Claims

1. A conjugate comprising a water-insoluble hydrogel Z, wherein said conjugate comprises a plurality of moieties -L^2-L^1-D covalently conjugated to Z,

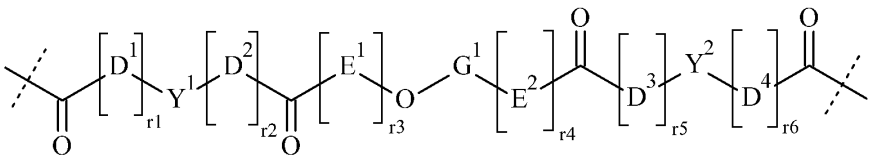
wherein

each -D is drug moiety;

each -L^1- is independently a linker moiety to which -D is covalently and reversibly conjugated;

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

Z is a PEG-based hydrogel comprising a plurality of backbone moieties that are crosslinked via crosslinker moieties -CL-, either directly or via a spacer moiety -SP- between a crosslinker moiety and -CL-, and wherein -CL- is of formula (A)

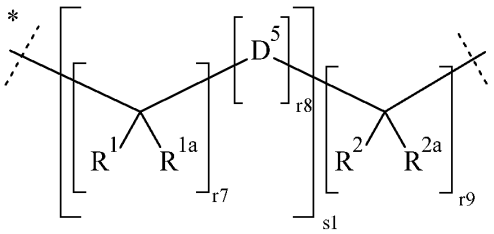


(A),

wherein

dashed lines indicate attachment to a backbone moiety or to a spacer moiety -SP-;

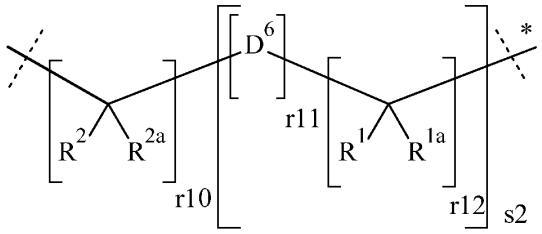
-Y^1- is of formula



,

wherein the dashed line marked with the asterisk indicates attachment to -D^1- and the unmarked dashed line indicates attachment to -D^2-;

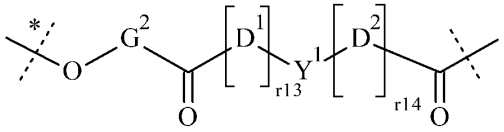
-Y^2- is of formula



,

wherein the dashed line marked with the asterisk indicates attachment to -D^4- and the unmarked dashed line indicates attachment to -D^3-;

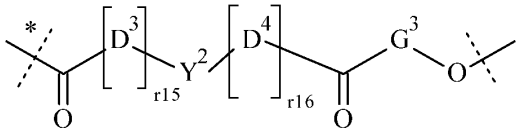
-E^1- is of formula



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wherein the dashed line marked with the asterisk indicates attachment to -(C=O)- and the unmarked dashed line indicates attachment to -O-;

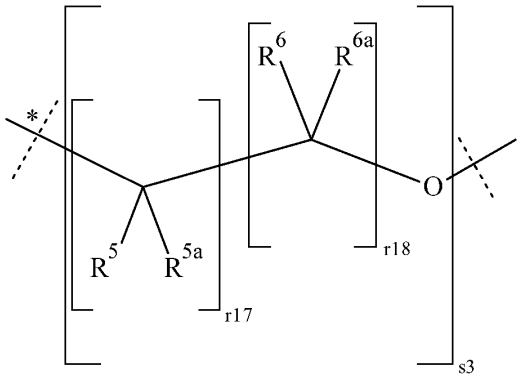
-E^2- is of formula



,

wherein the dashed line marked with the asterisk indicates attachment to -G^1- and the unmarked dashed line indicates attachment to -(C=O)-;

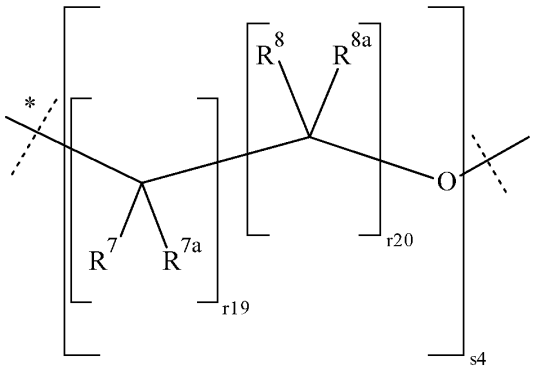
-G^1- is of formula



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wherein the dashed line marked with the asterisk indicates attachment to -O- and the unmarked dashed line indicates attachment to -E^2-;

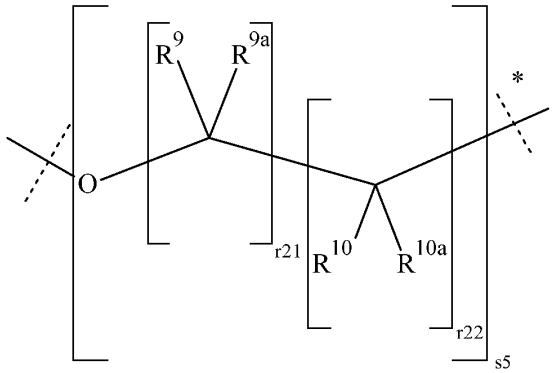
-G^2- is of formula



,

wherein the dashed line marked with the asterisk indicates attachment to -O- and the unmarked dashed line indicates attachment to -(C=O)-;

