Electronic Supporting Information (ESI) for:

Pseudopeptidic Compounds for the Generation of Dynamic Combinatorial Libraries of Chemically Diverse Macrocycles in Aqueous Media

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General methods

Reagents and solvents were purchased from commercial suppliers (Aldrich, Fluka, Merck or Iris Biotech) and were used without further purification. Chromatographic purifications were performed on Biotage® Isolera Prime™ equipment using Biotage® SNAP KP-Sil and Biotage® SNAP KP-C18-HS cartridges for normal- and reversed-phase purifications respectively. TLCs were performed using 6 x 3 cm SiO₂ pre-coated aluminium plates (ALUGRAM® SIL G/UV₂₅₄).

RP-HPLC analyses were performed on a Hewlett Packard Series 1100 (UV detector 1315A) modular system using a reversed-phase X-Terra C₁₈ (15 x 0.46 cm, 5 µm) column. (MeCN + 0.07% (v/v) TFA and H₂O + 0.1% (v/v) TFA) mixtures at 1 mL/min were used as mobile phase and the monitoring wavelengths were set at 220 and 254 nm. The temperature of the column was set at 25 °C. The HPLC samples were prepared by dilution with an acidic solution of 89% H₂O, 10% MeCN and 1% TFA. For the analysis of the DCLs a reversed-phase kromaphase C₁₈ (25 x 0.46 cm, 5µm) column was used, (MeCN + 20 mM HCOOH and H₂O + 20 mM HCOOH) mixtures at 1 mL/min were used as mobile phase and the monitoring wavelength was set at 254 nm.

Nuclear Magnetic Resonance (NMR) spectroscopic experiments were carried out on a Varian INOVA 500 spectrometer (500 MHz for ¹H and 126 MHz for ¹³C), a Varian Mercury 400 instrument (400 MHz for ¹H and 101 MHz for ¹³C) and a Varian Unity 300 (300 MHz for ¹H and 75 MHz for ¹³C). The chemical shifts (δ) are reported in ppm relative to trimethylsilane (TMS), and coupling constants (J) are reported in Hertz (Hz). Signal assignment was carried out using the necessary 2D NMR spectra including ¹H-¹H gCOSY, ¹H-¹³C gHSQC and ¹H-¹³C gHMBC. For describing signals of ¹H NMR spectra de following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, ABq = AB quartet, quint = quintet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, dq = doublet of quartets, qd = quartet of doublets, ddd = double doublet of doublets, ddt = double doublet of triplets, m = multiplet, and br = broad signal.

HRMS analyses were carried out at the IQAC Mass Spectrometry Facility, using UPLC-ESI-TOF equipment: [Acquity UPLC® BEH C₁₈ 1.7 mm, 2.1x100 mm, LCT Premier Xe, Waters]. (MeCN + 20 mM HCOOH and H₂O + 20 mM HCOOH) mixtures at 0.3 mL/min were used as mobile phase. The characterization of the pure products and intermediates was performed in flow injection analysis (FIA) mode.

S3
Synthesis of the building blocks

Synthesis of tritylsulfanyl acetic acid

This compound was prepared as previously described.1 To a solution of mercaptoacetic acid (4.60 g, 49.9 mmol) and triphenylmethanol (13.0 g, 49.9 mmol) in chloroform (50 mL), trifluoroacetic acid (TFA, 5.0 mL, 65 mmol) was added. After the mixture was stirred at room temperature for 2 hours, volatiles were removed in vacuum. The crude product was recrystallized from dichloromethane/hexane to give 13.9 g of tritylsulfanyl acetic acid (83% yield) as a white solid. Rf of the product in AcOEt/Hexane, 3:7, (v/v): 0.39. 1H NMR (500 MHz, CDCl3): δ = 7.42 (d, J = 7.3 Hz, 6H, CHAr), 7.30 (t, J = 7.6 Hz, 6H, CHAr), 7.23 (t, J = 7.3 Hz, 3H, CHAr), 3.03 (s, 2H, CH2). 13C NMR (75 MHz, CDCl3): δ = 174.7 (1 x CO), 144.0 (3 x CAr), 129.6 (6 x CHAr), 128.3 (6 x CHAr), 127.2 (3 x CHAr), 67.4 (1 x C), 34.5 (1 x CH2). HRMS (ESI–) calcd. for C21H18O2S [2M–H]– (m/z): 667.1982, found: 667.1996.

Synthesis of intermediates 1a-j and 1l

Synthesis of 1a: to a solution of Fmoc-L-Asn(Trt)-OH (4.24 g, 7.11 mmol) in dry DMF (15 mL), HOBt (1.25 g, 9.27 mmol) and DCCD (2.23 g, 10.8 mmol) were added under inert atmosphere of Ar. The resulting mixture was cooled down to 0 °C in an ice-water bath. Then, a solution of m-phenylenediamine (334 mg, 3.09 mmol) in dry DMF (10 mL) was added via cannula under inert atmosphere of Ar. The mixture was stirred at room temperature for 60 hours, after which complete conversion of the starting material was observed by TLC (Rf of 1a in AcOEt/hexane, 1:1 (v/v): 0.58). The mixture was filtered, and the filtrate was diluted with DCM, washed with saturated aqueous NaHCO3 and saturated aqueous NaCl, dried over MgSO4 and concentrated under reduced pressure. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 30% to 50% AcOEt) to give 2.05 g of 1a (52% yield) as a white solid. HRMS (ESI+) calcd. for C82H68N6O8 [M+H]+ (m/z): 1265.5171, found: 1265.5183. 1H NMR (400 MHz, CDCl3): δ = 8.77 (br s, 2H, NHCOC*H), 7.81–7.66 (m, 5H, CHAr), 7.61–7.51 (m, 4H, CHAr), 7.38 (t, J = 7.5 Hz, 4H, CHAr), 7.32–7.04 (m, 37H, CHAr), 6.97 (s, 2H, CONHTrt), 6.54 (br s, 2H, NHFmoc), 4.68 (br s, 2H, C*H), 4.51–4.32 (m, 4H, COOCH2), 4.20 (t, J = 7.0 Hz, 2H, CH), 3.16 (d, J = 15.7 Hz, 2H, CH2C*H), 2.66 (dd, J = 15.7, 6.9 Hz, 2H, CH2C*H). 13C NMR (101 MHz, CDCl3): δ = 170.8 (2 x CO), 169.0 (2 x CO), 156.4 (2 x

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**Synthesis of 1b:** this compound was obtained as described above for 1a, starting from Fmoc-L-Gln(Trt)-OH. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 25% to 40% AcOEt, Rf of 1b in AcOEt/hexane, 3:2 (v/v): 0.50) to give 1.12 g of 1b (47% yield) as a white solid.

HRMS (ESI+) calcd. for C₈₄H₇₂N₆O₈ [M+H]^+ (m/z): 1293.5484, found: 1293.5472. ¹H NMR (500 MHz, CDCl₃): δ = 8.84 (s, 2H, NHCOCH₃), 7.89 (s, 1H, CH₃Ar), 7.75 (d, J = 7.1 Hz, 4H, CH₂Ar), 7.61–7.52 (m, 4H, CH₂Ar), 7.38 (t, J = 7.1 Hz, 4H, CH₂Ar), 7.31–7.18 (m, 34H, CH₂Ar), 7.10 (t, J = 8.0 Hz, 1H, CH₃Ar), 7.03 (s, 2H, NH-Fmoc), 4.43–4.30 (m, 4H, COOCH₂₂), 4.20 (t, J = 7.1 Hz, 2H, CH₂), 4.17–4.08 (m, 2H, CH₂), 2.67–2.55 (m, 2H, CH₂CO), 2.50–2.38 (m, 2H, CH₂CO), 2.19–2.08 (m, 2H, CH₂), 2.03–1.89 (m, 2H, CH₂).

**Synthesis of 1c:** this compound was obtained as described above for 1a, starting from Fmoc-L-Ser(tBu)-OH. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 25% to 40% AcOEt, Rf of 1c in AcOEt/hexane, 3:2 (v/v): 0.83) to give 1.05 g of 1c (45% yield) as a white solid.

HRMS (ESI+) calcd. for C₅₀H₅₄N₄O₈ [M+H]^+ (m/z): 839.4014, found: 839.4029. ¹H NMR (400 MHz, CDCl₃): δ = 8.80 (br s, 2H, NHCOCH₃), 7.96 (s, 1H, CH₃Ar), 7.77 (d, J = 7.6 Hz, 4H, CH₂Ar), 7.62 (d, J = 7.1 Hz, 4H, CH₂Ar), 7.41 (t, J = 7.4 Hz, 4H, CH₂Ar), 7.32 (t, J = 7.8 Hz, 4H, CH₂Ar), 7.29–7.20 (m, 3H, CH₂Ar), 5.87 (br s, 2H, C*HNCO), 4.44 (d, J = 7.0 Hz, 4H, COOCH₂₂), 4.35 (br s, 2H, C*H), 4.25 (t, J = 6.9 Hz, 2H, CH₂), 3.92 (br s, 2H, C*HC₃H₃₂), 3.45 (t, J = 8.7 Hz, 2H, C*HC₃H₃₂), 1.28 (s, 18H, CH₃). ¹³C NMR (101 MHz, CDCl₃): δ = 168.5 (2 x CO), 156.2 (2 x CO), 143.9 (4 x CH₃), 141.4 (4 x CH₃), 138.4 (2 x CH₃), 129.9 (1 x CH₃), 127.9 (4 x CH₂), 127.2 (4 x CH₂), 125.2 (4 x CH₂), 120.2 (4 x CH₂), 115.5 (2 x CH₂), 111.0 (1 x CH₂), 75.1 (2 x CH₂), 67.3 (2 x COOCH₂₂), 61.9 (2 x C*HC₃H₃₂), 54.8 (2 x C*H), 47.3 (2 x CH₂), 34.0 (2 x C*HC₃H₃₂), 30.4 (2 x C*HC₃H₃₂).
Supporting Information

Synthesis of 1d: this compound was obtained as described above for 1a, starting from Fmoc-L-Thr(tBu)-OH. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 25% to 40% AcOEt, Rf of 1d in AcOEt/hexane, 3:7 (v/v): 0.46) to give 1.61 g of 1d (67% yield) as a white solid. HRMS (ESI–) calcd. for C_{52}H_{58}N_{4}O_{8} [M+HCOO]– (m/z): 911.4237, found: 911.4254. 1H NMR (400 MHz, CDCl₃): δ = 9.24 (s, 2H, NHCOCH), 7.92 (s, 1H, CH₆), 7.78 (d, J = 7.5 Hz, 4H, CH₂Ar), 7.63 (d, J = 7.5 Hz, 4H, CH₂Ar), 7.41 (t, J = 7.5 Hz, 4H, CH₂Ar), 7.37–7.19 (m, 7H, CH₂Ar), 6.12 (d, J = 4.9 Hz, 2H, C*HNCO), 4.49–4.21 (m, 10H, 4H x CH₂ + 2H x CH + 2H x C*NH₂ + 2H x C*H₂), 1.38 (s, 18H, C(CH₃)₃), 1.10 (d, J = 6.3 Hz, 6H, C*HC₆H₃).

13C NMR (101 MHz, CDCl₃): δ = 167.6 (2 x CO), 156.2 (2 x CO), 143.8 (4 x CAr), 141.4 (4 x CAr), 138.4 (2 x CAr), 129.8 (1 x CHAr), 127.9 (4 x CHAr), 127.2 (4 x CHAr), 125.3 (4 x CHAr), 120.2 (4 x CHAr), 115.3 (2 x CHAr), 110.9 (1 x CHAr), 76.3 (2 x C), 67.2 (2 x CH₂), 67.1 (2 x C*HCH₃), 59.1 (2 x C*NH), 47.3 (2 x CH), 28.3 (6 x C(CH₃)₃), 16.9 (2 x C*HCH₃).

Synthesis of 1e: this compound was obtained as described above for 1a, starting from Fmoc-L-Tyr(tBu)-OH. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 25% to 40% AcOEt, Rf of 1e in AcOEt/hexane, 2:3 (v/v): 0.46) to give 1.46 g of 1e (53% yield) as a white solid. HRMS (ESI+) calcd. for C_{62}H_{62}N_{4}O_{8} [M+H]⁺ (m/z): 991.4640, found: 991.4622. 1H NMR (500 MHz, CDCl₃): δ = 7.91 (br s, 2H, NHCOCH), 7.74 (d, J = 7.6 Hz, 4H, CH₂Ar), 7.60–7.48 (m, 5H, CH₂Ar), 7.37 (t, J = 7.5 Hz, 4H, CH₂Ar), 7.31–7.22 (m, 4H, CH₂Ar), 7.14–6.99 (m, 7H, CH₂Ar), 6.86 (d, J = 8.4 Hz, 4H, CH₂Ar), 5.57 (br s, 2H, C*NHCOH), 4.50 (br s, 2H, C*H), 4.44–4.25 (m, 4H, COOCH₂), 4.19 (t, J = 6.9 Hz, 2H, CH), 3.14–2.93 (m, 4H, C*HCH₂), 1.26 (s, 18H, CH₃). 13C NMR (101 MHz, CDCl₃): δ = 169.5 (2 x CO), 156.5 (2 x CO), 154.6 (2 x CAr), 143.7 (4 x CAr), 141.4 (4 x CAr), 137.8 (2 x CAr), 131.1 (2 x CAr), 129.9 (4 x CH₂Ar), 129.5 (1 x CHAr), 127.9 (4 x CH₂Ar), 127.3 (4 x CH₂Ar), 125.2 (4 x CH₂Ar), 124.6 (4 x CH₂Ar), 120.1 (4 x CH₂Ar), 116.1 (2 x CH₂Ar), 111.7 (1 x CH₂Ar), 78.7 (2 x C), 67.4 (2 x COOCH₂), 57.3 (2 x C*H), 47.2 (2 x CH), 38.0 (2 x C*HCH₂), 28.9 (6 x C(CH₃)₃).

