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)–,

(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;

wherein the at least one backbone reagent is selected from the group consisting of a compound of formula (I)

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

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,

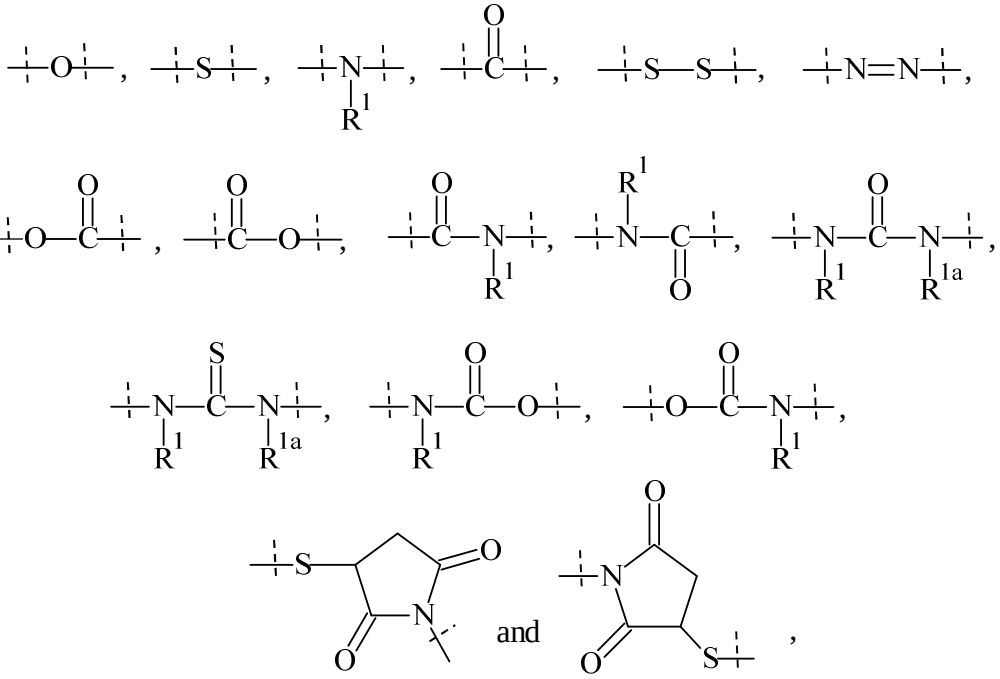
P is a PEG-based polymeric chain comprising at least 80% PEG, preferably at least 85% PEG, more preferably at least 90% PEG and most preferably at least 95% PEG,

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)

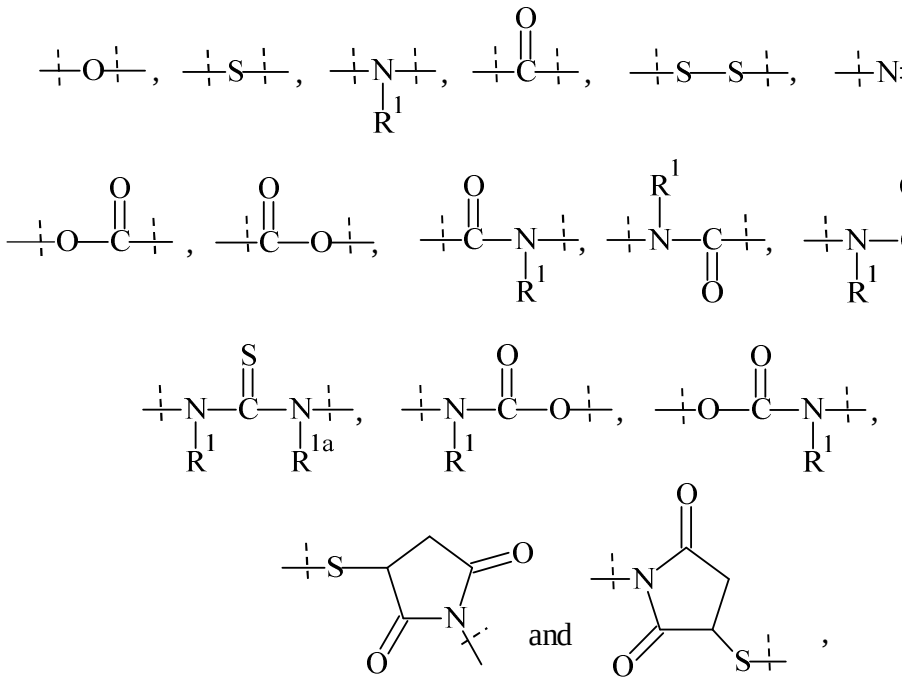
$$Hyp^2 - A^3 - P - A^4 - Hyp^3 \qquad (II),$$

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)

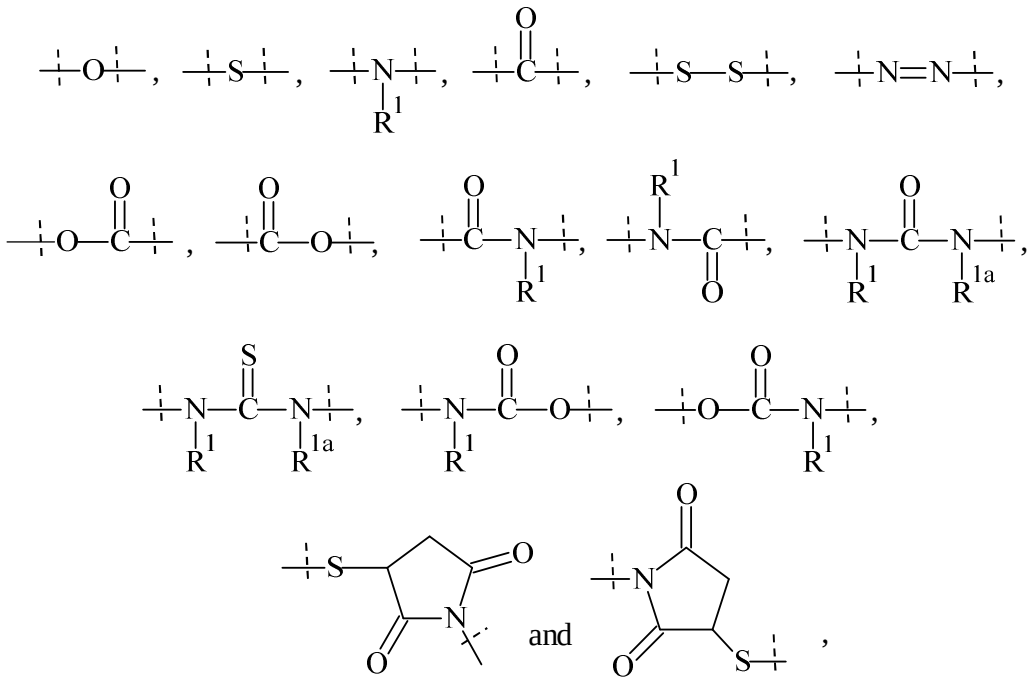
$$P^1 - A^5 - Hyp^4 \qquad (III),$$

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.

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

3. The process of claim 1 or 2, wherein the polymerization in step (b) is initiated by adding a base.

4. The process of claim 3, wherein the base is selected from *N*,*N*,*N*′,*N*′-tetramethylethylene diamine, 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, 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.

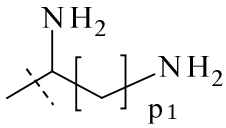
5. The process of any one of claims 1 to 4, wherein the mixture of step (a) is an emulsion.

6. The process of any one of claims 1 to 5, wherein the process further comprises the step of:

(c) working-up the hydrogel.

7. The process of any one of claims 1 to 6, 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)



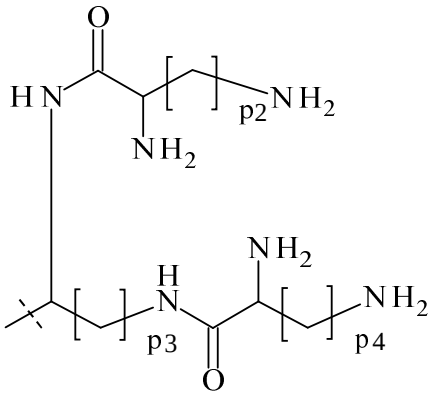
(e-i)

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)



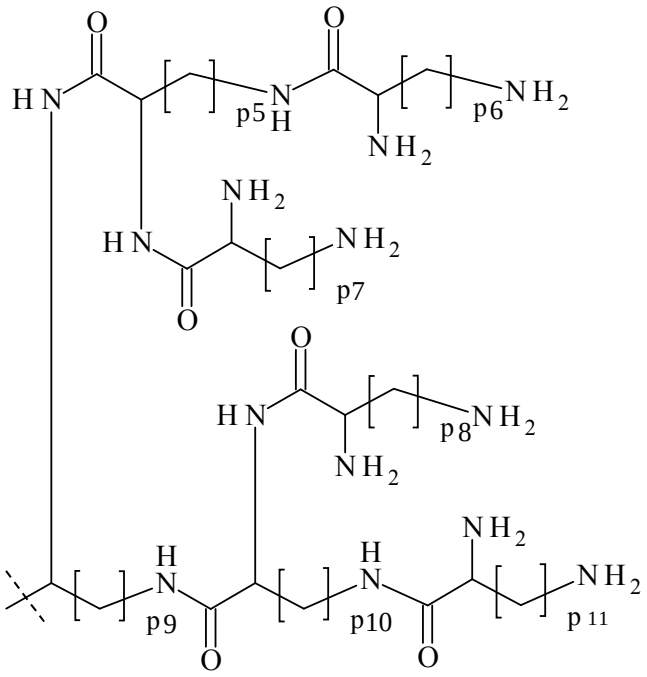
(e-ii)

