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Synthesis of novel polymerizable molecules bearing bisphosphonate

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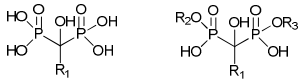
S. Kachbi Khelfallah,[a] M. Monteil,[a] J. Deschamp,[a] O. Gager,[a] E. Migianu-Griffoni[a] and M. Lecouvey*[a]

In recent years, bisphosphonates chemistry has taken an exponential growth due to the potential applications of these compounds in medicine and nanobiomaterial research. In this paper we describe the synthetic methods of different families of methacrylic monomers bearing a bisphosphonate with varying lengths of chain, PEG linkers and more or less hydrolysable functions such as ester, carbamate or amide.

Introduction

Among the organic derivatives of phosphorus, the phosphonic acids occupy a prominent position. For many decades, there has been significant interest in the preparation and investigation of phosphonic acids and their derivatives. [1] At the beginning, phosphonic acids were considered as analogues of natural phosphate and can be incorporated into a lot of molecules which are involved in numerous biological functions.[2] The substitution of the oxygen atom of phosphate by a carbon atom in phosphonate rendered the latter chemically stable and resistant to enzymatic hydrolysis. The strong structural relationship to natural compounds, together with high stability and low toxicity, allowed their possible activity as antimetabolites, enzymatic inhibitors and cellular receptor inhibitors.[3] Since the late 1970s, phosphonic acids were also used for the surface modification of material.[4] It has been shown that these phosphorylated compounds react with a wide range of metal salts or oxides to lead metal organic frameworks or metal phosphonates. Later, with the nanotechnology development, phosphonic acids were used to functionalize the surface of metals or oxides. They present some advantages compared to other ligands because the PO-metal bond is robust and stable. Moreover, the phosphonic acid group is compatible with other functional groups allowing further organic reactions. In recent years, the development and exploitation of highly functional hybrid materials have been applied in areas as diverse as biomedical field, catalysis or optoelectronic.[5]

In our laboratory we are focused on a particular family of phosphorylated derivatives called bisphosphonates (Fig. 1).



A B

Figure 1 General structures of BPs (**A**) or esterified BPs (**B**).

Bisphosphonates (BPs) are currently the most widely used treatment of common skeletal disorders. They are used as inhibitors of bone resorption, in particular osteoporosis, solid tumor bone metastases and myeloma bone disease.[6] Most BPs contain a hydroxyl group on their P-C-P structure that confers high affinity binding to calcium phosphate (hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) and is the basis for the bone-targeting properties of BPs.[7, 8]

BPs also exhibit direct and indirect antitumor effects *in vitro* against a broad variety of tumor cell lines, including melanoma, mesothelioma, prostate, breast, lung and myeloma cancer cells. [9-11] However, the major drawback of these drugs is their poor bioavailability: only 7% of the administered dose reaches the target. This is mainly due to their rapid elimination from the blood circulation due to their charged nature and their preferential accumulation in bone. To enhance the antitumor activity of BPs, various strategies have been considered such as the use of BP prodrugs.[12]) We have demonstrated that partly esterified BPs (Fig.1) display antitumor growth and antiangiogenic activities on A431 tumors and MDA-MB-231 tumors being more effective *in vivo* than *in vitro*.[13, 14] Esterified BPs act like prodrug molecules being hydrolysed by cellular or serum environment containing phosphoesterase enzymes, leading to the release of the tetraacid active molecule.[15] These BP analogues possess a lower affinity for bone mineral because the chelating power for Ca^{2+} ions decreases with the number of phosphonic esters on the molecule.[16] In order to increase the pharmacological properties of BPs, several drug delivery systems can be used, like liposomes[17] or nanoparticles.[18] BPs can be attached to the inorganic phase by the formation of strong M–O–P bonds

[a] *Université Paris 13, Sorbonne Paris Cité, Laboratoire de Chimie, Structure, Propriétés de Biomatériaux et d'Agents Thérapeutiques (CSPBAT), CNRS UMR 7244, F-93017 Bobigny, France. E-mail : marc.lecouvey@univ-paris13.fr*

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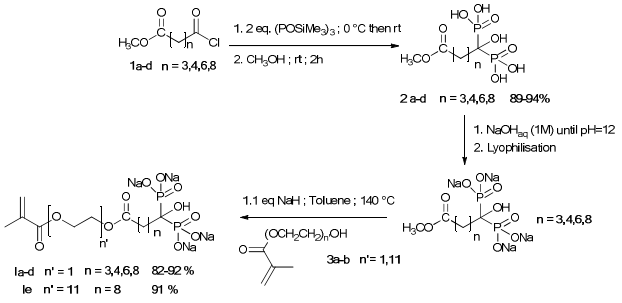
through heterocondensation and coordination.[5] Surface functionalization of γFe_2O_3 nanocrystals with HMBP–$(CH_2)_3$–COOH has been described. We demonstrated the potential of this hybrid nanomaterial, which has no cytotoxicity, as an MRI contrast agent.[19] More recently, we developed new macromolecular produgs to increase the pharmacokinetic properties of BPs. We have shown that the use of modified polysaccharides such as dextran modify the biodistribution of BPs. Thanks to EPR effect, the concentration of macromolecular prodrug has been increased and after release of the drug in the tumor site, a significate reduction of tumor growth has been observed after four weeks of treatment.[20]

For this study we selected an acrylic synthetic polymer to design the novel conjugates with BPs. The low toxicity of acrylic polymers allows these high molecular mass substances to be widely used in various fields of pharmacy[21] and their high bioadhesive properties offers good prospects for using these polymers in controlled drug delivery systems for local application.[22] Two strategies can be used. The first is the incorporation of BPs onto reactive side chains of polymers. Unfortunately, the amount of BPs incorporated is quite limited. To avoid such limitation, a second strategy has been developed using a versatile BP-based monomer, as recently demonstrated by Schrader and co-workers.[23] To our knowledge, few studies relate directly to the synthesis of these bifunctional hydroxymethylene bisphosphonates (HMBPs) monomers.[24] Therefore, we designed different new bifunctional monomers bearing a methacrylate and HMBP function linked by carbon chain or/and PEG spacer with different labile links (ester, carbamate, amide). We report herein the synthesis of five novel families of monomers.

Results and discussion

Synthesis of acrylic ester bisphosphonates via an ester bond Ia-e

The first family of acrylic derivatives **I** that we designed possess two ester functions, the first one between the methacrylic acid and one hydroxyl function of PEG and the second between a BP bearing a carboxylic acid on the side chain and the second free PEG alcohol. Four steps were necessary to obtain this first family and allowed to synthesize a monomer with two labile functions and various biocompatible chain lengths (Scheme 1).



Scheme 1 Synthesis of acrylic ester bisphosphonates **Ia-e**.

The first step of this strategy is to introduce HMBP. The standard procedure using the mixture PCl_3/H_3PO_3 followed by an aqueous hydrolysis is not compatible with the presence of ester group on the side chain. These drastic conditions do not allow the use of fragile substrates and the obtaining of functionalized HMBPs. As an alternative to this pathway our group proposed a very mild and one-pot synthesis of HMBPs from tris(trimethylsilyl) phosphite and acyl chlorides followed by a methanolysis.[25] This method enables the access of various substituted hydroxymethylene bisphosphonic acids in a one-pot procedure under mild conditions. Moreover, reaction times were shortened and purifications were easier. This reaction was successfully extended to anhydride, aliphatic and aromatic substrates in excellent yields.[26] Starting materials **1a–d** were commercially available with various chain lengths (n=3, 4, 6 and 8). The addition of two equivalents of tris(trimethylsilyl)-phosphite onto the acyl chloride derivatives **1a-d** at 0 °C led to corresponding silylated HMPBPs. The complete conversion of starting phosphite was monitored by ^{31}P NMR. The volatile by-products were then evaporated under vacuum and the silylated HMBPs were stirred in methanol at room temperature for two hours. After solvent evaporation, the crude products were washed several times with dry diethyl ether to remove residual phosphorous acid. HMBPs **2a-d** were obtained in excellent yields (Table 1, entries 1-4).

The compounds **2a-d** were then neutralized with aqueous sodium hydroxide solution until pH = 12 and lyophilized. The acrylic ester BPs **Ia-e** were obtained via a transesterification reaction between methacrylic PEG alcohol **3a-b** deprotonated by sodium hydride and HMPB **2a-d** salts. The reaction was carried out in toluene at 140 °C using a Dean-Stark apparatus. The transesterification was monitored by ^{31}P NMR and a peak around 19 ppm was observed. After addition of water, the solution was extracted by chloroform and the aqueous layer was lyophilized. ^{31}P and ^{1}H NMR analysis showed that pure products were obtained as white solids in good yields (Table 1, entries 5-9). Our methodology is very effective to introduce as well short PEG chain (Table 1, entries 5-8) as long PEG chain (Table 1, entries 9) allowing variations of linker length.

