Claims

1. A process for the preparation of a hydrogel comprising the steps of:

(a) providing a mixture comprising

(a-i) at least one backbone reagent, wherein the at least one backbone reagent has a molecular weight ranging from 1 to 100 kDa, and comprises at least three amines ($-NH_2$ and/or -NH-);

(a-ii) at least one crosslinker reagent, wherein the at least one crosslinker reagent has a molecular weight ranging from 6 to 40 kDa, the at least one crosslinker reagent comprising

(i) at least two carbonyloxy groups (–(C=O)–O– or –O–(C=O)–), and additionally

(ii) at least two activated functional end groups selected from the group consisting of activated ester groups, activated carbamate groups, activated carbonate groups and activated thiocarbonate groups,

and being PEG-based comprising at least 70% PEG; and

(a-iii) a first solvent and at least a second solvent, which second solvent is immiscible in the first solvent,

in a weight ratio of the at least one backbone reagent to the at least one crosslinker reagent ranging from 1:99 to 99:1; and

(b) polymerizing the mixture of step (a) in a suspension polymerization to a hydrogel.

2. The process of claim 1, wherein the mixture of step (a) further comprises a detergens.

3. The process of claim 2, wherein the detergens is Cithrol DPHS, Hypermer 70A, Hypermer B246, Hypermer 1599A, Hypermer 2296, or Hypermer 1083.

4. The process of any one of claims 1 to 3, wherein the polymerization in step (b) is initiated by adding a base.

5. The process of claim 4, wherein the base is selected from *N,N,N',N'*-tetramethylethylene diamine (TMEDA), 1,4-dimethylpiperazine, 4-methylmorpholine, 4-ethylmorpholine, 1,4-diazabicyclo[2.2.2]octane, 1,1,4,7,10,10-hexamethyltriethylenetetramine, 1,4,7-trimethyl-1,4,7-triazacyclononane, tris[2-(dimethylamino)ethyl]amine, triethylamine, diisopropylethylamine (DIPEA), trimethylamine, N,N-dimethylethylamine, N,N,N',N'-tetramethyl-1,6-hexanediamine, N,N,N',N'',N''-pentamethyldiethylenetriamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, and hexamethylenetetramine.

6. The process of any one of claims 1 to 5, wherein the mixture of step (a) is an emulsion.

7. The process of any one of claims 1 to 6, wherein the process further comprises the step of:

(c) working-up the hydrogel.

8. The process of any one of claims 1 to 7, wherein the at least one backbone reagent is selected from the group consisting of

a compound of formula (I)

$$B(-(A^0)_{x1}-(SP)_{x2}-A^1-P-A^2-Hyp^1)_x \quad (I),$$

wherein

B is a branching core,

SP is a spacer moiety selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl,

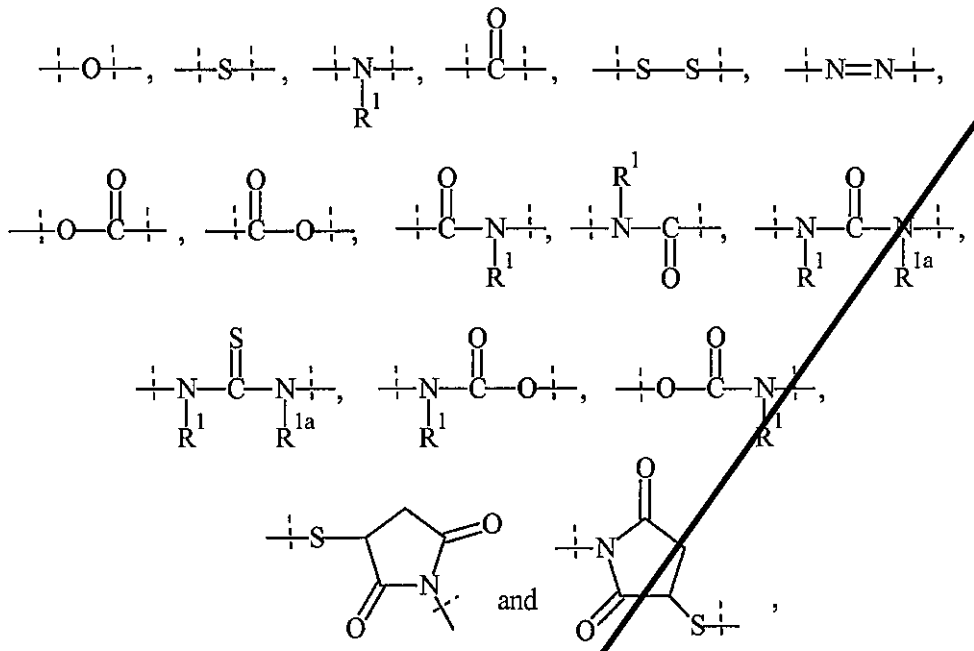
P is a PEG-based polymeric chain comprising at least 80% PEG, preferably at least 85% PEG, more preferably at least 90% PEG and most preferably at least 95% PEG,

Hyp^1 is a moiety comprising an amine ($-NH_2$ and/or -NH-) or a polyamine comprising at least two amines ($-NH_2$ and/or -NH-),

x is an integer from 3 to 16,

x1, x2 are independently of each other 0 or 1, provided that x1 is 0, if x2 is 0,

A^0, A^1, A^2 are independently of each other selected from the group consisting of



wherein R^1 and R^{1a} are independently of each other selected from H and C_{1-6} alkyl;

a compound of formula (II)

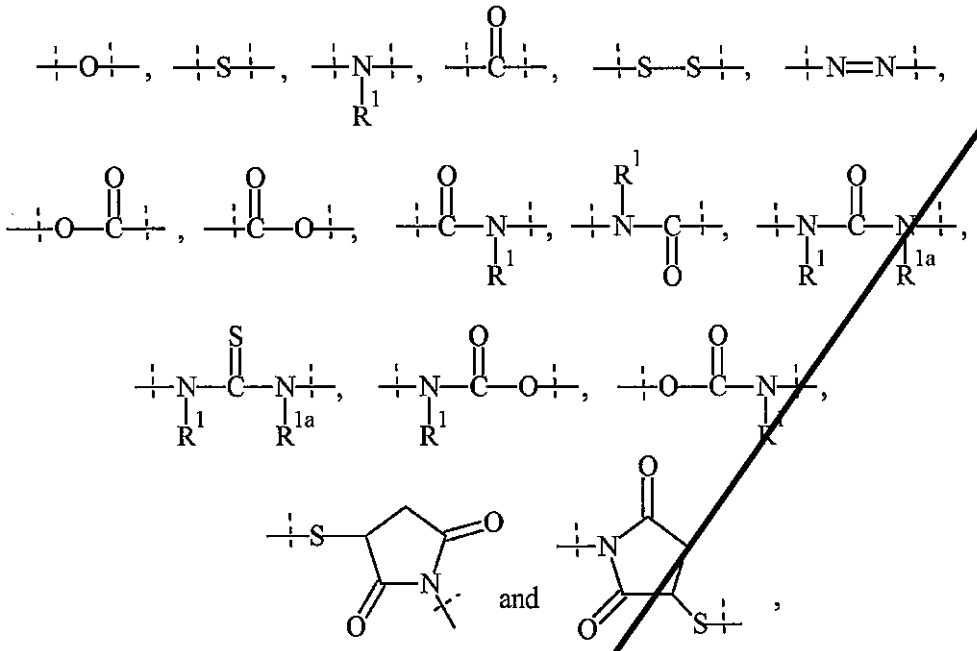
$Hyp^2 - A^3 - P - A^4 - Hyp^3$ (II),

wherein

P is defined as above in the compound of formula (I),

Hyp^2, Hyp^3 are independently of each other a polyamine comprising at least two amines (-NH_2 and/or -NH-), and

A^3 and A^4 are independently selected from the group consisting of



wherein R^1 and R^{1a} are independently of each other selected from H and C_{1-6} alkyl;

a compound of formula (III)

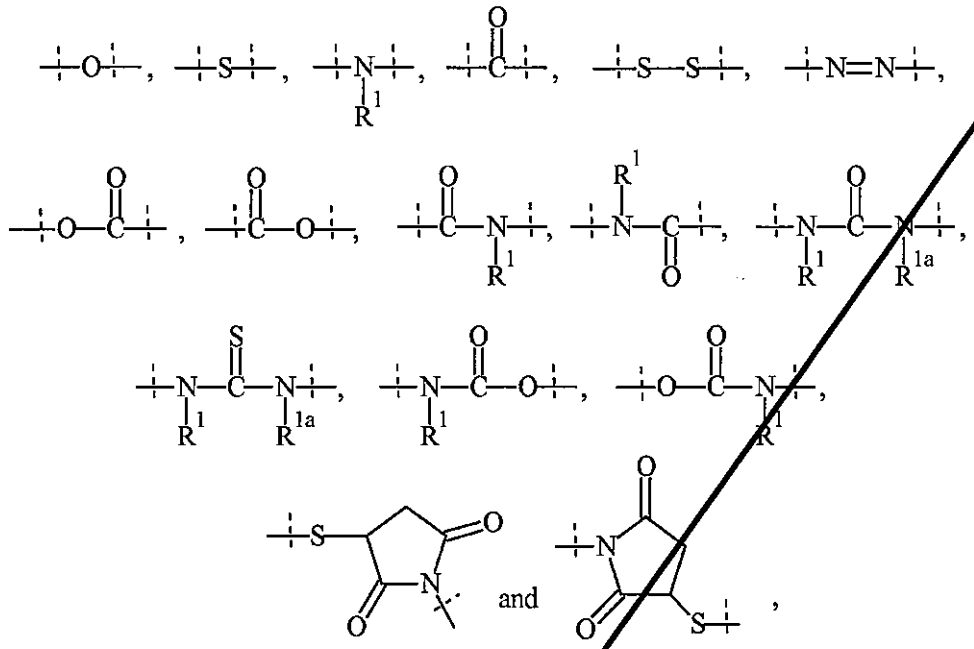
$$P^1 - A^5 - Hyp^4 \qquad (III),$$

wherein

P^1 is a PEG-based polymeric chain comprising at least 80% PEG, preferably at least 85% PEG, more preferably at least 90% PEG and most preferably at least 95% PEG,

Hyp^4 is a polyamine comprising at least three amines ($-NH_2$ and/or -NH), and

A^5 is selected from the group consisting of



wherein R^1 and R^{1a} are independently of each other selected from H and C_{1-6} alkyl;

and

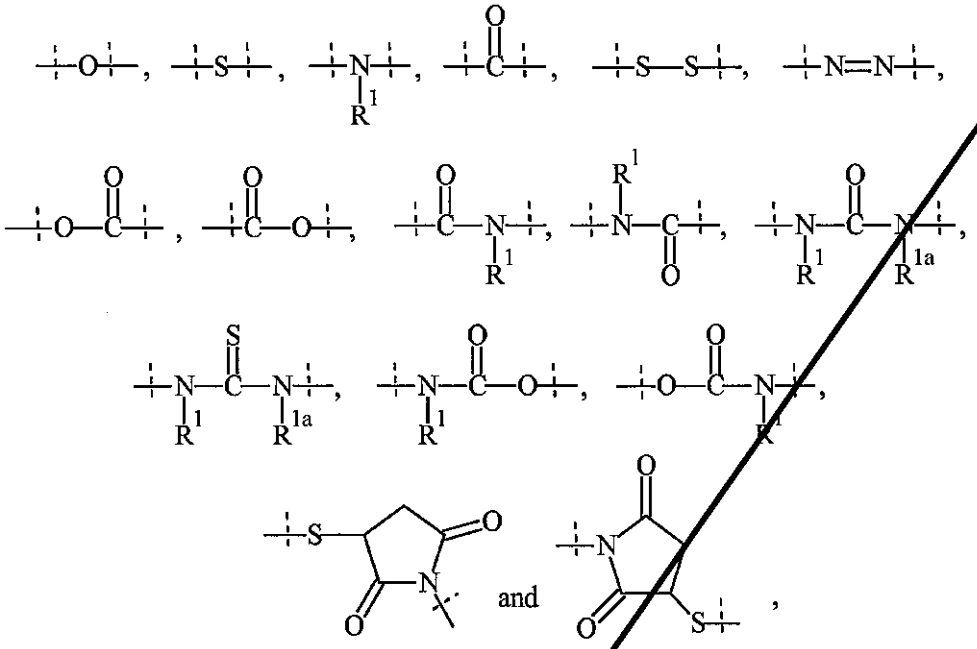
a compound of formula (IV),

$T^1 - A^6 - Hyp^5$ (IV),

wherein

Hyp^5 is a polyamine comprising at least three amines ($-NH_2$ and/or -NH), and

A^6 is selected from the group consisting of

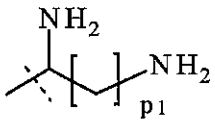


wherein R^1 and R^{1a} are independently of each other selected from H and C_{1-6} alkyl; and

T^1 is selected from the group consisting of C_{1-50} alkyl, C_{2-50} alkenyl or C_{2-50} alkynyl, which fragment is optionally interrupted by one or more group(s) selected from -NH-, -N(C_{1-4} alkyl)-, -O-, -S-, -C(O)-, -C(O)NH-, -C(O)N(C_{1-4} alkyl)-, -O-C(O)-, -S(O)-, -$S(O)_2$-, 4- to 7-membered heterocyclyl, phenyl or naphthyl.

9. The process of claim 8, wherein Hyp^1, Hyp^2, Hyp^3, Hyp^4, and Hyp^5 are selected from the group consisting of

a moiety of formula (e-i)



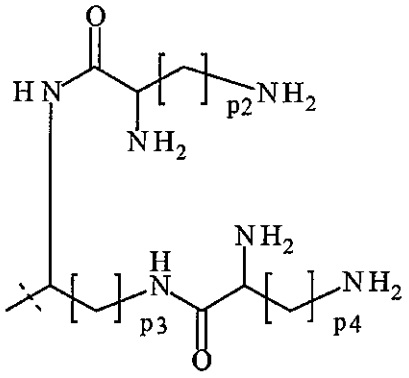
(e-i)

wherein

p1 is an integer from 1 to 5, preferably p1 is 4, and

the dashed line indicates attachment to A^2 if the backbone reagent has a structure of formula (I) and to A^3 or A^4 if the backbone reagent has the structure of formula (II);

a moiety of formula (e-ii)



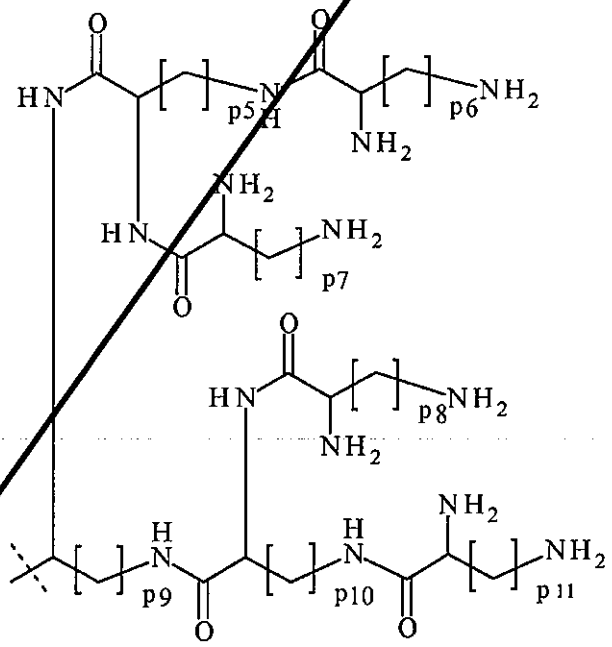
(e-ii)

wherein

p2, p3 and p4 are identical or different and each is independently of the others an integer from 1 to 5, preferably p2, p3 and p4 are 4, and

the dashed line indicates attachment to A^2 if the backbone reagent has a structure of formula (I), to A^3 or A^4 if the backbone reagent has a structure of formula (II), to A^5 if the backbone reagent has a structure of formula (III) and to A^6 if the backbone reagent has a structure of formula (IV);

a moiety of formula (e-iii)



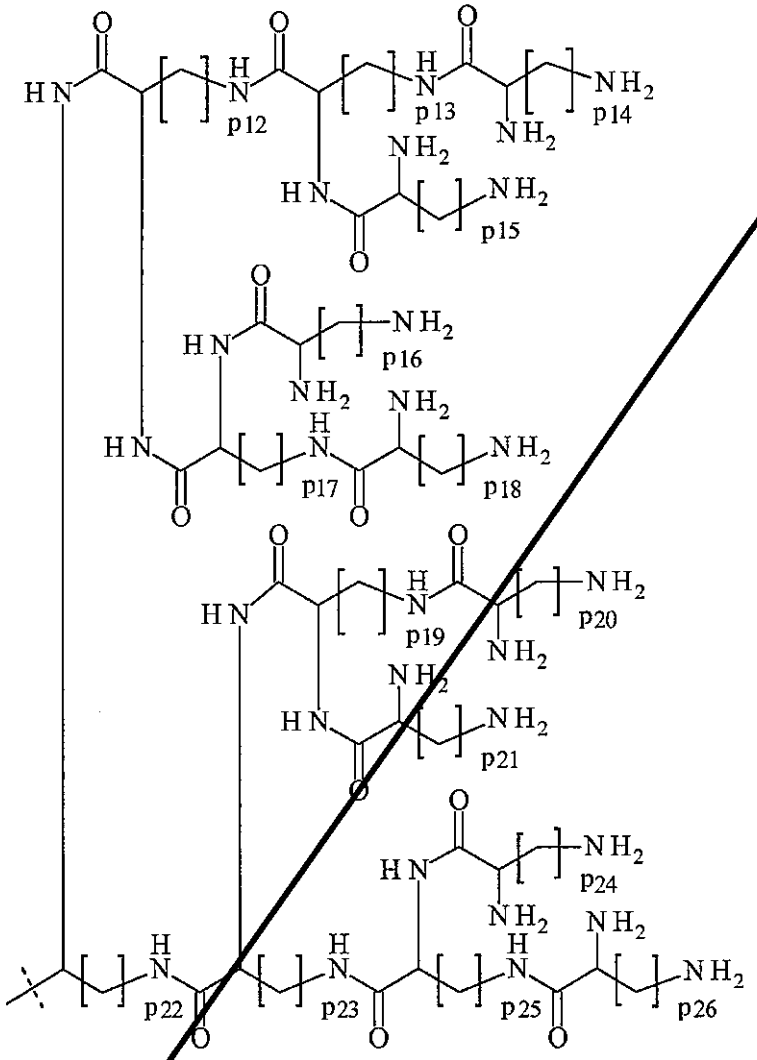
(e-iii)

wherein

p5 to p11 are identical or different and each is independently of the others an integer from 1 to 5, preferably p5 to p11 are 4, and

the dashed line indicates attachment to A^2 if the backbone reagent is of formula (I), to A^3 or A^4 if the backbone reagent is of formula (II), to A^5 if the backbone reagent is of formula (III) and to A^6 if the backbone reagent is of formula (IV);

a moiety of formula (e-iv)



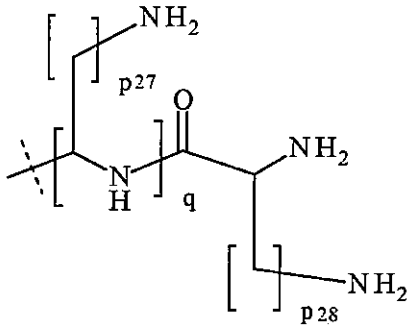
(e-iv)

wherein

p12 to p26 are identical or different and each is independently of the others an integer from 1 to 5, preferably p12 to p26 are 4, and

the dashed line indicates attachment to A^2 if the backbone reagent has a structure of formula (I), to A^3 or A^4 if the backbone reagent has a structure of formula (II), to A^5 if the backbone reagent has a structure of formula (III) and to A^6 if the backbone reagent has a structure of formula (IV);

a moiety of formula (e-v)



(e-v)

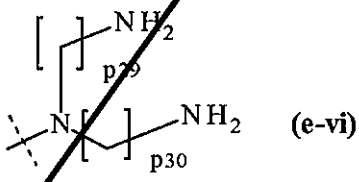
wherein

p27 and p28 are identical or different and each is independently of the other an integer from 1 to 5, preferably p27 and p28 are 4,

q is an integer from 1 to 8, preferably q is 2 or 6 and most preferably 1 is 6, and

the dashed line indicates attachment to A^2 if the backbone reagent has a structure of formula (I), to A^3 or A^4 if the backbone reagent has a structure of formula (II), to A^5 if the backbone reagent has a structure of formula (III) and to A^6 if the backbone reagent has a structure of formula (IV);

a moiety of formula (e-vi)



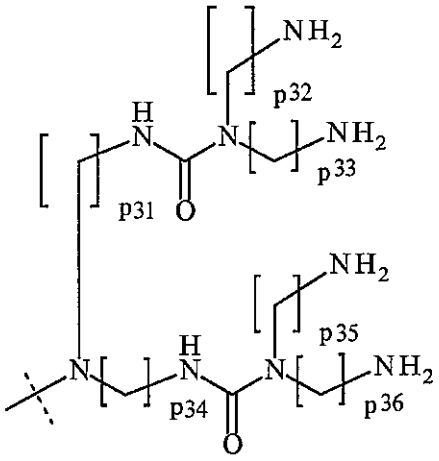
(e-vi)

wherein

p29 and p30 are identical or different and each is independently of the other an integer from 2 to 5, preferably p29 and p30 are 3, and

the dashed line indicates attachment to A^2 if the backbone reagent has the structure of formula (I), to A^3 or A^4 if the backbone reagent has the structure of formula (II), to A^5 if the backbone reagent has the structure of formula (III) and to A^6 if the backbone reagent has the structure of formula (IV);

a moiety of formula (e-vii)