-G^3- is of formula



,

wherein the dashed line marked with the asterisk indicates attachment to -O- and the unmarked dashed line indicates attachment to -(C=O)-;

-D^1-, -D^2-, -D^3-,-D^4-, -D^5- and -D^6- are identical or different and each is independently of the others selected from the group comprising -O-, -NR^{11}-, -$N^+R^{12}R^{12a}$-, -S-, -(S=O)-, -$(S(O)_2)$-, -C(O)-, -$P(O)R^{13}$-, -$P(O)(OR^{13})$ and -$CR^{14}R^{14a}$-;

$-R^{1}$, $-R^{1a}$, $-R^{2}$, $-R^{2a}$, $-R^{3}$, $-R^{3a}$, $-R^{4}$, $-R^{4a}$, $-R^{5}$, $-R^{5a}$, $-R^{6}$, $-R^{6a}$, $-R^{7}$, $-R^{7a}$, $-R^{8}$, $-R^{8a}$, $-R^{9}$, $-R^{9a}$, $-R^{10}$, $-R^{10a}$, $-R^{11}$, $-R^{12}$, $-R^{12a}$, $-R^{13}$, $-R^{14}$ and $-R^{14a}$ are identical or different and each is independently of the others selected from the group consisting of -H and C_{1-6} alkyl;

optionally, one or more of the pairs $-R^{1}/-R^{1a}$, $-R^{2}/-R^{2a}$, $-R^{3}/-R^{3a}$, $-R^{4}/-R^{4a}$, $-R^{1}/-R^{2}$, $-R^{3}/-R^{4}$, $-R^{1a}/-R^{2a}$, $-R^{3a}/-R^{4a}$, $-R^{12}/-R^{12a}$, and $-R^{14}/-R^{14a}$ form a chemical bond or are joined together with the atom to which they are attached to form a C_{3-8} cycloalkyl or to form a ring A or are joined together with the atom to which they are attached to form a 4- to 7-membered heterocyclyl or 8- to 11-membered heterobicyclyl or adamantyl;

A is selected from the group consisting of phenyl, naphthyl, indenyl, indanyl and tetralinyl;

r1, r2, r5, r6, r13, r14, r15 and r16 are independently 0 or 1;

r3, r4 are independently 0, 1, 2, 3, or 4, with the provision that $r3 + r4 \geq 1$;

r7, r8, r9, r10, r11, r12 are independently 0, 1, 2, 3, or 4;

r17, r18, r19, r20, r21 and r22 are independently 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

s1, s2, s4, s5 are independently 1, 2, 3, 4, 5 or 6; and

s3 ranges from 1 to 900.

2. The conjugate of claim 1, wherein r3 and r4 are both 1.

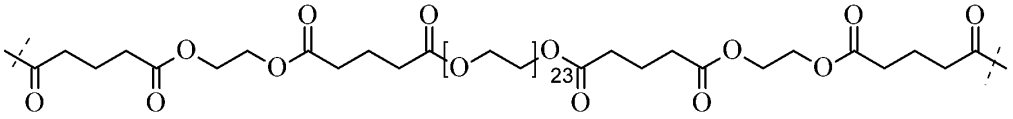
3. The conjugate of claim 1 or 2, wherein r1, r2, r5 and r6 are 0.

4. The conjugate of any one of claims 1 to 3, wherein s3 ranges from 15 to 100.

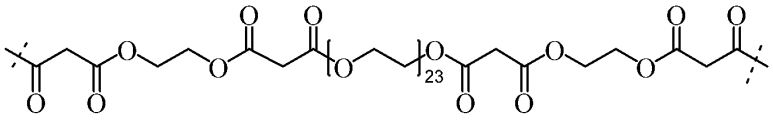
5. The conjugate of any one of claims 1 to 4, wherein s3 ranges from 20 to 50.

6. The conjugate of any one of claims 1 to 5, wherein a moiety -CL- has a molecular weight ranging from 0.2 kDa to 25 kDa

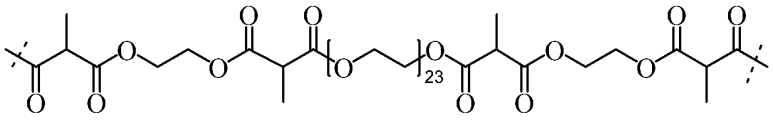
7. The conjugate of any one of claims 1 to 6, wherein a moiety -CL- is selected from the group consisting of