Table 1 Synthesis of acrylic ester bisphosphonates **Ia-e**

Entry		n	n'	Time (h)	Yield (%)	^{31}P δ (ppm)
1	**2a**	3	-	0.5	94	18.20
2	**2b**	4	-	0.5	90	19.50
3	**2c**	6	-	1	89	18.90
4	**2d**	8	-	1	91	19.75
5	**Ia**	3	1	2	84	18.78
6	**Ib**	4	1	2	82	18.85
7	**Ic**	6	1	3	86	19.28
8	**Id**	8	1	3	92	18.88
9	**Ie**	8	11	3	91	18.81

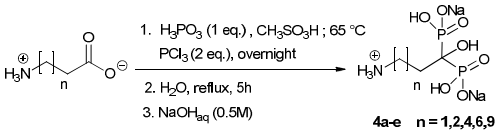
Synthesis of acrylic ester bisphosphonates via a carbamate bond If-g

To synthesise the second type of acrylic ester BPs via a carbamate bond, we had to prepare several aminoalkylBPs with variable chain lengths. For that, a large-scale one-step procedure reported by Kieczykowski *et al.* was used.[27] After neutralization until pH = 4 and precipitation, aminoalkylBPs were obtained very pure in satisfying yields (Table 2).

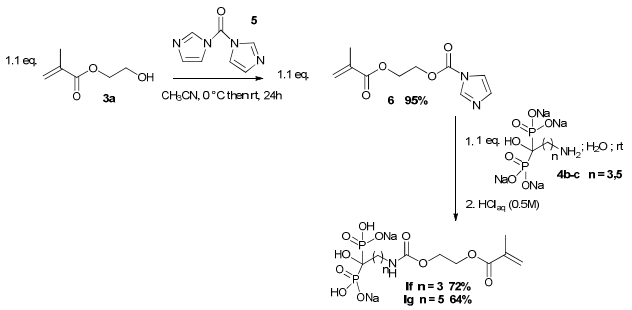
The second type of monomers was synthesized in two steps according to Scheme 2. AminoalkylBPs **4** were coupled to methacrylic derivative **3a** carrying a PEG unit via a carbamate linkage. This type of bonding more sensitive to pH, is selected in order to compare the kinetics of release of the drug. We previously described a one-pot method allowing the coupling reaction between an unprotected aminoalkylBP and an alcohol modified first by carbonyldiimidazole.[28] This method was applied for the synthesis of acrylic ester BPs **If-g.** After changing the free alcohol of **3a** by *N,N*-carbonyldiimidazole **5** (CDI), the carbamate **6** reacted with amine group of BPs **4b-c** by nucleophilic substitution under basic conditions (pH = 12). The reaction was monitored by ^{31}P NMR.

The chemical shift of the coupling product was slightly deshielded (0.2 ppm) from the starting aminoalkyl-BP. After a chloroform extraction to remove all unreacted organic substances, compounds **If-g** were precipitated in a mixture of diethyl ether and acetone. The crude products were also purified by column chromatography on reversed phase silica C18 (eluent: water/methanol 95/5). After lyophilization, the monomers **If-g** were obtained in good yields.

Table 2 Synthesis of aminobisphosphonates **4a-e**



Entry	Compound	n	Yield (%)	^{31}P δ (ppm)
1	**4a**	1	71	17.65
2	**4b**	2	91	18.58
3	**4c**	4	89	19.18
4	**4d**	6	88	19.25
5	**4e**	9	78	19.23

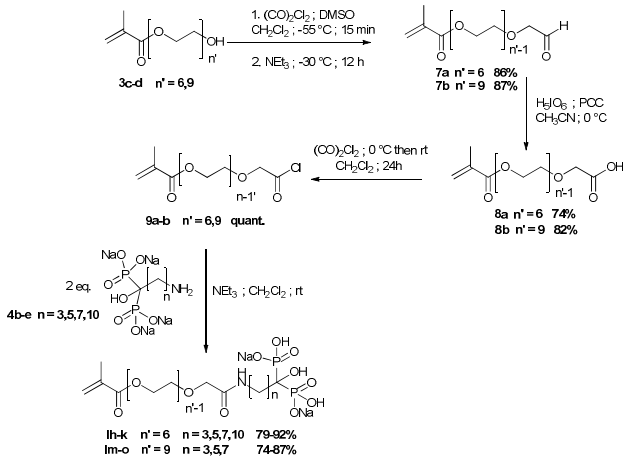


Scheme 2 Synthesis of acrylic ester bisphosphonates **If-g**.

Synthesis of acrylic ester bisphosphonates via an amide bond Ih-k and Im-o

The third type of acrylic ester bisphosphonates presents an amide bond between PEG acrylic derivatives and aminoalkylbisphosphonates. The introduction of aminoalkyl-BP moiety can only be done after oxidation of the primary alcohol function of PEG. Starting materials **3c-d** were commercially available. Several direct oxidation tests were carried out using conventional reagents such as Jones reagent (CrO_3/H_2SO_4) or potassium permanganate. A partial oxidation was obtained with the presence of several secondary products. To obtain carboxylic acids **8a-b**, we proceeded an oxidation in two steps (Scheme 3).

Alcohols **3c-d** were oxidized to aldehydes in the Swern conditions. The corresponding products **7a-b** were isolated in respectively 86 and 87 % yield. The second step was to oxidize the aldehyde into carboxylic acid. An easy and quantitative preparation of carboxylic acids by pyridinium chlorochromate (PCC) in catalytic amount (2 mol %) using 2.2 equivalents of aldehyde and 1.1 equivalents of periodic acid (H_5IO_6) in acetonitrile was used. The carboxylic acids **8a-b** were then obtained in 74 and 82% yield. They were then quantitatively converted into the acyl chlorides **9a-b** in presence of oxalyl chloride at room temperature for 24 hours. The difficulty for the last coupling step was the solubility of the reactants. Indeed, the BP is soluble in water and the acrylic derivative is soluble in organic solvents and has a low stability in aqueous media. We choose to couple the deprotected BP and methacrylic acyl chloride in an organic solvent. The aminoalkylBPs **4a-e** were first basified to pH = 12 and lyophilized. Acyl chloride **9a-b** reacted with aminoalkylBPs **4a-e** in the presence of triethylamine in dichloromethane under argon. The coupling reaction takes place in heterogeneous phase. The evolution of the reaction was monitored by ^{31}P NMR.



Scheme 3 Synthesis of acrylic ester bisphosphonates **Ih-k** and **Im-o**.

Table 3 Synthesis of acrylic ester bisphosphonates **Ih-k** and **Im-o**

Entry		n	n'	Time (h)	Yield (%)	^{31}P δ (ppm)
1	**Ih**	3	6	36	91	18.03
2	**Ii**	5	6	48	92	18.38
3	**Ij**	7	6	48	84	18.77
4	**Ik**	10	6	72	79	18.72
5	**Im**	3	9	48	87	17.86
6	**In**	5	9	72	82	18.46
7	**Io**	7	9	72	74	18.64

As shown in Table 3, coupling reaction was very effective whatever the nature of BPs and acyl chlorides. In all examples, acrylic ester BPs via an amide bond were synthesized in good yields. However, the kinetic of the reaction depended on the nature of the reactants. Their lipophilicity increased significantly time of reaction. This methodology allowed us to obtain another type of monomers with a more robust amide bond but hydrolysable *in vivo*.

Synthesis of acrylic ester bisphosphonates via a methyl ether bond Ip-q

The last type of acrylic ester BPs that we designed have an acrylic ester moiety, a PEG linker and a BP grafted via a non-hydrolysable methylether bond. These compounds do not allow the drug release but can be used for surface functionalization of metals or oxides to obtain surface modified hybrid materials. The presence of free methacrylic ester enables further functionalization via a Michael reaction. Those ligands may find application in biomedical field.

To prepare these new monomers, we used the procedure previously described for the synthesis of HMBP **2.** The addition of two equivalents of tris(trimethylsilyl) phosphite onto the acyl chloride derivatives **9a-b** at 0 °C led to corresponding silylated HMBPs (Scheme 4). The complete conversion of starting phosphite was monitored by ^{31}P NMR. The methanolysis was carried out in the presence of triethylamine at room temperature for two hours. The triethylammonium cations were exchanged using cation-exchange resin DOWEX Na^+. After lyophilization, two new monomers **Ip** and **Iq** were isolated in 83 and 81% yield respectively.

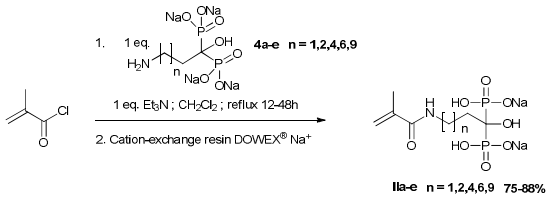
Synthesis of methacrylamide bisphosphonates IIa-e

The last family of acrylic monomers that we designed presents methacrylic structure directly linked to aminoalkyl-BPs via an amide bond. These monomers will be useful to study the influence of linker on drug release. Besides, they could represent a new generation of ligands for the passivation of nanoparticles. To perform the amidification reaction, the same procedure developed for the synthesis of **Ih-k** was used (Scheme 5). As before, the same synthesis difficulties have been encountered, particularly the solubility of the reactants. Methacrylic acyl chloride being totally hydrolyzed in water, the coupling reaction was done in organic solvent in heterogeneous phase. Due to the stability of the reactants, the temperature could be increased improving the solubility and a coupling reaction more efficient. Moreover the solubility of BP should be increased with the length of carbon side chain. The aminoalkylBPs **4a-e** were first basified to pH = 12 and lyophilized. Methacrylic acyl chloride freshly distilled reacted with aminoalkyl-BPs **4a-e** in the presence of triethylamine in dichloromethane under argon. The heterogeneous solution was then heated under reflux. The evolution of the reaction was monitored by ^{31}P NMR and by the Kaiser test.

