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(54) Title: NEW COMPOUNDS FOR USE AS INTERMEDIATES IN LINEAR BLOCK POLYMER AND NEW LINEAR BLOCK POLYMER

(57) Abstract: The present invention relates to a compound according to Formula (1) wherein R<sub>1</sub> and R<sub>2</sub> which R<sub>1</sub> and R<sub>2</sub> can be the same or different, are amino((C<sub>2</sub>-C<sub>5</sub>)alkyl), ((C<sub>1</sub>-C<sub>4</sub>)alkyl[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]], or A, wherein A is [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl); or R<sub>1</sub> is amino((C<sub>1</sub>-C<sub>5</sub>)alkyl) when R<sub>2</sub> is [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]([2-4, 2-4]bis(R<sub>p</sub>)(C<sub>2</sub>-C<sub>5</sub>)alkyl); or R<sub>2</sub> is a substituent according to Formula (1A) wherein R is (C<sub>2</sub>-C<sub>4</sub>)alkyl, and I is from 1 to 20, preferably 1 to 10, and R<sub>1</sub> is then ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)], or [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl); and new linear block polymers.



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New compounds for use as intermediates in linear block polymer and new linear block polymer.

#### FIELD OF THE INVENTION

- 5 The present invention relates to a new compound according to Formula (1), a method for preparing said compound, intermediates formed during preparation of said compound and use of said compound. Furthermore, the present invention relates to a method for preparing a linear block polymer, a new linear block polymer, use of said linear block polymer and new implants, pharmaceutical preparations,  
10 microencapsules, suspensions, emulsions and material for promoting wound healing.

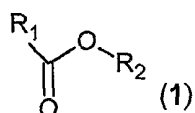
#### PRIOR ART

- 15 In the event of human or animal injury or disease, damaged organs or damaged tissue must on occasions be temporarily or permanently replaced by some form of implant. In order for the function of such an implant to be acceptable, not only must the implant have properties, for example strength, that enable it to replace the functions of the damaged organ or tissue, but it must also be biocompatible.  
20 Various materials such as pure titanium and certain plastics have been shown to have acceptable function, and are extensively used. It is often desirable that an implant promotes the growth of damaged tissue, while at the same time the implant should in many cases be biologically degradable .
- 25 SE, C2, 505703 describes a linear block polymer with a molecular weight of  $10^4$  Dalton, preferably  $10^5$  Dalton, comprising urea and urethane groups and ester groups at such a distance from each other that after hydrolysis of the same, fragments are created that are so small that they can be excreted from a human body. Said linear block polymer comprising urea and urethane groups is a suitable  
30 material for implants for humans and animals.

## DESCRIPTION OF THE INVENTION

The present invention relates to a compound according to Formula (1)

5



10

wherein

R<sub>1</sub> and R<sub>2</sub>, which R<sub>1</sub> and R<sub>2</sub> can be the same or different, are

15 amino((C<sub>2</sub>-C<sub>5</sub>)alkyl) wherein (C<sub>2</sub>-C<sub>5</sub>)alkyl is saturated,  
((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)] or A,

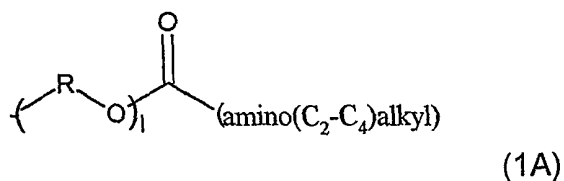
wherein A is [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl); or

20 R<sub>1</sub> is amino((C<sub>1</sub>-C<sub>5</sub>)alkyl) when R<sub>2</sub> is

[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)][(2-4, 2-4]bis(R<sub>p</sub>)(C<sub>2</sub>-C<sub>5</sub>)alkyl), wherein

25 each R<sub>p</sub>, which R<sub>p</sub> can be the same or different, is  
hydroxy((C<sub>1</sub>-C<sub>5</sub>)alkyl) or [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl);  
or

R<sub>2</sub> is a substituent according to Formula (1A)



30

wherein R is (C<sub>2</sub>-C<sub>4</sub>)alkyl, and

l is from 1 to 20, preferably 1 to 10, and R<sub>1</sub> is then

- 5 ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)], or  
[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl); or

salts, together with all possible stereoisomers either pure or as racemic compounds  
or as mixtures of stereoisomers, of said compound according to Formula (1); and

10

provided that neither of 2-aminoethyl 3-aminopropanoate,  
2-aminoethyl 4-aminobutanoate, 2-aminoethyl 3-amino-3-methylbutanoate or  
2-aminoethyl 6-aminohexanoate is included in Formula (1).

- 15 Each alkyl and each alkanooate in Formula (1) can, with exception for when the  
opposite is stated, independently of each other, be straight or branched, saturated  
or unsaturated, and/or substituted with, for example, methyl, phenyl, 4-  
hydroxyphenyl, 4-aminobutyl, 2-butyl, 2-hydroxymethyl, 3-aminopropyl, 2-  
aminoethyl, 2-mercaptomethyl, or similar.

20

Salts of said compound of Formula (1) comprise, for example, its trifluoroacetic acid  
salt, acetic acid salt, p-toluenesulphonic acid salt, chloride salt, bromide salt or  
methanesulphonic acid salt.

- 25 Said compound according to Formula (1) has been shown to be useful during the  
preparation of new linear block polymers of the polyurea or polyurethaneurea type,  
wherein said linear block polymers comprise ester groups at such a distance from  
each other that after hydrolysis of the same, fragments are created that are so  
small, namely less than 2,000 Dalton, that they can be excreted from a human or  
30 animal body. Said linear block polymers comprise blocks that contain urea groups,  
known as "hard" blocks, the size of which blocks is more than halved by hydrolysis  
of said ester groups, which ester groups are derived from said compound according  
to Formula 1, wherein the hydrolysis promotes excretion of residues in that it gives a  
smaller fragment size, less than 2,000 Dalton.

A further embodiment according to the present invention relates to the compound having Formula (1), wherein

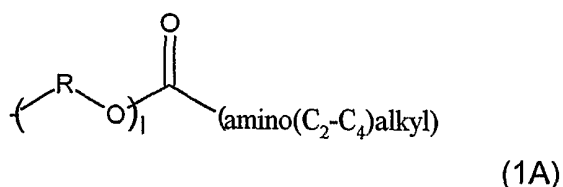
5  $R_1$  and  $R_2$ , which  $R_1$  and  $R_2$  can be the same or different, are

amino((C<sub>2</sub>-C<sub>5</sub>)alkyl), ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)] or A,

wherein A is [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl); or

10

$R_2$  is a substituent according to Formula (1A)



wherein R is (C<sub>2</sub>-C<sub>4</sub>)alkyl, and

15

l is from 1 to 20, preferably 1 to 10, and  $R_1$  is then

((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)], or

[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl); or

20

salts, together with all possible stereoisomers either pure or as racemic compounds or as mixtures of stereoisomers, of said compound according to Formula (1).

25 Still a further embodiment according to the present invention relates to a compound according to Formula (1), wherein

$R_1$  is amino((C<sub>1</sub>-C<sub>5</sub>)alkyl) when  $R_2$  is

[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]([2-4, 2-4]bis( $R_p$ )(C<sub>2</sub>-C<sub>5</sub>)alkyl), wherein

30

each  $R_p$ , which  $R_p$  can be the same or different, is hydroxy((C<sub>1</sub>-C<sub>5</sub>)alkyl) or [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl).

A further embodiment according to the present invention relates to a compound  
5 having Formula (1), wherein

$R_1$  is amino((C<sub>3</sub>-C<sub>5</sub>)alkyl),  
((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)], or  
[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl); and  
10

$R_2$  is amino((C<sub>2</sub>-C<sub>5</sub>)alkyl),  
((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)], or  
[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl).

15 A further embodiment according to the present invention relates to a compound having Formula (1), wherein  $R_2$  is A,

wherein A is [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>3</sub>-C<sub>5</sub>)alkyl).

20 A yet further embodiment according to the present invention relates to a compound having Formula (1), wherein

$R_2$  is a substituent according to Formula (1A), as above, and

25  $R_1$  is ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)], or  
[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>3</sub>-C<sub>5</sub>)alkyl).

Further embodiments according to the present invention relate to the compounds:

30 4-[(4-aminobutanoyl)oxy]butyl 4-aminobutanoate,  
5-[(2S)-2-amino-3-methoxy-3-oxopropyl] 1-methyl (2S)-2-aminopentanedioate,  
5-(2-aminoethyl) 1-methyl (2S)-2-aminopentanedioate,  
5-(3-aminopropyl) 1-methyl (2S)-2-aminopentanedioate,  
5-(4-aminobutyl) 1-methyl (2S)-2-aminopentanedioate,

methyl (2S)-2-amino-3-[(3-aminopropanoyl)oxy] propanoate,  
 2-[(2-aminoacetyl)oxy]ethyl 3-aminopropanoate,  
 2-[(2-aminoacetyl)oxy]ethyl 4-aminobutanoate,  
 2-[(2-aminoacetyl)oxy]ethyl aminoacetate,  
 5 or 4-(2-aminoethyl) 1-methyl (2R)-2-aminobutanedioate; or

salts, together with all possible stereoisomers either pure or as racemic compounds or as mixtures of stereoisomers, thereof.

10 Furthermore, a further embodiment according to the present invention relates to the compounds:

4-[(4-aminobutanoyl)oxy]butyl 4-aminobutanoate,  
 5-[(2S)-2-amino-3-methoxy-3-oxopropyl] 1-methyl (2S)-2-aminopentanedioate; or  
 15

salts, together with all possible stereoisomers either pure or as racemic compounds or as mixtures of stereoisomers, thereof.

20 A further embodiment according to the present invention relates to a compound according to Formula (1), wherein

$R_1$  is amino((C<sub>1</sub>-C<sub>5</sub>)alkyl) when  $R_2$  is

[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)][(2, 2]bis( $R_p$ )(C<sub>3</sub>)alkyl), wherein  
 25

each  $R_p$ , which  $R_p$  can be the same or different, is hydroxy((C<sub>1</sub>-C<sub>3</sub>)alkyl) or [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoat)]((C<sub>3</sub>)alkyl).

30 In a further embodiment, the present invention relates to the compounds:

3-[(aminoacetyl)oxy]-2,2-bis(hydroxymethyl)propyl aminoacetate or

3-({aminoacetyl}oxy)-2,2-bis[({aminoacetyl}oxy)methyl]propyl aminoacetate.

The present invention further relates to a method for preparing the compound described by Formula (1), which method comprises

5 a) preparation of a compound having Formula (1) by deprotecting the corresponding compound with protected amines, or

b) conversion of a compound having Formula (1) to a salt thereof, or vice versa, or

10 c) conversion of a salt of a compound having Formula (1) to another salt.

Protective groups in method a) that protect said protected amines, and reaction conditions are well known from similar reactions. The protecting groups can be tert-butyloxycarbonyl groups or benzyloxycarbonyl groups, wherein said deprotection can occur by acidic hydrolysis or by catalytic hydrolysis, or  
15 fluorenylmethyloxycarbonyl protecting groups (Fmoc-) and deprotection with piperidine or another suitable base, by base-catalysed B-elimination.

