

Impact of amino acids on the aqueous self-assembly of benzenetrispeptides into supramolecular polymer bottlebrushes

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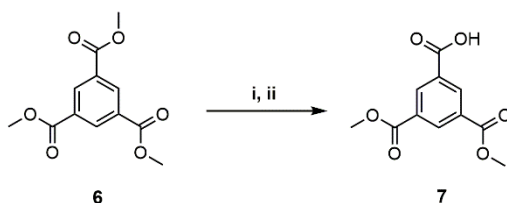
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1. Synthesis

Materials and Methods. All reagents and solvents were commercial products purchased from Sigma-Aldrich, abcr, Iris BioTech, Rapp Polymere or TCI and were used without further purification. Flash chromatography was performed on a *CombiFlash* Rf 4x Module by TeledyneIsco using a UV detector for compound purity monitoring. ¹H-NMR spectra were measured with a Bruker spectrometer (300 MHz) equipped with an Avance I console, a dual ¹H and ¹³C sample head and a 120x BACS automatic sample changer. The chemical shifts of the peaks were determined by using the residual solvent signal as reference and are given in ppm in comparison to TMS. Size-exclusion chromatography (SEC) of polymers was performed on an Agilent system (series 1200) equipped with a PSS degasser, a G1310A pump, a G1362A refractive index detector and a PSS GRAM 30 and 1000 column with DMAc (+ 0.21 wt.% LiCl) as eluent at a flow rate of 1 mL min⁻¹. The column oven was set to 40 °C and poly(ethylene glycol) (PEO) standards were used for calibration. Fluorescence spectra were recorded on a JASCO FP-8300 spectrometer equipped with a Peltier element. DLS correlograms were measured on a ZetaSizer Nano ZS (Malvern, Herrenberg, Germany) equipped with a He–Ne laser with a wavelength of $\lambda = 633$ nm. *Cryo*TEM measurements were performed on a FEI Tecnai G2 20 platform with a LaB6 filament at 200 kV acceleration voltage. Analytical ultracentrifuge experiments were performed with a ProteomeLab XL-I analytical ultracentrifuge (Beckman Coulter Instruments, Brea, CA). Small angle X-ray scattering was performed at the beamline BL40B2 of the Super Photon Ring – 8 GeV (SPring-8) in Hyōgo Prefecture, Japan. CD spectra were measured using a JASCO J-820KS spectrophotometer.

1.1 Synthetic routes

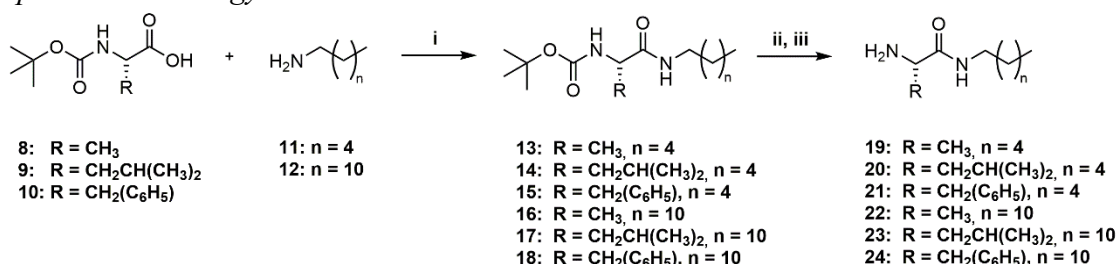
Core unit



Scheme S 1: Synthesis of 3,5-bis(methoxycarbonyl)benzoic acid **7**. i) NaOH (aq), MeOH, overnight; ii) 1M HCl, H₂O.

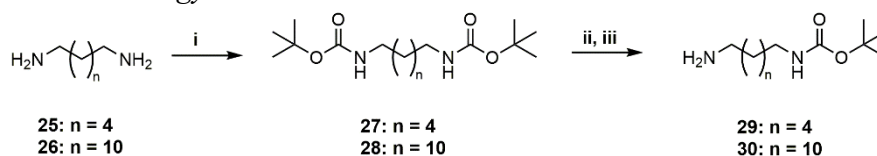
Amino acid arms

Boc-protection strategy

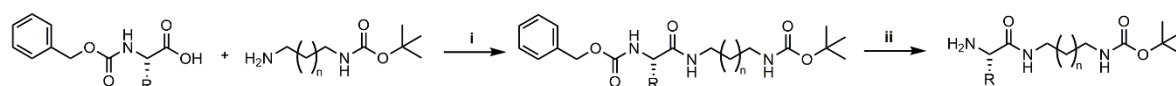


Scheme S 2: Synthesis of alkylated amino acids **19-24**. i) DMAP, EDC-HCl, DCM, 20 °C, 6 h; ii) TFA, TIPS, H₂O, DCM, 20 °C, 6 h; iii) Na₂CO₃ (aq), 20 °C, overnight.

Cbz-Boc-protection strategy



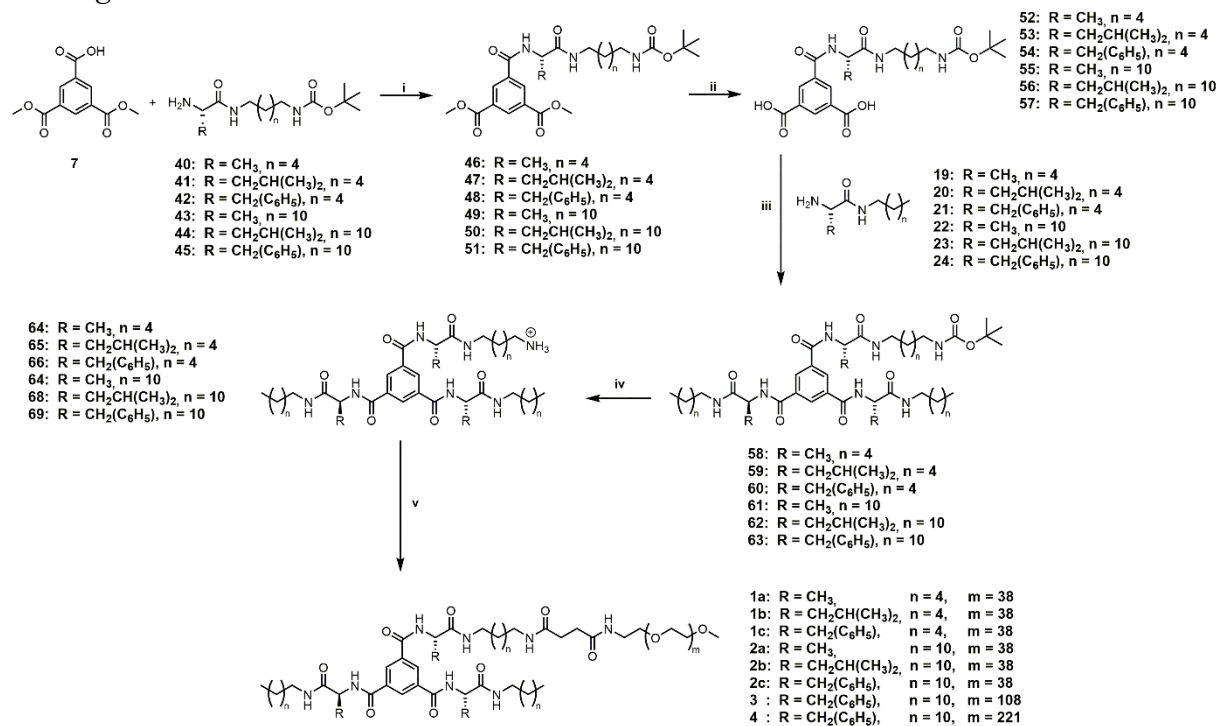
Scheme S 3: Synthesis of semi-Boc-protected hexyl- and dodecyl-diamines **29** and **30**, respectively. i) DiBoc, DCM/MeOH 1:1, 20 °C, overnight; ii) HCl, DCM/Et₂O 1:1, 20 °C, overnight; iii) NaHCO₃ (aq), 20 °C, overnight.



Scheme S 4: Synthesis of alkylated amino acids bearing a terminal Boc-protected amino group **40-45**. i) DMAP, EDC-HCl, DCM, 20 °C, 6 h; ii) H₂, Pd-C, MeOH or THF, 20 °C, overnight.

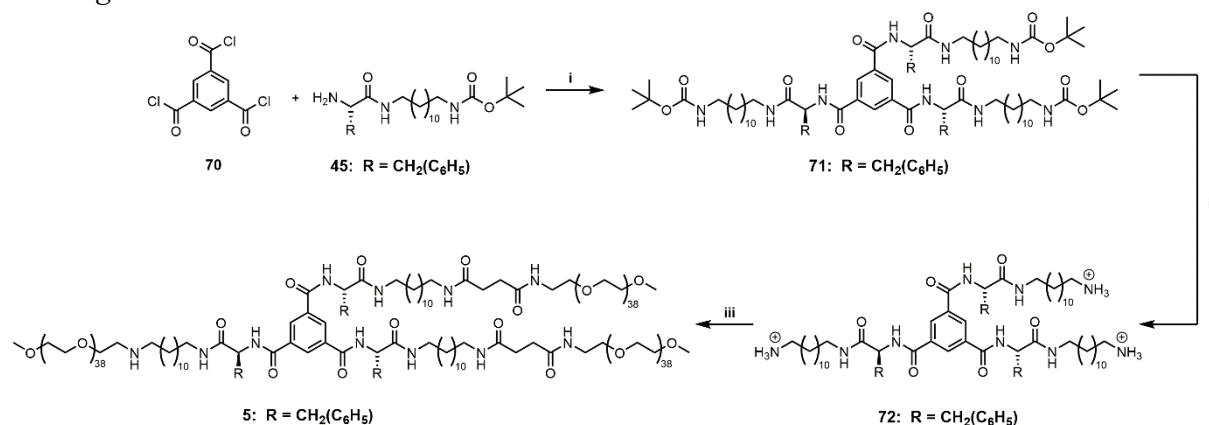
Benzenetrispeptide building blocks

Bearing one PEO chain



Scheme S 5: Synthetic route to the benzenetrispeptide conjugates **1a**, **1b**, **1c**, **2a**, **2b**, **2c**, **3** and **4** bearing one PEO chain. i) DMAP, EDC-HCl, CHCl₃, rt, overnight; ii) KOH, EtOH/H₂O, reflux, 30 min; iii) DMAP, EDC-HCl, CHCl₃ or DMF, rt, overnight; iv) TFA/TIPS/H₂O, DCM, rt, 2 h; v) MeO-PEO-NHS, TEA, DMF, rt, overnight.

Bearing three PEO chains

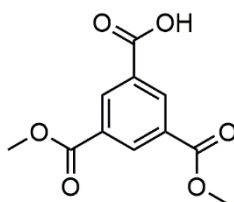


Scheme S 6: Synthetic route to the benzenetrispeptide conjugate **5** bearing three PEO chains. i) TEA, CHCl₃, 0 °C, overnight; ii) TFA, TIPS, H₂O, DCM, 20 °C, 2 h; iii) MeO-PEO-NHS, TEA, DMF, 20 °C, overnight.

1.2 Synthetic protocols

1.2.1 Core unit

3,5-bis(methoxycarbonyl)benzoic acid - 7



7

Trimethyl benzene-1,3,5-tricarboxylate (30 g, 119 mmol, 1.0 eq) was dissolved in 1.5 L methanol and 107 mL of a 1 M aq. NaOH solution (107 mmol, 0.9 eq) dropwise added under vigorous stirring and the solution stirred overnight at rt. Afterwards, the solvent was removed under reduced pressure and the residue resuspended in DCM to dissolve residual starting material. The suspension was then filtered and the solid residue dried in a vacuum oven (40 °C) overnight. To convert the sodium-carboxylate into its corresponding carboxylic acid, the dried solid (27.7 g, 106.5 mmol) was dissolved in 500 mL water to which 106.5 mL of a 1 M aq. HCl solution (106.5 mmol) were added dropwise under vigorous stirring. The formed precipitate was filtered and wash with a little amount of water to remove remaining sodium-carboxylate. The obtained white solid was dried overnight in the vacuum oven (40 °C).

Yield: 20 g, 84 mmol (78%), white solid.

Molecular formula: C₁₁H₁₀O₆.

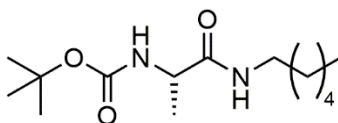
¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 13.69 (s, 1H, COOH), 8.61 (d, *J* = 1.6 Hz, 2H, CH_{aromat}), 8.58 (t, *J* = 1.6 Hz, 1H, CH_{aromat}), 2.50 (s, 6H, CH₃).

ESI-ToF-MS (negative mode, acetonitrile) (m/z): calculated for [M-H]⁻: 237.0405; found: 237.0351.

1.2.2 Amino acid arms

Boc-protection strategy

Boc-L-Ala-C(O)NH-C₆ - **13**



13

Boc-L-Ala-OH **8** (10 g, 52.9 mmol, 1.0 eq) and DMAP (646 mg, 5.29 mmol, 0.1 eq) were dissolved in 192 mL DCM. To this solution 7.64 mL hexylamine (58.1 mmol, 1.1 eq) were added dropwise. Thereafter, 12.16 g EDC-HCl (63.4 mmol, 1.2 eq) were added portion wise under vigorous stirring and the solution stirred for 4 h at rt. Afterwards, the reaction mixture was extracted with 1 M HCl (3x 50 mL), sat. aq. NaHCO₃ (1x, 50 mL) and brine (1x, 50 mL). The combined organic phases were dried over MgSO₄, filtered and reduced *in vacuo*. The obtained product was dried in the vacuum oven (40 °C) overnight.

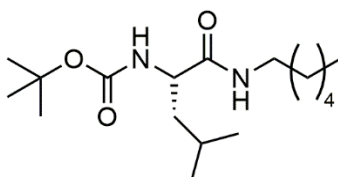
Yield: 13.23 g, 48.6 mmol (92%), yellowish liquid.

Molecular formula: C₁₄H₂₈N₂O₃.

¹H-NMR (300 MHz, CDCl₃, 298 K): δ [ppm] = 6.42 (s, 1H, NH), 5.18 (d, J = 6.8 Hz, 1H, NH), 4.21 – 4.04 (m, 1H, CH), 3.20 (q, J = 6.9, 6.4 Hz, 2H, CH₂), 1.46 (m, 2H, CH₂), 1.42 (s, 9H, CH₃), 1.32 (d, J = 7.0 Hz, 3H, CH₃), 1.25 (m, 4H, CH₂), 0.85 (t, J = 6 Hz, 3H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 295.1992; found: 295.1984.

Boc-L-Leu-C(O)NH-C₆ – **14**



14

The compound was synthesized according to the procedure of compound **13**.

Yield: 24.064 g, 76.5 mmol (95%), yellowish liquid.

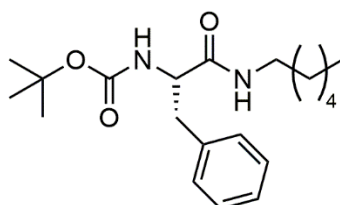
Molecular formula: C₁₇H₃₄N₂O₃.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 7.74 (d, J = 5.7 Hz, 1H, NH), 6.77 (d, J = 8.5 Hz, 1H, NH), 3.89 (q, J = 8.6 Hz, 1H, CH), 3.02 (dt, J = 13.9, 6.9 Hz, 2H, CH₂), 1.36 (dd,

J = 12.6, 7.5 Hz, 1H, CH₂, CH), 1.36 (m, 13H, CH₃, CH₂), 1.23 (s, 6H, CH₂), 0.84 (m, 9H, CH₃) ppm.

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 337.2462; found: 337.2472.

Boc-L-Phe-C(O)NH-C₆ - **15**



15

The compound was synthesized according to the procedure of compound **13**.

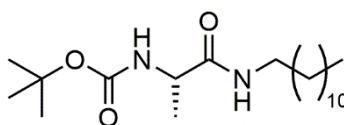
Yield: 25.66 g, 73.6 mmol (98%), white solid.

Molecular formula: C₂₀H₃₂N₂O₃.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 7.82 (t, J = 5.4 Hz, 1H, NH), 7.24 (m, 5H, CH_{aromat}), 6.86 (d, J = 8.5 Hz, 1H, NH), 4.09 (td, J = 9.3, 5.1 Hz, 1H, CH), 3.12 – 2.94 (m, 2H, CH₂), 2.89 (dd, J = 13.6, 5.0 Hz, 1H, CH₂), 2.72 (dd, J = 13.5, 9.8 Hz, 1H, CH₂), 1.26 (m, 17H, CH₃, CH₂, CH₂, CH₂, CH₂), 0.85 (t, J = 6.7 Hz, 3H).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 371.2305; found: 371.2314.

Boc-L-Ala-C(O)NH-C₁₂ - **16**



16

Boc-L-Ala-OH **8** (5 g, 26.4 mmol, 1.0 eq) and DMAP (323 mg, 2.64 mmol, 0.1 eq) were dissolved in 117 mL DCM. To this solution 4.41 g dodecylamine (23.78 mmol, 0.9 eq) were added. Thereafter, 6.08 g EDC-HCl (31.7 mmol, 1.2 eq) were added portion wise under vigorous stirring and the solution stirred for 4 h at rt. Afterwards, the reaction mixture was extracted with 1 M HCl (4x, 50 mL), sat. aq. NaHCO₃ (3x, 50 mL) and brine (1x, 50 mL). The combined organic phases were dried over MgSO₄, filtered and reduced *in vacuo*. The obtained product was dried in the vacuum oven (40 °C) overnight.

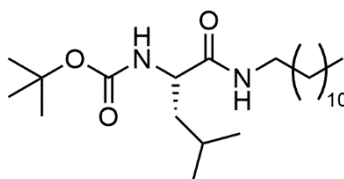
Yield: 8.52 g, 23.9 mmol (90%), white solid.

Molecular formula: C₂₀H₄₀N₂O₃.

¹H-NMR (300 MHz, CDCl₃, 298 K): δ [ppm] = 6.12 (s, 1H, NH), 4.98 (s, 1H, NH), 4.10 (p, J = 6.2 Hz, 1H, CH), 3.23 (q, J = 6.6 Hz, 2H, CH₂), 1.44 (m, 7H, CH₂, CH₃), 1.34 (d, J = 7.1 Hz, 3H, CH₃), 1.25 (m, 11H, CH₂), 0.87 (t, J = 7.5 Hz, 3H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 379.2931; found: 379.2940.

Boc-L-Leu-C(O)NH-C₁₂ – **17**



17

The compound was synthesized according to the procedure of compound **16**.

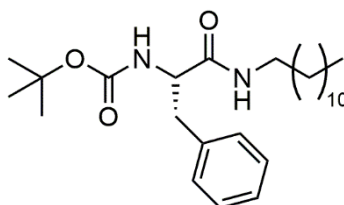
Yield: 22.91 g, 57.5 mmol (89%), yellow liquid.

Molecular formula: C₂₃H₄₆N₂O₃.

¹H-NMR (300 MHz, CDCl₃, 298 K): δ [ppm] = 6.05 (t, J = 4.9 Hz, 1H, NH), 4.83 (s, 1H, NH), 4.01 (q, J = 8.2 Hz, 1H, CH), 3.21 (q, J = 6.8 Hz, 2H, CH₂), 1.64 (dt, J = 12.0, 6.7 Hz, 2H, CH₂), 1.42 (m, 13H, CH₂, CH₃), 1.23 (m, 18H, CH₂), 0.91 (dd, J = 6.2, 2.2 Hz, 6H, CH₃), 0.86 (t, J = 7.5 Hz, 3H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 421.3401; found: 421.3332.

Boc-L-Phe-C(O)NH-C₁₂ - **18**



18

The compound was synthesized according to the procedure of compound **16**.

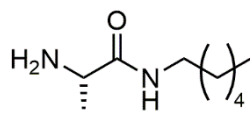
Yield: 23.3 g, 56.5 mmol (95%), white solid.

Molecular formula: C₂₆H₄₄N₂O₃.

¹H-NMR (300 MHz, CDCl₃, 298 K): δ [ppm] = 7.36 – 7.15 (m, 4H, C_{aromat}), 5.64 (s, 1H, NH), 5.08 (s, 1H, NH), 4.25 (q, J = 7.5 Hz, 1H, CH), 3.21 – 2.93 (m, 4H, CH₂), 1.41 (s, 9H, CH₃), 1.28 (m, 20H, CH₂), 0.88 (t, J = 7.5 Hz, 3H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 455.3244; found: 455.3255.

H₂N-L-Ala-C(O)NH-C₆ - **19**



19

Compound **13** (3.07 g, 11.28 mmol, 1.0 eq) was dissolved in 26 mL DCM. To this solution, 26.1 mL trifluoroacetic acid (338 mmol, 25.0 eq) added dropwise under vigorous stirring. Afterwards, the reaction mixture was stirred for 4 h at rt. Then, the reaction mixture was reduced *in vacuo*. The residue was re-dissolved in 250 mL DCM and again reduced *in vacuo*. This step was repeated 4x in order to remove most of the residual TFA. The obtained salt product (3.5 g) was then dissolved in 55 mL sat. NaHCO₃ (aq.) and stirred overnight in order to convert the ammonium-TFA salt into the free amine. The aqueous solution was then extracted with DCM (5x, 50 mL). The combined organic phases were then washed with brine (1x, 50 mL), dried over MgSO₄, filtered and reduced *in vacuo*. The obtained product was dried in the vacuum oven (40 °C) overnight.

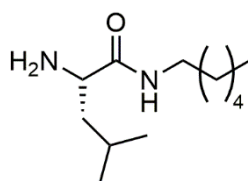
Yield: 1.55 g, 9 mmol (80%), yellow liquid.

Molecular formula: C₉H₂₀N₂O.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 7.78 (s, 1H, NH), 3.22 (q, J = 6.9 Hz, 1H, CH), 3.04 (q, J = 6.6 Hz, 2H, CH₂), 2.06 (s, 2H, NH₂), 1.37 (q, J = 6.6 Hz, 2H, CH₂), 1.23 (m, 6H, CH₂), 1.09 (d, J = 6.9 Hz, 3H, CH₃), 0.84 (t, J = 7.5 Hz, 3H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 173.1648; found: 173.1649.

H₂N-L-Leu-C(O)NH-C₆ - **20**



20

The compound was synthesized according to the procedure of compound **19**.

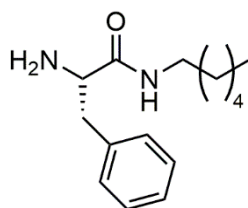
Yield: 13.82 g, 64.5 mmol (85%), white solid.

Molecular formula: C₁₂H₂₆N₂O.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 7.80 (t, J = 5.4 Hz, 1H, NH), 3.06 (m, 3H, CH, CH₂), 1.66 (dq, J = 12.9, 6.5 Hz, 2H), 1.36 (ddd, J = 13.5, 8.2, 5.6 Hz, 2H, CH₂), 1.24 (m, 3H, CH, CH₂), 0.85 (m, 9H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 215.2118; found: 215.2177.

H₂N-L-Phe-C(O)NH-C₆ - **21**



21

The compound was synthesized according to the procedure of compound **19**.

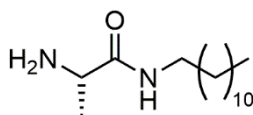
Yield: 7.63 g, 30.7 mmol (93%), white solid.

Molecular formula: C₁₅H₂₄N₂O.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 7.76 (t, J = 5.1 Hz, 1H, NH), 7.31 – 7.13 (m, 4H, C_{aromat}), 3.01 (hept, J = 6.6 Hz, 2H, CH₂), 2.88 (dd, J = 13.0, 5.0 Hz, 1H, CH₂), 2.60 (dd, J = 13.1, 7.9 Hz, 1H, CH₂), 1.63 (s, 2H, NH₂), 1.39 – 1.12 (m, 8H, CH₂), 0.85 (t, J = 6.1 Hz, 3H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 249.1961; found: 249.1978.

H₂N-L-Ala-C(O)NH-C₁₂ – **22**



22

The compound was synthesized according to the procedure of compound **19**.

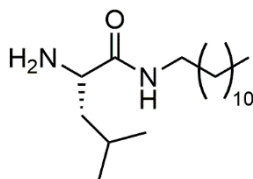
Yield: 4.94 g, 19.3 mmol (88%), yellowish solid.

Molecular formula: C₁₅H₃₂N₂O.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 7.73 (t, J = 5.5 Hz, 1H, NH), 3.19 (q, J = 7.9, 7.0 Hz, 1H, CH), 3.02 (q, J = 6.5 Hz, 2H, CH₂), 1.45 – 1.31 (m, 2H, CH₂), 1.23 (m, 16H, CH₂), 1.08 (d, J = 5.6 Hz, 3H, CH₃), 0.85 (t, J = 6.1 Hz, 3H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 257.2587; found: 257.2638.

H₂N-L-Leu-C(O)NH-C₁₂ – **23**



23

The compound was synthesized according to the procedure of compound **19**.

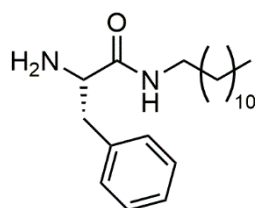
Yield: 15.7 g, 52.6 mmol (93%), yellowish solid.

Molecular formula: C₁₈H₃₈N₂O.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 7.79 (t, J = 5.5 Hz, 1H), 3.12 – 2.93 (m, 3H, CH, CH₂), 1.67 (m, 3H, NH₂, CH), 1.43 – 1.29 (m, 4H, CH₂), 1.23 (m, 18H, CH₂), 0.85 (m, 9H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 299.3057; found: 299.3051.

H₂N-L-Phe-C(O)NH-C₁₂ – **24**



24

The compound was synthesized according to the procedure of compound **19**.

Yield: 14.56 g, 43.8 mmol (95%), yellow resin-like liquid.

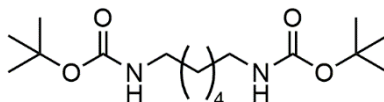
Molecular formula: C₂₁H₃₆N₂O.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 7.75 (t, J = 4.7 Hz, 1H, NH), 7.30 – 7.12 (m, 4H, C_{aromat}), 3.00 (m, 2H, CH₂), 2.87 (dd, J = 13.6, 4.8 Hz, 1H, CH₂), 2.60 (dd, J = 12.6, 8.5 Hz, 1H, CH₂), 1.67 (s, 2H, NH₂), 1.23 (m, 20H, CH₂), 0.85 (t, J = 5.8 Hz, 3H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 333.2900; found: 333.2910.

Cbz-Boc-protection strategy

N,N'-Boc-1,6-hexanediamine – **27**



27

Hexane-1,6-diamine **25** (15 g, 129 mmol, 1.0 eq) were dissolved in 430 mL DCM/MeOH (1:1 v:v). To this solution, 62.3 mL di-*tert*-butyl dicarbonate (59.2 g, 271 mmol, 2.1 eq) were added dropwise under vigorous stirring. The reaction mixture was stirred overnight at rt. Afterwards, the solvents were removed under reduced pressure and the obtained crude product recrystallised from methanol. The obtained crystals were dried in the vacuum oven (40 °C) overnight.

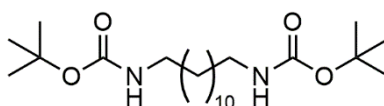
Yield: 40.7 g, 129 mmol (100%), white powder.

Molecular formula: C₁₆H₃₂N₂O₄.

¹H-NMR (300 MHz, d₄-MeOD, 298 K): δ [ppm] = 3.02 (t, J = 6.9 Hz, 4H, CH₂), 1.43 (m, 22H, CH₂, CH₃), 1.32 (dt, J = 7.4, 3.4 Hz, 4H, CH₂).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+K]⁺: 355.1994; found: 355.2068.

N,N'-Boc-1,12-dodecanediamine – **28**



28

The compound was synthesized according to the procedure of compound **27**.

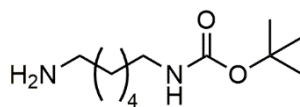
Yield: 33.2 g, 83 mmol (95%), white powder.

Molecular formula: C₂₂H₄₄N₂O₄.

¹H-NMR (300 MHz, d₄-MeOD, 298 K): δ [ppm] = 3.01 (t, J = 7.0 Hz, 4H, CH₂), 1.43 (m, 22H, CH₂, CH₃), 1.30 (m, 16H, CH₂).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 423.3193; found: 423.3144.

N-Boc-1,6-hexanediamine – **29**



29

Compound **27** (20 g, 63.2 mmol, 1.0 eq) was dissolved in 95 mL DCM. To this 95 mL of a 1 M HCl in diethyl ether (190 mmol, 3.0 eq) was added dropwise under vigorous stirring. The solution turned turbid (precipitation of product) and was further stirred overnight at rt. The precipitate was filtered and washed with cold diethyl ether (3x, 50 mL). The obtained ammonium chloride salt product was dried in the vacuum oven (40 °C) overnight. Afterwards, the crude product was dissolved in sat. NaHCO₃ (aq., 700 mL) and stirred overnight at rt in order to obtain the free amine. Thereafter, the aqueous solution was extracted with DCM (5x, 100 mL). The combined organic phases were dried over MgSO₄, filtered and reduced *in vacuo*.

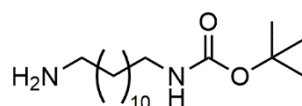
Yield: 10.603 g, 49 mmol (78%), white solid.

Molecular formula: C₁₁H₂₄N₂O₂.

¹H-NMR (300 MHz, d₄-MeOD, 298 K): δ [ppm] = 3.02 (t, J = 6.9 Hz, 2H, CH₂), 2.66 (t, J = 7.2 Hz, 2H, CH₂), 1.42 (m, 13H, CH₂, CH₃), 1.39 – 1.29 (m, 4H, CH₂).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 217.1911; found: 217.1896.

N-Boc-1,12-dodecanediamine – 30



30

Compound **28** (33 g, 82 mmol, 1.0 eq) was dissolved in 124 mL DCM. To this 124 mL of a 1 M HCl in diethyl ether (247 mmol, 3.0 eq) was added dropwise under vigorous stirring. The solution turned turbid (precipitation of product) and was further stirred overnight at rt. The precipitate was filtered and washed with cold diethyl ether (3x, 50 mL). The obtained ammonium chloride salt product was dried in the vacuum oven (40 °C) overnight. Afterwards, the crude product was dissolved in sat. NaHCO₃ (aq., 350 mL) and stirred overnight at rt in order to obtain the free amine. Thereafter, the formed precipitate was filtered and thoroughly washed with water to remove residual salt traces. The obtained product was dried in the vacuum oven (40 °C) overnight.

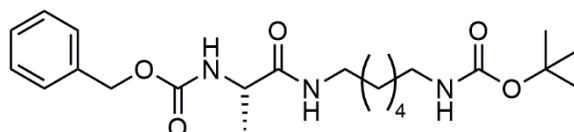
Yield: 24.163 g, 80 mmol (98%), white solid.

Molecular formula: C₁₇H₃₆N₂O₂.

¹H-NMR (300 MHz, d₄-MeOD, 298 K): δ [ppm] = 3.01 (t, J = 7.0 Hz, 2H, CH₂), 2.80 – 2.73 (m, 2H, CH₂), 1.61 – 1.51 (m, 2H, CH₂), 1.43 (m, 11H, CH₂,CH₃), 1.31 (m, 16H, CH₂).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 301.2850; found: 301.3650.

Cbz-L-Ala-C(O)NH-C₆-NH-Boc – 34



34

Cbz-L-Ala-OH **31** (3 g, 13.44 mmol, 1.0 eq) and DMAP (164 mg, 1.34 mmol, 0.1 eq) were dissolved in 59.7 mL DCM. To this solution 3.2 g tert-butyl 6-aminohexylcarbamate **29** (14.78 mmol, 1.1 eq) were added. Thereafter, 3.09 g EDC-HCl (16.13 mmol, 1.2 eq) were added portion wise under vigorous stirring and the solution stirred for 4 h at rt. Afterwards, the reaction mixture was extracted with 1 M HCl (3x, 50 mL), sat. aq. NaHCO₃ (1x, 50 mL) and brine (1x, 50 mL). The combined organic phases were dried over MgSO₄, filtered and reduced *in vacuo*. The obtained product was dried in the vacuum oven (40 °C) overnight.

