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Supporting Information

Generalizing the Aromatic δ-Amino Acid Foldamer Helix

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Contents

List of Abbreviations

AcOH	acetic acid
CD	circular dichroism
CyHex	Cyclohexane
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EI	electron ionization
ESI	electrospray ionization
EtOAc	ethyl acetate
Fmoc	fluorenylmethoxycarbonyl
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum correlation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
MeOH	methanol
MW	molecular weight
NMR	nuclear magnetic resonance
RP	reversed phase
RT	room temperature
SPFS	solid phase foldamer synthesis
***t*BuOH**	*tert*-butanol
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropyl silane
TLC	thin layer chromatography
TMSP	3-(trimethylsilyl)propionic-2,2,3,3-d4 acid sodium salt
UV/Vis	ultraviolet-visible

1 Supplementary figures

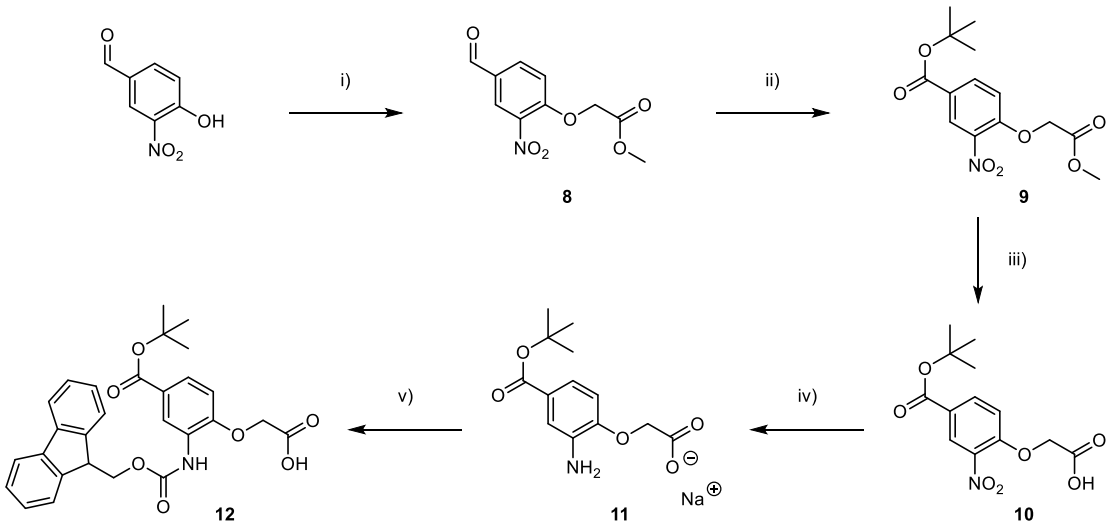


Figure S1: Synthetic route to the Fmoc-**B**$^{\mathbf{Acd}}$-OH monomer (**12**): i) methyl bromoacetate, K_2CO_3, acetonitrile, 70 °C (48%); ii) 1) Jones reagent, acetone, 2) *t*BuOH, EDC·HCl, DMAP, DMF (70%); iv) LiOH, H_2O, THF (quant.); v) H_2, Pd/C, Na_2CO_3, MeOH (quant.); vi) Fmoc-Cl, $NaHCO_3$, H_2O, 1,4-dioxane (76%). For detailed synthetic procedures see section 2.3.

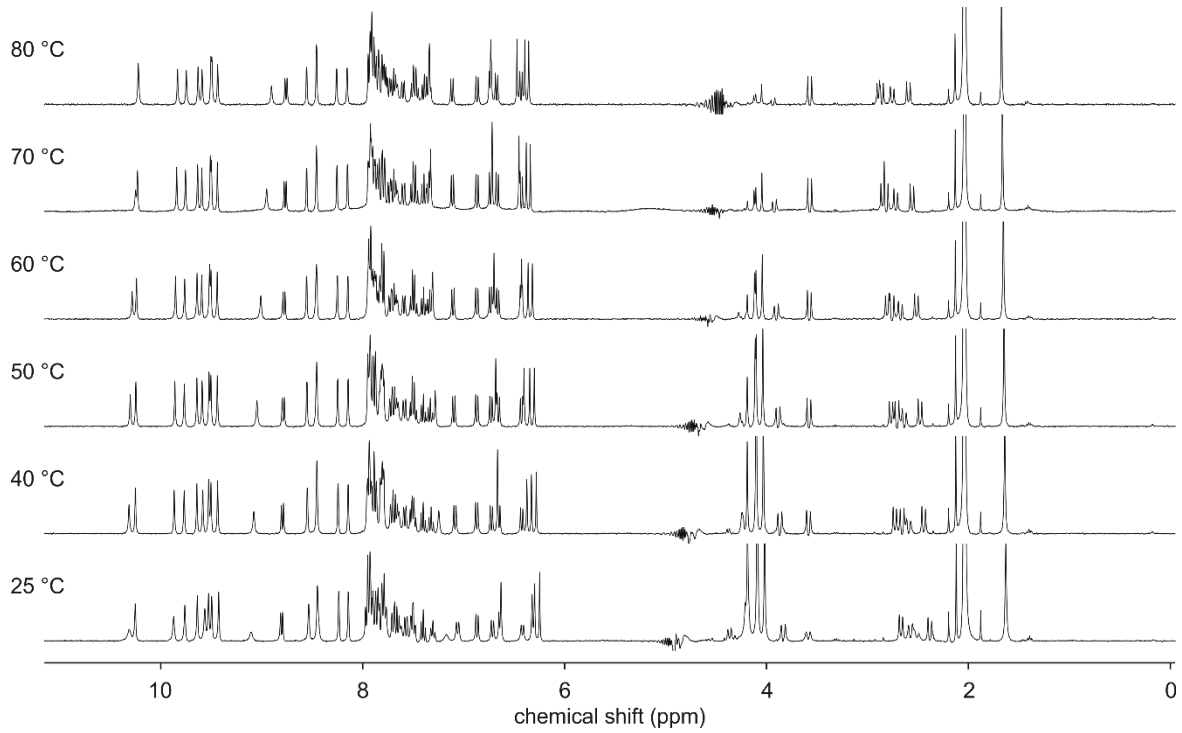


Figure S2: Variable temperature ^{1}H NMR spectra of oligomer **1** (500 MHz, 0.6 mM in 12 mM NH_4OAc buffer pH 8.5 H_2O/D_2O 9:1, H_2O suppression).

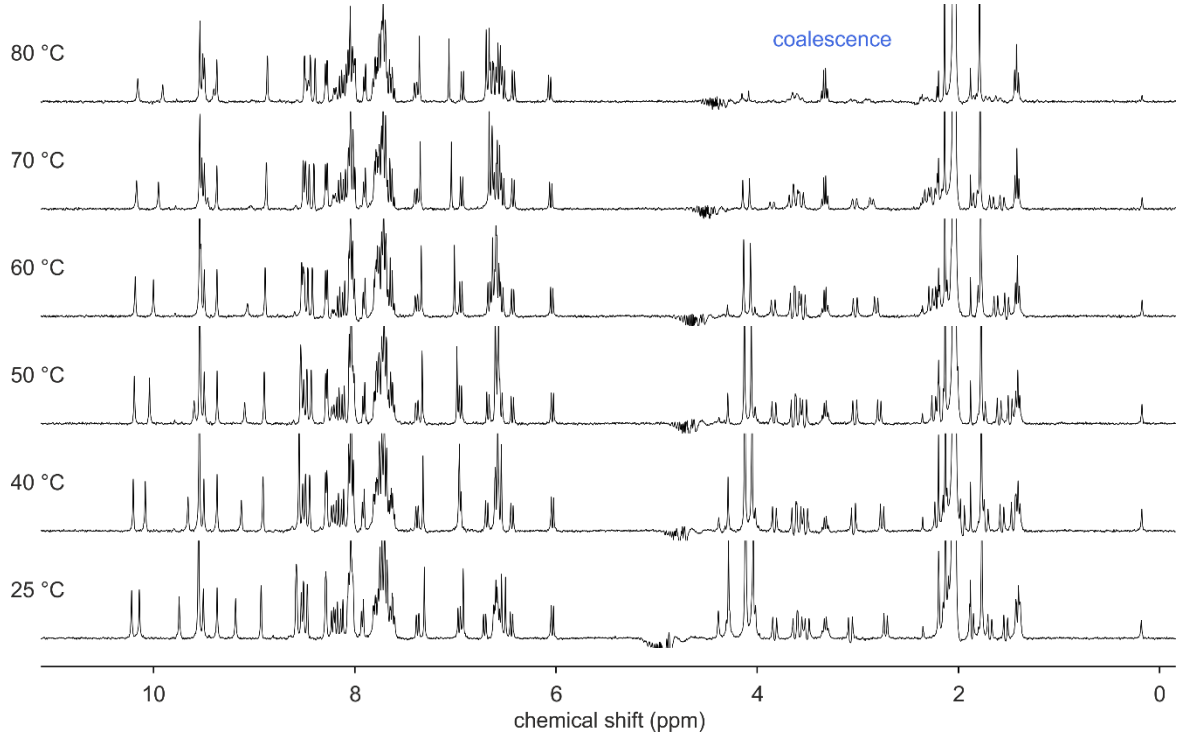


Figure S3: Variable temperature ^{1}H NMR spectra of oligomer **2** (500 MHz, 0.26 mM in 12 mM NH_4OAc buffer pH 8.5 H_2O/D_2O 9:1, H_2O suppression).

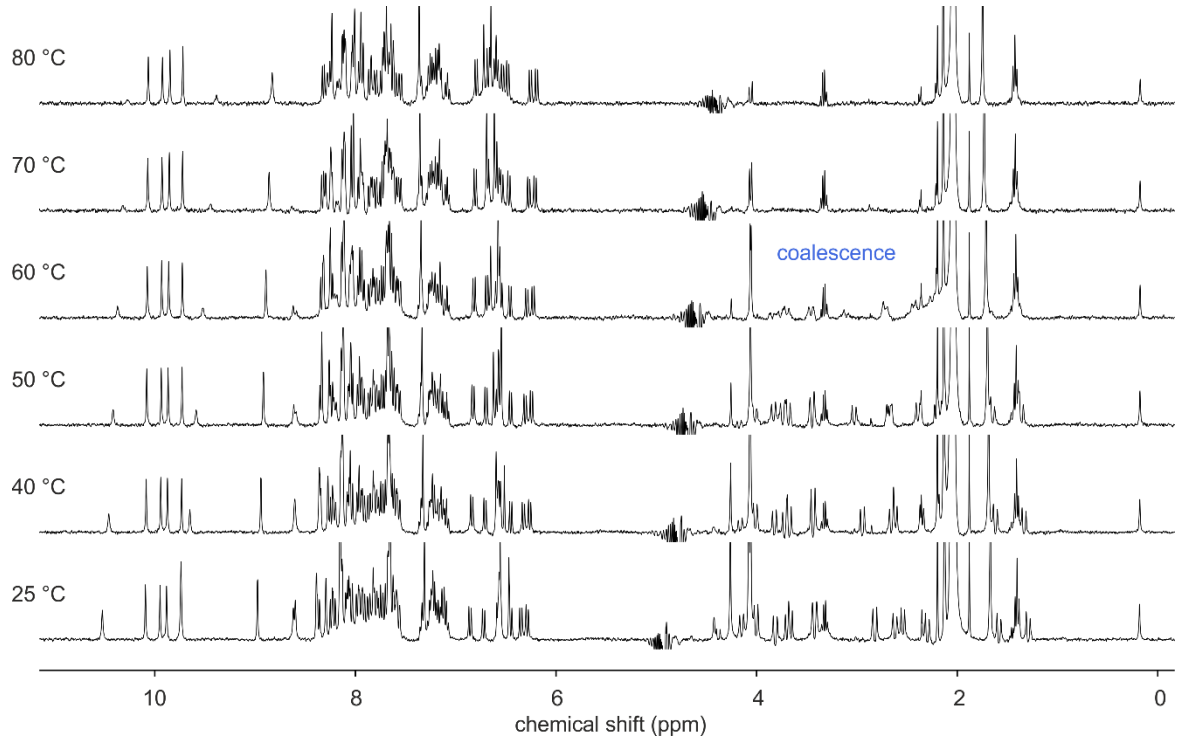


Figure S4: Variable temperature ^{1}H NMR spectra of oligomer **3** (500 MHz, 0.16 mM in 12 mM NH_4OAc buffer pH 8.5 H_2O/D_2O 9:1, H_2O suppression).

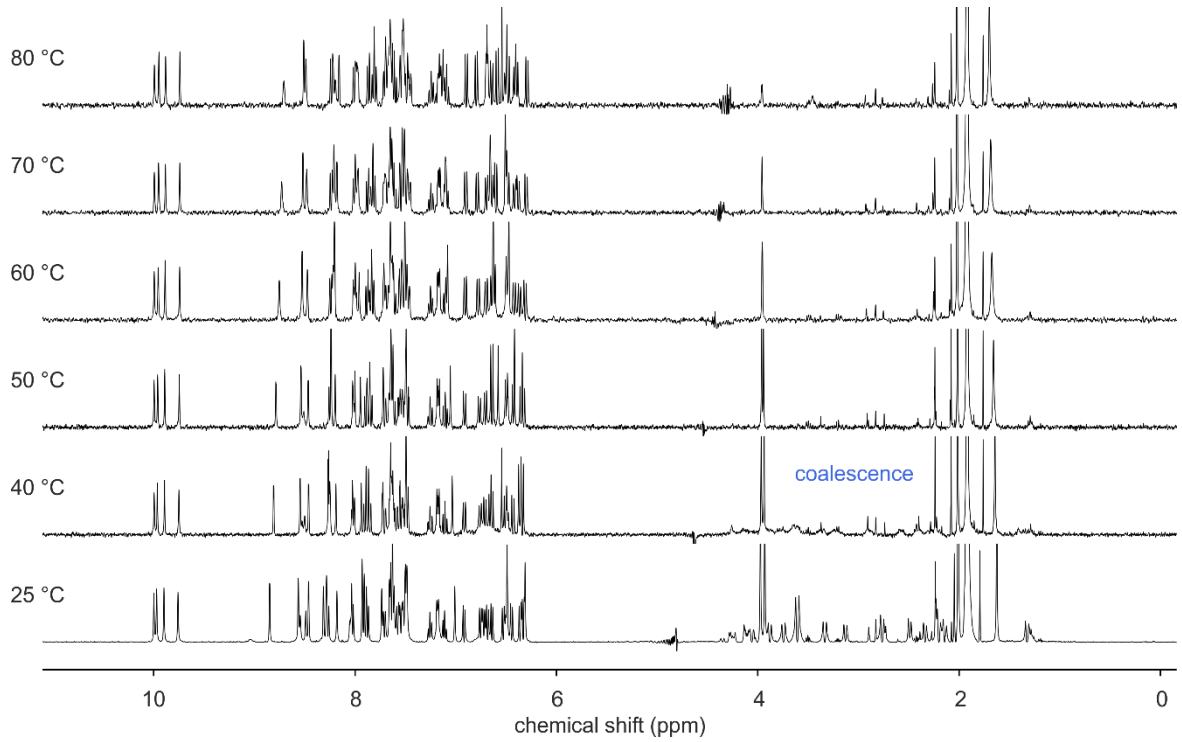


Figure S5: Variable temperature ^{1}H NMR spectra of oligomer **4** (500 MHz, 0.18 mM in 12 mM NH_4OAc buffer pH 8.5 H_2O/D_2O 9:1, H_2O suppression).