Several extractions in acid and basic medium by dichloromethane were necessary to purify monomers **IIa-e.** Finally, they were obtained after several cation-exchanges with Na^+ DOWEX resin followed by a lyophilisation. As shown in Table 4, the efficiency of the procedure was not affected by the nature of the aminoalkylBP. In all cases, methacrylamide BPs **II** were prepared pure in excellent yields**.** Longest times were observed for long chain BPs except for the compound **IIa** (entry 1). In this case, the amino group is less nucleophile due to the proximity of withdrawing groups such as hydroxyl and phosphonate functions.

Conclusions

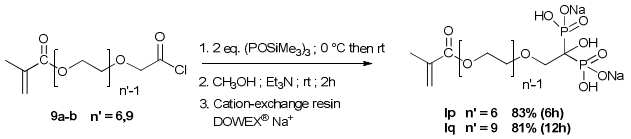
In this work, we have described efficient procedures to synthesize different families of methacrylic monomers bearing a BP. We designed these derivatives with varying lengths of chain, PEG linkers and more or less hydrolysable functions such as ester, carbamate or amide.



Scheme 5 Synthesis of acrylamide bisphosphonates **IIa-e**.

Table 4 Synthesis of acrylamide bisphosphonates **IIa-e**

Entry		n	Time (h)	Yield (%)	^{31}P δ (ppm)
1	**IIa**	1	36	75	18.04
2	**IIb**	2	12	86	19.37
3	**IIc**	4	16	91	18.59
4	**IId**	6	24	78	19.79
5	**IIe**	9	36	88	19.14



Scheme 4 Synthesis of acrylic ester bisphosphonates **Ip-q**.

These compounds may have numerous applications in biomedical fields. Copolymerization with HPMA could lead to new polymeric biocompatible delivery system of BPs. First tests of polymerization using RAFT technique yielded copolymers bearing BP with a narrow size distribution and controlled molecular weight. These monomers or copolymers could be used for the coating of nanoparticles improving their stability and their biocompatibility.

Experimental

General

Reagents were purchased from common commercial suppliers (Alfa-Aesar, Acros Organics, Sigma-Aldrich) and used without prior purification, unless otherwise stated. Solvents were extra-dried grade or distilled over drying agents.

Aminoalkylbisphosphonates **4a-e** are known compounds and were prepared according to literature procedures.[27, 29, 30]

Column chromatographies in a reverse phase were performed using Polygoprep 60-130 C18 phase (Macherey-Nagel).

NMR spectra were recorded on a Bruker AVANCE III 400 MHz spectrometer. ^{1}H and ^{13}C spectra were calibrated on non-deuterated solvent residual peak ($CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR; D_2O: 4.79 ppm for ^{1}H NMR). H_3PO_4 (85 % in water) was used as an external standard for ^{31}P NMR. Chemical shifts (δ) and coupling constants (*J*) were expressed in ppm and Hz respectively. NMR multiplicities were abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, m = multiplet, br = broad signal. All ^{31}P spectra were realised with ^{1}H decoupling.

Infrared spectra were recorded on a Thermo Electron Corporation Nicolet 380 FT-IR spectrometer between 4000 and 500 cm^{-1} (16 scans, resolution = 1 to 2 cm^{-1}). The samples were analyzed as KBr pellets for solids and as films placed between two pieces of KBr for oils.

High resolution mass spectroscopy spectra were acquired using a WATERS Micromass Q-tof spectrometer in positive mode (ES+).

Melting points were determined using a Stuart SMP3 melting point apparatus version 5.0 and were given in Celsius degrees (°C).

Synthesis of acrylic ester bisphosphonates via an ester bond Ia-e

General procedure for the synthesis of carboxylate alkylbisphosphonates 2a-d. In a flame-dried 50 mL three-necked flask under argon equipped with a thermometer and a dropping funnel was introduced the adequate commercial acyl chloride **1a-d** (5 mmol, 1 eq.). Then, tris(trimethylsilyl) phosphite (2.98 g, 10 mmol, 2 eq.) was added dropwise at 0 °C. Once the addition was completed, the reaction mixture was stirred at room temperature and the progress of the reaction was then monitored by ^{31}P NMR. The reaction times depended on the carbon chain length. Volatile fractions were then evaporated under reduced pressure (10^{-2} mbar) and the resulting oil was hydrolysed in methanol at room temperature for 2 hours. The pure products **2a-d** were obtained after solvent evaporation without furthermore purification.

*(1-Hydroxy-5-methoxy-5-oxopentane-1,1-diyl) diphosphonic acid (**2a**).* The compound was isolated as a colorless oil; yield: 94%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 18.20; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 3.54 (3H, s), 2.26 (2H, q, $^{3}J_{H,H}$ = 7.2 Hz), 2.03 - 1.68 (4H, m); νmax/cm^{-1} 3240 (OH), 1732 (C=O), 1180 (P=O), 982 (P-O); HRMS (EI): *m/z* calcd. for $C_6H_{14}O_9P_2$ $[M+H]^+$: 293.0113; found: 293.0119.

*(1-Hydroxy-6-methoxy-6-oxohexane-1,1-diyl) diphosphonic acid (**2b**).* The compound was isolated as a colorless oil; yield: 90%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 19.50; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 3.65 (3H, s), 2.39 (2H, t, $^{3}J_{H,H}$ = 8.0 Hz), 2.02 - 1.93 (2H, m), 1.67 - 1.51 (4H, m); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 177.3, 73.1 (t, $^{1}J_{P,C}$ = 146.9 Hz), 52.0, 33.4, 33.1, 24.8, 22.6 (t, $^{2}J_{P,C}$ = 6.3 Hz); νmax/cm^{-1} 3194 (OH), 1734 (C=O), 1250 (P=O), 1122 (P-O), 939 (P-O); HRMS (EI): *m/z* calcd. for $C_7H_{16}O_9P_2$ $[M+H]^+$: 307.0269; found: 307.0261.

*(1-Hydroxy-8-methoxy-8-oxooctane-1,1-diyl) diphosphonic acid (**2c**).* The compound was isolated as a colorless oil; yield: 89%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 18.90; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 3.55 (3H, s), 2.26 (2H, t, $^{3}J_{H,H}$ = 8.0 Hz), 1.91 - 1.80 (2H, m), 1.55 - 1.39 (4H, m), 1.55 - 1.29 (4H, m); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 177.3, 73.1 (t, $^{1}J_{P,C}$ = 147.5 Hz), 52.0, 33.3 (d, $^{2}J_{P,C}$ = 15.0 Hz), 33.1, 24.8, 22.6 (t, $^{3}J_{P,C}$ = 5.0 Hz); νmax/cm^{-1} 3374 (OH), 1731 (C=O), 1102 (P=O), 957 (P-O); HRMS (EI): *m/z* calcd. for $C_9H_{20}O_9P_2$ $[M+H]^+$: 335.0582; found: 335.0584.

*(1-Hydroxy-10-methoxy-10-oxodecane-1,1-diyl) diphosphonic acid (**2d**).* The compound was isolated as a colorless oil; yield: 91%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 19.75; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 3.58 (3H, s), 2.28 (2H, t, $^{3}J_{H,H}$ = 8.0 Hz), 1.95 - 1.83 (2H, m), 1.55 - 1.41 (4H, m), 1.28 - 1.12 (8H, m); νmax/cm^{-1} 3422 (OH), 1737 (C=O), 1107 (P=O), 958 (P-O); HRMS (EI): *m/z* calcd. for $C_{11}H_{24}O_9P_2$ $[M+H]^+$: 363.0895; found: 363.0891.

General procedure for the synthesis of acrylic ester bisphosphonates via an ester bond Ia-e. In a 100 mL single-necked flask equipped with a Dean-Stark apparatus were introduced 2-hydroxyethyl methacrylate **3a** or methacrylate-PEG **3b** (6 mmol, 1 eq.) and 40 mL of dry toluene. After addition of sodium hydride (0.024 g, 1 mmol, 1/6 eq.), the reaction was stirred for a few minutes at room temperature. Appropriate carboxylate alkylbisphosphonate **2a-d** previously adjusted to pH = 12 and lyophilized, was then added in small portions. Once the addition was complete, the reaction mixture was stirred at 140 °C and the evolution of the reaction was then monitored by ^{31}P NMR. The reaction was completed between 2 and 3 hours. After quenching the reaction with water and removal of solvent in vacuum, the resulting aqueous phase was washed 3 times with chloroform. The aqueous medium was evaporated under vacuum and lyophilised. The attended products **Ia-e** were obtained with sufficient purity and no further purification was necessary.