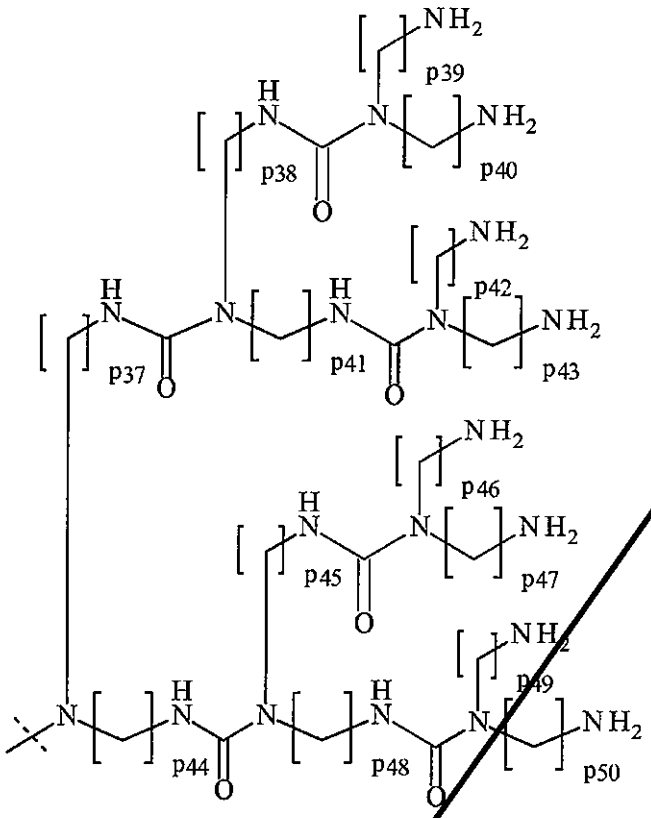
(e-vii)

wherein

p31 to p36 are identical or different and each is independently of the others an integer from 2 to 5, preferably p31 to p36 are 3, and

the dashed line indicates attachment to A^2 if the backbone reagent has a structure of formula (I), to A^3 or A^4 if the backbone reagent has a structure of formula (II), to A^5 if the backbone reagent has a structure of formula (III) and to A^6 if the backbone reagent has a structure of formula (IV);

a moiety of formula (e-viii)



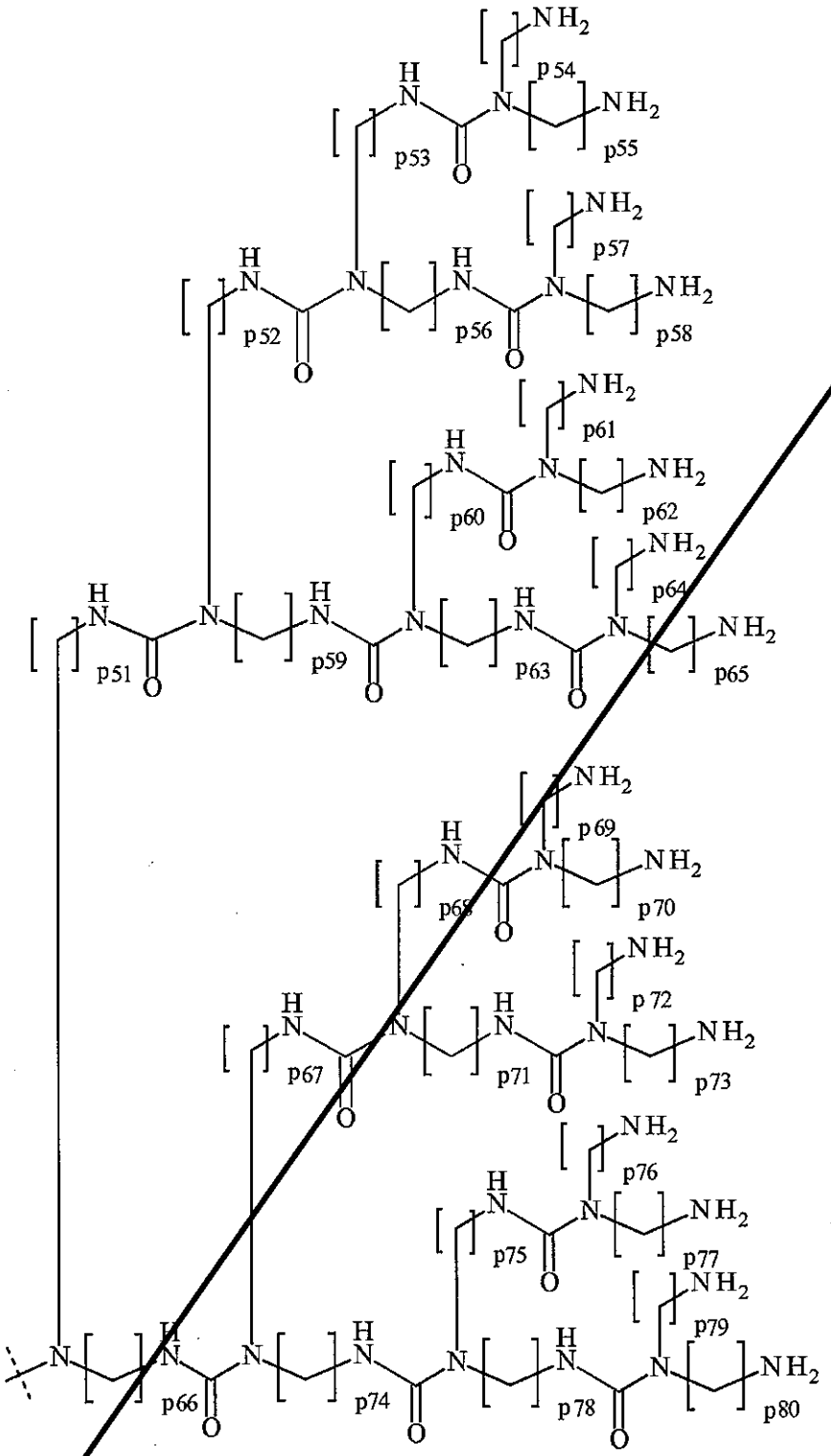
(e-viii)

wherein

p37 to p50 are identical or different and each is independently of the others an integer from 2 to 5, preferably p37 to p50 are 3, and

the dashed line indicates attachment to A^2 if the backbone reagent has a structure of formula (I), to A^3 or A^4 if the backbone reagent has a structure of formula (II), to A^5 if the backbone reagent has a structure of formula (III) and to A^6 if the backbone reagent has a structure of formula (IV); and

a moiety of formula (e-ix):



(e-ix)

wherein

p51 to p80 are identical or different and each is independently of the others an integer from 2 to 5, preferably p51 to p80 are 3, and

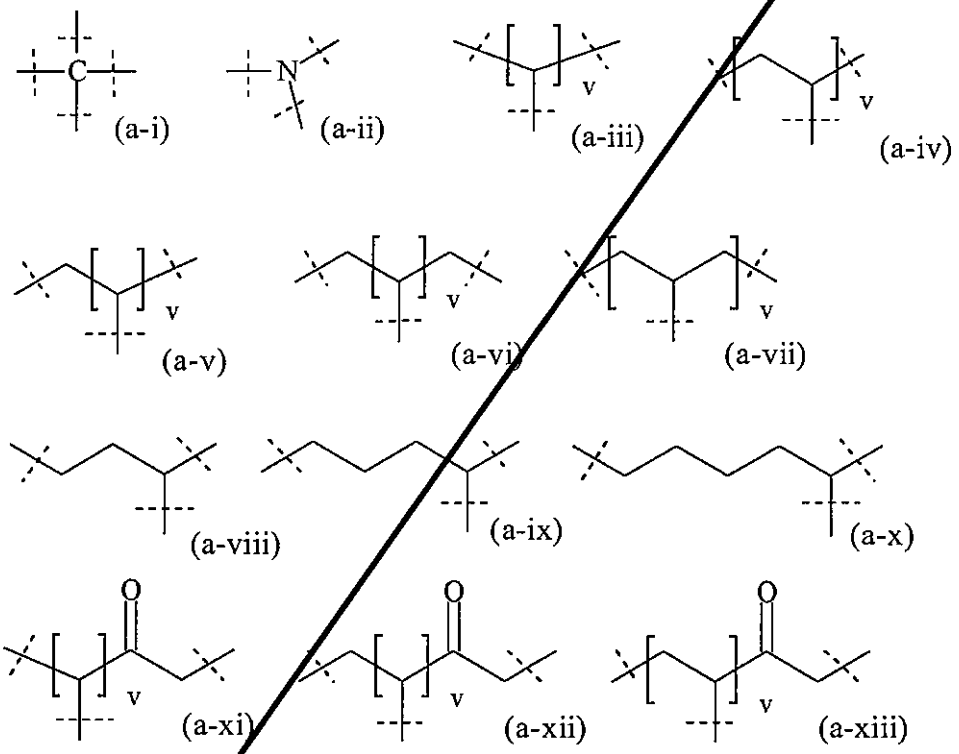
the dashed line indicates attachment to A^2 if the backbone reagent has a structure of formula (I), to A^3 or A^4 if the backbone reagent has a structure of formula (II), to A^5 if

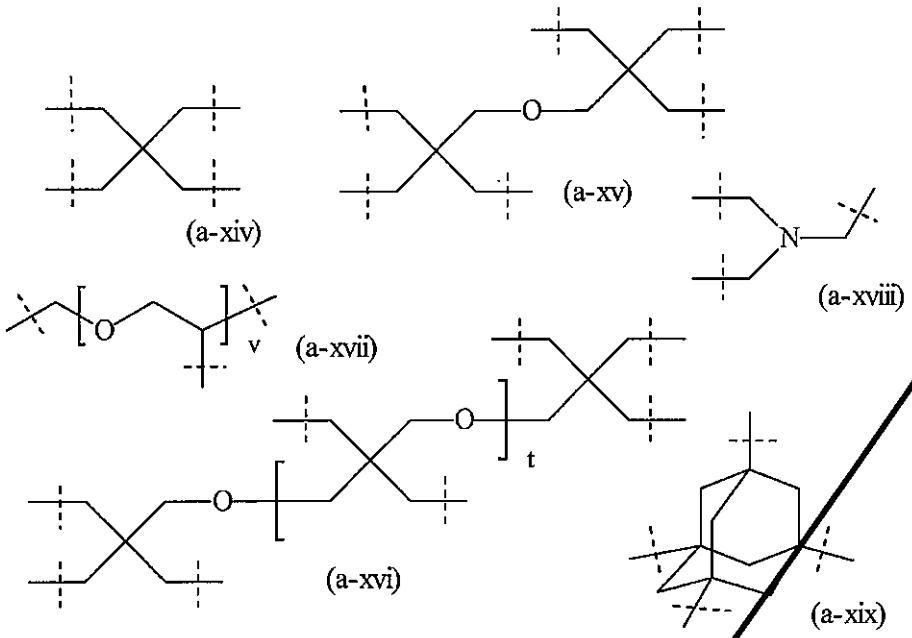
the backbone reagent has a structure of formula (III) and to A^6 if the backbone reagent has a structure of formula (IV); and

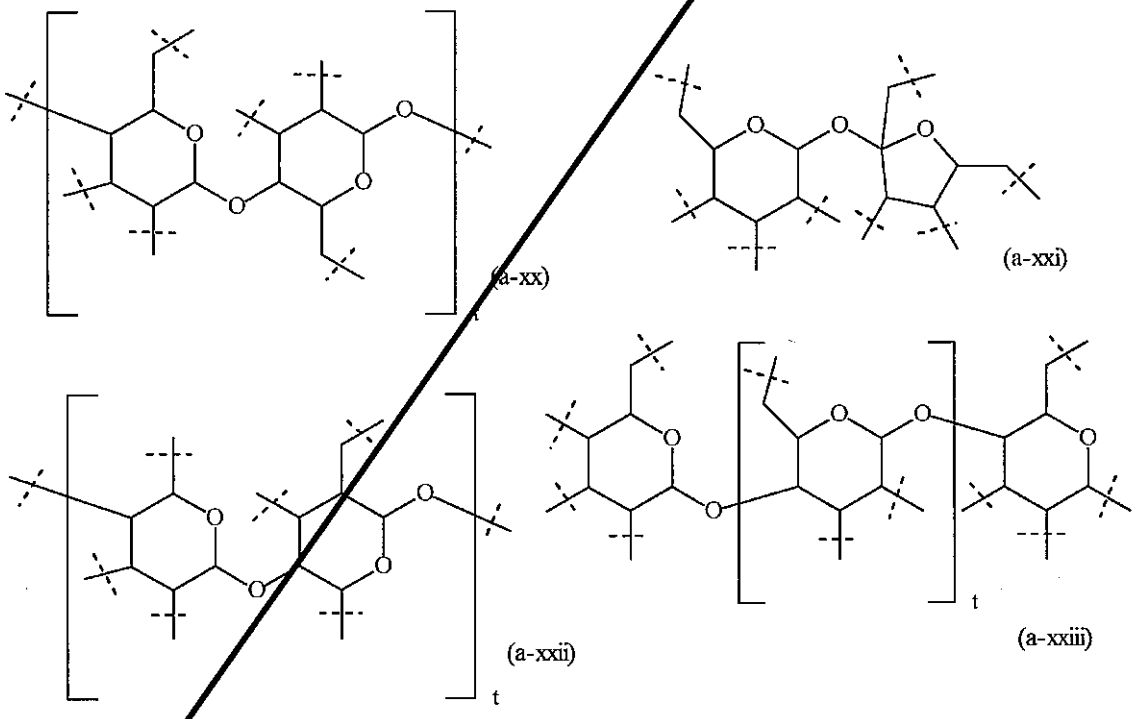
wherein the moieties (e-i) to (e-v) may at each chiral center be in either R- or S-configuration, preferably, all chiral centers of a moiety (e-i) to (e-v) are in the same configuration.

10. The process of claim 8 or 9, wherein the backbone reagent is a compound of formula (I).

11. The process of any one of claims 8 to 10, wherein the branching core B is selected from the following structures:







wherein

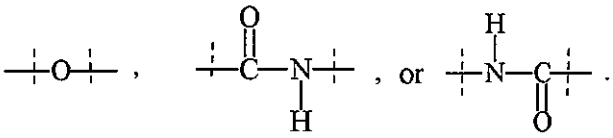
dashed lines indicate attachment to A^0 or, if x1 and x2 are both 0, to A^1,

t is 1 or 2; preferably t is 1,

v is 1, 2, 3, 4, 5, ,6 ,7 ,8 , 9, 10, 11, 12, 13 or 14; preferably, v is 2, 3, 4, 5, 6; more preferably, v is 2, 4 or 6; most preferably, v is 2.

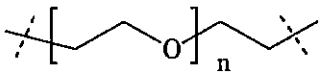
12. The process of claim 11, wherein B is of formula (a-xiv).

13. The process of any one of claims 8 to 12, wherein A^0 is



14. The process of any one of claims 8 to 13, wherein x1 and x2 are 0.

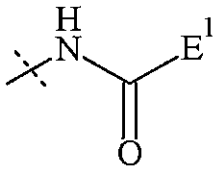
15. The process of any one of claims 8 to 14, wherein P has the structure of formula (c-i):



(c-i),

wherein n ranges from 6 to 900, more preferably n ranges from 20 to 700 and most preferably n ranges from 20 to 250.

16. The process of any one of claims 8 to 15, wherein the moiety – A^2 – Hyp^1 is a moiety of the formula



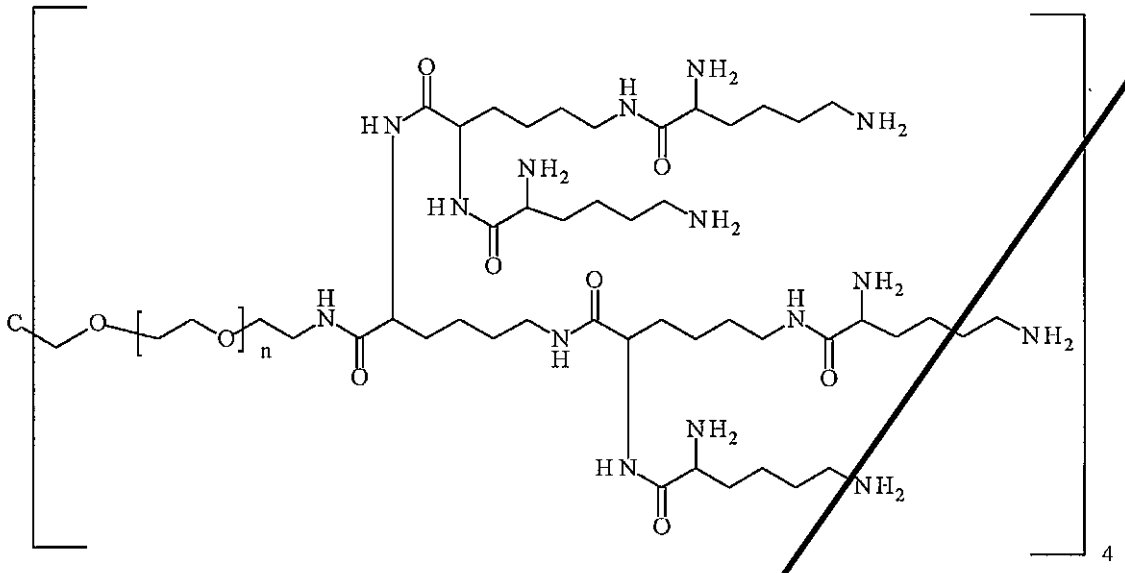
,

wherein

the dashed line indicates attachment to P; and

E^1 is selected from formulas (e-i) to (e-ix).

17. The process of any one of claims 1 to 16, wherein the backbone reagent has the following formula:



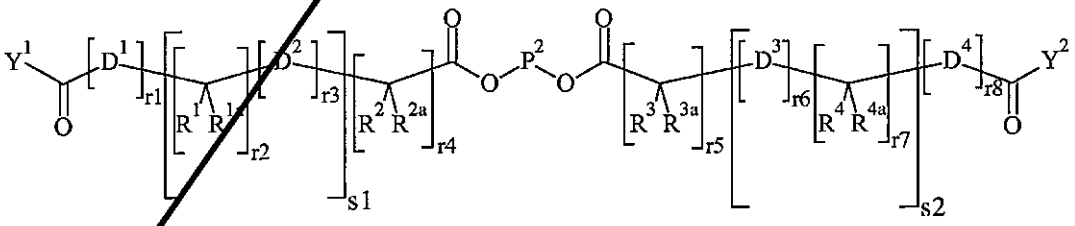
wherein

n ranges from 10 to 40, preferably from 10 to 30, more preferably from 10 to 20.

18. The process of claim 17, wherein n ranges from 20 to 30 kDa and most preferably n is 28.

19. The process of any one of claims 1 to 18, wherein the backbone reagent is present in the form of its acidic salt.

20. The process of any one of claims 1 to 19, wherin the crosslinker reagent is a compound of formula (V-II):



(V-II),

wherein

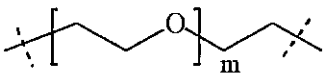
D^1, D^2, D^3 and D^4 are identical or different and each is independently of the others selected from the group comprising O, NR^5,S and CR^5R^{5a};

R^1, R^{1a}, R^2, R^2, R^3, R^{3a}, R^4, R^{4a}, R^5 and R^{5a} are identical or different and each is independently of the others selected from the group comprising H and C_{1-6} alkyl; optionally, one or more of the pair(s) 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}, and R^{3a}/R^{4a} 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;

P^2 is



m ranges from 120 to 920, preferably from 120 to 460 and more preferably from 120 to 230;

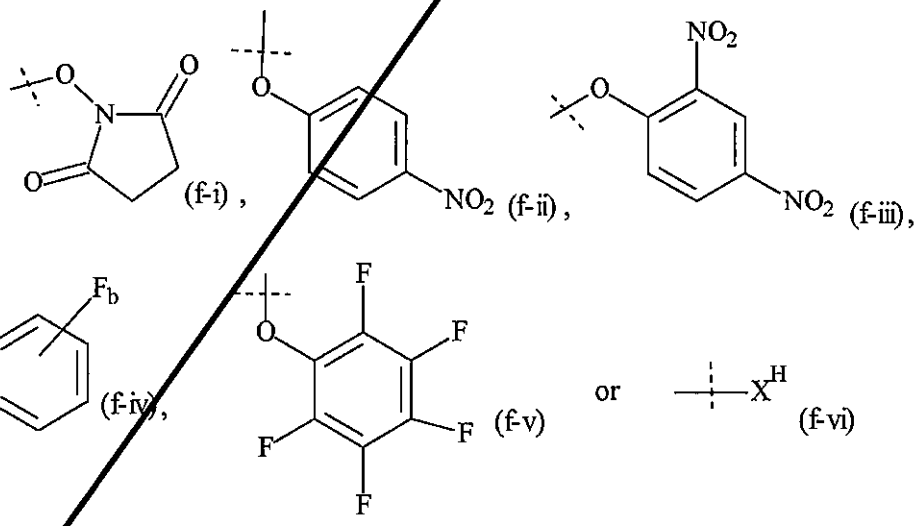
r1, r2, r7, r8 are independently 0 or 1;

r3, r6 are independently 0, 1, 2, 3, or 4;

r4, r5 are independently 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

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

Y^1, Y^2 are identical or different and each is independently of the other selected from formulas (f-i) to (f-vi):



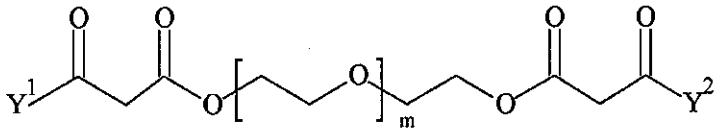
wherein

the dashed lines indicate attachment to the rest of the molecule,

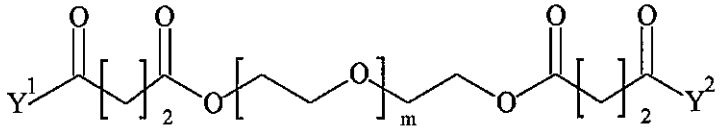
b is 1, 2, 3 or 4

X^H is Cl, Br, I, or F.