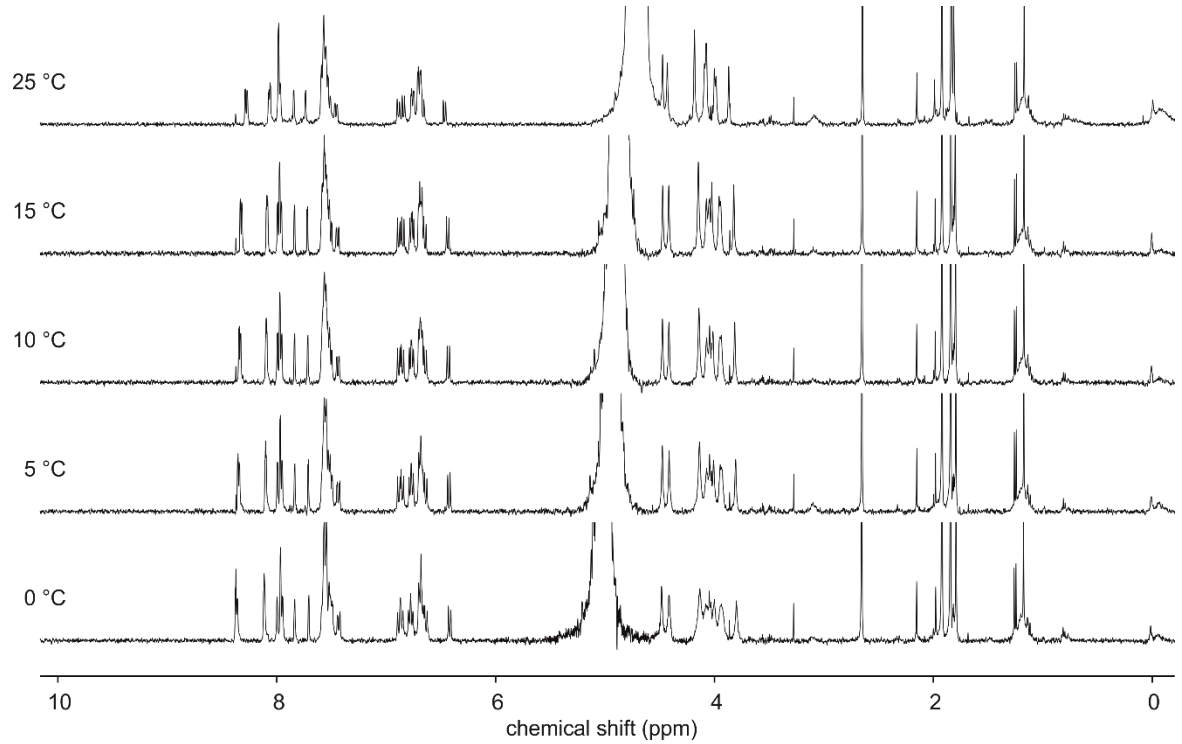


Figure S6: Variable temperature ^{1}H NMR spectra of oligomer **5** (400 MHz, 0.6 mM in 60 mM ND_4 + 15 mM AcOH-d_4 in D_2O).

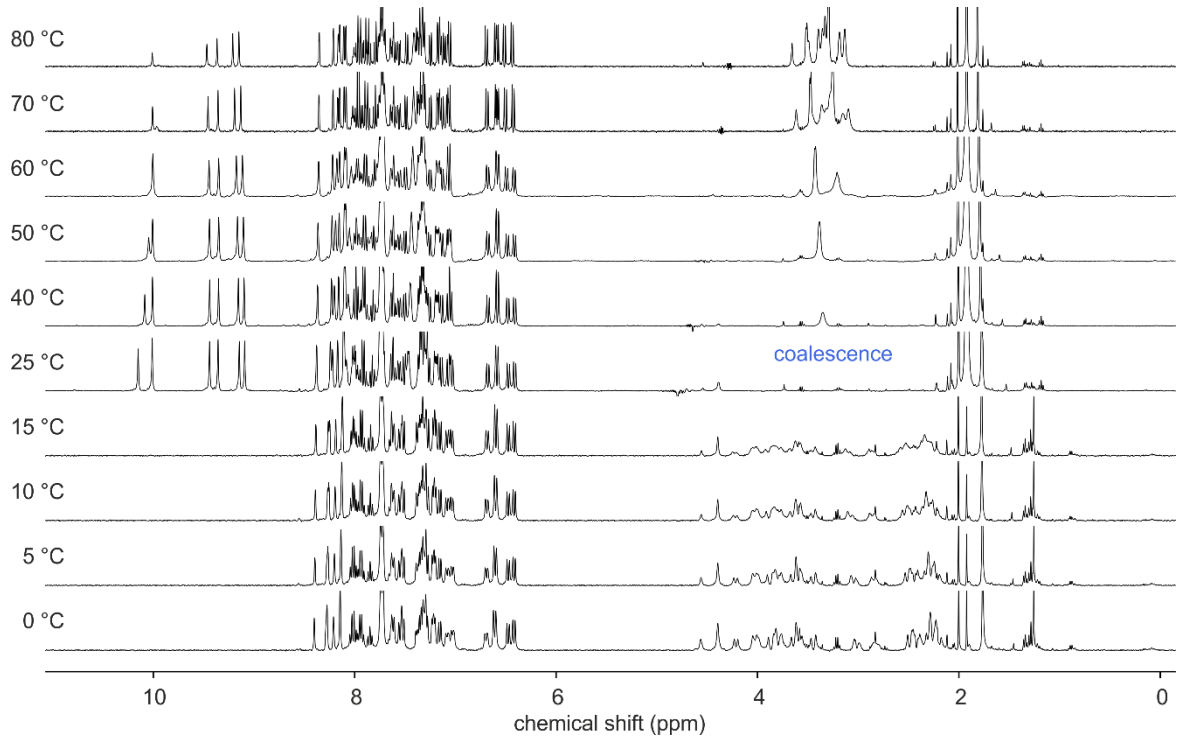


Figure S7: Variable temperature ^{1}H NMR spectra of oligomer **6** (25–80 °C: 500 MHz, 0.66 mM in 12 mM NH_4OAc buffer pH 8.5 H_2O/D_2O 9:1, H_2O suppression; 0–15 °C: 400 MHz, 0.66 mM in 60 mM ND_4 + 15 mM AcOH-d_4 in D_2O).

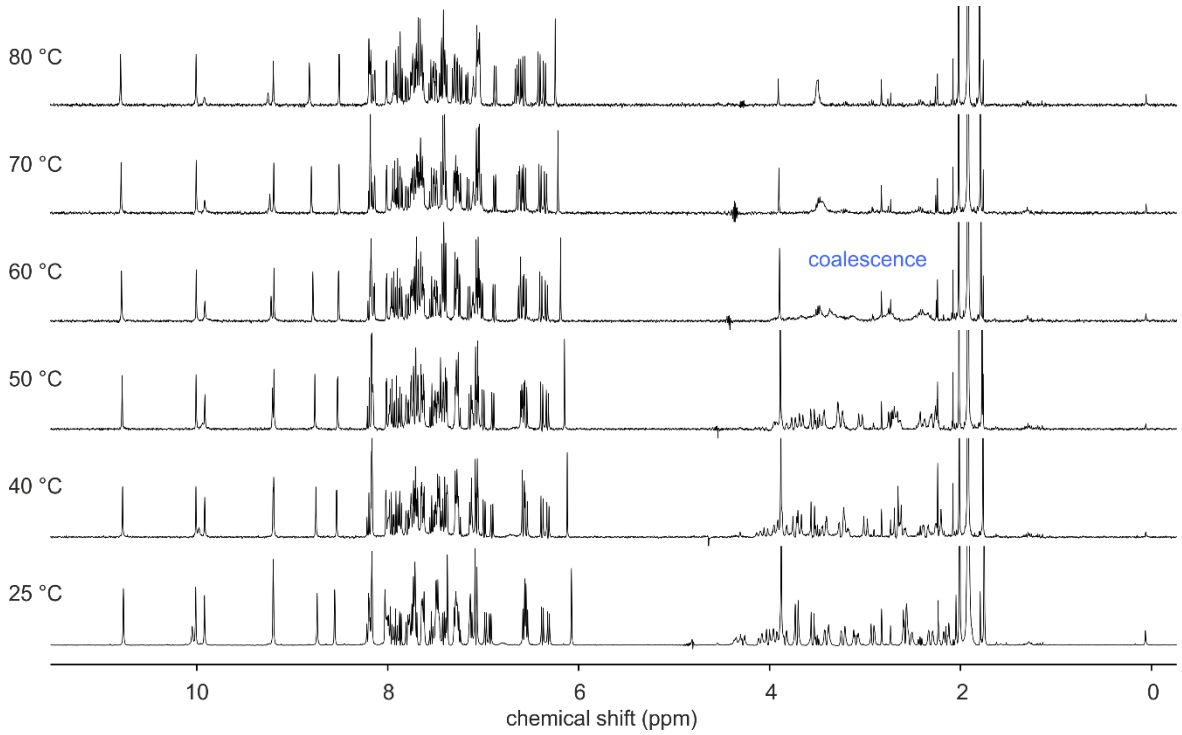


Figure S8: Variable temperature ^{1}H NMR spectra of oligomer **7** (500 MHz, 0.36 mM in 12 mM NH_4OAc buffer pH 8.5 H_2O/D_2O 9:1, H_2O suppression).

2 Materials and Methods

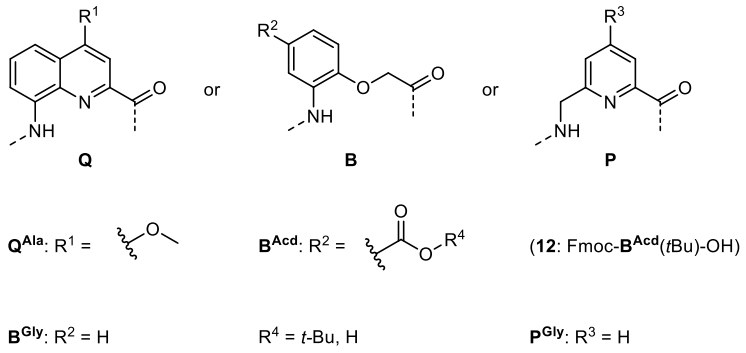


Figure S9: Fmoc-acid building blocks used in this study. Fmoc-**Q**$^{\mathbf{Ala}}$-OH[1], Fmoc-**B**$^{\mathbf{Gly}}$-OH[2] and Fmoc-**P**$^{\mathbf{Gly}}$-OH[3] have been described previously. For a detailed procedure to Fmoc-**B**$^{\mathbf{Acd}}$(*t*Bu)-OH, see section 2.3.

2.1 General

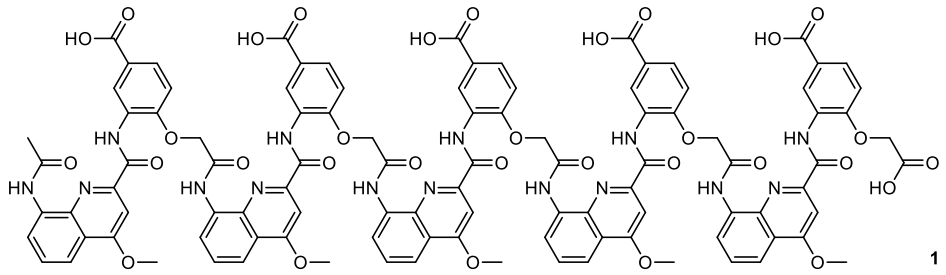
Commercial reagents (Suppliers: Abcr, Fisher Scientific, Merck, Sigma-Aldrich, TCI or VWR) were used without further purification unless otherwise stated. Wang resin LL (100–200 mesh) was purchased from Novabiochem, Cl-MPA ProTide™ resin LL was purchased from CEM. Peptide grade *N*,*N*-dimethylformamide (DMF) was purchased from Carlo Erba. Anhydrous chloroform, triethylamine (TEA) and *N*,*N*-diisopropylethylamine (DIPEA) were obtained via distillation over CaH_2 prior to use. Anhydrous tetrahydrofuran (THF) and dichloromethane (DCM) were obtained via an MBRAUN SPS-800 solvent purification system. Ultrapure water was obtained via a Sartorius arium® pro VF ultrapure water system. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60-F254 plates and observed under UV light. Column chromatography purifications were carried out on Merck GEDURAN Si60 (40–63 μm). Nuclear magnetic resonance (NMR) spectra were recorded on an Avance III HD 400MHz Bruker BioSpin spectrometer or an Avance III HD 500MHz Bruker BioSpin spectrometer equipped with a broad band observe 5-mm BB-H&FD CryProbe™ Prodigy. Measurements were performed at 25 °C unless stated otherwise. Water suppression was performed with excitation sculpting. Processing was done with MestReNova (v.12.0.0-20080) NMR processing software from Mestrelab Research. Chemical shifts are reported in ppm and calibrated via residual solvent signals or 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid sodium salt (TMSP) when water suppression was applied.[4] Signal multiplicities are abbreviated as s, singlet; d, doublet; t, triplet; q, quartet, and m, multiplet. Signals were assigned using ^{1}H-^{13}C HMQC and ^{1}H-^{13}C HMBC spectra. Electrospray ionization (ESI) mass spectra were recorded on Bruker microTOF II and Thermo Finnigan LTQ FT Ultra spectrometers. Electron ionization (EI) mass spectra were recorded on a Thermo Q

Exactive GC Orbitrap or a Finnigan MAT 95 sector mass spectrometer. Analytical and semi-preparative reversed phase (RP) high performance liquid chromatography (HPLC) was performed on a Thermo Fisher Scientific Ultimate 3000 HPLC System using Macherey-Nagel Nucleodur C18 Gravity columns (4 × 100 mm, 5 µm and 10 × 250 mm, 5 µm) and Macherey-Nagel Nucleodur C8 Gravity columns (4 × 50 mm, 5 µm and 10 × 100 mm, 5 µm). UV absorbance was monitored at 300 nm if not stated otherwise. Simple ultraviolet–visible (UV/Vis) absorbance measurements were done with a Thermo Fisher Scientific Nanodrop One instrument using a 1 cm quartz cuvette. Circular dichroism (CD) spectra were measured on a Jasco J-810 spectrometer. Measurements were performed at 20 °C if not stated otherwise. Manual microwave-assisted solid-phase foldamer synthesis (SPFS) was performed via a CEM® Discover Bio microwave peptide synthesizer. The temperature within the reactor vessel was monitored with an optical fiber probe. Automated SPFS was done via a Gyros Protein Technologies PurePep Chorus synthesizer with induction heating.

2.2 Solid phase synthesis procedures

Oligomers were synthesized according to previously reported SPFS protocols,[5] hereafter referred to as standard method. Fmoc acid building blocks were activated *in situ* by generating the respective acid chlorides prior to coupling.

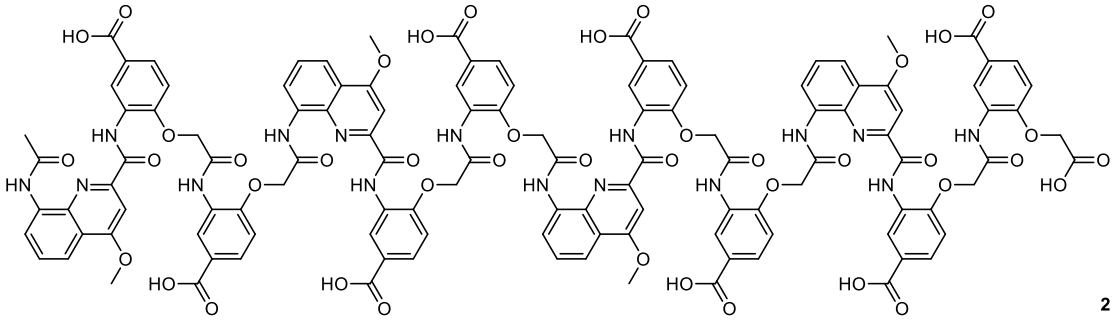
Acetylation: In the microwave vessel: after the resin (1.0 equiv.) was washed with anhydrous THF (4 ×), DIPEA (10.0 equiv.) and acetyl chloride (5.0 equiv.) in anhydrous THF (1 mL per 100 mg resin; not less than 2 mL) were added and the suspension was heated to 50 °C for 15 min (25 W, ramp to 50 °C over 5 min, hold at 50 °C for 15 min). The resin was washed with anhydrous THF (3×) and the coupling step was repeated once. Then, the resin was washed again with anhydrous THF (1×) and DMF (5×), and kept suspended in DMF (if stored longer than 24 h, it was kept at 4 °C).



