Supporting Information

Regulating H_2S Release from Self-Assembled Peptide H_2S-Donor Conjugates Using Cysteine Derivatives

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Materials

4-Formylbenzoic acid (FBA) was purchased from Chem-Impex International, Inc (Wood Dale, IL, USA). Thiobenzoic acid was purchased from Sigma-Aldrich (St. Louis, MO, USA). Trifluoroacetic acid (TFA) was purchased from Millipore Sigma (Burlington, MA, USA). Unless otherwise stated, all other reagents were sourced from Fisher Scientific (Hampton, NH, USA) or VWR (Radnor, PA, USA). TsO-EG_4-OMe was synthesized as reported earlier.[1] DCM = dichloromethane.

General Methods for Synthesis and Analysis

Column chromatography

For column chromatography, silica gel with a particle size of 0.035–0.070 mm and a pore size of 60 Å by Acros Organics (New Jersey, USA) was used. The eluents were freshly prepared of technical grade solvents, unless stated otherwise. For flash chromatography a pressure of 0.2–0.6 bar was applied with nitrogen. The analysis of the collected fractions was performed *via* thin layer chromatography.

Centrifugation

Centrifugation was performed on a VWR MicroStar 12 by Avantor (Darmstadt, Germany) using 1.5 mL Eppendorf-tubes, or on a VWR Mega Star 600 by Avantor (Darmstadt, Germany) using 15 mL or 50 mL Falcon-tubes.

NMR spectroscopy

All ^{1}H- and ^{13}C-NMR spectra and corresponding 2D NMR-experiments were performed on an Avance II 400 (^{1}H-NMR: 400 MHz, ^{13}C-NMR 101 MHz) spectrometer or Avance III HD 400 (^{1}H-NMR: 400 MHz, ^{13}C-NMR 101 MHz) spectrometer by Bruker (Rheinstätten, Germany) equipped with a 5 mm broadband observe probe head (z gradient) or Avance III 600 (^{1}H-NMR: 600 MHz, ^{13}C-NMR 151 MHz) spectrometer by Bruker (Rheinstätten, Germany) equipped with a 5 mm cryogenic triple-band inverse probe head (z gradient) using standard Bruker release pulse sequences. All samples were dissolved in deuterated solvents by Deutero (Kastellaun, Germany). Evaluations of the spectra were carried out with MestReNova 14.1.0 by Mestrelab Research *S.L.* (Santiago de Compostela, Spain). The chemical shifts of the signals were locked relative to the residual solvent peaks reported in literature[2] and are given in parts per million (ppm) relative to tetramethylsilane (0 ppm). Coupling constants were measured in Hz and the nomenclature of the multiplicity of the signals was used as follows:

br = broad signal, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet and m = multiplet.

Mass spectrometry

All mass spectra were recorded on an G6545A Q-TOF-MS by Agilent (Santa Clara, USA), ionized using electron spray ionization (ESI). Sample injection is performed via 1260 Infinity II HPLC-System by Agilent (Santa Clara, USA) with G7111B 1260 Quaternary Pump, G7129A 1260 Vial sampler and G7116A 1260 Multicolumn Thermostat.

High performance liquid chromatography (HPLC)

The HPLC system consisted of a PU-4086 semi-preparative binary pump module, an AS-4050 HPLC Autosampler, a MD-4015 Photo Diode Array Detector, a CO-4060 column oven by Jasco (Pfungstadt, Germany) and a CHF122SC fraction collector by Advantec *MFS Inc.* (Dublin, USA).

Purification using NUCLEODUR C18 Pyramid by Macherey-Nagel was performed at a flowrate of 18.9 mL/min with the solvents and the time program shown below. The particle size of the column was 5 µm, the length 250 mm and the diameter 21 mm.

Table S1.1: Gradient of the solvents used in Method A.

Time /min	ultrapure water /vol%	Acetonitrile /vol%
0	95	5
3	95	5
28	5	95
40	5	95

Table S1.2: Gradient of the solvents used in Method B.

Time /min	ultrapure water +0.1% TFA /vol%	Acetonitrile + 0.1% TFA /vol%
0	95	5
3	95	5
28	5	95
40	5	95

Solid Phase Peptide Synthesis

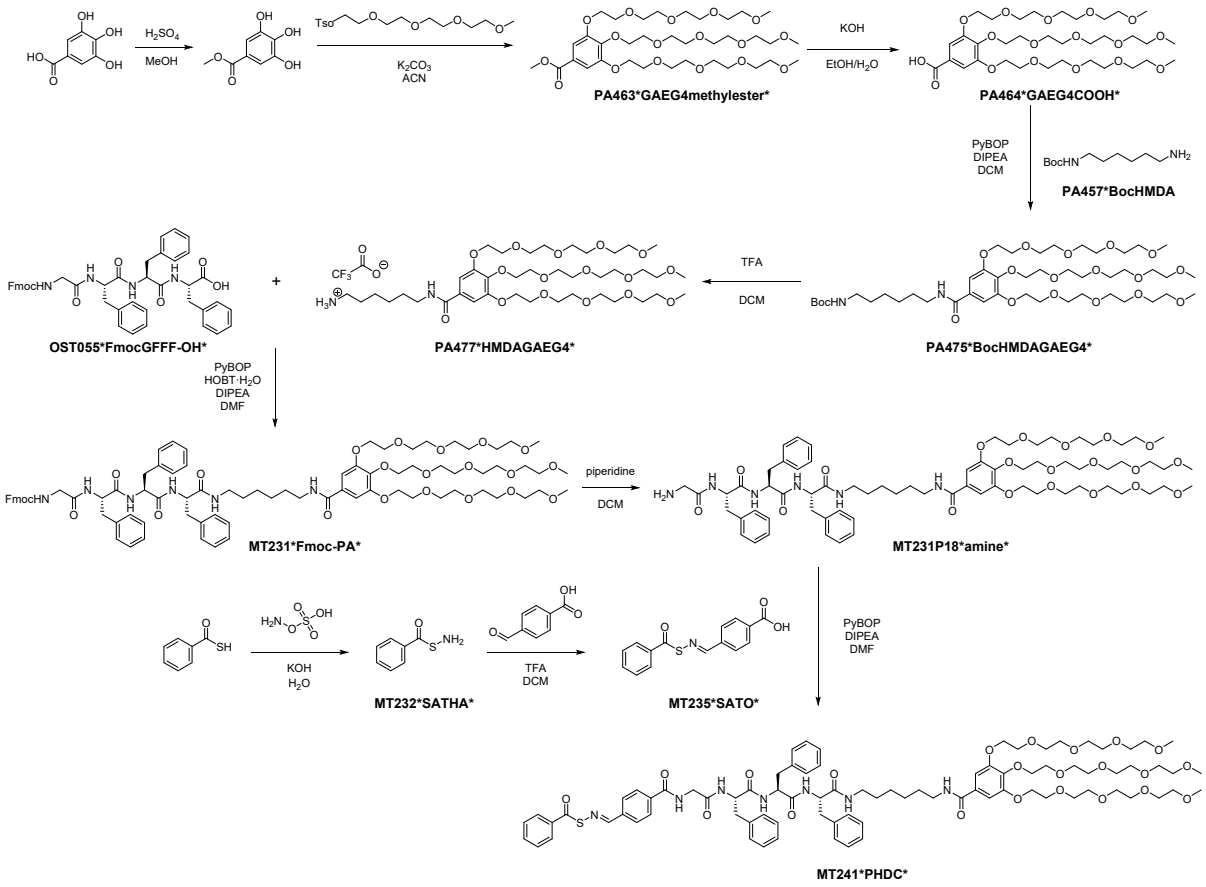
Solid phase peptide synthesis was carried out on a CS136XT Peptide Synthesizer by CS Bio Co. (Menlo Park, USA). Peptide grade solvents and reagents were used. Peptide synthesis was carried out by a modified version of the standard Fmoc-protocol shown by Atherton and Sheppard.[3]

Solid phase peptide synthesis was performed using the standard Fmoc-protocol without capping, hence consisting of the following two steps:

- Fmoc-deprotection: The Fmoc protecting group was cleaved from the amino acid using an excess of 20% piperidine in DMF.
- Coupling: To couple the amino acid, 4 eq. the Fmoc protected amino acid was used with 4 eq. of 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 4 eq. 1-hydroxybenzotriazol (HOBt) and 6 eq. diisopropylethylamine (DIPEA) in DMF, added to the free amine of the amino acid on the resin.

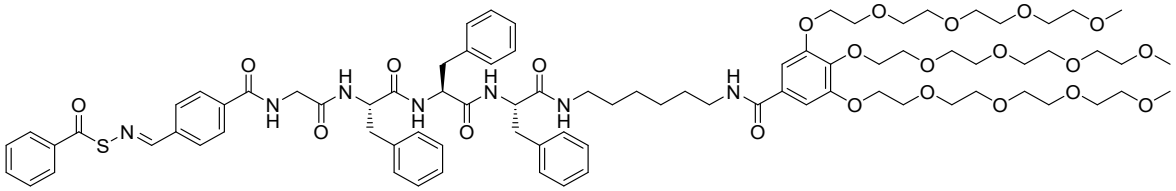
For each amino acid only one coupling step was performed. The procedure was repeated for all amino acids in the sequence.

Synthesis of H_2S Donating Peptide-Dendron Conjugate



Scheme S1 Synthesis of H_2S donating peptide-dendron conjugate.

Compound MT241*PHDC*



MT231P18*amine* (20.0 mg, 0.015 mmol, 1.0 eq.) was dissolved in degassed DMF (2 mL) and cooled down in an ice bath. **MT235*SATO*** (8.5 mg, 0.030 mmol, 2.0 eq.) and PyBOP (15.6 mg, 0.030 mmol, 2.0 eq.) were added, before DIPEA (7.8 µL, 0.045 mmol, 3.0 eq.) was added in three equal portions, after waiting 10 min each time. The ice bath was removed, and the reaction mixture was stirred at rt for 2 h. The solvent was removed *in vacuo* and the crude product was purified *via* HPLC (Method A)

Yield: 8.0 mg (0.005 mmol, 33 %) colorless lyophilizate.

Molecular formular: $C_{84}H_{113}N_7O_{22}S$.

Exact mass: 1603.7659.

HR-TOF-MS (ESI, pos.), *m*/*z*: 1642.7309 $[M+K]^+$ (calc. 1642.7291),

840.8481 $[M+2K]^{2+}$ (calc. 840.8461).

^{1}H NMR (300 MHz, DMSO-d_6, 296 K, COSY) δ/ppm: 9.09 (s, 1H, CH^{Imin}), 8.87 (t, 1H, J = 5.9 Hz, NH^{Gly}), 8.36 (t, 1H, J = 5.7 Hz, NH^{HMDA}), 8.18 (d, 1H, J = 8.1 Hz, NH^{Phe1}), 8.14–8.06 (m, 2H, NH^{Phe2}, NH^{Phe3}), 8.03–7.89 (m, 6H, *H*-2$^{\text{SATO}}$, *H*-6$^{\text{SATO}}$, *H*-2'$^{\text{SATO}}$, *H*-3'$^{\text{SATO}}$, *H*-5'$^{\text{SATO}}$, *H*-6'$^{\text{SATO}}$,), 7.80–7.73 (m, 2H, *H*-4$^{\text{SATO}}$,NH^{HMDA}), 7.63 (t, 2H, J = 7.6 Hz, *H*-3$^{\text{SATO}}$, *H*-5$^{\text{SATO}}$), 7.28–7.11 (m, 17H, 6x Phe$^{\delta}$, 6x Phe$^{\varepsilon}$, 3x Phe$^{\zeta}$, *H*-2$^{\text{gallic acid}}$, *H*-6$^{\text{gallic acid}}$), 4.57–4.40 (m, 3H, 3x Phe$^{\alpha}$), 4.14 (t, 4H, J = 4.7 Hz, 2x *meta*-OCH_2), 4.06 (t, 2H, J = 4.9 Hz, *para*-OCH_2), 3.97–3.79 (m, 2H, Gly$^{\alpha}$), 3.76 (t, 4H, J = 4.7 Hz, 2x *meta*-OCH$_2$CH_2), 3.67 (t, 2H, J = 4.9 Hz, *para*-OCH$_2$CH_2), 3.63–3.39 (m, 36H, 18x OCH_2^{TEG}), 3.26–3.18 (m, 11H, 3x OCH_3, CH_2^{HMDA}), 3.04–2.66 (m, 8H, 3x Phe$^{\beta}$, CH_2^{HMDA}), 1.54–1.41 (m, 2H, CH_2^{HMDA}), 1.33–1.15 (m, 6H, 3x CH_2^{HMDA}).

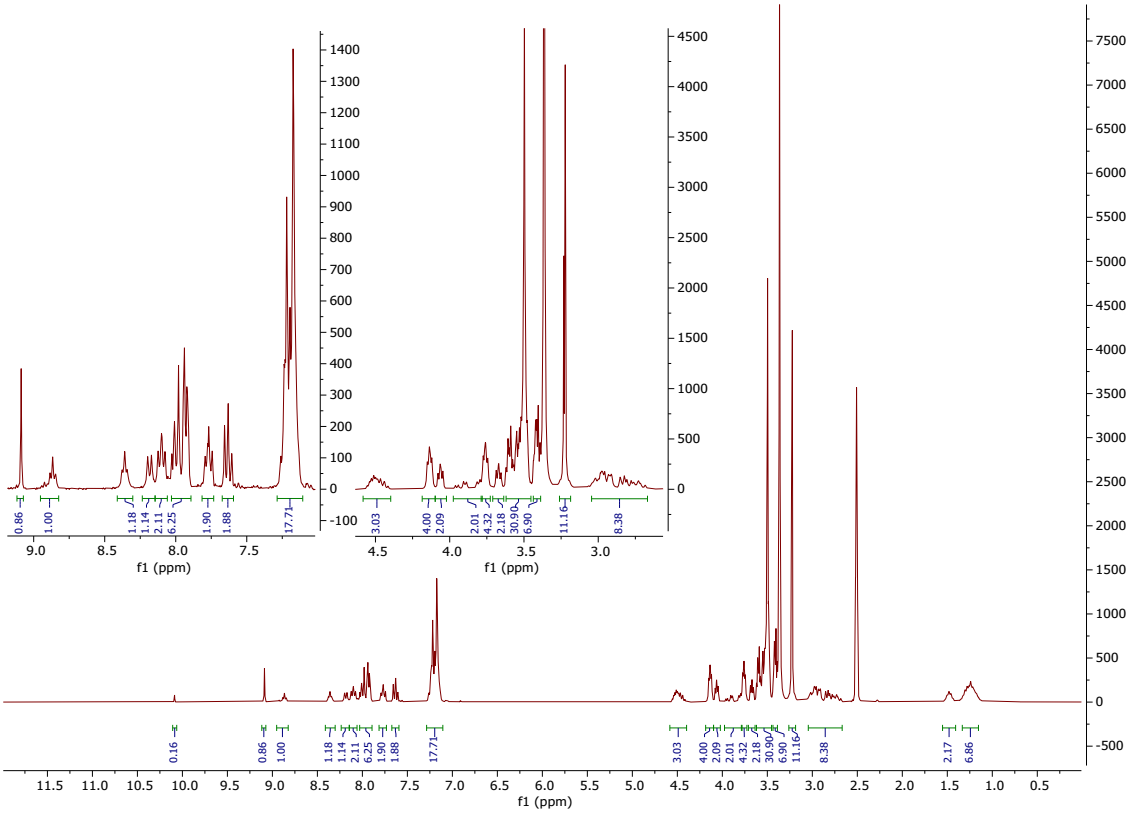


Figure S1 ^{1}H NMR spectrum of compound **MT241P25*PHDC*** in DMSO-d_6.