The conversion in methods b) and c) can be carried out by conventional methods, which are known per se, for example, reaction of the free base with an acid  
20 containing the desired anion, or by precipitation of the salt at basic pH. The reaction is carried out in a suitable solvent such as N,N-dimethylformamide (DMF), N-methylpyrrolidone (NMP), N,N-dimethylacetamide (DMAC) or dimethylsulphoxide (DMSO).

25 Starting material for the above-mentioned methods for preparing the described compound having Formula (1) can be obtained through methods that are described in the Examples or by methods equivalent to these. Other conventional methods for obtaining starting material are clear for one skilled in the art.

30 In the methods that are described in the Examples, the following general intermediate is obtained, which intermediate is also an embodiment according to the invention:

a compound having Formula (1B) that is defined as in Formula (1) above, but

in which "amino" in Formula (1) is replaced throughout by "[protected amine]".

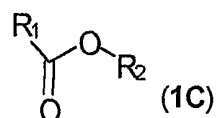
The present invention also relates to a method for preparing a linear block polymer, wherein the method comprises

5

prepolymers, which prepolymers can be the same or different, and compounds according to Formula (1C), which compounds can be the same or different, and

chain extension of said prepolymer, with two isocyanate end-groups per molecule, with said compound according to Formula (1C)

10



15

wherein

R<sub>1</sub> and R<sub>2</sub>, which R<sub>1</sub> and R<sub>2</sub> can be the same or different, are

20

amino((C<sub>1</sub>-C<sub>5</sub>)alkyl), ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)] or A, wherein,

when R<sub>1</sub> is A,

A is [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>1</sub>-C<sub>5</sub>)alkyl); and

25

when R<sub>2</sub> is A,

A is [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>3</sub>-C<sub>5</sub>)alkyl); or wherein

R<sub>1</sub> is diamino((C<sub>1</sub>-C<sub>5</sub>)alkyl) and

30

R<sub>2</sub> is hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl or benzyl; or wherein

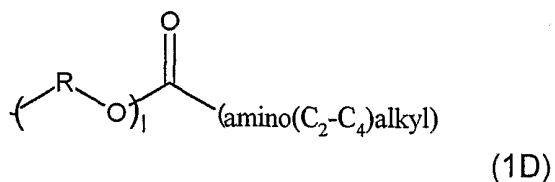
$R_1$  is amino((C<sub>1</sub>-C<sub>5</sub>)alkyl) when  $R_2$  is

[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)][[2-4, 2-4]bis( $R_p$ )(C<sub>2</sub>-C<sub>5</sub>)alkyl], wherein

5 each  $R_p$ , which  $R_p$  can be the same or different, is hydroxy((C<sub>1</sub>-C<sub>5</sub>)alkyl) or [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl); or wherein

$R_2$  is a substituent according to Formula (1D)

10



wherein R is (C<sub>2</sub>-C<sub>4</sub>)alkyl, and

15 l is from 1 to 20, preferably 1 to 10, and  $R_1$  is then

amino((C<sub>1</sub>-C<sub>5</sub>)alkyl),  
((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)], or  
[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>1</sub>-C<sub>5</sub>)alkyl); or

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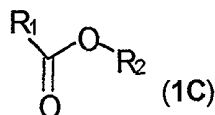
salts, together with all possible stereoisomers either pure or as racemic compounds or as mixtures of stereoisomers, thereof.

Each alkyl and each alkanoate in Formula (1C) can, independently of each other, be  
25 straight or branched, saturated or unsaturated, and/or substituted with, for example, methyl, phenyl, 4-hydroxyphenyl, 4-aminobutyl, 2-butyl, 2-hydroxymethyl, 3-aminopropyl, 2-aminoethyl, 2-mercaptomethyl, or similar.

Salts of said compound of Formula (1C) comprise, for example, its trifluoroacetic acid salt, acetic acid salt, p-toluenesulphonic acid salt, chloride salt, bromide salt or methanesulphonic acid salt.

- 5 The prepolymer can be prepared by, for example, the reaction of oligoesters and oligoethers, that have HO-terminations at both ends, with diisocyanate, with the molar ratio between diisocyanate and the OH-group being approximately 1:1 during the reaction.
- 10 A further embodiment according to the present invention relates to said method for preparing a linear block polymer, wherein the method comprises
- prepolymers, which prepolymers can be the same or different, and compounds according to Formula (1C), which compounds can be the same or different, and
- 15 chain extension of said prepolymers having two isocyanate end-groups per molecule with said compound according to Formula (1C)

20



wherein

25

$R_1$  and  $R_2$ , which  $R_1$  and  $R_2$  can be the same or different, are

amino((C<sub>1</sub>-C<sub>5</sub>)alkyl), ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)] or A, wherein,

30

when  $R_1$  is A,

A is [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)]((C<sub>1</sub>-C<sub>5</sub>)alkyl); and

when  $R_2$  is A,

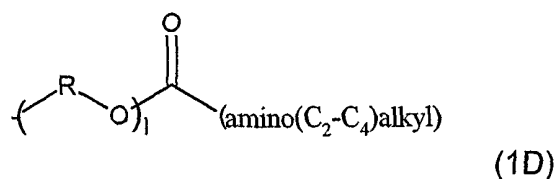
A is [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)]((C<sub>3</sub>-C<sub>5</sub>)alkyl); or wherein

R<sub>1</sub> is diamino((C<sub>1</sub>-C<sub>5</sub>)alkyl) and

R<sub>2</sub> is hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl or benzyl; or wherein

5

R<sub>2</sub> is a substituent according to Formula (1D)



wherein R is (C<sub>2</sub>-C<sub>4</sub>)alkyl, and

10

l is from 1 to 20, preferably 1 to 10, and R<sub>1</sub> is then

amino((C<sub>1</sub>-C<sub>5</sub>)alkyl),

((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)], or

15 [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>1</sub>-C<sub>5</sub>)alkyl); or

salts, together with all possible stereoisomers either pure or as racemic compounds or as mixtures of stereoisomers, thereof.

20 A further embodiment according to the present invention relates to said method for preparing a linear block polymer, wherein A is

[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>3</sub>-C<sub>5</sub>)alkyl).

25 A yet further embodiment relates to a method for preparing linear block polymers according to the present invention, wherein said prepolymers are chain-extended with one or more of

2-aminoethyl 4-aminobutanoate,

30 4-[(4-aminobutanoyl)oxy]butyl 4-aminobutanoate,

- 5-[(2S)-2-amino-3-methoxy-3-oxopropyl] 1-methyl (2S)-2-aminopentanedioate,  
 5-(2-aminoethyl) 1-methyl (2S)-2-aminopentanedioate,  
 5-(3-aminopropyl) 1-methyl (2S)-2-aminopentanedioate,  
 5-(4-aminobutyl) 1-methyl (2S)-2-aminopentanedioate,  
 5 methyl (2S)-2-amino-3-[(3-aminopropanoyl)oxy] propanoate,  
 2-[(2-aminoacetyl)oxy]ethyl 3-aminopropanoate,  
 2-[(2-aminoacetyl)oxy]ethyl 4-aminobutanoate,  
 2-[(2-aminoacetyl)oxy]ethyl aminoacetate,  
 4-(2-aminoethyl) 1-methyl (2R)-2-aminobutanedioate,  
 10 2-aminoethyl aminoacetate  
 4-[(2-aminoacetyl)oxy]butyl aminoacetate,  
 2-[(3-aminopropanoyl)oxy]ethyl 3-aminopropanoate,  
 2-[(2-aminoacetyl)oxy]ethyl aminoacetate,  
 methyl (2S)-2-amino-3-[(aminoacetyl)oxy] propanoate,  
 15 tert-butyl 2,6-diaminohexanoate  
 and benzyl 2,6-diaminohexanoate; or

salts, together with all possible stereoisomers either pure or as racemic compounds  
 or as mixtures of stereoisomers, thereof.

20

Furthermore, a further embodiment relates to a method for preparing linear block  
 polymers according to the present invention, wherein said prepolymers are chain-  
 extended with one or more of

- 25 2-aminoethyl 4-aminobutanoate,  
 4-[(4-aminobutanoyl)oxy]butyl 4-aminobutanoate,  
 5-[(2S)-2-amino-3-methoxy-3-oxopropyl] 1-methyl (2S)-2-aminopentanedioate,  
 2-aminoethyl aminoacetate,  
 4-[(2-aminoacetyl)oxy]butyl aminoacetate,  
 30 tert-butyl 2,6-diaminohexanoate,  
 2-[(3-aminopropanoyl)oxy]ethyl 3-aminopropanoate, and  
 2-[(2-aminoacetyl)oxy]ethyl aminoacetate; or

salts, together with all possible stereoisomers either pure or as racemic compounds or as mixtures of stereoisomers, thereof.

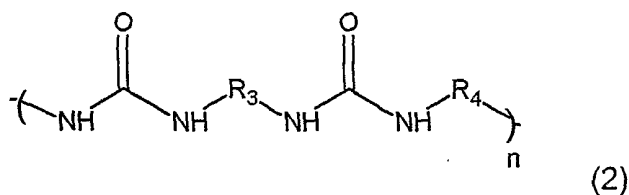
Another embodiment relates to said method for preparing a linear block polymer,  
5 wherein said prepolymer is chain-extended with one or more of

3-[(aminoacetyl)oxy]-2,2-bis(hydroxymethyl)propyl aminoacetate or

3-({aminoacetyl}oxy)-2,2-bis[({aminoacetyl}oxy)methyl]propyl aminoacetate.

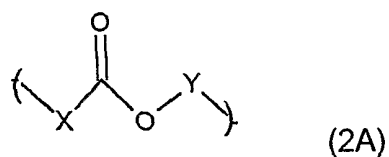
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The present invention also relates to a linear block polymer with a molecular weight of at least  $10^4$  Dalton, which linear block polymer consists of internally and linearly linked sequences, which sequences can be described according to Formula (2)



15 wherein each  $\text{R}_3$  and each  $\text{R}_4$  can be the same or different; and

$\text{R}_3$  can be described according to Formula (2A)



20

wherein

X and Y, which X and Y can be the same or different, are  $(\text{C}_1-\text{C}_5)$ alkyl, or are

derived from  $((\text{C}_1-\text{C}_4)\text{alkyl})[(2-4)\text{-amino}((\text{C}_2-\text{C}_4)\text{ alcanoate})]$  or

25

derived from A, wherein,

when X is A ,

A is [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanoate)]((C<sub>1</sub>-C<sub>5</sub>)alkyl); and

5 when Y is A,

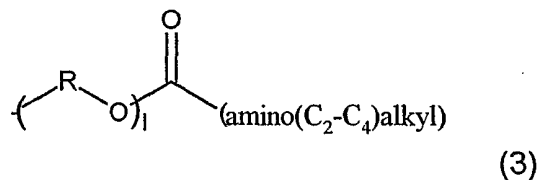
A is [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanoate)]((C<sub>3</sub>-C<sub>5</sub>)alkyl); or

10 X is derived from amino((C<sub>1</sub>-C<sub>5</sub>)alkyl) when Y is derived from

[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]([2-4, 2-4]bis(R<sub>p</sub>)(C<sub>2</sub>-C<sub>5</sub>)alkyl), wherein

15 each R<sub>p</sub>, which R<sub>p</sub> can be the same or different, is  
hydroxy((C<sub>1</sub>-C<sub>5</sub>)alkyl) or [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl);  
or