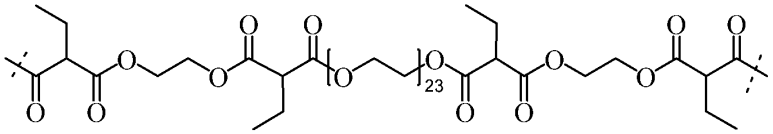
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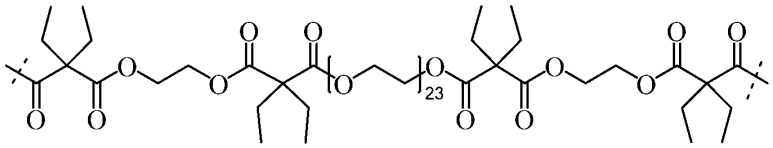
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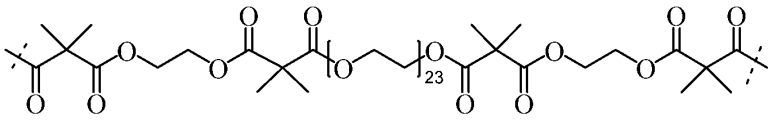
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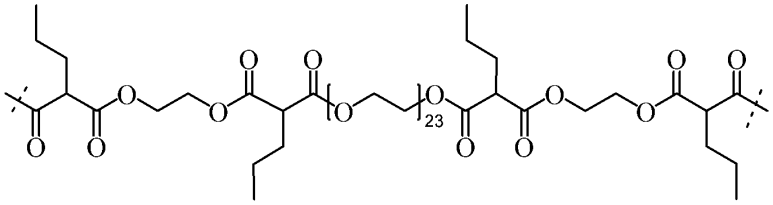
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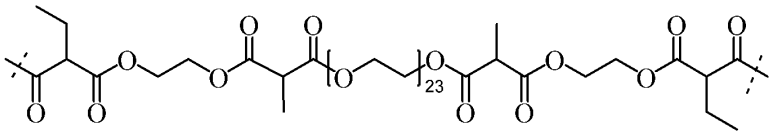
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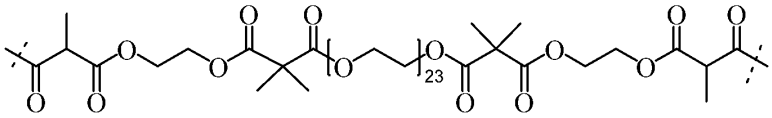


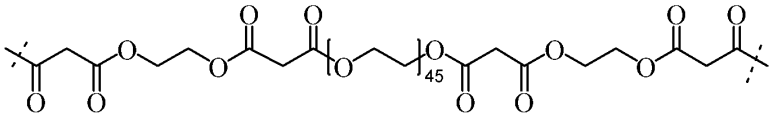
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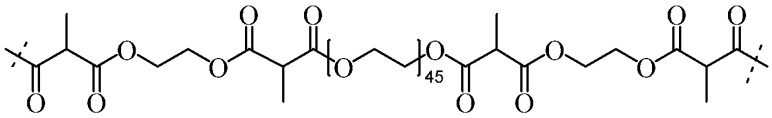


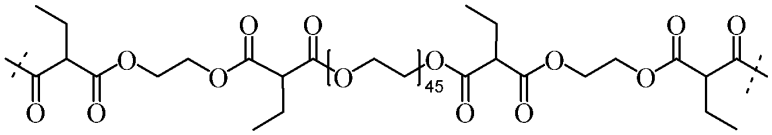
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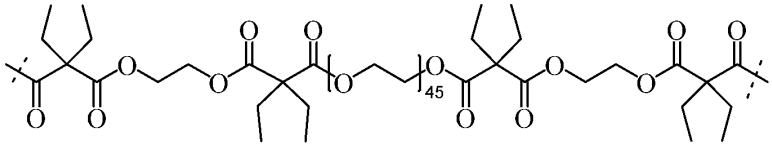

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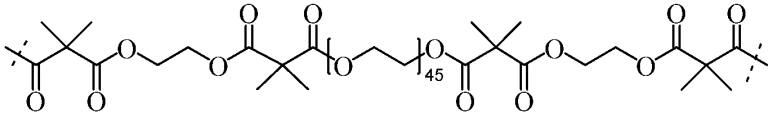

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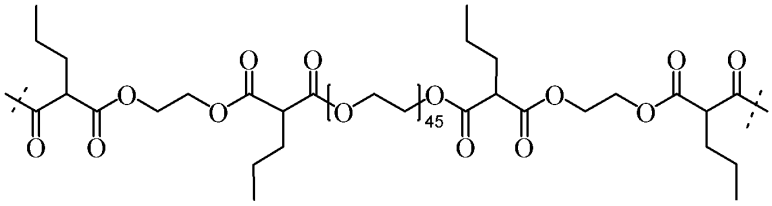

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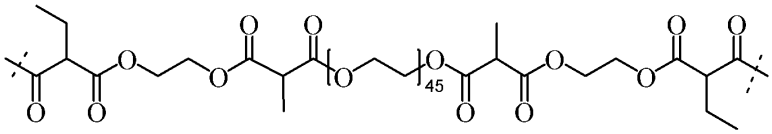

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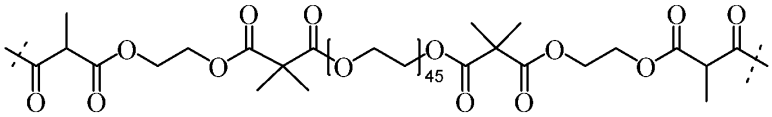

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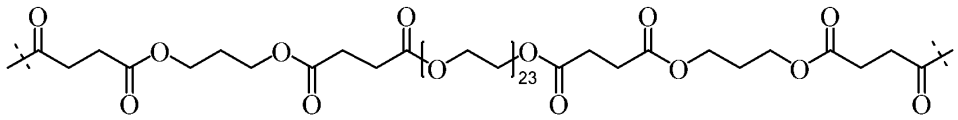