Figure S2 COSY spectrum of compound **MT241P25*PHDC*** in DMSO-d_6.

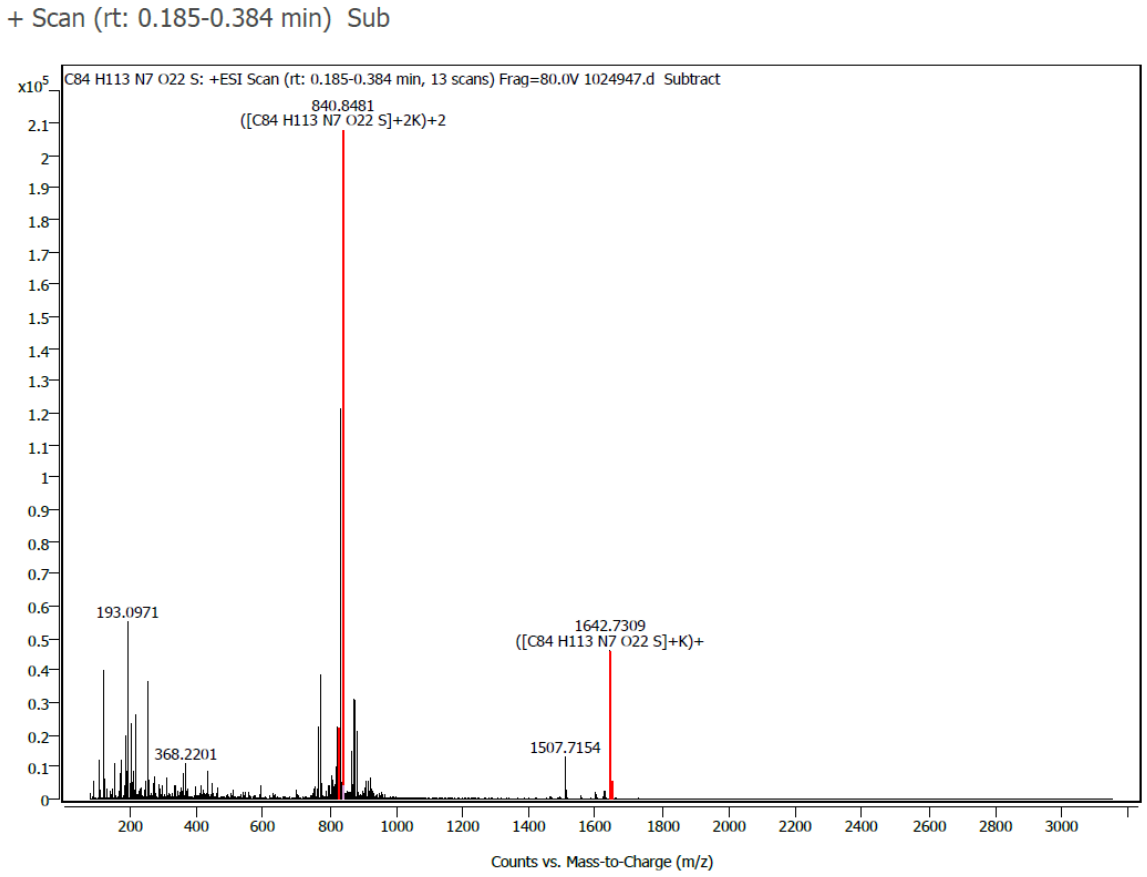
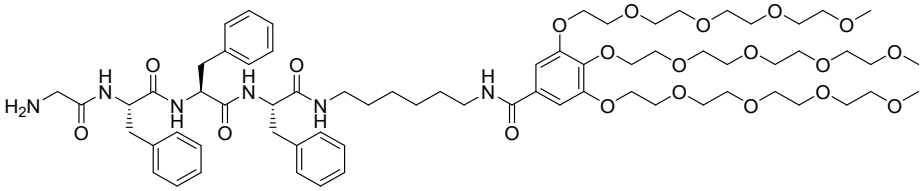


Figure S3 positive ESI-HR-QTOF-MS spectrum of **MT241P25*PHDC***.

Compound MT231P18*amine*



MT231*Fmoc-PA* (90.0 mg, 0.058 mmol, 1.0 eq.) was dissolved in DCM/piperidine (8/2, 10 mL) and stirred for 2 h at rt. The solvent was removed *in vacuo* and co-distilled with toluene (6×6 mL). The crude product was taken up in DCM (50 mL) and washed with Milli-Q water (50 mL) once. The aqueous phase was extracted with DCM (3×50 mL) and the combined organic layer dried over Na_2SO_4. After evaporation of the solvent the crude product was purified *via* HPLC (Method A).

Yield: 11 mg (0.008 mmol, 14 %) colorless lyophilizate.

Molecular formular: $C_{69}H_{104}N_6O_{20}$.

Exact mass: 1336.7305.

HR-TOF-MS (ESI, pos.), *m*/*z*: 1337.7399 $[M+Na]^+$ (calc. 1337.7378).

680.3657 $[M+H+Na]^{2+}$ (calc. 680.3635).

^{1}H NMR (300 MHz, DMSO-d_6, 296 K, COSY) δ/ppm: 8.53 (d, 1H, J = 8.5 Hz, NH^{Phe1}), 8.42–8.34 (m, 2H, NH^{Phe2}, NH^{HMDA}), 8.17 (d, 1H, J = 8.1 Hz, NH^{Phe3}), 7.93–7.82 (m, 2H, NH_3^{Gly}, NH^{HMDA}), 7.26–7.12 (m, 17H, 6x Phe$^{\delta}$, 6x Phe$^{\varepsilon}$, 3x Phe$^{\zeta}$, H-2$^{gallic\ acid}$, H-6$^{gallic\ acid}$), 4.65–4.42 (m, 3H, 3x Phe$^{\alpha}$), 4.13 (t, 4H, J = 4.4 Hz, 2x *meta*-OCH_2), 4.06 (t, 2H, J = 5.0 Hz, *para*-OCH_2), 3.79-3.70 (m, 4H, 2x *meta*-OCH$_2$CH_2), 3.66 (t, 2H, J = 5.0 Hz, *para*-OCH$_2$CH_2), 3.62–3.38 (m, 96H, 18x OCH_2^{TEG}, HDO), 3.26–3.17 (m, 11H, 3x OCH_3, CH_2^{HMDA}), 3.07–2.64 (m, 8H, 3x Phe$^{\beta}$, CH_2^{HMDA}), 1.53–1.41 (m, 2H, CH_2^{HMDA}), 1.33–1.11 (m, 6H, 3x CH_2^{HMDA}).

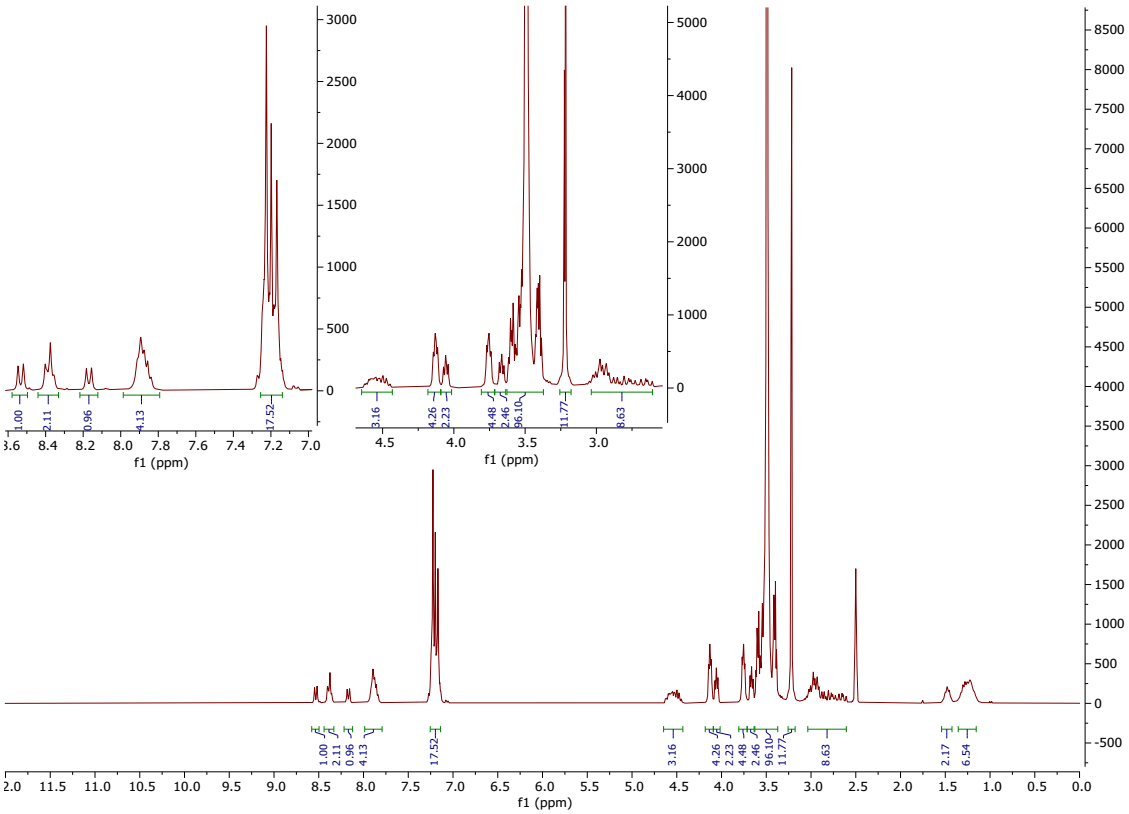
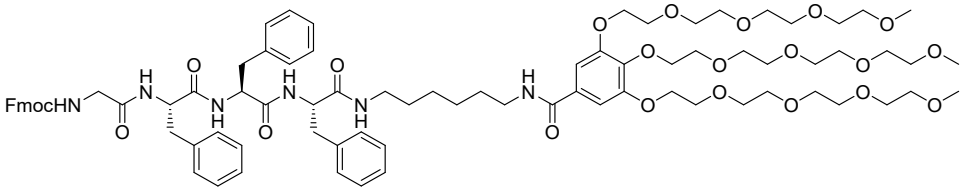


Figure S4 ^{1}H NMR spectrum of compound **MT231P18*amine*** in DMSO-d_6.

Compound MT231*Fmoc-PA*



OST089*FmocGFFF-OH* (105.7 mg, 0.143 mmol, 1.0 eq.) and **PA477* HMDAGAEG4*** (150.0 mg, 0.157 mmol, 1.1 eq.) was dissolved in degassed DMF (10 mL) and HOBt·H_2O

(32.7 mg, 0.215 mmol, 1.5 eq.) and PyBOP (111.7 mg, 0.215 mmol, 1.5 eq.) was added. The solution was cooled down in an ice bath, before DIPEA (52.5 µL, 0,.300 mmol, 2.1 eq.) was added in two portions after waiting 10 min each time. The ice bath was removed, and the reaction mixture was stirred under exclusion of light at rt for 4 d. An additional portion of PyBOP (50.0 mg, 0.096 mmol, 0.7 eq.) was added and reacted further for 6 h. The reaction mixture was concentrated to 1 mL and precipitated in ice cold diethyl ether (20 mL). The precipitate was collected by centrifugation and purified *via* size exclusion chromatography (Bio-Beads S-X1, DMF) to yield 101.5 mg of colorless amorphous solid. The impure fractions were further purified via HPLC (Method B) to yield another 6.0 mg of colorless amorphous solid. The combined solids were suspended in water and subjected to lyophilization.

Yield: 107.5 mg (0.069 mmol, 48 %) colorless lyophilizate.

Molecular formular: $C_{84}H_{114}N_6O_{22}$.

Exact mass: 1558.7986.

HR-TOF-MS (ESI, pos.), *m*/*z*: 1581.7913 $[M+Na]^+$ (calc. 1581.7878).

802.3904 $[M+2Na]^{2+}$ (calc. 802.3885).

^{1}H NMR (300 MHz, DMSO-d_6, 296 K, COSY) δ/ppm: 8.34 (t, 1H, J = 5.4 Hz, NH^{HMDA}), 8.17 (d, 1H, J = 8.1 Hz, NH^{Phe1}), 8.11 (d, 2H, J = 8.0 Hz, NH^{Phe2}), 7.96 (d, 1H, J = 8.3 Hz, NH^{Phe3}), 7.88 (d, 2H, J = 7.5 Hz, *H*-4^{Fmoc}, *H*-5^{Fmoc}), 7.78 (t, 1H, J = 5.6 Hz, NH^{HMDA}), 7.69 (d, 2H, J = 7.4 Hz, *H*-1^{Fmoc}, *H*-8^{Fmoc}), 7.48 (t, 2H, J = 6.0 Hz, NH^{Gly}), 7.41 (t, 2H, J = 7.4 Hz, *H*-3^{Fmoc}, *H*-6^{Fmoc}), 7.31 (d, 2H, J = 7.4 Hz, *H*-2^{Fmoc}, *H*-7^{Fmoc}), 7.26–7.08 (m, 17H, 6x Phe$^{\delta}$, 6x Phe$^{\varepsilon}$, 3x Phe$^{\zeta}$, *H*-2$^{gallic\ acid}$, *H*-6$^{gallic\ acid}$), 4.57–4.41 (m, 3H, 3x Phe$^{\alpha}$), 4.22 (d, 2H, J = 5.5 Hz, *H*-10^{Fmoc}) ,4.13 (t, 4H, J = 4.7 Hz, 2x *meta*-OCH_2), 4.06 (t, 2H, J = 4.8 Hz, *para*-OCH_2), 3.79-3.72 (m, 4H, 2x *meta*-OCH$_2$CH_2), 3.66 (t, 2H, J = 4.9 Hz, *para*-OCH$_2$CH_2), 3.62–3.37 (m, 36H, 18x OCH_2^{TEG}), 3.27–3.16 (m, 11H, 3x OCH_3, CH_2^{HMDA}), 3.09–2.63 (m, 8H, 3x Phe$^{\beta}$, CH_2^{HMDA}), 1.53–1.40 (m, 2H, CH_2^{HMDA}), 1.37–1.13 (m, 6H, 3x CH_2^{HMDA}).

