

Electronic Supplementary Information

Folding Induced Supramolecular Assembly into pH Responsive Nanorods with a Protein Repellent Shell

Ronja Otter^{1,†}, Kristina Klinker^{1,2,†}, Daniel Spitzer¹, Meike Schinnerer³, Matthias Barz^{1,*}, Pol Besenius^{1,*}

¹Institute of Organic Chemistry, Johannes Gutenberg University, Duesbergweg 10-14, 55128 Mainz, Germany

²Graduate School of Materials Science in Mainz, Staudingerweg 9, 55128 Mainz, Germany

³Institute of Physical Chemistry, Johannes Gutenberg University, Duesbwegweg 10-14, 55128 Mainz, Germany

[†] These authors contributed equally.

*barz@uni-mainz.de, besenius@uni-mainz.de

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1. Additional experimental data

Fluorescence Spectroscopy

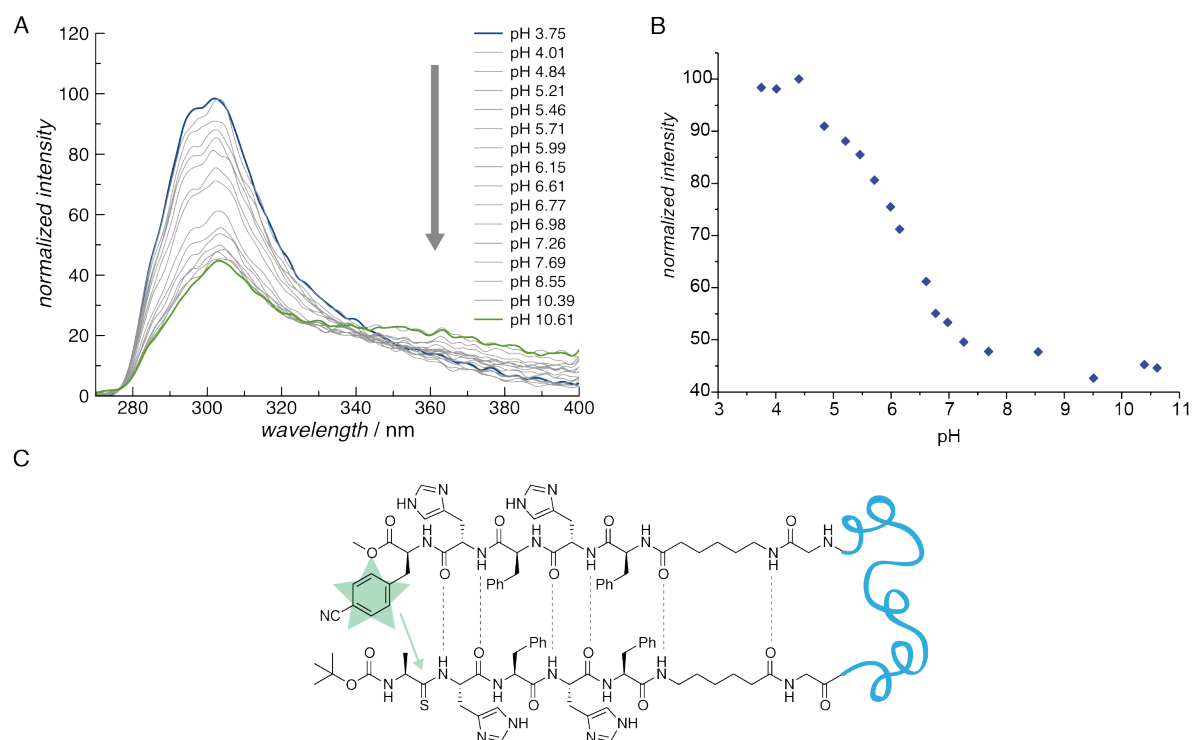


Figure S1. A) Fluorescence spectra of a 50 μM aqueous solution of **C4** at different pH values, $\lambda_{\text{exc}} = 240$ nm, maximum Intensity normalized to 100. B) Corresponding titration curve following the intensity of the fluorescence at $\lambda = 302.5$ nm. C) Chemical structure of **C4**.

Characterization of P4 and C4

Table S1: Analytical data of **P4** and **C4**

	M/I	$X_n(\text{NMR})^a$	$M_{n(\text{GPC})}^b / \text{g mol}^{-1}$	\bar{D}^b
P4	200	189	30709	1.23
C4	-	-	31509	1.32

^a Determined by ^1H NMR. ^b Determined by HFIP GPC relative to PMMA standards.

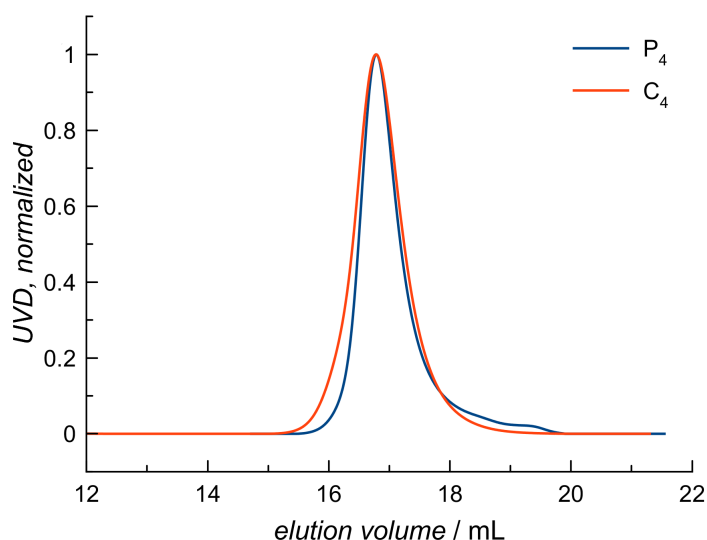


Figure S2. GPC elugrams of **P4** and **C4** in HFIP.

CD-Measurements of **C5**

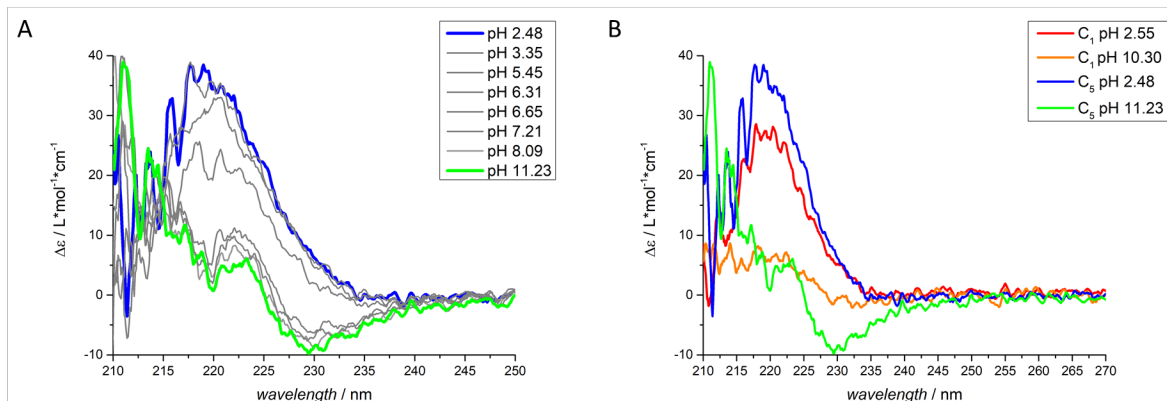


Figure S3. A) pH-dependent CD-Measurements of **C5** (50 μ M) in 10 mM phosphate buffer. B) Comparison of CD-measurements of **C1** and **C5** at acidic and basic pH-values in 10 mM phosphate buffer.

Characterization of **P5** and **C5**

Table S2: Analytical data of **P5** and **C5**

	M/I	$X_{\text{n(NMR)}}^{\text{a)}}$	$M_{\text{n(GPC)}}^{\text{b)}} / \text{g mol}^{-1}$	\bar{D}^{b}
P5	25	28	9760	1.13
C5		-	11895	1.19

^a Determined by ^1H NMR. ^b Determined by HFIP GPC relative to PMMA standards.

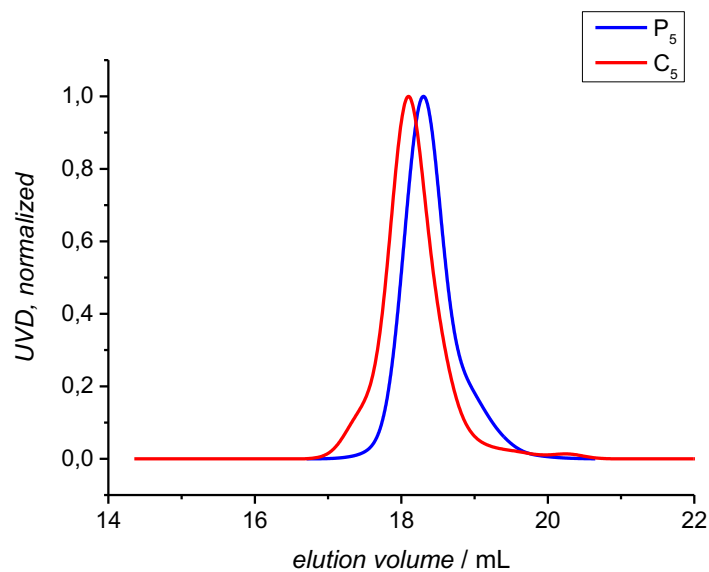


Figure S4. GPC elugrams of **P5** and **C5** in HFIP.

Transmission Electron Microscopy (TEM)

The lengths of individual rods were measured using the software Image J.

Values of L_n and L_w were calculated as previously reported.^[1]

$$L_n = \frac{\sum_{i=1}^n n_i L_i}{\sum_{i=1}^n n_i} \quad L_w = \frac{\sum_{i=1}^n n_i L_i^2}{\sum_{i=1}^n n_i L_i}$$

L_n = number average rod length in nm, L_w = weighted average rod length in nm, n = sample size and the dispersity $\mathcal{D} = L_w / L_n$ for nanorods.

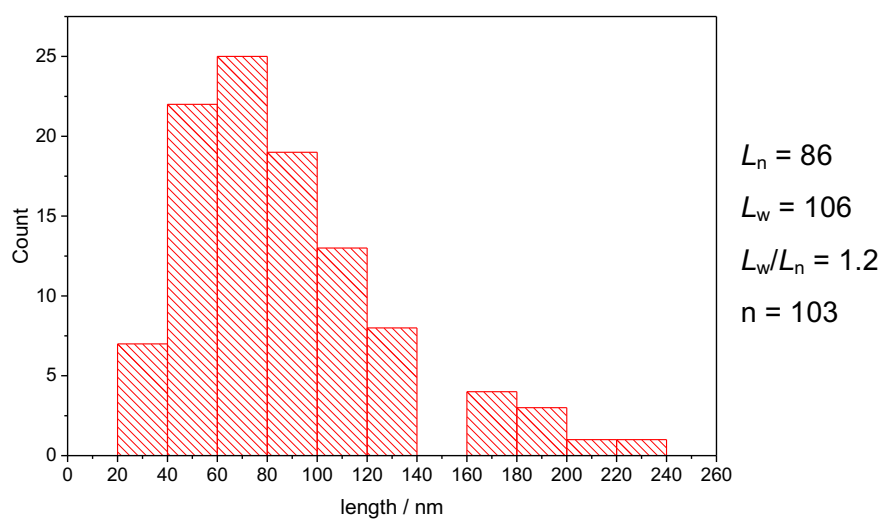


Figure S5. Length histogram of **C2**.

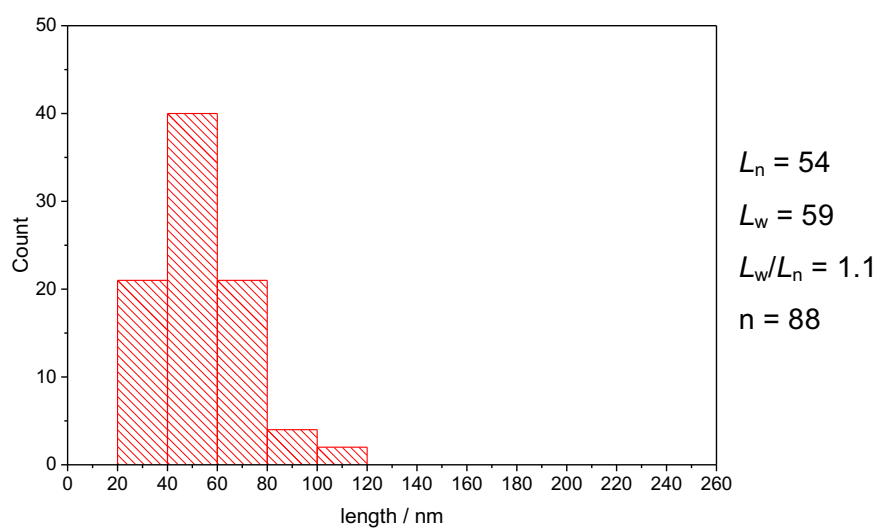


Figure S6. Length histogram of **C3**.