1

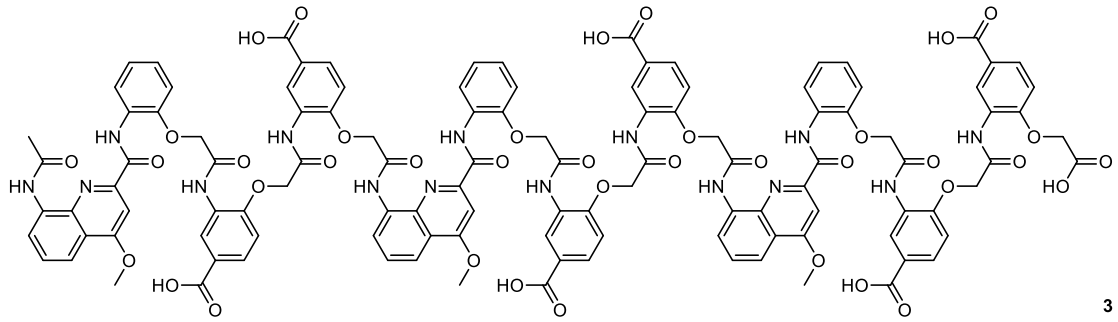
Compound 1: Oligomer **1** was synthesized on Wang resin (0.37 mmol g^{-1}, 27.8 µmol scale) according to the standard method (automated). Loading of the first monomer: 0.25 mmol g^{-1} (68%). The final acetyl group was installed via the general acetylation method. After purification by semi-prep HPLC (C18, 0–30B, 50 °C; A: 13 mmol NH_4OAc buffer pH 8.5, B: acetonitrile), the title compound was

obtained as a white solid (13.8 mg, 6.8 µmol, 24%; HPLC-purity: 97.5%). **^{1}H NMR** (500 MHz, 12 mmol NH_4OAc buffer pH 8.5 in H_2O/D_2O 9:1): δ = 10.19 (s, 1H), 10.13 (s, 1H), 9.75 (s, 1H), 9.64 (s, 1H), 9.52 (s, 1H), 9.44 (s, 1H), 9.41 (s, 1H), 9.38 (s, 1H), 9.31 (s, 1H), 8.98 (s, 1H), 8.68 (d, *J* = 8.40 Hz, 1H), 8.42 (s, 1H), 8.33 (s, 1H), 8.12 (s, 1H), 8.02 (d, *J* = 2.01 Hz, 1H), 7.85 (s, 1H), 7.83 (s, 1H), 7.82 – 7.79 (m, 2H), 7.78 (d, *J* = 4.48 Hz, 1H), 7.75 (s, 1H), 7.73 (s, 1H), 7.71 (s, 1H), 7.69 (d, *J* = 4.22 Hz, 1H), 7.67 (s, 1H), 7.65 (s, 1H), 7.59 (s, 1H), 7.58 – 7.55 (m, 1H), 7.54 (s, 1H), 7.53 – 7.48 (m, 1H), 7.48 – 7.42 (m, 1H), 7.38 (td, *J* = 8.61, 3.80 Hz, 1H), 7.28 (t, *J* = 8.64 Hz, 1H), 7.19 (t, *J* = 8.91 Hz, 1H), 7.06 (s, 1H), 6.94 (d, *J* = 10.04 Hz, 1H), 6.75 (d, *J* = 9.33 Hz, 1H), 6.60 (d, *J* = 9.56 Hz, 1H), 6.53 (s, 1H), 6.51 (s, 1H), 6.30 (d, *J* = 9.75 Hz, 1H), 6.20 (s, 1H), 6.18 (s, 1H), 6.13 (s, 1H), 4.28 (d, *J* = 13.23 Hz, 1H), 4.22 (d, *J* = 13.88 Hz, 1H), 4.10 (s, 1H), 4.07 (s, 2H), 3.97 (s, 6H), 3.90 (s, 3H), 3.72 (d, *J* = 16.33 Hz, 1H), 3.47 (d, *J* = 15.24 Hz, 1H), 2.55 (d, *J* = 12.82 Hz, 1H), 2.46 (d, *J* = 16.20 Hz, 1H), 2.40 (d, *J* = 18.53 Hz, 1H), 2.27 (d, *J* = 14.44 Hz, 1H), 1.51 (s, 3H). **HRMS** (ESI^-) *m/z* calcd. for $C_{102}H_{78}N_{15}O_{32}$: 2024.4943 $(M-H)^-$; found: 2024.5504.



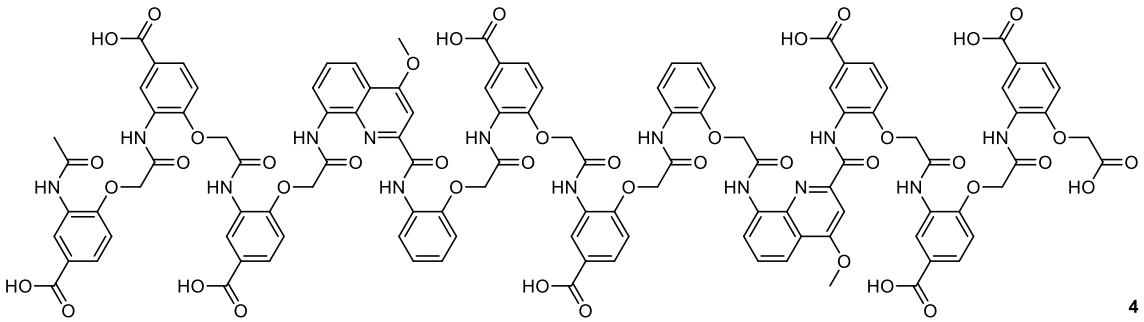
2

Compound 2: Oligomer **2** was synthesized on Wang resin (0.37 mmol g^{-1}, 27.8 µmol scale) according to the standard method (automated). Loading of the first monomer: 0.37 mmol g^{-1} (quant.). The final acetyl group was installed via the general acetylation method. After purification by semi-prep HPLC (C18, 0–15B, 50 °C; A: 13 mmol NH_4OAc buffer pH 8.5, B: acetonitrile), the title compound was obtained as a white solid (14.1 mg, 5.88 µmol, 21%; HPLC-purity: 99.9%). **^{1}H NMR** (500 MHz, 12 mmol NH_4OAc buffer pH 8.5 in H_2O/D_2O 9:1): δ = 10.10 (s, 1H), 10.02 (s, 1H), 9.63 (s, 1H), 9.43 (s, 3H), 9.39 (s, 1H), 9.25 (s, 1H), 9.07 (s, 1H), 8.81 (s, 1H), 8.47 (d, *J* = 2.17 Hz, 1H), 8.46 (d, *J* = 2.10 Hz, 1H), 8.41 (s, 1H), 8.39 (s, 1H), 8.35 (s, 1H), 8.20 – 8.14 (m, 2H), 8.10 (d, *J* = 8.62 Hz, 1H), 8.07 (d, *J* = 9.23 Hz, 1H), 8.01 (d, *J* = 9.28 Hz, 1H), 7.98 – 7.86 (m, 6H), 7.81 (d, *J* = 7.91 Hz, 1H), 7.72 – 7.64 (m, 2H), 7.63 (s, 1H), 7.61 (s, 13H), 7.60 – 7.57 (m, 2H), 7.56 (s, 2H), 7.51 (td, *J* = 8.46, 3.44 Hz, 2H), 7.30 – 7.23 (m, 1H), 7.19 (s, 1H), 6.84 (d, *J* = 9.41 Hz, 1H), 6.80 (s, 1H), 6.59 (d, *J* = 9.39 Hz, 1H), 6.52 – 6.43 (m, 4H), 6.42 (s, 1H), 6.38 (s, 1H), 6.32 (d, *J* = 9.40 Hz, 1H), 5.92 (d, *J* = 9.39 Hz, 1H), 4.27 (s, 1H), 4.17 (s, 2H), 4.00 (s, 5H), 3.92 (s, 3H), 3.90 (s, 1H), 3.71 (d, *J* = 15.54 Hz, 1H), 3.51 (d, *J* = 16.12 Hz, 1H), 3.46 (d, *J* = 15.78 Hz, 1H), 3.39 (d, *J* = 15.74 Hz, 1H), 2.95 (d, *J* = 15.86 Hz, 2H), 2.61 (d, *J* = 13.15 Hz, 1H), 2.06 (d, *J* = 13.51 Hz, 1H), 1.75 (d, *J* = 15.83 Hz, 1H), 1.65 (s, 3H), 1.57 (d, *J* = 15.54 Hz, 1H), 1.41 (d, *J* = 15.05 Hz, 1H), 1.30 (d, *J* = 11.21 Hz, 2H). **HRMS** (ESI^-) *m/z* calcd. for $C_{118}H_{91}N_{16}O_{42}$: 2403.5482 $(M-H)^-$; found: 2403.6165.



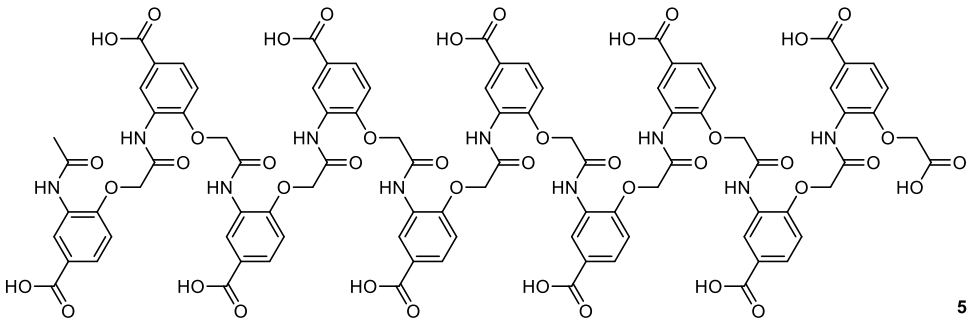
3

Compound 3: Oligomer **3** was synthesized on Wang resin (0.37 mmol g^{-1}, 27.8 µmol scale) according to the standard method (automated). Loading of the first monomer: 0.37 mmol g^{-1} (quant.). The final acetyl group was installed via the general acetylation method. After purification by semi-prep HPLC (C18, 0–20B, 50 °C; A: 13 mmol NH_4OAc buffer pH 8.5, B: acetonitrile), the title compound was obtained as a white solid (3.99 mg, 1.76 µmol, 6.3%; HPLC-purity: 98.8%). **^{1}H NMR** (500 MHz, 12 mmol NH_4OAc buffer pH 8.5 in H_2O/D_2O 9:1): δ = 10.40 (s, 1H), 9.97 (s, 1H), 9.83 (s, 1H), 9.76 (s, 1H), 9.62 (s, 2H), 8.86 (s, 1H), 8.49 (d, *J* = 10.09 Hz, 1H), 8.27 (d, *J* = 2.16 Hz, 1H), 8.25 (d, *J* = 8.52 Hz, 1H), 8.18 (s, 1H), 8.12 (d, *J* = 8.39 Hz, 1H), 8.09 (d, *J* = 8.62 Hz, 1H), 8.06 – 7.99 (m, 5H), 7.96 (dd, *J* = 9.19, 6.35 Hz, 2H), 7.92 (d, *J* = 9.61 Hz, 1H), 7.86 (d, *J* = 9.93 Hz, 1H), 7.83 (d, *J* = 9.68 Hz, 1H), 7.80 (d, *J* = 9.05 Hz, 1H), 7.78 – 7.73 (m, 1H), 7.72 – 7.68 (m, 2H), 7.68 – 7.64 (m, 1H), 7.63 (s, 1H), 7.61 (d, *J* = 6.30 Hz, 1H), 7.58 (s, 1H), 7.58 – 7.52 (m, 4H), 7.52 – 7.49 (m, 1H), 7.49 – 7.45 (m, 1H), 7.44 (d, *J* = 2.15 Hz, 1H), 7.25 – 7.15 (m, 3H), 7.14 (d, *J* = 1.62 Hz, 1H), 7.13 (s, 1H), 7.11 (s, 1H), 7.09 (s, 1H), 7.07 (s, 1H), 7.05 (d, *J* = 9.56 Hz, 1H), 7.02 (s, 1H), 7.00 (d, *J* = 4.38 Hz, 1H), 6.97 (d, *J* = 8.06 Hz, 1H), 6.74 (d, *J* = 9.37 Hz, 1H), 6.60 (d, *J* = 9.30 Hz, 1H), 6.45 (dt, *J* = 10.81, 5.44 Hz, 4H), 6.38 – 6.31 (m, 3H), 6.23 (d, *J* = 9.52 Hz, 1H), 6.17 (d, *J* = 9.53 Hz, 1H), 4.31 (s, 1H), 4.26 (d, *J* = 14.51 Hz, 1H), 4.14 (s, 2H), 4.03 (d, *J* = 15.33 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.89 (d, *J* = 14.91 Hz, 1H), 3.70 (d, *J* = 15.91 Hz, 1H), 3.56 (t, *J* = 15.60 Hz, 2H), 3.30 (d, *J* = 18.89 Hz, 2H), 2.70 (d, *J* = 15.56 Hz, 1H), 2.50 (d, *J* = 15.66 Hz, 1H), 2.42 (d, *J* = 13.68 Hz, 1H), 2.18 (d, *J* = 14.77 Hz, 1H), 1.55 (s, 3H), 1.47 (d, *J* = 15.82 Hz, 2H), 1.17 (d, *J* = 15.64 Hz, 1H). **HRMS** (ESI^-) *m/z* calcd. for $C_{113}H_{90}N_{15}O_{38}$: 2264.5577 $(M-H)^-$; found: 2264.6101.



4

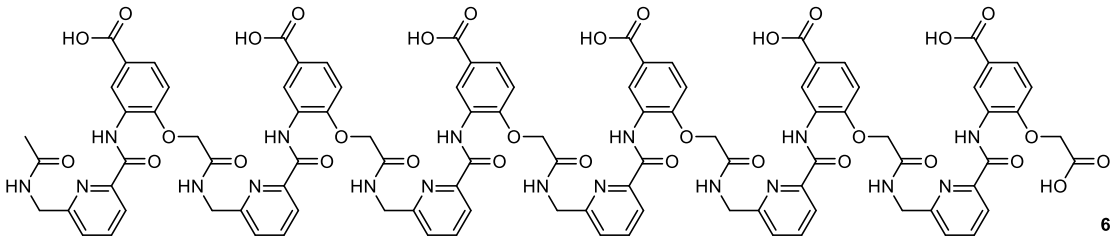
Compound 4: Oligomer **4** was synthesized on ProTide™ resin (0.15 mmol g^{-1}, 25 µmol scale) according to the standard method (automated). Loading of the first monomer: 0.15 mmol g^{-1} (quant.). The final acetyl group was installed via the general acetylation method. After purification by semi-prep HPLC (C18, 0–5B, 50 °C; A: 13 mmol NH_4OAc buffer pH 8.5, B: acetonitrile), the title compound was obtained as a white solid (4.15 mg, 1.8 µmol, 7.2%; HPLC-purity: 90.31%). **^{1}H NMR** (500 MHz, 12 mmol NH_4OAc buffer pH 8.5 in H_2O/D_2O 9:1): δ = 10.00 (s, 1H), 9.97 (s, 1H), 9.90 (s, 1H), 9.76 (s, 1H), 9.04 (s, 1H), 8.85 (s, 1H), 8.56 (s, 1H), 8.54 (s, 1H), 8.49 (s, 1H), 8.46 (s, 1H), 8.31 (s, 1H), 8.30 – 8.24 (m, 2H), 8.18 (s, 1H), 8.08 – 8.00 (m, 2H), 7.92 (d, *J* = 10.34 Hz, 3H), 7.88 (d, *J* = 10.43 Hz, 1H), 7.74 (s, 1H), 7.71 (d, *J* = 10.15 Hz, 1H), 7.68 – 7.60 (m, 4H), 7.58 (d, *J* = 10.15 Hz, 1H), 7.54 (d, *J* = 10.68 Hz, 1H), 7.53 (s, 1H), 7.52 – 7.46 (m, 4H), 7.26 (t, *J* = 8.48 Hz, 1H), 7.22 – 7.14 (m, 2H), 7.11 (t, *J* = 8.40 Hz, 1H), 7.01 (s, 1H), 6.92 (d, *J* = 9.41 Hz, 1H), 6.75 (d, *J* = 9.51 Hz, 1H), 6.72 (d, *J* = 9.38 Hz, 1H), 6.68 (d, *J* = 9.60 Hz, 1H), 6.64 (d, *J* = 9.32 Hz, 1H), 6.53 (d, *J* = 9.60 Hz, 1H), 6.51 – 6.47 (m, 2H), 6.45 (d, *J* = 9.37 Hz, 1H), 6.36 (d, *J* = 9.42 Hz, 1H), 6.33 (d, *J* = 9.90 Hz, 2H), 6.31 (s, 1H), 4.35 (d, *J* = 15.53 Hz, 1H), 4.30 – 4.20 (m, 1H), 4.16 – 4.06 (m, 1H), 4.03 (d, *J* = 9.62 Hz, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.88 (d, *J* = 14.97 Hz, 1H), 3.74 (d, *J* = 16.58 Hz, 1H), 3.61 (d, *J* = 16.36 Hz, 3H), 3.33 (d, *J* = 16.44 Hz, 1H), 3.13 (d, *J* = 15.02 Hz, 1H), 2.76 (d, *J* = 16.02 Hz, 1H), 2.49 (d, *J* = 13.58 Hz, 1H), 2.34 (d, *J* = 15.12 Hz, 1H), 2.25 – 2.22 (m, 1H), 2.20 (d, *J* = 15.54 Hz, 1H), 2.14 (d, *J* = 16.26 Hz, 1H), 1.63 (s, 3H), 1.32 (d, *J* = 16.40 Hz, 1H). **HRMS** (ESI^-) *m/z* calcd. for $C_{112}H_{89}N_{14}O_{42}$: 2301.5264 $(M-H)^-$; found: 2301.3943.