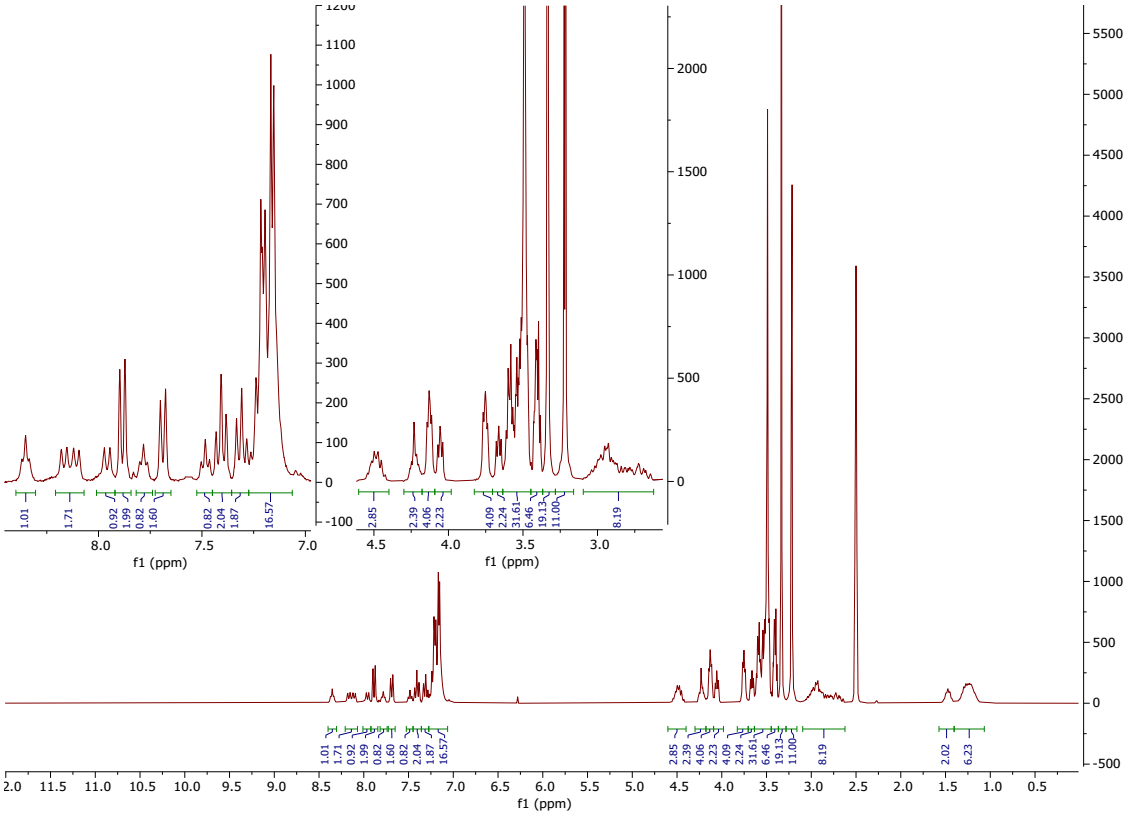
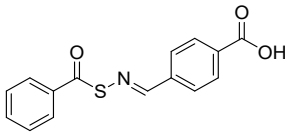


Figure S5 ^{1}H NMR spectrum of compound **MT231*Fmoc-PA*** in DMSO-d_6.

Compound MT235*SATO*



MT232*SATHA* (238.0 mg, 1.554 mmol, 1.0 eq.) was dissolved in dry DCM (10 mL) in a flame dried *Schlenk* tube under argon atmosphere. 4-Carboxy benzaldehyde (333.5 mg, 2.222 mmol, 1.4 eq.) and TFA (10 µL) was added under argon counterflow. The contents were stirred for 21 h to turn into a colorless suspension. The precipitate was filtered and washed with DCM (5 mL). For purification the solid was recrystallized from ethyl acetate (30 mL), filtered, washed with ethyl acetate (2×5 mL) and dried under reduced pressure.

Yield: 309 mg (1.083 mmol, 70 %) colorless solid.

Molecular formular: $C_{15}H_{11}NO_3S$.

Exact mass: 285.0460.

HR-TOF-MS (ESI, pos.), *m/z*: 286.0524 $[M+H]^+$ (calc. 286.0533).

^{1}H NMR (300 MHz, DMSO-d_6, 296 K, COSY) δ/ppm: 13.24 (bs, 1H, COO*H*), 9.10 (s, 1H, C*H*^{Imin}), 8.07 (d, 2H, J = 8.4 Hz, *H*-3',*H*-5'), 7.98–7.89 (m, 4H, *H*-2, *H*-6, *H*-2', *H*-6'), 7.79–7.72 (m, 1H, *H*-4), 7.67–7.58 (m, 2H, *H*-3, *H*-5). The spectrum matched a previous report.[4]

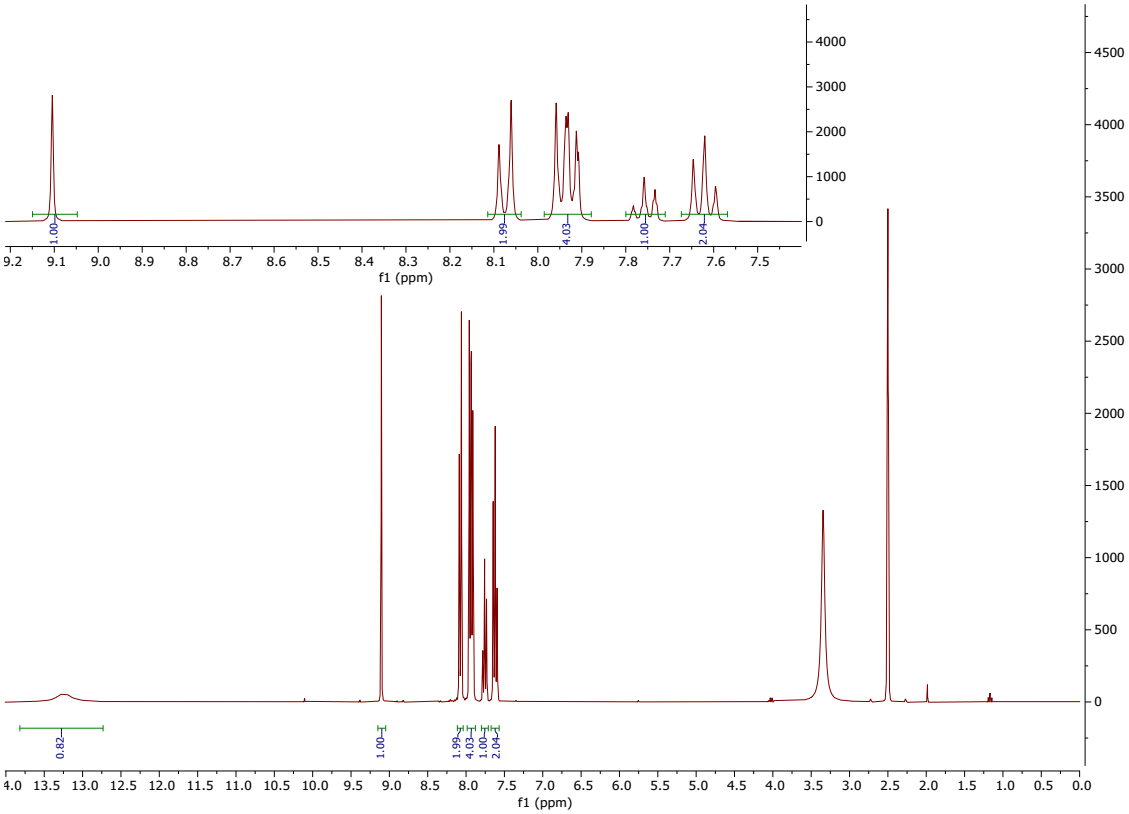
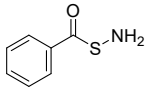


Figure S6 ^{1}H NMR spectrum of compound **MT235*SATO*** in DMSO-d_6.

Compound MT232*SATHA*



Thiobenzoic acid (500.0 mg, 3.618 mmol, 1.0 eq.) and KOH (406.1 mg, 7.237 mmol, 2.0 eq.) were dissolved in Milli-Q water (10 mL). Hydroxylamine-*O*-sulfonic acid (409.2 mg, 3.618 mmol, 1.0 eq.) was added and the mixture was stirred for 20 min. The precipitate was collected by filtration and washed with Milli-Q water (2×10 mL) before drying under reduced pressure. The colorless solid was purified *via* column chromatography (SiO_2, DCM).

Yield: 245 mg (1.599 mmol, 44 %) colorless solid.

Molecular formular: C_7H_7NOS.

Exact Mass: 153.0248.

^{1}H NMR (400 MHz, $CDCl_3$, 296 K) δ/ppm: 7.90–7.85 (m, 1H, *H*-2, *H*-6), 7.63–7.56 (m, 1H, *H*-4), 7.51–7.44 (m, 1H, *H*-3, *H*-5), 2.75 (s, 2H, NH_2). The spectrum matched a previous report.[4]

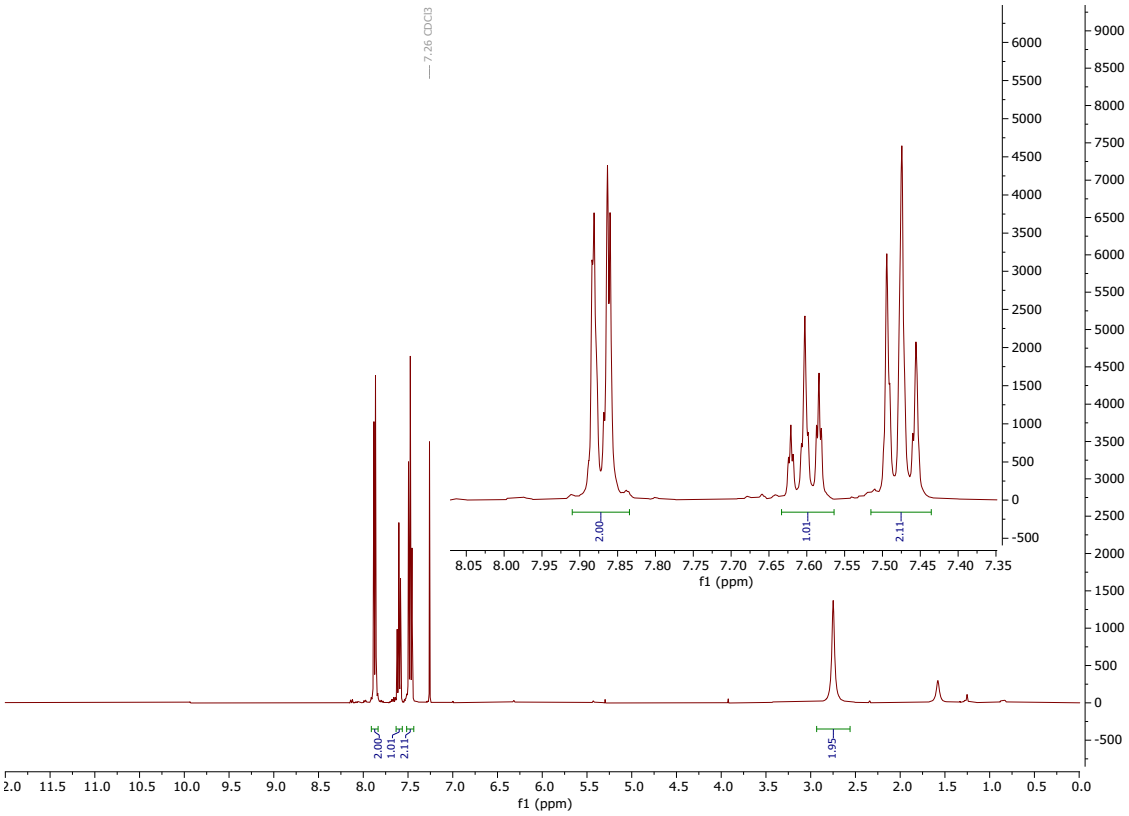
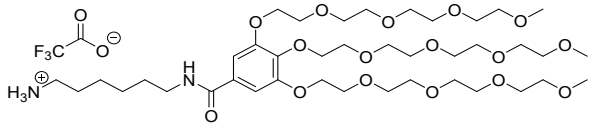


Figure S7 ^{1}H NMR spectrum of compound **MT232*SATHA*** in $CDCl_3$.

Compound PA477*HMDAGAEG4*



PA475*BocHMDAGAEG4* (1440 mg, 1.533 mmol, 1.0 eq.) was dissolved in TFA/DCM (1/1, 20 mL) and stirred at rt for 1 h. The solvent was removed under reduced pressure and the remainder was co-distilled with toluene (5×10 mL). The desired product was obtained without further purification.

Yield: 1460 mg (1.532 mmol, quant.) viscous, pale yellow oil.

Molecular formular: $C_{40}H_{74}N_2O_{16}\cdot$TFA.

Exact mass: 952.4967.

HR-TOF-MS (ESI, pos.), *m*/*z*: 861.4922 $[M\text{-}TFA+Na]^+$ (calc. 861.4931).

^{1}H NMR (400 MHz, DMSO-d_6, 296 K, COSY) δ/ppm: 8.37 (t, 1H, J = 5.6 Hz, N*H*), 7.68 (bs, 3H, NH_3^+) 7.16 (s, 2H, H-2$^{\text{gallic acid}}$, H-6$^{\text{gallic acid}}$), 4.16–4.11 (m, 4H, 2x *meta*-OCH_2), 4.08–4.04 (m, 2H, *para*-OCH_2), 3.78–3.74 (m, 4H, 2x *meta*-O$CH_2C\mathit{H}_2$), 3.69–3.65 (m, 2H, *para*-O$CH_2C\mathit{H}_2$), 3.63–

3.39 (m, 38H, 18x OCH_2^{TEG}, CH_2^{HMDA}), 3.23 (s, 3H, *para*-CH_3^{OMe}), 3.22 (s, 6H, 2x *meta*-CH_3^{OMe}), 2.82–2.72 (m, 2H, NH_3CH_2), 1.58–1.45 (m, 4H, 2x CH_2^{HMDA}), 1.38–1.25 (m, 4H, 2x CH_2^{HMDA}).

^{13}C NMR (101 MHz, DMSO-d_6, 296 K, HSQC, HMBC) δ/ppm: 165.3 (*C*=O$^{gallic\ acid}$), 158.3 (q, J = 36.8 Hz, CF_3*C*OOH), 151.8 (*meta*-*C*^{Ar}), 139.9 (*para*-*C*^{Ar}), 129.5 (*C*^{Ar}C=O), 117.0 (NH_3*C*H_2), 114.1 (*C*F_3COOH), 106.3 (*ortho*-*C*H^{Ar}), 71.9 (*para*-C^{Ar}O*C*H_2), 71.3, 70.0, 69.9, 69.8, 69.8, 69.8, 69.6, 69.0 (O*C*H_2*C*H_2O), 68.4 (*meta*-C^{Ar}O*C*H_2), 58.0 (*meta*-*C*H_3^{OMe}, *para*-*C*H_3^{OMe}), 38.8 (*C*H_2^{HMDA}), 29.1 (*C*H_2^{HMDA}), 27.0 (*C*H_2^{HMDA}), 26.0 (*C*H_2^{HMDA}), 25.57 (*C*H_2^{HMDA}).