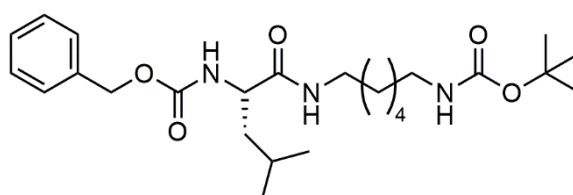
Yield: 4.99 g, 11.84 mmol (88%), white solid.

Molecular formula: C₂₂H₃₅N₃O₅.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 7.80 (t, J = 5.5 Hz, 1H, NH), 7.34 (m, 6H, Caromat, NH), 6.77 (t, J = 5.4 Hz, 1H, NH), 5.00 (d, J = 2.6 Hz, 2H, CH₂), 3.97 (p, J = 7.0 Hz, 1H, CH), 3.02 (hept, J = 6.4 Hz, 3H, CH₂), 2.88 (q, J = 6.5 Hz, 2H, CH₂), 1.36 (m, 13H, CH₂, CH₃), 1.21 (m, 4H, CH₂), 1.17 (d, J = 7.2 Hz, 3H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 444.2469; found: 444.2487.

Cbz-L-Leu-C(O)NH-C₆-NH-Boc – **35**



35

The compound was synthesized according to the procedure of compound **34**.

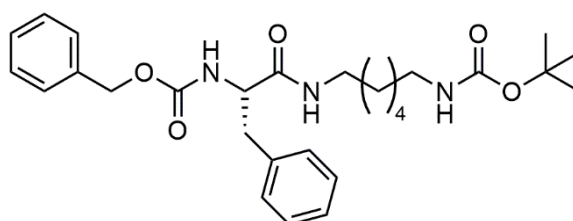
Yield: 11.191 g, 24.13 mmol (83%), yellow liquid.

Molecular formula: C₂₅H₄₁N₃O₅.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 7.86 (t, J = 5.7 Hz, 1H, NH), 7.34 (m, 6H, Caromat, NH), 6.77 (t, J = 5.3 Hz, 1H, NH), 5.01 (s, 2H, CH₂), 4.04 – 3.89 (m, 1H, CH), 3.11 – 2.91 (m, 2H, CH₂), 2.87 (q, J = 6.4 Hz, 2H, CH₂), 1.56 (m, 2H, CH₂), 1.36 (m, 15H, CH₂, CH₃), 1.21 (m, 4H, CH₂), 0.85 (t, J = 6.9 Hz, 6H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 486.2938; found: 486.2897.

Cbz-L-Phe-C(O)NH-C₆-NH-Boc – **36**



36

The compound was synthesized according to the procedure of compound **34**.

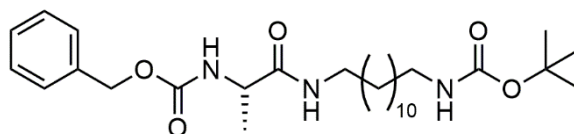
Yield: 5.655 g, 11.36 mmol (68%), yellowish solid.

Molecular formula: C₂₈H₃₉N₃O₅.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 7.94 (t, J = 5.4 Hz, 1H, NH), 7.47 (d, J = 8.6 Hz, 1H, NH), 7.39 – 7.13 (m, 10H, C_{aromat}), 6.77 (t, J = 5.5 Hz, 1H, NH), 4.94 (s, 2H, CH₂), 4.18 (td, J = 9.6, 5.0 Hz, 1H, CH), 2.96 (m, 5H, CH₂), 2.74 (dd, J = 13.5, 10.0 Hz, 1H, CH₂), 1.37 (m, 13H, CH₂, CH₃), 1.19 (m, 4H, CH₂).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 520.2782; found: 520.2785.

Cbz-L-Ala-C(O)NH-C₁₂-NH-Boc – **37**



37

The compound was synthesized according to the procedure of compound **34**.

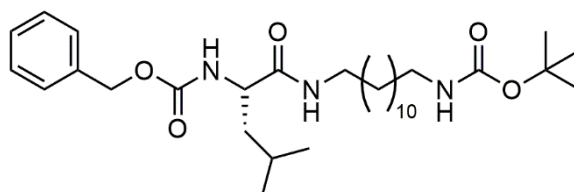
Yield: 6.87 g, 13.59 mmol (82%), white solid.

Molecular formula: C₂₈H₄₇N₃O₅.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 7.79 (t, J = 5.4 Hz, 1H, NH), 7.44 – 7.24 (m, 5H, C_{aromat}, NH), 6.75 (t, J = 5.6 Hz, 1H, NH), 5.00 (s, 2H, CH₂), 3.96 (q, J = 7.3 Hz, 1H, CH), 3.02 (hept, J = 6.5 Hz, 3H, CH₂), 2.87 (q, J = 6.6 Hz, 2H, CH₂), 1.36 (m, 13H, CH₂, CH₃), 1.22 (m, 16H, CH₂), 1.17 (d, J = 7.2 Hz, 3H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 528.3408; found: 528.3412.

Cbz-L-Leu-C(O)NH-C₁₂-NH-Boc – **38**



38

The compound was synthesized according to the procedure of compound **34**.

Yield: 14.341 g, 26.18 mmol (98%), white solid.

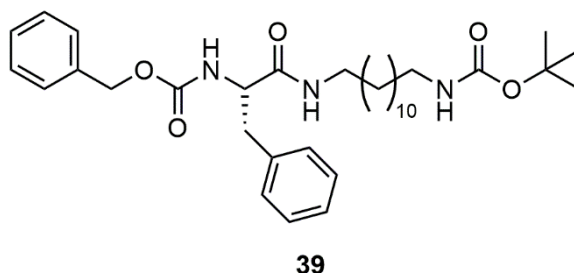
Molecular formula: C₃₁H₅₃N₃O₅.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 7.85 (t, J = 5.4 Hz, 1H, NH), 7.33 (m, 6H, C_{aromat}, NH), 6.75 (t, J = 5.3 Hz, 1H, NH), 5.01 (s, 2H, CH₂), 4.03 – 3.90 (m, 1H, CH), 3.01 (m,

2H, CH₂), 2.87 (q, J = 6.5 Hz, 2H, CH₂), 1.64 – 1.51 (m, 2H, CH₂), 1.36 (m, 15H, CH₂, CH₃), 1.22 (m, 16H, CH₂), 0.85 (t, J = 6.9 Hz, 6H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 570.3877; found: 570.3772.

Cbz-L-Phe-C(O)NH-C₁₂-NH-Boc – 39



The compound was synthesized according to the procedure of compound **34**.

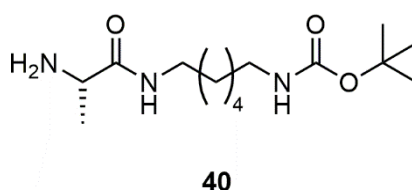
Yield: 7.82 g, 13.44 mmol (81%), white solid.

Molecular formula: C₃₄H₅₁N₃O₅.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 7.93 (t, J = 5.5 Hz, 1H, NH), 7.47 (d, J = 8.6 Hz, 1H, NH), 7.41 – 7.13 (m, 10H, C_{aromat}), 6.75 (t, J = 5.3 Hz, 1H, NH), 4.94 (s, 2H, CH₂), 4.18 (td, J = 9.6, 4.9 Hz, 1H, CH), 3.13 – 2.82 (m, 5H, CH₂), 2.74 (dd, J = 13.7, 10.0 Hz, 1H, CH₂), 1.36 (m, 13H, CH₂, CH₃), 1.22 (m, 16H, CH₂).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 604.3721 ; found: 604.3721.

H₂N-L-Ala-C(O)NH-C₆-NH-Boc – 40



Cbz-L-Ala-C(O)NH-C₆-NH-Boc **34** (7 g, 17.18 mmol, 1.0 eq) was dissolved in 68.7 mL methanol. To this solution 700 mg palladium on activated charcoal (10 wt%) were added and the flask sealed with a septum. By using a balloon, hydrogen was purged through this solution 5x and afterwards a sixth balloon was left on the flask as a hydrogen reservoir. The reaction mixture was stirred overnight at rt. The solution was then filtered over Celite® and reduced *in vacuo*. The obtained product was dried in the vacuum oven (40 °C) overnight.

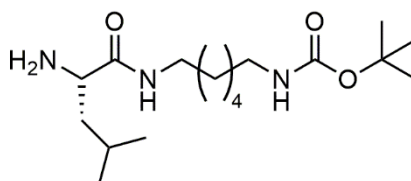
Yield: 4.78 g, 16.63 mmol (98%), white/brownish solid.

Molecular formula: C₁₄H₂₉N₃O₃.

¹H-NMR (300 MHz, CDCl₃, 298 K): δ [ppm] = 7.28 (s, 1H, NH), 4.59 (s, 1H, NH), 3.46 (q, J = 5.8 Hz, 1H, CH), 3.21 (q, J = 6.8 Hz, 2H, CH₂), 3.08 (q, J = 6.5 Hz, 2H, CH₂), 1.63 (s, 2H, NH₂), 1.42 (m, 13H, CH₂, CH₃), 1.31 (m, 7H, CH₂, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 288.2282; found: 288.2347.

H₂N-L-Leu-C(O)NH-C₆-NH-Boc – **41**



41

The compound was synthesized according to the procedure of compound **40**.

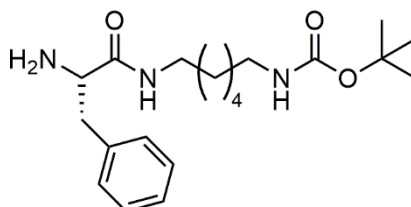
Yield: 3.341 g, 10.14 mmol (93%), white solid.

Molecular formula: C₁₇H₃₅N₃O₃.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 7.82 (t, J = 5.5 Hz, 1H, NH), 6.77 (t, J = 5.4 Hz, 1H, NH), 3.18 – 2.95 (m, 3H, CH₂, CH), 2.88 (q, J = 6.6 Hz, 2H, CH₂), 1.90 (s, 2H, NH₂), 1.65 (m, 1H, CH), 1.36 (m, 13H, CH₂, CH₃), 1.22 (m, 4H, CH₂), 0.85 (d, J = 10.1, 6.6 Hz, 6H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 330.2751; found: 330.2759.

H₂N-L-Phe-C(O)NH-C₆-NH-Boc – **42**



42

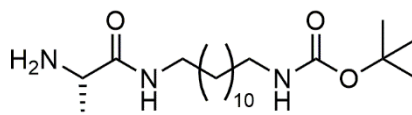
The compound was synthesized according to the procedure of compound **40**.

Yield: 1.313 g, 3.61 mmol (90%), yellowish wax/solid.

Molecular formula: C₂₀H₃₃N₃O₃.

¹H-NMR (300 MHz, CDCl₃, 298 K): δ [ppm] = 7.37 – 7.16 (m, 5H, C_{aromat}), 4.54 (s, 1H, NH), 3.59 (dd, J = 9.3, 4.1 Hz, 1H, CH), 3.32 – 3.17 (m, 3H, CH₂), 3.10 (q, J = 6.5 Hz, 1H, CH₂), 2.69 (dd, J = 13.7, 9.3 Hz, 1H, CH₂), 1.44 (m, 16H, CH₂, CH₃, NH₂), 1.36 – 1.26 (m, 4H, CH₂).
ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 364.2595; found: 364.2605.

H₂N-L-Ala-C(O)NH-C₁₂-NH-Boc – **43**



43

The compound was synthesized according to the procedure of compound **40**.

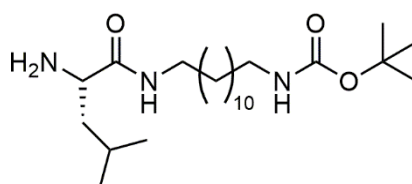
Yield: 3.265 g, 8.79 mmol (89%), yellowish solid.

Molecular formula: C₂₀H₄₁N₃O₃.

¹H-NMR (300 MHz, CDCl₃, 298 K): δ [ppm] = 7.24 (s, 1H, NH), 4.51 (s, 1H, NH), 3.50 (q, J = 7.0 Hz, 1H, CH), 3.23 (q, J = 7.0 Hz, 2H, CH₂), 3.09 (q, J = 6.7 Hz, 2H, CH₂), 1.69 (s, 2H, NH₂), 1.44 (m, 13H, CH₂, CH₃), 1.33 (d, J = 7.0 Hz, 3H, CH₃), 1.25 (m, 16H, CH₂).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 372.3221; found: 372.3207.

H₂N-L-Leu-C(O)NH-C₁₂-NH-Boc – **44**



44

The compound was synthesized according to the procedure of compound **40**.

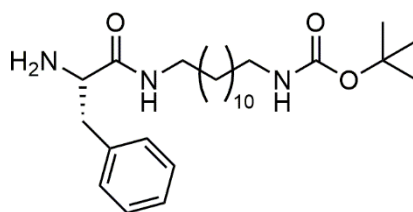
Yield: 6.944 g, 16.79 mmol (92%), white solid.

Molecular formula: C₂₃H₄₇N₃O₃.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 7.79 (t, J = 5.6 Hz, 1H, NH), 6.76 (t, J = 5.5 Hz, 1H, NH), 3.13 – 2.96 (m, 3H, CH, CH₂), 2.87 (q, J = 6.5 Hz, 2H, CH₂), 1.67 (m, 2H, CH₂), 1.36 (m, 15H, CH₂, CH₃), 1.23 (m, 16H, CH₂), 0.85 (dd, J = 10.3, 6.6 Hz, 6H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 414.3690; found: 414.3690.

H₂N-L-Phe-C(O)NH-C₁₂-NH-Boc – **45**



45

The compound was synthesized according to the procedure of compound **40**.

Yield: 5.535 g, 12.36 mmol (91%), white solid.

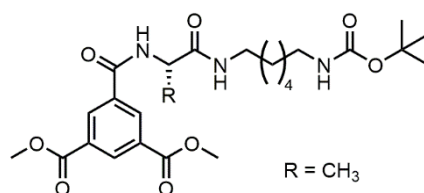
Molecular formula: C₂₆H₄₅N₃O₃.

¹H-NMR (300 MHz, CDCl₃, 298 K): δ [ppm] = 7.37 – 7.15 (m, 5H, C_{aromat}), 4.51 (s, 1H, NH), 3.59 (dd, J = 9.3, 4.1 Hz, 1H, CH), 3.33 – 3.16 (m, 3H, CH, CH₂), 3.09 (q, J = 6.6 Hz, 2H, CH₂), 2.69 (dd, J = 13.7, 9.3 Hz, 1H, CH₂), 1.59 (s, 2H, NH₂), 1.44 (m, 13H, CH₂, CH₃), 1.25 (m, 16H, CH₂).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 448.3539; found: 448.3509.

1.2.3 Benzenetrispeptide building blocks bearing one PEO chain

(S)-dimethyl 5-(1-(6-(*tert*-butoxycarbonylamino)hexylamino)-1-oxopropan-2-ylcarbamoyl)-isophthalate – **46**



46

3,5-bis(methoxycarbonyl)benzoic acid **7** (0.5 g, 2.099 mmol, 1.0 eq) and DMAP (26 mg, 0.21 mmol, 0.1 eq) were dissolved in 10.5 mL chloroform. Compound **40** (0.664 g, 2.309 mmol, 1.1 eq) was added to the reaction mixture. Afterwards, EDC-HCl (0.483 g, 2.52 mmol, 1.2 eq) was added portion wise and the reaction mixture stirred overnight at rt. After removal of the solvent, the crude product was purified via flash chromatography (DCM/MeOH 96.5:3.5, v:v).

Yield: 0.834 g, 1.643 mmol (78%), white solid.

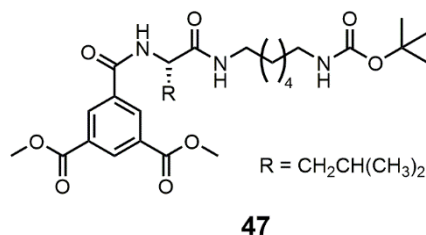
Molecular formula: C₂₅H₃₇N₃O₈.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 9.02 (d, J = 7.4 Hz, 1H, NH), 8.72 (d, J = 1.6 Hz, 2H, CH_{aromat}), 8.58 (t, J = 1.5 Hz, 1H, CH_{aromat}), 6.74 (t, J = 5.4 Hz, 1H, NH), 4.46 (t, J

= 7.3 Hz, 1H, CH), 3.93 (s, 6H, CH₃), 3.05 (p, J = 6.8 Hz, 2H, CH₂), 2.87 (q, J = 6.6 Hz, 2H, CH₂), 1.44 – 1.29 (m, 16H, CH₂, CH₃), 1.29 – 1.17 (m, 4H, CH₂).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 530.2473; found: 530.2468.

dimethyl (*S*)-5-((1-((6-((*tert*-butoxycarbonyl)amino)hexyl)amino)-4-methyl-1-oxopentan-2-yl)carbamoyl)isophthalate – **47**



The compound was synthesized according to the procedure of compound **46**, except using a different eluent composition (here: DCM/MeOH 96:4, v:v) for flash chromatography.

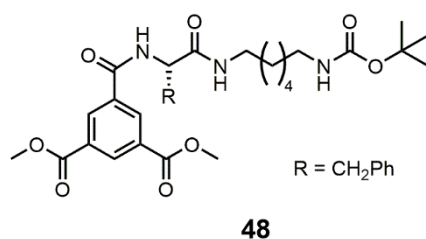
Yield: 1.736 g, 3.158 mmol (83%), white solid.

Molecular formula: C₂₈H₄₃N₃O₈.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.99 (d, J = 8.1 Hz, 1H, NH), 8.73 (d, J = 1.6 Hz, 2H, CH_{aromat}), 8.59 (t, J = 1.5 Hz, 1H, CH_{aromat}), 6.75 (t, J = 4.8 Hz, 1H, NH), 4.56 – 4.43 (m, 1H, CH), 3.93 (s, 6H, CH₃), 3.12 – 2.96 (m, 2H, CH₂), 2.86 (q, J = 7.3, 6.7 Hz, 2H), 1.76 – 1.46 (m, 3H, CH, CH₂), 1.36 (m, 13H, CH₂, CH₃), 1.21 (m, 4H, CH₂), 0.88 (dd, J = 11.2, 6.1 Hz, 6H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 572.2942; found: 572.2926.

dimethyl (*S*)-5-((1-((6-((*tert*-butoxycarbonyl)amino)hexyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamoyl)isophthalate – **48**



The compound was synthesized according to the procedure of compound **46**, except using a different eluent composition (here: DCM/MeOH 97:3, v:v) for flash chromatography.

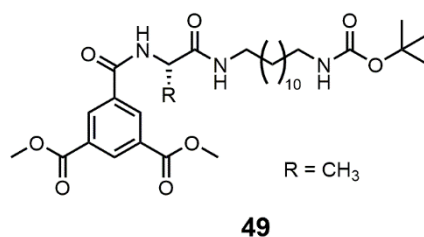
Yield: 0.307 g, 0.526 mmol (84%), white solid.

Molecular formula: C₃₁H₄₁N₃O₈.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 9.15 (d, J = 8.5 Hz, 1H, NH), 8.63 (d, J = 1.5 Hz, 2H, CH_{aromat}), 8.56 (t, J = 1.5 Hz, 1H, CH_{aromat}), 8.11 (t, J = 5.4 Hz, 1H, NH), 7.34 – 7.10 (m, 5H, CH_{aromat}), 6.76 (t, J = 5.5 Hz, 1H, NH), 4.76 – 4.64 (m, 1H, CH), 3.93 (s, 6H, CH₃), 3.14 – 2.93 (m, 4H, CH₂), 2.87 (q, J = 6.3 Hz, 2H, CH₂), 1.42 – 1.27 (m, 13H, CH₂, CH₃), 1.27 – 1.12 (m, 2H, CH₂).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 606.2786; found: 606.2802.

(S)-dimethyl 5-(1-(12-(*tert*-butoxycarbonylamino)dodecylamino)-1-oxopropan-2-ylcarbamoyl)isophthalate – **49**



The compound was synthesized according to the procedure of compound **46**, except using a different eluent composition (here: DCM/MeOH 98:2, v:v) for flash chromatography.

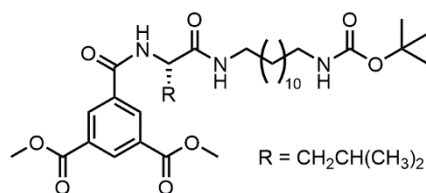
Yield: 0.738 g, 3.158 mmol (79%), white solid.

Molecular formula: C₃₁H₄₉N₃O₈.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 9.04 (d, J = 7.3 Hz, 1H, NH), 8.73 (d, J = 1.6 Hz, 2H, CH_{aromat}), 8.59 (t, J = 1.6 Hz, 1H, CH_{aromat}), 7.93 (t, J = 5.6 Hz, 1H, NH), 6.75 (t, J = 5.3 Hz, 1H, NH), 4.46 (p, J = 7.1 Hz, 1H, CH), 3.93 (s, 6H, CH₃), 3.04 (q, J = 6.2 Hz, 2H, CH₂), 2.87 (q, J = 6.5 Hz, 2H, CH₂), 1.44 – 1.29 (m, 16H, CH₂, CH₃), 1.20 (m, 16H, CH₂).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 614.3412; found: 614.3447.

dimethyl (*S*)-5-((1-((12-((*tert*-butoxycarbonyl)amino)dodecyl)amino)-4-methyl-1-oxopentan-2-yl)carbamoyl)isophthalate – **50**



50

The compound was synthesized according to the procedure of compound **46**, except using a different eluent composition (here: DCM/MeOH 96:4, v:v) for flash chromatography.

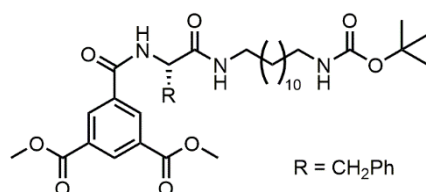
Yield: 1.736 g, 2.739 mmol (83%), white solid.

Molecular formula: C₃₄H₅₅N₃O₈.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.99 (d, *J* = 8.1 Hz, 1H, NH), 8.73 (d, *J* = 1.6 Hz, 2H, CH_{aromat}), 8.59 (t, *J* = 1.5 Hz, 1H, CH_{aromat}), 8.01 (t, *J* = 5.5 Hz, 1H, NH), 6.75 (t, *J* = 5.1 Hz, 1H, NH), 4.57 – 4.45 (m, 1H, CH), 3.93 (s, 6H, CH₃), 3.11 – 2.98 (m, 2H, CH₂), 2.87 (q, *J* = 6.6 Hz, 2H, CH₂), 1.77 – 1.45 (m, 3H, CH, CH₂), 1.36 (m, 13H, CH₂, CH₃), 1.19 (m, 16H, CH₂), 0.88 (dd, *J* = 11.2, 6.1 Hz, 6H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 656.3881; found: 656.3789.

(*S*)-dimethyl 5-(1-(12-((*tert*-butoxycarbonyl)amino)dodecyl)amino)-1-oxo-3-phenylpropan-2-ylcarbamoyl)isophthalate – **51**



51

The compound was synthesized according to the procedure of compound **46**, except using a different eluent composition (here: DCM/MeOH 96:4, v:v) for flash chromatography.

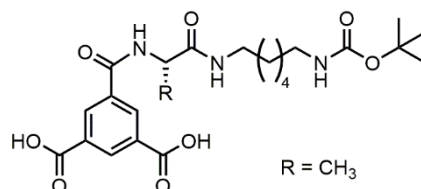
Yield: 1.174 g, 2.739 mmol (93%), white solid.

Molecular formula: C₃₇H₅₃N₃O₈.

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 9.15 (d, *J* = 8.4 Hz, 1H, NH), 8.63 (d, *J* = 1.6 Hz, 2H, CH_{aromat}), 8.56 (t, *J* = 1.6 Hz, 1H, CH_{aromat}), 8.09 (t, *J* = 5.5 Hz, 1H, NH), 7.35 – 7.10 (m, 5H, CH_{aromat}), 6.75 (t, *J* = 5.4 Hz, 1H, NH), 4.72 (m, 1H, CH), 3.92 (s, 6H, CH₃), 3.07 (m, 4H, CH₂), 2.87 (q, *J* = 6.6 Hz, 2H, CH₂), 1.36 (m, 13H, CH₂, CH₃), 1.20 (m, 16H, CH₂).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for $[M+Na]^+$: 690.3725; found: 690.3733.

(S)-5-(1-(6-(*tert*-butoxycarbonylamino)hexylamino)-1-oxopropan-2-ylcarbamoyl)isophthalic acid – **52**



52

Compound **46** (0.819 g, 1.614 mmol, 1.0 eq) was dissolved in 32.23 ml of a 0.7 M KOH-solution in EtOH/H₂O (9:1, v:v) and stirred under reflux for 30 min. Afterwards, 1M aq. HCl was added dropwise under vigorous stirring until the product starts to precipitate. Then, the ethanol was removed *in vacuo* in order to allow an extraction with ethyl acetate. The remaining aqueous phase was extracted with ethyl acetate (3x, 50 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and reduced *in vacuo*. The obtained product was then dried in the vacuum oven (40 °C) overnight.

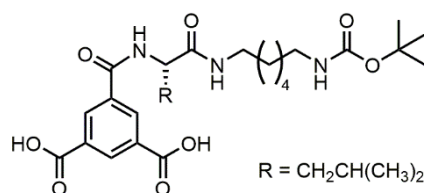
Yield: 0.549 g, 1.145 mmol (71%), white solid.

Molecular formula: C₂₃H₃₃N₃O₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 13.47 (s, 2H, COOH), 8.97 (d, J = 7.4 Hz, 1H, NH), 8.68 (d, J = 1.6 Hz, 2H, CH_{aromat}), 8.58 (t, J = 1.6 Hz, 1H, CH_{aromat}), 7.93 (t, J = 5.6 Hz, 1H, NH), 6.75 (t, J = 5.6 Hz, 1H, NH), 4.45 (p, J = 7.1 Hz, 1H, CH), 3.04 (m, 4H, CH₂), 2.87 (q, J = 6.6 Hz, 2H, CH₂), 1.35 (m, 16H, CH₂, CH₃), 1.22 (m, 4H, CH₂).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for $[M+Na]^+$: 502.2160; found: 502.2158.

(S)-5-((1-((6-((*tert*-butoxycarbonyl)amino)hexyl)amino)-4-methyl-1-oxopentan-2-yl)carbamoyl)isophthalic acid – **53**



53

The compound was synthesized according to the procedure of compound **52**.

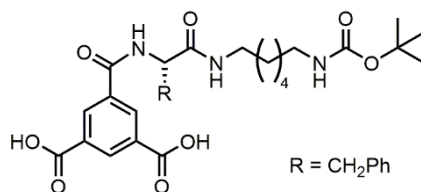
Yield: 0.323 g, 0.619 mmol (99%), white solid.

Molecular formula: C₂₆H₃₉N₃O₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 13.48 (s, 2H, COOH), 8.92 (d, J = 8.1 Hz, 1H, NH), 8.68 (d, J = 1.6 Hz, 2H, CH_{aromat}), 8.57 (t, J = 1.6 Hz, 1H, CH_{aromat}), 8.00 (t, J = 5.6 Hz, 1H, NH), 6.75 (t, J = 5.7 Hz, 1H, NH), 4.55 – 4.44 (m, 1H, CH), 3.03 (m, 2H, CH₂), 2.87 (q, J = 6.7 Hz, 2H, CH₂), 1.75 – 1.47 (m, 4H, CH₂), 1.33 (m, 13H, CH₂, CH₃), 1.23 (s, 4H, CH₂), 0.88 (dd, J = 11.1, 6.2 Hz, 6H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 544.2690; found: 544.2557.

(S)-5-((1-(((6-((*tert*-butoxycarbonyl)amino)hexyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamoyl)isophthalic acid – **54**



54

The compound was synthesized according to the procedure of compound **52**.

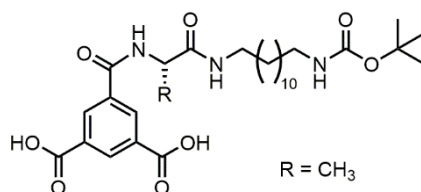
Yield: 0.248 g, 0.446 mmol (99%), white solid.

Molecular formula: C₂₉H₃₇N₃O₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 9.08 (d, J = 8.0 Hz, 1H, NH), 8.59 (d, J = 1.5 Hz, 2H, CH_{aromat}), 8.55 (t, J = 1.4 Hz, 1H, CH_{aromat}), 8.11 (t, J = 5.1 Hz, 1H, NH), 7.36 – 7.10 (m, 5H, CH_{aromat}), 6.77 (t, J = 5.3 Hz, 1H, NH), 4.76 – 4.63 (m, 1H, CH), 3.15 – 2.94 (m, 4H, CH₂), 2.87 (q, J = 6.8 Hz, 2H, CH₂), 1.42 – 1.27 (m, 13H, CH₂, CH₃), 1.27 – 1.14 (m, 4H, CH₂).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 578.2473; found: 578.2467.

(S)-5-(1-(12-(*tert*-butoxycarbonylamino)dodecylamino)-1-oxopropan-2-ylcarbamoyl)isophthalic acid – **55**



55

The compound was synthesized according to the procedure of compound **52**.

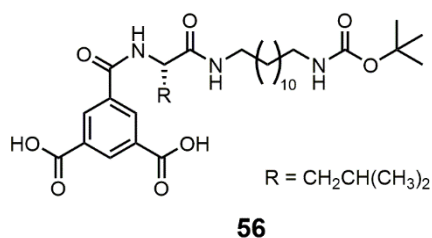
Yield: 0.511 g, 0.907 mmol (94%), white solid.

Molecular formula: C₂₉H₄₅N₃O₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 13.50 (s, 2H, COOH), 8.97 (d, J = 7.3 Hz, 1H, NH), 8.73 – 8.65 (m, 2H, CH_{aromat}), 8.60 – 8.56 (m, 1H, CH_{aromat}), 7.90 (t, J = 5.2 Hz, 1H, NH), 6.79 – 6.70 (m, 1H, NH), 4.45 (p, J = 6.9, 6.4 Hz, 1H), 3.04 (q, J = 7.3, 6.8 Hz, 2H, CH₂), 2.87 (q, J = 6.2 Hz, 2H, CH₂), 1.35 (m, 17H, CH₂, CH₃), 1.20 (m, 16H, CH₂).

ESI-ToF-MS (negative mode, acetonitrile) (m/z): calculated for [M-H]⁻: 638.3447; found: 638.3283.

(S)-5-((1-((12-((*tert*-butoxycarbonyl)amino)dodecyl)amino)-4-methyl-1-oxopentan-2-yl)carbamoyl)isophthalic acid – **56**



The compound was synthesized according to the procedure of compound **52**.

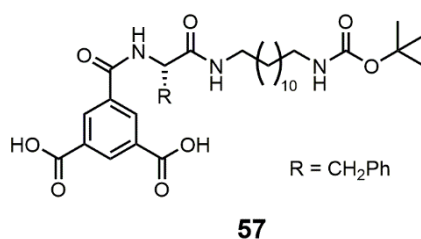
Yield: 1.404 g, 2.318 mmol (94%), white solid.

Molecular formula: C₃₂H₅₁N₃O₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.93 (d, J = 8.5 Hz, 1H, NH), 8.67 (d, J = 1.6 Hz, 2H, CH_{aromat}), 8.57 (t, J = 1.5 Hz, 1H, CH_{aromat}), 8.00 (t, J = 5.5 Hz, 1H, NH), 6.75 (t, J = 5.5 Hz, 1H, NH), 4.54 – 4.43 (m, 1H, CH), 3.08 – 2.99 (m, 2H, CH₂), 2.86 (q, J = 6.5 Hz, 2H, CH₂), 1.75 – 1.48 (m, 3H, CH, CH₂), 1.35 (m, 13H, CH₂, CH₃), 1.19 (m, 16H, CH₂), 0.88 (dd, J = 11.3, 6.2 Hz, 6H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 628.3568; found: 628.3444.