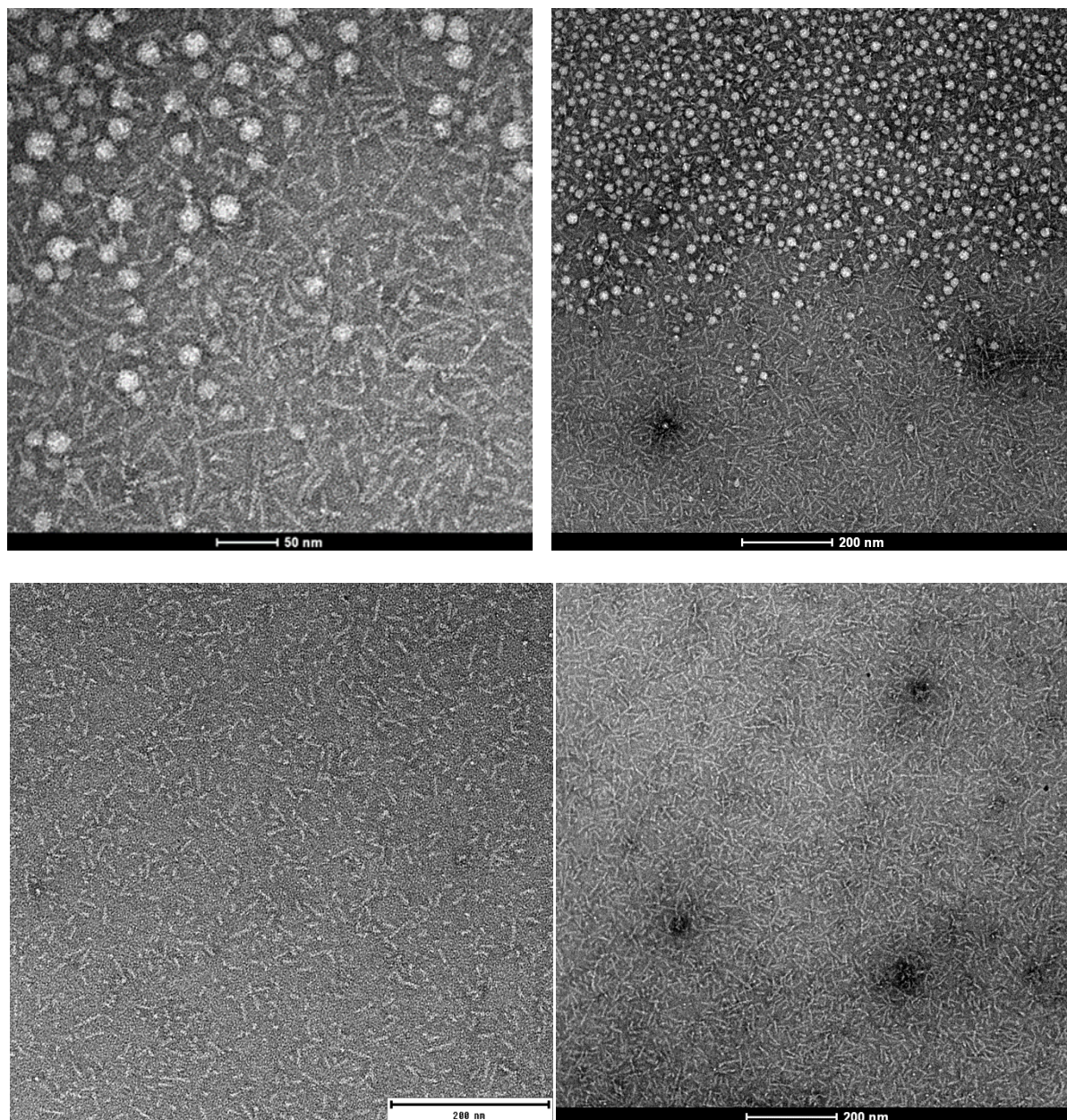


Figure S7. Representative TEM images of **C1** at pH 7.8.

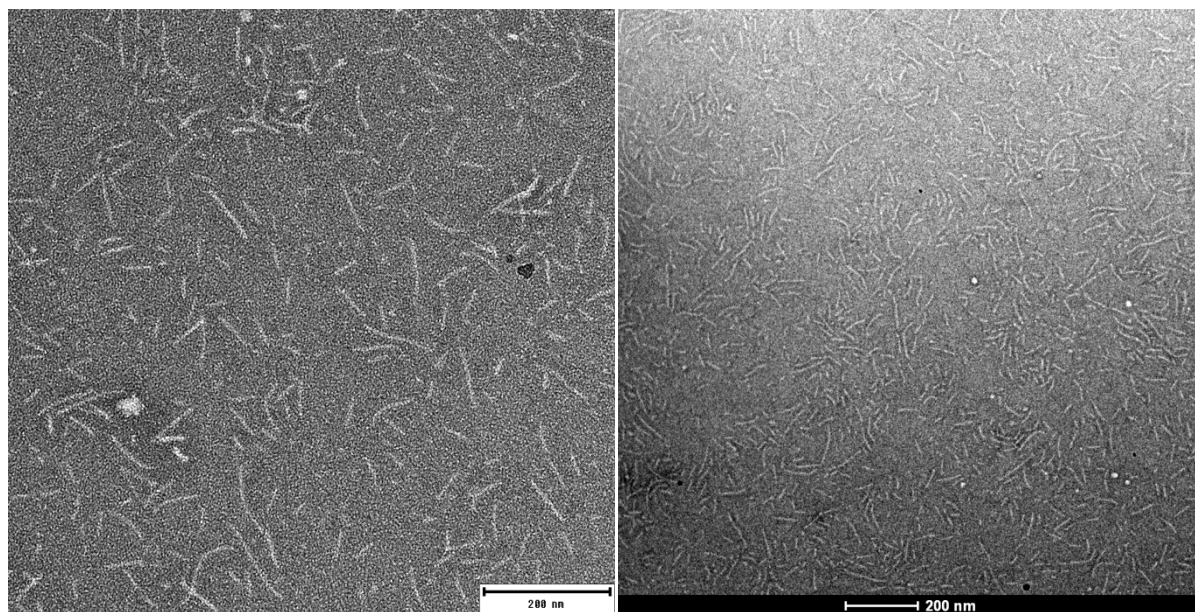


Figure S8. Representative TEM images of **C2** at pH 7.8.

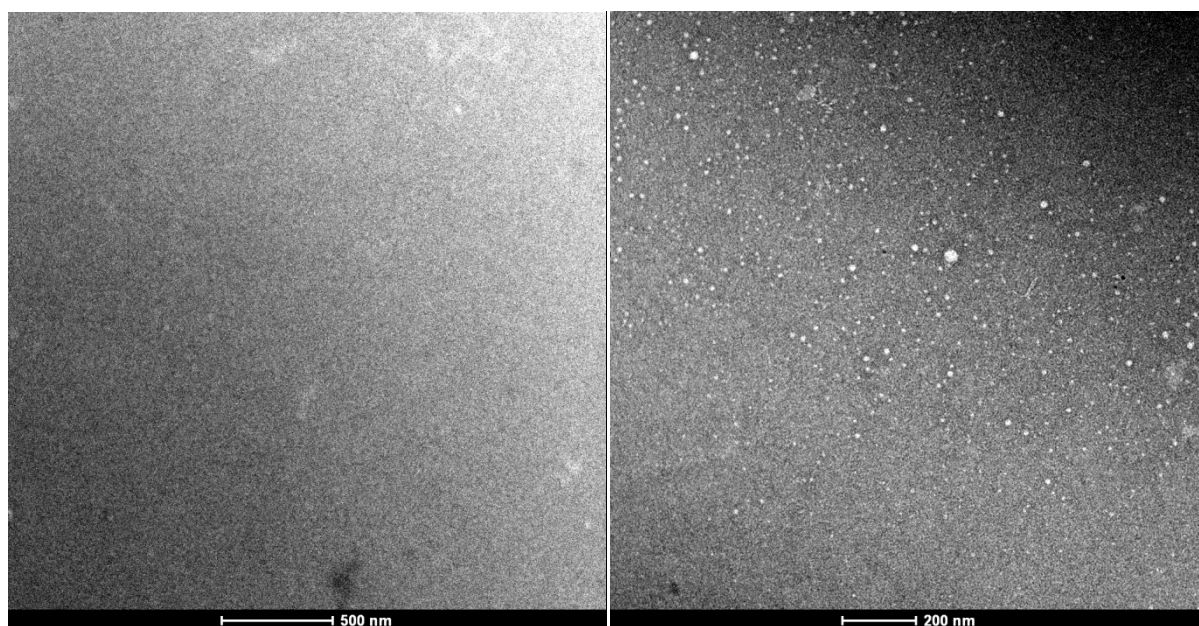


Figure S9. Representative TEM images of **C3** at pH 1.7.

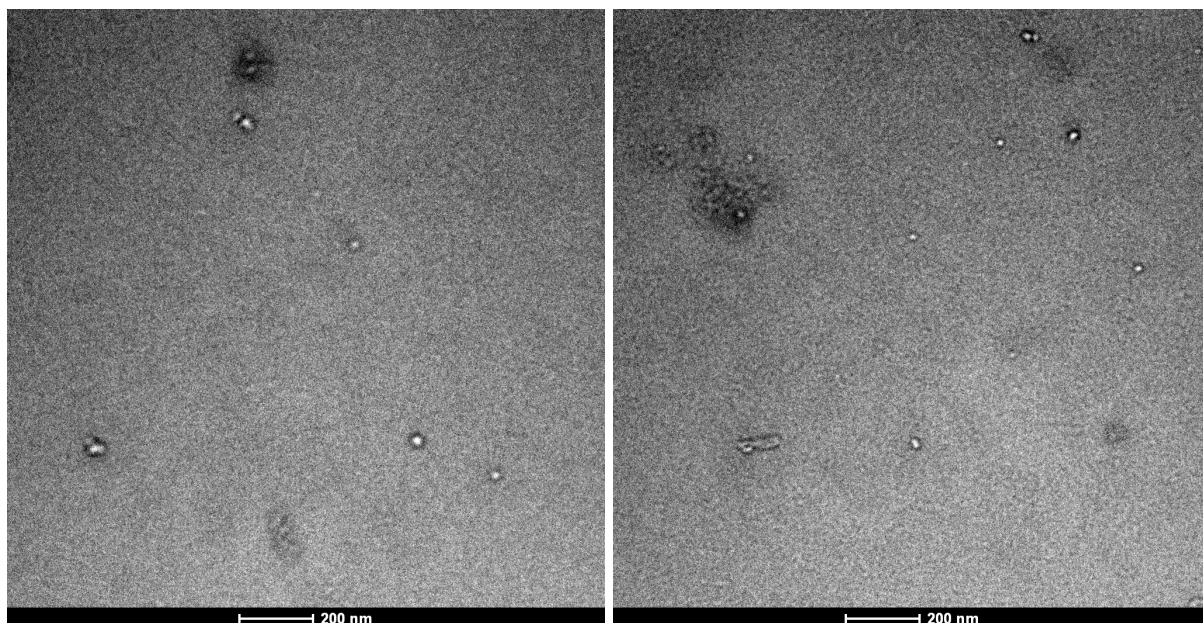


Figure S10. Representative TEM images of **C3** at pH 5.1.

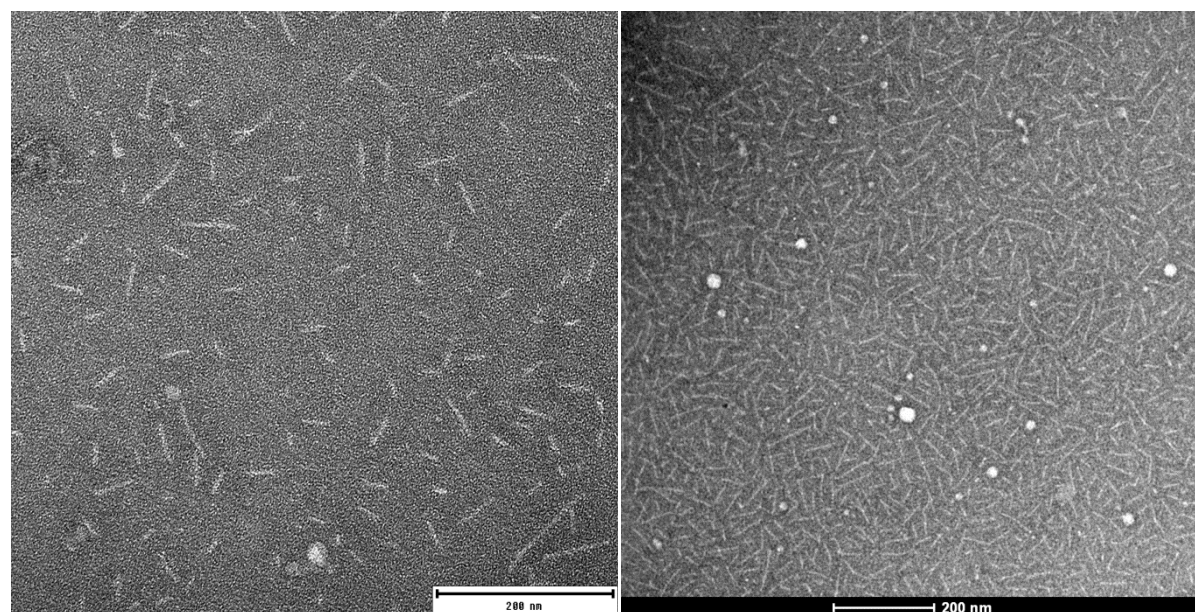
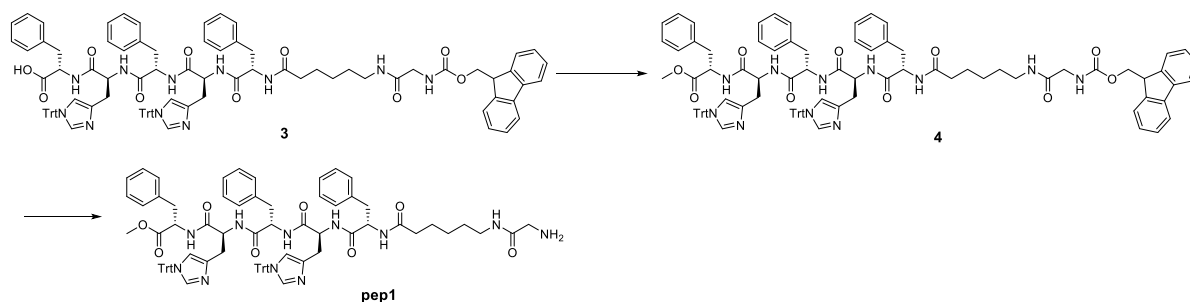


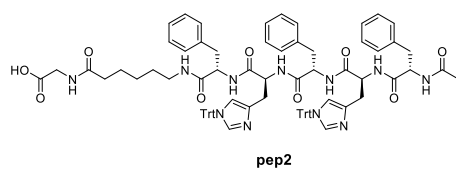
Figure S11. Representative TEM images of **C3** at pH 7.8.