Synthesis of 1f: this compound was obtained as described above for 1a, starting from Fmoc-L-Trp(Boc)-OH. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 30% to 35% AcOEt, Rf of 1f in AcOEt/hexane, 2:3 (v/v): 0.59) to give 1.33 g of 1f (43% yield) as a white solid. HRMS (ESI–) calcd. for C_{68}H_{64}N_{6}O_{10} [M+HCOO]– (m/z): 1169.4666, found:1169.5189. 1H NMR (500 MHz, CDCl₃): δ = 8.23 (br s, 2H, NHCOCH), 8.08 (br s, 2H, CH₂Ar), 7.71 (d, J = 7.6 Hz, 4H, CH₂Ar), 7.62–7.40 (m, 9H, CH₂Ar), 7.16–7.03 (m, 9H, CH₂Ar), 6.87 (d, J = 8.4 Hz, 4H, CH₂Ar), 5.60 (br s, 2H, C*NHCOH), 4.50 (br s, 2H, C*H), 4.44–4.25 (m, 4H, COOCH₂), 4.19 (t, J = 6.9 Hz, 2H, CH), 3.14–2.93 (m, 4H, C*HCH₂), 1.26 (s, 18H, CH₃).
7.34 (t, J = 7.5 Hz, 4H, CH\textsubscript{Ar}), 7.29–6.98 (m, 11H, CH\textsubscript{Ar}), 5.72 (br s, 2H, C*HNH\textsubscript{CO}), 4.67 (br s, 2H, C*H), 4.33 (br s, 4H, COOCH\textsubscript{2}), 4.18–4.10 (m, 2H, COOCH\textsubscript{2}CH\textsubscript{3}), 3.30–3.06 (m, 4H, C*HCH\textsubscript{2}), 1.56 (s, 18H, CH\textsubscript{3}). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): δ = 169.7 (2 x CO), 156.6 (2 x CO), 149.6 (2 x CO), 143.7 (4 x C\textsubscript{Ar}), 141.4 (4 x C\textsubscript{Ar}), 137.8 (2 x C\textsubscript{Ar}), 135.6 (2 x C\textsubscript{Ar}), 130.2 (2 x C\textsubscript{Ar}), 129.4 (1 x C\textsubscript{Ar}), 127.8 (4 x CH\textsubscript{Ar}), 127.2 (4 x CH\textsubscript{Ar}), 125.2 (4 x CH\textsubscript{Ar}), 124.8 (2 x CH\textsubscript{Ar}), 124.6 (2 x CH\textsubscript{Ar}), 122.9 (2 x CH\textsubscript{Ar}), 120.1 (4 x CH\textsubscript{Ar}), 119.1 (2 x CH\textsubscript{Ar}), 116.3 (2 x CH\textsubscript{Ar}), 115.5 (2 x CH\textsubscript{Ar}), 115.3 (2 x C\textsubscript{Ar}), 112.0 (1 x CH\textsubscript{Ar}), 83.9 (2 x C), 67.5 (2 x COOCH\textsubscript{2}), 55.8 (2 x C*H), 47.1 (2 x CH), 28.2 (6 x CH\textsubscript{3}), 28.1 (2 x C*HCH\textsubscript{2}).

**Synthesis of 1g:** this compound was obtained as described above for 1a, starting from Fmoc-L-Asp('Bu)-OH. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 25% to 40% AcOEt, Rf of 1g in AcOEt/hexane, 2:3 (v/v): 0.34) to give 978 mg of 1g (42% yield) as a white solid. HRMS (ESI+) calcd. for C\textsubscript{52}H\textsubscript{54}N\textsubscript{3}O\textsubscript{10} [M+Na]\textsuperscript{+} (m/z): 917.3732, found: 917.3764. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ = 8.57 (s, 2H, NHCO*C*H), 7.80 (s, 1H, CH\textsubscript{Ar}), 7.76 (d, J = 7.4 Hz, 4H, CH\textsubscript{Ar}), 7.59 (d, J = 6.3 Hz, 4H, CH\textsubscript{Ar}), 7.39 (t, J = 7.3 Hz, 4H, CH\textsubscript{Ar}), 7.34 – 7.20 (m, 7H, CH\textsubscript{Ar}), 6.11 (d, J = 7.4 Hz, 2H, C*HNH\textsubscript{CO}), 4.66 (br s, 2H, C*H), 4.45 (d, J = 6.4 Hz, 4H, COOCH\textsubscript{2}), 4.23 (t, J = 6.9 Hz, 2H, CH), 2.96 (d, J = 16.0 Hz, 2H, C*HCH\textsubscript{2}), 2.69 (dd, J = 17.0, 6.7 Hz, 2H, C*HCH\textsubscript{2}), 1.45 (s, 18H, CH\textsubscript{3}). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): δ = 171.5 (2 x CO), 168.7 (2 x CO), 156.4 (2 x CO), 143.8 (4 x C\textsubscript{Ar}), 141.5 (4 x C\textsubscript{Ar}), 138.2 (2 x C\textsubscript{Ar}), 129.7 (1 x CH\textsubscript{Ar}), 128.0 (4 x CH\textsubscript{Ar}), 127.3 (4 x CH\textsubscript{Ar}), 125.2 (4 x CH\textsubscript{Ar}), 120.2 (4 x CH\textsubscript{Ar}), 116.1 (2 x CH\textsubscript{Ar}), 111.5 (1 x CH\textsubscript{Ar}), 82.5 (2 x C), 67.5 (2 x COOCH\textsubscript{2}), 51.9 (2 x C*H), 47.3 (2 x CH), 37.5 (2 x C*HCH\textsubscript{2}), 28.2 (6 x CH\textsubscript{3}).

**Synthesis of 1h:** this compound was obtained as described above for 1a, starting from Fmoc-L-Glu('Bu)-OH. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 30% to 40% AcOEt, Rf of 1h in AcOEt/hexane, 2:3 (v/v): 0.43) to give 1.79 g of 1h (70% yield) as a white solid. HRMS (ESI+) calcd. for C\textsubscript{54}H\textsubscript{58}N\textsubscript{4}O\textsubscript{10} [M+H]\textsuperscript{+} (m/z): 923.4226, found: 923.4225. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ = 8.62 (s, 2H, NHCO*C*H), 7.84 (s, 1H, CH\textsubscript{Ar}), 7.75 (d, J = 7.5 Hz, 4H, CH\textsubscript{Ar}), 7.59 (t, J = 6.8 Hz, 4H, CH\textsubscript{Ar}), 7.38 (t, J = 7.4 Hz, 4H, CH\textsubscript{Ar}), 7.33–7.16 (m, 7H, CH\textsubscript{Ar}), 5.94 (d, J = 7.1 Hz, 2H, C*HNH\textsubscript{CO}), 4.38–4.28 (m, 6H, 4H x COOCH\textsubscript{2} + 2H x C*H), 4.21 (t, J = 7.0 Hz, 2H, CH), 2.59 – 2.46 (m, 2H, C*HCH\textsubscript{2}CH\textsubscript{3}), 2.43–2.30 (m, 2H, C*HCH\textsubscript{2}CH\textsubscript{2}), 2.22–2.09 (m, 2H, C*HCH\textsubscript{2}), 2.04–1.93 (m, 2H, C*HCH\textsubscript{2}), 1.46 (s, 18H, CH\textsubscript{3}). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): δ = 173.4 (2 x CO), 169.7 (2 x CO), 156.7 (2 x CO), 143.8 (4 x C\textsubscript{Ar}), 141.4 (4 x C\textsubscript{Ar}), 138.2 (2 x C\textsubscript{Ar}), 129.6 (1 x CH\textsubscript{Ar}), 127.9 (4 x CH\textsubscript{Ar}), 127.2
Synthesis of 1i: To a solution of Boc-L-Lys(Cbz)-OH (2.30 g, 6.05 mmol) in dry DMF (15 mL), HBTU (2.55 g, 6.74 mmol) and DIPEA (2.3 mL, 13 mmol) were added. The resulting mixture was cooled down to 0 °C in an ice-water bath. Then, a solution of m-phenylenediamine (302 mg, 2.79 mmol) in dry DMF (10 mL) was added via cannula under inert atmosphere of Ar. The mixture was stirred at room temperature for 60 hours, after which complete conversion of the starting material was observed by TLC (Rf of 1i in AcOEt/hexane, 3:2 (v/v): 0.41). The mixture was diluted with DCM, washed with saturated aqueous NaHCO₃ and saturated aqueous NaCl, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 40% to 50% AcOEt) to give 1.77 g of 1i (56% yield) as a white solid. HRMS (ESI+) calcd. for C₄₄H₆₀N₆O₁₀ [M+H]+ (m/z): 833.4444, found: 833.4453.

1H NMR (400 MHz, CDCl₃): δ = 8.95 (br s, 2H, NHCO(O)b), 7.73 (br s, 1H, CHAr), 7.55–7.16 (m, 12H, CHAr), 7.16–6.97 (m, 1H, CHAr), 5.72 (br s, 2H, C=Nb), 5.33–4.84 (m, 6H, 4H x NHCOOCH₂ + 2H x NHCOCbz), 4.24 (br s, 2H, C*H), 3.16 (br s, 4H, C₂H₂NHCbz), 2.00–1.59 (m, 4H, C*HC₂H₂), 1.58–1.18 (m, 26H, 4H x C₂H₂CH₂Cbz + 4H x C*HCH₂C₂H₂ + 18H x CH₃). 13C NMR (101 MHz, CDCl₃): δ = 171.5 (2 x CO), 156.8 (2 x CO), 156.4 (2 x CO), 138.5 (2 x CHAr), 136.7 (2 x CHAr), 129.5 (1 x CHAr), 128.6 (4 x CHAr), 128.2 (6 x CHAr), 115.7 (2 x CHAr), 111.3 (1 x CHAr), 80.4 (2 x C), 66.8 (2 x NHCOOCH₂), 55.4 (2 x CH₃), 40.7 (2 x CH₂NHCbz), 32.2 (2 x C*HCH₂), 29.5 (2 x CH₂CH₂NHCbz), 28.5 (6 x CH₃), 22.9 (2 x C*HCH₂CH₂).

Synthesis 1j: This compound was synthesized following the procedure described for 1i starting from Boc-L-Orn(Alloc)-OH. The crude product was purified by flash chromatography using AcOEt/hexane as eluent (from 45% to 55% AcOEt, Rf of 1j in AcOEt/hexane, 2:3 (v/v): 0.23) to give 1.43 g of 1j (85% yield) as a white solid. HRMS (ESI+) calcd. for C₃₄H₅₂N₆O₁₀ [M+H]+ (m/z): 705.3818, found: 705.3813. 1H NMR (400 MHz, CDCl₃): δ = 8.92 (br s, 2H, NHOC*H), 7.77 (br s, 1H, CHAr), 7.36–6.97 (m, 3H, CHAr), 5.89 (ddt, J = 17.2, 10.8, 5.6 Hz, 2H, NHCOOCH₂CHCH₂), 5.66 (br s, 2H, C*HNCb), 5.28 (dq, J = 17.2, 1.6 Hz, 2H, NHCOOCH₂CHCH₂), 5.22–5.07 (m, 4H, 2H x NHCOOCH₂CHCH₂ + 2H x NHAlloc), 4.58 (d, J = 5.5 Hz, 4H, NHCOOCH₂CHCH₂), 4.43 (br s, 2H, C*H), 3.40 (br s, 2H, CH₃NHAlloc), 3.24–3.02 (m, 2H, CH₂NHAlloc), 1.96–1.77 (m, 2H, C*HCH₂), 1.76–1.54 (m, 6H, 2H x C*HCH₂ + 4H x C*HCH₂CH₂), 1.43 (s, 18H, CH₃). 13C NMR (101 MHz, CDCl₃): δ = 171.3 (2 x CO), 157.2 (2 x CO),
156.4 (2 x CO), 138.5 (2 x C\text{Ar}), 133.0 (2 x NH\text{COOCH}_2\text{CHCH}_2), 129.4 (1 x CH\text{Ar}), 117.7 (2 x NH\text{COOCH}_2\text{CHCH}_2), 115.7 (2 x CH\text{Ar}), 111.5 (1 x CH\text{Ar}), 80.3 (2 x C), 65.9 (2 x NH\text{COOCH}_2\text{CHCH}_2), 53.9 (2 x C\text{H}_2\text{NHAlloc}), 38.9 (2 x C\text{H}_2\text{NHAlloc}), 30.3 (2 x C\text{H}_2\text{NHAlloc}), 28.5 (6 x CH\text{CH}_3), 26.6 (2 x C\text{H}_2\text{NHAlloc}), 26.6 (2 x C\text{H}_2\text{NHAlloc}).