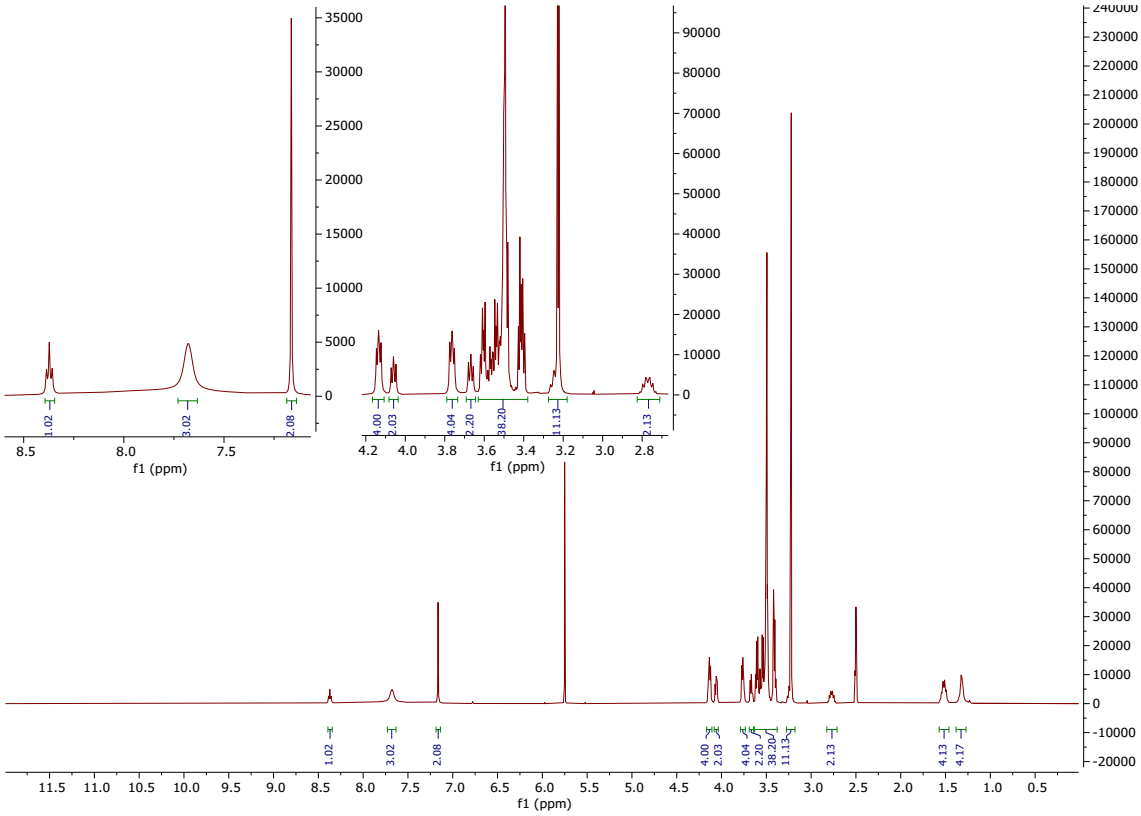


Figure S8 ^{1}H NMR spectrum of compound PA477*HMDAGAEG4* in DMSO-d_6.

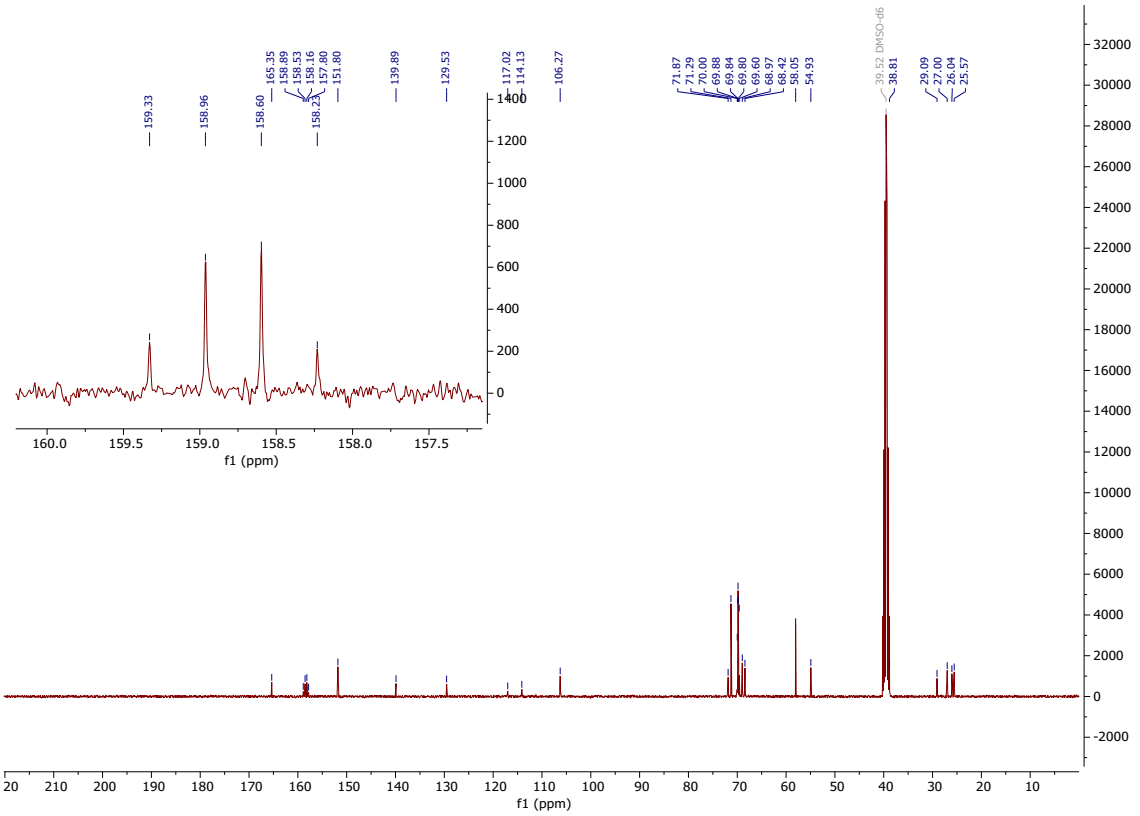
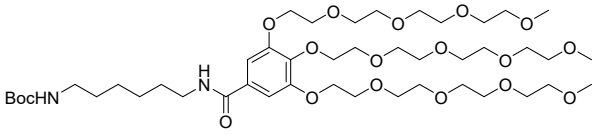


Figure S9 ^{13}C NMR spectrum of compound **PA477*HMDAGAEG4*** in DMSO-d_6.

Compound PA475*BocHMDAGAEG4*



PA464*GAEG4COOH* (1180 mg, 1.593 mmol, 1.0 eq.) was dissolved in DCM. **PA457*BocHMDA*** (450 mg, 2.080 mmol, 1.3 eq.) in DCM was added to the stirring solution. In the following PyBOP (1990 mg, 3.824 mmol, 2.4 eq.) and DIPEA (1.030 g, 7.99 mmol, 5.0 eq.) were added and the mixture stirred under argon atmosphere for 3 h at room temperature. The solvent was removed *in vacuo* and the residue was purified *via* size exclusion chromatography (Sephadex® LH 20, MeOH).

Yield: 1.440 mg (1.533 mmol, 96 %) colorless lyophilizate.

Molecular formular: $C_{45}H_{82}N_2O_{18}$.

Exact mass: 938.5563.

HR-TOF-MS (ESI, pos.), *m*/*z*: 961.5422 $[M+Na]^+$ (calc. 961.5455).

^{1}H NMR (400 MHz, DMSO-d_6, 296 K, COSY) δ/ppm: 8.33 (t, 1H, J = 5.6 Hz, NH^{HMDA}), 7.16 (s, 2H, H-2$^{gallic\ acid}$, H-6$^{gallic\ acid}$), 6.76 (t, 1H, J = 5.9 Hz, NH^{Boc}), 4.16–4.11 (m, 4H, 2x *meta*-OCH_2),

4.08–4.04 (m, 2H, para-OCH_2), 3.78–3.74 (m, 4H, *meta*-OCH$_2$CH_2), 3.69–3.64 (m, 2H, *para*-OCH$_2$CH_2), 3.63–3.38 (m, 38H, 18x OCH_2^{TEG}, CH_2^{HMDA}), 3.23 (s, 3H, *para*-CH_3^{OMe}), 3.22 (s, 6H, *meta*-CH_3^{OMe}), 2.89 (td, 2H, J = 7.0 Hz, J = 5.8 Hz, CH_2^{HMDA}), 1.54–1.44 (m, 2H, CH_2^{HMDA}), 1.40–1.32 (m, 11H, CH_3^{OtBu}, CH_2^{HMDA}), 1.31–1.21 (m, 4H, 2x CH_2^{HMDA}).

^{13}C NMR (101 MHz, DMSO-d_6, 296 K, HSQC, HMBC) δ/ppm: 165.3 (C=O$^{gallic\ acid}$), 155.6 (C=O^{Boc}), 151.8 (*meta*-C^{Ar}), 139.80 (*para*-C^{Ar}), 129.5 (C^{Ar}C=O), 106.2 (*ortho*-CH^{Ar}), 77.3 (C_q^{tBu}), 71.8 (*para*-C^{Ar}OCH$_2$), 71.3, 70.0, 69.9, 69.8, 69.8, 69.7, 69.6, 68.9 (OCH$_2$CH$_2$O), 68.4 (*meta*-C^{Ar}OCH$_2$), 58.03 (*meta*-CH$_3^{OMe}$, *para*-CH$_3^{OMe}$), 39.2 (CH$_2^{HMDA}$), 29.5 (CH$_2^{HMDA}$), 29.2 (CH$_2^{HMDA}$), 28.3 (CH$_3^{tBu}$), 26.2 (CH$_2^{HMDA}$), 26.1 (CH$_2^{HMDA}$).

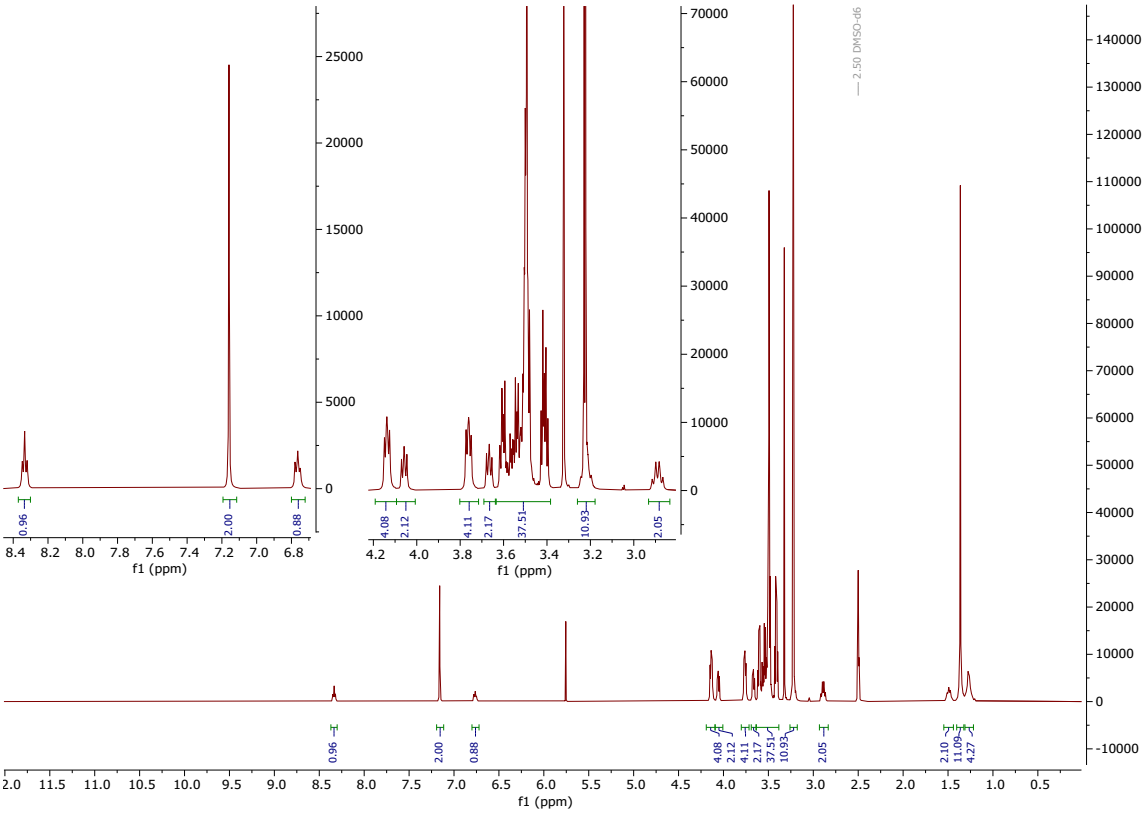


Figure S10 ^{1}H NMR spectrum of compound **PA475*BocHMDAGAEG4*** in DMSO-d_6.

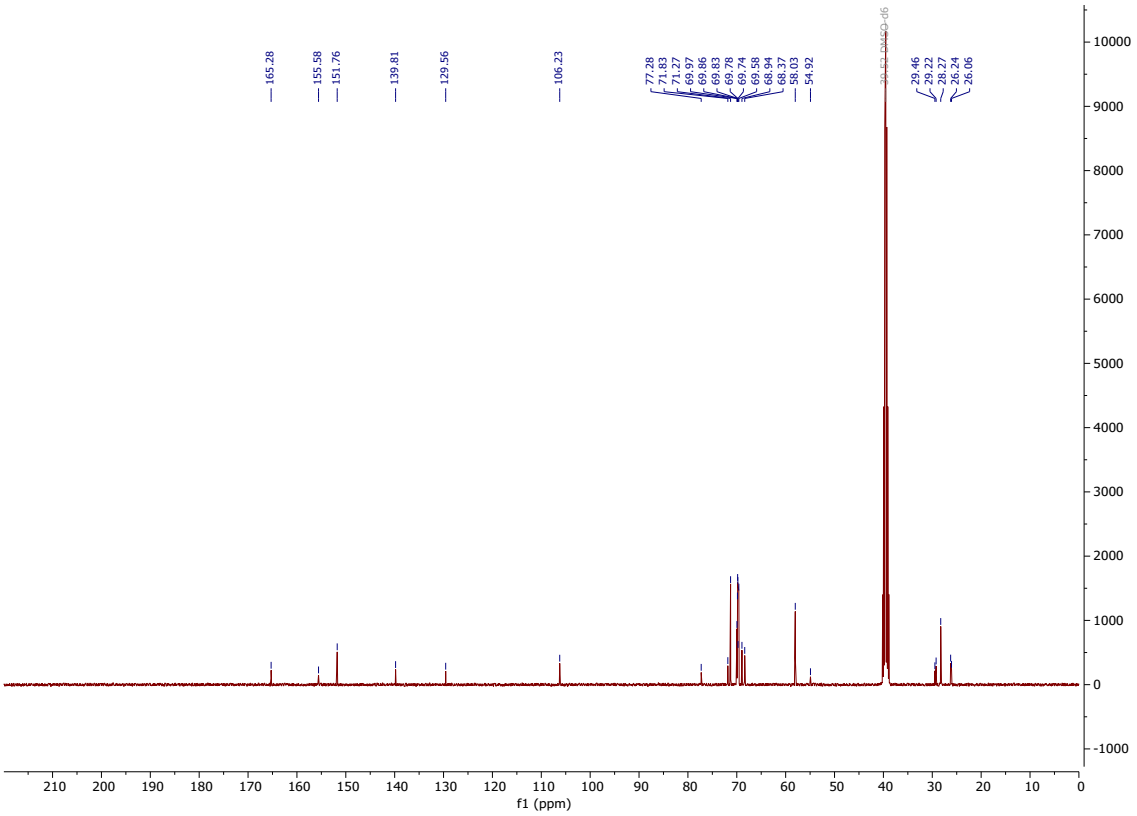
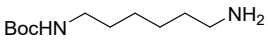


Figure S11 ^{13}C NMR spectrum of compound **PA475*BocHMDAGAEG4*** in DMSO-d_6.

