Supporting Information

Design and Synthesis of Cyclic RGD-Pentapeptoids by Consecutive Ugi Reactions

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General Remarks

All commercially available chemicals were used without further purification. Methanol HPLC grade was used in Ugi reactions. Analytical thin layer chromatography (TLC) was performed using silica gel 60 F_{254} aluminum sheets and detected by UV absortion (254 nm) or by charring with a solution of $(NH_4)_6Mo_7O_{24}$ (25.0 g), $Ce(SO_4)_2$ (5.0 g) in concd. H_2SO_4 (50 mL) and water (450 mL) or with a solution of ninhydrin in n-butanol (3:1 w/v) and 3% acetic acid. Flash column chromatography was performed using silica gel (0.040- 0.063

mm). Melting points are uncorrected. ^{1}H and ^{13}C NMR were recorded at 25°C at 300.2 MHz and 75.5 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the TMS (^{1}H NMR) and to the solvent signal (^{13}C NMR). High resolution ESI mass spectra were obtained from a Bruker Apex III Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer equipped with an Infinity™ cell, a 7.0 Tesla superconducting magnet, an RF-only hexapole ion guide and an external electrospray ion source (off axis spray). Preparative HPLC was performed using a Waters YMC-Pack ODS column AA 12505-1520 WT SH-342-5 150 x 20 mm, reference number 20154895.

Experimental Section

General procedure for the Ugi reactions: To a solution of the amine (2.0 mmol) in methanol (50 mL) was added sodium sulfate (0.20 g) and paraformaldehyde (2.0 mmol) [TEA (2.0 mmol) was also added when the amine hydrochloride was used] and stirred for 1h at rt. The acid (1.0 mmol) was added and, after 30 min, the methyl or ethyl isocyanoacetate (1.0 mmol). The reaction was stirred for 24 h at rt. After filtration, the solution was concentrated in vacuum and the residue was purified by column chromatography to yield the respective ester.

General procedure for ester hydrolysis: To a solution of the ester (1.0 mmol) in THF/H_2O (2:1, 35 mL) was added LiOH (2.5 mmol) at 0°C. The reaction was stirred for 1.5 h at 0°C. The solution was acidified with a 2M solution of $NaHSO_4$ to pH 2 and extracted twice with diethyl ether (25 mL). The ether phase was dried with sodium sulfate and concentrated to yield the respective acid, which was used without further purification.

General procedure for Cbz cleavage: To a solution of Cbz-amine (1.0 mmol) in MeOH (50 mL) was added 0.10 g of 10% Pd-C. The reaction vessel were evacuated, purged with hydrogen and kept under a H_2 atmosphere (balloon). The suspension was stirred for 24 h at rt. After filtration through Celite®, the solvent was concentrated and the obtained amine was used without further purification.

General procedure for macrocyclization: To a solution of paraformaldehyde (1.0 mmol) in MeOH (100 mL) was added simultaneously, using a syringe pump, a solution of amino acid (1.0 mmol) in 50 mL of MeOH and a solution of *t*-butyl isocyanide (1.0 mmol) in 50 mL of MeOH at a rate of 0.6 mL/h at rt. After the addition was complete, the reaction mixture was stirred for 24 h, filtered and the solvent was removed. The resulting residue was purified by flash column chromatography.

3-Azidopropyl-1-amine (**12**): A solution of 3-chloropropyl-1-amine **11** (10.0 g, 76.9 mmol) and NaN_3 (15.0 g, 230.7 mmol) in water (77 mL) was heated at 80°C for 15 h. Half of the water was removed under vacuum. The resulting solution was cooled in an ice bath and diethyl ether (50 mL) and KOH (4.0 g) were added, keeping the temperature under 10°C. After separation, the aqueous phase was extracted with diethyl ether (2 x 70 mL). The combined organic layers were dried with Na_2SO_4 and concentrated to furnish the azide **12** (5.8 g, 58.4 mmol) in 76% yield. R_f (CH_2Cl_2/MeOH 10%) = 0.37. IR (ATR, cm^{-1}) : 2090, 1258. ^1H NMR ($CDCl_3$): δ 3.38 [t, *J* = 6.8 Hz, 2H], 2.81 [t, *J* = 6.8 Hz, 2H], 2.25 [s, 2H], 1.74 [quint, *J* = 6.8 Hz, 2H]. ^{13}C NMR ($CDCl_3$): δ 49.0, 39.2, 31.9. Caution: azides maybe explosive in high concentration. They should not be heated or treated with transition metal ions.

***N*-(2,4-dimethoxybenzyl)-3-azidopropyl-1-amine** (**13**): A solution of azide **12** (2.0 g, 20.0 mmol) and 2,4-dimethoxybenzaldehyde (2.76 g, 16.6 mmol) in MeOH (60 mL) was stirred for 2h at rt. $NaBH_4$ (1.14 g, 30.0 mmol) was added to the reaction mixture in small portions at 4°C. The solution was stirred for 2 h at rt and then diluted in diethyl ether (50 mL). A solution of NaOH 2 M (20 mL) was added carefully. The organic layer was washed with water (2 x 50 mL) and brine (50 mL) and then dried with Na_2SO_4, filtered and concentrated to furnish the azide **13** (3.85 g, 18.4 mmol) in 92% yield. R_f (CH_2Cl_2/MeOH 10%) = 0.83. IR (ATR, cm^{-1}): 2091, 1611, 1504, 1250, 1033. ^1H NMR ($CDCl_3$): δ 7.12 [d, *J* = 8.0 Hz, 1H], 6.46 [d, *J* = 2.2 Hz, 1H], 6.43 [dd, *J* = 8.0 and 2.2 Hz, 1H], 3.81 [s, 3H], 3.80 [s, 3H], 3.71 [s, 2H], 3.36 [t, *J* = 6.8 Hz, 2H], 2.66 [t, *J* = 6.8 Hz, 2H], 1.77 [quint, *J* = 6.8 Hz, 2H], 1.57 [br s, 1H]. ^{13}C NMR ($CDCl_3$): δ 159.9, 158.4, 130.3, 120.6, 103.5, 98.4, 55.3, 55.2, 49.6, 48.8, 46.0, 29.3.

Azide 15: A solution of azide **13** (0.53 g, 2.12 mmol) and *N*-pmc-1-*H*-Pyrazole-1-carboxamidine **14**[1] (0.80 g, 2.12 mmol) in DMF (2.5 mL) was stirred at 130°C for 24 h in a sealed tube. After cooling to rt, the solution was diluted with EtOAc (20 mL), washed with saturated NH_4Cl (10 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated to furnish a yellow oil. After purification by column chromatography (silica gel, Hex/EtOAc 1:1), the azide **15** (1.0 g, 1.8 mmol) was obtained as a white powder in 85% yield. R_f (hexane/EtOAc 50%)= 0.77. m.p. (from EtOAc) = 127-130°C. IR (ATR, cm^{-1}): 3424, 3331, 2973, 2933, 2095, 1614, 1537, 1504, 1259, 1107. ^1H NMR ($CDCl_3$): δ 7.01 [d, *J* = 8.4 Hz, 1H], 6.45-6.40 [m, 4H], 4.33 [s, 2H], 3.79 [s, 3H], 3.78 [s, 3H], 3.40 [t, *J* = 6.8 Hz, 2H], 3.23 [t, *J* = 6.8 Hz, 2H], 2.62 [t, *J* = 6.8 Hz, 2H], 2.57 [s, 3H], 2.56 [s, 3H], 2.10 [s, 3H], 1.81-1.74 [m, 4H], 1.30 [s, 6H]. ^{13}C NMR ($CDCl_3$): δ 160.9, 157.7, 155.5, 153.2, 135.3, 134.6, 133.9, 130.0, 123.7, 117.7, 115.9, 104.4, 98.7, 73.5, 55.4, 55.3, 49.0, 46.2, 45.3, 32.8, 26.9, 26.7, 21.3, 18.5, 17.4, 12.0. HRMS (ESI-FT-ICR) *m/z*: 559.2685 $[M+H]^+$; calcd. for $C_{27}H_{39}N_6O_5S$: 559.2697.