Y can be derived from a substituent according to Formula (3)



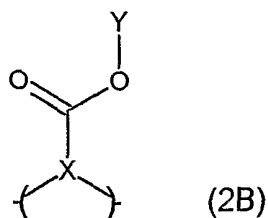
20

wherein R is (C<sub>2</sub>-C<sub>4</sub>)alkyl, and

I is from 1 to 20, preferably 1 to 10, and X can then be derived from

25 amino((C<sub>1</sub>-C<sub>5</sub>)alkyl), ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanoate)], or  
[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanoate)]((C<sub>1</sub>-C<sub>5</sub>)alkyl); or wherein

R<sub>3</sub> can be described according to Formula (2B)



wherein X is ((C<sub>1</sub>-C<sub>5</sub>)alkyl) and

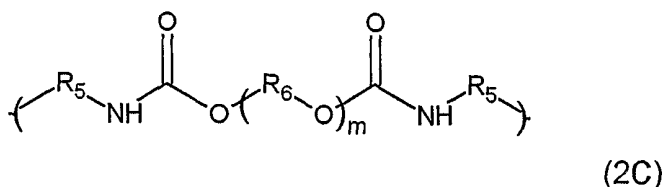
Y is hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl or benzyl; and

5

R<sub>4</sub> can be derived from diisocyanate and comprises none, one or several ester groups,

or R<sub>4</sub> can be described according to Formula (2C)

10



wherein each R<sub>5</sub>, the same or different, can be derived from diisocyanate,

15

R<sub>6</sub> is (C<sub>2</sub>-C<sub>4</sub>)alkyl, and

m is from 1 to 20, preferably 1 to 10.

20 Each alkyl and each alkanoate in Formula (2) can, independently of each other, be straight or branched, saturated or unsaturated, and/or substituted with, for example, methyl, phenyl, 4-hydroxyphenyl, 4-aminobutyl, 2-butyl, 2-hydroxymethyl, 3-aminopropyl, 2-aminoethyl, 2-mercaptomethyl, or similar.

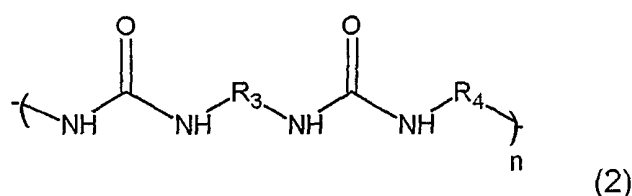
25 Said linear block polymer is of the polyurea or polyurethaneurea type when the polymer chain according to Formula (2) can contain urea groups as well as urethane and urea groups. Both urethane and urea groups in the block polymer form intermolecular hydrogen bonds, which provides the cohesive forces that are required to hold the molecules together to a material. Particularly strong  
30 intermolecular forces are obtained by the urea groups, especially when several urea

groups have the opportunity to cooperate. Those blocks in a block polymers that contain urea groups are often known as "hard", since they are responsible for the cohesion of the material, wherein the cohesion is a function of the number and lengths of the blocks that contain urea groups. In said linear block polymer according to Formula (2), the "hard" block is the block that is comprised in  $R_3$  and the neighbouring urea groups. In a corresponding manner, the blocks in a block polymer that give the material its extensibility and elasticity are often known as "soft". In said linear block polymer according to Formula (2), a "soft" block can be comprised within  $R_4$ , and, since  $R_4$  can be described according to Formula (2C), the neighbouring urethane groups can also be comprised in a "soft" block.

Each  $R_3$ , which is the same or different, can be described according to Formula (2A) or (2B) and each  $R_4$ , which is the same or different, comprises both one or several ester groups; wherein said linear block polymer comprises ester groups at such a distance from each other that after hydrolysis of said ester groups, fragments are created that are less than 2,000 Dalton, wherein the fragments can be excreted from a human or animal body. The created fragments are preferably less than 1,000 Dalton. For example, the fragments can, according to the present invention, be of the order of 400-500 Dalton.

Through the present invention a linear block polymer is obtained comprising urea groups or urea and urethane groups, which linear block polymer is suitable for use as an implant, wherein said linear block polymer is biologically degradable in a human or animal body. Said linear block polymer has degradation times when used as an implant, which degradation times can be varied from a few weeks to a couple of years through choice of said linear block polymer.

Further, the present invention also relates to a linear block polymer with a molecular weight of at least  $10^4$  Dalton, which linear block polymer consists of internally and linearly linked sequences, which sequences can be described according to Formula (2)

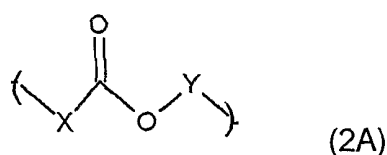


5

wherein each  $\text{R}_3$  and each  $\text{R}_4$  can be the same or different; and

$\text{R}_3$  can be described according to Formula (2A)

10



wherein

15

X and Y, which X and Y can be the same or different, are  $(\text{C}_1\text{-C}_5)\text{alkyl}$ , or are

derived from  $((\text{C}_1\text{-C}_4)\text{alkyl})[(2\text{-}4)\text{-amino}((\text{C}_2\text{-C}_4)\text{ alkanooate})]$  or

derived from A, wherein,

20

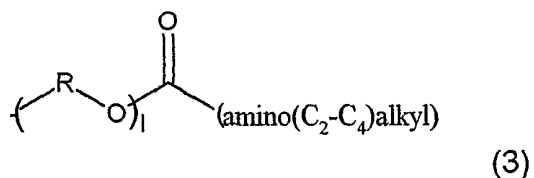
when X is A,

A is  $[(2\text{-}4)\text{-amino}((\text{C}_2\text{-C}_4)\text{ alkanooate})][(\text{C}_1\text{-C}_5)\text{alkyl}]$ ; and

when Y is A,

A is  $[(2\text{-}4)\text{-amino}((\text{C}_2\text{-C}_4)\text{ alkanooate})][(\text{C}_3\text{-C}_5)\text{alkyl}]$ ; or

Y can be derived from a substituent according to Formula (3)

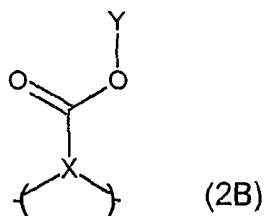


5                      wherein R is (C<sub>2</sub>-C<sub>4</sub>)alkyl, and

I is from 1 to 20, preferably 1 to 10, and X can then be derived from

amino((C<sub>1</sub>-C<sub>5</sub>)alkyl), ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)], or  
 10 [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)]((C<sub>1</sub>-C<sub>5</sub>)alkyl); or wherein

R<sub>3</sub> can be described according to Formula (2B)



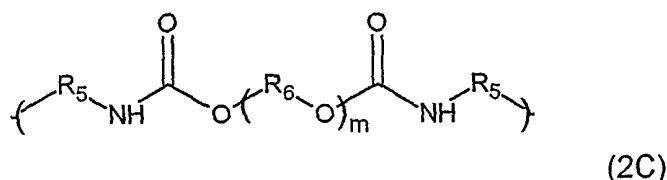
15

wherein X is ((C<sub>1</sub>-C<sub>5</sub>)alkyl)                      and

20    Y is hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl or benzyl; and

R<sub>4</sub> can be derived from diisocyanate and comprises none, one or several ester groups,

or  $R_4$  can be described according to Formula (2C)



5 wherein each  $R_5$ , the same or different, can be derived from diisocyanate,

$R_6$  is  $(\text{C}_2\text{-C}_4)$ alkyl, and

$m$  is from 1 to 20, preferably 1 to 10.

10

A further embodiment according to the present invention relates to said linear block polymers according to Formula (2), when  $Y$  can be derived from  $A$ , wherein  $A$  is

[(2-4)-amino( $(\text{C}_2\text{-C}_4)$  alkanooate)]( $(\text{C}_3\text{-C}_5)$ alkyl).

15

A further embodiment relates to a linear block polymer according to Formula (2), wherein each  $R_3$  can be the same or different and can be derived from one or several of

20

2-aminoethyl 4-aminobutanoate,

4-[(4-aminobutanoyl)oxy]butyl 4-aminobutanoate,

5-[(2S)-2-amino-3-methoxy-3-oxopropyl] 1-methyl (2S)-2-aminopentanedioate,

5-(2-aminoethyl) 1-methyl (2S)-2-aminopentanedioate,

5-(3-aminopropyl) 1-methyl (2S)-2-aminopentanedioate,

25

5-(4-aminobutyl) 1-methyl (2S)-2-aminopentanedioate,

methyl (2S)-2-amino-3-[(3-aminopropanoyl)oxy] propanoate,

2-[(2-aminoacetyl)oxy]ethyl 3-aminopropanoate,

2-[(2-aminoacetyl)oxy]ethyl 4-aminobutanoate,

2-[(2-aminoacetyl)oxy]ethyl aminoacetate,

30

4-(2-aminoethyl) 1-methyl (2R)-2-aminobutanedioate,

- 2-aminoethyl aminoacetate,  
 4-[(2-aminoacetyl)oxy]butyl aminoacetate,  
 2-[(3-aminopropanoyl)oxy]ethyl 3-aminopropanoate,  
 2-[(2-aminoacetyl)oxy]ethyl aminoacetate,  
 5 methyl (2S)-2-amino-3-[(aminoacetyl)oxy] propanoate,  
 tert-butyl 2,6-diaminohexanoate  
 and benzyl 2,6-diaminohexanoate; or

salts, together with all possible stereoisomers either pure or as racemic compounds  
 10 or as mixtures of stereoisomers, thereof.

Furthermore, a further embodiment relates to said linear block polymer according to Formula (2), wherein each  $R_3$  can be the same or different and can be derived from

- 15 2-aminoethyl 4-aminobutanoate,  
 4-[(4-aminobutanoyl)oxy]butyl 4-aminobutanoate,  
 5-[(2S)-2-amino-3-methoxy-3-oxopropyl] 1-methyl (2S)-2-aminopentanedioate,  
 2-aminoethyl aminoacetate,  
 4-[(2-aminoacetyl)oxy]butyl aminoacetate,  
 20 O-tert-butyl 2,6-diaminohexanoate,  
 2-[(3-aminopropanoyl)oxy]ethyl 3-aminopropanoate, or  
 2-[(2-aminoacetyl)oxy]ethyl aminoacetate; or

salts, together with all possible stereoisomers either pure or as racemic compounds  
 25 or as mixtures of stereoisomers, thereof.

Still a further embodiment relates to said linear block polymer according to Formula (2), wherein each  $R_3$  can be the same or different, may be derived from one or more of

- 30 3-[(aminoacetyl)oxy]-2,2-bis(hydroxymethyl)propyl aminoacetate or  
 3-[(aminoacetyl)oxy]-2,2-bis[(aminoacetyl)oxy]methyl]propyl aminoacetate.

A further embodiment according to the present invention relates to a linear block polymer wherein each  $R_4$ , the same or different, or when  $R_4$  is according to Formula

(2B), each  $R_5$ , the same or different, can be derived from diphenylmethane diisocyanate, toluylene diisocyanate, hexamethylene diisocyanate, tetramethylene diisocyanate, naphthylene diisocyanate or ethyl-2,6-diisocyanatohexanoate (LDI).