Compound PA457*BocHMDA*



Hexamethylene diamine (39.9 g, 343.5 mmol, 5.0 eq.) was dissolved in $CHCl_3$ (680 mL) and the solution cooled to 0 °C. Boc_2O (15.0 g, 68.7 mmol, 1.0 eq.) in $CHCl_3$ (340 mL) was added dropwise over 8 h at 0 °C. The obtained suspension was stirred for 18 h at room temperature. Next, the $CHCl_3$ phase was washed with H_2O (8×250 mL), dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified *via* column chromatography (SiO_2, $CHCl_3$ + 15% MeOH (+0.1% NH_3)).

Yield: 14.2 g (66.9 mmol, 97 %) viscous, colorless oil.

Molecular formular: $C_{11}H_{24}N_2O_2$.

Exact mass: 216.1838.

R_F: 0.33 (DCM + 15% MeOH (+0.1% NH_3)).

HR-TOF-MS (ESI, pos.), *m*/*z*: 217.1915 $[M+H]^+$ (calc. 217.1991).

^{1}H NMR (400 MHz, DMSO-d_6, 296 K, COSY) δ/ppm: 6.77 (t, 1H, J = 5.7 Hz, NH^{Boc}), 2.89 (td, 2H, J = 7.0 Hz, J = 5.8 Hz, NH^{Boc}CH_2), 2.55–2.49 (m, 2H, CH_2NH$_2$), 1.37 (s, 9H, $CH_3{}^{OtBu}$),

1.36–1.28 (m, 4H, $NH^{Boc}CH_2CH_2$, $NH^{Boc}[CH_2]_4CH_2$), 1.28–1.16 (m, 4H, $NH^{Boc}[CH_2]_2CH_2$, $NH^{Boc}[CH_2]_3CH_2$).

^{13}C NMR (101 MHz, DMSO-d_6, 296 K, HSQC, HMBC) δ/ppm: 155.6 (CO^{Boc}), 77.3 ($C_q{}^{t}Bu$), 41.4 (CH_2NH_2), 39.8 ($NH^{Boc}CH_2$), 32.8 ($NH^{Boc}[CH_2]_4CH_2$), 29.5 ($NH^{Boc}CH_2CH_2$), 28.3 ($CH_3{}^{t}Bu$), 26.2 ($NH^{Boc}[CH_2]_2CH_2$), 26.1 ($NH^{Boc}[CH_2]_3CH_2$).

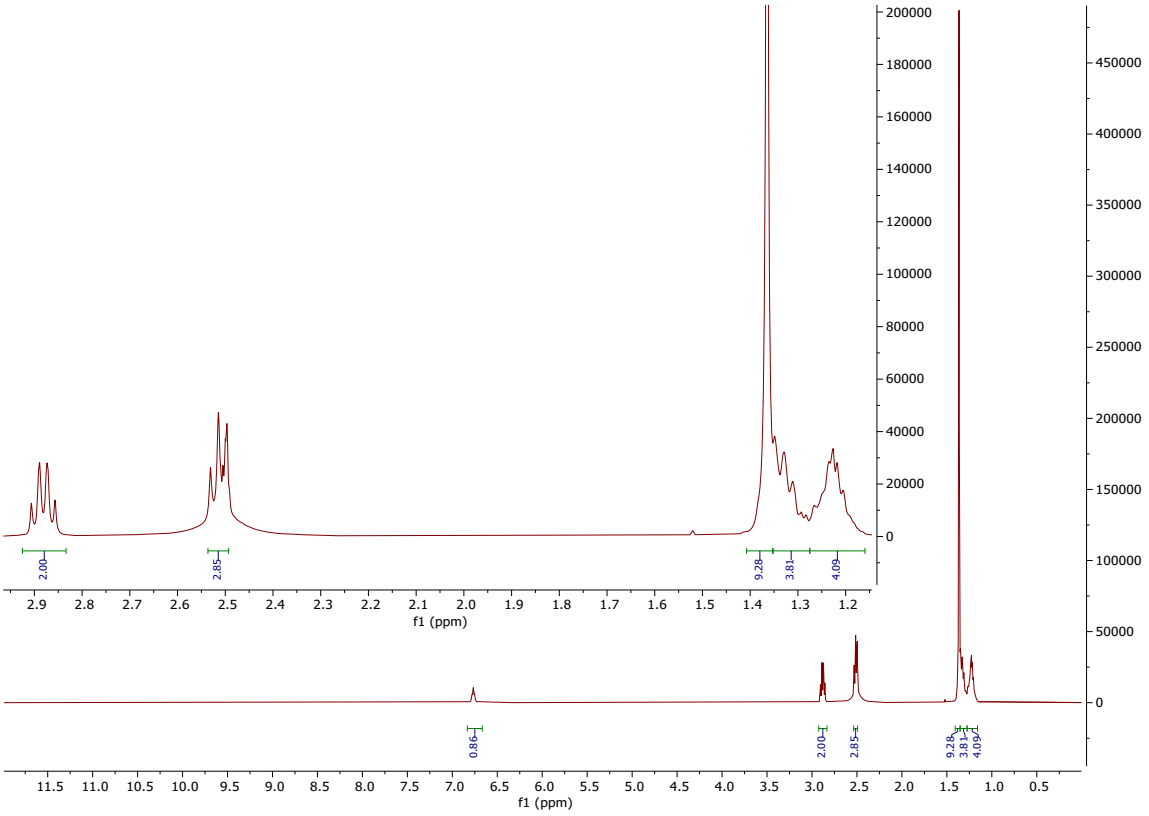


Figure S12 ^{1}H NMR spectrum of compound **PA457*BocHMDA*** in DMSO-d_6.

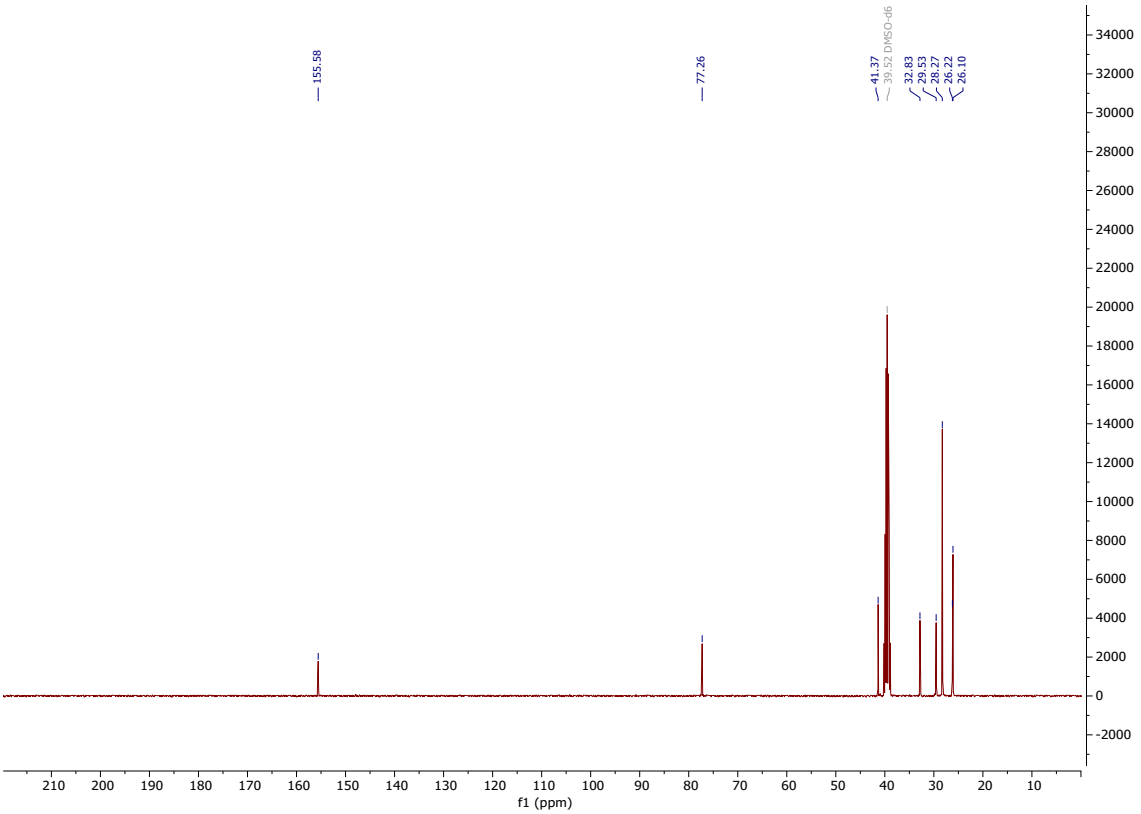
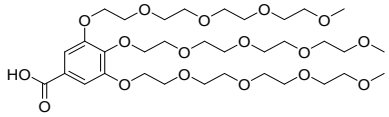


Figure S13 ^{13}C NMR spectrum of compound **PA457*BocHMDA*** in DMSO-d_6.

Compound PA464*GAEG4COOH*



PA463*GAEG4methylester* (1540 mg, 2.040 mmol, 1.0 eq.) was dissolved in a mixture of EtOH/H_2O (1/1, 40 mL) and KOH (572 mg, 10.194 mmol, 5.0 eq.) was added and the mixture stirred for 2 h at 90 °C. The pH of the solution was adjusted to pH 1 by addition of aqueous 1 M HCl and extracted with DCM (3×30 mL). The combined organic layers were washed with H_2O (2×30 mL), dried over Na_2SO_4 and the solvent removed *in vacuo.*

Yield: 1502 mg (2.027 mmol, 99 %) pale yellow oil.

Molecular formular: $C_{34}H_{60}O_{17}$.

Exact mass: 740.3831.

R_F: 0.24 (DCM + 5% MeOH).

HR-TOF-MS (ESI, pos.), *m/z*: 763.3719 $[M+Na]^+$ (calc. 763.3723).

^{1}H NMR (400 MHz, DMSO-d_6, 296 K, COSY) δ/ppm: 12.93 (bs, 1H, COOH), 7.22 (s, 2H, H-2$^{\text{gallic acid}}$, H-6$^{\text{gallic acid}}$), 4.16–4.08 (m, 6H, 2x *meta*-OCH_2, *para*-OCH_2), 3.78–3.73 (m, 4H, 2x *meta*-

OCH2CH_2), 3.69–3.65 (m, 2H, *para*-OCH2CH_2), 3.62–3.39 (m, 36H, 18x OCH_2^{TEG}), 3.23 (s, 3H, *para*-CH_3^{OMe}), 3.22 (s, 6H, 2x *meta*-CH_3^{OMe}).

^{13}C NMR (101 MHz, DMSO-d$_6$, 296 K, HSQC, HMBC) δ/ppm: 166.9 (COOH), 151.9 (*meta*-C^{Ar}), 145.5 (*para*-*C*^{Ar}), 125.7 (*C*COOH), 108.2 (*ortho*-*C*H^{Ar}), 71.9 (*para*-C^{Ar}O*C*H2), 71.3, 69.9, 69.9, 69.8, 69.8, 69.6, 68.9 (O*C*H2*C*H2O), 68.4 (*meta*-C^{Ar}O*C*H2), 58.0 (*meta*-*C*H$_3^{OMe}$, *para*-*C*H$_3^{OMe}$).

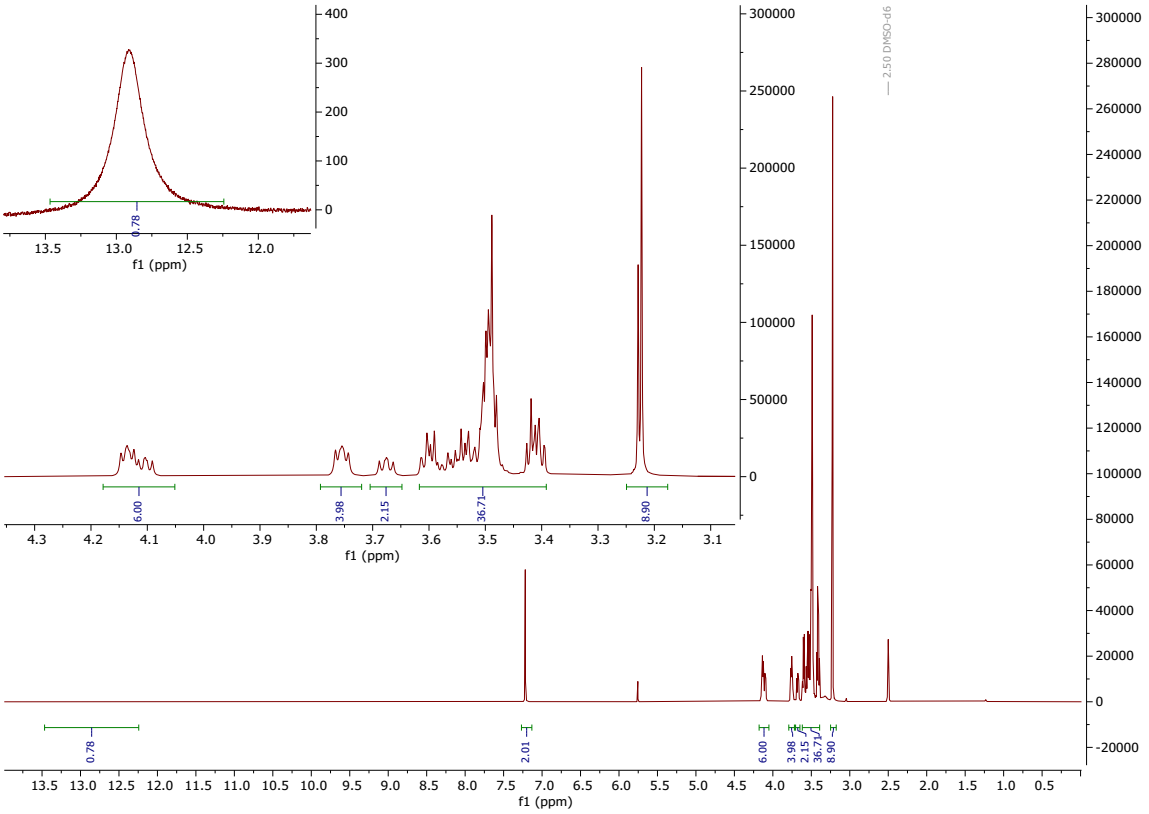


Figure S14 ^{1}H NMR spectrum of compound **PA464*GAEG4COOH*** in DMSO-d_6.