Amine 16: A suspension of active Lindlar catalyst (0.23 g) in a solution of azide **15** (0.65 g, 1.16 mmol) in ethanol (150 mL) was stirred under H_2 atmosphere for 6 h at rt. After filtration through Celite®. The solution was concentrated in vacuum to give amine **16** (0.61 g, 1.16 mmol) as a colorless oil in quantitative yield that was used without further purification in Ugi reactions. R_f (CH_2Cl_2/MeOH 10%) = 0.43. ^1H NMR ($CDCl_3$): δ 6.98 [d, *J* = 3.6 Hz, 1H], 6.38 [d, *J* = 2.0 Hz, 1H], 6.28 [bs, 1H], 4.46 [s, 2H], 3.75 [s, 3H], 3.73 [s, 3H], 3.36 [s, 2H], 3.37 [bs, 2H], 2.96 [bs, 2H], 2.73 [t, *J* = 6.0, 2H], 2.58 [t, *J* = 6.8 Hz, 2H], 2.53 [s, 3H], 2.52 [s, 3H], 2.07 [s, 3H], 1.78 [t, *J* = 6.8 Hz, 2H], 1.66 [bs, 2H], 1.29 [s, 6H]. ^{13}C NMR ($CDCl_3$): δ 160.3, 158.0, 156.9, 153.1, 135.4, 134.7, 134.0, 130.0, 123.6, 117.7, 104.1, 98.2, 73.4, 55.3, 55.2, 44.4, 43.4, 37.1, 32.8, 28.6, 26.7, 21.3, 18.4, 17.4, 12.0. HRMS (ESI-FT-ICR) *m/z*: 533.2782 $[M+H]^+$; calcd. for $C_{27}H_{41}N_4O_5S$: 533.2792.

Ester 8a: Compound **8a** was prepared following the general procedure for Ugi reactions using 3-amino-1-propanol (3.00 g, 40.0 mmol) and Cbz-glycine (4.18 g, 20.0 mmol) in 51% yield (4.20 g, 10.2 mmol) after flash column chromatography ($CHCl_3$/MeOH 99:1) as

a colorless oil. R_f (CH_2Cl_2/MeOH 3%)= 0.21. ^{1}H NMR ($CDCl_3$): δ 7.35-7.29 [m, 5H], 5.92 [br s, H], 5.09 [s, 2H], 4.16 [q, *J* = 7.2 Hz, 4H], 4.04-3.94 [m, 6H], 3.68 [br s, 1H], 3.58-3.50 [m, 4H], 1.84-1.71 [m, 2H], 1.25 [t, *J* = 7.2 Hz, 3H]. ^{13}C NMR ($CDCl_3$): δ 170.0, 169.8, 169.3, 156.6, 136.2, 128.4, 128.1, 127.9, 66.9, 61.4, 59.1, 50.5, 46.1, 42.2, 41.1, 30.1, 14.0. HRMS (ESI-FT-ICR) *m/z*: 432.1741 $[M+Na]^+$; calcd. for $C_{19}H_{27}N_3NaO_7$: 432.1741.

Ester 8b: Compound **8b** was prepared following the general procedure for Ugi reactions using Boc-monoprotected ethylenediamine[2] (4.00 g, 25 mmol) and Cbz-glycine (2.61 g, 12.5 mmol) in 98% yield (6.05g, 12.2 mmol) after flash column chromatography ($CHCl_3$/MeOH 99:1) as a viscous pale yellow oil. R_f (CH_2Cl_2/MeOH 3%) = 0.31.^{1}H NMR ($CDCl_3$): δ 7.35-7.28 [m, 5H], 5.86 [br s, 1H], 5.76 [br s, 1H], 5.10 [s, 2H], 4.19 [q, *J* = 7.0 Hz, 2H], 4.07-3.98 [m, 6H], 3.47 [t, *J* = 5.6 Hz, 2H], 3.28 [m, 2H], 2.09 [br s, 1H], 1.47 [s, 9H], 1.27 [t, *J* = 7.0 Hz, 3H]. ^{13}C NMR ($CDCl_3$): δ 170.1, 169.9, 169.4, 156.2, 136.3, 128.4, 128.0, 127.9, 79.4, 66.8, 61.5, 51.1, 49.1, 42.3, 41.1, 38.6, 28.4, 14.0. HRMS (ESI-FT-ICR) *m/z*: 517.2264 $[M+Na]^+$; calcd. for $C_{23}H_{34}N_4NaO_8$: 517.2269.

Ester 8c: Compound **8c** was prepared following the general procedure for Ugi reactions using glycine *t*-butyl ester hydrochloride (1.53 g, 9.14 mmol) and Cbz-glycine (0.96 g, 4.57 mmol) in 84% yield (1.85 g, 3.83 mmol) after flash column chromatography ($CHCl_3$/MeOH 99:1) as a pale yellow oil. R_f (CH_2Cl_2/MeOH 3%)= 0.49.^{1}H NMR($CDCl_3$): δ 7.35-7.27 [m, 5H], 5.79 [br s, 1H], 5.66 [br s, 1H], 5.10 [s, 2H], 4.20-4.14 [m, 2H], 4.12-3.96 [m, 8H], 1.47 [s, 9H], 1.28-1.23 [m, 3H]. ^{13}C NMR($CDCl_3$): δ 169.6, 168.4, 168.3, 156.2, 136.3, 128.4, 128.0, 127.9, 83.3, 66.9, 61.4, 52.9, 52.1, 42.4, 41.0, 27.9, 14.0. HRMS (ESI-FT-ICR) *m/z*: 488.1996 $[M+Na]^+$; calcd. for $C_{22}H_{31}N_3NaO_8$: 488.2003.

Ester 9a: Compound **8a** (3.04g, 7.42 mmol) was hydrolyzed following the general procedure for ester hydrolysis yielding the corresponding acid in 93% yield (2.65 g, 6.9 mmol). This was used following the general procedure for Ugi reactions with glycine *t*-butyl ester hydrochloride (2.33 g, 13.9 mmol) to give, after flash column chromatography

($CHCl_3$/MeOH 9:1), ester **9a** in 62% yield (2.75 g, 4.28 mmol) as a clear yellow oil. R_f (CH_2Cl_2/MeOH 3%) = 0.24. ^{1}H NMR ($CDCl_3$): δ 7.35-7.29 [m, 5H], 5.09 [s, 2H], 4.19-3.92 [m, 2H], 3.69-3.45 [m, 4H], 1.84-1.68 [m, 2H], 1.47 [s, 9H], 1,25 [t, *J* = 7.2 Hz, 3H]. ^{13}C NMR($CDCl_3$): δ 169.9, 169.8, 169.6, 169.3, 168.4, 156.6, 136.3, 128.4, 128.0, 127.9, 83.1, 81.1, 66.8, 61.4, 59.3, 52.5, 50.1, 45.9, 44.5, 42.3, 41.0, 40.0, 30.2, 27.9, 14.0. HRMS (ESI-FT-ICR) *m/z*: 660.2851 $[M+Na]^+$; calcd. for $C_{29}H_{43}N_5NaO_{11}$: 660.2856.

