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Supporting Information

Enhancing the Features of DNA Mimic Foldamers for Structural Investigations

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Supporting Information

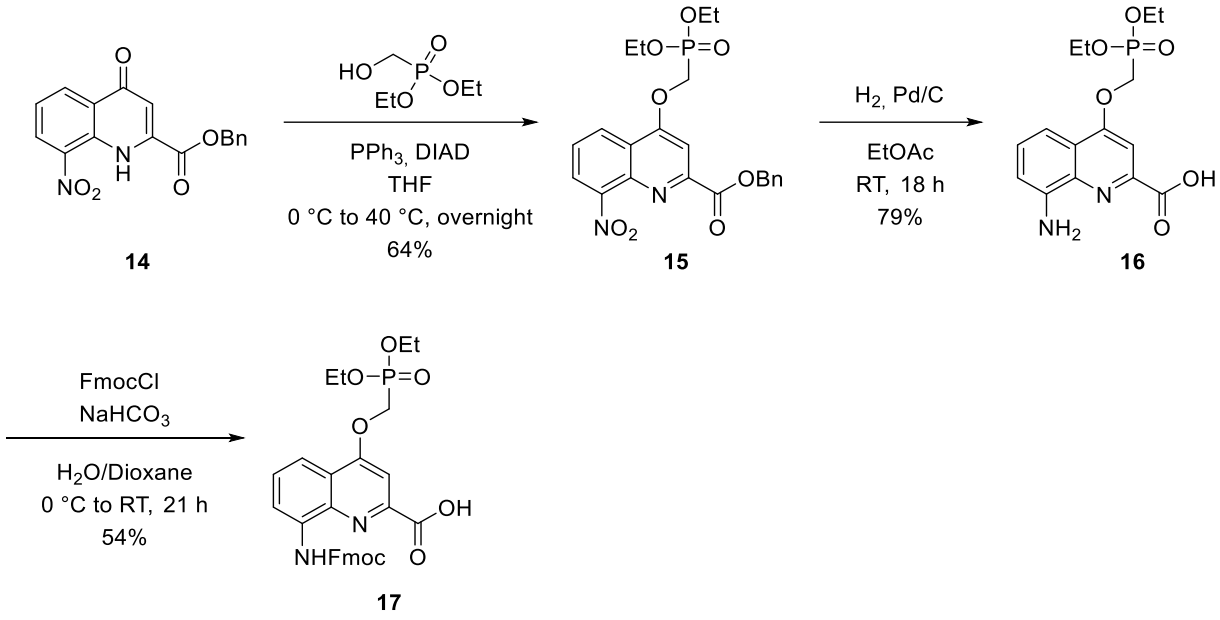
Contents

1. List of Abbreviations

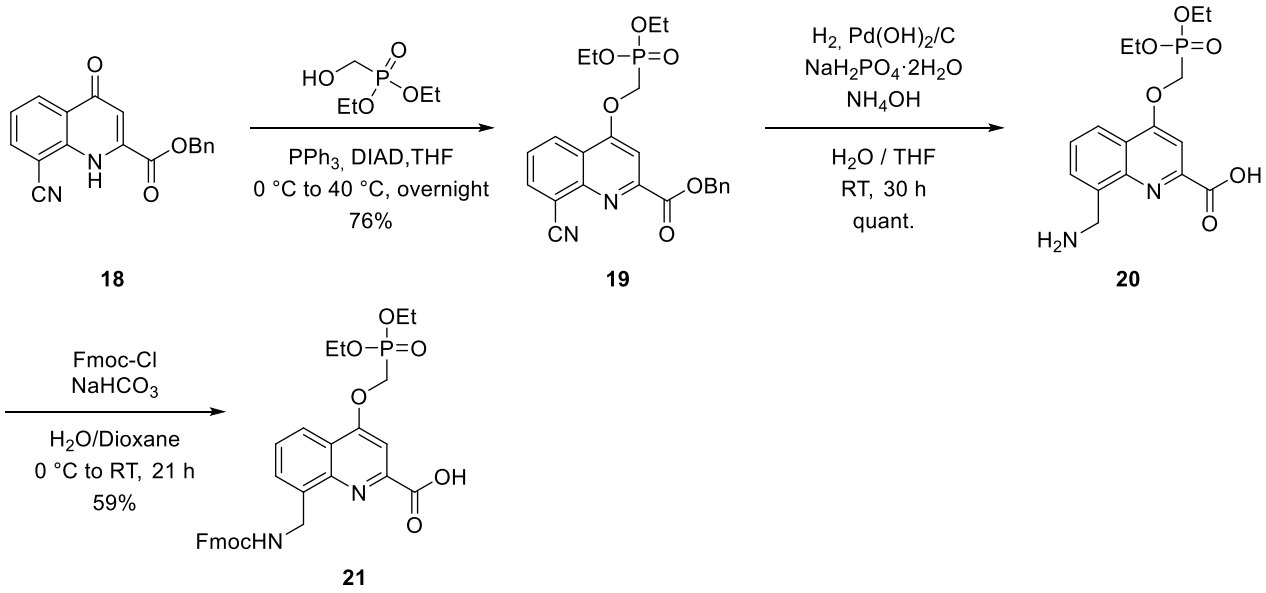
AcOH	acetic acid
Ac_2O	acetic anhydride
CD	circular dichroism
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DIPEA	*N,N*-diisopropylethylamine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
ESI	electrospray ionization
EtOAc	ethyl acetate
Et_2O	diethyl ether
Fmoc-Cl	fluorenylmethyloxycarbonyl chloride
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
LC-MS	liquid chromatography-mass spectrometry
MeOH	methanol
NMR	nuclear magnetic resonance
PPh_3	triphenylphosphine
PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
RP	reversed phase
RT	room temperature
SPS	solid phase synthesis
TCAN	trichloroacetonitrile
TEAA	triethylammonium acetate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMSBr	trimethylbromosilane
UV	ultraviolet

2. Supplementary Schemes and Figures

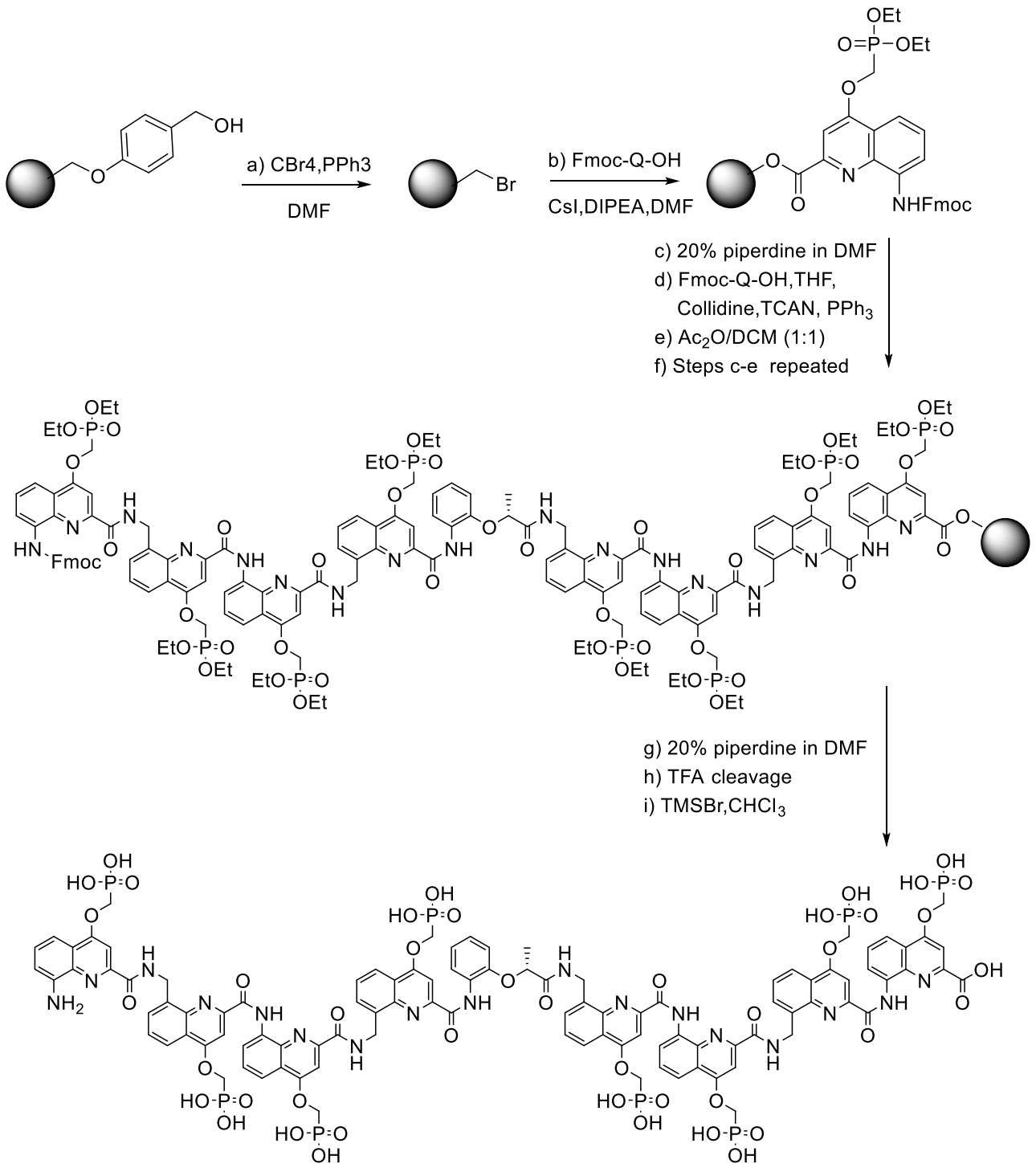
2.1 Supplementary Schemes



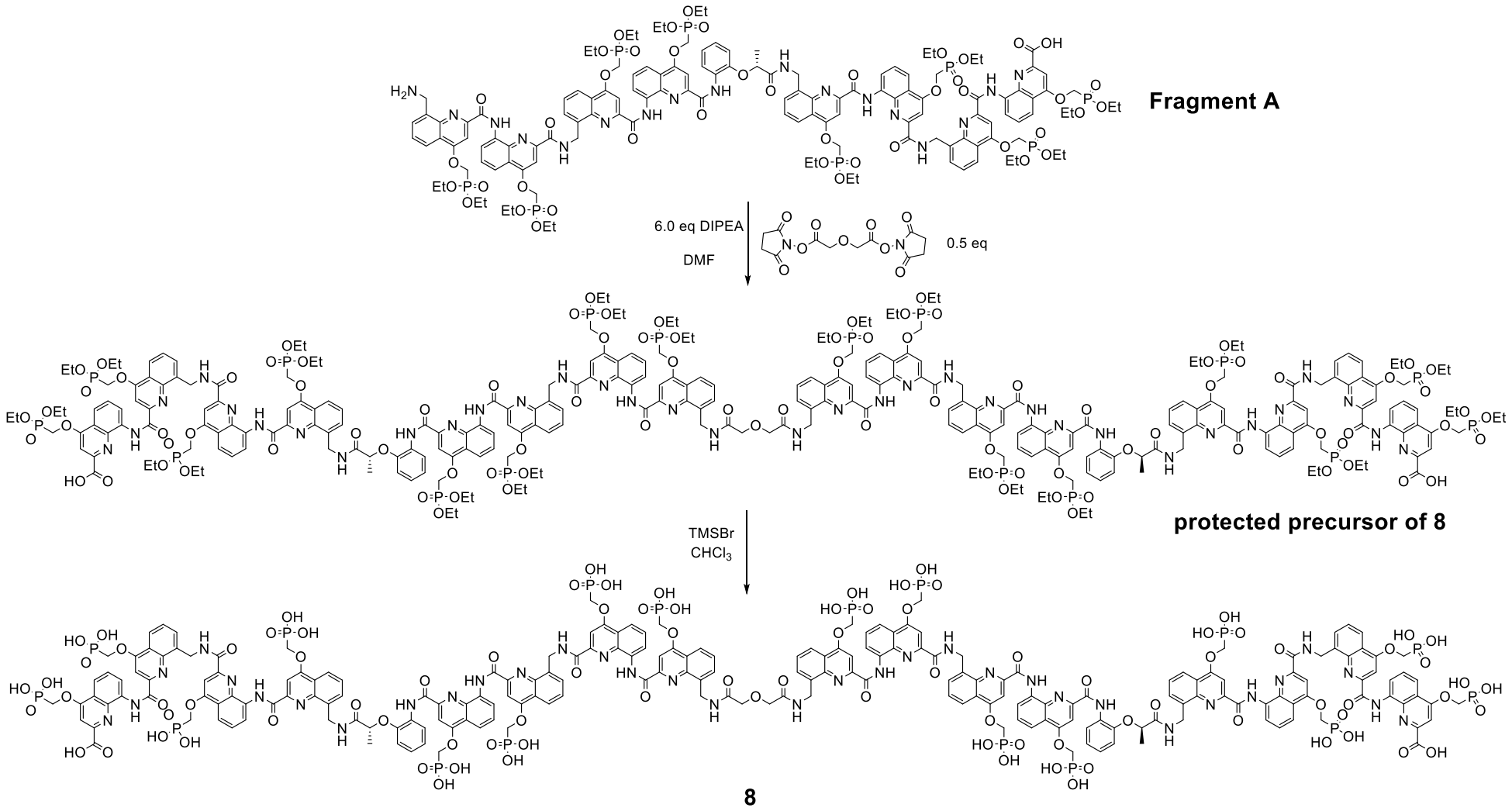
Scheme S1. Synthetic route to the Fmoc-Q^{Pho}-COOH monomer.



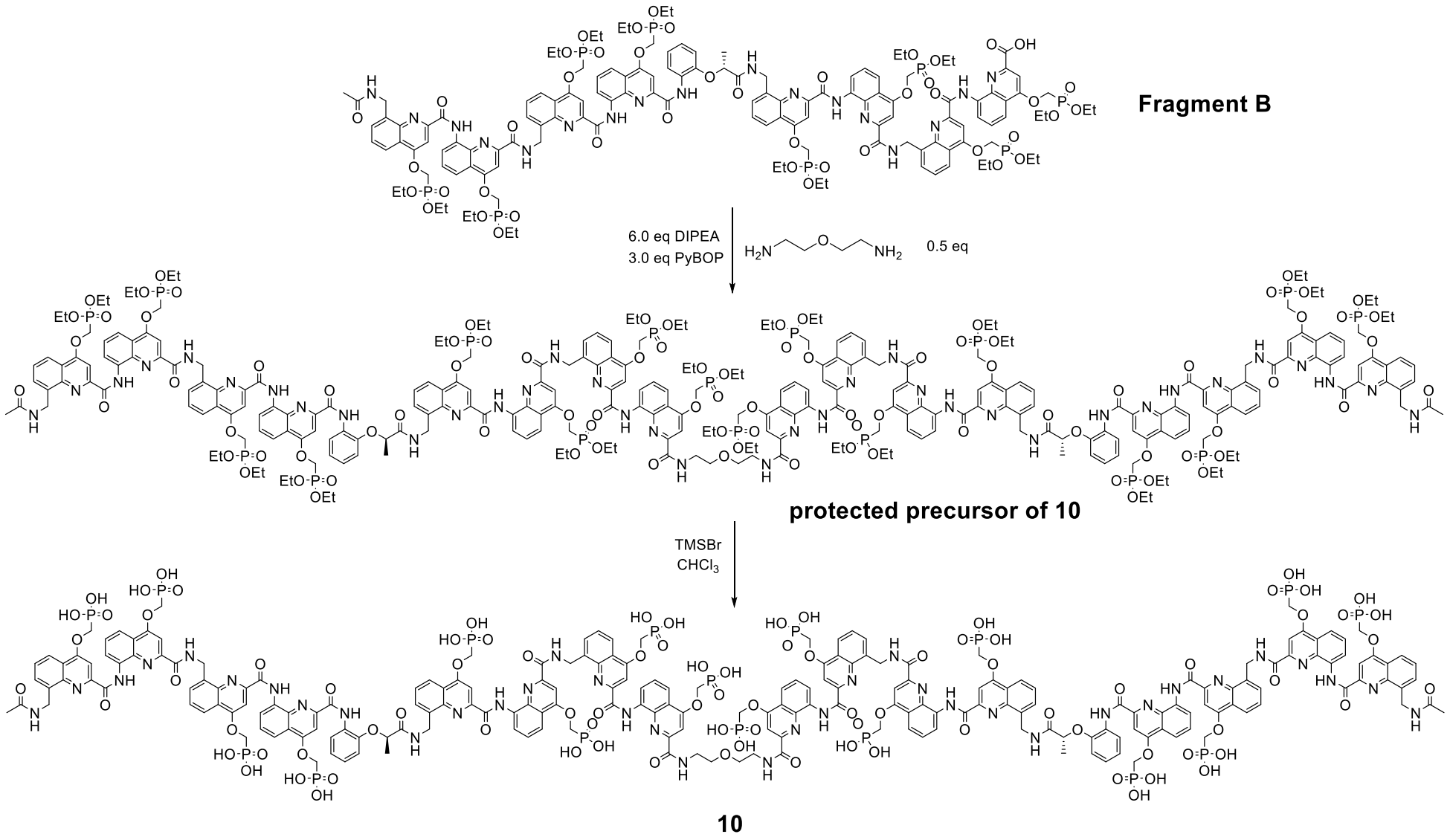
Scheme S2. Synthetic route to the Fmoc-M^{Pho}-COOH monomer.



Scheme S3. Representative example of SPS for oligomer **2**.



Scheme S4. Synthetic scheme for the N-terminus ligation to obtain oligomer **8**. A similar scheme leads to **9**.



Scheme S5. Synthetic scheme for the C-terminus ligation to obtain oligomer **10**. A similar scheme leads to **11**.

2.2 Supplementary Figures

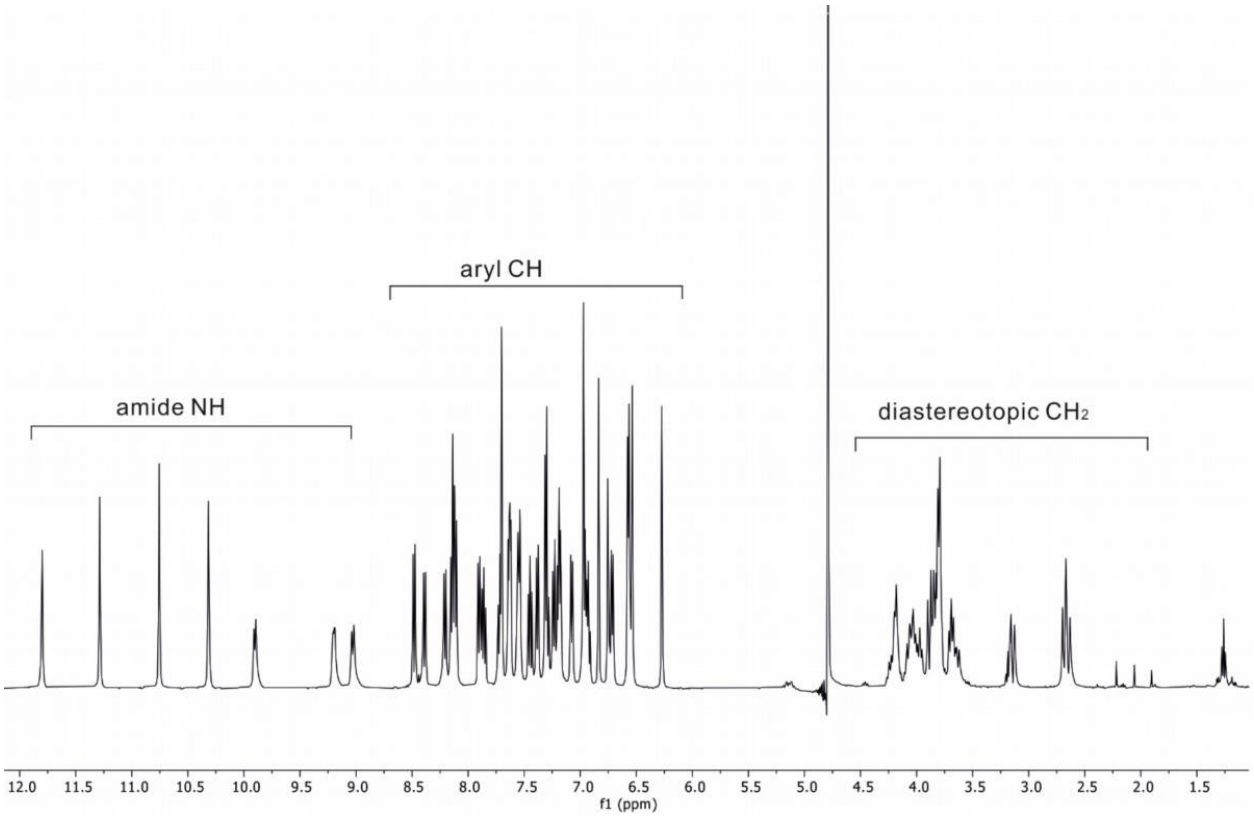


Figure S1. ^{1}H NMR spectrum of oligomer **1** (500 MHz, H_2O/D_2O 9:1 v/v, 50 mM NH_4HCO_3, pH 8.5, water suppression).

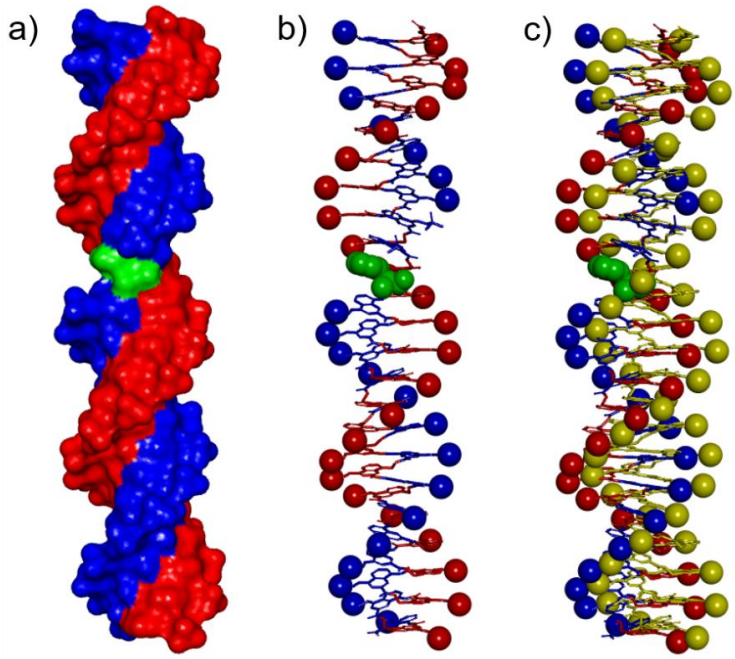


Figure S2. Energy minimized molecular models of extended-**2** as solvent accessible isosurface (a) and tube representation (b) except the phosphorous atoms which are shown in space-filling representation. The chiral B^{Rme} monomer is shown in bright green. The structure in (c) is an overlay of (b) and the reference DNA mimic structure $(M^{pho}Q^{Pho})_{24}$ displayed in yellow. Hydrogen atoms have been omitted for clarity.