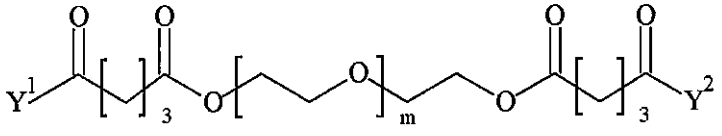
21. The process of any one of claims 1 to 20, wherein the crosslinker reagent is of formula (V-1) to (V-54):



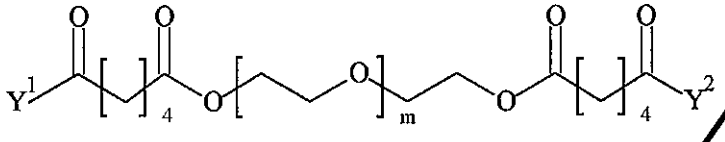
(V-1),



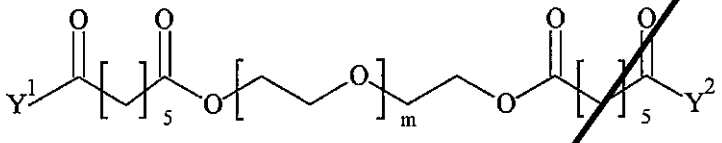
(V-2),



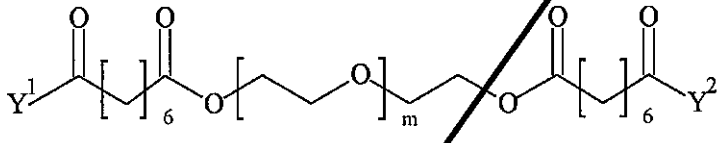
(V-3)



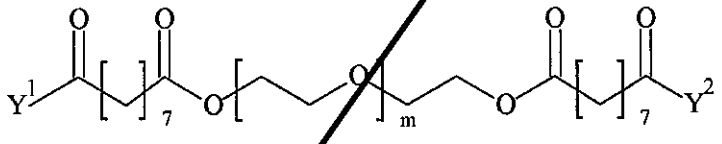
(V-4),



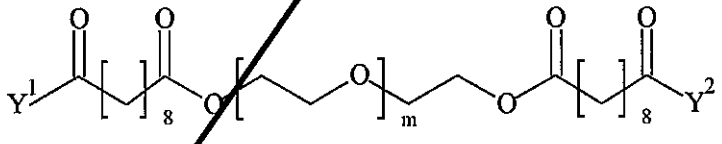
(V-5),



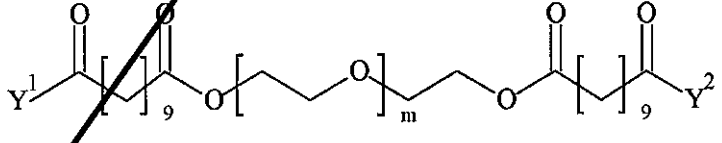
(V-6),



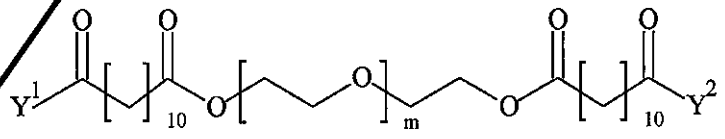
(V-7),



(V-8),



(V-9),



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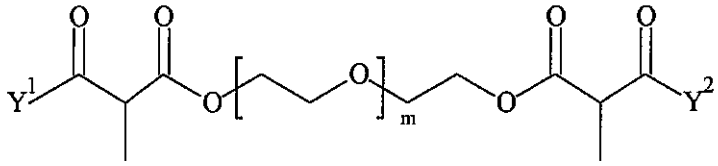

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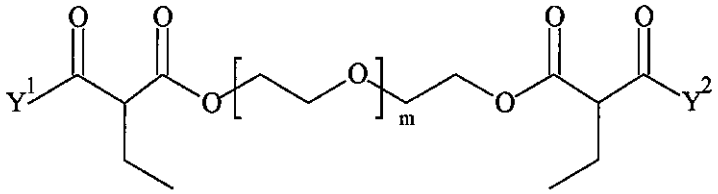

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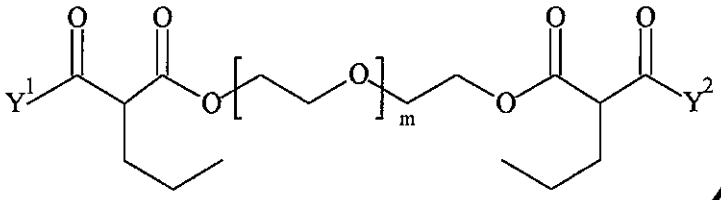

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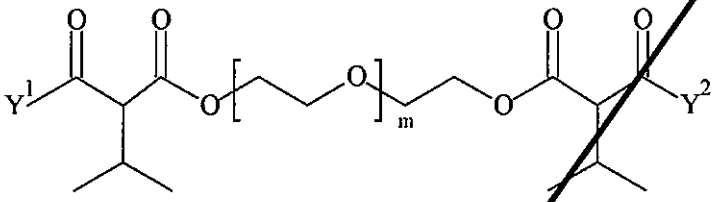

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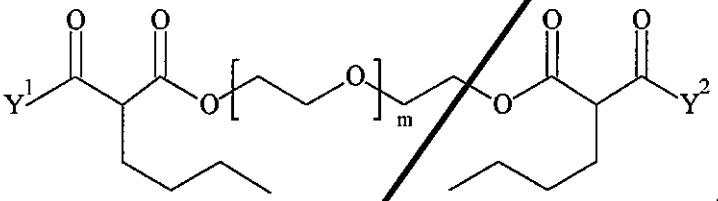

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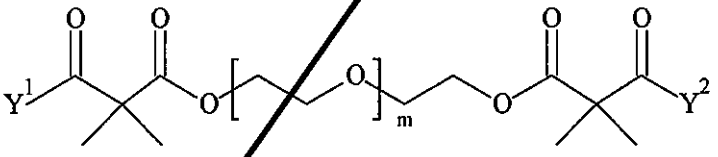

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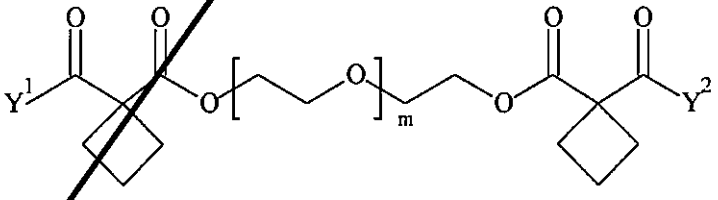

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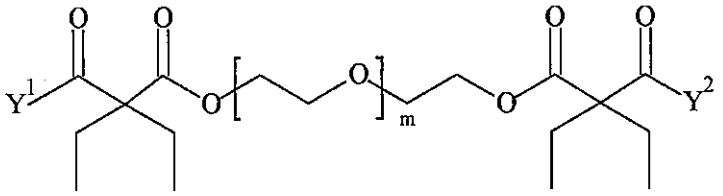

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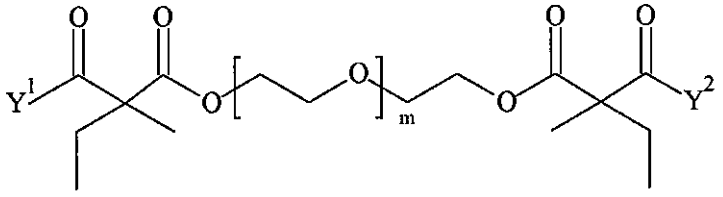

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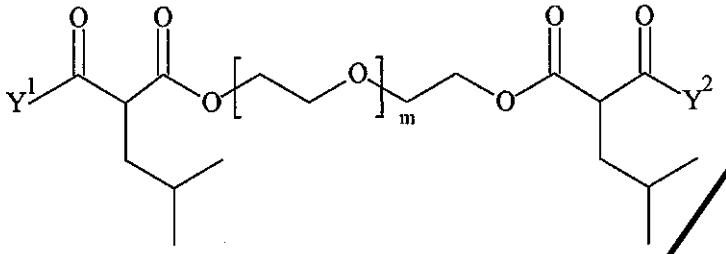

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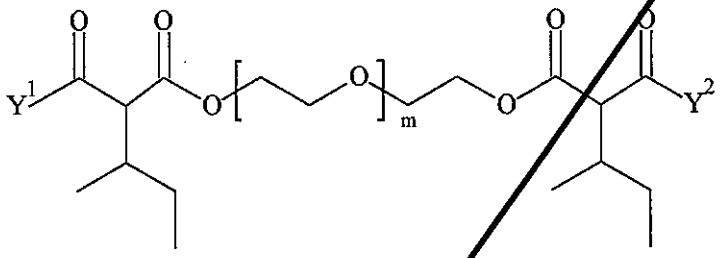

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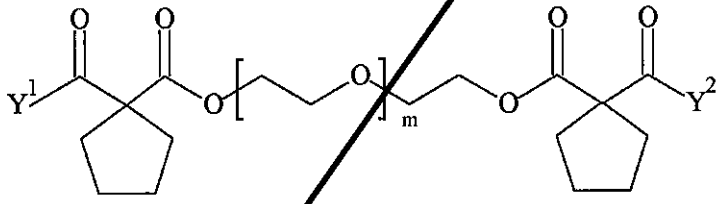

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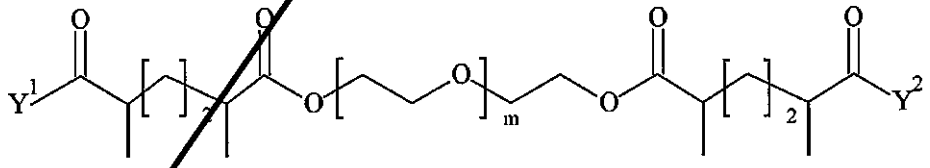

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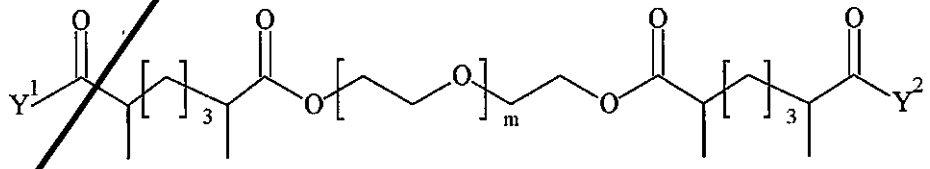

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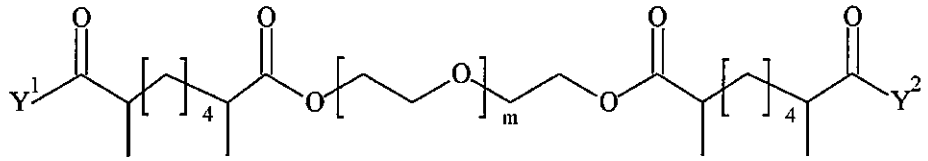

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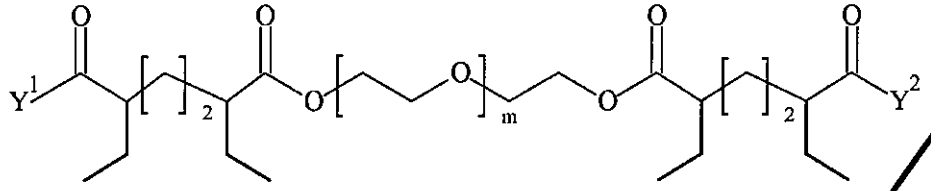

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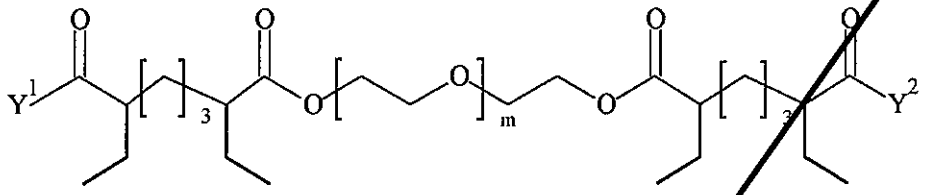

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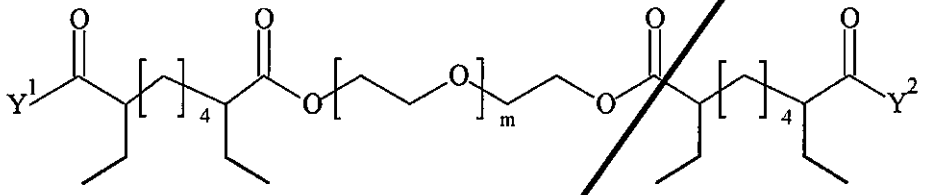

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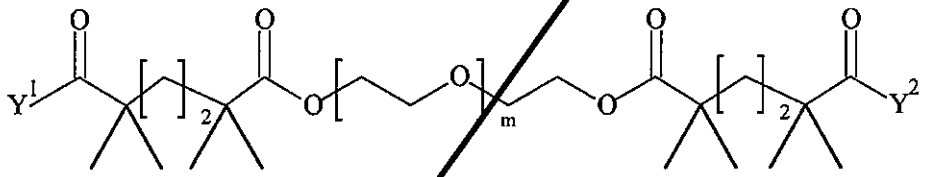

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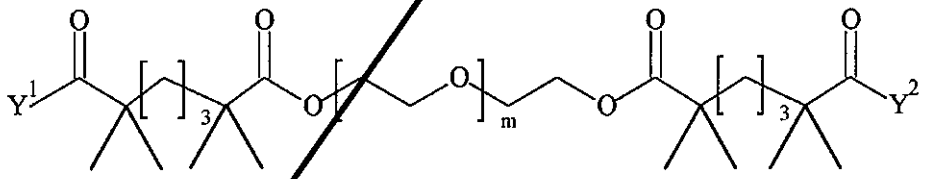

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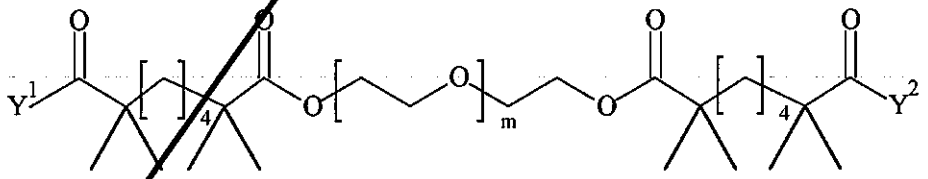

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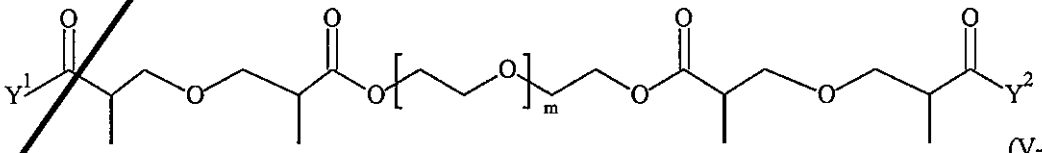

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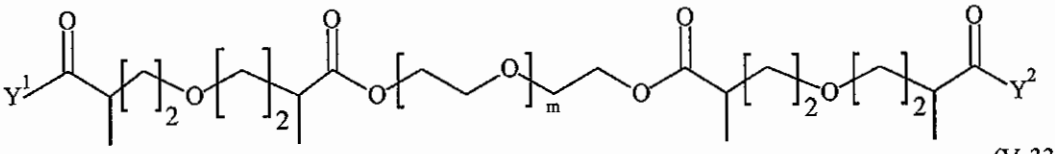

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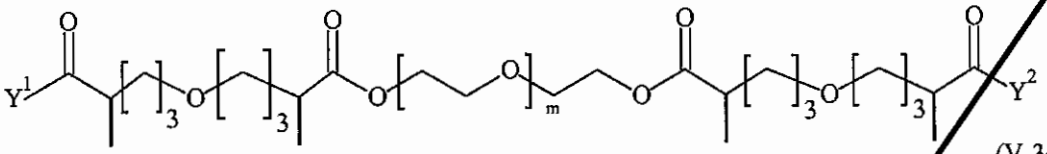

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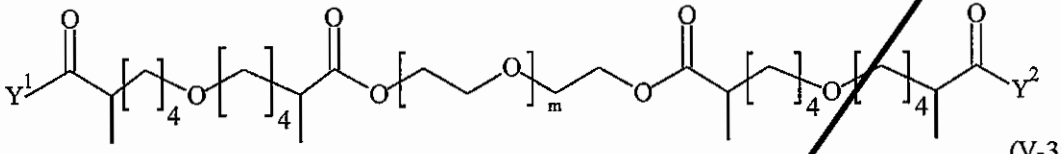

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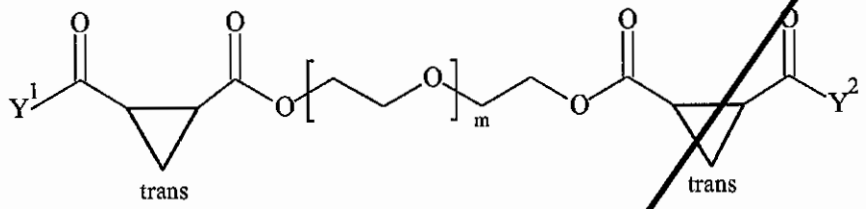

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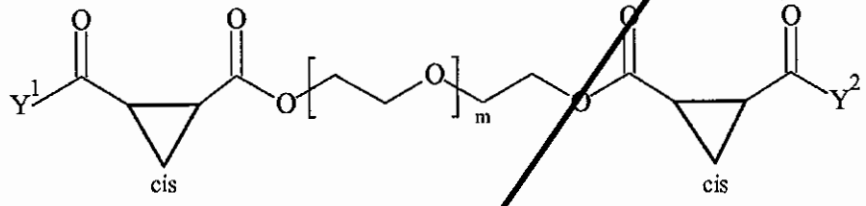

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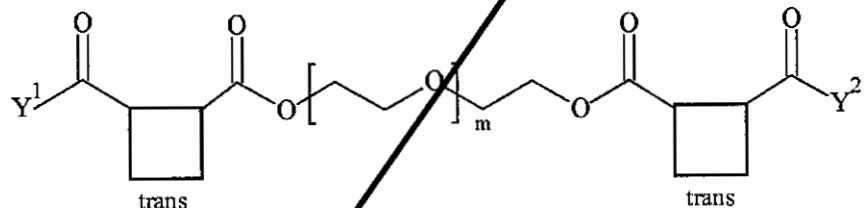

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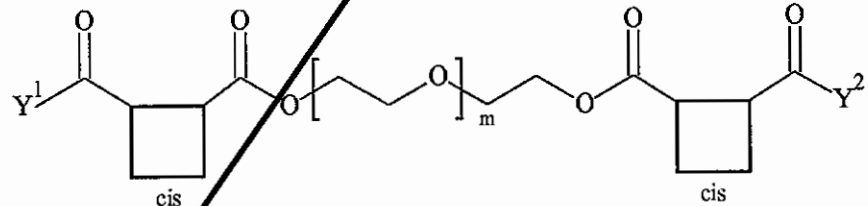

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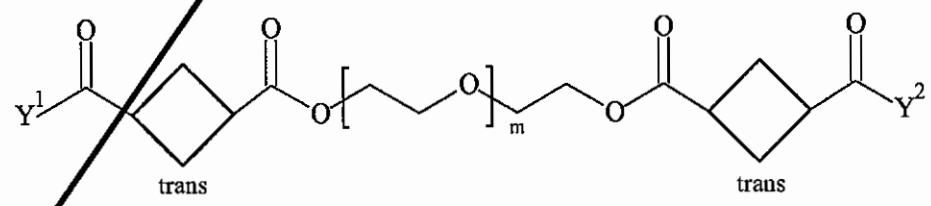

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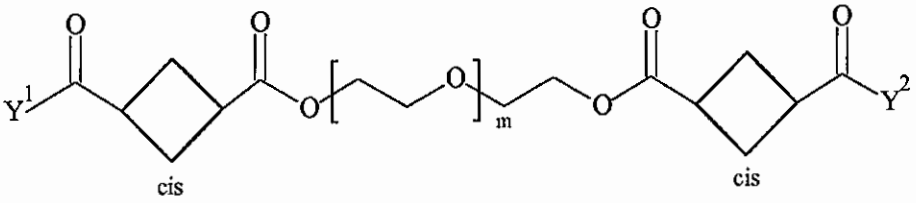

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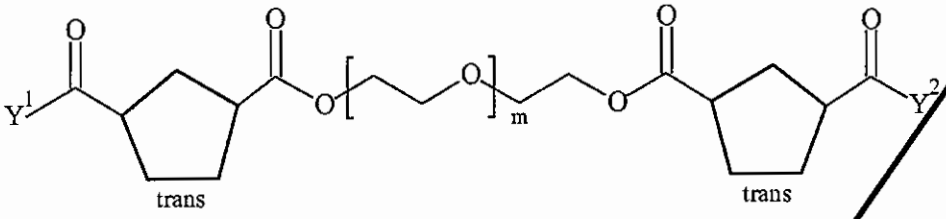

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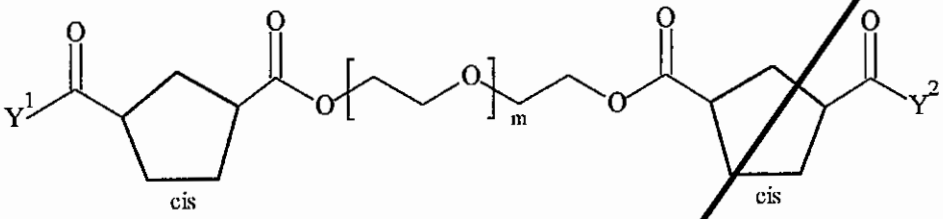

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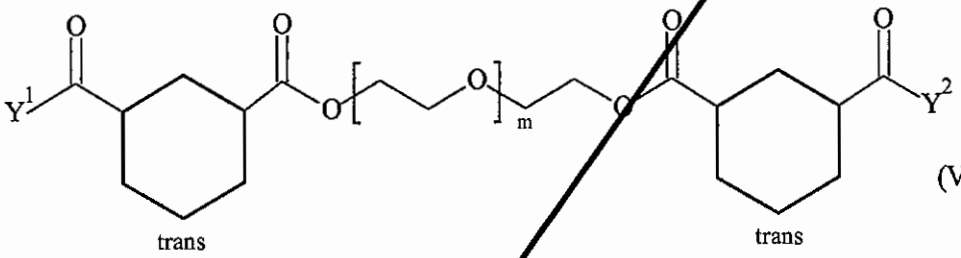