2. Synthetic Route

Synthesis of Initiator **pep1**:



Synthesis of Quencher **pep2**:



Synthesis of
Polymers/Conjugates:

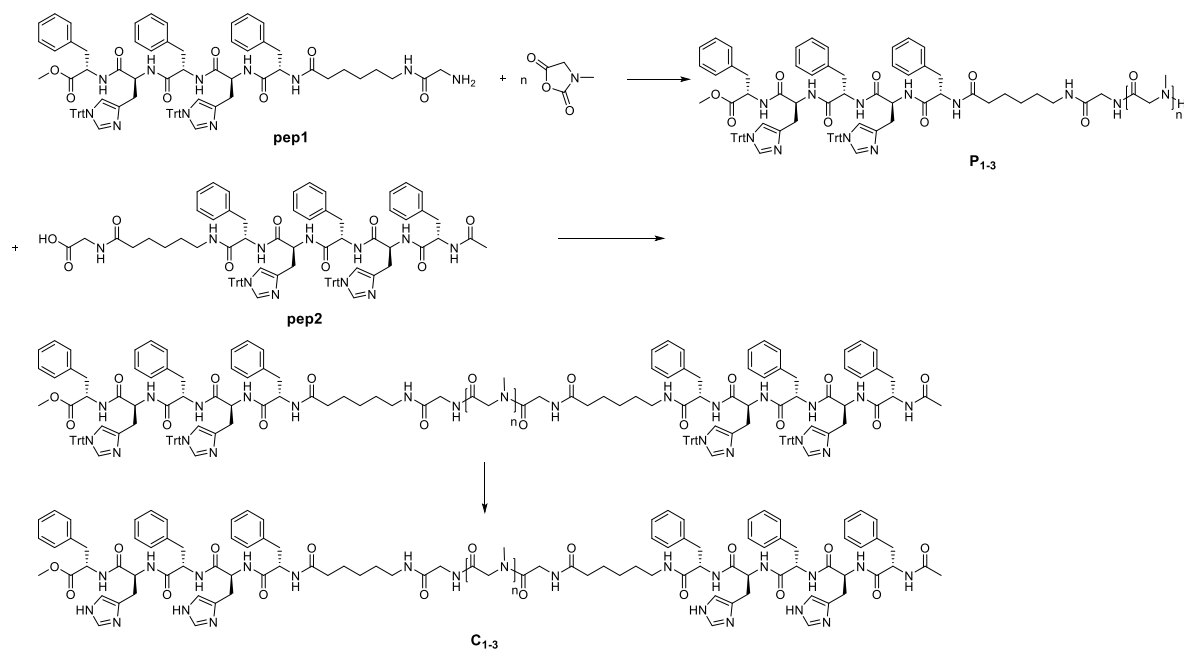
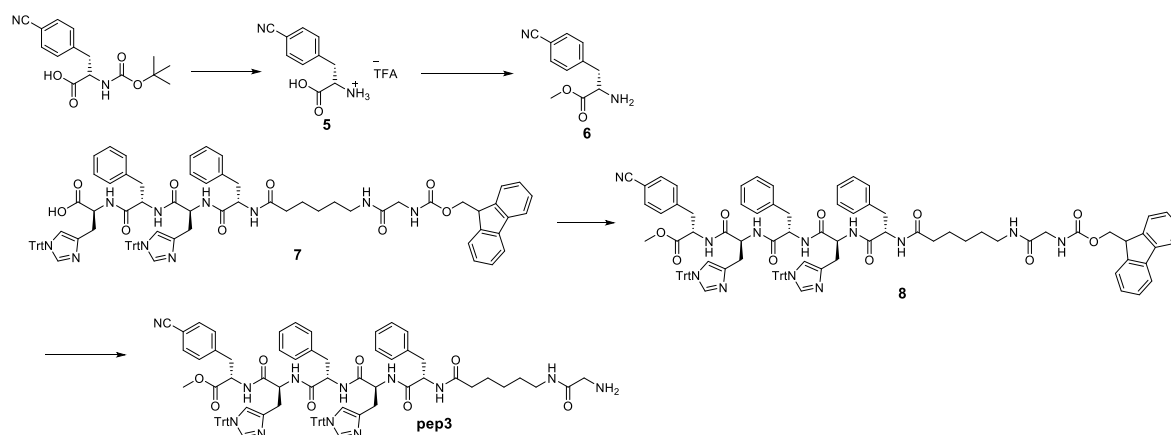
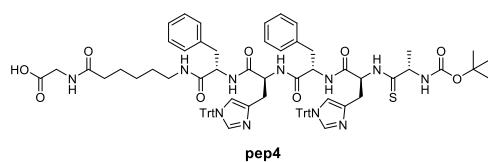


Figure S12. Synthetic route for the preparation of **C1-3**.

Synthesis of Initiator **pep3**



Synthesis of Quencher **pep4**



Synthesis of Polymer/Conjugate:

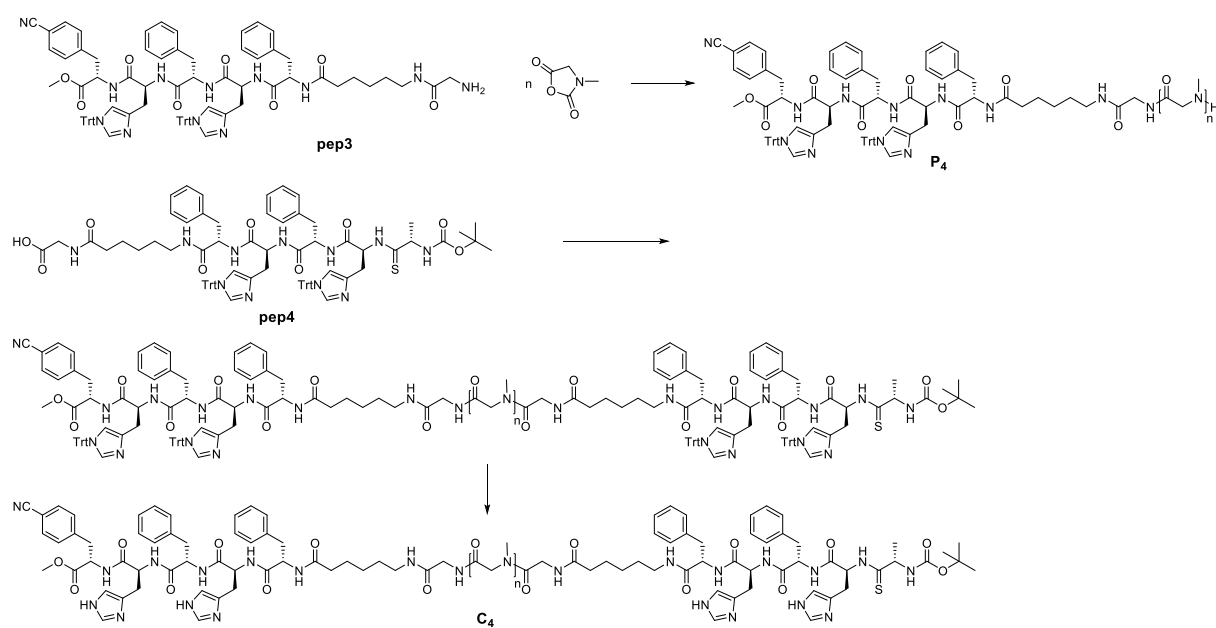
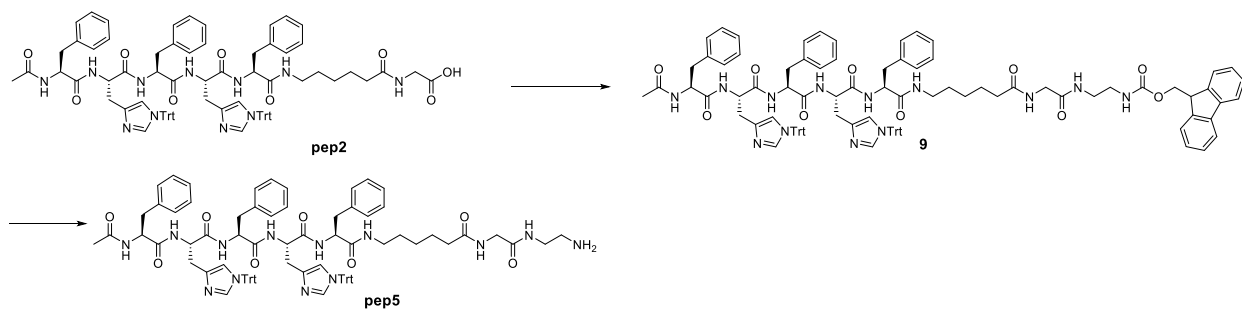
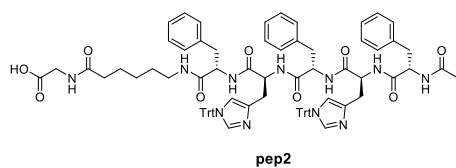


Figure S13. Synthetic route for the preparation of **C4**.

Synthesis of Initiator **pep5**:



Synthesis of Quencher **pep2**:



Synthesis of
Polymers/Conjugates:

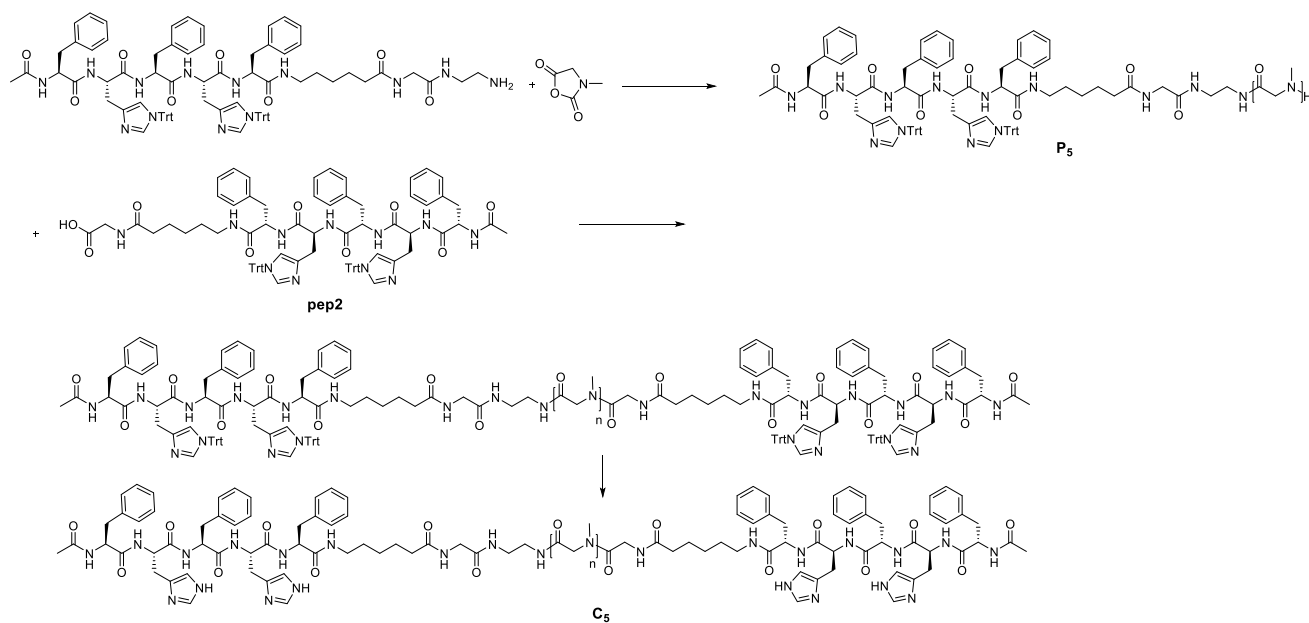


Figure S14. Synthetic route for the preparation of **C5**.

3. Materials and Methods

All reactions involving air- and moisture-sensitive compounds or intermediates were performed under argon atmosphere using standard Schlenk techniques. The glassware was dried in an oven at 120°C or heat gun dried under high vacuum prior to use. All reagents and solvents were added using disposable syringes and needles through septa. Solids were added using an argon or nitrogen counter flow. Degassing of solvents was achieved by performing multiple freeze-pump-thaw cycles until no more formation of gas bubbles could be observed. The vacuum level used for the removal of organic solvents was about 1 mbar and 0.1 mbar for the removal of water (Christ Alpha 1-2 LD plus freeze dryer).

Solvents and reagents

Unless stated otherwise, all solvents and reagents were obtained from commercial sources in the highest purity available and used without further purification. The list of suppliers includes SIGMA-ALDRICH (Sigma-Aldrich Chemie GmbH, Taufkirchen) ACROS ORGANICS (Thermo Scientific GmbH, Nidderau), MERCK (Merck KGaA, Darmstadt), ALFA AESAR (Alfa Aesar GmbH & Co. KG, Karlsruhe), CARBOLUTION Chemicals (Carbolution Chemicals GmbH, Saarbrücken), BACHEM (Bachem, Bubendorf) and IRIS BIOTECH (Iris Biotech GmbH, Marktredwitz). Water was demineralized prior to use. DMF, NMP and Piperidine were purchased in peptide grade quality. Solvents used for air- and moisture-sensitive reactions were purchased anhydrous. Solvents used for flash chromatography (FC) were purchased in technical quality and used without further purification. Sarcosine *N*-carboxyanhydride was synthesized according to a recently reported procedure.^[2]

Chromatography

Qualitative thin layer chromatography was carried out on silica-coated aluminium sheets (60, F254) with a fluorescence indicator from MERCK. The indication of the analytes was achieved by irradiation of the TLC plates with UV light ($\lambda = 254$ nm). Alternatively, the plates were dipped into a KMnO₄, cerium molybdate or ninhydrin solution followed by heating. Size-exclusion chromatography was performed using a Sephadex® LH-20 column with methanol or chloroform/methanol 2/1 (v/v) as the eluent. Flash chromatography was performed using silica gel.