- 5 A further embodiment according to the present invention relates to a linear block polymer wherein each  $R_4$ , the same or different, can be derived from one or several of polyesterdiol, polyetherdiol or monodiol and/or when  $R_4$  can be described according to Formula (2C), each  $R_6$ , the same or different, can be derived from one or several of polyesterdiol, polyetherdiol or monodiol.
- 10 A further embodiment of the present invention relates to a linear block polymer, wherein each  $R_4$ , the same or different, can be derived from one or more of polytetramethylenoxidediol, polyethylenoxidediol, polycaprolactonediol, polyethyleneglycoladipatediol, polydiethylenglycoladipatediol, toluylene
- 15 diisocyanate, diphenylmethane, hexamethylene diisocyanate, tetramethylene diisocyanate, naphthylene diisocyanate, glycerin monoallylether, trimethylolpropane monoallylether, glycerin monoglycidyl ether, ethyl-2,6-diisocyanatohexanoate (LDI), dimethylolpropionic acid methylester, dimethylolpropionic acid brombutylester, esters of monocarboxymethyl ethers, esters of glycerin, or esters of
- 20 trimethylpropane and/or when  $R_4$  can be described according to Formula (2C), each  $R_6$ , the same or different, can be derived from one or more of polytetramethylenoxidediol, polyethylenoxidediol, polycaprolactonediol, polyethyleneglycoladipatediol, polydiethylenglycoladipatediol, toluylene
- 25 diisocyanate, diphenylmethane, hexamethylene diisocyanate, tetramethylene diisocyanate, naphthylene diisocyanate, glycerin monoallylether, trimethylolpropane monoallylether, glycerin monoglycidyl ether, ethyl-2,6-diisocyanatohexanoate (LDI), dimethylolpropionic acid methylester, dimethylolpropionic acid brombutylester, esters of monocarboxymethylethers, esters of glycerin, or esters of
- 30 trimethylpropane.
- A further embodiment according to the present invention relates to a linear block polymer wherein said linear block polymer has a molecular weight of at least  $2 \times 10^4$  Dalton.

Further, the present invention relates to the use of a compound according to Formula (1) during preparation of linear block polymers.

5 The present invention also relates to the use of said linear block polymer, as has been described above, as material in implants for humans and animals.

Furthermore, the use of said linear block polymer according to the present invention also relates to, for example, pharmaceutical preparations, during microencapsulation, in suspensions, in emulsions or similar.

10

The present invention also relates to the use of said linear block polymer as material for promoting wound healing in humans and animals.

15 Furthermore, implants for humans and animals are concerned, wherein said implants comprise said linear block polymer.

The present invention also relates to pharmaceutical preparations, microencapsules, suspensions or emulsions that comprise said linear block polymer.

20 Furthermore the present invention also relates to material for promoting wound healing in humans and animals, which material comprises said linear block polymer.

## EXAMPLES

The following examples describe the invention, without in any way limiting it.

5 Example 1**2-{4-[(ammonioacetyl)oxy] butoxy}-2-oxethanaminium bis(trifluoroacetate)**

- a) 4-[(2-[(*tert*-butoxycarbonyl)amino]acetyl)oxy]butyl  
10 [*tert*-butoxycarbonyl)amino] acetate

17.52 g (100 mmol) *tert*-butoxycarbonyl glycine was dissolved in 50 ml dichloromethane (DCM) and the solution was added into a jacketed glass reactor cooled to 0°C. 4.5 g (50 mmol) butanediol was mixed with 50 ml dichloromethane  
15 and added into the reactor under stirring. When the mixture in the reactor had reached 0°C, a solution of 20.6 g (100 mmol) dicyclohexylcarbodiimide (DCC) in 100 ml dichloromethane was added. A catalytic amount of dimethylaminopyridine (DMAP) was added in order to catalyse the reaction. The temperature in the reactor rose rapidly to 10°C, after which it sank to its original value. The reaction was  
20 allowed to proceed for 3 hours at 0°C, after which it was warmed to approximately 30°C for one hour, and then left under stirring at room temperature until the next day. Processing of the reaction mixture commenced with filtration through a 40-100 µm glass filter, wherein the filtration separates out precipitated dicyclohexylurea (DCU). The dichloromethane that passed the filter was extracted with a 1M  
25 potassium hydrogen sulphate solution, followed by extraction with distilled water and with a saturated sodium hydrogen carbonate solution. The dichloromethane phase was then washed three times with distilled water. The washed dichloromethane phase was dried over water-free magnesium sulphate and evaporated to give an oil that crystallised slowly. Yield 80-90%. If the oil contains contaminant in the form of  
30 dicyclohexylurea, the oil can be dissolved in ethyl acetate and the contaminant filtered out, in order to then evaporate off the ethyl acetate and regain the final product in a more pure condition. Yield: 16.4 g (approximately 80%).

$^1\text{H}$ NMR ( 300 MHz ,  $\text{CDCl}_3$  , ppm): 1.42 (s, 9H, OtBu), 1.70-1.75 (m, 2H,  $\text{CH}_2$ ), 3.89 (d, 2H,  $\text{CN}_2\text{-N}$  ), 4.15-4.20 (m, 2H,  $\text{CH}_2\text{-O}$ ) and 5.0-5.1 (m, 1H, NH).  $\text{C}_2$ -symmetry halves the spectrum.

IR:  $\nu_{\text{max}}$  (Solid sample/ATR-FTIR), 3363s (N-H), 1730s (C=O, ester), 1676s (C=O, urethane).

MS: ESMS; m/z (calculated)  $\text{C}_{18}\text{H}_{32}\text{N}_2\text{O}_8$  404.455; (obtained) 405.2 [ $\text{MH}^+$ ] and 427.2 [ $\text{MNa}^+$ ].

10 b) 2-{4-[(ammonioacetyl)oxy] butoxy}-2-oxethanaminium bis(trifluoroacetate)

Deprotection of tert-butyloxycarbonyl protective groups by acidolysis.

50 ml dichloromethane (DCM) was added to 12.1g of the product from Step a) (molecular weight (Mw)=404.6, 30 mmol). 20 ml trifluoroacetic acid (TFA) was added under stirring to the partially dissolved substrate. Everything now became dissolved, while the solution took on a faint yellow colour and a powerful production of carbon dioxide could be seen. The procedure was interrupted after 45 minutes by evaporating the reaction to dryness (a yellow oil). 50 ml dry diethyl ether was added to the oil, after which the heterogeneous mixture was stirred vigorously. The TFA salt now precipitated during the stirring and the crystalline substance was washed twice with 50 ml diethyl ether. The crystals were then filtered out from the diethyl ether and vacuum-dried.

25 Yield: 12.45g (theoretical 12.96g ) 96%.

IR:  $\nu_{\text{max}}$  (solid sample/ATR-FTIR) 70°C, melted, 3050s (N-H), 1764s (C=O) and 1679s (C=O, TFA).

MS: ESMS; m/z (calculated)  $\text{C}_8\text{H}_{16}\text{N}_2\text{O}_4$  204.22; (obtained) 204.8 [ $\text{MH}^+$ ] and 409.1 [ $2\text{MH}^+$ ].

**Example 2****4-[(2-aminoacetyl)oxy]butyl aminoacetate**

- 5 a) 4-[(2-[(benzyloxy)carbonyl]amino)acetyl)oxy]butyl [(benzyloxy)carbonyl]amino  
acetate

Benzyloxycarbonylglycine, Z-Gly-OH (20.9 g, 100 mmol), was added into a 0.5 l  
jacketed reactor. 1,4-butanediol (4.56 g, 50 mmol) dispersed in 100 ml  
10 dichloromethane (DCM) was then added in batches. A catalytic amount of  
dimethylaminopyridine (DMAP) was added and the mixture then cooled to 0°C.  
Dicyclohexylcarbodiimide (DCC) dissolved in 100 ml DCM was added under stirring,  
wherein dicyclohexylurea (DCU) precipitated. The mixture was then allowed slowly  
to reach room temperature, at which it was allowed to proceed under stirring for  
15 three days. The reaction mixture was processed by filtering out the DCU that had  
formed, after which the remaining solution was washed by extraction with a 1M  
potassium hydrogen sulphate solution, distilled water, a saturated solution of sodium  
hydrogen carbonate and, finally, three times with distilled water. The thus purified  
organic phase was then dried over water-free magnesium sulphate, filtered and then  
20 evaporated to give a colourless oil that crystallised on reaching room temperature.  
Yield: 20 g (theoretical 23 g) 87%.

<sup>1</sup>HNMR (300 MHz, CDCl<sub>3</sub>, ppm): 1.71 (m, 2H, CH<sub>2</sub>), 3.96 (d, 2H, CH<sub>2</sub>-N), 4.17 (m,  
2H, CH<sub>2</sub>-O), 5.12 (s, 2H, CH<sub>2</sub>, benzyl), 5.3 (m, 1H, N-H) and 7.32 (s, 5H, phenyl).  
25 IR: ν<sub>max</sub> (solid sample/ATR-FTIR), 3300s (N-H), 1736s (C=O), 1201s (C-O).  
MS: ESMS; m/z (calculated) C<sub>24</sub>H<sub>28</sub>N<sub>2</sub>O<sub>8</sub> 472.488; (obtained) 473.1 [MH<sup>+</sup>] and 495.1  
[MNa<sup>+</sup>].

b) 4-[(2-aminoacetyl)oxy]butyl aminoacetate

30

9.44 g (20 mmol) of benzyloxycarbonyl-protected diamine from Step a) were  
dissolved in a mixture of 100 ml ethyl acetate and 50 ml methanol and transferred to  
a hydrogenation reactor. A catalytic amount of palladium on active carbon (Pd/C,  
10%, Merck) was added under a nitrogen atmosphere, after which the suspension

solution was evacuated three times with a water vacuum pump, with respect to dissolved gases. Hydrogen gas was loaded into the reactor between evacuations. A hydrogen gas pressure of 4 bar was then applied under vigorous stirring. Hydrogen gas was rapidly consumed, and hydrogen gas was consequently added at regular intervals. The product started to precipitate out in the reaction after a few hours, and it was consequently necessary to warm it to 40°C. Stirring was continued until the next day when the reaction mixture was warm-filtered through a 1µm glassfibre filter and evaporated to give an oil that crystallised.

10 Yield: 4.1 g (100%).

<sup>1</sup>HNMR (300 MHz/D<sub>2</sub>O, ppm): 1.56 (m, 2H, CH<sub>2</sub>), 3.59 (m, 2H, CH<sub>2</sub>-N), 3.99 (m, 2H, CH<sub>2</sub>-O) and 4.18 (t, 1H, partially exchanged, N-H)

IR: ν<sub>max</sub> (solid sample/ATR-FTIR), 3300s (N-H), 1736s (C=O), 1201s (C-O).

15 MS: ESMS; m/z (calculated) C<sub>8</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub> 204.22; (obtained) 204.8 [MH<sup>+</sup>].