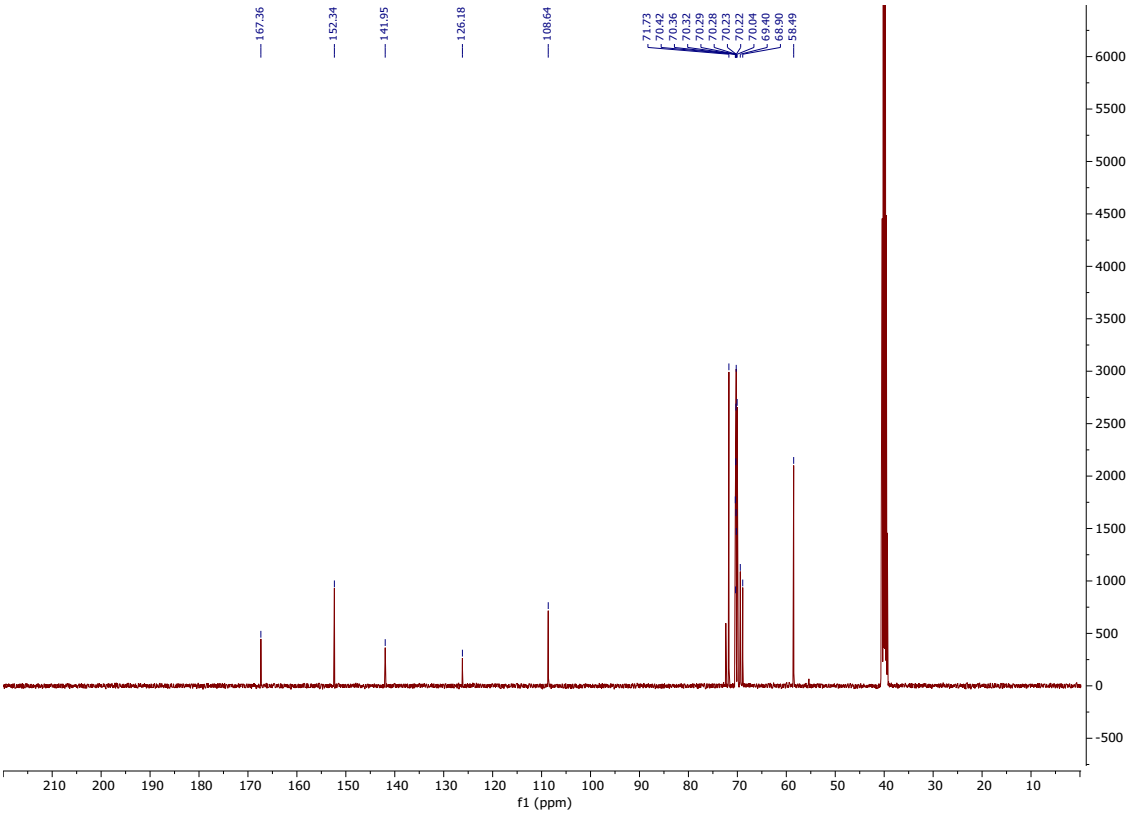
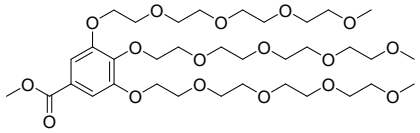


Figure S15 ^{13}C NMR spectrum of compound **PA464*GAEG4COOH*** in DMSO-d_6.

Compound PA463*GAEG4methylester*



PA462*GAmethylester* (451.0 mg, 2.449 mmol, 1.0 eq.) and **TsO-EG4-OMe** (3560 mg, 9.822 mmol, 4.0 eq.) were dissolved in CH_3CN (10 mL). K_2CO_3 (2370 mg, 17.147 mmol, 7.0 eq.) was added and the suspension stirred for 18 h at 85 °C. The solvent was removed *in vacuo* and the residue redissolved in H_2O. The aqueous layer was extracted with DCM (3×70 mL). The combined organic layers were washed with H_2O (3×50 mL) and brine (3×50 mL). The organic layer was dried over Na_2SO_4, and the solvent removed *in vacuo*. The obtained residue was purified *via* size exclusion chromatography (Sephadex® LH 20, MeOH).

Yield: 1570 mg (2.080 mmol, 85 %) pale yellow oil.

Molecular formular: $C_{35}H_{62}O_{17}$.

Exact mass: 754.3987.

R_F: 0.27 (DCM + 5% MeOH).

HR-TOF-MS (ESI, pos.), *m*/*z*: 777.3869 $[M+Na]^+$ (calc. 777.3879).

^{1}H NMR (400 MHz, DMSO-d_6, 296 K, COSY) δ/ppm: 7.24 (s, 2H, *H*-2$^{\text{gallic acid}}$, *H*-6$^{\text{gallic acid}}$), 4.17–4.10 (m, 6H, 2x *meta*-OCH_2, *para*-OCH_2), 3.83 (s, 3H, CH_3^{Me}), 3.78–3.74 (m, 4H, 2x *meta*-OCH$_2$CH_2), 3.70–3.66 (m, 2H, *para*-OCH$_2$CH_2), 3.62–3.39 (m, 36H, 18x OCH_2^{TEG}), 3.23 (s, 3H, *para*-CH_3^{OMe}), 3.22 (s, 6H, 2x *meta*-CH_3^{OMe}).

^{13}C NMR (101 MHz, DMSO-d_6, 296 K, HSQC, HMBC) δ/ppm: 165.8 (*C*OOMe), 152.0 (*meta*-*C*$^{\text{Ar}}$), 141.9 (*para*-*C*$^{\text{Ar}}$), 124.4 (*C*CO$_2$Me), 108.1 (*ortho*-*C*H$^{\text{Ar}}$), 71.9 (*p*-C$^{\text{Ar}}$O*C*H$_2$), 71.3, 70.00, 69.9, 69.8, 69.88, 69.6, 68.9 (O*C*H$_2$*C*H$_2$O), 68.5 (*meta*-C$^{\text{Ar}}$O*C*H2), 58.0 (*meta*-*C*H$_3^{\text{OMe}}$, *para*-*C*H$_3^{\text{OMe}}$), 52.2 (*C*H$_3^{\text{COOMe}}$).

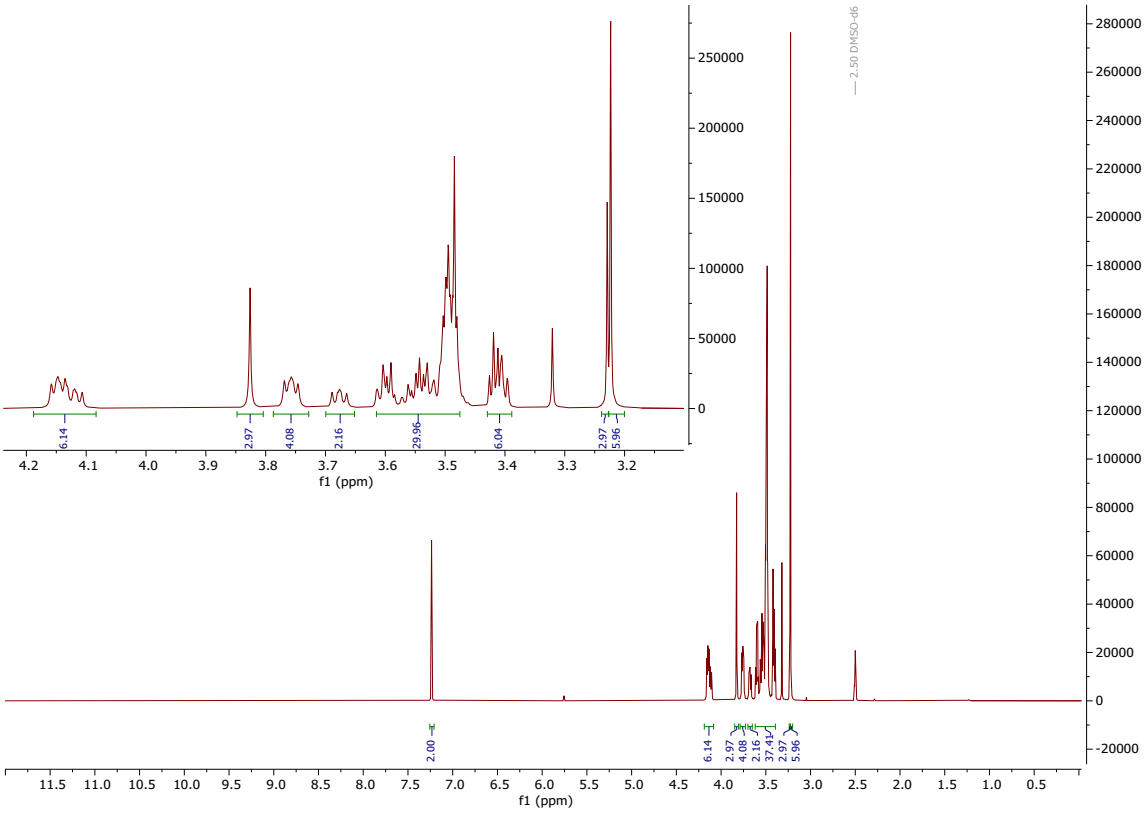


Figure S16 ^{1}H NMR spectrum of compound **PA463*GAEG4methylester*** in DMSO-d_6.

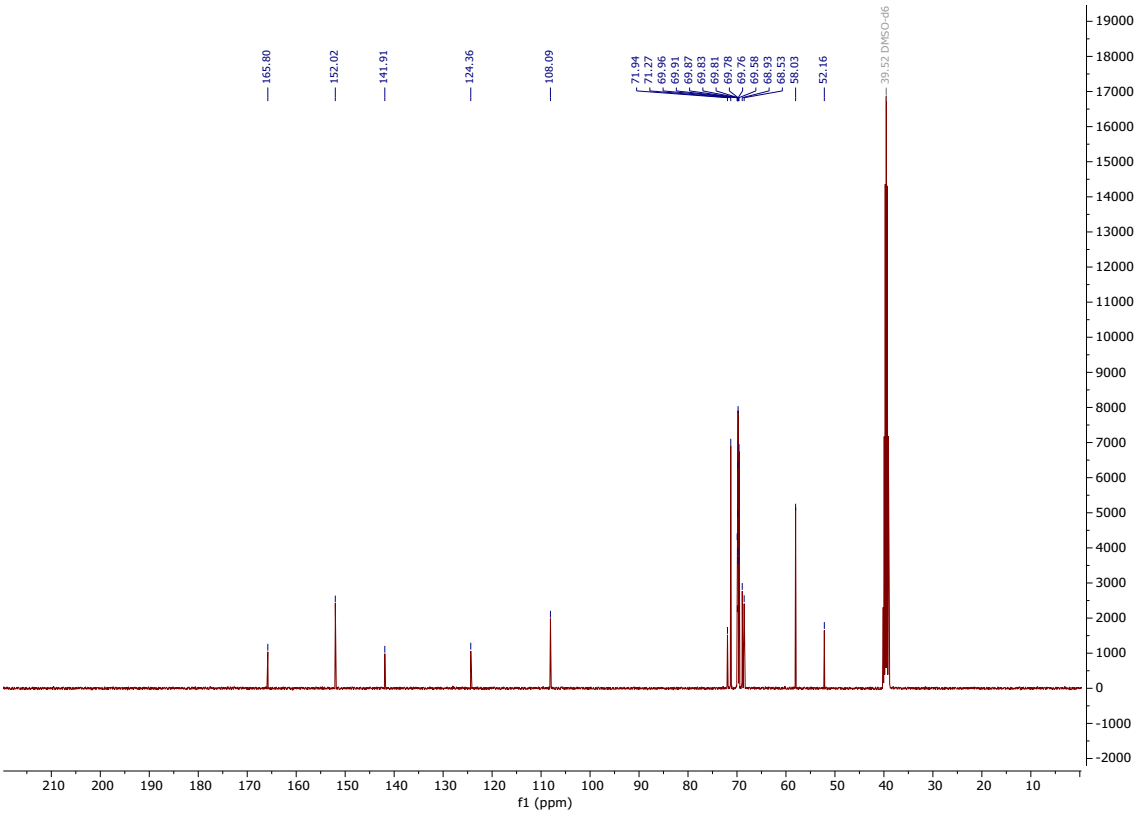
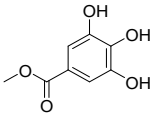


Figure S17 ^{13}C NMR spectrum of compound **PA463*GAEG4methylester*** in DMSO-d_6.

Compound PA462*GAmethylester*



3,4,5-Trihydroxybenzoic acid (5.45 g, 32.1 mmol, 1.0 eq) was dissolved in MeOH (50 mL). 10 drops of conc. H_2SO_4 were added, and the mixture refluxed for 18 h. MeOH was removed *in vacuo*, the residue redissolved in Et_2O/H_2O and extracted with Et_2O (3×200 mL). The combined organic layers were washed with H_2O (2x 100 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*.

Yield: 5.32 g (28.9 mmol, 90 %) colorless amorphous solid.

Molecular formular: $C_8H_4O_5$.

Exact mass: 184.0372.

R_F: 0.48 (CH:EA, 1:2).

FD-MS ($CHCl_3$, pos.), *m*/*z*: 184.42 $[M]^+$ (calc. 184.0372).

^{1}H NMR (300 MHz, DMSO-d_6, 296 K, COSY) δ/ppm: 9.17 (s, 3H, O*H*), 6.94 (s, 2H, *H*-2, *H*-6), 3.74 (s, 3H, CH_3^{Me}).

^{13}C NMR (75 MHz, DMSO-d_6, 296 K, HSQC, HMBC) δ/ppm: 166.4 (CO$_2$Me), 145.6 (*meta*-COH), 138.45 (CCOOMe), 119.3 (*para*-COH), 108.5 (*ortho*-CH^{Ar}), 51.65 (CH$_3^{Me}$).

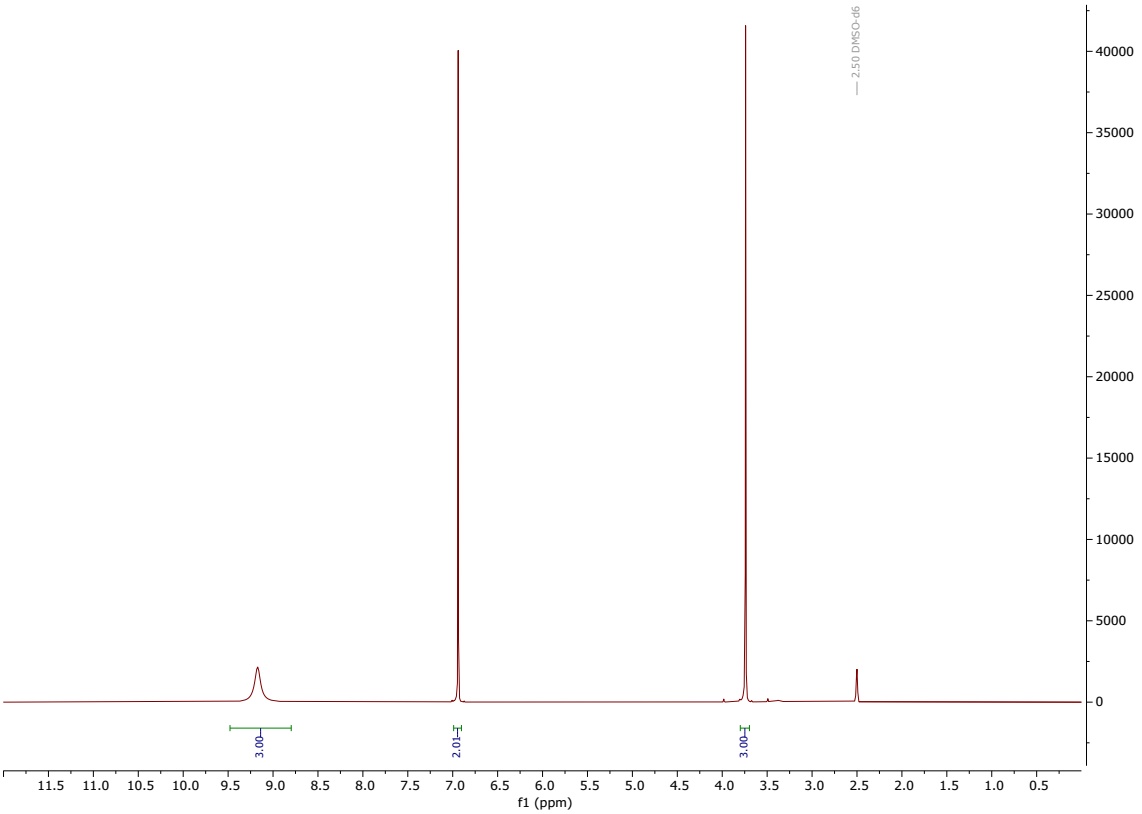


Figure S18 ^{1}H NMR spectrum of compound **PA462*GAmethylester*** in DMSO-d_6.