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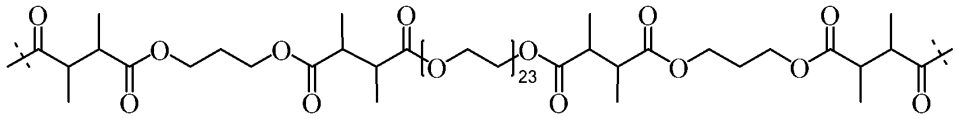

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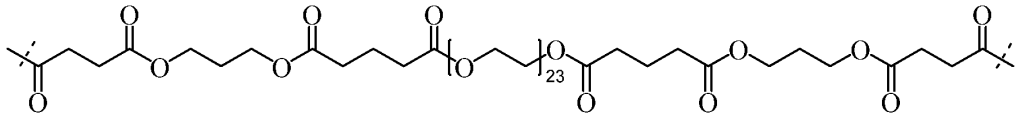

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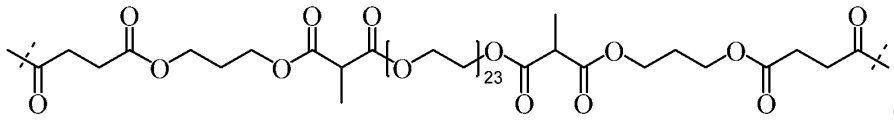
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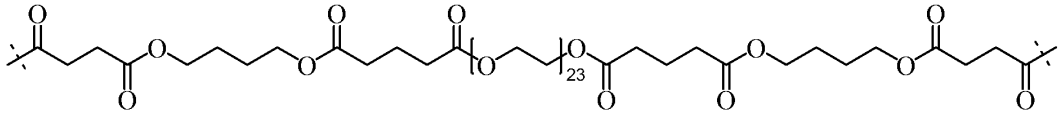
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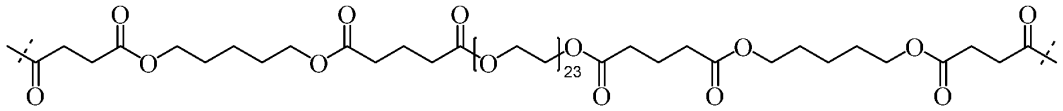
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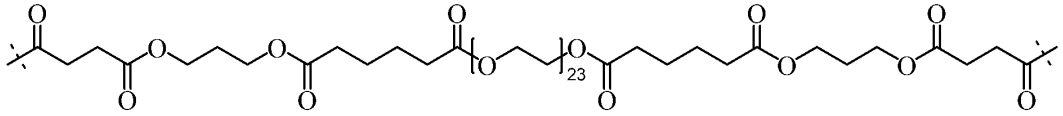
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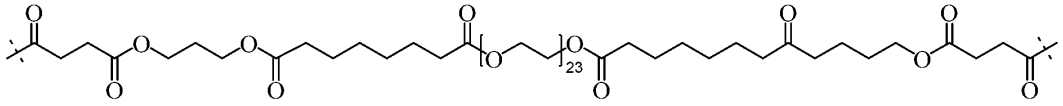
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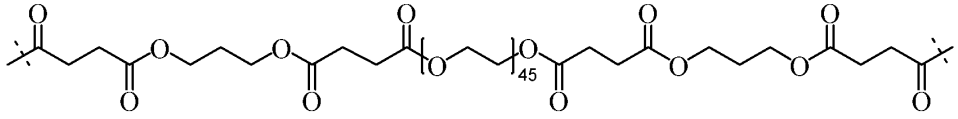
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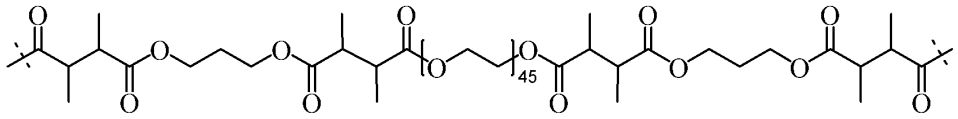
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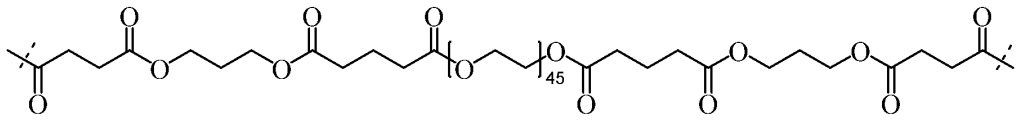
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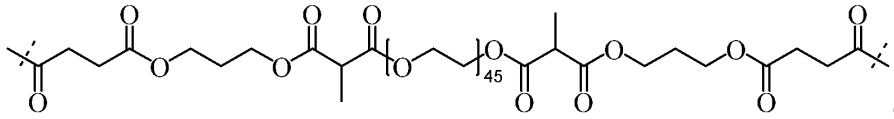
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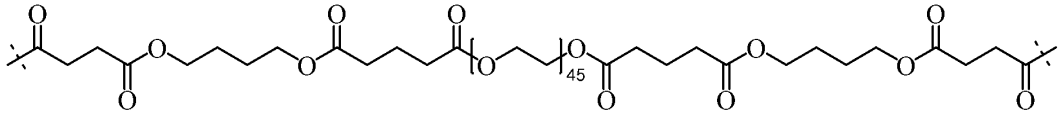
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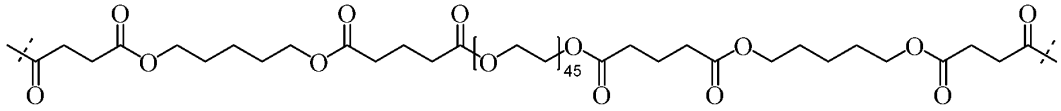