*Trisodium salt of (1-(hydrogenphosphonato)-1-hydroxy-5-(2-(methacryloyloxy)ethoxy)-5-oxopentyl)phosphonate (**Ia**).* The compound was isolated as a beige gum; yield: 84%; δ ^{31}P

NMR (162 MHz, D_2O, 25 °C) 18.78; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 5.60 (1H, bs), 5.28 (1H, bs), 3.59 (2H, bs), 2.03 - 2.01 (2H, m), 1.89 - 1.65 (3H, m); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 184.2, 177.5, 142.5, 120.3, 75.4 (t, $^1J_{P,C}$ = 134.4 Hz), 62.5, 38.6, 35.0, 21.4 (t, $^2J_{P,C}$ = 5.4 Hz), 18.9; νmax/cm^{-1} 3284 (OH), 1731 (C=O), 1613 (C=C), 1147 (P=O), 948 (P-O); HRMS (EI): *m/z* calcd. for $C_{11}H_{17}Na_3O_{11}P_2$ $[M+H]^+$: 456.9939; found: 456.9933.

*Trisodium salt of (1-(hydrogenphosphonato)-1-hydroxy-6-(2-(methacryloyloxy)ethoxy)-6-oxohexyl)phosphonate (**Ib**).* The compound was isolated as a brown solid; yield: 82%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 18.85; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 5.49 (1H, bs), 5.19 (1H, bs), 3.63 - 3.50 (4H, m), 2.28 (2H, t, $^3J_{H,H}$ = 7.0 Hz), 2.08 - 2.05 (4H, m), 1.84 - 1.57 (5H, m), 1.53 - 1.31 (4H, m); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 184.5, 177.5, 142.4, 120.2, 75.6 (t, $^1J_{P,C}$ = 132.0 Hz), 62.5, 37.8, 35.3, 27.2, 24.3 (t, $^2J_{P,C}$ = 6.2 Hz), 18.9; νmax/cm^{-1} 3194 (OH), 1733 (C=O), 1625 (C=C), 1150 (P=O), 968 (P-O); HRMS (EI): *m/z* calcd. for $C_{12}H_{19}Na_3O_{11}P_2$ $[M+H]^+$: 471.0095; found: 471.0096; mp: 290 °C.

*Trisodium salt of (1-(hydrogenphosphonato)-1-hydroxy-8-(2-(methacryloyloxy)ethoxy)-8-oxooctyl)phosphonate (**Ic**).* The compound was isolated as a brown solid; yield: 86%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 19.28; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 5.49 (1H, bs), 5.19 (1H, bs), 3.55 - 3.45 (4H, m), 2.03 (2H, t, $^3J_{H,H}$ = 7.4 Hz), 1.82 - 1.59 (5H, m), 1.48 - 1.26 (4H, m), 1.25 - 1.07 (4H, m); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 184.3, 177.5, 142.3, 120.3, 75.5 (t, $^1J_{P,C}$ = 129.5 Hz), 62.5, 48.9, 37.6, 35.2, 27.2, 24.3 (t, $^2J_{P,C}$ = 6.1 Hz), 18.9; νmax/cm^{-1} 3387 (OH), 1735 (C=O), 1648 (C=C), 1107 (P=O), 958 (P-O); HRMS (EI): *m/z* calcd. for $C_{14}H_{23}Na_3O_{11}P_2$ $[M+H]^+$: 499.0408; found: 499.0405; mp: 283 °C.

*Trisodium salt of (1-(hydrogenphosphonato)-1-hydroxy-10-(2-(methacryloyloxy)ethoxy)-10-oxodecyl)phosphonate (**Id**).* The compound was isolated as a brown solid; yield: 92%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 18.88; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 5.68 (1H, bs), 5.38 (1H, bs), 3.74 - 3.60 (4H, m), 2.20 (2H, t, $^3J_{H,H}$ = 7.5 Hz), 1.91 (3H, s), 1.68 - 1.49 (2H, m), 1.41 - 1.21 (10H, m); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 184.4, 177.4, 142.3, 120.3, 76.7 (t, $^1J_{P,C}$ = 129.3 Hz), 62.5, 37.6, 36.2, 30.4, 29.0 - 28.4, 25.9, 24.3 (t, $^2J_{P,C}$ = 6.3 Hz), 18.9; νmax/cm^{-1} 3332 (OH), 1736 (C=O), 1571 (C=C), 1103 (P=O), 968 (P-O); HRMS (EI): *m/z* calcd. for $C_{16}H_{27}Na_3O_{11}P_2$ $[M+H]^+$: 527.0721; found: 527.0726; mp: 314° C.

*Trisodium salt of (47-hydroxy-2-methyl-3,38-dioxo-4,7,10,-13,16,19,22,25,28,31,34,37-dodecaoxaheptatetracont-1-ene-47,47-diyl) bis(hydrogenphosphonate) (**Ie**).* The compound was isolated as a brown solid; yield: 91%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 18.81; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 5.68 (1H, bs), 5.37 (1H, bs), 3.83 - 3.62 (44H, m), 2.20 (2H, t, $^3J_{H,H}$ = 7.5 Hz), 1.90 (3H, s), 1.64 - 1.50 (4H, m), 1.42 - 1.24 (8H, m); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 184.3, 171.1, 142.4, 120.3, 71.8 (t, $^1J_{P,C}$ = 131.1 Hz), 69.8 - 69.2, 37.7, 36.3, 30.5, 29.1 - 28.4, 25.9, 24.4 (t, $^2J_{P,C}$ =7.1 Hz), 18.8; νmax/cm^{-1} 3235 (OH), 1726 (C=O), 1629 (C=C), 1113 (P=O), 988 (P-O); HRMS (EI): *m/z* calcd. for $C_{36}H_{67}Na_3O_{21}P_2$ $[M+H]^+$: 967.3343; found: 967.3347; mp: 320 °C.

Synthesis of acrylic ester bisphosphonates via a carbamate bond If-g

Synthesis of 2-(methacryloyloxy)ethyl 1*H*-imidazole-1-carboxylate 6. In a flame-dried and argon flushed 250 mL four-necked flask equipped with a mechanical stirrer, a thermometer, an argon inlet and an addition funnel were introduced carbonyldiimidazole (1.83 g, 11 mmol, 1.1 eq.) and 150 mL of freshly distilled acetonitrile. After stirring at room temperature for 1 hour, a solution of the commercial 2-hydroxyethyl methacrylate **3a** (1.3 g, 10 mmol, 1 eq.) in 50 mL of distilled acetonitrile was added dropwise at 0 °C. The resulting reaction mixture was next stirred at room temperature for 24 hours. After evaporation of the volatile fractions, 50 mL of ethyl acetate were added and the organic layer was washed with water (3 x 15 mL), brine (1 x 15 mL), dried over sodium sulfate, filtered and vacuum evaporated. The compound **6** was isolated pure as a yellow oil; yield: 95%; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 8.10 (1H, dd, $^4J_{H,H}$ = 0.9 Hz), 7.30 (1H, dd, $^3J_{H,H}$ = 2.0 Hz, $^4J_{H,H}$ = 1.4 Hz), 6.93 (1H, dd, $^3J_{H,H}$ = 1.6 Hz, $^4J_{H,H}$ = 0.8 Hz), 6.17 - 6.02 (1H, m), 5.50 – 5.46 (1H, m), 4.59 - 4.50 (2H, m), 4.40 - 4.34 (2H, m), 1.80 (3H, dd, $^4J_{H,H}$ = 1.4 Hz); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 166.8, 148.4, 137.1, 135.6, 130.7, 126.5, 117.1, 65.8, 61.6, 18.2; νmax/cm^{-1} 1708 (C=O), 1637 (C=C), 1263 (C=N), 1088 (C-O); HRMS (EI): *m/z* calcd. for $C_{10}H_{12}N_2O_4$ $[M+H]^+$: 225.0797; found: 225.0793.

General procedure for the synthesis of acrylic ester bisphosphonates via a carbamate bond If-g. In a 10 mL flask, the aminobisphosphonate derivative, previously adjusted to pH = 12 and lyophilised, (alendronate **4b** or neridronate **4c**) (1 mmol, 1 eq.) was dissolved in water (2 mL). The imidazole-carboxylate **6** (0.25 g, 1.1 mmol, 1.1 eq.) was then added dropwise and the pH was checked and adjusted to pH = 12 with aqueous 1M sodium hydroxide solution. The evolution of the reaction was monitored by ^{31}P NMR and an excess of compound **6** was added if necessary. When the reaction was complete, the reaction mixture was washed 3 times with chloroform at pH = 4.5. The aqueous phase was concentrated under vacuum and the crude product was precipitated several times in acetone in order to remove the residual imidazole. Purification was performed using a column chromatography in a reverse phase (C_{18} resin) with a mixture water/methanol 95/5 as eluent.