**Synthesis of 1l**: this compound was obtained as described above for 1a starting from Boc-L-Cys(Trt)-OH. In this case dry DCM was used instead of dry DMF as solvent. The crude product was purified by flash chromatography using AcOEt/hexane as eluent (from 25% to 40% AcOEt, Rf of 1l in AcOEt/hexane, 1:2 (v/v): 0.39) to give 1.49 g of 1l. (29% yield) as a white solid. HRMS (ESI+) calcd. for C\text{60}H\text{62}N\text{4}O\text{6}S\text{2} [M+H]^+ (m/z): 999.4184, found: 999.4145. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ = 8.02 (br s, 2H, NH\text{COC*H}), 7.64 (s, 1H, CH\text{Ar}), 7.44 (d, J = 7.1 Hz, 12H, CH\text{Ar}), 7.30 (t, J = 7.6 Hz, 12H, CH\text{Ar}), 7.25–7.13 (m, 9H, CH\text{Ar}), 4.81 (br s, 2H, C\text{HNNHCOC*H}), 3.94 (br s, 2H, C\text{HNNHCOC*H}), 2.85–2.70 (m, 2H, CH\text{CH}_2), 2.62 (dd, J = 13.2, 5.1 Hz, 2H, CH\text{CH}_2), 1.43 (s, 18H, CH\text{CH}_3). 13C NMR (126 MHz, CDCl\textsubscript{3}): δ = 168.9 (2 x CO), 156.0 (2 x CO), 144.5 (6 x C\text{Ar}), 138.1 (2 x C\text{Ar}), 129.7 (12 x CH\text{Ar}), 129.5 (1 x CH\text{Ar}), 128.2 (12 x CH\text{Ar}), 127.1 (6 x CH\text{Ar}), 115.7 (2 x CH\text{Ar}), 111.0 (1 x CH\text{Ar}), 80.9 (2 x C), 67.5 (2 x C), 54.4 (2 x C\text{H}_2\text{NHAlloc}), 33.6 (2 x CH\text{CH}_2), 28.4 (6 x CH\text{CH}_3).
Supporting Information

Synthesis of intermediates 2a-j

Synthesis of 2a: compound 1a (600 mg, 0.47 mmol) was dissolved in 4.0 mL of 20% piperidine in dry DMF. After several minutes stirring at room temperature the product precipitated as a white solid but the mixture was allowed to react for 4 hours until complete conversion of starting material. Diethyl ether was added over the reaction mixture and the product was filtered off and washed with diethyl ether, obtaining 293 mg of diamine 2a (75% yield) as a white solid.

HRMS (ESI+) calcd. for C_{52}H_{48}N_{6}O_{4} [M+H]^+ (m/z): 821.3810, found: 821.3832. ¹H NMR (400 MHz, MeOD-d₄): δ = 7.93 (s, 1H, CH₂Ar), 7.38–7.31 (m, 31H, CH₂Ar), 3.77 (dd, J = 7.5, 5.5 Hz, 2H, C*H), 2.77 (dd, J = 15.3, 5.5 Hz, 2H, CH₂), 2.68 (dd, J = 15.3, 7.6 Hz, 2H, CH₂). ¹³C NMR (101 MHz, MeOD-d₄): δ = 174.6 (2 x CO), 172.5 (2 x CO), 145.9 (6 x CAr), 144.7 (6 x CAr), 140.1 (1 x CAr), 303.0 (12 x CH₂Ar), 128.7 (12 x CH₂Ar), 127.8 (6 x CH₂Ar), 117.0 (2 x CH₂Ar), 112.8 (1 x CH₂Ar), 71.7 (2 x C), 54.0 (2 x C*H), 42.3 (2 x CH₂).

Synthesis of 2b: 531 mg of 2b (white solid, 74% yield) were obtained from 1b as described above for 2a. HRMS (ESI+) calcd. for C_{54}H_{52}N_{6}O_{4} [M+H]^+ (m/z): 849.4123, found: 849.4135. ¹H NMR (400 MHz, CDCl₃): δ = 9.46 (s, 2H, NHCOCH₂), 7.82 (t, J = 1.8 Hz, 1H, CH₂Ar), 7.35–7.19 (m, 33H, CH₂Ar), 6.93 (s, 2H, NHTrt), 3.40 (t, J = 6.5 Hz, 2H, C*H), 2.53–2.45 (m, 4H, CH₂C*H₂C*H₂), 2.13–1.94 (m, 4H, NH₂), 70.7 (2 x C), 54.8 (2 x C*H), 34.1 (2 x C*HCH₂C*H₂), 31.0 (2 x C*H₂C*H₂).

Synthesis of 2c: 522 mg of 2c (white solid, quantitative yield) were obtained from 1c as described above for 2a. HRMS (ESI+) calcd. for C_{20}H_{34}N_{4}O_{4} [M+H]^+ (m/z): 395.2653, found: 395.2672. ¹H NMR (400 MHz, CDCl₃): δ = 9.54 (s, 2H, NH), 7.91 (t, J = 2.1 Hz, 1H, CH₂Ar), 7.39–7.35 (m, 2H, CH₂Ar), 7.29–7.23 (m, 1H, CH₂Ar), 3.67 (dd, J = 7.2, 3.3 Hz, 2H, CH₂), 3.62–3.55 (m, 4H, 2H x C*H + 2H x CH₂), 2.00 (br s, 4H, NH₂), 1.21 (s, 18H, CH₃). ¹³C NMR (101 MHz, CDCl₃): δ = 171.6 (2 x CO), 138.6 (2 x CAr), 129.6 (1 x CAr), 128.8 (12 x CH₂Ar), 128.1 (12 x CH₂Ar), 127.2 (6 x CH₂Ar), 115.2 (2 x CH₂Ar), 101.5 (1 x CH₂Ar), 70.7 (2 x C), 54.8 (2 x C*H), 34.1 (2 x C*HCH₂C*H₂), 31.0 (2 x C*HCH₂C*H₂).

Synthesis of 2d: 445 mg of 2d (white solid, 64% yield) were obtained from 1d as described above for 2a. HRMS (ESI+) calcd. for C_{22}H_{38}N_{4}O_{4} [M+H]^+ (m/z): 423.2966, found: 423.2956. ¹H NMR (400 MHz, CDCl₃): δ = 9.63 (s, 2H, NHCOCH₂), 7.82 (t, J = 2.1 Hz, 1H, CH₂Ar), 7.40–7.33 (m, 2H, CH₂Ar), 7.32–7.23 (m, 1H, CH₂Ar), 4.23 (qd, J = 6.3, 2.5 Hz, 2H, C*HCH₃), 3.25 (d, J = 2.5 Hz, 2H, NHCOCH₂).
C*HNNH₂), 1.95 (br s, 4H, NH₂), 1.21 (d, J = 6.3 Hz, 6H, C*HCH₃), 1.17 (s, 18H, C(CH₃)₃).

¹³C NMR (101 MHz, CDCl₃): δ = 172.3 (2 x CO), 138.7 (2 x C₆H₄), 129.6 (1 x CH₆H₄), 115.0 (2 x CH₆H₄), 110.4 (1 x CH₆H₄), 74.4 (2 x C), 67.8 (2 x C*HCH₃), 60.4 (2 x C*HNNH₂), 28.6 (6 x C(CH₃)₃), 20.5 (2 x C*HCH₃).

**Synthesis of 2e:** 812 g of 2e (white solid, quantitative yield) were obtained from 1e as described above for 2a. HRMS (ESI+) calcd. for C₃₂H₄₂N₄O₄ [M+H]⁺ (m/z): 547.3279, found: 547.3280. ¹H NMR (500 MHz, CDCl₃): δ = 9.48 (s, 2H, NH₁COC*H), 7.92 (t, J = 8.3 Hz, 2H, CH₆H₄), 7.94 (t, J = 2.1 Hz, 1H, CH₆H₄), 7.65 (dd, J = 7.7, 1.0 Hz, 2H, CH₆H₄), 7.50 (s, 2H, CH₆H₄), 7.43 (dd, J = 7.8, 2.1 Hz, 2H, CH₆H₄), 7.38–7.22 (m, 5H, CH₆H₄), 3.84 (dd, J = 9.8, 3.6 Hz, 2H, C*H), 3.49 (ddd, J = 14.7, 3.7, 1.2 Hz, 2H, C*HCH₂), 2.88 (dd, J = 14.8, 9.6 Hz, 2H, C*HCH₂), 1.66 (s, 18H, CH₃), 1.58 (s, 4H, NH₂). ¹³C NMR (101 MHz, CDCl₃): δ = 172.8 (2 x CO), 154.5 (2 x C₆H₄), 138.4 (2 x C₆H₄), 132.5 (2 x C₆H₄), 129.8 (4 x CH₆H₄), 129.7 (1 x CH₆H₄), 124.6 (4 x CH₆H₄), 115.2 (2 x CH₆H₄), 110.4 (1 x CH₆H₄), 78.6 (2 x C), 57.0 (2 x C*H), 40.2 (2 x CH₂), 29.0 (6 x CH₃).

**Synthesis of 2f:** 781 mg of 2f (white solid, quantitative yield) were obtained from 1f as described above for 2a. HRMS (ESI+) calcd. for C₃₈H₄₄N₆O₆ [M+H]⁺ (m/z): 681.3395, found: 681.3399. ¹H NMR (400 MHz, CDCl₃): δ = 9.57 (s, 2H, NH₁COC*H), 8.14 (d, J = 8.3 Hz, 2H, CH₆H₄), 7.94 (t, J = 2.1 Hz, 1H, CH₆H₄), 7.65 (dd, J = 7.7, 1.0 Hz, 2H, CH₆H₄), 7.50 (s, 2H, CH₆H₄), 7.43 (dd, J = 7.8, 2.1 Hz, 2H, CH₆H₄), 7.38–7.22 (m, 5H, CH₆H₄), 3.84 (dd, J = 9.8, 3.6 Hz, 2H, C*H), 3.49 (ddd, J = 14.7, 3.7, 1.2 Hz, 2H, C*HCH₂), 2.88 (dd, J = 14.8, 9.6 Hz, 2H, C*HCH₂), 1.66 (s, 18H, CH₃), 1.58 (s, 4H, NH₂). ¹³C NMR (101 MHz, CDCl₃): δ = 172.7 (2 x CO), 149.7 (2 x CO), 138.4 (2 x C₆H₄), 135.8 (2 x C₆H₄), 130.3 (2 x C₆H₄), 129.7 (1 x CH₆H₄), 124.9 (2 x CH₆H₄), 124.3 (2 x CH₆H₄), 122.9 (2 x CH₆H₄), 119.3 (2 x CH₆H₄), 116.7 (2 x CH₆H₄), 115.5 (2 x CH₆H₄), 115.2 (2 x CH₆H₄), 110.5 (1 x CH₆H₄), 83.9 (2 x C), 55.4 (2 x C*H), 30.6 (2 x CH₂), 28.3 (6 x CH₃).

**Synthesis of 2g:** 531 mg of 2g (white solid, quantitative yield) were obtained from 1g as described above for 2a. HRMS (ESI+) calcd. for C₂₂H₃₄N₄O₆ [M+H]⁺ (m/z): 451.2551, found: 451.2560. ¹H NMR (400 MHz, MeOD-d₄): δ = 7.92 (t, J = 2.0 Hz, 1H, CH₆H₄), 7.38–7.34 (m, 2H, CH₆H₄), 7.29–7.24 (m, 1H, CH₆H₄), 3.75 (dd, J = 6.7, 6.0 Hz, 2H, C*H), 2.74 (dd, J = 16.2, 6.0 Hz, 2H, CH₂), 2.62 (dd, J = 16.2, 6.7 Hz, 2H, CH₂), 1.43 (s, 18H, CH₃). ¹³C NMR (101 MHz, MeOD-d₄): δ = 174.5 (2 x CO), 172.1 (2 x CO), 140.0 (2 x C₆H₄), 130.2(1 x CH₆H₄), 116.9 (2 x CH₆H₄), 112.8 (1 x CH₆H₄), 82.3 (2 x C), 53.6 (2 x C*H), 41.5 (2 x CH₂), 28.3 (6 x CH₃).
Supporting Information

Synthesis of 2h: 1.05 g of 2h (white solid, quantitative yield) were obtained from 1h as described above for 2a. HRMS (ESI+) calcd. for C_{34}H_{38}N_{10}O_{6} [M+H]^+ (m/z): 479.2864, found: 479.2882. \(^1\)H NMR (400 MHz, MeOD-d_4): \(\delta = 7.94\) (t, \(J = 2.0\) Hz, 1H, CH\(_{Ar}\)), 7.37–7.33 (m, 2H, CH\(_{Ar}\)), 7.30–7.23 (m, 1H, CH\(_{Ar}\)), 3.45 (dd, \(J = 7.2, 6.1\) Hz, 2H, C*H), 2.44–2.30 (m, 4H, C*HCH\(_2\)CH\(_2\)), 2.07–1.96 (m, 2H, C*HCH\(_2\)), 1.92–1.80 (m, 2H, C*HCH\(_2\)), 1.43 (s, 18H, CH\(_3\)). \(^{13}\)C NMR (101 MHz, MeOD-d_4): \(\delta = 175.5\) (2 x CO), 174.2 (2 x CO), 140.0 (2 x CH\(_{Ar}\)), 130.2 (1 x CH\(_{Ar}\)), 117.1 (2 x CH\(_{Ar}\)), 81.7 (2 x C), 56.1 (2 x C*H), 32.7 (2 x C*HCH\(_2\)CH\(_2\)), 31.5 (2 x C*HCH\(_2\)), 28.3 (6 x CH\(_3\)).