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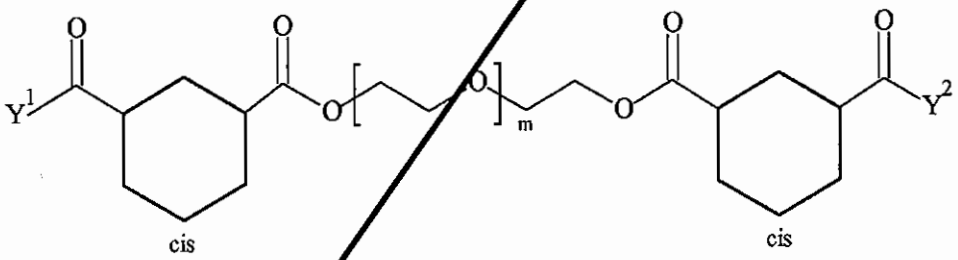

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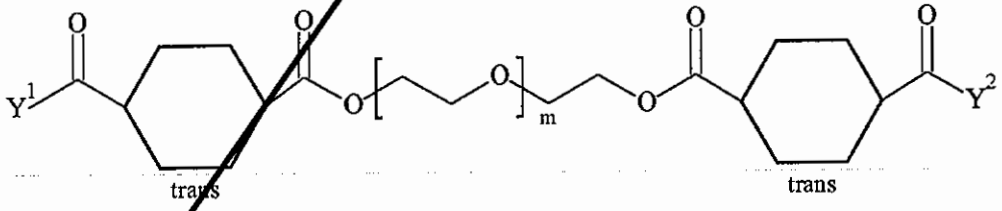

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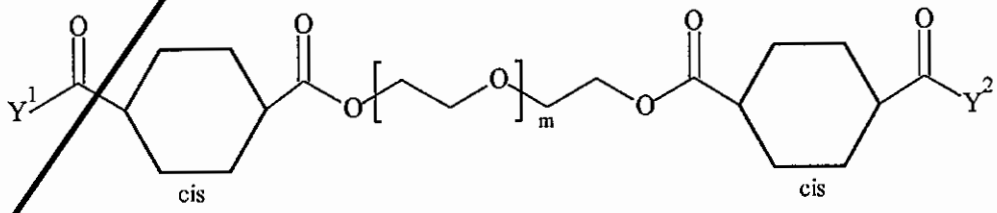

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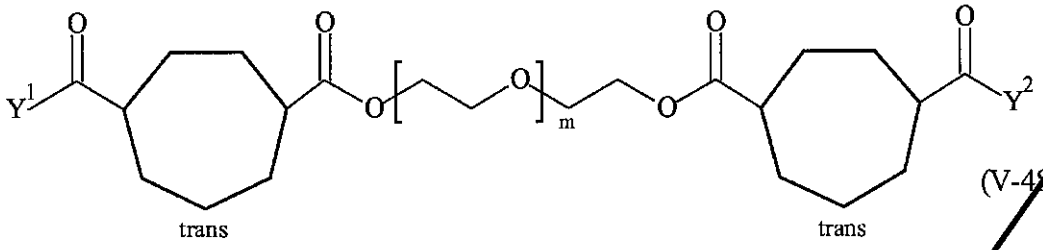

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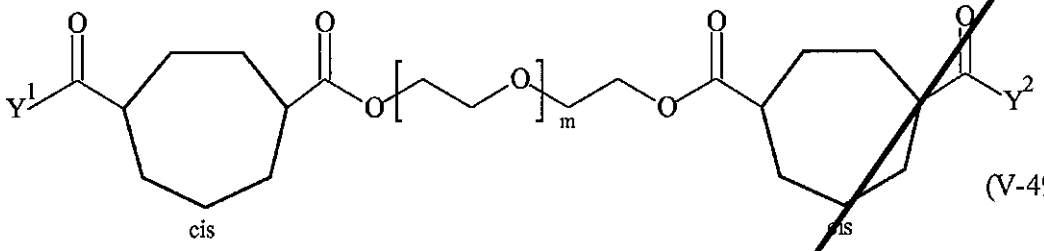

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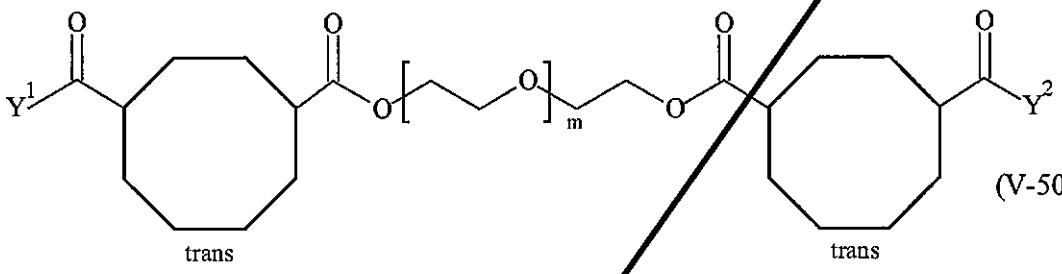

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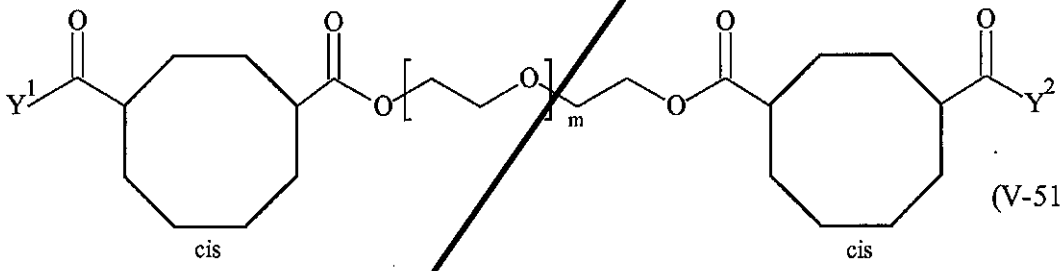

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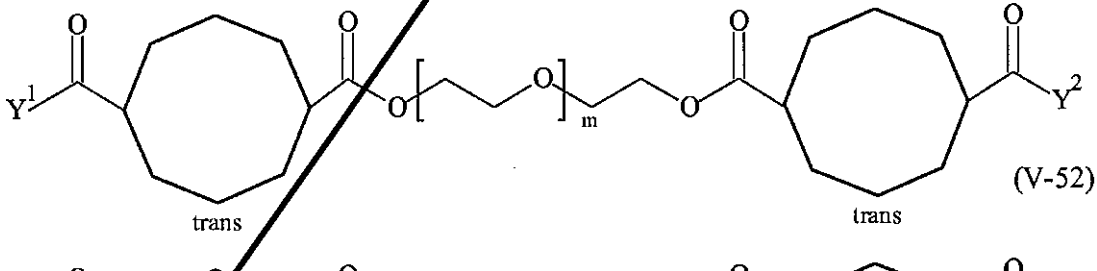

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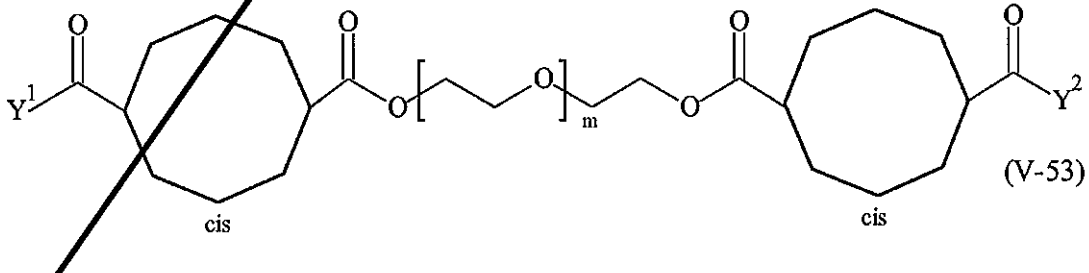
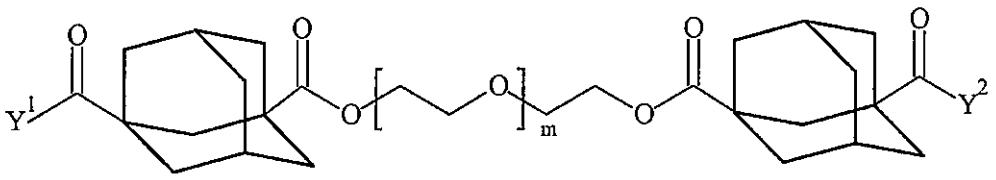


(V-53)



(V-54)

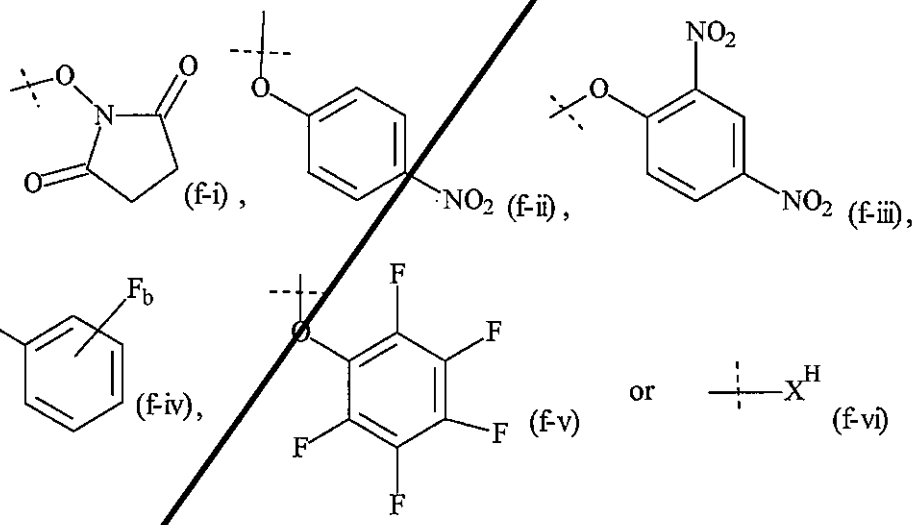
wherein

each crosslinker reagent may be in the form of its racemic mixture, where applicable;

and

m ranges from 120 to 920, preferably from 120 to 460 and more preferably from 120 to 230;

Y^1, Y^2 are identical or different and each is independently of the other selected from formulas (f-i) to (f-vi):



(f-i), (f-ii), (f-iii),

(f-iv), (f-v) or (f-vi)

wherein

the dashed lines indicate attachment to the rest of the molecule,

b is 1, 2, 3 or 4

X^H is Cl, Br, J, or F.

22. The process of any one of claims 1 to 21, wherein the hydrogel obtained from the polymerization is a shaped article.

23. The process of claim 22, wherein the hydrogel is in the form of microparticular beads having a diameter of 1 to 500 micrometer.

24. A hydrogel obtainable by a process of any one of claims 1 to 23.

25. A process for the preparation of a hydrogel-spacer conjugate comprising the step of:

(d) reacting the hydrogel from claim 24 with a spacer reagent of the formula (VI)

A^{x1}-S^0-A^{x2} (VI),

wherein

S^0 is selected from the group comprising C_{1-50} alkyl, C_{2-50} alkenyl and C_{2-50} alkynyl, which fragment is optionally interrupted by one or more group(s) selected from -NH-, -N(C_{1-4} alkyl)-, -O-, -S, -C(O)-, -C(O)NH, -C(O)N(C_{1-4} alkyl)-, -O-C(O)-, -S(O)-, -$S(O)_2$-, 4- to 7-membered heterocyclyl, phenyl and naphthyl;

A^{x1} is a functional group for reaction with an amine group of the hydrogel; and

A^{x2} is a functional group;

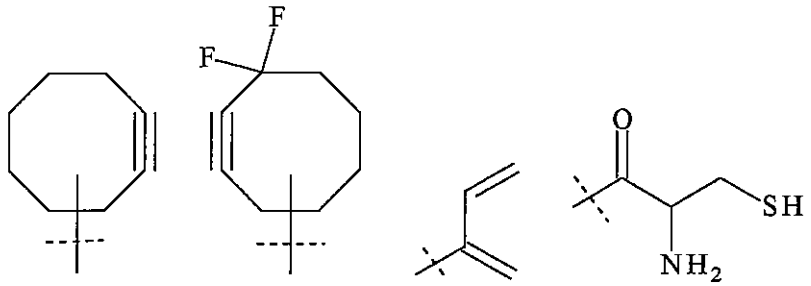
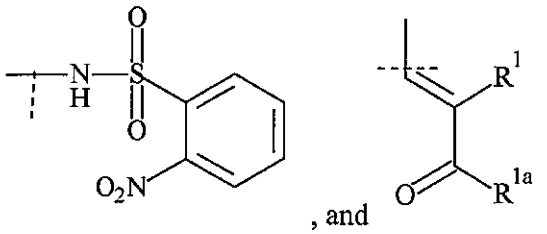
in the presence of a solvent to obtain a hydrogel-spacer conjugate.

26. The process of claim 25, wherein A^{x1} is selected from the group comprising activated carboxylic acid; Cl-(C=O)-; NHS-(C=O)-, wherein NHS is N-hydroxysuccinimide; $ClSO_2$-; R^1(C=O)-; I-; Br-; Cl-; SCN-; and CN-,

wherein

R^1 is selected from the group comprising H, C_{1-6} alkyl, alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 4- to 7-membered heterocyclyl, 8- to 11-membered heterobicyclyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl.

27. The process of claim 25 or 26, wherein A^{x2} is selected from the group comprising -maleimide, -SH, -NH_2, -SeH, -N_3, -C≡CH, -CR^1=$CR^{1a}R^{1b}$, -OH, -(CH=X^0)–R^1, -(C=O)–S–R^1, -(C=O)-H, -NH-NH_2, -O-NH_2, -Ar–X^0, -Ar–Sn(R^1)(R^{1a})(R^{1b}), -Ar–B(OH)(OH),

; with optional protecting groups;

wherein

X^0 is -OH, $-NR^1R^{1a}$, -SH, and -SeH,

Ar is selected from phenyl, naphthyl, indenyl, indanyl, and tetralinyl, and

R^1, R^{1a}, R^{1b} are independently of each other selected from the group comprising H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 4- to 7-membered heterocyclyl, 8- to 11-membered heterobicyclyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl.

28. A hydrogel-spacer conjugate obtainable by the process of any one of claims 26 to 27.

29. A process for the preparation of a carrier-linked prodrug comprising the step of:

(e) reacting a hydrogel of claim 24 or a hydrogel-spacer conjugate of claim 28 with a prodrug linker–biologically active moiety reagent of formula (VII)

A^{y1}-L-D (VII),

wherein

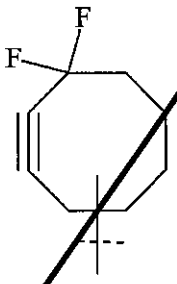
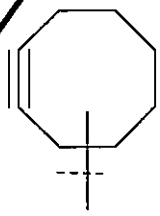
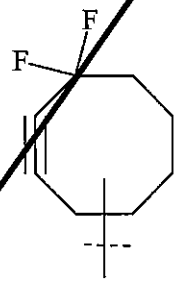
A^{y1} is a functional group for reaction with an amine of the hydrogel of step (b) or (c) or for reaction with the functional group A^{x2} of the hydrogel-spacer conjugate of step (d),

L is a prodrug linker;

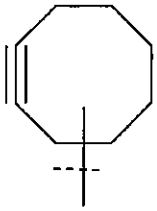
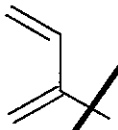
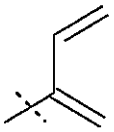
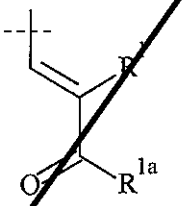
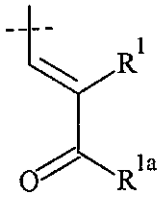
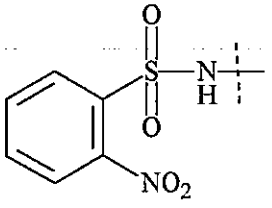
D is a biologically active moiety;

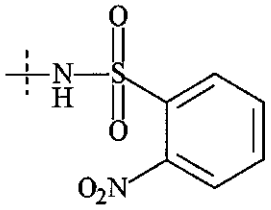
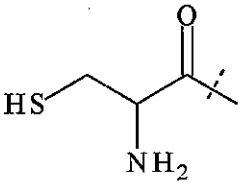
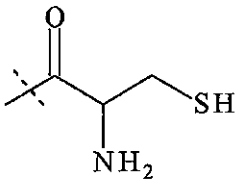
in the presence of a solvent, to obtain a carrier linked prodrug.

30. The process of claim 29, wherein A^{x2}/A^{y1} are selected from the following:

A^{x2}	A^{y1}
–maleimide	HS–, H_2N–, or HSe–
–SH, $–NH_2$, or –SeH	maleimide–
$–N_3$	HC≡C–,  , or 
–C≡CH,  , or	N_3–

-continued-

	
$-CR^{1a}=CR^{1a}R^{1b}$	 $R^{1b}R^{1a}C=CR^{1}-$ or
	$R^{1b}R^{1a}C=CR^{1}-$
$-(C=X^{0})-R^{1}$	
	$R^{1}-(C=X)-$
$-OH$	H_2N- or 
$-NH_2$ or	$HO-$

	
–(C=O)–S–R^1	
	R^1–S–(C=O)–
–(C=O)–H	H_2N–NH– or H_2N–O–
–NH–NH_2 or –O–NH_2	H–(C=O)–
–Ar–X^0	–Ar–Sn(R^1)(R^{1a})(R^{1b}) or -Ar–B(OH)(OH)
(R^{1b})(R^{1a})(R^1)Sn–Ar– or –Ar–B(OH)(OH)	X^0–Ar–

wherein

X^0 is -OH, -NR^1R^{1a}, -SH, and –SeH;

R^1, R^{1a}, R^{1b} are independently of each other selected from the group comprising H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 4- to 7-membered heterocyclyl, 8- to 11-membered heterobicyclyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl; and

Ar is selected from phenyl, naphthyl, indenyl, indanyl, and tetralinyl.

31. The process of claim 29 or 30, wherein A^{x2} is a thiol and A^{y1} is of formula (VIIa)

$$T-PG^0-S- \quad (VIIa),$$

wherein

T is H or a tag moiety;

PG^0 is a sulfur-activating moiety; and

S is sulfur.

32. The process of any one of claims 29 to 31, wherein D has a molecular weight ranging between 2 and 500 kDa, more preferably between 5 and 250 kDa, more preferably between 5 and 100 kDa and most preferably between 10 and 60 kDa.

33. A carrier-linked prodrug obtainable by a process for the preparation of a carrier-linked prodrug of any one of claims 29 to 32.

34. A pharmaceutical composition comprising the carrier-linked prodrug of claim 33 or a pharmaceutical salt thereof together with a pharmaceutically acceptable excipient.

35. The carrier-linked prodrug of claim 33 or the pharmaceutical composition of claim 34 for use as a medicament.

Claims

1. A process for the preparation of a hydrogel comprising the steps of:

(a) providing a mixture comprising

(a-i) at least one backbone reagent, wherein the at least one backbone reagent has a molecular weight ranging from 1 to 100 kDa, and comprises at least three amines ($-NH_2$ and/or -NH-);

(a-ii) at least one crosslinker reagent, wherein the at least one crosslinker reagent has a molecular weight ranging from 6 to 40 kDa, the at least one crosslinker reagent comprising

(i) at least two carbonyloxy groups (–(C=O)–O– or –O–(C=O)–), and additionally

(ii) at least two activated functional end groups selected from the group consisting of activated ester groups, activated carbamate groups, activated carbonate groups and activated thiocarbonate groups,

and being PEG-based comprising at least 70% PEG; and

(a-iii) a first solvent and at least a second solvent, which second solvent is immiscible in the first solvent,

in a weight ratio of the at least one backbone reagent to the at least one crosslinker reagent ranging from 1:99 to 99:1; and

(b) polymerizing the mixture of step (a) in a suspension polymerization to a hydrogel.

2. The process of claim 1, wherein the mixture of step (a) further comprises a detergens.

3. The process of claim 2, wherein the detergens is Cithrol DPHS, Hypermer 70A, Hypermer B246, Hypermer 1599A, Hypermer 2296, or Hypermer 1083.

4. The process of any one of claims 1 to 3, wherein the polymerization in step (b) is initiated by adding a base.

5. The process of claim 4, wherein the base is selected from *N,N,N',N'*-tetramethylethylene diamine (TMEDA), 1,4-dimethylpiperazine, 4-methylmorpholine, 4-ethylmorpholine, 1,4-diazabicyclo[2.2.2]octane, 1,1,4,7,10,10-hexamethyltriethylenetetramine, 1,4,7-trimethyl-1,4,7-triazacyclononane, tris[2-(dimethylamino)ethyl]amine, triethylamine, diisopropylethylamine (DIPEA), trimethylamine, N,N-dimethylethylamine, N,N,N',N'-tetramethyl-1,6-hexanediamine, N,N,N',N'',N''-pentamethyldiethylenetriamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, and hexamethylenetetramine.

6. The process of any one of claims 1 to 5, wherein the mixture of step (a) is an emulsion.

7. The process of any one of claims 1 to 6, wherein the process further comprises the step of:

(c) working-up the hydrogel.