4. Instrumentation

pH-electrode

All pH-values were adjusted using the MI-410 Micro-Combination pH-probe. The electrode was calibrated using Mettler-Toledo certified buffer solutions at pH 4.01 and pH 10. All pH values were adjusted using aqueous NaOH or HCl solutions, the samples were measured after the pH value was stable and the samples were left to equilibrate for 5 min.

Mass spectrometry

The mass-spectroscopic analyses were performed by the mass spectroscopic department of the Johannes Gutenberg University in Mainz. All test samples were prepared at a concentration of 0.1 g L^{-1} using MeOH as a solvent. Mass spectra were recorded on the electrospray ionization spectrometer (ESI) QToF Ultima.

NMR-spectroscopy

NMR spectra were recorded on a BRUKER ARX 300 spectrometer and a BRUKER Avance II 400 spectrometer. All measurements were carried out using DMSO- d_6 or MeOD- d_4 as deuterated solvent. Chemical shifts (δ) are reported in parts per million (ppm) relative to the chemical shifts of the residual protons in the deuterated solvent. The spin multiplicities of the signals are assigned as follows: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). All measured coupling constants are stated in Hertz (Hz). All NMR spectra were analyzed using the software MestReNova Version: 11.0.4-18998.

GPC

Gel permeation chromatography (GPC) was performed using HFIP, which contained 3 g L^{-1} potassium trifluoroacetate (KTFA) as eluent at 40°C and a flow rate of 0.8 mL min^{-1} . GPC columns were packed with modified silica (PFG columns, particle size: $7 \mu\text{m}$ porosity: 100 \AA and 1000 \AA , respectively). Poly(methyl methacrylate) standards (PMMA, Polymer Standards Services GmbH) were used for calibration and toluene was used as the internal standard. A refractive index detector (G1362A RID) and an UV/Vis detector (230 nm ; Jasco UV-2075 Plus) were used for polymer detection.

DLS

For dynamic light scattering (DLS) cylindrical quartz cuvettes (Hellma, Mühlheim, Germany) were cleaned by dust-free distilled acetone and transferred to a dust free flow box. Solutions were filtered into the cuvettes. DLS measurements were performed by the following instrument at 20°C . The apparatus consists of a Uniphase He/Ne Laser (22.5 mW output power at $\lambda =$

632.8 nm), an ALV/SP125 goniometer with an ALV 5000/E/PCI correlator and an ALV/High QEAPD Avalanche photodiode detector.

To investigate the aggregation behavior of the particles in human plasma, plasma pooled from 6 probands was used. The plasma was obtained from the University Medical Center Mainz and filtered through a Millex GS 0.22 μm filter. 20 mg polymer was dissolved in 2.5 mL 0.15 M NaCl (pH 4-5). The solution was filtered through a 0.2 μm pore size Pall GHP filter. By addition of 0.2 μm GHP filtered 0.1 M NaOH, the pH was adjusted to 7-8, the samples were measured after one hour. The following mixtures have been prepared: plasma/PBS 9:1 and plasma/polymer solution 9:1. The cuvettes were incubated for 20 min at room temperature before measurement.

Matrix-assisted laser desorption/ionization (MALDI)

MALDI-ToF measurements were obtained with a Shimadzu Axima CFR MALDI-ToF mass spectrometer, equipped with a nitrogen laser delivering 3 ns laser pulses at 337 nm. HABA (2-(4'-hydroxybenzeneazo)benzoic acid) was used as a matrix. Samples were prepared by dissolving the polymer in MeOH at a concentration of 10 g L⁻¹. A 10 μL aliquot of this solution was added to 10 μL aliquot of 10 g L⁻¹ solution of the matrix in MeOH. A 1.5 μL aliquot of the resulting mixture was applied to a multistage target to evaporate and create a thin matrix/analyte film. The samples were measured in positive ion and in linear mode of the spectrometer.

Circular dichroism (CD) spectroscopy

All spectra were recorded using a monomer concentration of 50 μM in 10 mM phosphate buffer using a quartz cell with a path length of 2 mm. The pH values were adjusted by addition of aqueous HCl and NaOH. CD-spectra were recorded on a J-815 CD spectrometer (JASCO) using the software Spectra Manager 2.08.04. All Spectra were corrected by the subtraction of the buffer (background). All data was processed using OriginPro 9.1.

Transmission electron microscopy (TEM)

TEM samples were prepared from 50 μM solutions in TRIS buffer, the pH was adjusted by the addition of HCl and NaOH. The samples were prepared on freshly glow-discharged copper grids (CF300-Cu, 300 mesh) coated with a 3-4 nm carbon layer followed by negative staining using a 2% v/v solution of uranyl acetate. TEM images were accomplished on a FEI TecnaiTM T12 transmission electron microscope equipped with a BioTWIN lens and a LaB₆ cathode operated at 120 kV. Digital electron micrographs were recorded with a 4k x 4k CMOS camera (TVIPS) and a 1k x 1k CCD camera (Megasis).

Fluorescence Spectroscopy

Fluorescence spectra were recorded on a Perkin–Elmer LS 50B spectrophotometer and processed using OriginPro 9.1. All spectra were recorded at room temperature using a monomer concentration of 20 μM in 5 μM phosphate buffer. The pH values were adjusted by the addition of aqueous NaOH and HCl. A quartz fluorometer cell with a path length of 1 cm was used. The excitation wavelength was 240 nm and the emission data was collected from 260 nm to 400 nm. The slit width was 5 nm, the scan rate 250 nm min⁻¹ and the data interval 0.5 nm.

5. Synthesis

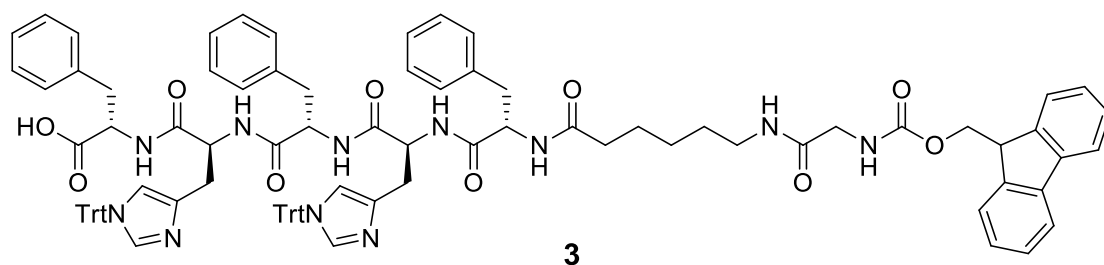
Synthesis of Peptides *via* SPPS

The loading of the 2-chlorotrityl chloride resin was performed according to literature procedures. The first Fmoc-protected amino acid (2 eq. relative to the resin loading capacity) to be coupled to the 2-chlorotrityl chloride resin (1.0 g, loading capacity 1.6 mmol g⁻¹) was dissolved in 10 mL DCM. A slight amount of DMF was added due to the low solubility of some amino acids in pure DCM. The solution was added to the vessel containing the resin under an argon atmosphere. DIPEA (2.0 eq. relative to the resin loading capacity) was added and the mixture was shaken for 5 minutes at room temperature. This was followed by the addition of additional DIPEA (3 eq.). The reaction mixture was shaken for one hour at room temperature followed by the addition of MeOH (1 mL g⁻¹ resin) and shaken for 15 minutes. After draining the vessel the resin was washed consecutively three times with 10 mL DCM, DMF, DCM and MeOH. The resin was dried *in vacuo* overnight.

The following step-wise chain elongation was performed using a CS136XT peptide synthesizer, which is an automated batch peptide synthesizer. The beads were swollen in DCM while shaking the reaction vessel. After draining the DCM, a piperidine solution (20% in DMF) was added to the vessel, which was shaken for 20 minutes. Afterwards, the piperidine solution was sucked off and the beads were washed four times with DMF and two times with DCM. After the addition of the Fmoc-protected amino acid (4.0 eq relative to the resin loading capacity), HBTU (4.0 eq) and DIPEA (6.0 eq) in DMF were added to the reaction vessel. After shaking for one hour, the solution was removed and the beads were washed with DMF five times. This procedure was repeated for the following amino acids, starting with the Fmoc deprotection of the resin-bound amino acid. In some peptides an N-terminal acetylation was performed. For this purpose, the Fmoc-protecting group was cleaved off followed by the acetylation of the amine-group using a capping solution (0.5 M acetic anhydride, 0.125 M DIPEA, 0.015 M HOBt) in NMP. In the final step the resin was washed with DCM.

To cleave the resin-bound peptide the beads were shaken in a mixture of DCM and trifluoroethanol (4/1) for 45 minutes. The solution was drained and the beads washed two times with a small amount of DCM. The collected solutions were concentrated under reduced pressure. The product precipitated out of a cooled mixture of cyclohexan and diethyl ether (1/1) and was isolated through centrifugation. The procedure was carried out three times.

Fmoc-Gly-Ahx-Phe-His(Trt)-Phe-His(Trt)-Phe-OH (3)



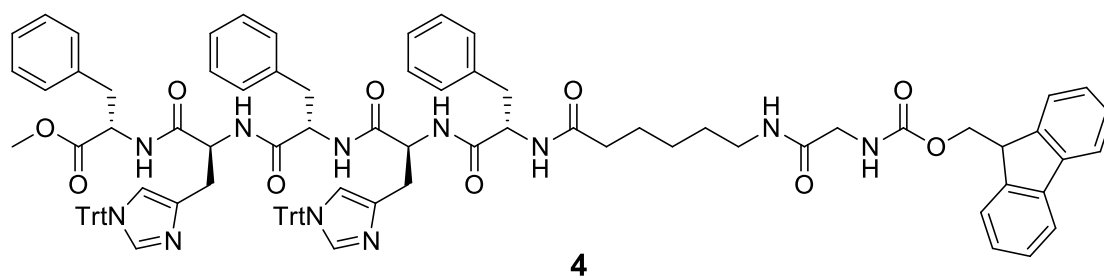
The synthesis was carried out according to the Synthesis of Peptides via SPPS (page S16).

Molecular formula: C₁₀₀H₉₅N₁₁O₁₀.

ESI-HRMS (MeOH) (m/z): Calculated for [C₁₀₀H₉₆N₁₁O₁₀]⁺: 1610.7355, found: 1610.7342.

¹H-NMR (400 MHz, DMSO-*d*₆, 298 K): δ/ppm: 13.00 (s, 1H, COOH), 8.47 (d, *J* = 8.1 Hz, 1H, α-NH), 8.15 (d, *J* = 7.6 Hz, 1H, α-NH), 8.01-7.86 (m, 5H, α-NH/CH^{FMOC}), 7.75 (t, *J* = 5.9 Hz, 1H, α-NH^{Ahx}), 7.71 (d, *J* = 7.5 Hz, 2H, CH^{FMOC}), 7.50 (t, *J* = 6.1 Hz, 1H, α-NH^{Gly}), 7.38-6.97 (m, 51H, CH^{FMOC}/Trt/CH^{His}/CH^{Ar}), 6.67 (s, 1H, CH^{His}), 6.62 (s, 1H, CH^{His}), 4.54-4.31 (m, 5H, α-CH), 4.32-4.16 (m, 3H, CH^{FMOC}/CH₂^{FMOC}), 3.56 (d, *J* = 6.1 Hz, 2H, CH₂^{Gly}), 3.07-2.57 (m, 12H, CH₂^{His}/CH₂^{Phe}/CH₂^{Ahx}), 1.96-1.87 (m, 2H, CH₂^{Ahx}), 1.30-1.20 (m, 4H, CH₂^{Ahx}), 1.04-0.95 (m, 2H, CH₂^{Ahx}).

Fmoc-Gly-Ahx-Phe-His(Trt)-Phe-His(Trt)-Phe-CH₃ (4)



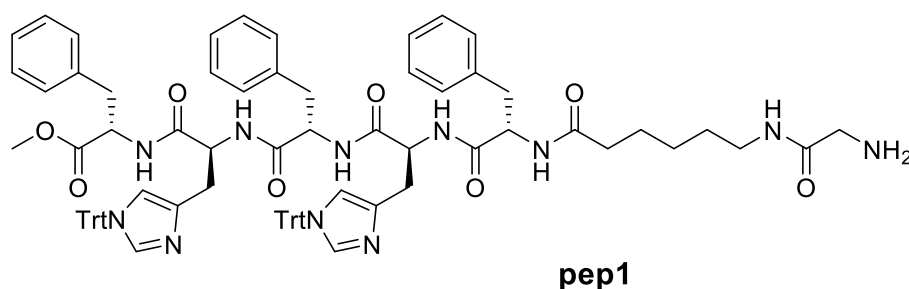
3 (200 mg, 124 μ mol, 1 eq.) was dissolved in 3 mL of DCM and 3 mL of MeOH in a dried Schlenk-flask equipped with a stir-bar under an argon atmosphere. Thionylchloride (46 μ L, 620 mmol, 5 eq.) was added through a septum using a syringe. The solution was stirred at room temperature for 3 hours, after which all volatiles were removed *in vacuo*. The residue was purified *via* flash chromatography on silica gel (DCM:MeOH = 25:2, R_f = 0.55). After drying *in vacuo*, a colorless solid (150 mg, 92 μ mol, **74%**) could be obtained.

Molecular formula: C₁₀₁H₉₇N₁₁O₁₀.

ESI-HRMS (MeOH) (m/z): Calculated for [C₁₀₁H₉₈N₁₁O₁₀]⁺: 1624.7498, found: 1624.7483.

