SUPPORTING INFORMATION

Fabrication of Hydrophilic Polymer Nanocontainers by Use of Supramolecular Templates

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General

All reactions were carried out in heat-gun-dried glassware under an argon atmosphere and were performed by using standard *Schlenk* techniques. ^{1}H NMR and ^{13}C NMR spectra were recorded on a *Bruker* DPX-300 (^{1}H: 300 MHz, ^{13}C: 75 MHz), a *Varian* Inova 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz), or *Varian* Unity plus 600 (^{1}H: 600 MHz, ^{13}C: 150 MHz). Chemical shifts δ in ppm are referenced to the solvent residual peak. Thin layer chromatography was carried out on *Merck* silica gel 60 F254 plates; detection by UV or dipping into a solution of $KMnO_4$ (1.5 g), $NaHCO_3$ (5.0 g) in H_2O (400 mL) followed by heating. Flash chromatography (FC) was carried out on *Merck* silica gel 60 (40 – 63 μm) at an argon pressure of 0-0.5 bar. IR spectra were recorded on a *Varian* 3100 FT-IR equipped with a MKII Golden Gate Single Reflection ATR unit. ESI-MS (m/z) and HRMS (m/z) were performed using a *Bruker* MicroTof and a *LTQ Orbitrap XL* (nanospray inlet, 1.1 KV, resolution: 30 000). Size exclusion chromatography (SEC) was carried out with degassed THF as eluent at a flow rate of 1.0 mL/min at rt on a system consisting of an HPLC Pump 64 (*Knauer*), a set of two PLgel 5 μm MIXED-C columns (300 × 7.5 mm, *Polymer Laboratories*) and a *Shodex* RI differential refractometer detector. Data were analyzed with *PSS* WinGPC Compact V.7.20 software (*Polymer Standards Service*) based on calibration curves built upon poly(methyl methacrylate) standards (*Polymer Laboratories* Poly(methyl methacrylate) Medium MW Calibration Kit M-M-10 to determine the molecular weight of polymers) with peak molecular weights ranging from 1 660 to 1 000 000 g/mol.

Materials and Methods

All chemicals were purchased from *Sigma Aldrich*, *Acros Organics*, *ABCR*, *VWR* or *TCI* and used as received unless otherwise stated. Free nitroxide **6** was prepared according to a previously reported procedure.[1] Benzene was freshly distilled from Na and CH_2Cl_2 was distilled from P_2O_5.

Preparation of CDV: Unilamellar bilayer vesicles of **CDV** were prepared by extrusion. In short, several milligrams of amphiphilic β-cyclodextrin in 1 ml of chloroform were dried by slow rotary evaporation to yield a thin film in a glass vial. Residual solvent was removed under high vacuum. 10 ml of aqueous buffer (20 mM HEPES, 0.15 M NaCl, pH 7.4) was

(1) Miele, S.; Nesvadba, P.; Studer, A. *Macromolecules* **2009**, *42*, 2419-2427.

added and stirred overnight. The resulting suspension was repeatedly passed through a polycarbonate membrane with 100 nm pore size in a Liposofast manual extruder.

Preparation of PSV: A 0.1 mM buffered solution of **CDV** was taken in a vial. 25 μM **Ad-PAA** (50% coverage of total β-CD cavities at the outward surface of vesicles) was added to the vesicle solution and incubated for 30 min. To this polymer decorated vesicle (**PDV**) solution 8 mM of EDCI (4 eq. of total –COOH groups at **PDV** surface, assuming 100% incorporation of **Ad-PAA** at the surface) was added to activate the carboxylic acids in PAA residues outside **PDV**. After 25 min, 2,2'-(ethylendioxy)bis(ethylamine) (0.5 mM, 0.25 equiv to the total carboxylic acid groups for 50% cross-linking) was added and the mixture was slowly stirred for 12 h. The byproducts were removed by dialysis (MWCO 6,000-10,000) against 20 mM HEPES (600 mL, pH 7.4, 150 mM NaCl) for 48 h.

Preparation of PC: 2% Triton X-100 was added to a solution of **PSV**. To remove the surfactant, dialysis was done (MWCO 6,000-10,000) for 3 days with changing the buffer in every 12 h.

Dynamic Light Scattering: DLS measurements were performed by using a *Malvern Nano-ZS instrument (Malvern Instruments)* with low-volume disposable cuvettes kept at 25 ^{o}C. Typical concentrations: **[CDV]** = 0.1 mM, **[Ad-PAA]** = 0.025 mM and **[C] =** 0.5 mM, [**EDCI**] = 8 mM in aqueous buffer (20 mM HEPES and 0.15M NaCl, pH 7.4).

Dye Encapsulation: A 20 mM solution of sulforhodamine B was prepared in buffer solution (20 mM HEPES, 90 mM NaCl, pH 7.2). **CDV** were obtained by the hydration of a film of amphiphiles with sulforhodamine B containing buffer solution. The total concentration of amphiphiles was 1 mM. **Ad-PAA** (250 μM) was added to the dye encapsulated vesicle solution. The dye encapsulated **PDV** solution (500 μL) was loaded onto a Sephadex G-50 size-exclusion column with buffer solution as eluent to separate the vesicles free dye. A fraction of around 2 mL was collected and filled up to 5 mL to end up with an amphiphile concentration of around 0.1 mM. For preparation of dye encapsulated **PSV**, cross-linking of the carboxylic acid groups was done with 2,2'-(ethylendioxy)bis(ethylamine) (5 mM) and EDCI (80 mM) before the gel filtration separation of the dye. The fluorescence spectrum of the fraction was measured using a *JASCO FP6500 Spectrofluorometer* at an excitation wavelength of 540 nm. A reference sample was prepared by the addition of 0.2% Triton X-100.

The percentage of leakage was calculated by using the following equation:

$$\% \text{ Leakage} = \frac{\left(\frac{F_t}{F_t^T} - \frac{F_0}{F_0^T}\right)}{\left(1 - \frac{F_0}{F_0^T}\right)} X\ 100$$

F_t = fluorescence intensity at time t, F_0= fluorescence intensity at time zero, F_t^T = fluorescence intensity at time t in presence of Triton X − 100 and F_0^T = maximum fluorescence intensity at time zero in presence of Triton X − 100.

Scanning Electron Microscopy

5 µL of the sample solution was casted on carbon coated Cu-grid and simultaneously on cleaned silicon wafer. Samples were kept on grid/wafer for 2 min for sedimentation. The samples were washed one time with double distilled water, and then the residual water was dried off completely by filter paper. The air-dried samples were rotary-coated with 2 nm of platinium/carbon (Pt/C) at an elevation angle of 65° (*BAF 300*, Balzers, Liechtenstein). For secondary electron (SE) imaging, an "in-lens" FESEM S-5000 (Hitachi Ltd., Japan) equipped by a *digital imaging scanning system DISS5* (*point electronic* GmbH, Germany) was used.