5

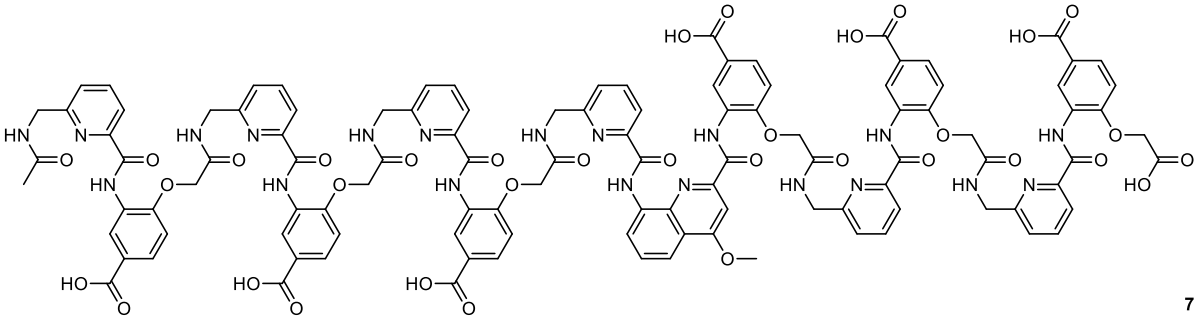
Compound 5: Oligomer **5** was synthesized on Wang resin (0.37 mmol g^{-1}, 27.8 µmol scale) according to the standard method (manual). Loading of the first monomer: 0.25 mmol g^{-1} (68%). The final acetyl group was installed via the general acetylation method. After purification by semi-prep HPLC (C18, 0–15B, 50 °C; A: 13 mmol NH_4OAc buffer pH 8.5, B: acetonitrile), the title compound was obtained as a white solid (9.03 mg, 4.46 µmol, 16%; HPLC-purity: 95.4%). **^{1}H NMR** (500 MHz, 12 mmol NH_4OAc buffer pH 8.5 in H_2O/D_2O 9:1): δ = 9.32 (s, 1H), 9.20 (s, 1H), 8.34 (s, 1H), 8.30 (s, 1H), 8.13 (s, 3H), 8.11 (s, 1H), 8.08 – 8.00 (m, 4H), 7.92 (s, 1H), 7.83 (s, 1H), 7.71 – 7.59 (m, 8H), 7.56 (d, *J* = 8.97 Hz, 1H), 6.97 (d, *J* = 9.71 Hz, 1H), 6.93 (d, *J* = 9.53 Hz, 1H), 6.89 – 6.76 (m, 7H), 6.60 (d, *J* = 9.58 Hz, 1H),

4.37 (s, 2H), 4.27 (s, 4H), 4.20 (s, 2H), 4.19 (s, 2H), 4.04 (s, 4H), 2.01 (s, 5H). **HRMS** (ESI^-) *m/z* calcd. for $C_{92}H_{73}N_{10}O_{42}$: 1989.3889 $(M-H)^-$; found: 1989.4469.



6

Compound 6: Oligomer **6** was synthesized on Wang resin (0.37 mmol g^{-1}, 24 µmol scale) according to the standard method (automated). Loading of the first monomer: 0.37 mmol g^{-1} (quant.). The final acetyl group was installed via the general acetylation method. After purification by semi-prep HPLC (C18, 0–10B, 50 °C; A: 13 mmol NH_4OAc buffer pH 8.5, B: acetonitrile), the title compound was obtained as a white solid (14.8 mg, 7.33 µmol, 31%; HPLC-purity: 95.5%). **^{1}H NMR** (500 MHz, 12 mmol NH_4OAc buffer pH 8.5 in H_2O/D_2O 9:1): δ = 10.15 (s, 1H), 10.01 (s, 1H), 9.44 (s, 1H), 9.36 (s, 1H), 9.15 (s, 1H), 9.09 (s, 1H), 8.38 (d, *J* = 2.19 Hz, 1H), 8.23 (dd, *J* = 10.50, 2.12 Hz, 2H), 8.17 (d, *J* = 2.18 Hz, 1H), 8.11 (dd, *J* = 4.03, 2.17 Hz, 2H), 8.08 (t, *J* = 4.25 Hz, 1H), 8.04 – 8.00 (m, 1H), 8.00 (d, *J* = 4.71 Hz, 1H), 7.98 (d, *J* = 4.86 Hz, 0H), 7.94 (d, *J* = 8.14 Hz, 1H), 7.90 (d, *J* = 8.19 Hz, 1H), 7.83 (t, *J* = 8.20 Hz, 1H), 7.77 – 7.70 (m, 6H), 7.66 – 7.59 (m, 2H), 7.59 – 7.54 (m, 1H), 7.51 (d, *J* = 8.40 Hz, 1H), 7.47 (dt, *J* = 7.58, 3.87 Hz, 3H), 7.37 (s, 1H), 7.35 (s, 1H), 7.34 – 7.32 (m, 2H), 7.31 (s, 1H), 7.30 (s, 0H), 7.28 (d, *J* = 3.69 Hz, 1H), 7.26 (s, 1H), 7.20 (d, *J* = 6.03 Hz, 2H), 7.19 (d, *J* = 6.91 Hz, 2H), 7.14 (d, *J* = 8.69 Hz, 1H), 7.07 (d, *J* = 9.18 Hz, 1H), 7.04 (d, *J* = 8.57 Hz, 1H), 6.68 (d, *J* = 9.18 Hz, 1H), 6.59 (d, *J* = 10.98 Hz, 2H), 6.47 (d, *J* = 9.20 Hz, 1H), 6.41 (d, *J* = 9.05 Hz, 1H), 4.54 (s, 0H), 4.39 (s, 0H), 1.77 (s, 4H). **HRMS** (ESI^-) *m/z* calcd. for $C_{98}H_{81}N_{18}O_{32}$: 2021.5270 $(M-H)^-$; found: 2021.6454.

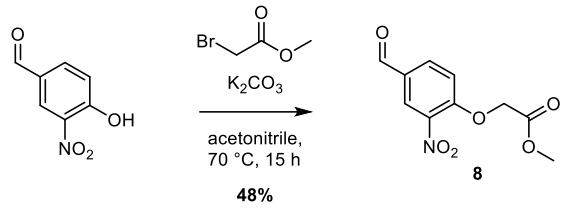


7

Compound 7: Oligomer **7** was synthesized on ProTide™ resin (0.15 mmol g^{-1}, 25 µmol scale) according to the standard method (automated). Loading of the first monomer: 0.15 mmol g^{-1} (quant.). The final acetyl group was installed via the general acetylation method. After purification by semi-prep HPLC (C18, 0–10B, 50 °C; A: 13 mmol NH_4OAc buffer pH 8.5, B: acetonitrile), the title compound

was obtained as a white solid (12.0 mg, 5.4 µmol, 22%; HPLC-purity: 95.7%). **^{1}H NMR** (500 MHz, 12 mmol NH_4OAc buffer pH 8.5 in H_2O/D_2O 9:1): δ = 10.77 (s, 1H), 10.05 (s, 1H), 10.01 (s, 1H), 9.92 (s, 1H), 9.20 (s, 2H), 8.74 (s, 1H), 8.56 (s, 1H), 8.23 – 8.15 (m, 4H), 8.05 – 8.01 (m, 1H), 8.00 (d, *J* = 7.09 Hz, 1H), 7.96 (d, *J* = 8.26 Hz, 1H), 7.93 (d, *J* = 8.15 Hz, 1H), 7.90 (s, 1H), 7.87 (d, *J* = 8.41 Hz, 1H), 7.81 (d, *J* = 2.03 Hz, 1H), 7.78 (d, *J* = 7.64 Hz, 1H), 7.75 (s, 1H), 7.74 – 7.70 (m, 4H), 7.69 (s, 1H), 7.66 – 7.60 (m, 3H), 7.54 (t, *J* = 8.23 Hz, 1H), 7.51 – 7.45 (m, 3H), 7.42 (d, *J* = 8.50 Hz, 1H), 7.38 (d, *J* = 7.92 Hz, 2H), 7.32 – 7.26 (m, 3H), 7.25 (d, *J* = 8.25 Hz, 1H), 7.17 – 7.11 (m, 2H), 7.08 (d, *J* = 9.50 Hz, 3H), 6.98 (d, *J* = 8.60 Hz, 1H), 6.93 (d, *J* = 8.69 Hz, 1H), 6.57 (d, *J* = 9.05 Hz, 2H), 6.54 (d, *J* = 8.70 Hz, 2H), 6.38 (d, *J* = 9.11 Hz, 1H), 6.32 (d, *J* = 9.38 Hz, 1H), 6.08 (s, 1H), 4.55 (s, 1H), 4.41 – 4.23 (m, 1H), 4.10 (d, *J* = 17.84 Hz, 1H), 4.02 (d, *J* = 15.87 Hz, 1H), 3.94 (d, *J* = 17.40 Hz, 1H), 3.88 (s, 3H), 3.84 (d, *J* = 14.03 Hz, 1H), 3.72 (d, *J* = 15.35 Hz, 2H), 3.55 (d, *J* = 15.01 Hz, 1H), 3.40 (d, *J* = 20.37 Hz, 1H), 3.23 (d, *J* = 20.11 Hz, 1H), 3.17 – 3.04 (m, 1H), 2.92 (d, *J* = 15.61 Hz, 1H), 2.63 – 2.47 (m, 3H), 2.31 (d, *J* = 21.86 Hz, 1H), 2.26 – 2.10 (m, 2H), 1.75 (s, 3H). **HRMS** (ESI^-) *m/z* calcd. for $C_{109}H_{89}N_{20}O_{34}$: 2221.5856 $(M-H)^-$; found: 2221.4344.

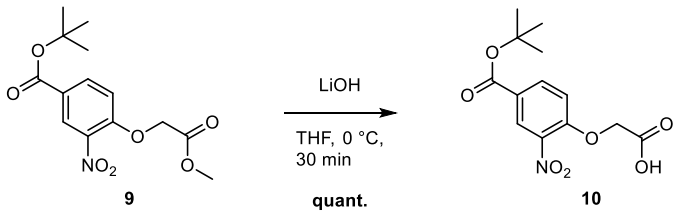
2.3 Monomer synthesis procedures



Compound 8: 4-hydroxy-3-nitrobenzaldehyde (8.40 g, 50.3 mmol, 1.0 equiv.) and K_2CO_3 (7.64 g, 55.3 mmol, 1.1 equiv.) was suspended in acetonitrile (300 ml). After the addition of methyl bromoacetate (5.23 ml, 55.3 mmol, 1.1 equiv.), the reaction mixture was stirred at 70 °C for 15 h under N_2 atmosphere. The resulting suspension was filtered, washed with acetonitrile and the filtrate evaporated *in vacuo*. Then, the residue was dissolved in water and $CHCl_3$. After the organic phase was removed, the aqueous phase was extracted with $CHCl_3$ (2×), the combined organic phases were washed with brine, dried over $MgSO_4$, evaporated *in vacuo*, and the residue was dried under high vacuum overnight. Finally, it was redissolved in a minimum amount of DCM. Et_2O was added until precipitation occurred. The solution was kept at 4 °C for 2 h, filtered and washed with cold Et_2O yielding the final compound (5.79 g, 24.2 mmol, 48%) as an off white crystalline solid. ($C_{10}H_9NO_6$; MW = 239.18 g mol^{-1}). $\mathbf{R_f}$ (CyHex/EtOAc 6:4) = 0.34. **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 9.95 (s, 1H, C10-H), 8.39 (d, *J* = 2.05 Hz, 1H, C3-H), 8.06 (dd, *J* = 8.69, 2.10 Hz, 1H, C5-H), 7.09 (d, *J* = 8.68 Hz, 1H, C6-H), 4.90 (s, 2H; C7-H), 3.83 (s, 3H, C9-H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 188.7 (C10), 167.5 (C8), 155.4 (C1), 140.4 (C2), 134.5 (C5), 130.2 (C4), 127.8 (C3), 114.9 (C6), 66.2 (C7), 52.9 (C9). **HRMS**

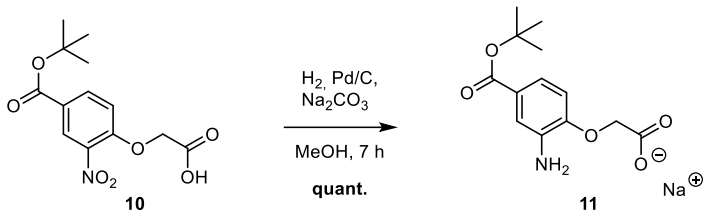
(ESI$^-$) *m/z* calcd. for $C_{10}H_9NO_6Cl$: 274.0124 $(M+Cl)^-$; Found: 274.0124. (Modified literature procedure[6]; analytical data is in line with the literature).

Compound 9: Compound **8** (19.6 g, 81.9 mmol, 1.0 equiv.) was dissolved in acetone (150 ml). Jones reagent (2 M CrO_3 in 6 M $H_2SO_{4\,(aq.)}$) was added dropwise at 23 °C until the starting material was consumed by TLC analysis (45 ml). Remaining Jones reagent was quenched by adding an excess of *i*PrOH and the suspension was filtered and washed with acetone. The solvent was evaporated under reduced pressure, and the residue was redissolved in DCM (THF may be added to help solubilization). H_2O was added, the organic phase removed, and the aqueous phase extracted with DCM (2×). The combined organic phases were dried over $MgSO_4$ and evaporated *in vacuo* to give the crude carboxylic acid (20.3 g with 20% impurity by NMR). Then, the solid was redissolved in anhydrous DMF (105 ml) under N_2 atmosphere. *t*BuOH (22.4 ml, 239 mmol, 3.0 equiv.), EDC·HCl (22.9 g, 119 mmol, 1.5 equiv.) and DMAP (9.74 g, 79.6 mmol, 1.0 equiv.) were added at 0 °C and the reaction mixture was stirred at 23 °C for 15 h. After evaporating the solvents *in vacuo*, the residue was dissolved in EtOAc and H_2O. The organic phase was removed, and the aqueous phase was extracted with EtOAc (2×). Combined organic phases were washed with sat. $NH_4Cl_{\,(aq.)}$ and brine, dried over Na_2SO_4 and evaporated *in vacuo*. After purification by column chromatography (SiO_2, CyHex/EtOAc 8:2), the title compound (17.8 g, 57.2 mmol, 70%) was obtained as a white solid ($C_{14}H_{17}NO_7$; MW = 311.29 g mol^{-1}). $\mathbf{R_f}$ (CyHex/EtOAc 8:2) = 0.20. **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 2.15 Hz, C3-H), 8.14 (dd, *J* = 8.75, 2.16 Hz, 1H, C5-H), 6.97 (d, *J* = 8.82 Hz, 1H, C6-H), 4.85 (s, 2H, C7-H), 3.81 (s, 3H, C9-H), 1.59 (s, 9H, C12-H, C13-H, C14-H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 167.8 (C8), 163.4 (C10), 154.0 (C1), 139.9 (C2), 135.0 (C5), 127.4 (C3), 126.0 (C4), 114.1 (C6), 82.4 (C11), 66.3 (C7), 52.8 (C9), 28.3 (C12, C13, C14). **HRMS** (ESI$^-$) *m/z* calcd. for $C_{14}H_{17}NO_7Cl$: 346.0699 $(M+Cl)^-$; Found: 346.0702. (Modified literature procedure[6]; analytical data is in line with the literature).