Ester 9b: Ester **8b** (1.32 g, 2.65 mmol) was hydrolyzed following the general procedure yielding the corresponding acid (1.12 g, 2.4 mmol, 91% yield). This was subsequently used in the Ugi reaction with glycine *t*-butyl ester hydrochloride **3c** (0.80 g, 4.8 mmol), following the general procedure, to give ester **9b** (1.19 g, 1.63 mmol, 68% yield) after flash column chromatography ($CHCl_3$/MeOH 99:1) as a yellow oil. R_f (CH_2Cl_2/MeOH 3%) = 0.32. ^{1}H NMR($CDCl_3$): δ 7.35-7.29 [m, 5H], 5.96 [br s, 1H], 5.85 [br s, 1H], 5.10 [s, 2H], 4.20-3.93 [m, 14H], 3.53 [s, 1H], 3.47-3.38 [m, 2H], 3.27 [m, 2H], 1.46 [s, 9H], 1.41 [s, 9H], 1.27-1.23 [m, 3H]. ^{13}C NMR($CDCl_3$): δ 169.9, 169.5, 169.3, 168.5, 168.3, 167.8, 156.2, 136.4, 128.4, 128.0, 127.9, 83.2, 79.5, 66.8, 61.4, 52.8, 51.8, 51.3, 50.5, 49.0, 42.3, 41.0, 38.4, 28.3, 27.9, 14.1. HRMS (ESI-FT-ICR) *m/z*: 745.3374 $[M+Na]^+$; calcd. for $C_{33}H_{50}N_6NaO_{12}$: 745.3379.

Ester 9c: After hydrolysis of ester **8c** (1.45 g, 3.12 mmol) following the general procedure, the resulting acid (1.30 g, 2.97 mmol) was used in the Ugi reaction with Boc-monoprotected ethylenediamine[2] (0.95 g, 5.94 mmol) following the general procedure to give ester **9c** (1.84 g, 2.60 mmol, 87% yield) after flash column chromatography (AcOEt/MeOH 9:1) as a pale yellow oil. R_f (CH_2Cl_2/MeOH 3%) = 0.31. ^{1}H NMR ($CDCl_3$): δ 7.36-7.29 [m, 5H], 5.94 [br s, 2H], 5.82 [br s, 1H], 5.09 [d, *J* = 7.6 Hz, 2H], 4.20-3.96 [m, 14H], 3.51-3.47 [m, 2H], 3.30-3.28 [m, 2H], 2.26 [s, 1H], 1.46 [s, 9H], 1.41 [s, 9H], 1.27-1.23 [m, 3H]. ^{13}C NMR ($CDCl_3$): δ 170.3, 170.0, 169.6, 169.4, 168.4, 156.3, 136.3, 128.4, 128.0, 128.0, 83.4, 82.8, 66.8, 61.5, 50.9, 49.0, 42.4, 41.2, 41.0, 40.7, 38.9, 28.3, 27.9, 14.0. HRMS (ESI-FT-ICR) *m/z*: 745.3386 $[M+Na]^+$; calcd. for $C_{33}H_{50}N_6NaO_{12}$: 745.3379.

Cyclic peptoid 10a: Ester **9a** (1.09 g, 1.75 mmol) was hydrolyzed and the Cbz protection removed following the general procedures to give the acyclic amino acid (0.73 g, 1.53 mmol) which was submitted to macrocyclization according to the general procedure, to yield the cyclic peptoid **10a** (0.19 g, 0.30 mmol, 20% yield) as a colourless oil after flash column chromatography ($CHCl_3$/MeOH 8:2). R_f (CH_2Cl_2/MeOH 6%) = 0.19. ^{1}H NMR (CD_3OD): δ 4.09-3.83 [m, 7H], 3.67-3.55 [m, 4H], 1.88-1.76 [m, 2H], 1.50 [s, 9H], 1.40 [s, 9H]. ^{13}C NMR (CD_3OD): δ 171.3, 170.6, 169.6, 169.5, 168.5, 168.0, 166.5, 83.6, 77.2, 58.3, 51.7, 51.3, 50.7, 49.7, 46.7, 44.9, 43.2, 40.3, 31.8, 28.3, 27.9. HRMS (ESI-FT-ICR) *m/z*: 593.2906 $[M+Na]^+$; calcd. for $C_{25}H_{42}N_6NaO_9$: 593.2905.

Cyclic peptoid 10b: The free amino acid (1.00 g, 1.78 mmol) prepared from ester **9b** (1.29 g, 1.78 mmol, quantitative yield) following the general procedures of ester hydrolysis and Cbz cleavage, was submitted to macrocyclization according to the general procedure to furnish the cyclic peptoid **10b** (0.22 mg, 0.34 mmol, 19% yield) after flash column chromatography ($CHCl_3$/MeOH 95:5) as a colourless foam. R_f (CH_2Cl_2/MeOH 6%) = 0.46. ^{1}H NMR (CD_3OD): δ 4.18-3.31 [m, 18H], 1.50 [s, 9H], 1.42 [s, 9H], 1.41 [s, 9H]. ^{13}C NMR (CD_3OD): δ 171.2, 170.7, 169.5, 169.4, 168.2, 167.9, 166.2, 156.0, 83.3, 79.9, 77.2, 53.3, 51.7, 50.5, 50.4, 49.4, 42.0, 40.2, 39.2, 28.3, 28.3, 27.9. HRMS (ESI-FT-ICR) *m/z*: 678.3433 $[M+Na]^+$; calcd. for $C_{29}H_{49}N_7NaO_{10}$: 678.3437.

Cyclic peptoid 10c: After cleavage and Cbz deprotection of ester **9c** (0.47 g, 0.66 mmol), the resulting amino acid (0.36 g, 0.64 mmol) was submitted to macrocyclization according to the general procedure to furnish cyclic peptoid **10c** (0.09 g, 0.13 mmol, 21% yield) after flash column chromatography ($CHCl_3$/MeOH 95:5) as a white foam. R_f (CH_2Cl_2/MeOH 6%) = 0.46. ^{1}H NMR (CD_3OD): δ 4.20-3.29 [m, 18H], 1.49 [s, 9H], 1.43 [s, 9H], 1.40 [s, 9H]. ^{13}C NMR (CD_3OD): δ 171.1, 170.7, 169.5, 169.5, 168.8, 167.9, 166.6, 156.1, 83.2, 79.8, 77.6, 53.7, 51.7, 51.5, 50.4, 49.9, 42.1, 40.1, 38.8, 28.3, 28.2, 27.8. HRMS (ESI-FT-ICR) *m/z*: 678.3439 $[M+Na]^+$; calcd. for $C_{29}H_{49}N_7NaO_{10}$: 678.3437.