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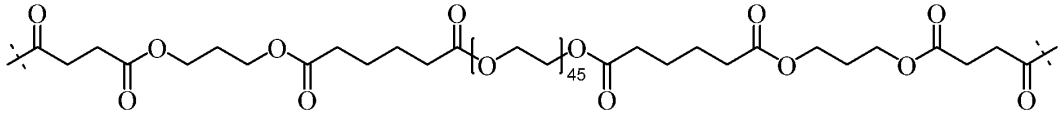
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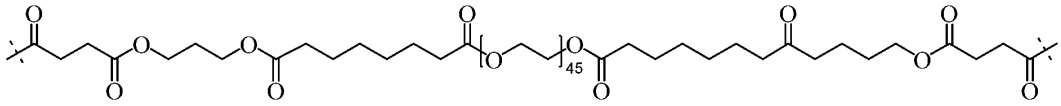
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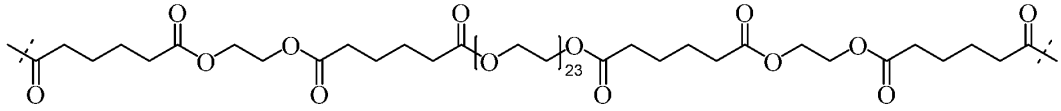
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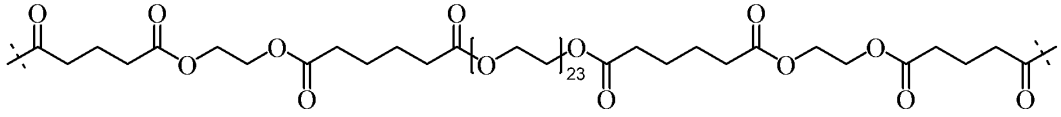
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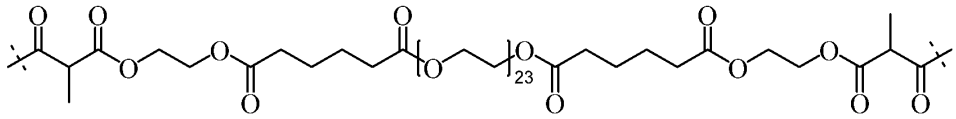
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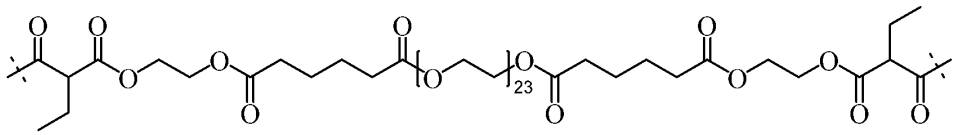
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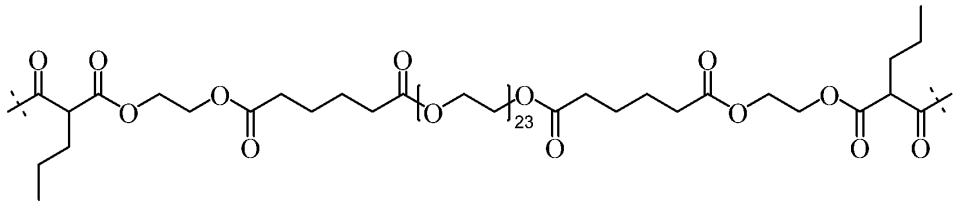
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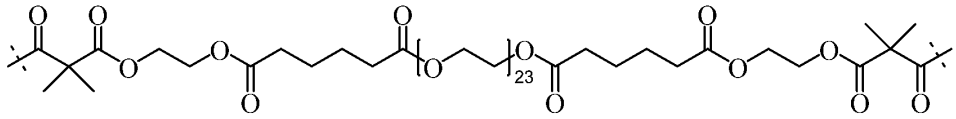
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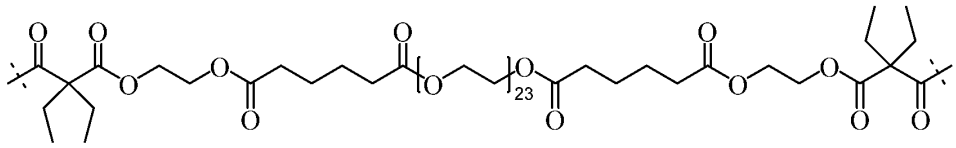
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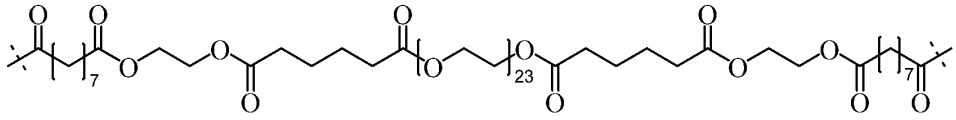
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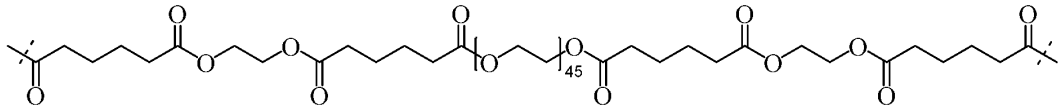
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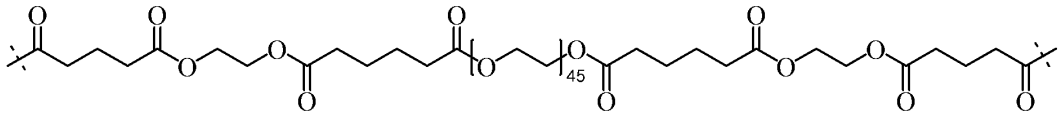