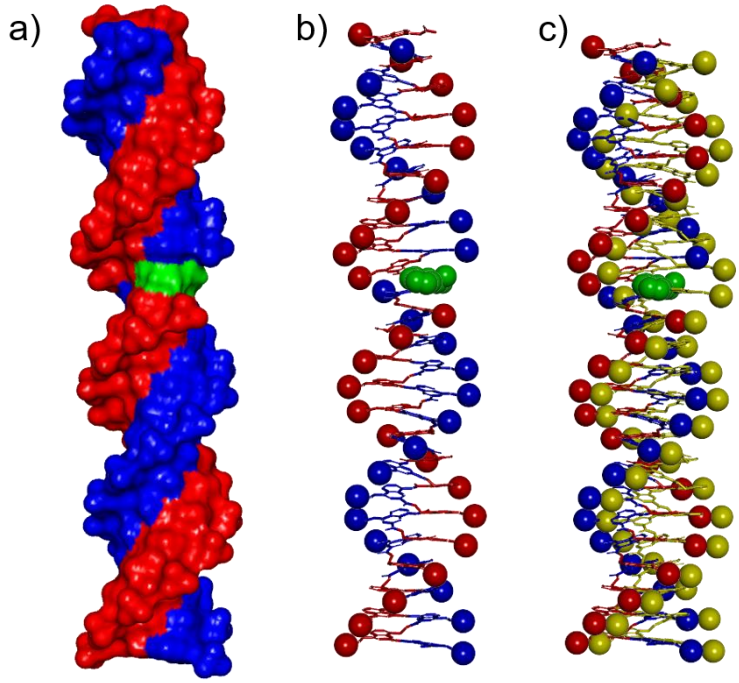


Figure S3. Energy minimized molecular models of extended-**5** as solvent accessible isosurface (a) and tube representation (b) except the phosphorous atoms which are shown in space-filling representation. The chiral B^{Rme} monomer is shown in bright green. The structure in (c) is an overlay of (b) and the reference DNA mimic structure $(M^{pho}Q^{Pho})_{24}$ displayed in yellow. Hydrogen atoms have been omitted for clarity.

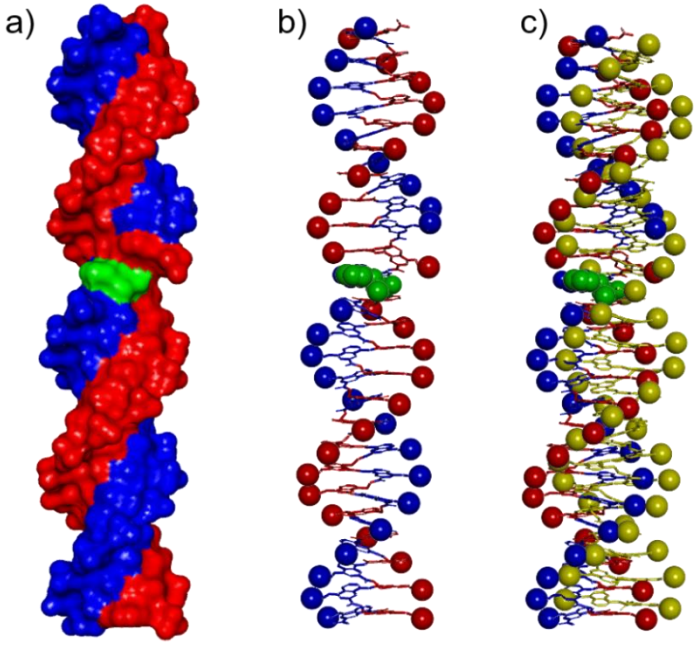


Figure S4. Energy minimized molecular models of extended-**7** as solvent accessible isosurface (a) and tube representation (b) except the phosphorous atoms which are shown in space-filling representation. The double insertion of B^{Rme} and of M^{pho} creates minor distortions in the overall structure. The chiral B^{Rme} monomer is shown in bright green. The structure in (c) is an overlay of (b) and the reference DNA mimic structure $(M^{pho}Q^{Pho})_{24}$ displayed in yellow. Hydrogen atoms have been omitted for clarity.

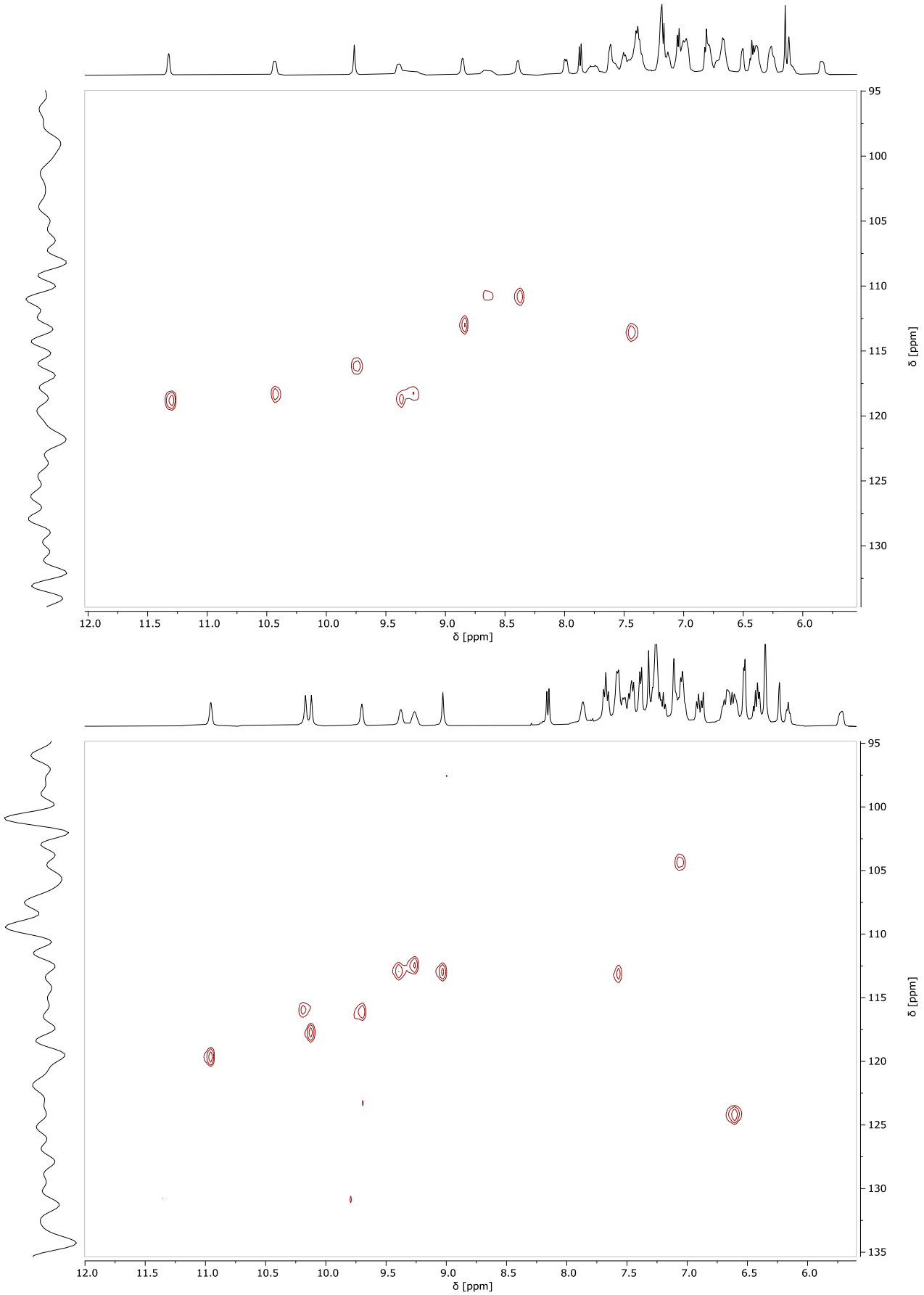


Figure S5. 500 MHz ^{15}N-^{1}H HSCQ spectra of **9** (top) and **10** (bottom) in 50 mM NH_4HCO_3 (pH 8.5) in H_2O/D_2O (9:1, vol/vol). In both case, the number of correlations matches with the expected number of different N*H* resonances in C_2-symmetrical structures.

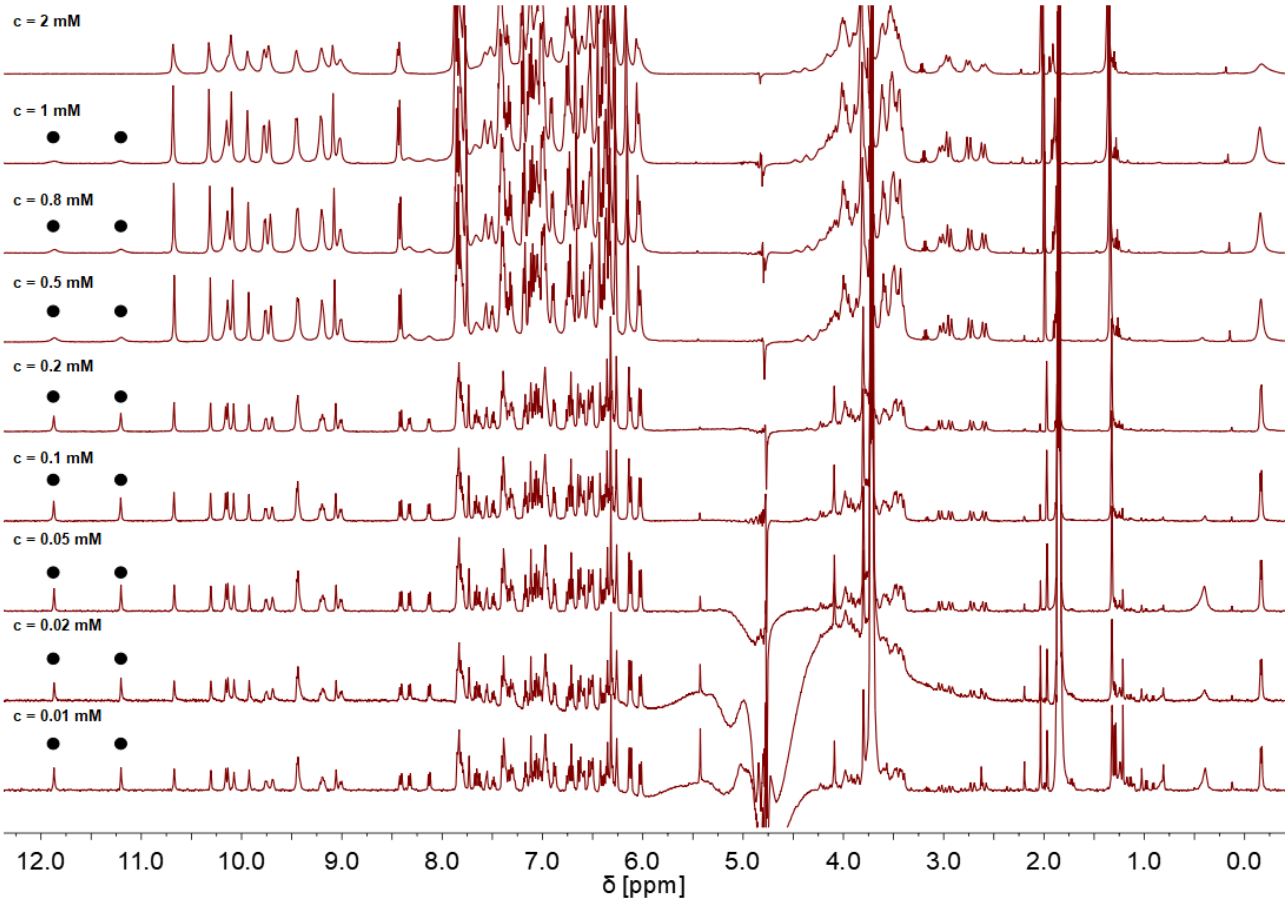


Figure S6. ^{1}H NMR dilution study of oligomer **12** (500 MHz, H_2O/D_2O 9:1 v/v, 27 mM sodium phosphate buffer, pH 7.2) from 2 mM to 0.01 mM. Black circles indicate the monomeric species forming upon dilution.

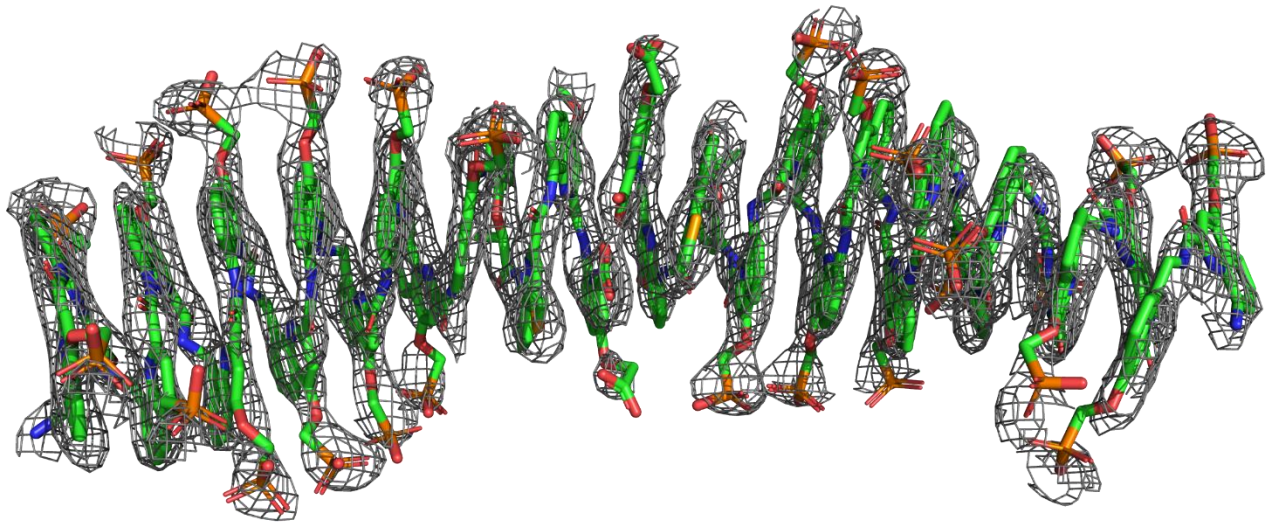


Figure S7. Sigma weighted $2F_o$-F_c electron density map (grey mesh) contoured at 1 σ superimposed on helices of **13**.

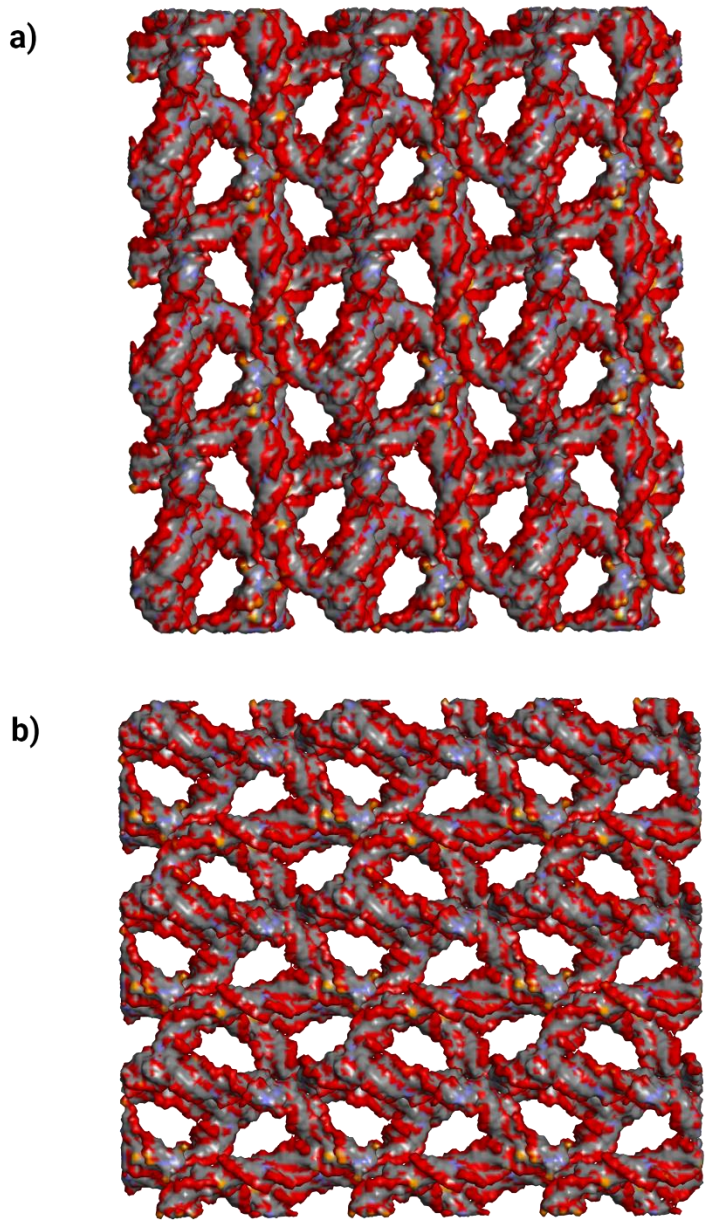


Figure S8. Packing of **13** (PDB # 8QHM) in the crystal lattice viewed down the a) a-axis and b) b-axis. Helices are shown in surface representation.

3. Materials and Methods

3.1 General

Chemicals and reagents were used as commercially supplied without any further purification unless otherwise stated. Low loading Wang resin (0.41 mmol g^{-1}) was purchased from Novabiochem. Analytical grade organic solvents were used for SPS. Anhydrous THF and DCM for SPS were dispensed from an *MBRAUN Solvent Purification System-800* solvent purification system. Reactions requiring anhydrous conditions were performed under nitrogen. Protected Fmoc-acid building blocks are shown in Figure S9.

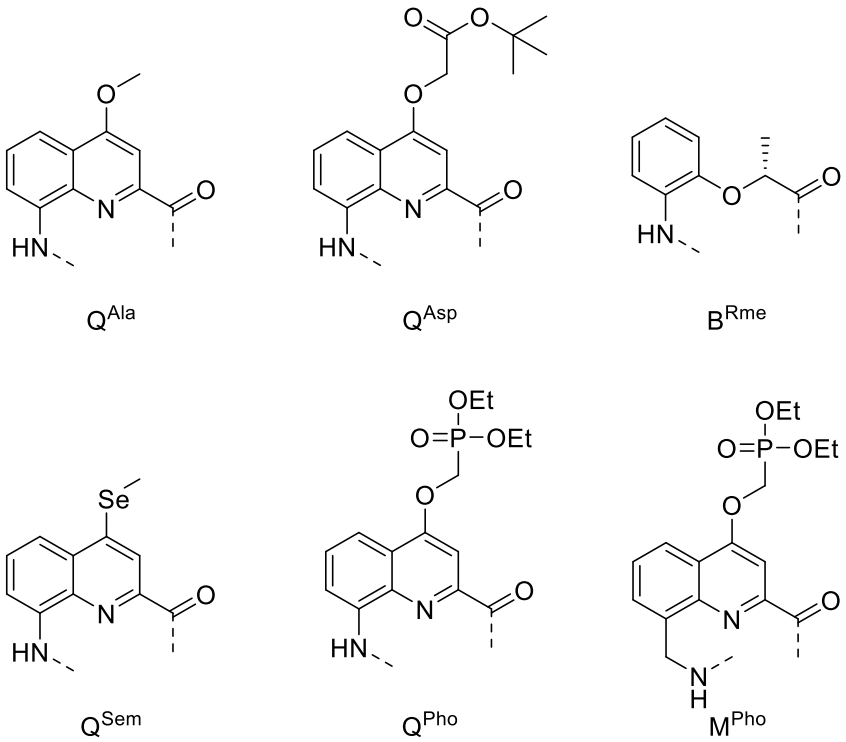


Figure S9. Side chain-protected Fmoc-acid building blocks used in this study. Fmoc-Q^{Ala}-OH,[27] Fmoc-Q^{Asp}-OH[12a] and Fmoc-B^{Rme}-OH[11] have been described previously. Fmoc-Q^{Sem}-OH will be described elsewhere. For a detailed procedure to Fmoc-Q^{Pho}-OH and Fmoc-M^{Pho}-OH, see section 3.2.

Analytical and semi-preparative RP-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). When using acidic conditions, 0.1% TFA was added to aqueous mobile phase (referred to as mobile phase A) and to acetonitrile (referred to as mobile phase B). When using basic conditions, the mobile phase was composed of 12.5 mM TEAA in water at pH 8.5 (solvent A) and 12.5 mM TEAA in water: acetonitrile 1:2 vol/vol at pH 8.5 (solvent B). For RP-HPLC analyses, a flow rate of 1.0 mL/min was applied; semi-preparative RP-HPLC purification were performed at a flow rate of 5.0 mL/min. UV absorbance was monitored at 300 nm if not stated otherwise.

NMR spectra were recorded on the *Avance III HD 500 MHz Bruker Biospin* spectrometer. DMSO-d_6 (δH: 2.50, δC: 39.4) and D_2O (δH: 4.79) were used as solvents. Water suppression was performed with excitation sculpting. Measurements were performed at 298 K unless stated otherwise. NMR spectra of the oligomers were recorded in H_2O/D_2O (9:1 v/v), 50 mM NH_4HCO_3. The raw data were evaluated using Mnova version 14.0.0 from Mestrelab Research. Signal multiplicities are abbreviated as s, singlet; d, doublet; t, triplet; q, quartet, and m, multiplet.

LC-MS spectra were recorded on a *Thermo Scientific Dionex UltiMate 3000* equipped with a Nucleodur C18 gravity column (2 x 50 mm, 1.8 µm) with a flow of 0.3 mL min^{-1}. 0.1% of formic acid in water (solvent A) and 0.1% of formic acid in acetonitrile (solvent B) were used as mobile phase for the ionization of the quinoline monomers. For water soluble oligomers, 12.5 mM aqueous NH_4OAc buffer adjusted to pH 8.5 and LC-MS grade acetonitrile were used as mobile phase for the ionization of the polyanionic foldamers. Elution was monitored by UV detection at 214, 254 and 300 nm with a diode array detector. The LC system was coupled to a *micrOTOF II* mass spectrometer by *Bruker Daltonics* and molecules were ionized by ESI.

CD spectra were recorded on a *J-815 Circular Dichroism spectrometer* by *Jasco* using quartz cells (2 mm optical path length). Scans were measured at 20 °C, over a wavelength range of 300–500 nm, with a response time of 0.5 s and a scanning speed of 50 nm/min. Molar extinction values were normalized per quinoline units. Foldamers (60 µM) were dissolved in 50 mM NH_4HCO_3 buffer pH 8.5.