Ester 17: Compound **17** was prepared following the general procedure for Ugi reactions using amine **16** (0.62 g, 1.16 mmol) and Cbz-glycine (0.12 g, 0.74 mmol) in 68% yield (0.43 g, 0.5 mmol) after flash column chromatography (CH_2Cl_2/MeOH 99:1) as a pale yellow foam. R_f (CH_2Cl_2/MeOH 3%) = 0.36. ^{1}H NMR ($CDCl_3$): δ 7.48 [bs, 1H], 7.34-7.29 [m, 5H], 7.03-6.90 [m, 1H], 6.60 [br s, 1H], 6.45-6.33 [m, 2H], 5.78-5.72 [m, 1H], 5.09 [s, 1H], 5.08 [s, 1H], 4.36 [br s, 2H], 4.04-3.94 [m, 4H], 3.80-3.73[m, 6H], 3.71[d, *J* = 3.4 Hz, 3H], 3.42-3.23 [m, 4H], 2.62-2.59[m, 2H], 2.54-2.52 [m, 6H], 2.09 [s, 3H], 1.93-1.77 [m, 2H], 1.30 [s, 3H], 1.29 [s, 3H]. ^{13}C NMR ($CDCl_3$): δ 169.9, 169.5, 169.1, 160.7, 157.7, 156.2, 155.5, 153.3, 136.4, 135.3, 134.6, 130.0, 129.7, 128.4, 127.9, 127.8, 123.8, 117.8, 104.5, 98.6, 73.6, 66.7, 55.3, 55.2, 52.2, 45.5, 42.5, 41.0, 32.7, 26.6, 25.9, 21.3, 18.4, 17.3, 12.0. HRMS (ESI-FT-ICR) *m/z*: 875.3599 $[M+Na]^+$; calcd. for $C_{42}H_{56}N_6NaO_{11}SNa$: 875.3620.

Ester 18: Ester **18** was obtained following the general procedure for Ugi reactions with glycine *t*-butyl ester hydrochloride (0.13 g, 0.78 mmol) and the acid (0.37 g, 0.39 mmol), prepared from ester **17**, following the general procedure for ester hydrolysis, in 85% yield (0.36 g, 0.33 mmol) after flash column chromatography (CH_2Cl_2/MeOH 99:1) as a white foam. R_f (CH_2Cl_2/MeOH 3%) = 0.34.^{1}H NMR ($CDCl_3$): δ 7.34-7.29 [m, 5H], 7.07-6.90 [m,1H], 6.44-6.39 [m, 2H], 5.09 [s, 1H], 5.08 [s, 1H], 4.39-4.31 [m, 2H], 4.22-3.86 [m, 12H], 3.80-3.65 [m, 9H], 3.41-3.23 [m, 4H], 2.60-2.59 [m, 2H], 2.52 [s, 3H], 2.49 [s, 3H], 2.07 [s, 3H], 1.80-1.77 [m, 4H], 1.48-1.45 [m, 11H], 1.29 [s, 6H]. ^{13}C NMR ($CDCl_3$): δ 170.0, 169.9, 169.7, 169.2, 168.5, 167.9, 160.8, 157.9, 156.3, 155.5, 153.3, 136.4, 135.3, 134.7, 129.9, 128.5, 128.0, 127.9, 127.8, 123.8, 117.8, 104.4, 98.7, 83.6, 73.5, 66.7, 55.3, 52.2, 51.5, 51.2, 50.4, 42.7, 40.8, 32.7, 27.9, 26.7, 21.3, 18.4, 17.4, 12.0. HRMS (ESI-FT-ICR) *m/z*: 1103.4748 $[M+Na]^+$; calcd. for $C_{52}H_{72}N_8O_{15}SNa$: 1103.4730.

Cyclic peptoid 2: After cleavage and Cbz deprotection of ester **18** (1.46 g, 1.35 mmol), the resulting amino acid (1.26 g, 1.35 mmol) was submitted to macrocyclization according to the general procedure to furnish after flash column chromatography ($CHCl_3$/MeOH 90:10), the protected cyclic peptoid (0.65 g, 47% yield). This was submitted to TFA/CH_2Cl_2 1:1 (6

mL) for 2h, removal of the TFA by co-evaporation with toluene, giving the cyclic peptoid **2** in 70% yield after preparative HPLC (r.t. = 13.2 min., solvent A: H_2O + 0.1% TFA, solvent B: CH_3CN + 0.1% TFA, gradient 2% to 50% B in 30 min, flow: 25mL/min) as a white powder. m.p. (from H_2O) = 162-164°C. ^{1}H NMR (CD_3OD): δ 4.47 [bs, 1H], 4.37-3.48 [m, 15H], 3.27-3.18 [m, 2H], 1.80 [t, *J*=6 Hz, 1H], 1.40 [d, *J*=4.8 Hz, 2H], 1.37-1.32 [m, 9H]. ^{13}C NMR (CD_3OD): δ 174.5, 172.6, 172.4, 172.2, 171.5, 170.9, 169.9, 158.4, 55.2, 54.4, 52.3, 51.8, 51.2, 47.8, 46.5, 42.0, 41.0, 40.4, 28.9, 28.3. HRMS (ESI-FT-ICR) *m/z*: 556.2845 $[M+H]^+$; calcd. for $C_{22}H_{38}N_9O_8$: 556.2843.

Ester 19: Ester **19** was obtained following the general procedure for Ugi reaction with amine **16** (0.94 g, 1.76 mmol) and the acid (0.70 g, 1.60 mmol) prepared from ester **8c** following the general procedure for ester hydrolysis, in 53% yield (0.92 g, 0.85 mmol) after flash column chromatography (CH_2Cl_2/MeOH 97:3) as a white foam. R_f (CH_2Cl_2/MeOH 3%) = 0.34. ^{1}H NMR ($CDCl_3$): δ 7.34-7.30 [m, 5H], 7.01-6.92 [m,1H], 6.69 [br s, 1H], 6.44-6.34 [m, 2H], 5.84-5.74 [m, 1H], 5.09 [s, 1H], 5.07 [s, 1H], 4.39-4.34 [m, 2H], 4.18-3.93 [m, 12H], 3.79-3.68 [m, 9H], 3.44-3.27 [m, 4H], 2.63-2.59 [m, 2H], 2.53 [s, 6H], 2.08 [s, 4H], 1.90-1.78 [m, 4H], 1.46-1.45 [m, 9H], 1.30 [s, 6H]. ^{13}C NMR ($CDCl_3$): δ 170.1, 169.9, 169.8, 169.2, 168.3, 167.6, 160.9, 157.8, 156.3, 155.6, 153.5, 136.4, 135.4, 134.8, 130.1, 128.4, 128.0, 127.9, 127.8, 124.0, 117.9, 104.5, 98.7, 82.7, 73.6, 66.8, 55.4, 52.2, 51.8, 50.8, 50.3, 42.4, 41.1, 32.7, 28.0, 26.7, 21.4, 18.5, 17.4, 12.1. HRMS (ESI-FT-ICR) *m/z*: 1081.4895 $[M+H]^+$; calcd. for $C_{52}H_{73}N_8O_{15}S$: 1081.4911.

Cyclic peptoid 3: After cleavage and Cbz deprotection of ester **20** (0.43 g, 0.4 mmol), the obtained intermediate amino acid (0.37 g, 0.4 mmol) was submitted to macrocyclization according to the general procedure. The resulting cyclic peptoid (0.21 g, 30% yield) was purified by flash column chromatography ($CHCl_3$/MeOH 90:10), and subsequently was submitted to treatment with TFA/CH_2Cl_2 1:1 (6 mL) for 2h, removal of TFA by coevaporation with toluene, giving the cyclic peptoid **3** in 71% yield after preparative HPLC (r.t. = 12.6min., solvent A: H_2O + 0.1% TFA, solvent B: CH_3CN + 0.1% TFA, gradient 2% to 50% B in 30 min, flow: 25mL/min) as a pale yellow powder. m.p. (from

methanol) = 152-154°C. ^{1}H NMR (CD_3OD): δ 4.40-3.39 [m, 16H], 3.26-3.15 [m, 2H], 1.79-1.70 [m, 1H], 1.39 [s, 2H], 1.35-1.30 [m, 9H]. ^{13}C NMR (CD_3OD): δ 173.9, 173.2, 172.6, 172.0, 171.3, 170.7, 169.7, 158.4, 55.8,54.1, 53.2, 52.8, 52.2, 51.9, 47.6, 46.0, 45.6, 39.9, 28.8, 27.7. HRMS (ESI-FT-ICR) *m/z*: 578.2669 $[M+Na]^+$; calcd. for $C_{22}H_{37}N_9NaO_8$: 578.2663.