(S)-5-(1-(12-((*tert*-butoxycarbonyl)amino)dodecylamino)-1-oxo-3-phenylpropan-2-yl)carbamoyl)isophthalic acid – **57**



The compound was synthesized according to the procedure of compound **52**.

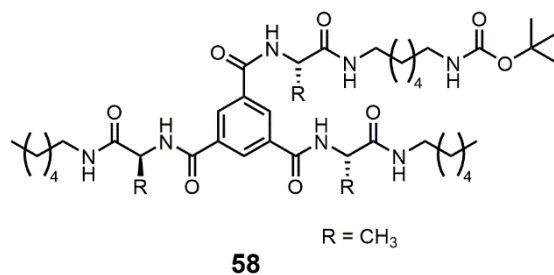
Yield: 1.029 g, 1.608 mmol (99%), white solid.

Molecular formula: C₃₅H₄₉N₃O₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 13.34 (s, 1H, COOH), 9.08 (d, J = 8.4 Hz, 1H, NH), 8.60 (d, J = 1.6 Hz, 2H, CH_{aromat}), 8.55 (t, J = 1.5 Hz, 1H, CH_{aromat}), 8.07 (t, J = 5.5 Hz, 1H, NH), 7.34 – 7.10 (m, 5H, CH_{aromat}), 6.75 (t, J = 5.2 Hz, 1H, NH), 4.70 (td, J = 9.5, 5.1 Hz, 1H, CH), 3.13 – 2.94 (m, 4H, CH₂), 2.87 (q, J = 6.6 Hz, 2H, CH₂), 1.36 (m, 13H, CH₂, CH₃), 1.20 (m, 16H, CH₂).

ESI-ToF-MS (negative mode, acetonitrile) (m/z): calculated for [M-H]⁻: 638.3447; found: 638.3283.

[B][Ala][C₆] Boc-protected – **58**



Compound **52** (0.549 g, 1.145 mmol, 1.0 eq) and DMAP (14 mg, 0.114 mmol, 0.1 eq) were dissolved in 5.7 mL chloroform. To this, compound **19** (0.434 g, 2.52 mmol, 2.2 eq) was added. Consequently, EDC-HCl (0.658 g, 3.43 mmol, 3 eq) was added and the solution stirred overnight at rt. Afterwards, the solvent was removed and crude product purified via flash chromatography (DCM/MeOH, 92:8, v:v).

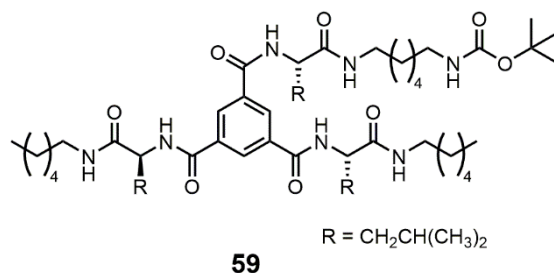
Yield: 0.703 g, 0.892 mmol (78%), white solid.

Molecular formula: C₄₁H₆₉N₇O₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.67 (d, J = 7.4 Hz, 3H, NH), 8.47 (d, J = 1.1 Hz, 3H, CH_{aromat}), 7.96 (t, J = 5.3 Hz, 3H, NH), 6.77 (t, J = 5.4 Hz, 1H, NH), 4.50 (p, J = 7.2 Hz, 3H, CH), 3.05 (m, 6H, CH₂), 2.88 (q, J = 6.5 Hz, 2H, CH₂), 1.34 (m, 23H, CH₂, CH₃), 1.24 (m, 16H, CH₂), 0.84 (t, J = 7.5 Hz, 6H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 810.5100; found: 810.5124.

[B][Leu][C₆] Boc-protected – 59



The compound was synthesized according to the procedure of compound **58**, except using a different eluent composition (here: DCM/MeOH 96:4, v:v) for flash chromatography.

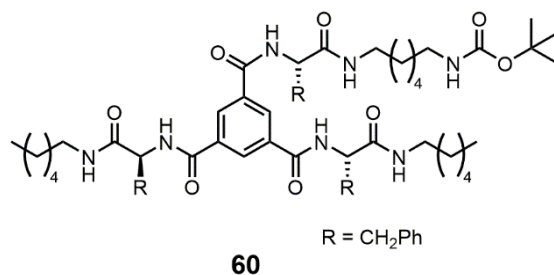
Yield: 0.155 g, 0.157 mmol (44%), light yellow solid.

Molecular formula: C₅₀H₈₇N₇O₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.63 (d, J = 8.2 Hz, 3H, NH), 8.43 (s, 3H, CH_{aromat}), 8.01 (t, J = 5.3 Hz, 3H, NH), 6.75 (t, J = 5.4 Hz, 1H, NH), 4.54 (m, 3H, CH), 3.14 – 2.96 (m, 6H, CH₂), 2.87 (q, J = 6.6 Hz, 2H, CH₂), 1.73 – 1.58 (m, 6H, CH₂), 1.57 – 1.46 (m, 3H, CH), 1.45 – 1.30 (m, 17H, CH₂, CH₃), 1.29 – 1.15 (m, 16H, CH₂), 0.90 (dd, J = 9.0, 6.4 Hz, 18H, CH₃), 0.84 (t, J = 7.5 Hz, 6H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 936.6508; found: 936.6489.

[B][Phe][C₆] Boc-protected – 60



The compound was synthesized according to the procedure of compound **58**, except using DMF as reaction solvent and a different eluent composition (here: DCM/MeOH 90:10, v:v) for flash chromatography.

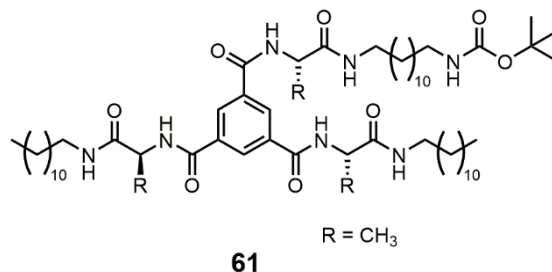
Yield: 0.765 g, 0.753 mmol (49%), light yellow solid.

Molecular formula: C₅₉H₈₁N₇O₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.75 – 8.63 (m, 3H, NH), 8.34 – 8.25 (m, 3H, CH_{aromat}), 8.15 – 8.06 (m, 3H, NH), 7.37 – 7.11 (m, 15H, CH_{aromat}), 6.76 (t, J = 5.4 Hz, 1H, NH), 4.77 – 4.68 (m, 3H, CH), 3.14 – 2.94 (m, 12H, CH₂), 2.88 (q, J = 6.1 Hz, 3H, CH₂), 1.36 (m, 17H, CH₂, CH₃), 1.22 (m, 16H, CH₂), 0.84 (t, J = 6.9 Hz, 6H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for $[M+Na]^+$: 1038.6039; found: 1038.6000.

[B][Ala][C₁₂] Boc-protected – **61**



The compound was synthesized according to the procedure of compound **58**, except using DMF as reaction solvent and a different eluent composition (here: DCM/MeOH 96:4, v:v) for flash chromatography.

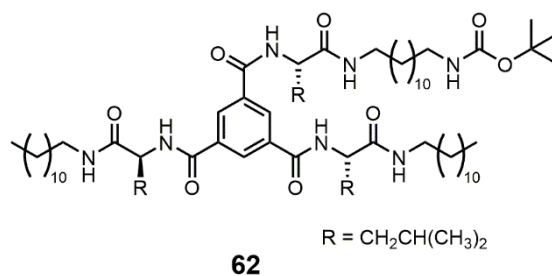
Yield: 0.605 g, 0.581 mmol (37.5%), light yellow solid.

Molecular formula: C₅₉H₁₀₅N₇O₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.66 (d, J = 7.5 Hz, 3H, NH), 8.47 (d, J = 1.0 Hz, 3H, CH_{aromat}), 7.95 (t, J = 7.5 Hz, 3H, NH), 6.75 (t, J = 5.6 Hz, 1H, NH), 4.49 (p, J = 7.0 Hz, 3H, CH), 3.05 (q, J = 6.3, 5.9 Hz, 6H, CH₂), 2.88 (q, J = 6 Hz, 1H), 1.45 – 1.30 (m, 26H, CH₂, CH₃), 1.22 (m, 52H, CH₂), 0.84 (t, J = 7.5 Hz, 6H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for $[M+Na]^+$: 1062.7917; found: 1062.7879.

[B][Leu][C₁₂] Boc-protected – **62**



The compound was synthesized according to the procedure of compound **58**, except using a different eluent composition (here: DCM/MeOH 96:4, v:v) for flash chromatography.

Yield: 0.288 g, 0.247 mmol (74%), light yellow solid.

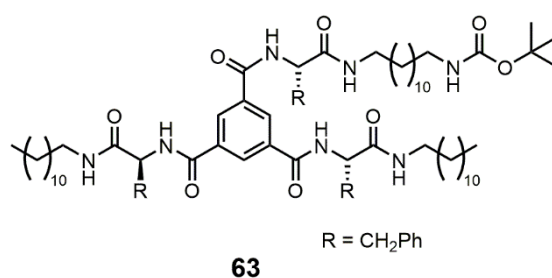
Molecular formula: C₆₈H₁₂₃N₇O₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.63 (d, J = 8.3 Hz, 3H, NH), 8.43 (s, 3H, CH_{aromat}), 8.01 (t, J = 5.4 Hz, 3H, NH), 6.74 (t, J = 5.3 Hz, 1H, NH), 4.58 – 4.47 (m, 3H, CH),

3.05 (hept, $J = 6.5$ Hz, 6H, CH₂), 2.87 (q, $J = 6.7$ Hz, 2H, CH₂), 1.75 – 1.47 (m, 9H, CH, CH₂), 1.36 (m, 17H, CH₂, CH₃), 1.21 (s, 52H, CH₂), 0.98 – 0.77 (m, 24H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 1188.9325; found: 1188.9310.

[B][Phe][C₁₂] Boc-protected – **63**



The compound was synthesized according to the procedure of compound **58**, except using DMF as reaction solvent and a different eluent composition (here: DCM/MeOH 96:4, v:v) for flash chromatography.

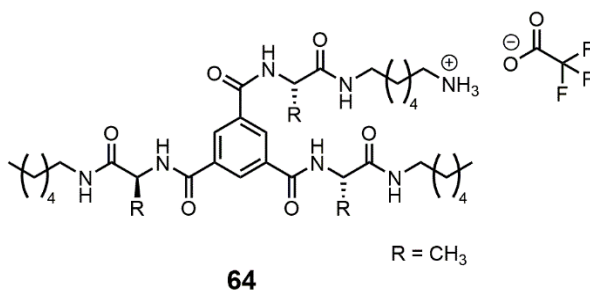
Yield: 0.442 g, 0.348 mmol (45%), light yellow solid.

Molecular formula: C₇₇H₁₁₇N₇O₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.72 (t, $J = 7.9$ Hz, 3H, NH), 8.35 – 8.25 (m, 3H, CH_{aromat}), 8.16 – 8.04 (m, 3H, NH), 7.37 – 7.09 (m, 15H, CH_{aromat}), 6.75 (t, $J = 5.2$ Hz, 1H, NH), 4.80 – 4.63 (m, 3H, CH), 3.16 – 2.92 (m, 12H, CH₂), 2.87 (q, $J = 6.6$ Hz, 2H, CH₂), 1.36 (m, 17H, CH₂, CH₃), 1.21 (m, 52H, CH₂), 0.84 (t, $J = 6.6$ Hz, 6H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+Na]⁺: 1290.8856; found: 1290.8791.

[B][Ala][C₆] Boc-deprotected – **64**



Compound **58** (0.690 g, 0.876 mmol, 1.0 eq) was dissolved in 8.76 mL DCM. To this, 2.82 mL of an 18:1:1 solution of TFA/TIPS/H₂O (TFA: 2.429 mL, 31.5 mmol, 36 eq; TIPS: 0.359 mL, 1.751 mmol, 2 eq; H₂O: 0.032 mL, 1.751 mmol, 2 eq) was added dropwise and the solution stirred for 2 h at rt. Afterwards, half of the DCM volume was removed and the concentrated

reaction mixture precipitated in cold diethyl ether. The suspension was centrifuged (3 min, 8,000 rpm) and the supernatant decanted. The obtained product was dried in the vacuum oven (40 °C overnight).

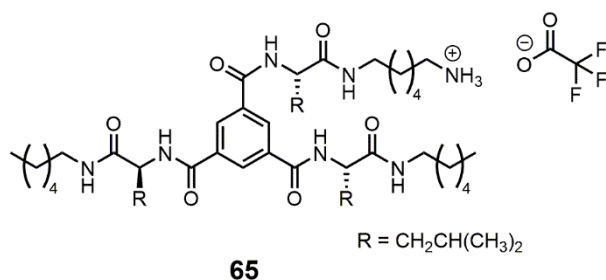
Yield: 0.636 g, 0.739 mmol (91%), white solid.

Molecular formula: C₃₂H₆₂N₇O₂F₃

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.67 (t, J = 6.5 Hz, 3H, NH), 8.50 – 8.45 (m, 3H, CH_{aromat}), 7.98 (t, J = 5.4 Hz, 3H, NH), 7.63 (s, 3H, NH₃), 4.49 (p, J = 6.2, 5.5 Hz, 3H, CH), 3.06 (hept, J = 6.3 Hz, 6H, CH₂), 2.84 – 2.69 (m, 2H, CH₂), 1.57 – 1.46 (m, 2H, CH₂), 1.36 (m, 11H, CH₂, CH₃), 1.26 (m, 16H), 0.85 (t, J = 7.5 Hz, 6H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 688.4756; found: 688.4741.

[B][Leu][C₆] Boc-protected – **65**



The compound was synthesized according to the procedure of compound **64**.

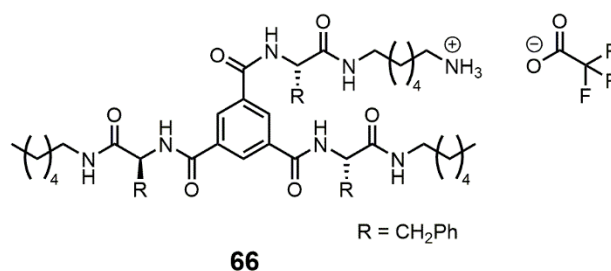
Yield: 0.099 g, 0.107 mmol (98%), white solid.

Molecular formula: C₄₂H₈₀N₇O₂F₃

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.63 (d, J = 8.3 Hz, 3H, NH), 8.43 (s, 3H, CH_{aromat}), 8.03 (t, J = 5.2 Hz, 3H, NH), 7.60 (s, 3H, NH₃), 4.52 (t, J = 7.0 Hz, 3H, CH), 3.07 (m, 6H, CH₂), 2.83 – 2.69 (m, 2H, CH₂), 1.75 – 1.32 (m, 17H, CH, CH₂), 1.24 (m, 16H, CH₂), 0.98 – 0.75 (m, 24H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 814.6165; found: 814.6142.

[B][Phe][C₆] Boc-deprotected – 66



The compound was synthesized according to the procedure of compound 64.

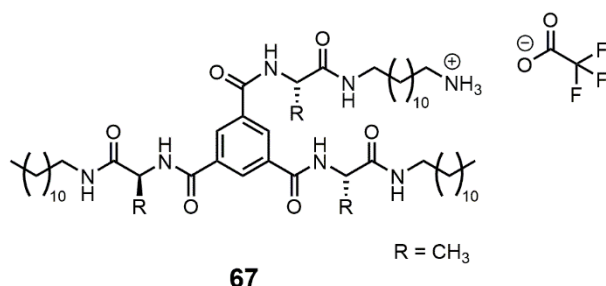
Yield: 0.621 g, 0.603 mmol (88%), white solid.

Molecular formula: C₅₂H₇₄N₇O₂F₃

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.80 – 8.64 (m, 3H, NH), 8.37 – 8.25 (m, 3H, CH_{aromat}), 8.22 – 8.07 (m, 3H, NH), 7.79 (s, 3H, NH₃), 7.39 – 7.08 (m, 15H, CH_{aromat}), 4.82 – 4.64 (m, 3H, CH_{aromat}), 3.19 – 2.92 (m, 12H, CH₂), 2.84 – 2.68 (m, 2H, CH₂), 1.50 (q, J = 7.6, 7.0 Hz, 2H, CH₂), 1.37 (m, 6H, CH₂), 1.22 (m, 17H, CH₂), 0.84 (t, J = 6.5 Hz, 6H, CH₃).

ESI-ToF-MS (mode, acetonitrile) (m/z): calculated for [M+H]⁺: 916.5695; found: 916.5658.

[B][Ala][C₁₂] Boc-deprotected – 67



The compound was synthesized according to the procedure of compound 64.

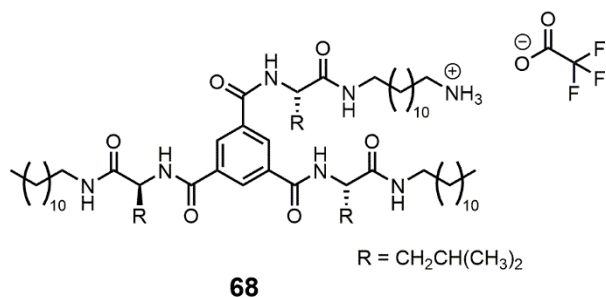
Yield: 0.533 g, 0.505 mmol (87%), white solid.

Molecular formula: C₅₆H₉₈N₇O₈F₃

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.67 (d, J = 7.4 Hz, 3H, NH), 8.48 (d, J = 1.4 Hz, 3H, CH_{aromat}), 7.97 (t, J = 5.5 Hz, 3H, NH), 7.70 (s, 3H, NH₃), 4.49 (p, J = 6.9 Hz, 3H, CH), 3.06 (q, J = 6.6 Hz, 6H, CH₂), 2.76 (dq, J = 12.8, 5.7 Hz, 2H, CH₂), 1.59 – 1.46 (m, 2H, CH₂), 1.36 (m, 15H, CH₂, CH₃), 1.23 (m, 48H, CH₂), 0.85 (t, J = 7.5 Hz, 6H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 940.7573; found: 940.7574.

[B][Leu][C₁₂] Boc-deprotected – 68



The compound was synthesized according to the procedure of compound **64**.

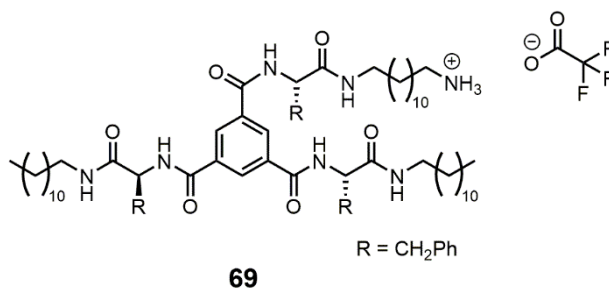
Yield: 0.195 g, 0.165 mmol (96%), white solid.

Molecular formula: C₆₅H₁₁₆N₇O₈F₃

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.63 (d, J = 8.2 Hz, 3H, NH), 8.43 (s, 3H, CH_{aromat}), 8.02 (t, J = 5.3 Hz, 3H, NH), 7.59 (s, 3H, NH₃), 4.62 – 4.45 (m, 3H, CH), 3.13 – 2.95 (m, 6H, CH₂), 2.81 – 2.74 (m, 2H, CH₂), 1.75 – 1.33 (m, 17H, CH₂, CH₃), 1.22 (m, 52H, CH₂), 0.97 – 0.74 (m, 24H, CH₃).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+H]⁺: 1066.8982; found: 1066.8958.

[B][Phe][C₁₂] Boc-deprotected – 69



The compound was synthesized according to the procedure of compound **64**.

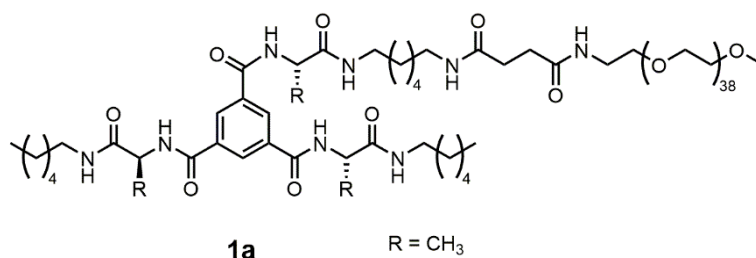
Yield: 0.311 g, 0.242 mmol (80%), white solid.

Molecular formula: C₇₄H₁₁₀N₇O₈F₃

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.73 (t, J = 7.4 Hz, 3H, NH), 8.38 – 8.24 (m, 3H, CH_{aromat}), 8.11 (t, J = 4.7 Hz, 3H, NH), 7.70 (s, 3H, NH₃), 7.38 – 7.08 (m, 15H, CH_{aromat}), 4.72 (q, J = 8.9 Hz, 3H, CH), 3.18 – 2.91 (m, 12H, CH₂), 2.83 – 2.64 (m, 2H, CH₂), 1.59 – 1.44 (m, 2H, CH₂), 1.36 (m, 6H, CH₂), 1.22 (m, 52H, CH₂), 0.84 (t, J = 6.5 Hz, 6H, CH₃).

ESI-ToF-MS (mode, acetonitrile) (m/z): calculated for [M+H]⁺: 1168.8512; found: 1168.8467.

[B][Ala]₃[C₆]₃[PEO_{2k}] – **1a**



Compound **64** (0.599 g, 0.747 mmol, 1.0 eq) was dissolved in 9.96 mL DMF. To this, 1.041 mL triethylamine (7.47 mmol, 10 eq) were added dropwise. After stirring at rt for 15 min, 1.784 g of MeO-PEO_{2k}-NHS ester (0.896 mmol, 1.2 eq) were added and the reaction mixture stirred at rt overnight. Afterwards, the reaction mixture was precipitated into cold diethyl ether, the suspension centrifuged (3 min, 8,000 rpm) and the supernatant decanted. Then a mixture of diethyl ether and acetone (9:1, v:v) was added to the precipitate and the suspension exposed to sonication for 5 min in order to remove all residual DMF and some unconjugated MeO-PEO_{2k}-NHS ester. Afterwards, the suspension was again centrifuged (3 min, 8,000 rpm) and the supernatant decanted. Still remaining MeO-PEO_{2k}-NHS ester was then removed via continuous centrifugal washing using Amicon® Ultra-15 centrifugal filter units (MWCO: 10 kDa). The obtained product was then dissolved in water and lyophilised overnight.

Yield: 1.734 g, 0.677 mmol (91%), white powder.

Molecular formula: C₁₂₁H₂₂₈N₈O₄₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.66 (d, J = 7.4 Hz, 3H, NH), 8.47 (s, 3H, CH_{aromat}), 7.96 (t, J = 5.0 Hz, 3H, NH), 7.87 (t, J = 5.3 Hz, 1H, NH), 7.76 (t, J = 5.2 Hz, 1H, NH), 4.49 (p, J = 6.6 Hz, 3H, CH), 3.77 – 3.70 (m, 2H, CH₂), 3.50 (s, 148H, PEO), 3.45 – 3.41 (m, 2H, CH₂), 3.23 (s, 2H, CH₂), 3.16 (q, J = 5.6 Hz, 2H, CH₂), 3.12 – 2.93 (m, 6H, CH₂), 2.27 (s, 4H, CH₂), 1.47 – 1.30 (m, 11H, CH₂, CH₃), 1.24 (s, 16H, CH₂), 0.84 (t, J = 6.4 Hz, 6H, CH₃).

MALDI-ToF-MS (positive mode, DHB) (m/z): calculated for [C₁₁₉H₂₂₄N₈O₄₇Na]⁺: 2541.5309; found: 2541.6358.

SEC (DMAc + 0.21 wt.% LiCl): M_n = 2,400 g mol⁻¹; M_w = 3,000 g mol⁻¹; Đ = 1.26.

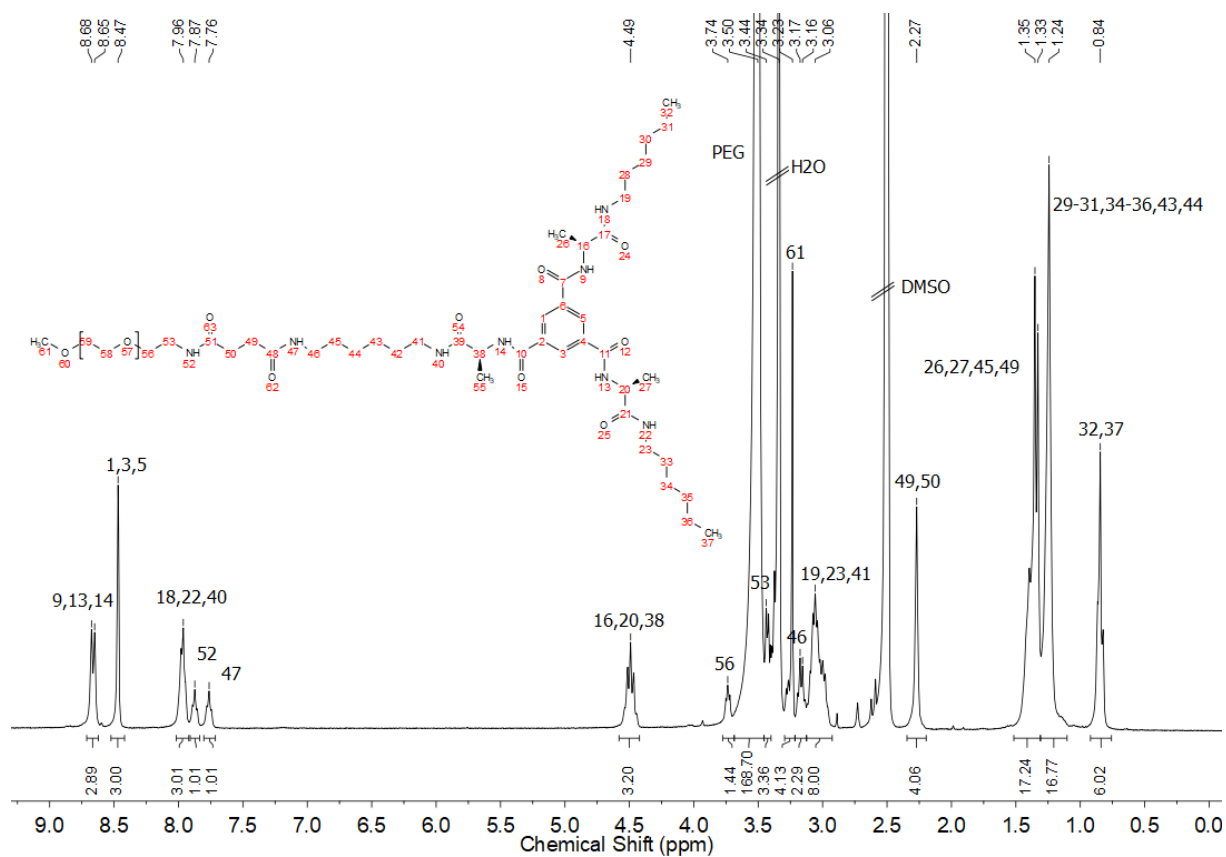


Figure S 1: ¹H-NMR spectrum of **1a** measured in d₆-DMSO.

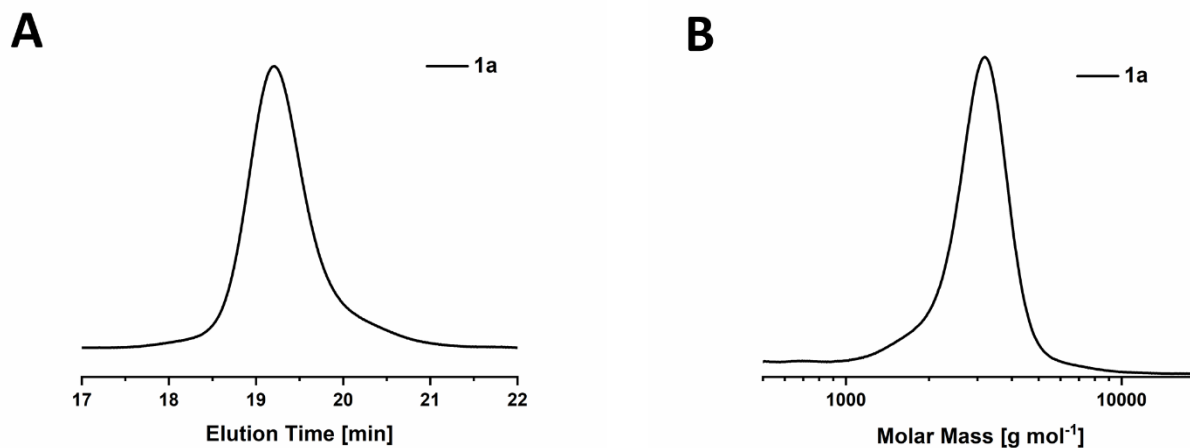
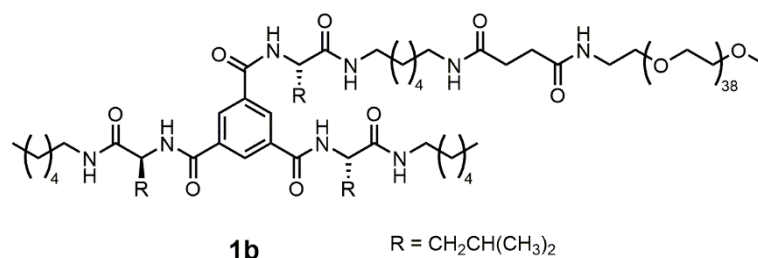


Figure S 2: SEC traces of **1a** recorded in DMAc (+0.21 wt% LiCl; 25 °C, RI, detection, PEO-Standard). A) Elution profile, B) Molar Mass distribution.

[B][Leu]₃[C₆]₃[PEO_{2k}] – **1b**



The compound was synthesized according to the procedure of compound **1a**.

Yield: 0.148 g, 0.055 mmol (68%), white powder.

Molecular formula: C₁₃₀H₂₄₆N₈O₄₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.65 (d, J = 8.1 Hz, 3H, NH), 8.43 (s, 3H, CH_{aromat}), 8.03 (t, J = 4.8 Hz, 3H, NH), 7.87 (t, J = 5.1 Hz, 1H, NH), 7.76 (t, J = 4.7 Hz, 1H, NH), 4.60 – 4.47 (m, 3H, CH), 3.78 – 3.70 (m, 2H, CH₂), 3.50 (s, 148H, PEO), 3.45 – 3.41 (m, 2H, CH₂), 3.23 (s, 2H, CH₂), 3.17 (q, J = 5.4 Hz, 2H, CH₂), 3.13 – 2.94 (m, 8H, CH₂), 2.27 (s, 4H, CH₂), 1.66 (q, J = 8.1, 6.5 Hz, 6H, CH₂), 1.59 – 1.46 (m, 3H, CH), 1.46 – 1.32 (m, 8H, CH₂), 1.24 (s, 14H, CH₂) 0.90 (t, J = 6.2 Hz, 18H, CH₃), 0.84 (t, J = 6.2 Hz, 6H, CH₃).

MALDI-ToF-MS (positive mode, DHB) (m/z): calculated for [C₁₂₈H₂₄₂N₈O₄₇Na]⁺: 2667.6718; found: 2667.8208.

SEC (DMAc + 0.21 wt.% LiCl): M_n = 3,100 g mol⁻¹; M_w = 3,200 g mol⁻¹; Đ = 1.05.