Synthesis of 2i·2TFA: 530 mg of 1i (0.72 mmol) were dissolved in DCM (10 mL) and TFA (1.5 mL) was added. The mixture was stirred at room temperature for 4 hours and then concentrated under reduced pressure. Diethyl ether was then added over the residue and the precipitate formed was filtered and washed with diethyl ether, obtaining 474 mg of 2i·2TFA (white solid, 93% yield) HRMS (ESI+) calcd. for C_{34}H_{44}N_{10}O_{6} [M+H]^+ (m/z): 633.3395, found: 633.3389. \(^1\)H NMR (500 MHz, MeOD-d_4): \(\delta = 8.10\) (t, \(J = 2.0\) Hz, 1H, CH\(_{Ar}\)), 7.41–7.24 (m, 13H, CH\(_{Ar}\)), 5.01 (ABq, \(\delta_A = 5.04, \\delta_B = 4.99\), \(J = 12.5\) Hz, 4H, NHCOOC\(_2\)H), 3.95 (t, \(J = 6.5\) Hz, 2H, C*H), 3.13 (t, \(J = 6.8\) Hz, 4H, CH\(_2\)NHCbz), 2.04–1.84 (m, 4H, C*HCH\(_2\)), 1.56 (quint, \(J = 7.0\) Hz, 4H, CH\(_2\)CH\(_2\)NHCbz), 1.51–1.38 (m, 4H, C*HCH\(_2\)CH\(_2\)). \(^{13}\)C NMR (101 MHz, MeOD-d_4): \(\delta = 168.6\) (2 x CO), 159.0 (2 x CO), 139.7 (2 x CH\(_{Ar}\)), 138.3 (2 x CH\(_{Ar}\)), 130.5 (1 x CH\(_{Ar}\)), 129.4 (4 x CH\(_{Ar}\)), 128.9 (2 x CH\(_{Ar}\)), 128.7 (4 x CH\(_{Ar}\)), 117.4 (2 x CH\(_{Ar}\)), 113.0 (1 x CH\(_{Ar}\)), 67.4 (2 x NHCOOC\(_2\)H), 55.1 (2 x C*H), 41.1 (2 x CH\(_2\)NHCbz), 32.3 (2 x C*HCH\(_2\)), 30.5 (2 x CH\(_2\)CH\(_2\)NHCbz), 23.0 (2 x C*HCH\(_2\)).

Synthesis of 2j·2TFA: 1.27 g of 2j·2TFA (white solid, 94% yield) were obtained from 1j as described above for 2i·2TFA. HRMS (ESI+) calcd. for C_{34}H_{36}N_{10}O_{6} [M+H]^+ (m/z): 505.2769, found: 505.2786. \(^1\)H NMR (400 MHz, MeOD-d_4): \(\delta = 8.08\) (t, \(J = 1.8\) Hz, 1H, CH\(_{Ar}\)), 7.40–7.35 (m, 2H, CH\(_{Ar}\)), 7.34–7.29 (m, 1H, CH\(_{Ar}\)), 5.90 (ddt, \(J = 17.3, 10.6, 5.4\) Hz, 2H, NHCOOC\(_2\)HCH\(_2\)CH\(_2\)), 5.27 (dd, \(J = 17.3, 1.7\) Hz, 2H, NHCOOC\(_2\)HCH\(_2\)CH\(_2\)), 5.15 (dd, \(J = 10.3, 1.0\) Hz, 2H, NHCOOC\(_2\)HCH\(_2\)CH\(_2\)), 4.52 (dt, \(J = 5.4, 1.5\) Hz, 4H, NHCOOC\(_2\)HCH\(_2\)CH\(_2\)), 4.02 (t, \(J = 6.5\) Hz, 2H, C*H), 3.18 (td, \(J = 6.8, 1.7\) Hz, 4H, CH\(_2\)NHAlloc), 2.0–1.85 (m, 4H, C*HCH\(_2\)), 1.74–1.55 (m, 4H, C*HCH\(_2\)CH\(_2\)). \(^{13}\)C NMR (101 MHz, MeOD-d_4): \(\delta = 168.5\) (2 x CO), 159.0 (2 x CO), 139.7 (2 x CH\(_{Ar}\)), 134.4 (2 x NHCOOC\(_2\)HCH\(_2\)), 130.5 (1 x CH\(_{Ar}\)), 117.5 (2 x NHCOOC\(_2\)HCH\(_2\)CH\(_2\)), 117.3 (2 x CH\(_{Ar}\)), 112.9 (1 x CH\(_{Ar}\)), 66.4 (2 x NHCOOC\(_2\)HCH\(_2\)CH\(_2\)), 54.8 (2 x C*H), 40.8 (2 x CH\(_2\)NHAlloc), 30.1 (2 x C*HCH\(_2\)), 26.6 (2 x C*HCH\(_2\)).
Synthesis of intermediates 3a-k

Synthesis of 3a: tritylsulfanyl acetic acid (501 mg, 1.50 mmol) was dissolved in dry DMF (20 mL) and EDC·HCl (312 mg, 1.63 mmol), HOBT (228 mg, 1.69 mmol) and DIPEA (1.6 mL, 4.59 mmol) were added over the solution. The reaction mixture was cooled down to 0 °C in an ice-water bath and 2a (585 mg, 0.715 mmol) was added over the mixture. The mixture was stirred at room temperature under an inert atmosphere of Ar for 48 hours, and the formation of the product was followed by TLC. The mixture was diluted with DCM, washed with saturated aqueous NaHCO$_3$ and saturated aqueous NaCl, and dried under reduced pressure. The crude product was purified by flash chromatography using AcOEt/hexane as eluent (from 40% to 60% AcOEt, Rf of 3a in AcOEt/hexane, 1:1 (v/v): 0.46) to give 758 mg of 3a (73% yield) as a white solid. HRMS (ESI+) calcd. for C$_{94}$H$_{80}$N$_6$O$_6$S$_2$ [M+H]$^+$ (m/z): 1453.5654, found: 1453.5665. $^1$H NMR (400 MHz, CDCl$_3$): δ = 8.84 (s, 2H, NHCO*C*H), 7.60 (t, $J$ = 2.0 Hz, 1H, CH$_{Ar}$), 7.54–7.00 (m, 65H, 2H x C*HNHCO + 63H x CH$_{Ar}$), 6.91 (s, 2H, NHTrt), 4.49 (td, $J$ = 7.5, 3.0 Hz, 2H, C*H), 3.05 (ABq, δ$_A$ = 3.08, δ$_B$ = 3.02, $J$ = 15.7 Hz, 4H, CH$_2$STrt), 2.96–2.83 (m, 2H, C$_2$H$_2$C*H), 2.39 (dd, $J$ = 15.7, 7.8 Hz, 2H, CH$_2$C*H). $^{13}$C NMR (101 MHz, CDCl$_3$): δ = 170.7 (2 x CO), 169.0 (2 x CO), 168.3 (2 x CO), 144.2 (6 x C$_{Ar}$), 144.1 (6 x C$_{Ar}$), 138.11 (2 x C$_{Ar}$), 129.7 (12 x CH$_{Ar}$), 129.2 (1 x CH$_{Ar}$), 128.7 (12 x CH$_{Ar}$), 128.3 (12 x CH$_{Ar}$), 128.2 (12 x CH$_{Ar}$), 127.3 (6 x CH$_{Ar}$), 127.1 (6 x CH$_{Ar}$), 116.3 (2 x CH$_{Ar}$), 111.8 (1 x CH$_{Ar}$), 71.1 (2 x C), 67.9 (2 x C), 50.7 (2 x C*H), 38.4 (2 x CH$_2$C*H), 36.2 (2 x CH$_2$STrt).

Synthesis of 3b: this compound was obtained as described above for 3a, starting from 2b. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 30% to 40% AcOEt, Rf of 3b in AcOEt/hexane, 1:1 (v/v): 0.23) to give 593 mg of 3b (66% yield) as a white solid. HRMS (ESI+) calcd. for C$_{96}$H$_{84}$N$_6$O$_6$S$_2$ [M+H]$^+$ (m/z): 1481.5967, found: 1481.5916. $^1$H NMR (400 MHz, CDCl$_3$): δ = 8.76 (s, 2H, NHCO*C*H), 7.73 (t, $J$ = 1.9 Hz, 1H, CH$_{Ar}$), 7.44–7.38 (m, 55H, 51H x CH$_{Ar}$ + 2H x C*HCO*CO + 2H x NHTrt), 4.03 (q, $J$ = 6.8 Hz, 2H, C*H), 3.06 (ABq, δ$_A$ = 3.07, δ$_B$ = 3.05, $J$ = 15.8Hz, 4H, CH$_3$STrt), 2.59–2.49 (m, 2H, C*HCH$_2$CH$_2$), 2.39–2.29 (m, 2H, C*HCH$_2$CH$_2$), 2.03–1.92 (m, 2H, C*HCH$_2$), 1.81–1.70 (m, 2H, C*HCH$_2$). $^{13}$C NMR (101 MHz, CDCl$_3$): δ = 172.5 (2 x CO), 168.8 (2 x CO), 168.6 (2 x CO), 144.5 (6 x C$_{Ar}$), 144.1 (6 x C$_{Ar}$), 138.2 (2 x C$_{Ar}$), 129.7 (12 x CH$_{Ar}$), 129.2 (1 x CH$_{Ar}$), 128.8 (12 x CH$_{Ar}$), 128.3 (12 x CH$_{Ar}$), 128.1 (12 x CH$_{Ar}$), 127.2 (6 x CH$_{Ar}$), 127.1(6 x CH$_{Ar}$), 115.9 (2 x CH$_{Ar}$), 111.4 (1 x CH$_{Ar}$), 70.9 (2 x C), 68.0 (2 x C).
Supporting Information

Synthesis of 3c: this compound was obtained as described above for 3a starting from 2c. The crude product was purified by flash chromatography using AcOEt/hexane as eluent (from 35% to 45% AcOEt, Rf of 3c in AcOEt/hexane, 2:3 (v/v): 0.27) to give 612 mg of 3c (51% yield) as a white solid. HRMS (ESI+) calcd. for \( \text{C}_{62}\text{H}_{66}\text{N}_4\text{O}_6\text{S}_2 [\text{M}+\text{H}]^+ \) (m/z): 1027.4497, found: 1027.4492. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 8.68 \) (s, 2H, N\( \text{HOC}\)C\*H), 7.79 (t, \( J = 1.8 \) Hz, 1H, CH\(_{Ar}\)), 7.43 (d, \( J = 7.3 \) Hz, 12H, CH\(_{Ar}\)), 7.28 (t, \( J = 7.6 \) Hz, 12H, CH\(_{Ar}\)), 7.25–7.18 (m, 9H, CH\(_{Ar}\)), 7.10 (d, \( J = 5.8 \) Hz, 2H, C*HN\( \text{HCO} \)), 4.24–4.18 (dt, \( J = 9.7, 4.6 \) Hz, 2H, C*H), 3.71 (dd, \( J = 8.6, 4.3 \) Hz, 2H, C*HC\( \text{H}_2 \)), 3.20–3.08 (m, 6H, 2H x C*HC\( \text{H}_2 \) + 4H x C\( \text{H}_2 \)STrt), 1.22 (s, 18H, CH\(_3\)). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta = 168.7 \) (2 x CO), 168.2 (2 x CO), 144.1 (6 x C\(_{Ar}\)), 138.4 (2 x C\(_{Ar}\)), 129.9 (1 x CH\(_{Ar}\)), 129.7 (12 x CH\(_{Ar}\)), 128.3 (12 x CH\(_{Ar}\)), 127.1 (6 x CH\(_{Ar}\)), 115.5 (2 x CH\(_{Ar}\)), 110.9 (1 x CH\(_{Ar}\)), 75.0 (2 x C), 68.0 (2 x C), 61.0 (2 x C*H\( \text{H}_2 \)), 53.8 (2 x C*H), 36.2 (2 x C\( \text{H}_2 \)STrt), 27.6 (6 x CH\(_3\)).

Synthesis of 3d: this compound was obtained as described above for 3a starting from 2d. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 20% to 35% AcOEt, Rf of 3d in AcOEt/hexane, 3:7 (v/v): 0.28) to give 608 mg of 3d (57% yield) as a white solid. HRMS (ESI–) calcd. for \( \text{C}_{64}\text{H}_{70}\text{N}_4\text{O}_6\text{S}_2 [\text{M}+\text{HCOO}^-] \) (m/z): 1099.4719, found: 1099.4722. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 9.16 \) (s, 2H, N\( \text{HOC}\)C*H), 7.70 (s, 1H, CH\(_{Ar}\)), 7.43 (d, \( J = 7.5 \) Hz, 12H, CH\(_{Ar}\)), 7.33–7.17 (m, 23H, 21H x CH\(_{Ar}\) + 2H x C*HN\( \text{HCO} \)), 4.24–4.13 (m, 4H, 2H x C*H\( \text{HN} \)+ 2H x C*H\( \text{CH}_3 \)), 3.07 (ABq, \( \delta_A = 3.10, \delta_B = 3.03, J = 15.4 \) Hz, 4H, CH\(_2\)), 1.33 (s, 18H, C(CH\(_3\))\(_3\)), 0.94 (d, \( J = 6.4 \) Hz, 6H, C*H\( \text{CH}_3 \)). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta = 168.5 \) (2 x CO), 167.4 (2 x CO), 144.1 (6 x C\(_{Ar}\)), 138.4 (2 x C\(_{Ar}\)), 129.9 (1 x CH\(_{Ar}\)), 129.7 (12 x CH\(_{Ar}\)), 128.3 (12 x CH\(_{Ar}\)), 127.1 (6 x CH\(_{Ar}\)), 115.5 (2 x CH\(_{Ar}\)), 110.9 (1 x CH\(_{Ar}\)), 75.0 (2 x C), 68.0 (2 x C), 61.0 (2 x C*H\( \text{H}_2 \)), 36.2 (2 x C\( \text{H}_2 \)STrt), 27.6 (6 x CH\(_3\)).