Spectra of selected compounds

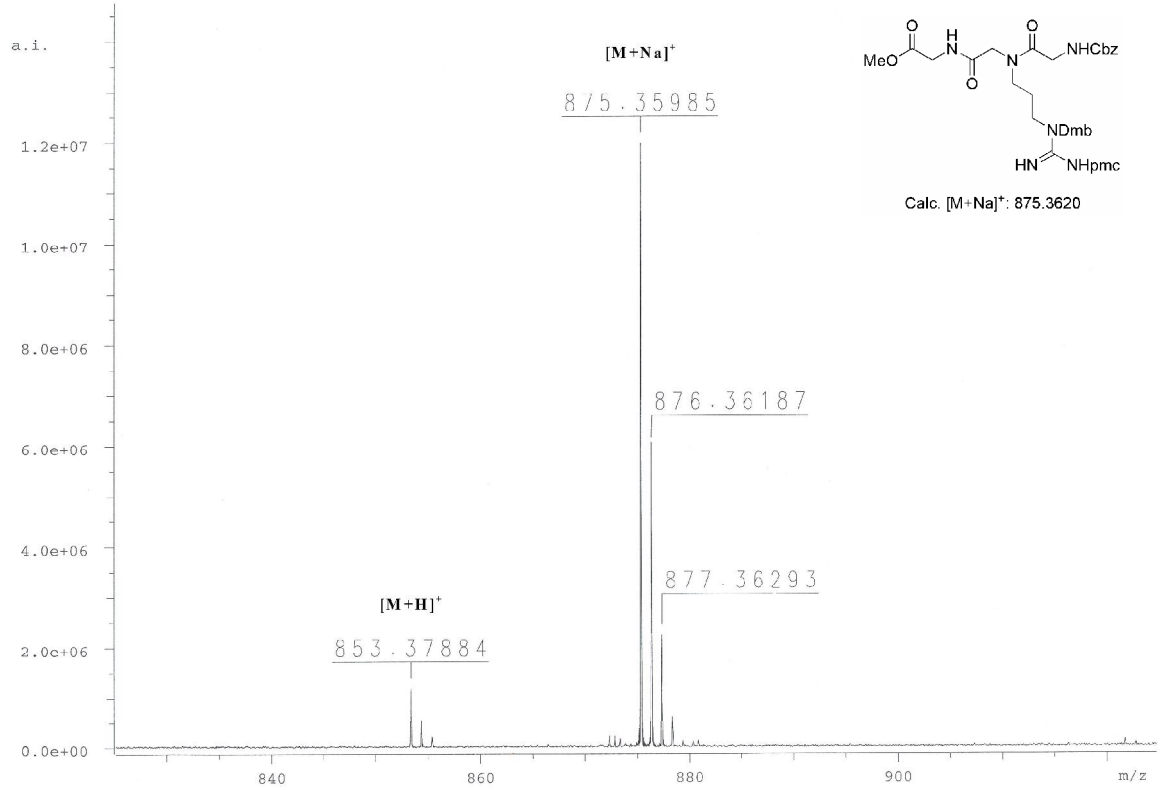

Figure 1. HRMS (ESI-FT-ICR) spectrum of ester **17**.

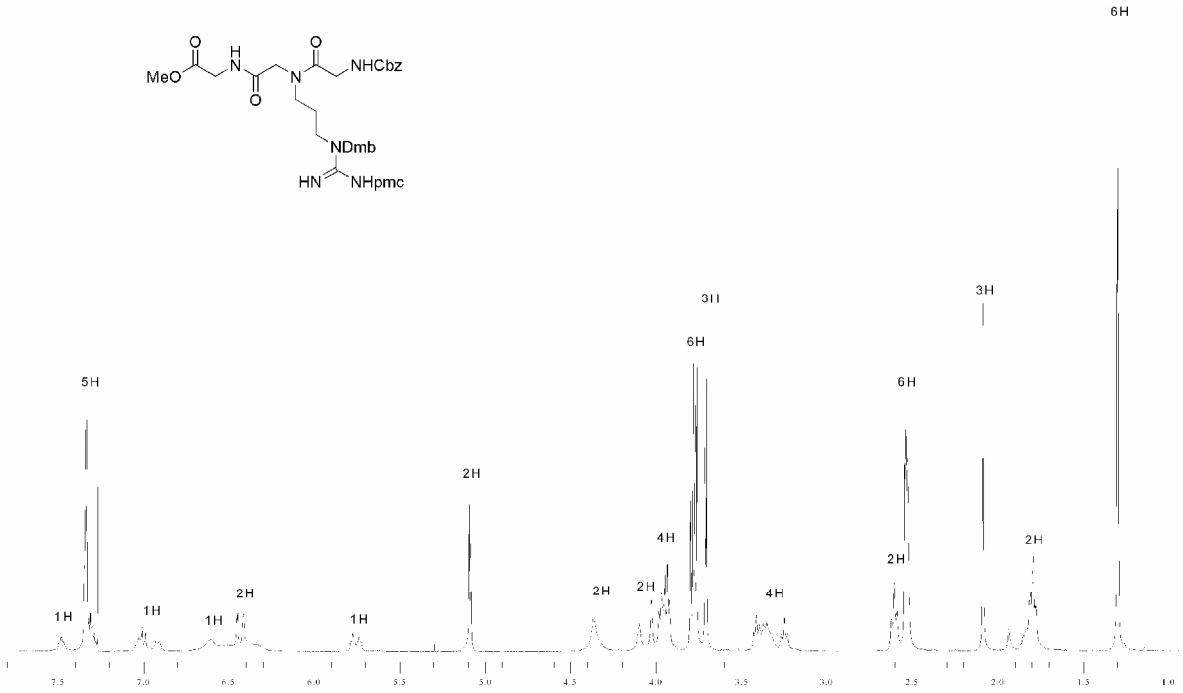

Figure 2. ^{1}H NMR spectrum of ester **17**.