*Disodium salt of (1-hydroxy-4-(((2-(methacryloyloxy)-ethoxy)carbonyl)amino)butane-1,1-diyl) bis(hydrogenphosphonate) (**If**).* The compound was isolated as a colorless oil; yield: 72%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 18.69; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 5.48 (1H, bs), 5.17 (1H, bs), 3.96 (2H, t,$^3J_{H,H}$ = 4.0 Hz), 3.60 (2H, t, $^3J_{H,H}$ = 4.0 Hz), 2.98 (2H, t, $^3J_{H,H}$ = 6.4 Hz), 1.91 - 1.54 (7H, m); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 167.6, 156.5, 139.9, 123.2, 74.3 (t, $^1J_{P,C}$ = 137.7 Hz), 60.4, 42.2, 24.6, 23.9 - 23.6, 17.1; νmax/cm^{-1} 3150 (NH), 1708 (C=O), 1648 (C=O), 1234 (P=O), 1152 (P=O), 965 (P-O); HRMS (EI): *m/z* calcd. for $C_{11}H_{19}NNa_2O_{11}P_2$ $[M+H]^+$: 450.0228; found: 450.0225.

Disodium salt of (1-hydroxy-6-(((2-(methacryloyloxy)-ethoxy)carbonyl)amino)hexane-1,1-diyl) bis(hydrogenphospho-

*nate) (**Ig**).* The compound was isolated as a colorless oil; yield: 64%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 18.75; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 5.53 – 5.49 (1H, m), 5.22 – 5.18 (1H, m), 3.99 (2H, t, $^{3}J_{H,H}$ = 4.0 Hz), 3.62 (2H, t, $^{3}J_{H,H}$ = 8.0 Hz), 2.99 (2H, t, $^{3}J_{H,H}$ = 8.0 Hz), 1.80 - 1.73 (5H, m), 1.44 - 1.36 (4H, m), 1.28 - 1.18 (2H, m); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 169.5, 158.2, 135.1, 127.1, 74.3 (t, $^{1}J_{P,C}$ = 134.3 Hz), 62.5, 40.4, 33.9, 28.6, 26.9, 26.3, 23.4, 17.3; νmax/cm^{-1} 3408 (NH), 1711 (C=O), 1702 (C=O), 1254 (P=O), 1139 (P=O), 962 (P-O); HRMS (EI): *m/z* calcd. for $C_{13}H_{23}NNa_2O_{11}P_2$ $[M+H]^+$: 478.0541; found: 478.0547.

Synthesis of acrylic ester bisphosphonates via an amide bond Ih-k and Im-o

General procedure for the synthesis of aldehydes 7. In a dry and argon flushed 100 mL four-necked flask, equipped with a mechanical stirrer, a thermometer, an argon inlet and a septum, a solution of DMSO (1.7 g, 21.8 mmol, 2.18 eq.) in 4.5 mL of dichloromethane was added dropwise at -55 °C to a solution of oxalyl chloride (2.16 g, 17.2 mmol, 1.72 eq.) in 22.5 mL of dichloromethane. After two minutes, a solution of methacrylic alcohol **3c-d** (10 mmol, 1 eq.) in 10 mL of dichloromethane was added dropwise. After stirring for 15 minutes, the mixture was allowed to warm to -30 °C. Then, freshly distilled triethylamine was added dropwise (5.1 g, 50.4 mmol, 5.04 eq.). After 12 hours at room temperature, the mixture was quenched with 20 mL of water. The aqueous phase was extracted twice with 20 mL of dichloromethane. The combined organic phases were washed successively with aqueous solution of hydrochloric acid (20 % v/v) and aqueous solution of sodium bicarbonate (5 % w/w), dried over sulfate magnesium and concentrated in vacuo to furnish expected aldehydes **7** sufficiently pure to be used without furthermore purification.

*17-Oxo-3,6,9,12,15-pentaoxaheptadecyl methacrylate (**7a**).* The compound was isolated as a brown oil; yield: 86%; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 9.59 (1H, s), 6.00 (1H, bs), 5.45 (1H, bs), 5.22 (2H, s), 4.27 – 3.93 (2H, m), 3.71 - 3.34 (18H, m), 1.81 (3H, bs); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 201.1, 166.9, 136.0, 125.6, 76.7, 71.4 - 69.8, 68.9, 63.7, 18.2; νmax/cm^{-1} 2878 (CHO), 1718 (C=O), 1651 (C=C), 1170 (C-O); HRMS (EI): *m/z* calcd. for $C_{16}H_{28}O_8$ $[M+H]^+$: 349.1784; found: 349.1788.

26-Oxo-3,6,9,12,15,18,21,24-octaoxahexacosyl methacrylate (***7b***). The compound was isolated as a brown oil; yield: 87%; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 9.56 (1H, s), 6.07 (1H, bs), 5.52 (1H, bs), 4.24 (t, $^{3}J_{H,H}$ = 8.0 Hz), 4.11 (2H, s), 3.77 - 3.32 (30H, m), 1.88 (3H, s); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 201.0, 167.4, 136.1, 125.8, 71.2, 70.8 - 70.4, 69.1, 63.9, 18.3; νmax/cm^{-1} 2875 (CHO), 1728 (C=O), 1647 (C=C), 1114 (C-O); HRMS (EI): *m/z* calcd. for $C_{22}H_{40}O_{11}$ $[M+H]^+$: 481.2570; found: 481.2576.

General procedure for the synthesis of carboxylic acids 8. In a three-necked 500 mL flask, equipped with a dropping funnel and a thermometer, were introduced 257.5 mL of dry acetonitrile and periodic acid H_5IO_6 (8.07 g, 35.4 mmol, 1.1 eq.). The resulting mixture was stirred at room temperature for 15 minutes. Then, a solution of the adequate aldehyde **7a-b** (32.2 mmol, 1 eq.) in 30 mL of dry acetonitrile was added dropwise at 0 °C, followed by dropwise addition of a solution of pyridinium chlorochromate PCC (0.14 g, 0.65 mmol, 0.02 eq.) in 30 mL of dry acetonitrile. The reaction evolution was monitored by TLC (eluent: dichloromethane/ethanol 95/5). When the reaction was complete, 70 mL of ethyl acetate were added to the mixture and the resulting solution was washed successively with aqueous saturated sodium chloride solution, aqueous saturated sodium bisulfite solution and aqueous saturated sodium chloride solution again. The organic layer was dried over magnesium sulfate and evaporated under vacuum to give pure carboxylic acids **8** without furthermore purification.

*20-Methyl-19-oxo-3,6,9,12,15,18-hexaoxahenicos-20-en-1-oic acid (**8a**).* The compound was isolated as a brown oil; yield: 74%; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 6.06 (1H, bs), 5.52 (1H, bs), 4.28 - 4.18 (2H, m), 4.11 – 4.07 (2H, m), 3.75 – 3.50 (20H, m), 1.87 (3H, s); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 172.7, 167.4, 136.1, 125.9, 71.2 - 69.2, 69.0, 63.9, 18.3; νmax/cm^{-1} 3105 (OH), 1736 (C=O), 1723 (C=O), 1654 (C=C), 1242 (C-O); HRMS (EI): *m/z* calcd. for $C_{16}H_{28}O_9$ $[M+H]^+$: 365.1733; found: 365.1735.

*29-Methyl-28-oxo-3,6,9,12,15,18,21,24,27-nonaoxatriacont-29-en-1-oic acid (**8b**).* The compound was isolated as a brown oil; yield: 82%; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 6.01 (1H, bs), 5.47 (1H, bs), 4.19 - 4.17 (2H, m), 4.04 (2H, bs), 3.63 - 3.36 (30H, m), 1.83 (3H, s); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 172.1, 167.2, 136.0, 125.7, 71.9 - 69.0, 68.4, 63.8, 18.2; νmax/cm^{-1} 3072 (OH), 1738 (C=O), 1645 (C=C), 1219 (C-O); HRMS (EI): *m/z* calcd. for $C_{22}H_{40}O_{12}$ $[M+H]^+$: 497.2519; found: 497.2513.

General procedure for the synthesis of acyl chlorides 9. In a flame-dried 100 mL three-necked flask equipped with an argon inlet and a dropping funnel were introduced the appropriate carboxylic acid **8a-b** (1 mmol, 1 eq.) and 25 mL of freshly distilled dichloromethane. The flask was placed in ice bath (0 °C) and a solution of oxalyl chloride (0.63 g, 5 mmol, 5 eq.) in 10 mL of distilled dichloromethane was added dropwise. The reaction mixture was then stirred at room temperature during 24 hours. After slow evaporation under reduced pressure (10^{-2} mbar), the crude product was washed twice with 5 mL of dry dichloromethane then twice with 5 mL of dry diethyl ether. The obtained compound was in the end dried under vacuum (10^{-2} mbar) for a few minutes to lead to acyl chloride **9a-b** used in the next step without purification.