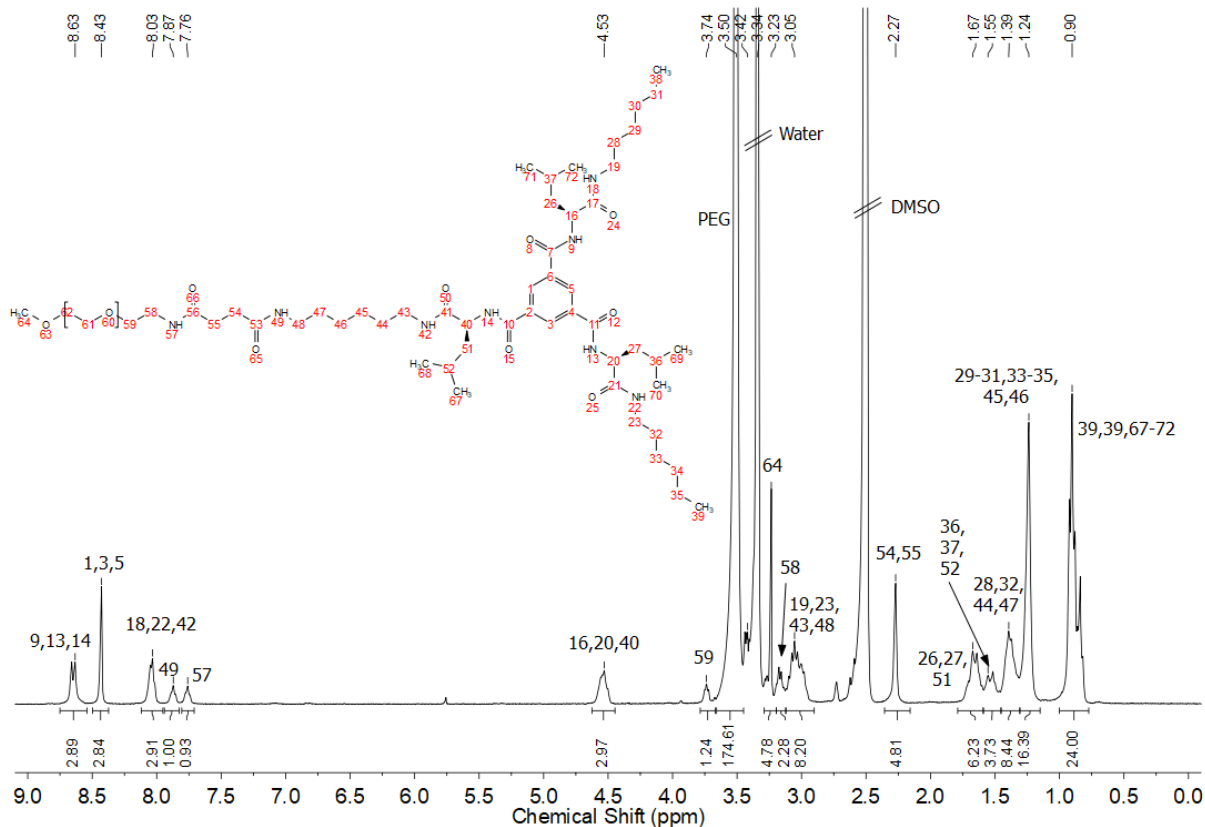


Figure S 3: ¹H-NMR spectrum of **1b** measured in d₆-DMSO.

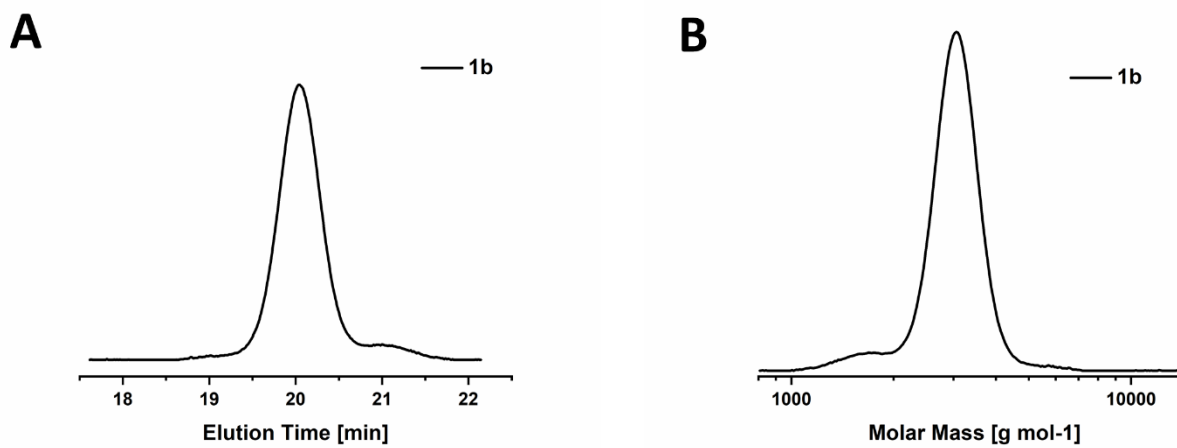
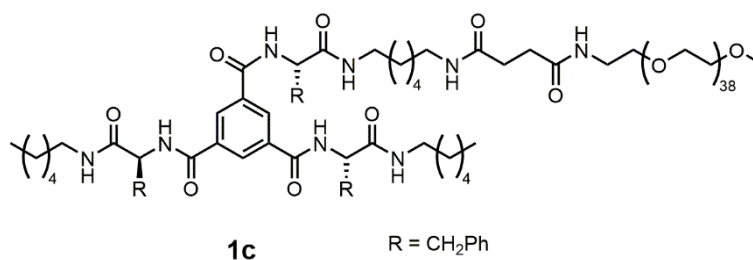


Figure S 4: SEC traces of **1b** recorded in DMAc (+0.21 wt% LiCl; 25 °C, RI, detection, PEO-Standard). A) Elution profile, B) Molar Mass distribution.

[B][Phe]₃[C₆]₃[PEO_{2k}] – **1c**



The compound was synthesized according to the procedure of compound **1a**.

Yield: 1.191 g, 0.427 mmol (75%), white powder.

Molecular formula: C₁₃₉H₂₄₀N₈O₄₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.78 – 8.62 (m, 3H, NH), 8.36 – 8.23 (m, 3H, CH_{aromat}), 8.17 – 8.05 (m, 3H, NH), 7.87 (t, J = 5.4 Hz, 1H, NH), 7.76 (t, J = 5.8 Hz, 1H, NH), 7.37 – 7.09 (m, 15H, CH_{aromat}), 4.79 – 4.64 (m, 3H, CH), 3.78 – 3.70 (m, 2H, CH₂), 3.50 (s, 148H, PEO), 3.45 – 3.40 (m, 2H, CH₂), 3.23 (s, 2H, CH₂), 3.17 (q, J = 5.9 Hz, 2H, CH₂), 3.13 – 2.92 (m, 12H, CH₂), 2.28 (s, 4H, CH₂), 1.36 (m, 8H, CH₂), 1.22 (m, 18H, CH₂), 0.84 (t, J = 6.6 Hz, 6H, CH₃).

MALDI-ToF-MS (positive mode, DHB) (m/z): calculated for [C₁₃₇H₂₃₈N₈O₄₇Na]⁺: 2769.6249; found: 2769.8914.

SEC (DMAc + 0.21 wt.% LiCl): M_n = 2,700 g mol⁻¹; M_w = 3,100 g mol⁻¹; Đ = 1.16.

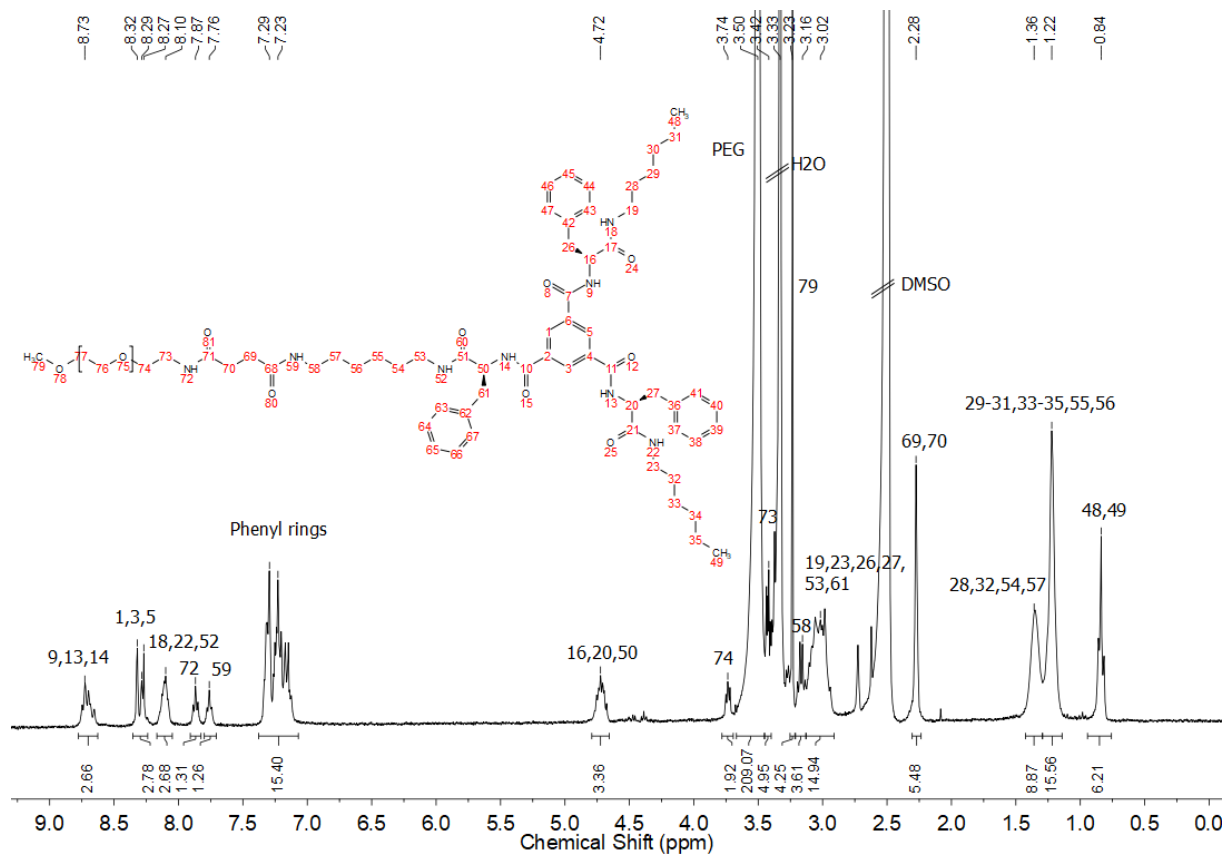


Figure S 5: ¹H-NMR spectrum of **1c** measured in d₆-DMSO.

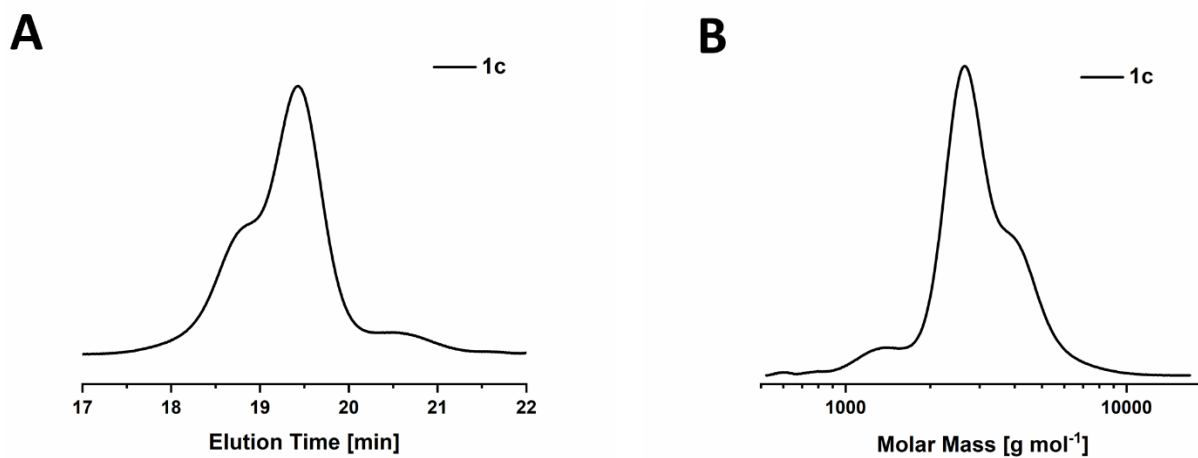
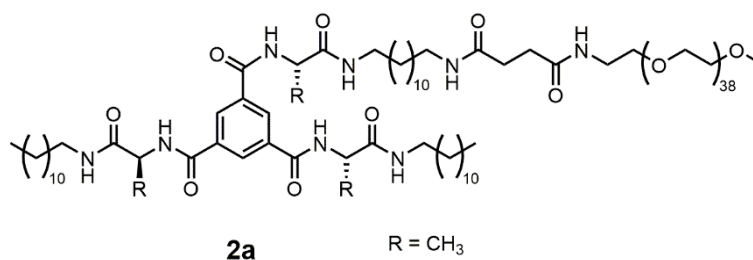


Figure S 6: SEC traces of **1c** recorded in DMAc (+0.21 wt% LiCl; 25 °C, RI, detection, PEO-Standard). A) Elution profile, B) Molar Mass distribution. The peak at around 1500 g mol⁻¹ is caused by residual NHS-PEO2k-MeO and the shoulder at higher molar masses most likely originates from assembly of **1c**.

[B][Ala]₃[C₁₂]₃[PEO_{2k}] – **2a**



The compound was synthesized according to the procedure of compound **1a**.

Yield: 0.359 g, 0.128 mmol (90%), white powder.

Molecular formula: C₁₃₉H₂₆₄N₈O₄₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.65 (d, J = 7.4 Hz, 3H, NH), 8.47 (s, 3H, CH_{aromat}), 7.95 (t, J = 5.5 Hz, 3H), 7.87 (t, J = 5.5 Hz, 1H, NH), 7.75 (t, J = 5.4 Hz, 1H, NH), 4.49 (p, J = 6.9 Hz, 3H, CH), 3.74 (t, J = 4.8 Hz, 2H, CH₂), 3.50 (s, 148H, PEO), 3.46 – 3.39 (m, 2H, CH₂), 3.23 (s, 2H, CH₂), 3.16 (q, J = 5.9 Hz, 2H, CH₂), 3.12 – 2.93 (m, 6H, CH₂), 2.27 (s, 4H, CH₂), 1.46 – 1.30 (m, 17H, CH₂, CH₃), 1.22 (m, 54H, CH₂), 0.89 – 0.80 (m, 6H, CH₃).

MALDI-ToF-MS (positive mode, DHB) (m/z): calculated for [C₁₃₇H₂₆₀N₈O₄₇Na]⁺: 2793.8127; found: 2793.8134.

SEC (DMAc + 0.21 wt.% LiCl): M_n = 3,500 g mol⁻¹; M_w = 3,700 g mol⁻¹; Đ = 1.06.

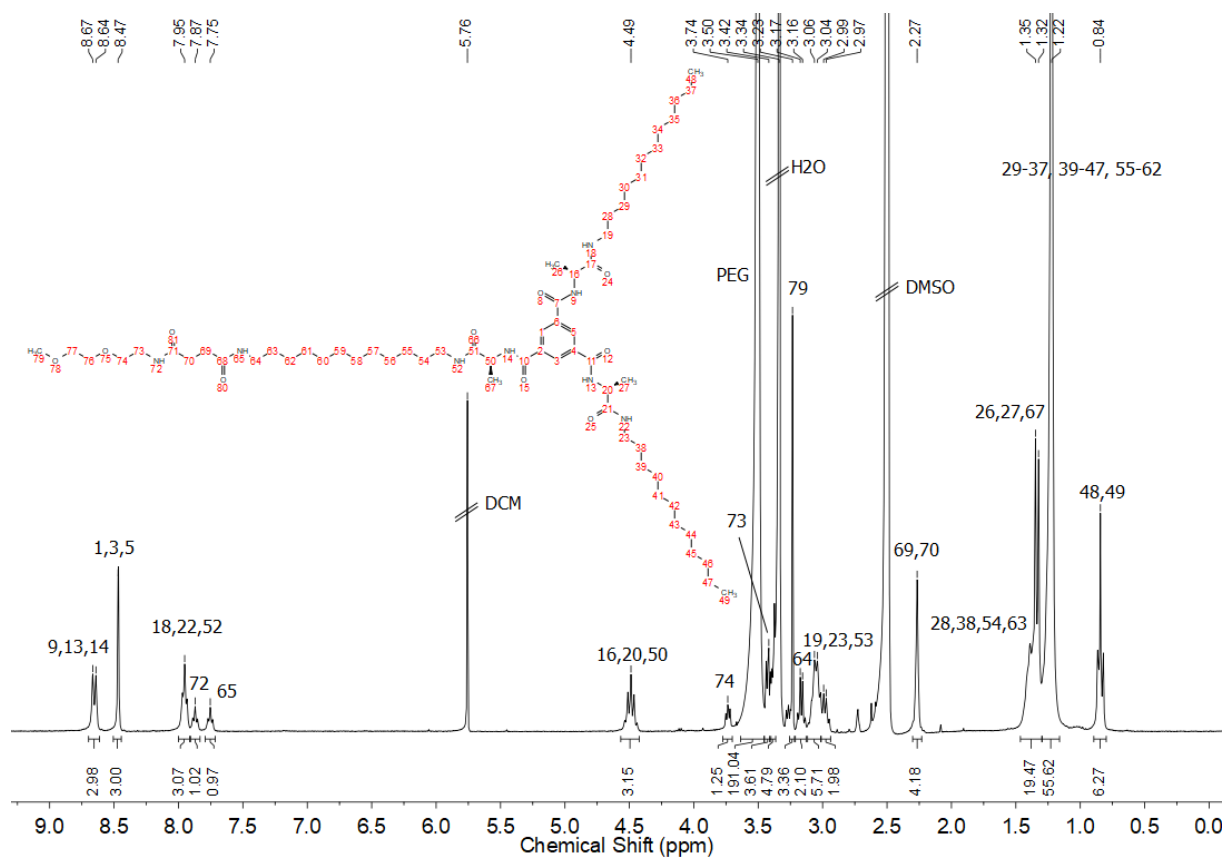


Figure S 7: ^1H -NMR spectrum of **2a** measured in d_6 -DMSO.

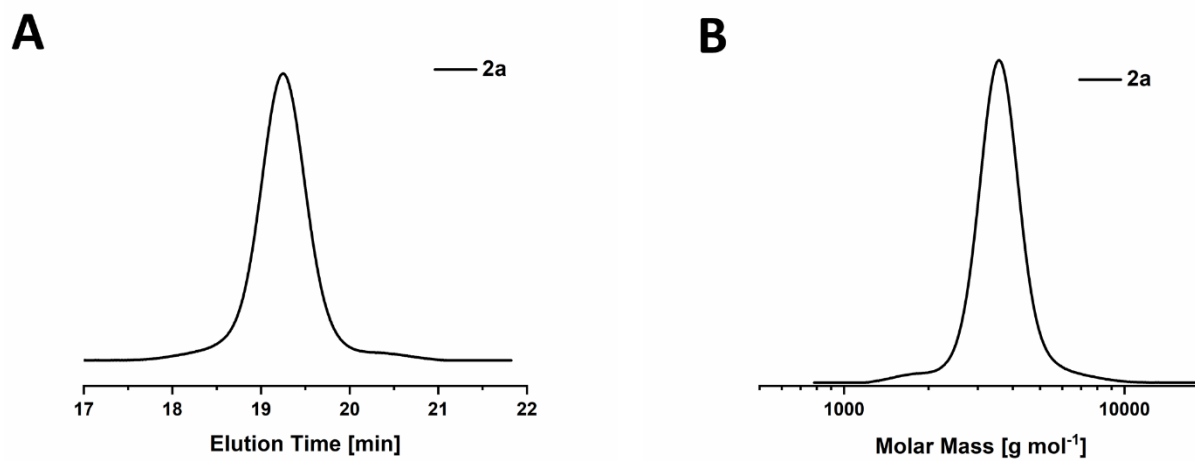
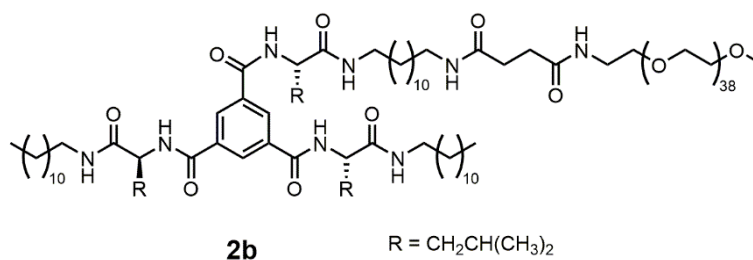


Figure S 8: SEC traces of **2a** recorded in DMAc (+0.21 wt% LiCl; 25 °C, RI, detection, PEO-Standard). A) Elution profile, B) Molar Mass distribution.

[B][Leu]₃[C₁₂]₃[PEO_{2k}] – **2b**



The compound was synthesized according to the procedure of compound **1a**.

Yield: 0.221 g, 0.075 mmol (97%), white powder.

Molecular formula: C₁₄₈H₂₈₂N₈O₄₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.63 (d, J = 8.1 Hz, 3H, NH), 8.43 (s, 3H, CH_{aromat}), 8.02 (t, J = 4.9 Hz, 3H, NH), 7.87 (t, J = 5.1 Hz, 1H, NH), 7.75 (t, J = 5.4 Hz, 1H, NH), 4.61 – 4.48 (m, 3H, CH), 3.78 – 3.70 (m, 2H, CH₂), 3.50 (s, 148H, PEO), 3.28 (m, 2H, CH₂), 3.23 (s, 2H, CH₂), 3.17 (q, J = 5.6 Hz, 2H, CH₂), 3.13 – 2.93 (m, 6H, CH₂), 2.27 (s, 4H, CH₂), 1.75 – 1.32 (m, 17H, CH, CH₂), 1.22 (m, 54H, CH₂), 0.90 (t, J = 6.4 Hz, 18H, CH₃), 0.84 (t, J = 6.7 Hz, 3H, CH₃).

MALDI-ToF-MS (positive mode, DHB) (m/z): calculated for [C₁₄₆H₂₇₈N₈O₄₇Na]⁺: 2919.9537; found: 2919.8889.

SEC (DMAc + 0.21 wt.% LiCl): M_n = 3,600 g mol⁻¹; M_w = 3,800 g mol⁻¹; Đ = 1.05.

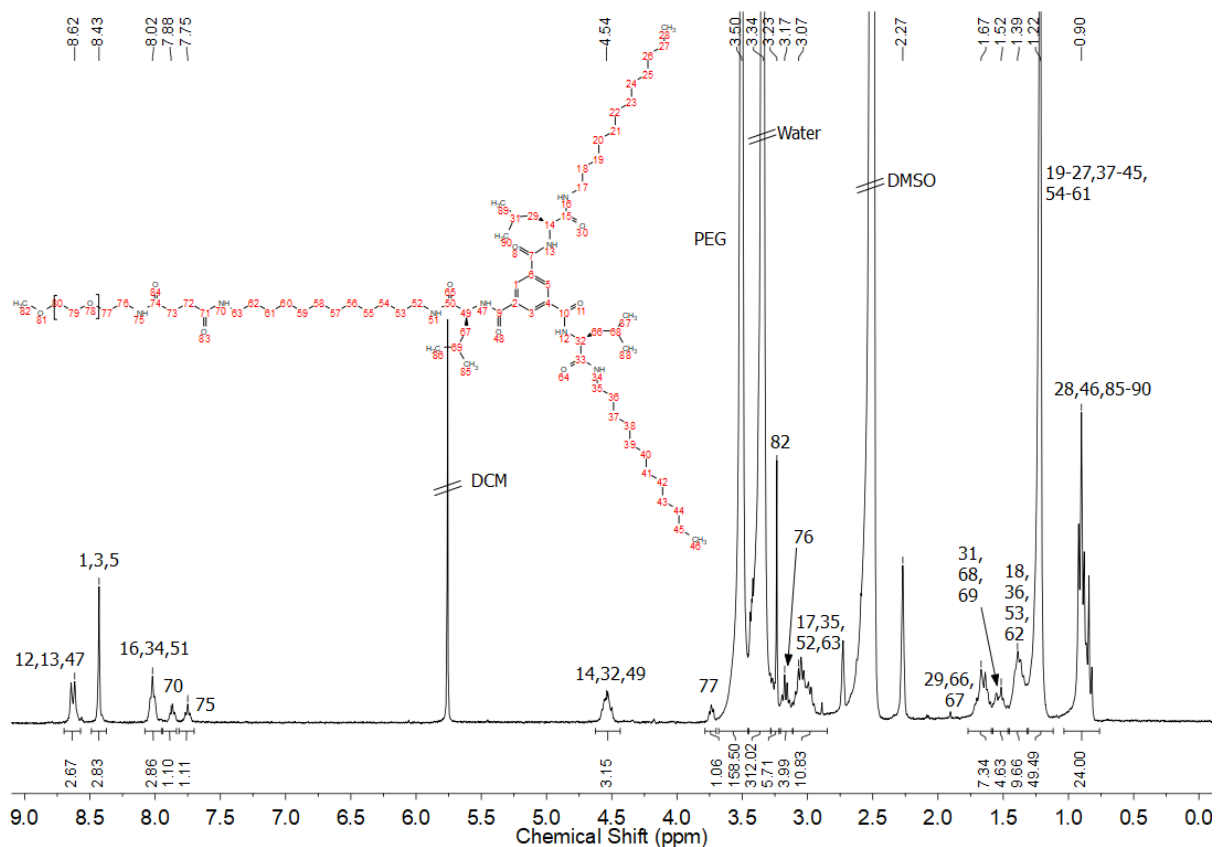


Figure S 9: $^1\text{H-NMR}$ spectrum of **2b** measured in $d_6\text{-DMSO}$.

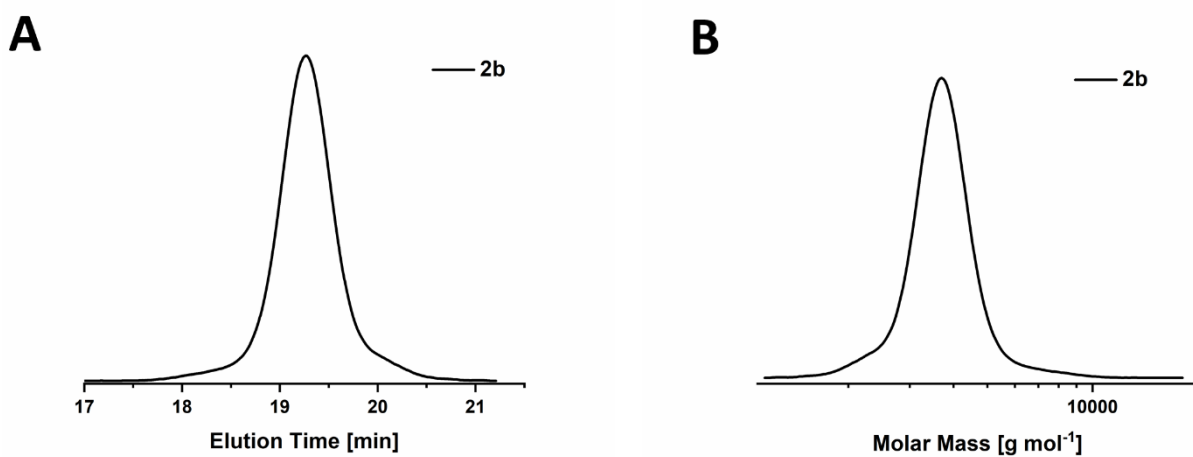
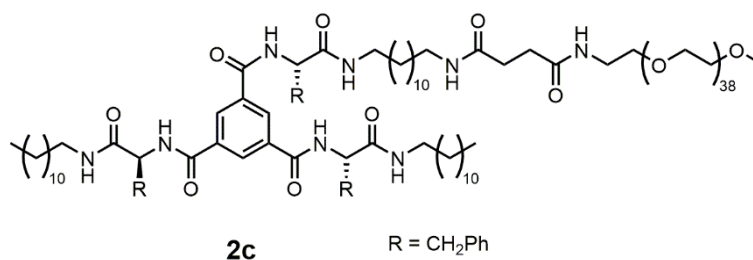


Figure S 10: SEC traces of **2b** recorded in DMAc (+0.21 wt% LiCl; 25 °C, RI, detection, PEO-Standard). A) Elution profile, B) Molar Mass distribution.

[B][Phe]₃[C₁₂]₃[PEO_{2k}] – **2c**



The compound was synthesized according to the procedure of compound **1a**.

Yield: 0.7 g, 0.230 mmol (97%), white powder.

Molecular formula: C₁₅₇H₂₇₆N₈O₄₈

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.72 (t, J = 7.6 Hz, 3H, NH), 8.36 – 8.24 (m, 3H, CH_{aromat}), 8.09 (s, 3H, NH), 7.87 (t, J = 5.5 Hz, 1H, NH), 7.75 (t, J = 5.1 Hz, 1H, NH), 7.37 – 7.08 (m, 15H, CH_{aromat}), 4.78 – 4.63 (m, 3H, CH), 3.78 – 3.70 (m, 2H, CH₂), 3.50 (s, 148H, PEO), 3.46 – 3.40 (m, 2H, CH₂), 3.23 (s, 2H, CH₂), 3.16 (q, J = 5.6 Hz, 2H, CH₂), 3.12 – 2.89 (m, 12H, CH₂), 2.27 (s, 4H, CH₂), 1.35 (m, 8H, CH₂), 1.22 (m, 54H), 0.84 (t, J = 6.4 Hz, 6H, CH₃).

MALDI-ToF-MS (positive mode, DHB) (m/z): calculated for [C₁₅₅H₂₇₂N₈O₄₇Na]⁺: 3021.9070; found: 3021.8116.

SEC (DMAc + 0.21 wt.% LiCl): M_n = 3,400 g mol⁻¹; M_w = 3,700 g mol⁻¹; Đ = 1.07.

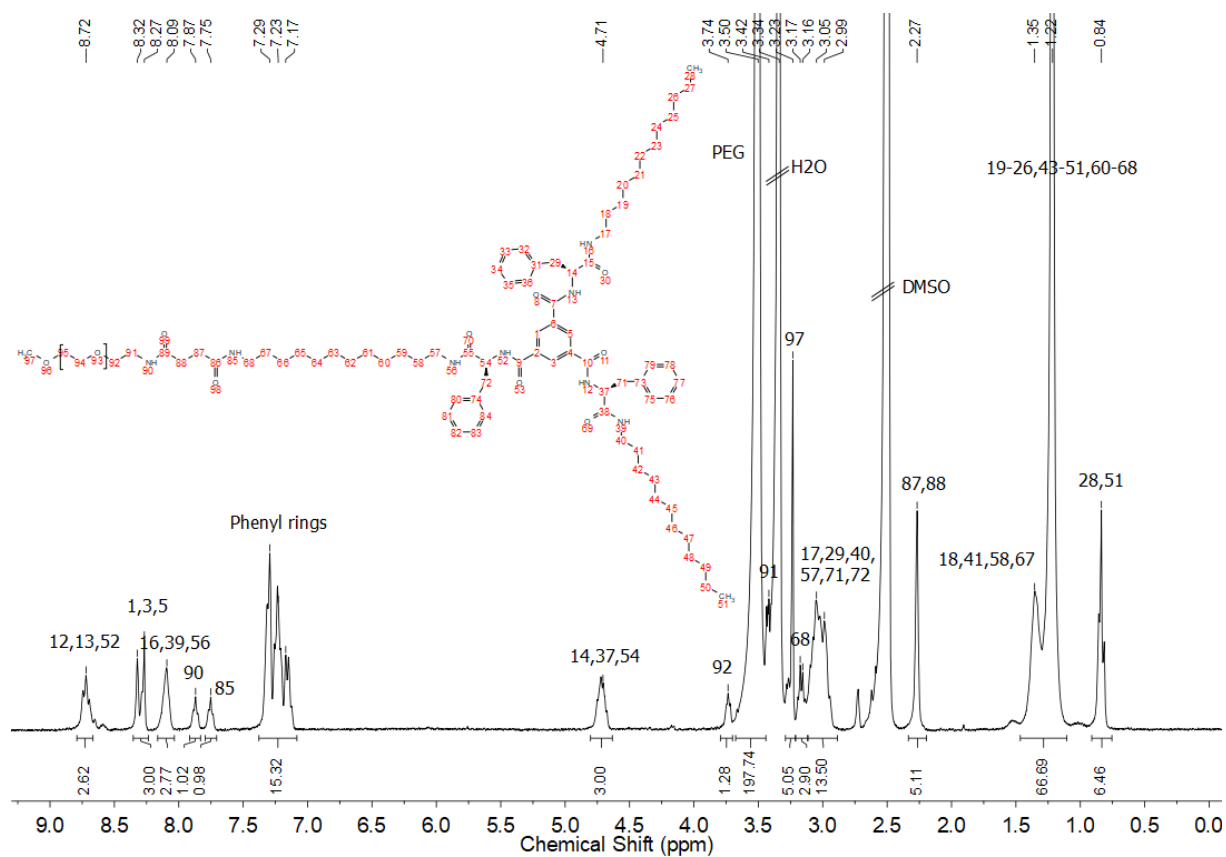


Figure S 11: $^1\text{H-NMR}$ spectrum of **2c** measured in $\text{d}_6\text{-DMSO}$.