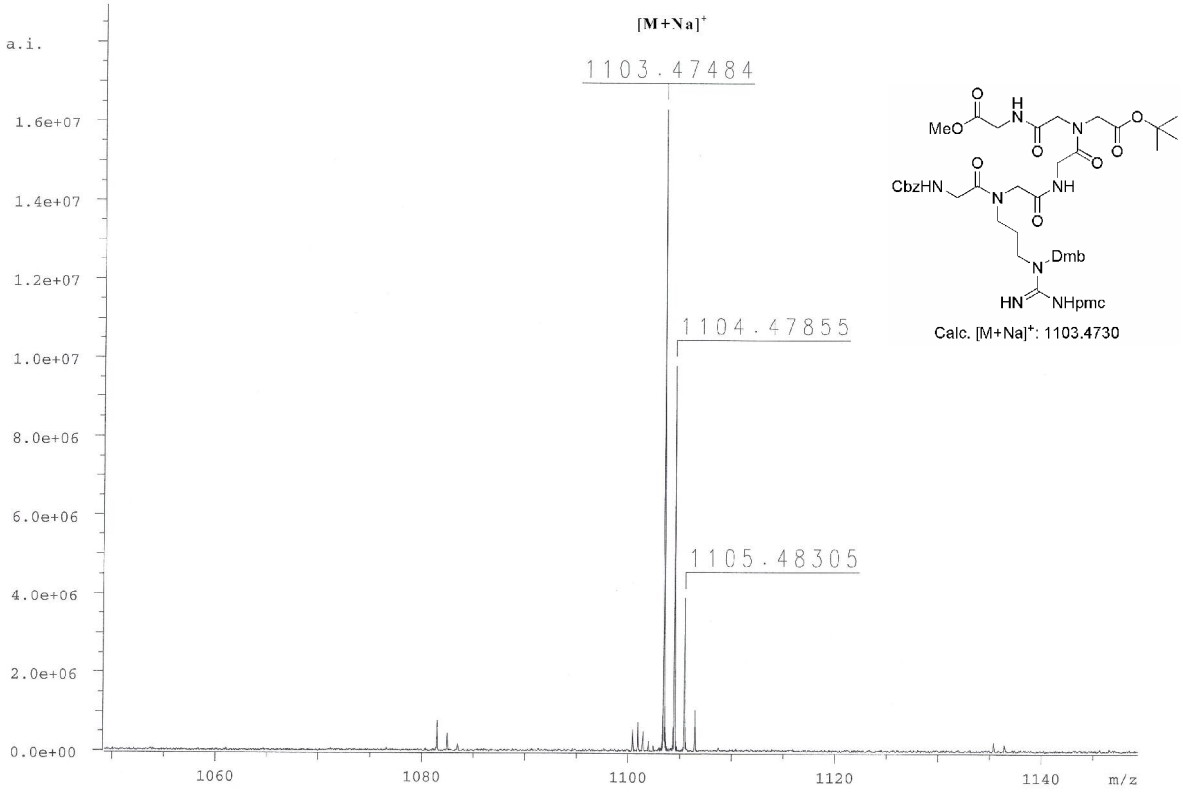

Figure 3. HRMS (ESI-FT-ICR) spectrum of ester **18**.

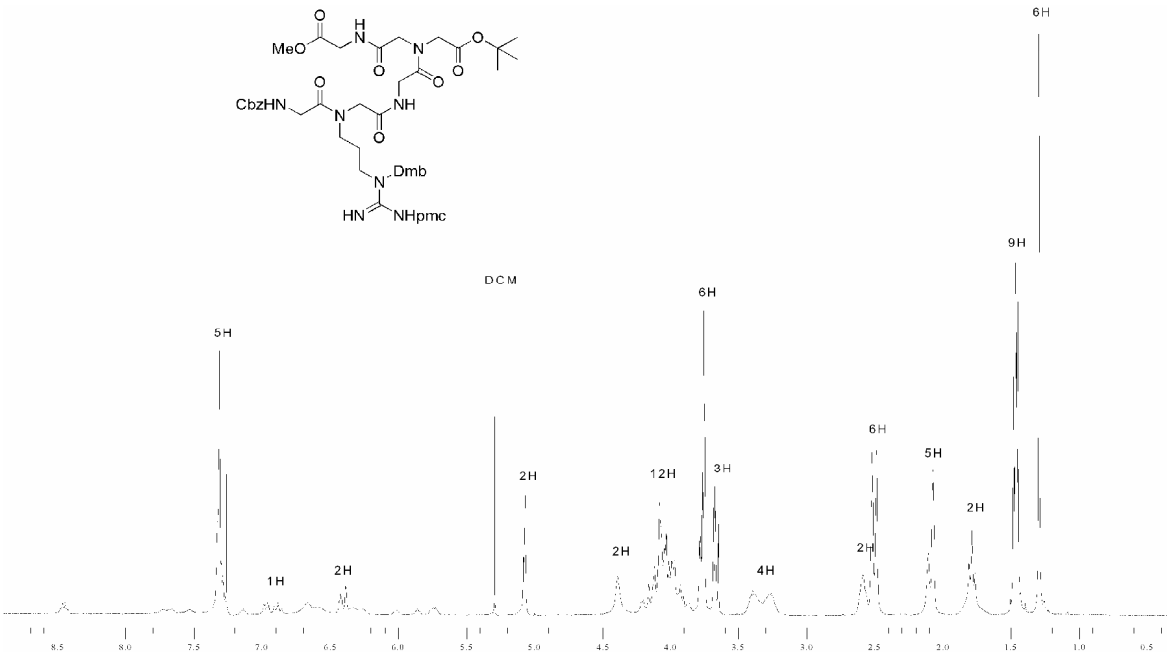

Figure 4. ^{1}H NMR spectrum of ester **18**.

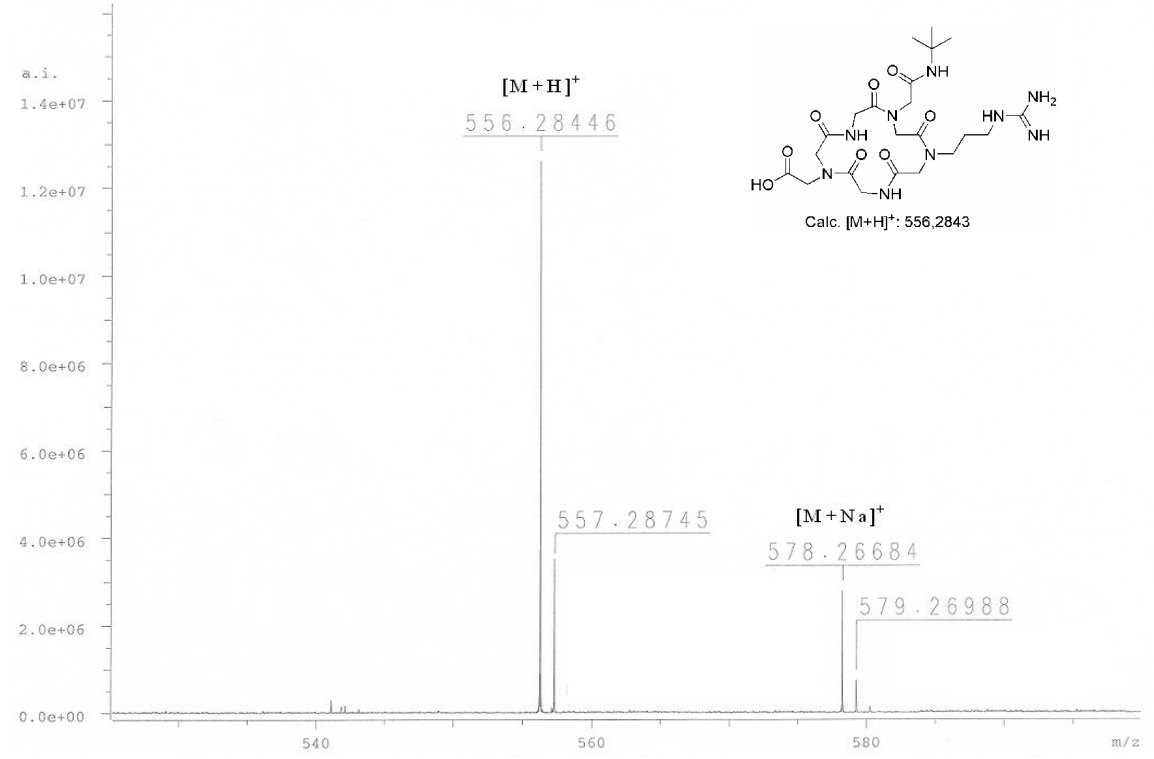

Figure 5. HRMS (ESI-FT-ICR) spectrum of cyclopeptoid **2**.