*17-Chloro-17-oxo-3,6,9,12,15-pentaoxaheptadecyl methacrylate (**9a**).* The compound was isolated as a brown oil; yield: quantitative; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 6.09 (1H, bs), 5.54 (1H, bs), 4.49 (2H, bs), 4.25 (2H, t, $^{3}J_{H,H}$ = 8.0 Hz), 3.82 - 3.52 (18H, m), 1.92 (3H, s); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 172.2, 167.5, 136.2, 125.8, 76.6, 71.4 - 70.1, 63.7, 18.4; νmax/cm^{-1} 1806 (C=O), 1718 (C=O), 1635 (C=C), 1168 (C-O), 749 (C-Cl); HRMS (EI): *m/z* calcd. for $C_{16}H_{27}ClO_8$ $[M+H]^+$: 383.1394; found: 383.1392.

*26-Chloro-26-oxo-3,6,9,12,15,18,21,24-octaoxahexacosyl methacrylate (**9b**).* The compound was isolated as a brown oil; yield: quantitative; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 6.12 (1H,

bs), 5.57 (1H, bs), 4.47 (2H, bs), 4.29 (2H, t, $^3J_{H,H}$ = 8.0 Hz), 3.78 - 3.51 (30H, m), 1.94 (3H, s); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 172.1, 167.3, 136.2, 125.7, 76.4, 71.3 - 69.1, 63.9, 18.3; νmax/cm^{-1} 1804 (C=O), 1716 (C=O), 1638 (C=C), 1171 (C-O), 741 (C-Cl); HRMS (EI): *m/z* calcd. for $C_{22}H_{39}ClO_{11}$ $[M+H]^+$: 515.2180; found: 515.2183.

General procedure for the synthesis of acrylic ester bisphosphonates via an amide bond Ih-k and Im-o. In a flame-dried and argon flushed 100 mL four-necked flask, equipped with a mechanical stirrer, a thermometer, an argon inlet and a septum were introduced the acyl chloride **9a** or **9b** (3 mmol, 1.2 eq.) and dry dichloromethane (25 mL). Then, freshly distilled triethylamine (0.5 g, 5 mmol, 2 eq.) was added and the resulting reaction mixture was stirred for a few minutes at room temperature. The appropriate aminobisphosphonate **4b-e** (2.5 mmol, 1 eq.) was next added per portion and the mixture was stirred at room temperature. After full disappearance of the starting bisphosphonate (monitored by ^{31}P NMR), the reaction was quenched with water and the solution was concentrated under vacuum. The excess of triethylamine and acyl chloride derivative were removed successively from the aqueous layer at pH = 12 and 4.5 respectively, by washing with chloroform (3 x 20 mL) and diethyl ether (3 x 20 mL). Expected product was obtained as a disodium salt after multiple passes through a cation-exchange resin using DOWEX® Na^+ form.

*Disodium salt of (26-hydroxy-2-methyl-3,21-dioxo-4,7,10,13,16,19-hexaoxa-22-azahexacos-1-ene-26,26-diyl) bis-(hydrogenphosphonate) (**Ih**).* The compound was isolated as a beige solid; yield: 91%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 18.03; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 6.04 (1H, bs), 5.62 (1H, bs), 4.95 (1H, bs), 4.23 (2H, t, $^4J_{H,H}$ = 4.0 Hz), 3.82 (2H, bs), 3.72 (2H, t, $^4J_{H,H}$ = 4.0 Hz), 3.66 - 3.52 (14H, m), 2.93 (2H, t, $^3J_{H,H}$ = 5.9 Hz), 1.88 – 1.84 (4H, m), 1.82 (3H, s); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 177.9, 169.7, 135.7, 126.9, 73.5 (t, $^1J_{P,C}$ = 133.4 Hz), 69.7 - 69.3, 68.5, 64.1, 62.1, 52.2, 40.0, 30.9, 22.4 (t, $^2J_{P,C}$ = 7.0 Hz), 17.4; νmax/cm^{-1} 3040 (NH), 1722 (C=O), 1656 (C=C), 1180 (P=O), 1050 (P-O), 934 (P-O); HRMS (EI): *m/z* calcd. for $C_{20}H_{37}NNa_2O_{15}P_2$ $[M+H]^+$: 640.1433; found: 640.1435; mp: 198°C.

*Disodium salt of (28-hydroxy-2-methyl-3,21-dioxo-4,7,10,-13,16,19-hexaoxa-22-azaoctacos-1-ene-28,28-diyl) bis(hydro-genphosphonate) (**Ii**).* The compound was isolated as a brown solid; yield: 92%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 18.38; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 6.04 (1H, bs), 5.61 (1H, bs), 4.22 (2H, t, $^4J_{H,H}$ = 4.0 Hz), 3.82 (2H, bs), 3.71 (2H, t, $^4J_{H,H}$ = 4.0 Hz), 3.64 - 3.51 (16H, m), 2.90 (2H, t, $^3J_{H,H}$ = 7.3 Hz), 1.81 - 1.72 (5H, m), 1.63 - 1.44 (4H, m), 1.59 (2H, qt, $^3J_{H,H}$ = 7.5 Hz), 1.29 (2H, qt, $^3J_{H,H}$ = 8.0 Hz); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 177.9, 169.7, 135.6, 127.0, 74.3 (t, $^1J_{P,C}$ = 134.4 Hz), 69.7 - 64.1, 39.2, 33.6, 30.2, 26.2 (d, $^2J_{P,C}$ = 16.1 Hz), 23.0 (t, $^3J_{P,C}$ = 6.3 Hz), 17.3; νmax/cm^{-1} 3434 (NH), 1719 (C=O), 1651 (C=C), 1172 (P=O), 1109 (P-O), 953 (P-O); HRMS (EI): *m/z* calcd. for $C_{22}H_{41}NNa_2O_{15}P_2$ $[M+H]^+$: 668.1746; found: 668.1742; mp: 217°C.

*Disodium salt of (30-hydroxy-2-methyl-3,21-dioxo-4,7,10,13,16,19-hexaoxa-22-azatriacont-1-ene-30,30-diyl) bis-(hydrogenphosphonate) (**Ij**).* The compound was isolated as a beige solid; yield: 84%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 18.77; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 6.05 (1H, bs), 5.63 (1H, bs), 4.95 (1H, bs), 4.23 (2H, t, $^4J_{H,H}$ = 4.0 Hz), 3.96 - 3.55 (20H, m), 2.89 (2H, t, $^3J_{H,H}$ = 7.2 Hz), 1.90 - 1.72 (5H, m), 1.62 - 1.50 (2H, m), 1.49 - 1.39 (2H, m), 1.38 - 1.22 (6H, m); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 177.9, 169.6, 135.7, 126.9, 74.4 (t, $^1J_{P,C}$ = 129.2 Hz), 70.3 – 69.1, 68.5, 64.1, 62.1, 52.3, 39.4, 33.9, 29.2, 27.8, 26.5, 25.2, 23.5 (t, $^2J_{P,C}$ = 6.6 Hz), 17.3; νmax/cm^{-1} 3384 (NH), 1715 (C=O), 1657 (C=C), 1200 (P=O), 1089 (P-O), 929 (P-O); HRMS (EI): *m/z* calcd. for $C_{24}H_{45}NNa_2O_{15}P_2$ $[M+H]^+$: 696.2059; found: 696.2054; mp: 269°C.

*Disodium salt of (33-hydroxy-2-methyl-3,21-dioxo-4,7,10,13,16,19-hexaoxa-22-azatritriacont-1-ene-33,33-diyl) bis (hydrogenphosphonate) (**Ik**).* The compound was isolated as a beige solid; yield: 79%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 18.72; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 6.02 (1H, bs), 5.59 (1H, bs), 4.92 (1H, bs), 4.20 (2H, t, $^3J_{H,H}$ = 7.2 Hz), 3.80 (2H, bs), 3.70 (2H, t, $^3J_{H,H}$ = 7.2 Hz), 3.60 - 3.50 (20H, m), 2.78 (2H, t, $^3J_{H,H}$ = 7.3 Hz), 1.82 - 1.71 (5H, m), 1.54 - 1.32 (4H, m), 1.24 - 1.09 (12H, m); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 177.9, 169.7, 135.7, 125.9, 74.10 (t, $^1J_{P,C}$ = 131.2 Hz), 69.4 - 68.2, 64.2, 62.2, 39.4, 33.7, 29.0, 28.4 - 25.4, 24.0, 23.4 (t, $^2J_{P,C}$ = 6.7 Hz), 17.4; νmax/cm^{-1} 3448 (NH), 1716 (C=O), 1657 (C=C), 1233 (P=O), 1108 (P-O), 950 (P-O); HRMS (EI): *m/z* calcd. for $C_{27}H_{51}NNa_2O_{15}P_2$ $[M+H]^+$: 738.2529; found: 738.2521; mp: 207°C.

*Disodium salt of (35-hydroxy-2-methyl-3,30-dioxo-4,7,10,13,16,19,22,25,28-nonaoxa-31-azapentatriacont-1-ene-35,35-diyl) bis(hydrogenphosphonate) (**Im**).* The compound was isolated as a brown solid; yield: 87%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 17.86; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 6.02 (1H, bs), 5.60 (1H, bs), 4.93 (1H, bs), 4.21 (2H, t, $^4J_{H,H}$ = 4.0 Hz), 3.80 (2H, bs), 3.70 (2H, t, $^4J_{H,H}$ = 4.0 Hz), 3.64 - 3.46 (26H, m), 2. 95 – 2.86 (6H, m), 1.89 - 1.77 (7H, m); νmax/cm^{-1} 3334 (NH), 1721 (C=O), 1636 (C=C), 1238 (P=O), 1111 (P-O), 935 (P-O); HRMS (EI): *m/z* calcd. for $C_{26}H_{49}NNa_2O_{18}P_2$ $[M+H]^+$: 772.2220; found: 772.2227; mp: 209°C.

