Electronic Supplementary Material (ESI) for Green Chemistry.

Greener peptoid synthesis in additive-free water-based media

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CONTENTS

PROCEDURES FOR SYNTHESIS OF PEPTOID MONOMERS

Commercially available peptoid monomers (protected proline **1b** and peptoid amine **2h**·HCl) were purchased from TCI and Fluka, respectively. All other peptoid monomers required for the study could readily be synthesised from commercially available reagents (TCI) as detailed below.

General procedure S1: Synthesis of peptoid amine

To a mixture of the primary amine (3.0 equiv., 0.6 M) in H_2O, EtOAc or THF at room temperature were added triethylamine (3.0 equiv.) and *tert*-butyl, methyl or ethyl bromoacetate (1.0 equiv.). The resulting mixture was stirred for 30 min at 45 °C and then for 24 h at room temperature. The mixture was washed with EtOAc and the organic layer was concentrated under reduced pressure to furnish the crude peptoid monomer. No further purification was required when the primary amine starting material had a low boiling point (removed by evaporation under reduced pressure).

General procedure S2: Cbz-protection of peptoid amine

To a suspension of the peptoid (1.0 equiv.) in satd. aq. $NaHCO_3$ (2 mL/mmol) at 0 °C was added 1,4-dioxane (2 mL/mmol). Benzyl chloroformate (1.05 equiv.) was then added dropwise over 5 min and the resulting mixture was stirred for at least 4 h at room temperature. After completion of the reaction, EtOAc was added. The organic layer was isolated, washed with H_2O (2×), dried over Na_2SO_4, filtered and evaporated under reduced pressure to furnish the crude Cbz-protected peptoid monomer.

General procedure S3: Peptoid acid by deprotection of *tert*-butyl ester

The *tert*-butyl ester peptoid (0.014 M) was stirred in TFA/CH_2Cl_2 1:1. Evaporation under reduced pressure furnished the crude peptoid acid which was used without purification in the next step.

Peptoid acid 1a

Peptoid acid **1a** was obtained in three steps starting from reaction of isobutylamine with triethylamine and *tert*-butyl bromoacetate according to General procedure S1, followed by Cbz-protection according to General procedure S2, and then finally *tert*-butyl ester

deprotection using General procedure S3. Peptoid acid **1a** was used directly in the next step without purification. R_f (cyclohexane/EtOAc 80:20) = 0.10; 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.88 and 0.91 (6H, 2×d, *J* = 6.6 Hz), 1.86 (1H, m), 3.17 (2H, m), 4.02 and 4.07 (2H, 2×s), 5.15 and 5.17 (2H, 2×s), 7.27-7.39 (5H, m), 9.29 (1H, bs).

Data for peptoid amine intermediate: Colorless oil (0.185 g, 0.987 mmol, 99%). R_f (cyclohexane/EtOAc 80:20) = 0.43; 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.92 (6H, d, *J* = 5.4 Hz), 1.46 (9H, s), 1.73 (1H, m), 2.40 (2H, d, *J* = 5.4 Hz), 3.29 (2H, s).

Data for Cbz-protected peptoid intermediate: Colorless oil (0.56 g, 1.74 mmol, 92%). R_f (cyclohexane/EtOAc 90:10) = 0.34; 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.86 and 0.91 (6H, 2×d, *J* = 6.6 Hz), 1.36 and 1.45 (9H, 2×s, 9H), 1.79-1.89 (1H, m), 3.11 and 3.15 (2H, 2×d, *J* = 5.9 Hz), 3.82 and 3.89 (2H, 2×s), 5.10 and 5.14 (2H, 2×s), 7.31-3.35 (5H, m).

Peptoid amine 2a

Peptoid amine **2a** was obtained by reaction of benzylamine with triethylamine and *tert*-butyl bromoacetate according to General procedure S1 in EtOAc. Peptoid amine **2a** was obtained as a colorless oil (2.17 g, 9.81 mmol, 98%) after flash chromatography on silica gel using cyclohexane/EtOAc 90:10 as eluent. R_f (cyclohexane/EtOAc 80:20) = 0.31; 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.46 (9H, s), 2.39 (1H, br s), 3.29 (2H, s), 3.80 (2H, s), 7.32-7.34 (5H, m).

Peptoid amine 2b

Peptoid amine **2b** was obtained by reaction of benzylamine with triethylamine and methyl bromoacetate according to General procedure S1 in EtOAc. Peptoid amine **2b** was obtained as a colorless oil (4.16 g, 23.2 mmol, 97%) after flash chromatography on silica gel using cyclohexane/EtOAc 90:10 as eluent. R_f (cyclohexane/EtOAc 80:20) = 0.37; 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.89 (1H, s), 3.43 (2H, s), 3.73 (3H, s), 3.81 (2H, s), 7.26-7.33 (5H, m).

Peptoid amine 2c

Peptoid amine **2c** was obtained by reaction of isobutylamine with triethylamine and methyl bromoacetate according to General procedure S1 in EtOAc. Peptoid amine **2c** was obtained as a colorless oil (1.02 g, 7.02 mmol, 88%). R_f (cyclohexane/EtOAc 80:20) = 0.43; 1H NMR

(400 MHz, $CDCl_3$) δ (ppm): 0.93 (6H, d, *J* = 6.6 Hz), 1.79 (1H, m), 2.45 (2H, d, *J* = 6.8 Hz), 2.66 (1H, br s), 3.44 (2H, s), 3.73 (3H, s).

Peptoid amine 2d

Peptoid amine **2d** was obtained by reaction of isopropylamine with triethylamine and ethyl bromoacetate according to General procedure S1 in EtOAc. Peptoid amine **2d** was obtained as a colorless oil (5.68 g, 39.1 mmol, 81%). R_f (cyclohexane/EtOAc 40:60) = 0.34; 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.00 (6H, d, *J* = 6.2 Hz), 1.22 (3H, t, *J* = 7.16 Hz), 1.64 (1H, s), 2.75 (1H, m), 3.34 (2H, s), 4.13 (2H, q, *J* = 7.16 Hz).

Peptoid amine 2e

Peptoid amine **2e** was obtained in two steps by mono-protection of 1,3-diaminopropane using a procedure adapted from General procedure S2 (5.0 equiv. 1,3-diaminopropane, 1.0 equiv. benzyl chloroformate), followed by reaction of the derived crude *N*-Cbz-1,3-diaminopropane with triethylamine and ethyl bromoacetate according to General procedure S1. Peptoid amine **2e** was purified by flash chromatography on silica gel.

Data for *N*-Cbz-1,3-diaminopropane: Colorless oil (2.78 g, 11.4 mmol, 57%). R_f (CH_2Cl_2/MeOH 90:10) = 0.22; 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.31 (2H, br s), 1.60-1.62 (2H, m), 2.73-2.76 (2H, t, *J* = 5.2 Hz), 3.20-3.29 (2H, m), 5.11-5.12 (2H, m), 5.40 (1H, br s), 7.25-7.34 (5H, m).

Data for peptoid amine **2e**: Colorless oil (1.75 g, 6.00 mmol, 57%). R_f (cyclohexane/EtOAc 10:90) = 0.22; 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.23-1.27 (3H, m), 1.56 (1H, s), 1.65-1.67 (2H, m), 2.65-2.67 (2H, m), 3.27-3.28 (2H, m), 3.35 (2H, m), 4.13-4.19 (2H, m), 5.07 (2H, s), 5.45 (1H, s), 7.29-7.34 (5H, m).

Peptoid amine 2f

Peptoid amine **2f** was obtained by reaction of isobutylamine with triethylamine and ethyl bromoacetate according to General procedure S1. Peptoid amine **2f** was obtained as a colorless oil (6.54 g, 41.1 mmol, 98%). R_f (cyclohexane/EtOAc 80:20) = 0.43; 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.90 (6H, d, *J* = 6.8 Hz), 1.25 (3H, t, *J* = 7.1 Hz), 1.71 (1H, m), 2.29 (2H, d, *J* = 6.8 Hz), 3.36 (2H, s), 4.16 (2H, q, *J* = 7.1 Hz).

Peptoid amine 2g

Peptoid amine **2g** was obtained by reaction of benzylamine with triethylamine and ethyl bromoacetate according to General procedure S1. Peptoid amine **2g** was obtained as a colorless oil (6.61 g, 34.2 mmol, 82%) after flash chromatography on silica gel using cyclohexane/EtOAc 80:20 as eluent. R_f (cyclohexane/EtOAc 90:10) = 0.24; 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.26 (3H, t, *J* = 7.1 Hz), 1.90 (1H, s), 3.39 (2H, s), 3.79 (2H, s), 4.18 (2H, q, *J* = 7.1 Hz), 7.23-7.32 (5H, m).

Peptoid amine 2i

Peptoid amine **2i** was obtained by reaction of 4-benzyloxy-benzylamine with triethylamine and methyl bromoacetate according to General procedure S1. Peptoid amine **2i** was obtained as a pale yellow solid (206 mg, 0.72 mmol, 72%) after flash chromatography on silica gel using cyclohexane/EtOAc 50:50 as eluent. R_f (cyclohexane/EtOAc 50:50) = 0.28; 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.07 (1H, bs), 3.41 (2H, s), 3.72 (3H, s), 3.74 (2H, s), 5.06 (2H, s), 6.93 (2H, d, *J* = 8.7 Hz), 7.24 (2H, d, *J* = 8.7 Hz), 7.31-7.44 (5H, m).

Peptoid methyl ester 16

Peptoid methyl ester **16** was obtained by Cbz protection of peptoid amine **2c** according to General procedure S2. Peptoid methyl ester **16** was obtained as a colorless oil (4.16 g, 14.9 mmol, 91%) after flash chromatography on silica gel using cyclohexane/EtOAc 80:20 as eluent. R_f (cyclohexane/EtOAc 90:10) = 0.34; 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.87 and 0.91 (6H, 2×d, *J* = 6.6 Hz), 1.79-1.89 (1H, m), 3.15 and 3.18 (2H, 2×d, *J* = 7.4 Hz), 3.64 and 3.73 (3H, 2×s), 3.96 and 4.02 (2H, 2×s), 5.12 and 5.16 (2H, 2×s), 7.27-7.36 (5H, m).

NMR SPECTRA OF PEPTOID MONOMERS

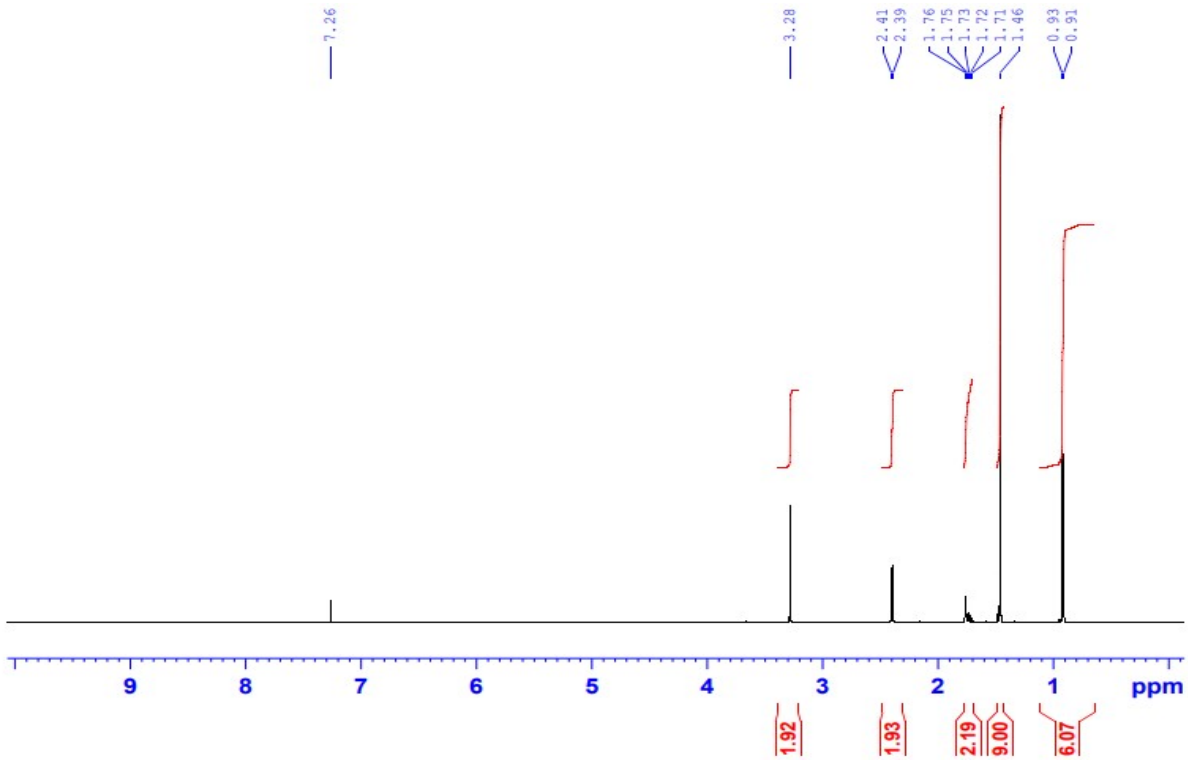


Figure S1. 1H NMR ($CDCl_3$) of peptoid amine intermediate for synthesis of peptoid acid **1a**.

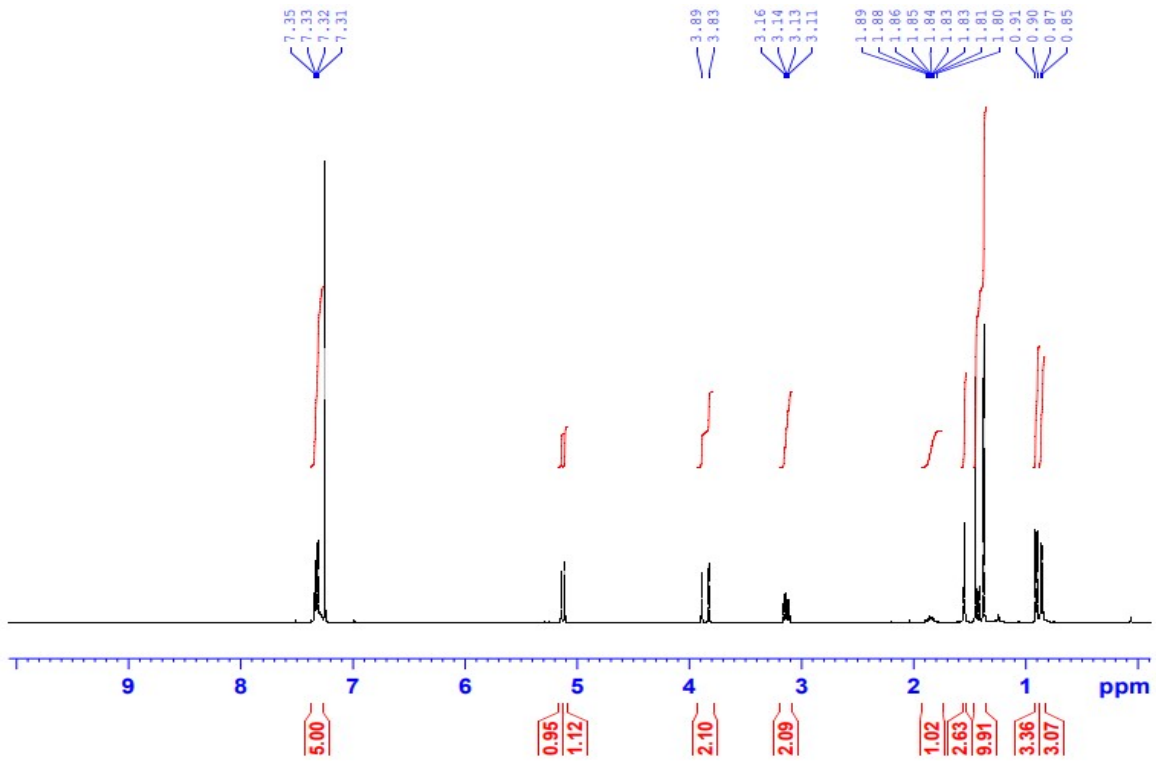


Figure S2. 1H NMR ($CDCl_3$) of Cbz-protected peptoid intermediate for synthesis of peptoid acid **1a**.