### Example 3

#### **4-(2-ammonioethoxy)-4-oxo-1-butanaminium bis(trifluoroacetate)**

20

a) 2-[(*tert*-butoxycarbonyl)amino]ethyl 4-[(*tert*-butoxycarbonyl)amino] butanoate

8.13 g (Mw=203, 40 mmol) of Boc-GABA-OH and 6.45 g (40 mmol, Mw=161) of Boc-aminoethanol were added to a reaction vessel together with a small amount of DCM (40 ml). DCC, 8.24 g, 40 mmol dissolved in 40 ml DCM was added at room temperature. A catalytic amount of DMAP was also added. DCU precipitated within a few seconds. The mixture was stirred overnight. The reaction mixture was filtered and evaporated to give an oil that was dissolved in ethyl acetate and refiltered. The reaction mixture was extracted by washing with a sodium hydrogen carbonate solution, dried and evaporated to dryness. The residue crystallised. Yield 11 g, approximately 80%.

<sup>1</sup>HNMR (300 MHz/CDCl<sub>3</sub>, ppm): 1.42 (s, 18H, tBu), 1.8 (m, 2H, -CH<sub>2</sub>-), 2.36 (t, 2H, -CH<sub>2</sub>-CO-), 3.15 (d, 2H, -CH<sub>2</sub>-N, GABA), 3.39 (d, 2H, CH<sub>2</sub>-N, aminoethanol), 4.16 (d, CH<sub>2</sub>-O), 4.7 (s, 1H, NH) and 5.15 (s, 1H, NH).

IR:  $\nu_{\max}$  (Solid sample/ATR-FTIR), 3339s (N-H), 1727s (C=O) and 1685s (C=O, tBu).

MS: ESMS; m/z (calculated) C<sub>16</sub>H<sub>30</sub>N<sub>2</sub>O<sub>6</sub> 346.42; (obtained) 369.2 [MNa<sup>+</sup>].

b) 4-(2-ammonioethoxy)-4-oxo-1-butanaminium bis(trifluoroacetate)

3.79 g (10.9 mmol) of Boc-protected diamine from Step a) was dissolved in a mixture of 15 ml DCM and 15 ml TFA at room temperature. Carbon dioxide was produced when the reaction mixture was stirred. The reaction mixture was evaporated to dryness after two hours. The residue, which contained an excess of TFA, was precipitated at alkali pH by sodium carbonate solution and extracted three times with chloroform. The chloroform phases were combined, dried, and evaporated to dryness. The residue, an oil that crystallised. Yield: 3.3 g (theoretical 4.08 g) 81%.

IR:  $\nu_{\max}$  (Solid sample/ATR-FTIR), 3340s, 2927s, 2855s, 1686s (C=O), 1641s (C=O, TFA).

MS: ESMS; m/z (Calculated) C<sub>6</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> 146.19 ; obtained 146.8 [MH<sup>+</sup>].

**Example 4**

**4-[[4-(4-aminobutanoyl)oxy]butyl 4-aminobutanoate**

a) 4-[[4-[[[(benzyloxy)carbonyl]amino}butanoyl) oxy]butyl 4-[[[(benzyloxy)carbonyl]amino} butanoate

7.99 g (33.6 mmol, Mw=237) Z-GABA-OH and 1.51 g (16.8 mmol, Mw=90.13) butanediol were mixed in a reactor together with 100 ml DCM and a catalytic amount of DMAP. The mixture was cooled to 0°C, after which 7.2 g (approximately 35 mmol, Mw=206) of DCC dissolved in 50 ml DCM was added under stirring. DCU

started to precipitate immediately. The mixture was allowed to reach room temperature slowly and stirred overnight.

The reaction mixture was warmed for a short period to 30°C before processing. After  
5 cooling, the DCU was filtered out and the residue washed by extraction with  
potassium hydrogen sulphate (1 M), distilled water, sodium hydrogen carbonate  
(saturated) and three times with distilled water. The organic phase was then dried  
over water-free magnesium sulphate and evaporated to give an oil. The oil was  
dissolved in absolute ethanol and placed in the cold to crystallise. The crystals were  
10 filtered out and dried. Yield: approximately 8 g (theoretical 8.8 g) 90%.

<sup>1</sup>HNMR (300 MHz/CDCl<sub>3</sub>, ppm): 1.69 (d, undissolved, 2H, O-C-CH<sub>2</sub>), 1.82 (m, 2H,  
C-CH<sub>2</sub>-C), 2.35 (t, 2H, CH<sub>2</sub>-CO), 3.22 (m, 2H, N-CH<sub>2</sub>), 4.07 (d, undissolved, 2H, O-  
CH<sub>2</sub>), 4.94 (m, 1H, N-H), 5.08 (s, 2H, benzyl) and 7.3 (s, 5H, phenyl).  
15 MS: ESMS; m/z (calculated) C<sub>28</sub>H<sub>36</sub>N<sub>2</sub>O<sub>6</sub> 528.59; (obtained) 529.2 [MH<sup>+</sup>] and 551.2  
[MNa<sup>+</sup>].

IR: ν<sub>max</sub> (Solid sample/ATR-FTIR), 3332s (N-H), 1722s (C=O) and 1686s (C=O).

b) 4-[(4-aminobutanoyl)oxy]butyl 4-aminobutanoate

20

Approximately 8 g (approximately 16 mmol, Mw=528) of the product from Step a)  
was dissolved in absolute ethanol. A catalytic amount of palladium on active carbon  
(Pd/C 10%) was added and dissolved gases evacuated from the mixture. A  
hydrogen gas pressure of 4 bar was then applied and the mixture stirred vigorously.  
25 When no more hydrogen gas was consumed in the reaction mixture, the procedure  
was interrupted and the catalyst filtered out. The residual solution was evaporated to  
an oil, 6 g, which dried slowly. Yield: approximately 3.5 g (80%).

IR: ν<sub>max</sub> (Solid sample/ATR-FTIR), 3300s (N-H) and 1682s (C=O).

30 MS: ESMS; m/z (calculated) C<sub>12</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub> 260.33; (obtained) 261 [MH<sup>+</sup>].

**Example 5****5-[(2S)-2-amino-3-methoxy-3-oxopropyl] 1-methyl (2S)-2-aminopentandioate**

- 5 a) 5-((2S)-2-(((benzyloxy)carbonyl)amino)-3-methoxy-3-oxopropyl) 1-methyl (2S)-2-(((benzyloxy)carbonyl)amino) pentandioate

8.86 g (30 mmol, Mw=295.3) Z-Glu-OMe and 7.6 g (30 mmol, Mw=253.3) Z-Ser-OMe were dissolved in 100 ml DCM, after which a catalytic amount of DMAP was  
 10 added. The mixture was cooled to 0°C, and 6.39 g (31 mmol, Mw=206) of DCC dissolved in 20 ml DCM was added under stirring. The mixture was allowed to reach room temperature and was stirred overnight. DCU precipitated out from the reaction mixture slowly.

15 The mixture was processed after being warmed to 30°C for approximately one hour. The residue was dissolved in ethyl acetate after filtering and evaporation, on which further DCU precipitated out. The product mixture was therefore allowed to stand for three days before being refiltered. The reaction mixture was washed by extraction with potassium hydrogen sulphate (1 M), distilled water, sodium hydrogen carbonate  
 20 (saturated) and finally three times with distilled water. The organic phase was then dried over water-free magnesium sulphate, filtered and evaporated to dryness.

Yield: 17 g (theoretical 16 g).

25 <sup>1</sup>HNMR (300 MHz/CDCl<sub>3</sub>, ppm): 1.92 (m, 2H, C-CH<sub>2</sub>-C), 2.18 (m, 1H, -CH-CO), 2.38 (m, 2H, CH<sub>2</sub>-CO), 3.72 (s, 3H, OCH<sub>3</sub>), 3.76 (s, 3H, OCH<sub>3</sub>), 4.38 (m, 2H, CH<sub>2</sub>-O), 4.64 (m, 1H, α-H), 5.06 (s, 2H, benzyl), 5.11 (s, 2H, benzyl), 5.43 (d, 1H, N-H), 5.91 (d, 1H, N-H), 7.32 (s, 5H, phenyl) and 7.324 (s, 5H, phenyl).

IR: ν<sub>max</sub> (Solid sample/ATR-FTIR), 3330s (N-H) and 1720s (C=O, broad).

30

MS: ESMS; m/z (calculated) C<sub>26</sub>H<sub>30</sub>N<sub>2</sub>O<sub>10</sub> 530.52; (obtained) 531.3 [MH<sup>+</sup>] and 553.3 [MNa<sup>+</sup>].

b) 5-[(2S)-2-amino-3-methoxy-3-oxopropyl] 1-methyl (2S)-2-aminopentandioate

Benzyloxycarbonyl-protected diamine, 16 g, 30 mmol, Mw=530.5 was dissolved in 50 ml absolute ethanol and a catalytic amount of palladium on active carbon (Pd/C 10%) was added, after which dissolved gases were evacuated from the mixture by applying a water vacuum. A hydrogen gas pressure of 2.5 bar was then applied and the mixture stirred vigorously. When no further hydrogen gas was consumed in the reactor on the following day, the procedure was interrupted and the contents filtered through celite and evaporated to an oil.

10

Yield: 7.65 g (theoretical 7.86 g ) 97%.

IR:  $\nu_{\max}$ (Solid sample/ATR-FTIR), 3360s (N-H), 3280s (N-H), 1733s (C=O), 1676s (C=O) and 1204s (C-O).

15 MS: ESMS; m/z (calculated)  $C_{10}H_{18}N_2O_6$  262.26; (obtained), 262.9  $[MH^+]$  and 284.9  $[MNa^+]$ .

Example 6

20 Preparation of a di-substituted pentaerythritol, here 3-[(aminoacetyl)oxy]-2,2-bis(hydroxymethyl)propyl aminoacetate

a) 3-([[(tert-butoxycarbonyl)amino]acetyl]oxy)-2,2-bis(hydroxymethyl)propyl [(tert-butoxycarbonyl)amino]acetate

25

6.8 g (50 mmol, Mw=136.15 g) pentaerythritol and 17.55 g (100 mmol, Mw=175.2 g) Boc-glycine was suspended in 75 ml dichloromethane. 20.6 g (100 mmol, Mw=206g) dicyclohexylcarbodiimide (DCC) was dissolved in 40 ml DCM together with a catalytic amount of DMAP, and this solution was added to the above solution in a reactor at room temperature (approximately 25 ° C). DCU (a by-product of the reaction) started to precipitate. The reaction was allowed to continue for five days during stirring, and then it was filtered and evaporated to a oil. The oil was then solved in ethylacetate and processed as in Example 1.

30

b) 3-[(aminoacetyl)oxy]-2,2-bis(hydroxymethyl)propyl aminoacetate

The product from Step a), in the form of a viscous substance, was treated with HCl/isopropylalcohol (5-6M) which gave the deblocked diamine as a dihydrochloride-salt. The dihydrochloride-salt was then used as a chain extender in polymerisation reactions.