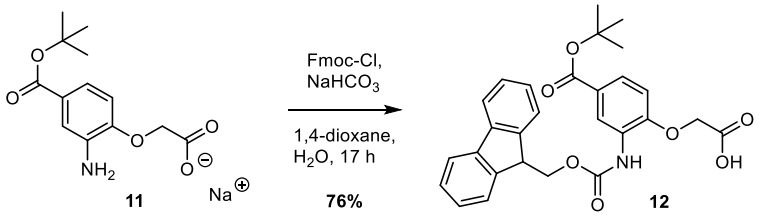


Compound 10: Compound **9** (17.8 g, 57.2 mmol, 1.0 equiv.) was dissolved in THF (800 ml) and cooled to 0 °C. LiOH (1.37 g, 57.2 mmol, 1.0 equiv.) in H_2O (200 ml) was added and the reaction mixture was stirred at 0 °C for 30 min. After the addition of citric acid $_{(aq.)}$ (1 M, 57.2 ml, 1 equiv.) the mixture was

extracted with DCM (3×). The combined organic phases were washed with brine, dried over Na_2SO_4 and solvents were removed *in vacuo*. The final product (17.0 g, 57.2 mmol, quant.) was obtained as a white solid. ($C_{13}H_{15}NO_7$; MW = 297.26 g mol^{-1}). $\mathbf{R_f}$ (DCM/MeOH 95:5 + 1% AcOH) = 0.51. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 13.34 (s, 1H, O9-H), 8.30 (d, *J* = 2.18 Hz, 1H, C3-H), 8.09 (dd, *J* = 8.88, 2.23 Hz, 1H, C5-H), 7.38 (d, *J* = 8.93 Hz, 1H, C6-H), 5.02 (s, 2H, C7-H), 1.55 (s, 9H, C12-H, C13-H, C14-H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 168.9 (C8), 163.0 (C10), 153.7 (C1), 139.2 (C2), 134.4 (C5), 125.7 (C3), 123.9 (C4), 115.3 (C6), 81.6 (C11), 65.6 (C7), 27.7 (C12, C13, C14). **HRMS** (ESI$^-$) *m/z* calcd. for $C_{13}H_{14}NO_7$: 296.0776 (M-H)$^-$; Found: 296.0776. (Modified literature procedure[6]; analytical data is in line with the literature).



Compound 11: Compound **10** (17.0 g, 57.2 mmol, 1.0 equiv.) and Na_2CO_3 (6.28 g, 57.2 mmol, 1.0 equiv.) were dissolved in MeOH (750 ml). The solution was quickly degassed by vacuum N_2 cycles (3×), then Pd/C (1.70 g, 10 wt. % loading) was added and the N_2 atmosphere was replaced by H_2. After stirring for 7 h the reaction mixture was filtered over celite©, washed with MeOH and solvents were removed *in vacuo*. The crude product (16.5 g, 57.2 mmol, quant.) was obtained as a slightly brown solid and was used in the next step without further purification. ($C_{13}H_{16}NO_5Na$; MW = 289.26 g mol^{-1}). $\mathbf{R_f}$ (EtOH) = 0.60. **^{1}H-NMR** (400 MHz, DMSO-d_6): δ = 7.16 (d, *J* = 2.12 Hz, 1H, C3-H), 7.05 (dd, *J* = 8.30, 2.17 Hz, 1H, C5-H), 6.62 (d, *J* = 8.38 Hz, 1H, C6-H), 4.96 (s, 2H, N15-H), 4.11 (s, 2H, C7-H), 1.50 (s, 9H, C12-H, C13-H, C14-H). **^{13}C-NMR** (101 MHz, DMSO-d_6): δ = 170.5 (C8), 165.5 (C10), 150.3 (C1), 138.0 (C2), 123.3 (C4), 118.2 (C5), 113.9 (C3), 111.8 (C6), 79.3 (C11), 69.2 (C7), 27.9 (C12, C13, C14). **HRMS** (ESI$^-$) *m/z* calcd. for $C_{13}H_{16}NO_5$: 266.1034 (M-H)$^-$; Found: 266.1033.



Compound 12: Compound **11** (16.5 g, 57.2 mmol, 1.0 equiv.) was added to $NaHCO_3$ (24.0 g, 286 mmol, 5.0 equiv.) in H_2O (400 ml). After the suspension was cooled to 0 °C, Fmoc-Cl (19.2 g, 74.4 mmol, 1.3 equiv.) in 1,4-dioxane (400 ml) was added dropwise at 0 °C over 1 h. The reaction mixture was stirred at 0 °C for 1 h, then at 23 °C for 15 h. After acidifying to pH 2 using citric acid $_{(aq.)}$ (1 M) the mixture was extracted with DCM (3×). The combined organic phases were washed with brine, dried over $MgSO_4$ and solvents were evaporated *in vacuo*. The crude product was purified by trituration:

the residue was dissolved in a minimal amount of THF, a larger amount of Et_2O was added and the suspension was cooled to 4 °C over night to help precipitation. The suspension was filtered and washed with cold Et_2O. This procedure was repeated once yielding the title compound (21.9 g, 44.8 mmol, 76%, HPLC purity: 99%) as a white solid ($C_{28}H_{27}NO_7$; MW = 489.52 g mol^{-1}). $\mathbf{R_f}$ (EtOAc/MeOH 98:2 + 1% AcOH) = 0.36. **^{1}H NMR** (500 MHz, DMSO-d_6): δ = 13.20 (s, 1H, O9-H), 8.88 (s, 1H, N15-H), 8.28 (s, 1H, C3-H), 7.91 (d, *J* = 7.62 Hz, 2H, C22-H, C23-H), 7.76 (d, *J* = 7.50 Hz, 2H, C19-H, C26-H), 7.62 (dd, *J* = 8.58, 2.16 Hz, 1H, C5-H), 7.43 (t, *J* = 7.50 Hz, 2H, C21-H, C24-H), 7.34 (t, *J* = 7.47 Hz, 2H, C20-H, C25-H), 7.06 (d, *J* = 8.70 Hz, 1H, C6-H), 4.83 (s, 2H, C7-H), 4.41 (d, *J* = 7.26 Hz, 2H, C17-H), 4.31 (t, *J* = 7.18 Hz, 1H, C18-H), 1.52 (s, 9H, C12-H, C13-H, C14-H). **^{13}C NMR** (126 MHz, DMSO-d_6): δ = 169.8 (C8), 164.5 (C10), 153.7 (C16), 152.1 (C1), 143.7 (C18a, C26a), 140.7 (C22a, C22b, 127.7 (C2), 127.4 (C20, C25), 127.1 (C5), 125.7 (C19, C26), 125.4 (C4), 121.8 (C3), 120.2 (C22, C23), 112.5 (C6), 80.3 (C11), 66.3 (C17), 65.7 (C7), 46.5 (C18), 27.8 (C12, C13, C14). **HRMS** (ESI^+) *m/z* calcd. for $C_{28}H_{28}NO_7$: 490.1860 $(M+H)^+$; Found: 490.1863.

3 X-ray Crystallography

Aqueous solutions of compounds **1** and **6** were prepared from lyophilized samples to final concentrations of 2 mM (in 15 mM NH4OAc buffer pH 8.5) and 8 mM (in H_2O) respectively. Crystallization screening trials were carried out by vapor diffusion method using commercial sparse matrix screens at 293 K.[7] Diffraction-quality crystals of **1** (Figure S10a) was obtained by sitting drop method by adding 1 µL of 1 and 2 µL of the reservoir solution containing 20% w/v polyethylene glycol 8000, 10 mM TRIS buffer (pH 7.5), and 10 mM calcium chloride. Volume of reservoir solution was 500 µL. Diffraction-quality crystals (Figure S10b) of **6** was obtained by hanging drop method by adding 1.2 µL of **6** and 1.8 µL of the reservoir solution containing 30% v/v polyethylene glycol 400, 100 mM HEPES buffer (pH 7.5), and 200 mM calcium chloride. 400 µL of the reservoir solution was layered by 100 µL of Silicon oil to slow the rate of vapor diffusion.[8] Single crystals of **1** were fished using MiTeGen microloops, quickly soaked in a cryo-protectant solution of 20% w/v polyethylene glycol 8000 and 40% v/v polyethylene glycol 400 and flash frozen in liquid nitrogen. Single crystals of **6** were fished and directly plunged into liquid nitrogen without cryo-protection.

Synchrotron data for **1** and **6** were collected at P14 and P13[9] beam lines operated by EMBL Hamburg at the Petra III storage ring (DESY, Hamburg, Germany) using EIGER 16M detector. Diffraction data for **1** was processed using *xia2*[10] with *DIALS*[11] for integration and using *Pointless*/*Aimless*[12] for scaling and merging respectively. Diffraction data for **6** was processed using *CrysAlis*^{Pro}.[*] Both structures were solved using dual space method with the program *ShelxD*[13] and refined by a full-matrix least squares method on F^2 with *ShelxL*-2014[14] within *Olex2* suite.[15] The initial structures of both **1** and **6** revealed most of the main-chain atoms. After each refinement step, visual inspection of the model and the electron-density maps were carried out using *Olex2* and *Coot*.[16] AFIX, DFIX, EADP, SADI and FLAT instructions were used to improve the geometry of molecules and temperature parameters. All non-H atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed at idealized positions. Restraints on anisotropic displacement parameters were implemented with DELU, SIMU, RIGU and ISOR instructions. In the final stage of refinement *SQUEEZE*[17] procedure from Platon suite was introduced to remove unmodeled electron density.

Statistics of data collection and refinement are described in Table S1. The final cif file was checked using IUCr's checkcif algorithm. Due to large volume fractions of disordered solvent molecules, weak diffraction intensity and poor resolution, a number of A- and B-level remain in the checkcif file. These alerts are inherent to the data and refinement procedures and illustrate the limited practicality of the checkcif tool for medium- size molecule crystallography. They are listed below and have been divided into two groups. The first group illustrates weak quality of the data and refinement statistics if compared to that expected for small molecule structures from highly diffracting crystals. The second group is

[*] Agilent, CrysAlisPRO. Agilent Technologies Ltd, Yarnton, Oxfordshire, England (2014).

connected to decisions made during refinement and explained below. Atomic coordinates and structure factors for **1** and **6** were deposited in the Cambridge Crystallographic Data Centre (CCDC) with accession codes 2125508 and 2125515 respectively. The data is available free of charge upon request (www.ccdc.cam.ac.uk/).

CheckCIF validation of **1**:

Group 1 alerts:

THETM01_ALERT_3_A	The value of sine(theta_max)/wavelength is less than 0.550
PLAT029_ALERT_3_A _	diffrn_measured_fraction_theta_full value Low. Why?
PLAT084_ALERT_3_A	High wR2 Value (i.e. > 0.25) ..... 0.36 Report
PLAT242_ALERT_2_B	Low 'MainMol' Ueq as Compared to Neighbors
PLAT250_ALERT_2_B	Large U3/U1 Ratio for Average U(I,j) Tensor.. Note
PLAT340_ALERT_3_B	Low Bond Precision on C-C Bonds.. 0.03562 Ang.

Group 2 alerts:

PLAT306_ALERT_2_B Isolated Oxygen Atom Check

Unrecognized electron density was introduced to refinement as dummy oxygen atoms.

PLAT412_ALERT_2_A Short Intra XH3 .. XHn Check

These alerts concern H atoms placed geometrically.

PLAT430_ALERT_2_A Short Inter D...A Contact Check

These alerts concern contacts with solvent molecules whose positions were poorly determined.

CheckCIF validation of **6**:

Group 1 alerts:

THETM01_ALERT_3_A	The value of sine(theta_max)/wavelength is less than 0.550
PLAT029_ALERT_3_A _	diffrn_measured_fraction_theta_full value Low. Why?
PLAT082_ALERT_2_B	High R1 Value ..... 0.17 Report
PLAT084_ALERT_3_A	High wR2 Value (i.e. > 0.25) ..... 0.46 Report
PLAT250_ALERT_2_B	Large U3/U1 Ratio for Average U(I,j) Tensor.. Note
PLAT340_ALERT_3_B	Low Bond Precision on C-C Bonds.. 0.01523 Ang.

Group 2 alerts:

PLAT316_ALERT_2_A Too many H on C in C=N Moiety in Main Residue Check

Concerned C in C–N moiety in main residue and H atoms checked.

PLAT306_ALERT_2_B Isolated Oxygen Atom Check

Unrecognized electron density was introduced to the refinement as dummy oxygen atoms

PLAT430_ALERT_2_B Short Inter D...A Contact Check

These alerts concern contacts with solvent molecules which positions were poorly determined

Table S1: Crystallographic data and refinement details for **1** and **6**.

Foldamers	**1**	**6**
Chemical formula	$C_{102}H_{71.75}Ca_1N_{15}O_{37.25}$	$C_{98}H_{75}Ca_{2.25}N_{18}O_{49.25}$
Formula weight	2143.57	2382.94
Temperature	100 K	100.15
Wavelength	0.9762 Å	0.8000 Å
Crystal system	Triclinic	Orthorhombic
Space group	P1	Pbcn
Unit cell dimensions	a = 21.833 (4) Å b = 26.901 (4) Å c = 27.093 (3) Å α = 93.876 (1)° β = 108.543 (1)° γ = 111.116 (13)°	a = 48.968 (8) Å b = 43.383 (2) Å c = 27.123 (19) Å α = 90° β = 90° γ = 90°
Volume	13772 (4) $Å^3$	57620.1 (10) $Å^3$
Z	4	16
Density (calculated)	1.034 g/cm^3	1.099 g/cm^3
Absorption coefficient	0.215 μ/mm^{-1}	0.230 μ/mm^{-1}
Color and shape	Pale yellow, needles	Colorless, plates
Crystal size	0.15 x 0.02 x 0.02 mm	0.15 x 0.05 x 0.01 mm
Index ranges	$-18 \leq h \leq 18$ $-22 \leq k \leq 22$ $-22 \leq l \leq 22$	$-19 \leq h \leq 44$ $-40 \leq k \leq 42$ $-23 \leq l \leq 26$
Reflections collected	57803	96340
R_{int}	0.1337	0.0838
Data/restraints/parameters	29422/675/1376	22635/467/2493
Goodness-of-fit on F^2	1.006	1.786
Final R indexes [$I > 2\sigma(I)$]	$R_1 = 0.1210$ $wR_2 = 0.2838$	$R_1 = 0.1681$ $wR_2 = 0.4348$
Final R indexes [all data]	$R_1 = 0.2104$ $wR_2 = 0.3613$	$R_1 = 0.1947$ $wR_2 = 0.4615$
Largest diff. peak and hole	0.69/-0.56 e $Å^{-3}$	1.07/-0.70 e $Å^{-3}$
Total potential solvent accessible void volume from SQUEEZE	3592.0 $Å^3$	16882.8 $Å^3$
Electron count/cell	1126	4517
CCDC #	2125508	2125515

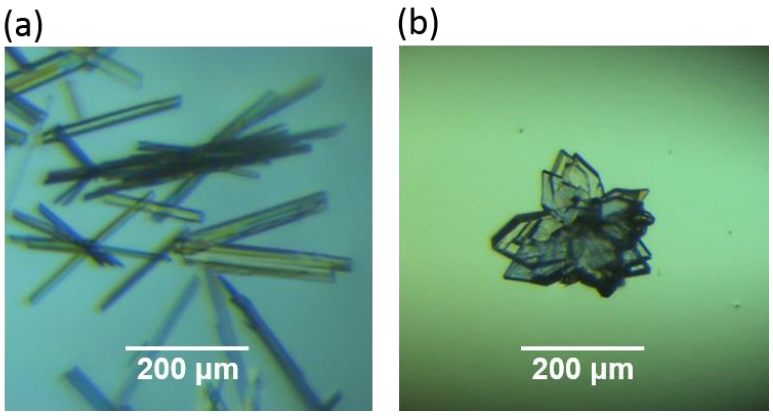


Figure S10: Crystals of (a) **1** and (b) **6** observed under cross polarizing microscope.