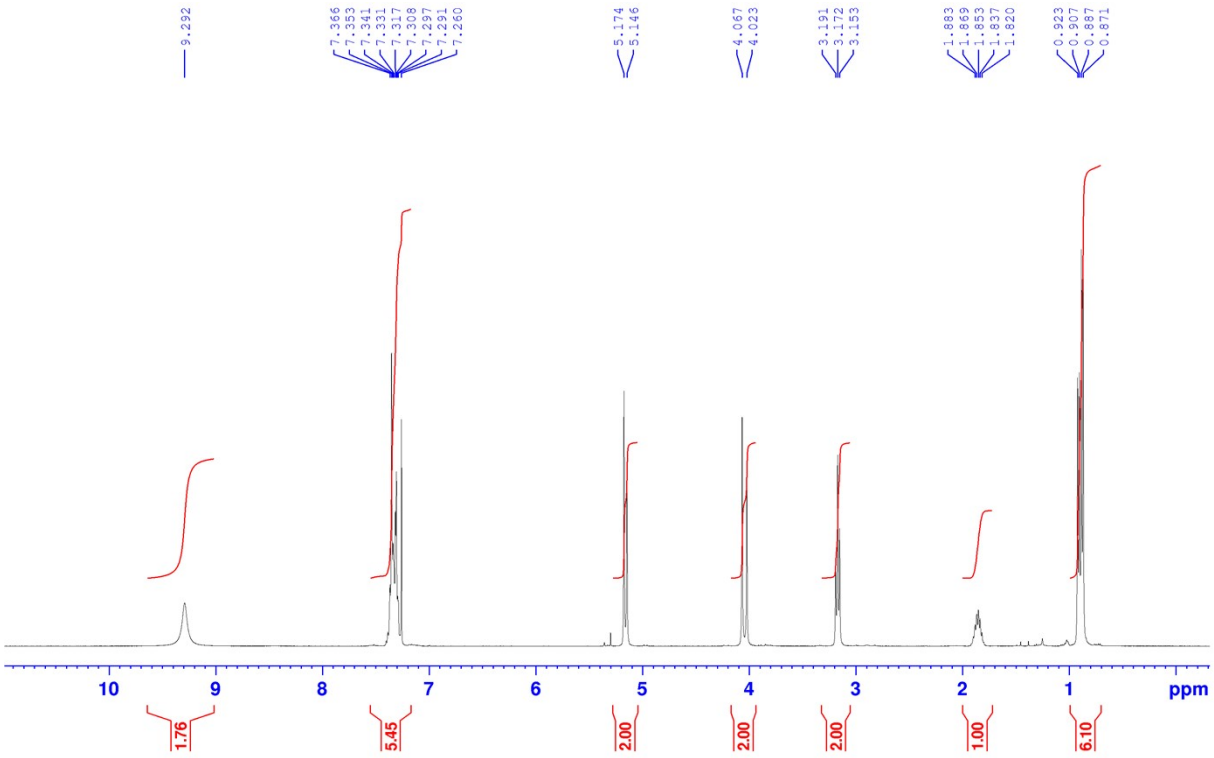


Figure S3. 1H NMR ($CDCl_3$) of peptoid acid **1a**.

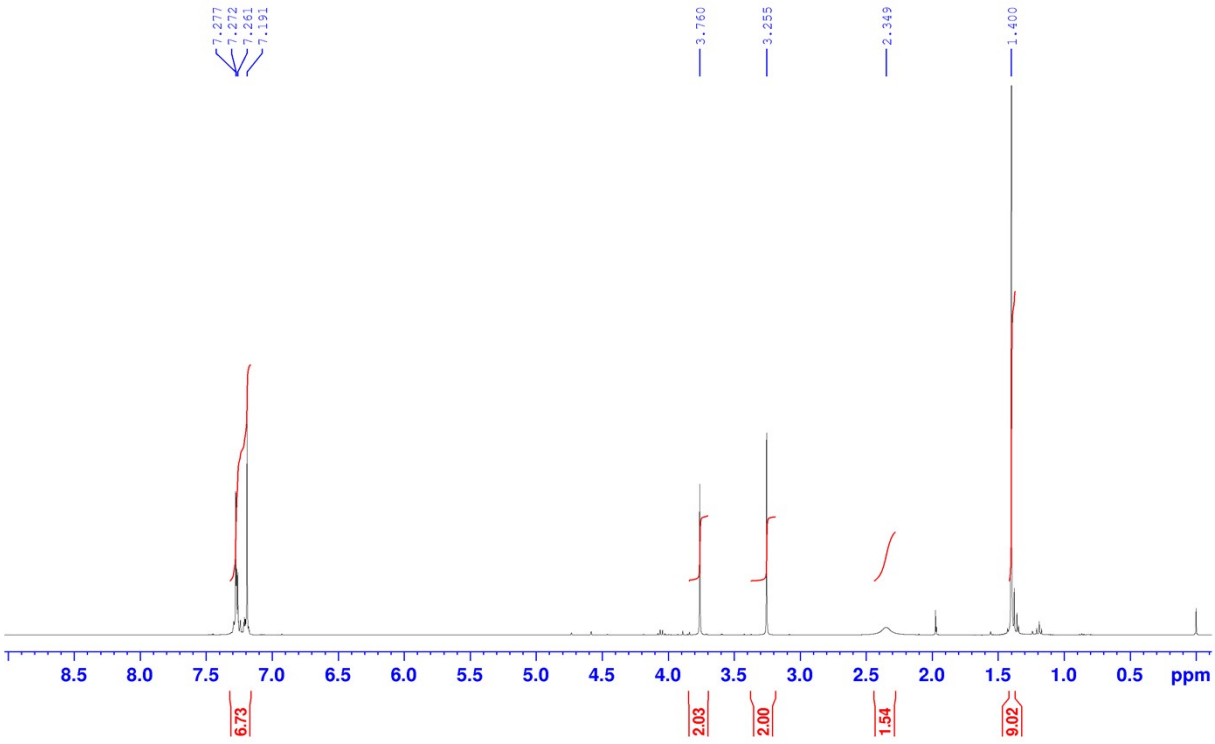


Figure S4. 1H NMR ($CDCl_3$) of peptoid amine **2a**.

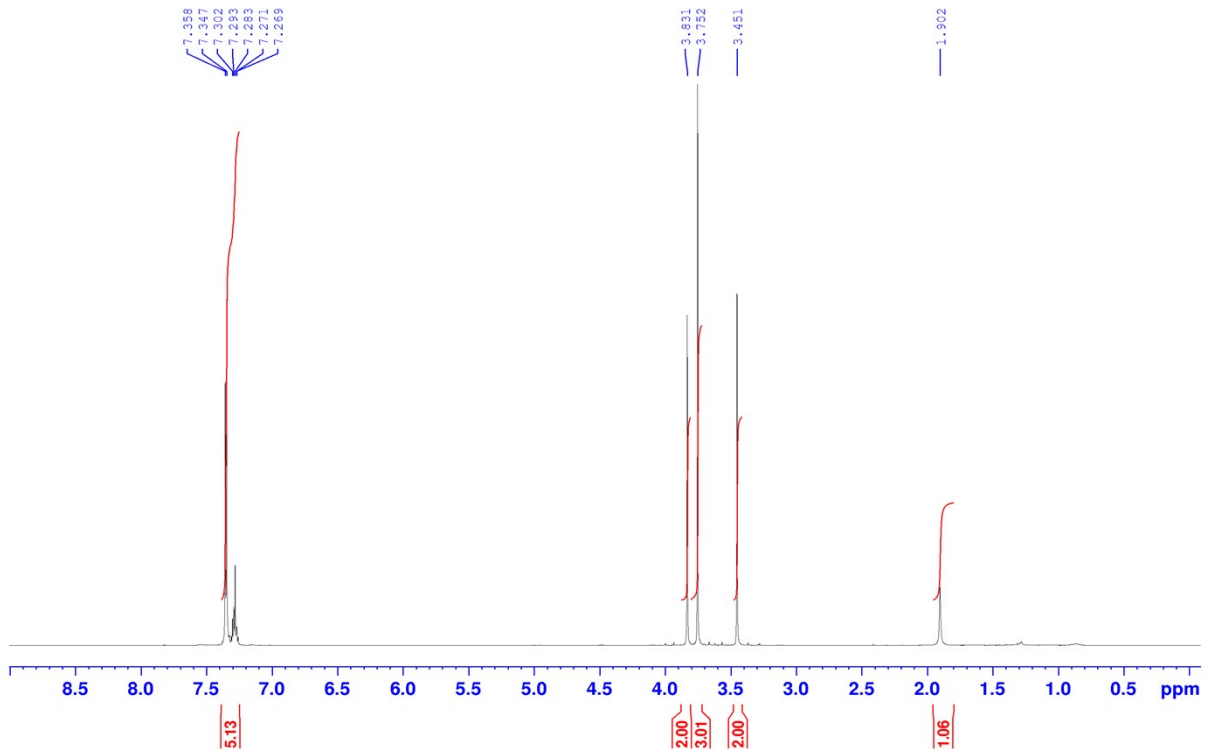


Figure S5. 1H NMR ($CDCl_3$) of peptoid amine **2b**.

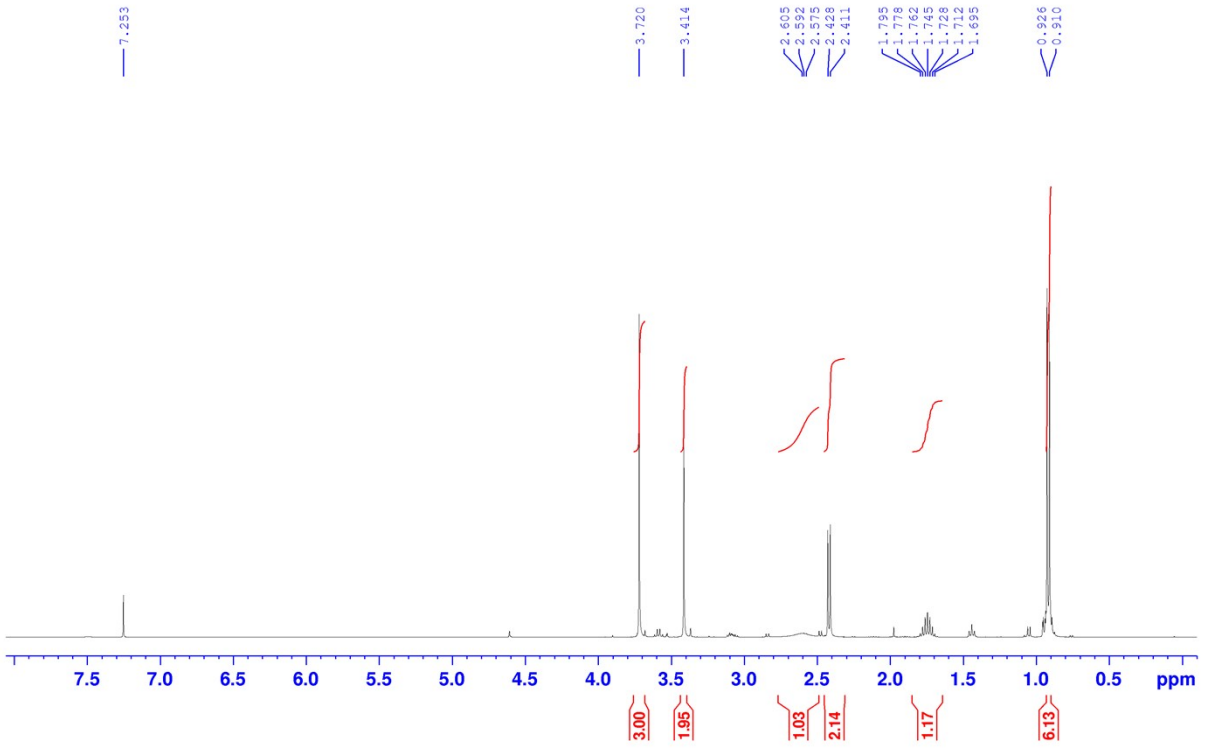


Figure S6. 1H NMR ($CDCl_3$) of peptoid amine **2c**.

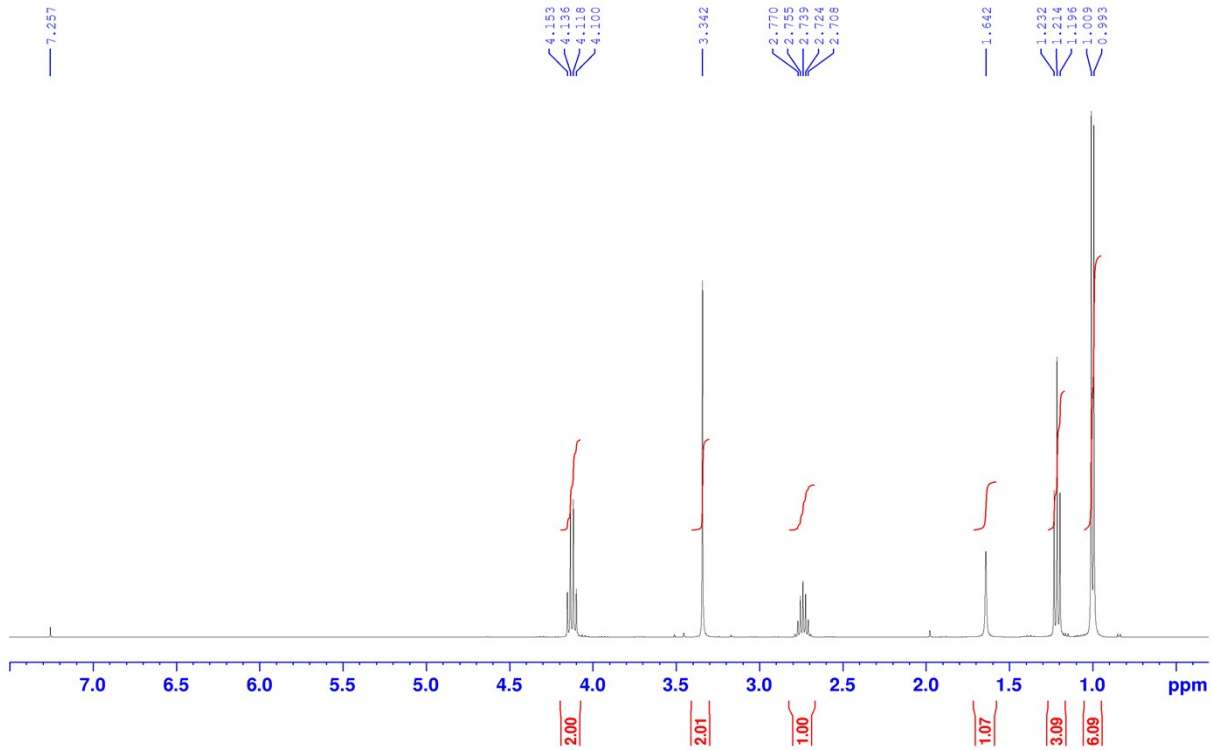


Figure S7. 1H NMR ($CDCl_3$) of peptoid amine **2d**.

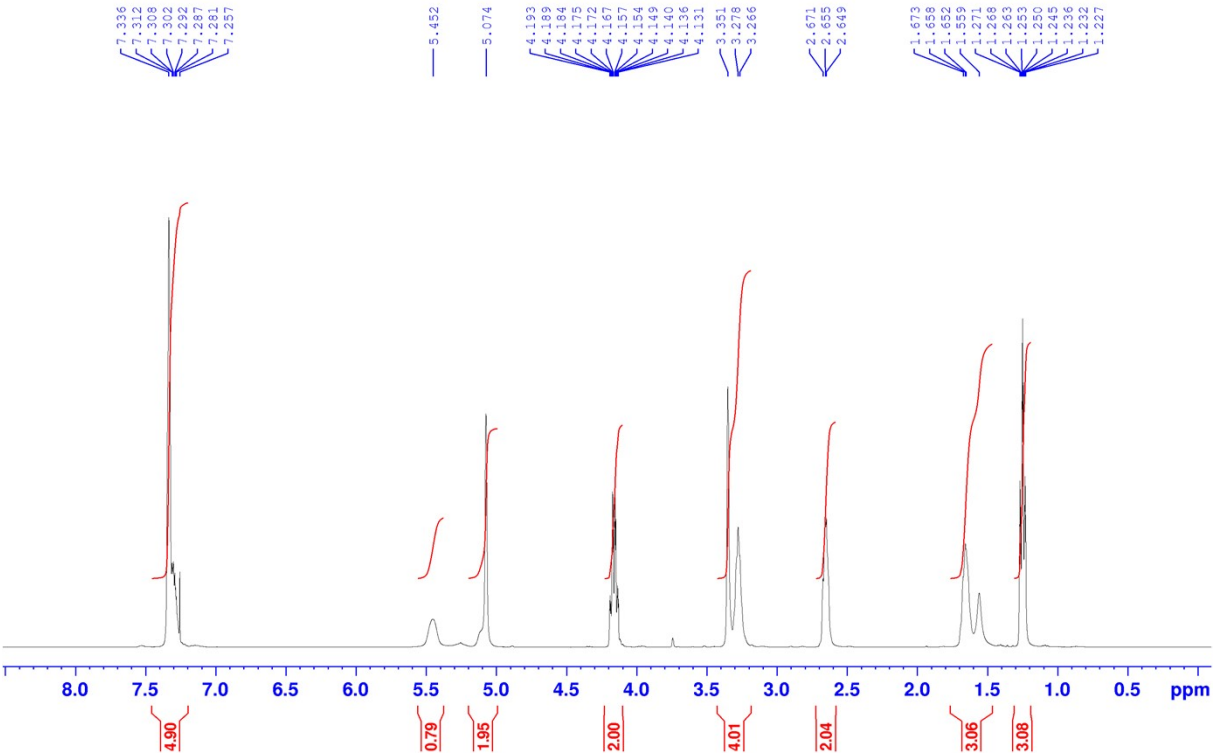


Figure S8. 1H NMR ($CDCl_3$) of peptoid amine **2e**.