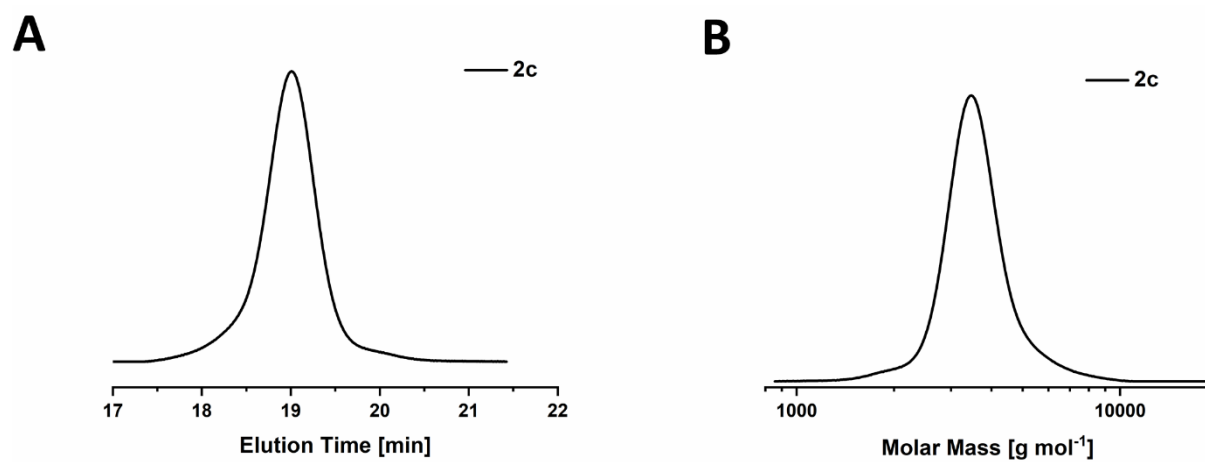
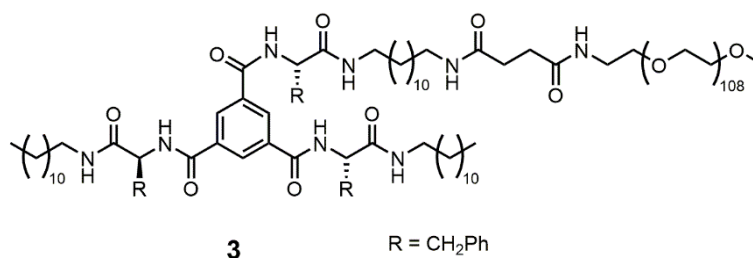


Figure S 12: SEC traces of **2c** recorded in DMAc (+0.21 wt% LiCl; 25 °C, RI, detection, PEO-Standard). A) Elution profile, B) Molar Mass distribution.

[B][Phe]₃[C₁₂]₃[PEO_{5k}] – 3



The compound was synthesized according to the procedure of compound **1a**.

Yield: 0.846 g, 0.139 mmol (119%, residual PEO_{5k} left), white powder.

Molecular formula: C₂₉₅H₅₅₂N₈O₁₁₇

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.72 (t, J = 7.4 Hz, 3H, NH), 8.37 – 8.24 (m, 3H, CH_{aromat}), 8.09 (m, 3H, NH), 7.87 (t, J = 5.2 Hz, 1H, NH), 7.75 (t, J = 4.9 Hz, 1H, NH), 7.37 – 7.03 (m, 15H, CH_{aromat}), 4.78 – 4.66 (m, 3H, CH), 3.78 – 3.70 (m, 2H, CH₂), 3.50 (s, 432H, PEO), 3.45 – 3.41 (m, 2H, CH₂), 3.23 (s, 2H, CH₂), 3.17 (q, J = 5.8 Hz, 2H, CH₂), 3.12 – 2.92 (m, 12H, CH₂), 2.27 (s, 4H, CH₂), 1.36 (m, 8H, CH₂), 1.22 (m, 54H, CH₂), 0.84 (t, J = 6.5 Hz, 6H, CH₃).

MALDI-ToF-MS (positive mode, DHB) (m/z): calculated for [C₃₀₃H₅₆₈N₈O₁₂₁Na]⁺: 6281.9637; found: 6282.000.

SEC (DMAc + 0.21 wt.% LiCl): M_n = 6,200 g mol⁻¹; M_w = 6,900 g mol⁻¹; Đ = 1.11.

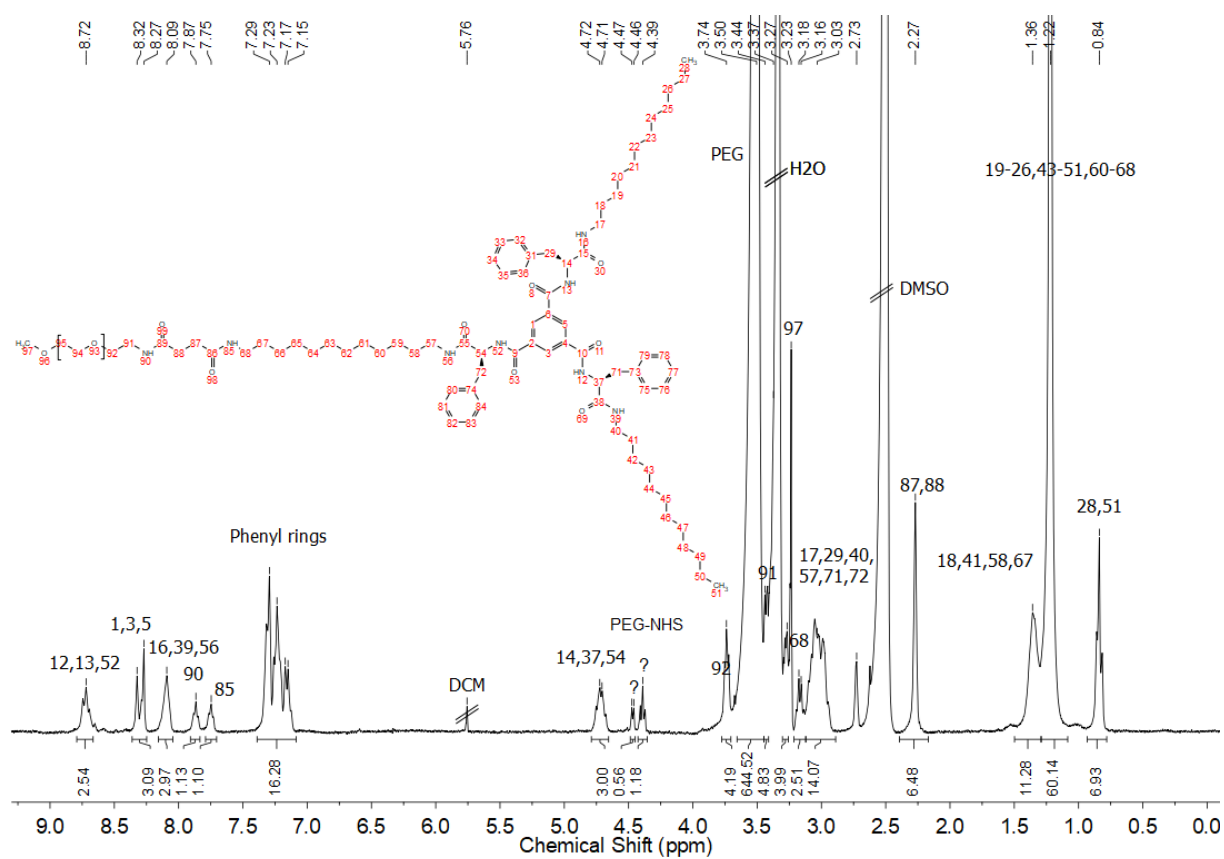


Figure S 13: $^1\text{H-NMR}$ spectrum of **3** measured in $\text{d}_6\text{-DMSO}$.

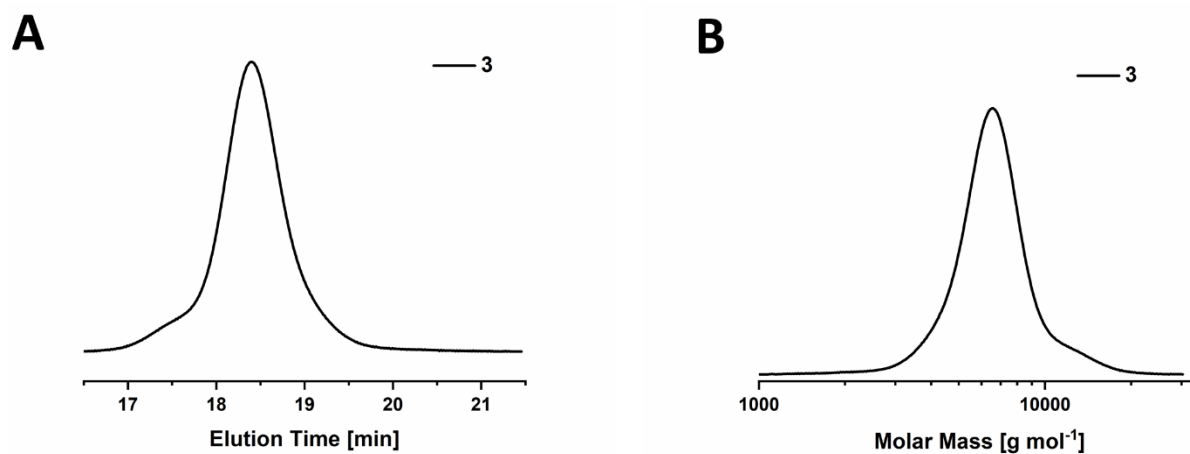
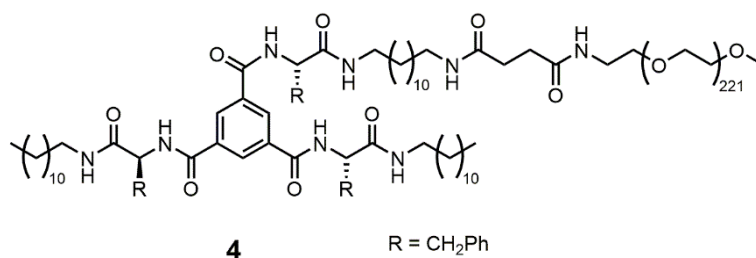


Figure S 14: SEC traces of **3** recorded in DMAc (+0.21 wt% LiCl; 25 °C, RI, detection, PEO-Standard). A) Elution profile, B) Molar Mass distribution.

[B][Phe]₃[C₁₂]₃[PEO_{10k}] – 4



The compound was synthesized according to the procedure of compound **1a**.

Yield: 0.914 g, 0.083 mmol (141%, residual PEO_{10k} left), white powder.

Molecular formula: C₅₂₁H₁₀₀₄N₈O₂₃₀

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.74 (t, J = 7.6 Hz, 3H, NH), 8.36 – 8.26 (m, 3H, CH_{aromat}), 8.10 (s, 3H, NH), 7.87 (t, J = 5.2 Hz, 1H, NH), 7.75 (t, J = 5.0 Hz, 1H, NH), 7.37 – 7.07 (m, 15H, CH_{aromat}), 4.78 – 4.64 (m, 3H, CH), 3.79 – 3.68 (m, 2H, CH₂), 3.50 (s, 884H, PEO), 3.44 (m, 2H, CH₂), 3.24 (s, 2H, CH₂), 3.22 – 3.11 (m, 2H, CH₂), 3.12 – 2.92 (m, 12H, CH₂), 2.27 (s, 4H, CH₂), 1.36 (m, 8H, CH₂), 1.22 (m, 54H, CH₂), 0.84 (t, J = 6.7 Hz, 6H, CH₃).

MALDI-ToF-MS (positive mode, CHCA) (m/z): calculated for [C₅₂₁H₁₀₀₄N₈O₂₃₀Na]⁺: 11,083.4190; found: 11,083.3760.

SEC (DMAc + 0.21 wt.% LiCl): M_n = 11,800 g mol⁻¹; M_w = 13,600 g mol⁻¹; Đ = 1.15.

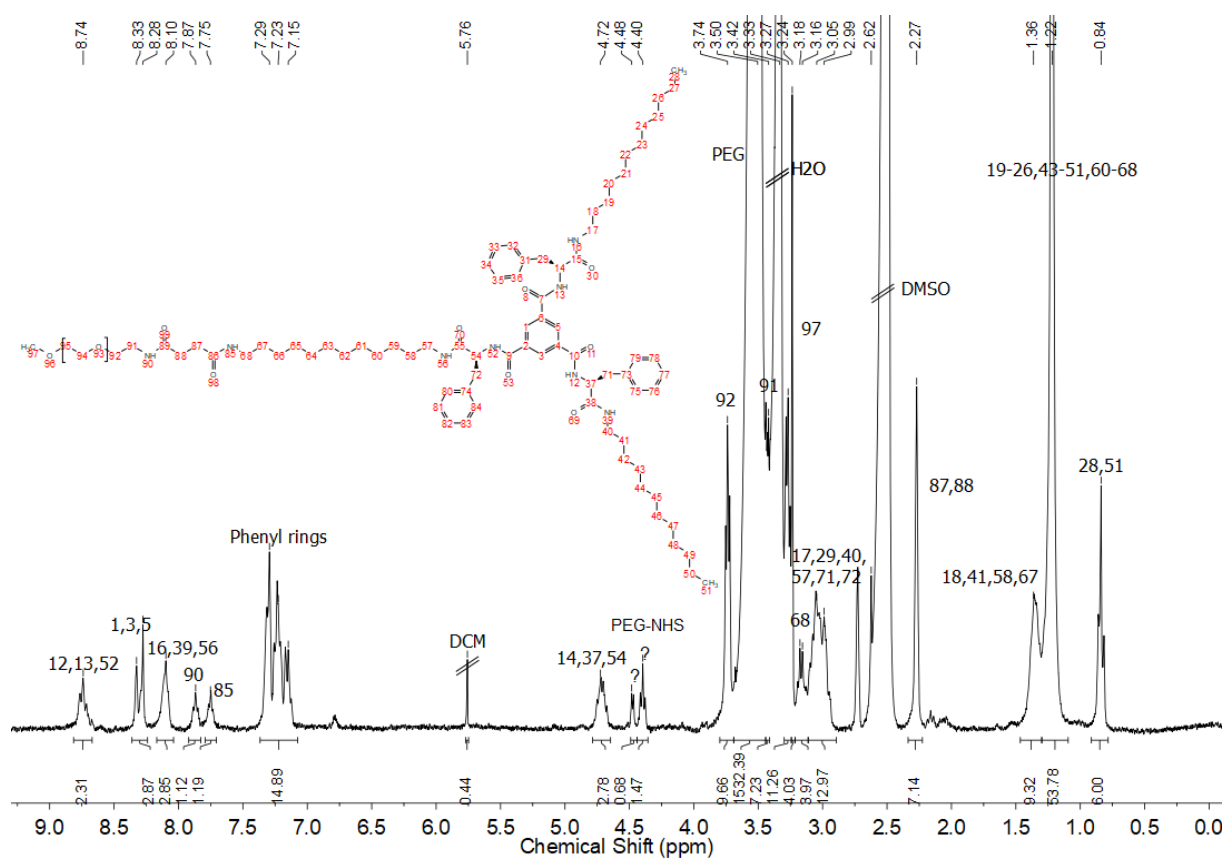


Figure S 15: $^1\text{H-NMR}$ spectrum of **4** measured in $\text{d}_6\text{-DMSO}$.

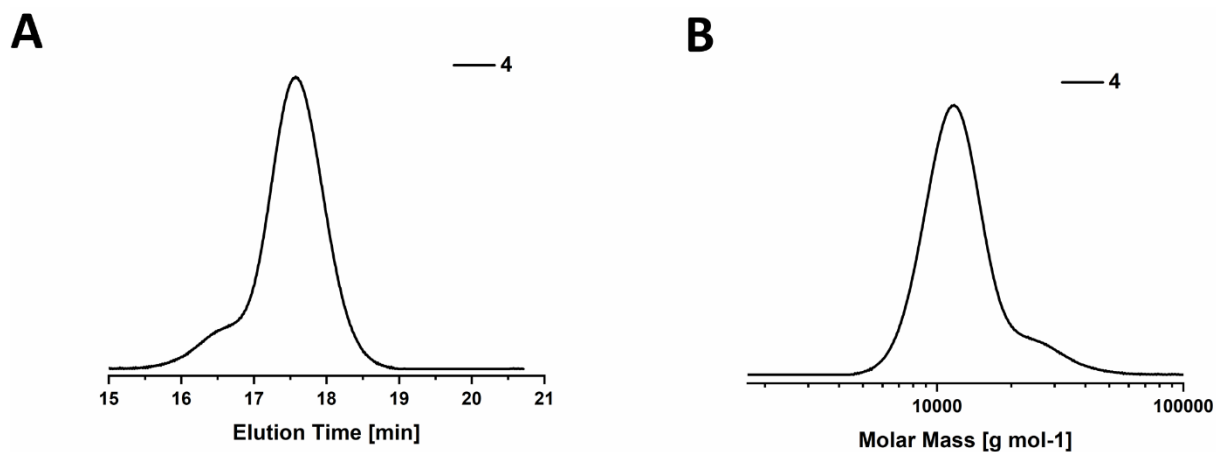
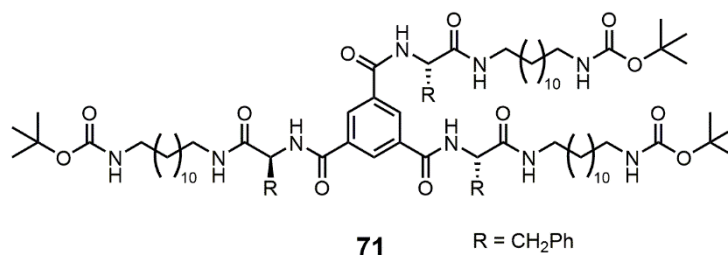


Figure S 16: SEC traces of **4** recorded in DMAc (+0.21 wt% LiCl; 25 °C, RI, detection, PEO-Standard). A) Elution profile, B) Molar Mass distribution.

1.2.4 Benzenetrispeptide building blocks bearing three PEO chains

[B][Phe]₃[C₁₂]₃ Boc-protected – 71



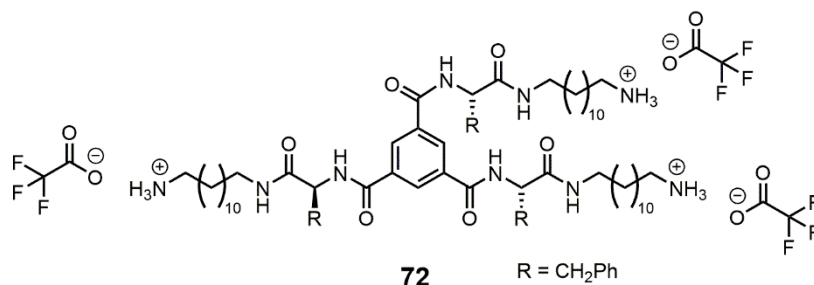
Benzene-1,3,5-tricarbonyl trichloride (96 mg, 0.360 mmol, 1.0 eq) was dissolved in 7.21 mL anhydrous chloroform under Argon atmosphere and the solution cooled to 0 °C. Compound **45** (0.5 g, 1.117 mmol, 3.1 eq) and triethylamine (201 μL, 1.441 mmol, 4 eq) were added. The solution was allowed to warm to rt and then stirred overnight. The solvent was removed and the crude product purified via flash chromatography (DCM/MeOH; 93:7, v:v). The obtained product was dried in the vacuum oven (40 °C) overnight.

Yield: 0.238 g, 0.159 mmol (44%), white solid.

Molecular formula: C₈₇H₁₃₅N₉O₁₂

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.74 (d, J = 8.4 Hz, 3H, NH), 8.27 (s, 3H, CH_{aromat}), 8.09 (t, J = 5.4 Hz, 3H, NH), 7.35 – 7.09 (m, 15H, CH_{aromat}), 6.75 (t, J = 5.4 Hz, 3H, NH), 4.79 – 4.64 (m, 3H, CH), 3.17 – 2.93 (m, 12H, CH₂), 2.87 (q, J = 6.6 Hz, 6H, CH₂), 1.36 (m, 43H, CH₂, CH₃), 1.21 (m, 48H, CH₂).

[B][Phe]₃[C₁₂]₃ Boc-protected – 72



Compound **71** (0.24 g, 0.16 mmol, 1.0 eq) was dissolved in 1.6 mL DCM. To this, 515 μ L of an 18:1:1 solution of TFA/TIPS/H₂O (TFA: 444 μ L, 5.76 mmol, 36 eq; TIPS: 66 μ L, 0.32 mmol, 2 eq; H₂O: 5 μ L, 0.32 mmol, 2 eq) was added dropwise and the solution stirred for 3 h at rt. Afterwards, half of the DCM volume was removed and the concentrated reaction mixture precipitated in cold diethyl ether. The suspension was centrifuged (3 min, 8,000 rpm) and the supernatant decanted. The obtained product was dried in the vacuum oven (40 °C) overnight.

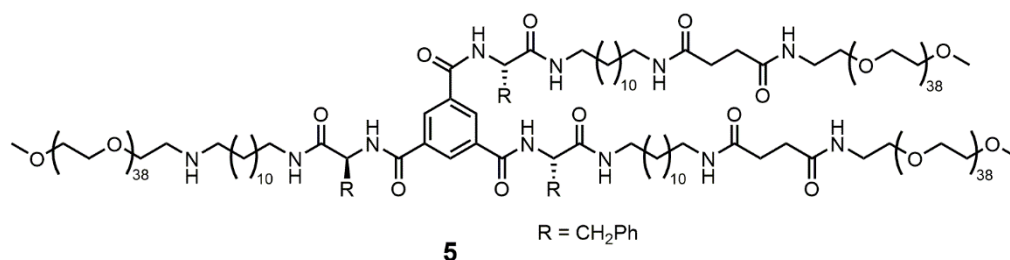
Yield: 0.171 g, 0.111 mmol (69%), light yellow wax.

Molecular formula: C₇₈H₁₁₄N₉O₁₂F₉

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.73 (d, J = 8.4 Hz, 3H, NH), 8.27 (s, 3H, CH_{aromat}), 8.12 (t, J = 5.5 Hz, 3H, NH), 7.69 (s, 9H, NH₃), 7.36 – 7.11 (m, 15H, CH_{aromat}), 4.79 – 4.65 (m, 3H, CH), 3.18 – 2.91 (m, 12H, CH₂), 2.83 – 2.67 (m, 6H, CH₂), 1.57 – 1.40 (m, 6H, CH₂), 1.42 – 1.31 (m, 6H, CH₂), 1.23 (m, 48H, CH₂).

ESI-ToF-MS (positive mode, acetonitrile) (m/z): calculated for [M+2H]²⁺: 599.9401; found: 599.9424.

[B][Phe]₃[C₁₂]₃[PEO_{2k}]₃ – 5



Compound **72** (0.171 g, 0.111 mmol, 1.0 eq) was dissolved in 9.96 mL DMF. To this, 0.309 mL triethylamine (2.22 mmol, 20 eq) were added dropwise. After stirring at rt for 15 min, 0.663 g of MeO-PEO_{2k}-NHS ester (0.333 mmol, 3.0 eq) were added and the reaction mixture stirred at rt overnight. Afterwards, the reaction mixture was precipitated into cold diethyl ether, the suspension centrifuged (3 min, 8,000 rpm) and the supernatant decanted. Then a mixture of diethyl ether and acetone (9:1, v:v) was added to the precipitate and the suspension exposed to sonication for 5 min in order to remove all residual DMF and some unconjugated MeO-PEO_{2k}-NHS ester. Afterwards, the suspension was again centrifuged (3 min, 8,000 rpm) and the supernatant decanted. Still remaining MeO-PEO_{2k}-NHS ester was then removed via continuous centrifugal washing using Amicon® Ultra-15 centrifugal filter units (MWCO: 10 kDa). The obtained product was then dissolved in water and lyophilised overnight.

Yield: 0.622 g, 0.091 mmol (82%), white powder.

Molecular formula: C₃₂₇H₆₁₂N₁₂O₁₃₂

¹H-NMR (300 MHz, d₆-DMSO, 298 K): δ [ppm] = 8.72 (d, J = 7.8 Hz, 3H, NH), 8.26 (s, 3H, CH_{aromat}), 8.09 (t, J = 5.0 Hz, 3H, NH), 7.87 (t, J = 5.3 Hz, 3H, NH), 7.75 (t, J = 5.5 Hz, 3H, NH), 7.34 – 7.08 (m, 15H, CH_{aromat}), 4.71 (q, J = 8.8 Hz, 3H, CH), 3.78 – 3.70 (m, 6H, CH₂), 3.50 (m, 468H, PEO), 3.29 – 3.25 (m, 6H, CH₂), 3.23 (s, 6H, CH₂), 3.16 (q, J = 5.8 Hz, 6H, CH₂), 3.12 – 2.91 (m, 12H, CH₂), 2.27 (s, 12H, CH₂), 1.34 (m, 12H, CH₂), 1.21 (m, 48H, CH₂).

MALDI-ToF-MS (positive mode, dithranol) (m/z): calculated for [C₃₂₇H₆₁₂N₁₂O₁₃₂Na]⁺: 6847.0805; found: 6843.9496.

SEC (DMAc + 0.21 wt.% LiCl): M_n = 6,600 g mol⁻¹; M_w = 7,200 g mol⁻¹; Đ = 1.16.

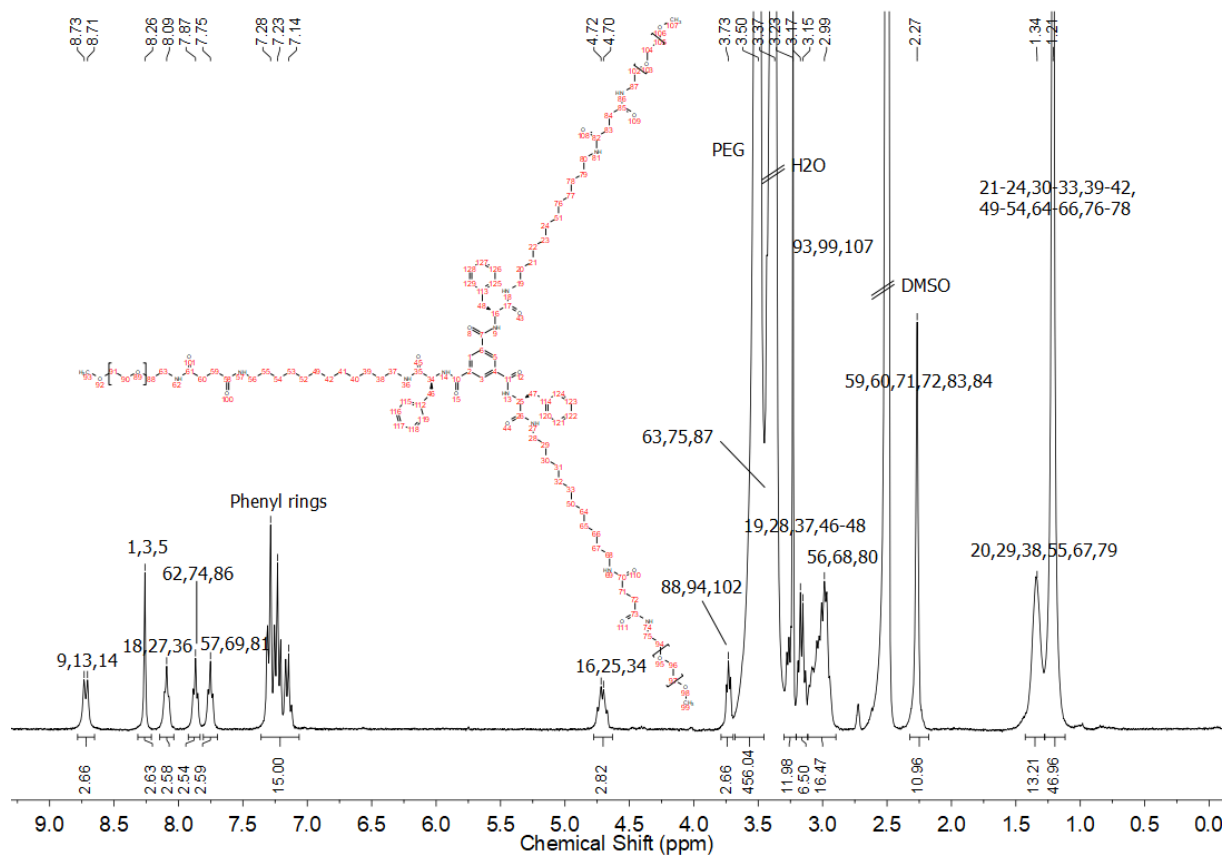


Figure S 17: ¹H-NMR spectrum of **5** measured in d₆-DMSO.

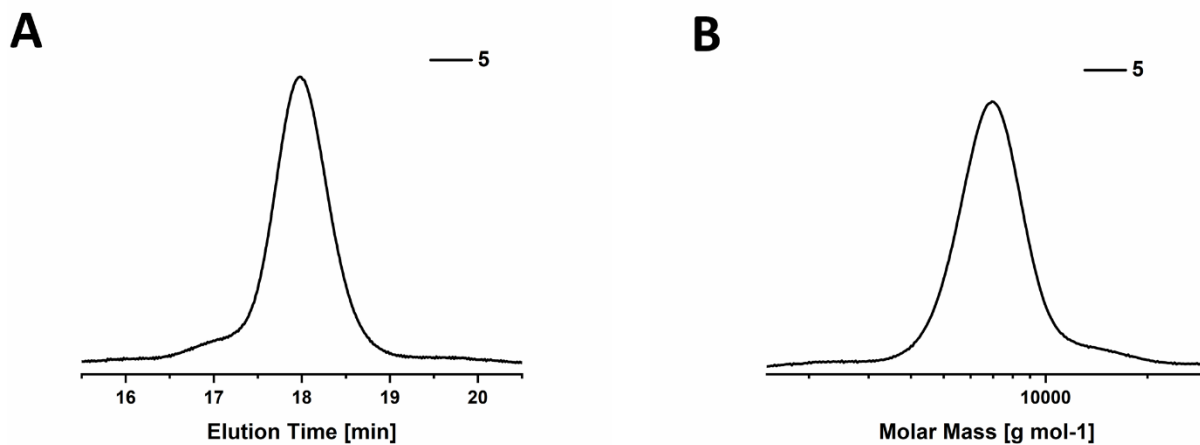


Figure S 18: SEC traces of **5** recorded in DMAc (+0.21 wt% LiCl; 25 °C, RI, detection, PEO-Standard). A) Elution profile, B) Molar Mass distribution.

2. Characterisation

2.1 Sample preparation

All investigated samples were initially dissolved in water and lyophilized afterwards, in order to obtain a fluffy powder. We observed that this powder dissolves easier in water compared to the precipitate obtained out of the PEO-conjugation reaction.