¹H-NMR (400 MHz, DMSO-*d*₆, 298 K): δ /ppm: 8.45 (d, J =8.1 Hz, 1H, α -NH), 8.21 (d, J =7.4 Hz, 1H, α -NH), 8.13 (d, J =7.6 Hz, 1H, α -NH), 8.02 (d, J =7.3 Hz, 1H, α -NH), 7.94-7.83 (m, 3H, α -NH/ CH^{Fmoc}), 7.79-7.68 (m, 3H, α -NH^{Ahx}/ CH^{Fmoc}), 7.49 (t, 1H, J = 6.1 Hz, α -NH^{Gly}), 7.41 (t, 2H, J = 7.4, CH^{Fmoc}), 7.38-6.98 (m, 49H, CH^{Fmoc} / Trt / CH^{His} / CH^{Ar}), 6.68 (s, 1H, CH^{His}), 6.61 (s, 1H, CH^{His}), 4.54-4.36 (m, 5H, α -CH), 4.31-4.17 (m, 3H, CH^{Fmoc} / CH_2^{Fmoc}), 3.56 (d, J = 6.1 Hz, 2H, CH_2^{Gly}), 3.44 (s, 3H, CH₃), 3.02-2.58 (m, 12H, CH_2^{His} / CH_2^{Phe} / CH_2^{Ahx}), 1.97-1.87 (m, 2H, CH_2^{Ahx}), 1.32-1.20 (m, 4H, CH_2^{Ahx}), 1.06-0.96 (m, 2H, CH_2^{Ahx}).

H-Gly-Ahx-Phe-His(Trt)-Phe-His(Trt)-Phe-CH₃ (pep1)



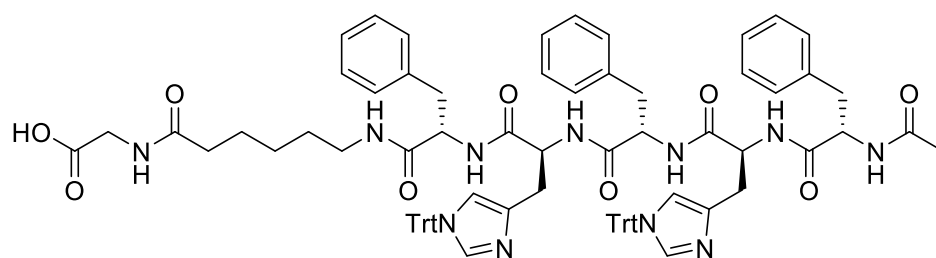
4 (400 mg, 0.25 mmol, 1 eq.) was dissolved in a mixture of 4 mL DCM and 1 mL Piperidine. After stirring for 45 minutes at room temperature the volatiles were removed via reduced pressure. The residue was purified via size exclusion chromatography (Sephadex® LH 20, CCl₃H/MeOH 2/1). The resulting solid was lyophilized out of a DCM/benzene mixture resulting in a colorless solid (339 mg, 0.24 mmol, **98%**).

Molecular formula: C₈₆H₈₇N₁₁O₈.

ESI-HRMS (MeOH) (m/z): Calculated for [C₈₆H₈₈N₁₁O₈]⁺: 1402.6817, found: 1402.6791.

¹H-NMR (400 MHz, DMSO-d₆, 298 K): δ/ppm: 8.46 (d, *J* = 8.1 Hz, 1H, α-NH), 8.20 (d, *J* = 7.3 Hz, 1H, α-NH), 8.13 (d, *J* = 7.6 Hz, 1H, α-NH), 8.02 (d, *J* = 7.3 Hz, 1H, α-NH), 7.90 (d, *J* = 8.2 Hz, 1H, α-NH), 7.71 (t, *J* = 5.7 Hz, 1H, α-NH^{Ahx}), 7.41-6.95 (m, 47 H, *Trt*/CH^{His}/CH^{Ar}), 6.67 (s, 1H, CH^{His}), 6.61 (s, 1H, CH^{His}), 4.54-4.36 (m, 5H, α-CH), 3.44 (s, 3H, CH₃), 3.03 (s, 2H, CH₂^{Gly}), 3.01-2.56 (m, 12H, CH₂^{His}/CH₂^{Phe}/CH₂^{Ahx}), 2.00-1.86 (m, 2H, CH₂^{Ahx}), 1.32-1.18 (m, 4H, CH₂^{Ahx}), 1.06-0.95 (m, 2H, CH₂^{Ahx}).

CH₃CO-Phe-His(Trt)-Phe-His(Trt)-Phe-Ahx-Gly-OH (pep2)



pep2

The synthesis was carried out according to the Synthesis of Peptides via SPPS (page S16).

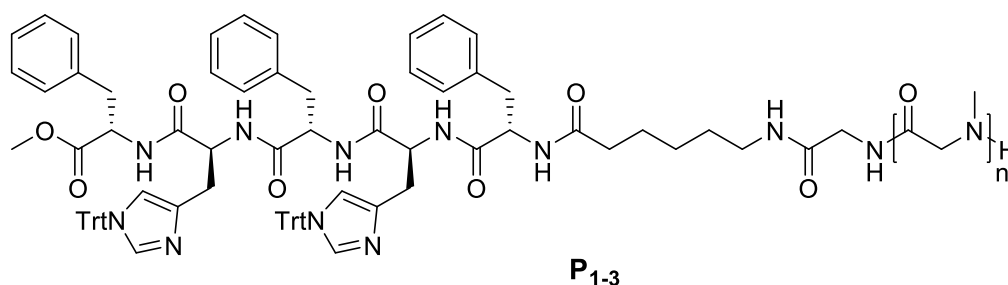
Yield: 850.2 mg (0.59 mmol) colorless solid.

Molecular formula: C₈₇H₈₇N₁₁O₉.

ESI-HRMS (MeOH) (m/z): Calculated for [C₈₇H₈₈N₁₁O₉]⁺: 1430.6766, found: 1430.6730.

¹H-NMR (400 MHz, DMSO-*d*₆, 298 K): δ/ppm: 12.54 (s, 1H, COOH), 8.50 (d, *J* = 7.5 Hz, 1H, α-NH), 8.19 (d, *J* = 7.5 Hz, 1H, α-NH), 8.10-8.00 (m, 3H, α-NH), 7.96 (t, *J* = 5.6 Hz, 1H, α-NH^{Gly}), 7.91 (d, *J* = 8.1 Hz, 1H, α-NH), 7.42-6.95 (m, 47H, *Trt*/CH^{His}/CH^{Ar}), 6.67 (s, 1H, CH^{His}), 6.57 (s, 1H, CH^{His}), 4.46-4.31 (m, 5H, α-CH), 3.70 (d, *J* = 5.9 Hz, 2H, CH₂^{Gly}), 3.08-2.58 (m, 12H, CH₂^{His}/CH₂^{Phe}/CH₂^{Ahx}), 2.09-2.02 (m, 2H, CH₂^{Ahx}), 1.67 (s, 3H, CH₃), 1.43-1.35 (m, 2H, CH₂^{Ahx}), 1.29-1.21 (m, 2H, CH₂^{Ahx}), 1.15-1.06 (m, 2H, CH₂^{Ahx}).

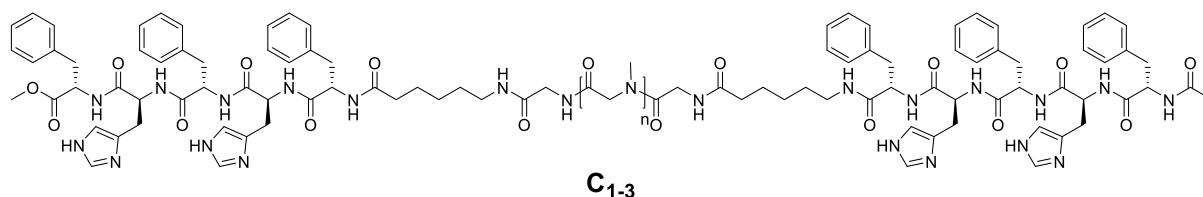
Synthesis of P1-3 (NCA Polymerization)



In a typical experiment, *n* eq. of sarsosine NCA were transferred into a pre-dried Schlenk tube equipped with a stir bar and dried in high vacuum. 1 eq. of the initiator **pep1** was added into another pre-dried Schlenk tube and dried in high vacuum. Subsequently, both compounds were dissolved in a minimum amount of dry DMF. The solution of the initiator peptide was added to the NCA solution through the septum using a syringe. The solution was stirred at room temperature while a constant stream of dry nitrogen was kept on the flask *via* the Schlenk line to allow CO₂ to escape and to prevent impurities from entering the flask. The reaction progress of the polymerization was monitored by IR spectroscopy (disappearance of the NCA peaks (1853 and 1786 cm⁻¹)). After completion of the reaction the polymer was precipitated into cold diethyl ether and centrifuged (4°C, 3500 rpm, 15 minutes). The liquid fraction was discarded and the polymer was resuspended and centrifuged again. After the repeat of the procedure, the polymer was dissolved in water and lyophilized resulting in a colorless solid.

¹H-NMR (400 MHz, DMSO-*d*₆, 298 K): δ/ppm: 8.46 (d, *J* = 8.0 Hz, 1H, α-NH), 8.21 (d, *J* = 7.3 Hz, 1H, α-NH), 8.13 (d, *J* = 7.7 Hz, 1H, α-NH), 8.03 (d, *J* = 7.2 Hz, 1H, α-NH), 7.90 (d, *J* = 8.0 Hz, 1H, α-NH), 7.72 (s(br), 1H, α-NH), 7.39-7.00 (m, 48H, α-NH/CH^{His}/CH^{Phe}/Trt), 6.67 (s, 1H, CH^{His}), 6.61 (s, 1H, CH^{His}), 4.55-3.86 (m, 5H+2nH, α-CH/CH₂^{PSar}), 3.73-3.58 (m, 2H, CH₂^{Gly}), 3.44 (s, 3H, COOCH₃), 3.02-2.66 (m, 12H+3nH, CH₃^{PSar}/CH₂^{His}/CH₂^{Phe}/CH₂^{Ahx}), 2.01-1.83 (m, 2H, CH₂^{Ahx}), 1.31-1.20 (m, 4H, CH₂^{Ahx}), 1.08-0.94 (m, 2H, CH₂^{Ahx}).

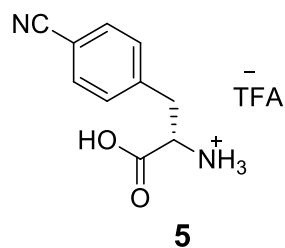
Synthesis of C1-3 (Conjugation and Deprotection)



All end group modifications were carried out in the same way. The polymer (80 mg, 24 μmol , 1 eq.) was transferred into a pre-dried Schlenk flask equipped with a stir bar and dissolved in 2.5 mL of dry DMF. **Pep2** (91 mg, 63 μmol , 3 eq.), HOBt (9.5 mg, 70 μmol , 3.3 eq.), HBTU (26.5 mg, 70 μmol , 3.3 eq.) and DIPEA (24 μL , 140 μmol , 6.6 eq.) were added and the solution was stirred at room temperature for 3 days. The polymer was precipitated in diethyl ether and centrifuged (4°C, 3500 rpm, 15 minutes). After discarding the liquid fraction, the resulting solid was dried *in vacuo*, dissolved in HFIP/water (9/1 v/v) and stirred overnight. After deprotection, all volatiles were removed through reduced pressure. The residue was purified *via* size exclusion chromatography (Sephadex® LH 20, MeOH (acidic 0.1% HCl)). The solid residue was dissolved in water and extracted with ether. The aqueous phase was lyophilized resulting in a colorless solid (54.7 mg, 14.7 mmol). The following yields 61% for **C1**, 56% for **C2** and 59% for **C3** could be achieved.

¹H-NMR of C₁₋₃ (400 MHz, DMSO-*d*₆, 298 K): δ /ppm: 14.55-14.25 (m, 8H, $\text{NH}_2^{+\text{His}}$), 9.09-7.75 (m, 18H, $\alpha\text{-NH}/\text{CH}^{\text{His}}$), 7.45-7.10 (m, 34H, $\text{CH}^{\text{His}}/\text{CH}^{\text{Phe}}$), 4.81-4.57 (m, 10H, $\alpha\text{-CH}$), 4.58-3.90 (m, 2nH, $\text{CH}_2^{\text{PSar}}$), 3.76-3.64 (m, 4H, CH_2^{Gly}), 3.57 (s, 3H, COOCH_3), 3.14-2.68 (m, 24H+3nH, $\text{CH}_3^{\text{PSar}}/\text{CH}_2^{\text{His}}/\text{CH}_2^{\text{Phe}}/\text{CH}_2^{\text{Ahx}}$), 2.10 (m, 2H, CH_2^{Ahx}), 2.02-1.95 (m 2H, CH_2^{Ahx}), 1.74 (s, 3H, NHCOCH_3) 1.50-1.41 (m, 2H, CH_2^{Ahx}), 1.35-1.23 (m, 4H, CH_2^{Ahx}), 1.19-1.12 (m, 2H, CH_2^{Ahx}), 1.06-0.97 (m, 2H, CH_2^{Ahx}).

4-cyano-L-phenylalanine (Cnf) (5)

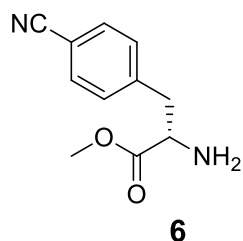


N-(tert-Butoxycarbonyl)-4-cyano-L-phenylalanine (100 mg, 0.34 mmol, 1 eq.) was dissolved in a mixture 2 mL DCM and 2 mL TFA. After stirring for 30 minutes at room temperature, the volatiles were removed by reduced pressure. A colorless solid (**quant.**) could be obtained.

Molecular formula: C₁₀H₁₀N₂O₂.