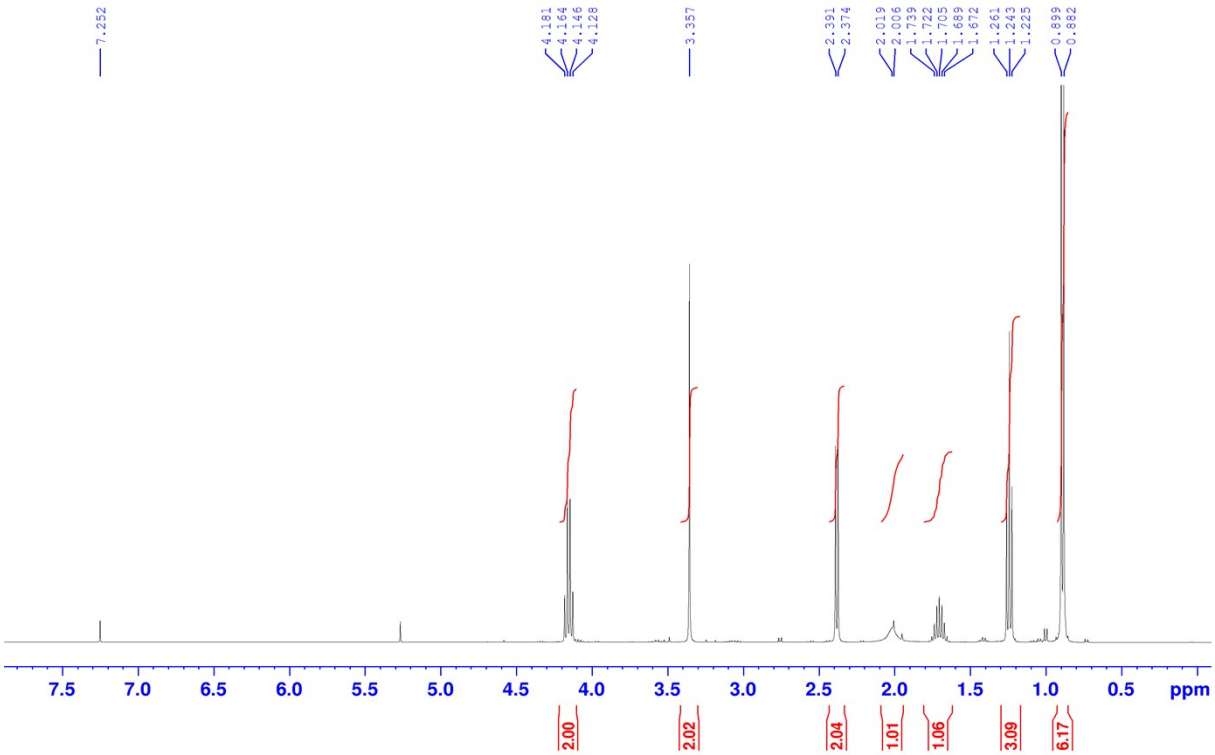


Figure S9. 1H NMR ($CDCl_3$) of peptoid amine **2f**.

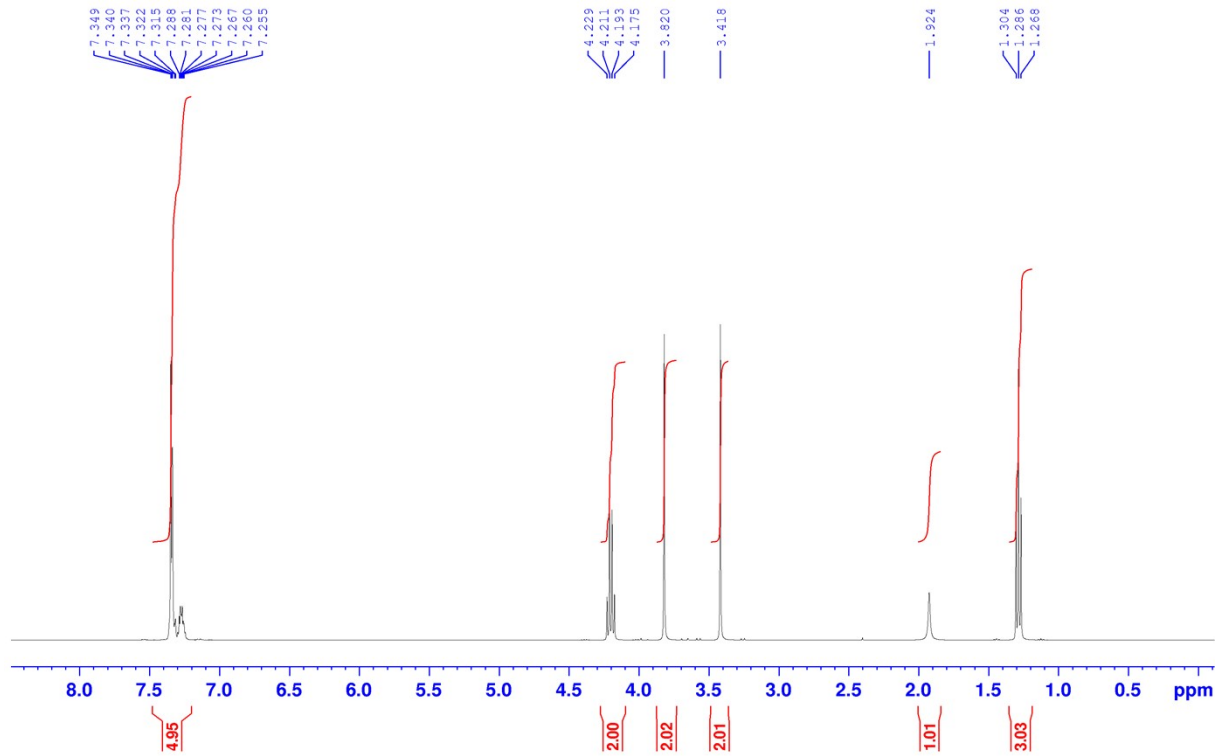


Figure S10. 1H NMR ($CDCl_3$) of peptoid amine **2g**.

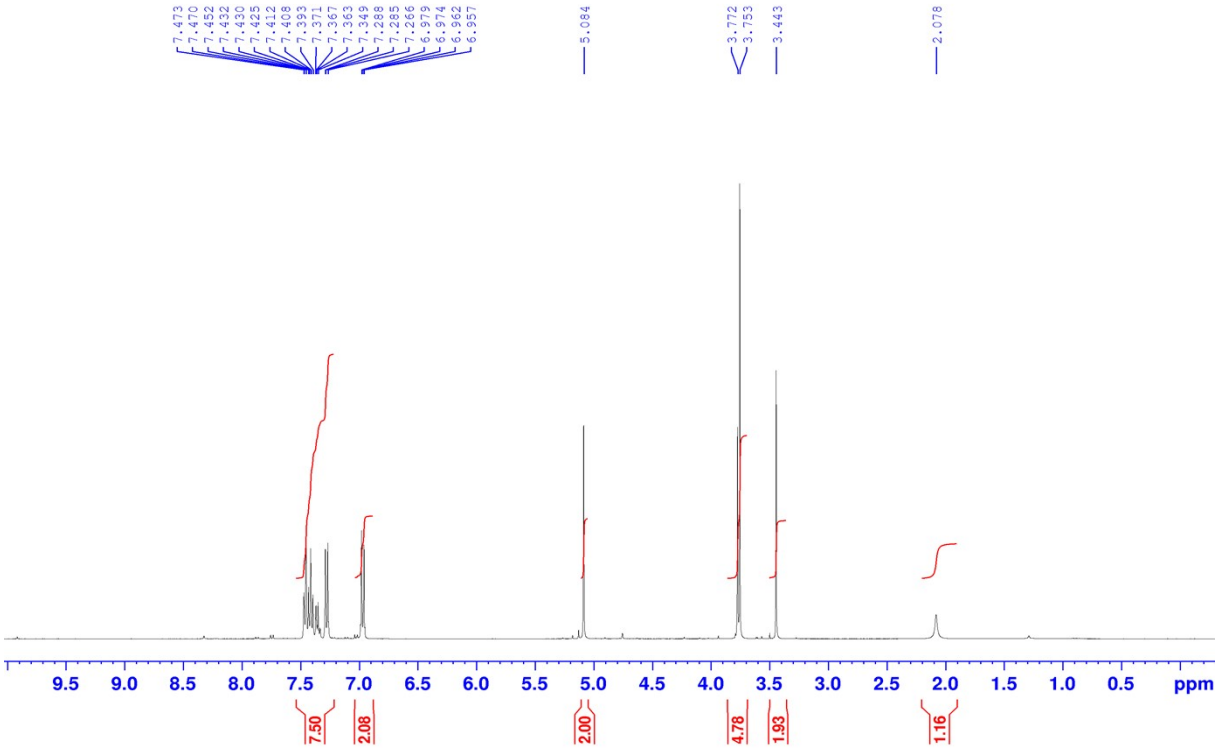


Figure S11. 1H NMR ($CDCl_3$) of peptoid amine **2i**.

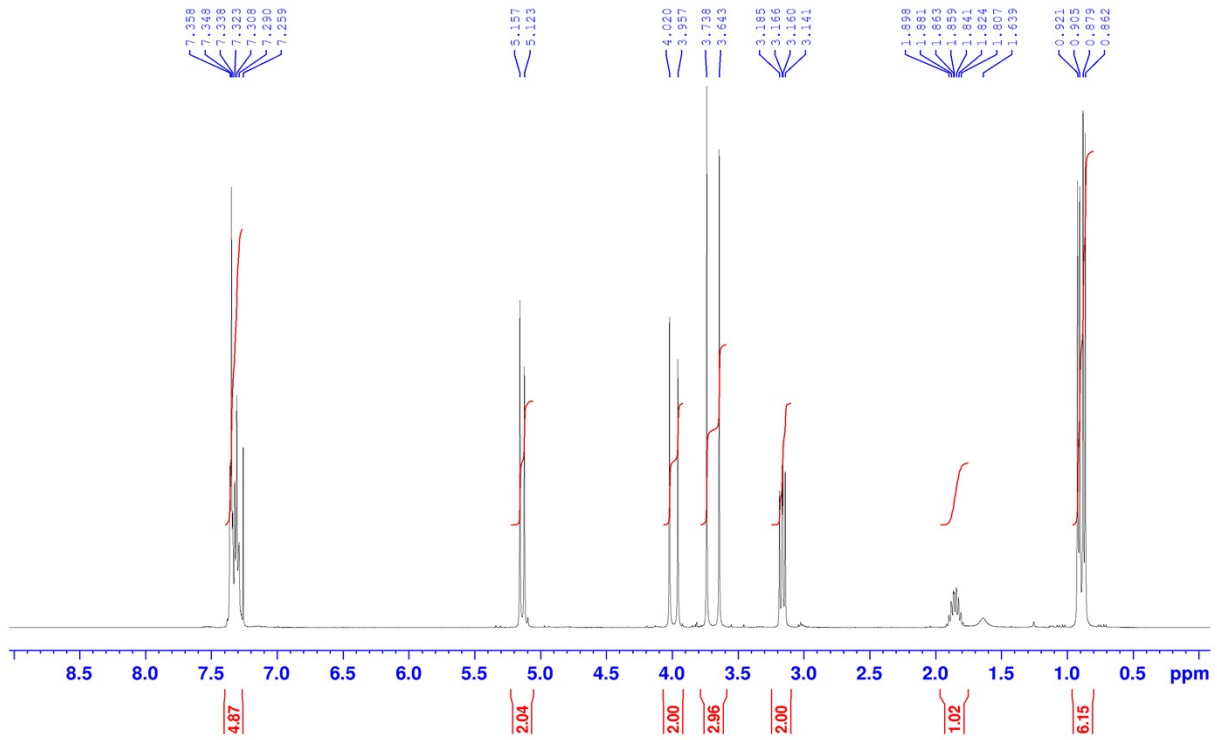


Figure S12. 1H NMR ($CDCl_3$) of peptoid methyl ester **16**.

NMR SPECTRA OF PEPTOID OLIGOMERS

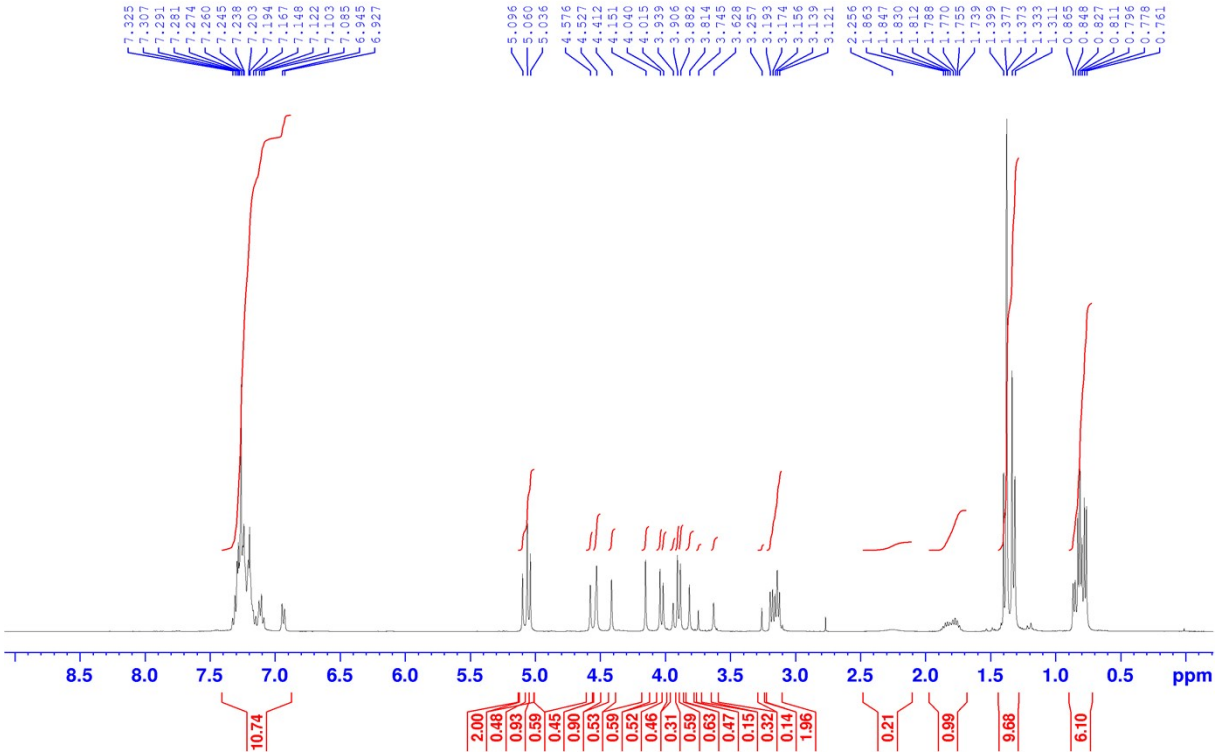


Figure S13. 1H NMR ($CDCl_3$) of dipeptoid **3**.