4 Spectra and Chromatograms

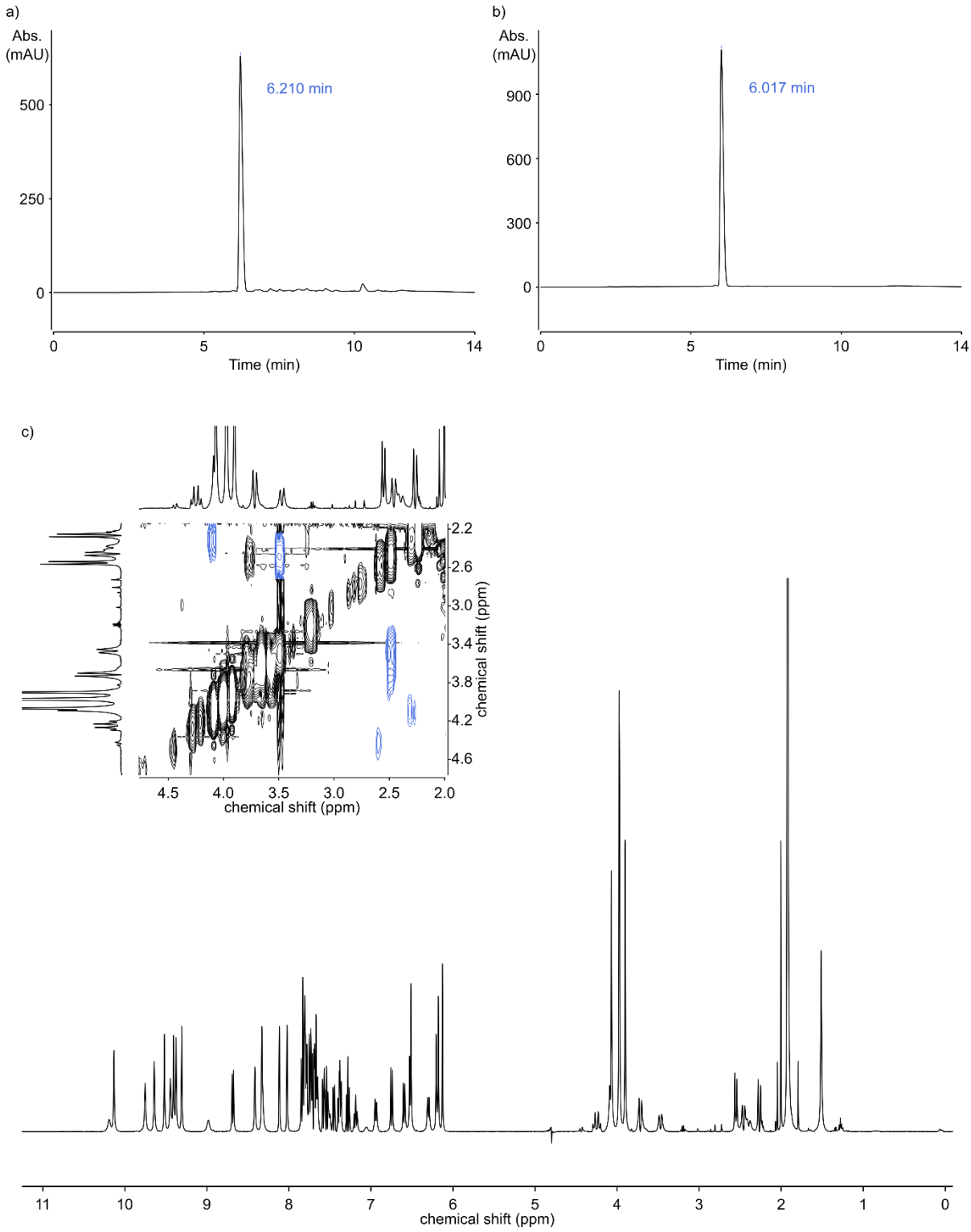


Figure S11: Analytical data of compound **1**. HPLC chromatograms after cleavage from the resin (a) and after purification (b) (C18, 0–30B, 50 °C; A: 13mM NH_4OAc buffer pH 8.5, B: acetonitrile). c) ^1H NMR and part of the COSY NMR spectrum (500 MHz, 0.6 mM in 12 mM NH_4OAc buffer pH 8.5 H_2O/D_2O 9:1, H_2O suppression), some cross-signals of diastereotopic methylene groups are exemplary highlighted in blue.

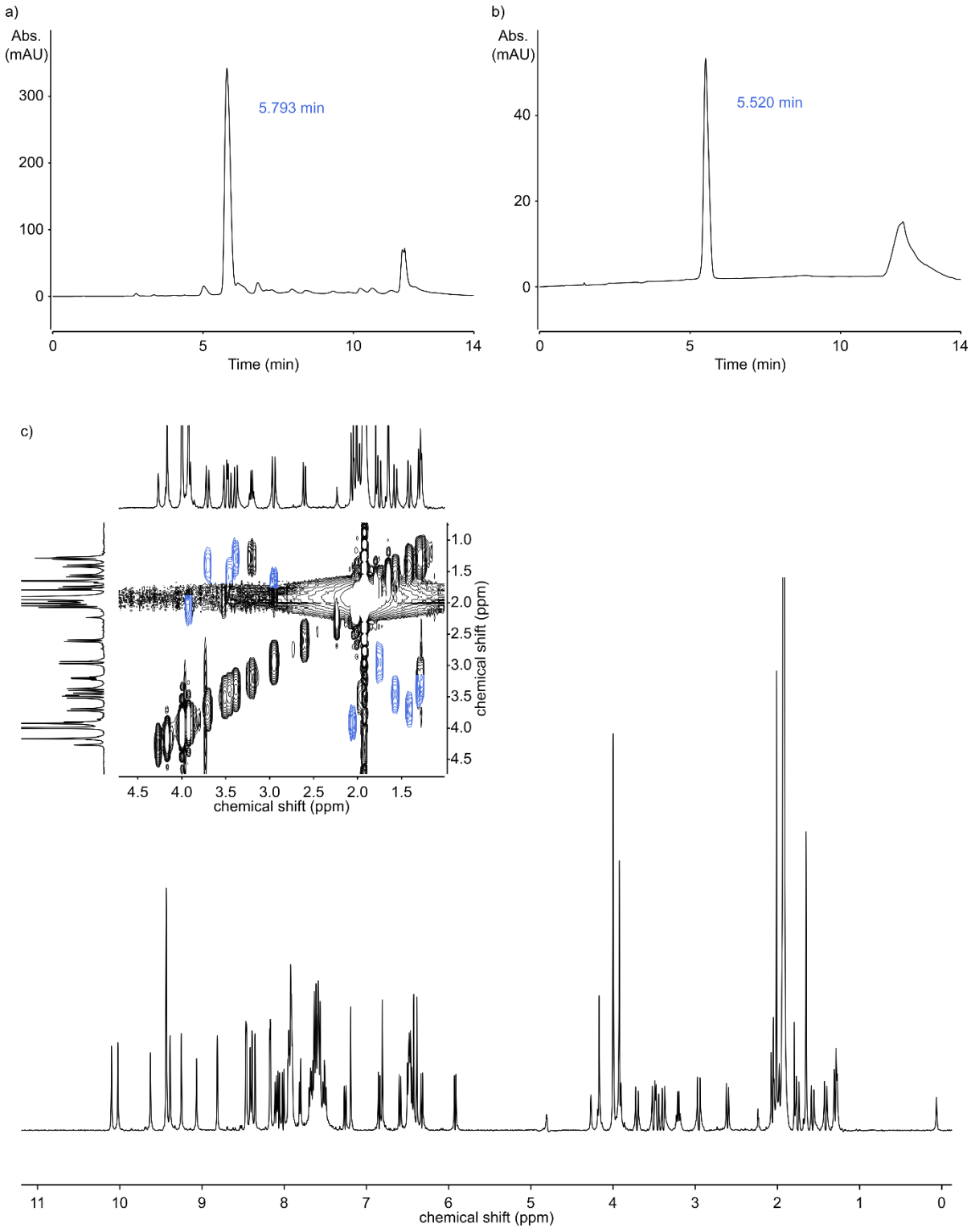


Figure S12: Analytical data of compound **2**. HPLC chromatograms after cleavage from the resin (a) and after purification (b) (C18, 0–15B, 50 °C; A: 13mM NH_4OAc buffer pH 8.5, B: acetonitrile). c) ^1H NMR and part of the COSY NMR spectrum (500 MHz, 0.26 mM in 12 mM NH_4OAc buffer pH 8.5 H_2O/D_2O 9:1, H_2O suppression), some cross-signals of diastereotopic methylene groups are exemplary highlighted in blue.

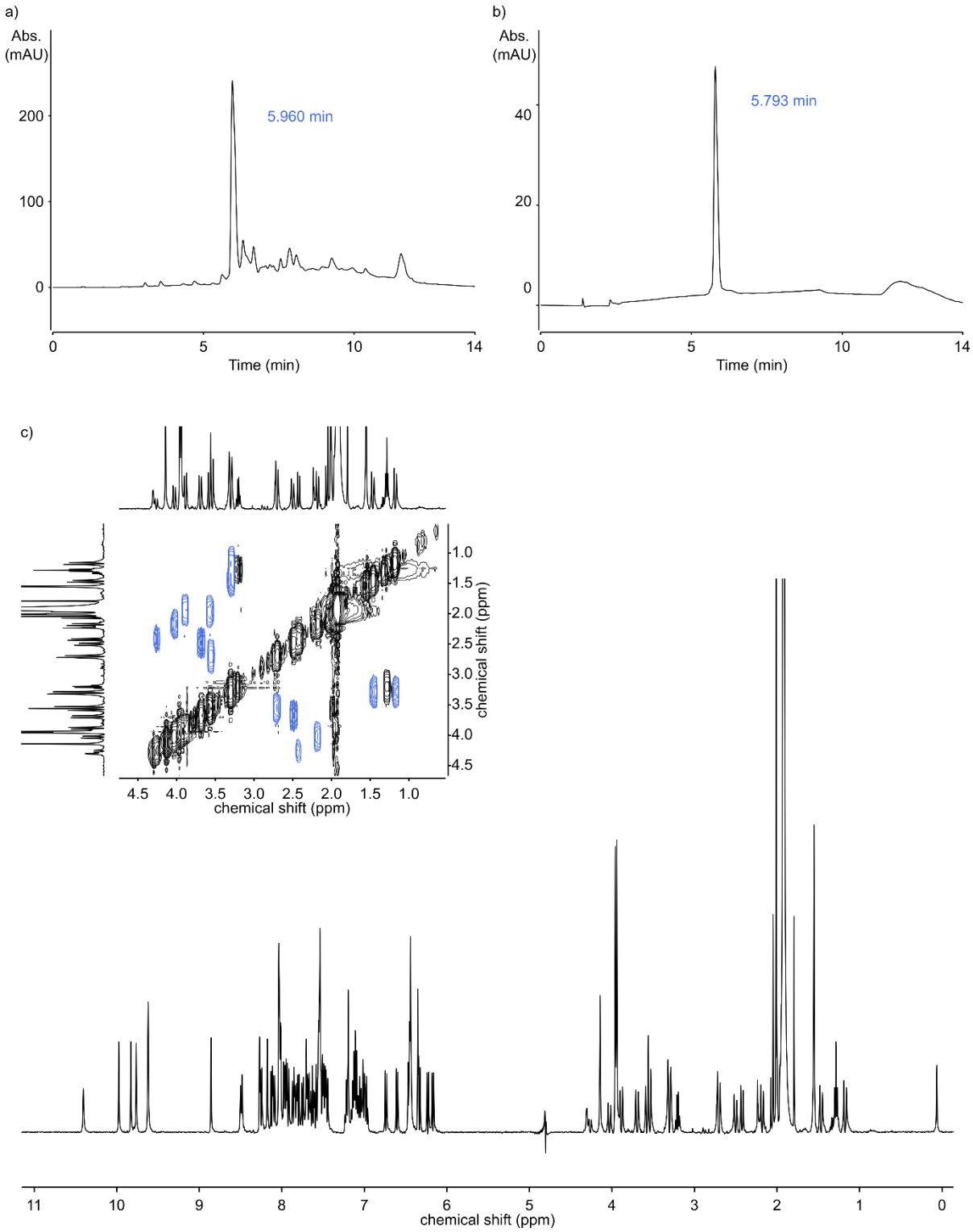


Figure S13: Analytical data of compound **3**. HPLC chromatograms after cleavage from the resin (a) and after purification (b) (C18, 0–30B, 50 °C; A: 13mM NH_4OAc buffer pH 8.5, B: acetonitrile). c) ^1H NMR and part of the COSY NMR spectrum (500 MHz, 0.16 mM in 12 mM NH_4OAc buffer pH 8.5 H_2O/D_2O 9:1, H_2O suppression), some cross-signals of diastereotopic methylene groups are exemplary highlighted in blue.

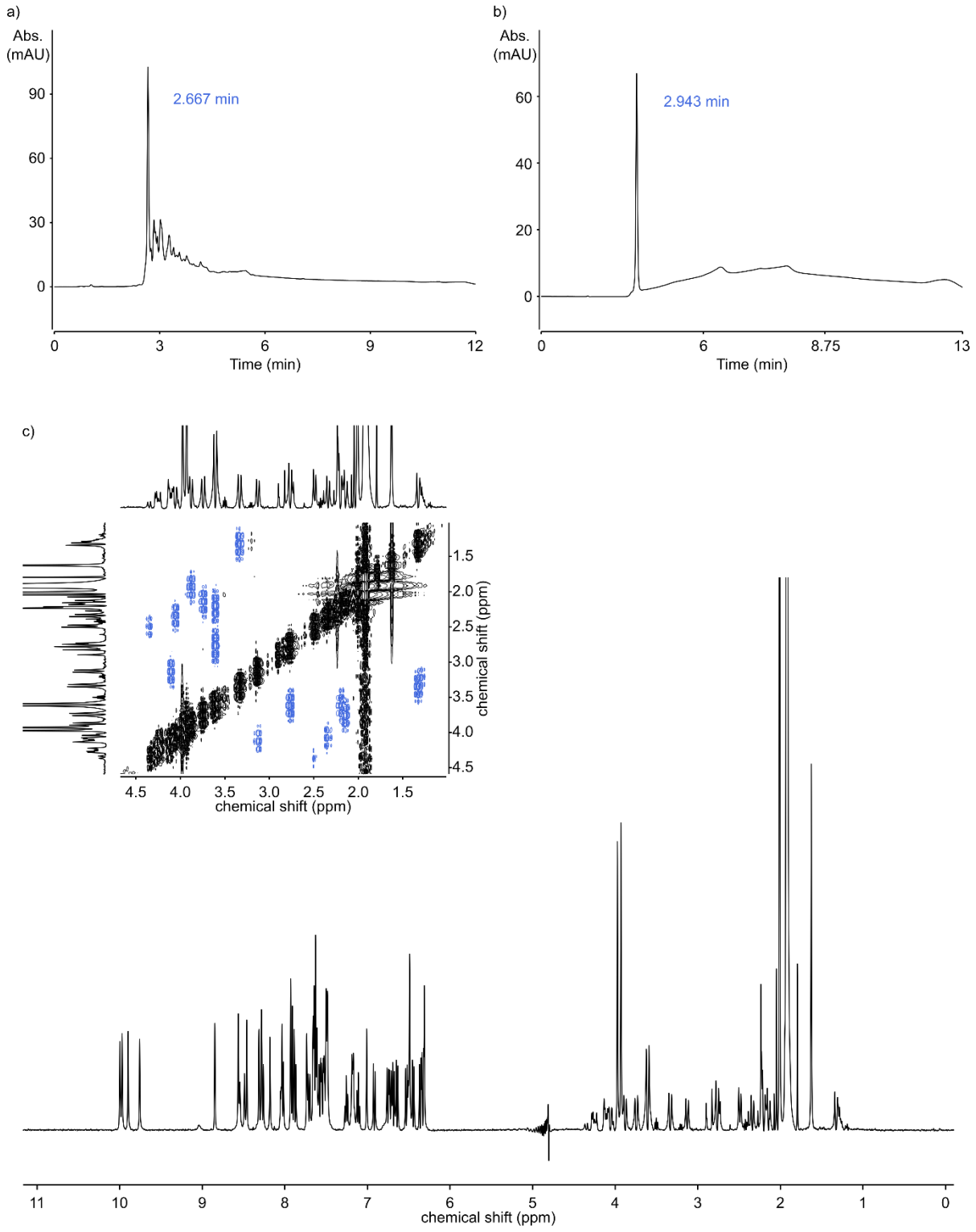


Figure S14: Analytical data of compound **4**. HPLC chromatograms after cleavage from the resin (a) (C18, 0–100B, 50 °C; A: 13mM NH_4OAc buffer pH 8.5, B: acetonitrile) and after purification (b) (C18, 0–50B, 50 °C; A: 13mM NH_4OAc buffer pH 8.5, B: acetonitrile). c) ^1H NMR and part of the COSY NMR spectrum (500 MHz, 0.18 mM in 12 mM NH_4OAc buffer pH 8.5 H_2O/D_2O 9:1, H_2O suppression), some cross-signals of diastereotopic methylene groups are exemplary highlighted in blue.