Additional Experiments

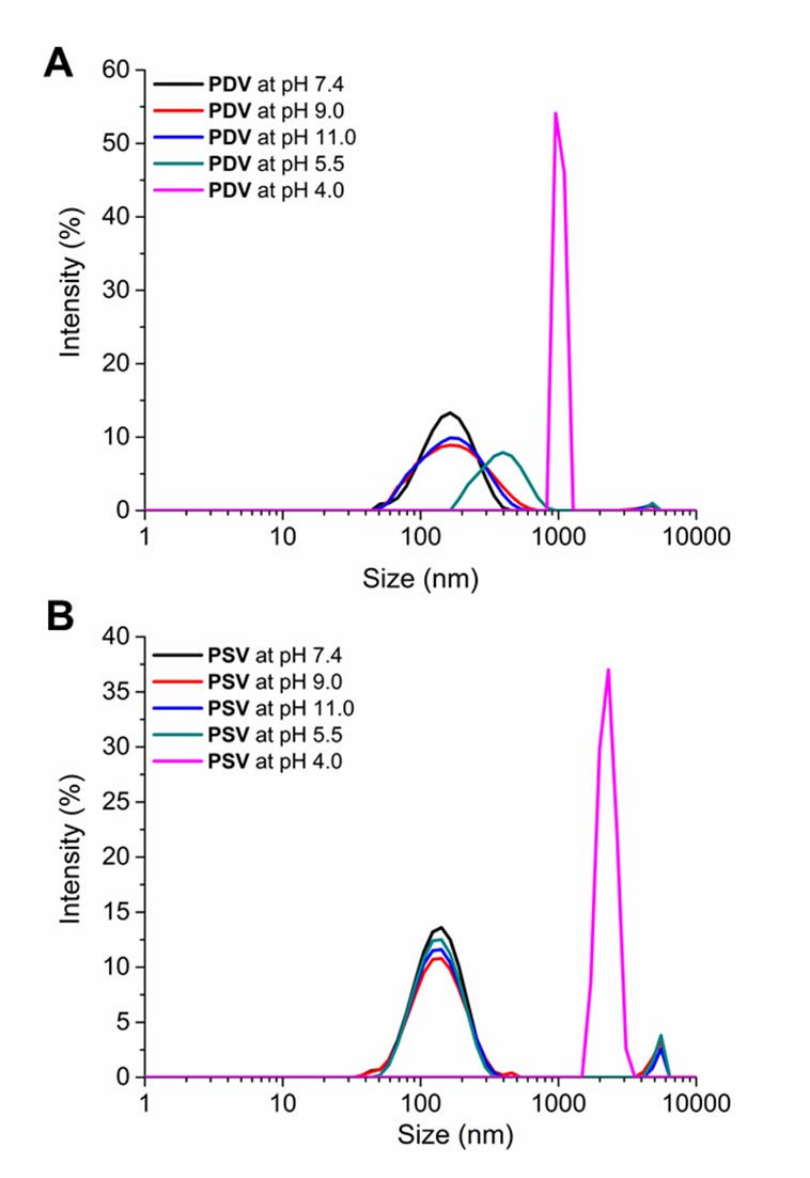


Fig. S1 A) Size distribution of **PDV** at different pH according to dynamic light scattering. B) Size distribution of **PSV** at different pH according to dynamic light scattering.

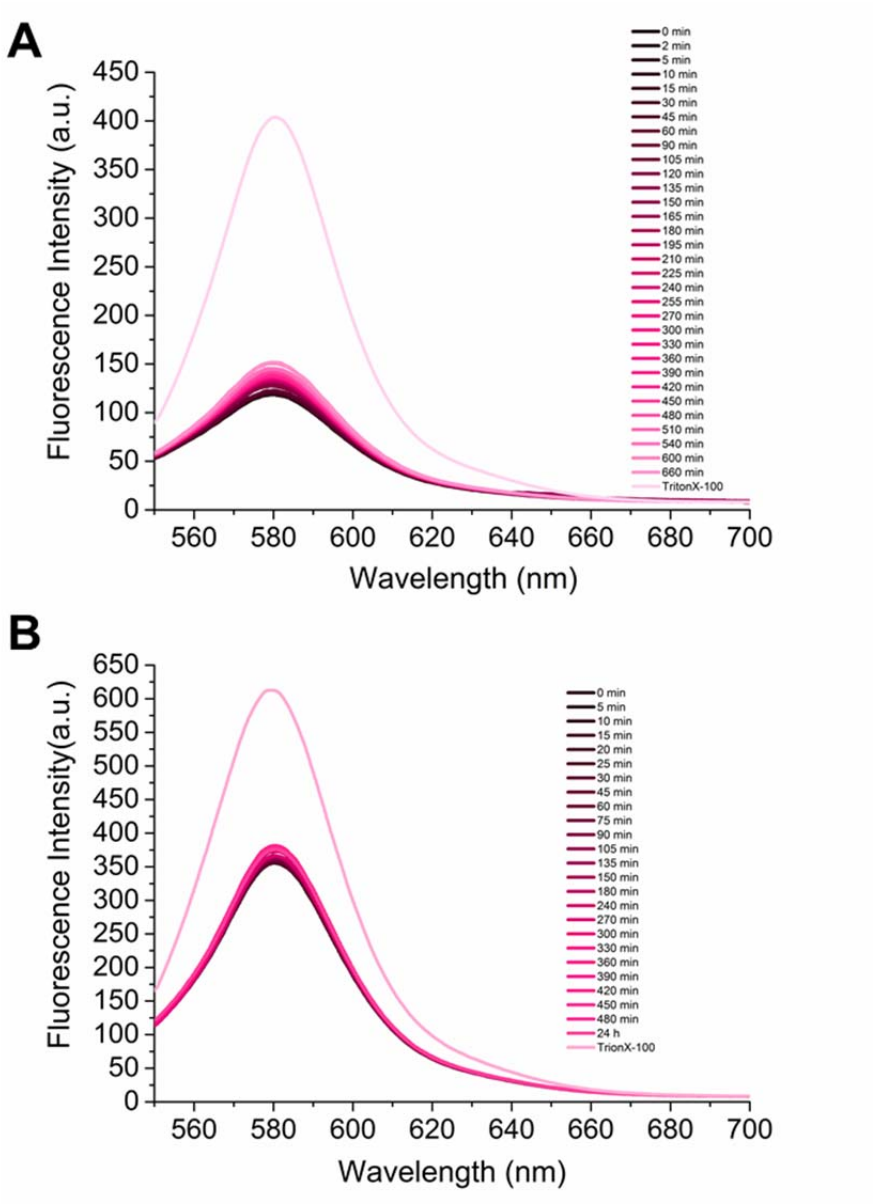


Fig. S2 Encapsulation of sulforhodamine in vesicles with **PDV** and **PSV**. All experiments were performed at room temperature. Fluorescence spectra collected after sephadex column at different times and finally after addition of 0.2% TritonX 100.

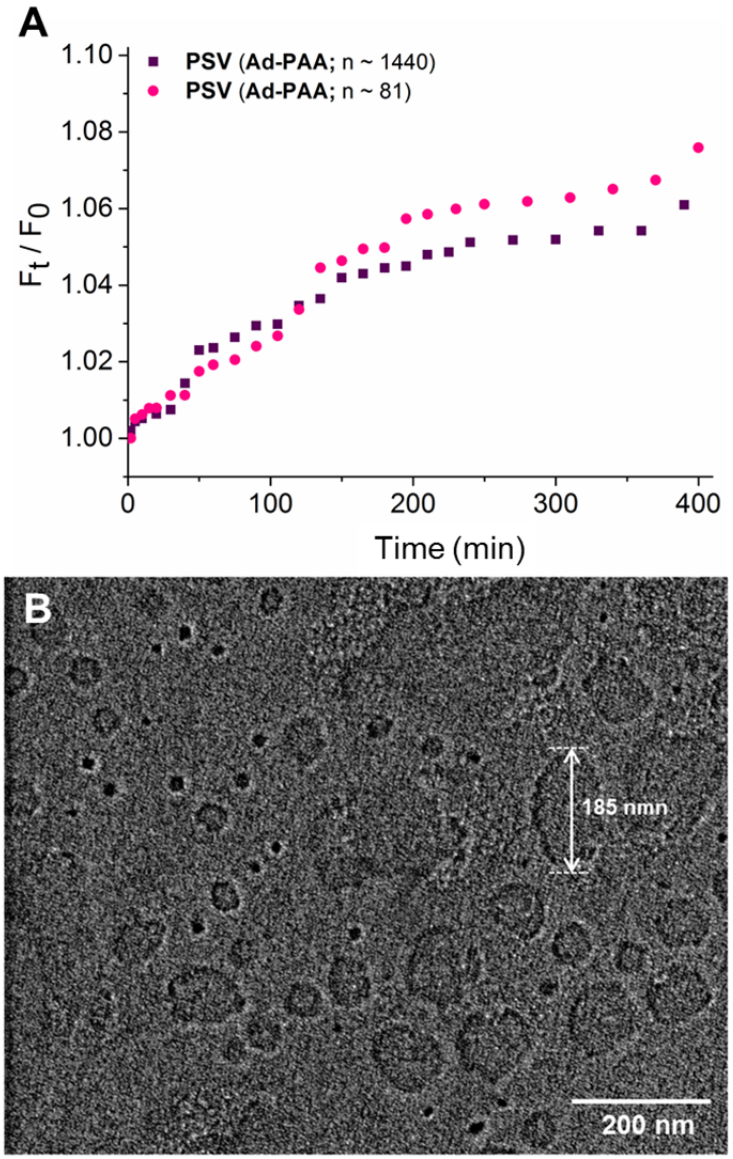


Fig. S3 A) Leakage of sulforhodamine B from **PSV** (**Ad-PAA**; n ~ 81) and **PSV** (**Ad-PAA**; n ~ 1440). Normalized fluorescence intensity F_t/F_0 plotted with time. B) FESEM image of **PC** (**AD-PAA**; n ~ 1440).