Synthesis of 3e: this compound was obtained as described above for 3a, starting from 2e. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 30% to 40% AcOEt, Rf of 3e in AcOEt/hexane, 2:3 (v/v): 0.39) to give 1.07 g of 3e (79% yield) as a white solid. HRMS (ESI–) calcd. for \( \text{C}_{74}\text{H}_{74}\text{N}_4\text{O}_6\text{S}_2 [\text{M}+\text{HCOO}^-] \) (m/z): 1223.5032, found: 1223.4956. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 7.73 \) (s, 2H, N\( \text{HOC}\)C*H), 7.51 (t, \( J = 2.0 \) Hz, 1H, CH\(_{Ar}\)), 7.36 (d, \( J = 7.2 \) Hz, 12H, CH\(_{Ar}\)), 7.29–7.22 (m, 14H, CH\(_{Ar}\)), 7.18 (t, \( J = 7.3 \) Hz, 6H,
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CH$_2$Ar), 7.14–7.09 (m, 1H, CH$_2$Ar), 7.06 (d, $J = 8.4$ Hz, 4H, CH$_2$Ar), 6.86 (d, $J = 8.4$ Hz, 4H, CH$_2$Ar), 6.61 (d, $J = 7.3$ Hz, 2H, C*HNHCO), 4.37 (q, $J = 7.1$ Hz, 2H, C*H), 3.12 (ABq, $\delta_A = 3.15$, $\delta_B = 3.09$, $J = 16.3$ Hz, 4H, CH$_2$STrt), 2.91 (d, $J = 7.1$ Hz, 4H, C*HCH$_2$), 1.28 (s, 18H, CH$_3$).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta =$ 169.0 (2 x CO), 168.4 (2 x CO), 154.6 (2 x C$_{Ar}$), 144.0 (6 x C$_{Ar}$), 138.0 (2 x C$_{Ar}$), 131.1 (2 x C$_{Ar}$), 130.0 (4 x CH$_2$Ar), 129.6 (12 x CH$_{Ar}$), 128.4 (12 x CH$_{Ar}$), 127.3 (6 x CH$_{Ar}$), 124.6 (4 x CH$_{Ar}$), 115.9 (2 x CH$_{Ar}$), 111.3 (1 x CH$_{Ar}$), 78.6 (2 x C), 68.2 (2 x C), 55.9 (2 x C*H), 36.9 (2 x C*HCH$_2$), 36.0 (2 x CH$_2$STrt), 29.0 (6 x CH$_3$).

**Synthesis of 3f**: This compound was obtained as described above for 3a starting from 2f. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 30% to 40% AcOEt, Rf of 3f in AcOEt/hexane, 2:3 (v/v): 0.54) to give 977 mg of 3f (88% yield) as a white solid. HRMS (ESI+) calcd. for C$_{80}$H$_{76}$N$_6$O$_8$S$_2$ [M+Na]$^+$ (m/z): 1335.50, found: 1335.5060.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 8.10 (d, $J = 8.4$ Hz, 2H, CH$_2$Ar), 7.94 (s, 2H, NHCO*C*H), 7.55 (d, $J = 7.8$ Hz, 2H, CH$_2$Ar), 7.46 (s, 1H, CH$_2$Ar), 7.40 (s, 2H, CH$_2$Ar), 7.34 (d, $J = 7.4$ Hz, 12H, CH$_2$Ar), 7.29–7.02 (m, 25H, CH$_2$Ar), 6.61 (d, $J = 7.2$ Hz, 2H, C*HNHCO), 4.52 (q, $J = 7.0$ Hz, 2H, C*H), 3.21–2.98 (m, 8H, 4H x C$_2$H$_2$STrt + 4H x C*HC$_2$H$_2$), 1.59 (s, 18H, CH$_3$).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta =$ 169.2 (2 x CO), 168.5 (2 x CO), 149.6 (2 x CO), 144.0 (6 x C$_{Ar}$), 138.0 (2 x C$_{Ar}$), 135.6 (2 x C$_{Ar}$), 130.2 (2 x C$_{Ar}$), 129.6 (12 x CH$_2$Ar), 128.4 (12 x CH$_2$Ar), 127.3 (6 x CH$_2$Ar), 124.6 (4 x CH$_2$Ar), 115.9 (2 x CH$_2$Ar), 111.3 (1 x CH$_2$Ar), 78.6 (2 x C), 68.2 (2 x C), 55.9 (2 x C*H), 36.9 (2 x C*HCH$_2$), 36.0 (2 x CH$_2$STrt), 29.0 (6 x CH$_3$).

**Synthesis of 3g**: This compound was obtained as described above for 3a starting from 2g. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 30% to 40% AcOEt, Rf of 3g in AcOEt/hexane, 2:3 (v/v): 0.54) to give 644 mg of 3g (69% yield) as a white solid. HRMS (ESI+) calcd. for C$_{64}$H$_{66}$N$_6$O$_8$S$_2$ [M+Na]$^+$ (m/z): 1105.4214, found: 1105.4236.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 8.54 (s, 2H, NHCO*C*H), 7.63 (s, 1H, CH$_2$Ar), 7.40 (s, 2H, CH$_2$Ar), 7.34 (d, $J = 7.4$ Hz, 12H, CH$_2$Ar), 7.29–7.02 (m, 25H, CH$_2$Ar), 6.61 (d, $J = 7.2$ Hz, 2H, C*HNHCO), 4.52 (q, $J = 7.0$ Hz, 2H, C*H), 3.21–2.98 (m, 8H, 4H x C$_2$H$_2$STrt + 4H x C*HC$_2$H$_2$), 1.59 (s, 18H, CH$_3$).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta =$ 171.3 (2 x CO), 169.0 (2 x CO), 168.0 (2 x CO), 144.0 (6 x C$_{Ar}$), 138.3 (2 x C$_{Ar}$), 129.6 (13 x CH$_2$Ar), 128.3 (12 x CH$_2$Ar), 127.26 (6 x CH$_2$Ar), 116.0 (2 x CH$_2$Ar), 111.3 (1 x CH$_3$).
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CH_{Ar}, 82.3 (2 x C), 68.2 (2 x C), 50.4 (2 x C\*H), 36.6 (2 x CH_2), 36.0 (2 x CH_2), 28.2 (6 x CH_3).

**Synthesis of 3h:** this compound was obtained as described above for 3a, starting from 2h. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 30% to 40% AcOEt, Rf of 3h in AcOEt/hexane, 2:3 (v/v): 0.20) to give 285 mg of 3h (74% yield) as a white solid. HRMS (ESI+) calcd. for C_{66}H_{70}N_{4}O_{8}S_{2} [M+H]^+ (m/z): 1111.4708, found: 1111.4696. ^1H NMR (400 MHz, CDCl_3): \( \delta = 8.72 \) (s, 2H, NHCOC*H), 7.78 (t, \( J = 1.8 \) Hz, 1H, CH_{Ar}), 7.44–7.37 (m, 12H, CH_{Ar}), 7.30–7.14 (m, 21H, CH_{Ar}), 6.80 (d, \( J = 7.2 \) Hz, 2H, C*NHCO), 4.26 (q, \( J = 6.8 \) Hz, 2H, C*H), 3.14 (ABq, \( \delta_A = 3.16, \delta_B = 3.12, J = 16.1 \)Hz, 4H, CH_2STrt), 2.45–2.34 (m, 2H, C*HCH_2CH_2), 2.28–2.17 (m, 2H, C*HCH_2H), 2.08–1.96 (m, 2H, C*HCH_2), 1.83–1.71 (m, 2H, C*HCH_2), 1.44 (s, 18H, CH_3). ^13C NMR (101 MHz, CDCl_3): \( \delta = 173.1 \) (2 x CO), 169.0 (2 x CO), 168.8 (2 x CO), 144.0 (6 x C_{Ar}), 138.4 (2 x C_{Ar}), 129.6 (12 x CH_{Ar}), 129.5 (1 x CH_{Ar}), 128.3 (12 x CH_{Ar}), 127.2 (6 x CH_{Ar}), 115.7 (2 x CH_{Ar}), 111.0 (1 x CH_{Ar}), 81.3 (2 x C), 68.1 (2 x C), 53.5 (2 x C*H), 36.1 (2 x CH_2STrt), 32.0 (2 x C*HCH_2CH_2), 28.2 (6 x CH_3), 27.8 (2 x C*HCH_2H).

**Synthesis of 3i:** this compound was obtained as described above for 3a starting from 2i. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 50% to 65% AcOEt, Rf of 3i in AcOEt/hexane, 3:2 (v/v): 0.47) to give 1.70 g of 3i (83% yield) as a white solid. HRMS (ESI+) calcd. for C_{76}H_{76}N_{6}O_{8}S_{2} [M+H]^+ (m/z): 1265.5239, found: 1265.5187. ^1H NMR (400 MHz, CDCl_3): \( \delta = 8.64 \) (br s, 2H, NHCOC*H), 7.62 (br s, 1H, CH_{Ar}), 7.47–7.03 (m, 43H, CH_{Ar}), 6.60 (d, \( J = 7.4 \) Hz, 2H, C*NHCO), 5.03 (s, 4H, NHCOOCH_{2}), 4.97 (br s, 2H, NHCbz), 4.23 (br s, 2H, C*H), 3.22–2.99 (m, 8H, 4H x CH_2NHCbz + 4H x CH_2STrt), 1.92–1.64 (m, 4H, C*HCH_2), 1.57–1.34 (m, 4H, CH_2CH_2NHCbz), 1.33–1.09 (m, 4H, C*HCH_2CH_2). ^13C NMR (101 MHz, CDCl_3): \( \delta = 169.7 \) (2 x CO), 169.2 (2 x CO), 156.6 (2 x CO), 144.1 (6 x C_{Ar}), 138.4 (2 x C_{Ar}), 136.8 (2 x C_{Ar}), 129.6 (13 x CH_{Ar}), 128.6 (4 x CH_{Ar}), 128.3 (12 x CH_{Ar}), 128.2 (6 x CH_{Ar}), 127.2 (6 x CH_{Ar}), 115.9 (2 x CH_{Ar}), 111.4 (1 x CH_{Ar}), 68.1 (2 x C), 59.6 (2 x NHCOOCH_{2}), 54.3 (2 x C*H), 40.6 (2 x CH_2NHCbz), 36.2 (2 x CH_2STrt), 31.6 (2 x C*HCH_2), 29.5 (2 x CH_2CH_2NHCbz), 22.7 (2 x C*HCH_2CH_2).