Prior to characterization, the powder was dissolved in MilliQ water at the desired concentration. For dissolution, the solution was put into the vortex and shaken at room temperature until the solution was fully clear (at least 24 h). No stirring, heating, sonication or filtration was applied to facilitate the dissolution in water, in order to keep the parameters affecting dissolution and self-assembly to a minimum.

2.2 Dynamic Light Scattering (DLS)

A scattering angle of 173° was used to record intensity fluctuations of the different samples in solution. All measurements were conducted in triplicate at a temperature of 25°C in disposable macro cuvettes containing 3 mL solution and after allowing for an equilibration time of 60 s. The acquisition time was 60 s. The apparent distribution of intensity-weighted hydrodynamic radii, d_h , was obtained from the Stokes–Einstein equation:

$$d_h = \frac{kT}{3\pi\eta D} \quad (\text{Equation S1})$$

with k being the Boltzmann constant, T the temperature in units K, η the viscosity of the solvent, and D the apparent translational diffusion coefficient at the utilized concentrations. The intensity-weighted distributions were transformed into number-weighted distributions.

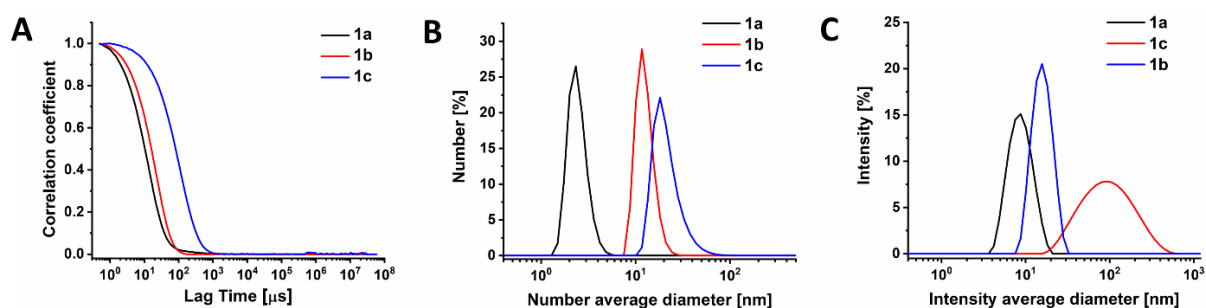


Figure S 19: A) DLS correlograms of **1a** (black), **1b** (red) and **1c** (blue); B) corresponding distributions of the number-weighted hydrodynamic diameter (**1a**: $d_{H,\text{number}} = 2.5 \pm 0.2$ nm; **1b**: $d_{H,\text{number}} = 11.5 \pm 0.1$ nm; **1c**: $d_{H,\text{number}} = 16.2 \pm 5.0$ nm) and C) intensity-weighted hydrodynamic diameter (**1a**: $d_{H,\text{intensity}} = 9.0 \pm 2.0$ nm; **1b**: $d_{H,\text{intensity}} = 16.2 \pm 4.2$ nm; **1c**: $d_{H,\text{intensity}} = 115.0 \pm 81.2$ nm) at a concentration of 5 mg mL^{-1} .

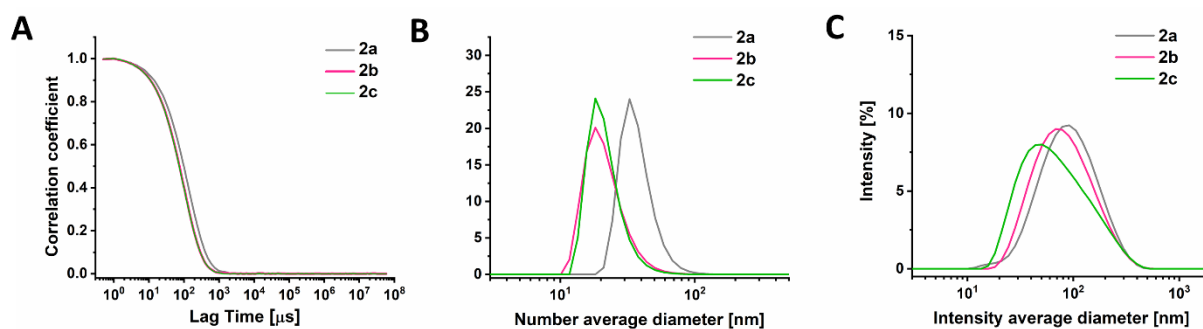


Figure S 20: A) DLS correlograms of **2a** (grey), **2b** (magenta) and **2c** (green); B) corresponding distributions of the number-weighted hydrodynamic diameter (**2a**: $d_{H,number} = 27.0 \pm 9.3$ nm; **2b**: $d_{H,number} = 20.3 \pm 8.1$ nm; **2c**: $d_{H,number} = 22.6 \pm 1.0$ nm) and C) intensity-weighted hydrodynamic diameter (**2a**: $d_{H,intensity} = 113.0 \pm 71.4$ nm; **2b**: $d_{H,intensity} = 95.6 \pm 63.5$ nm; **2c**: $d_{H,intensity} = 84.5 \pm 65.9$ nm) at a concentration of 5 mg mL^{-1} .

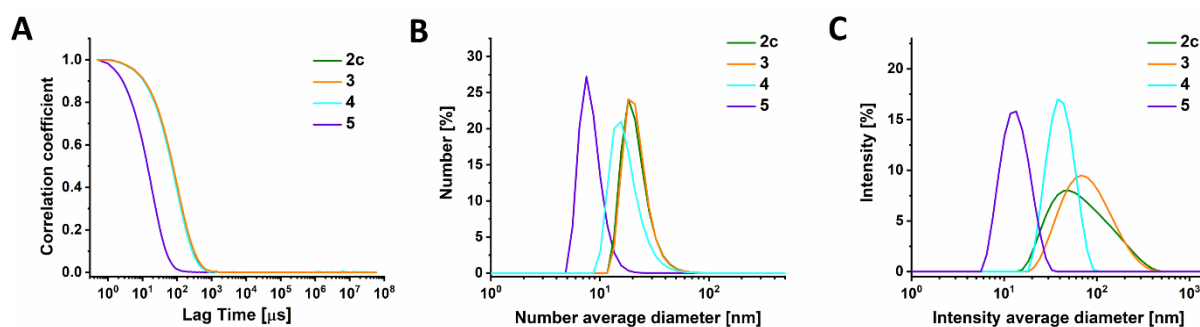


Figure S 21: A) DLS correlograms of **2c** (green), **3** (orange), **4** (cyan) and **5** (purple); B) corresponding distributions of the number-weighted hydrodynamic diameter (**2c**: $d_{H,number} = 22.6 \pm 1.0$ nm; **3**: $d_{H,number} = 22.4 \pm 2.7$ nm; **4**: $d_{H,number} = 23.3 \pm 4.8$ nm; **5**: $d_H = 8.5 \pm 0.2$ nm) and C) intensity-weighted hydrodynamic diameter (**2c**: $d_{H,intensity} = 84.5 \pm 65.9$ nm; **3**: $d_{H,intensity} = 90.9 \pm 57.8$ nm; **4**: $d_{H,intensity} = 42.4 \pm 13.4$ nm; **5**: $d_{H,intensity} = 13.9 \pm 4.7$ nm) at a concentration of 5 mg mL^{-1} .

2.3 Small Angle X-Ray Scattering (SAXS)

Small angle X-ray scattering was performed at the beamline BL40B2 of the Super Photon Ring – 8 GeV (SPring-8) in Hyogo Prefecture, Japan. The sample-to-detector distance was 4.0 m (detector: PILATUS 2M (Dectris)) and the wavelength of the incident beam (λ) was adjusted to 0.10 nm. Each sample was measured at a concentration of 1.5 mg mL⁻¹ in water at 25 °C and exposed for 180 s.

Each recorded 2D profile was azimuthally averaged to obtain 1D profile of $I(q)$ vs. q , followed by being divided by the incident X-ray intensity. After that, the solvent scattering data (background scattering) was subtracted from the solution data to obtain the excess scattering intensity. The excess scattering intensity was normalized to be the differential scattering cross-section (absolute intensity) by using the scattering intensity of water.¹

The obtained reduced SAXS data was analysed with the open access software SASfit (version: 0.94.11).² All parameters for the respective fits can be found in the following tables. The radius of the sphere or cylinder were fitted by applying a Gaussian distribution to the fit, which has a concentration parameter N , a width parameter σ and a mean radius parameter R .

1b – [B][Leu]₃[C₆]₃[PEO_{2k}]**Table S 1:** SAXS fitting parameters for compound **1b** using a form factor for a sphere.

Parameter	Values
R_{sphere} [nm]	5.27
Σ	1.32
N	7.45×10^{-2}
<i>subtracted background</i>	2.70×10^{-4}
η^a [nm ⁻²]	1.019×10^{-3}

^a The X-ray scattering length density (SLD) η was calculated using the SLD calculator given in SASfit.

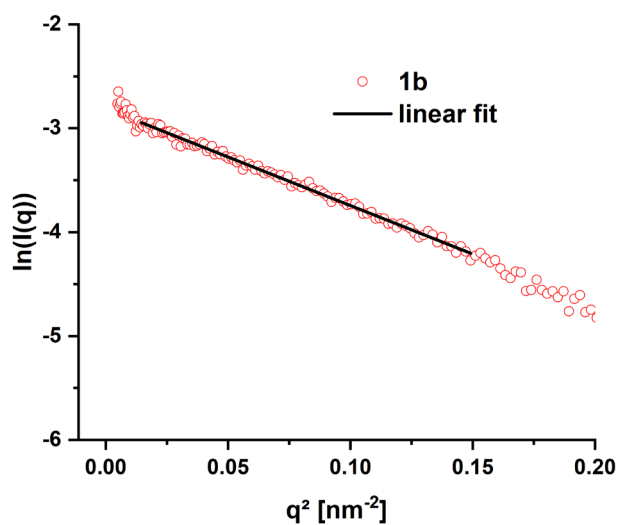


Figure S 22: Guinier plot ($\ln(I(q))$ vs. q^2) of the SAXS data of compound **1b**. The slope of the linear fit was used to determine the radius of gyration R_g (here: $R_g = 5.3$ nm) using the Guinier approximation.

Table S 2: SAXS fitting parameters for compound **1b** using a form factor for a cylinder.

Parameter	Values
R_{cylinder} [nm]	6.24
L_{cylinder} [nm]	8.12
Σ	0.52
N	5.5×10^{-2}
<i>subtracted background</i>	2.70×10^{-4}
η^a [nm ⁻²]	1.019×10^{-3}

^a The X-ray scattering length density (SLD) η was calculated using the SLD calculator given in SASfit.

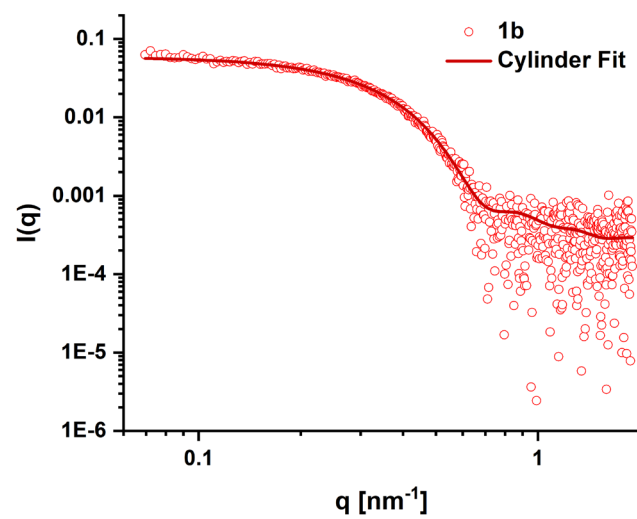


Figure S 23: SAXS trace for **1b** (circles) in water ($c = 1.5 \text{ mg mL}^{-1}$) fitted with form factor for cylinder (solid line).

1c – [B][Phe]₃[C₆]₃[PEO_{2k}]

Table S 3: SAXS fitting parameters for compound **1c** using a form factor for a cylinder.

Parameter	Values
R_{cylinder} [nm]	5.08
L_{cylinder}^a [nm]	700
Σ	1.22
N	1.59×10^{-3}
subtracted background	2.00×10^{-4}
η^b [nm ⁻²]	1.014×10^{-3}

^a The length L for the cylinder fit was estimated from the lengths observed in the corresponding cryoTEM images of compound **1c**. Due to the absence of a plateau at low q -values for the SAXS data, this value does not represent the real average cylinder length.

^b The X-ray scattering length density (SLD) η was calculated using the SLD calculator given in SASfit.

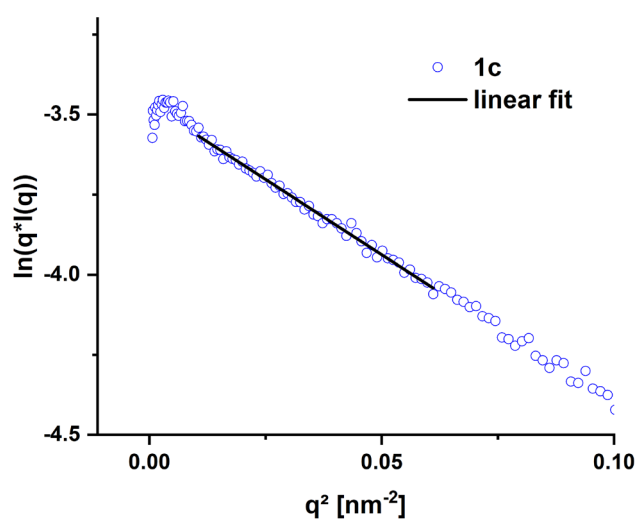


Figure S 24: Cross-sectional diameter plot ($\ln(qI(q))$ vs. q^2) of the SAXS data of compound **1c**. The slope of the linear fit was used to determine the cross-sectional radius $R_{\text{c-s}}$ (here: $R_{\text{c-s}} = 6.1$ nm).

2a – [B][Ala]₃[C₁₂]₃[PEO_{2k}]

Table S 4: SAXS fitting parameters for compound **2a** using a form factor for a cylinder.

Parameter	Values
R_{cylinder} [nm]	6.14
L_{cylinder}^a [nm]	100
Σ	1.36
N	6.43×10^{-2}
subtracted background	9.00×10^{-5}
η^b [nm ⁻²]	1.021×10^{-3}

^a The length L for the cylinder fit was estimated from the lengths observed in the corresponding cryoTEM images of compound **2a**. Due to the absence of a plateau at low q -values for the SAXS data, this value does not represent the real average cylinder length.

^b The X-ray scattering length density (SLD) η was calculated using the SLD calculator given in SASfit.

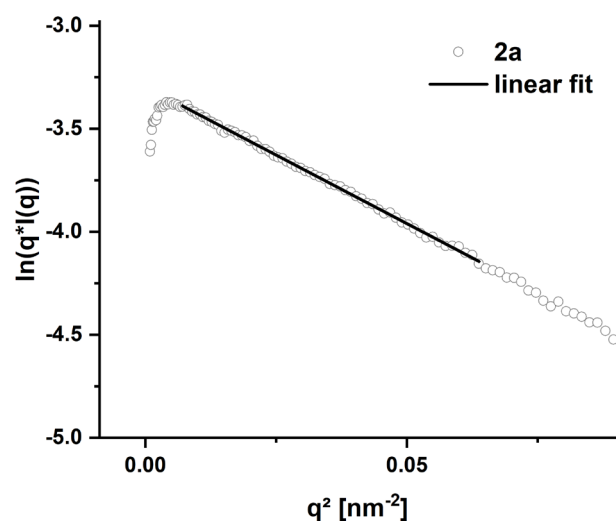


Figure S 25: Cross-sectional diameter plot ($\ln(qI(q))$ vs. q^2) of the SAXS data of compound **2a**. The slope of the linear fit was used to determine the cross-sectional radius $R_{\text{c-s}}$ (here: $R_{\text{c-s}} = 7.3$ nm).

2b – [B][Leu]₃[C₁₂]₃[PEO_{2k}]

Table S 5: SAXS fitting parameters for compound **2b** using a form factor for a cylinder.

Parameter	Values
R_{cylinder} [nm]	7.57
L_{cylinder}^a [nm]	320
Σ	4.00×10^{-3}
N	5.02×10^{-4}
subtracted background	2.71×10^{-4}
η^b [nm ⁻²]	1.023×10^{-3}

^a The length L for the cylinder fit was estimated from the lengths observed in the corresponding cryoTEM images of compound **2b**. Due to the absence of a plateau at low q -values for the SAXS data, this value does not represent the real average cylinder length.

^b The X-ray scattering length density (SLD) η was calculated using the SLD calculator given in SASfit.

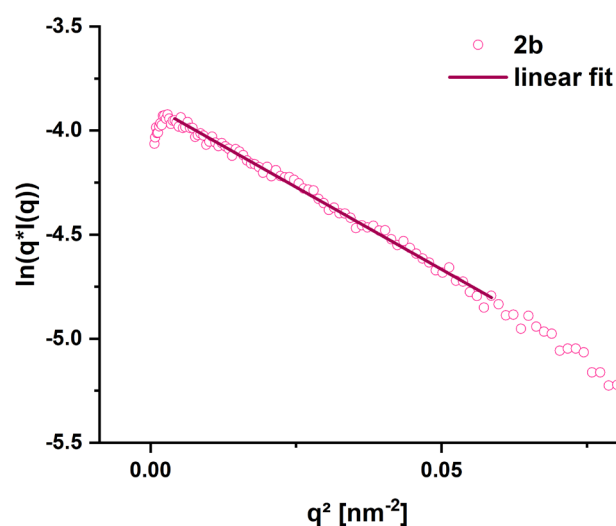


Figure S 26: Cross-sectional diameter plot ($\ln(qI(q))$ vs. q^2) of the SAXS data of compound **2b**. The slope of the linear fit was used to determine the cross-sectional radius $R_{\text{c-s}}$ (here: $R_{\text{c-s}} = 8.0$ nm).

2c – [B][Phe]₃[C₁₂]₃[PEO_{2k}]

Table S 6: SAXS fitting parameters for compound **2c** using a form factor for a cylinder.

Parameter	Values
R_{cylinder} [nm]	6.56
L_{cylinder}^a [nm]	200
Σ	1.42
N	1.91×10^{-3}
subtracted background	1.00×10^{-4}
η^b [nm ⁻²]	1.018×10^{-3}

^a The length L for the cylinder fit was estimated from the lengths observed in the corresponding cryoTEM images of compound **2c**. Due to the absence of a plateau at low q -values for the SAXS data, this value does not represent the real average cylinder length.

^b The X-ray scattering length density (SLD) η was calculated using the SLD calculator given in SASfit.

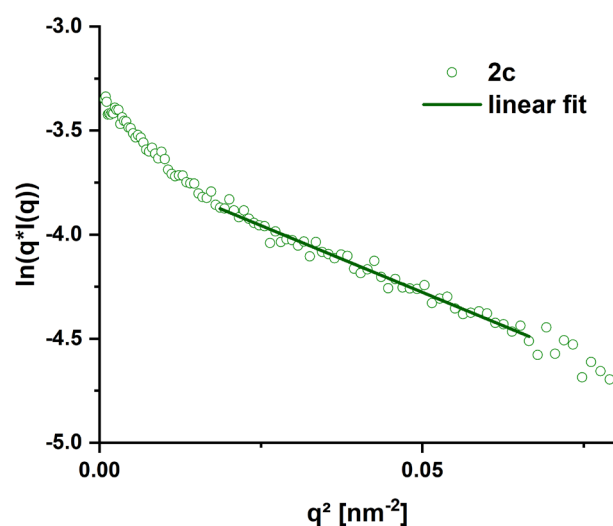


Figure S 27: Cross-sectional diameter plot ($\ln(qI(q))$ vs. q^2) of the SAXS data of compound **2c**. The slope of the linear fit was used to determine the cross-sectional radius $R_{\text{c-s}}$ (here: $R_{\text{c-s}} = 7.2$ nm).

3 – [B][Phe]₃[C₁₂]₃[PEO]_{5k}

Table S 7: SAXS fitting parameters for compound **3** using a form factor contribution for a sphere.

Parameter	Values
R_{sphere} [nm]	9.34
Σ	3.34
N	4.87×10^{-3}
<i>subtracted background</i>	4.00×10^{-4}
η^a [nm ⁻²]	1.018×10^{-3}

^a The X-ray scattering length density (SLD) η was calculated using the SLD calculator given in SASfit.

Table S 8: SAXS fitting parameters for compound **3** using a form factor contribution for a cylinder.

Parameter	Values
R_{cylinder} [nm]	9.87
L_{cylinder}^a [nm]	200
Σ	1.03
N	1.45×10^{-4}
<i>subtracted background</i>	1.00×10^{-4}
η^b [nm ⁻²]	1.018×10^{-3}

^a The length L for the cylinder fit was estimated from the lengths observed in the corresponding cryoTEM images of compound **3**. Due to the absence of a plateau at low q -values for the SAXS data, this value does not represent the real average cylinder length.

^b The X-ray scattering length density (SLD) η was calculated using the SLD calculator given in SASfit.

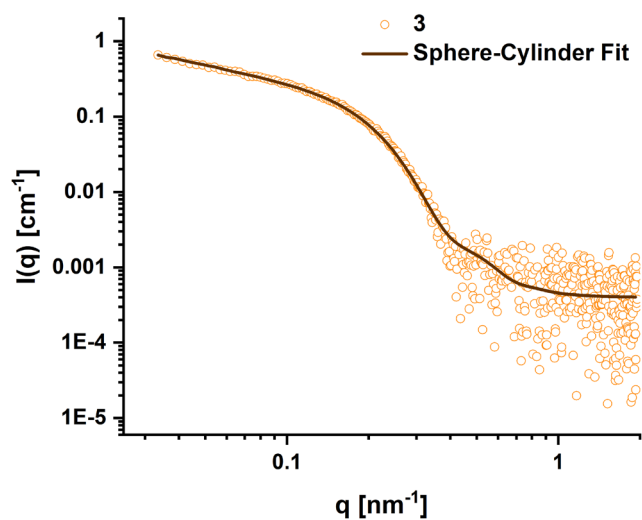


Figure S 28: SAXS trace for **3** (circles) in water ($c = 1.5 \text{ mg mL}^{-1}$) fitted with form factor contributions for a sphere and cylinder (solid line).

4 – [B][Phe]₃[C₁₂]₃[PEO_{10k}]

Table S 9: SAXS fitting parameters for compound **4** using a form factor for a sphere.

Parameter	Values
R_{sphere} [nm]	10.53
Σ	4.85
N	2.10×10^{-3}
<i>subtracted background</i>	4.00×10^{-4}
η^a [nm ⁻²]	1.019×10^{-3}

^a The X-ray scattering length density (SLD) η was calculated using the SLD calculator given in SASfit.

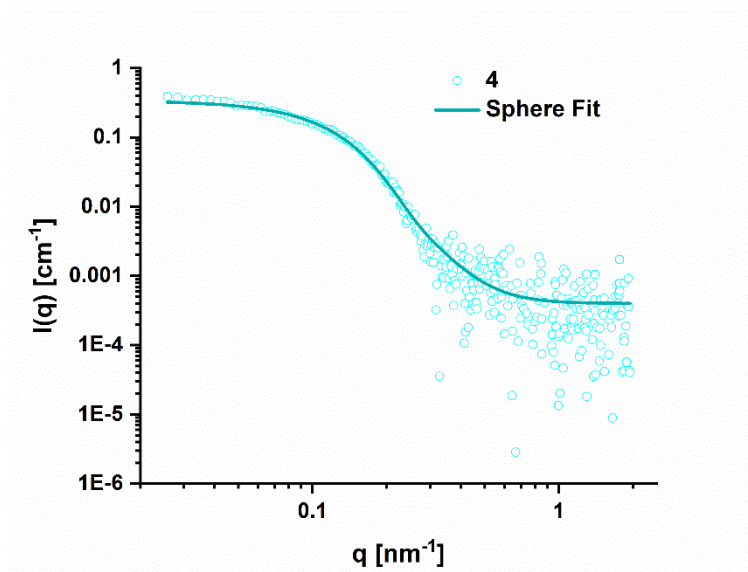


Figure S 29: SAXS trace for **4** (circles) in water ($c = 1.5 \text{ mg mL}^{-1}$) fitted with a form factor for a sphere (solid line).

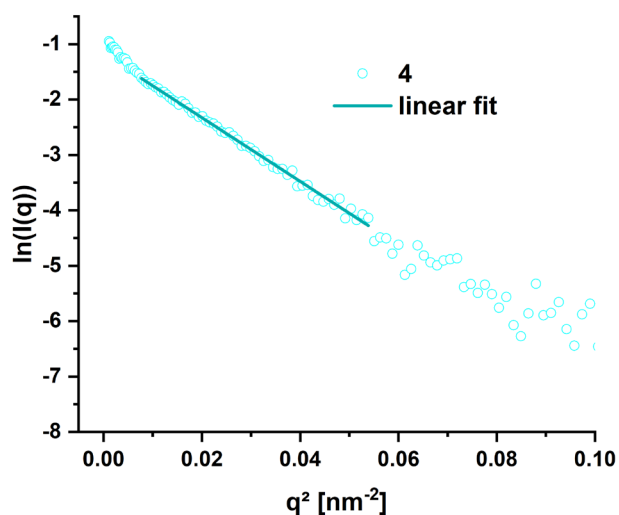


Figure S 30: Guinier plot ($\ln(I(q))$ vs. q^2) of the SAXS data of compound **4**. The slope of the linear fit was used to determine the radius of gyration R_g (here: $R_g = 13.1 \text{ nm}$) using the Guinier approximation.

5 – [B][Phe]₃[C₁₂]₃[PEO_{2k}]₃

Table S 10: SAXS fitting parameters for compound 4 using a form factor for a sphere.

Parameter	Values
R_{sphere} [nm]	3.91
Σ	1.05
N	2.10×10^{-3}
subtracted background	4.00×10^{-4}
η^a [nm ⁻²]	1.019×10^{-3}

^a The X-ray scattering length density (SLD) η was calculated using the SLD calculator given in SASfit.

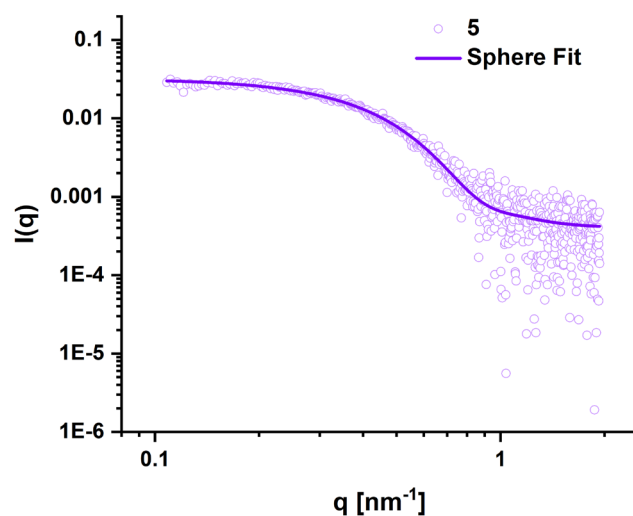


Figure S 31: SAXS trace for 5 (circles) in water ($c = 1.5 \text{ mg mL}^{-1}$) fitted with a form factor for a sphere (solid line).

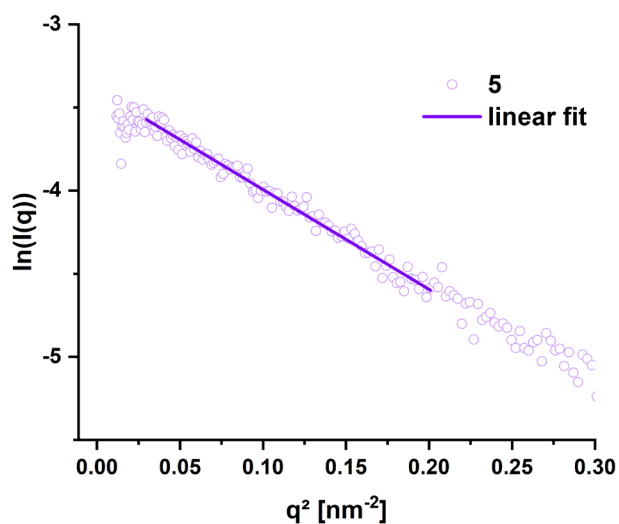


Figure S 32: Guinier plot ($\ln(I(q))$ vs. q^2) of the SAXS data of compound 5. The slope of the linear fit was used to determine the radius of gyration R_g (here: $R_g = 4.2 \text{ nm}$) using the Guinier approximation.

Molecules per cross-section calculation

The weight-average molar mass, M_w , of the spherical aggregates of **5** can be calculated from a Guinier plot of $\ln\left(\frac{I(q)}{K \cdot C}\right)$ against q^2 . To this end, the intersection of the linear plot with the y-axis is determined which yields the weight-average molar mass according to the following equation:³

$$M_w = e^{y, \text{intersection}} = e^{\left(\frac{I(q)}{K \cdot C}\right)_{x,0}} \quad (\text{Equation S2})$$

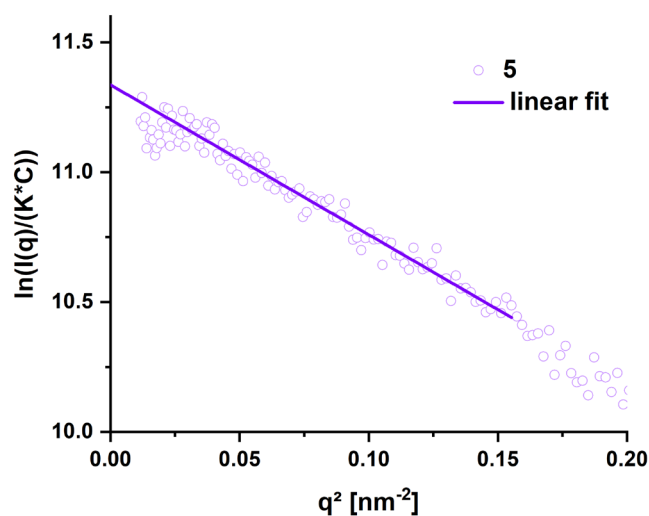


Figure S 33: Weight-average molar mass, M_w , calculation from a Guinier plot of $\ln(I(q)/(K \cdot C))$ against q^2 . M_w can be derived from the intersection of the linear fit with the y-axis.

This results in a M_w of 83800 g mol⁻¹ for the spherical micelle of **5**. Assuming a cylindrical arrangement of the BTP-PEO compound inside the micelles via the formation of a triple helix as known for benzenetrisamides,⁴ the number of aggregation, N_{agg} , and from this the number of molecules per cross-section can be determined. To support the assumption of a cylindrical arrangement of **5** within the spherical micelle, we fitted the SAXS data of **5** with a cylindrical form factor. The resulting fit was of similar quality as the originally applied fit using a spherical form factor (Table S 11 and Figure S 34).

Table S 11: SAXS fitting parameters for compound **5** using a form factor contribution for a cylinder.

Parameter	Values
$R_{cylinder}$ [nm]	5.14
$L_{cylinder}$ [nm]	5.28
σ	0.55
N	1.49×10^{-1}
<i>subtracted background</i>	4.00×10^{-4}
η^a [nm ⁻²]	1.017×10^{-3}

^a The X-ray scattering length density (SLD) η was calculated using the SLD calculator given in SASfit.