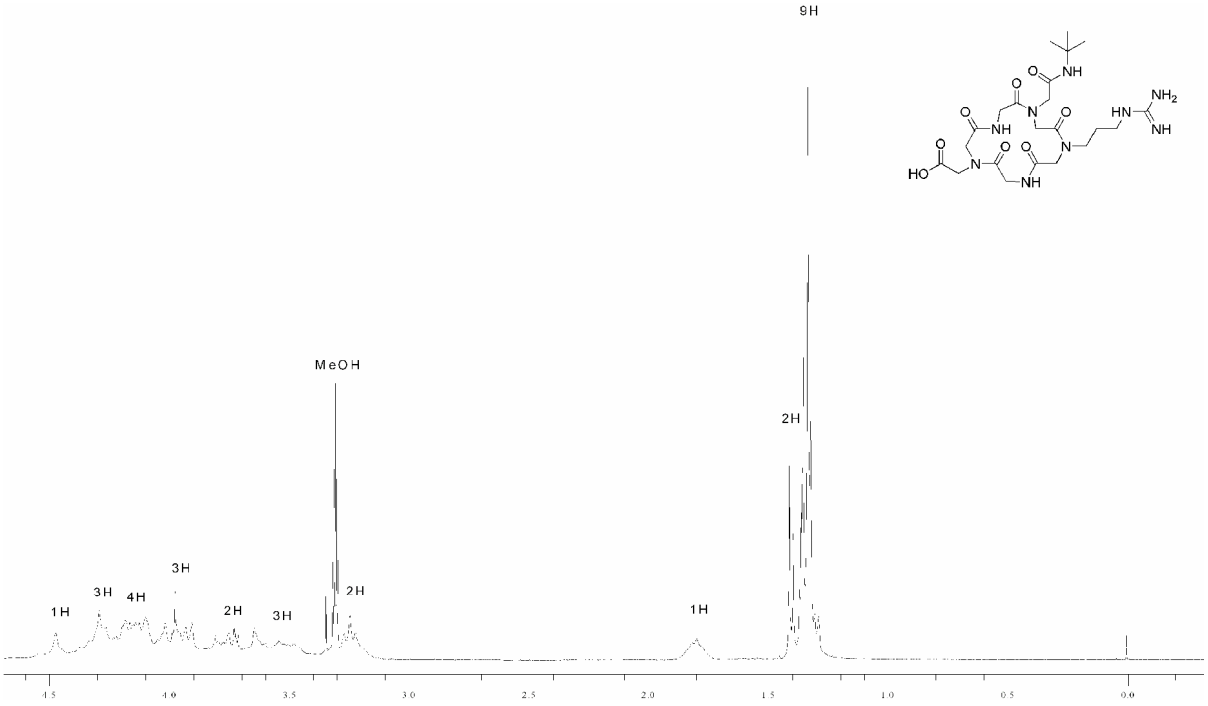

Figure 6. ^{1}H NMR spectrum of cyclopeptoid **2**.

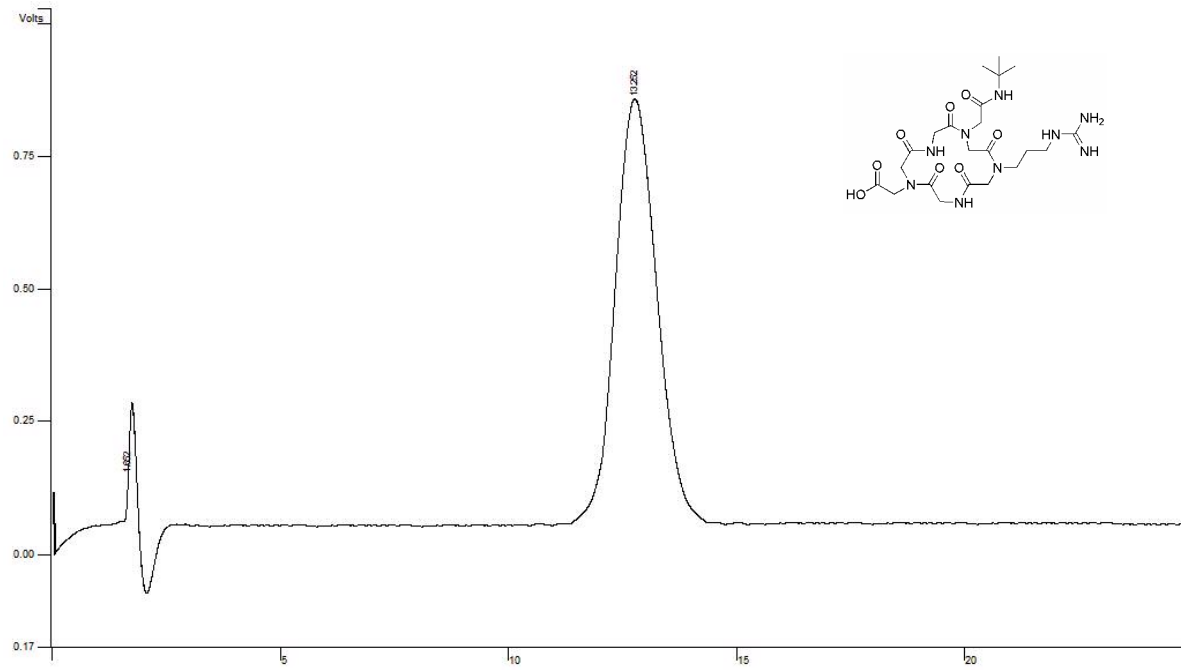

Figure 7. HPLC chromatogram of pure cyclopeptoid **2**.