3.2 Monomer synthesis procedures

Compound (15). Benzyl 8-nitro-4-quinolinone-2-carboxylate intermediate **14** was prepared according to previously described methods.[1a] Freshly dried compound **14** (12.0 g, 37.0 mmol, 1 eq.), PPh_3 (12.6 g, 48.1 mmol, 1.3 eq.) and diethyl hydroxymethyl phosphonate (6.84 g, 6 mL, 40.7 mmol, 1.1 eq.) were suspended in anhydrous THF under N_2 and cooled to 0 °C. DIAD (9.44 mL, 48.1 mmol, 1.3 eq.) was added dropwise over 20 min at 0 °C. The resulting solution was stirred at 0 °C for 1.5 h, at RT for another 1 h, and at 50 °C overnight. THF was removed *in vacuo* and co-evaporated with DCM (2 x 100 mL) and Et_2O (2 x 100 mL). The resulting solid was dried overnight under vacuum to remove residual THF. The crude product was purified by flash column chromatography (100% EtOAc, dry-load using silica gel). After evaporation of the solvent, the purified product was dissolved in DCM (5 mL), Et_2O (100 mL) was layered on top and the product was crystallized at –14 °C overnight, filtered and washed with cold Et_2O (200 mL). Crystallization was repeated twice, until the HPLC analysis of an aliquot showed no residual triphenylphosphine oxide, to yield the title compound (11.2 g, 64%) as a white crystalline solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ [ppm] = 8.48 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.13 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.74 – 7.66 (m, 2H), 7.55 – 7.50 (m, 2H), 7.43 – 7.38 (m, 2H), 7.38 – 7.32 (m, 1H), 5.49 (s, 2H), 4.57 (d, *J* = 10.2 Hz, 2H), 4.28 (dq, *J* = 8.4, 7.0 Hz, 4H), 1.38 (t, *J* = 7.0 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ [ppm] = 164.8, 162.4 (d, *J* = 13.2 Hz), 151.5, 148.7, 140.3, 135.5, 128.8, 128.5, 128.3, 126.7, 126.2, 125.4, 123.0, 102.4, 68.1, 63.4(d, *J* = 6.4 Hz), 63.0 (d, *J* = 171.5 Hz), 16.7(d, *J* = 5.6 Hz). **HRMS** (ESI^+) *m/z* calcd. for $C_{22}H_{23}N_2O_8P$: 475.1265 $[M+H]^+$; found: 475.1319.

Compound (17). Compound **15** (11.2 g, 23.4 mmol, 1 eq.) was dissolved in EtOAc (350 mL), split over two flasks under N_2 and the solvent was degassed for 15 min by bubbling N_2 through the solution while sonicating. Pd/C (1.30 g) was added and the solution was further degassed for 10 min. Under vigorous stirring, a H_2 balloon was placed on top of the round bottom flask and the reaction mixture was stirred for 18 h until full conversion. The catalyst was filtered with a paper filter and the residual solid washed with hot THF. The filtrate was removed *in vacuo,* the resulting solid suspended in water/acetonitrile (30 mL, 1:1 v/v), sonicated, and freeze-dried to give **16** (7.22 g, 79%) as a green solid that was used without further purification. Compound **16** (7.22 g, 18.5 mmol, 1.0 eq) was suspended in dioxane (350 mL) and $NaHCO_3$ (36.0 g, 426 mmol, 21 eq.) dissolved in water (370 mL) was added. The suspension was cooled to 0 °C and Fmoc-Cl (5.31 g, 20.5 mmol, 1.1 eq.) in dioxane (200 mL) was added dropwise over 1 h at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then stirred at RT for 21 h. The reaction mixture was concentrated by rotary evaporation to remove most of the dioxane and the resulting suspension was diluted with water to a volume of 800 mL. The reaction mixture was acidified to pH 3 with a saturated $KHSO_4$ solution, extracted with DCM (1 L, then 2 x 500 mL), and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*, and the resulting solid was dried under vacuum to remove residual dioxane. The crude product was precipitated from acetonitrile (50 mL), sonicated shortly to allow full precipitation,

filtered, and washed with cold acetonitrile (−14 °C). The resulting solid was purified by flash column chromatography (5% MeOH in DCM with 0.1% AcOH, dry-load with silica from DCM) and the combined fractions were concentrated and washed with water (3 x 500 mL). After removal of the solvent *in vacuo*, the resulting solid was precipitated from acetonitrile, washed with cold acetonitrile (−14 °C), and lyophilized to yield the title compound (6.25 g, 58%) as a pale yellow solid. **^{1}H NMR (500 MHz, DMSO-d_6):** δ [ppm] = 13.56 (s, 1H), 10.46 (s, 1H), 8.37 (s, 1H), 7.94 (d, *J* = 7.5, 2H), 7.84 (s, 1H), 7.82 – 7.76 (m, 2H), 7.76 (d, *J* = 1.3 Hz, 1H), 7.69 – 7.65 (m, 1H), 7.45 (td, *J* = 7.7, 1.0 Hz, 2H), 7.37 (td, *J* = 7.5, 1.2 Hz, 2H), 4.93 (d, *J* = 9.7 Hz, 2H), 4.63 (d, *J* = 6.8 Hz, 2H), 4.46 (t, *J* = 6.8 Hz, 1H), 4.19 (d, *J* = 8.4, 7.0 Hz, 4H), 1.28 (t, *J* = 7.0 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$):** δ [ppm] = 165.3, 162.4 (d, *J* = 13.2 Hz), 153.5, 146.7, 143.7, 140.8, 137.5, 135.8, 128.9, 127.8, 127.2, 125.2, 121.6, 120.3, 116.6, 114.2, 101.3, 66.4, 62.5 (d, *J* = 5.9 Hz), 62.1(d, *J* = 164.3 Hz), 46.6, 16.3 (d, *J* = 5.4 Hz). **HRMS** (ESI$^+$) *m/z* calcd. for $C_{30}H_{29}N_2O_8P$: 577.1734 $[M+H]^+$; found: 577.1949.

Compound (20). Compound **19**[1a] (4.35 g, 9.61 mmol, 1.0 eq.) was dissolved in THF (360 mL) under N_2 and $NaH_2PO_4{\cdot}2H_2O$ (15.0 g, 96.1 mmol,10 eq.) dissolved in water (130 mL) was added. The solvent was degassed for 15 min by bubbling N_2 through the solution while sonicating, $Pd(OH)_2/C$ (0.41 g) and NH_4OH (20%, 5.49 mL, 28.8 mmol, 3.0 eq.) were added and the solution was further degassed for 10 min. Under vigorous stirring, a H_2 balloon was placed on top of the round bottom flask and the reaction mixture was stirred for 30 h at RT under H_2 until the reaction was complete. The catalyst was filtered with a paper filter and the residual solid washed with THF. The filtrate was removed *in vacuo* and the crude product was used in the next step without further purification (HPLC purity in acidic condition was 93%).

Compound (21): Compound **20** (7.07 g, 17.8 mmol, 1.0 eq.) was suspended in dioxane (350 mL) and 10% $NaHCO_3$ in water (340 mL) was added. The suspension was cooled to 0 °C and Fmoc-Cl (5.54 g, 21.4 mmol, 1.2 eq.) in dioxane (150 mL) was added dropwise over 1 h at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then stirred at RT for 13 h. The solvents were removed *in vacuo* and the resulting solid was suspended in water (500 mL). The suspension was acidified to pH 3 with a saturated $KHSO_4$ solution, extracted with DCM (3 x 500 mL) and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*, and the resulting solid was dried under vacuum to remove residual dioxane. The crude product was precipitated from acetonitrile (50 mL), sonicated to allow full precipitation, filtered and washed with cold acetonitrile (−14 °C). Precipitation from the filtrates and freeze-drying of the combined solids, yielded the title compound (6.18 g, 59%) as a white solid. **^{1}H NMR (500z MHz, DMSO-d_6):** δ [ppm] = 13.12 (s, 1H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.93 – 7.86 (m, 3H), 7.76 (s, 1H), 7.73 – 7.66 (m, 3H), 7.62 (d, *J* = 6.9 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 4.89 (d, *J* = 9.9 Hz, 2H), 4.84 (d, *J* = 6.1 Hz, 2H), 4.40 (d, *J* = 6.7 Hz, 2H), 4.26 (d, *J* = 6.7 Hz, 1H), 4.22 – 4.15 (m, 4H), 1.27 (t, *J* = 7.0 Hz, 6H). **^{13}C NMR (126 MHz, DMSO-d_6):** δ [ppm] = 165.3, 162.1 (*J* = 13.1Hz), 153.5, 146.7, 143.7, 140.8, 137.5, 135.8, 128.9, 127.8, 127.2, 125.2, 121.6, 120.3, 116.6, 114.2, 101.3, 65.3, 62.4 (d, *J* = 6.0 Hz), 61.9 (d, *J* = 164.1 Hz), 46.8, 40.6, 16.3 (d, *J* = 5.4 Hz).**HRMS** (ESI$^+$) *m/z* calcd. for $C_{31}H_{31}N_2O_8P$: 591.1891 $[M+H]^+$; found: 591.2121.

3.3 Oligomer synthesis procedures

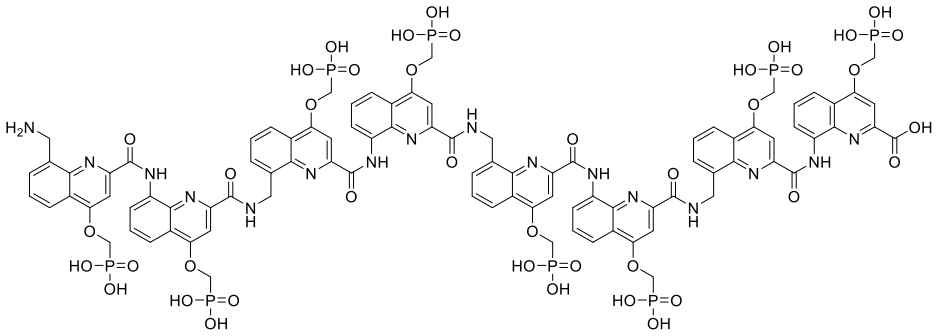
Oligomers **2**–**7** were synthesized according to previously reported SPS protocols,[11,12a,28] see Scheme S3. Oligomers **8**–**9** and oligomers **10**–**11** were synthesized following Schemes S4 and Scheme S5, respectively. Oligomers **12**–**13** were synthesized by recently reported automated SPS procedures.[12b] Fmoc acid building blocks were activated *in situ* by generating the respective acid chlorides prior to coupling.

Acetylation: The resin (1.0 equiv.) was washed with DCM (3 x 3 mL) and incubated in Ac_2O/DCM (1:1 v:/v) for 10 min. Then, the resin was washed with DCM (2 x 3 mL) and DMF (3 x 3 mL).

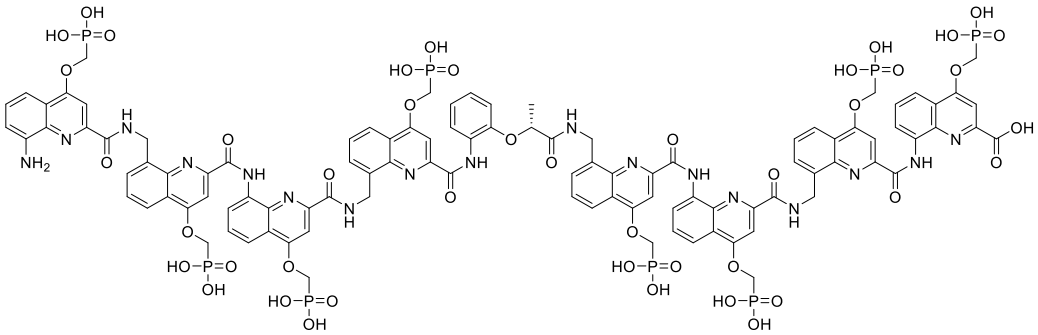
Resin cleavage and Preparative HPLC purification: The resin-bound oligomer was placed in a syringe equipped with a filter, washed with DMF (3 x 3 mL), DCM (3 x 3 mL), and dried by passing N_2 flow through it. It was then suspended in a solution of TFA. The resin was next shaken for at least

2 h at RT and then filtered off and washed one time with TFA. The combined solvent was removed in vacuo. After precipitation in cold Et_2O, the crude oligomer with protecting groups was purified by semi prep RP-HPLC under acidic condition to give the oligomer as a yellow solid.

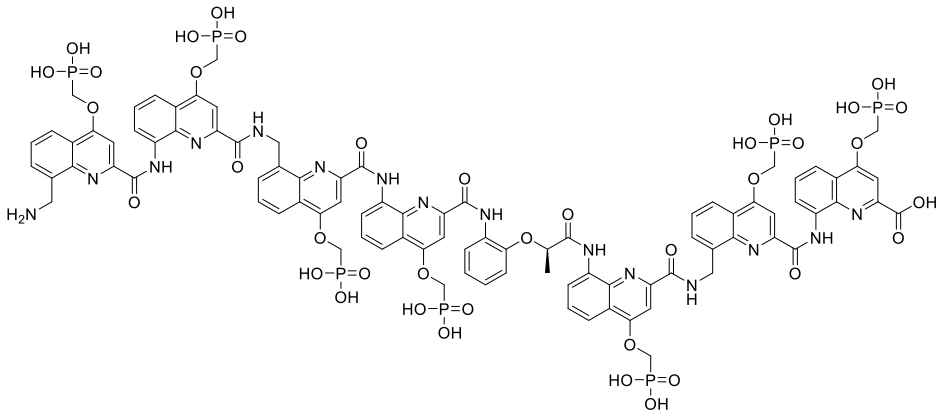
Synthesis of water-soluble oligomers: The previously purified oligomer was treated by TMSBr to remove the ethyl groups. Subsequently, the crude was purified by semi prep RP-HPLC under basic conditions (as described in section 3.1) to give the oligomer as a yellow solid. Following this, an ion exchange process was performed to obtain the side chains as water-soluble ammonium phosphonate salts. The removal of ethyl phosphonate protecting groups and ion exchange were performed as previously described.[1a]



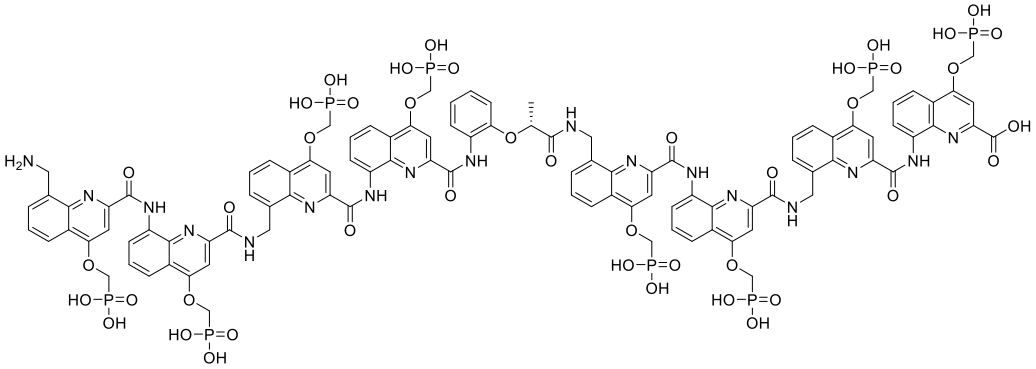
Oligomer (1): The ^{1}H NMR spectrum of **1** in Figure S1 matched with that described.[1a]



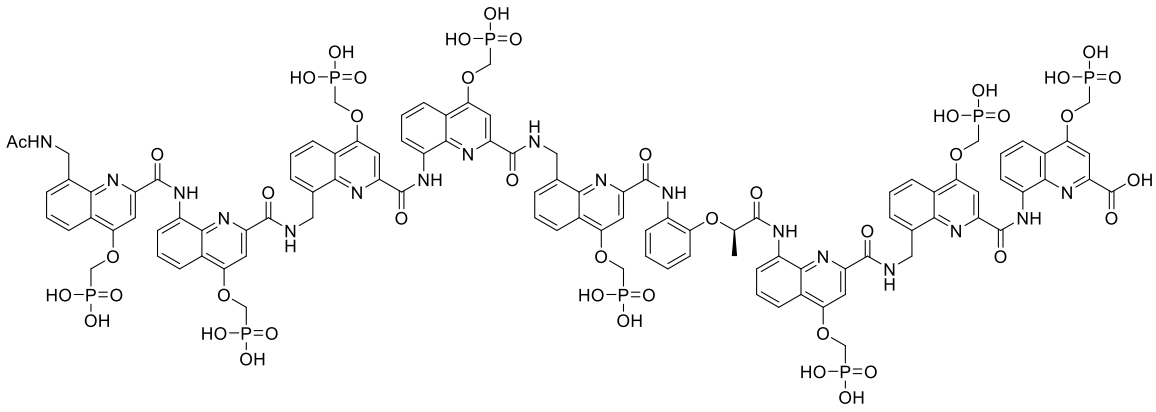
Oligomer (2): Oligomer **2** was synthesized on Wang resin (0.41 mmol g^{-1}, 30 µmol scale) following procedures reported previously.[11,12a,28] After ion exchange, the title compound was obtained as a light yellow solid (10 mg, 15%; HPLC-purity: >99%).**^{1}H NMR (500 MHz, H_2O/D_2O 9:1): amide NHs** δ [ppm] = 11.93 (s, 1H), 11.14 (s, 1H), 11.06 (s, 1H), 9.24 (s, 1H), 9.15 (s, 1H), 8.98 (d, *J* = 8.5 Hz, 1H), 8.86 (d, *J* = 11.9 Hz, 1H), 8.56 (dd, *J* = 15.9, 9.6 Hz, 1H); **aromatic CHs** δ [ppm] =8.39 (d, *J* = 9.4 Hz), 8.22 (d, *J* = 9.8 Hz), 8.18 – 8.12 (m), 8.02-7.92 (m), 7.79 (dd, *J* = 11.9, 8.7 Hz), 7.69 (d, *J* = 12.3 Hz), 7.58 (dd, *J* = 13.5, 8.8 Hz), 7.43-7.33 (m), 7.31 – 7.21 (m), 7.23 – 7.03 (m), 6.72 (t, *J* = 8.8 Hz), 6.67 (s), 6.60 (s), 6.53 (d, *J* = 6.1 Hz), 6.47 (s), 6.32 (s); **aliphatic CHs** δ [ppm] = 5.50 (s), 4.17 – 3.83 (m), 3.76 (t, *J* = 10.2 Hz), 3.71 (s), 3.29 (s), 3.10 – 2.88 (m), 2.00 (s), 1.32 – 1.12 (m), 0.21 (s). **HRMS** (ESI) *m/z* calcd. for: $C_{101}H_{91}N_{17}O_{43}P_8$: 1238.1623 $[M-2H]^{2-}$; found: 1238.2223.



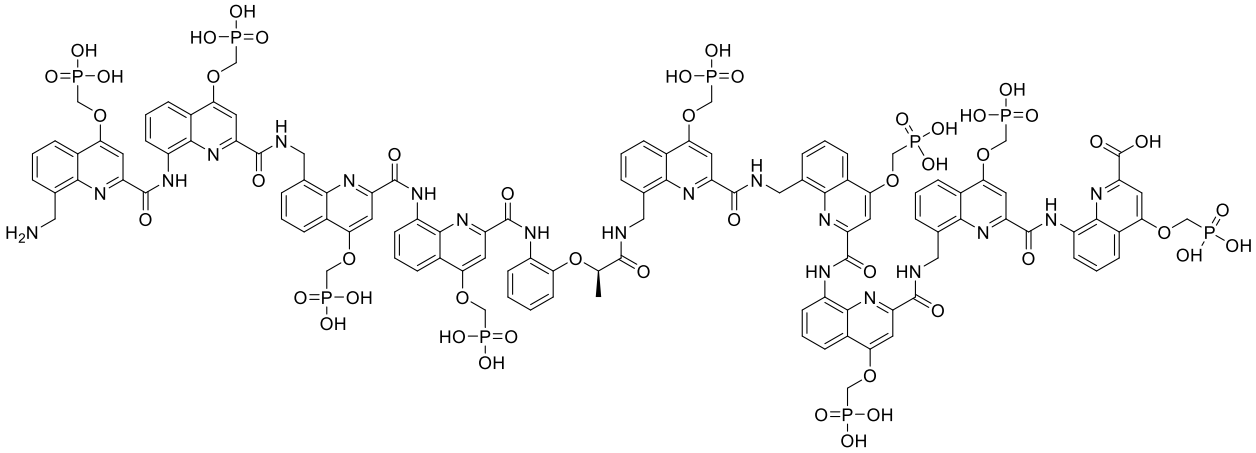
Oligomer (3): Oligomer **3** was synthesized on Wang resin (0.41 mmol g^{-1}, 30 µmol scale) following procedures reported previously.[11,12a,28] After ion exchange, the title compound was obtained as a light yellow solid (10 mg, 15%; HPLC-purity: >97%).**^{1}H NMR (500 MHz, H_2O/D_2O 9:1): amide NHs** δ [ppm] = 11.35 (s, 1H), 11.14 (s, 1H), 10.60 (s, 1H), 9.80 (d, *J* = 9.4 Hz, 2H), 9.67 (d, *J* = 9.4 Hz, 1H), 9.54 (s, 1H) , 8.46 (d, *J* = 9.2 Hz, 1H); **aromatic CHs** δ [ppm] = 8.26 – 8.18 (m), 8.07 (d, *J* = 8.6 Hz), 7.89 – 7.75 (m), 7.78 (d, *J* = 8.6 Hz), 7.67 (d, *J* = 9.2 Hz), 7.65 – 7.56 (m), 7.54 – 7.47 (m), 7.50 – 7.42 (m), 7.45 – 7.37 (m), 7.24 (t, *J* = 8.4 Hz), 7.17 (q, *J* = 9.0 Hz), 7.07 (s, 1H), 7.01 (t, *J* = 8.4 Hz), 6.98 – 6.92 (m), 6.84 (d, *J* = 8.0 Hz), 6.48 (d, *J* = 9.3 Hz), 6.36 (s), 6.08 (s); **aliphatic CHs** δ [ppm] = 4.25 – 4.06 (m), 3.96 (s), 3.94 – 3.79 (m), 2.63 - 2.59 (m), 2.22 (s), 1.35 – 1.22 (m), 0.17 (s). **HRMS** (ESI^-) *m/z* calcd. for: $C_{89}H_{80}N_{15}O_{38}P_7$: 1090.6403 $[M-2H]^{2-}$; found: 1090.6515.