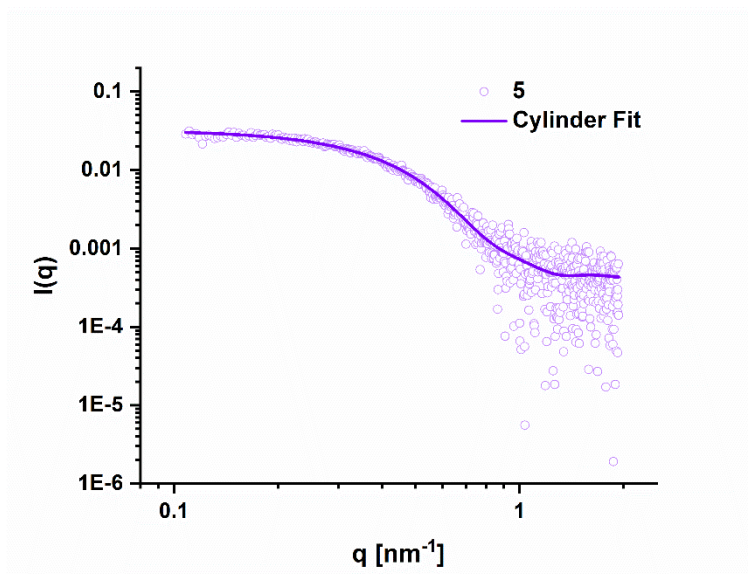


Figure S 34: SAXS trace for **5** (circles) in water ($c = 1.5 \text{ mg mL}^{-1}$) fitted with a form factor for a cylinder (solid line).

The number of aggregation, N_{agg} , can then be calculated by dividing M_w by the molar mass of compound **5**.

$$N_{agg} = \frac{M_w}{M_{w,5}} \quad (\text{Equation S3})$$

This yields a N_{agg} of 12.3. Assuming an intermolecular distance of 0.362 nm between individual BTP-PEO molecules,⁵ the number of molecules per cross-section, $\#_{cross}$, can be calculated when considering the length of the cylinder, L_{cyl} , obtained from the cylindrical fit (Table S 11):

$$\#_{cross} = \frac{N_{agg}}{\left(\frac{L_{cyl}}{0.362 \text{ nm}}\right)} \quad (\text{Equation S4})$$

According to this, approximately 0.87 molecules of **5** are present in the cross-section of the spherical micelles.

2.4 CryoTransmission Electron Microscopy (cryoTEM)

Samples were prepared on Ar plasma treated Quantifoil grids (R2/2). 8.5 μL of the solutions (3 mg mL^{-1} in H_2O) were applied onto the grids and vitrified into liquid ethane utilizing a FEI Vitrobot Mark IV system (offset: -3 mm, blotting time: 1 s). Samples were transferred into the cryo holder (Gatan 626) utilizing the Gatan cryo stage, followed by transfer into the microscope keeping the temperature below -172 $^{\circ}\text{C}$ during the whole transfer and measurement process after vitrification. Measurements were performed using a FEI Technai G² 20 at an acceleration voltage of 200 kV. Images were acquired with a Mega View (OSIS, Olympus Soft Imaging Systems) or an Eagle 4k CCD camera. In the cryoTEM images in this study, only specific regions of interest are shown, that are representative for the whole sample.

1a – [B][Ala]₃[C₆]₃[PEO]_{2k}

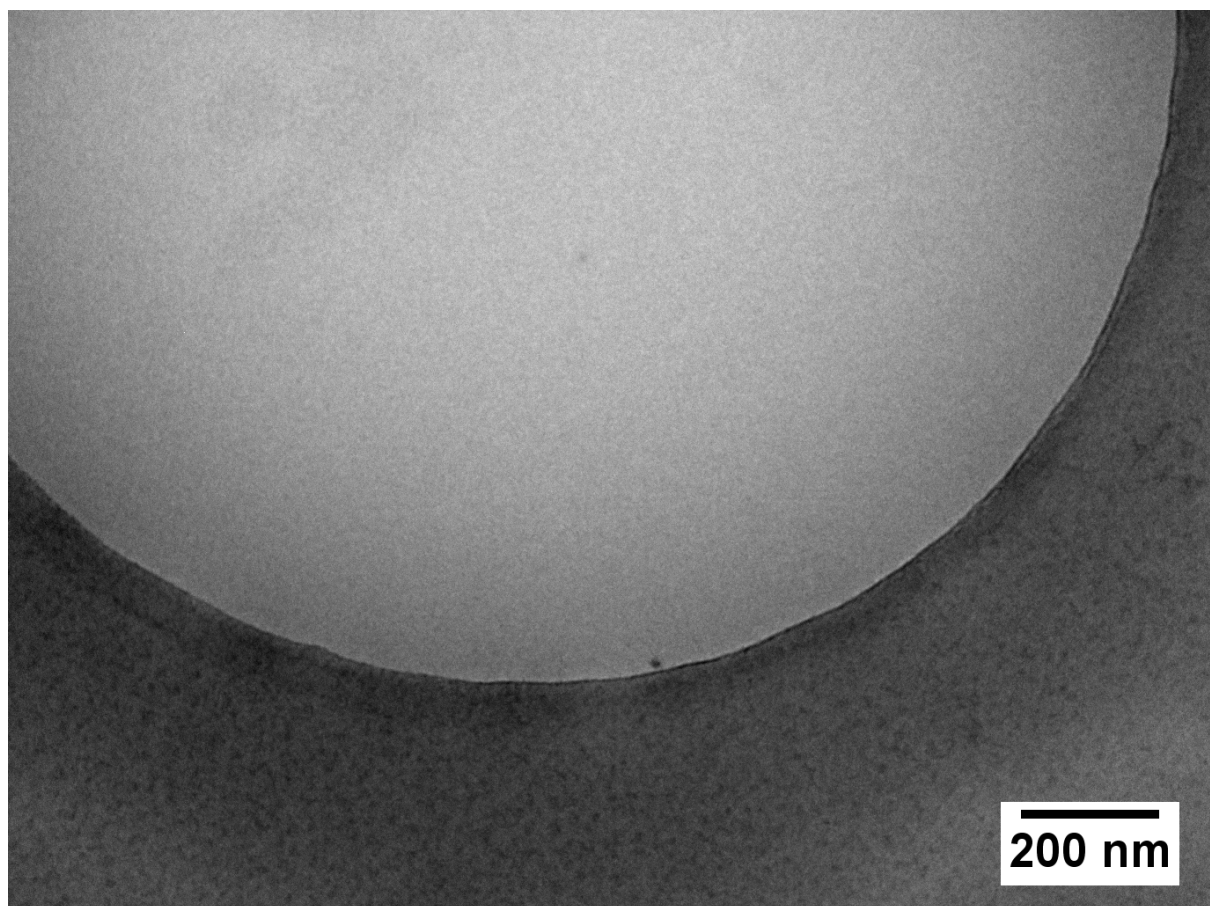


Figure S 35: cryoTEM micrograph of *1a* in water (3 mg mL^{-1}).

1b – [B][Leu]₃[C₆]₃[PEO_{2k}]

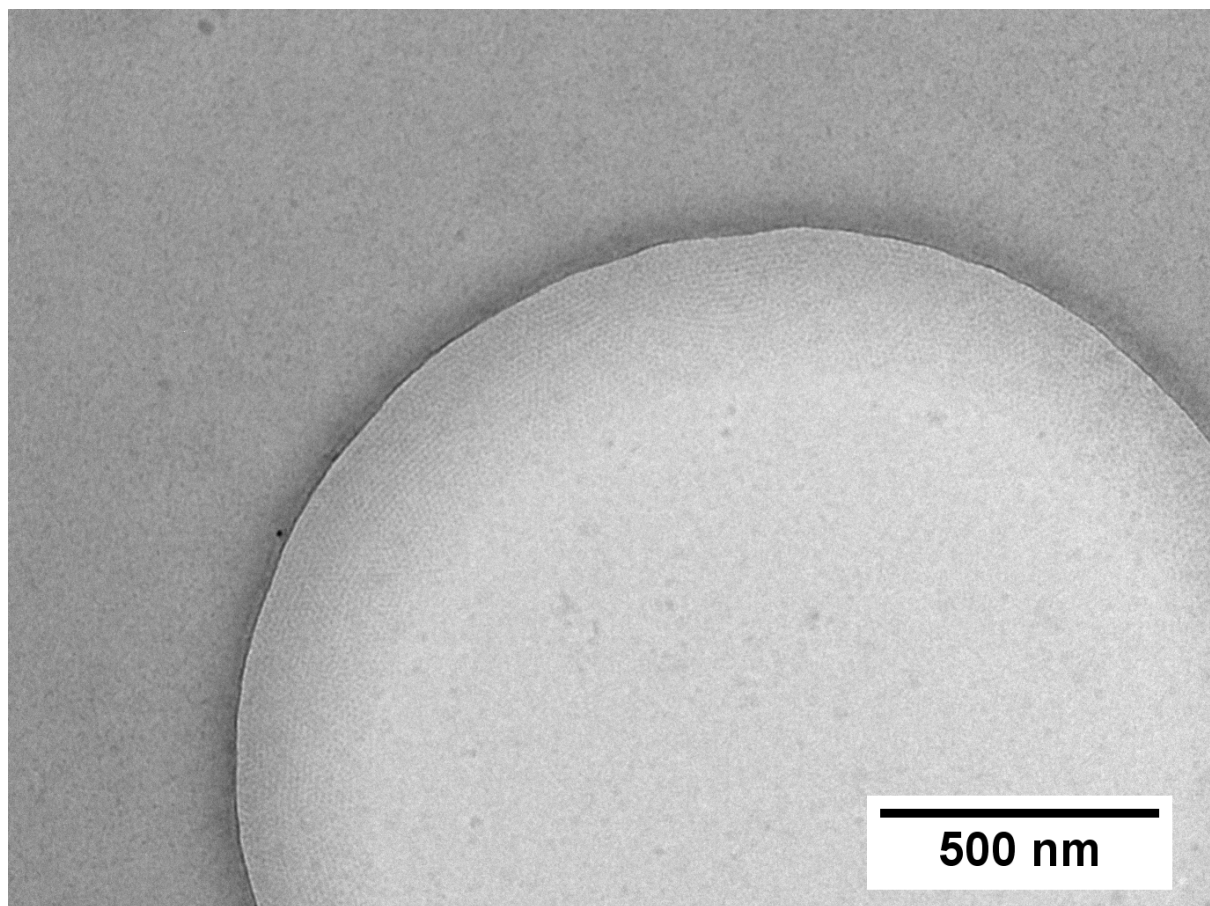


Figure S 36: cryoTEM micrograph of **1b** in water (3 mg mL⁻¹).

1c – [B][Phe]₃[C₆]₃[PEO_{2k}]

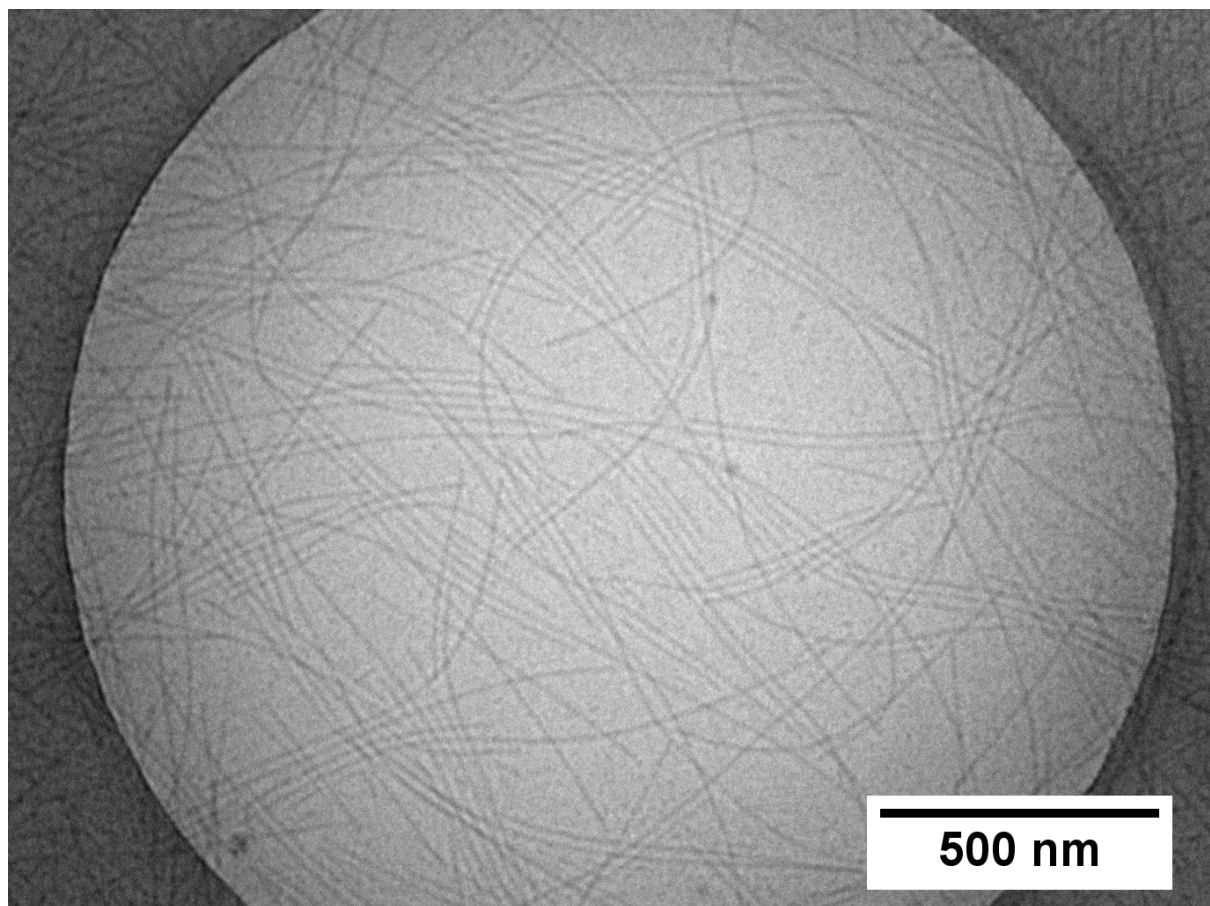


Figure S 37: cryoTEM micrograph of **1c** in water (3 mg mL⁻¹).

2a – [B][Ala]₃[C₁₂]₃[PEO_{2k}]

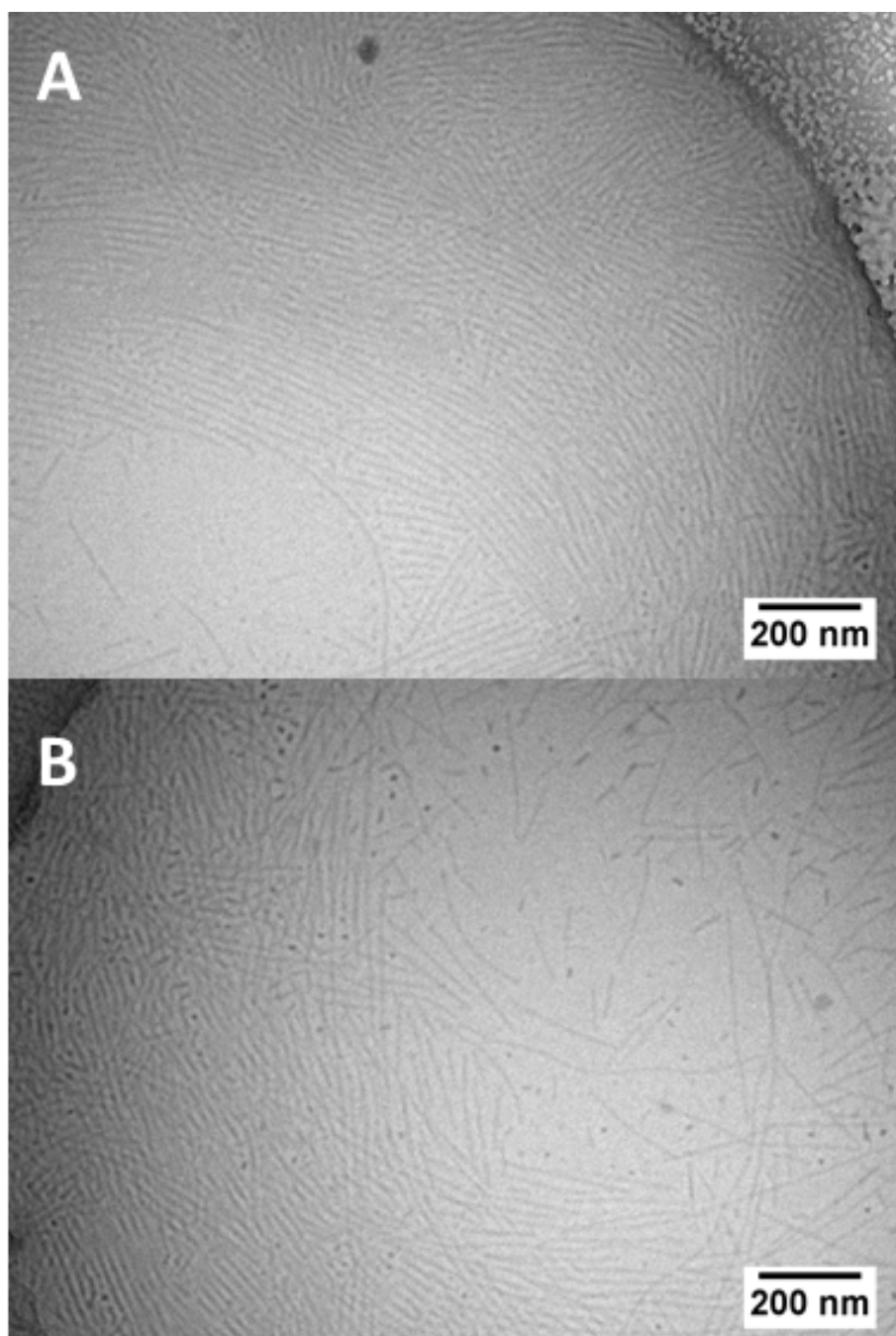


Figure S 38: cryoTEM micrographs of **2a** in water (3 mg mL⁻¹).

2b – [B][Leu]₃[C₁₂]₃[PEO_{2k}]

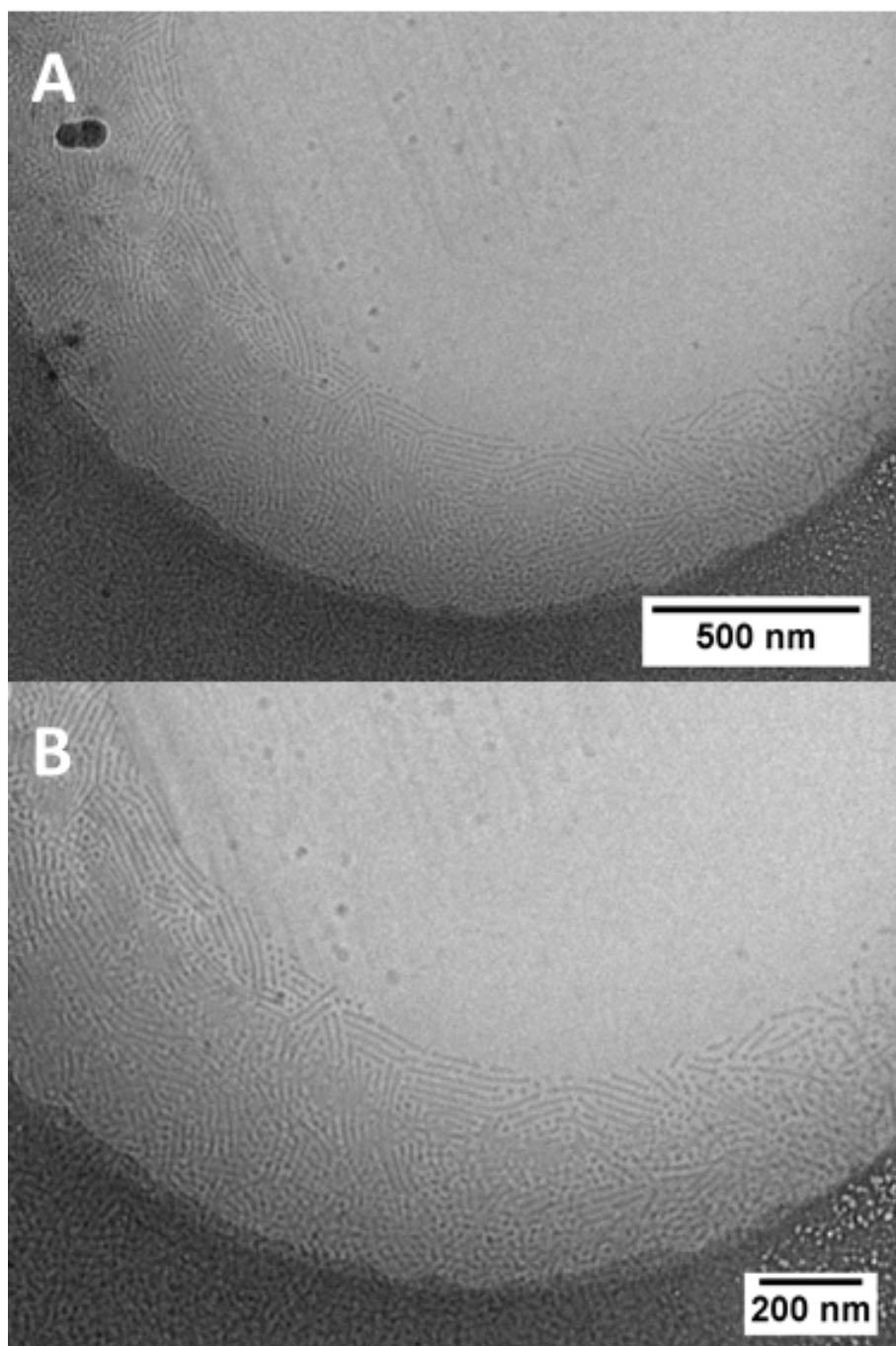


Figure S 39: cryoTEM micrographs of **2b** in water (3 mg mL⁻¹).

2c – [B][Phe]₃[C₁₂]₃[PEO_{2k}]

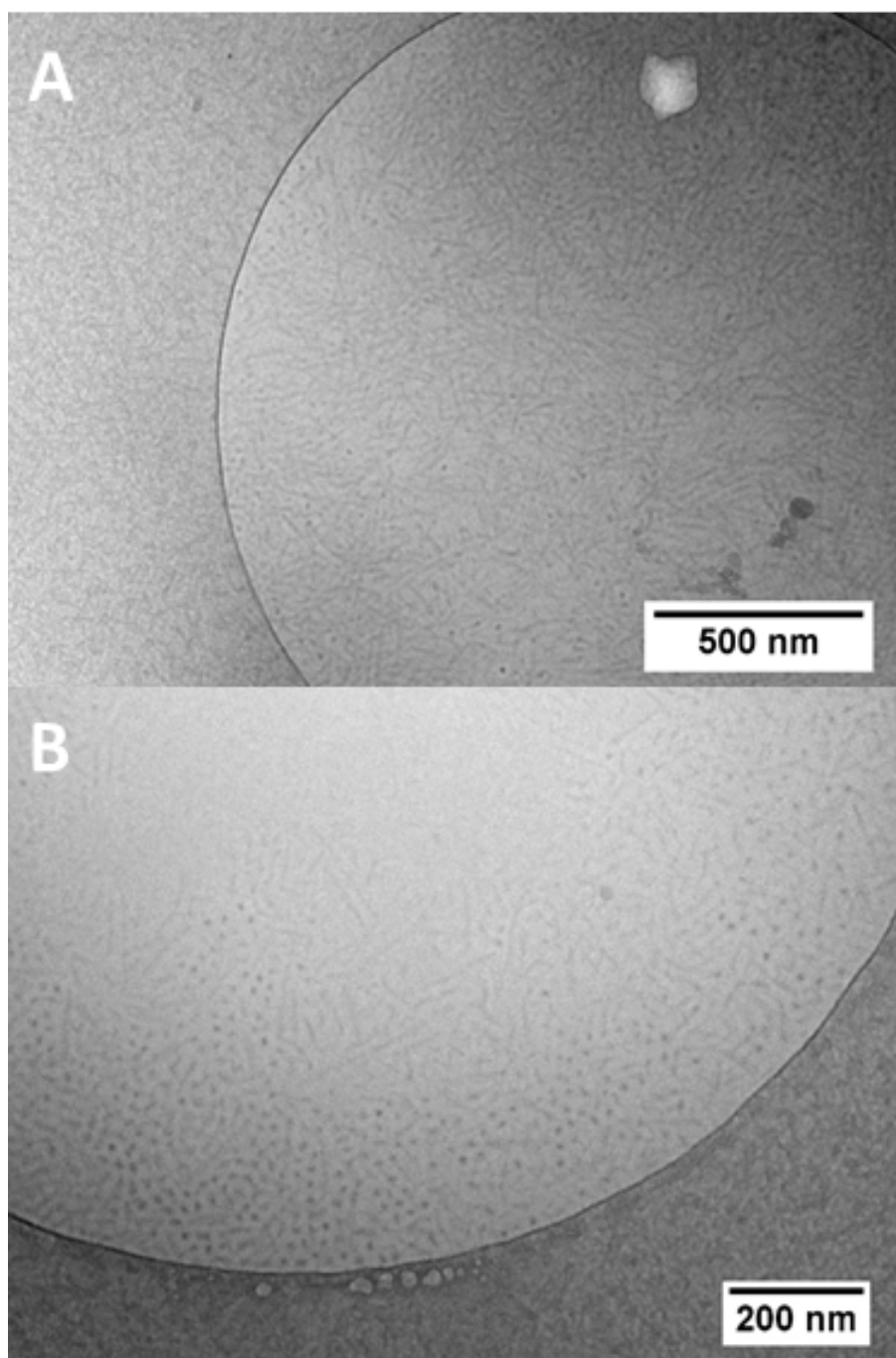


Figure S 40: cryoTEM micrographs of **2c** in water (3 mg mL⁻¹).

3 – [B][Phe]₃[C₁₂]₃[PEO_{5k}]

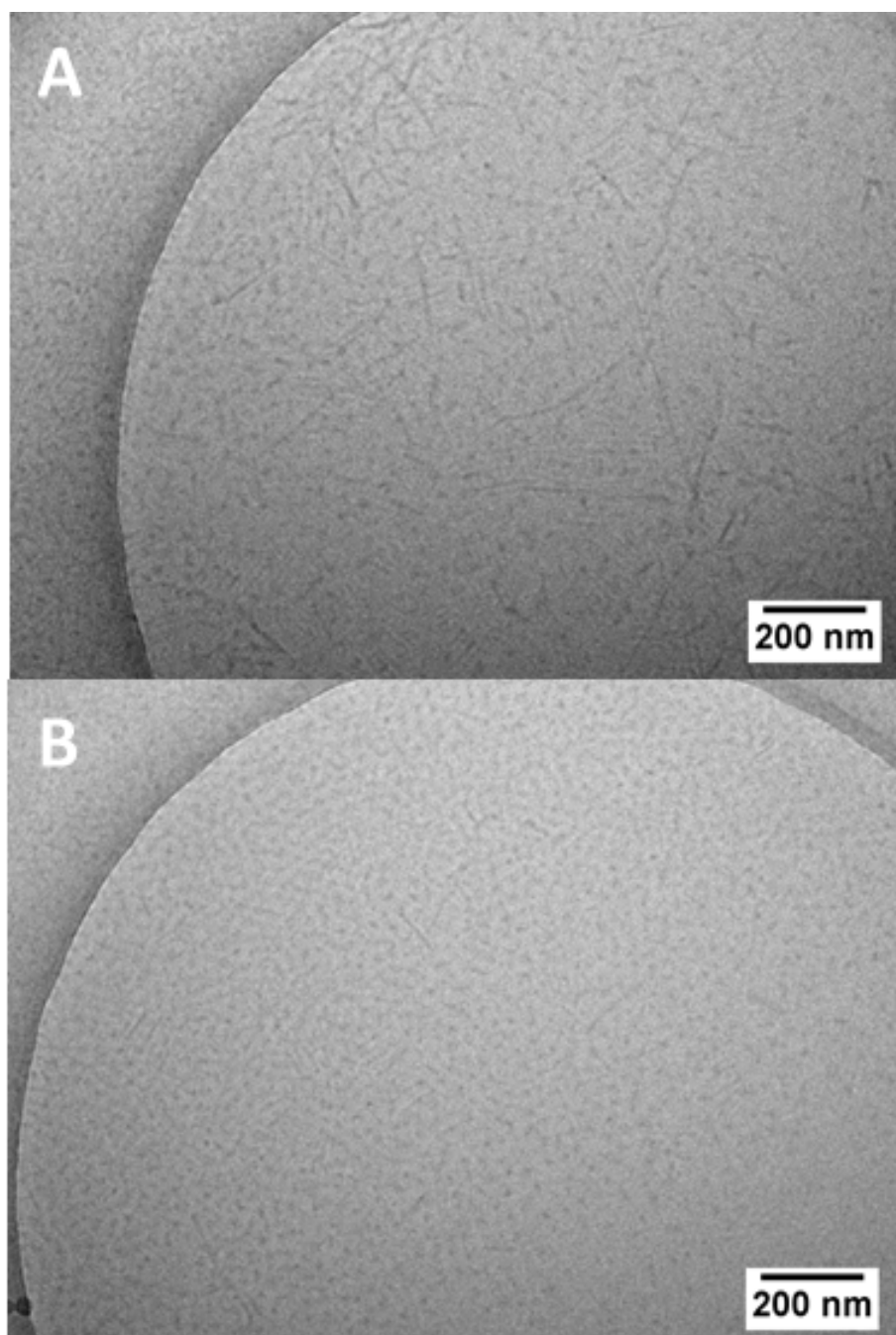


Figure S 41: cryoTEM micrographs of **3** in water (3 mg mL⁻¹).

4 – [B][Phe]₃[C₁₂]₃[PEO_{10k}]

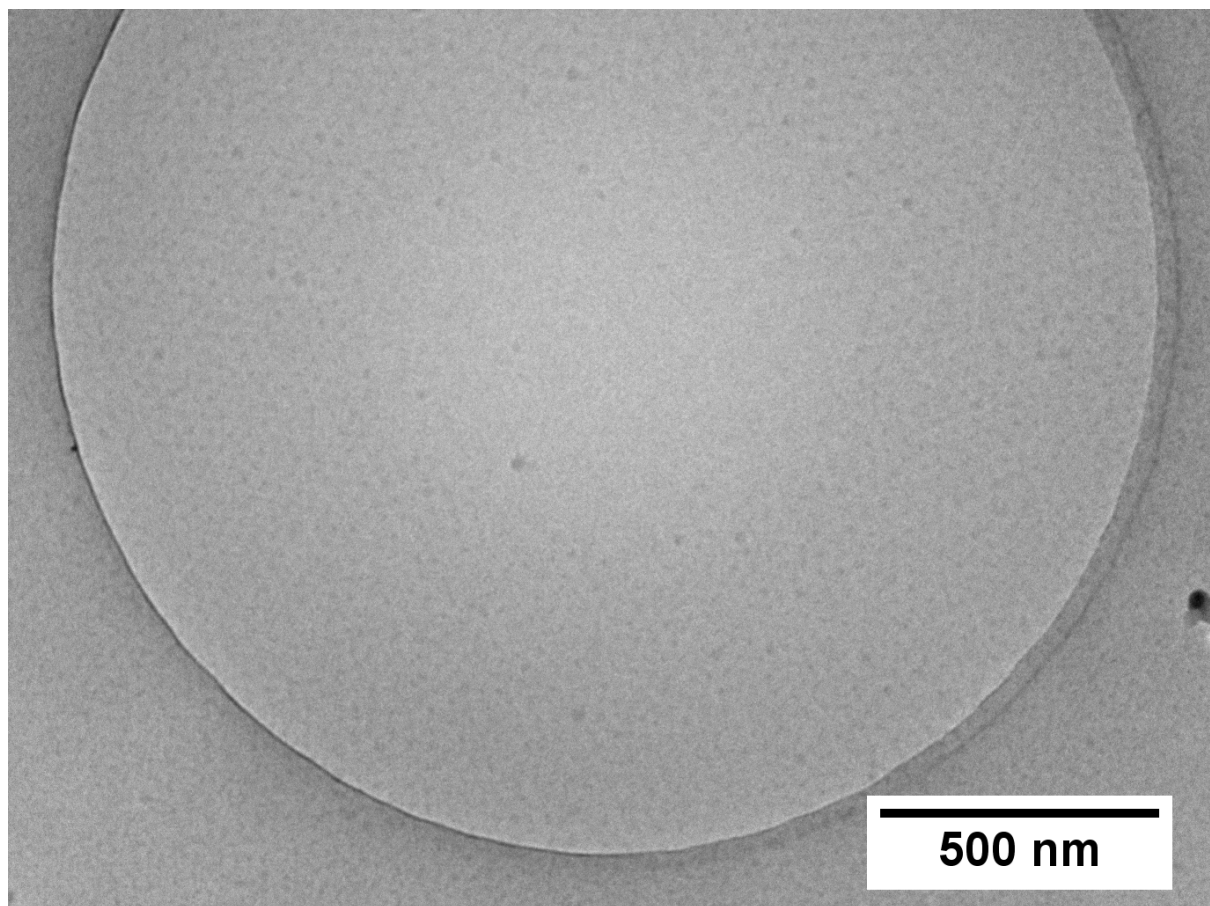


Figure S 42: cryoTEM micrograph of **4** in water (3 mg mL^{-1}).