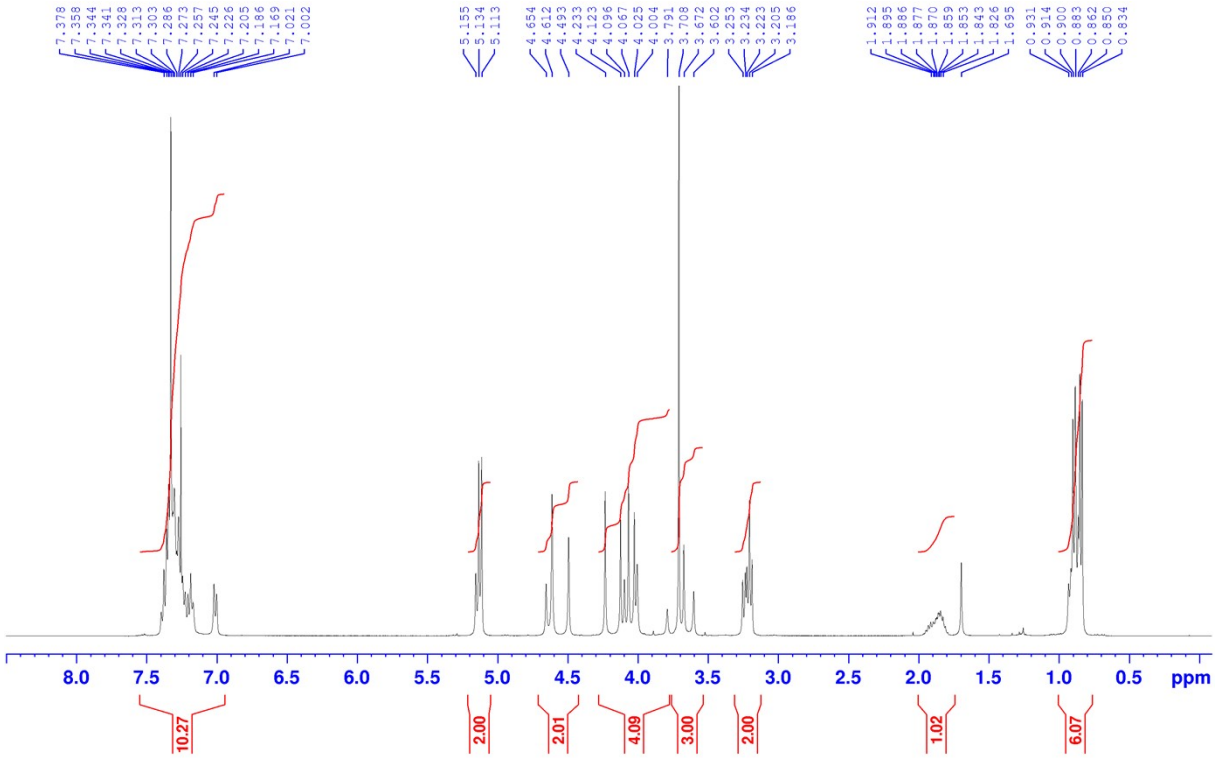


Figure S14. 1H NMR ($CDCl_3$) of dipeptoid **4**.

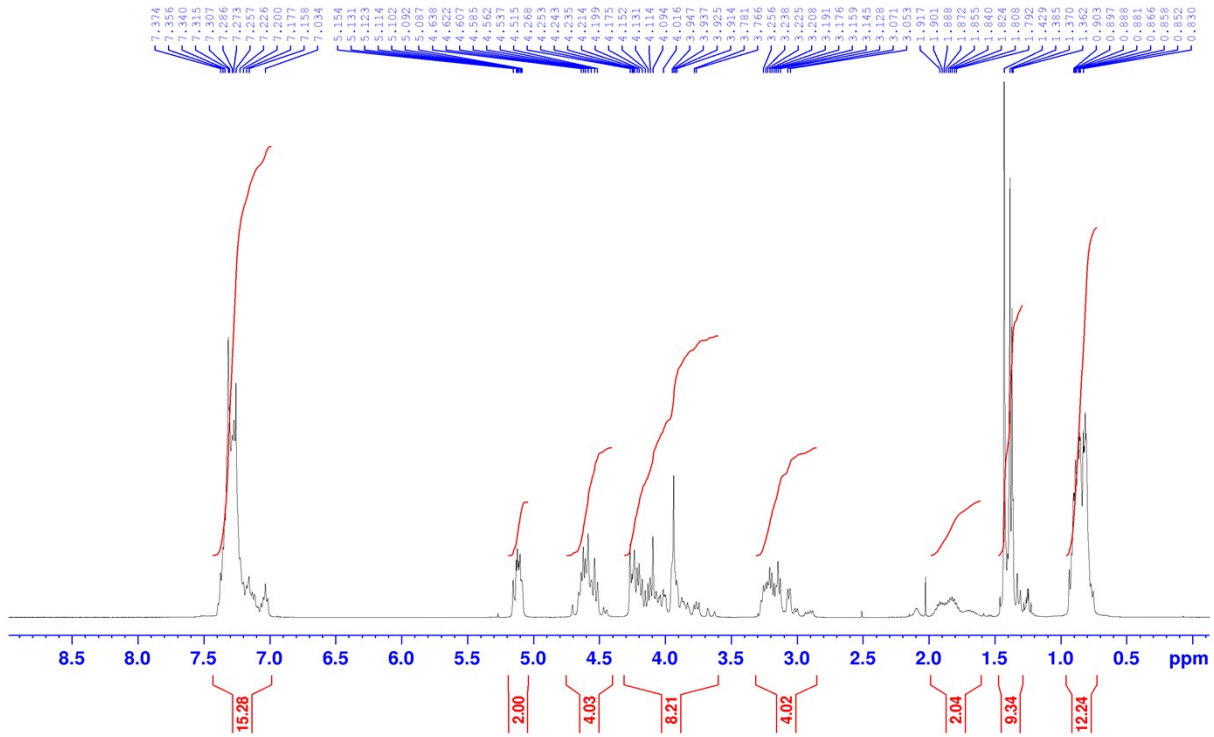


Figure S15. 1H NMR ($CDCl_3$) of tetrapeptoid **6**.

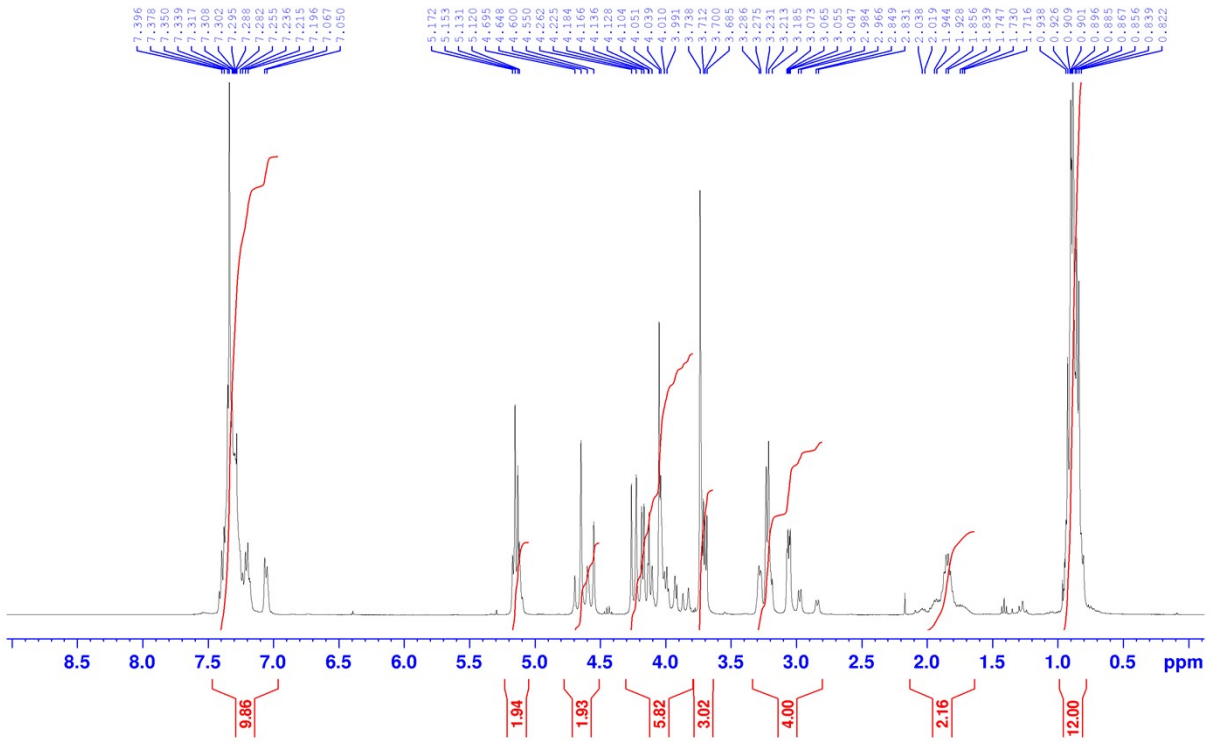


Figure S16. 1H NMR ($CDCl_3$) of tripeptoid **8**.

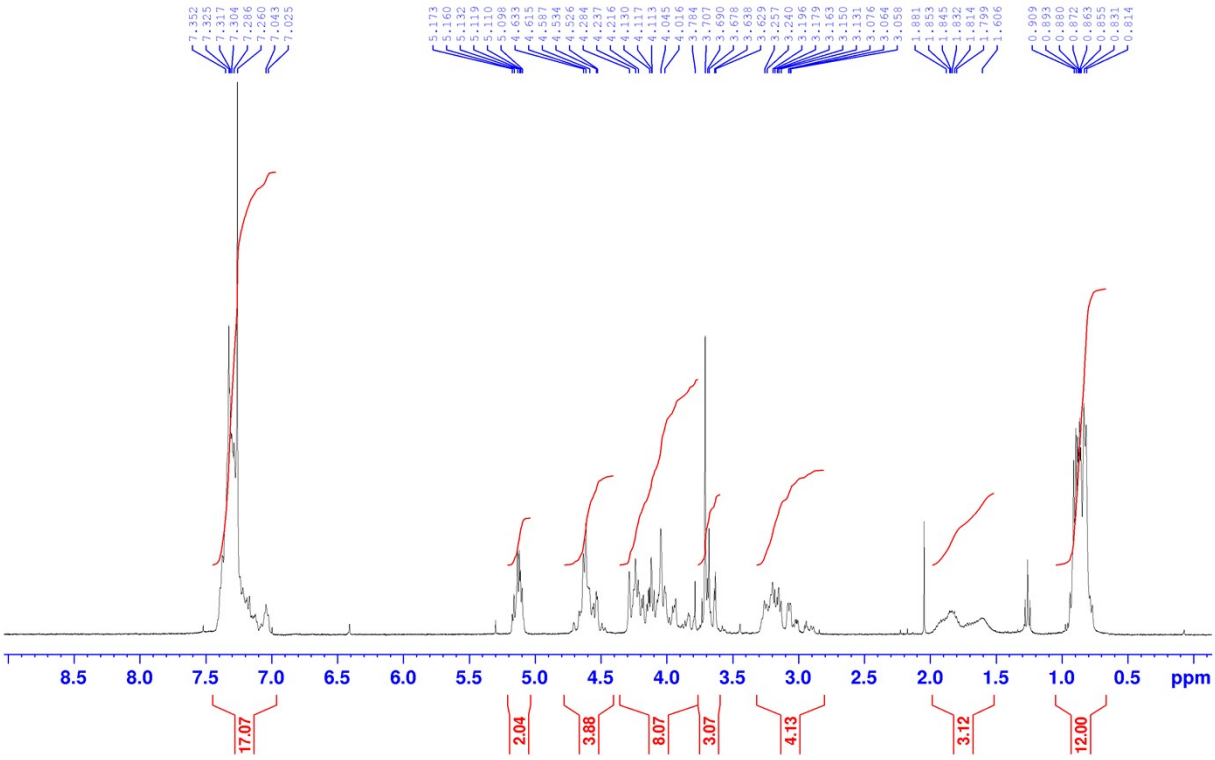


Figure S17. 1H NMR ($CDCl_3$) of tetrapeptoid **9**.

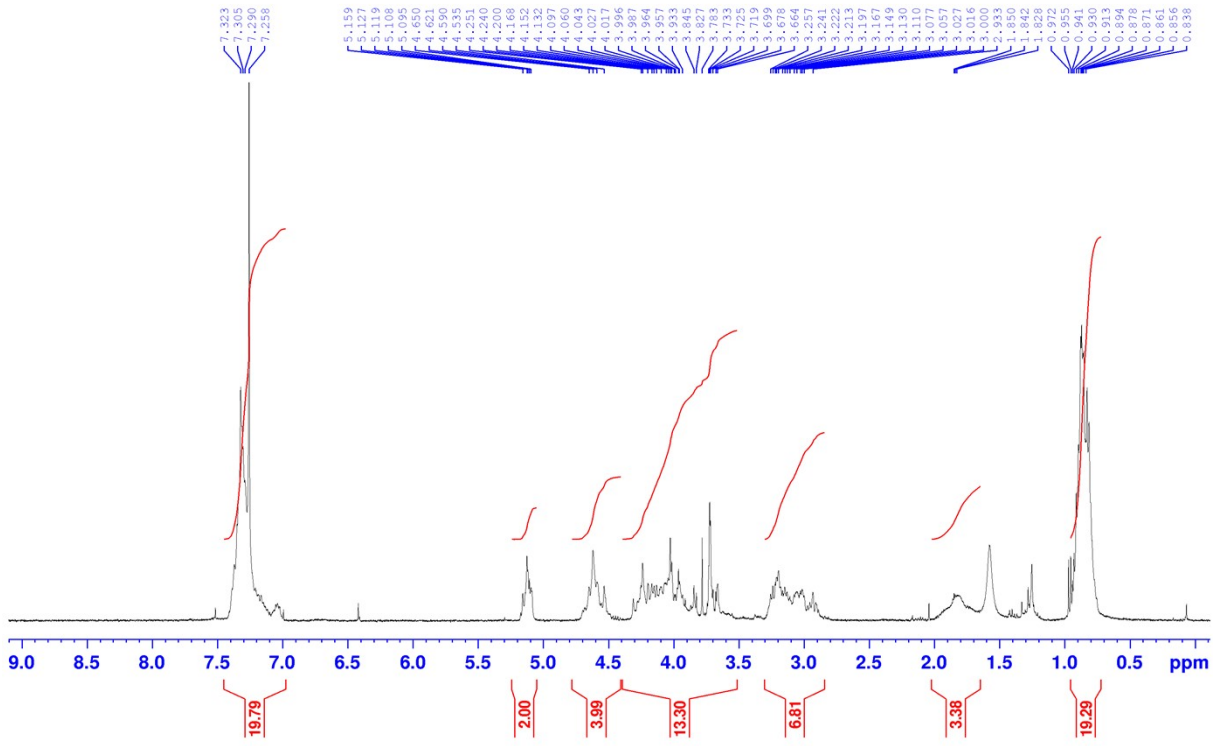


Figure S18. 1H NMR ($CDCl_3$) of pentapeptoid **10**.

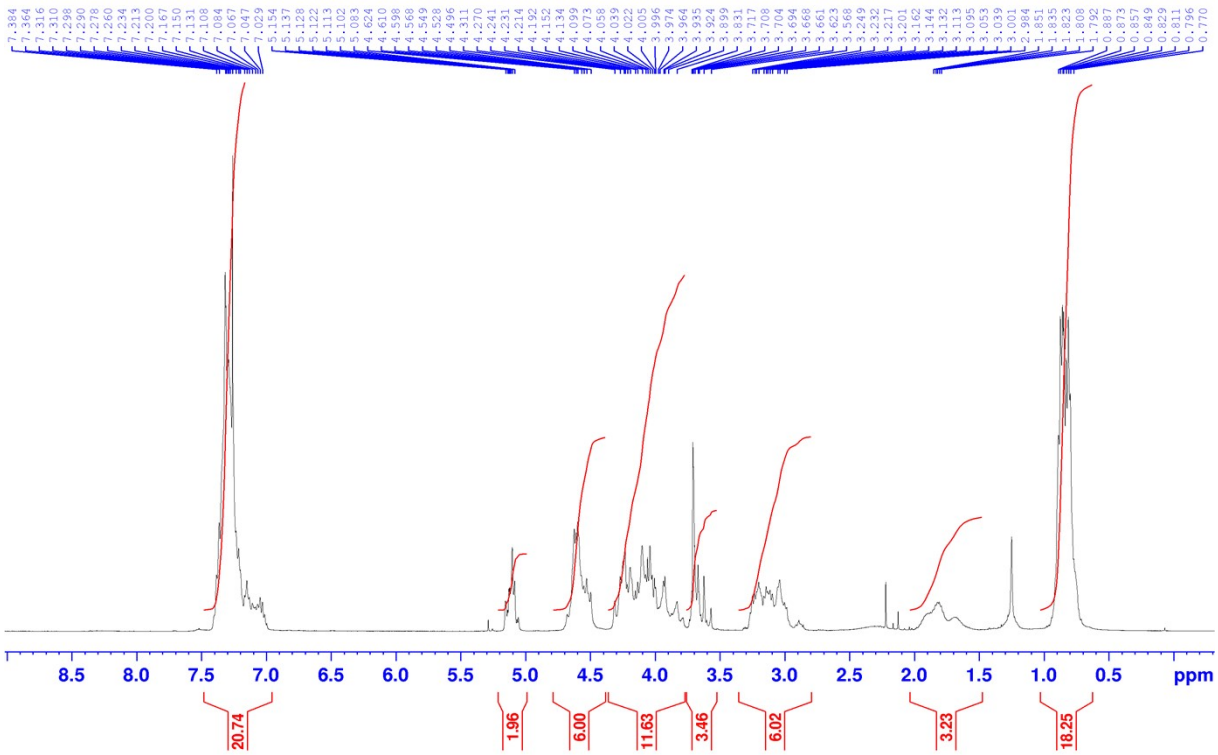


Figure S19. 1H NMR ($CDCl_3$) of hexapeptoid **11**.