8. The process of any one of claims 1 to 7, wherein the at least one backbone reagent is selected from the group consisting of

a compound of formula (I)

$$B(-(A^0)_{x1}-(SP)_{x2}-A^1-P-A^2-Hyp^1)_x \quad (I),$$

wherein

B is a branching core,

SP is a spacer moiety selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl,

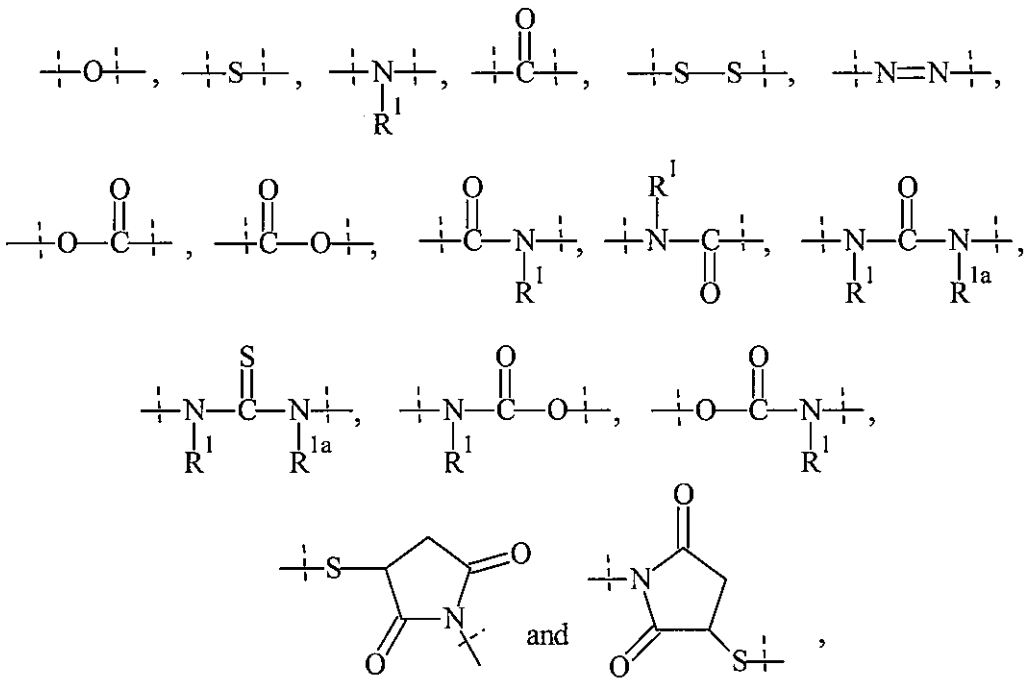
P is a PEG-based polymeric chain comprising at least 80% PEG, preferably at least 85% PEG, more preferably at least 90% PEG and most preferably at least 95% PEG,

Hyp^1 is a moiety comprising an amine ($-NH_2$ and/or -NH-) or a polyamine comprising at least two amines ($-NH_2$ and/or -NH-),

x is an integer from 3 to 16,

x1, x2 are independently of each other 0 or 1, provided that x1 is 0, if x2 is 0,

A^0, A^1, A^2 are independently of each other selected from the group consisting of



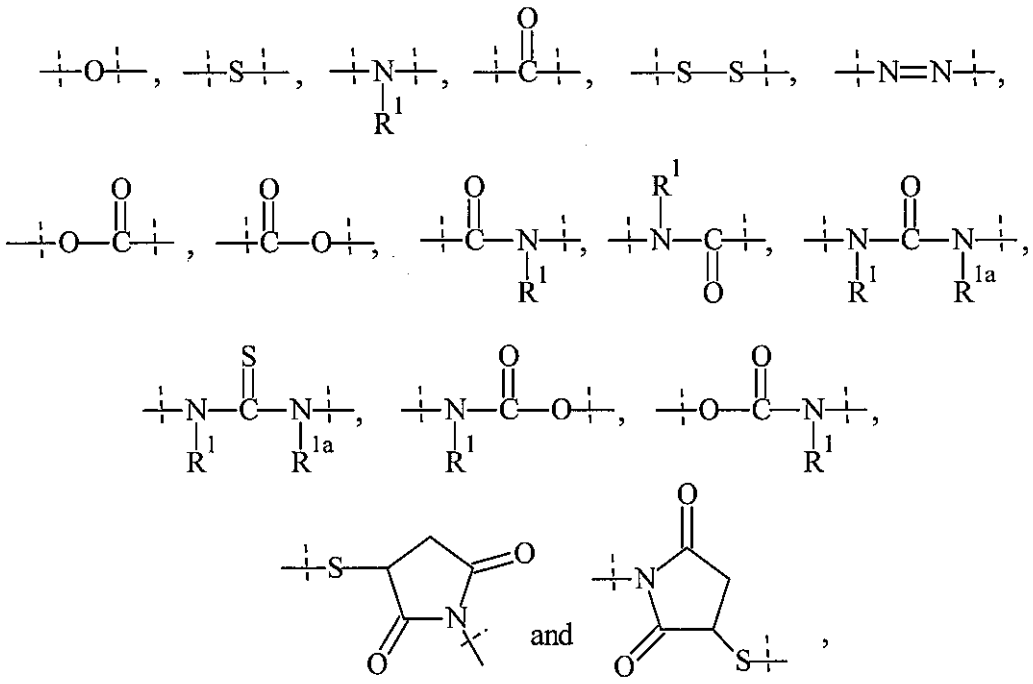
wherein R^I and R^{Ia} are independently of each other selected from H and C_{1-6} alkyl;

a compound of formula (II)

$Hyp^2 - A^3 - P - A^4 - Hyp^3$ (II),

wherein

P	is defined as above in the compound of formula (I),
Hyp^2, Hyp^3	are independently of each other a polyamine comprising at least two amines ($-NH_2$ and/or -NH-), and
A^3 and A^4	are independently selected from the group consisting of



wherein R^1 and R^{1a} are independently of each other selected from H and C_{1-6} alkyl;

a compound of formula (III)

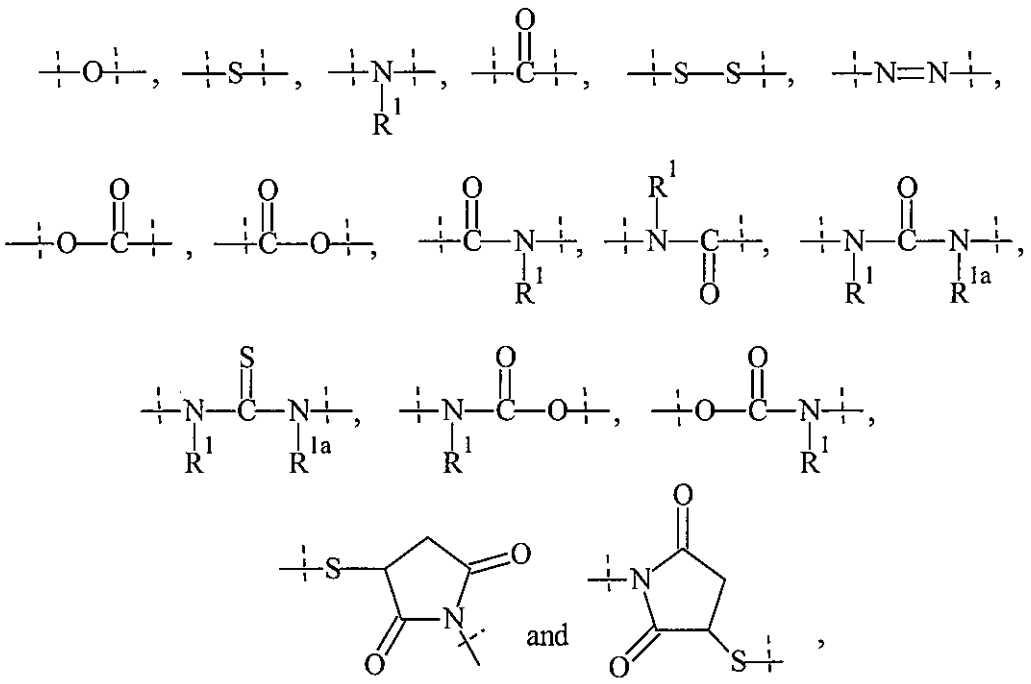
$$P^1 - A^5 - Hyp^4 \qquad \text{(III)},$$

wherein

P^1 is a PEG-based polymeric chain comprising at least 80% PEG, preferably at least 85% PEG, more preferably at least 90% PEG and most preferably at least 95% PEG,

Hyp^4 is a polyamine comprising at least three amines (-NH_2 and/or -NH), and

A^5 is selected from the group consisting of



wherein R^1 and R^{1a} are independently of each other selected from H and C_{1-6} alkyl;

and

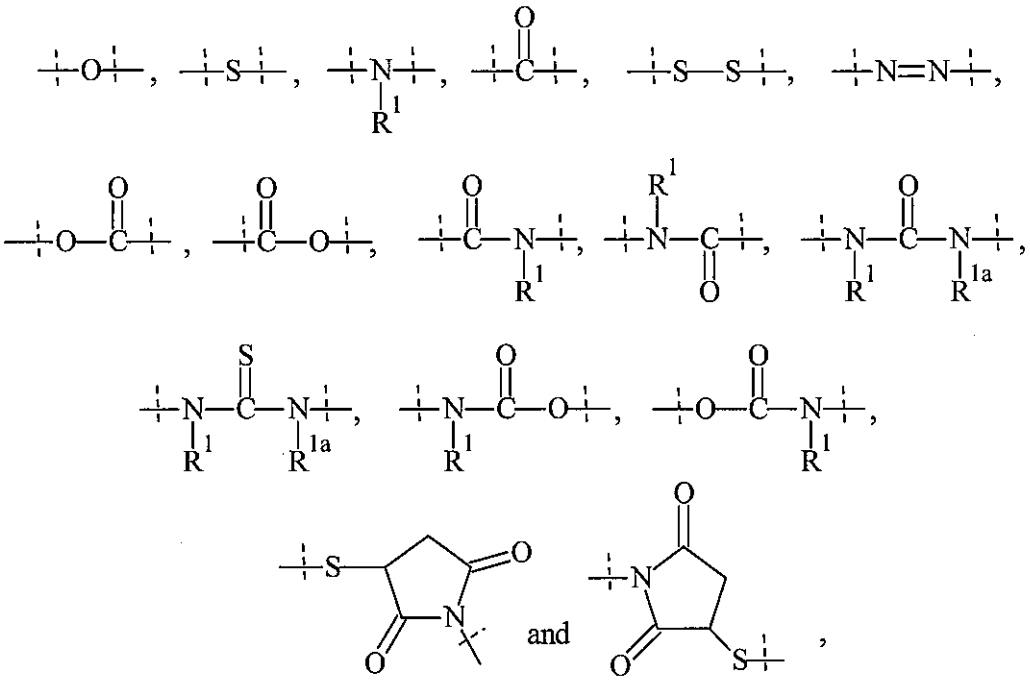
a compound of formula (IV),

$$T^1 - A^6 - Hyp^5 \qquad (IV),$$

wherein

Hyp^5 is a polyamine comprising at least three amines ($-NH_2$ and/or -NH), and

A^6 is selected from the group consisting of

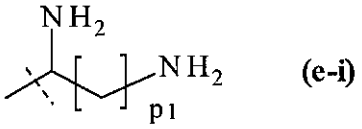


wherein R^1 and R^{1a} are independently of each other selected from H and C_{1-6} alkyl; and

T^1 is selected from the group consisting of C_{1-50} alkyl, C_{2-50} alkenyl or C_{2-50} alkynyl, which fragment is optionally interrupted by one or more group(s) selected from -NH-, -N(C_{1-4} alkyl)-, -O-, -S-, -C(O)-, -C(O)NH-, -C(O)N(C_{1-4} alkyl)-, -O-C(O)-, -S(O)-, -$S(O)_2$-, 4- to 7-membered heterocyclyl, phenyl or naphthyl.

9. The process of claim 8, wherein Hyp^1, Hyp^2, Hyp^3, Hyp^4, and Hyp^5 are selected from the group consisting of

a moiety of formula (e-i)



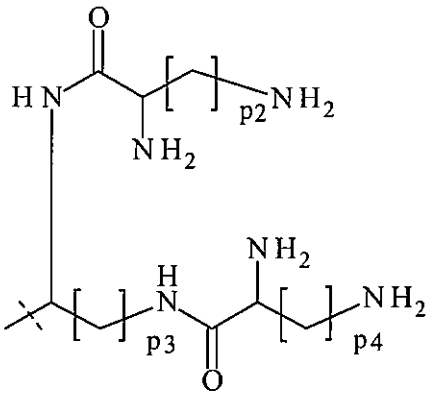
(e-i)

wherein

p1 is an integer from 1 to 5, preferably p1 is 4, and

the dashed line indicates attachment to A^2 if the backbone reagent has a structure of formula (I) and to A^3 or A^4 if the backbone reagent has the structure of formula (II);

a moiety of formula (e-ii)



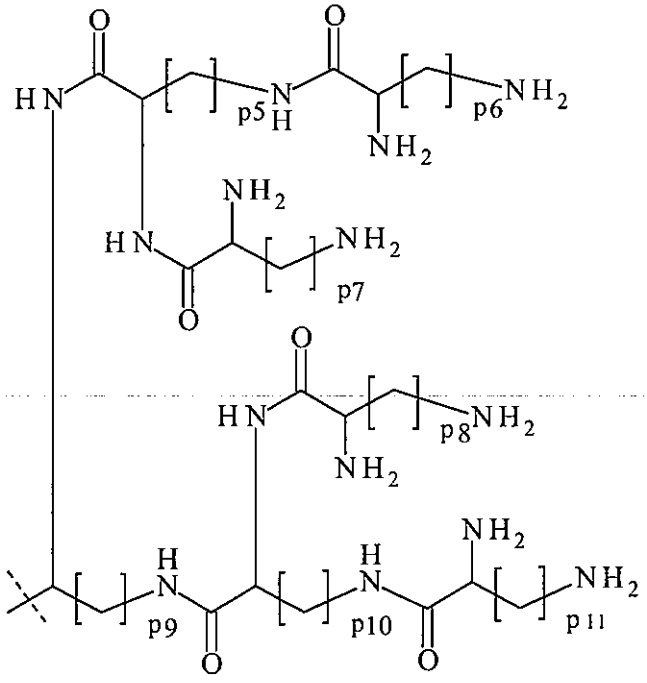
(e-ii)

wherein

p2, p3 and p4 are identical or different and each is independently of the others an integer from 1 to 5, preferably p2, p3 and p4 are 4, and

the dashed line indicates attachment to A^2 if the backbone reagent has a structure of formula (I), to A^3 or A^4 if the backbone reagent has a structure of formula (II), to A^5 if the backbone reagent has a structure of formula (III) and to A^6 if the backbone reagent has a structure of formula (IV);

a moiety of formula (e-iii)



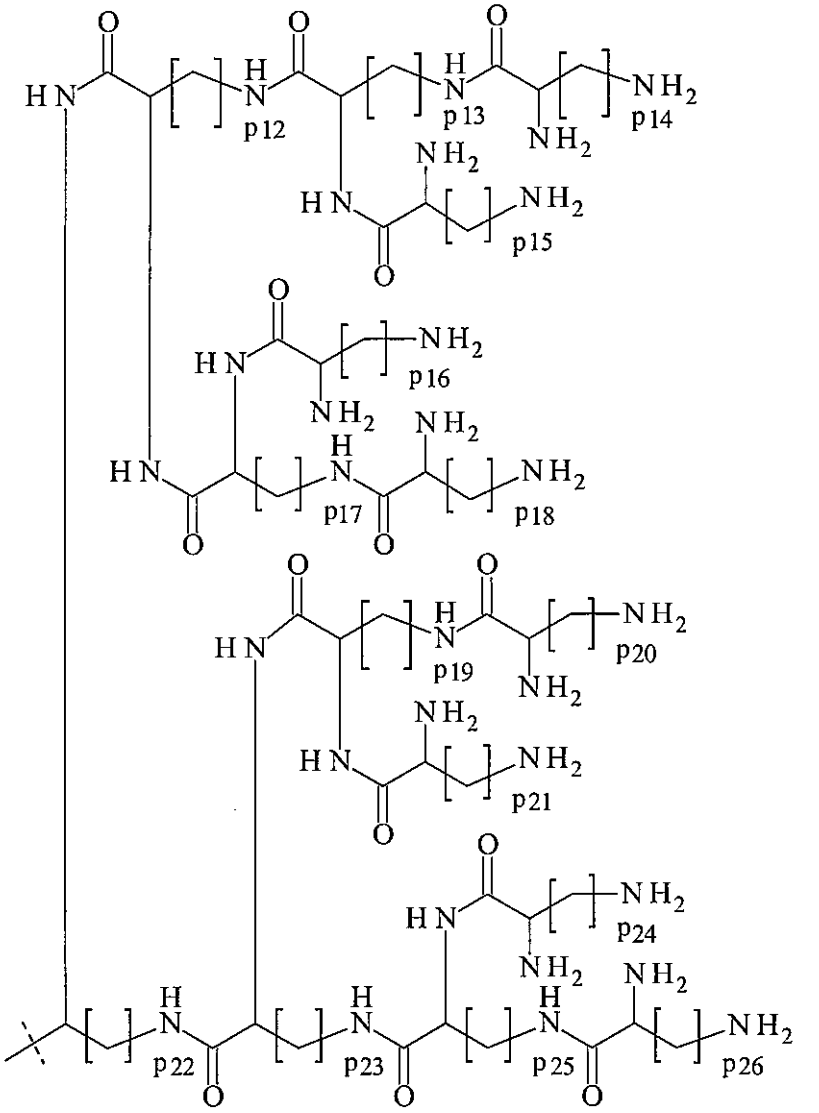
(e-iii)

wherein

p5 to p11 are identical or different and each is independently of the others an integer from 1 to 5, preferably p5 to p11 are 4, and

the dashed line indicates attachment to A^2 if the backbone reagent is of formula (I), to A^3 or A^4 if the backbone reagent is of formula (II), to A^5 if the backbone reagent is of formula (III) and to A^6 if the backbone reagent is of formula (IV);

a moiety of formula (e-iv)



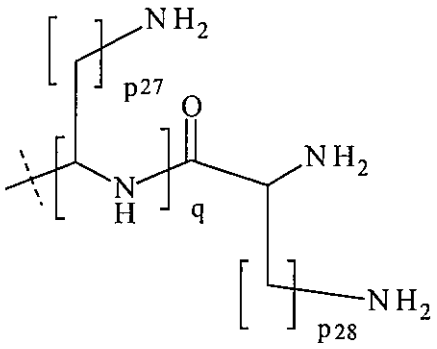
(e-iv)

wherein

p12 to p26 are identical or different and each is independently of the others an integer from 1 to 5, preferably p12 to p26 are 4, and

the dashed line indicates attachment to A^2 if the backbone reagent has a structure of formula (I), to A^3 or A^4 if the backbone reagent has a structure of formula (II), to A^5 if the backbone reagent has a structure of formula (III) and to A^6 if the backbone reagent has a structure of formula (IV);

a moiety of formula (e-v)



(e-v)

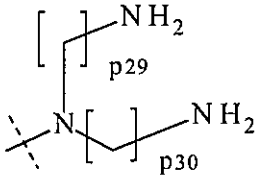
wherein

p27 and p28 are identical or different and each is independently of the other an integer from 1 to 5, preferably p27 and p28 are 4,

q is an integer from 1 to 8, preferably q is 2 or 6 and most preferably 1 is 6, and

the dashed line indicates attachment to A^2 if the backbone reagent has a structure of formula (I), to A^3 or A^4 if the backbone reagent has a structure of formula (II), to A^5 if the backbone reagent has a structure of formula (III) and to A^6 if the backbone reagent has a structure of formula (IV);

a moiety of formula (e-vi)



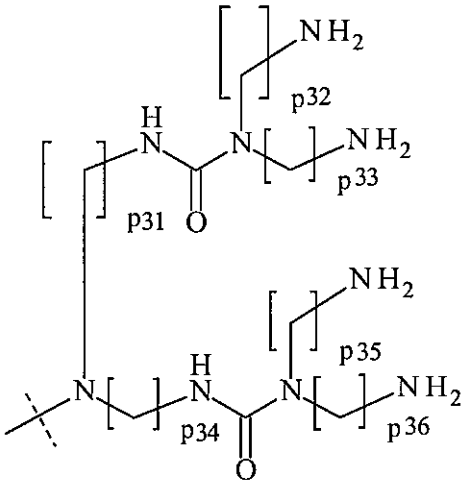
(e-vi)

wherein

p29 and p30 are identical or different and each is independently of the other an integer from 2 to 5, preferably p29 and p30 are 3, and

the dashed line indicates attachment to A^2 if the backbone reagent has the structure of formula (I), to A^3 or A^4 if the backbone reagent has the structure of formula (II), to A^5 if the backbone reagent has the structure of formula (III) and to A^6 if the backbone reagent has the structure of formula (IV);

a moiety of formula (e-vii)



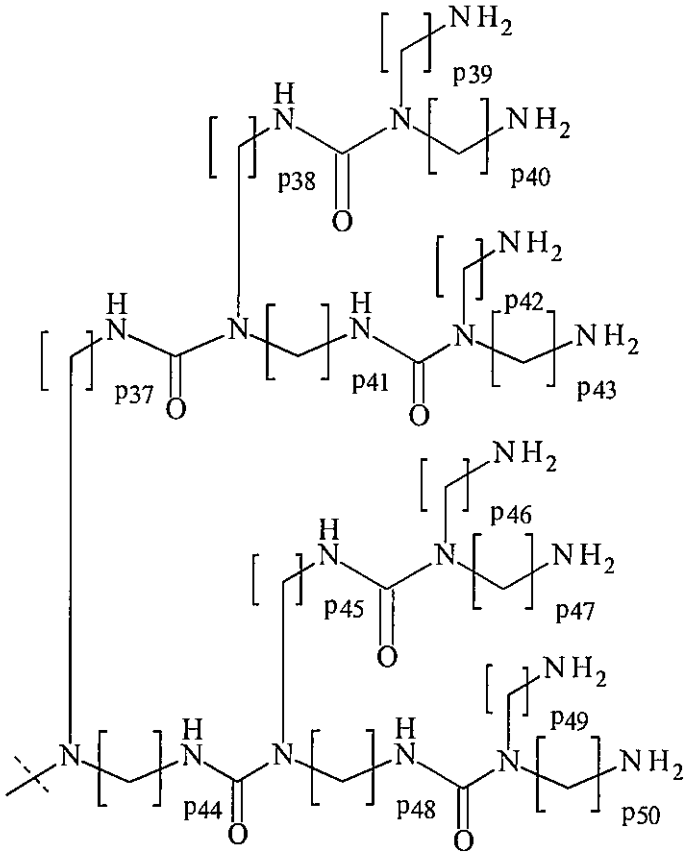
(e-vii)

wherein

p31 to p36 are identical or different and each is independently of the others an integer from 2 to 5, preferably p31 to p36 are 3, and

the dashed line indicates attachment to A^2 if the backbone reagent has a structure of formula (I), to A^3 or A^4 if the backbone reagent has a structure of formula (II), to A^5 if the backbone reagent has a structure of formula (III) and to A^6 if the backbone reagent has a structure of formula (IV);

a moiety of formula (e-viii)