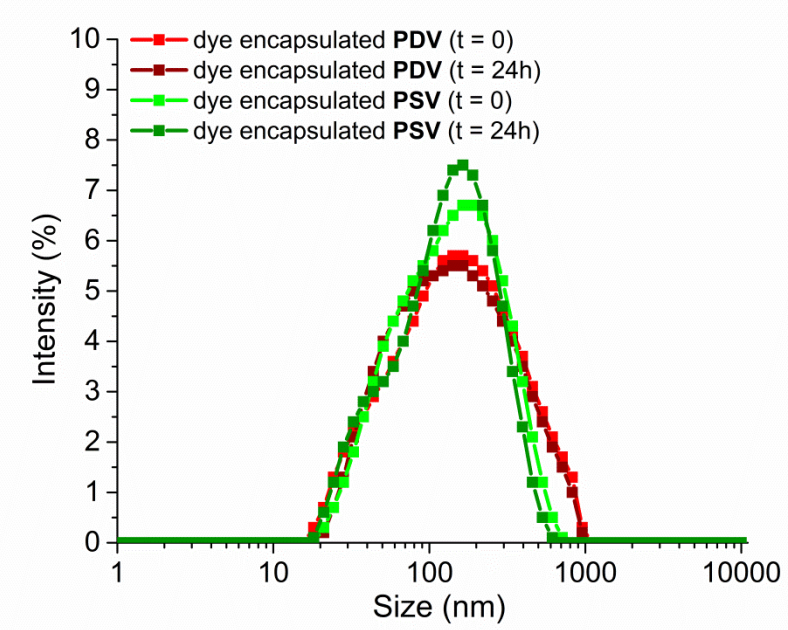
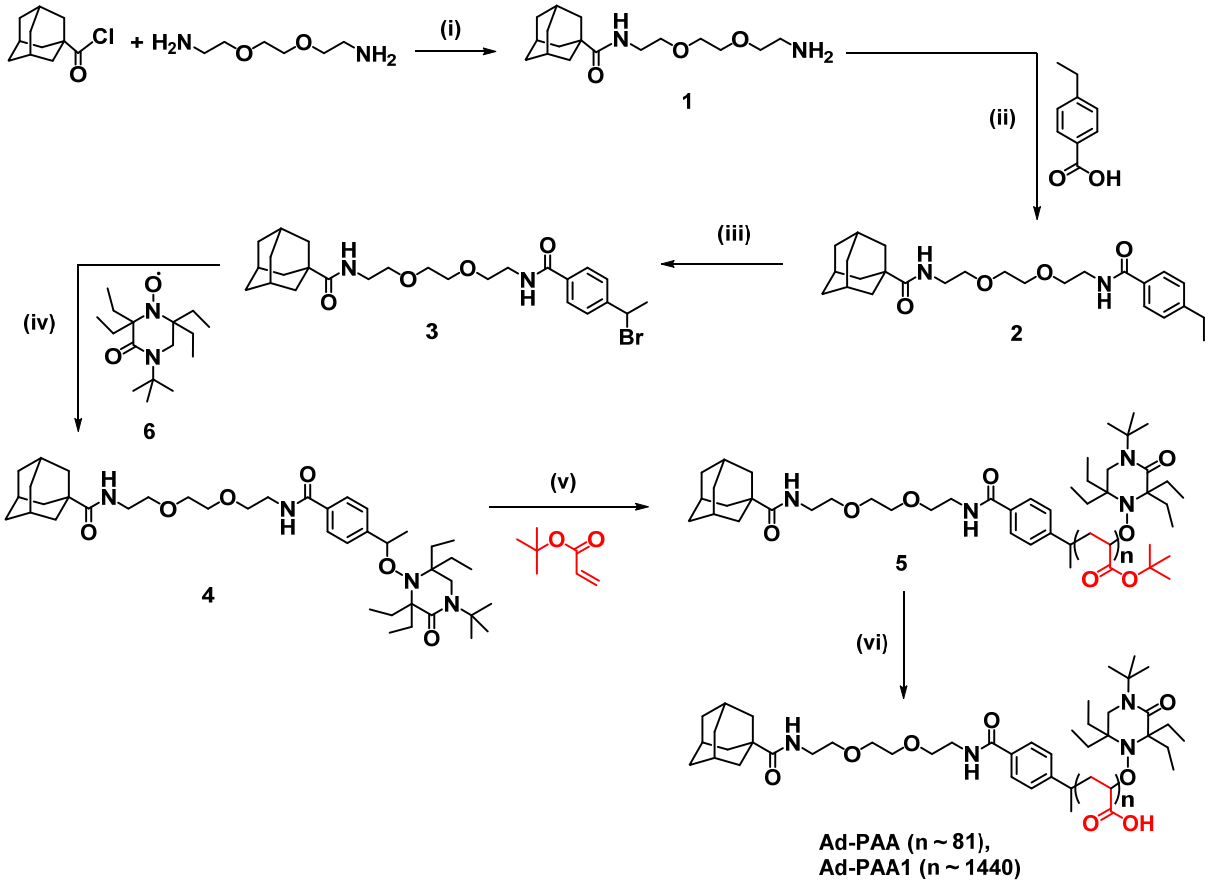


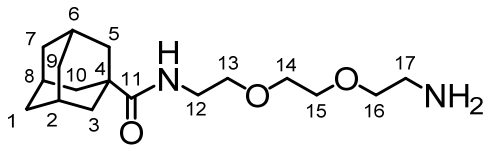
Fig. S4 Size distribution of sulforhodamine B encapsulated in **PDV** and **PSV** at t = 0 and t = 24 h according to dynamic light scattering. The template vesicles ([**CDV**] = 1 mM) were prepared by sonication in a 20 mM solution of sulforhodamine B followed by a Sephadex G-50 size-exclusion column chromatographic separation of encapsulated and non-encapsulated dye.

Synthesis



Scheme S1 Synthesis of adamantane terminated poly(acrylic acid): (i) dry DCM, -78 °C – rt, 18 h; 52% (ii) EDC, HOBt, NMM, DMF, rt, overnight, 63%; (iii) NBS, AIBN, CCl_4, reflux, 18 h, 69%; (iv) Cu powder, $Cu(OTf)_2$, 4,4'-di-*tert*-butyl-2,2'dipyridyl, benzene, 75 °C, 24 h; (v) 130 °C, 2-6 h; (vi) trifluoroacetic acid, DCM, rt, 24 h.

N-(2-(2-(2-aminoethoxy)ethoxy)ethyl)adamantane-1-carboxamide (1)



To a solution of 1.48 g 2,2'-(ethylendioxy)bis(ethylamine) (10.0 mmol, 4.0 eq.) in dry DCM, 500 mg adamantane acid chloride (2.50 mmol, 1.0 eq.) were added dropwise at -78 °C under rigorous stirring. The resulting suspension was stirred another 12 h at room temperature. The reaction mixture was quenched by 5% HCl and extracted with 30 ml of DCM, unreacted di-amine and mono-substituted amine went into the aqueous phase. The aqueous phase was neutralized by NaOH solution and extracted twice with DCM. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was further purified by column chromatography using a 2:1 mixture of DCM and EtOH (silica gel, 1% NH_3, R_f = 0.25) to result the product as sticky white solid (406 mg, 1.31 mmol, 52%).

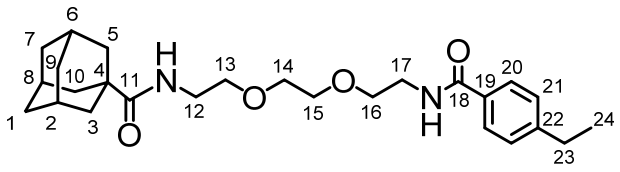
^{1}H NMR (300 MHz, $CDCl_3$, 298K): δ = 6.15 (*s*, 1H, amide NH), 3.61 (*m*, 4H, 13,16-H), 3.57 – 3.49 (*m*, 4H, 14,15-H), 3.47 – 3.40 (*m*, 2H, 12-H), 2.88 (*t*, *J* = 5.2 Hz, 2H, 17-H), 1.96 (*s*, 3H, 2,6,8-H), 1.84 (*d*, *J* = 2.9 Hz, 6H, 3,5,10-H), 1.77 – 1.64 (*m*, 6H, 1,7,9-H), 1.47 – 1.19 (*m*, 1H, NH_2), 0.94 – 0.86 (*m*, NH_2) ppm.

^{13}C NMR (75 MHz, $CDCl_3$, 298K): δ = 178.20, 77.16, 73.25, 70.35, 70.30, 70.09, 41.77, 40.71, 39.31, 39.07, 36.65, 28.25 ppm.

ESI-HRMS (m/z): calculated for $[C_{17}H_{30}N_2O_3H]^+$: 311.2329, found: 311.2340, calculated for $[C_{17}H_{30}N_2O_3Na]^+$: 333.2149, found: 333.2148.