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), and to A^5 if the backbone reagent has a structure of formula (III);

a moiety of formula (e-iii)



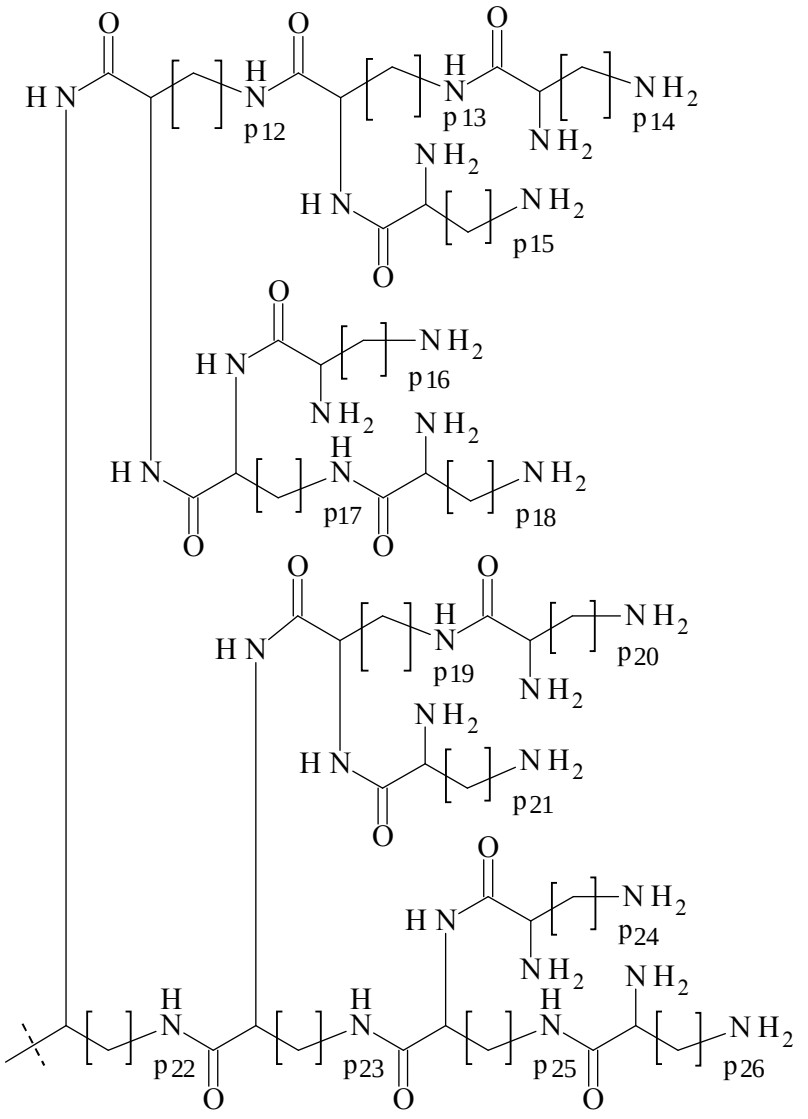
(e-iii)

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), and to A^5 if the backbone reagent is of formula (III);

a moiety of formula (e-iv)



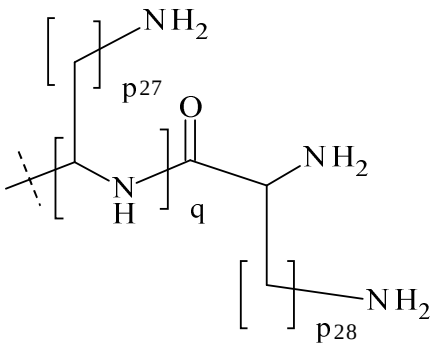
(e-iv)

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), and to A^5 if the backbone reagent has a structure of formula (III);

a moiety of formula (e-v)



(e-v)

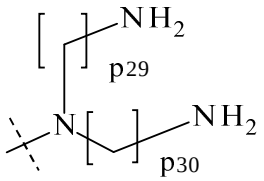
wherein

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 q 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), and to A^5 if the backbone reagent has a structure of formula (III);

a moiety of formula (e-vi)



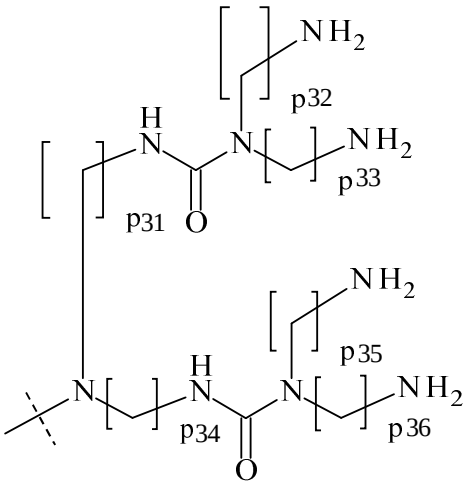
(e-vi)

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), and to A^5 if the backbone reagent has the structure of formula (III);

a moiety of formula (e-vii)



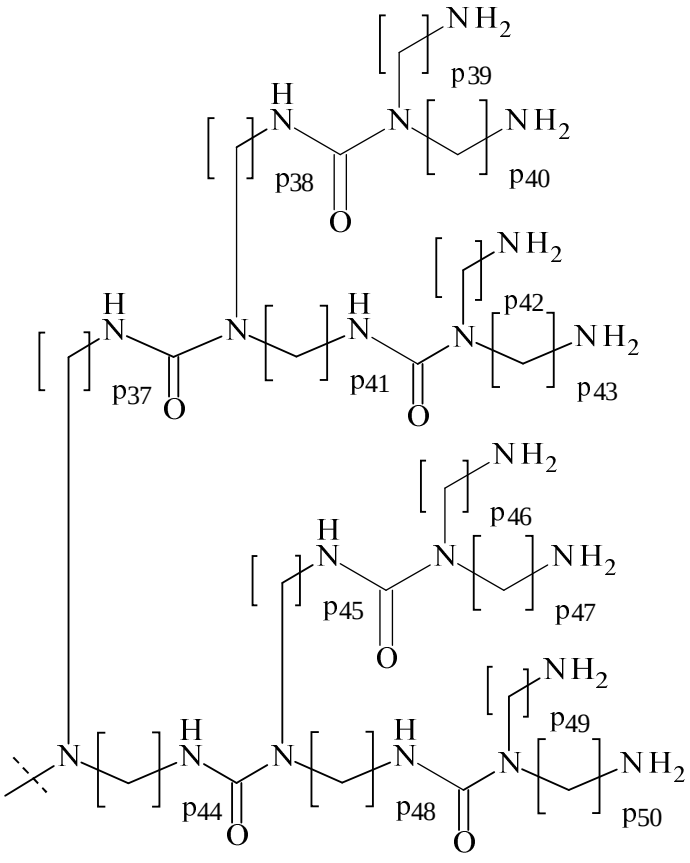
(e-vii)

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), and to A^5 if the backbone reagent has a structure of formula (III);

a moiety of formula (e-viii)



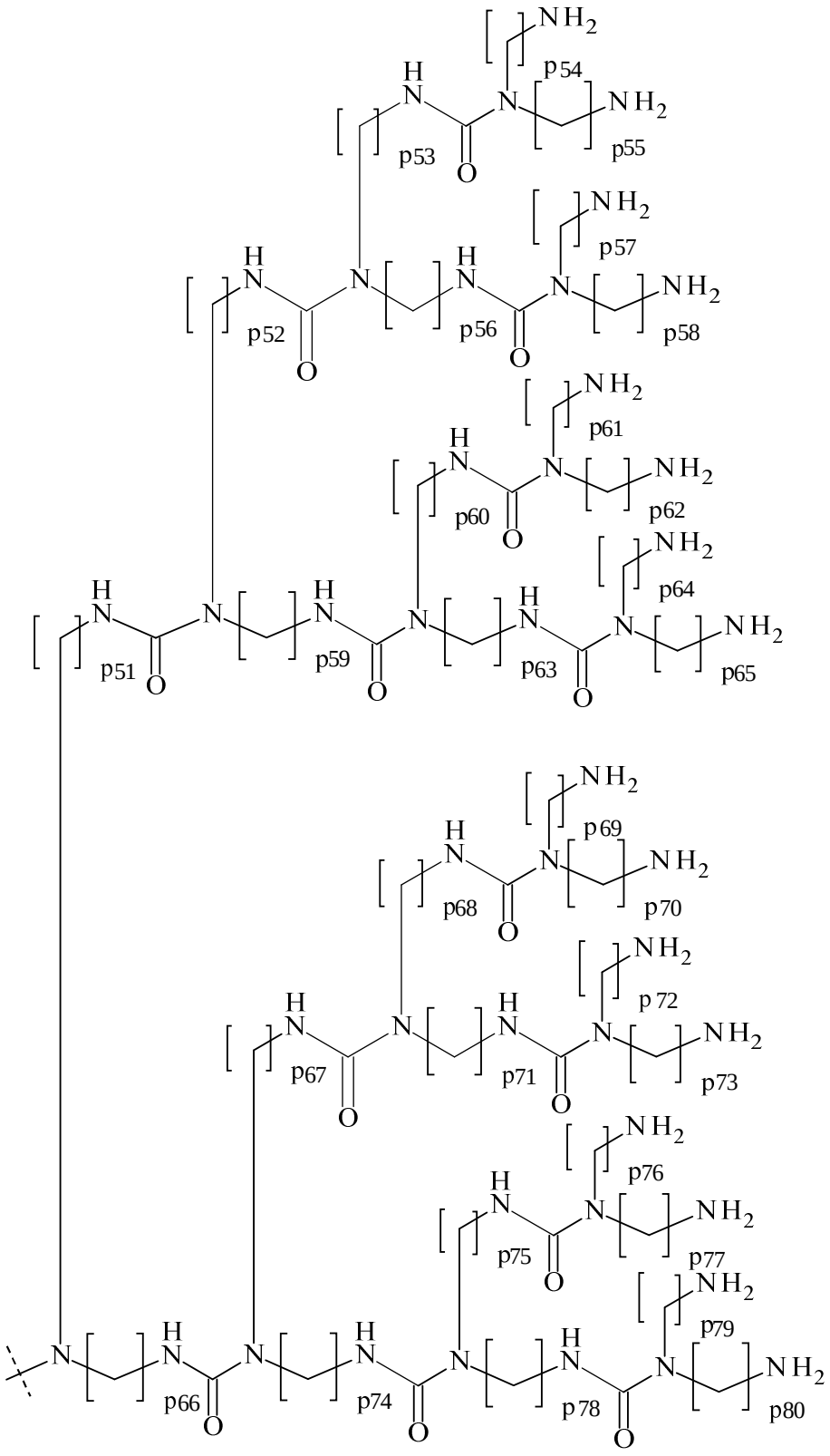
(e-viii)