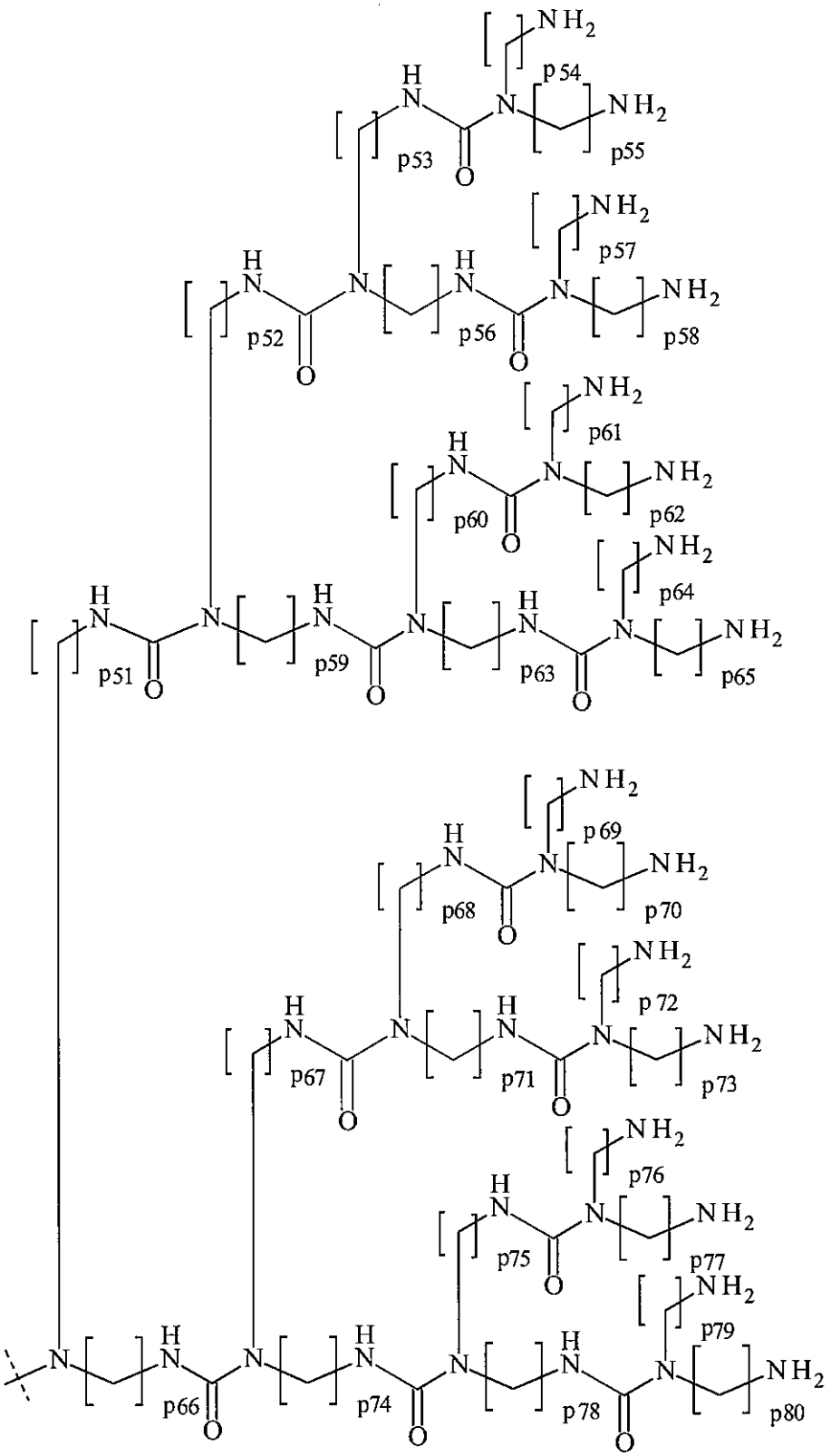
(e-viii)

wherein

p37 to p50 are identical or different and each is independently of the others an integer from 2 to 5, preferably p37 to p50 are 3, and

the dashed line indicates attachment to A^2 if the backbone reagent has a structure of formula (I), to A^3 or A^4 if the backbone reagent has a structure of formula (II), to A^5 if the backbone reagent has a structure of formula (III) and to A^6 if the backbone reagent has a structure of formula (IV); and

a moiety of formula (e-ix):



(e-ix)

wherein

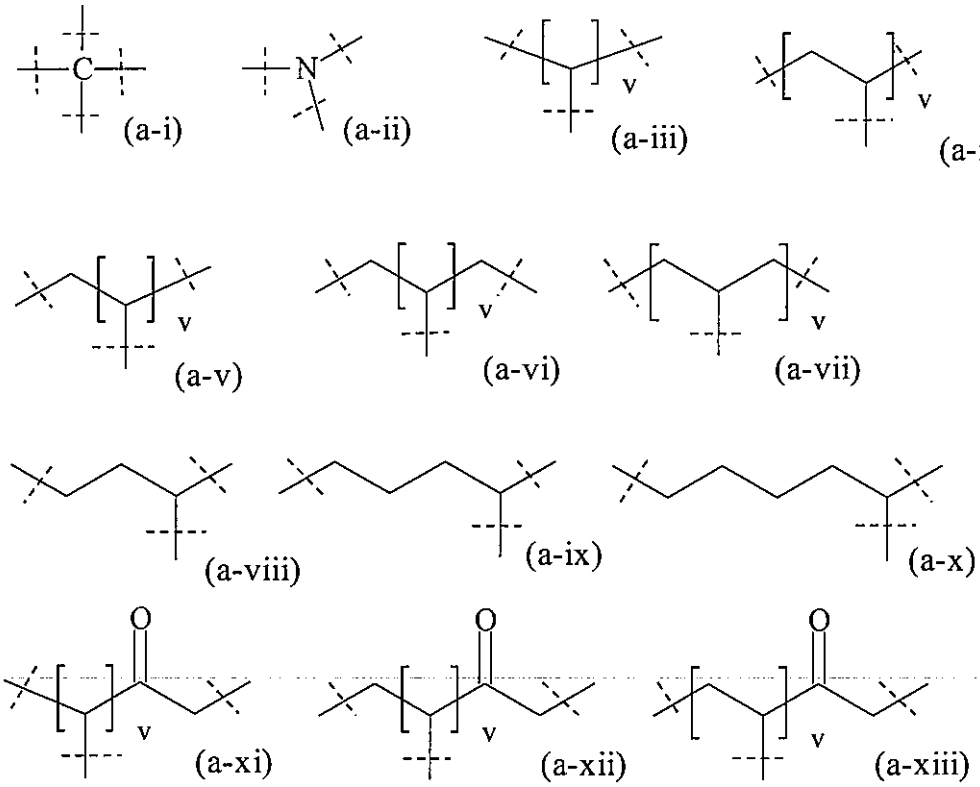
p51 to p80 are identical or different and each is independently of the others an integer from 2 to 5, preferably p51 to p80 are 3, and

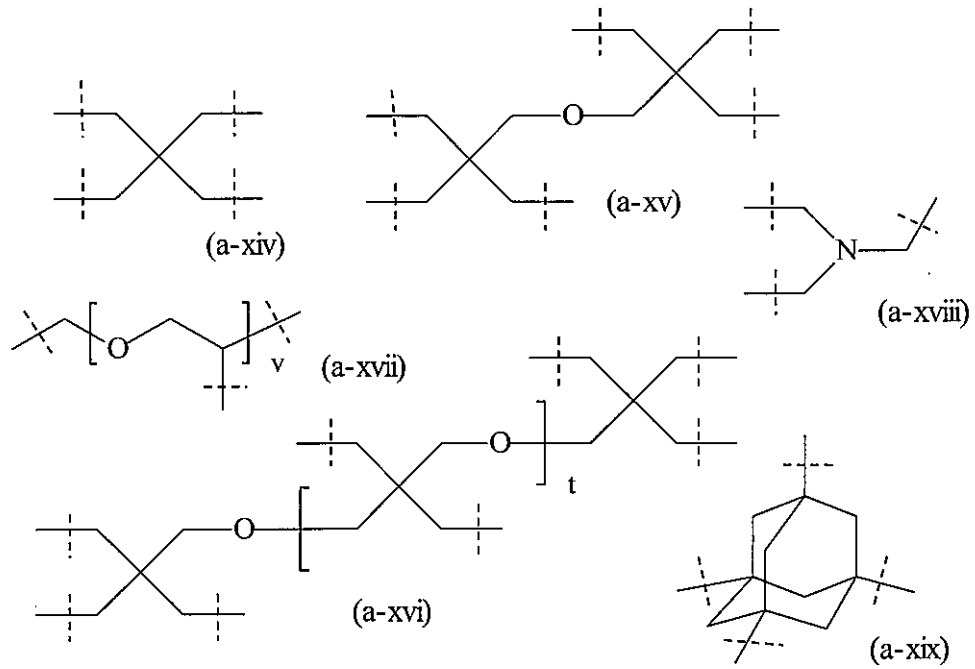
the dashed line indicates attachment to A^2 if the backbone reagent has a structure of formula (I), to A^3 or A^4 if the backbone reagent has a structure of formula (II), to A^5 if the backbone reagent has a structure of formula (III) and to A^6 if the backbone reagent has a structure of formula (IV); and

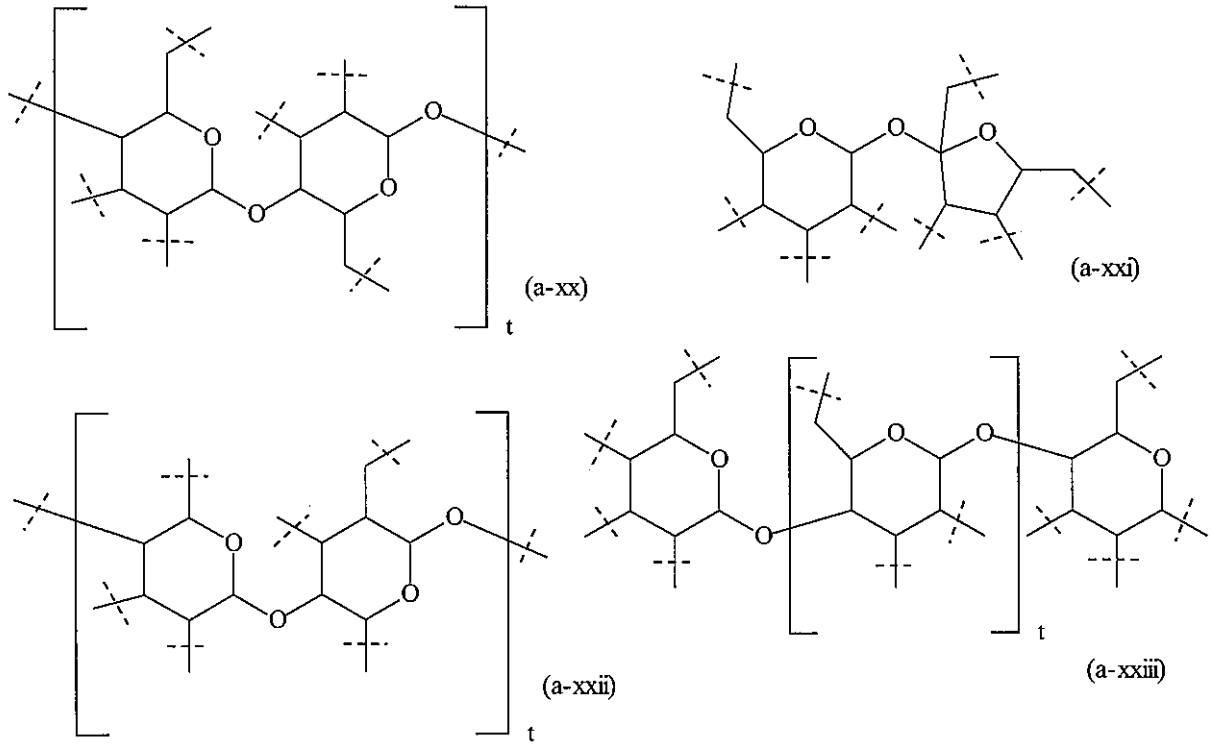
wherein the moieties (e-i) to (e-v) may at each chiral center be in either R- or S-configuration, preferably, all chiral centers of a moiety (e-i) to (e-v) are in the same configuration.

10. The process of claim 8 or 9, wherein the backbone reagent is a compound of formula (I).

11. The process of any one of claims 8 to 10, wherein the branching core B is selected from the following structures:







wherein

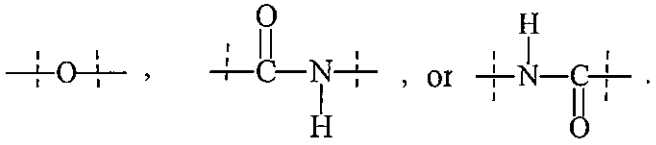
dashed lines indicate attachment to A^0 or, if x1 and x2 are both 0, to A^1,

t is 1 or 2; preferably t is 1,

v is 1, 2, 3, 4, 5, ,6 ,7 ,8 , 9, 10, 11, 12, 13 or 14; preferably, v is 2, 3, 4, 5, 6; more preferably, v is 2, 4 or 6; most preferably, v is 2.

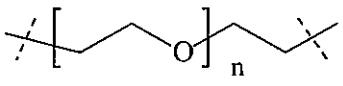
12. The process of claim 11, wherein B is of formula (a-xiv).

13. The process of any one of claims 8 to 12, wherein A^0 is



14. The process of any one of claims 8 to 13, wherein x1 and x2 are 0.

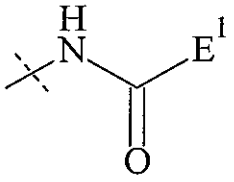
15. The process of any one of claims 8 to 14, wherein P has the structure of formula (c-i):



(c-i),

wherein n ranges from 6 to 900, more preferably n ranges from 20 to 700 and most preferably n ranges from 20 to 250.

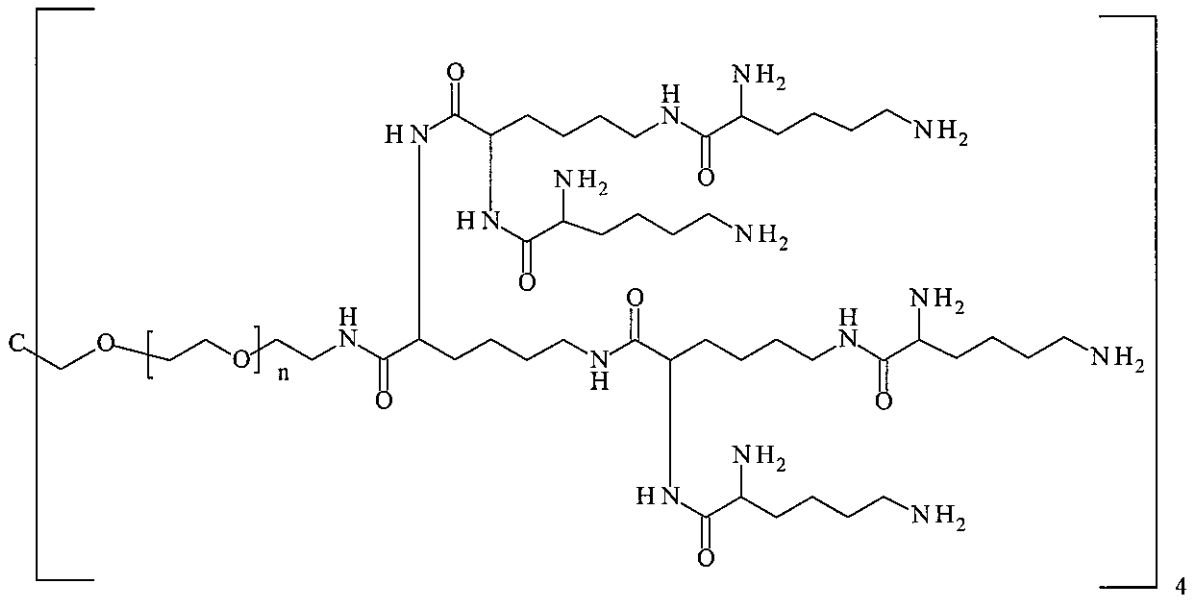
16. The process of any one of claims 8 to 15, wherein the moiety – A^2 – Hyp^1 is a moiety of the formula



,

wherein
the dashed line indicates attachment to P; and
E^1 is selected from formulas (e-i) to (e-ix).

17. The process of any one of claims 1 to 16, wherein the backbone reagent has the following formula:



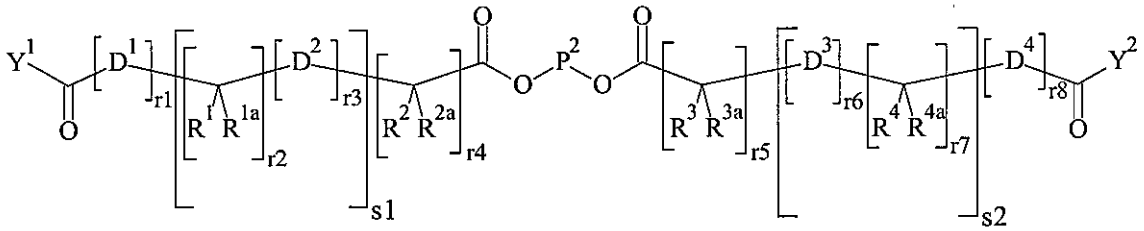
wherein

n ranges from 10 to 40, preferably from 10 to 30, more preferably from 10 to 20.

18. The process of claim 17, wherein n ranges from 20 to 30 kDa and most preferably n is 28.

19. The process of any one of claims 1 to 18, wherein the backbone reagent is present in the form of its acidic salt.

20. The process of any one of claims 1 to 19, wherin the crosslinker reagent is a compound of formula (V-II):



(V-II),

wherein

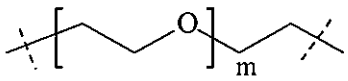
D^1, D^2, D^3 and D^4 are identical or different and each is independently of the others selected from the group comprising O, NR^5,S and CR^5R^{5a};

R^1, R^{1a}, R^2, R^2, R^3, R^{3a}, R^4, R^{4a}, R^5 and R^{5a} are identical or different and each is independently of the others selected from the group comprising H and C_{1-6} alkyl; optionally, one or more of the pair(s) 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}, and R^{3a}/R^{4a} 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;

P^2 is



m ranges from 120 to 920, preferably from 120 to 460 and more preferably from 120 to 230;

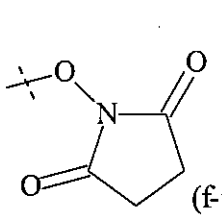
r1, r2, r7, r8 are independently 0 or 1;

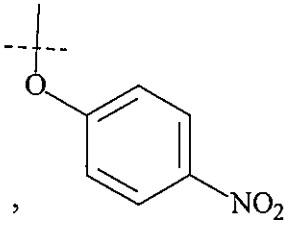
r3, r6 are independently 0, 1, 2, 3, or 4;

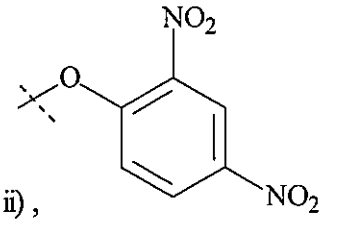
r4, r5 are independently 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

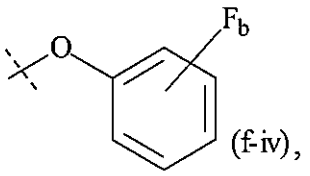
s1, s2 are independently 1, 2, 3, 4, 5 or 6;

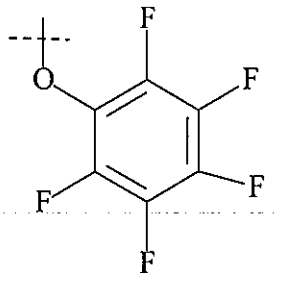
Y^1, Y^2 are identical or different and each is independently of the other selected from formulas (f-i) to (f-vi):


(f-i),

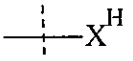

(f-ii),


(f-iii),


(f-iv),


(f-v)

or


(f-vi)

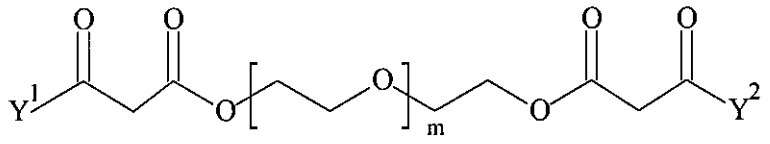
wherein

the dashed lines indicate attachment to the rest of the molecule,

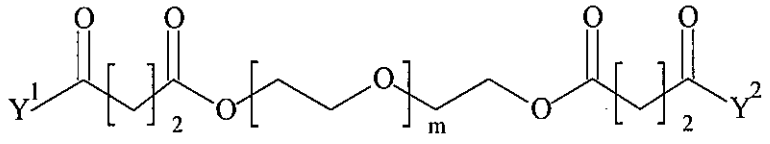
b is 1, 2, 3 or 4

X^H is Cl, Br, I, or F.