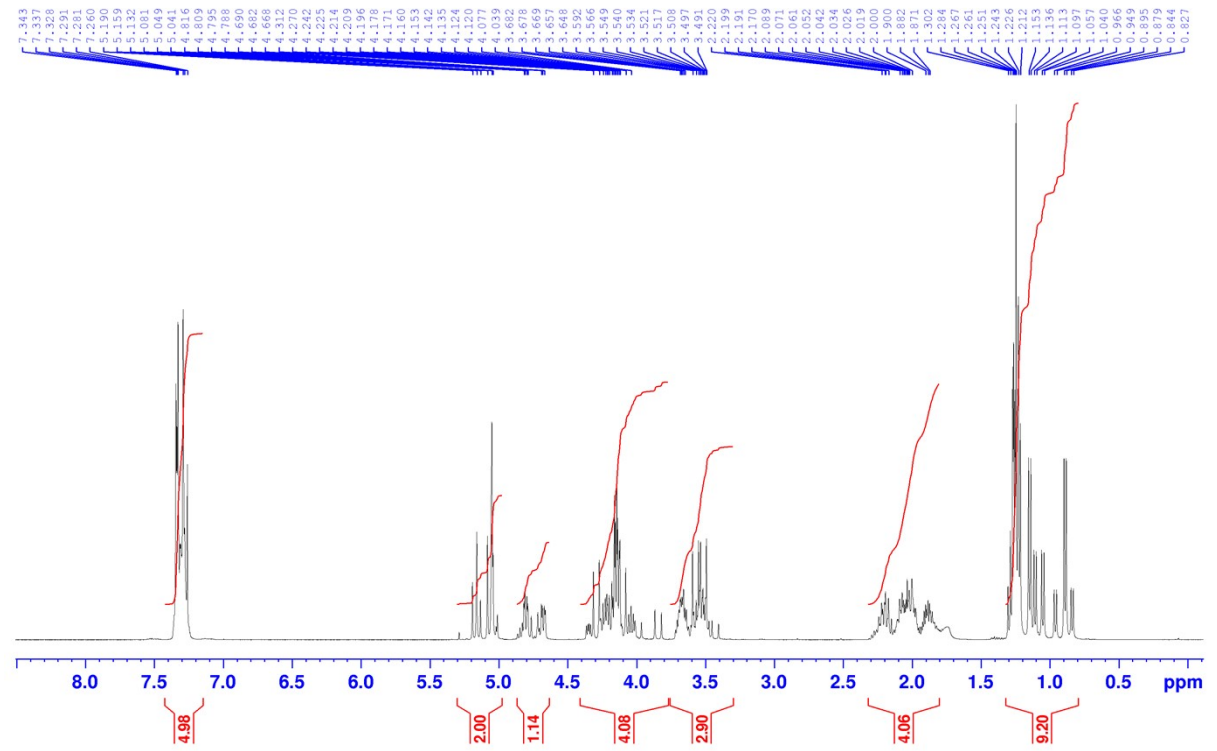


Figure S20. 1H NMR ($CDCl_3$) of dipeptoid **12**.

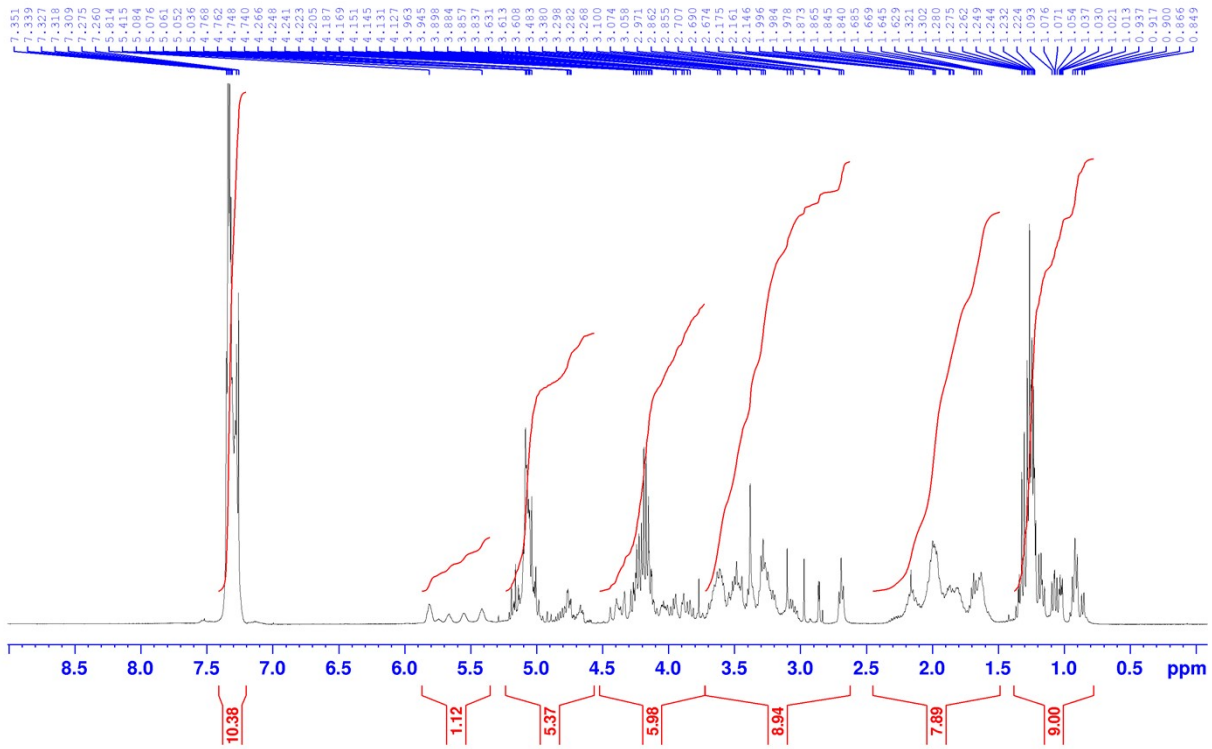


Figure S21. 1H NMR ($CDCl_3$) of tripeptoid **13**.

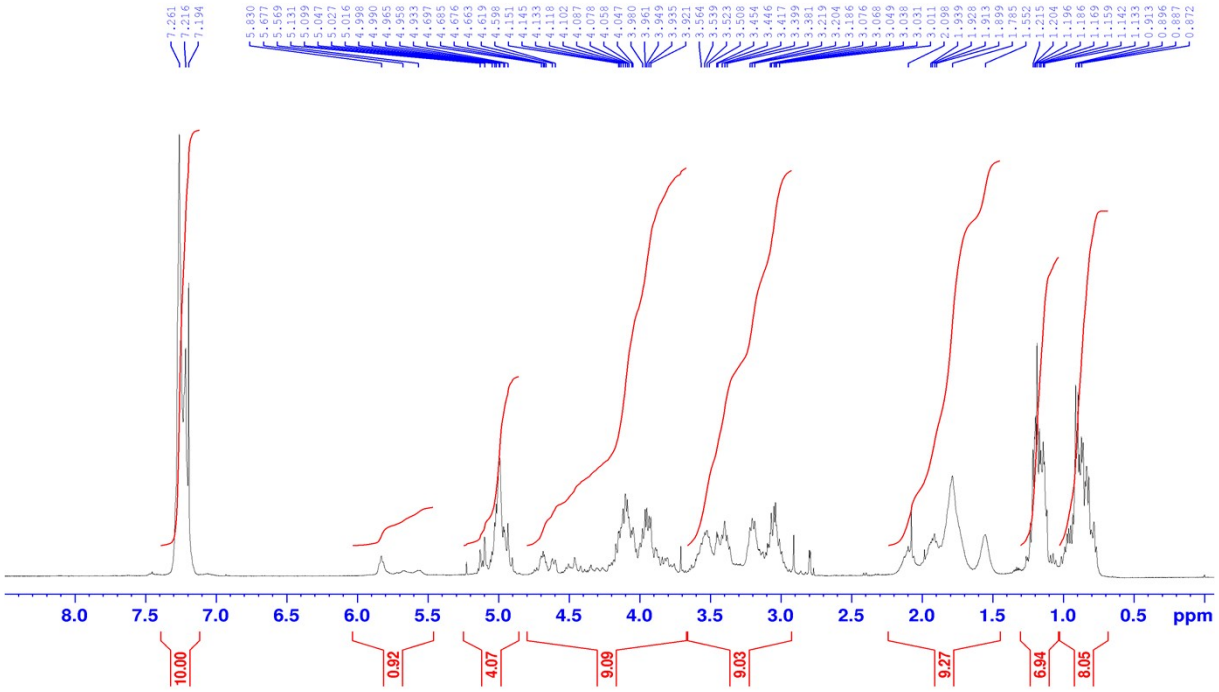


Figure S22. 1H NMR ($CDCl_3$) of tetrapeptoid **14**.

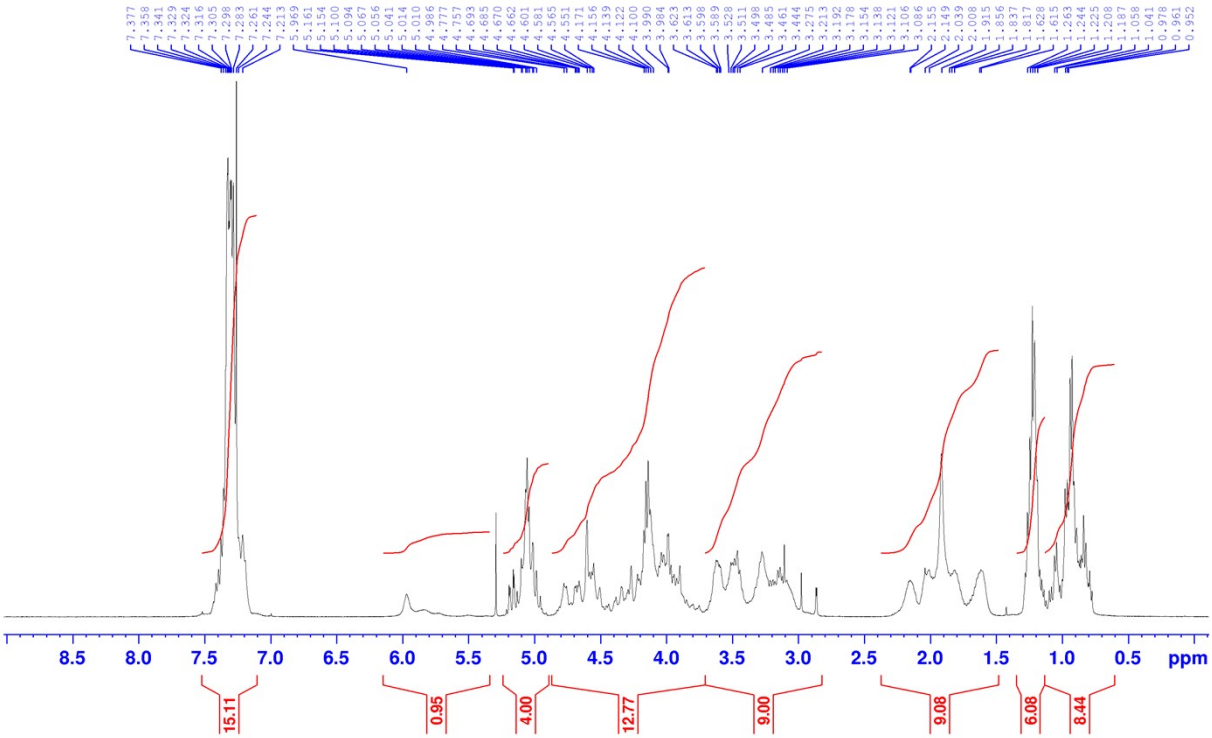


Figure S23. 1H NMR ($CDCl_3$) of pentapeptoid **15**.

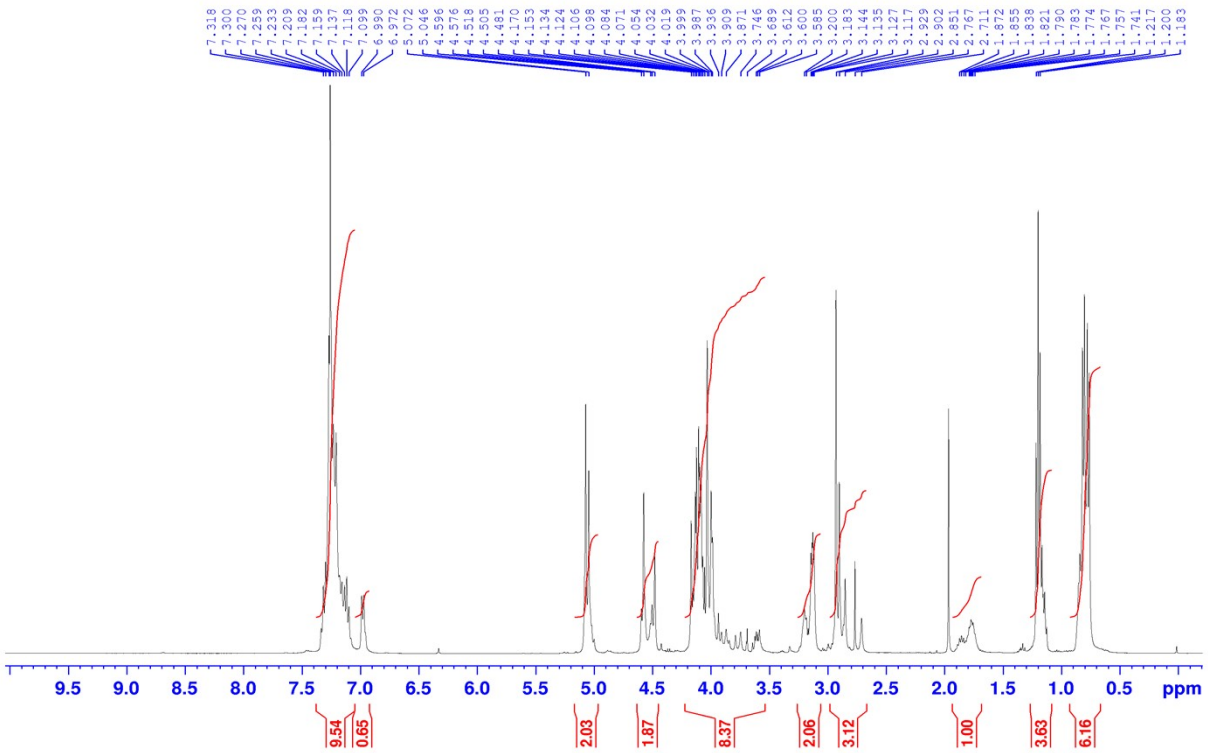


Figure S24. 1H NMR ($CDCl_3$) of tripeptoid **17**.