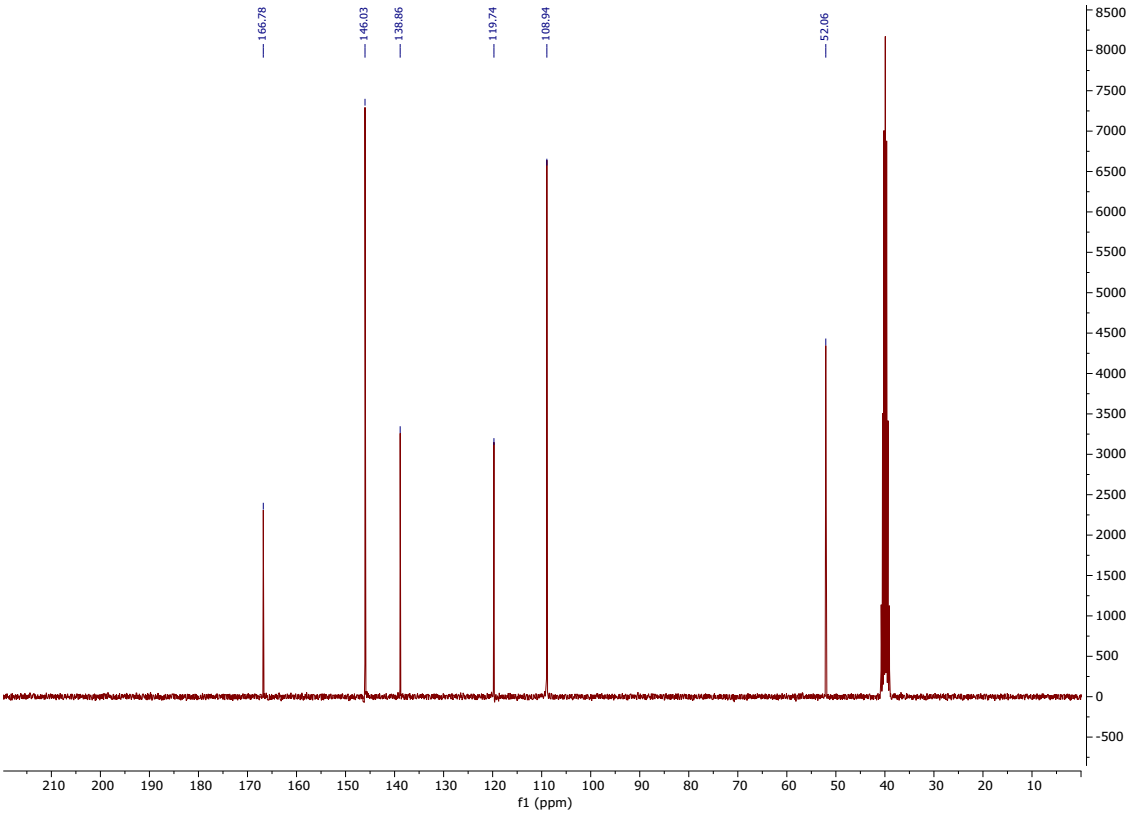
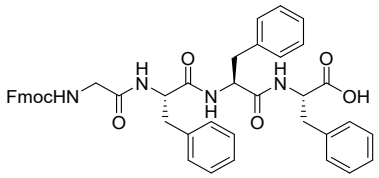


Figure S19 ^{13}C NMR spectrum of compound **PA462*GAmethylester*** in DMSO-d_6.

Compound OST055*FmocGFFF-OH*



To load the amino acid on the resin, Fmoc-Phe-OH (1.17 g, 3.02 mmol, 2.0 eq.) was dissolved in DCM (10 mL). The solution was added to 2-chlorotritylchloride resin (1.51 mmol/g loading capacity, 1.00 g, 1.51 mmol, 1.0 eq.) in a *Merrifield* reactor and DIPEA (0.53 mL, 3.02 mmol, 2.0 eq.) was added. The reaction mixture was shaken for 5 min at room temperature. Then another portion of DIPEA (0.79 mL, 4.53 mmol, 3.0 eq.) was added and shaking continued for 60 min. To cap non-functionalized sites on the resin, methanol (2 mL) was added, and the suspension was shaken for 15 min at room temperature. After the reaction the vessel was drained and washed with DCM (3x10 mL), with DMF (3x10 mL) and with DCM (3x10 mL) again. The loaded resin was used without further drying and was subjected to the solid phase peptide synthesis as described above.

After solid phase peptide synthesis, the resin was transferred to a *Merrifield* reactor to cleave the peptide from the resin. A cleavage cocktail of TFA (10 mL) in DCM (10 mL) was added and the suspension was shaken for one hour. The solution was filtered, and the cleavage procedure was

repeated three times. The solutions were combined, and the solvent removed *in vacuo* and co-distilled with toluene (5×12 mL). The residue was taken up in Milli-Q water and subjected to lyophilization to yield the peptide as colorless amorphous solid.

Yield: 0.95 g (1.28 mmol, 85 %) colorless amorphous solid.

Molecular formular: $C_{44}H_{42}N_4O_7$

Exact mass: 738.3053.

HR-TOF-MS (ESI, neg.), *m/z*: 737.2963 $[M-H]^-$ (calc.: 737.2980).

^{1}H NMR (400 MHz, DMSO-d_6, 296 K, COSY) δ/ppm: 12.78 (bs, 1H, COO*H*), 8.29 (d, 1H, J = 7.7 Hz, N*H*^{Phe}), 8.17 (d, 1H, J = 8.3 Hz, N*H*^{Phe}), 7.92 (d, 1H, J = 8.6 Hz, N*H*^{Phe}), 7.89 (d, 2H, J = 7.6 Hz, *H*-4^{Fmoc}, *H*-5^{Fmoc}), 7.70 (d, 2H, J = 7.4 Hz, *H*-1^{Fmoc}, *H*-8^{Fmoc}), 7.48 (t, 1H, J = 6.1 Hz, N*H*^{Gly}), 7.41 (t, 2H, J = 7.4 Hz, *H*-3^{Fmoc}, *H*-6^{Fmoc}), 7.31 (t, 2H, J = 7.3 Hz, *H*-2^{Fmoc}, *H*-7^{Fmoc}–7.08 (m, 15H, , 6x Phe$^{\delta}$, 6x Phe$^{\varepsilon}$, 3x Phe$^{\zeta}$), 4.63–4.40 (m, 3H, 3x Phe$^{\alpha}$), 4.29–4.03 (m, 3H, *H*-9^{Fmoc},*H*-10^{Fmoc}), 3.60 (dd, 1H, J = 16.8 Hz, J = 6.2 Hz, Gly$^{\alpha\text{-}a}$) 3.48 (dd, 1H, J = 16.8 Hz, J = 6.2 Hz, Gly$^{\alpha\text{-}b}$), 3-11–2.84 (m, 4H, 2x Phe$^{\beta}$), 2.83–2.61 (m, 2H, Phe$^{\beta}$).

^{13}C NMR (100 MHz, DMSO-d_6, 296 K, HSQC, HMBC) δ/ppm: 172.7, 171.0, 170.7 (*C*=O^{Phe}), 168.7 (*C*=O^{Gly}), 156.4 (*C*=O^{Fmoc}), 143.9 (C_q^{Fmoc}), 140.7 (C_q^{Fmoc}), 137.6, 137.4 (Phe$^{\gamma}$), 129.3, 129.2, 129.2 (Phe$^{\delta}$), 128.2, 128.1, 128.0 (Phe$^{\varepsilon}$), 127.7 (*C*-3^{Fmoc}, *C*-6^{Fmoc}), 127.1 (*C*-2^{Fmoc}, *C*-7^{Fmoc}), 126.5, 126.3 126.2 (Phe$^{\zeta}$), 125.3 (*C*-1^{Fmoc}, *C*-8^{Fmoc}), 120.1 (*C*-4^{Fmoc}, *C*-5^{Fmoc}), 65.8 (*C*-10^{Fmoc}), 53.7, 53.5 (Phe$^{\alpha}$), 46.6 (*C*-9^{Fmoc}), 43.3 (Gly$^{\alpha}$), 37.6, 37.6, 36.7 (Phe$^{\beta}$).

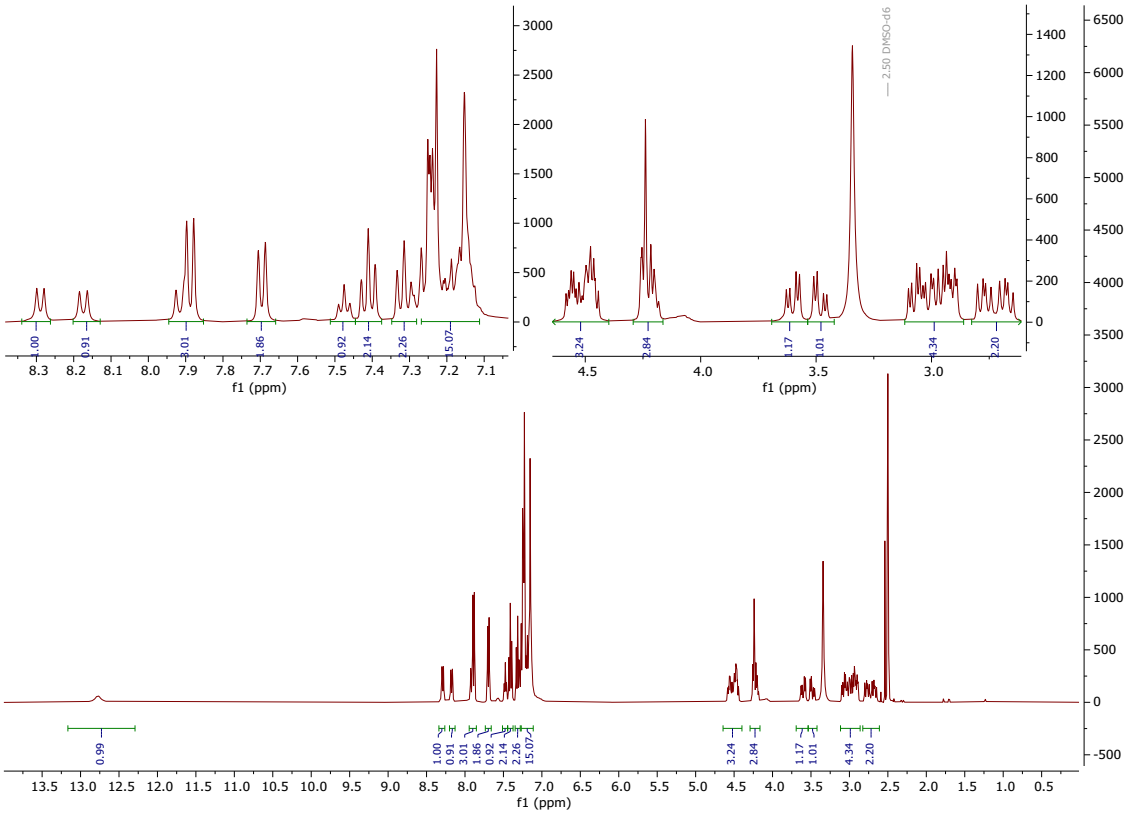


Figure S20 ^{1}H NMR spectrum of compound **OST055*FmocGFFF*** in DMSO-d_6.

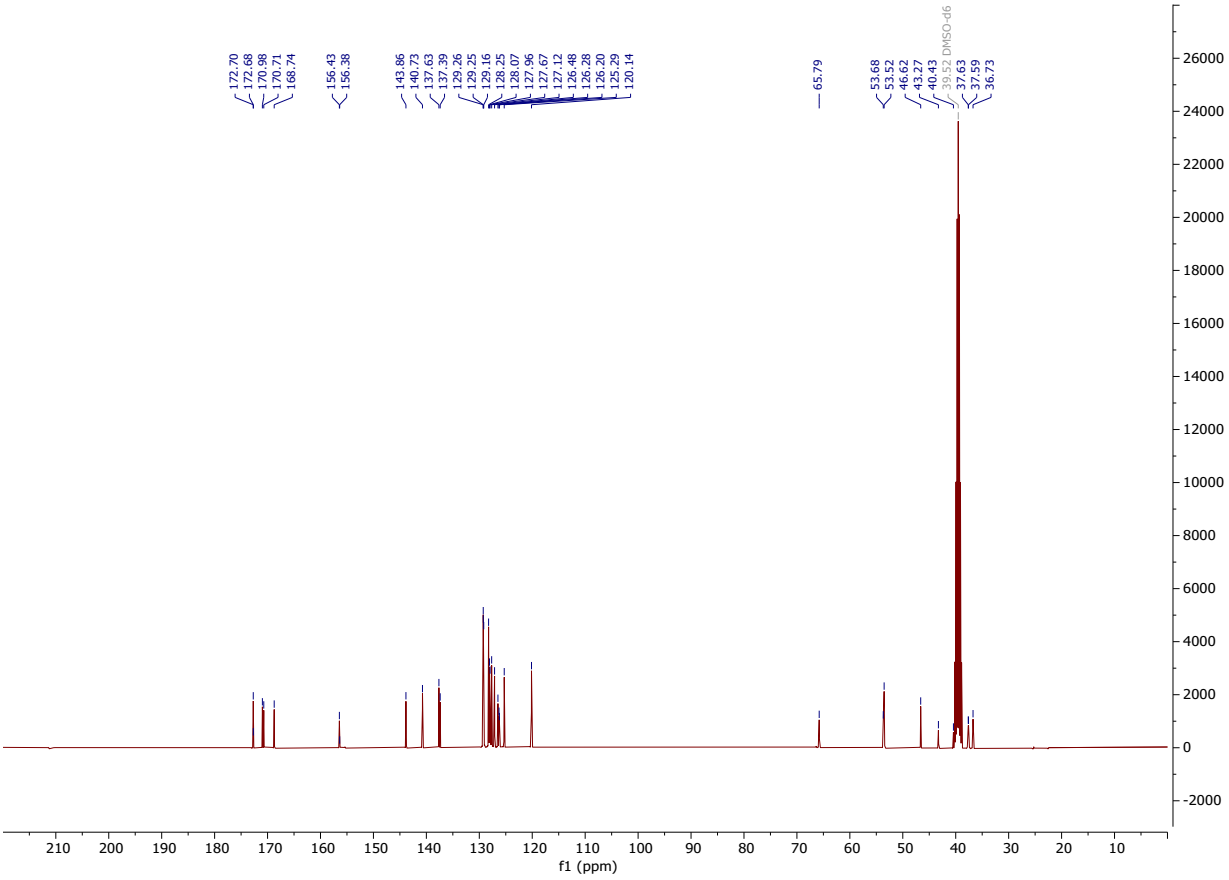


Figure S21 ^{13}C NMR spectrum of compound **OST055*FmocGFFF*** in DMSO-d_6.