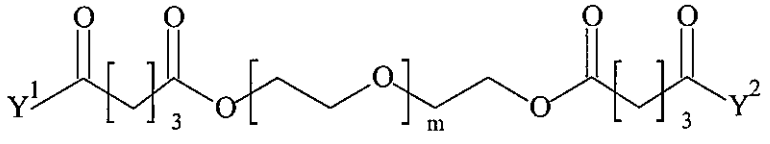
21. The process of any one of claims 1 to 20, wherein the crosslinker reagent is of formula (V-1) to (V-54):



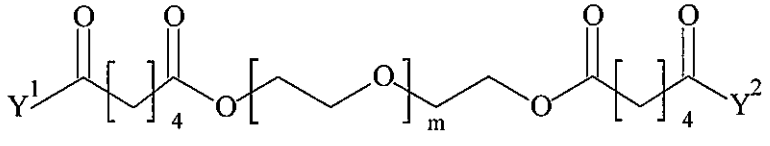
(V-1),



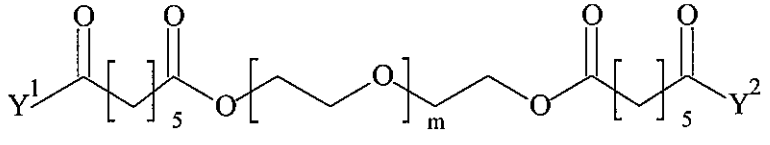
(V-2),



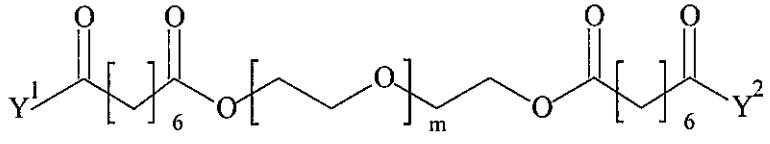
(V-3),



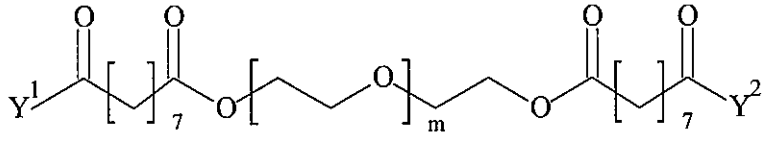
(V-4),



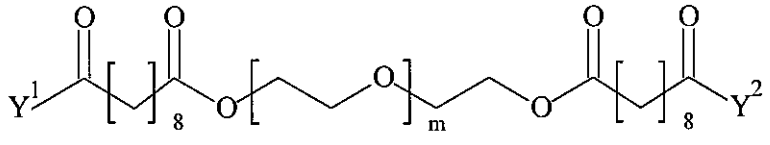
(V-5),



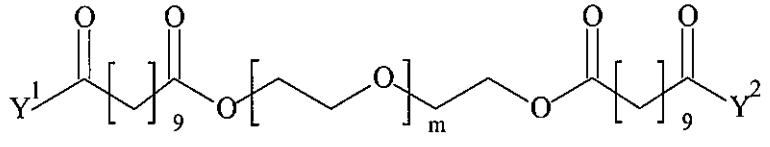
(V-6),



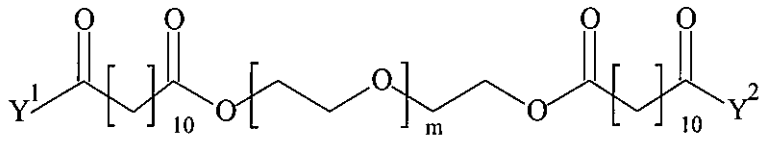
(V-7),



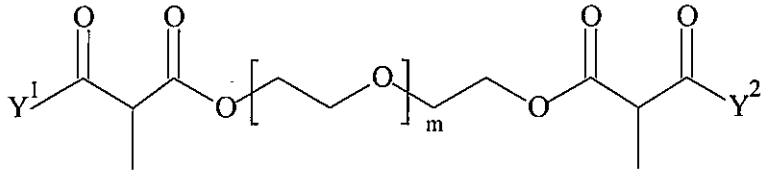
(V-8),



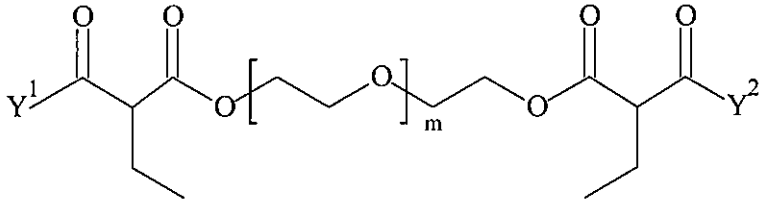
(V-9),



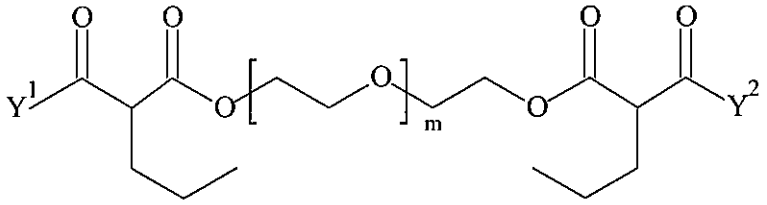
(V-10),



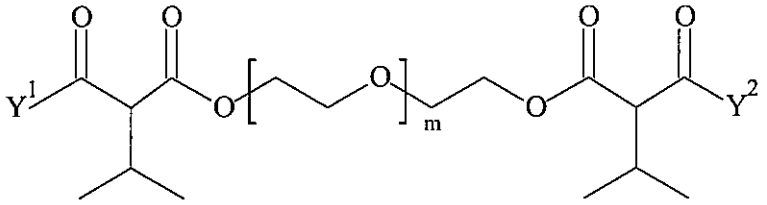
(V-11),



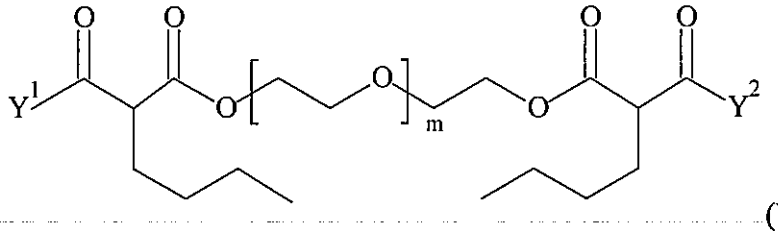
(V-12),



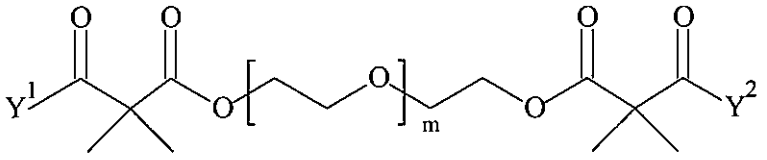
(V-13),



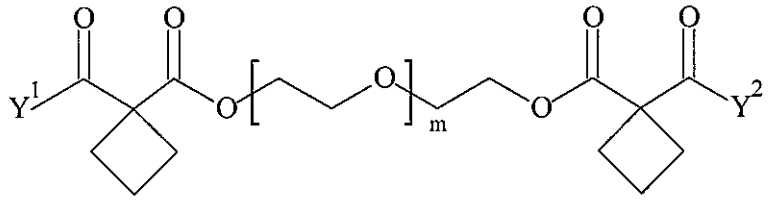
(V-14),



(V-15),



(V-16),



(V-17)

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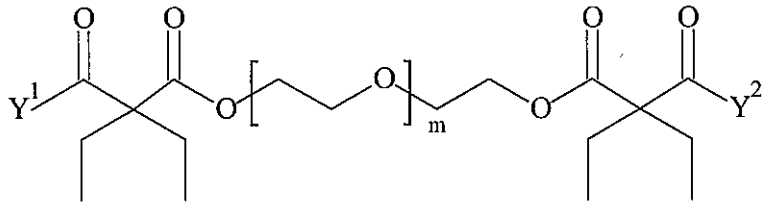

(V-18)

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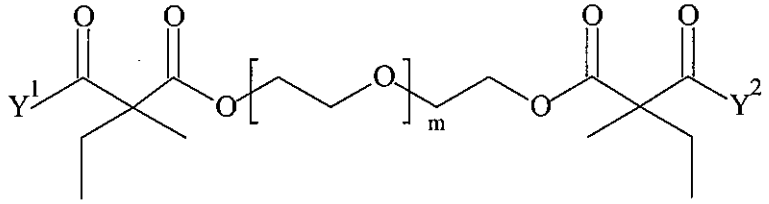
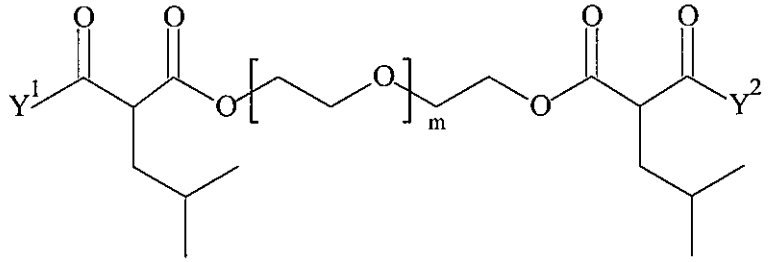
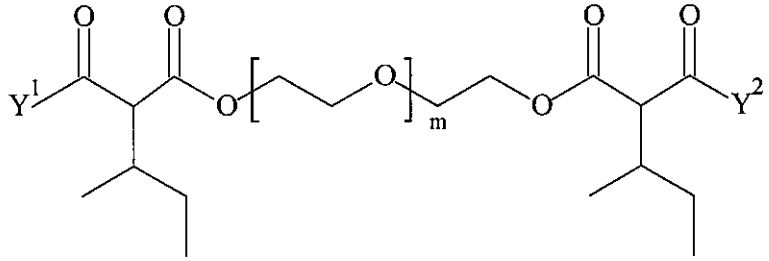


(V-19)

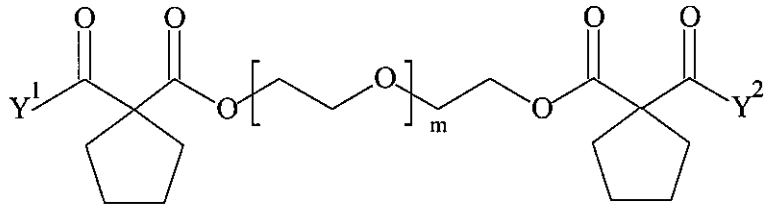


(V20)



(V-21)

5



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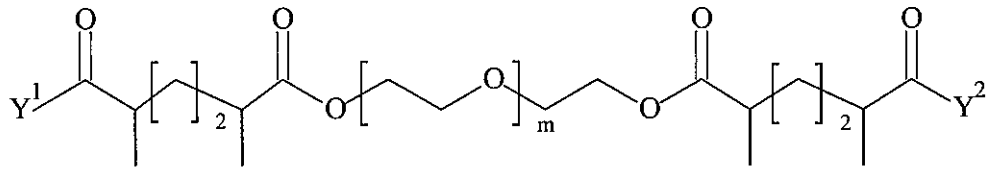
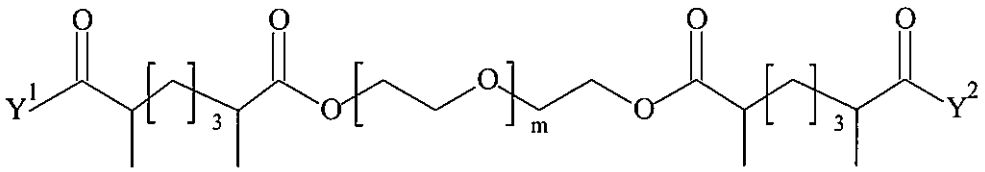
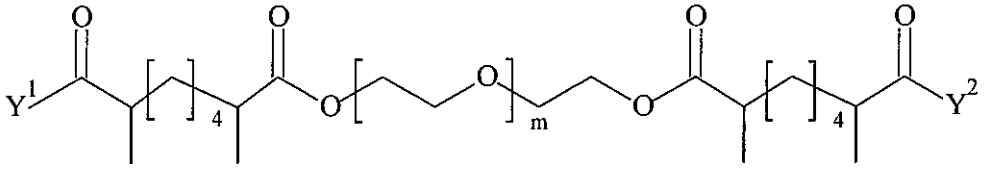


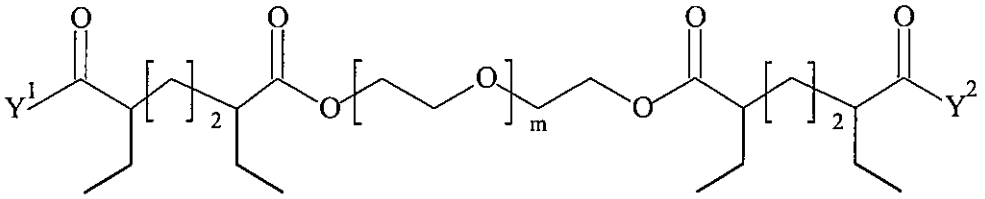
(V-23)



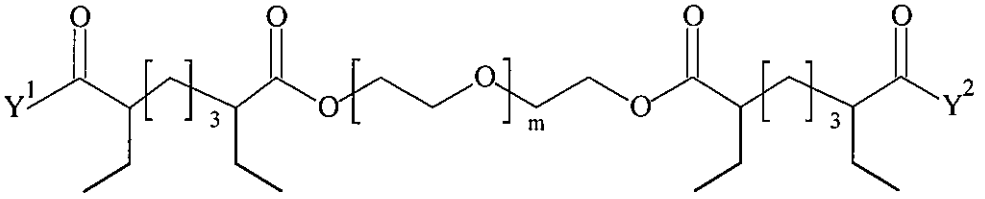
(V-24)



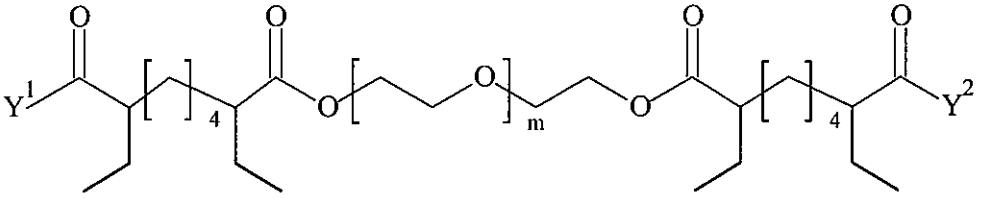
(V-25)



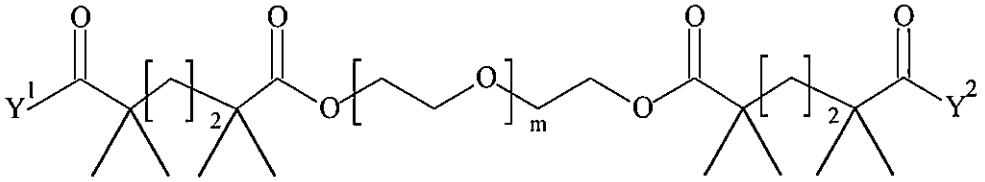
(V-26)



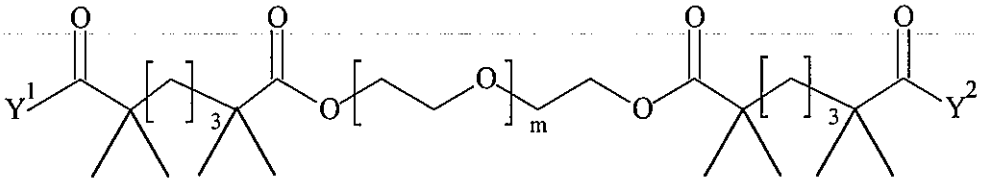
(V-27)



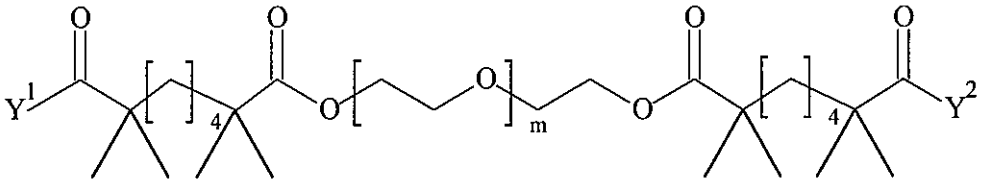
(V-28)



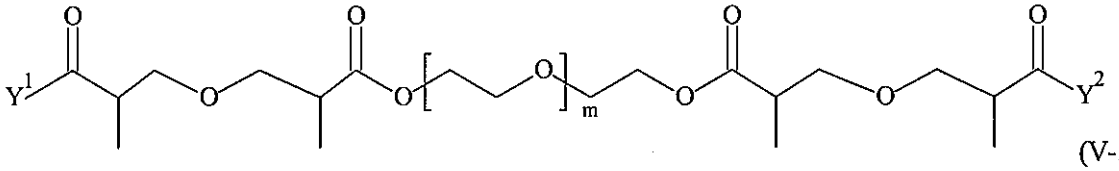
(V-29)



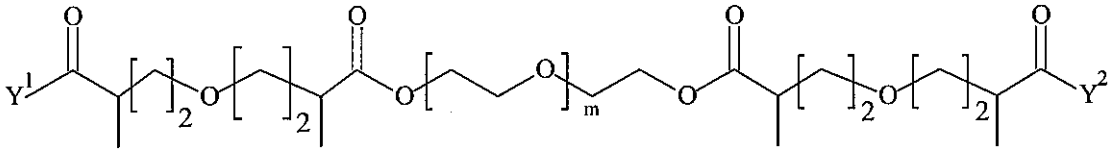
(V-30)



(V-31)



(V-32)



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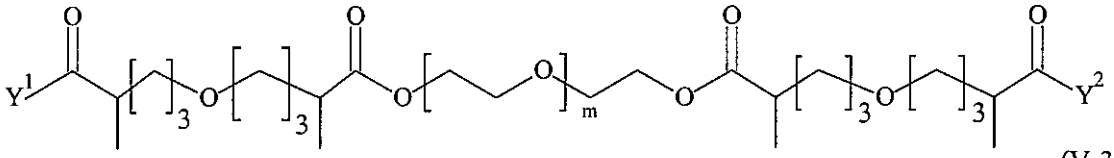
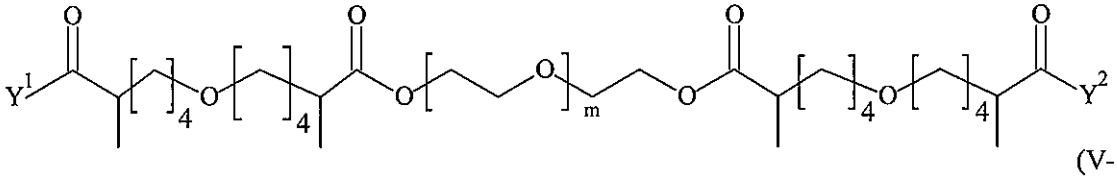
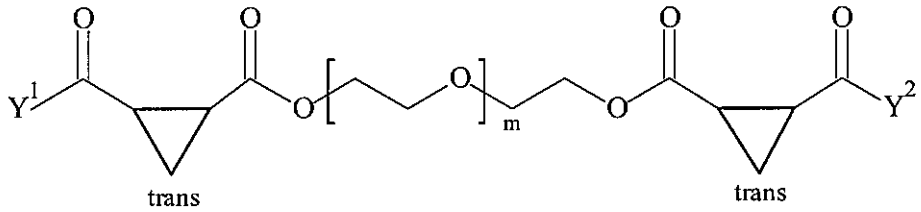


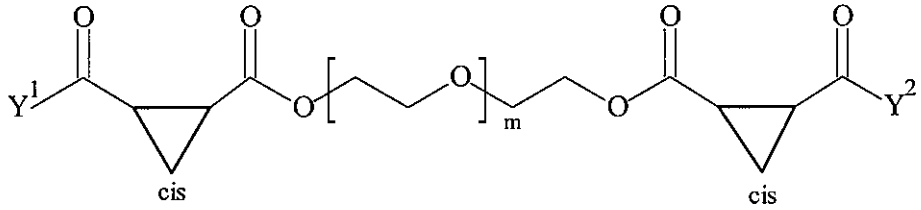
(V-34)



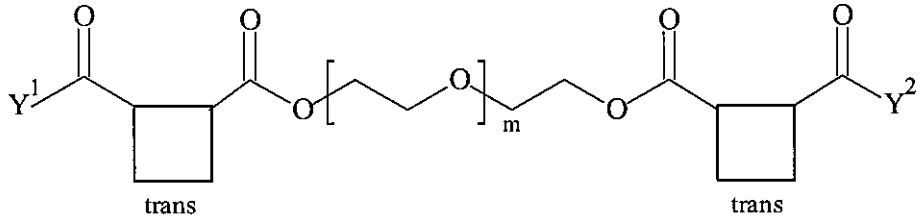
(V-35)



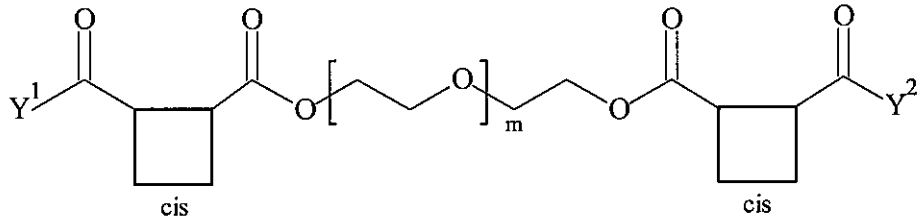
(V-36)



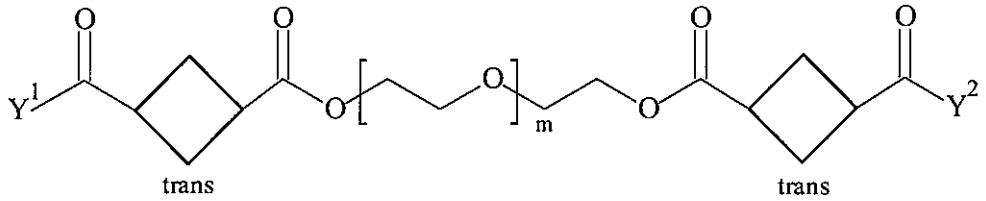
(V-37)