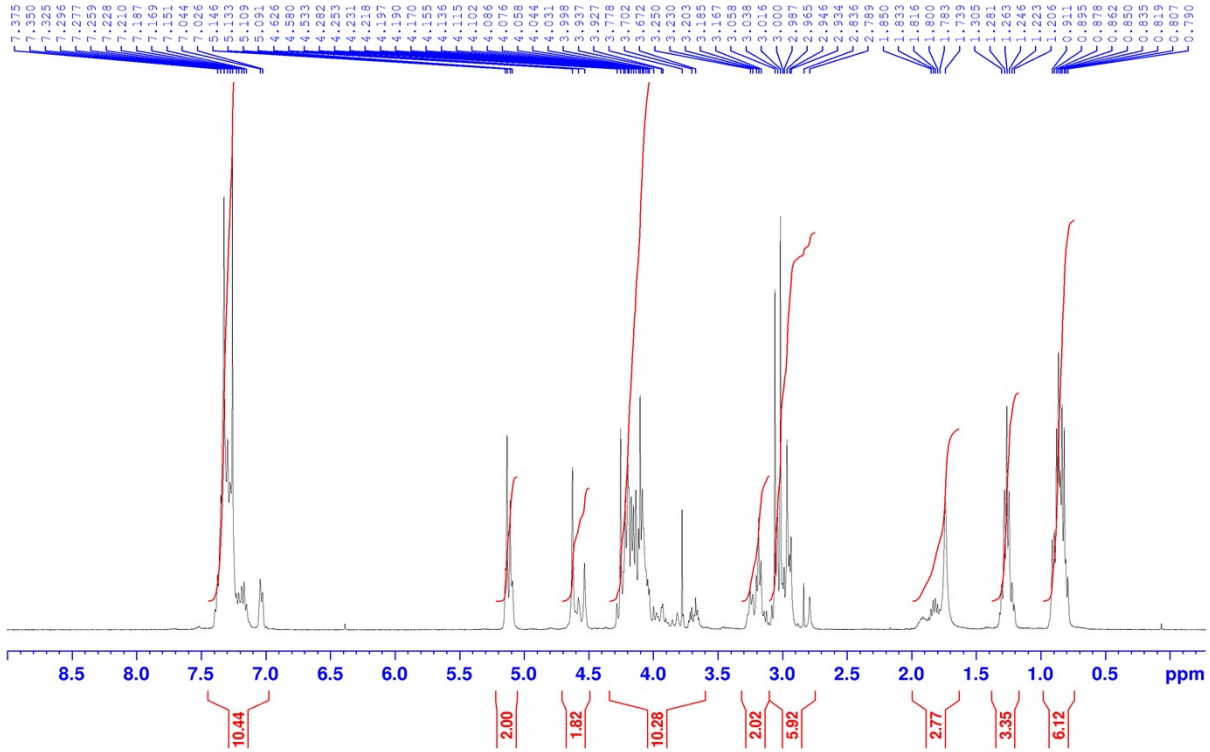


Figure S25. 1H NMR ($CDCl_3$) of tetrapeptoid **18**.

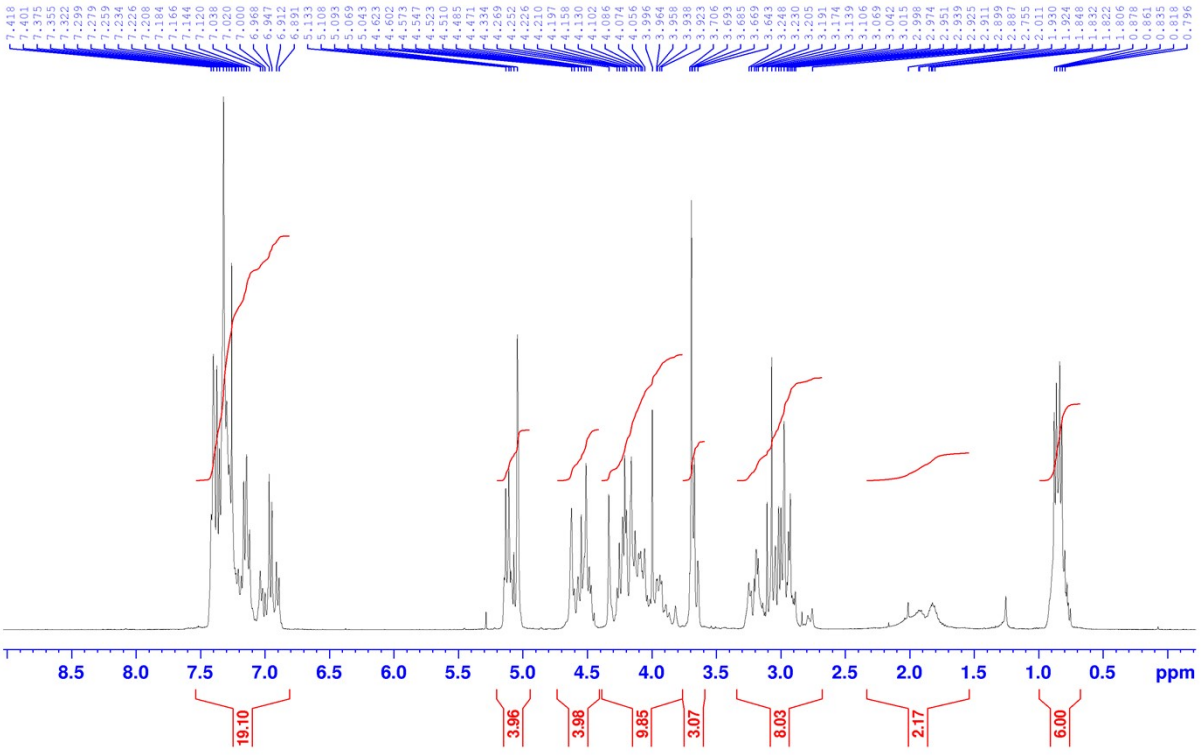


Figure S26. 1H NMR ($CDCl_3$) of pentapeptoid **19**.

ANALYTICAL HPLC PROFILES

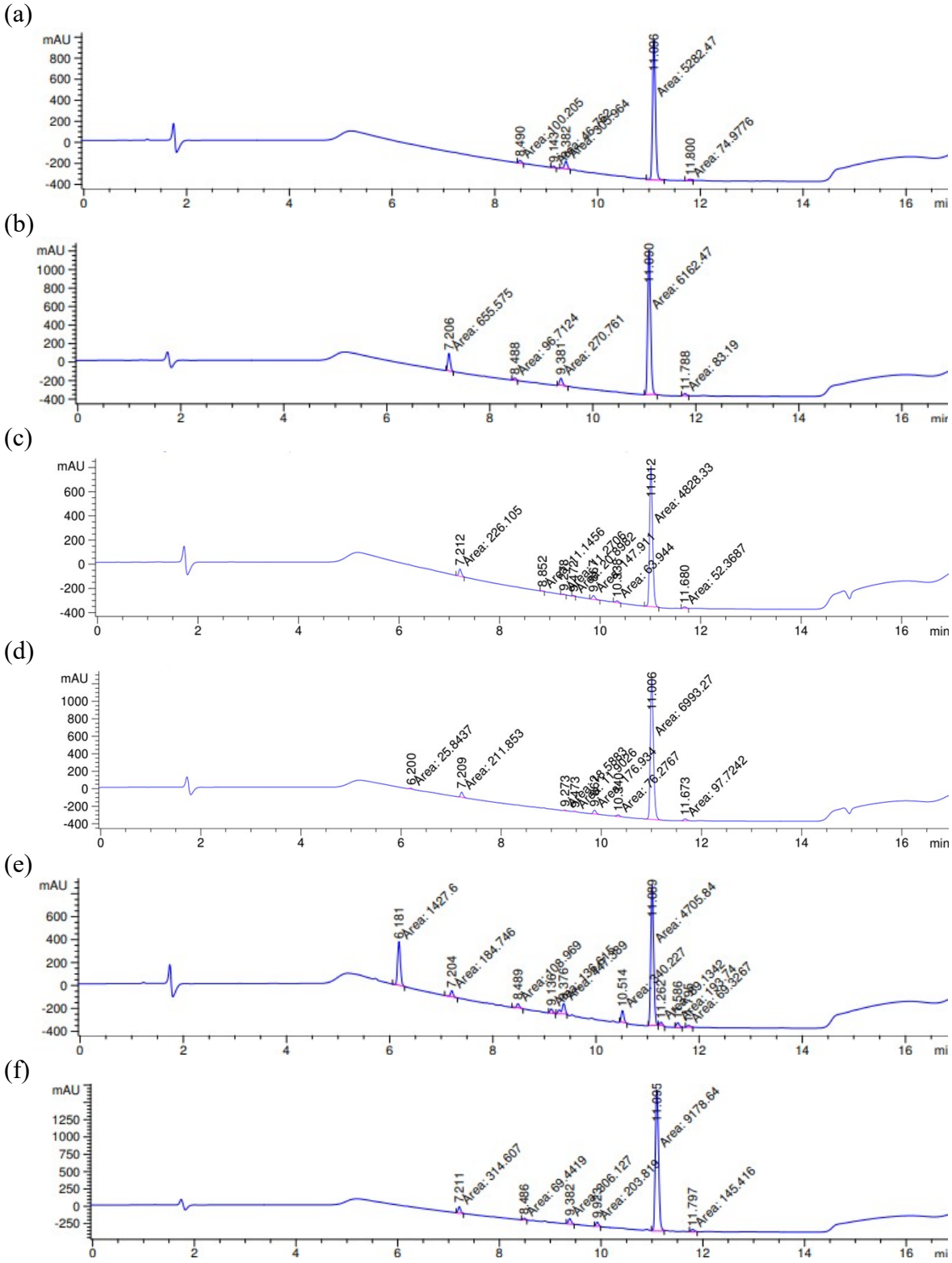


Figure S27. Analytical HPLC of dipeptoid **3** synthesised by 1+1 coupling as detailed in Table 1: (a) entry 1, crude; (b) entry 2, crude; (c) entry 3, crude; (d) entry 4, crude; (e) entry 5, crude; (f) entry 1, purified.

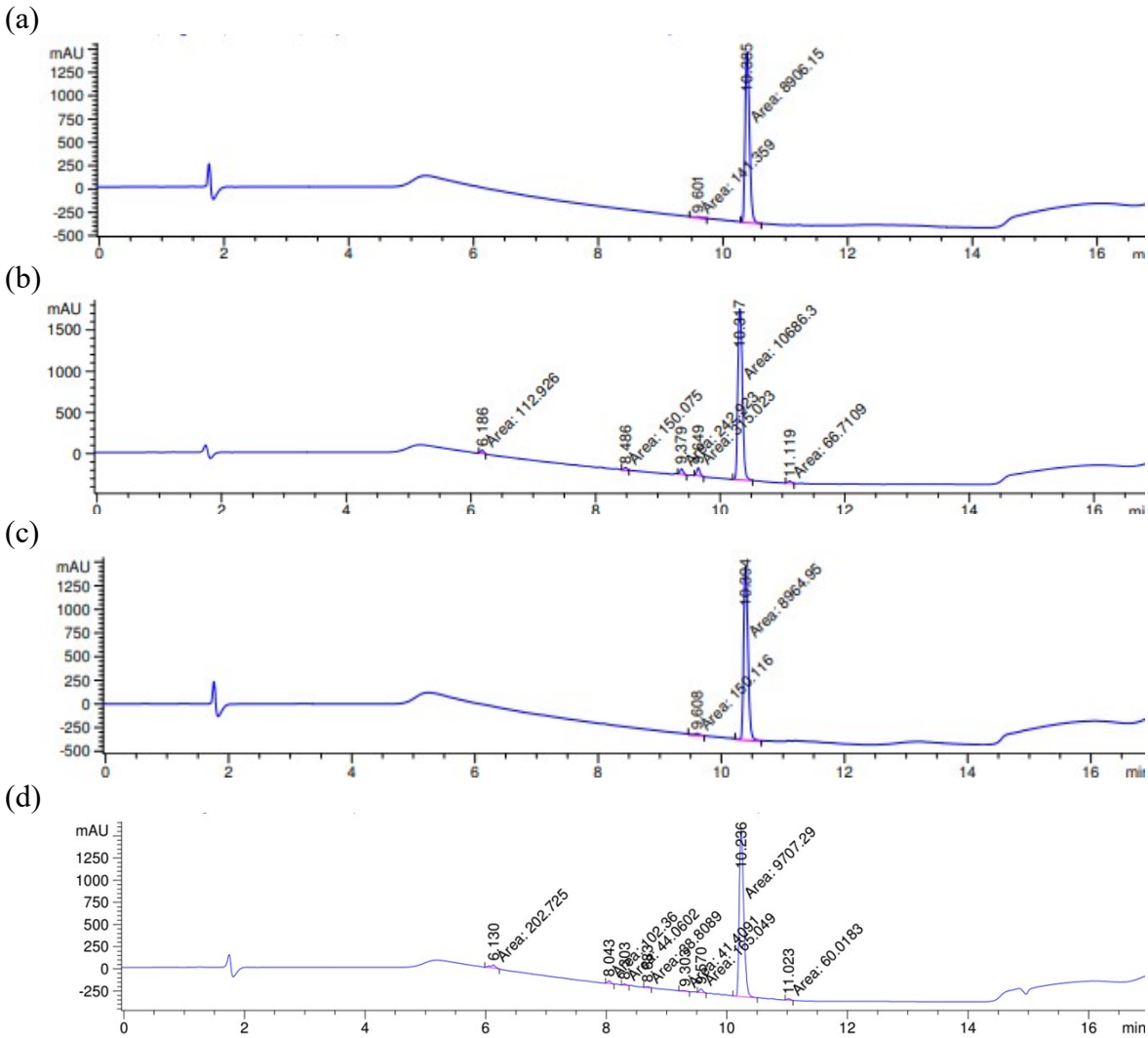
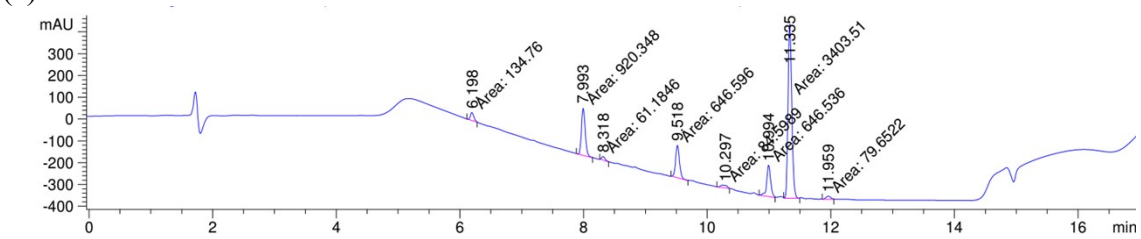


Figure S28. Analytical HPLC of dipeptoid **4** synthesised by 1+1 coupling as detailed in Table 1: (a) entry 6, crude; (b) entry 7, crude; (c) entry 8, crude; (d) entry 9, crude.

(a)



(b)

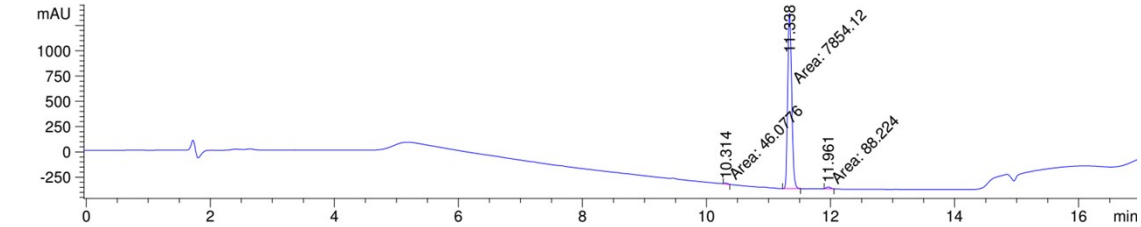


Figure S29. Analytical HPLC of tetrapeptoid **6** synthesised by 2+2 coupling as detailed in Table 2: (a) entry 3, crude purity 57%; (b) entry 3, purified purity 98%, t_r = 11.34 min.