¹H-NMR (400 MHz, DMSO-*d*₆, 298 K): δ/ppm: 14.01 (s, 1H, COOH), 8.31 (s, 3H, NH₃), 7.83 (d, *J* = 8.3 Hz, 2H, CH^{Cnf}), 7.48 (d, *J* = 8.3 Hz, 2H, CH^{Cnf}), 4.28 (s, 1H, CH^{Cnf}), 3.39-2.98 (m, 2H, CH₂^{Cnf}).

4-cyano-L-phenylalanine methylester (6)



5 (0.34 mmol, 1 eq.) was dissolved in a mixture of 1 mL DCM and 2 mL MeOH and cooled in an ice bath. Thionyl chloride (74 μ L, 1.02 mmol, 3 eq.) was added to the solution. The mixture was stirred at room temperature for 2 hours; afterwards the same amount of thionyl chloride (74 μ L, 1.02 mmol, 3 eq.) was added. The solution was heated to 40°C and stirred for 4 hours. After removing the volatiles *in vacuo*, the solid was dissolved in a mixture of water and methanol. After removing the methanol under reduced pressure, the remaining solution was lyophilized resulting in a colorless solid (71.2 mg, 34 mmol, **quant.**).

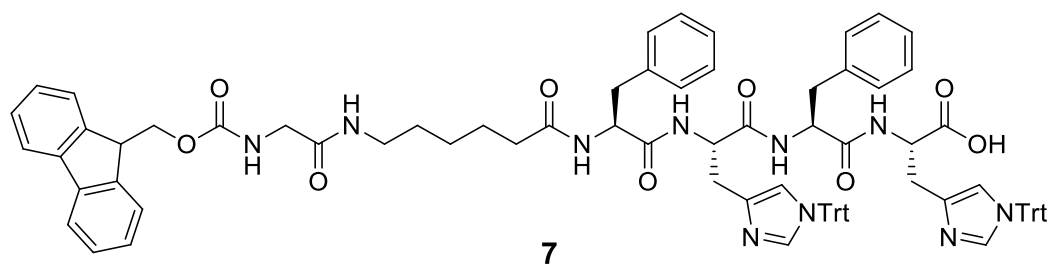
Molecular formula: C₁₁H₁₂N₂O₂.

ESI-HRMS (MeOH) (m/z): Calculated for [C₁₁H₁₃N₂O₂]⁺: 205.0977, found: 205.0981.

¹H-NMR (400 MHz, MeOD-*d*₄, 298 K): δ /ppm: 7.72 (d, *J* = 8.3 Hz, 2H, CH^{Cnf}), 7.45 (d, *J* = 8.0 Hz, 2H, CH^{Cnf}), 4.32 (t, *J* = 6.9 Hz, 1H, CH^{Cnf}), 3.77 (s, 3H, CH₃), 3.36-3.18 (m, 2H, CH₂^{Cnf}).

¹³C-NMR (101 MHz, MeOD-*d*₄, 298 K): δ /ppm: 170.25 (CO) 141.45 (CH^{ipso}), 133.86 (CH^{meta}), 131.61 (CH^{ortho}), 119.44 (CN), 112.81 (CH^{para}), 54.72 (CH^{Phe}), 53.69 (CH₃), 37.37 (CH₂^{Phe}).

Fmoc-Ahx-Phe-His(Trt)-Phe-His(Trt)-Cnf-CH₃ (7)



The synthesis was carried out according to Synthesis of Peptides via SPPS (page S16).

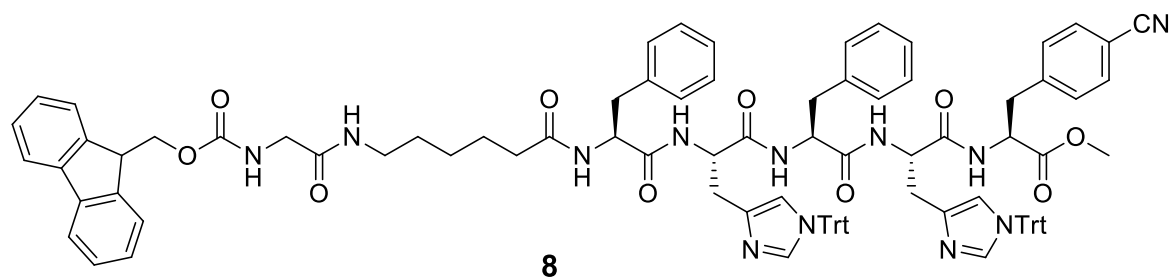
Yield: 423 mg (0.29 mmol) colorless solid.

Molecular formula: C₉₁H₈₆N₁₀O₉.

ESI-HRMS (MeOH) (m/z): Calculated for [C₉₁H₈₇N₁₀O₉]⁺: 1463.6652, found: 1463.6679.

¹H-NMR (400 MHz, DMSO-d₆, 298 K): δ/ppm: 12.63 (s, 1H, COOH), 8.06 (d, *J* = 7.8 Hz, 1H, α-NH), 7.95 (d, *J* = 7.9 Hz, 1H, α-NH), 7.92-7.83 (m, 3H, α-NH/CH^{FMOC}), 7.75 (t, *J* = 5.6 Hz, 1H, α-NH^{Ahx}), 7.71 (d, *J* = 7.4 Hz, 2H, CH^{FMOC}), 7.50 (t, *J* = 6.1 Hz, 1H, α-NH^{Gly}), 7.45-6.91 (m, 46H, CH^{FMOC}/Trt/CH^{His}/CH^{Phe}), 6.66 (s, 1H, CH^{His}), 6.64 (s, 1H, CH^{His}), 4.62-4.16 (m, 7H, α-CH/CH^{FMOC}/CH₂^{FMOC}), 3.56 (d, *J* = 6.1 Hz, 2H, CH₂^{Gly}), 3.13-2.55 (m, 10H, CH₂^{His}/CH₂^{Phe}/CH₂^{Ahx}), 2.08-1.78 (m, 2H, CH₂^{Ahx}), 1.32-1.10 (m, 4H, CH₂^{Ahx}), 1.04-0.97 (m, 2H, CH₂^{Ahx}).

Fmoc-Gly-Ahx-Phe-His(Trt)-Phe-His(Trt)-Cnf-CH₃ (8)



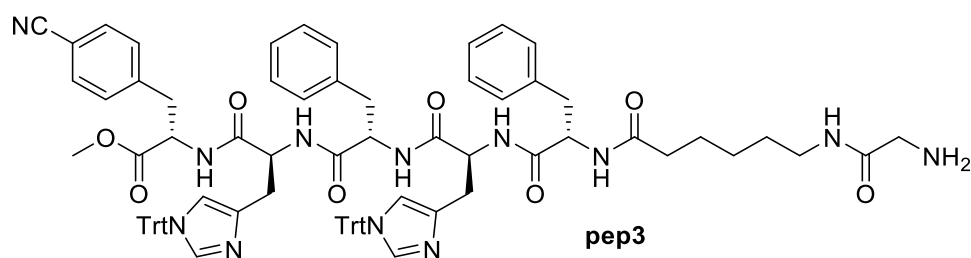
7 (100 mg, 68 μ mol, 1 eq.) was dissolved in 2 mL DMF in a pred-ried Schlenk flask equipped with a stir bar under an argon atmosphere. **6** (23 mg, 75 μ mol, 1.1 eq), PyBOP (39 mg, 75 μ mol, 1.1 eq.), HOBt (10 mg, 75 μ mol, 1.1 eq.) and DIPEA (27 μ L, 150 μ mol, 2.2 eq.) were added under argon counter flow. The mixture was stirred overnight at room temperature. After removal of the solvent through reduced pressure, the residue was purified *via* flash chromatography on silica gel (DCM/MeOH = 17:3, R_f = 0.9). After drying *in vacuo*, a colorless solid (73.7 mg, 45 μ mol, **66%**) could be obtained.

Molecular formula: C₁₀₂H₉₆N₁₂O₁₀.

ESI-HRMS (MeOH) (m/z): Calculated for [C₁₀₂H₉₆N₁₀₂O₁₀Na]⁺: 1671.7265, found: 1671.7283.

¹H-NMR (400 MHz, DMSO-*d*₆, 298 K): δ /ppm: 8.48 (d, J = 8.0 Hz, 1H, α -NH), 8.27 (d, J = 7.5 Hz, 1H, α -NH), 8.13 (d, J = 7.4 Hz, 1H, α -NH), 8.02 (d, J = 7.3 Hz, 1H, α -NH), 7.94-7.84 (m, 3H, CH^{FMOC}/ α -NH), 7.78-7.65 (m, 3H, CH^{FMOC}/ α -NH), 7.63 (d, J = 8.3 Hz, 2H, CH^{Cnf}), 7.49 (t, J = 6.1 Hz, 1H, α -NH^{Gly}), 7.44-6.96 (m, 48 H, CH^{FMOC}/Trt/CH^{His}/CH^{Phe}/CH^{Cnf}), 6.67 (s, 1H, CH^{His}), 6.63 (s, 1H, CH^{His}), 4.52-4.34 (m, 5H, α -CH), 4.29-4.15 (m, 3H, CH^{FMOC}/CH₂^{FMOC}), 3.56 (d, J = 6.1 Hz, 2H, CH₂^{Gly}), 3.46 (s, 3H, CH₃), 3.13-2.56 (m, 12H, CH₂^{His}/CH₂^{Phe}/CH₂^{Ahx}/CH₂^{Cnf}), 1.97-1.85 (m, 2H, CH₂^{Ahx}), 1.32-1.20 (m, 4H, CH₂^{Ahx}), 1.05-0.95 (m, 2H, CH₂^{Ahx}).

NH₂-Gly-Ahx-Phe-His(Trt)-Phe-His(Trt)-Cnf-CH₃ (pep3)

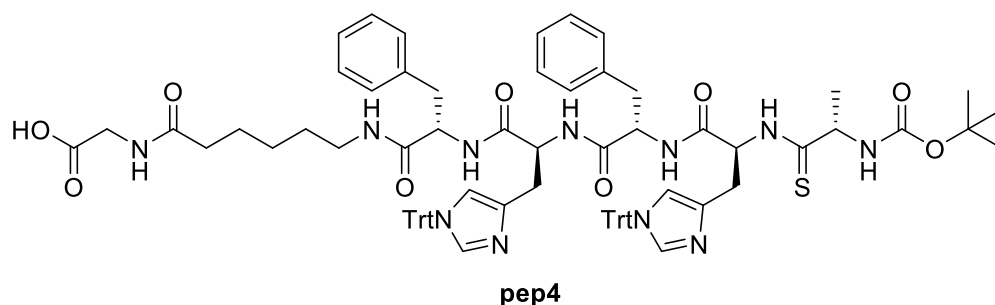


8 (69 mg, 42 μ mol, 1 eq.) was dissolved in a mixture of 4 mL DCM and 1 mL piperidine and stirred at room temperature for 45 minutes. After removal of the volatiles through reduced pressure, the mixture was precipitated in diethyl ether. The solid residue was dissolved in DCM and extracted with water. DCM was removed through reduced pressure and the residue was dissolved in 4 mL DCM and 1 mL piperidine. After stirring for one hour at room temperature, the volatiles were removed *via* reduced pressure. The residue was purified by size exclusion chromatography (Sephadex® LH 20, CCl₃H/MeOH 2/1). The resulting solid was lyophilized out of a DCM/benzene mixture resulting in a colorless solid (25.4 mg, 18 μ mol, **43%**).

Molecular formula: C₈₇H₈₆N₁₂O₈.

ESI-HRMS (MeOH) (m/z): Calculated for [C₈₇H₈₇N₁₂O₈]⁺: 1427.6770, found: 1427.6786.

¹H-NMR (400 MHz, DMSO-*d*₆, 298 K): δ /ppm: 8.49 (d, *J* = 8.2 Hz, 1H, α -NH), 8.29 (d, *J* = 7.2 Hz, 1H, α -NH), 8.15 (d, *J* = 8.0 Hz, 1H, α -NH), 8.03 (d, *J* = 7.4 Hz, 1H, α -NH), 7.92 (d, *J* = 8.2 Hz, 1H, α -NH), 7.87 (t, *J* = 5.5 Hz, 1H, α -NH), 7.64 (d, *J* = 8.2 Hz, 2H, CH^{Cnf}), 7.51-6.92 (m, 44H, Trt/CH^{His}/CH^{Phe}/CH^{Cnf}), 6.67 (s, 1H, CH^{His}), 6.63 (s, 1H, CH^{His}), 4.55-4.34 (m, 5H, α -CH), 3.46 (s, 3H, CH₃), 3.13 (s, 2H, CH₂^{Gly}), 3.09-2.60 (m, 12H, CH₂^{His}/CH₂^{Phe}/CH₂^{Ahx}/CH₂^{Cnf}), 2.03-1.84 (m, 2H, CH₂^{Ahx}), 1.36-1.13 (m, 4H, CH₂^{Ahx}), 1.05-0.94 (m, 2H, CH₂^{Ahx}).

Boc-Ala^{*}-His(Trt)-Phe-His(Trt)-Phe-Ahx-Gly-OH (pep4)

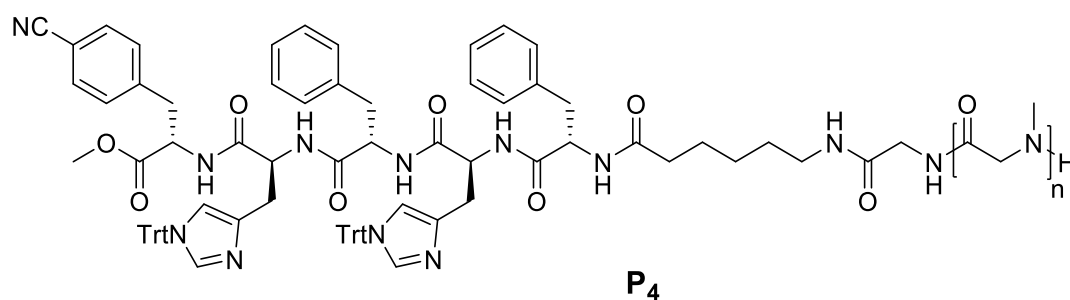
The synthesis was carried out according to the Synthesis of Peptides via SPPS (page S16) until the Fmoc deprotection of the second histidine amino acid. After that Boc-Thionoala-1-(6-nitro)benzotriazolide (2 eq.) and DIPEA (6 eq.) in DMF were added to the reaction vessel. After shaking for three hours the solution was removed and the beads washed with DMF five times. In the final step the resin was washed with DCM.