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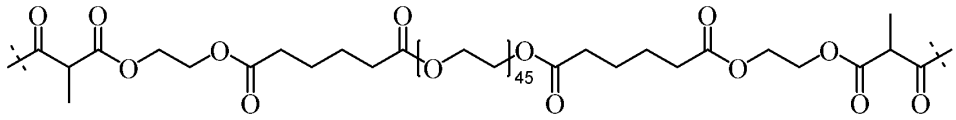
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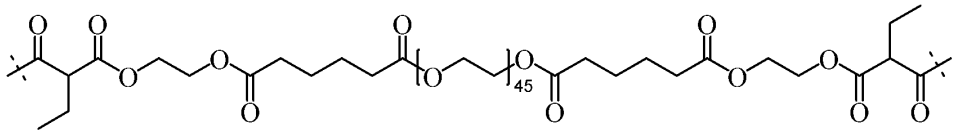
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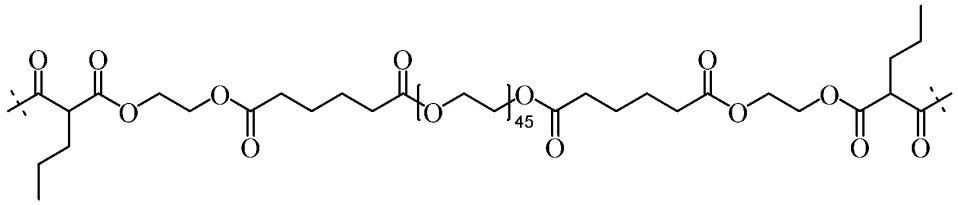
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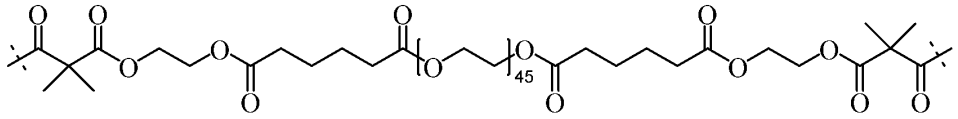
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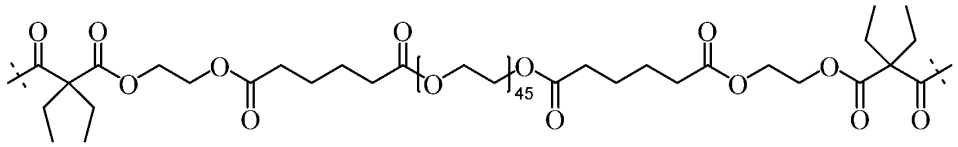
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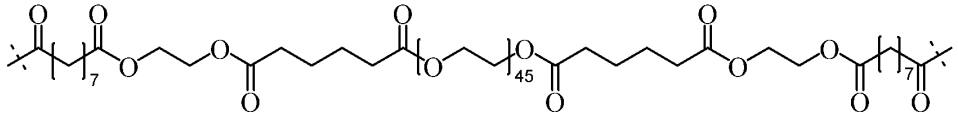
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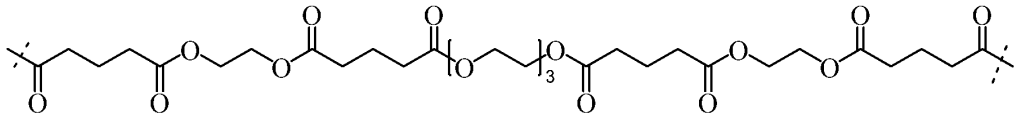
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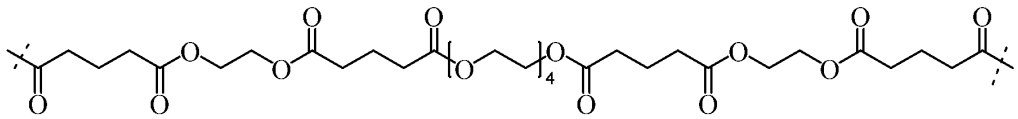
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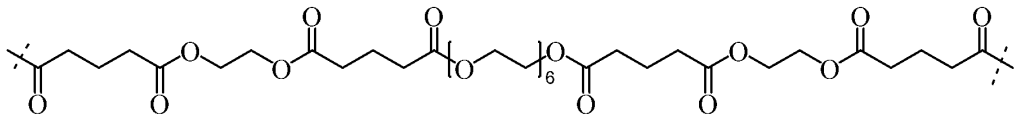
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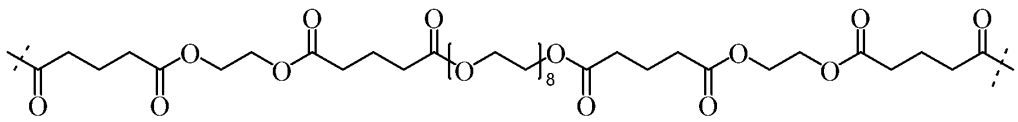
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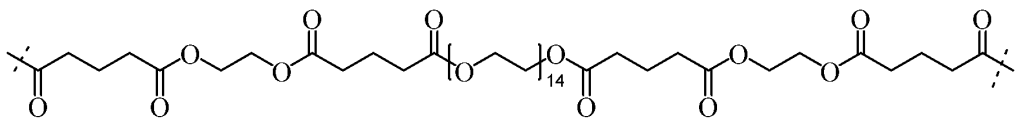
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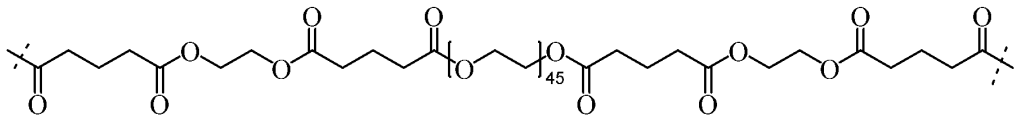
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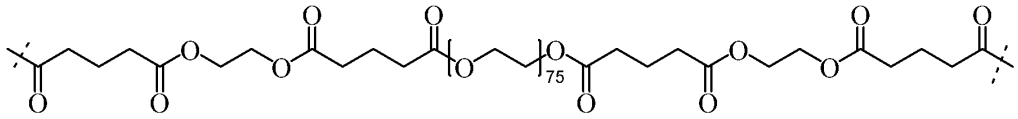