*Disodium salt of (37-hydroxy-2-methyl-3,30-dioxo-4,7,10,-13,16,19,22,25,28-nonaoxa-31-azaheptatriacont-1-ene-37,37-diyl) bis(hydrogenphosphonate) (**In**).* The compound was isolated as a brown solid; yield: 82%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 18.46; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 6.12 (1H, bs), 5.69 (1H, bs), 4.90 (1H, bs), 4.30 (2H, t, $^4J_{H,H}$ = 4.0 Hz), 3.90 (2H, bs), 3.80 (2H, t, $^4J_{H,H}$ = 4.0 Hz), 3.76 - 3.53 (34H, m), 2.98 (2H, t, $^3J_{H,H}$ = 7.3 Hz), 1.93 – 1.79 (4H, m), 1.67 (2H, qt, $^3J_{H,H}$ = 8.0 Hz), 1.62 – 1.51 (2H, m), 1.37 (2H, qt, $^3J_{H,H}$ = 8.0 Hz); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 177.8, 169.7, 135.4, 126.9, 74.4 (t, $^1J_{P,C}$ = 133.2 Hz), 70.0 – 69.1, 68.5, 64.1, 60.3, 39.3, 33.5, 30.2, 26.2 (d, $^3J_{P,C}$ = 16 Hz), 23.0 (t, $^2J_{P,C}$ = 6.3 Hz), 17.3; νmax/cm^{-1} 3401 (NH), 1711 (C=O), 1633 (C=O), 1230 (P=O), 1113 (P-O), 946 (P-O); HRMS (EI): *m/z* calcd. for $C_{28}H_{53}NNa_2O_{18}P_2$ $[M+H]^+$: 800.2533; found: 800.2538; mp: 286 °C.

*Disodium salt of (39-hydroxy-2-methyl-3,30-dioxo-4,7,10,-13,16,19,22,25,28-nonaoxa-31-azanonatriacont-1-ene-39,39-diyl) bis(hydrogenphosphonate) (**Io**).* The compound was isolated as a dark brown solid; yield: 74%; δ ^{31}P NMR (162

MHz, D_2O, 25 °C) 18.64; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 6.13 (1H, bs), 5.70 (1H, bs), 5.03 (1H, bs), 4.31 (2H, t, $^4J_{H,H}$ = 4.0 Hz), 3.91 (2H, bs), 3.81 (2H, t, $^4J_{H,H}$ = 4.0 Hz), 3.77 - 3.58 (36H, m), 2.98 (2H, t, $^3J_{H,H}$ = 7.3 Hz), 1.96 - 1.78 (6H, m), 1.68 - 1.58 (2H, m), 1.58 – 1.44 (2H, m), 1.43 – 1.31 (2H, m); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 177.9, 173.4, 169.6, 135.7, 126.9, 74.3 (t, $^1J_{P,C}$ = 129.2 Hz), 69.7 - 69.4, 68.5, 64.1, 52.1, 39.4, 33.8, 29.2, 27.7, 26.4, 25.1, 23.4 (t, $^2J_{P,C}$ = 5.3 Hz), 17.3; νmax/cm^{-1} 3376 (NH), 1715 (C=O), 1637 (C=O), 1235 (P=O), 1108 (P-O), 954 (P-O); HRMS (EI): *m/z* calcd. for $C_{30}H_{57}NNa_2O_{18}P_2$ $[M+H]^+$: 828.2846; found: 828.2842; mp: 290°C.

Synthesis of acrylic ester bisphosphonates via an ether bond Ip-q

General procedure. In a flame-dried 25 mL three-necked flask under argon equipped with a thermometer and a dropping funnel was introduced the acyl chloride (5 mmol, 1 eq.). Then, tris(trimethylsilyl) phosphite (2.98 g, 10 mmol, 2 eq.) was added dropwise at 0 °C. Once the addition is complete, the reaction mixture was stirred at room temperature and the progress of the reaction was monitored by ^{31}P NMR. The reaction was completed between 6 and 12 hours depending on the chain length. Volatile fractions were evaporated under reduced pressure (10^{-2} mbar) and the resulting oil was hydrolyzed in methanol in presence of triethylamine at room temperature for 4 hours. The crude product was precipitated in dry diethyl ether for several times. The excepted bisphosphonate **Ip** or **Iq** was obtained as a disodium salt after multiple passes through a cation-exchange resin using DOWEX® Na^+ form.

*Disodium salt of (1-hydroxy-20-methyl-19-oxo-3,6,9,12,15,-18-hexaoxahenicos-20-ene-1,1-diyl) bis(hydrogenphosphonate) (**Ip**).* The compound was isolated as a yellow solid; yield: 83%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 15.66; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 6.11 (1H, bs), 5.68 (1H, bs), 4.36 - 4.24 (2H, m), 3.99 - 3.55 (12H, m) 1.89 (3H, s); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 169.7, 135.7, 126.9, 73.2 (t, $^1J_{P,C}$ = 132.5 Hz), 69.9 - 69.2, 68.5, 64.1, 17.3; νmax/cm^{-1} 3415 (OH), 1719 (C=O), 1638 (C=C), 1127 (P=O), 950 (P-O); HRMS (EI): *m/z* calcd. for $C_{16}H_{30}Na_2O_{14}P_2$ $[M+H]^+$: 555.0906; found: 555.0901; mp: 208 °C.

*Disodium salt of (1-hydroxy-29-methyl-28-oxo-3,6,9,12,15,-18,21,24,27-nonaoxatriacont-29-ene-1,1-diyl) bis(hydrogen-phosphonate) (**Iq**).* The compound was isolated as a yellow solid; yield: 81%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 15.94; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 6.06 (1H, bs), 5.63 (1H, bs), 4.34 - 4.10 (2H, m), 3.89 - 3.48 (32H, m), 1.83 (3H, s); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 169.6, 135.8, 126.9, 73.4 (t, $^1J_{P,C}$ = 123.4 Hz), 70.3 - 68.7, 68.5, 64.1, 17.4; νmax/cm^{-1} 3428 (OH), 1722 (C=O), 1637 (C=C), 1113 (P=O), 955 (P-O); HRMS (EI): *m/z* calcd. for $C_{22}H_{42}Na_2O_{17}P_2$ $[M+H]^+$: 687.1692; found: 687.1697; mp: 231 °C.

Synthesis of acrylamide bisphosphonates IIa-e

General procedure. In a dry 100 mL three-necked flask equipped with an argon inlet, a thermometer and a condenser was introduced the freshly distilled acryloyl chloride (for compounds IIf-g) or methacryloyl chloride (for compounds IIa-e) (9 mmol, 2 eq.) and dry dichloromethane (25 mL). After addition of freshly distilled triethylamine (0.9 g, 9 mmol, 2 eq.), the reaction mixture was stirred for few minutes at room temperature. Then, the aminobisphosphonate 4a-e, previously adjusted to pH = 12 and lyophilised (4.5 mmol, 1 eq.) was added per portion and the reaction mixture was stirred firstly at room temperature for a few minutes and then refluxed (the reaction time depended on the length of the carbon chain). The end of the reaction was confirmed with ninhydrin test and ^{31}P NMR. After completion of the reaction, the mixture was quenched with water and concentrated in vacuo. The excess of triethylamine and acyl chloride derivative were removed successively from the aqueous layer at pH = 12 and 1.5 respectively, by washing with chloroform (3 x 20 mL) and diethyl ether (3 x 20 mL). Expected product was obtained as a disodium salt after multiple passes through a cation-exchange resin using DOWEX® Na^+ form.

*Disodium salt of (1-hydroxy-3-methacrylamidopropane-1,1-diyl) bis(hydrogenphosphonate) (**IIa**).* The compound was isolated as a yellow oil; yield: 75%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 18.04; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 5.72 (1H, bs), 5.45 (1H, bs), 3.56 (2H, t, $^3J_{H,H}$ = 6.8 Hz), 2.25 - 2.08 (2H, m), 1.93 (3H, s); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 171.6, 139.1, 121.2, 73.1 (t, $^1J_{P,C}$ = 136.1 Hz), 35.6 (t, $^2J_{P,C}$ = 7.8 Hz), 32.8, 17.7; νmax/cm^{-1} 3361 (NH), 1654 (C=O), 1619 (C=C), 1226 (P=O), 1145 (P-O), 1100 (P-O); HRMS (EI): *m/z* calcd. for $C_7H_{13}NNa_2O_8P_2$ $[M+H]^+$: 347.9911; found: 347.9918.