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), and to A^5 if the backbone reagent has a structure of formula (III); and

a moiety of formula (e-ix):



(e-ix)

wherein

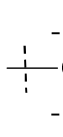
p51 to p80 are identical or different and each is independently of the others an integer from 2 to 5, preferably p51 to p80 are 3, and

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), and to A^5 if the backbone reagent has a structure of formula (III); and

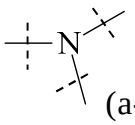
wherein the moieties (e-i) to (e-v) may at each chiral center be in either R- or S-configuration, preferably, all chiral centers of a moiety (e-i) to (e-v) are in the same configuration.

8. The process of any one of claims 1 or 7, wherein the backbone reagent is a compound of formula (I).

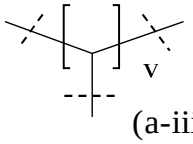
9. The process of any one of claims 1 to 8, wherein the branching core B is selected from the following structures:



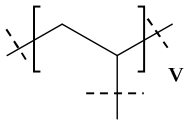
(a-i)



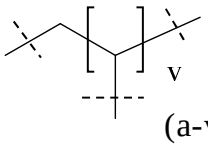
(a-ii)



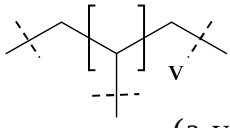
(a-iii)



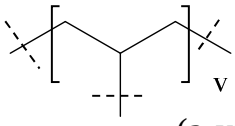
(a-iv)



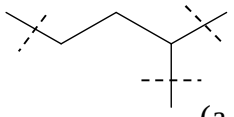
(a-v)

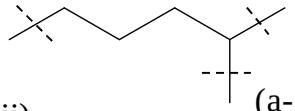


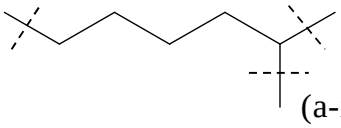
(a-vi)

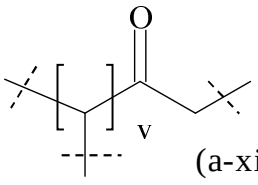


(a-vii)

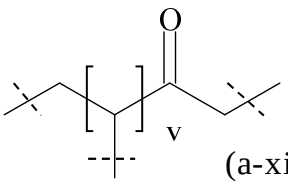

(a-viii)


(a-ix)

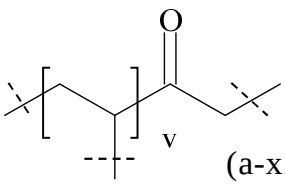

(a-x)



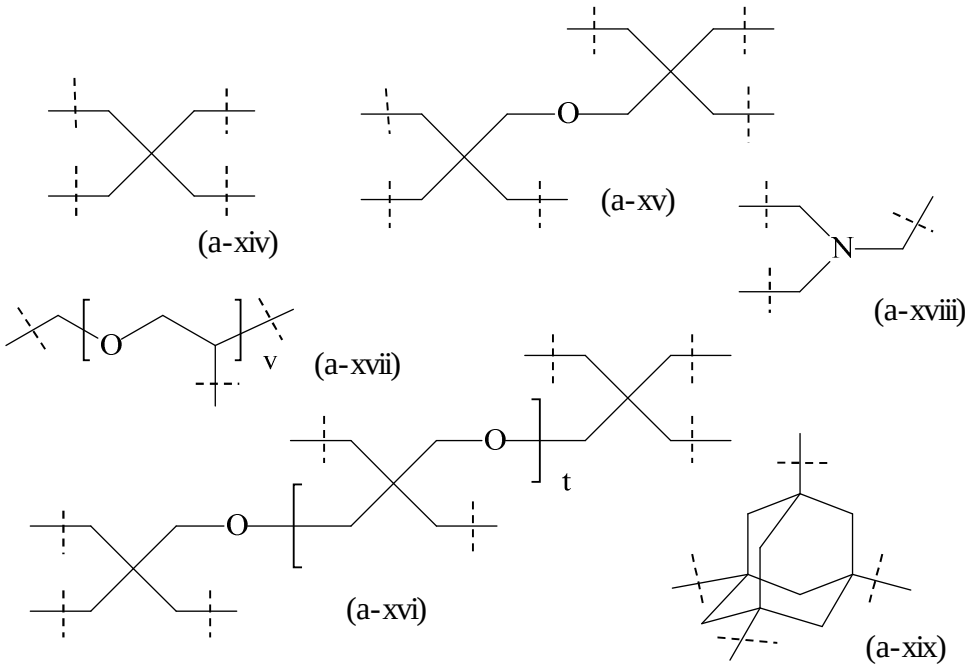
(a-xi)

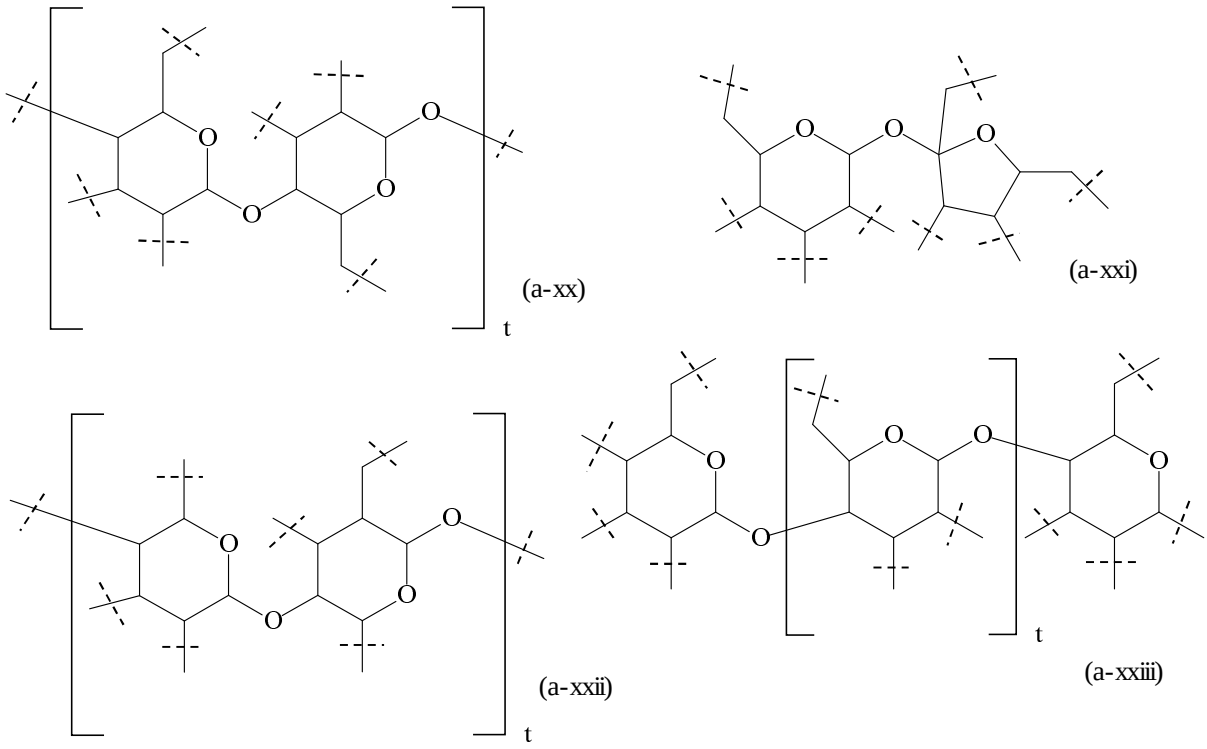


(a-xii)



(a-xiii)





wherein

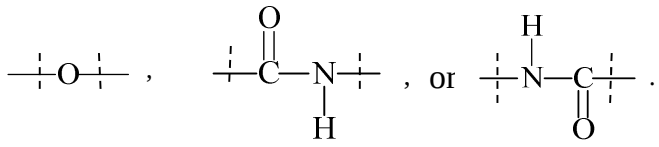
dashed lines indicate attachment to A^0 or, if x1 and x2 are both 0, to A^1,

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.

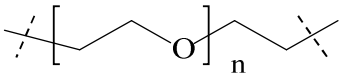
10. The process of claim 9, wherein B is of formula (a-xiv).