IR (ATR): ν = 2980*m*, 2946*m*, 2907*w*, 2603*s*, 2531*w*, 2497*m*, 1630*w*, 1533*w*, 1476*m*, 1444*m*, 1398*s*, 1384*w*, 1365*w*, 1331*w*, 1290*w*, 1173*m*, 1064*m*, 1036*s*, 851*m*, 808*m* cm^{-1}.

***N*-(2-(2-(2-(4-ethylbenzamido)ethoxy)ethoxy)ethyl)adamantane-1-carboxamide (2)**



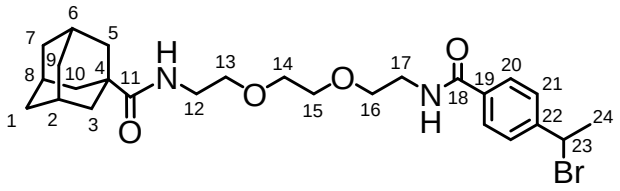
To a stirred solution of **1** (183 mg, 0.591 mmol, 1.0 eq) and 4-ethylbenzoic acid (98 mg, 0.650 mmol, 1.1 eq) in dry DMF, EDC (130 mg, 0.678 mmol, 1.15 eq), HOBt (108 mg, 0.705 mmol, 1.2 eq) and NMM (119.58 mg, 1.182 mmol, 2 eq) were added. After stirring for 12 h at room temperature 100 ml DCM was added. The organic phase was washed with 20 mL of an aqueous solution of citric acid (10 wt%) and 20 mL of an aqueous solution of $NaHCO_3$ (5 wt%). The organic layer was dried over $MgSO_4$. Purification of the crude product by column chromatography (DCM/MeOH 98:2, R_f = 0.4) yielded the product (0.165 mg, 0.372 mmol, 63%) as colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$, 298K): δ = 7.86 – 7.57 (*d*, *J* = 8.2 Hz, 2H, 20-H), 7.33 – 7.14 (*d*, *J* = 7.6, 2H, 21-H), 6.68 (*s*, 1H, amide-H), 6.01 (*s*, 1H, amide-H), 3.68 – 3.61 (*m*, 8H, 13,14,15,16-H), 3.54 (*t*, *J* = 5.1 Hz, 2H), 3.42 (*q*, *J* = 5.3 Hz, 2H), 2.68 (*q*, *J* = 7.7 Hz, 2H), 2.01 – 1.99 (*m*, 3H, 2,6,8-H), 1.81 – 1.79 (*d*, *J* = 2.97 Hz, 6H, 3,5,10-H), 1.73 – 1.63 (*m*, 6H, 1,7,9-H), 1.25 – 1.22 (*t*, *J* = 7.6 Hz, 3H, 24-H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$, 298K): δ = 178.20, 167.55, 148.27, 131.97, 128.14, 127.16, 77.16, 70.33, 70.29, 70.10, 70.02, 40.70, 39.75, 39.30, 39.04, 36.61, 28.89, 28.21, 15.47 ppm.

ESI-HRMS (m/z): Calculated for $[C_{26}H_{38}N_2O_4H]^+$: 443.2910; found: 443.2904.

***N*-(2-(2-(2-(4-(1-bromoethyl)benzamido)ethoxy)ethoxy)ethyl)adamantane-1-carboxamide (3)**



To a stirred solution of **2** (154 mg, 0.348 mmol, 1 eq) dry CCl_4, N-bromosuccinimide (NBS) (93.2 mg, 0.523, 1.5 eq) and azobisisobutyronitrile (AIBN) (2.9 mg, 0.018 mmol, 0.05 eq) were added under argon atmosphere. The reaction mixture was refluxed for 18 h. The organic phase was washed with 50 ml of brine solution and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (DCM/MeOH 97:3; R_f = 0.4), providing the target bromide **3** as colorless liquid (0.126 mg, 0.24 mmol, 69%).

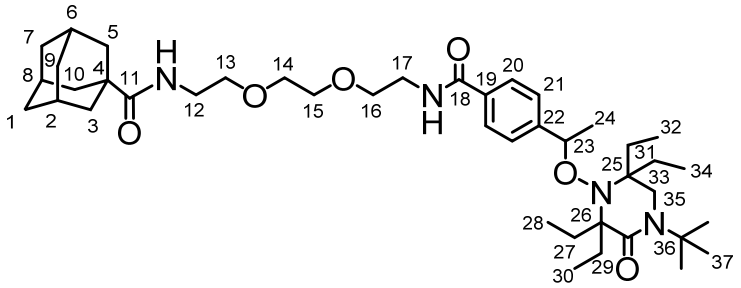
^{1}H NMR (300 MHz, $CDCl_3$, 298K): δ = 7.77 – 7.73 (*d*, *J* = 8.3 Hz, 2H, 20-H), 7.49 – 7.48 (*d*, *J* = 8.3 Hz, 1H, 21-H), 6.71 (*s*, 1H, amide-H), 5.98 (*s*, 1H, amide-H), 5.23 – 5.16 (*q*, *J* = 6.9 Hz, 1H, 23-H), 3.67 – 3.61 (*m*, 8H, 13,14,15,16-H), 3.57 – 3.53 (*t*, *J* = 5.2 Hz, 2H, 17-H), 3.45 – 3.39 (*m*, 2H, 12-H), 2.05 – 2.03 (*m*, 6H, 2,6,8,24-H), 1.83 – 1.82 (*d*, *J* = 2.9 Hz, 6H, 3,5,10), 1.76 – 1.62 (*m*, 6H, 1,7,9-H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$, 298K): δ = 178.23, 166.97, 146.74, 134.58, 127.58, 127.20, 77.16, 70.46, 70.35, 70.14, 69.98, 48.21, 40.78, 39.92, 39.41, 39.12, 36.68, 28.28, 26.72 ppm.

ESI-HRMS (m/z): Calculated for $[C_{26}H_{37}BrN_2O_4Na]^+$: 543.1834 and 545.1814; found: 543.1833 and 545.1819.

IR (ATR): 3350*w*, 2902*m*, 2851*m*, 1710*w*, 1630*vs*, 1537*s*, 1504*w*, 1451*m*, 1345*m*, 1302*m*, 1283*m*, 1214*w*, 1186*w*, 1118*s*, 1091*m*, 1044*w*, 1017*w*, 976*m*, 939*m*, 896*w*, 854*s*, 770*m*, 693*w* cm^{-1}.

***N*-(2-(2-(2-(4-(1-((4-(tert-butyl)-2,2,6,6-tetraethyl-3-oxopiperazin-1-yl)oxy)ethyl)-benzamido)ethoxy)ethoxy)ethyl)adamantane-1-carboxamide (4)**



In a heat gun-dried *Schlenk* tube, bromide **3** (160 mg, 0.307 mmol, 1.0 eq.), free nitroxide **6** (87.0 mg, 0.307 mmol, 1.0 eq.), copper powder (22.0 mg, 0.338 mmol, 1.1 eq.), copper(II) triflate (1.1 mg, 3.0 µmol, 1.0 mol%), and 4,4'-di-*tert*-butyl-2,2'dipyridyl (3.3 mg, 12 µmol, 4.0 mol%) were dissolved in benzene (4 mL). The mixture was degassed by conducting one freeze-thaw cycle.[2] The reaction was carried out in the sealed tube at 75 °C for 24 h. After the mixture was cooled to rt it was filtered through celite, washing with EtOAc. The solvents were removed using a rotary evaporator and the crude product was purified by FC (DCM/MeOH 95:5; $R_f = 0.4$), providing the target alkoxyamine **4** (177 mg, 80 %) as pale yellow and sticky solid.

^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.75 (*d*, 20-H *J* = 8.1 Hz, 2H), 7.34 (*d*, *J* = 6.4 Hz, 2H, 21-H), 6.70 (*s*, 1H, amide-H), 6.00 (*s*, 1H, amide-H), 4.80 – 4.67 (*q*, 1H, 23-H), 3.65 (*dd*, *J* = 9.9, 2.3 Hz, 8H, 13,14,15,16-H), 3.55 (*t*, *J* = 5.1 Hz, 2H, 17-H), 3.43 (*t*, *J* = 5.3 Hz, 2H, 12-H), 3.25 – 2.93 (*m*, 2H, 31-H), 2.77 – 2.59 (*m*, 1H, 23-H), 2.01 (*s*, 3H, 2,6,8-H), 1.95 – 1.53 (*m*, 18H), 1.50 – 1.34 (*m*, 12H), 1.24 (*m*, *J* = 9.2, 6.0 Hz, 1H), 1.12 – 0.93 (*m*, 6H, 32,34-H), 0.88 – 0.59 (*m*, 6H, 28,30-H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$, 298K): δ = 178.11, 172.68, 167.27, 148.10, 147.84, 133.57, 133.33, 131.93, 128.03, 127.11, 126.98, 126.82, 126.68, 82.60, 82.49, 73.56, 73.17, 70.31, 70.25, 70.01, 69.92, 62.67, 62.41, 60.40, 57.15, 47.05, 46.09, 40.66, 39.79, 39.29, 39.02, 36.57, 34.61, 33.39, 29.65, 29.28, 29.06, 28.80, 28.23, 28.18, 26.92, 26.66, 24.65, 23.28, 22.25, 21.06, 15.29, 14.24, 11.67, 11.24, 9.60, 9.35, 9.14, 8.29, 7.72 ppm.