**Synthesis of 3j:** this compound was obtained as described above for 3a, starting from 2j. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 50% to 75% AcOEt, Rf of 3j in AcOEt/hexane, 4:1 (v/v): 0.51) to give 281 mg of 3j (15% yield) as a white solid. HRMS (ESI+) calcd. for
C_{66}H_{68}N_{6}O_{8}S_{2} \ [M+Na]^+ \ (m/z): 1159.4432, \text{ found: 1159.4454.} \ \ ^1H \text{ NMR (400 MHz, CDCl}_3\): \ \delta = 8.75 \text{ (br s, 2H, NHCO*C*H), 7.74 \text{ (br s, 1H, CH}_A), 7.42–7.35 \text{ (m, 12H, CH}_A), 7.33–7.23 \text{ (m, 15H, CH}_A), 7.22–7.14 \text{ (m, 6H, CH}_A), 6.79 \text{ (d, J = 6.1 Hz, 2H, C*HNHCO), 5.86 \text{ (dd, J = 16.3, 10.7, 5.5 Hz, 2H, NHCOOCH}_2CHCH}_2, 5.25 \text{ (dd, J = 17.2, 1.6 Hz, 2H, NHCOOCH}_2CHCH}_2, 5.14 \text{ (dd, J = 10.6, 1.4 Hz, 2H, NHCOOCH}_2CHCH}_2, 5.02 \text{ (br s, 2H, NHAlloc), 4.56 \text{ (d, J = 5.2 Hz, 4H, NHCOOCH}_2CHCH}_2, 4.52 \text{ (s, 2H, C*H), 3.41 \text{ (br s, 2H, C*_H2NHAlloc), 3.21–2.96 \text{ (m, 6H, 2H x C*_H2NHAlloc + 4H x C*_H2STrt), 1.89–1.66 \text{ (m, 2H, C*HCH}_2, 1.58–1.35 \text{ (m, 6H, 2H x C*HCH}_2C*HCH}_2, 1.35 \text{ (m, 6H, C*HCH}_2C*HCH}_2).} \ \ ^13C \text{ NMR (101 MHz, CDCl}_3\): \ \delta = 169.9 \text{ (2 x CO), 169.1 \text{ (2 x CO), 157.1 \text{ (2 x CO), 144.1 \text{ (6 x C}_A), 138.5 \text{ (2 x C}_A), 133.0 \text{ (2 x NHCOOCH}_2CHCH}_2, 129.7 \text{ (12 x CH}_A), 129.4 \text{ (1 x CH}_A), 128.3 \text{ (12 x CH}_A), 127.2 \text{ (6 x CH}_A), 117.7 \text{ (2 x NHCOOCH}_2CHCH}_2, 115.6 \text{ (2 x CH}_A), 111.0 \text{ (1 x CH}_A), 68.0 \text{ (2 x C), 65.8 \text{ (2 x NHCOOCH}_2CHCH}_2, 52.9 \text{ (2 x C*H), 39.7 \text{ (2 x C}_2NHAlloc), 36.3 \text{ (2 x CH}_2STrt), 30.0 \text{ (2 x C*HCH}_2, 26.4 \text{ (2 x C*HCH}_2CH}_2).} \ \ \text{Synthesis of 3k: To a solution of 3j (132 mg, 0.116 mmol) in dry DCM (3.0 mL), PhSiH}_3 \text{ (343 \mu L, 2.79 mmol) was added under inert atmosphere of Ar. Then a solution of Pd(PPh}_3)_4 \text{ (18 mg, 15 \eta mol) in dry DCM (2.0 mL) was added. The mixture was stirred at room temperature for 1 hour, after which complete conversion of the starting material was observed by TLC. The crude mixture was filtered through a bed of Celite® and the filtrate was concentrated to dryness under reduced pressure, obtaining diamine 5j as a brownish solid that was no further purified. HRMS (ESI+) calcd. for C_{58}H_{60}N_{6}O_{4}S_{2} \ [M+H]^{+} \ (m/z): 969.4190, \text{ found: 969.4178. The residue was re-dissolved in DCM (5.0 mL), and triethylamine (54 \mu L, 0.39 mmol) and N,N’-di-Boc-N’’-triflylguanidine (139 mg, 0.355 mmol) were added. The mixture was stirred for 2 hours under inert atmosphere of Ar, until the reaction was completed as evidenced by TLC (Rf of 3k in AcOEt/Hexane, 2:3 (v/v): 0.30). The mixture was diluted with DCM, washed with 2M aqueous NaHSO}_4, saturated aqueous NaHCO}_3 and saturated aqueous NaCl, dried over MgSO}_4 and concentrated under reduced pressure. The residue was purified by flash chromatography using AcOEt/hexane as eluent (from 40% to 45% AcOEt) to give 106.7 mg of 3k (63% yield over the last two steps) as a white solid. HRMS (ESI–) calcd. for C_{80}H_{96}N_{10}O_{12}S_{2} \ [M–H]^{-} \ (m/z): 1451.6578, \text{ found: 1451.6572.} \ \ ^1H \text{ NMR (400 MHz, CDCl}_3\): \ \delta = 11.46 \text{ (s, 2H, NH), 8.51–8.33 \text{ (m, 4H, 2H x NHCO*C*H + 2H x NH), 7.67–7.63 \text{ (m, 1H, CH}_A), 7.41 \text{ (d, J = 7.2 Hz, 12H, CH}_A), 7.31–7.16 \text{ (m, 21H, CH}_A), 7.08 \text{ (d, J = 7.7 Hz, 2H, C*HNHCO), 4.34 \text{ (q, J = 6.8 Hz, 2H, C*H), 3.43 \text{ (q, J = 5.8 Hz, 4H, CH}_2NH), 3.14 \text{ (s, 4H, CH}_2STrt), 1.90–1.75 \text{ (m, 2H, C*HCH}_2, 1.72–1.13 \text{ (m,}
42H, 2H x C*HCH₂ + 4H x C*HCH₂CH₂ + 36H x CH₃). $^{13}$C NMR (101 MHz, CDCl₃): δ = 169.3 (2 x CO), 168.9 (2 x CO), 167.5 (2 x C-guanidine), 152.5 (2 x CO), 147.0 (2 x CO), 144.1 (6 x C₆H₅), 138.6 (2 x C₆H₅), 129.7 (12 x CH₆H₅), 129.3 (1 x CH₆H₅), 128.3 (12 x CH₆H₅), 127.2 (6 x CH₆H₅), 116.2 (2 x CH₆H₅), 111.8 (1 x CH₆H₅), 90.1 (2 x C), 81.0 (2 x C), 68.0 (2 x C), 53.1 (2 x C*H), 41.9 (2 x CH₂NH), 36.3 (2 x C₂H₂STrt), 29.9 (2 x C*HCH₂), 28.1 (12 x CH₃), 25.5 (2 x C*HCH₂CH₂).
Synthesis of building blocks 4a-l

Synthesis of 4a: to a solution of 3a (230 mg, 0.16 mmol) in DCM (1.0 mL), TFA (8.5 mL), TIS (332 μL, 1.28 mmol) and EDT (160 μL, 1.91 mmol) were added rapidly and under stirring. The reaction mixture was stirred at room temperature for 2 hours, after which the solvents were partially evaporated using a N₂ flow. Diethyl ether was added over the reaction mixture and the product was filtered off and washed with diethyl ether. The product was purified by reversed-phase flash chromatography using a mixture of MeCN + 0.07% (v/v) TFA and H₂O + 0.1% (v/v) TFA as mobile phase (gradient: from 5% to 30% MeCN in H₂O). After lyophilisation 37.8 mg of 4a (52% yield) were obtained as a white solid. HRMS (ESI+) calcd. for C₁₈H₂₄N₆O₆S₂ [M+H]⁺ (m/z): 485.1277, found: 485.1279.

¹H NMR (400 MHz, DMSO- d₆): δ = 9.97 (s, 2H, NHCOC*H), 8.34 (d, J = 7.7 Hz, 2H, C*HNHCO), 7.93 (t, J = 2.0 Hz, 1H, H¹), 7.36 (s, 2H, NH₂), 7.29 (dd, J = 7.6, 2.0 Hz, 2H, H³), 7.24–7.15 (m, 1H, H⁴), 6.91 (s, 2H, NH₂), 4.67 (q, J = 7.1 Hz, 2H, C*H), 3.17 (d, J = 7.9 Hz, 4H, C₂H₂SH), 2.73 (t, J = 7.9 Hz, 2H, SH), 2.62–2.41 (m, 4H, C₂H₂C*H).

¹³C NMR (101 MHz, DMSO- d₆): δ = 171.1 (2 x CONH₂), 169.5 (2 x COC*H), 169.4 (2 x COCH₂), 139.1 (2 x C), 128.6 (1 x C⁴), 114.3 (2 x C³), 110.4 (1 x C¹), 50.9 (2 x C*H), 37.1 (2 x CH₂C*H), 27.0 (2 x CH₂SH).

Synthesis of 4b: this compound was obtained as described above for 4a, starting from 3b. The product was purified by reversed-phase flash chromatography using a mixture of MeCN + 0.07% (v/v) TFA and H₂O + 0.1% (v/v) TFA as mobile phase (gradient: from 5% to 30% MeCN in H₂O) and 31.3 mg of 4b (48% yield) were obtained as a white solid. HRMS (ESI+) calcd. for C₂₀H₂₈N₆O₆S₂ [M+H]⁺ (m/z): 513.1590, found: 513.1592.

¹H NMR (400 MHz, DMSO- d₆): δ = 10.09 (s, 2H, NHCOC*H), 8.30 (d, J = 7.7 Hz, 2H, C*HNHCO), 7.96 (t, J = 2.0 Hz, 1H, H¹), 7.35–7.27 (m, 4H, 2H x H³ + 2H x NH₂), 7.26–7.20 (m, 1H, H⁴), 6.77 (s, 2H, NH₂), 4.39 (td, J = 8.0, 5.7 Hz, 2H, C*H), 3.25–3.12 (m, 4H, CH₂SH), 2.75 (t, J = 8.0 Hz, 2H, SH), 2.22–2.04 (m, 4H, C*HCH₂CH₂), 1.99–1.88 (m, 2H, C*HCH₂), 1.88–1.76 (m, 2H, C*HCH₂). ¹³C NMR (101 MHz, DMSO- d₆): δ = 173.3 (2 x CONH₂), 170.0 (2 x COC*H), 169.6 (2 x COCH₂), 139.0 (2 x C²), 128.6 (1 x C⁴), 114.3 (2 x C³), 110.4 (1 x C¹), 53.1 (2 x C*H), 31.1 (2 x C*HCH₂CH₂), 27.8 (2 x C*HCH₂), 26.7 (2 x CH₂SH).

Synthesis of 4c: this compound was obtained as described above for 4a starting from 3c. The product was purified by reversed-phase flash chromatography using a mixture of MeCN + 0.07% (v/v) TFA and H₂O + 0.1% (v/v) TFA as mobile phase (gradient: from 5% to 30% MeCN in H₂O) and 42.4 mg of 4c (51% yield)
were obtained as a white solid. HRMS (ESI+) calcd. for C_{16}H_{22}N_{4}O_{8}S_{2} [M+H]^+ (m/z): 431.1059, found: 431.1054. \(^1\)H NMR (400 MHz, MeOD-d₄): \(\delta = 7.92\) (t, \(J = 2.0\) Hz, 1H, H\(^1\)), 7.37–7.30 (m, 2H, H\(^3\)), 7.29–7.23 (m, 1H, H\(^4\)), 4.56 (t, \(J = 5.3\) Hz, 2H, C\(^*\)H), 3.93–3.82 (m, 4H, CH₃OH), 3.28 (s, 4H, CH₂SH). \(^{13}\)C NMR (101 MHz, MeOD-d₄): \(\delta = 173.1\) (2 x COCH), 170.3 (2 x COC\(^*\)H), 139.7 (2 x C\(^2\)), 129.9 (1 x C\(^3\)), 117.3 (2 x C\(^3\)), 113.4 (1 x C\(^4\)), 62.8 (2 x CH₂OH), 57.2 (2 x C\(^*\)H), 27.9 (2 x CH₂SH).

**Synthesis of 4d**: this compound was obtained as described above for 4a starting from 3d; 79.6 mg of 4d (92% yield) were obtained as a white solid which required no further purification. HRMS (ESI+) calcd. for C_{18}H_{26}N_{4}O_{8}S_{2} [M+H]^+ (m/z): 459.1372, found: 459.1371. \(^1\)H NMR (400 MHz, MeOD-d₄): \(\delta = 9.80\) (s, 2H, NHCO\(^*\)H), 8.18 (d, \(J = 8.2\) Hz, 2H, C\(^*\)HNHCO), 7.95–7.89 (m, 1H, H\(^1\)), 7.36–7.30 (m, 2H, H\(^3\)), 7.29–7.23 (m, 1H, H\(^4\)), 4.48–4.42 (m, 2H, C\(^*\)HNH), 4.24 (qd, \(J = 6.4, 3.9\) Hz, 2H, C\(^*\)HCH₃), 3.35–3.29 (m, 4H, CH₂), 1.24 (d, \(J = 6.3\) Hz, 6H, CH₃). \(^{13}\)C NMR (101 MHz, MeOD-d₄): \(\delta = 173.3\) (2 x COCH), 170.4 (2 x COC\(^*\)H), 139.5 (2 x C\(^2\)), 129.8 (1 x C\(^3\)), 117.2 (2 x C\(^3\)), 113.3 (1 x C\(^4\)), 68.4 (2 x C\(^*\)HCH₃), 60.6 (2 x C\(^*\)HNH), 28.0 (2 x CH₂), 20.0 (2 x CH₃).

**Synthesis of 4e**: this compound was obtained as described above for 4a starting from 3e; 63.7 mg of 4e (91% yield) were obtained as a white solid which required no further purification. HRMS (ESI+) calcd. for C_{20}H_{30}N_{4}O_{8}S_{2} [M+H]^+ (m/z): 583.1685, found: 583.1696. \(^1\)H NMR (400 MHz, DMSO-d₆): \(\delta = 10.11\) (s, 2H, NHCO\(^*\)H), 9.17 (br s, 2H, OH), 8.34 (d, \(J = 8.1\) Hz, 2H, C\(^*\)HNHCO), 7.88 (t, \(J = 2.1\) Hz, 1H, H\(^1\)), 7.32–7.25 (m, 2H, H\(^3\)), 7.25–7.18 (m, 1H, H\(^4\)), 7.06 (d, \(J = 8.5\) Hz, 4H, H\(^6\)), 6.64 (d, \(J = 8.5\) Hz, 4H, H\(^7\)), 4.58 (td, \(J = 8.4, 5.5\) Hz, 2H, C\(^*\)H), 3.12 (d, \(J = 7.9\) Hz, 4H, CH₂SH), 2.92 (dd, \(J = 13.8, 5.4\) Hz, 2H, C\(^*\)HCH₃), 2.75 (dd, \(J = 13.8, 8.9\) Hz, 2H, C\(^*\)HCH₃), 2.63 (t, \(J = 7.9\) Hz, 2H, SH). \(^{13}\)C NMR (101 MHz, DMSO-d₆): \(\delta = 170.0\) (2 x COC\(^*\)H), 169.4 (2 x COCH), 155.8 (2 x C\(^8\)), 139.0 (2 x C\(^2\)), 130.1 (4 x C\(^6\)), 128.8 (1 x C\(^4\)), 127.4 (2 x C\(^5\)), 114.9 (4 x C\(^7\)), 114.6 (2 x C\(^3\)), 110.6 (1 x C\(^1\)), 55.3 (2 x C\(^*\)H), 37.1 (2 x C\(^*\)HCH₂), 26.9 (2 x CH₂SH).

**Synthesis of 4f**: this compound was obtained as described above for 4a starting from 3f. The product was purified by reversed-phase flash chromatography using a mixture of MeCN + 0.07% (v/v) TFA and H₂O + 0.1% (v/v) TFA as mobile phase (gradient: from 30% to 65% MeCN in H₂O) and 51.3 mg of 4f (44% yield) were obtained as a white solid. HRMS (ESI+) calcd. for C_{32}H_{32}N_{6}O_{3}S_{2} [M+H]^+ (m/z): 629.2004, found: 629.2003. \(^1\)H NMR (400 MHz, DMSO-d₆): \(\delta = 10.82\) (d, \(J = 2.4\) Hz, 2H, H\(^5\)), 10.17 (s, 2H, NHCO\(^*\)H), 8.37 (d, \(J = 7.9\) Hz, 2H,
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$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 7.93 (s, 1H, H$^1$), 7.64 (d, $J = 7.8$ Hz, 2H, H$^2$), 7.35–7.27 (m, 4H, 2H x H$^3$ + 2H x H$^7$), 7.24–7.18 (m, 1H, H$^4$), 7.16 (d, $J = 2.4$ Hz, 2H, H$^5$), 7.05 (ddd, $J = 8.1$, 6.9, 1.2 Hz, 2H, H$^8$), 6.97 (ddd, $J = 8.0$, 7.0, 1.1 Hz, 2H, H$^9$), 7.9 (s, 1H, H$^{10}$), 7.64 (d, $J = 7.8$ Hz, 2H, C*H), 3.23–3.11 (m, 6H, 4H x C$^2$H$_2$SH + 2H x C*$^2$H$_2$), 3.02 (dd, $J = 14.6$, 8.2 Hz, 2H, C*HC$^2$H$_2$), 2.65 (t, $J = 8.0$ Hz, 2H, SH).