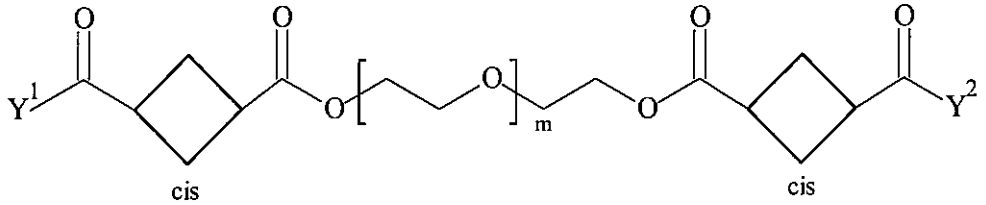
(V-38)



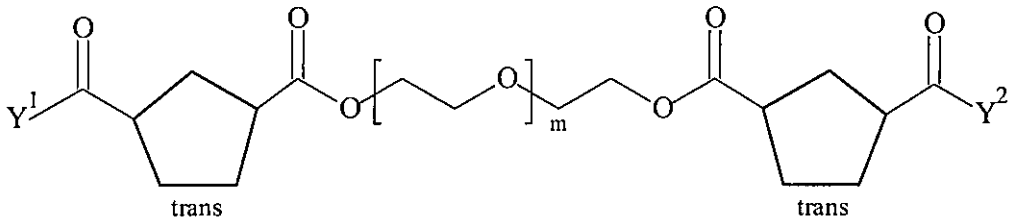
(V-39)



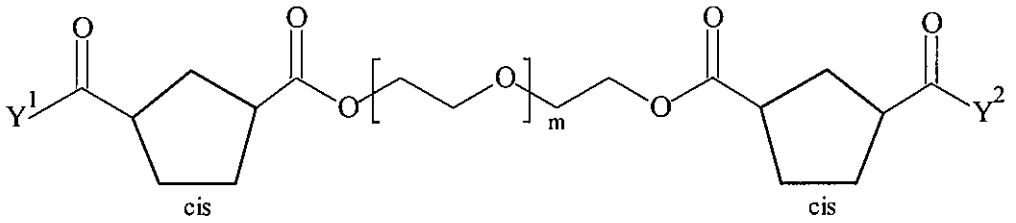
(V-40)



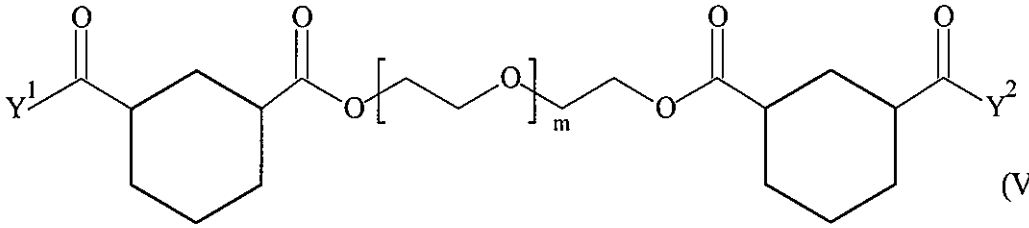
(V-41)



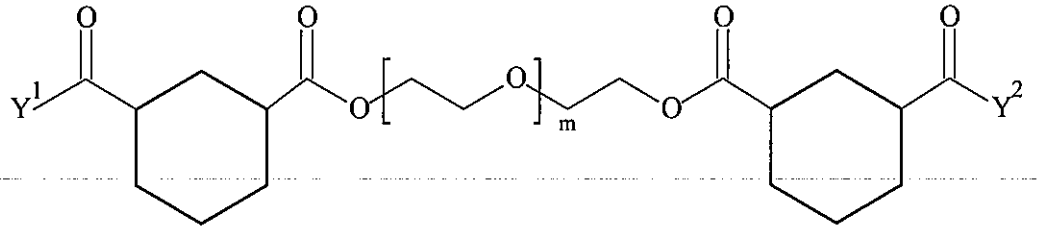
(V-42)



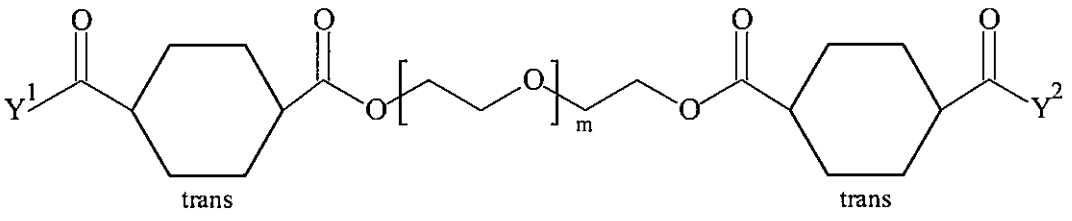
(V-43)



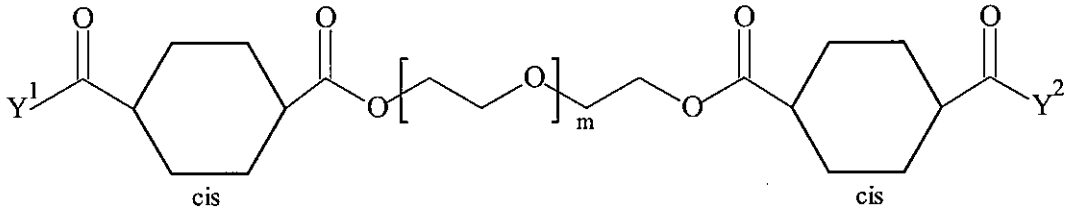
(V-44)



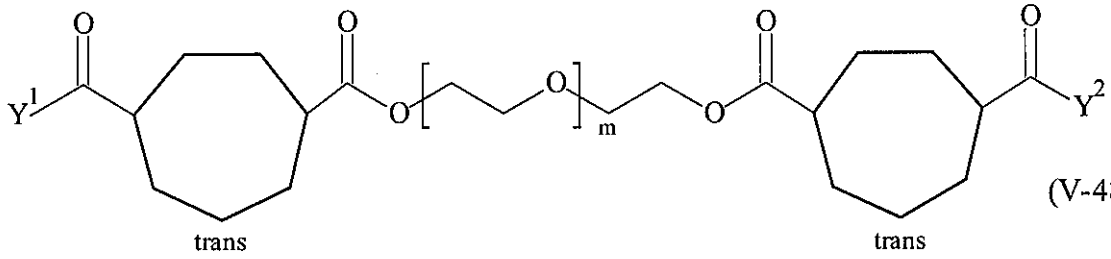
(V-45)



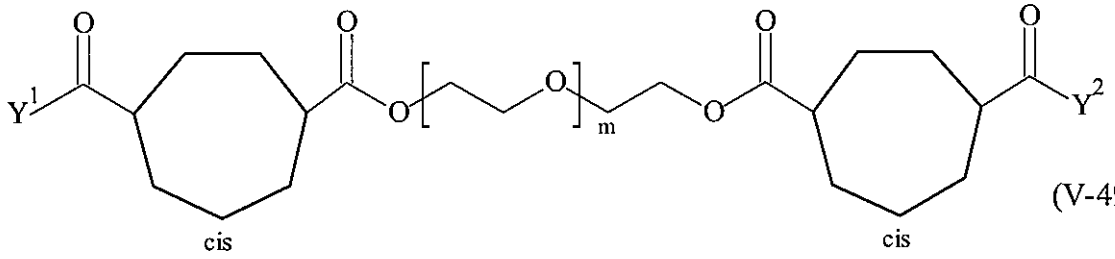
(V-46)



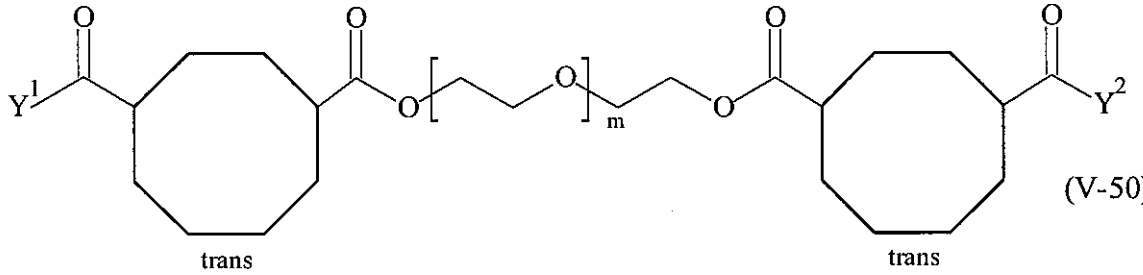
(V-47)



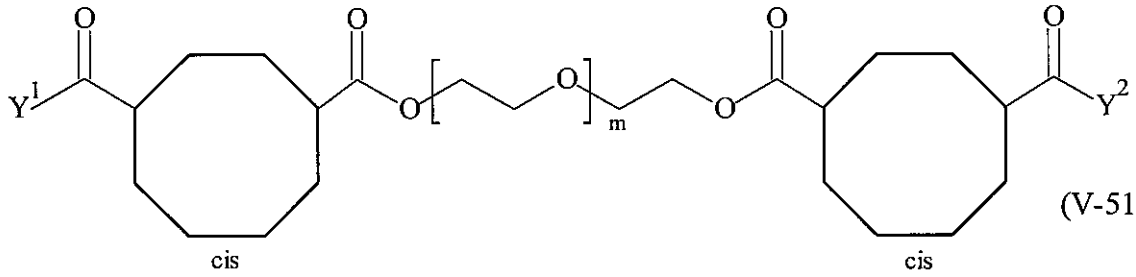
(V-48)



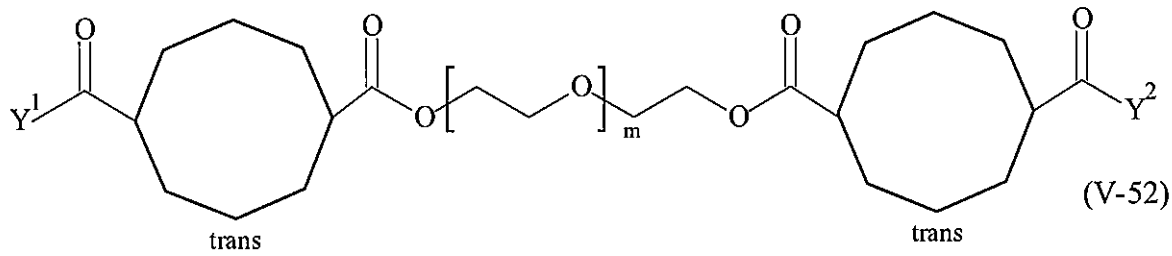
(V-49)



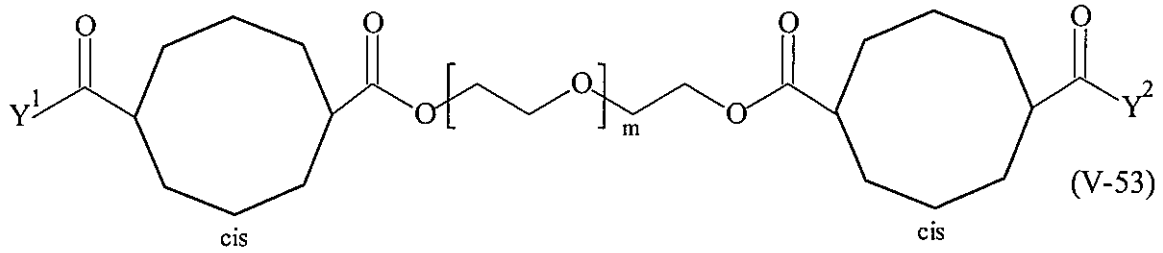
(V-50)



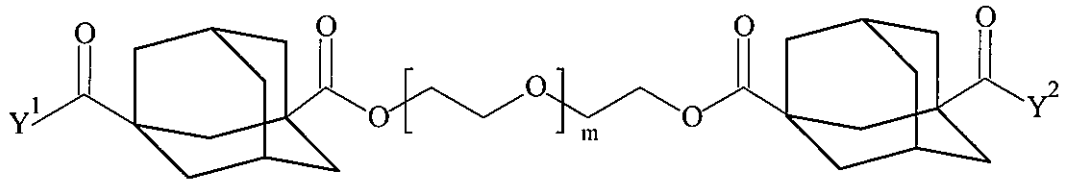
(V-51)



(V-52)



(V-53)



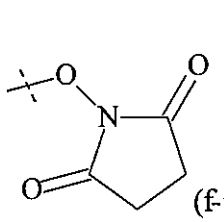
(V-54)

wherein

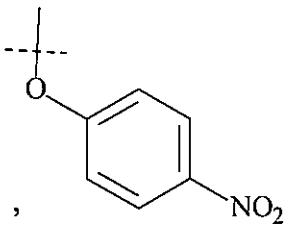
each crosslinker reagent may be in the form of its racemic mixture, where applicable; and

m ranges from 120 to 920, preferably from 120 to 460 and more preferably from 120 to 230;

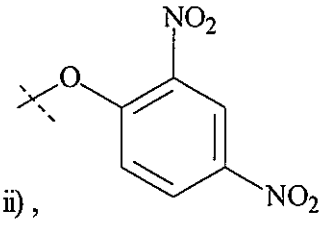
Y^1, Y^2 are identical or different and each is independently of the other selected from formulas (f-i) to (f-vi):



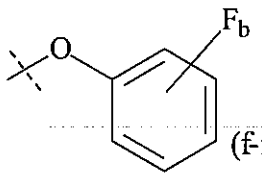
(f-i),



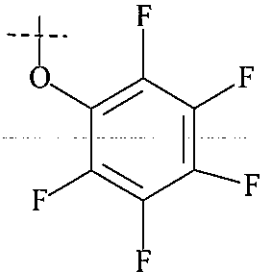
(f-ii),



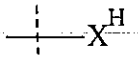
(f-iii),



(f-iv),



(f-v) or



(f-vi)

wherein

the dashed lines indicate attachment to the rest of the molecule,

b is 1, 2, 3 or 4

X^H is Cl, Br, J, or F.

22. The process of any one of claims 1 to 21, wherein the hydrogel obtained from the polymerization is a shaped article.

23. The process of claim 22, wherein the hydrogel is in the form of microparticular beads having a diameter of 1 to 500 micrometer.

24. A hydrogel obtainable by a process of any one of claims 1 to 23.

25. A process for the preparation of a hydrogel-spacer conjugate comprising the step of:

(d) reacting the hydrogel from claim 24 with a spacer reagent of the formula (VI)

A^{x1}-S^0-A^{x2} (VI),

wherein

S^0 is selected from the group comprising C_{1-50} alkyl, C_{2-50} alkenyl and C_{2-50} alkynyl, which fragment is optionally interrupted by one or more group(s) selected from -NH-, -N(C_{1-4} alkyl)-, -O-, -S, -C(O)-, -C(O)NH, -C(O)N(C_{1-4} alkyl)-, -O-C(O)-, -S(O)-, -$S(O)_2$-, 4- to 7-membered heterocyclyl, phenyl and naphthyl;

A^{x1} is a functional group for reaction with an amine group of the hydrogel; and

A^{x2} is a functional group;

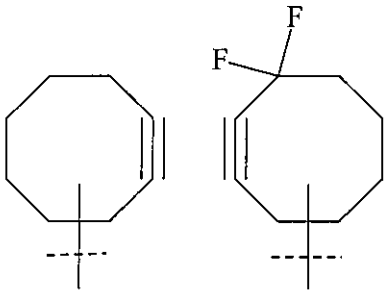
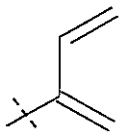
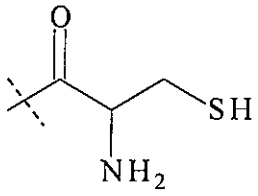
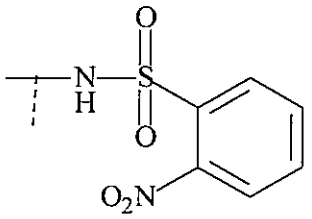
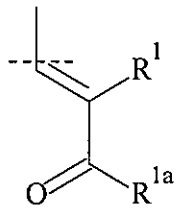
in the presence of a solvent to obtain a hydrogel-spacer conjugate.

26. The process of claim 25, wherein A^{x1} is selected from the group comprising activated carboxylic acid; Cl-(C=O)-; NHS-(C=O)-, wherein NHS is N-hydroxysuccinimide; $ClSO_2$-; R^1(C=O)-; I-; Br-; Cl-; SCN-; and CN-,

wherein

R^1 is selected from the group comprising H, C_{1-6} alkyl, alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 4- to 7-membered heterocyclyl, 8- to 11-membered heterobicyclyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl.

27. The process of claim 25 or 26, wherein A^{x2} is selected from the group comprising -maleimide, -SH, -NH_2, -SeH, -N_3, -C≡CH, -CR^1=$CR^{1a}R^{1b}$, -OH, -(CH=X^0)–R^1, -(C=O)–S–R^1, -(C=O)-H, -NH-NH_2, -O-NH_2, -Ar–X^0, -Ar–Sn(R^1)(R^{1a})(R^{1b}), -Ar–B(OH)(OH),

, and ; with optional protecting groups;

wherein

X^0 is -OH, $-NR^1R^{1a}$, -SH, and -SeH,

Ar is selected from phenyl, naphthyl, indenyl, indanyl, and tetralinyl, and

R^1, R^{1a}, R^{1b} are independently of each other selected from the group comprising H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 4- to 7-membered heterocyclyl, 8- to 11-membered heterobicyclyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl.

28. A hydrogel-spacer conjugate obtainable by the process of any one of claims 26 to 27.

29. A process for the preparation of a carrier-linked prodrug comprising the step of:

(e) reacting a hydrogel of claim 24 or a hydrogel-spacer conjugate of claim 28 with a prodrug linker–biologically active moiety reagent of formula (VII)

A^{yl}-L-D (VII),

wherein

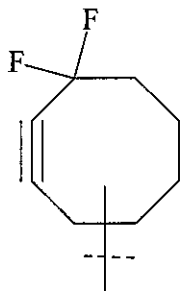
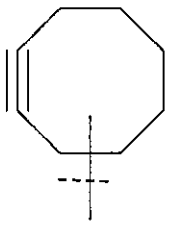
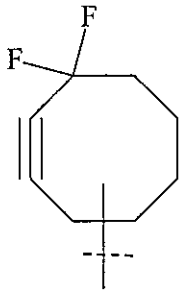
A^{yl} is a functional group for reaction with an amine of the hydrogel of step (b) or (c) or for reaction with the functional group A^{x2} of the hydrogel-spacer conjugate of step (d),

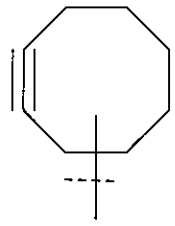
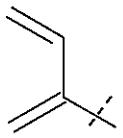
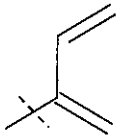
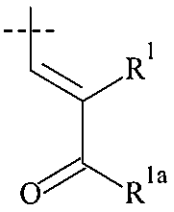
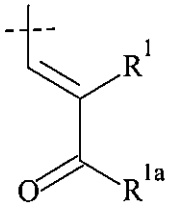
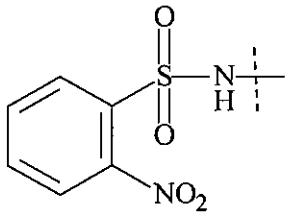
L is a prodrug linker;

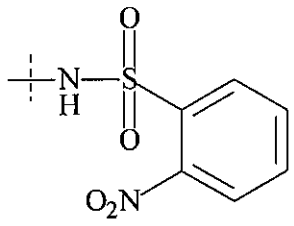
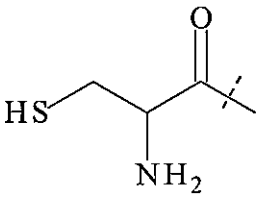
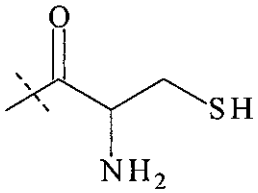
D is a biologically active moiety;

in the presence of a solvent, to obtain a carrier linked prodrug.

30. The process of claim 29, wherein A^{x2}/A^{y1} are selected from the following:

A^{x2}	A^{y1}
–maleimide	HS–, H_2N–, or HSe–
–SH, $–NH_2$, or –SeH	maleimide–
$–N_3$	HC≡C–,  , or 
–C≡CH,  , or -continued-	N_3–

	
$-CR^{1a}=CR^{1a}R^{1b}$	$R^{1b}R^{1a}C=CR^{1}-$ or 
	$R^{1b}R^{1a}C=CR^{1}-$
$-(C=X^{0})-R^{1}$	
	$R^{1}-(C=X)-$
$-OH$	H_2N- or 
$-NH_2$ or	$HO-$

	
–(C=O)–S–R^1	
	R^1–S–(C=O)–
–(C=O)–H	H_2N–NH– or H_2N–O–
–NH–NH_2 or –O–NH_2	H–(C=O)–
–Ar–X^0	–Ar–Sn(R^1)(R^{1a})(R^{1b}) or -Ar–B(OH)(OH)
(R^{1b})(R^{1a})(R^1)Sn–Ar– or –Ar–B(OH)(OH)	X^0–Ar–

wherein

X^0 is -OH, -NR^1R^{1a}, -SH, and –SeH;

R^1, R^{1a}, R^{1b} are independently of each other selected from the group comprising H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 4- to 7-membered heterocyclyl, 8- to 11-membered heterobicyclyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl; and

Ar is selected from phenyl, naphthyl, indenyl, indanyl, and tetralinyl.

31. The process of claim 29 or 30, wherein A^{x2} is a thiol and A^{yl} is of formula (VIIa)

$$T-PG^0-S- \quad \text{(VIIa)},$$

wherein

T is H or a tag moiety;

PG^0 is a sulfur-activating moiety; and

S is sulfur.

32. The process of any one of claims 29 to 31, wherein D has a molecular weight ranging between 2 and 500 kDa, more preferably between 5 and 250 kDa, more preferably between 5 and 100 kDa and most preferably between 10 and 60 kDa.

33. A carrier-linked prodrug obtainable by a process for the preparation of a carrier-linked prodrug of any one of claims 29 to 32.

34. A pharmaceutical composition comprising the carrier-linked prodrug of claim 33 or a pharmaceutical salt thereof together with a pharmaceutically acceptable excipient.

35. The carrier-linked prodrug of claim 33 or the pharmaceutical composition of claim 34 for use as a medicament.