ESI-HRMS (m/z): calculated for $[(C_{42}H_{68}N_4O_6)Na]^+$: = 747.5031; found : 747.5022.

(2) Freeze-thaw cycles were conducted as follows: Under a strong flow of argon, the tube was placed in a dewar filled with liquid nitrogen. After 1 min, high vacuum was applied for 5 min maintaining a strong argon flow; the tube was removed from the Dewar flask and kept at rt for 12 min.

IR (ATR): 3346*w*, 2905*m*, 2852*m*, 1713*w*, 1639*vs*, 1533*s*, 1453*m*, 1365*m*, 1303*m*, 1280*m*, 1243*m*, 1205*m*, 1119*s*, 1098*s*, 1062*m*, 992*m*, 939*w*, 915*m*, 853*m*, 812*w*, 770*w*, 624*m* cm^{-1}.

General Procedure for the 6-Mediated NMP of *tert*-Butyl Acrylate (5)

Under argon, a heat gun-dried *Schlenk* tube was charged with initiator **4** (1.0 eq.) and *tert*-butyl acrylate (100-1 000 eq.). The solution was degassed by conducting three freeze-thaw cycles. After the mixture was brought to rt the tube was sealed and the polymerization was carried out at 130 °C for 7-19 h. The reaction was cooled to rt and transferred to a round bottom flask using DCM. Solvent and residual monomer were removed under reduced pressure and the polymer was dried *in vacuo*. Conversion was determined gravimetrically. Molecular weight and PDI were determined by GPC at 25 °C against PMMA standards using THF as eluent.

IR (ATR): 2978*w*, 2935*w*, 1724*s*, 1446*w*, 1392*m*, 1366*s*, 1256*s*, 1143*vs*, 845*m* cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$, 298K)**: δ = 2.22 (br *s*, 1H), 1.77 (*m*, 1H), 1.53 (br *s*, 1H), 1.44 (br *s*, 9H) ppm.

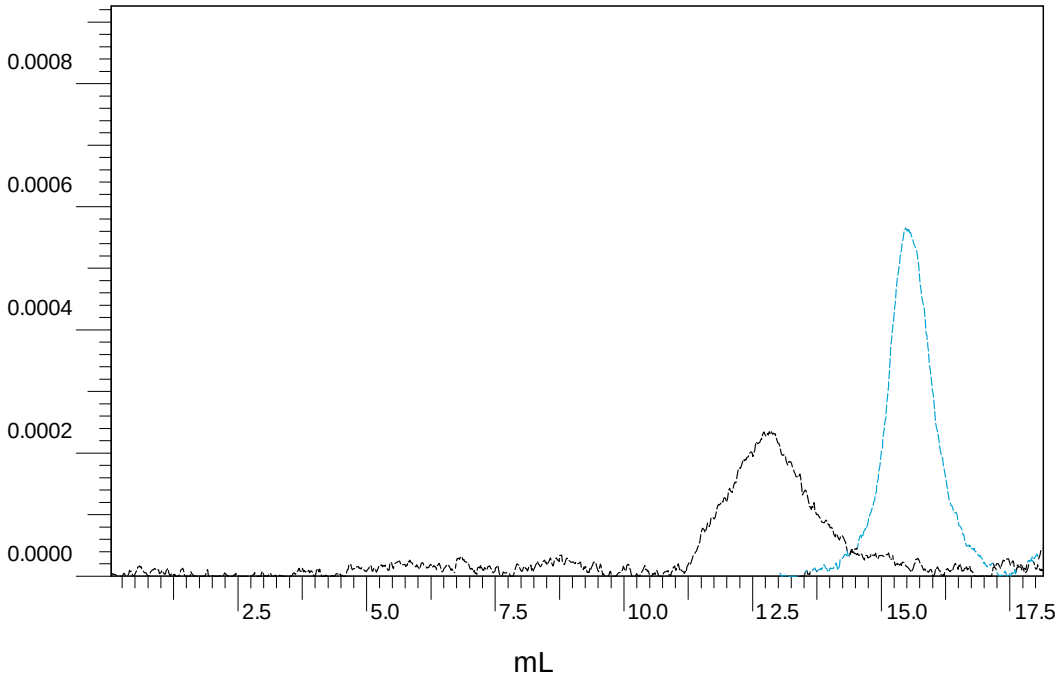
General Procedure for the Ester Hydrolysis of Poly[*tert*-Butyl Acrylate] to Ad-PAA

Poly[*tert*-butyl acrylate] (33.0 mg, 0.260 mmol, 1.0 eq.) was dissolved in DCM (2 mL) and trifluoroacetic acid (293 mg, 2.60 mmol, 10 eq.) was added slowly at rt. The mixture was stirred at rt for 24-48 h, forming a white precipitate. The solvent was removed under reduced pressure and the residual polymer was dissolved in ultra-pure water (3 mL) and purified by dialysis (cellulose tube, MWCO = 1000 g/mol) against ultra-pure water (600 mL, exchanged every 12 h) for 5 d. The polymer was freeze-dried to give a bulky white solid. Yield was determined gravimetrically, conversion was determined by ^{1}H NMR spectroscopy.

IR (ATR): 1709*vs*, 1614*w*, 1451*m*, 1246*s*, 1170*s*, 803*m* cm^{-1}.

^{1}H NMR (300 MHz, D_2O, 298K): δ = 2.45 (br *s*, 1H), 2.12 – 1.53 (*m*, 2H) ppm.

GPC (SEC) Traces of Poly[*tert*-Butyl Acrylate] (5)



Curve	eq. *tert*-butyl acrylate	time [h]	M_n [g/mol]	DP	PDI
-----	1 000	7.5	185 000	1 440	1.5
-----	100	19	11 100	81	1.2

Molecular weight and PDI were determined by GPC at 25 °C against PMMA standards using THF as eluent.