To cleave the resin-bound peptide the beads were shaken in a mixture of DCM and Trifluoroethanol (4/1) for 45 minutes. The solution was drained and the beads washed two times with a small amount of DCM. The collected solutions were concentrated under reduced pressure. The product precipitated out of a cooled mixture of Cyclohexan and Diethylether (1/1) and was isolated through centrifugation. The procedure was carried out three times. The residue was purified *via* flash chromatography on silica gel (DCM/MeOH 9/1, $R_f = 0.15$). After drying *in vacuo* a colorless solid (48 mg, 34 μ mol) could be obtained.

Molecular formula: C₈₄H₈₉N₁₁O₉S.

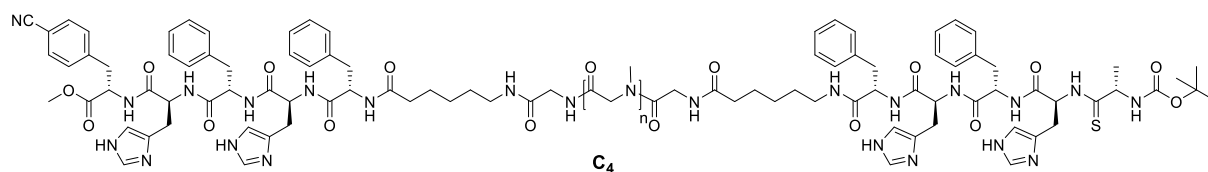
ESI-HRMS (MeOH) (m/z): Calculated for [C₈₄H₈₉N₁₁O₉S]⁺: 1428.6638, found: 1428.6600.

¹H-NMR (400 MHz, DMSO-d₆, 298 K): δ /ppm: 9.87 (s, 1H, COOH), 8.78 (s (br), 1H, α -NH^{Thioamide}), 8.35 (s (br), 1H, α -NH), 8.09 (s (br), 2H, α -NH), 7.54 (s (br), 1H, α -NH), 7.46-6.90 (m, 42H, $Trt/CH^{His}/CH^{Phe}$), 6.64 (s, 1H, CH^{His}), 6.53 (s, 1H, CH^{His}), 5.05-4.97 (m, 1H, α -CH^{Ala}), 4.68-4.14 (m, 4H, α -CH), 3.69-3.46 (m, 2H, CH_2^{Gly}), 3.09-2.55 (m, 10H, $CH_2^{His}/CH_2^{Phe}/CH_2^{Ahx}$), 2.18-1.91 (m, 2H, CH_2^{Ahx}), 1.43-1.35 (m, 2H, CH_2^{Ahx}), 1.31-1.12 (m, 13H, CH_2^{Ahx}/Boc), 1.04 (d, $J = 6.1$ Hz, 3H, CH_3^{Ala}).

P4

The synthesis was carried out the same way as **P1-3** (page S21), using **pep3** instead of **pep1** as the initiator.

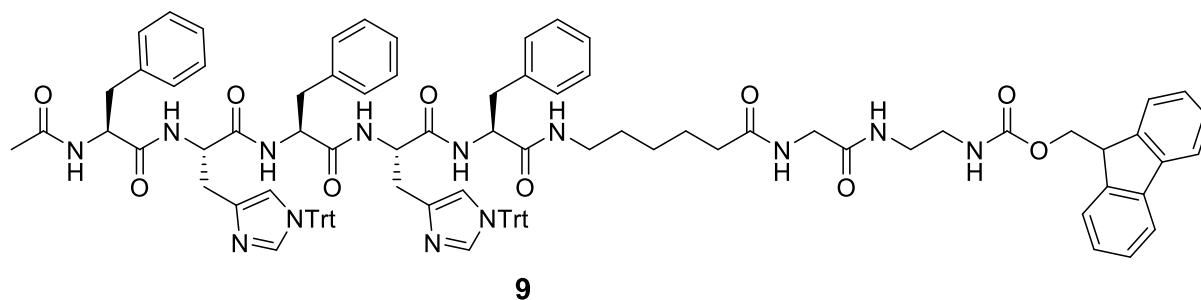
¹H-NMR (400 MHz, DMSO-*d*₆, 298 K): δ/ppm: 8.53-8.46 (m, 1H, α-NH), 8.29 (d, *J* = 7.2 Hz, 1H, α-NH), 8.18-8.11 (m, 1H, α-NH), 8.06-7.99 (m, 1H, α-NH), 7.92-7.86 (m, 1H, α-NH), 7.63 (d, *J* = 8.2 Hz, 2H, CH^{Cnf}), 7.44-6.98 (m, 45H, α-NH/CH^{His}/CH^{Phe}/Trt/ CH^{Cnf}), 6.67 (s, 1H, CH^{His}), 6.63 (s, 1H, CH^{His}), 4.69-3.85 (m, 5H+2nH, α-CH/ CH₂^{PSar}), 3.74-3.61 (m, 2H, CH₂^{Gly}), 3.46 (s, 3H, COOCH₃), 3.11-2.64 (m, 12H+3nH, CH₃^{PSar}/CH₂^{His}/ CH₂^{Phe}/ CH₂^{Ahx}), 2.05-1.83 (m, 2H, CH₂^{Ahx}), 1.30-1.19 (m, 4H, CH₂^{Ahx}), 1.05-0.95 (m, 2H, CH₂^{Ahx}).

C4

The synthesis was carried out the same way as **C1-3** (page S22), using **pep4** instead of **pep2** for the functionalization. After dialysis against acetate buffer (pH 5) using a MWCO 8000 membrane **C4** (1.28 μ mol, 24.8 mg, **29%**) could be obtained as a colorless solid.

¹H-NMR (400 MHz, DMSO-*d*₆, 298 K): δ /ppm: 14.76-14.28 (m, 8H, $\text{NH}_2^{+\text{His}}$), 10.94 (d, $J = 6.0$ Hz, 1H, $\alpha\text{-NH}^{\text{Thioamide}}$), 9.03-8.08 (m, 17H, $\alpha\text{-NH}/\text{CH}^{\text{His}}$), 7.71 (d, $J = 8.1$ Hz, 2H CH^{Cnf}), 7.48 (d, $J = 7.9$ Hz, 2H, CH^{Cnf}), 7.40-7.10 (m, 24H, $\text{CH}^{\text{His}}/\text{CH}^{\text{Phe}}$), 5.19-5.13 (m, 1H, $\alpha\text{-CH}^{\text{Ala}}$), 4.72-3.75 (m, 13H+2nH, $\alpha\text{-CH}/\text{CH}_2^{\text{PSar}}/\text{CH}_2^{\text{Gly}}$), 3.59 (s, 1H, COOCH_3), 3.18-2.63 (m, 22H+3nH, $\text{CH}_3^{\text{PSar}}/\text{CH}_2^{\text{His}}/\text{CH}_2^{\text{Phe}}/\text{CH}_2^{\text{Ahx}}$), 2.15-2.06 (m, 2H, CH_2^{Ahx}), 2.03-1.94 (m, 2H, CH_2^{Ahx}), 1.51-1.39 (m, 2H, CH_2^{Ahx}), 1.36-1.21 (m, 16 H $\text{CH}_2^{\text{Ahx}}/\text{Boc}/\text{CH}_3^{\text{Ala}}$), 1.20-1.12 (m, 2H, CH_2^{Ahx}), 1.06-0.97 (m, 2H, CH_2^{Ahx}).

CH₃CO-Phe-His(Trt)-Phe-His(Trt)-Phe-Ahx-Gly-Ethylendiamine-Fmoc (9)



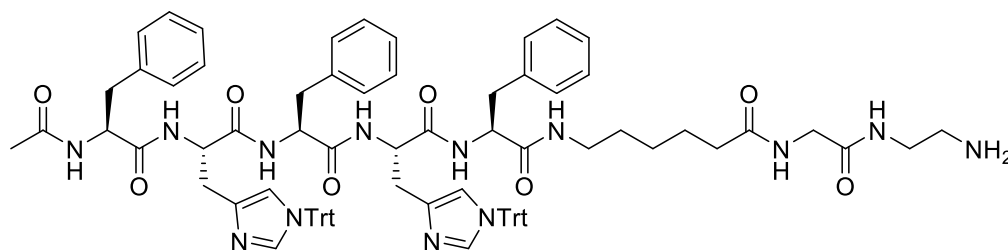
Pep2 (2350 mg, 1.64 mmol, 1 eq.) was dissolved in 12 mL DMF in a predried Schlenk flask equipped with a stir bar under an argon atmosphere. Fmoc ethylene diamine hydrochloride (550 mg, 1.72 mmol, 1.05 eq), PyBOP (940 mg, 1.81 mmol, 1.1 eq.), HOBt (246 mg, 1.81 μ mol, 1.1 eq.) and DIPEA (585 μ L, 3.45 mmol, 2.1 eq.) were added under argon counter flow. The mixture was stirred overnight at room temperature. After removal of the solvent through reduced pressure, the residue was purified *via* flash chromatography on silica gel (DCM/MeOH = 10:1, R_f = 0.6). After drying *in vacuo*, a colorless solid (2709 mg, 1.59 μ mol, **97%**) could be obtained.

Molecular formula: C₁₀₄H₁₀₃N₁₃O₁₀.

ESI-HRMS (MeOH) (m/z): Calculated for [C₁₀₄H₁₀₃N₁₃O₁₀Na]⁺: 1716.7843, found: 1716.7831.

¹H-NMR (400 MHz, DMSO-*d*₆, 298 K): δ /ppm: 8.47 (d, J = 7.5 Hz, 1H, α -NH), 8.19 (d, J = 7.5 Hz, 1H, α -NH), 8.06-8.00 (m, 2H, α -NH), 8.00-7.97 (m, 1H, α -NH), 7.92-7.85 (m, 4H, α -NH, CH^{Fmoc}), 7.74-7.65 (m, 2H, CH^{Fmoc}), 7.49-6.96 (m, 51H, CH^{Fmoc}/Trt/CH^{His}/CH^{Phe}), 6.68 (s, 1H, CH^{His}), 6.58 (s, 1H, CH^{His}), 4.48-4.16 (m, 8H, α -CH/CH^{Fmoc}/CH₂^{Fmoc}), 3.64 (d, J = 5.8 Hz, 2H, CH₂^{Gly}), 3.14-2.60 (m, 16H, CH₂^{His}/CH₂^{Phe}/CH₂^{Ahx}/CH₂^{Ethylendiamine}), 2.07 (t, J = 7.6 Hz, 2H, CH₂^{Ahx}), 1.67 (s, 3H, CH₃), 1.43-1.36 (m, 2H, CH₂^{Ahx}), 1.28-1.20 (m, 2H, CH₂^{Ahx}), 1.13-1.06 (m, 2H, CH₂^{Ahx}).

CH₃CO-Phe-His(Trt)-Phe-His(Trt)-Phe-Ahx-Gly-Ethylendiamine-NH₂ (pep5)



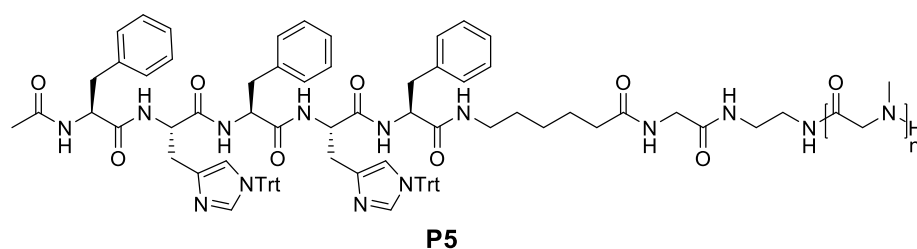
pep5

9 (2700 mg, 1.59 mmol, 1 eq.) was dissolved in a mixture of 8 mL DCM and 2 mL Piperidine. After stirring for 45 minutes at room temperature the volatiles were removed via reduced pressure. The residue was dissolved in DCM and precipitated in Diethylether. The solid residue was dissolved in DCM and washed with water, after the removal of the solvent through reduced pressure a colourless solid (2140 mg, 1.45 mmol, **91%**) could be obtained.

Molecular formula: C₈₉H₉₃N₁₃O₈.

ESI-HRMS (MeOH) (m/z): Calculated for [C₈₉H₉₄N₁₃O₈]⁺: 1472.7348, found: 1472.58.

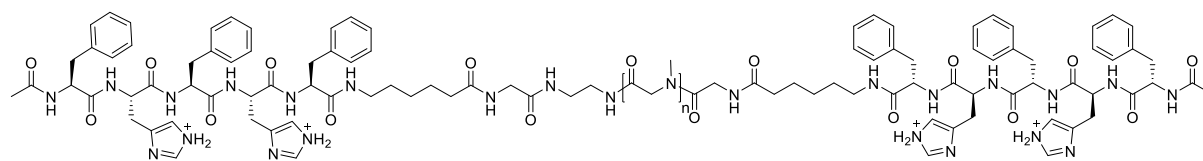
¹H-NMR (400 MHz, DMSO-*d*₆, 298 K): δ/ppm: 8.48 (d, *J* = 7.5 Hz, 1H, α-NH), 8.19 (d, *J* = 7.5 Hz, 1H, α-NH), 8.07-7.94 (m, 4H, α-NH), 7.91-7.85 (m, 1H, α-NH), 7.76 (t, *J* = 5.6 Hz, 1H, α-NH^{Gly}), 7.70-7.66 (m, 1H, α-NH), 7.45-6.98 (m, 47 H, *Trt*/CH^{His}/CH^{Phe}), 6.68 (s, 1H, CH^{His}), 6.58 (s, 1H, CH^{His}), 4.46-4.31 (m, 5H, α-CH), 3.65 (d, *J* = 5.8 Hz, 2H, CH₂^{Gly}), 3.08-2.60 (m, 16H, CH₂^{His}/CH₂^{Phe}/CH₂^{Ahx}/CH₂^{Ethylendiamine}), 2.11-2.04 (m, 2H, CH₂^{Ahx}), 1.67 (s, 3H, CH₃), 1.44-1.36 (m, 2H, CH₂^{Ahx}), 1.29-1.21 (m, 2H, CH₂^{Ahx}), 1.15-1.06 (m, 2H, CH₂^{Ahx}).