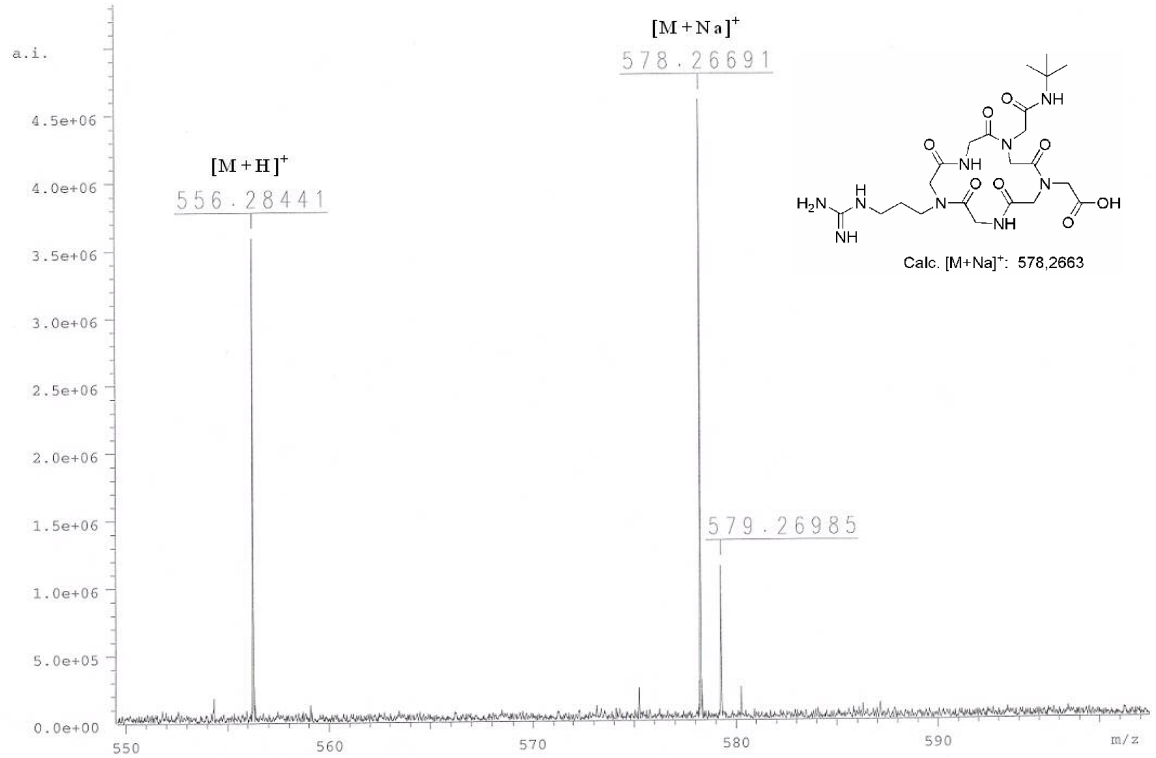

Figure 8. HRMS (ESI-FT-ICR) spectrum of cyclopeptoid **3**.

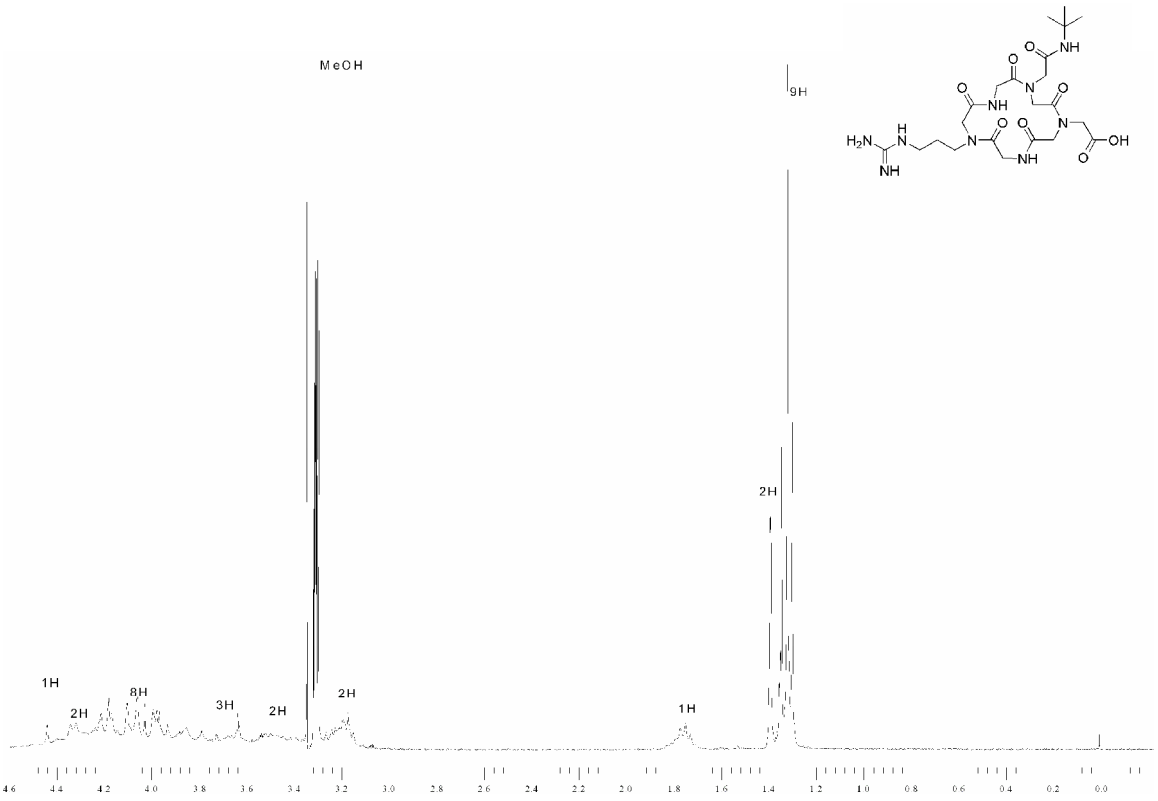

Figure 9. ^{1}H NMR spectrum of cyclopeptoid **3**.

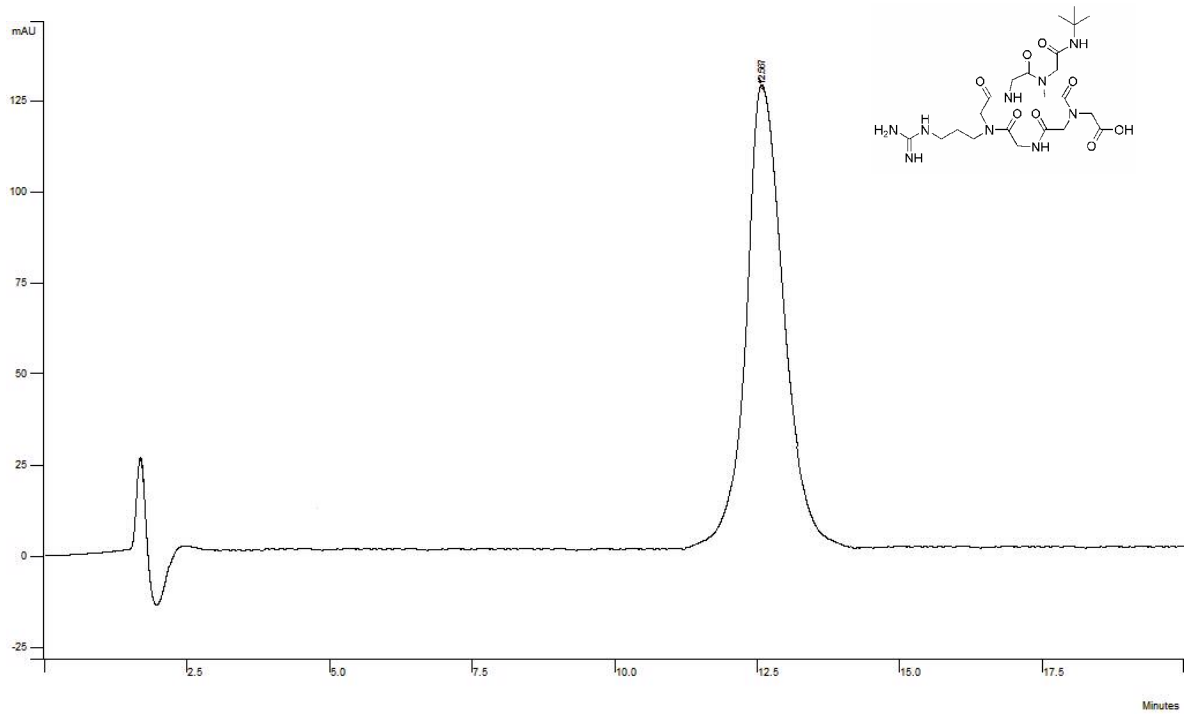

Figure 10. HPLC chromatogram of compound **3**.

[1] Uno, T.; Beausoleil, E.; Goldsmith, R. A.; Levine, B. H.; Zuckermann, R. N. *Tetrahedron Lett.* **1999**, *40*, 1475.
[2] Pittelkow, M.; Lewinsky, R.; Christensen, J. B. *Synthesis*, **2002**, 2195.