11. The process of any one of claims 1 to 10, wherein A^0 is



12. The process of any one of claims 1 to 11, wherein x1 and x2 are 0.

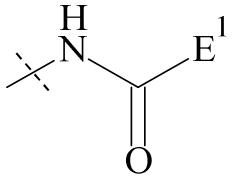
13. The process of any one of claims 1 to 12, wherein P has the structure of formula (c-i):



(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.

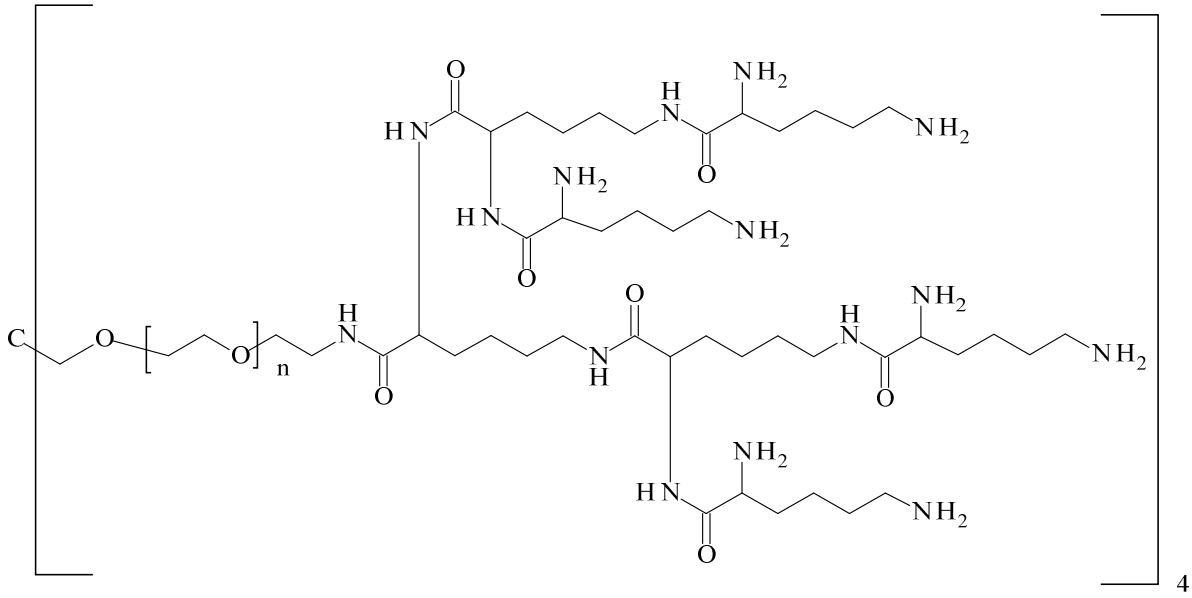
14. The process of any one of claims 1 to 13, wherein the moiety $– A^2 – Hyp^1$ is a moiety of the formula



,

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

15. The process of any one of claims 1 to 14, wherein the backbone reagent has the following formula:



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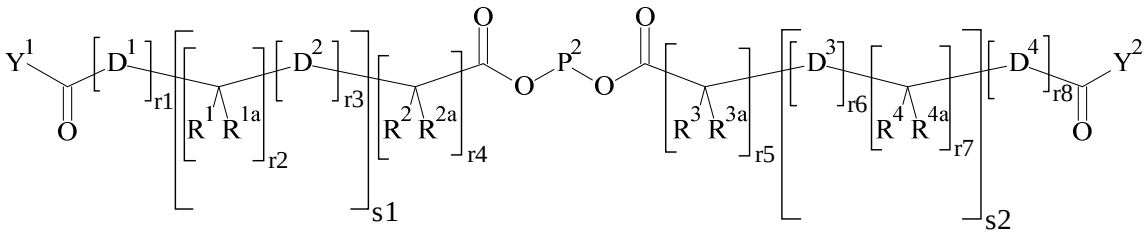
wherein

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

16. The process of claim 15, wherein n ranges from 20 to 30 and most preferably n is 28.

17. The process of any one of claims 1 to 16, wherein the backbone reagent is present in the form of its acidic salt.

18. The process of any one of claims 1 to 17, wherein the crosslinker reagent is a compound of formula (V-II):



(V-II),

wherein

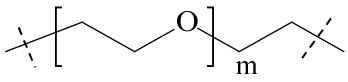
D^1, D^2, D^3 and D^4 are identical or different and each is independently of the others selected from the group comprising O, NR^5,S and CR^5R^{5a};

R^1, R^{1a}, R^2, R^{2a}, 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;

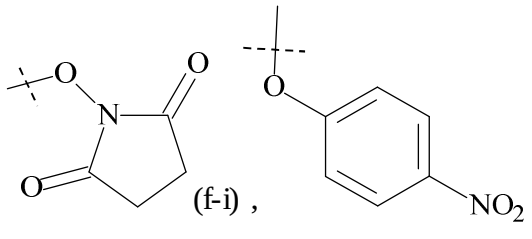
r1, r2, r7, r8 are independently 0 or 1;

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

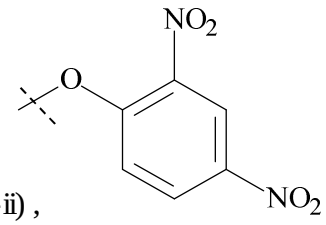
r4, r5 are independently 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

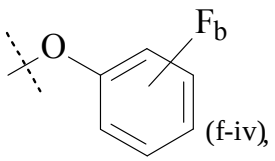
s1, s2 are independently 1, 2, 3, 4, 5 or 6;

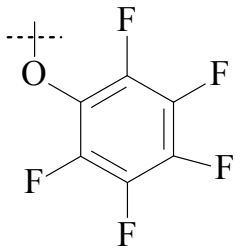
Y^1, Y^2 are identical or different and each is independently of the other selected from formulas (f-i) to (f-vi):

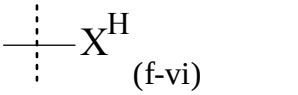

(f-i),

(f-ii),


(f-iii),


(f-iv),


(f-v) and


(f-vi)

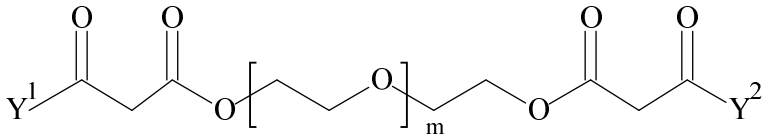
wherein

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

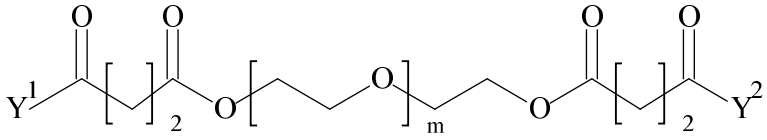
b is 1, 2, 3 or 4

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

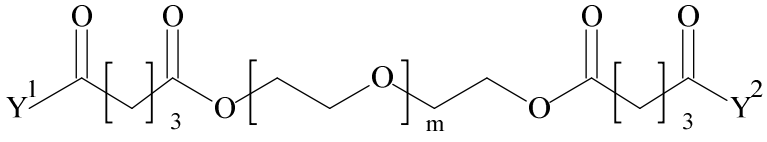
19. The process of any one of claims 1 to 18, wherein the crosslinker reagent is of formula (V-1) to (V-54):