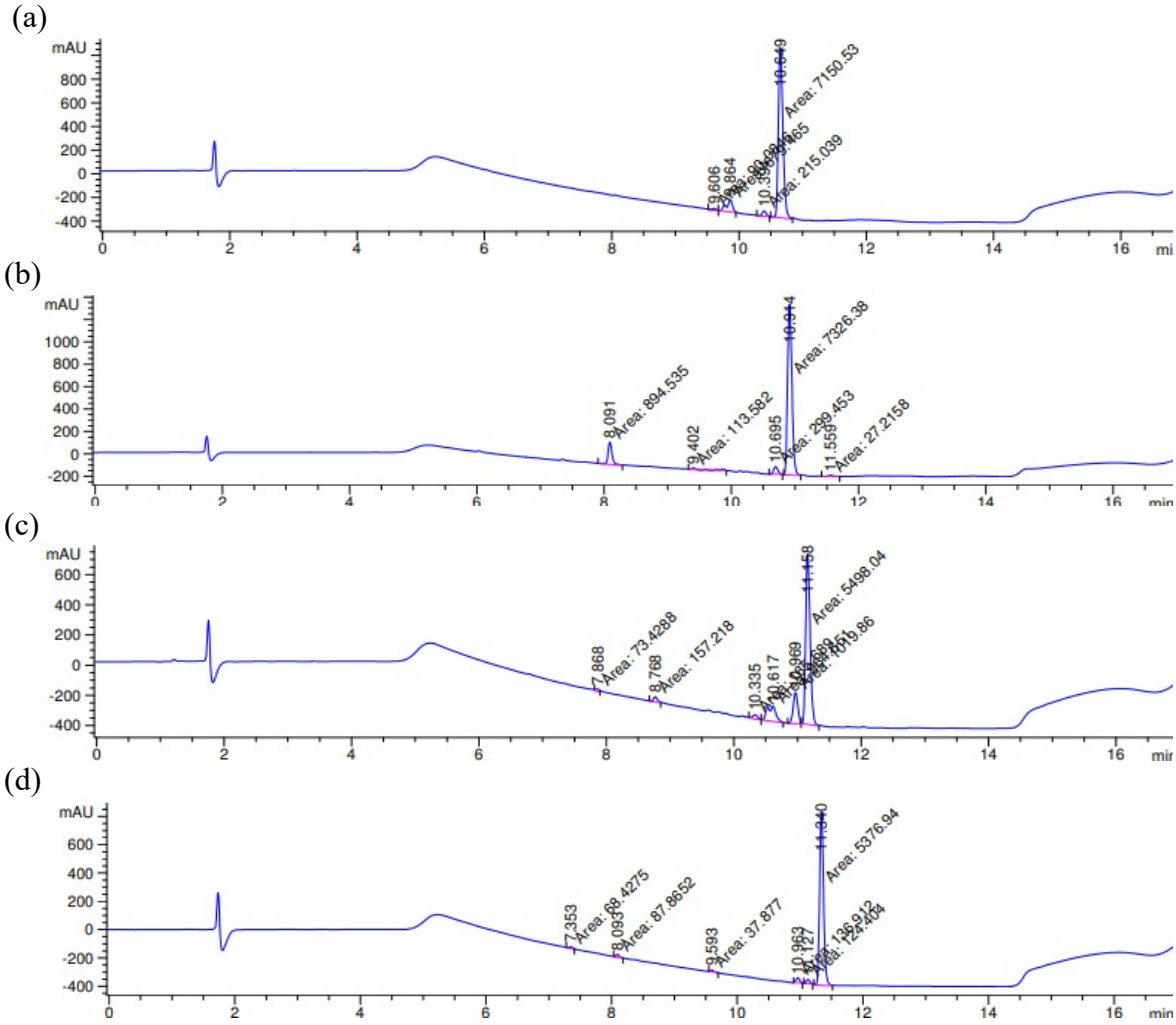


Figure S30. Analytical HPLC of peptoids **8**, **9**, **10** and **11** synthesised as detailed in Table 3, Method A: (a) tripeptoid **8**, crude purity 88%, t_r = 10.65 min; (b) tetrapeptoid **9**, crude purity 81%, t_r = 10.91 min; (c) pentapeptoid **10**, crude purity 70%, t_r = 11.16 min; (d) hexapeptoid **11**, purified purity 84%, t_r = 11.34 min.

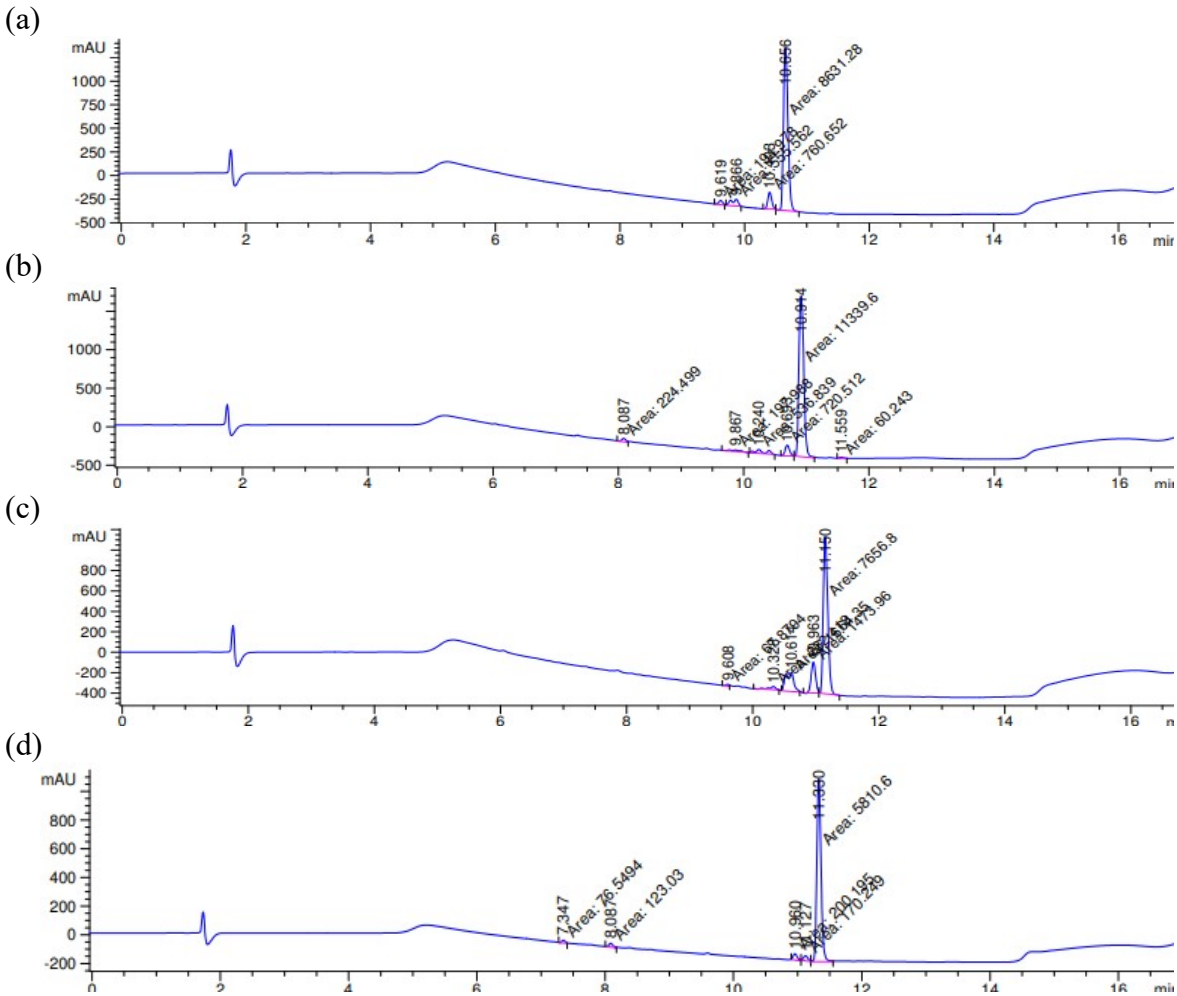


Figure S31. Analytical HPLC of peptoids **8**, **9**, **10** and **11** synthesised as detailed in Table 3, Method B: (a) tripeptoid **8**, crude purity 85%, t_r = 10.65 min; (b) tetrapeptoid **9**, crude purity 87%, t_r = 10.91 min; (c) pentapeptoid **10**, crude purity 69%, t_r = 11.15 min; (d) hexapeptoid **11**, purified purity 85%, t_r = 11.33 min.

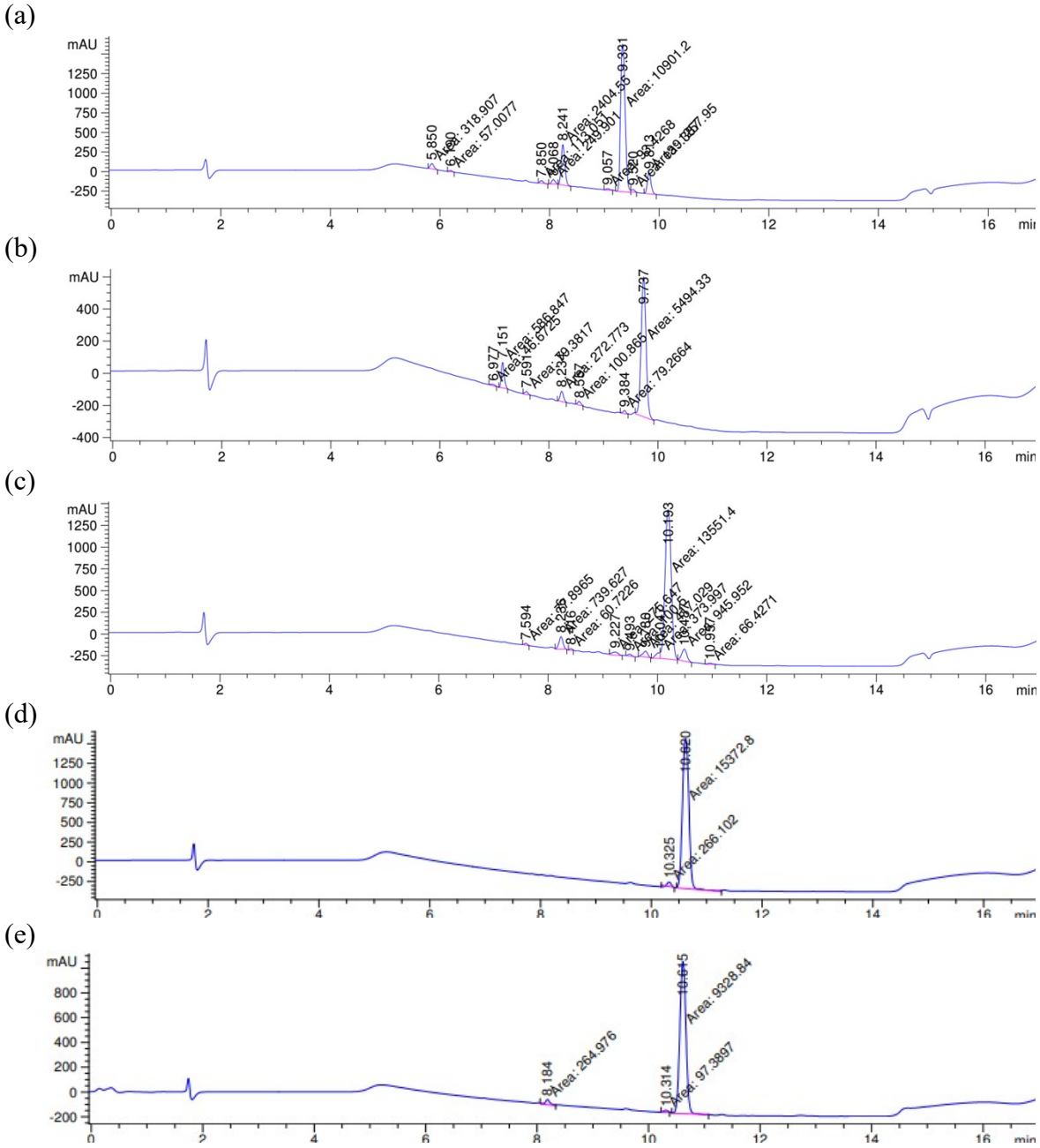


Figure S32. Analytical HPLC of peptoids **12**, **13**, **14** and **15** (mimic of Gramicidin S sequence) synthesised as detailed in Scheme 2: (a) dipeptoid **12**, crude puirity 70%, t_r = 9.33 min; (b) tripeptoid **13**, crude purity 82%, t_r = 9.74 min; (c) tetrapeptoid **14**, crude purity 82%, t_r = 10.19 min; (d) pentapeptoid **15**, purified purity 96%, t_r = 10.62 min; (e) pentapeptoid **15** synthesised with inclusion of 2 wt % TPGS-750-M in the coupling steps, purified purity 98%, t_r = 10.62 min.

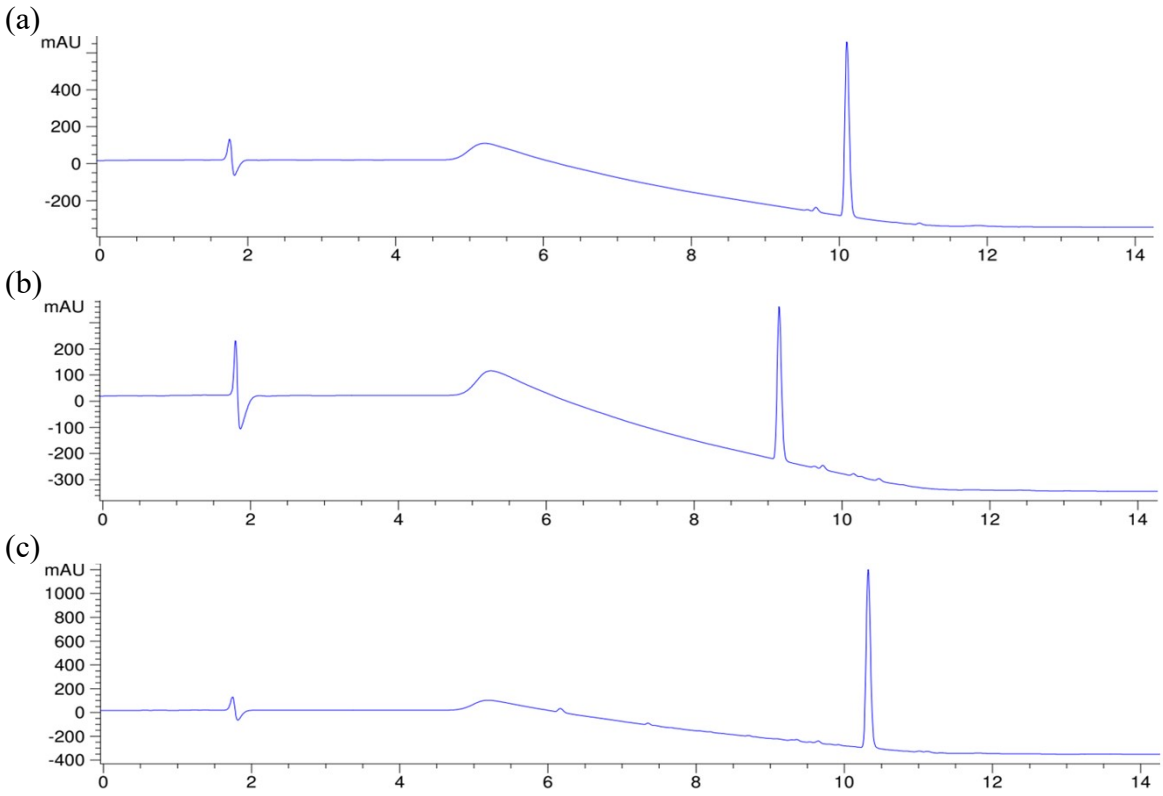


Figure S33. HPLC monitoring for the synthesis of dipeptoid **4** from peptoid methyl ester **16** using the one-pot two-step procedure as detailed in Scheme 3: (a) peptoid methyl ester **16**, t = 0 min; (b) peptoid acid intermediate after hydrolysis step, t = 30 min; (c) crude dipeptoid **4** after coupling step.