*Disodium salt of (1-hydroxy-4-methacrylamidobutane-1,1-diyl) bis(hydrogenphosphonate) (**IIb**).* The compound was isolated as a yellow oil; yield: 86%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 19.37; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 5.64 (1H, bs), 5.39 (1H, bs), 3.14 (2H, t, $^3J_{H,H}$ = 6.6 Hz), 1.97 - 1.61 (7H, m); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 171.9, 139.2, 121.0, 72.9 (t, $^1J_{P,C}$ = 136.1 Hz), 39.7, 30.8, 23.1 (t, $^2J_{P,C}$ = 7.8 Hz), 17.7; νmax/cm^{-1} 3359 (NH), 1657 (C=O), 1623 (C=C), 1173 (P=O), 1059 (P-O); HRMS (EI): *m/z* calcd. for $C_8H_{15}NNa_2O_8P_2$ $[M+H]^+$: 362.0068; found: 362.0064.

Disodium salt of (1-hydroxy-4-methacrylamidobutane-1,1-diyl) bis(hydrogenphosphonate) (**IIc**). The compound was isolated as a yellow oil; yield: 91%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 18.59; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 5.60 (1H, bs), 5.37 (1H, bs), 3.23 (2H, t, $^3J_{H,H}$ = 7.0 Hz), 1.96 - 1.83 (5H, m), 1.60 - 1.51 (4H, m), 1.38 - 1.24 (2H, m); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 172.0, 139.4, 120.6, 74.3 (t, $^1J_{P,C}$ = 133.9 Hz), 39.7, 33.7, 30.4, 27.0, 23.4 (t, $^2J_{P,C}$ = 6.3 Hz), 17.8; νmax/cm^{-1} 3374 (NH), 1655 (C=O), 1627 (C=C), 1172 (P=O), 1060 (P-O); HRMS (EI): *m/z* calcd. for $C_{10}H_{19}NNa_2O_8P_2$ $[M+H]^+$: 390.0381; found: 390.0388.

*Disodium salt of (1-hydroxy-8-methacrylamidooctane-1,1-diyl) bis(hydrogenphosphonate (**IId**).* The compound was isolated as a yellow solid; yield: 78%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 19.79; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 5.59 (1H, bs), 5.36 (1H, bs), 3.18 (2H, t, $^3J_{H,H}$ = 6.9 Hz), 2.01 - 1.81 (5H, m), 1.59 - 1.41 (4H, m), 1.34 – 1.18 (6H, m); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 171.9, 139.3, 120.5, 73.8 (t, $^1J_{P,C}$ = 135.4 Hz),

39.5, 33.5, 29.4, 28.2, 28.1, 25.9, 23.1 (t, $^{2}J_{P,C}$ = 6.1 Hz), 17.7; νmax/cm^{-1} 3273 (NH), 1652 (C=O), 1617 (C=C), 1116 (P=O), 966 (P-O); HRMS (EI): *m/z* calcd. for $C_{12}H_{23}NNa_2O_8P_2$ $[M+H]^+$: 418.0694; found: 418.0699; mp: 312 °C.

*Disodium salt of (1-hydroxy-11-methacrylamidoundecane-1,1-diyl) bis(hydrogenphosphonate) (**IIe**).* The compound was isolated as a yellow solid; yield: 88%; δ ^{31}P NMR (162 MHz, D_2O, 25 °C) 19.14; δ ^{1}H NMR (400 MHz, D_2O, 25 °C) 5.65 (1H, bs), 5.37 (1H, bs), 3.20 (2H, t, $^{3}J_{H,H}$ = 6.8 Hz), 1.98 - 1.82 (5H, m), 1.58 - 1.42 (4H, m), 1.34 - 1.17 (12H, m); δ ^{13}C NMR (101 MHz, D_2O, 25 °C) 171.9, 139.2, 120.7, 74.1 (t, $^{1}J_{P,C}$ = 134.4 Hz), 52.3, 39.6, 33.7, 29.8, 28.8 – 28.1, 26.7, 24.1, 23.5 (t, $^{2}J_{P,C}$ = 6.2 Hz), 17.7; νmax/cm^{-1} 3393 (NH), 1654 (C=O), 1621 (C=C), 1222 (P=O), 1176 (P-O), 1061 (P-O); HRMS (EI): *m/z* calcd. for $C_{15}H_{29}NNa_2O_8P_2$ $[M+H]^+$: 460.1163; found: 460.1168; mp: 298 °C (dec.).

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Notes and references

1. C. S. Demmer, N. Krogsgaard-Larsen and L. Bunch, *Chem. Rev.*, 2011, **111**, 7981-8006.
2. R. Engel, *Chem. Rev.*, 1977, **77**, 349-367.
3. D. F. Wiemer, *Tetrahedron*, 1997, **53**, 16609-16644.
4. C. Queffélec, M. Petit, P. Janvier, D. A. Knight and B. Bujoli, *Chem. Rev.*, 2012, **112**, 3777-3807.
5. J. Galezowska and E. Gumienna-Kontecka, *Coord. Chem. Rev.*, 2012, **256**, 105-124.
6. R. G. Russell, *Bone*, 2011, **49**, 2-19.
7. G. H. Nancollas, R. Tang, R. J. Phipps, Z. Henneman, S. Gulde, W. Wu, A. Mangood, R. G. Russell and F. H. Ebetino, *Bone*, 2006, **38**, 617-627.
8. R. G. Russell, N. B. Watts, F. H. Ebetino and M. J. Rogers, *Osteoporos. int* .2008, **19**, 733-759.
9. M. Gnant and P. Clezardin, *Cancer Treat. Rev.*, 2012, **38**, 407-415.
10. E. Guenin, D. Ledoux, O. Oudar, M. Lecouvey and M. Kraemer, *Anticancer Res.*, 2005, **25**, 1139-1145.
11. S. Muller, E. Migianu, M. Lecouvey, M. Kraemer and O. Oudar, *Anticancer Res.*, 2005, **25**, 2655-2660.
12. J. J. Vepsalainen, *Curr. Med. Chem.*, 2002, **9**, 1201-1208.
13. M. Abdelkarim, E. Guenin, O. Sainte-Catherine, N. Vintonenko, N. Peyri, G. Y. Perret, M. Crepin, A. M. Khatib, M. Lecouvey and M. Di Benedetto, *PloS one*, 2009, **4**, e4685.
14. D. Ledoux, Y. Hamma-Kourbali, M. Di Benedetto, A. Foucault-Bertaud, O. Oudar, O. Sainte-Catherine, M. Lecouvey and M. Kraemer, *Anti-cancer drugs*, 2006, **17**, 479-485.
15. M. Monteil, E. Migianu-Griffoni, O. Sainte-Catherine, M. Di Benedetto and M. Lecouvey, *Eur. J. Med. Chem.*, 2014, **77**, 56-64.
16. E. Puljula, P. Turhanen, J. Vepsalainen, M. Monteil, M. Lecouvey and J. Weisell, *ACS Med. Chem. Lett*. 2015, **6**, 397-401.
17. I. Chebbi, E. Migianu-Griffoni, O. Sainte-Catherine, M. Lecouvey and O. Seksek, *Int. J. Pharm.*, 2010, **383**, 116-122.
18. F. Benyettou, Y. Lalatonne, I. Chebbi, M. Di Benedetto, J. M. Serfaty, M. Lecouvey and L. Motte, *Phys. Chem. Chem. Phys.*, 2011, **13**, 10020-10027.
19. Y. Lalatonne, C. Paris, J. M. Serfaty, P. Weinmann, M. Lecouvey and L. Motte, *Chem. Commun.* , 2008, 2553-2555.
20. E. Migianu-Griffoni, I. Chebbi, S. Kachbi, M. Monteil, O. Sainte-Catherine, F. Chaubet, O. Oudar and M. Lecouvey, *Bioconjug. Chem.*, 2014, **25**, 224-230.
21. R. Haag and F. Kratz, *Angew. Chem. Int. Ed. Engl.*, 2006, **45**, 1198-1215.
22. J. Nicolas, S. Mura, D. Brambilla, N. Mackiewicz and P. Couvreur, *Chem. Soc. Rev.*, 2013, **42**, 1147-1235.
23. C. Renner, J. Piehler and T. Schrader, *J. Am. Chem. Soc.*, 2006, **128**, 620-628.
24. E. Gluz, D. M. Mizrahi and S. Margel, *Polymer*, 2013, **54**, 565-571.
25. M. Lecouvey, I. Mallard, T. Bailly, R. Burgada and Y. Leroux, *Tetrahedron Lett.*, 2001, **42**, 8475-8478.
26. E. Guenin, E. Degache, J. Liquier and M. Lecouvey, *Eur. J. Org. Chem.*, 2004, 2983-2987.
27. G. R. Kieczykowski, R. B. Jobson, D. G. Melillo, D. F. Reinhold, V. J. Grenda and I. Shinkai, *J. Org. Chem.*, 1995, **60**, 8310-8312.
28. M. Lecouvey and Y. Leroux, *Synth. Comm.*, 2000, **30**, 23-30.
29. H. Blum and K. Worms, *US4407761 A1*, 2003.
30. V. Patel, T. Chitturi and R. Thennati, *WO/2005/044831* 2005.