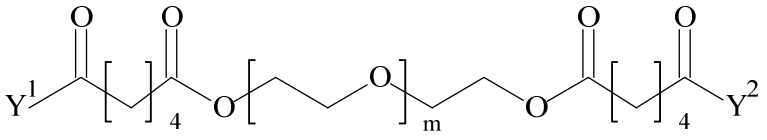
(V-1),



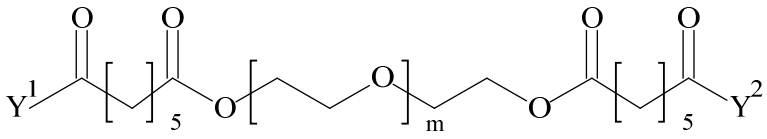
(V-2),



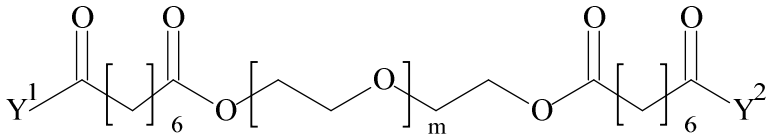
(V-3),



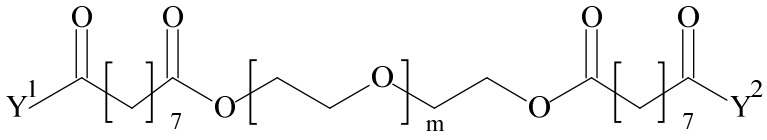
(V-4),



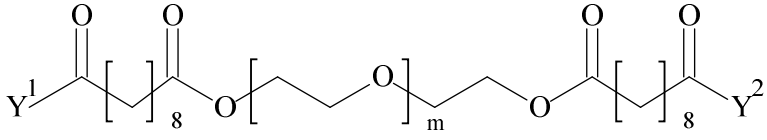
(V-5),



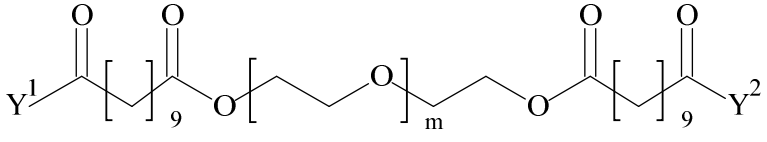
(V-6),



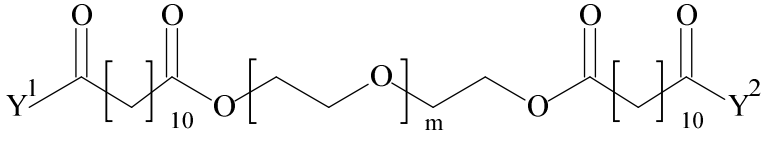
(V-7),



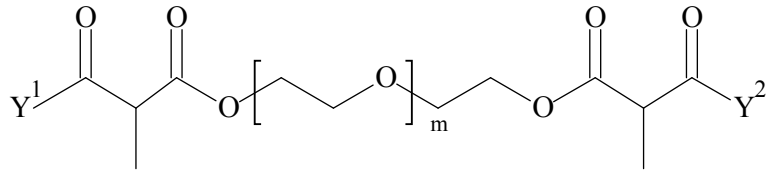
(V-8),



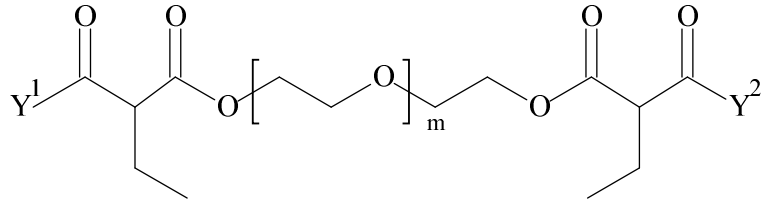
(V-9),



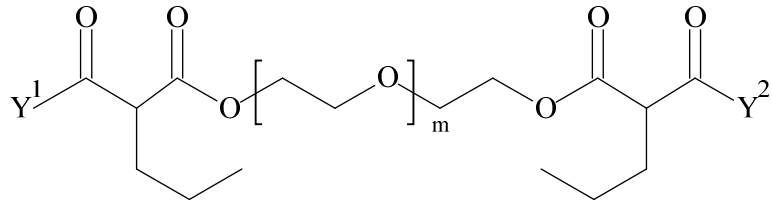
(V-10),



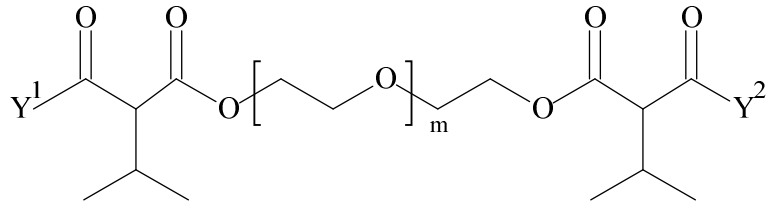
(V-11),



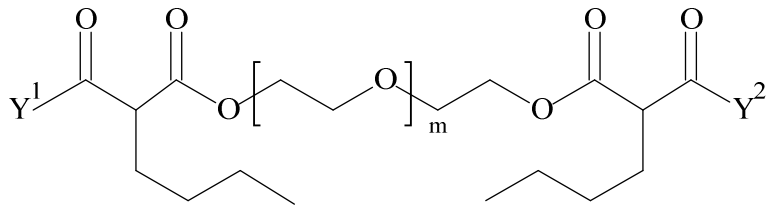
(V-12),



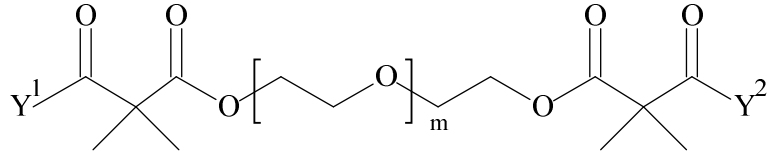
(V-13),



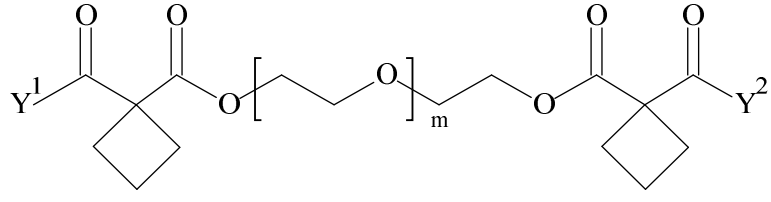
(V-14),



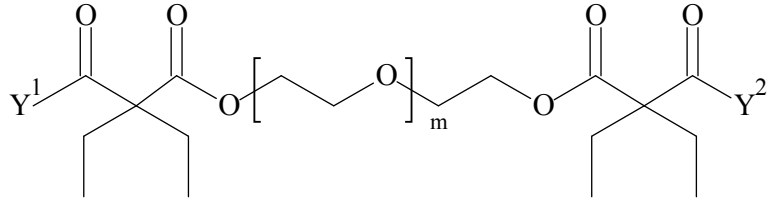
(V-15),



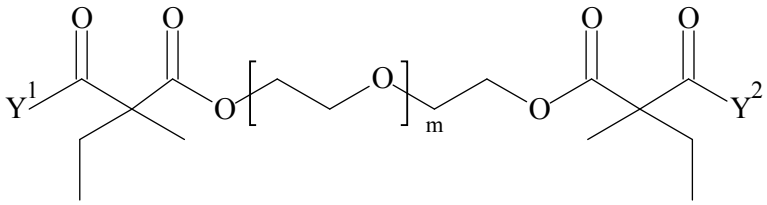
(V-16),



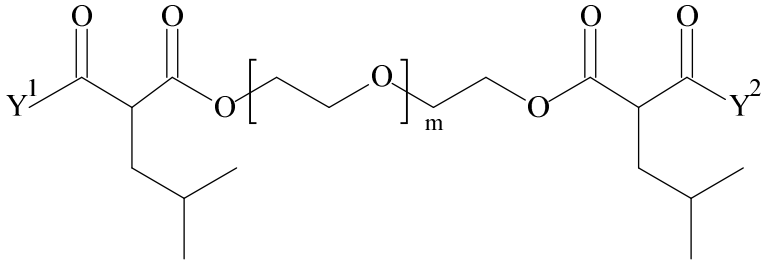
(V-17),



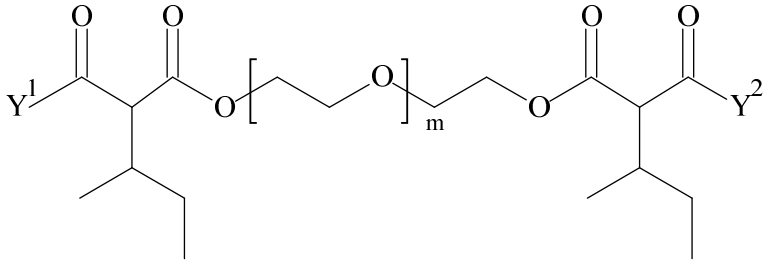
(V-18),



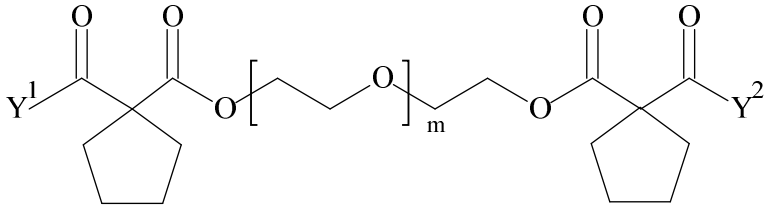
(V-19)



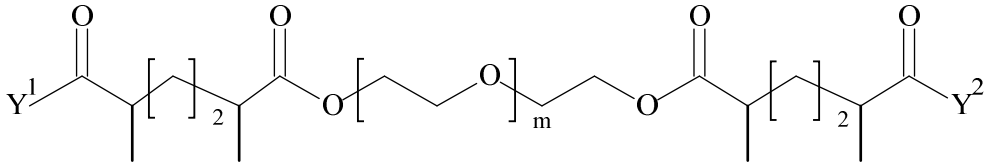
(V20)



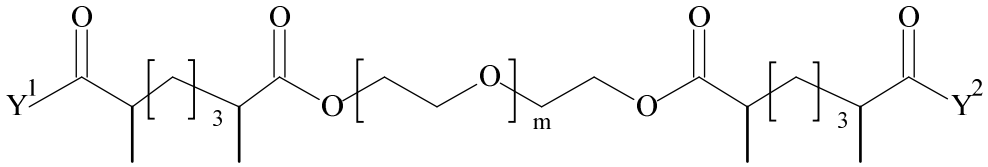
(V-21)



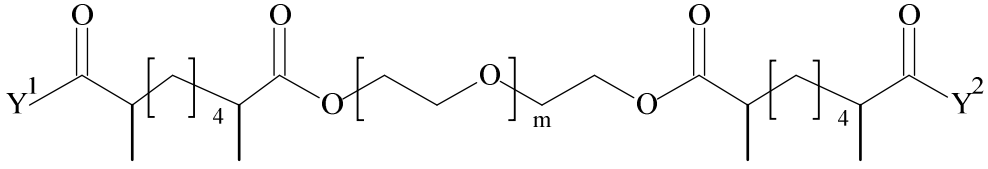
(V-22)



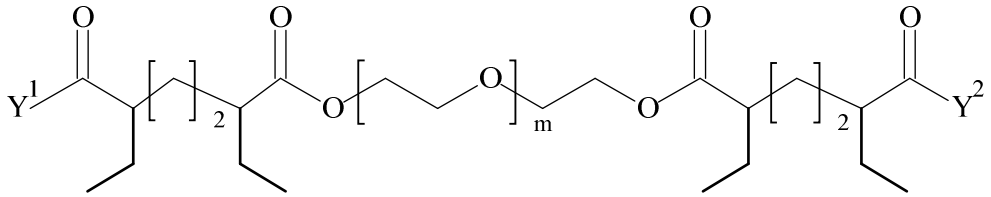
(V-23)