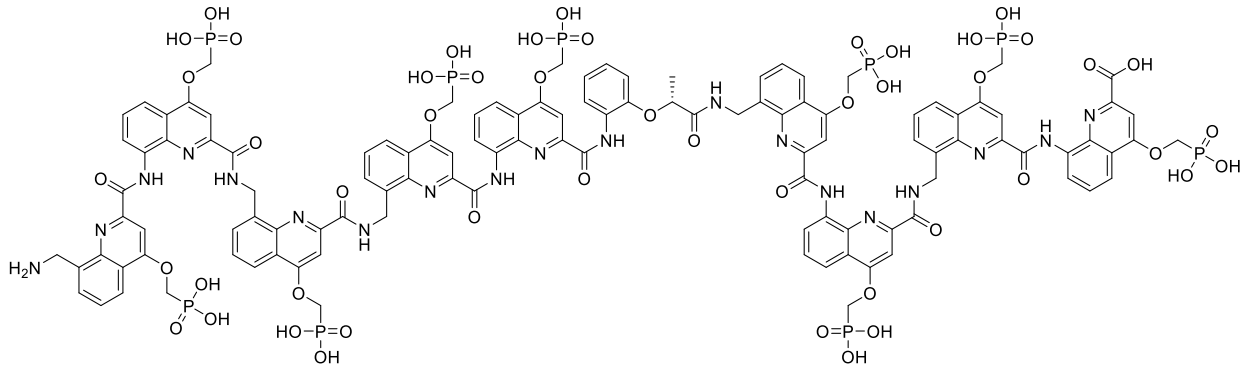
Oligomer (4): Oligomer **4** was synthesized on Wang resin (0.41 mmol g^{-1}, 30 µmol scale) following procedures reported previously.[11,12a,28] After ion exchange, the title compound was obtained as a light yellow solid (15 mg, 15%; HPLC-purity: >98%).**^{1}H NMR (500 MHz, H_2O/D_2O 9:1): amide NHs** δ [ppm] = 11.57 (s, 1H), 11.13 (s, 1H), 10.74 (s, 1H), 10.39 (s, 1H), 9.61 (s, 2H), 9.28 (s, 1H), 8.49 (d, *J* = 9.1 Hz, 1H); **aromatic CHs** δ [ppm] = 8.13 (d, *J* = 8.1 Hz), 8.05 – 8.00 (m), 7.97 (d, *J* = 8.9 Hz), 7.84 – 7.69 (m), 7.61 (d, *J* = 8.8 Hz), 7.58 (d, *J* = 6.1 Hz), 7.51 – 7.24 (m), 7.19 (s), 7.04 – 6.51 (m), 6.41 (s); **aliphatic CHs** δ [ppm] = 5.49 – 5.46 (m), 4.86 – 4.78 (m), 4.78 (s), 4.27 (s), 4.09 (d, *J* = 10.2 Hz), 3.98 (s), 3.86 (d, *J* = 14.3 Hz), 3.78 (d, *J* = 14.7 Hz), 3.75 – 3.67 (m), 3.63 – 3.55 (m), 3.32 – 3.24 (m), 3.12 – 2.59 (m), 2.21 (s), 2.05 (s), 1.33 – 1.21 (m), -0.40 (d, *J* = 6.9 Hz). **HRMS** (ESI^-) *m/z* calcd. for: $C_{101}H_{91}N_{17}O_{43}P_8$: 1238.1623 $[M-2H]^{2-}$; found: 1238.2073.



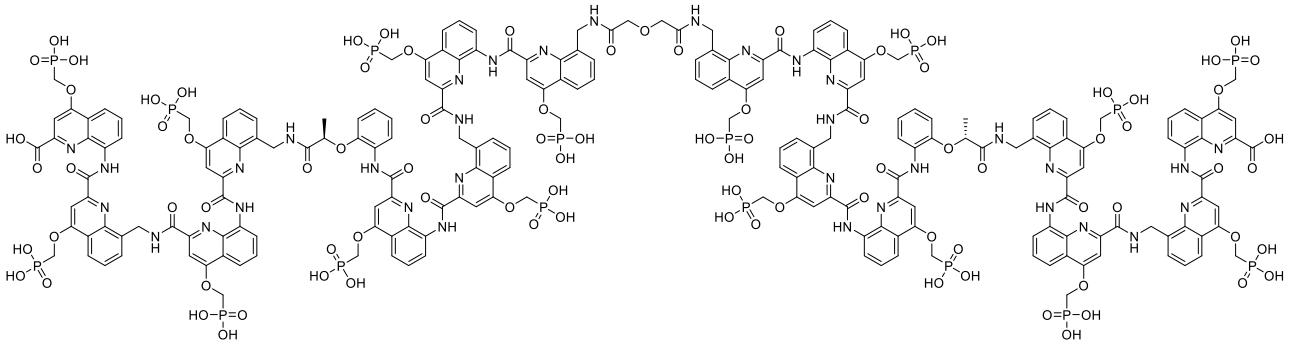
Oligomer (5): Oligomer **5** was synthesized on Wang resin (0.41 mmol g^{-1}, 30 µmol scale) following procedures reported previously.[11,12a,28] After ion exchange, the title compound was obtained as a light yellow solid (7 mg, 12%; HPLC-purity: >97%).**^{1}H NMR (500 MHz, H_2O/D_2O 9:1): amide NHs** δ [ppm] = 11.48 (s, 1H), 11.37 (s, 1H), 10.73 (s, 1H), 9.85 (s, 1H), 9.80 (d, *J* = 8.5 Hz, 1H), 9.73 (d, *J* = 9.3 Hz, 1H), 9.68 (d, *J* = 9.5 Hz, 1H), 9.04 (s, 1H), 8.40 (d, *J* = 9.2 Hz,1H); **aromatic CHs** δ [ppm] = 8.31 (d, *J* = 8.4 Hz), 8.11 (m), 8.02 (d, *J* = 8.6 Hz), 7.96 – 7.90 (m), 7.75 – 7.66 (m), 7.63 (d, *J* = 7.6 Hz), 7.51 – 7.44 (m), 7.37 – 7.23 (m), 7.17 – 7.06 (m), 6.96 (s), 6.83 – 6.79 (m), 6.77 (s), 6.69 – 6.64 (m), 6.57 – 6.52 (m), 6.31 – 6.27(m), 6.14 – 6.10 (m), 6.02 – 5.98 (m); **aliphatic CHs** δ [ppm] = 4.22 – 3.79 (m), 3.64 – 3.47 (m), 3.09 – 3.01 (m), 2.85 – 2.60 (m), 1.29 (s), 1.26 –1.22 (m), 0.30 (d, *J* = 6.6 Hz). **HRMS** (ESI^-) *m/z* calcd. for: $C_{103}H_{93}N_{17}O_{44}P_8$: 1259.1675 $[M-2H]^{2-}$; found: 1259.1859.



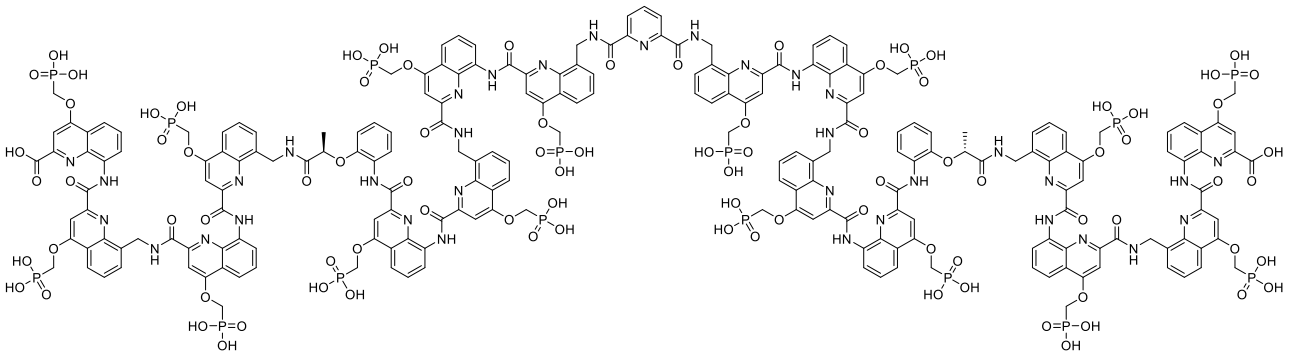
Oligomer (6): Oligomer **6** was synthesized on Wang resin (0.41 mmol g^{-1}, 30 µmol scale) following procedures reported previously.[11,12a,28] After ion exchange, the title compound was obtained as a light yellow solid (5 mg, 10%; HPLC-purity: >98%).**^{1}H NMR (500 MHz, H_2O/D_2O 9:1): amide NHs** δ [ppm] = 11.54 (s, 1H), 11.18 (s, 1H), 10.88 (s, 1H), 10.24 (s, 1H), 9.78 (t, *J* = 9.9 Hz, 2H), 9.24 (s, 1H), 8.84 (t, *J* = 4.8 Hz, 1H), 8.47 (d, *J* = 9.3 Hz, 1H); **aromatic CHs** δ [ppm] = 8.41 – 8.38 (m), 8.22 (d, *J* = 8.3 Hz), 8.17 (d, *J* = 9.0 Hz), 7.95 (d, *J* = 8.8 Hz), 7.75 (d, *J* = 8.5 Hz), 7.70 (d, *J* = 9.4 Hz), 7.59 – 7.26 (m), 7.24 (s), 7.13 – 6.75 (m), 6.65 (d, *J* = 5.5 Hz), 6.55 – 6.51 (m), 6.37 (d, *J* = 8.1 Hz); **aliphatic CHs** δ [ppm] = 5.78 (s), 5.58 (d, *J* = 9.4 Hz), 4.43 – 4.21 (m), 4.16 – 3.88 (m), 3.76 – 3.66 (m), 3.60 (s), 3.57 – 2.44 (m), 1.36 (s, 1H), 1.31 – 1.27 (m), -0.50 (d, *J* = 7.4 Hz). **HRMS** (ESI^-) *m/z* calcd. for: $C_{113}H_{102}N_{19}O_{48}P_9$: 1385.1825 $[M-2H]^{2-}$; found: 1385.2034.



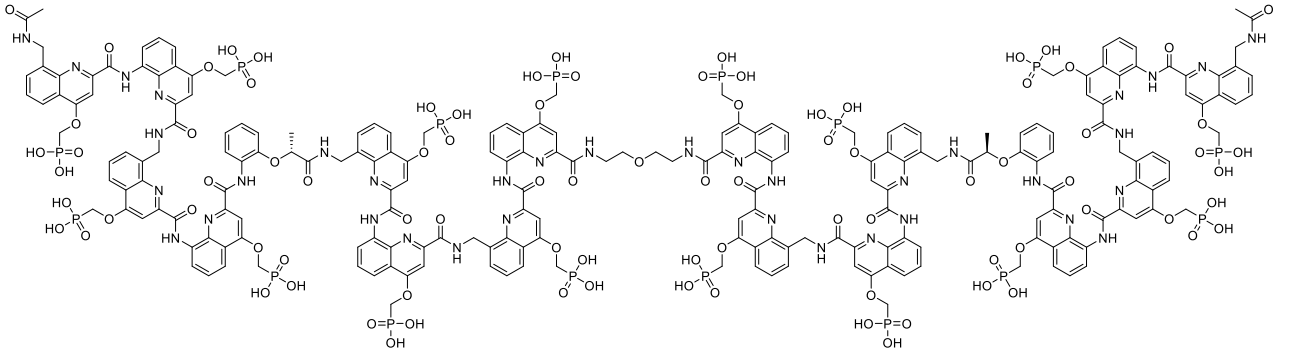
Oligomer (7): Oligomer **7** was synthesized on Wang resin (0.41 mmol g^{-1}, 30 µmol scale) following procedures reported previously.[11,12a,28] After ion exchange, the title compound was obtained as a light yellow solid (5 mg, 10%; HPLC-purity: >95%).**^{1}H NMR (500 MHz, H_2O/D_2O 9:1): amide NHs** δ [ppm] = 11.58 (s, 1H), 11.27 (s, 1H), 10.70 (s, 1H), 10.32 (d, *J* = 7.6 Hz, 1H), 10.25 (s, 1H), 9.42 (d, *J* = 9.7 Hz, 1H), 9.17 – 9.10 (m, 2H), 8.43 –8.39 (m, 2H); **aromatic CHs** δ [ppm] = 8.37 – 8.33 (m), 8.13 – 8.00 (m), 7.90 – 7.82 (m), 7.80 – 7.48 (m), 7.43 – 7.29 (m), 7.25 – 7.14 (m), 7.10 – 7.04 (m), 7.00 – 6.92 (m), 6.88 – 6.78 (m), 6.75 – 6.65 (m), 6.52 (s), 6.49 – 6.45 (m), 6.38 (s), 6.34 –6.30 (m), 5.99 (s); **aliphatic CHs** δ [ppm] = 5.46 –5.42 (m), 4.35 – 4.26 (m), 4.22 – 4.05 (m), 4.01 – 3.92 (m), 3.83 – 3.70 (m), 3.70 – 3.60 (m), 3.42 – 3.17 (m), 3.09 – 2.99 (m), 2.77 – 2.69 (m), 1.98 (s), 1.35 – 1.29 (m), 1.28 – 1.24 (m), -0.58 (d, *J* = 7.6 Hz). **HRMS** (ESI^-) *m/z* calcd. for: $C_{113}H_{102}N_{19}O_{48}P_9$: 1385.1825 $[M-2H]^{2-}$; found: 1385.2080.



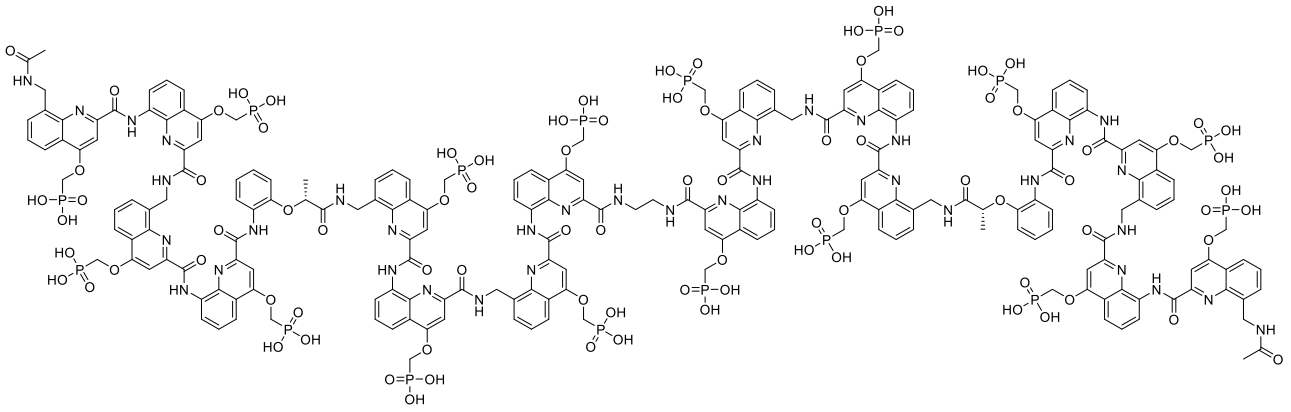
Oligomer (8): Fragment A (24 mg, 8.2 µmol, 2.0 equiv.) was dissolved in 1.35 mL DMF under N_2, DIPEA (17.1 µL, 6.0 eq) was added and wait for 15 min. 270 µL of the linker solution composed of bis(2,5-dioxopyrrolidin-1-yl) 2,2'-oxydiacetate were added dropwise over 40 min (a stock solution was prepared by dissolving 2 mg of the linker in 400 µL of DMF). The reaction mixture was stirred at RT for 2 h and monitored by RP-HPLC. The crude was lyophilized and purified on semi-preparative RP-HPLC with a gradient from 70% to 100% solvent B over 15 min at 50 °C (A: water + 0.1% TFA and B: acetonitrile + 0.1% TFA). After RP-HPLC purification, the protected precursor of **8** was obtained as a light yellow solid (12 mg, 50%; HPLC-purity: >97%). After removal of ethyl phosphonate groups and ion exchange, oligomer **8** was obtained as a light yellow solid (9 mg, 20%; HPLC-purity: >98%). ^{1}H **NMR (500 MHz, H_2O/D_2O 9:1): amide NHs** δ [ppm] = 11.52 (s, 1H), 10.57 (s, 1H), 9.96 (s, 1H), 9.79 (s, 1H), 9.26 (s, 1H), 9.03 (s, 1H), 8.78 (d, *J* = 13.9 Hz, 1H), 8.09 (m, 1H); **aromatic CHs** δ [ppm] = 8.10 (m), 8.04 (m), 7.87 – 7.77 (m), 7.71 (m), 7.60 (m), 7.58 – 7.47 (m), 7.45 – 7.15 (m), 7.09 – 6.94 (m), 6.77 – 6.65 (m), 6.59 (m), 6.54 (m), 6.43 (m), 6.31 (s, 1H), 6.26 (s), 5.91 (m); **aliphatic CHs** δ [ppm] = 5.43 (m), 4.26 – 4.18 (m), 4.12 (m), 4.11 – 3.80 (m), 3.79 – 3.64 (m), 3.60 – 3.46 (m), 3.30 (s), 2.78 (s), 2.59 (m), 1.34 – 1.21 (m), 0.33 (m), -0.20 (d, *J* = 14.9 Hz), -0.49 (d, *J* = 7.7 Hz). **HRMS** (ESI^-) *m/z* calcd. for: $C_{206}H_{184}N_{34}O_{89}P_{16}$: 1683.8856 $[M-3H]^{3-}$; found: 1683.8949.



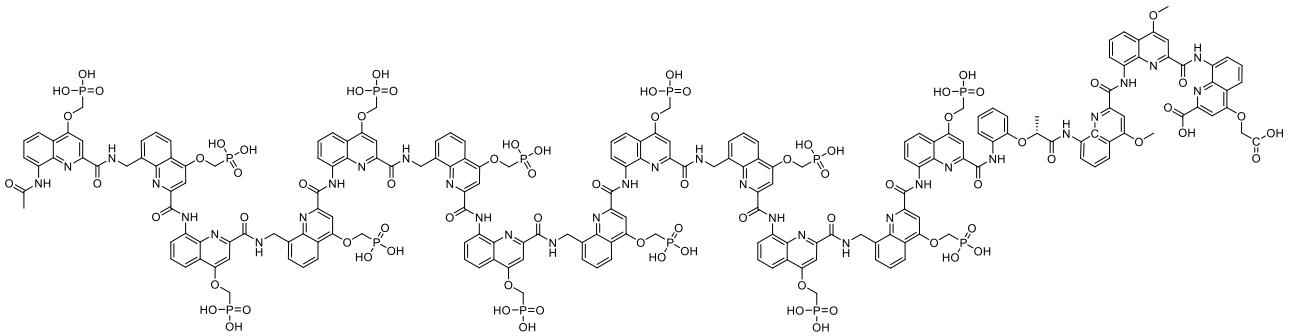
Oligomer (9): By using 2,6-bis(2,5-dioxo-1-pyrrolidinyl) 2,6-pyridinedicarboxylate as a linker, oligomer **9** was synthesized as previously described for oligomer **8**. After removal of ethyl phosphonate groups and ion exchange, oligomer **9** was obtained as a light yellow solid (9 mg, 19%; HPLC-purity: >98%). **^{1}H NMR (500 MHz, H_2O/D_2O 9:1): amide NHs** δ [ppm] = 11.49 (s, 1H), 10.53 (s, 1H), 9.90 (s, 1H), 9.47 (s, 1H), 9.27 – 9.21 (m, 1H), 8.96 (s, 1H), 8.64 (d, *J* = 10.4 Hz, 1H), 8.52 (d, *J* = 6.9 Hz, 1H), 8.11 (m,1H); **aromatic CHs** δ [ppm] = 8.01 (m), 7.80 (m), 7.69 (m), 7.57 (m), 7.53 (m), 7.47 (m), 7.41 – 7.28 (m), 7.26 – 7.12 (m), 6.97 (m), 6.85 – 6.76 (m, 2H), 6.73 (s), 6.68 (s), 6.57 (m), 6.51 (m), 6.43 (m), 6.37 (s), 6.30 – 6.22 (m); **aliphatic CHs** δ [ppm] = 5.92 (s), 5.63 (m), 4.10 (m), 4.04 (s), 4.01 (m), 3.93 – 3.84 (m), 3.80 (m), 3.69 (m), 3.47 (m), 3.36 – 3.25 (m), 3.15 – 3.07 (m), 2.79 (m), 2.58 (s, 1H), 1.33 – 1.21 (m), -0.47 (d, *J* = 7.5 Hz). **HRMS** (ESI^-) *m/z* calcd. for: $C_{209}H_{183}N_{35}O_{88}P_{16}$: 1694.8857 $[M-3H]^{3-}$; found: 1694.9024.



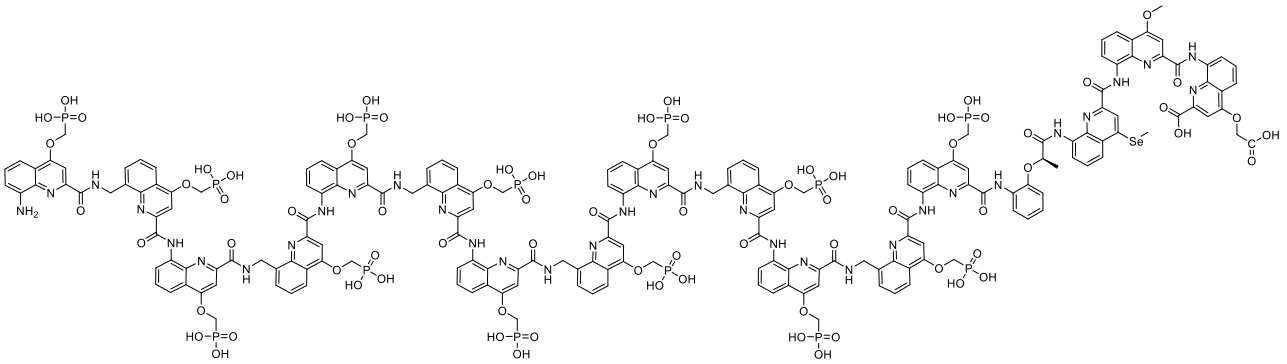
Oligomer (10): Fragment B (12 mg, 4 µmol, 2.0 equiv.) was dissolved in DMF (1.35 mL) under N_2, DIPEA (4.18 µL, 6.0 eq) and PyBOP (6.24 mg, 3.0 eq) were added and wait for 15 min. 100 µL of the linker solution composed of 2,2'-oxydiethanamine were added dropwise over 40 min (a stock solution was prepared by dissolving 21.5 µL of the linker in 1 mL of DMF). The reaction mixture was stirred at RT for 2 h and monitored by RP-HPLC. The crude was lyophilized and purified on semi-preparative RP-HPLC with a gradient from 30% to 100% solvent B over 20 min at 50 °C (A: water + 0.1% TFA and B: acetonitrile + 0.1% TFA). After RP-HPLC purification, the protected precursor of **10** was obtained as a light yellow solid (6 mg, 50%; HPLC-purity: >99%). After removal of ethyl phosphonate groups and ion exchange, oligomer **10** was obtained as a light yellow solid (4.8 mg, 95%; HPLC-purity: >99%). **^{1}H NMR (500 MHz, H_2O/D_2O 9:1): amide NHs** δ [ppm] =11.26 (s, 1H), 10.36 (s, 1H), 10.19 (s, 1H), 9.68 (d, *J* = 15.2 Hz, 2H), 9.57 (d, *J* = 7.9 Hz, 1H), 9.13 (s, 1H), 8.24 (d, *J* = 9.1 Hz, 1H); **aromatic CHs** δ [ppm] = 7.79 – 7.46 (m), 7.39 – 7.29 (m), 7.26 (m), 7.18 – 7.05 (m), 6.95 (m), 6.72 (m), 6.64 (s), 6.58 (m), 6.52 (m), 6.43 (m), 6.26 (m); **aliphatic CHs** δ [ppm] = 4.08 (m), 4.00 (m), 3.93 (m), 3.63 (m), 3.44 (m), 3.31 (m), 3.18 (m), 2.91 (m), 2.81 (m), 2.73 – 2.65 (m), 2.37 (m), 1.34 – 1.23 (m), 1.19 (s), 1.16 (m), -0.64 (d, *J* = 7.6 Hz). **HRMS** (ESI^-) *m/z* calcd. for: $C_{210}H_{194}N_{36}O_{87}P_{16}$: 1701.9171 $[M-3H]^{3-}$; found: 1702.0112.