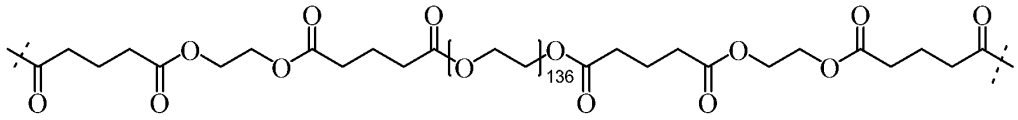
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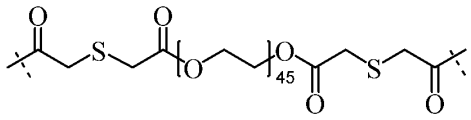


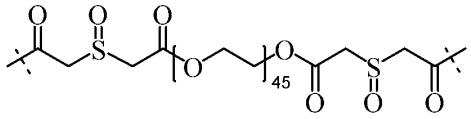
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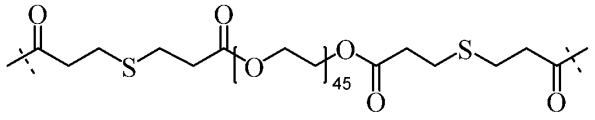

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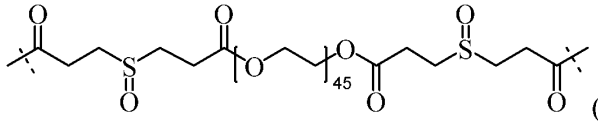

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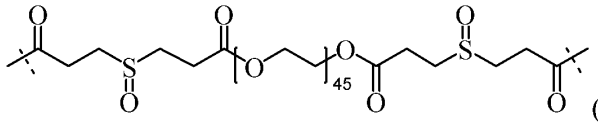

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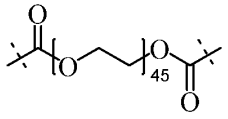

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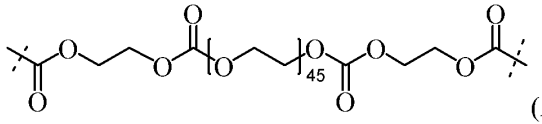

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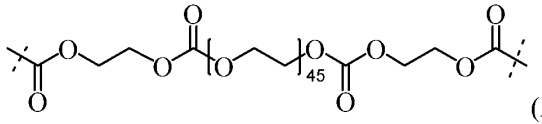

(A-60),

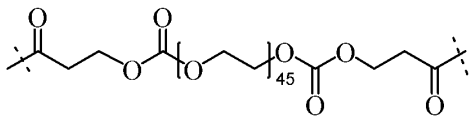

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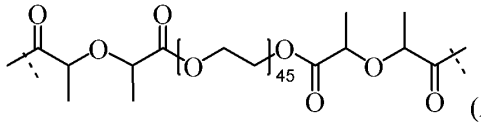

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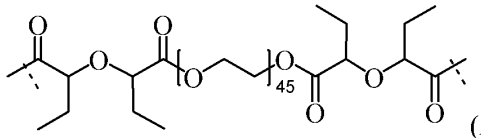

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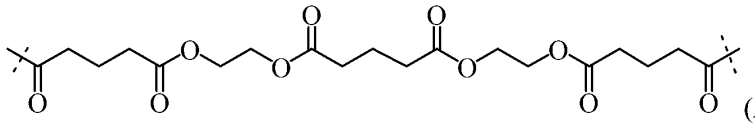

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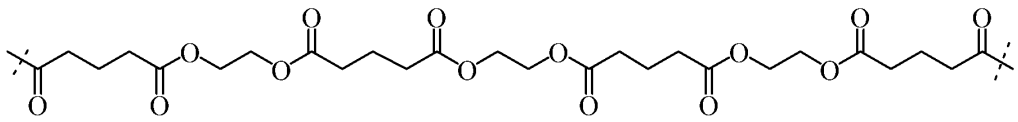

(A-65),


(A-66),


(A-67),


(A-68),


(A-69), and

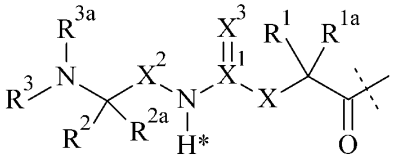

(A-70),

wherein

dashed lines indicate attachment to a backbone moiety or to a spacer moiety -SP-.