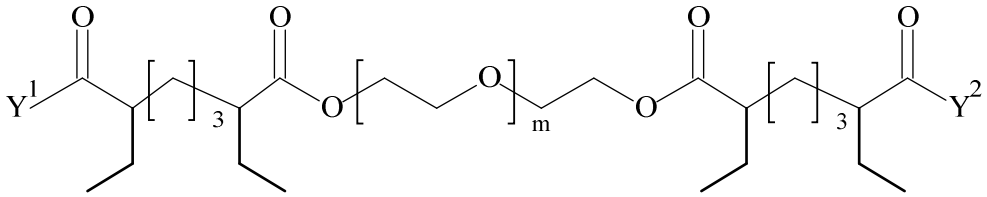
(V-24)



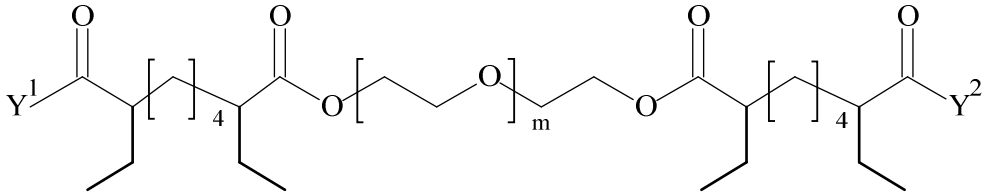
(V-25)



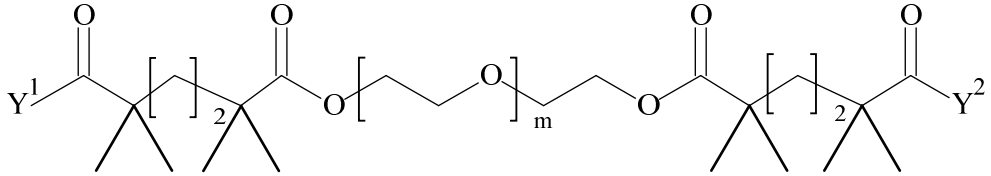
(V-26)



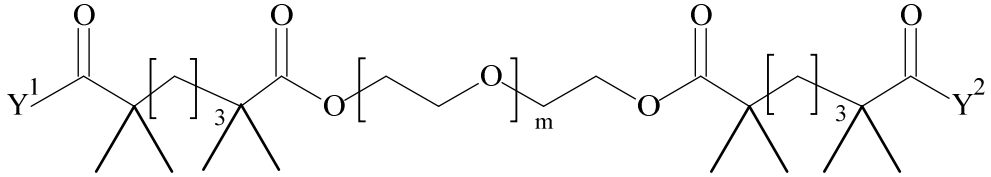
(V-27)



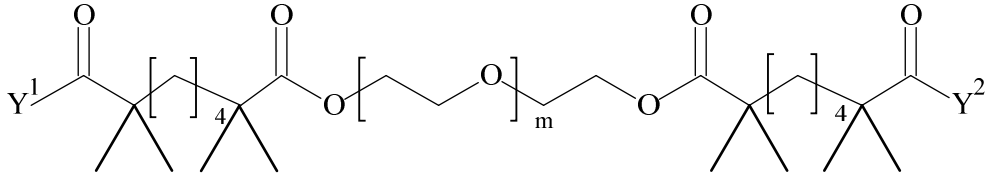
(V-28)



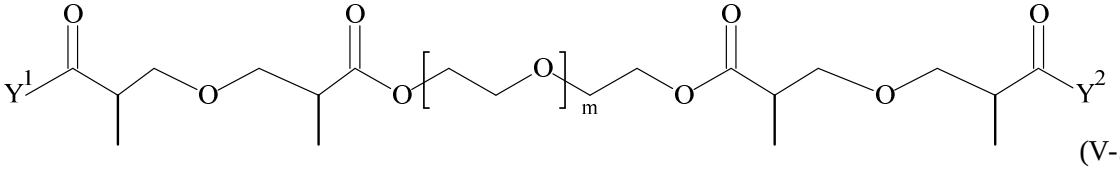
(V-29)



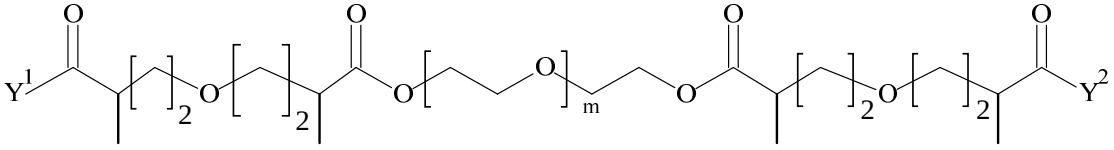
(V-30)



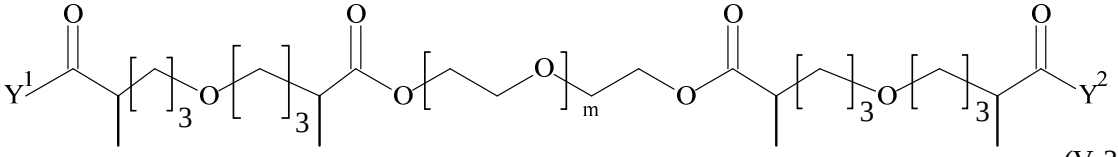
(V-31)



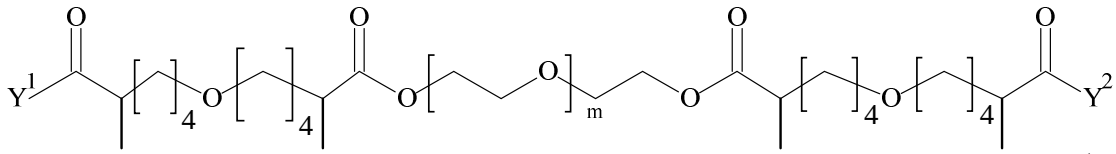
(V-32)



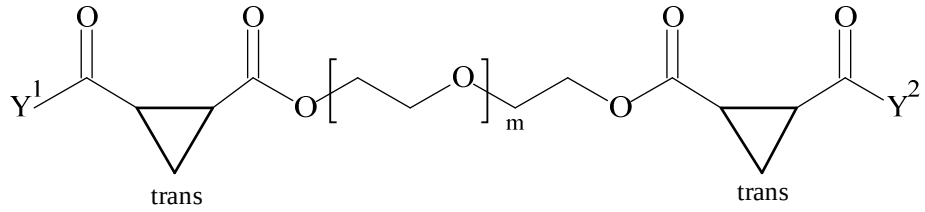
(V-33)



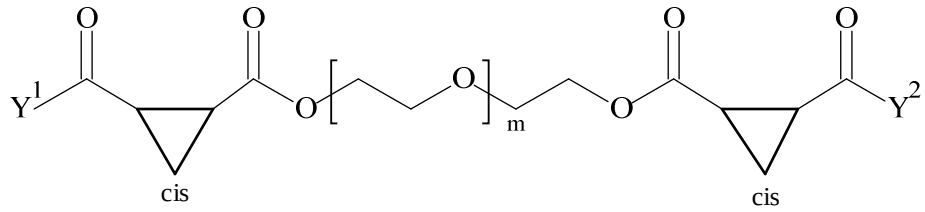
(V-34)



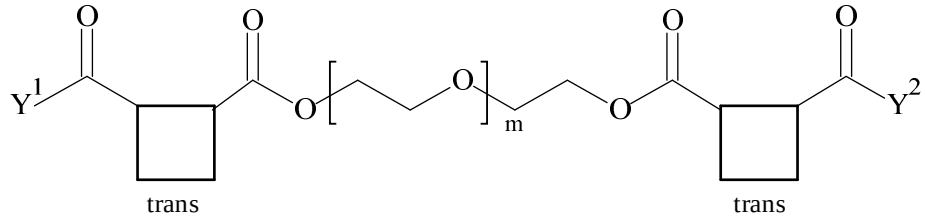
(V-35)



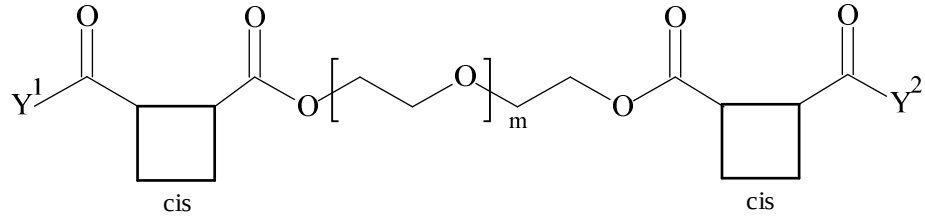
(V-36)



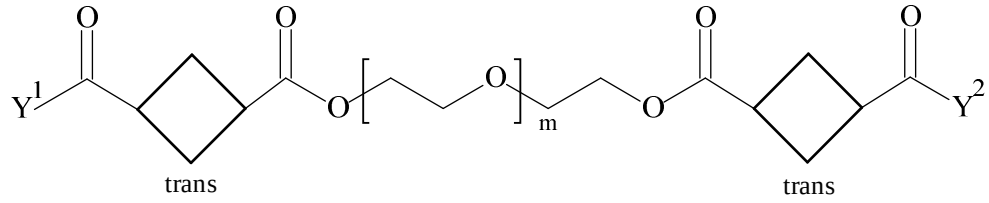
(V-37)