^{1}H and ^{13}C NMR Spectra of New Compounds

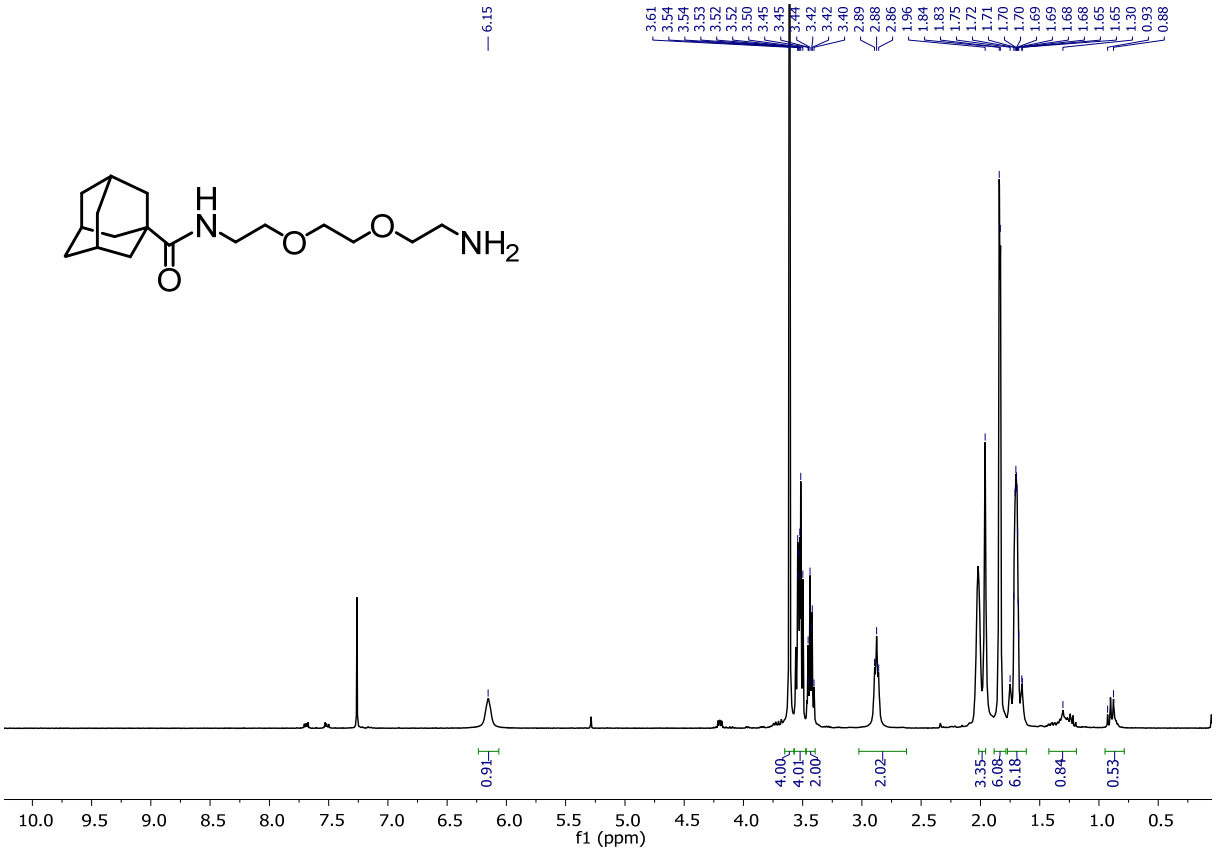


Fig. S5 ^{1}H-NMR of compound **1** in $CDCl_3$ at 298 K.

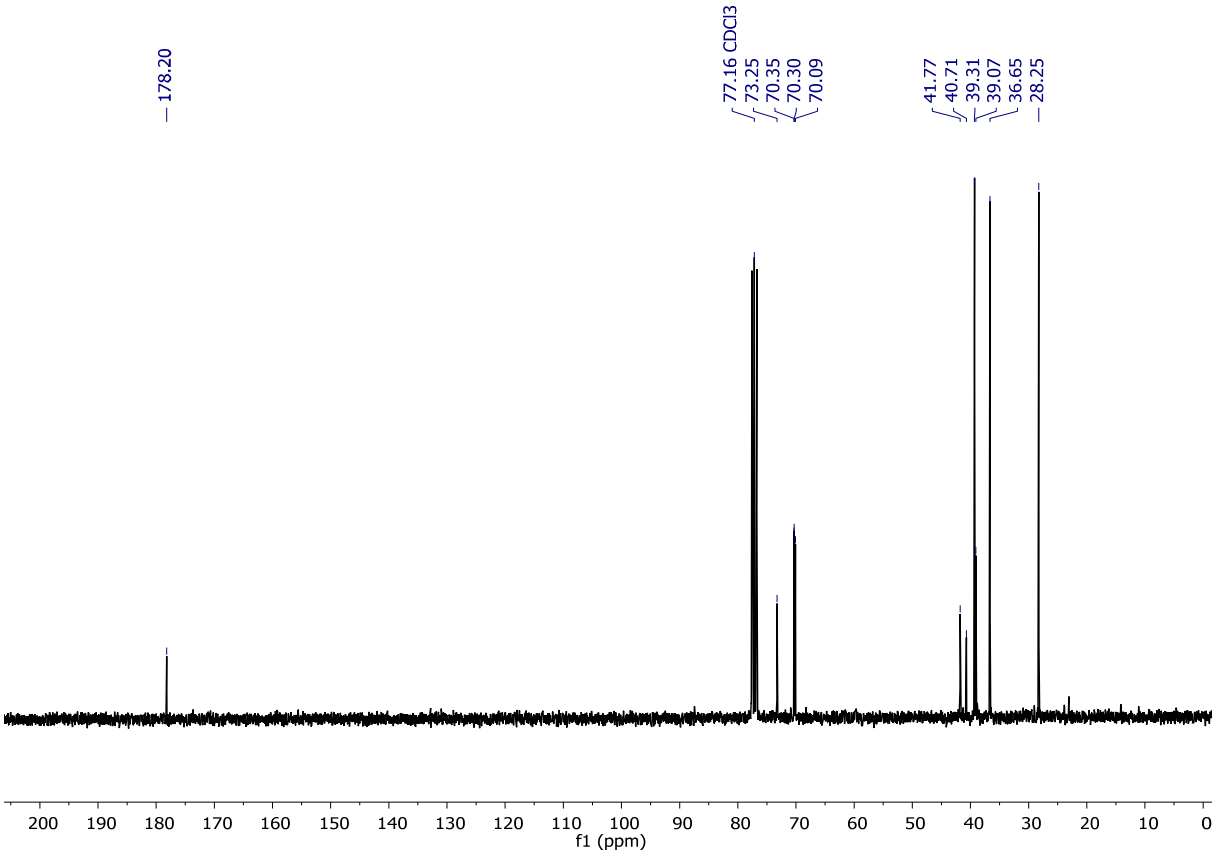


Fig. S6 ^{13}C-NMR of compound **1** in $CDCl_3$ at 298 K.

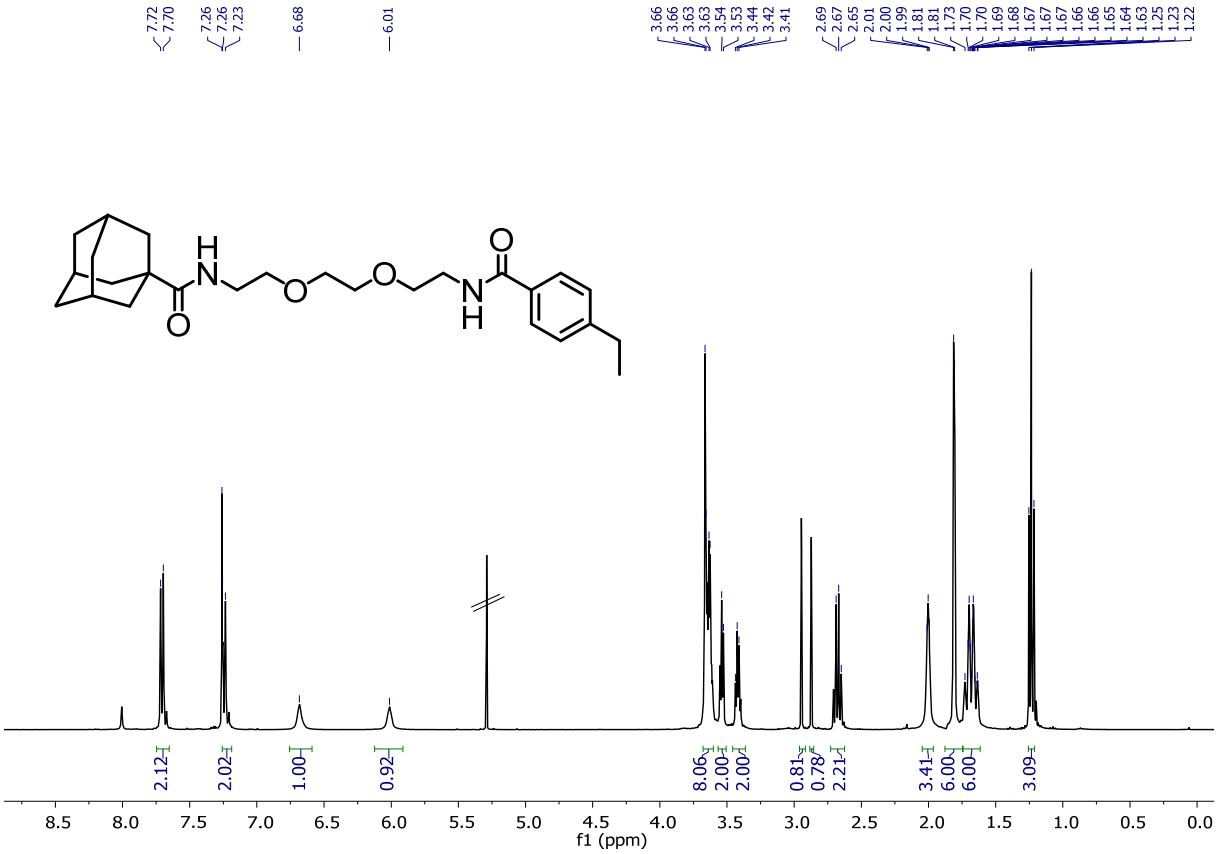


Fig. S7 ^{1}H-NMR of compound **2** in $CDCl_3$ at 298 K.