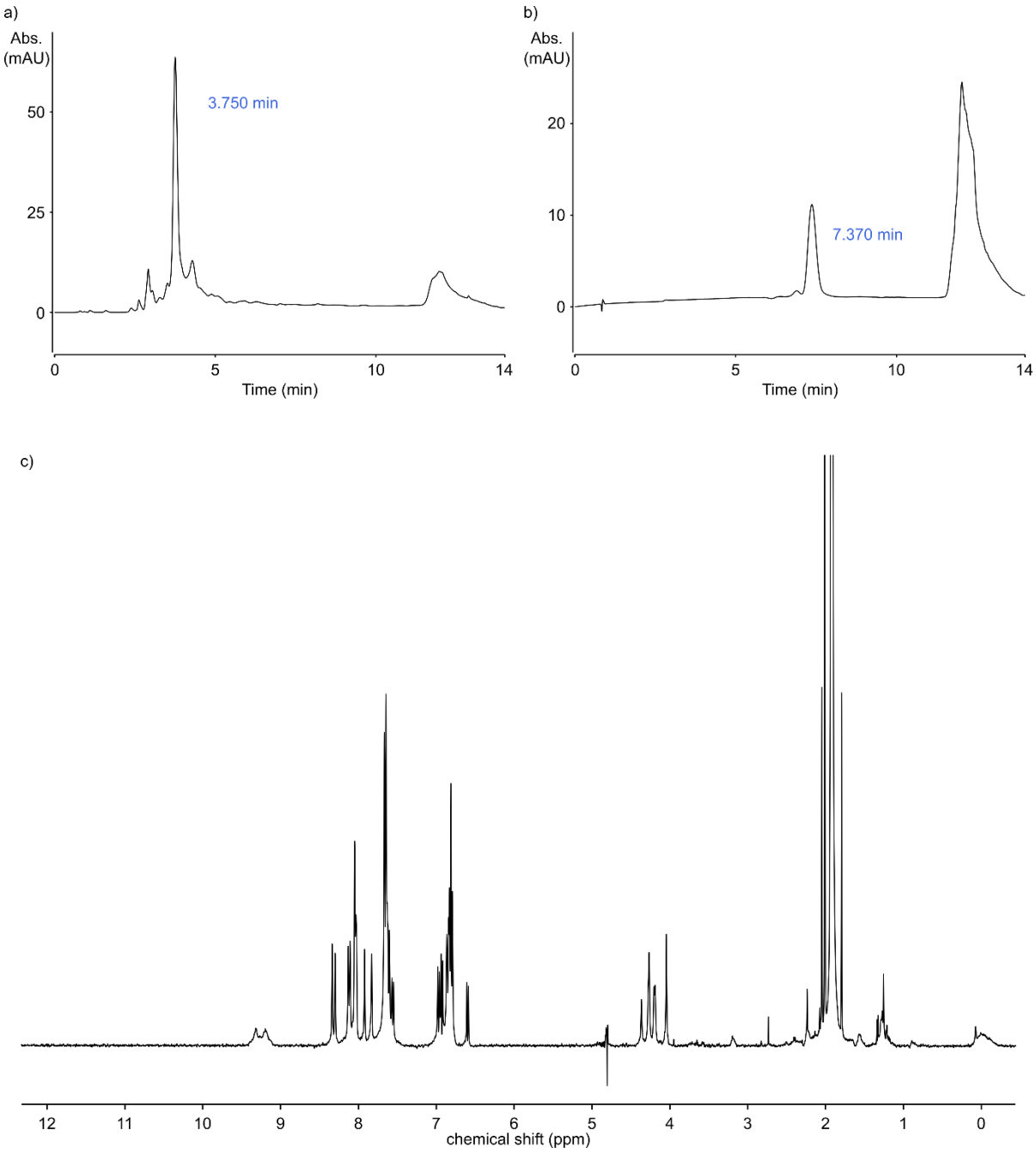


Figure S15: Analytical data of compound **5**. HPLC chromatograms after cleavage from the resin (a) (C18, 0–15B, 50 °C; A: 13mM NH_4OAc buffer pH 8.5, B: acetonitrile)and after purification (b) (C18, 0–5B, 50 °C; A: 13mM NH_4OAc buffer pH 8.5, B: acetonitrile). c) ^1H NMR spectrum (500 MHz, 0.6 mM in 12 mM NH_4OAc buffer pH 8.5 H_2O/D_2O 9:1, H_2O suppression.

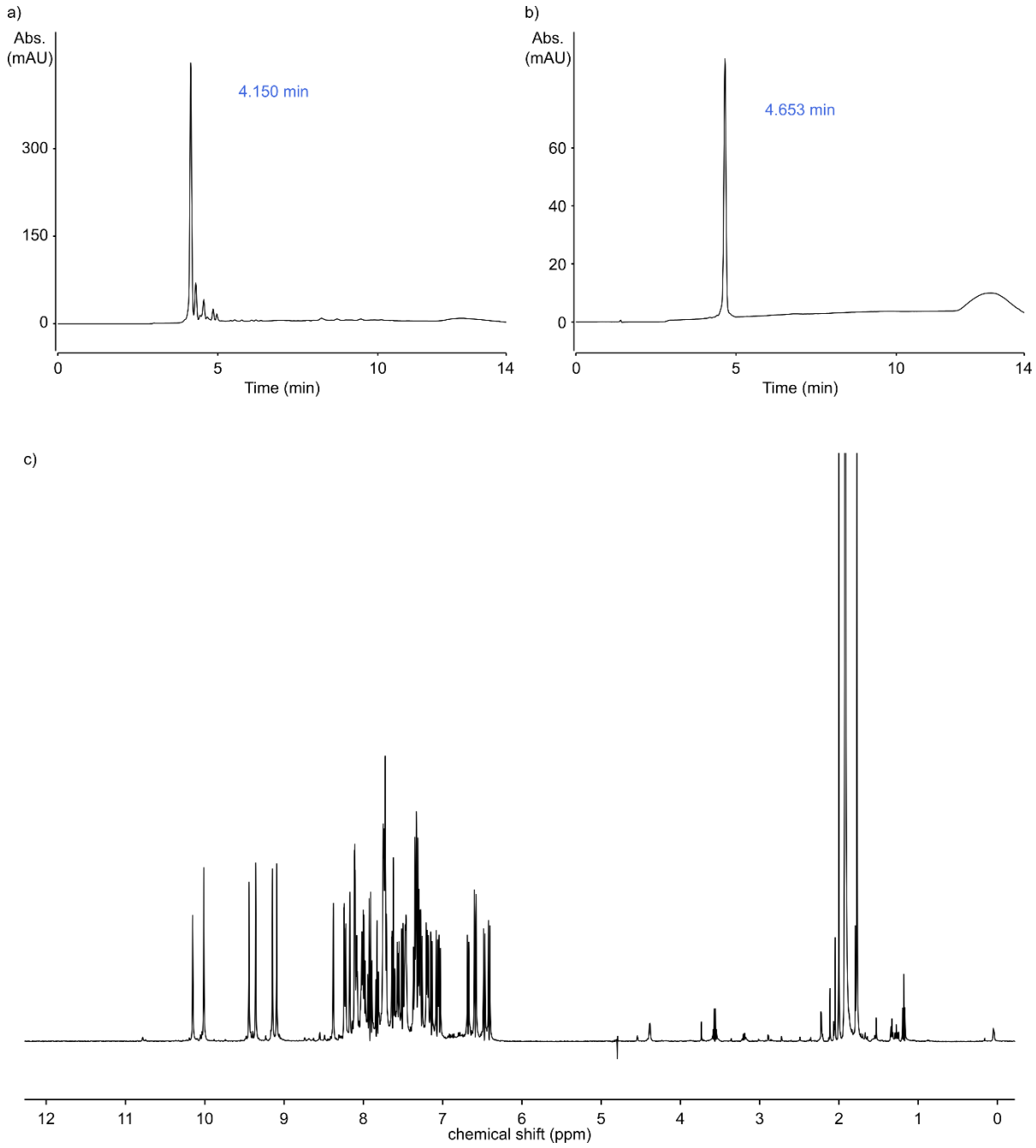


Figure S16: Analytical data of compound **6**. HPLC chromatograms after cleavage from the resin (a) (C18, 0–30B, 50 °C; A: 13mM NH_4OAc buffer pH 8.5, B: acetonitrile) and after purification (b) (C18, 0–10B, 50 °C; A: 13mM NH_4OAc buffer pH 8.5, B: acetonitrile). c) ^1H NMR spectrum (500 MHz, 0.66 mM in 12 mM NH_4OAc buffer pH 8.5 H_2O/D_2O 9:1, H_2O suppression).

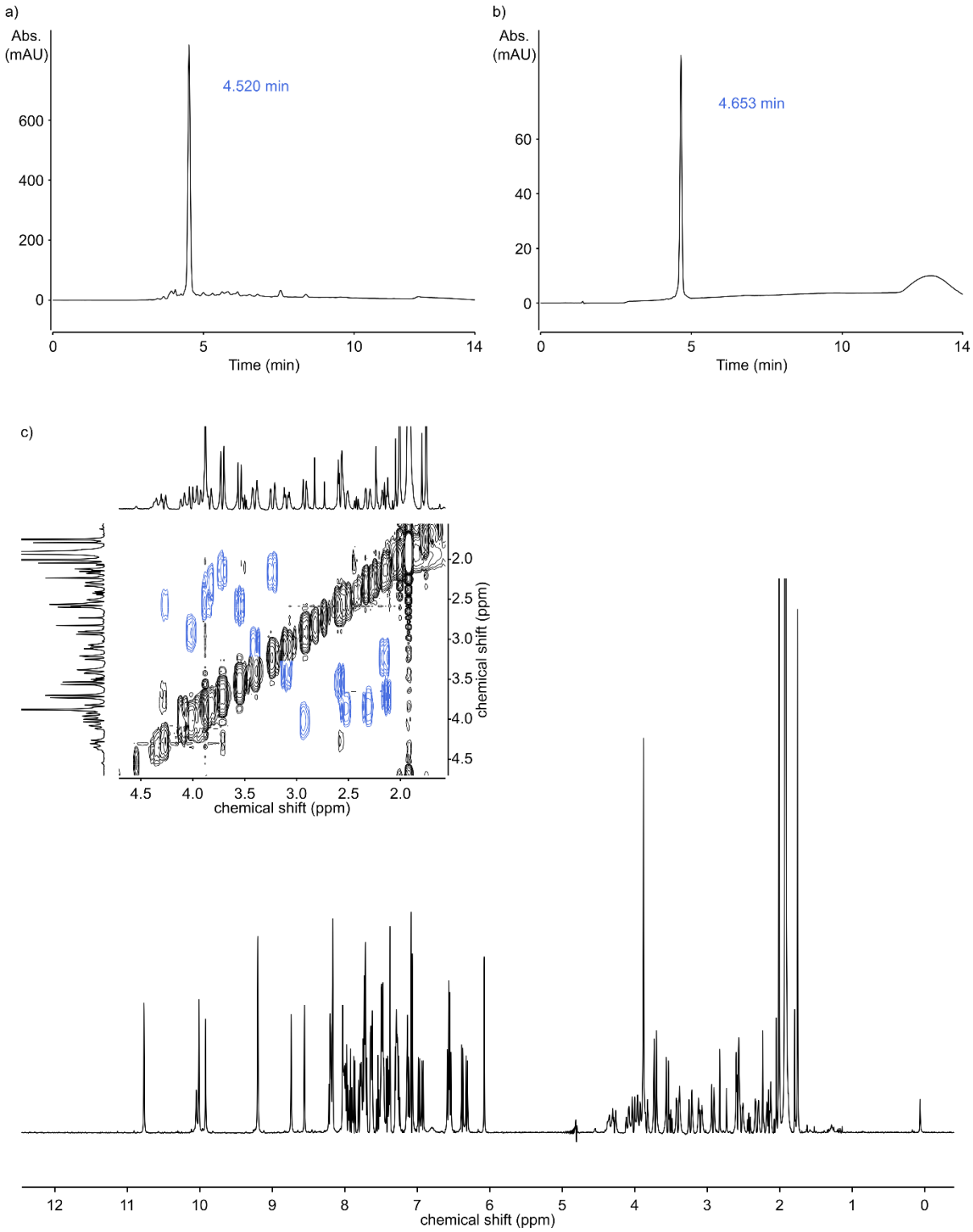


Figure S17: Analytical data of compound **7**. HPLC chromatograms after cleavage from the resin (a) and after purification (b) (C18, 0–30B, 50 °C; A: 13mM NH_4OAc buffer pH 8.5, B: acetonitrile). c) ^1H NMR and part of the COSY NMR spectrum (500 MHz, 0.36 mM in 12 mM NH_4OAc buffer pH 8.5 H_2O/D_2O 9:1, H_2O suppression), some cross-signals of diastereotopic methylene groups are exemplary highlighted in blue.

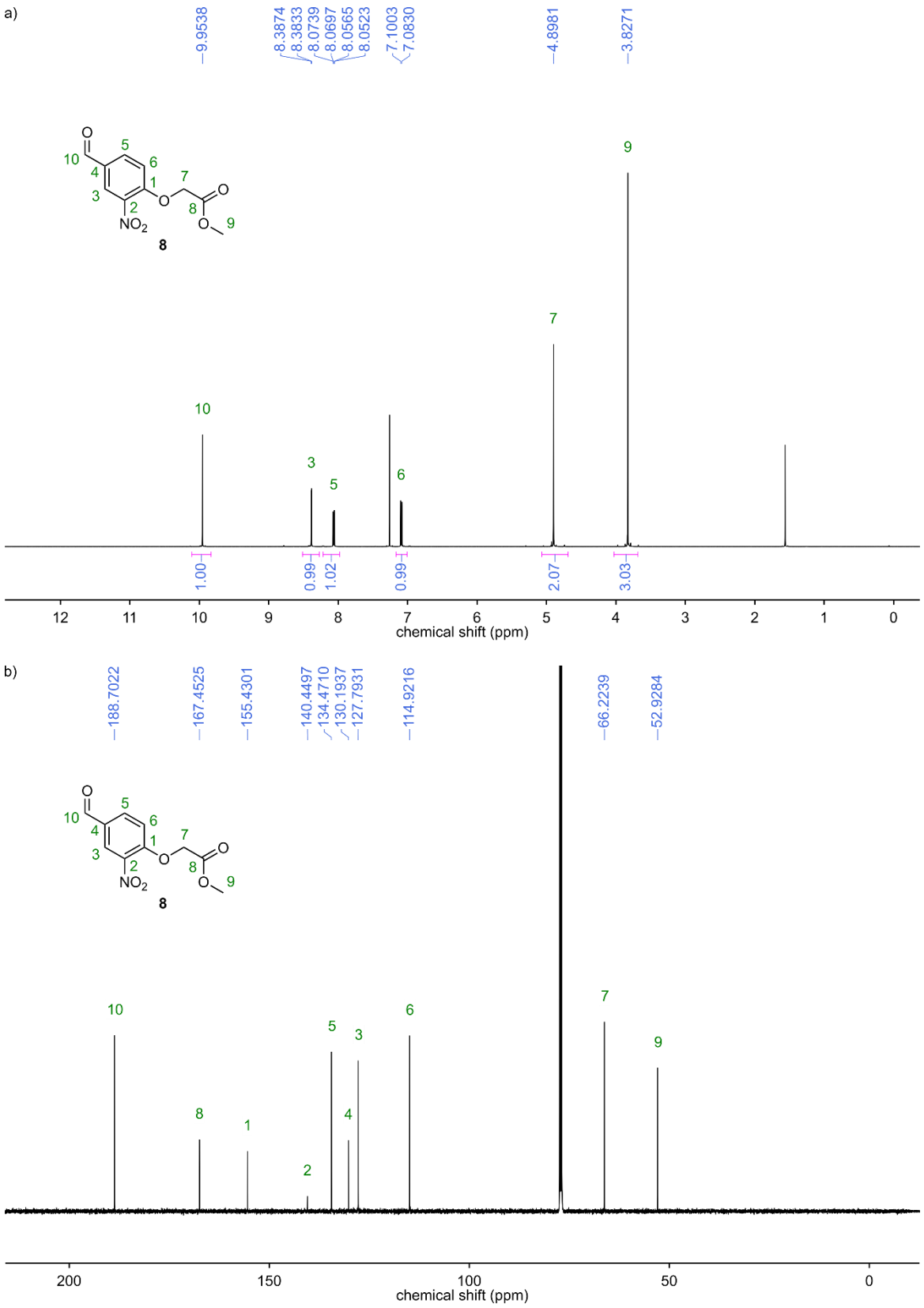


Figure S18: NMR spectra of compound **8**. a) ^{1}H NMR (500 MHz, $CDCl_3$). b) ^{13}C NHR (126 MHz, $CDCl_3$).