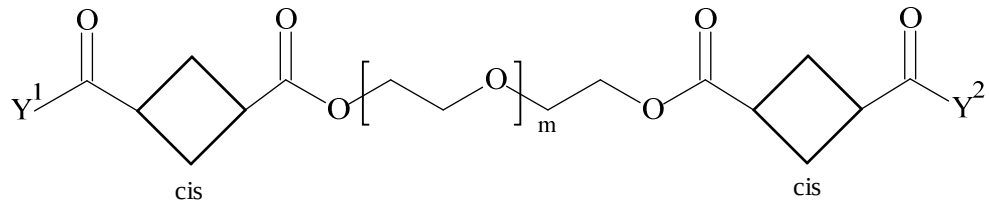
(V-38)



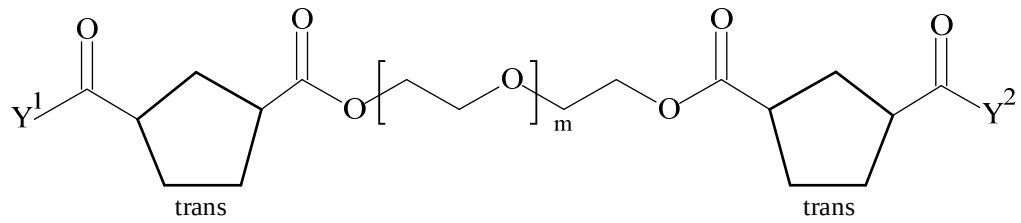
(V-39)



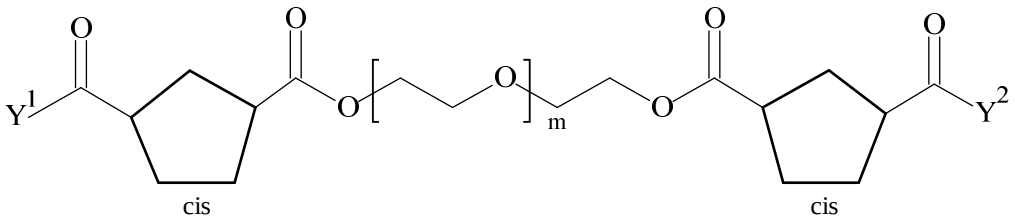
(V-40)



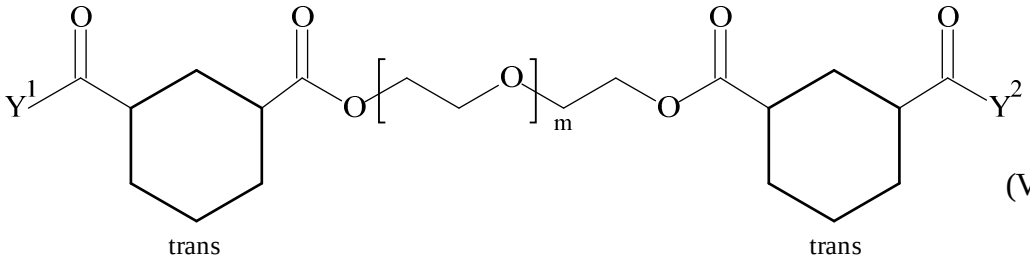
(V-41)



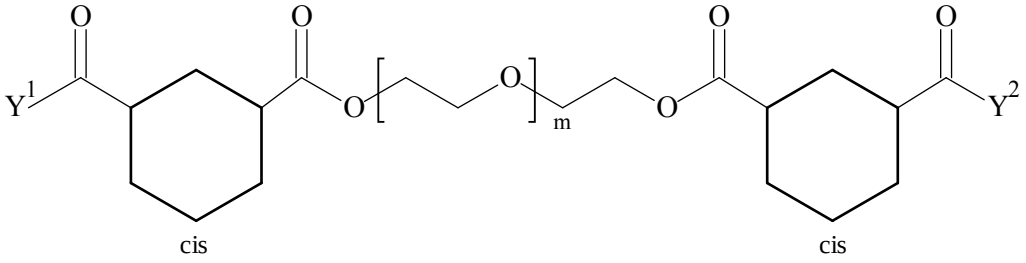
(V-42)



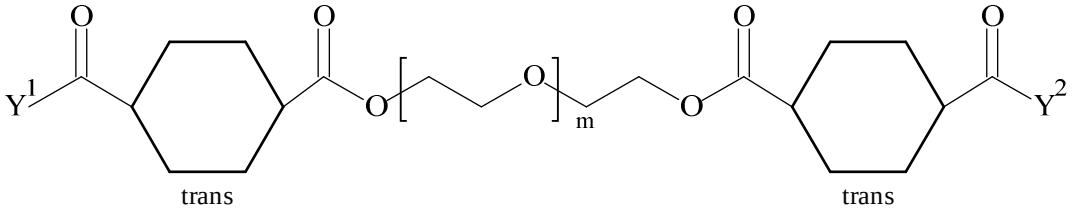
(V-43)



(V-44)

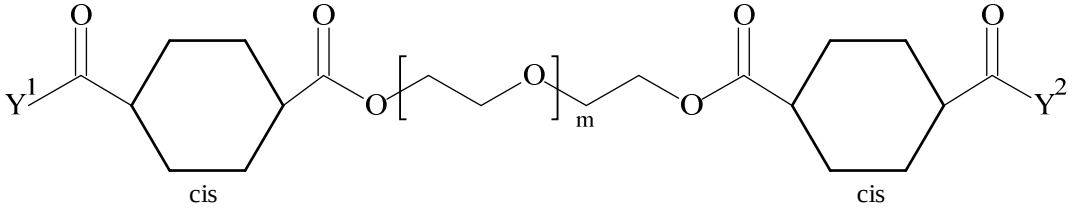


(V-45)

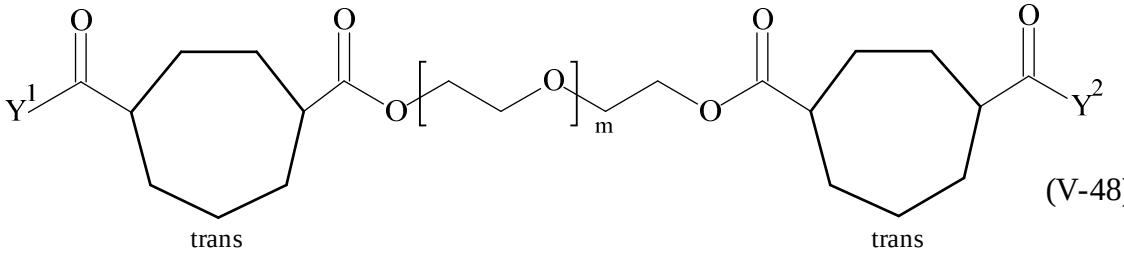


(V-46)

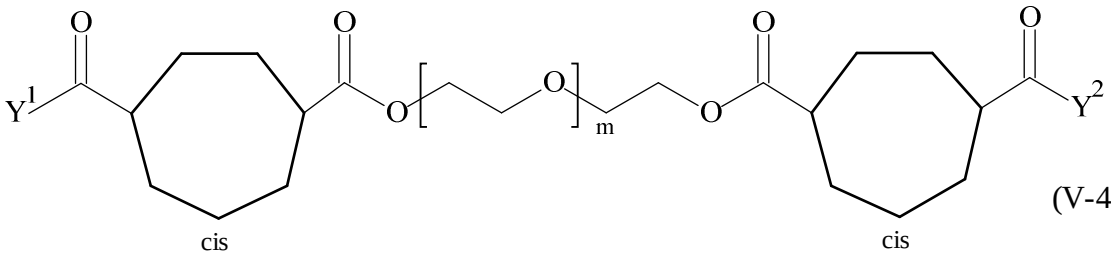
5



(V-47)

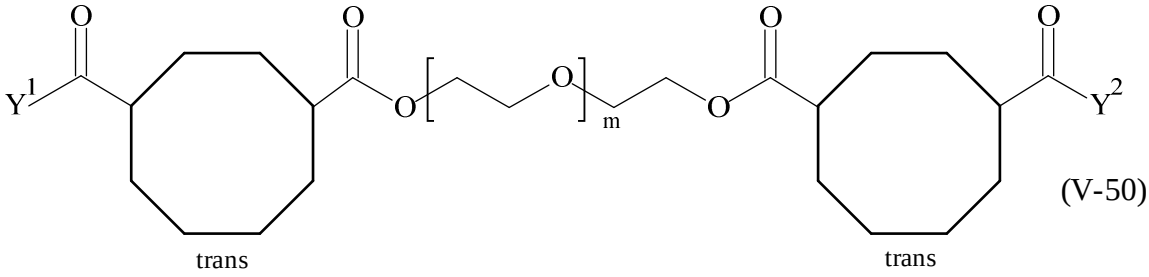


(V-48)



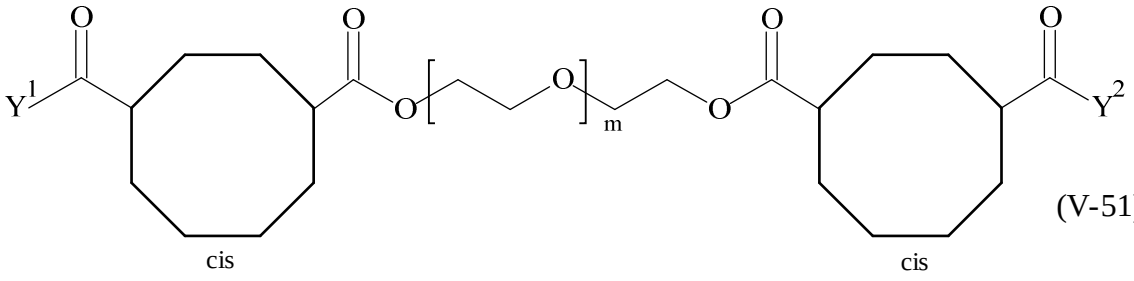
cis cis

(V-49)