$^{13}$C NMR (101 MHz, DMSO-$d_6$): δ = 170.3 (2 x COC), 169.4 (2 x COCH$_2$), 139.0 (2 x C$^2$), 136.0 (2 x C$^6$), 128.8 (1 x C$^4$), 127.3 (2 x C$^{11}$), 123.6 (2 x C$^{13}$), 120.9 (2 x C$^8$), 118.5 (2 x C$^{10}$), 118.2 (2 x C$^9$), 114.7 (2 x C$^3$), 111.3 (2 x C$^7$), 110.8 (1 x C$^1$), 109.6 (2 x C$^{12}$), 54.4 (2 x C$^*$H), 28.0 (2 x C*H$^2$C$^2$H$_2$), 27.0 (2 x CH$_2$SH).

**Synthesis of 4g:** this compound was obtained as described above for 4a starting from 3g. The product was purified by reversed-phase flash chromatography using a mixture of MeCN + 0.07% (v/v) TFA and H$_2$O + 0.1% (v/v) TFA as mobile phase (gradient: from 5% to 30% MeCN in H$_2$O) and 49.1 mg of 4g (53% yield) were obtained as a white solid.

HRMS (ESI+) calcd. for C$_{18}$H$_{22}$N$_4$O$_8$S$_2$ [M+H]$^+$ (m/z): 487.0957, found: 487.0956.

$^1$H NMR (400 MHz, MeOD-$d_4$): δ = 7.85 (t, $J = 2.1$ Hz, 1H, H$^1$), 7.35–7.29 (m, 2H, H$^3$), 7.28–7.22 (m, 1H, H$^4$), 4.90–4.81 (m, 2H, C*H), 3.24 (s, 4H, C$^2$H$_2$SH), 2.91 (dd, $J = 16.6$, 6.4 Hz, 2H, C*HC$^2$H$_2$), 2.78 (dd, $J = 16.6$, 7.0 Hz, 2H, C*HCH$_2$).

$^{13}$C NMR (101 MHz, MeOD-$d_4$): δ = 173.6 (2 x COOH), 173.4 (2 x COCH$_2$), 170.9 (2 x COC$^*$H), 139.8 (2 x C$^3$), 130.1 (1 x C$^4$), 117.6 (2 x C$^3$), 113.8 (1 x C$^1$), 52.3 (2 x C$^*$H), 36.8 (2 x C*HCH$_2$), 28.1 (2 x CH$_2$SH).

**Synthesis of 4h:** this compound was obtained as described above for 4a starting from 3h. The product was purified by reversed-phase flash chromatography using a mixture of MeCN + 0.07% (v/v) TFA and H$_2$O + 0.1% (v/v) TFA as mobile phase (gradient: from 5% to 30% MeCN in H$_2$O) and 49.6 mg of 4h (58% yield) were obtained as a white solid.

HRMS (ESI+) calcd. for C$_{20}$H$_{26}$N$_4$O$_8$S$_2$ [M+H]$^+$ (m/z): 515.1270, found: 515.1271.

$^1$H NMR (400 MHz, MeOD-$d_4$): δ = 7.90 (t, $J = 2.0$ Hz, 1H, H$^1$), 7.35–7.30 (m, 2H, H$^3$), 7.29–7.23 (m, 1H, H$^4$), 4.53 (dd, $J = 8.7$, 5.3 Hz, 2H, C*H), 3.24 (s, 4H, C$^2$H$_2$SH), 2.45 (t, $J = 7.6$ Hz, 4H, C*HCH$_2$C$^2$H$_2$), 2.25–2.12 (m, 2H, C*HCH$_2$), 2.08–1.96 (m, 2H, C*HCH$_2$).

$^{13}$C NMR (101 MHz, MeOD-$d_4$): δ = 176.0 (2 x COOH), 173.1 (2 x COCH$_2$), 171.4 (2 x COC$^*$H), 139.5 (2 x C$^3$), 129.8 (1 x C$^4$), 117.0 (2 x C$^3$), 113.1 (1 x C$^1$), 54.5 (2 x C$^*$H), 30.7 (2 x C*HCH$_2$C$^2$H$_2$), 28.3 (2 x C*HCH$_2$), 27.7 (2 x CH$_2$SH).

**Synthesis of 4i·2TFA:** a solution of 3i (64.3 mg, 0.051 mmol) in dry DCM (3.3 mL) was cooled down to 0 °C in an ice-water bath. Then triisobutylsilane (TIS, 55 µL, 0.21 mmol) and 800 µL of a solution of HBr in CH$_3$COOH (33 wt. %) were added under stirring. After 40 minutes stirring at 0 °C, diethyl ether was
added over the reaction mixture and the product was filtered off and washed with diethyl ether. The product was purified by reversed-phase flash chromatography using a mixture of MeCN + 0.07% (v/v) TFA and H₂O + 0.1% (v/v) TFA as mobile phase (gradient: from 2% to 12% MeCN in H₂O). During the purification the Br⁻ anions were exchanged by TFA⁻ and 31.8 mg of 4i·2TFA (84% yield) were obtained as a white solid. HRMS (ESI+) calcd. for C₂₂H₃₆N₆O₄S₂ [M+H]⁺ (m/z): 513.2318, found: 513.2319. ¹H NMR (400 MHz, MeOD-d₄): δ = 8.01–7.96 (m, 1H, H¹), 7.35–7.19 (m, 3H, 2H x H³ + 1H x H⁴), 4.49 (dd, J = 8.5, 5.5 Hz, 2H, C*H), 3.24 (s, 4H, CH₂SH), 2.93 (t, J = 7.6 Hz, 4H, CH₂NH₃⁺), 2.01–1.87 (m, 2H, C*HCH₂), 1.86–1.63 (m, 6H, 2H x C*HCH₂ + 4H x CH₂CH₂NH₃⁺), 1.62–1.39 (m, 4H, CH₂SH), 2.05–1.89 (m, 2H, C*HCH₂), 1.88–1.68 (m, 6H, 2H x C*HCH₂ + 4H, C*H CH₂CH₃). ¹³C NMR (101 MHz, MeOD-d₄): δ = 173.5 (2 x COCH₂), 172.1 (2 x COC*H), 139.9 (2 x C²), 130.2 (1 x C⁴), 117.5 (2 x C³), 113.6 (1 x C¹), 55.3 (2 x C*H), 40.5 (2 x CH₂NH₃⁺), 32.9 (2 x C*HCH₂), 28.2 (2 x CH₂CH₂NH₃⁺), 28.1 (2 x CH₂SH), 23.8 (2 x C*HCH₂CH₂).

**Synthesis of 4j·2TFA:** to a solution of 3j (133 mg, 0.117 mmol) in dry DCM (3.0 mL), PhSiH₃ (345 μL, 2.80 mmol) was added under inert atmosphere of Ar. Then a solution of Pd(PPh₃)₄ (18 mg, 15 μmol) in dry DCM (2.0 mL) was added. The mixture was stirred at room temperature for 1 hour, after which complete conversion of the starting material was observed by TLC. The crude mixture was filtered through a bed of Celite® and the filtrate was concentrated to dryness under reduced pressure. Diethyl ether was added over the reaction mixture and the product was filtered and washed with diethyl ether. The product was purified by reversed-phase flash chromatography using a mixture of MeCN + 0.07% (v/v) TFA and H₂O + 0.1% (v/v) TFA as mobile phase (gradient: from 2% to 10% MeCN in H₂O) and 46.9 mg of 4j·2TFA were obtained as a white solid (56% yield). HRMS (ESI+) calcd. for C₂₀H₃₂N₆O₄S₂ [M+H]⁺ (m/z): 485.2005, found: 485.2007. ¹H NMR (400 MHz, MeOD-d₄): δ = 8.02–7.97 (m, 1H, H¹), 7.34–7.18 (m, 3H, 2H x H³ + 1H x H⁴), 4.54 (dd, J = 8.0, 5.5 Hz, 2H, C*H), 3.25 (s, 4H, CH₂SH), 2.93 (t, J = 7.6 Hz, 4H, CH₂NH₃⁺), 2.01–1.87 (m, 2H, C*HCH₂), 1.86–1.63 (m, 6H, 2H x C*HCH₂ + 4H x CH₂CH₂NH₃⁺), 1.62–1.39 (m, 4H, CH₂SH), 2.05–1.89 (m, 2H, C*HCH₂), 1.88–1.68 (m, 6H, 2H x C*HCH₂ + 4H, C*H CH₂CH₃). ¹³C NMR (101 MHz, MeOD-d₄): δ = 173.5 (2 x COCH₂), 171.6 (2 x COC*H), 139.9 (2 x C²), 130.2 (1 x C⁴), 117.5 (2 x C³), 113.5 (1 x C¹), 54.8 (2 x C*H), 40.3 (2 x CH₂NH₃⁺), 30.4 (2 x C*HCH₂), 28.1 (2 x CH₂SH), 25.0 (2 x C*HCH₂CH₂).
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Synthesis of 4k·2TFA: this compound was obtained as described above for 4a, starting from 3k. The product was purified by reversed-phase flash chromatography using a mixture of MeCN + 0.07% (v/v) TFA and H2O + 0.1% (v/v) TFA as mobile phase (gradient: from 5% to 10% MeCN in H2O) and 14.6 mg of 4k·2TFA (27% yield) were obtained as a white solid. HRMS (ESI+) calcd. for C22H36N10O4S2 [M+H]+ (m/z): 569.2441, found: 569.2435. 1H NMR (400 MHz, MeOD-d4): δ = 7.99 (s, 1H, H1), 7.33–7.20 (m, 3H, 2 x H3 + 1 x H4), 4.52 (dd, J = 8.3, 5.6 Hz, 2H, C*H), 3.29–3.11 (m, 8H, 4H x CH2SH + 4H x CH2NH), 2.00–1.87 (m, 2H, C*HCH2), 1.86–1.57 (m, 6H, 2H x C*HCH2 + 4H x C*HCH2CH2). 13C NMR (101 MHz, MeOD-d4): δ = 172.1 (2 x CO), 170.5 (2 x COC*H), 157.2 (2 x C5), 138.4 (2 x C2), 128.8 (1 x C4), 116.1 (2 x C3), 112.2 (1 x C1), 53.6 (2 x C*H), 40.6 (2 x CH2NH), 29.2 (2 x C*HCH2), 26.7 (2 x CH2SH), 24.9 (2 x C*HCH2CH2).

Synthesis of 4l·2TFA: this compound was obtained as described above for 4a, starting from 2l. The product was purified by reversed-phase flash chromatography using a mixture of MeCN + 0.07% (v/v) TFA and H2O + 0.1% (v/v) TFA as mobile phase (gradient: from 0% to 10% MeCN in H2O) and 43.2 mg of 4l·2TFA (40% yield) were obtained as a white solid. HRMS (ESI+) calcd. for C12H18N4O2S2 [M+H]+ (m/z): 315.0949, found: 315.0950. 1H NMR (400 MHz, MeOD-d4): δ = 8.07 (t, J = 2.0 Hz, 1H, H1), 7.41–7.36 (m, 2H, H3), 7.36–7.30 (m, 1H, H4), 4.14 (dd, J = 7.2, 5.1 Hz, 2H, C*H), 3.16 (dd, J = 14.7, 5.1 Hz, 2H, CH2), 3.04 (dd, J = 14.7, 7.2 Hz, 2H, CH2). 13C NMR (101 MHz, MeOD-d4): δ = 166.7 (2 x CO), 139.6 (2 x C2), 130.5 (1 x C4), 117.5 (2 x C3), 113.0 (1 x C1), 56.9 (2 x C*H), 26.3 (2 x CH2).
Characterization of building blocks 4a-l

Building block 4a

Figure S1. $^1$H (400 MHz, 298 K in DMSO-$d_6$) and $^1$H-$^1$H gCOSY (400 MHz, 298 K in DMSO-$d_6$) spectra of 4a.
Figure S2. $^1$H-$^{13}$C gHSQC (400 MHz, 298 K in DMSO-$d_6$) and $^1$H-$^{13}$C gHMBC (400 MHz, 298 K in DMSO-$d_6$) spectra of 4a.
Figure S3. $^{13}$C (101 MHz, 298 K in DMSO-$d_6$) spectrum of 4a.