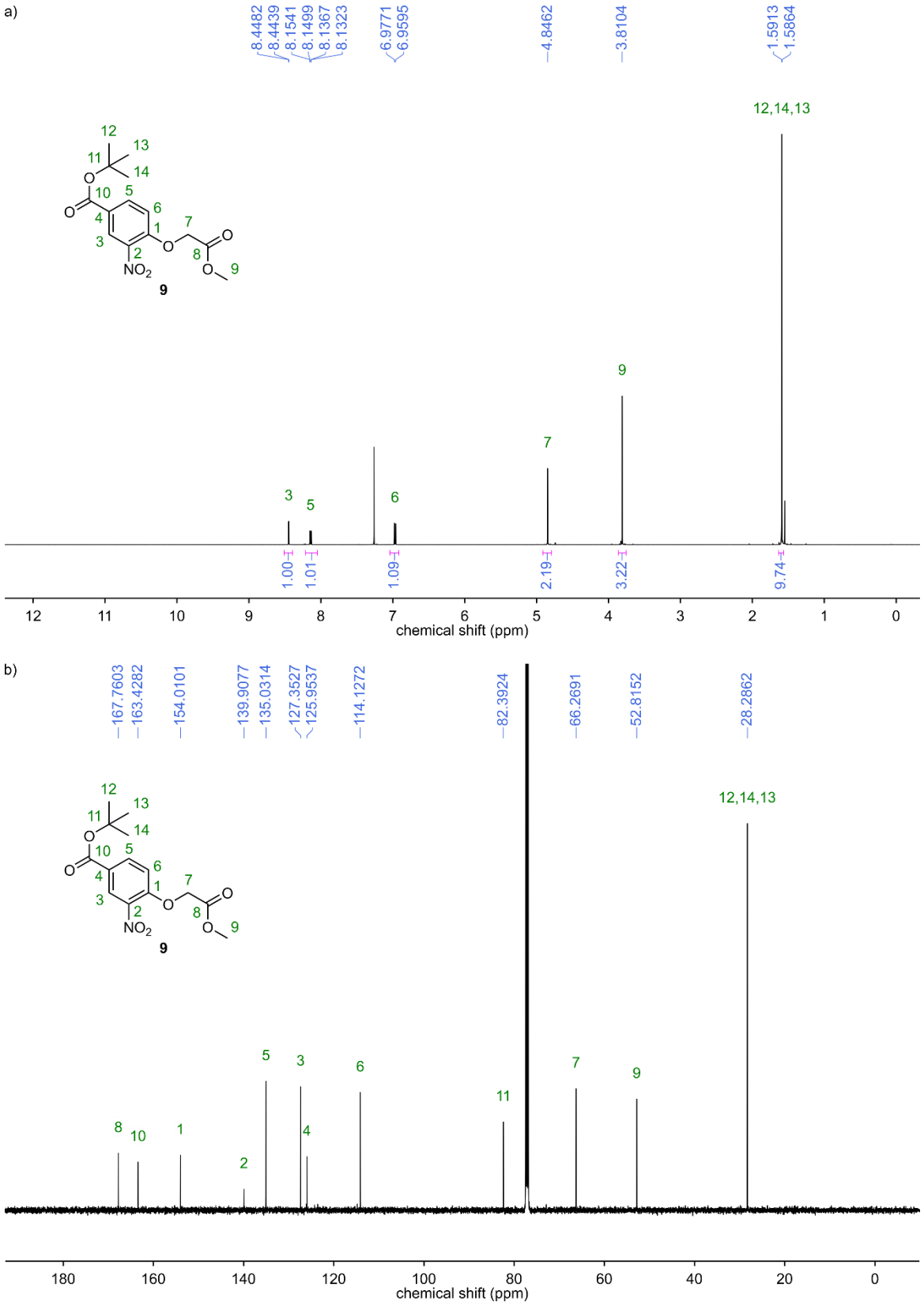


Figure S19: NMR spectra of compound **9**. a) ^{1}H NMR (500 MHz, $CDCl_3$). b) ^{13}C NHR (126 MHz, $CDCl_3$).

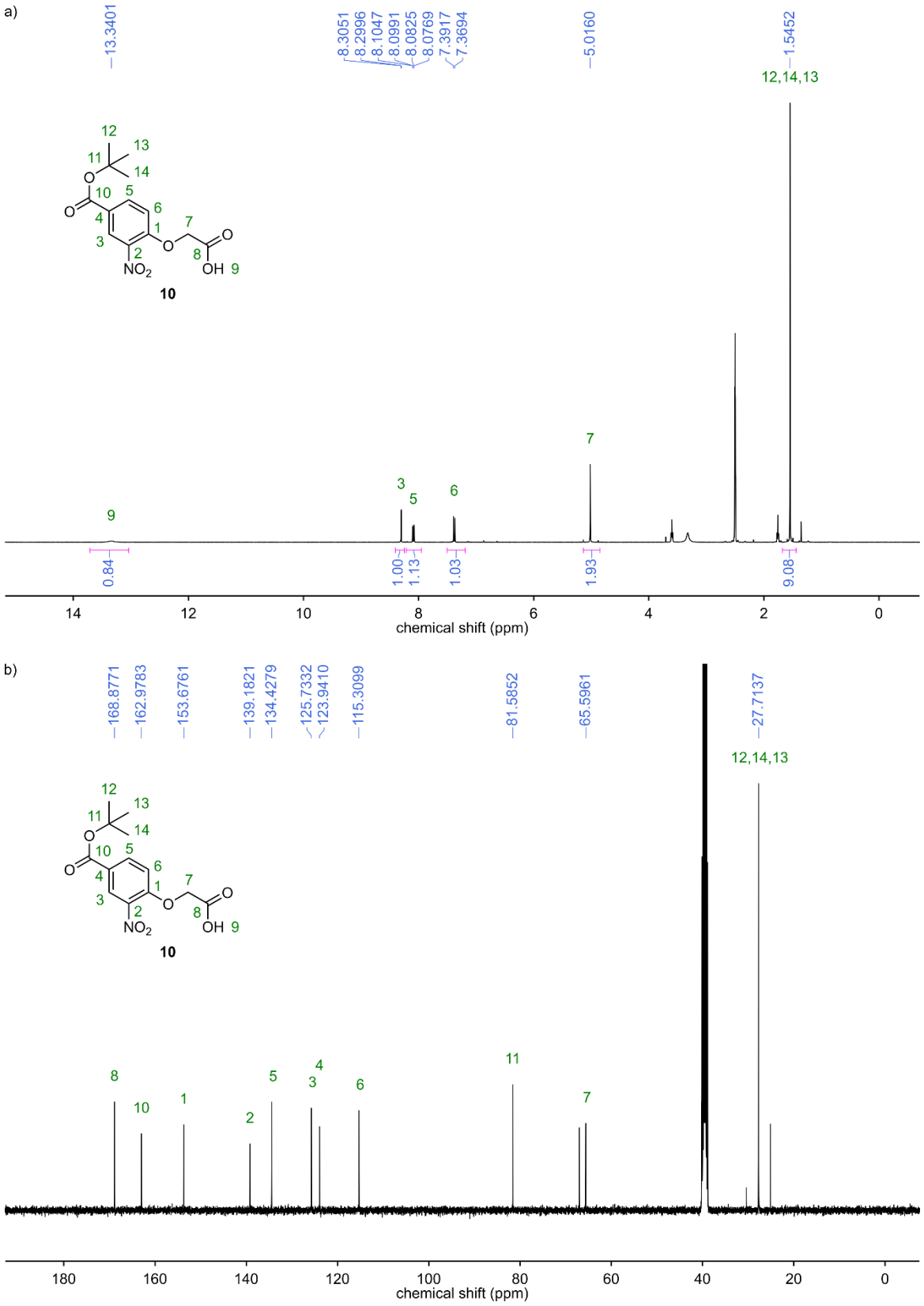


Figure S20: NMR spectra of compound **10**. a) ^{1}H NMR (400 MHz, DMSO-d_6). b) ^{13}C NHR (101 MHz, DMSO-d_6).

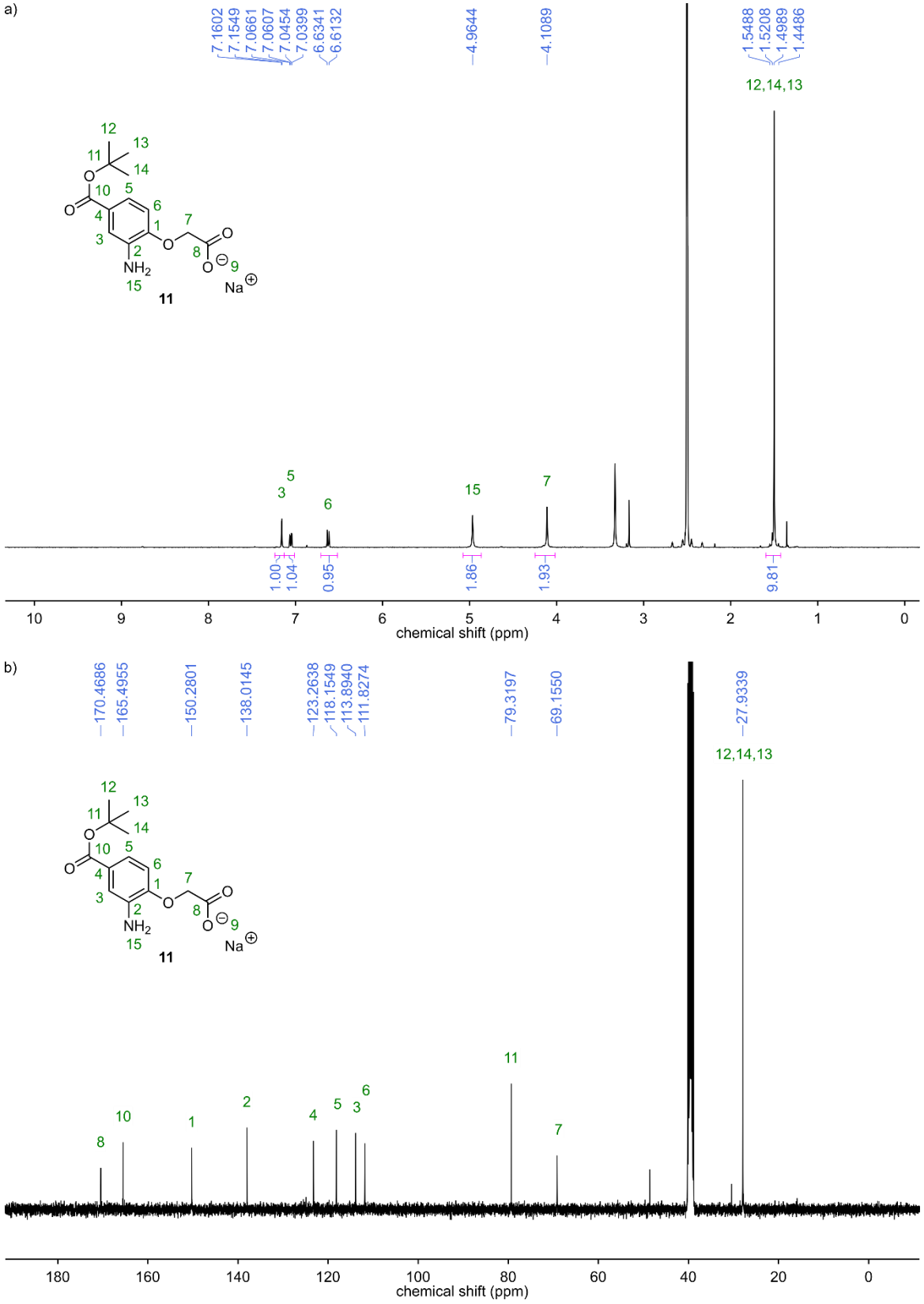


Figure S21: NMR spectra of compound **11**. a) ^{1}H NMR (400 MHz, DMSO-d_6). b) ^{13}C NHR (101 MHz, DMSO-d_6).

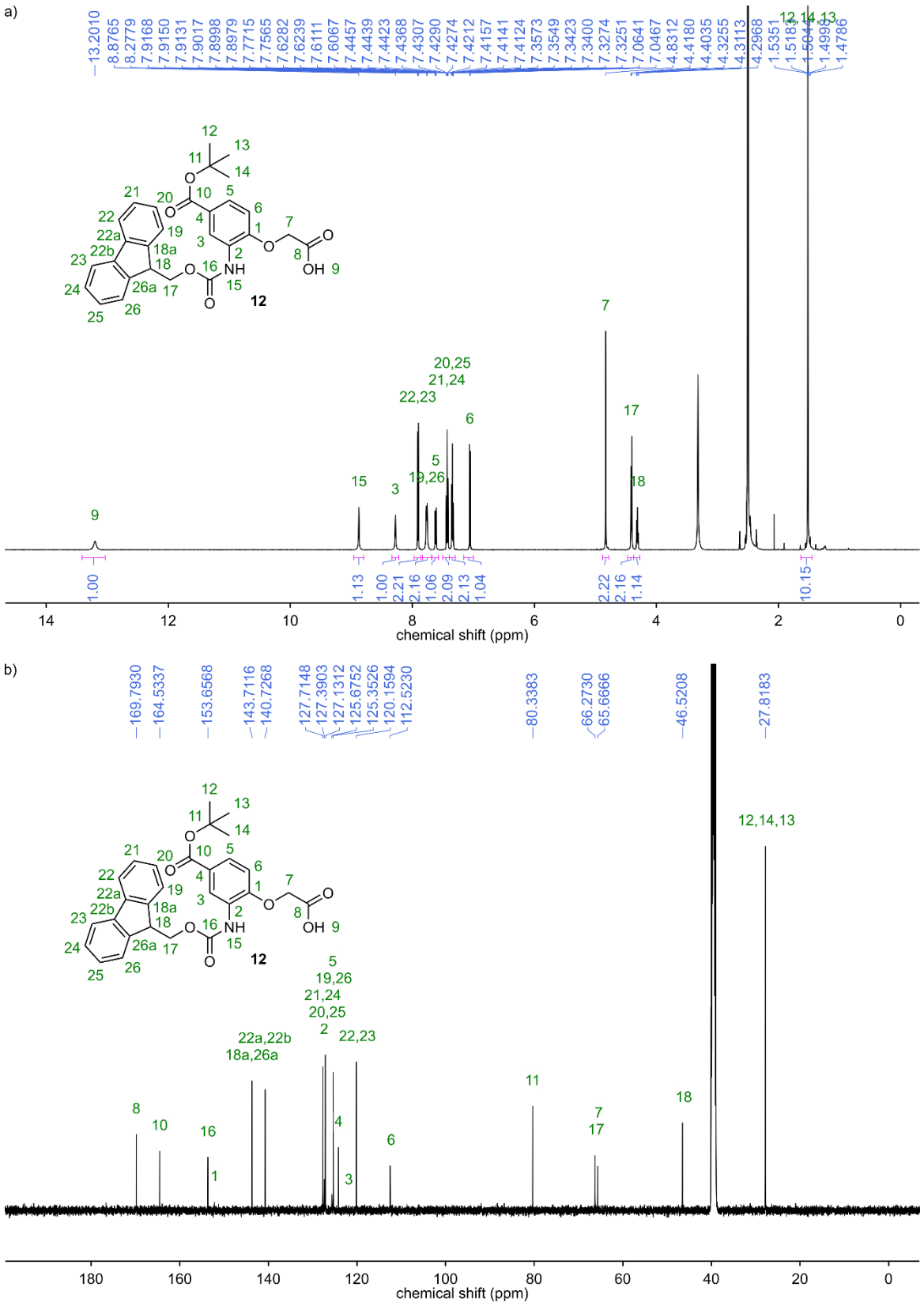


Figure S22: NMR spectra of compound **12**. a) 1H NMR (500 MHz, DMSO-d6). b) 13C NHR (126 MHz, DMSO-d6).

5 Literature

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