**Example 7**

**Preparation of a tetra-substituted pentaerythritol, here  
3-[(aminoacetyl)oxy]-2,2-bis[(aminoacetyl)oxy)methyl]propyl aminoacetate**

a) 3-[(tert-butoxycarbonyl)amino]acetyl]oxy)-2,2-bis[(tert-butoxycarbonyl)amino]acetyl]oxy)methyl]propyl [(tert-butoxycarbonyl)amino]acetate

3.4 g (25 mmol, Mw=136.15 g) pentaerythritol was suspended in 100 ml ethylacetate. 17.5 g (100 mmol, Mw=175.2 g) tert-butyloxykarbonylglycin (Boc-glycin) was dissolved in 100 ml ethylacetate and this solution was added to the above suspension of pentaerythritol in ethylacetate. A solution of 21 g (>100 mmol, Mw=206) dicyclohexylcarbodiimide in 100 ml ethylacetate was then added, and to this solution a catalytic amount of DMAP was added. DCU (a by-product of the reaction) started immediately to precipitate. The reaction was allowed to continue during stirring for 8 days at room temperature (with IR-monitoring of DCC), and then all by-product was filtered off. The remaining reaction solution was washed with 1M potassium hydrogen sulphate (1 M), distilled water, sodium hydrogen carbonate (saturated) and finally three times with distilled water. The reaction solution was then dried using water free magnesium sulphate. The remaining organic phase was evaporated to dryness, which did result in an amorphous foam. The yield was more than 15 g (theoretical 19.12 g, Mw=764.81 C<sub>33</sub>H<sub>56</sub>N<sub>4</sub>O<sub>16</sub>).

b) 3-[(aminoacetyl)oxy]-2,2-bis[(aminoacetyl)oxy)methyl]propyl aminoacetate

Treatment of the product from Step a) with trifluoroacetic acid (TFA) gave the TFA-salt of the above tetra-substituted pentaerythritol. After evaporation of excess

TFA, the TFA-salt of the tetra-substituted pentaerythritol may be used as a chain extender or a cross linking agent. Mw= 364.35 C<sub>13</sub>H<sub>24</sub>N<sub>4</sub>O<sub>8</sub>.

### **Example 8**

5

**Polymerisation experiments using 2-{4-[(aminoacetyl)oxy]butoxy}-2-oxethanaminium bis(trifluoroacetate), the product from Example 1**

11 g of a prepolymer, which is prepared from diphenylmethane diisocyanate that  
10 has reacted with polycaprolactonediol (PCL530) at a molar ratio of 2:1, were dissolved in 50 ml of dimethylformamide (DMF). 4.76 g (11 mmol) of the product from Example 1 were dissolved in 25 ml DMF under heating to give a clear solution that was added to the prepolymer solution. A mixture of 2.4 g triethylamine and 60 mg dibutylamine were added under gentle heating and vigorous stirring. Checking  
15 the pH showed that it was neutral, and for this reason a further 0.8 g triethylamine were added. The reaction was allowed to proceed overnight. The polymer was subsequently precipitated in absolute ethanol to form one solid lump. The polymer was dissolved in 30 ml DMF and samples were taken for SEC ("Size Exclusion Chromatography"). The molecular weight was estimated to be 33,000 Dalton by  
20 comparison with a polystyrene standard.

### **Example 9**

**Polymerisation experiments with 4-[(2-aminoacetyl)oxy]butyl aminoacetate,  
25 the product from Example 2**

17 g of a prepolymer, which is prepared from diphenylmethane diisocyanate that  
has reacted with polycaprolactonediol (PCL 530) at a molar ratio of 2:1, were dissolved in 60 ml of dimethylformamide (DMF). 3.47 g of the product from Example  
30 2 were suspended in 17 ml DMF and added to the prepolymer solution under vigorous stirring and gentle heating. The reaction was allowed to proceed overnight, after which it was precipitated with 250 ml absolute ethanol. The polymer was washed in ethanol, dried and dissolved in 50 ml DMF. A sample of the polymer

solution was taken for SEC. The molecular weight was estimated to be just under 30,000 Dalton.

#### **Example 10**

5

**Polymerisation experiments with 5-[(2S)-2-amino-3-methoxy-3-oxopropyl] 1-methyl (2S)-2-aminopentandioate, the product from Example 5**

15 g of a prepolymer, which is prepared from diphenylmethane diisocyanate that  
10 has reacted with polycaprolactonediol (PCL530) at a molar ratio of 2:1, were dissolved in 50 ml of dimethylformamide (DMF). The product from Example 5 dissolved readily in 25 ml DMF that was added to the prepolymer solution under vigorous stirring. The reaction was allowed to proceed until the next day, when it was precipitated with absolute ethanol. The polymer was washed in ethanol, dried  
15 and dissolved in DMF. A sample was removed for SEC analysis. The molecular weight was estimated to be approximately 21,000 Dalton by comparison with a polystyrene standard.

#### **Example 11**

20

**Degradation experiments of a polymer film made from the product from Example 7**

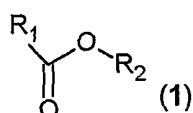
A polymer film of the product from Example 7, based on prepolymer and the diamine  
25 (the product from Example 5), was exposed to degradation experiments at 77°C in phosphate buffer at pH 7.4. The molecular weight was estimated to be 21,000 Dalton at the start of the experiment. Samples of the film were removed at regular intervals and analysed by SEC.

30 The molecular weight decreased rapidly during the experiment, and after 43 days the film was no longer conjunct, and the experiment was consequently interrupted. This means a halving of the breakdown time when compared with polymers that do not contain chain extenders with hydrolysable groups, i.e. in this case, polymers that do not contain compound (1), (1C) or R<sub>3</sub> according to the present invention.

## CLAIMS

1. A compound according to Formula (1)

5



10 wherein

R<sub>1</sub> and R<sub>2</sub>, which R<sub>1</sub> and R<sub>2</sub> can be the same or different, are

amino((C<sub>2</sub>-C<sub>5</sub>)alkyl) wherein (C<sub>2</sub>-C<sub>5</sub>)alkyl is saturated,

15 ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)] or A,

wherein A is [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl); or

R<sub>1</sub> is amino((C<sub>1</sub>-C<sub>5</sub>)alkyl) when R<sub>2</sub> is

20

[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]([2-4, 2-4]bis(R<sub>p</sub>)(C<sub>2</sub>-C<sub>5</sub>)alkyl), wherein

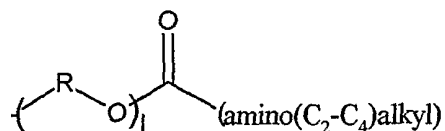
each R<sub>p</sub>, which R<sub>p</sub> can be the same or different, is

hydroxy((C<sub>1</sub>-C<sub>5</sub>)alkyl) or [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl);

25

or

R<sub>2</sub> is a substituent according to Formula (1A)



(1A)

wherein R is (C<sub>2</sub>-C<sub>4</sub>)alkyl, and

I is from 1 to 20, preferably 1 to 10, and R<sub>1</sub> is then

- 5 ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)], or  
 [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl); or

salts, together with all possible stereoisomers either pure or as racemic compounds  
 or as mixtures of stereoisomers, of said compound according to Formula (1); and

10

provided that neither of 2-aminoethyl 3-aminopropanoate,  
 2-aminoethyl 4-aminobutanoate, 2-aminoethyl 3-amino-3-methylbutanoate or  
 2-aminoethyl 6-aminohexanoate is included in Formula (1).

- 15 2. A compound according to claim 1, wherein

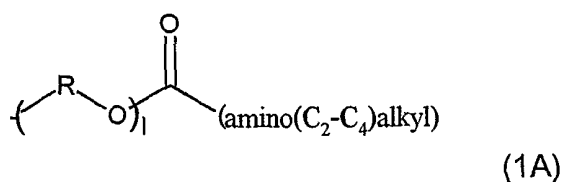
R<sub>1</sub> and R<sub>2</sub>, which R<sub>1</sub> and R<sub>2</sub> can be the same or different, are

amino((C<sub>2</sub>-C<sub>5</sub>)alkyl), ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)] or A,

20

wherein A is [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl); or

R<sub>2</sub> is a substituent according to Formula (1A)



25

wherein R is (C<sub>2</sub>-C<sub>4</sub>)alkyl, and

I is from 1 to 20, preferably 1 to 10, and R<sub>1</sub> is then

- 30 ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)], or

[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl).

3. A compound according to claim 1, wherein

5 R<sub>1</sub> is amino((C<sub>1</sub>-C<sub>5</sub>)alkyl) when R<sub>2</sub> is

[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]([2-4, 2-4]bis(R<sub>p</sub>)(C<sub>2</sub>-C<sub>5</sub>)alkyl), wherein

each R<sub>p</sub>, which R<sub>p</sub> can be the same or different, is hydroxy((C<sub>1</sub>-C<sub>5</sub>)alkyl) or

10 [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl).

4. A compound according to claim 1 or 2, wherein

R<sub>1</sub> is amino((C<sub>3</sub>-C<sub>5</sub>)alkyl),

15 ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)], or  
[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl); and

R<sub>2</sub> is amino((C<sub>2</sub>-C<sub>5</sub>)alkyl),

20 ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)], or  
[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl).

5. A compound according to claim 1, wherein R<sub>2</sub> is A,

wherein A is [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)]((C<sub>3</sub>-C<sub>5</sub>)alkyl).

25

6. A compound according to claim 1, wherein

R<sub>2</sub> is a substituent according to Formula (1A) and

30 R<sub>1</sub> is ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)], or  
[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)]((C<sub>3</sub>-C<sub>5</sub>)alkyl).

7. A compound according to any one of the claims 1 to 2 or 4 to 6, wherein

each alkyl and each alkanoate can, independently of each other, be substituted with methyl, phenyl, 4-hydroxyphenyl, 4-aminobutyl, 2-butyl, 2-hydroxymethyl, 3-aminopropyl, 2-aminoethyl, 2-mercaptomethyl, or similar.

8. A compound according to claim 1, which compound is

- 4-[(4-aminobutanoyl)oxy]butyl 4-aminobutanoate,  
 10 5-[(2S)-2-amino-3-methoxy-3-oxopropyl] 1-methyl (2S)-2-aminopentanedioate,  
 5-(2-aminoethyl) 1-methyl (2S)-2-aminopentanedioate,  
 5-(3-aminopropyl) 1-methyl (2S)-2-aminopentanedioate,  
 5-(4-aminobutyl) 1-methyl (2S)-2-aminopentanedioate,  
 methyl (2S)-2-amino-3-[(3-aminopropanoyl)oxy] propanoate,  
 15 2-[(2-aminoacetyl)oxy]ethyl 3-aminopropanoate,  
 2-[(2-aminoacetyl)oxy]ethyl 4-aminobutanoate,  
 2-[(2-aminoacetyl)oxy]ethyl aminoacetate,  
 or 4-(2-aminoethyl) 1-methyl (2R)-2-aminobutanedioate; or  
 salts, together with all possible stereoisomers either pure or as racemic compounds  
 20 or as mixtures of stereoisomers, thereof.

9. A compound according to claim 1, which compound is

- 4-[(4-aminobutanoyl)oxy]butyl 4-aminobutanoate, or  
 25 5-[(2S)-2-amino-3-methoxy-3-oxopropyl] 1-methyl (2S)-2-aminopentanedioate; or  
 salts, together with all possible stereoisomers either pure or as racemic compounds  
 or as mixtures of stereoisomers, thereof.

30 10. A compound according to claim 1 or 3, wherein

$R_1$  is amino((C<sub>1</sub>-C<sub>5</sub>)alkyl) when  $R_2$  is

[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]([2, 2]bis( $R_p$ )(C<sub>3</sub>)alkyl), wherein

each  $R_p$ , which  $R_p$  can be the same or different, is hydroxy((C<sub>1</sub>-C<sub>3</sub>)alkyl) or [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoat)]((C<sub>3</sub>)alkyl).