Characterization of self-assembled PHDC

Circular Dichroism (CD) Spectroscopy

The PHDC was dissolved in 10 mM phosphate buffer (PB) solution (pH 7.4) to make a 50 µM solution. The solution was kept at rt or 37 °C with or without stirring. CD spectroscopy was performed on a J-815 spectrometer (JASCO, Easton, MD). All samples were baseline corrected and measured using 110-QS (Thermo Fisher Scientific, Pittsburgh, PA) quartz glass cuvettes with a path length of 1 mm or 10 mm at varying temperatures, controlled by a PTC-423S/15 Peltier element. For prevention of noise increase, all concentrations were adjusted to keep the photomultiplier's high voltage (HV) value below 600 V at the respective wavelength area of interest (λ > 190 nm). Each sample was measured at least three times and averaged to minimize further errors.

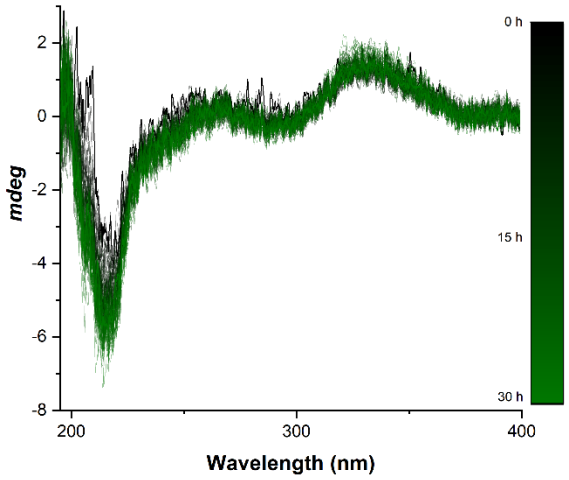


Figure S22 Full CD spectroscopic investigation of PHDC self-assembly process at rt without stirring. The concentration of PHDC was 50 μM in 10 mM PB (pH 7.4). Spectra were collected every 15 min over 30 h.

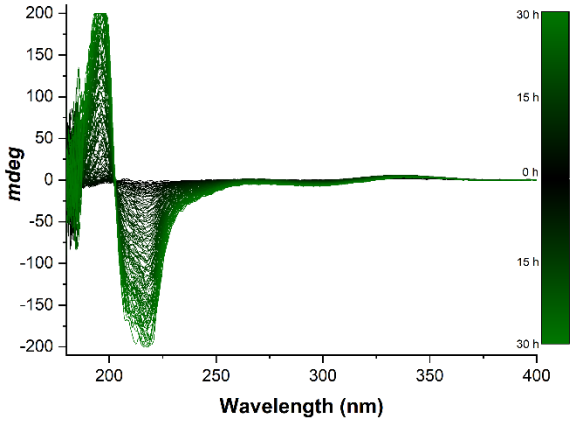


Figure S23 Full CD spectroscopic investigation of PHDC self-assembly process at 37 ℃ with stirring. The concentration of PHDC was 50 μM in 10 mM PB (pH 7.4). Spectra were collected every 15 min over 30 h.

Conventional Transmission Electron Microscopy (TEM)

The PHDC was dissolved in 10 mM PB solution (pH 7.4) to make a 50 μM solution. The solution was kept at rt without stirring or 37 ℃ with gentle stirring. At different time points, using a micropipette, 10 μL of the solution was deposited onto a carbon-coated copper grid (CF300-Cu-50, Electron Microscopy Services, Hatfield, PA, USA) and allowed to stand for 5 min. The excess solution was wicked away by a small piece of filter paper, and then DI water was deposited onto the grid, allowed to stand for 40 sec, and then wicked away to wash away excess salts. Finally, 10 μL of a 2 wt% aqueous uranyl acetate (UA) solution was deposited onto the grid and allowed to stand for 5 min. A thin layer was generated after carefully wicking away excess UA. The sample grid was then allowed to dry at rt prior to imaging. Bright-field TEM imaging was performed on

a Philips EM420 TEM operated at an acceleration voltage of 100 kV. TEM images were recorded by a slow scan CCD camera.

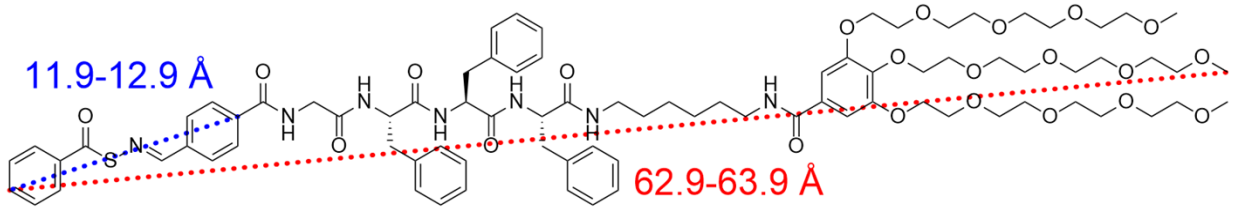


Figure S24 Calculated length of extended SATO group and PHDC by the 3D function of ChemDraw.

Figure S25 TEM image of PHDC self-assembled at 37 ℃ with stirring for 30 h. The concentration of PHDC was 50 μM in 10 mM PB (pH 7.4).

H_2S Release Determined by Methylene Blue Assay

Reactions for H_2S release determination were run in triplicate, with each reaction vial containing 0.93 mL of PHDC solution (268 μM in 10 mM PB, pH 7.4 with 10.75% DMSO, self-assembled at 37 ℃ with gentle stirring for 72 h), 20 μL of $Zn(OAc)_2$ solution (40 mM in H_2O), and 50 μL of Cys solution (50 mM in H_2O), making up to 1 mL total volume. The final concentration of the solution was 250 μM PHDC, 0.8 mM $Zn(OAc)_2$, and 2.5 mM Cys. A blank vial was run for each experiment using 10 mM PB solution instead of the PHDC solution. At predetermined time points, 100 μL aliquots were taken from each vial and diluted with 100 μL of $FeCl_3$ solution (30 mM in 1.2 M HCl) and 100 μL of *N,N*-dimethyl *p*-phenylenediamine dihydrochloride solution (20 mM in 7.2 M HCl). Each aliquot solution remained sealed in a microcentrifuge tube for a minimum of 2 h prior to the addition of 250 μL to a 96-well plate. The absorbance for each aliquot was measured at 750 nm and corrected by subtracting the absorbance for the blank samples at all time points. A calibration curve was prepared to determine the H_2S concentration by corrected absorbance. A series of Na_2S solutions were prepared in a glovebox with calculated concentrations as standards. Those standard solutions were also diluted similarly to each time point and measured by a plate

reader (BioTek, Winooski, VT). The corrected data were used to construct a linear calibration curve of concentration vs. absorbance.

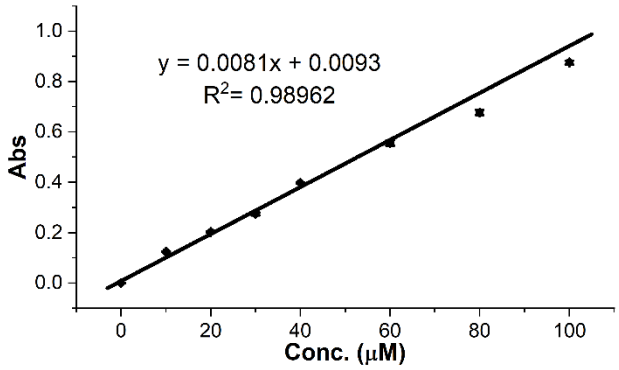


Figure S26 Calibration curve of methylene blue assay.

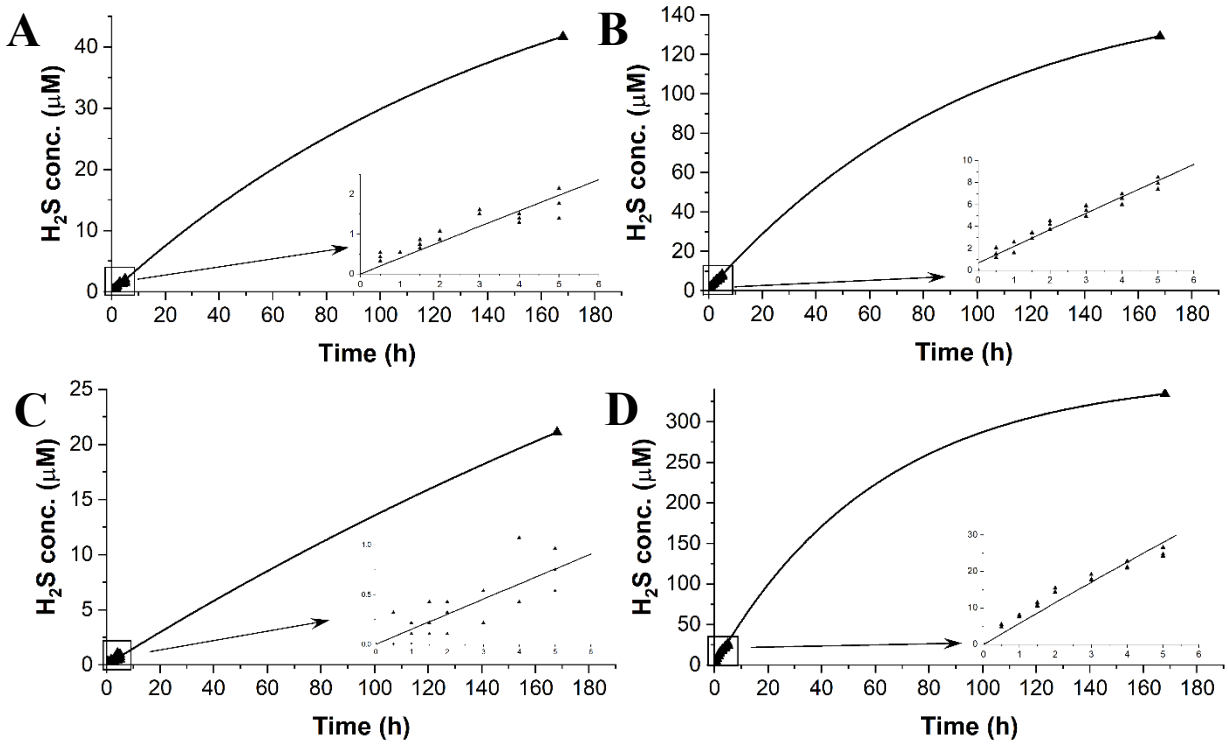


Figure S27 H_2S release kinetics of PHDCs triggered by (A) H-Cys-OH, (B) Ac-Cys-OMe, (C) Ac-Cys-OH, and (D) H-Cys-OMe.

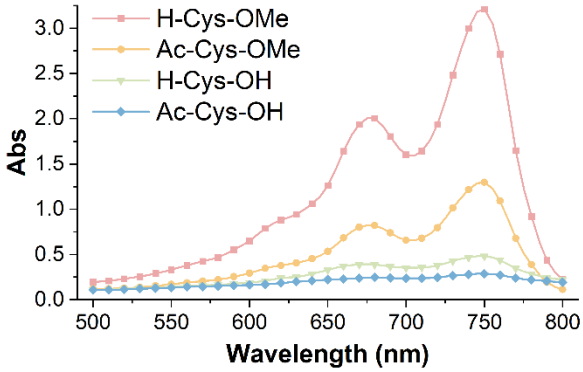


Figure S28. Methylene blue spectra at 7 d for PHDCs triggered by Cys derivatives.

H_2S Release Determined by Circular Dichroism

PHDC was dissolved in DMSO to yield a concentration of 3.3 mM and diluted with (PB) (10 mM, pH 7.4) at 37 °C to yield a solution at a concentration of 0.25 mM in PB with 7.7%vt DMSO. The solution was stirred at 37 °C for 72 h. After the pre-equilibration, 341.25 µL of sample solution was added into a 1 mm glass cuvette, along with 8.75 µL of a 100 mM solution of the Cys-derivative in DMSO to yield 350 µL of a 250 µM sample solution with 2.5 mM of Cys-derivative in PB with 10%vt DMSO. Then the measurement started immediately. The CD-signal was monitored at 337 nm with a data pitch of 10 sec at 20 °C on a J-815 CD-Spectrometer by Jasco (Pfungstadt, Germany).

Zeta Potential Measurements of Nanofibers

PHDC was dissolved in DMSO to yield a concentration of 3.3 mM and diluted with (PB) (10 mM, pH 7.4) at 37 °C to yield a solution at a concentration of 0.25 mM in PB with 7.7%vt DMSO. The solution was stirred at 37 °C for 72 h. After the pre-equilibration, 1 mL of sample solution was transferred into a capillary cuvette (Malvern DTS1070). Zeta-potential measurements were performed in a Malvern Zetasizer Nano ZS apparatus (Malvern, UK) at 25 °C with a position 2 mm, reference count rate 2072.3 Kcounts, Set attenuator 11, count rate 13.25 kcps. The results were shown in Table S2.

Table S2 Zeta potential measurements of nanofibers.

T (°C)	*ZP* (mV)	*Mob* ($m^2/Vs \times 10^{-8}$)	*Cond* (mS/cm)
25	-15.3	-1.203	1.45
25	-16.8	-1.321	1.57
25	-18.9	-1.486	1.65

Charge Calculation for Cys derivatives

To estimate the charge of the Cys derivative functional groups at pH 7.4 the general expressions for fraction of charge (1) and (2) derived from Henderson-Hasselbalch equation were used.

$$Q^- = \frac{-1}{1 + 10^{pK_a - pH}} \quad (1)$$

$$Q^+ = \frac{1}{1 + 10^{pH - pK_a}} \quad (2)$$

The sum over all charges at a specific pH yield the general expression of net charge (3) [5]:

$$Q_{net} = \sum Q^- + \sum Q^+$$
$$Q_{net} = \frac{-1}{1 + 10^{pK_a(COOH) - pH}} + \frac{-1}{1 + 10^{pK_a(SH) - pH}} + \frac{1}{1 + 10^{pH - pK_a(NH_3^+)}} \quad (3)$$

For the calculation of the net charge according to equation 3 the individual literature pK_a values for H-Cys-OH [6], Ac-Cys-OH [7], H-Cys-OMe [8] and Ac-Cys-OMe [9] were used. The value was shown in Table S3.

Table S3 Calculated net charge of Cys derivatives.[a]

Cys Derivatives	Net Charge Q_{net}
Ac-Cys-OH	-1.01
H-Cys-OH	-0.14
Ac-Cys-OMe	-0.02
H-Cys-OMe	+0.37

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9. Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2024 ACD/Labs).