5 – [B][Phe]₃[C₁₂]₃[PEO_{2k}]₃

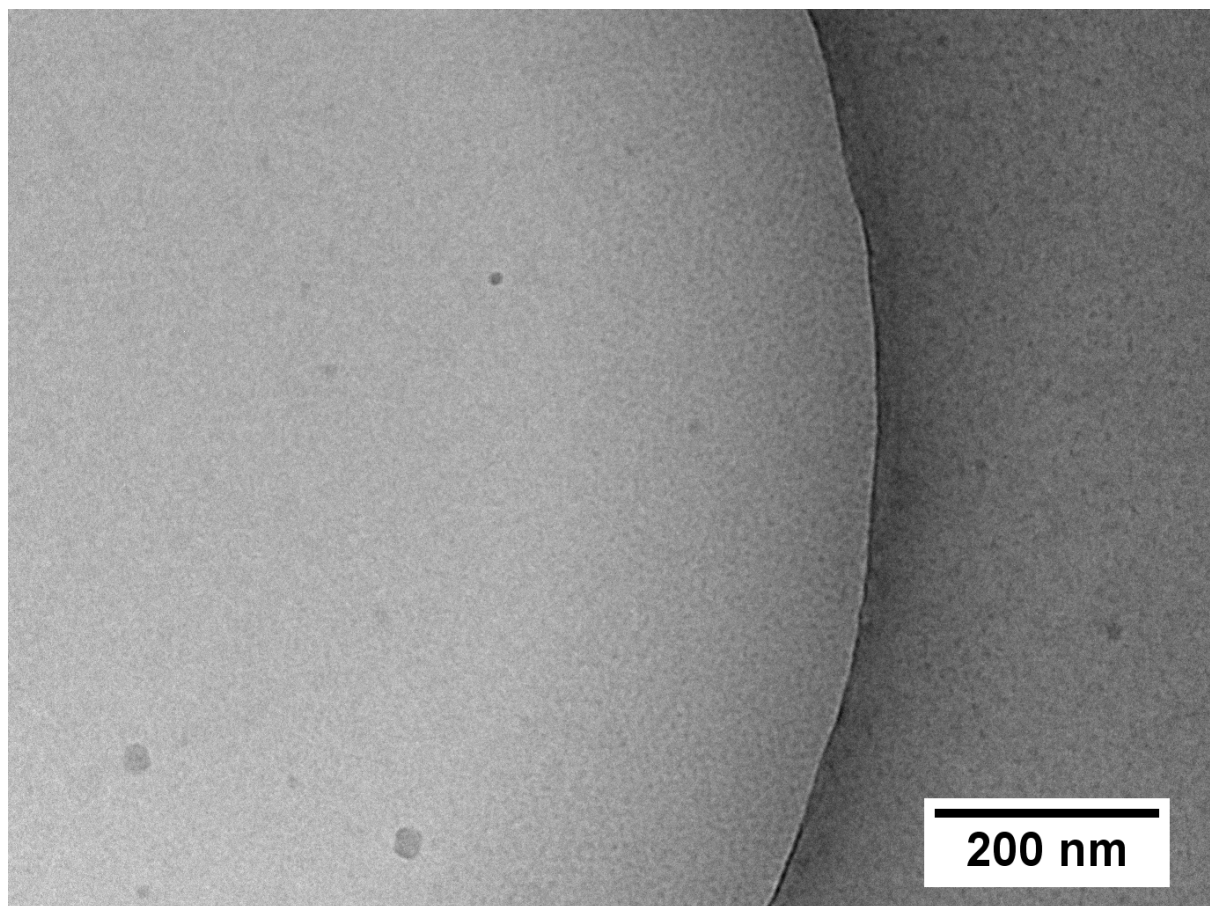


Figure S 43: cryoTEM micrograph of **5** in water (3 mg mL⁻¹).

2.5 Circular Dichroism (CD) spectroscopy

CD spectra were recorded on a JASCO J-820KS spectrophotometer. Each sample was measured five times at a concentration of 1.5 mg mL^{-1} in water using a quartz cell with a path length of 1 mm.

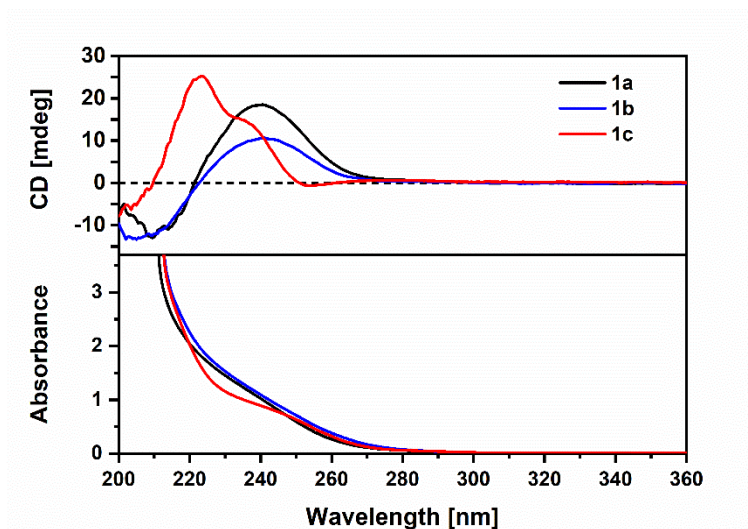


Figure S 44: CD (top) and UV absorption (bottom) spectra for compounds **1a** (black line), **1b** (red line) and **1c** (blue line) recorded in MilliQ water at a concentration of 1.5 mg mL^{-1} .

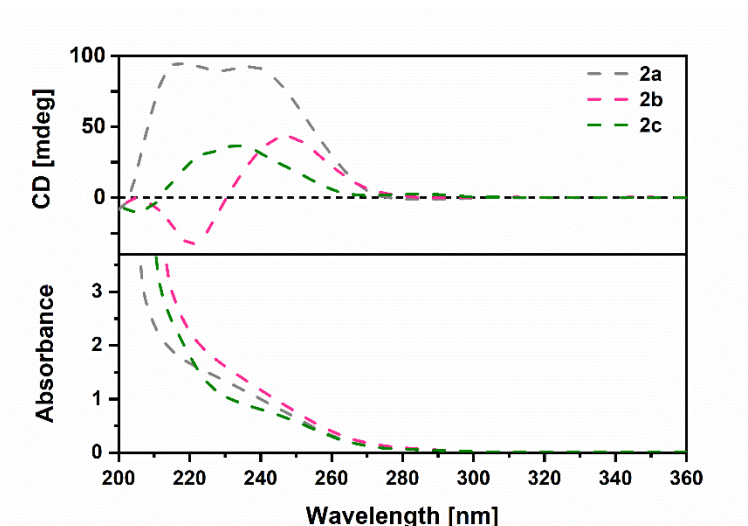


Figure S 45: CD (top) and UV absorption (bottom) spectra for compounds **2a** (grey line), **2b** (magenta line) and **2c** (green line) recorded in MilliQ water at a concentration of 1.5 mg mL^{-1} .

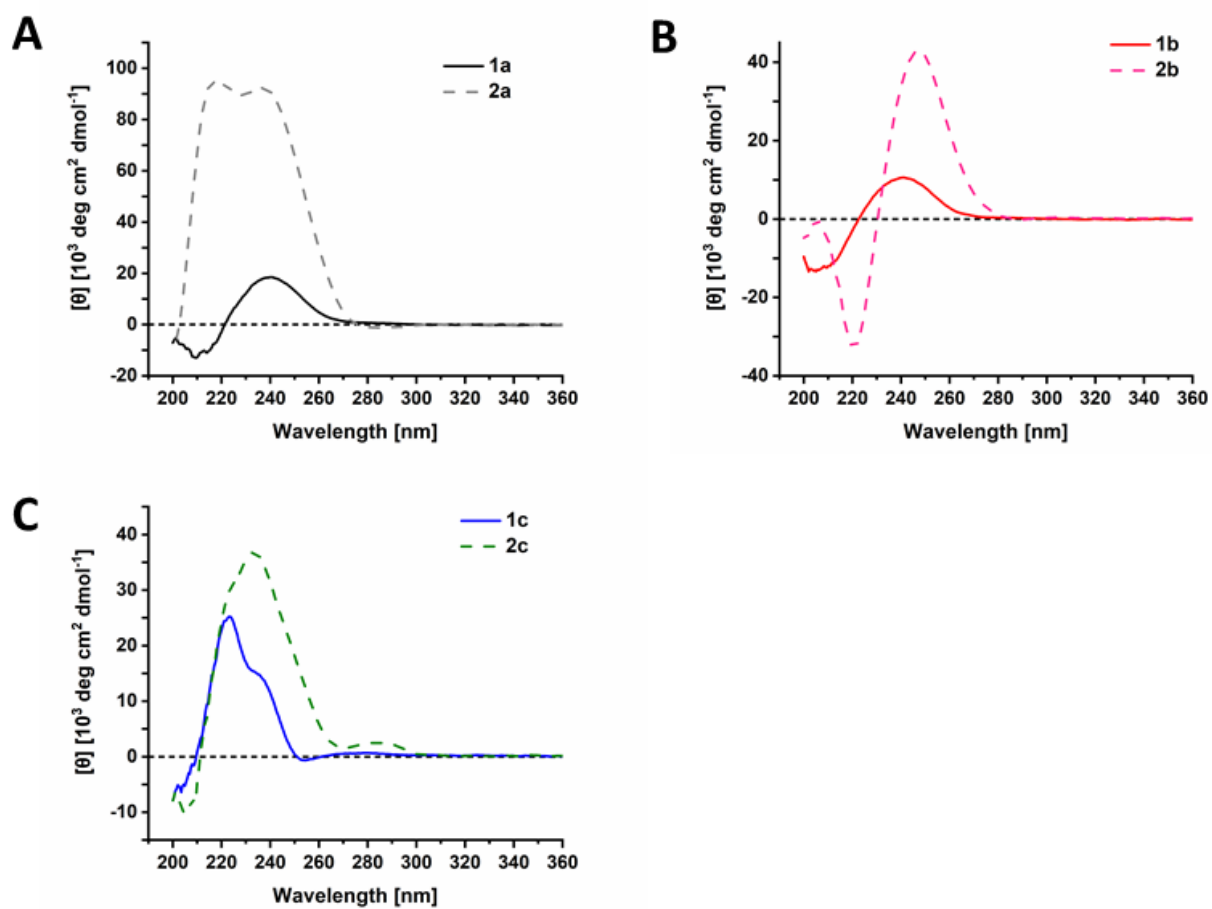


Figure S 46: CD spectra for compounds (A) **1a** (black line) and **2a** (grey line), (B) **1b** (red line) and **2b** (magenta line) and (C) **1c** (blue line) and **2c** (green line) recorded in MilliQ water at a concentration of 1.5 mg mL^{-1} .

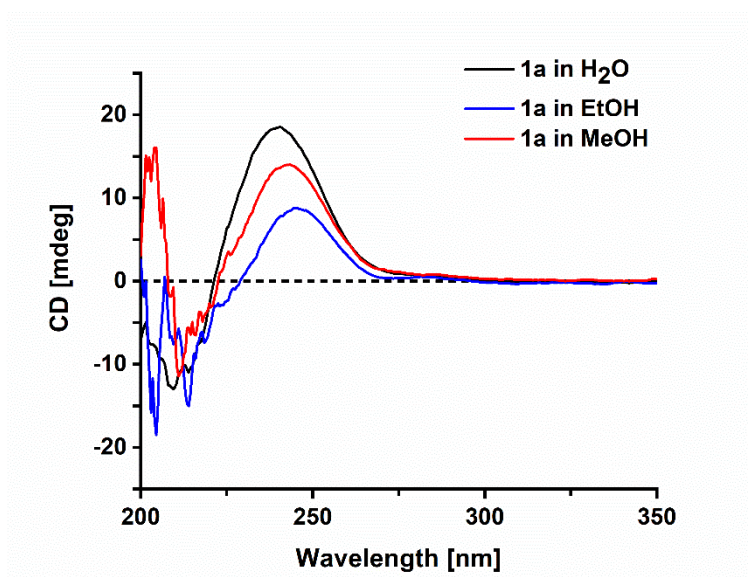


Figure S 47: CD spectra of **1a** recorded in water (black), ethanol (blue), and methanol (red).

2.6 CAC Determination

The critical aggregation concentrations (CAC) were determined by measuring the fluorescence intensity of Nile red incorporated in the benzenetrispeptide (BTP) poly(ethylene glycol) conjugates according to a literature procedure.⁶ To this end, BTP stock solutions were diluted with MilliQ water to obtain solutions of $V = 180 \mu\text{L}$ in a concentration range from $c = 1 \times 10^{-9}$ up to $c = 3 \text{ mg mL}^{-1}$. Then, $18 \mu\text{L}$ of a Nile red stock solution in THF ($c = 1 \text{ mg mL}^{-1}$) was added, and the samples equilibrated overnight in a thermoshaker device ($T = 25 \text{ }^\circ\text{C}$, 400 rpm). Afterwards, the samples were transferred to quartz cuvettes and the fluorescence of Nile red recorded (wavelength measurement range: 550 – 800 nm) from an excitation at a wavelength of $535 \pm 5 \text{ nm}$. The CAC was determined as the intersection point of the linear fits (performed with OriginPRO 2018b) from the emission intensity at a wavelength of 612 nm versus the \log of the BTP concentration.

Table S 12: CAC values of **1a-c** and **2a-c** in $\mu\text{g mL}^{-1}$ and $\mu\text{mol L}^{-1}$ using Nile red as a fluorescent probe.

Compound	CAC _{612nm} [$\mu\text{g mL}^{-1}$]	CAC _{612nm} [$\mu\text{mol L}^{-1}$]
1a	694.4	268.8
1b	177.7	66.2
1c	171.2	61.3
2a	125.9	44.5
2b	149.5	50.9
2c	113.2	37.2

1a – [B][Ala]₃[C₆]₃[PEO_{2k}]

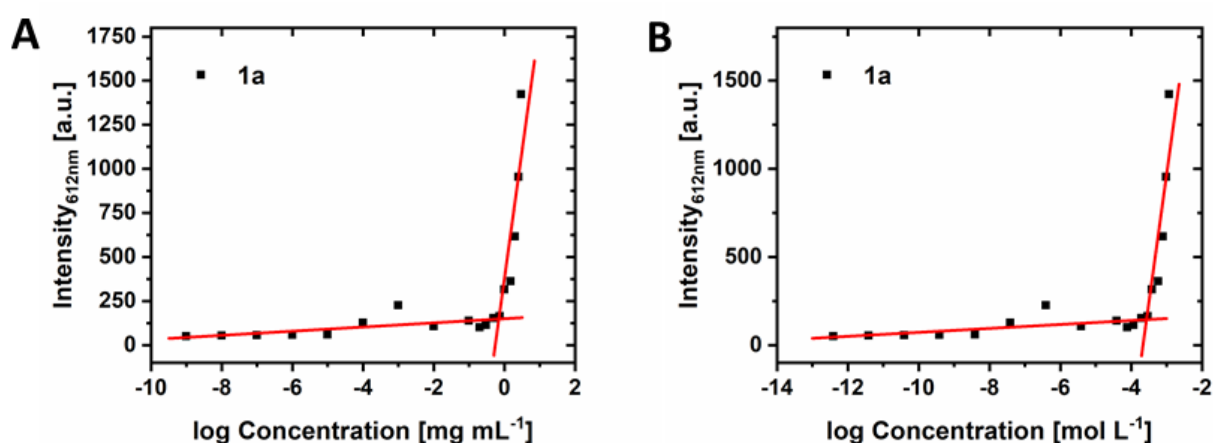


Figure S 48: CAC determination of **1a** via the Nile red fluorescence intensity method. A) Fluorescence intensity at 612 nm vs. logarithmic concentration in mg mL^{-1} (CAC: 694.4 $\mu\text{g mL}^{-1}$) and B) Fluorescence intensity at 612 nm vs. logarithmic concentration in mol L^{-1} (CAC: 268.8 $\mu\text{mol L}^{-1}$).

1b – [B][Leu]₃[C₆]₃[PEO_{2k}]

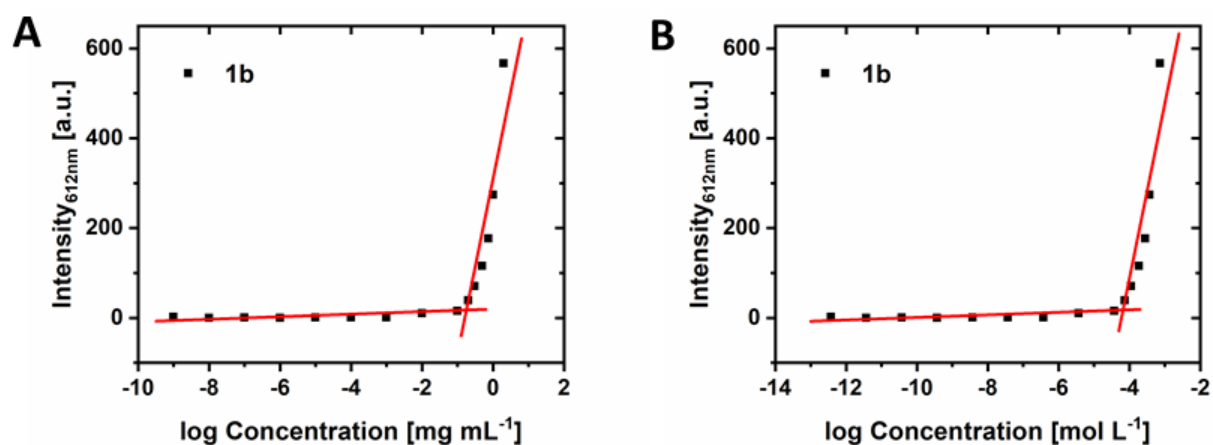


Figure S 49: CAC determination of **1b** via the Nile red fluorescence intensity method. A) Fluorescence intensity at 612 nm vs. logarithmic concentration in mg mL⁻¹ (CAC: 177.7 µg mL⁻¹) and B) Fluorescence intensity at 612 nm vs. logarithmic concentration in mol L⁻¹ (CAC: 66.2 µmol L⁻¹).

1c – [B][Phe]₃[C₆]₃[PEO_{2k}]

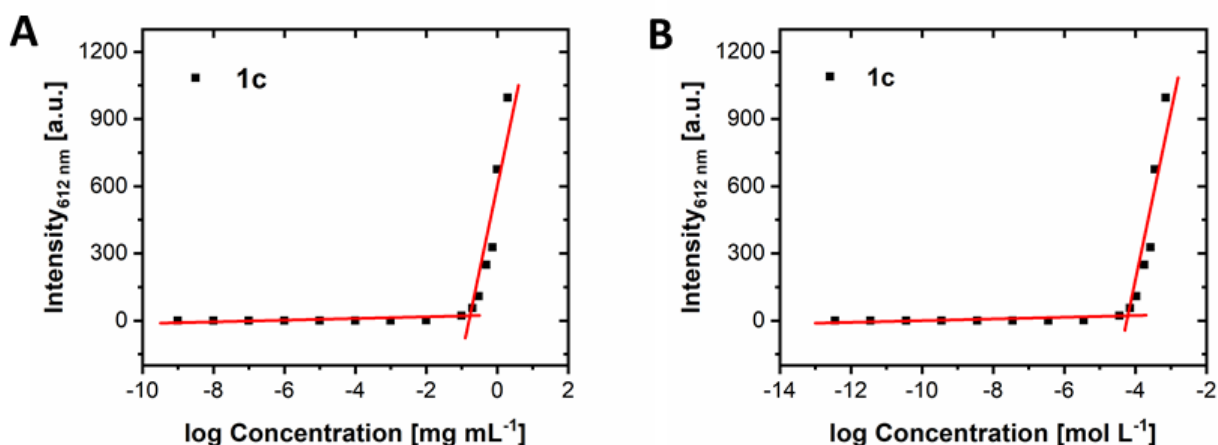


Figure S 50: CAC determination of **1c** via the Nile red fluorescence intensity method. A) Fluorescence intensity at 612 nm vs. logarithmic concentration in mg mL⁻¹ (CAC: 171.2 µg mL⁻¹) and B) Fluorescence intensity at 612 nm vs. logarithmic concentration in mol L⁻¹ (CAC: 61.3 µmol L⁻¹).

2a – [B][Ala]₃[C₁₂]₃[PEO_{2k}]

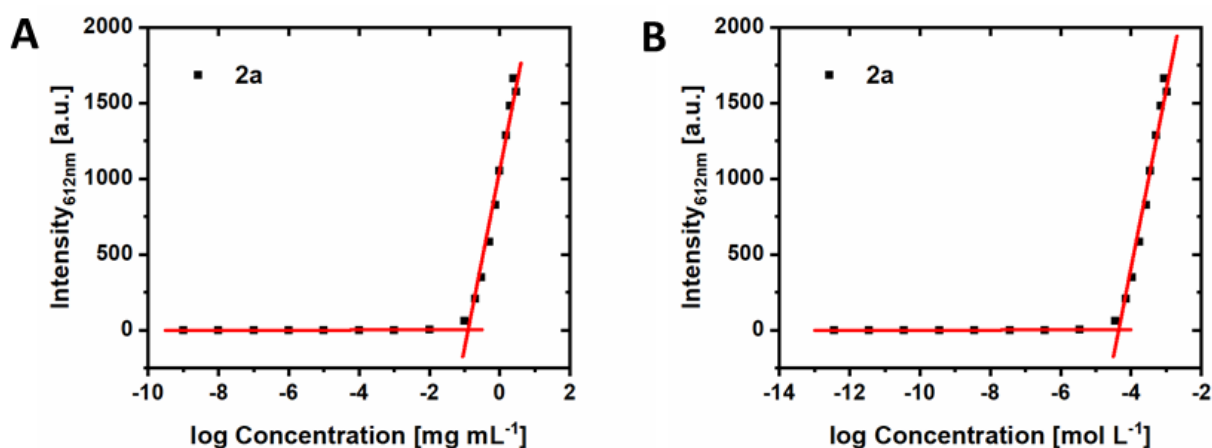


Figure S 51: CAC determination of **2a** via the Nile red fluorescence intensity method. A) Fluorescence intensity at 612 nm vs. logarithmic concentration in mg mL⁻¹ (CAC: 125.9 μg mL⁻¹) and B) Fluorescence intensity at 612 nm vs. logarithmic concentration in mol L⁻¹ (CAC: 44.5 μmol L⁻¹).

2b – [B][Leu]₃[C₁₂]₃[PEO_{2k}]

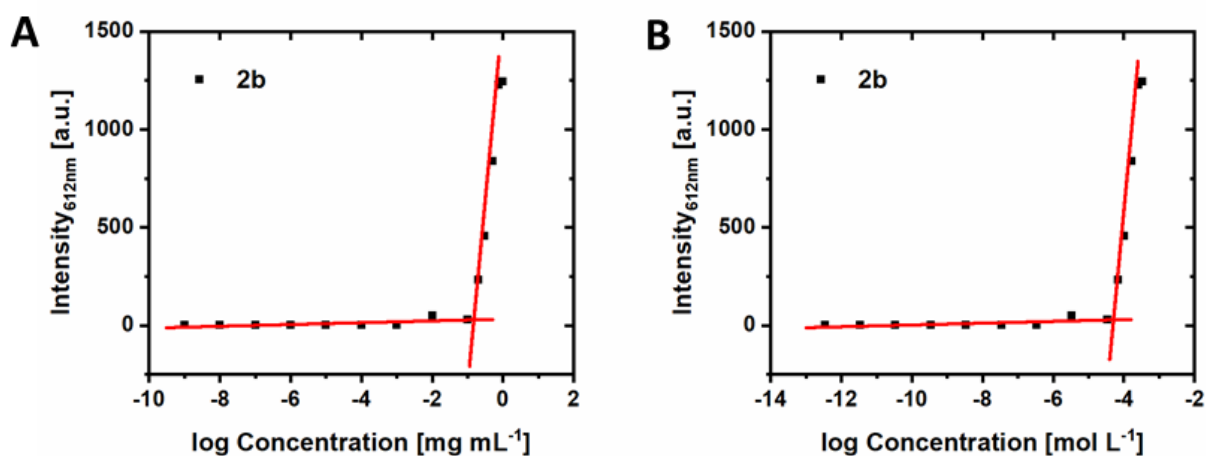


Figure S 52: CAC determination of **2b** via the Nile red fluorescence intensity method. A) Fluorescence intensity at 612 nm vs. logarithmic concentration in mg mL⁻¹ (CAC: 149.5 μg mL⁻¹) and B) Fluorescence intensity at 612 nm vs. logarithmic concentration in mol L⁻¹ (CAC: 50.9 μmol L⁻¹).

2c – [B][Phe]₃[C₁₂]₃[PEO_{2k}]

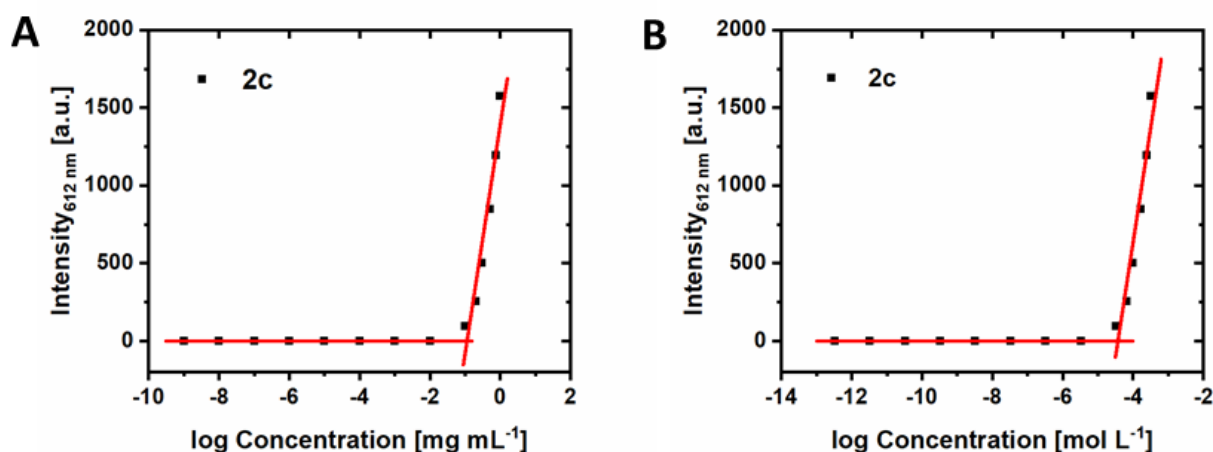


Figure S 53: CAC determination of 2c via the Nile red fluorescence intensity method. A) Fluorescence intensity at 612 nm vs. logarithmic concentration in mg mL⁻¹ (CAC: 113.2 μg mL⁻¹) and B) Fluorescence intensity at 612 nm vs. logarithmic concentration in mol L⁻¹ (CAC: 37.2 μmol L⁻¹).

2.7 Analytical Ultracentrifugation (AUC)

Sedimentation velocity experiments were performed with a ProteomeLab XL-I analytical ultracentrifuge (Beckman Coulter Instruments, Brea, CA). The cells, containing double-sector epon centerpieces with a 12 mm optical solution path length, were placed in an An-50 Ti eight-hole rotor. A rotor speed of 42,000 rpm was used. The cells were filled with 420 μL sample solution in water and with 440 μL of the solvent water in the reference sector. Typically, the experiments were conducted for a timescale of at least 24 hours and at a temperature of $T = 20$ °C. Sedimentation profile scans were recorded with the interference optics (refractive index (RI)).

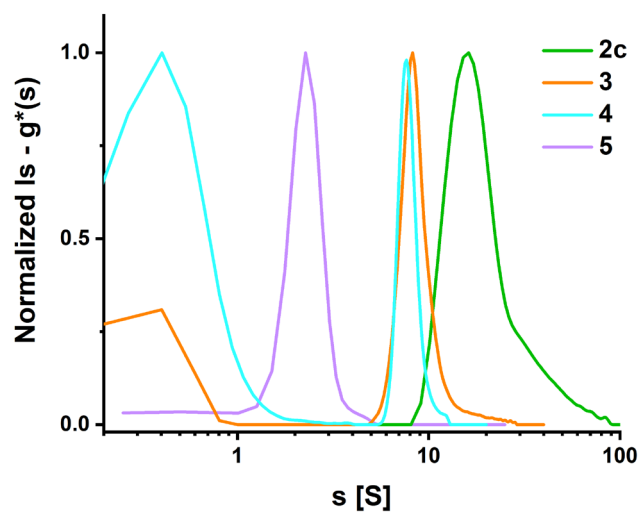


Figure S 54: Normalized differential distribution of sedimentation coefficients, $ls-g^*(s)$, of **2c** (green), **3** (orange), **4** (cyan) and **5** (purple) from sedimentation analysis in water ($c = 3 \text{ mg mL}^{-1}$). The signals below $S < 1$, visible in the curves of **3** and **4** originate from residual PEO_{5k} and PEO_{10k} unimeric species, respectively.⁷ These could not be removed from the BTP-PEO compounds via centrifugal washing, as described in the procedures in Chapter 1.

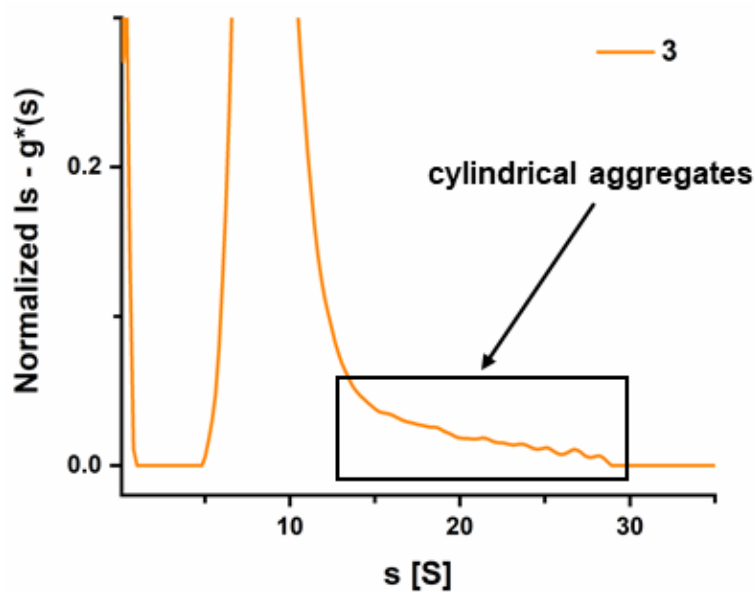


Figure S 55: Normalized differential distribution of sedimentation coefficients, $ls-g^*(s)$, of **3** from sedimentation-diffusion analysis in water ($c = 3 \text{ mg mL}^{-1}$). Zoomed view to clearly illustrate the presence of a minority of larger, cylindrical aggregates in accordance with the SAXS data and cryoTEM images of **3**.

3. References

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