8. The conjugate of any any one of claims 1 to 7, wherein a backbone moiety has a molecular weight ranging from 1 kDa to 20 kDa.

9. The conjugate of any one of claims 1 to 8, wherein $-L^1-$ is of formula (I):


(I)

,

wherein the dashed line indicates the attachment to a nitrogen, hydroxyl or thiol of -D;

-X- is selected from the group consisting of $-C(R^4R^{4a})-$, $-N(R^4)-$, -O-, $-C(R^4R^{4a})-C(R^5R^{5a})-$, $-C(R^5R^{5a})-C(R^4R^{4a})-$, $-C(R^4R^{4a})-N(R^6)-$, $-N(R^6)-C(R^4R^{4a})-$, $-C(R^4R^{4a})-O-$, $-O-C(R^4R^{4a})-$, and $-C(R^7R^{7a})-$,

X^1 is selected from the group consisting of C and S(O);

$-X^2-$ is selected from the group consisting of $-C(R^8R^{8a})-$ and $-C(R^8R^{8a})-C(R^9R^{9a})-$;

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

$-R^1$, $-R^{1a}$, $-R^2$, $-R^{2a}$, $-R^4$, $-R^{4a}$, $-R^5$, $-R^{5a}$, $-R^6$, $-R^8$, $-R^{8a}$, $-R^9$ and $-R^{9a}$ are independently selected from the group consisting of -H and C_{1-6} alkyl;

$-R^3$ and $-R^{3a}$ are independently selected from the group consisting of -H and C_{1-6} alkyl, provided that in case one of $-R^3$ and $-R^{3a}$ or both are other than -H they are connected to N to which they are attached through an sp^3-hybridized carbon atom;

$-R^7$ is selected from the group consisting of $-N(R^{10}R^{10a})$ and $-NR^{10}-(C=O)-R^{11}$;

$-R^{7a}$, $-R^{10}$, $-R^{10a}$ and $-R^{11}$ are independently selected from the group consisting of -H and C_{1-6} alkyl;

alternatively, one or more of the pairs $-R^{1a}/-R^{4a}$, $-R^{1a}/-R^{5a}$, $-R^{1a}/-R^{7a}$, $-R^{4a}/-R^{5a}$ and $-R^{8a}/-R^{9a}$ form a chemical bond;

alternatively, one or more of the pairs $-R^1/-R^{1a}$, $-R^2/-R^{2a}$, $-R^4/-R^{4a}$, $-R^5/-R^{5a}$, $-R^8/-R^{8a}$ and $-R^9/-R^{9a}$ are joined together with the atom to which they are attached to form a C_{3-10} cycloalkyl or 3- to 10-membered heterocyclyl;

alternatively, one or more of the pairs $-R^1/-R^4$, $-R^1/-R^5$, $-R^1/-R^6$, $-R^1/-R^{7a}$, $-R^4/-R^5$, $-R^4/-R^6$, $-R^8/-R^9$ and $-R^2/-R^3$ are joined together with the atoms to which they are attached to form a ring A;

alternatively, R^3/R^{3a} are joined together with the nitrogen atom to which they are attached to form a 3- to 10-membered heterocycle;

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; and

wherein $-L^1-$ is substituted with $-L^2-$ and wherein $-L^1-$ is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (II) is not replaced by $-L^2-$ or a substituent.

10. The conjugate of any one of claims 1 to 9, wherein $-L^2-$ is a spacer moiety.

11. The conjugate of any one of claims 1 to 10, wherein -D is an antibiotic moiety.

12. The conjugate of any one of claims 1 to 11, wherein -D is selected from the group consisting of aminoglycosides, tetracycline antibiotics, amphenicols, pleuromutilins,

macrolid antibiotics, lincosamides, steroid antibiotics, antifolate antibiotics, sulfonamides, topoisomerase inhibitors, quinolones, fluoroquinolones, nitroimidazole antibiotics, nitrofuran antibiotics, rifamycins, glycopeptides, penicillins, cephalosporins, monobactams, beta-lactamase inhibitors, polymyxin antibiotics, lipopeptide antibiotics, oxazolidinon, antimicrobial peptides, antimicrobial proteins, porphyrins, azole antifungals, polyenes, antiprotozoal drugs, fosfomycin, cycloserine, and bacitracin.

13. The conjugate of any one of claims 1 to 12, wherein -D is daptomycin.

14. A pharmaceutical composition comprising the conjugate of any one of claims 1 to 13 and at least one excipient.

15. The conjugate of any one of claims 1 to 13 or the pharmaceutical composition of claim 14 for use as a medicament.

16. The conjugate of any one of claims 11 to 13 or the pharmaceutical composition of claim 14 for use in the in the diagnosis, prophylaxis or treatment of a disease that can be treated with the conjugates of the present invention.

17. The conjugate of any one of claims 11 to 13 or the pharmaceutical composition of claim 14 for use as an antibiotic.

18. The conjugate of any one of claims 11 to 13 or the pharmaceutical composition of claim 14 for use in a method of preventing or treating a joint infection.