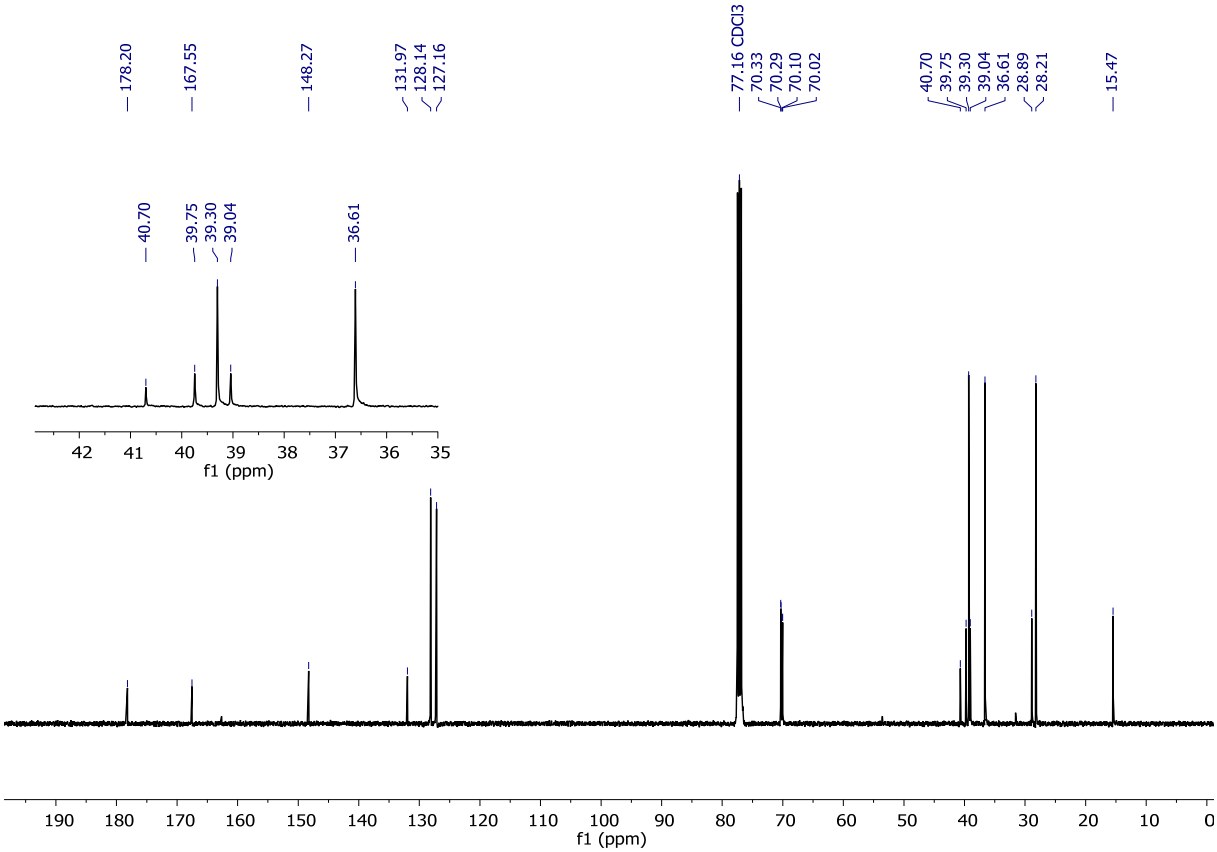


Fig. S8 ^{13}C-NMR of compound **2** in $CDCl_3$ at 298 K.

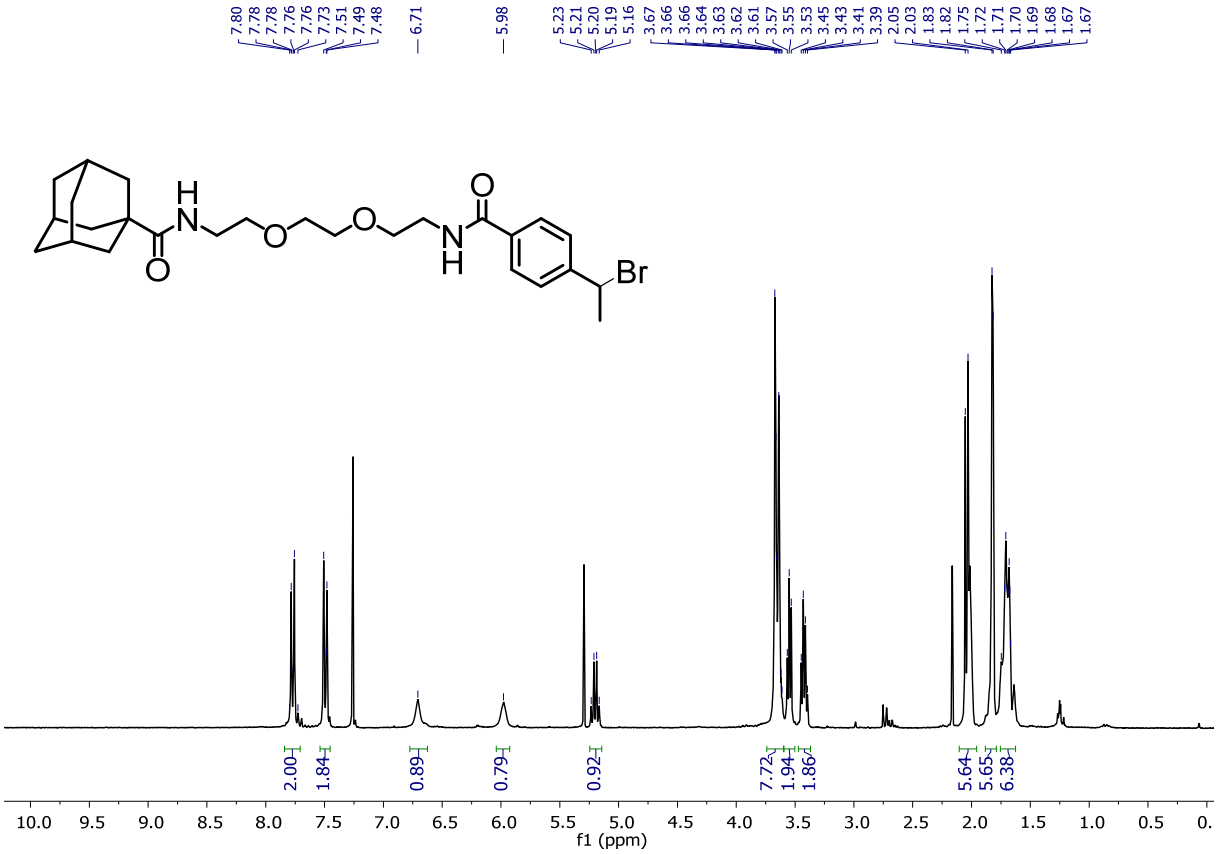


Fig. S9 ^{1}H-NMR of compound **3** in $CDCl_3$ at 298 K.