Oligomer (11): By using ethylenediamine as a linker, oligomer **11** was synthesized as above described for oligomer **10**. After removal of ethyl phosphonate groups and ion exchange, oligomer **11** was obtained as a light yellow solid (5.6 mg, 17%; HPLC-purity: >98%).**^{1}H NMR (500 MHz, H_2O/D_2O 9:1): amide NHs** δ [ppm] = 11.06 (s, 1H), 10.30 (s, 1H), 10.24 (s, 1H), 9.65 (d, *J* = 8.8 Hz, 1H), 9.44 (s, 1H), 9.37 (d, *J* = 9.6 Hz, 1H), 9.19 (s, 1H), 8.29 (d, *J* = 9.3 Hz, 1H); **aromatic CHs** δ [ppm] =7.99 (m), 7.94 (m), 7.81 (s), 7.82 – 7.75 (m), 7.69 (m), 7.63 (m), 7.58 (m), 7.51 – 7.41 (m), 7.39 (m), 7.33 (m), 7.24 – 7.14 (m), 7.12 – 7.00 (m), 6.85 (m), 6.81 (m), 6.75 (m), 6.67 (m), 6.59 (m), 6.49 – 6.40 (m), 6.38 (m), 6.14 (tm), 5.95 (s); **aliphatic CHs** δ [ppm] = 4.37 – 4.30 (m), 4.07 (m), 3.86 (m), 3.72 (m), 3.47 (m), 3.25 – 3.13 (m), 3.12 (s), 2.99 – 2.86 (m), 2.33 (m), 1.34 – 1.22 (m), 1.17 (m), -0.53 (d, *J* = 7.6 Hz). **HRMS** (ESI^-) *m/z* calcd. for: $C_{208}H_{190}N_{36}O_{86}P_{16}$: 1687.6663 $[M-3H]^{3-}$; found: 1687.6642.



Oligomer (12): Oligomer **12** was synthesized on Wang resin (0.41 mmol g^{-1}, 30 µmol scale) following recently reported procedures.[12b] After removal of the diethylphosphonate groups (scale: 6.39 µmol), the title compound was purified using a linear gradient of 0-15 B in A (A: 12.5 mmol NH_4OAc, B: acetonitrile), then lyophilized and obtained as a light yellow solid (17.7 mg, 62%; HPLC-purity: >99%).**^{1}H NMR (500 MHz, H_2O/D_2O 9:1): amide NHs** δ [ppm] = 11.90 (s, 1H), 11.22 (s, 1H), 10.66 (s, 1H), 10.21 – 10.16 (m, 2H), 9.94 (s, 1H), 9.80 (s, 1H), 9.65 (s, 1H), 9.63 – 9.57 (m, 2H), 9.49 (s, 1H), 9.39 (s, 1H), 9.28 (d, *J* = 8.2 Hz, 1H), 9.04 (d, *J* = 8.3 Hz, 1H), 9.01 (s, 1H), 8.94 (d, *J* = 9.6 Hz, 1H), 8.83 (d, *J* = 8.7 Hz, 1H); **aromatic CHs** δ [ppm] = 8.43 (d, *J* = 9.0 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 8.06 – 8.00 (m, 4H), 7.96 (d, *J* = 9.1 Hz, 3H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.71 – 7.54 (m, 6H), 7.54 – 7.46 (m, 3H), 7.47 – 7.38 (m, 3H), 7.34 – 7.25 (m, 3H), 7.25 – 7.19 (m, 2H), 7.17 – 7.11 (m, 4H), 7.08 (d, *J* = 8.1 Hz, 1H), 7.05 – 6.93 (m, 10H), 6.93 – 6.84 (m, 4H), 6.81 – 6.74 (m, 2H), 6.71 (d, *J* = 8.3 Hz, 1H), 6.65 – 6.56 (m, 6H), 6.56 – 6.43 (m, 10H), 6.39 (t, *J* = 8.3 Hz, 1H), 6.34 (s, 1H), 6.32 – 6.26 (fm, 4H), 6.18 (s, 3H), 6.14 (s, 1H), 6.03 (d, *J* = 7.2 Hz, 3H); **aliphatic CHs** δ [ppm] = 4.05 – 3.85 (m, 6H), 3.81 – 3.44 (m, 10H), 3.43 – 3.15 (m, 2H), 2.83 – 2.70 (m, 1H), 2.70 – 2.60 (m, 1H), 2.59 – 2.51 (m, 1H), 2.41 – 2.30 (m, 1H), -0.08 (d, *J* = 6.8 Hz, 3H). **HRMS** (ESI^-) *m/z* calcd. for: $C_{194}H_{163}N_{33}O_{77}P_{13}^{3-}$ $[M-3H]^{3-}$: 1530.2175; found: 1530.2348.



Oligomer (13): Oligomer **13** was synthesized on Wang resin (0.41 mmol g^{-1}, 30 µmol scale) following recently reported procedures.[12b] After removal of the diethylphosphonate groups (scale: 3.74 µmol), the title compound was purified using a linear gradient of 0-15 B in A (A: 12.5 mmol NH_4OAc, B: acetonitrile), then lyophilized and obtained as a light yellow solid (7.13 mg, 41%; HPLC-purity: >98%). **^{1}H NMR (500 MHz, H_2O/D_2O 9:1): amide NHs** δ [ppm] = 11.93 (s, 1H), 11.19 (s, 25H), 10.92 (s, 1H), 10.20 (s, 1H), 10.17 (s, 1H), 9.97 (s, 1H), 9.88 (s, 1H), 9.80 (s, 1H), 9.68 (s, 1H), 9.55 (s, 1H), 9.34 (s, 1H), 9.29 (s, 1H), 9.21 (d, *J* = 7.7 Hz, 1H), 8.94 (d, *J* = 7.9 Hz, 1H), 8.80 (d, *J* = 8.3 Hz, 1H), 8.71 (d, *J* = 7.8 Hz, 1H); **aromatic CHs** δ [ppm] = 8.42 – 8.32 (m, 2H), 8.15 – 7.96 (m, 7H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.64 – 7.48 (m, 6H), 7.47 – 7.29 (m, 5H), 7.24 (d, *J* = 8.7 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.10 – 6.92 (m, 12H), 6.91 – 6.84 (m, 1H), 6.81 – 6.39 (m, 12H), 6.34 (s, 1H), 6.30 (s, 1H), 6.25 (s, 1H), 6.20 (d, *J* = 8.7 Hz, 3H), 6.05 (s, 1H), 6.00 (s, 1H); **aliphatic CHs** δ [ppm] = 4.09 (s, 2H), 4.03 – 3.32 (m, 20H), 2.69 – 2.45 (m, 2H), -0.03 (d, *J* = 6.8 Hz, 3H). **HRMS** (ESI^-) *m/z* calcd. for: $C_{192}H_{161}N_{33}O_{75}P_{13}Se^{3-}$ $[M-3H]^{3-}$: 1537.5212; found: 1537.6029.

4. NMR spectra and HPLC chromatograms

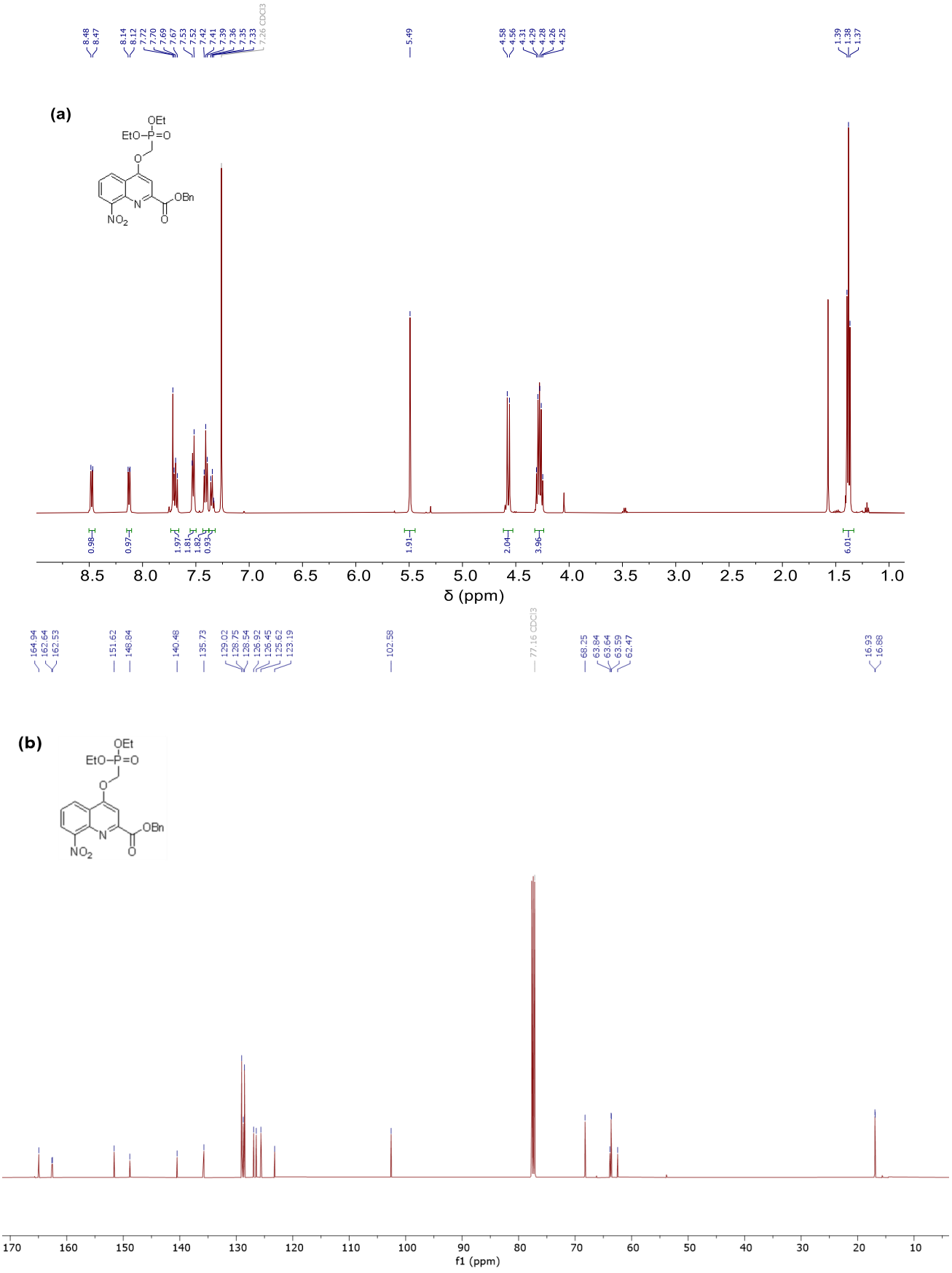


Figure S10. NMR spectra of compound **15**. (a) ^{1}H NMR (500 MHz, $CDCl_3$). (b) ^{13}C NMR (126 MHz, $CDCl_3$).

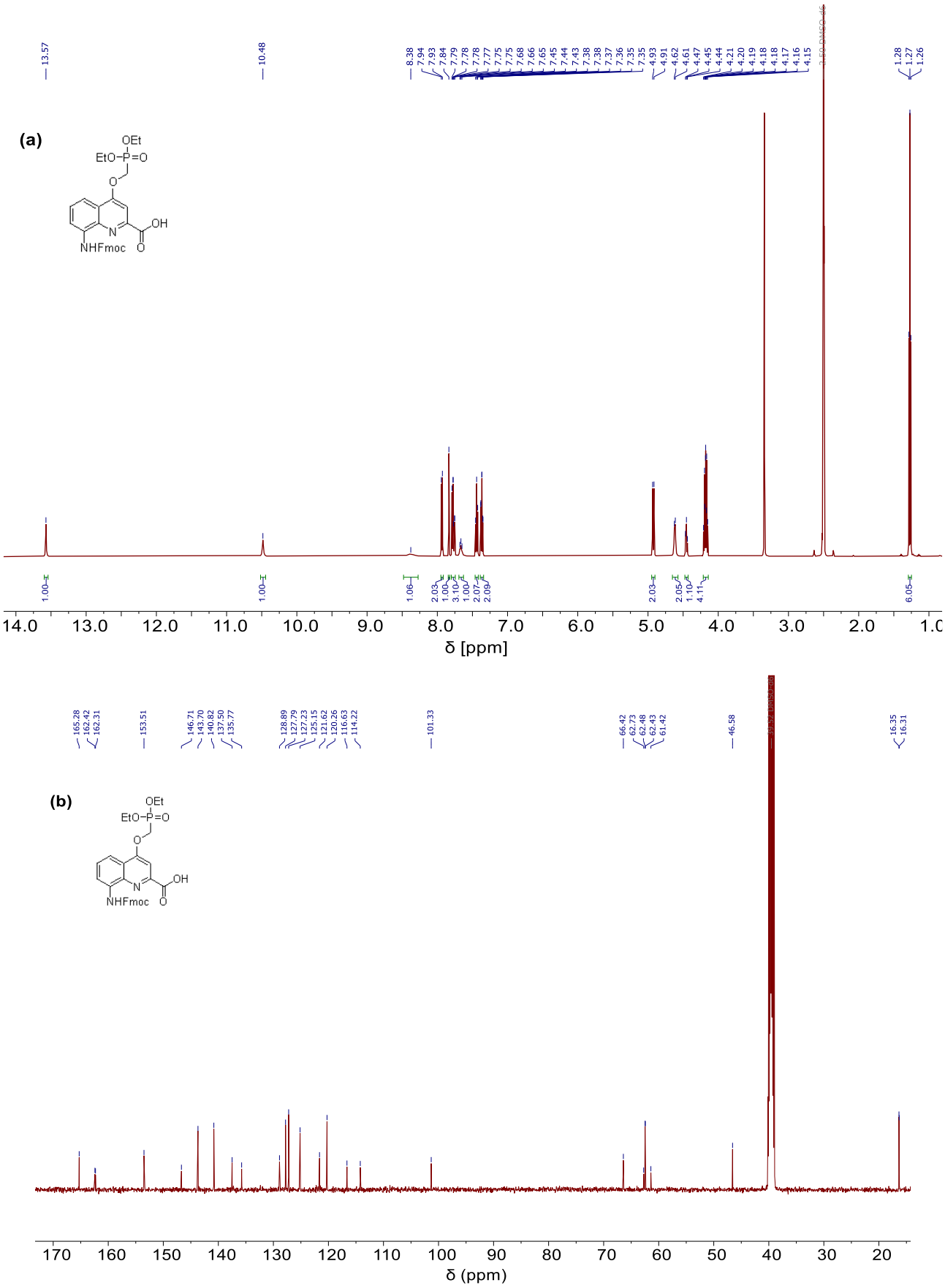


Figure S11. NMR spectra of compound **17**. (a) ^{1}H NMR (500 MHz, DMSO-d_6). (b) ^{13}C NMR (126 MHz, DMSO-d_6).

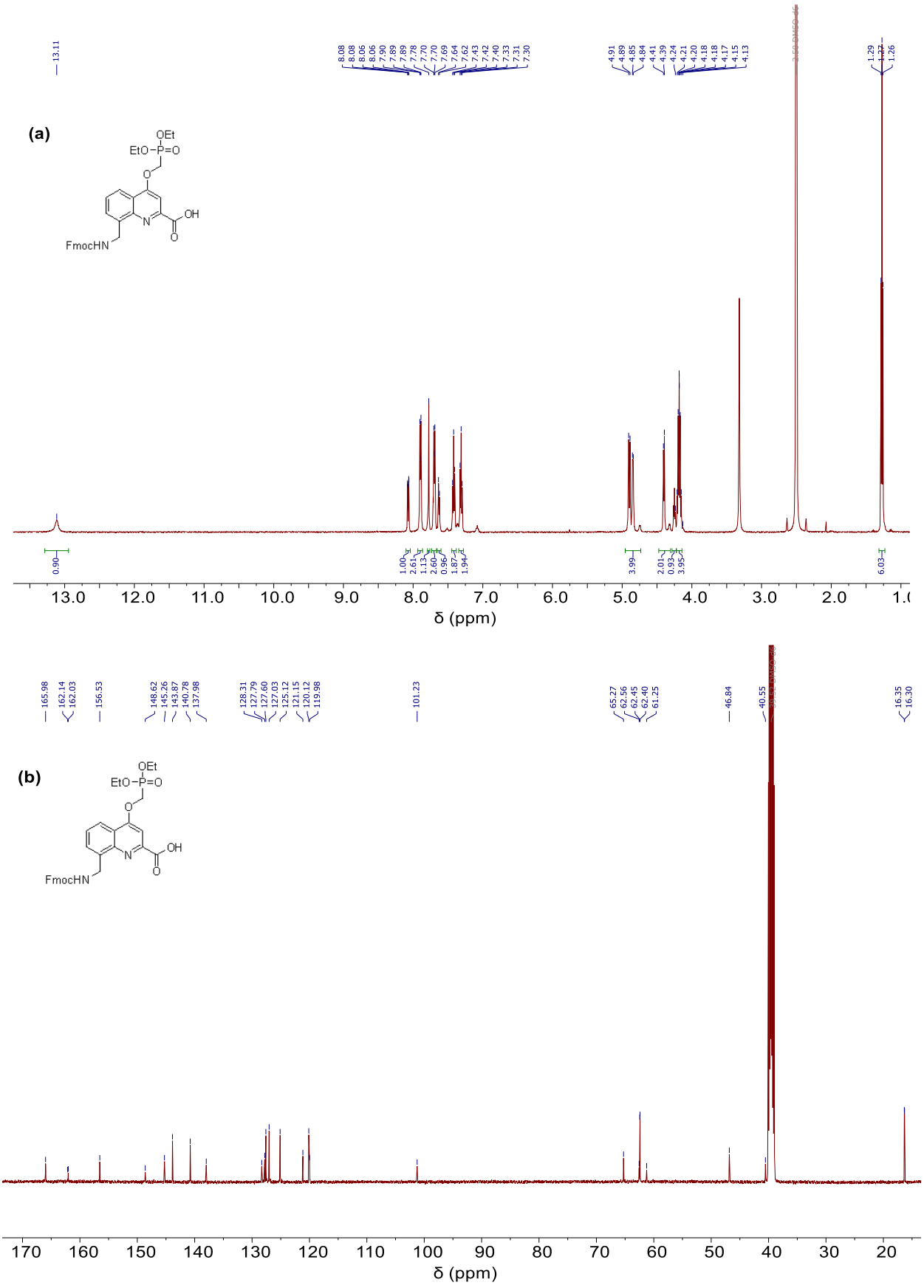


Figure S12. NMR spectra of compound **21**. (a) ^{1}H NMR (500 MHz, DMSO-d_6). (b) ^{13}C NMR (126 MHz, DMSO-d_6).

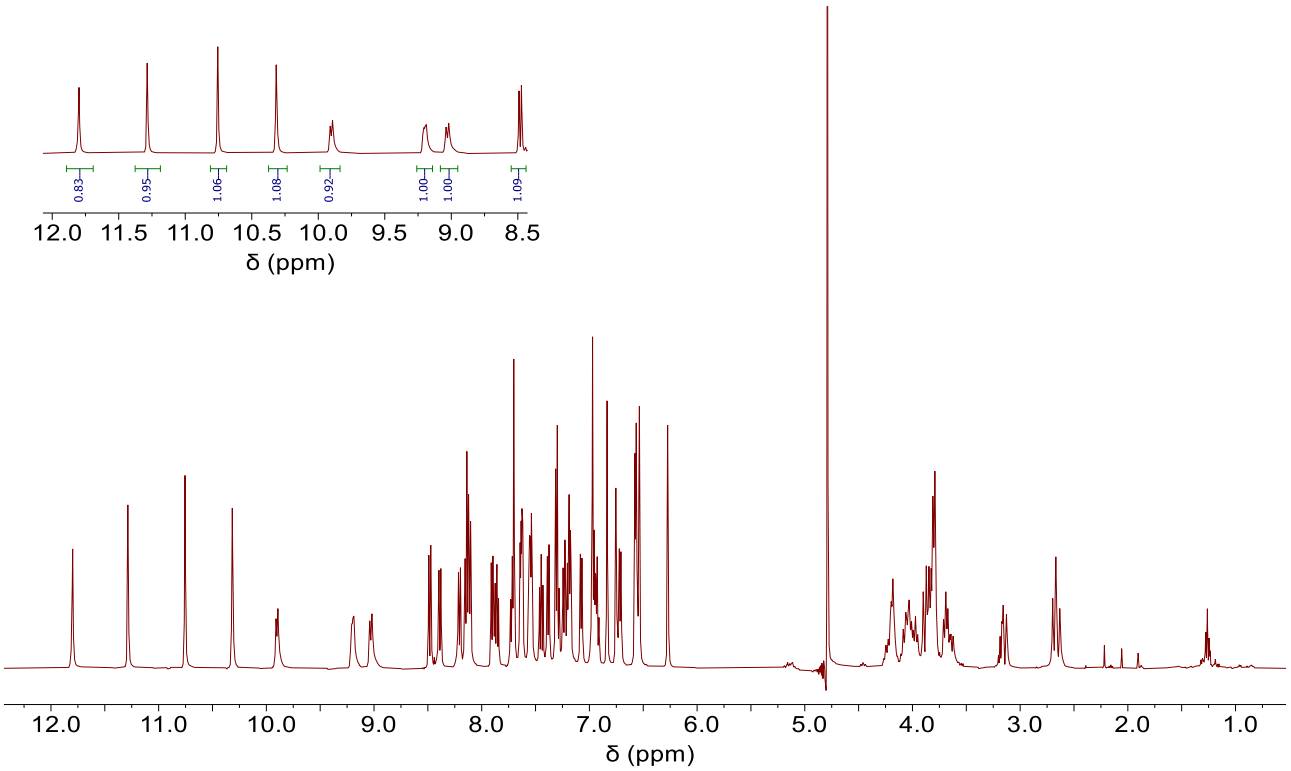


Figure S13. ^{1}H NMR spectrum of oligomer **1** (500 MHz, H_2O/D_2O 9:1 v/v, 50 mM NH_4HCO_3, pH 8.5, water suppression). The integrated protons are related to the NH amide region.