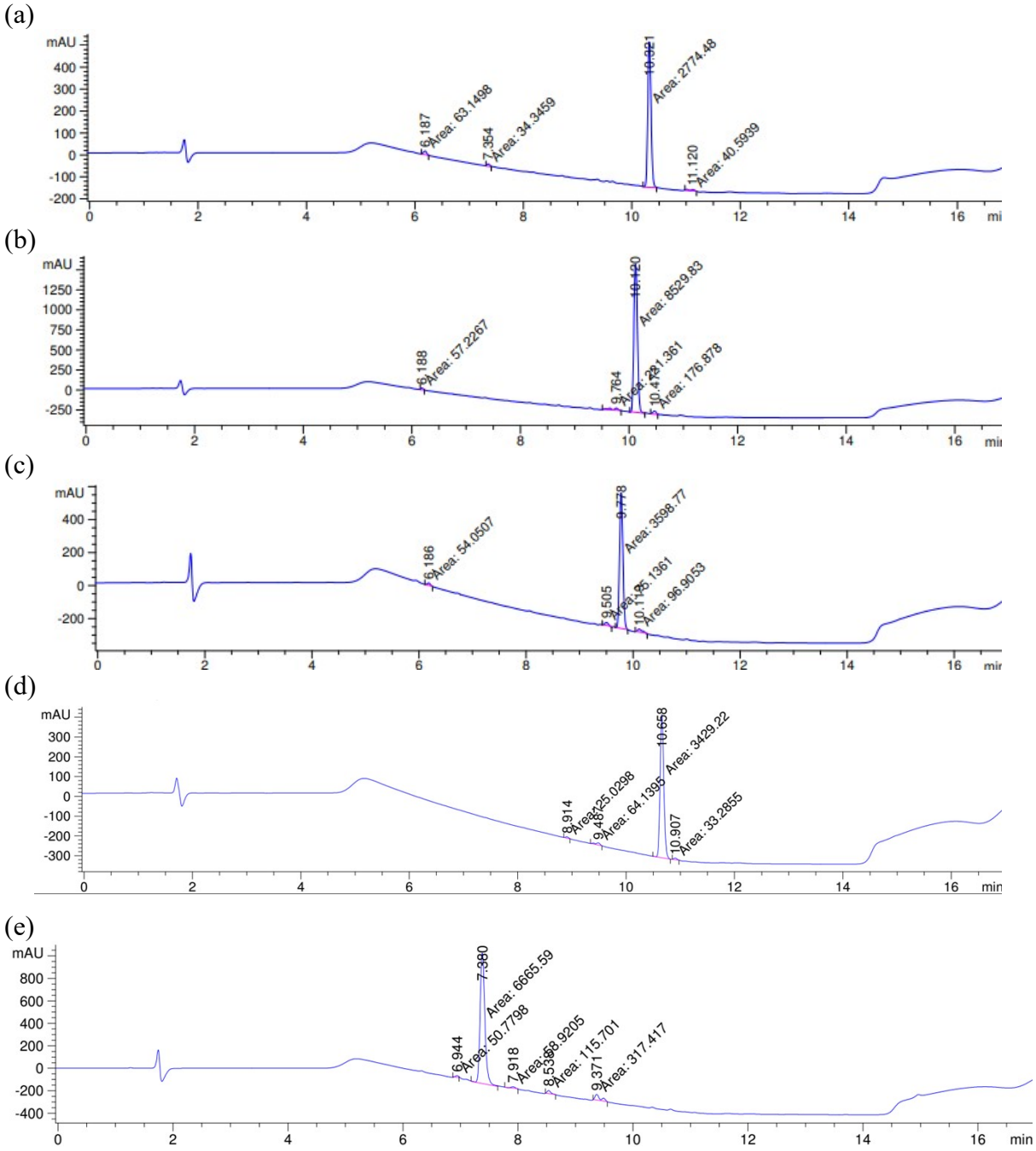


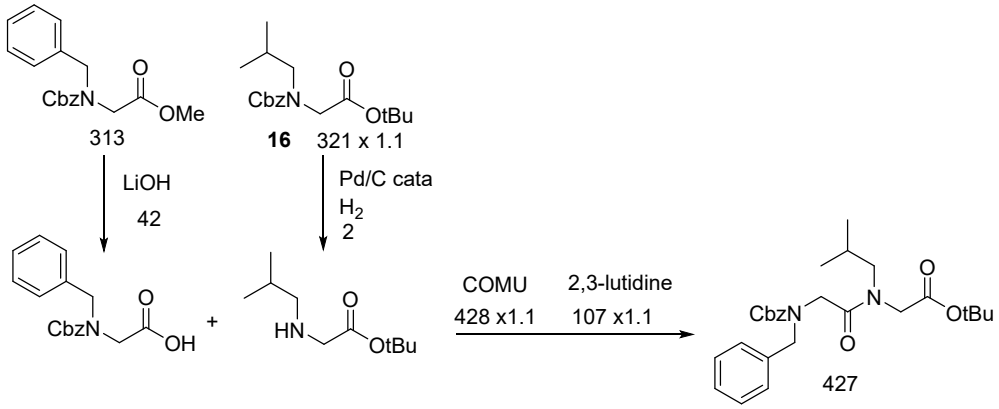
Figure S34. Analytical HPLC of peptoids **4**, **17**, **18** and **19** (retropeptoid mimic of Leu-enkephalin) synthesised as detailed in Scheme 3: (a) dipeptoid **4**, crude purity 97%, t_r = 10.32 min; (b) tripeptoid **17**, crude purity 95%, t_r = 10.12 min; (c) tetrapeptoid **18**, crude purity 94%, t_r = 9.78 min; (d) pentapeptoid **19**, purified purity 97%, t_r = 10.66 min (e) pentapeptoid **20**, purity 93%, t_r = 7.38 min.

ATOM ECONOMY CALCULATIONS

The atom economy percentage was calculated according to the methods described in the literature,[S1] using the formula:

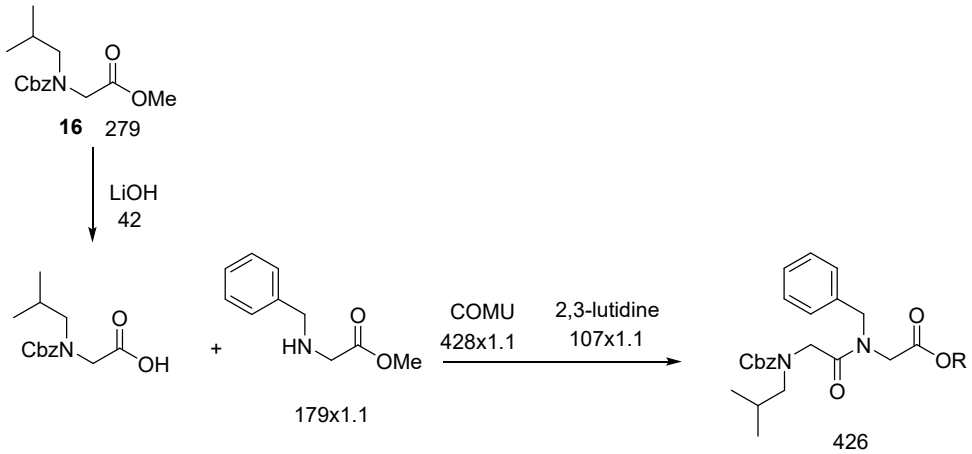
Atom economy = Molecular mass of desired product / Σ (Molecular mass of all reagents) × 100%.

Dipeptoid synthesis in the *C* to *N* direction in water-based media starting from monomer **16**



Atom economy = [427 / (313 + 42+ 353 + 2 + 471 + 118)] × 100 = 33 %.

Dipeptoid synthesis in the *N* to *C* direction in water-based media starting from monomer **16**



Atom economy = [427 / (279 + 42+ 197 + 471 + 118)] × 100 = 39 %.

E-FACTOR CALCULATIONS

E-factors for the synthesis of a retropeptoid mimic of Leu-enkephalin were calculated according to the recommendations described in the literature,[S2] using the formula:

E-factor = (Σ m(raw materials) + Σ m(reagents) + Σ m(solvents) + Σ m(water) – m product) / m product

The E-factor was calculated both for the method developed herein (one-pot two-step procedure in additive-free water-based media) as well as for a previously published synthesis employing the conventional solid-phase monomer method for comparison.

<u>E-factor for the synthesis of retropeptoid mimic of Leu-enkephalin using the method developed herein (one-pot two-step procedure in additive-free water-based media)</u>

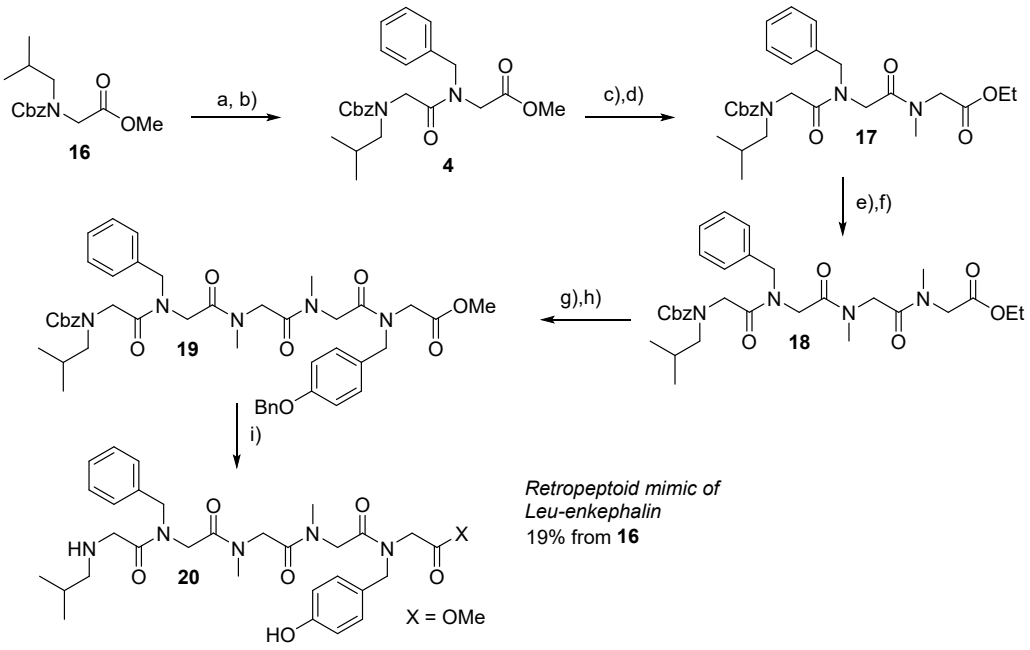


Table S1. Total mass of waste and E-factor for the nine-step synthesis of retropeptoid mimic of Leu-enkephalin using the one-pot two-step procedure in additive-free water-based media.

Steps	**Reagents/solvents**[a]	**Quantities**	**Mass (g)**
Starting material **16**	Cbz-NPhe-OMe **16**	0.025	0.070
First ester hydrolysis (a)	$LiOH·H_2O$	0.25 mmol	0.011
	EtOH	0.5 mL	0.394
	H_2O	0.75 mL	0.75
	HCl (1M)	5 drops	0.05
First coupling	H-NPhe-OMe **2b**	0.275 mmol	0.050

(b)	2,6-lutidine COMU EtOAc Aq. HCl (1M) Satd. aq. $NaHCO_3$ Satd. aq. NaCl $MgSO_4$	0.775 mmol 0.275 mmol 2x2 mL 2x2 mL 5x2 mL 2 mL	0.083 0.118 3.61 4.28 10.80 2.20 1
Second ester hydrolysis (c)	$LiOH·H_2O$ EtOH H_2O Aq. HCl (1M)	0.25 mmol 0.5 mL 0.75 mL 5 drops	0.011 0.394 0.75 0.05
Second coupling (d)	H-NAla-OEt **2h** 2,6-lutidine COMU EtOAc Aq. HCl (1M) Satd. aq. $NaHCO_3$ Satd. aq. NaCl $MgSO_4$	0.275 mmol 0.775 mmol 0.275 mmol 2x2 mL 2x2 mL 5x2 mL 2 mL	0.042 0.083 0.118 3.61 4.28 10.80 2.20 1
Third ester hydrolysis (e)	$LiOH·H_2O$ EtOH H_2O Aq. HCl (1M)	0.25 mmol 0.5 mL 0.75 mL 5 drops	0.011 0.394 0.75 0.05
Third coupling (f)	H-NAla-OEt **2h** 2,6-lutidine COMU EtOAc Aq. HCl (1M) Satd. aq. $NaHCO_3$ Satd. aq. NaCl $MgSO_4$	0.275 mmol 0.775 mmol 0.275 mmol 2x2 mL 2x2 mL 5x2 mL 2 mL	0.042 0.083 0.118 3.61 4.28 10.80 2.20 1
Fourth ester hydrolysis (g)	$LiOH·H_2O$ EtOH H_2O Aq. HCl (1M)	0.25 mmol 0.5 mL 0.75 mL 5 drops	0.011 0.394 0.75 0.05
Fourth coupling (h)	H-NTyr(Bn)-OEt **2i** 2,6-lutidine COMU EtOAc Aq. HCl (1M) Satd. aq. $NaHCO_3$ Satd. aq. NaCl $MgSO_4$	0.275 mmol 0.775 mmol 0.275 mmol 2x2 mL 2x2 mL 5x2 mL 2 mL	0.078 0.083 0.118 3.61 4.28 10.80 2.20 1
Deprotection (i)	Pd/C 10% EtOH Celite	Cat. 1 mL + 2 mL	0.002 2.36 1
		Total	96.828
Retropeptoid (yield)[b]	0.029 g (19%)	Total waste including water	96.799
		E-factor including water	**3337**
		Total waste without water	24.435
		E-factor without water	**842**

[a] Aqueous phase in blue and recommended solvent in green.

[b] The final purification of the retropeptoid is not considered in the calculations since the same final chromatography with identical impact is assumed regardless of the comparative synthetic procedures.

E-factor for the synthesis of retropeptoid mimic of Leu-enkephalin using a conventional solid-phase monomer procedure.

The solid-phase monomer method synthesis of a retropeptoid mimic of Leu-enkephalin previously reported in the literature[S3] was used for calculation of the E-factor for a conventional methodology.

Table S2. Total mass of waste and E-factor for the 12-step synthesis of retropeptoid mimic of Leu-enkephalin using the solid-phase monomer method.

Steps	**Reagents/solvents**[a]	**Quantities**	**Mass (g)**
Resin	TentaGel SRAM	0.25 mmol	1.05
	NMP (swelling)	2x4 mL	8.24
Fmoc deprotection	20% piperidine/NMP (x2)	2x4 mL	7.96
	NMP (washing)	5x4 mL	20.6
First coupling	Fmoc-NTyr(*t*Bu)-OH	1 mmol	0.459
	PyBOP	1 mmol	0.520
	DIPEA	2 mmol	0.259
	NMP	4 mL	4.12
	NMP (washing)	3x4 mL	12.36
Fmoc deprotection	20% piperidine/NMP (x2)	2x4 mL	7.96
	NMP (washing)	5x4 mL	20.6
Second coupling	Fmoc-NAla-OH	1 mmol	0.311
	PyBOP	1 mmol	0.520
	DIPEA	2 mmol	0.259
	NMP	4 mL	4.12
	NMP (washing)	3x4 mL	12.36
Fmoc deprotection	20% piperidine/NMP (x2)	2x4 mL	7.96
	NMP (washing)	5x4 mL	20.6
Third coupling	Fmoc-NAla-OH	1 mmol	0.311
	PyBOP	1 mmol	0.520
	DIPEA	2 mmol	0.259
	NMP	4 mL	4.12
	NMP (washing)	3x4 mL	12.36
Fmoc deprotection	20% piperidine/NMP (x2)	2x4 mL	7.96
	NMP (washing)	5x4 mL	20.6
Fourth coupling	Fmoc-NPhe-OH	1 mmol	0.387
	PyBOP	1 mmol	0.520
	DIPEA	2 mmol	0.259
	NMP	4 mL	4.12
	NMP (washing)	3x4 mL	12.36
Fmoc deprotection	20% piperidine/NMP (x2)	2x4 mL	7.96
	NMP (washing)	5x4 mL	20.6
Fifth coupling	Fmoc-NLeu-OH	1 mmol	0.353
	PyBOP	1 mmol	0.520
	DIPEA	2 mmol	0.259
	NMP	4 mL	4.12
	NMP (washing)	5x4 mL	20.6
Fmoc deprotection	20% piperidine/NMP (x2)	2x4 mL	7.96
	NMP (washing)	5x4 mL	20.6

	DCM (washing)	4x4 mL	21.21
Cleavage	TFA H_2O TIS	10 mL 0.25 mL 0.25 mL	14.9 0.25 0.193
		Total	313,559
Retropeptoid (yield)[b]	0.022 mg (15%)	Total waste with water	313.537
		E-factor including water	**14251**
		Total waste without water	313.287
		E-factor without water	**14240**

[a] Aqueous phase in blue and hazardous solvent in red.
[b] The final purification of the retropeptoid is not considered in the calculations since the same final chromatography with identical impact is assumed regardless of the comparative synthetic procedures.

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[S1] B. M. Trost, *Science.*, 1991, **254**, 1471.

[S2] R. A. Sheldon, *Green. Chem.*, 2017, **19**, 18.

[S3] J. A. W. Kruijtzer, L. J. F. Hofmeyer, W. Heerma, C. Versluis and R. M. J. Liskamp, *Chem. Eur. J.*, 1998, **4**, 1570.