5 11. A compound according to claim 1, 3 or 10, which compound is

3-[(aminoacetyl)oxy]-2,2-bis(hydroxymethyl)propyl aminoacetate or

3-({aminoacetyl}oxy)-2,2-bis[({aminoacetyl}oxy)methyl]propyl aminoacetate.

10

12. A method for preparing a compound according to any one of claims 1 to 11, which method comprises

15 a) preparation of a compound having Formula (1) by deprotecting the corresponding compound with protective amines,

b) conversion of a compound having Formula (1) to a salt thereof, or vice versa

c) conversion of a salt of a compound having Formula (1) to another salt.

20

13. A compound having Formula (1B) that is defined as in Formula (1) according to claim 1, but

in which "amino" in Formula (1) is replaced throughout by "[protected amine]".

25

14. A method for preparing a linear block polymer, wherein the method comprises

prepolymers, which prepolymers can be the same or different, and compounds according to Formula (1C), which compounds can be the same or different, and

30

chain extension of said prepolymer, with two isocyanate end-groups per molecule, with said compound according to Formula (1C)



wherein

10

R<sub>1</sub> and R<sub>2</sub>, which R<sub>1</sub> and R<sub>2</sub> can be the same or different, are

amino((C<sub>1</sub>-C<sub>5</sub>)alkyl), ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)] or A, wherein,

15

when R<sub>1</sub> is A,

A is [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>1</sub>-C<sub>5</sub>)alkyl); and

when R<sub>2</sub> is A,

A is [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>3</sub>-C<sub>5</sub>)alkyl); or wherein

20

R<sub>1</sub> is diamino((C<sub>1</sub>-C<sub>5</sub>)alkyl) and

R<sub>2</sub> is hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl or benzyl; or wherein

25

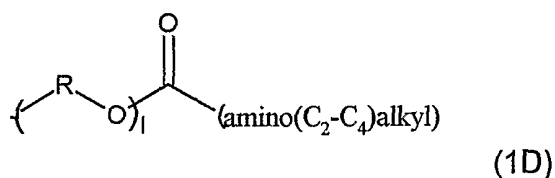
R<sub>1</sub> is amino((C<sub>1</sub>-C<sub>5</sub>)alkyl) when R<sub>2</sub> is

[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]([2-4, 2-4]bis(R<sub>p</sub>)(C<sub>2</sub>-C<sub>5</sub>)alkyl), wherein

30

each R<sub>p</sub>, which R<sub>p</sub> can be the same or different, is hydroxy((C<sub>1</sub>-C<sub>5</sub>)alkyl) or [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>2</sub>-C<sub>5</sub>)alkyl); or wherein

R<sub>2</sub> is a substituent according to Formula (1D)



5                      wherein R is (C<sub>2</sub>-C<sub>4</sub>)alkyl, and

I is from 1 to 20, preferably 1 to 10, and R<sub>1</sub> is then

amino((C<sub>1</sub>-C<sub>5</sub>)alkyl),

10    ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)], or  
      [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>)alkanoate)]((C<sub>1</sub>-C<sub>5</sub>)alkyl); or

salts, together with all possible stereoisomers either pure or as racemic compounds  
 or as mixtures of stereoisomers, thereof.

15

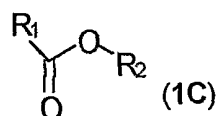
15. A method for preparing according to claim 14, wherein the method comprises

prepolymers, which prepolymers can be the same or different, and compounds  
 according to Formula (1C), which compounds can be the same or different, and

20

chain extension of said prepolymer, with two isocyanate end-groups per molecule,  
 with said compound according to Formula (1C)

25



wherein

$R_1$  and  $R_2$ , which  $R_1$  and  $R_2$  can be the same or different, are

5 amino(( $C_1$ - $C_5$ )alkyl), (( $C_1$ - $C_4$ )alkyl)[(2-4)-amino(( $C_2$ - $C_4$ ) alkanooate)] or A, wherein,

when  $R_1$  is A ,

A is [(2-4)-amino(( $C_2$ - $C_4$ ) alkanooate)](( $C_1$ - $C_5$ )alkyl); and

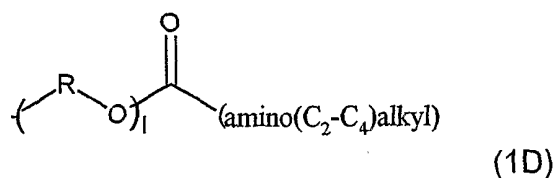
10 when  $R_2$  is A,

A is [(2-4)-amino(( $C_2$ - $C_4$ ) alkanooate)](( $C_3$ - $C_5$ )alkyl); or wherein

$R_1$  is diamino(( $C_1$ - $C_5$ )alkyl) and

15  $R_2$  is hydrogen, ( $C_1$ - $C_4$ )alkyl or benzyl; or wherein

$R_2$  is a substituent according to Formula (1D)



20

wherein R is ( $C_2$ - $C_4$ )alkyl, and

I is from 1 to 20, preferably 1 to 10, and  $R_1$  is then

25 amino(( $C_1$ - $C_5$ )alkyl),  
 (( $C_1$ - $C_4$ )alkyl)[(2-4)-amino(( $C_2$ - $C_4$ ) alkanooate)], or  
 [(2-4)-amino(( $C_2$ - $C_4$ ) alkanooate)](( $C_1$ - $C_5$ )alkyl).

16. The method for preparing a linear block polymer according to claim 14 or 15, wherein said prepolymer is chain-extended with one or more of

- 2-aminoethyl 4-aminobutanoate,
- 5 4-[(4-aminobutanoyl)oxy]butyl 4-aminobutanoate,
- 5-[(2S)-2-amino-3-methoxy-3-oxopropyl] 1-methyl (2S)-2-aminopentanedioate,
- 5-(2-aminoethyl) 1-methyl (2S)-2-aminopentanedioate,
- 5-(3-aminopropyl) 1-methyl (2S)-2-aminopentanedioate,
- 5-(4-aminobutyl) 1-methyl (2S)-2-aminopentanedioate,
- 10 methyl (2S)-2-amino-3-[(3-aminopropanoyl)oxy] propanoate,
- 2-[(2-aminoacetyl)oxy]ethyl 3-aminopropanoate,
- 2-[(2-aminoacetyl)oxy]ethyl 4-aminobutanoate,
- 2-[(2-aminoacetyl)oxy]ethyl aminoacetate,
- 4-(2-aminoethyl) 1-methyl (2R)-2-aminobutanedioate,
- 15 2-aminoethyl aminoacetate,
- 4-[(2-aminoacetyl)oxy]butyl aminoacetate,
- 2-[(3-aminopropanoyl)oxy]ethyl 3-aminopropanoate,
- 2-[(2-aminoacetyl)oxy]ethyl aminoacetate,
- methyl (2S)-2-amino-3-[(aminoacetyl)oxy] propanoate,
- 20 tert-butyl 2,6-diaminohexanoate
- and benzyl 2,6-diaminohexanoate; or

salts, together with all possible stereoisomers either pure or as racemic compounds or as mixtures of stereoisomers, thereof.

25

17. The method for preparing a linear block polymer according to claim 14 to 16, wherein said prepolymer is chain-extended with one or more of

- 2-aminoethyl 4-aminobutanoate,
- 30 4-[(4-aminobutanoyl)oxy]butyl 4-aminobutanoate,
- 5-[(2S)-2-amino-3-methoxy-3-oxopropyl] 1-methyl (2S)-2-aminopentanedioate,
- 2-aminoethyl aminoacetate,
- 4-[(2-aminoacetyl)oxy]butyl aminoacetate,
- O-tert-butyl 2,6-diaminohexanoate,

2-[(3-aminopropanoyl)oxy]ethyl 3-aminopropanoate, or  
2-[(2-aminoacetyl)oxy]ethyl aminoacetate; or

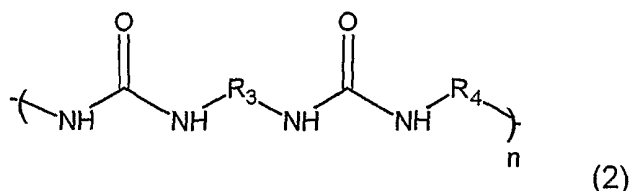
salts, together with all possible stereoisomers either pure or as racemic compounds  
5 or as mixtures of stereoisomers, thereof.

18. The method for preparing a linear block polymer according to claim 14, wherein  
said prepolymer is chain-extended with one or more of

10 3-[(aminoacetyl)oxy]-2,2-bis(hydroxymethyl)propyl aminoacetate or

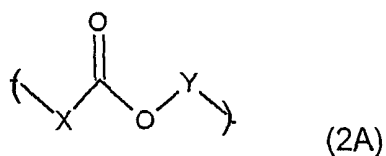
3-[(aminoacetyl)oxy]-2,2-bis[(aminoacetyl)oxymethyl]propyl aminoacetate.

19. A linear block polymer with a molecular weight of at least  $10^4$  Dalton, which  
15 linear block polymer consists of internally and linearly linked sequences, which  
sequences can be described according to Formula (2)



wherein each  $\text{R}_3$  and each  $\text{R}_4$  can be the same or different; and

20  $\text{R}_3$  can be described according to Formula (2A)



wherein

25 X and Y, which X and Y can be the same or different, are  $(\text{C}_1\text{-C}_5)$ alkyl, or are

derived from  $((C_1-C_4)\text{alkyl})[(2-4)\text{-amino}((C_2-C_4)\text{ alkanoate})]$  or

derived from A, wherein,

5 when X is A ,

A is  $[(2-4)\text{-amino}((C_2-C_4)\text{ alkanoate})][(C_1-C_5)\text{alkyl}]$ ; and

when Y is A,

A is  $[(2-4)\text{-amino}((C_2-C_4)\text{ alkanoate})][(C_3-C_5)\text{alkyl}]$ ; or

10

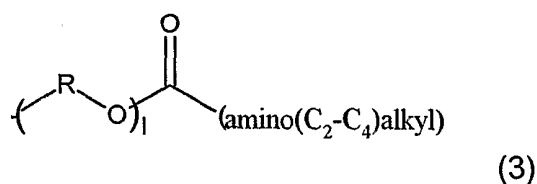
X is derived from  $\text{amino}((C_1-C_5)\text{alkyl})$  when Y is derived from

$[(2-4)\text{-amino}((C_2-C_4)\text{alkanoate})][(2-4, 2-4)\text{bis}(R_p)(C_2-C_5)\text{alkyl}]$ , wherein

15

each  $R_p$ , which  $R_p$  can be the same or different, is  
hydroxy $((C_1-C_5)\text{alkyl})$  or  $[(2-4)\text{-amino}((C_2-C_4)\text{alkanoate})][(C_2-C_5)\text{alkyl}]$ ;  
or

20 Y can be derived from a substituent according to Formula (3)



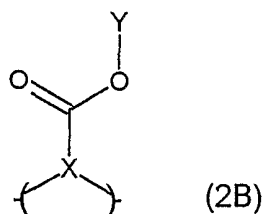
wherein R is  $(C_2-C_4)\text{alkyl}$ , and

25

I is from 1 to 20, preferably 1 to 10, and X can then be derived from

$\text{amino}((C_1-C_5)\text{alkyl})$ ,  $((C_1-C_4)\text{alkyl})[(2-4)\text{-amino}((C_2-C_4)\text{ alkanoate})]$ , or  
 $[(2-4)\text{-amino}((C_2-C_4)\text{ alkanoate})][(C_1-C_5)\text{alkyl}]$ ; or wherein

R<sub>3</sub> can be described according to Formula (2B)



5

wherein X is ((C<sub>1</sub>-C<sub>5</sub>)alkyl) and

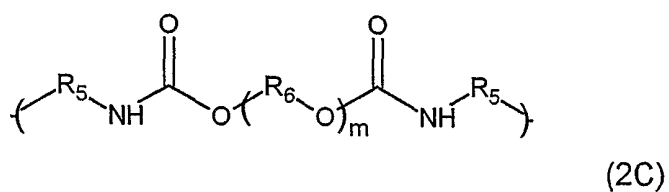
Y is hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl or benzyl; and

10

R<sub>4</sub> can be derived from diisocyanate and comprises none, one or several ester groups,

or R<sub>4</sub> can be described according to Formula (2C)

15



wherein each R<sub>5</sub>, the same or different, can be derived from diisocyanate,

20 R<sub>6</sub> is (C<sub>2</sub>-C<sub>4</sub>)alkyl, and

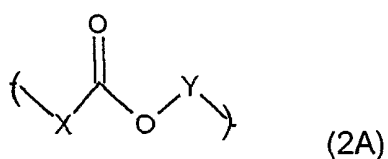
m is from 1 to 20, preferably 1 to 10.