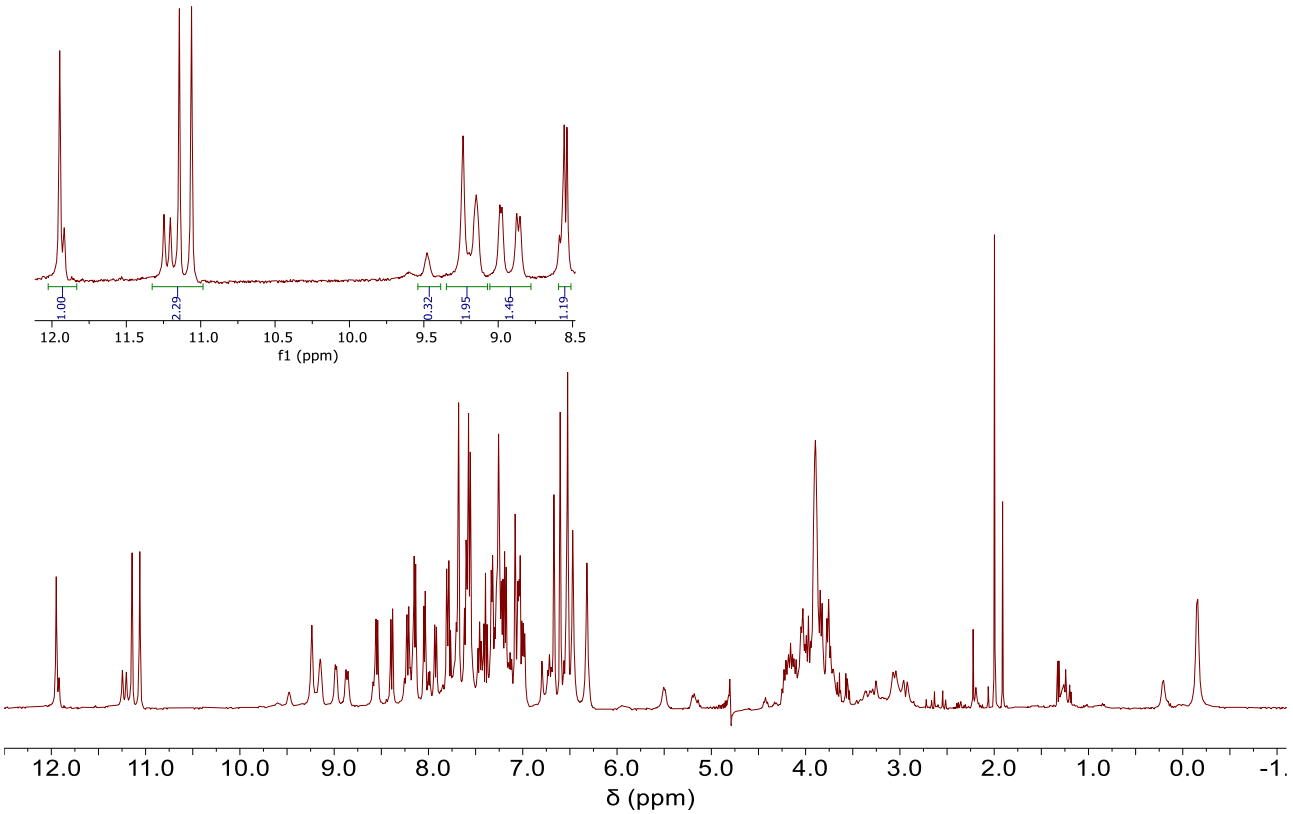


Figure S14. ^{1}H NMR spectrum of oligomer **2** (500 MHz, H_2O/D_2O 9:1 v/v, 50 mM NH_4HCO_3, pH 8.5, water suppression). The integrated protons are related to the NH amide region.

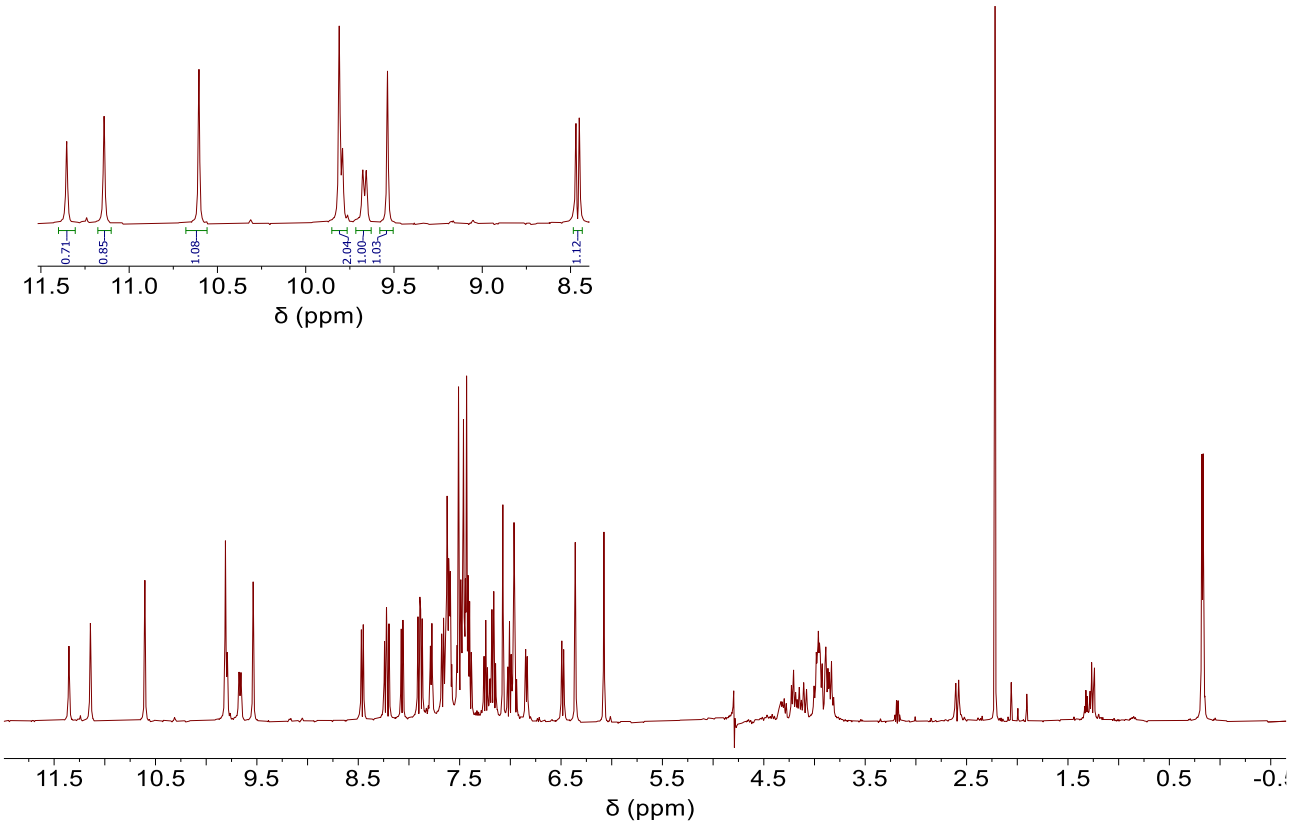


Figure S15. ^{1}H NMR spectrum of oligomer **3** (500 MHz, H_2O/D_2O 9:1 v/v, 50 mM NH_4HCO_3, pH 8.5, water suppression). The integrated protons are related to the NH amide region.

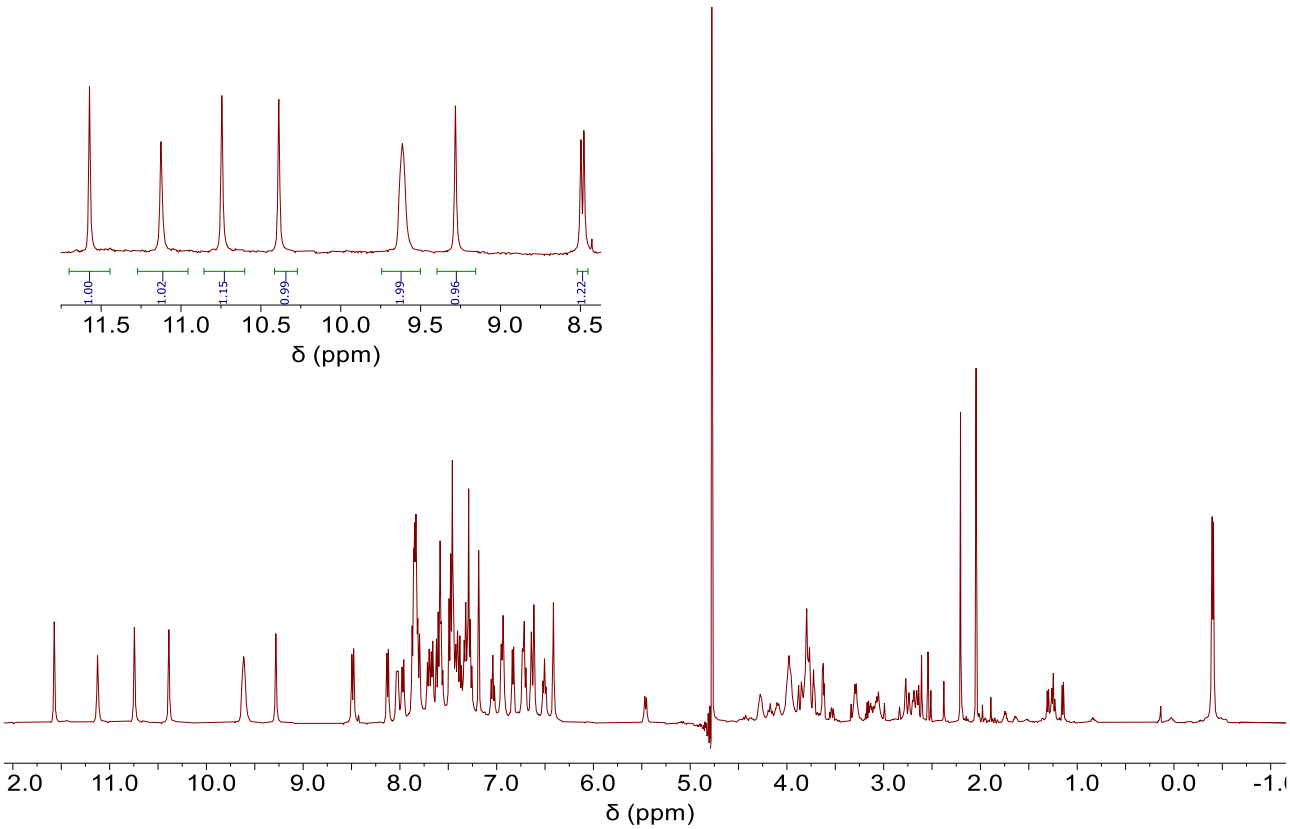


Figure S16. ^{1}H NMR spectrum of oligomer **4** (500 MHz, H_2O/D_2O 9:1 v/v, 50 mM NH_4HCO_3, pH 8.5, water suppression). The integrated protons are related to the NH amide region.

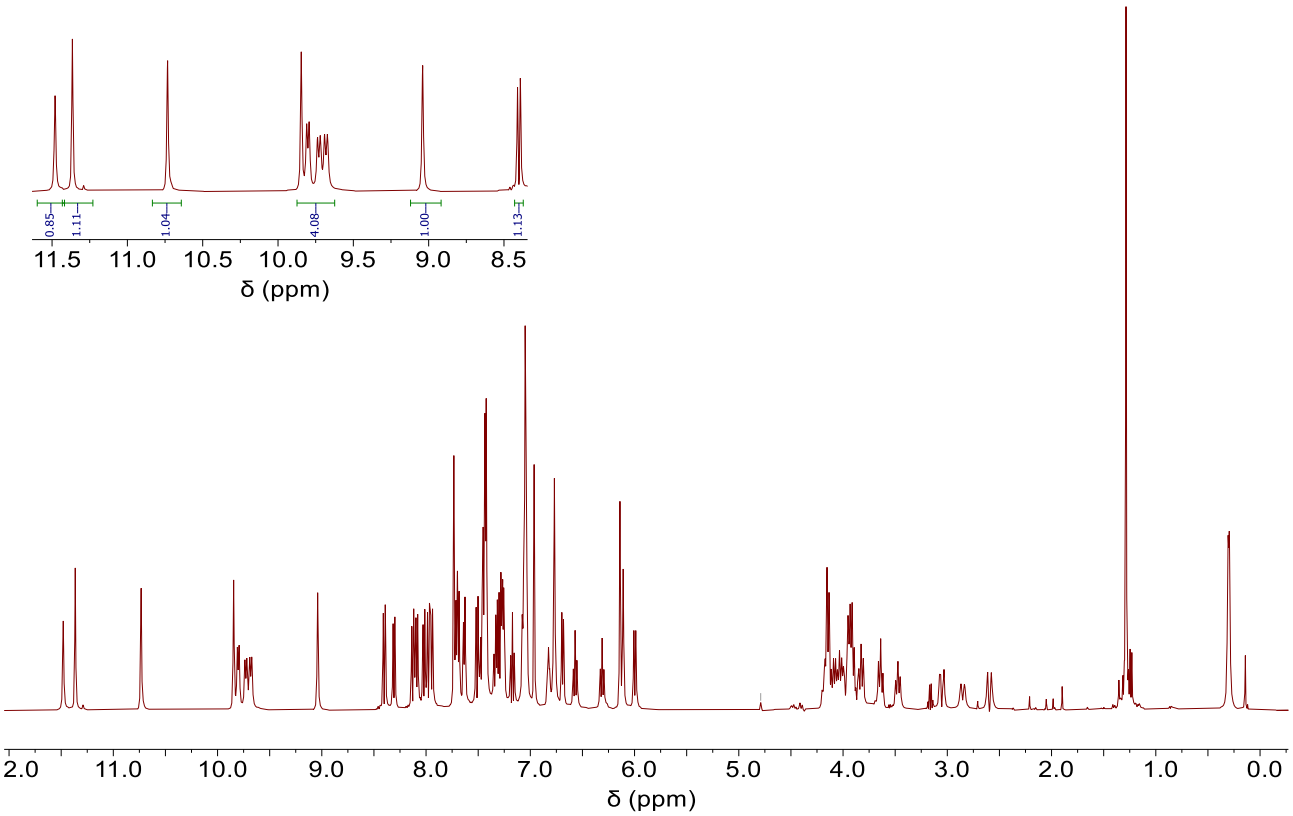


Figure S17. ^{1}H NMR spectrum of oligomer **5** (500 MHz, H_2O/D_2O 9:1 v/v, 50 mM NH_4HCO_3, pH 8.5, water suppression). The integrated protons are related to the NH amide region.

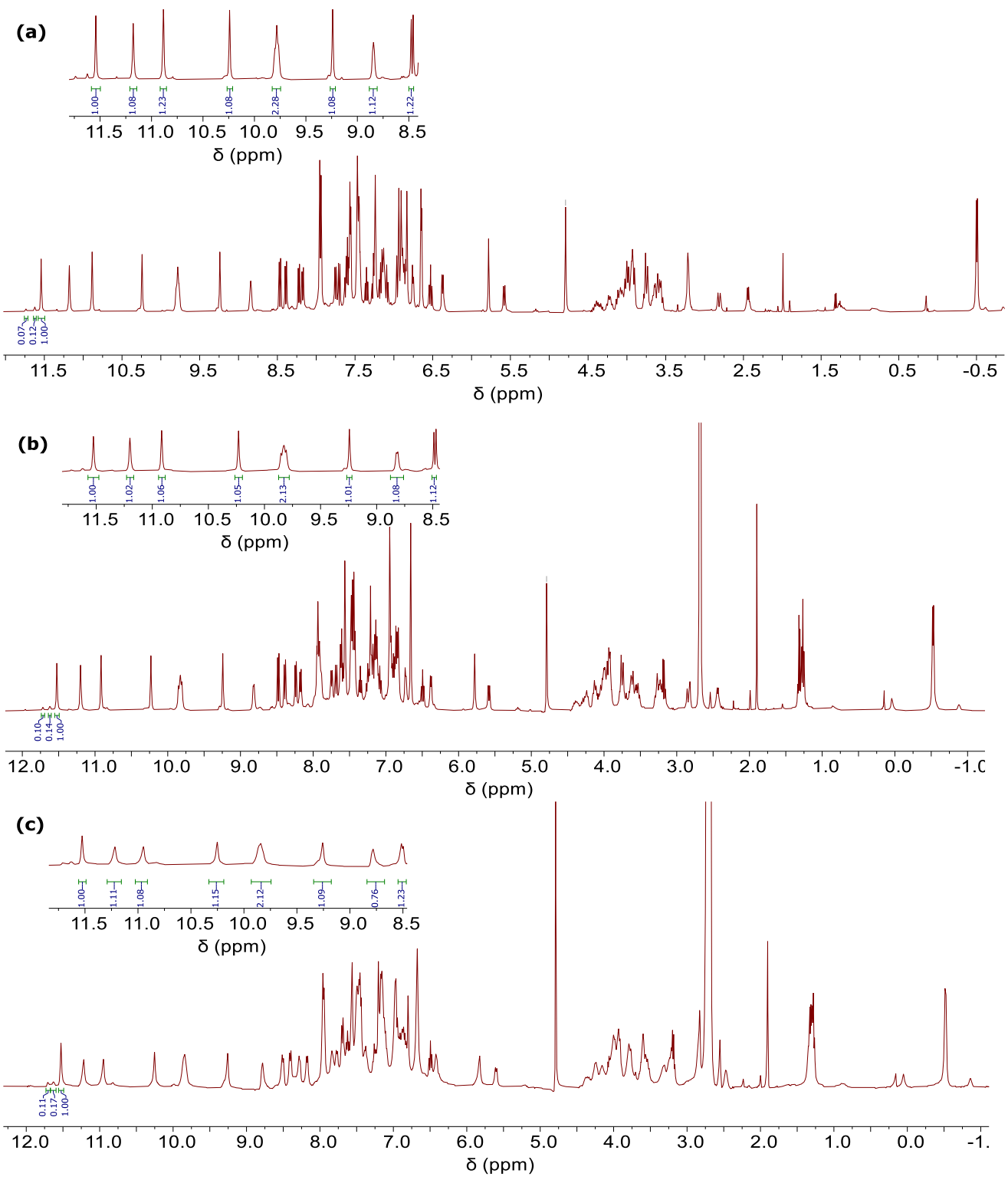


Figure S18. ^{1}H NMR spectra of oligomer **6**. (a) ^{1}H NMR (500 MHz, H_2O/D_2O 9:1 v/v, 50 mM NH_4HCO_3, pH 8.5). (b) ^{1}H NMR (500 MHz, 81% NH_4HCO_3 + 9% D_2O + **10% DMSO-*d*$_6$**). (c) ^{1}H NMR (500 MHz, 63% NH_4HCO_3 + 7% D_2O + **30% DMSO-*d*$_6$**). The integrated protons are related to the NH amide region. The proportion between signal integration of the major set of signals and minor set of signals near 11.5 ppm changed as a function of the amount of DMSO-*d*$_6$ added to the sample. The relative integration of the peaks from the minor signal set increases compared to the integration of the peaks of the major set of signals when the amount of DMSO changed from 0% to 30%. These data together with the clean HPLC profile support strong but not full handedness control of oligomer **6**.

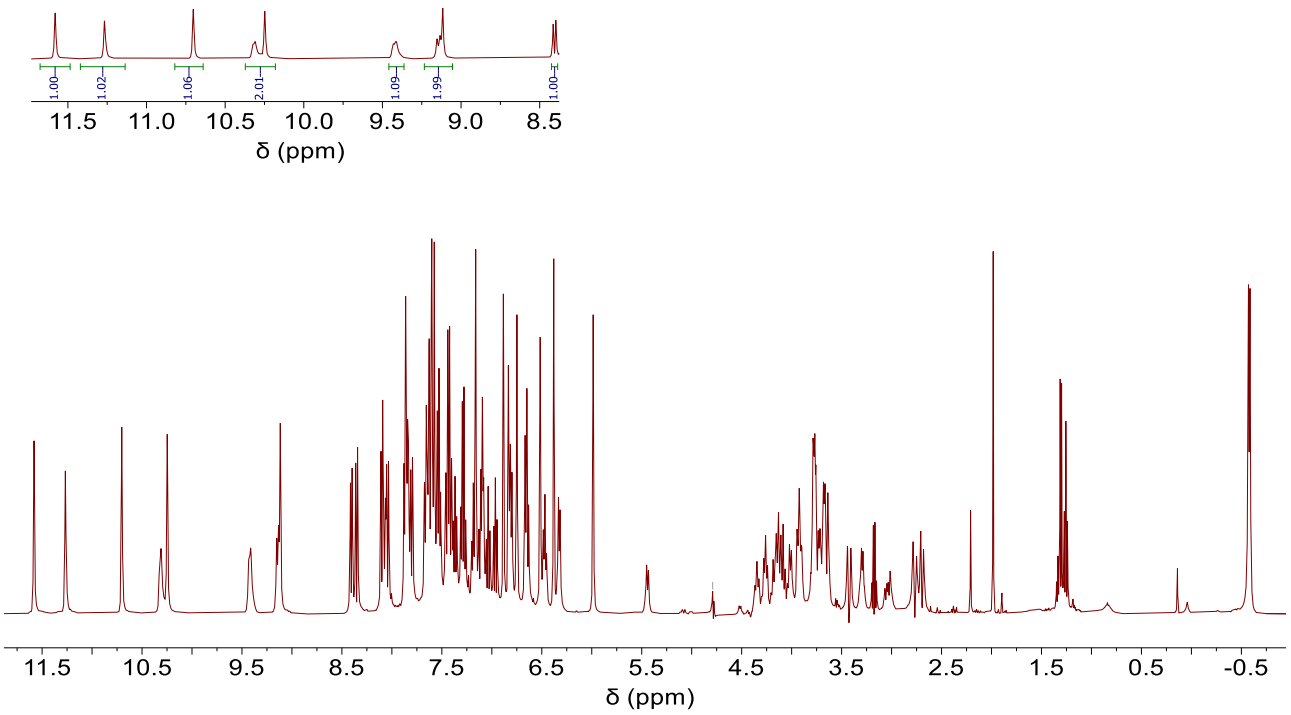


Figure S19. ^{1}H NMR spectrum of oligomer **7** (500 MHz, H_2O/D_2O 9:1 v/v, 50 mM NH_4HCO_3, pH 8.5, water suppression). The integrated protons are related to the NH amide region.

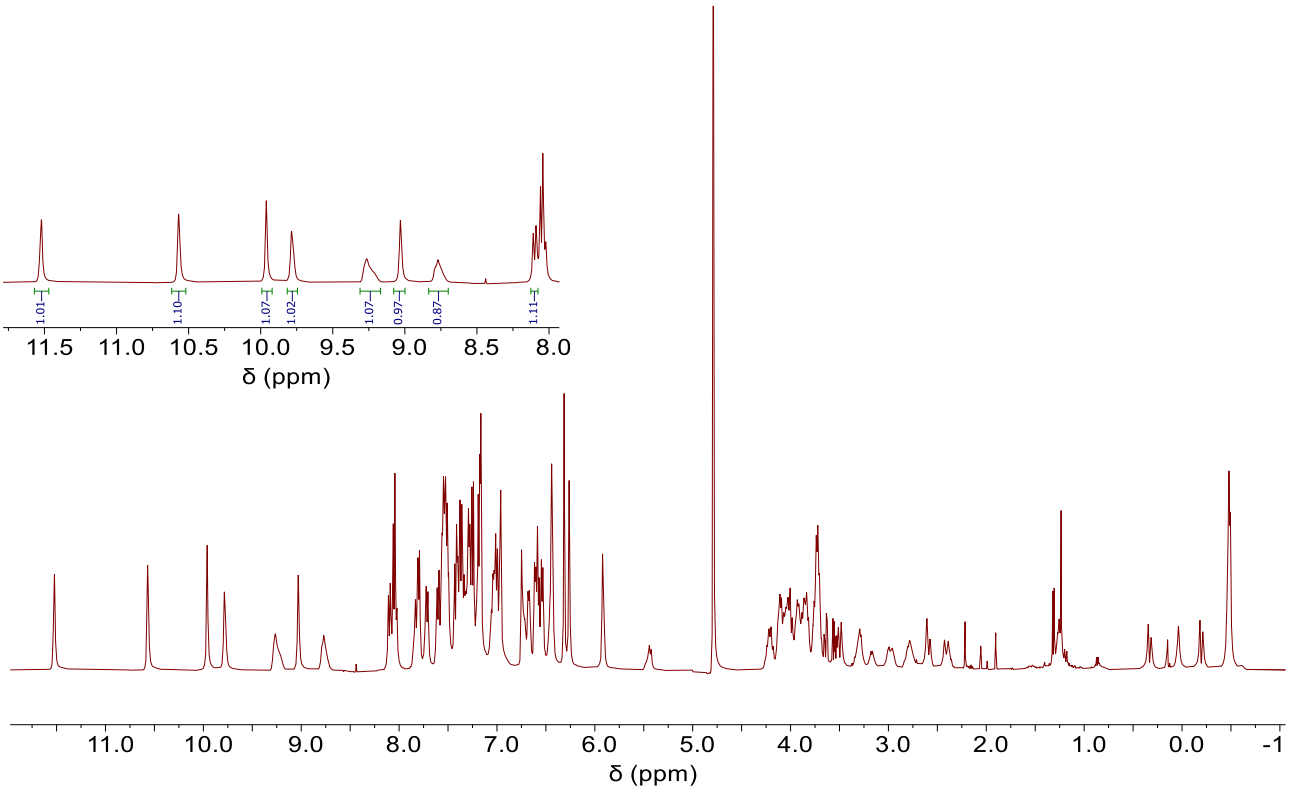


Figure S20. ^{1}H NMR spectrum of oligomer **8** (500 MHz, H_2O/D_2O 9:1 v/v, 50 mM NH_4HCO_3, pH 8.5, water suppression). The integrated protons are related to the NH amide region.