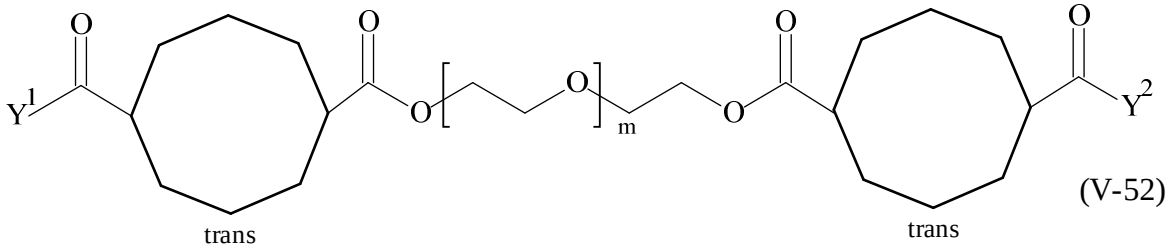
trans trans

(V-50)



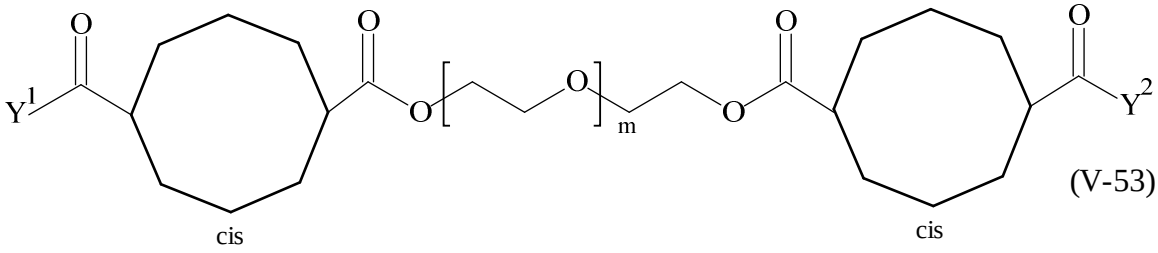
cis cis

(V-51)



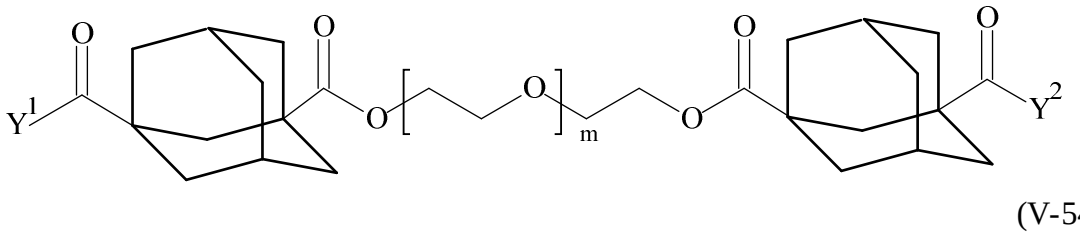
trans trans

(V-52)



cis cis

(V-53)



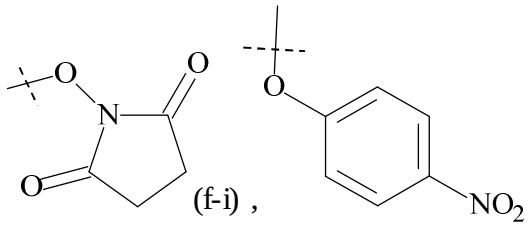
(V-54)

wherein

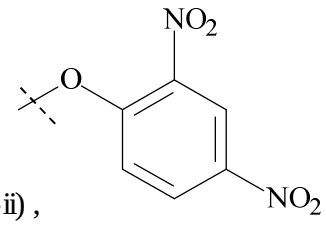
each crosslinker reagent may be in the form of its racemic mixture, where applicable; and

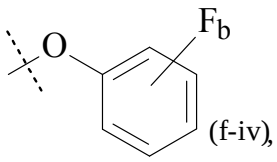
m ranges from 120 to 920, preferably from 120 to 460 and more preferably from 120 to 230*;*

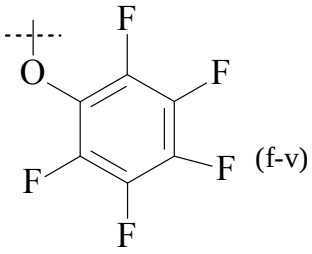
Y^1, Y^2 are identical or different and each is independently of the other selected from formulas (f-i) to (f-vi):

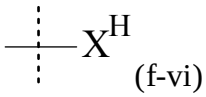

(f-i),

(f-ii),


(f-iii),


(f-iv),


(f-v)


(f-vi)

and

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.

20. The process of any one of claims 1 to 19, wherein the hydrogel obtained from the polymerization is a shaped article.

21. The process of claim 20, wherein the hydrogel is in the form of microparticular beads having a diameter of 1 to 500 micrometer.

22. A hydrogel obtainable by a process of any one of claims 1 to 21.

23. 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;

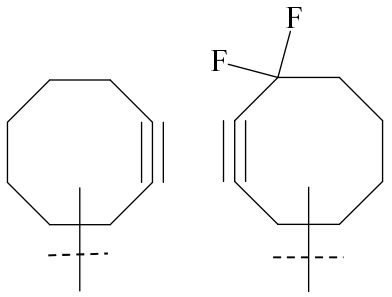
in the presence of a solvent to obtain a hydrogel-spacer conjugate.

24. The process of claim 23, 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, 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.

25. The process of claim 23 or 24, 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),



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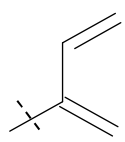
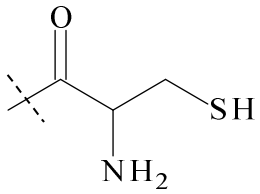
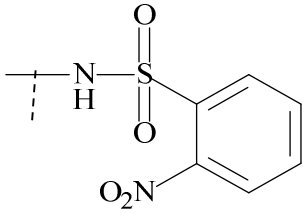
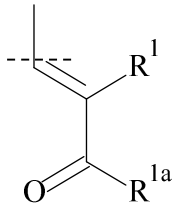

,




, and


; with optional protecting groups;

wherein

X^0 is -OH, -NR^1R^{1a}, -SH, or -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.

26. A hydrogel-spacer conjugate obtainable by the process of claim 24 or 25.

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

(e) reacting a hydrogel of claim 22 or a hydrogel-spacer conjugate of claim 27 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),

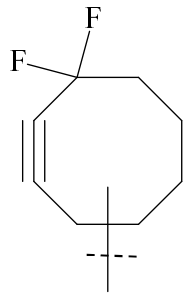
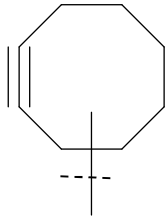
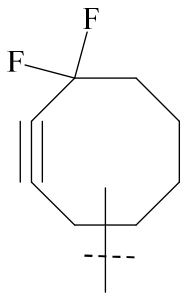
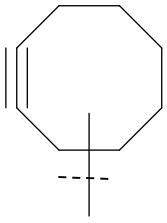
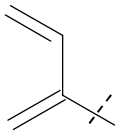
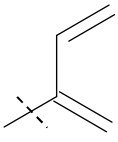
L is a prodrug linker;

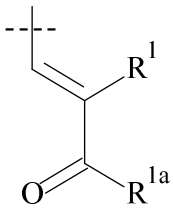
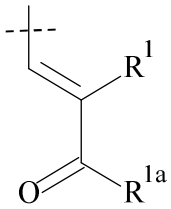
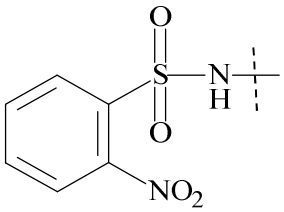
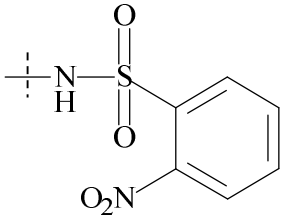
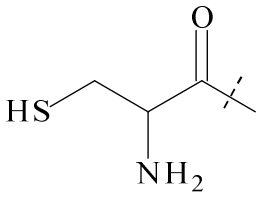
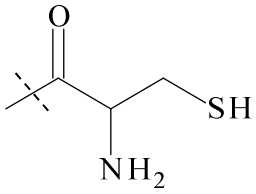
D is a biologically active moiety;

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

28. The process of claim 27, wherein A^{x2}/A^{y1} are selected from the following:

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

	 , or 
–C≡CH,  , or 	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, or –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.

29. The process of claim 27 or 28, wherein A^{x2} is a thiol and A^{y1} is of formula (VIIa)

T– PG^0 – S- (VIIa),

wherein

T is H or a tag moiety;

PG^0 is a sulfur-activating moiety; and

S is sulfur.

30. The process of any one of claims 27 to 29, 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.

31. The process of any one of claims 27 to 30, wherein D is a monoclonal or polyclonal antibody or a fragment or fusion thereof.

32. A carrier-linked prodrug obtainable by a process for the preparation of a carrier-linked prodrug of any one of claims 28 to 31.

33. A pharmaceutical composition comprising the carrier-linked prodrug of claim 32 or a pharmaceutical salt thereof together with a pharmaceutically acceptable excipient.

34. The carrier-linked prodrug of claim 32 or the pharmaceutical composition of claim 33 for use as a medicament.