46

20. A linear block polymer according to claim 19, wherein

each  $R_3$  and each  $R_4$  can be the same or different; and

5  $R_3$  can be described according to Formula (2A)



wherein

10 X and Y, which X and Y can be the same or different, are  $(C_1-C_5)$ alkyl, or are

derived from  $((C_1-C_4)$ alkyl)[(2-4)-amino $((C_2-C_4)$  alkanolate)] or

derived from A, wherein,

15

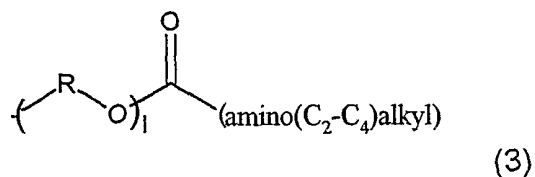
when X is A,

A is [(2-4)-amino $((C_2-C_4)$  alkanolate)] $((C_1-C_5)$ alkyl); and

when Y is A,

20 A is [(2-4)-amino $((C_2-C_4)$  alkanolate)] $((C_3-C_5)$ alkyl); or

Y can be derived from a substituent according to Formula (3)



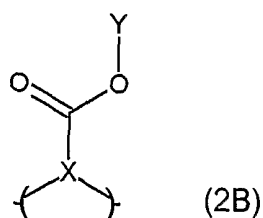
25

wherein R is (C<sub>2</sub>-C<sub>4</sub>)alkyl, and

I is from 1 to 20, preferably 1 to 10, and X can then be derived from

- 5 amino((C<sub>1</sub>-C<sub>5</sub>)alkyl), ((C<sub>1</sub>-C<sub>4</sub>)alkyl)[(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)], or [(2-4)-amino((C<sub>2</sub>-C<sub>4</sub>) alkanooate)]((C<sub>1</sub>-C<sub>5</sub>)alkyl); or wherein

R<sub>3</sub> can be described according to Formula (2B)



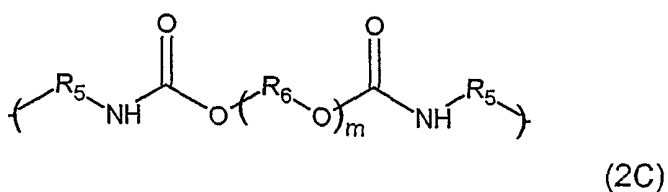
10

wherein X is ((C<sub>1</sub>-C<sub>5</sub>)alkyl) and

- 15 Y is hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl or benzyl; and

R<sub>4</sub> can be derived from diisocyanate and comprises none, one or several ester groups,

- 20 or R<sub>4</sub> can be described according to Formula (2C)



wherein each  $R_5$ , the same or different, can be derived from diisocyanate,

$R_6$  is  $(C_2-C_4)$ alkyl, and

5  $m$  is from 1 to 20, preferably 1 to 10.

21. The linear block polymer according to claim 19 or 20, wherein  $Y$  can be derived from  $A$ , wherein  $A$  is

10  $[(2-4)\text{-amino}((C_2-C_4)\text{ alkanooate})]((C_3-C_5)\text{alkyl})$ .

22. The linear block polymer according to claim 19 or 20, wherein each  $R_3$  can be the same or different and can be derived from one or several of

- 15 2-aminoethyl 4-aminobutanoate,  
 4-[(4-aminobutanoyl)oxy]butyl 4-aminobutanoate,  
 5-[(2S)-2-amino-3-methoxy-3-oxopropyl] 1-methyl (2S)-2-aminopentanedioate,  
 5-(2-aminoethyl) 1-methyl (2S)-2-aminopentanedioate,  
 5-(3-aminopropyl) 1-methyl (2S)-2-aminopentanedioate,  
 20 5-(4-aminobutyl) 1-methyl (2S)-2-aminopentanedioate,  
 methyl (2S)-2-amino-3-[(3-aminopropanoyl)oxy] propanoate,  
 2-[(2-aminoacetyl)oxy]ethyl 3-aminopropanoate,  
 2-[(2-aminoacetyl)oxy]ethyl 4-aminobutanoate,  
 2-[(2-aminoacetyl)oxy]ethyl aminoacetate,  
 25 4-(2-aminoethyl) 1-methyl (2R)-2-aminobutanedioate,  
 2-aminoethyl aminoacetate,  
 4-[(2-aminoacetyl)oxy]butyl aminoacetate,  
 2-[(3-aminopropanoyl)oxy]ethyl 3-aminopropanoate,  
 2-[(2-aminoacetyl)oxy]ethyl aminoacetate,  
 30 methyl (2S)-2-amino-3-[(aminoacetyl)oxy] propanoate,  
 tert-butyl 2,6-diaminohexanoate and  
 benzyl 2,6-diaminohexanoate; or

salts, together with all possible stereoisomers either pure or as racemic compounds or as mixtures of stereoisomers, thereof.

23. A linear block polymer according to claim 19, wherein each  $R_3$ , which  $R_3$  may  
5 be the same or different, may be derived from one or more of

3-[(aminoacetyl)oxy]-2,2-bis(hydroxymethyl)propyl aminoacetate or

3-({aminoacetyl}oxy)-2,2-bis[({aminoacetyl}oxy)methyl]propyl aminoacetate.  
10

24. The linear block polymer according to any one of claims 19 to 23, wherein each  $R_4$ , the same or different, or when  $R_4$  is according to Formula (2B), each  $R_5$ , the same or different, can be derived from diphenylmethane diisocyanate, toluylene diisocyanate, hexamethylene diisocyanate, tetramethylene diisocyanate,  
15 naphthylene diisocyanate or ethyl-2,6-diisocyanatoheaxanoate (LDI).

25. The linear block polymer according to any one of claims 19 to 24, wherein each  $R_4$ , the same or different, can be derived from one or several of polyesterdiol, polyetherdiol or monodiol and/or when  $R_4$  can be described according to Formula  
20 (2C), each  $R_6$ , the same or different, can be derived from one or several of polyesterdiol, polyetherdiol or monodiol.

26. The linear block polymer according to any one of claims 19 to 25, wherein  $R_4$ , the same or different, can be derived from one or more of  
25 polytetramethylenoxidediol, polyethylenoxidediol, polycaprolactonediol, polyethyleneglycoladipatediol, polydiethylenglycoladipatediol, toluylene diisocyanate, diphenylmethane, hexamethylene diisocyanate, tetramethylene diisocyanate, naphthylene diisocyanate, glycerin monoallylether, trimethylolpropane monallylether, glycerin monoglycidylether, ethyl-2,6-diisocyanatohexanoate (LDI),  
30 dimethylolpropionic acid methylester, dimethylolpropionic acid brombutylester, esters of monocarboxymethyl ethers, esters of glycerin, or esters of trimethylpropane and/or when  $R_4$  can be described according to Formula (2C), each  $R_6$ , the same or different, can be derived from one or more of polytetramethylenoxidediol, polyethylenoxidediol, polycaprolactonediol,

polyethyleneglycoladipatediol, polydiethylenglycoladipatediol, toluylene diisocyanate, diphenylmethane, hexamethylene diisocyanate, tetramethylene diisocyanate, naphthylene diisocyanate, glycerin monoallylether, trimethylolpropane monallylether, glycerin monoglycidylether, ethyl-2,6-diisocyanatohexanoate (LDI),  
5 dimethylolpropionic acid methylester, dimethylolpropionic acid brombutylester, esters of monocarboxymethyl ethers, esters of glycerin, or esters of trimethylpropane.

27. The linear block polymer according to any one of claims 19 to 26, wherein said  
10 linear block polymer has a molecular weight of at least  $2 \times 10^4$  Dalton.

28. Use of a compound according to any one of claims 1 to 11 during preparation of linear block polymers.

15 29. Use of the linear block polymer according to any one of claims 19 to 27 as material in implants for humans and animals.

30. Use of a linear block polymer according to any one of claims 19 to 27 for pharmaceutical preparations, during microencapsulation, in suspensions or in  
20 emulsions.

31. Use of the linear block polymer according to any one of claims 19 to 27 as material for promoting wound healing in humans and animals.

25 32. Implants for humans and animals, wherein said implants comprise a linear block polymer according to any one of claims 19 to 27.

33. Pharmaceutical preparations, microencapsules, suspensions or emulsions that comprise a linear block polymer according to any one of claims 19 to 27.

30 34. Material for promoting wound healing in humans and animals, which material comprises a linear block polymer according to any one of claims 19 to 27.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/02904

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 219/06, C07C 229/10, C07C 229/08, C08G 18/10, C08G 18/32, A61L 27/00  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C, C08G, A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, CHEM.ABS.DATA

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	GB 1251718 A (ALLIED CHEMICAL CORPORATION), 27 October 1971 (27.10.71) --	1-13
A	US 3567763 A (WILLIAM D. EMMONS), 2 March 1971 (02.03.71) --	1-13
A	WO 0045869 A1 (ARTIMPLANT AB), 10 August 2000 (10.08.00) --	14-34

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&amp;" document member of the same patent family

Date of the actual completion of the international search

11 April 2002

Date of mailing of the international search report

15-04-2002

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## INTERNATIONAL SEARCH REPORT

International application No.

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## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 6221997 B1 (WOODHOUSE ET AL), 24 April 2001 (24.04.01)  --	14-34
A	US 5236966 A (GRAHAM ET AL), 17 August 1993 (17.08.93)  --	14-34
A	US 4689353 A (HARRIS), 25 August 1987 (25.08.87)  --	14-28
A	US 4049632 A (MAGNUSSON ET AL), 20 Sept 1977 (20.09.77)  -- -----	14-28

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International application No.

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Information on patent family members

28/01/02

International application No.

PCT/SE 01/02904

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