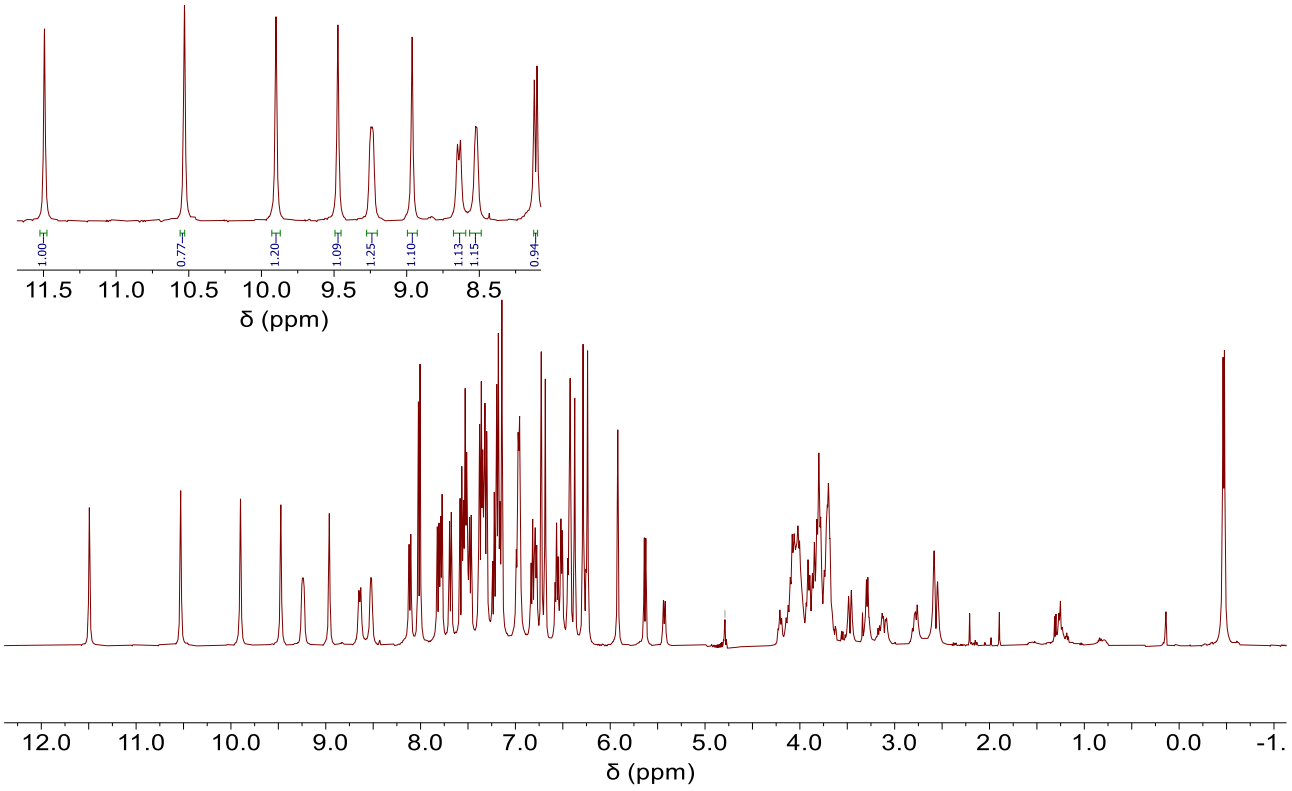


Figure S21. ^{1}H NMR spectrum of oligomer **9** (500 MHz, H_2O/D_2O 9:1 v/v, 50 mM NH_4HCO_3, pH 8.5, water suppression). The integrated protons are related to the NH amide region.

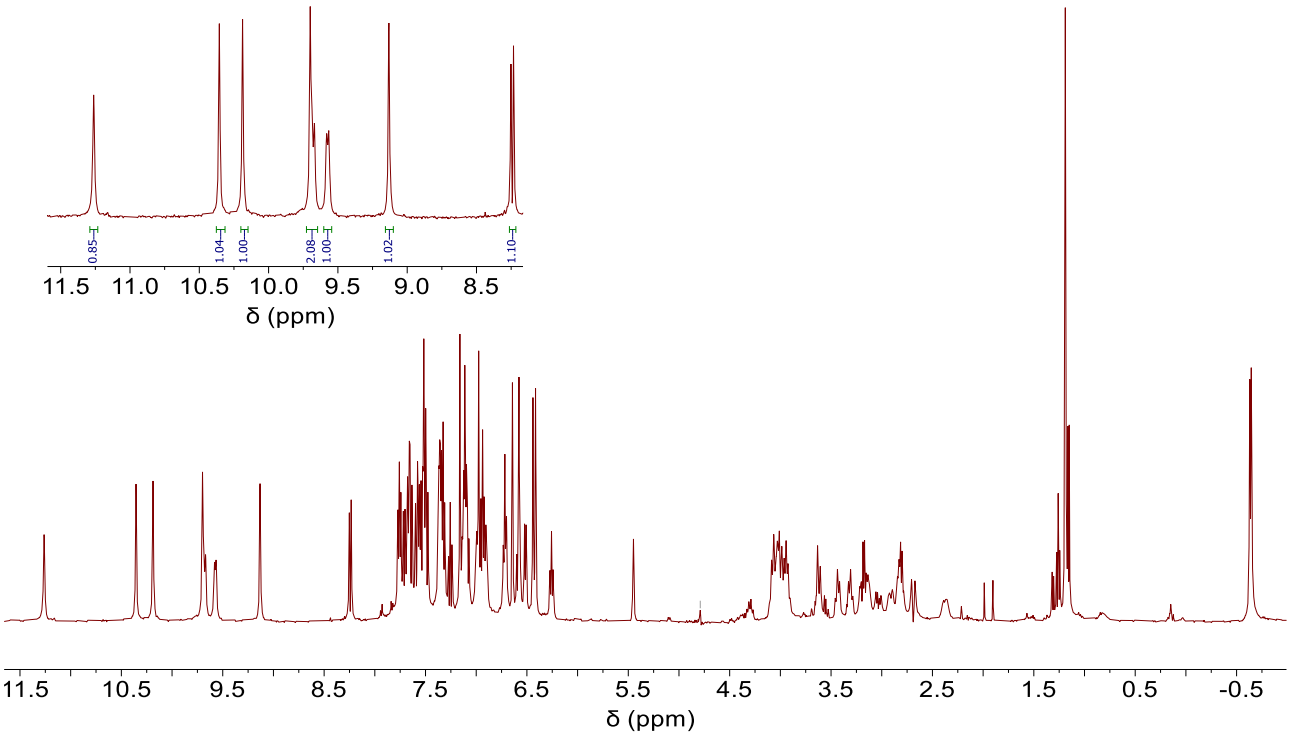


Figure S22. ^{1}H NMR spectrum of oligomer **10** (500 MHz, H_2O/D_2O 9:1 v/v, 50 mM NH_4HCO_3, pH 8.5, water suppression). The integrated protons are related to the NH amide region.

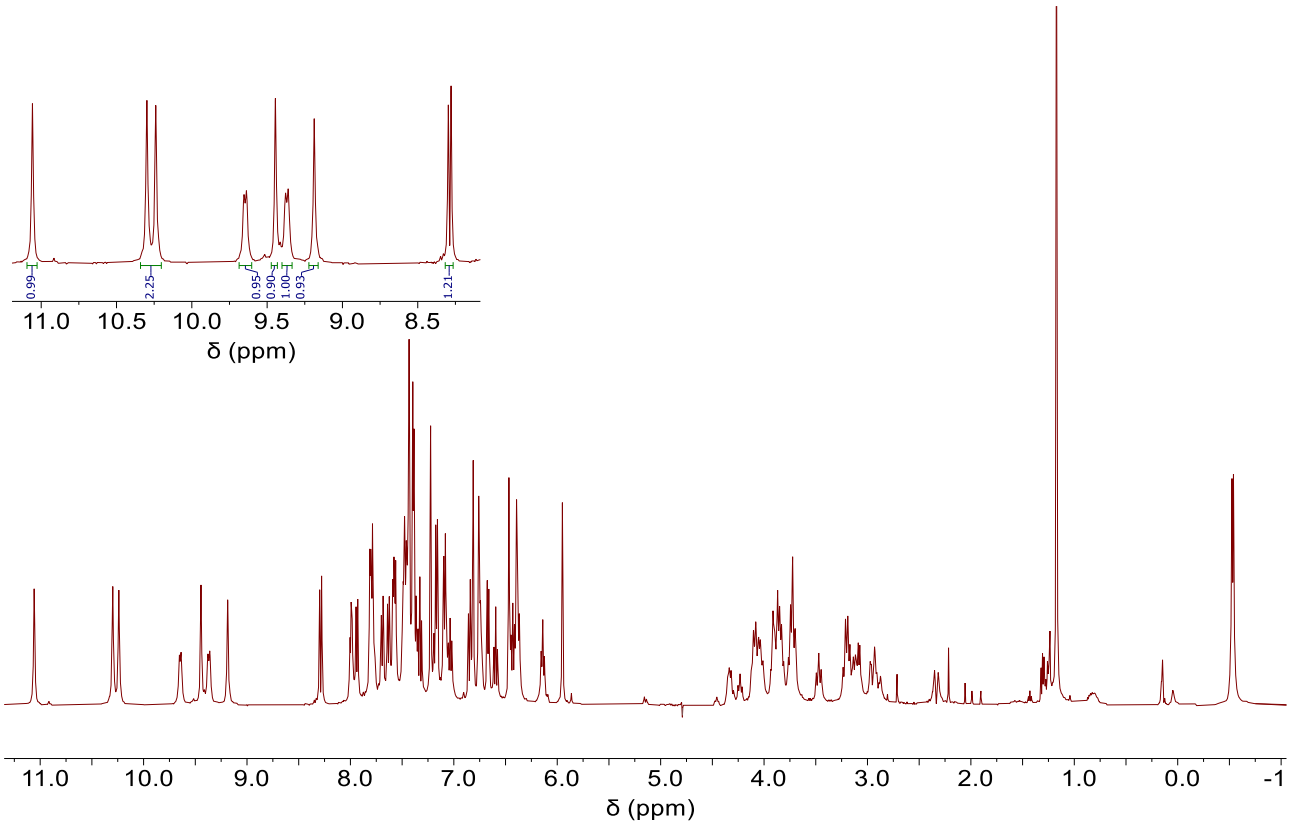


Figure S23. ^{1}H NMR spectrum of oligomer **11** (500 MHz, H_2O/D_2O 9:1 v/v, 50 mM NH_4HCO_3, pH 8.5, water suppression). The integrated protons are related to the NH amide region.

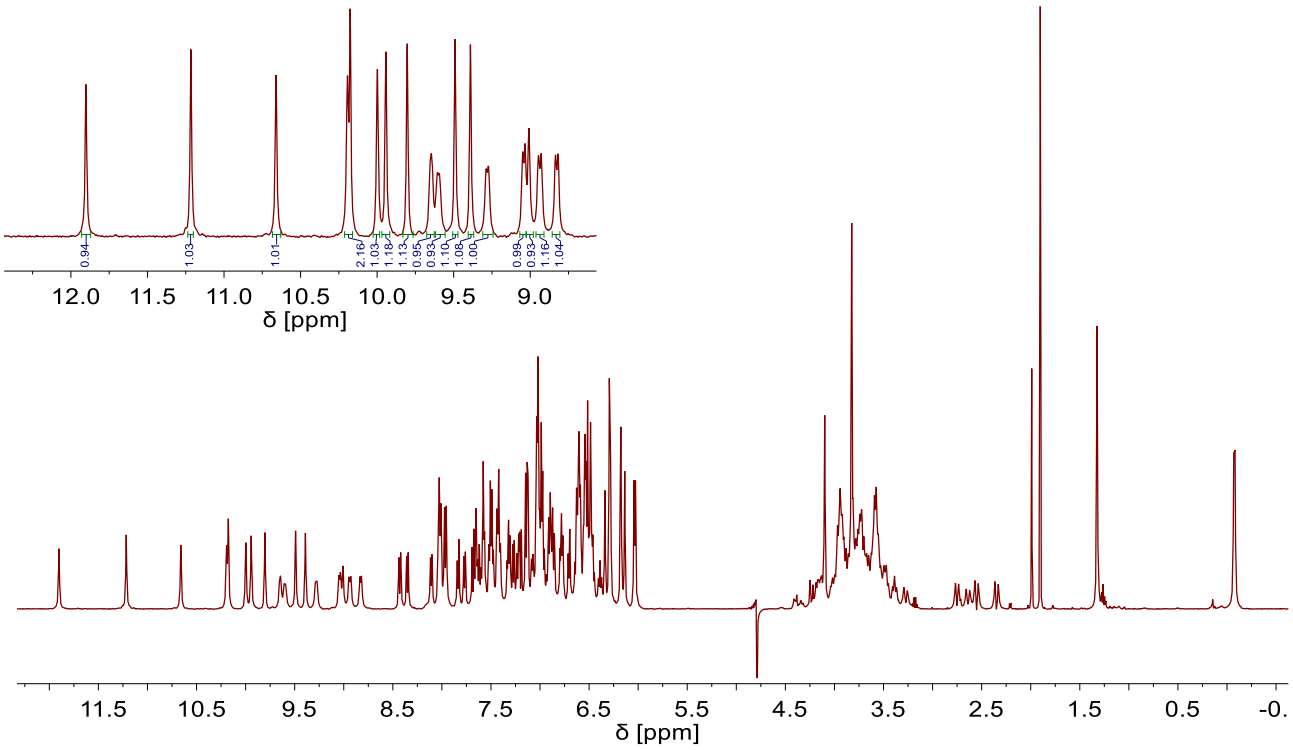


Figure S24. ^{1}H NMR spectrum of oligomer **12** (500 MHz, H_2O/D_2O 9:1 v/v, 50 mM NH_4HCO_3, pH 8.5, water suppression). The integrated protons are related to the NH amide region.

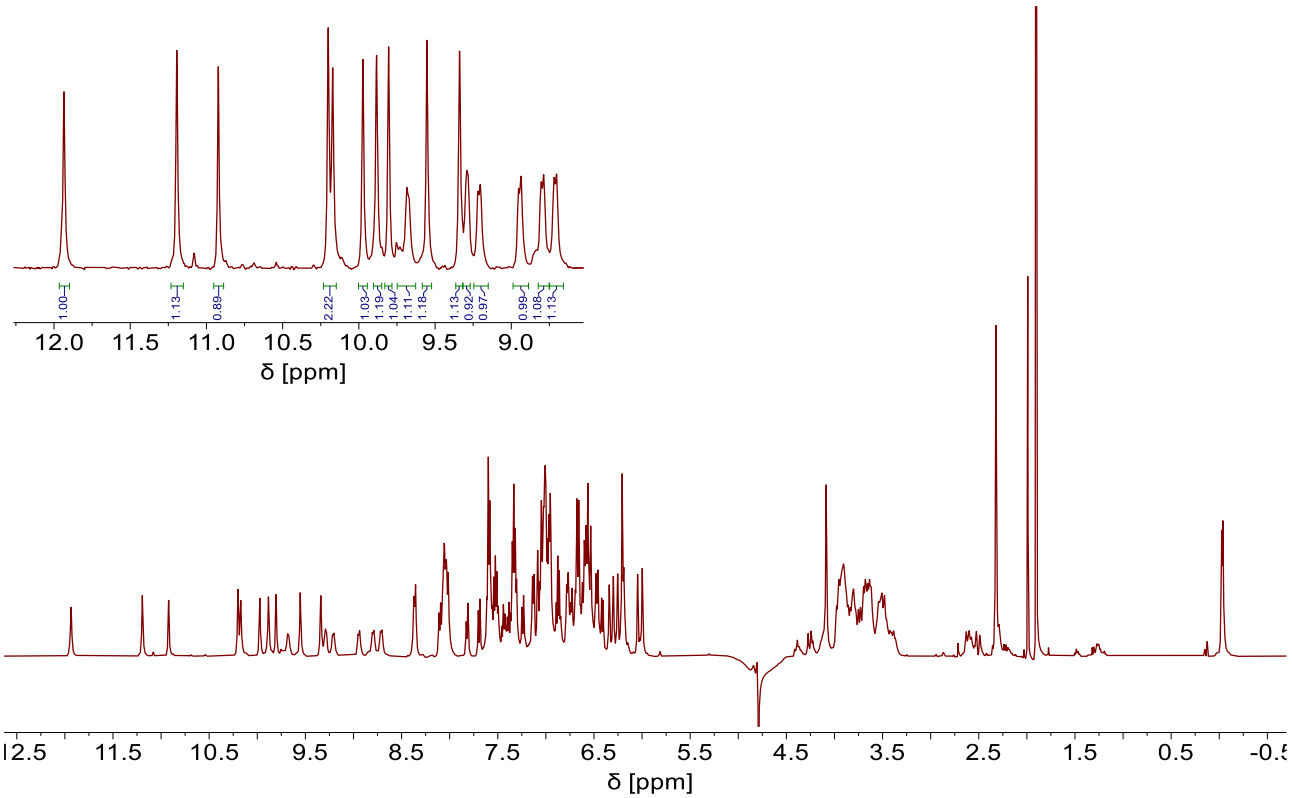


Figure S25. ^{1}H NMR spectrum of oligomer **13** (500 MHz, H_2O/D_2O 9:1 v/v, 50 mM NH_4HCO_3, pH 8.5, H_2O suppression). The integrated protons are related to the NH amide region.

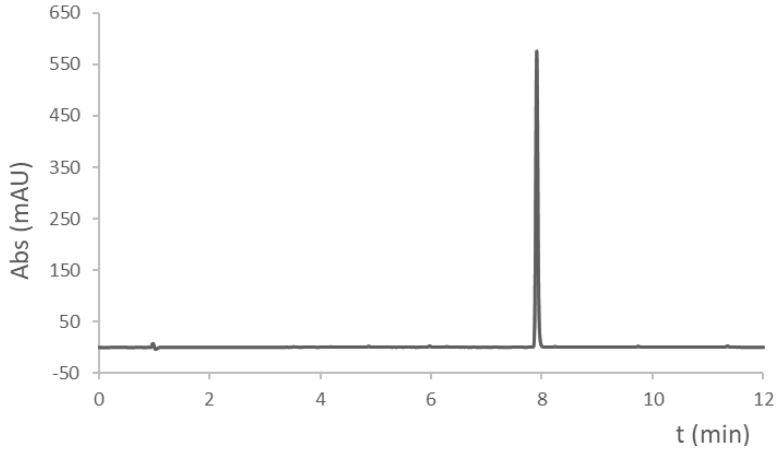


Figure S26. RP-HPLC chromatogram of **Fmoc-Q^{Pho}-COOH** using a linear gradient from 15% B to 100% B in 10 min; A: water + 0.1% TFA and B: acetonitrile + 0.1% TFA.

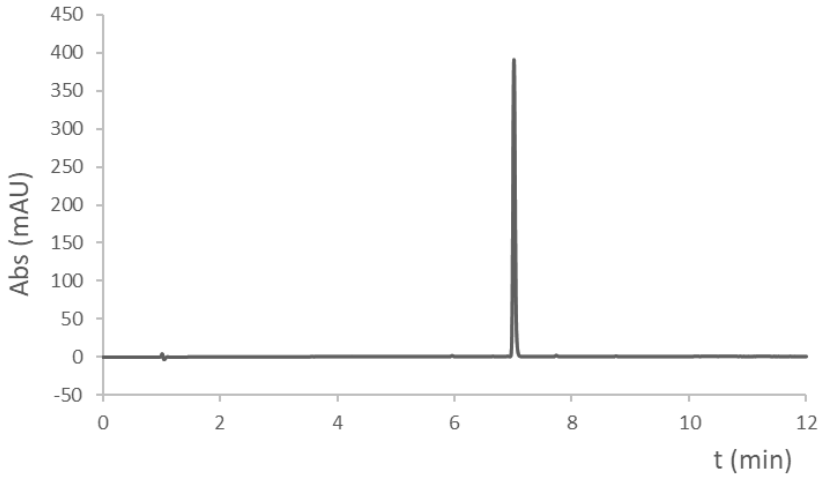


Figure S27. RP-HPLC chromatogram of **Fmoc-M^{Pho}-COOH** using a linear gradient from 15% B to 100% B in 10 min; A: water + 0.1% TFA and B: acetonitrile + 0.1% TFA.

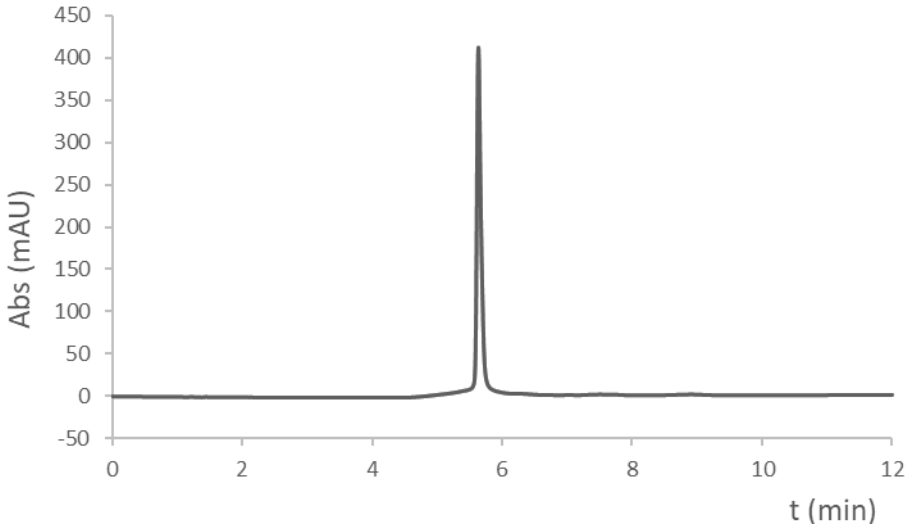


Figure S28. RP-HPLC chromatogram of oligomer **2** using a linear gradient from 5% B to 100% B in 10 min; A: 12.5 mM TEAA in water, pH 8.5; B: 12.5 mM TEAA in water:acetonitrile (1:2), pH 8.5.