P5

The synthesis was carried out the same way as **P1-3** (page S21), using **pep5** instead of **pep1** as the initiator.

¹H-NMR (400 MHz, DMSO-*d*₆, 298 K): δ/ppm: 8.46 (d, *J* = 7.5 Hz, 1H, α-NH), 8.19 (d, *J* = 7.5 Hz, 1H, α-NH), 8.06-7.84 (m, 6H, α-NH), 8.03 (d, *J* = 7.2 Hz, 1H, α-NH), 7.39-6.99 (m, 48H, α-NH/CH^{His}/CH^{Phe}/Trt), 6.67 (s, 1H, CH^{His}), 6.57 (s, 1H, CH^{His}), 4.48-3.81 (m, 5H+2nH, α-CH/CH₂^{PSar}), 3.64 (d, *J* = 5.7 Hz, 2H, CH₂^{Gly}), 3.03-2.61 (m, 16H+3nH, CH₃^{PSar}/CH₂^{His}/CH₂^{Phe}/CH₂^{Ahx}/CH₂^{Ethylendiamine}), 2.07 (t, *J* = 7.5 Hz, 2H, CH₂^{Ahx}), 1.44-1.37 (m, 2H, CH₂^{Ahx}), 1.30-1.20 (m, 2H, CH₂^{Ahx}), 1.14-1.06 (m, 2H, CH₂^{Ahx}).

C5



The synthesis was carried out the same way as **C1-3** (page S22), also using **pep2** for the functionalization, **C5** could be attained in a yield of **84%**.

¹H-NMR (400 MHz, DMSO-*d*₆, 298 K): δ/ppm: 14.50-14.18 (m, 8H, NH₂^{+His}), 9.10-7.77 (m, 20H, α-NH/ CH^{His}), 7.46-7.10 (m, 34H, CH^{His}/CH^{Phe}), 4.67-3.87 (m, 10H + 2nH, α-CH/CH₂^{PSar}), 3.73-3.61 (m, 4H, CH₂^{Gly}), 3.18-2.63 (m, 28H+3nH, CH₃^{PSar}/CH₂^{His}/ CH₂^{Phe}/ CH₂^{Ahx}/ CH₂^{Ethylenediamine}), 2.16-2.08 (m, 4H, CH₂^{Ahx}), 1.74 (s, 6H, NHCOCH₃) 1.51-1.41 (m, 4H, CH₂^{Ahx}), 1.38-1.28 (m, 4H, CH₂^{Ahx}), 1.20-1.13 (m, 4H, CH₂^{Ahx}).

6. Spectra

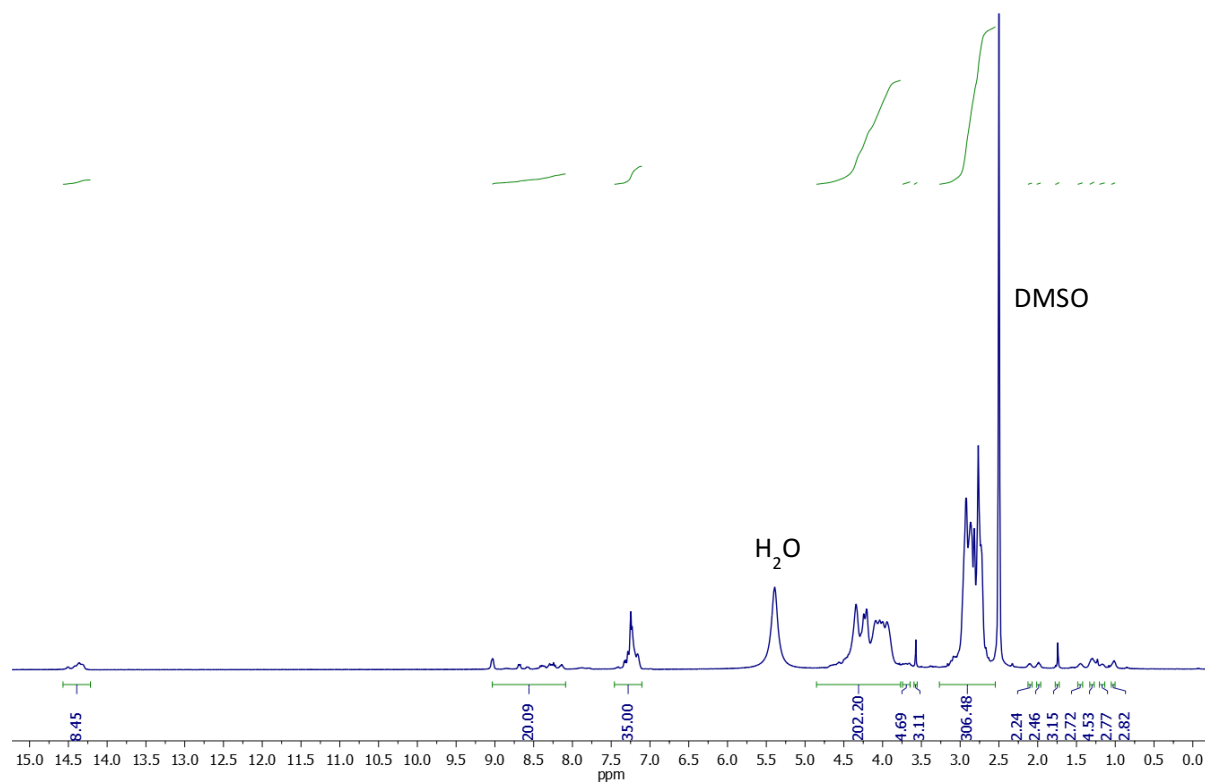


Figure S15. ¹H-NMR of **C2** in DMSO-*d*₆, 400 MHz.

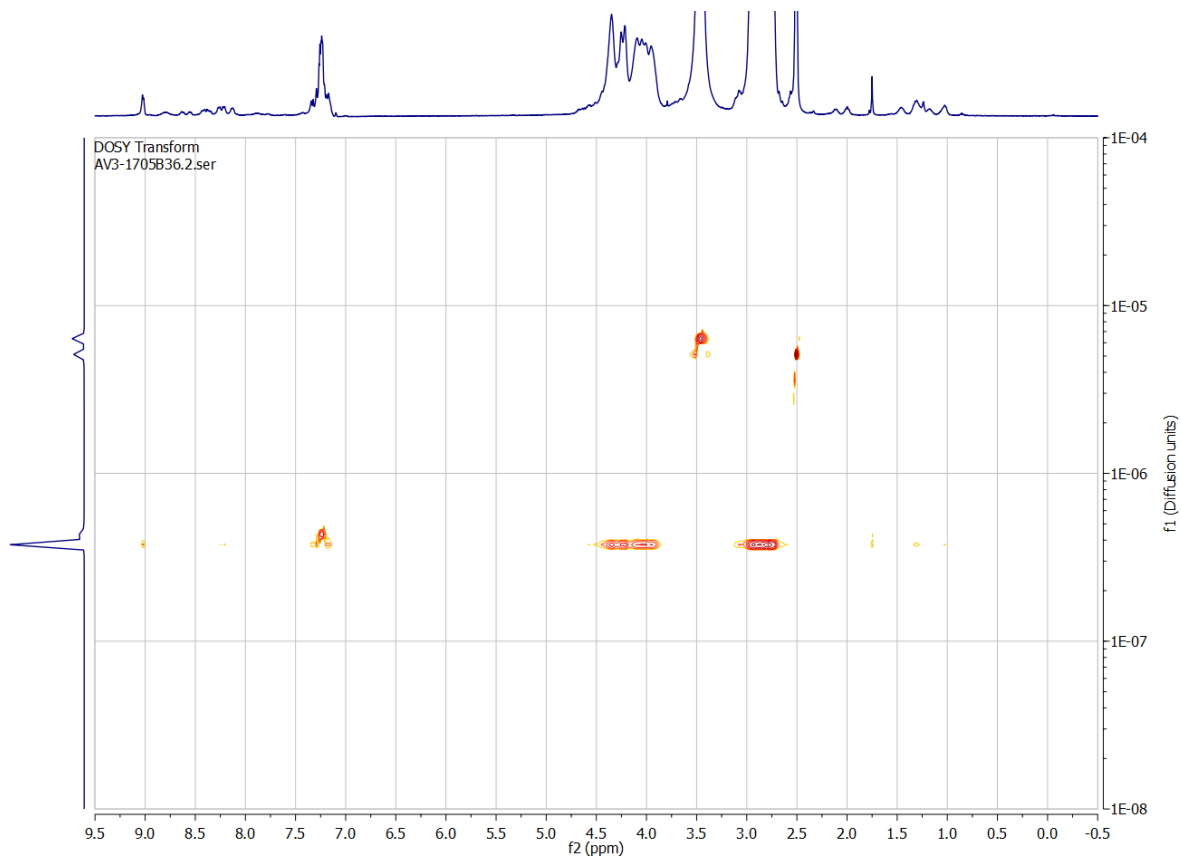


Figure S16. ¹H DOSY NMR of **C2** in DMSO-*d*₆, 400 MHz.

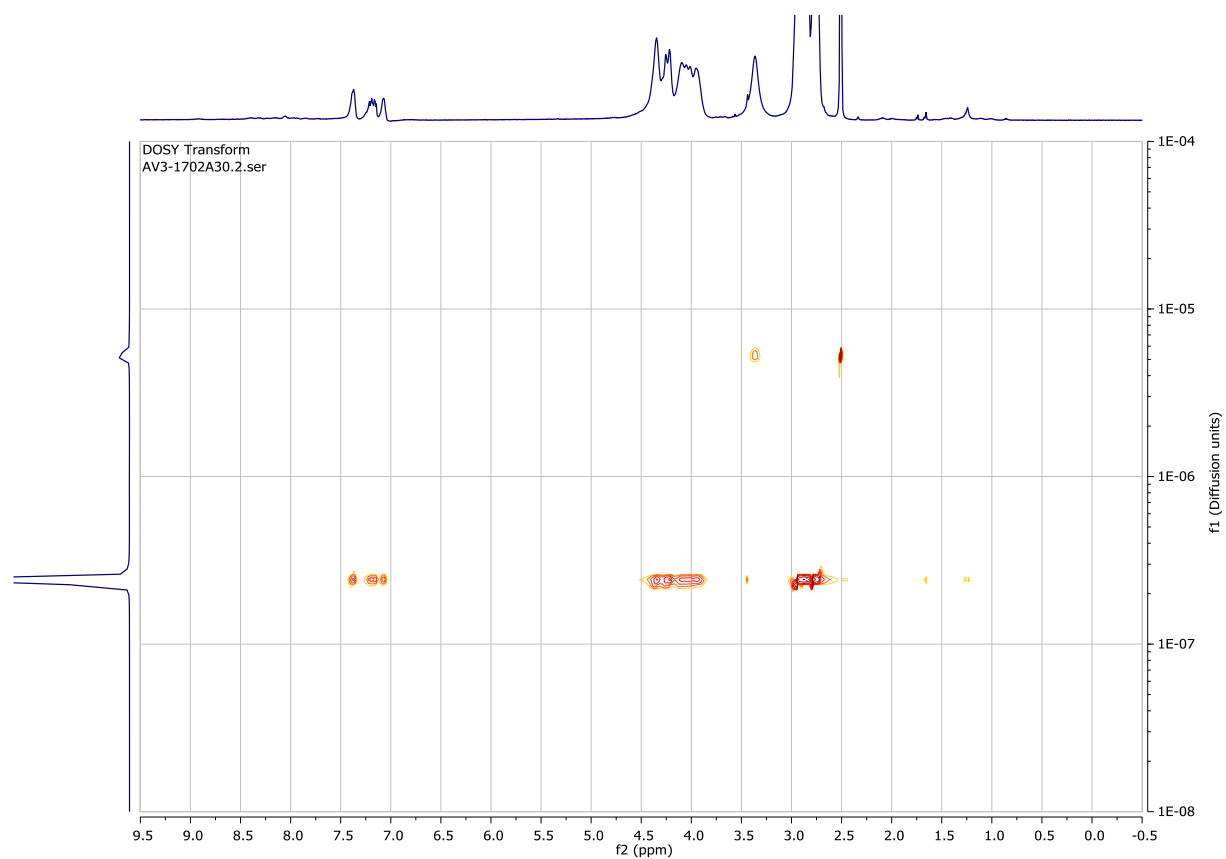


Figure S17. ^1H DOSY NMR of **C3** in $\text{DMSO-}d_6$, 400 MHz.

7. References

- [1] J. Qian, G. Guerin, Y. Lu, G. Cambridge, I. Manners, M. A. Winnik, *Angew. Chem., Int. Ed.* **2011**, *50*, 1622-1625; (b) P. A. Rugar, L. Chabanne, M. A. Winnik, I. Manners, *Science* **2012**, *337*, 559-562.
- [2] Birke, A.; Huesmann, D.; Kelsch, A.; Weilbacher, M.; Xie, J.; Bros, M.; Bopp, T.; Becker, C.; Landfester, K.; Barz, M. *Biomacromolecules* **2014**, *15*, 548-557.