Figure S4. Experimental (lower trace) and simulated (upper trace) ESI-TOF mass spectra for [M+H]$^+$ of 4a.
Building block 4b

Figure S5. $^1$H (400 MHz, 298 K in DMSO-$d_6$) and $^1$H-$^1$H gCOSY (400 MHz, 298 K in DMSO-$d_6$) spectra of 4b.
Figure S6. $^1$H-$^{13}$C gHSQC (400 MHz, 298 K in DMSO-$d_6$) and $^1$H-$^{13}$C gHMBC (400 MHz, 298 K in DMSO-$d_6$) spectra of 4b.
Figure S7. Experimental (lower trace) and simulated (upper trace) ESI-TOF mass spectra for [M+H]^+ of 4b.
Building block 4c

Figure S8. $^1$H (400 MHz, 298 K in MeOD-$d_4$) and $^1$H-$^1$H gCOSY (400 MHz, 298 K in MeOD-$d_4$) spectra of 4c.
Figure S9. $^1$H-$^{13}$C gHSQC (400 MHz, 298 K in MeOD-$d_4$) and $^1$H-$^{13}$C gHMBC (400 MHz, 298 K in MeOD-$d_4$) spectra of 4c.
Figure S10. Experimental (lower trace) and simulated (upper trace) ESI-TOF mass spectra for [M+H]$^+$ of 4c.
Building block 4d

Figure S11. $^1$H (400 MHz, 298 K in MeOD-$d_4$) and $^1$H-$^1$H gCOSY (400 MHz, 298 K in MeOD-$d_4$) spectra of 4d.
Figure S12. $^1$H-$^{13}$C gHSQC (400 MHz, 298 K in MeOD-d$_4$) and $^1$H-$^{13}$C gHMBC (400 MHz, 298 K in MeOD-d$_4$) spectra of 4d.
Figure S13. Experimental (lower trace) and simulated (upper trace) ESI-TOF mass spectra for [M+H]^+ of 4d.
Building block 4e

Figure S14. $^1$H (400 MHz, 298 K in DMSO-$d_6$) and $^1$H-$^1$H gCOSY (400 MHz, 298 K in DMSO-$d_6$) spectra of 4e.
Figure S15. $^1$H-$^{13}$C gHSQC (400 MHz, 298 K in DMSO-$d_6$) and $^1$H-$^{13}$C gHMBC (400 MHz, 298 K in DMSO-$d_6$) spectra of 4e.
Figure S16. $^{13}$C (101 MHz, 298 K in DMSO-$d_6$) spectrum of 4e.

Figure S17. Experimental (lower trace) and simulated (upper trace) ESI-TOF mass spectra for [M+H]$^+$ of 4e.
Building block 4f

Figure S18. $^1$H (400 MHz, 298 K in DMSO-$d_6$) and $^1$H-$^1$H gCOSY (400 MHz, 298 K in DMSO-$d_6$) spectra of 4f.
Figure S19. $^1$H-$^{13}$C gHSQC (400 MHz, 298 K in DMSO-$d_6$) and $^1$H-$^{13}$C gHMBC (400 MHz, 298 K in DMSO-$d_6$) spectra of 4f.
Figure S20. $^{13}$C (101 MHz, 298 K in DMSO-$d_6$) spectrum of 4f.

Figure S21. Experimental (lower trace) and simulated (upper trace) ESI-TOF mass spectra for [M+H]$^+$ of 4f.
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Building block 4g

Figure S22. $^1$H (400 MHz, 298 K in MeOD-$d_4$) and $^1$H-$^1$H gCOSY (400 MHz, 298 K in MeOD-$d_4$) spectra of 4g.
Figure S23. $^1$H-$^{13}$C gHSQC (400 MHz, 298 K in MeOD-$d_4$) and $^1$H-$^{13}$C gHMBC (400 MHz, 298 K in MeOD-$d_4$) spectra of $4g$. 
**Figure S24.** $^{13}$C (101 MHz, 298 K in MeOD-$d_4$) spectrum of 4g.

**Figure S25.** Experimental (lower trace) and simulated (upper trace) ESI-TOF mass spectra for [M+H]$^+$ of 4g.
Building block 4h

Figure S26. $^1$H (400 MHz, 298 K in MeOD-$d_4$) and $^1$H-$^1$H gCOSY (400 MHz, 298 K in MeOD-$d_4$) spectra of 4h.
Figure S27. \(^1\text{H}-^{13}\text{C}\) gHSQC (400 MHz, 298 K in MeOD-\(d_4\)) and \(^1\text{H}-^{13}\text{C}\) gHMBC (400 MHz, 298 K in MeOD-\(d_4\)) spectra of 4h.
**Figure S28.** Experimental (lower trace) and simulated (upper trace) ESI-TOF mass spectra for [M+H]$^+$ of 4h.
Building block 4i

Figure S29. $^1$H (400 MHz, 298 K in MeOD-$d_4$) and $^1$H-$^1$H gCOSY (400 MHz, 298 K in MeOD-$d_4$) spectra of 4i·2TFA.
Figure S30. $^1$H-$^{13}$C gHSQC (400 MHz, 298 K in MeOD-$d_4$) and $^1$H-$^{13}$C gHMBC (400 MHz, 298 K in MeOD-$d_4$) spectra of 4i-2TFA.
Figure S31. $^{13}$C (101 MHz, 298 K in MeOD-$d_4$) spectrum of 4i·2TFA.

Figure S32. Experimental (lower trace) and simulated (upper trace) ESI-TOF mass spectra for [M+H]$^+$ of 4i.
Building block 4j

Figure S33. $^1$H (400 MHz, 298 K in MeOD-$d_4$) and $^1$H-$^1$H gCOSY (400 MHz, 298 K in MeOD-$d_4$) spectra of 4j-2TFA.
Figure S34. $^1$H-$^{13}$C gHSQC (400 MHz, 298 K in MeOD-$d_4$) and $^1$H-$^{13}$C gHMBC (400 MHz, 298 K in MeOD-$d_4$) spectra of 4j·2TFA.
Figure S35. $^{13}$C (101 MHz, 298 K in MeOD-d$_4$) spectrum of 4j·2TFA.

Figure S36. Experimental (lower trace) and simulated (upper trace) ESI-TOF mass spectra for [M+H]$^+$ of 4j.
Building block 4k

Figure S37. $^1$H (400 MHz, 298 K in MeOD-$d_4$) and $^1$H-$^1$H gCOSY (400 MHz, 298 K in MeOD-$d_4$) spectra of 4k·2TFA.
Figure S38. $^1$H-$^{13}$C gHSQC (400 MHz, 298 K in MeOD-$d_4$) and $^1$H-$^{13}$C gHMBC (400 MHz, 298 K in MeOD-$d_4$) spectra of 4k·2TFA.
Figure S39. $^{13}$C (101 MHz, 298 K in MeOD-$d_4$) spectrum of 4k·2TFA.

Figure S40. Experimental (lower trace) and simulated (upper trace) ESI-TOF mass spectra for [M+H]$^+$ of 4k.
Building block 4l

Figure S41. $^1$H (400 MHz, 298 K in MeOD-$d_4$) and $^1$H-$^1$H gCOSY (400 MHz, 298 K in MeOD-$d_4$) spectra of 4l·2TFA.
Figure S42. $^1$H-$^{13}$C gHSQC (400 MHz, 298 K in MeOD-$d_4$) and $^1$H-$^{13}$C gHMBC (400 MHz, 298 K in MeOD-$d_4$) spectra of 4I-2TFA.
Figure S43. $^{13}$C (101 MHz, 298 K in MeOD-$d_4$) spectrum of 4l·2TFA.

Figure S44. Experimental (lower trace) and simulated (upper trace) ESI-TOF mass spectra for [M+H]$^+$ of 4l.
MS analysis of the oligomeric disulfides

Homodimers

Figure S45. Structure and isotopic pattern of [4a]₂.

Figure S46. Structure and isotopic pattern of [4b]₂.

Figure S47. Structure and isotopic pattern of [4c]₂.
Figure S48. Structure and isotopic pattern of [4d]₂.

Figure S49. Structure and isotopic pattern of [4e]₂.

Figure S50. Structure and isotopic pattern of [4f]₂.
Supporting Information

**Figure S51.** Structure and isotopic pattern of $[4g]_2$.

**Figure S52.** Structure and isotopic pattern of $[4h]_2$.

**Figure S53.** Structure and isotopic pattern of $[4i]_2$. 
Figure S54. Structure and isotopic pattern of [4j]₂.

Figure S55. Structure and isotopic pattern of [4k]₂.

Figure S56. Structure and isotopic pattern of [4l]₂.
Heterodimers

**Figure S57.** UPLC-UV (254 nm) trace of the mixture of 4d+4e+4f+4j corresponding to the RP-HPLC trace shown in Figure 2 of the manuscript.

**Figure S58.** UPLC-UV (254 nm) traces of the mixture of 4b+4e+4g+4l corresponding to the RP-HPLC trace shown in Figure 3 of the manuscript.
Figure S59. UPLC-UV (254 nm) traces of the mixture of 4d+4e+4h+4i corresponding to the RP-HPLC trace shown in Figure 4 of the manuscript.
Figure S60. Structure and isotopic pattern of [4j-4d] ($t_R = 10.9$ min in Figure S57).

Figure S61. Structure and isotopic pattern of [4j-4e] ($t_R = 15.5$ min in Figure S57).

Figure S62. Structure and isotopic pattern of [4j-4f] ($t_R = 21.1$ min in Figure S57).
Figure S63. Structure and isotopic pattern of [4d-4e] (t<sub>R</sub> = 22.4 min in Figure S57 and 13.5 min in Figure S59).

Figure S64. Structure and isotopic pattern of [4d-4f] (t<sub>R</sub> = 29.1 min in Figure S57).

Figure S65. Structure and isotopic pattern of [4e-4f] (t<sub>R</sub> = 31.9 min in Figure S57).
Figure S66. Structure and isotopic pattern of [4l-4b] ($t_R = 6.3$ min in Figure S58).

Figure S67. Structure and isotopic pattern of [4l-4g] ($t_R = 7.5$ min in Figure S58).

Figure S68. Structure and isotopic pattern of [4l-4e] ($t_R = 13.7$ min in Figure S58).
Figure S69. Structure and isotopic pattern of [4b-4g] ($t_R = 14.5$ min in Figure S58).

Figure S70. Structure and isotopic pattern of [4b-4e] ($t_R = 19.5$ min in Figure S58).

Figure S71. Structure and isotopic pattern of [4g-4e] ($t_R = 21.9$ min in Figure S58).
Figure S72. Structure and isotopic pattern of [4h-4i] \((t_R = 7.2 \text{ min in Figure S59})\).

Figure S73. Structure and isotopic pattern of [4d-4i] \((t_R = 7.3 \text{ min in Figure S59})\).

Figure S74. Structure and isotopic pattern of [4e-4i] \((t_R = 9.7 \text{ min in Figure S59})\).
Figure S75. Structure and isotopic pattern of [4d-4h] ($t_R = 10.4$ min in Figure S59).

Figure S76. Structure and isotopic pattern of [4e-4h] ($t_R = 13.0$ min in Figure S59).
Trimers

Figure S77. Structure and isotopic pattern of [(4d)\textsubscript{2}-4j] ($t\textsubscript{R} = 13.6$ min in Figure S57).

Figure S78. Structure and isotopic pattern of [4d-4e-4j] ($t\textsubscript{R} = 17.5$ min in Figure S57).

Figure S79. Structure and isotopic pattern of [4d-4h-4i] ($t\textsubscript{R} = 8.8$ min in Figure S59).
Stimuli responsiveness of a representative DCL

**Figure S80.** HPLC trace of a DCL formed by the mixture of 4d, 4e, 4h and 4i at 0.5 mM concentration of each BB, a) in the absence of stimulus b) in the presence of 0.125 mM spermine c) 0.5 mM spermine, d) 2 mM spermine, e) 10 mM spermine.

**Figure S81.** HPLC trace of a DCL formed by the mixture of 4d, 4e, 4h and 4i at 0.5 mM concentration of each BB, a) in the absence of stimulus, b) in the presence of 0.125 mM phytic acid c) 0.5 mM phytic acid, d) 2 mM phytic acid, e) 10 mM phytic acid.
NMR titration experiments

In order to confirm the host-guest interactions we decided to perform NMR-titrations of the amplified dimers with their corresponding guests, that is phytic acid for \([4d]_2\) and spermine for \([4h]_2\). To that end we prepared solutions containing the corresponding BBs that give rise to the amplified compounds under conditions similar to those of the libraries. Each homodimer \([4d]_2\) and \([4h]_2\) was prepared individually by oxidation of its component in a mixture of buffered H$_2$O:MeCN-$d_3$ and DMSO-$d_6$ at 0.5 mM concentration of BBs. The aqueous buffer was adjusted to pH 7.0 using tris(hydroxymethyl)aminomethane-$d_{11}$ (Tris-$d_{11}$) and the $^1$H NMR spectra were acquired after 8 days to ensure complete oxidation (also checked by HPLC). The $^1$H NMR data were consistent with the formation of the respective homodimers \([4d]_2\) (Thr) or \([4h]_2\) (Glu), although a minor formation of the trimer \([4h]_3\) (about 5% mol) could be observed in the latter. Titration of the \([4h]_2\) with spermine showed the shift of several signals (see Figure 5 in the main text and Figures S82-S83).

Figure S82. NMR titration experiment (500 MHz, 4:4:2 H$_2$O:CD$_3$CN:DMSO-$d_6$, Tris-$d_{11}$ buffer pH 7.0, 298 K) of \([4h]_2\) (125 $\mu$M) upon de addition of increasing amounts of spermine (from bottom up: 0, 0.125, 0.25, 0.5, 1.23, 2.41 mM).
Figure S83. Zoomed region of the spectra shown in Figure S82.

Unfortunately the NMR monitoring of the addition of phytate (up to 10 eq.) to [4d]₂ was hampered by the close proximity of the key CHOH proton signals (both in host and guest) to the water suppression region. Moreover, the appearance of a slight turbidity during the titration experiment additionally precluded to confirm the host-guest interaction.