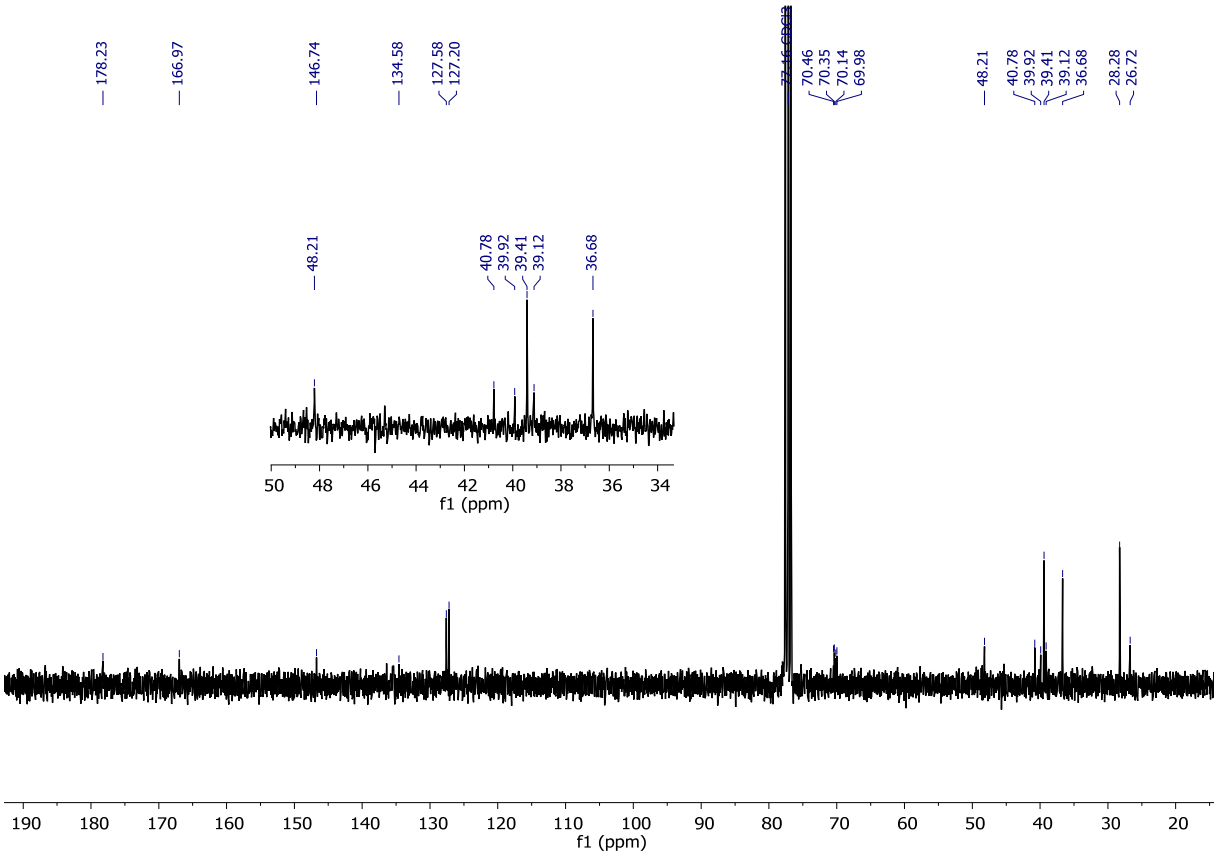


Fig. S10 ^{13}C-NMR of compound **3** in $CDCl_3$ at 298 K.

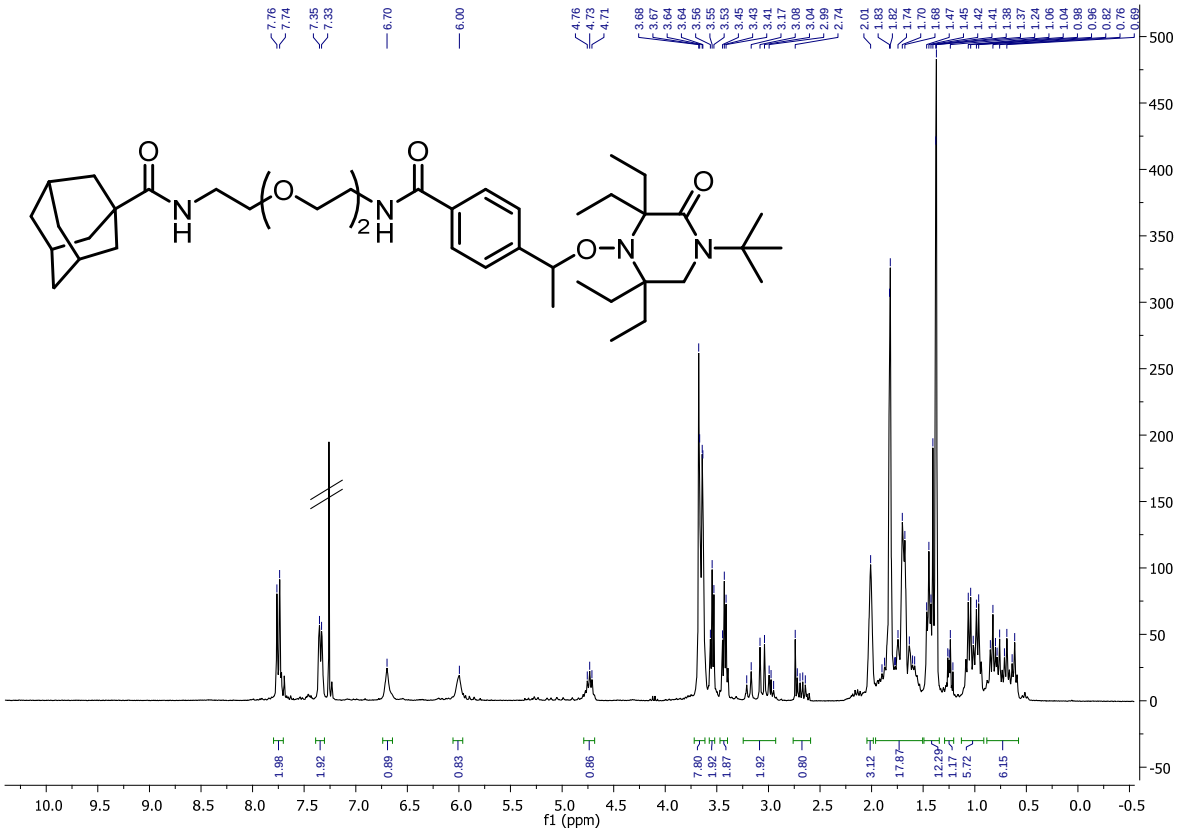


Fig. S11 ^{1}H-NMR of compound **4** in $CDCl_3$ at 298 K.

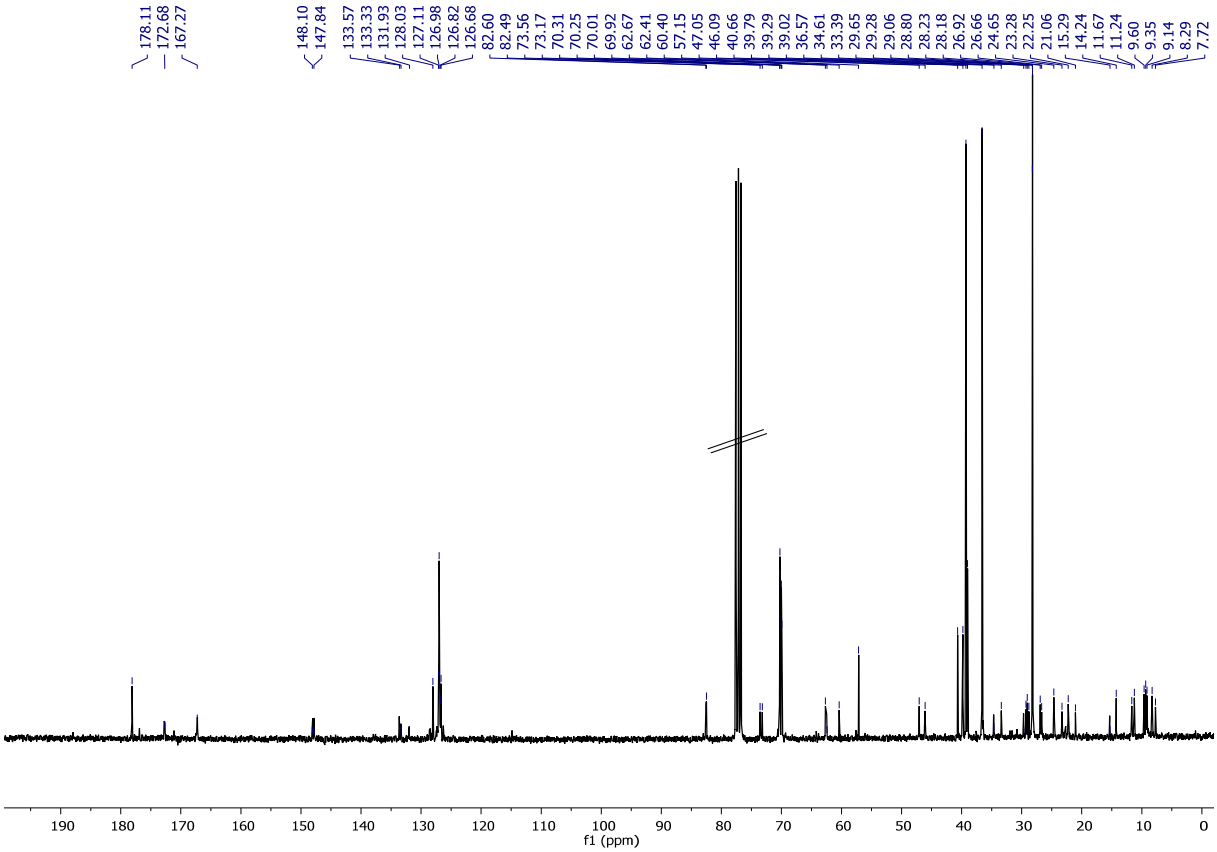


Fig. S12 ^{13}C-NMR of compound **4** in $CDCl_3$ at 298 K.