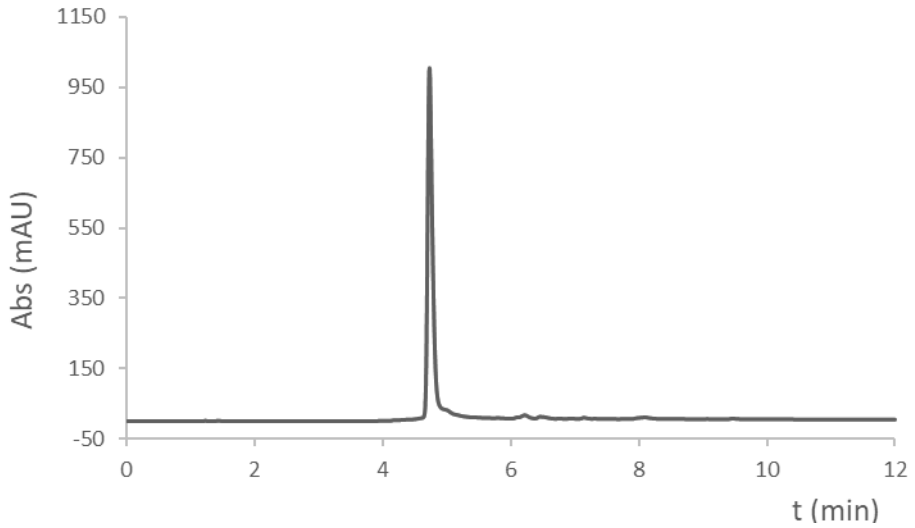


Figure S29. RP-HPLC chromatogram of oligomer **3** using a linear gradient from 5% B to 100% B in 10 min; A: 12.5 mM TEAA in water, pH 8.5; B: 12.5 mM TEAA in water:acetonitrile (1:2), pH 8.5.

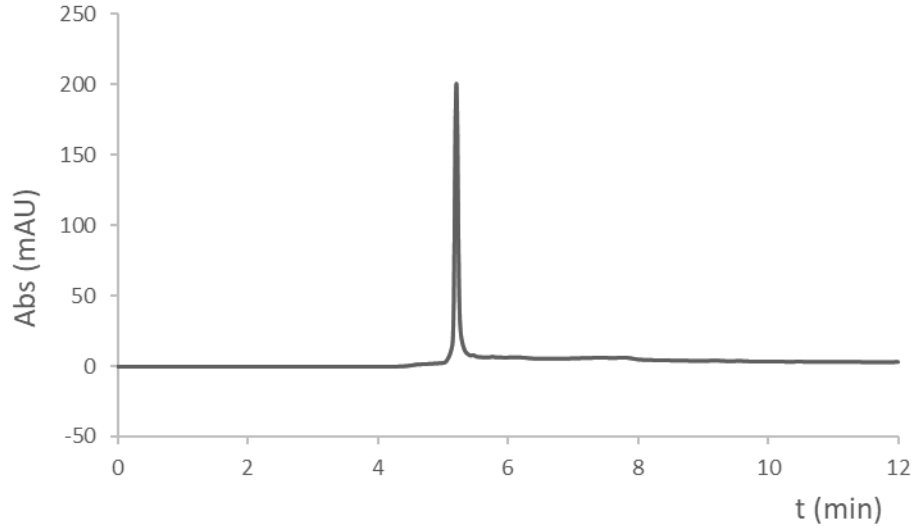


Figure S30. RP-HPLC chromatogram of oligomer **4** using a linear gradient from 5% B to 100% B in 10 min; A: 12.5 mM TEAA in water, pH 8.5; B: 12.5 mM TEAA in water:acetonitrile (1:2), pH 8.5.

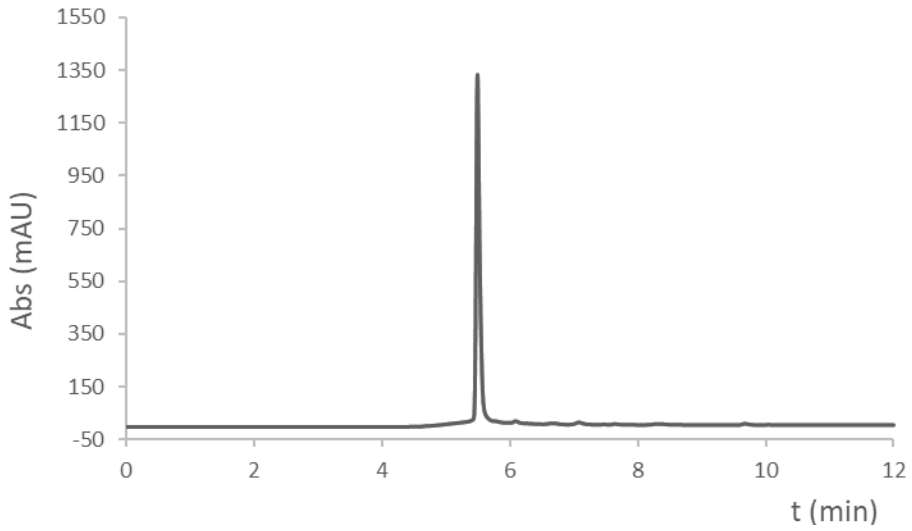


Figure S31. RP-HPLC chromatogram of oligomer **5** using a linear gradient from 5% B to 100% B in 10 min; A: 12.5 mM TEAA in water, pH 8.5; B: 12.5 mM TEAA in water:acetonitrile ((1:2), pH 8.5.

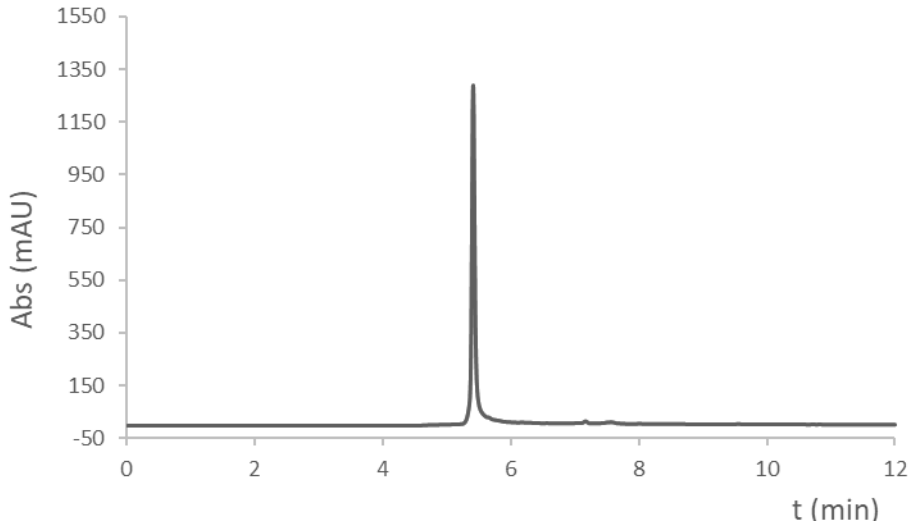


Figure S32. RP-HPLC chromatogram of oligomer **6** using a linear gradient from 5% B to 100% B in 10 min; A: 12.5 mM TEAA in water, pH 8.5; B: 12.5 mM TEAA in water:acetonitrile (1:2), pH 8.5.

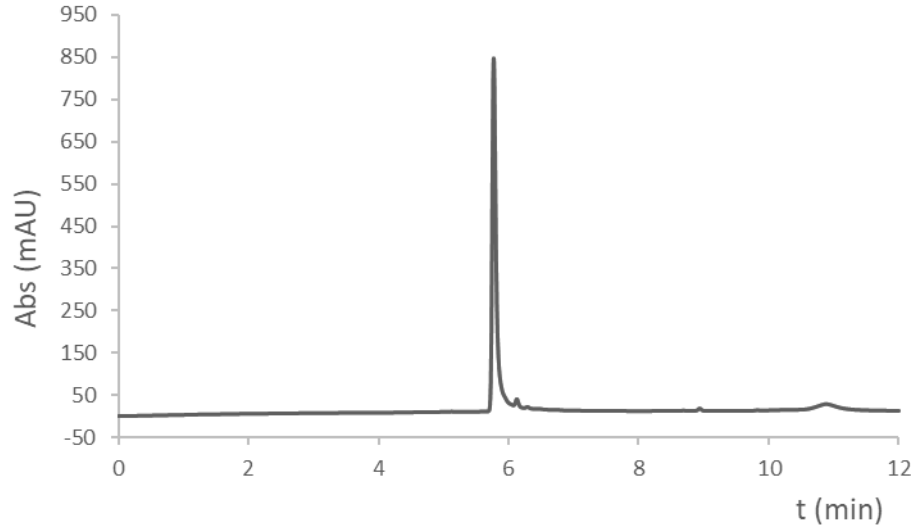


Figure S33. RP-HPLC chromatogram of oligomer **7** using a linear gradient from 5% B to 100% B in 10 min; A: 12.5 mM TEAA in water, pH 8.5; B: 12.5 mM TEAA in water:acetonitrile (1:2), pH 8.5.

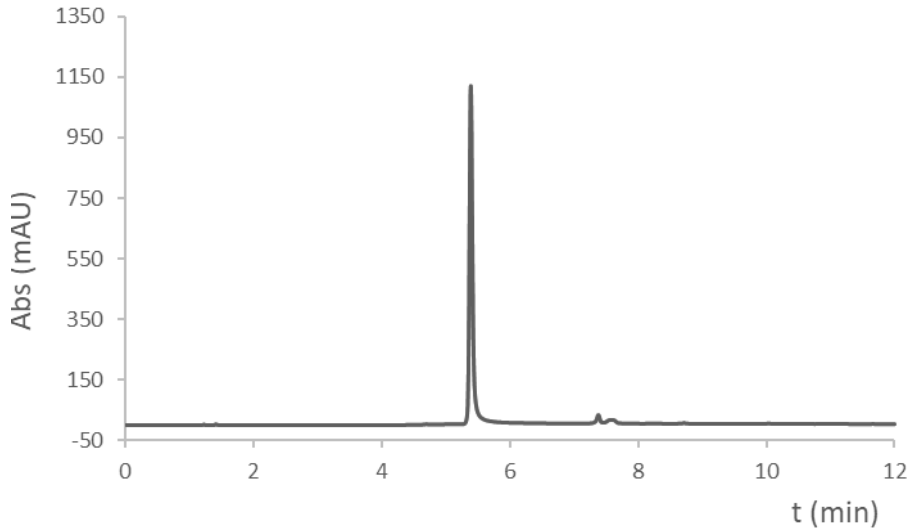


Figure S34. RP-HPLC chromatogram of oligomer **8** using a linear gradient from 5% B to 100% B in 10 min; A: 12.5 mM TEAA in water, pH 8.5; B: 12.5 mM TEAA in water:acetonitrile (1:2), pH 8.5.

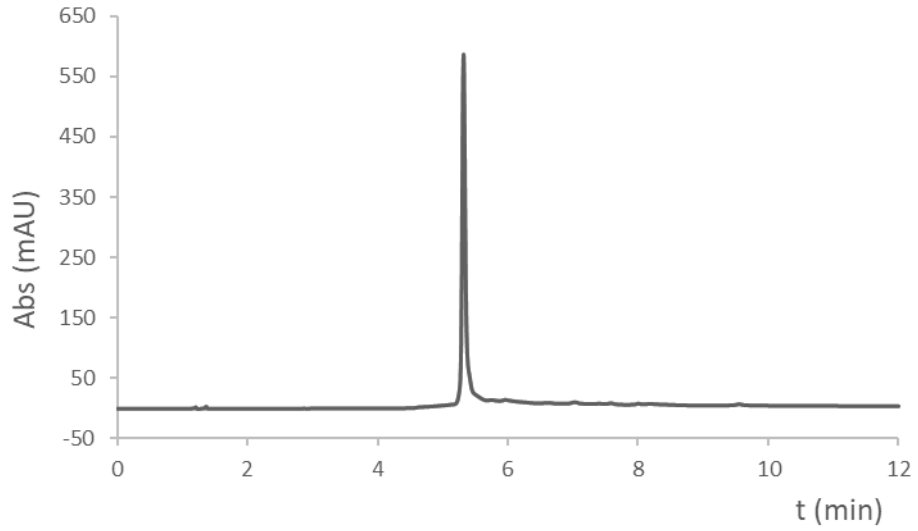


Figure S35. RP-HPLC chromatogram of oligomer **9** using a linear gradient from 5% B to 100% B in 10 min; A: 12.5 mM TEAA in water, pH 8.5; B: 12.5 mM TEAA in water:acetonitrile (1:2), pH 8.5.

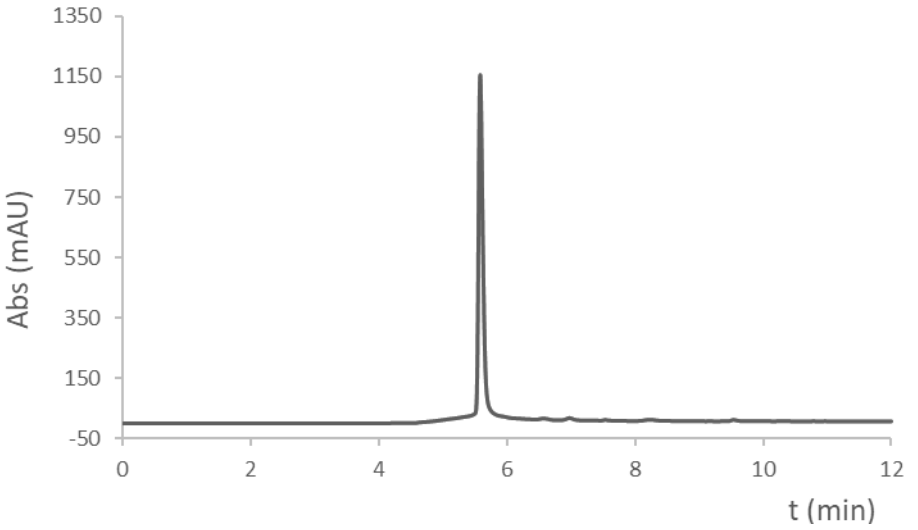


Figure S36. RP-HPLC chromatogram of oligomer **10** using a linear gradient from 5% B to 100% B in 10 min; A: 12.5 mM TEAA in water, pH 8.5; B: 12.5 mM TEAA in water:acetonitrile (1:2), pH 8.5.

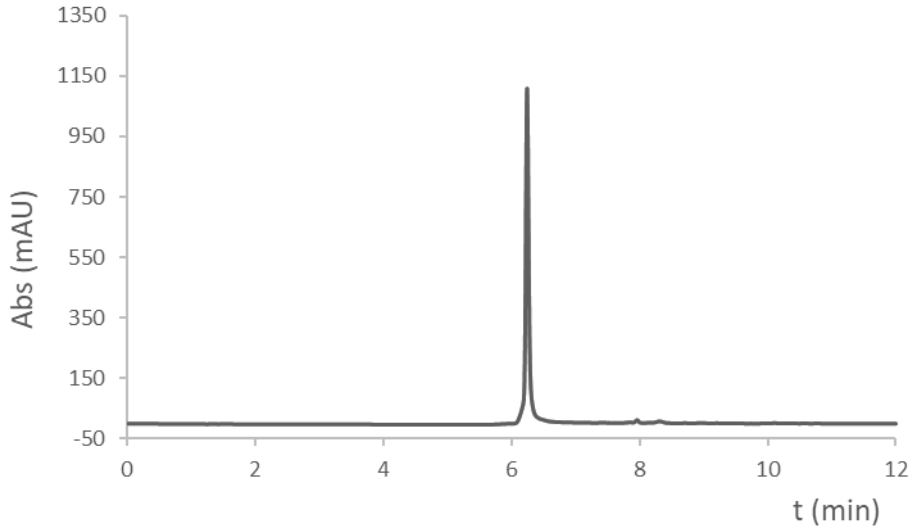


Figure S37. RP-HPLC chromatograms of oligomer **11** using a linear gradient from 5% B to 100% B in 10 min; A: 12.5 mM TEAA in water, pH 8.5; B: 12.5 mM TEAA in water:acetonitrile (1:2), pH 8.5.

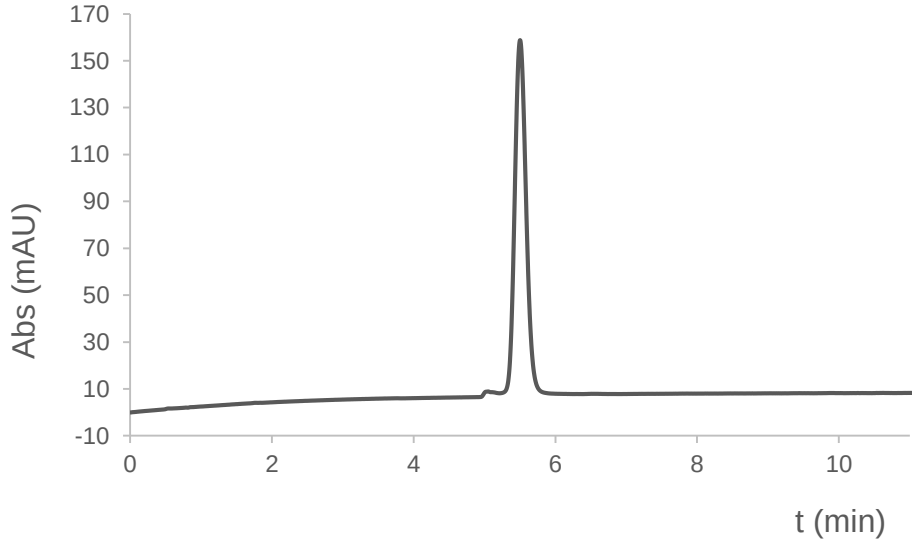


Figure S38. RP-HPLC chromatograms of oligomer **12** using a linear gradient from 0% B to 25% B in 10 min; A: 12.5 mmol NH_4OAc in water, pH 8.5; B: acetonitrile.

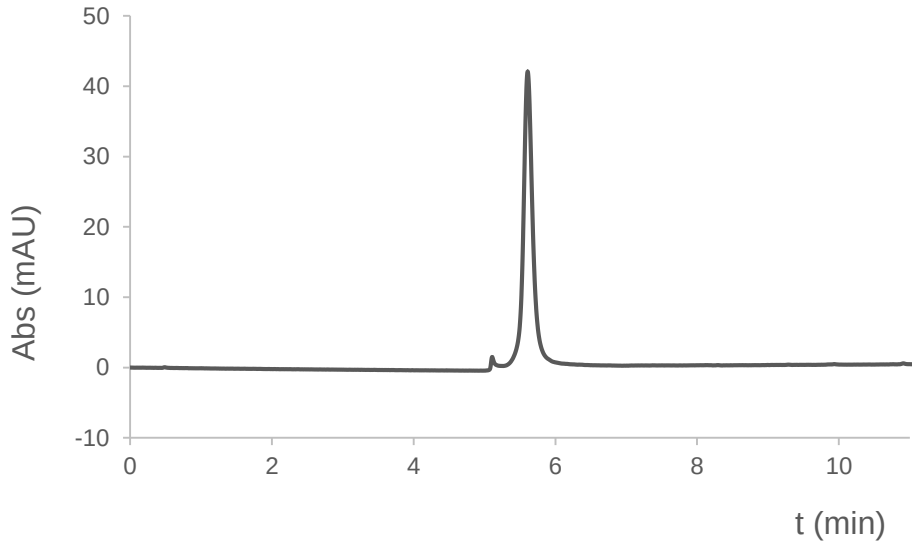


Figure S39. RP-HPLC chromatograms of oligomer **13** using a linear gradient from 0% B to 25% B in 10 min; A: 12.5 mmol NH_4OAc in water, pH 8.5; B: acetonitrile.

5. X-ray Crystallography

After preparative HPLC and ion exchange, the ammonium salt of oligomer **13** was dissolved in pure water to a concentration of 2.6 mM. Initially, **13** was mixed with Sac7d protein[20b] in 1:1 molar ratio to reach a 1.3 mM concentration. Various crystallization conditions were screened using the hanging drop vapor diffusion method. A precipitate formed in crystallization reagent composed of 20% PEG 6000, 0.1 M HEPES pH 7.0, 200 mM NaCl, but diamond-shaped crystals appeared in 30 days at 20 °C (Figure S40), which proved to be compound **13**. A single crystal was cryo-protected using 25% Glucose (*w/v*) prepared in crystallization reagent and flash-cooled in liquid nitrogen.
X-ray diffraction data were collected at 100K on beamline ID23-1 at the European Synchrotron Radiation Facility (ESRF, Grenoble) using a Dectris Eiger2 X 16M detector.[29] The dataset was processed using autoPROC pipeline (Global Phasing).[30] The crystal belonged to $P4_3\ 2_1\ 2$ (or $P4_1\ 2_1\ 2$) with 2 molecules in the asymmetric unit. The structure was solved by the Molecular Replacement (MR) method using PHASER[31] with a molecular model of compound **13**. The molecular model of **13** was built in Maestro (Version 11.5) based on previously crystallized foldamers containing a repeat of Q^{Pho} and M^{Pho} monomers (unpublished results) to which B^{Rme}, Q^{Sem}, Q^{Ala} and Q^{Asp} units were added at C terminus. Finally, the model was energy minimized using parameters described in Table S1. A single MR solution was found with a translation function Z-score (TFZ) of 16.0 and log-likelihood gain (LLG) of 223.12 in $P4_3\ 2_1\ 2$. Geometric restraints for each monomer were generated separately in eLBOW (Phenix suite).[32] Model building and refinement were performed in Phenix-Refine and Coot.[33] However, it is noteworthy that for chain F, the N-terminus monomer Q^{Pho} remained invisible in the electron density, even after multiple rounds of refinements. Consequently, it was not modeled. This observation raises the possibility that the Q^{Pho} monomer located at the N-terminus of chain F adopts an alternate conformation within the crystal lattice, leading to its absence in the observable electron density. In contrast, for chain A, the N-terminus Q^{Pho} monomer was readily discernible within the electron density maps during the refinement process and therefore, it was modeled accordingly. Data collection and structure refinement statistics are given in Table S2. The structure was deposited in PDB database with accession ID 8QHM.

Table S1. Parameters used to build the molecular model of compound **13**.

Forcefield	OPLS3
Solvent	Water
Charges from	Force Field
Cutoff	Extended
Method	PRCG
Converge on	Gradient
Convergence threshold	0.05
Minimization mode	Minimization of non-conformers
Maximum iterations	2500

Table S2. Crystallography data collection and structure refinement statistics for compound **13**.

Wavelength	0.95
Resolution range	19.43 - 3.0 (3.107 - 3.0)
Space group	P 43 21 2
Unit cell	74.146 74.146 83.693 90 90 90
Total reflections	21196 (1975)
Unique reflections	4874 (395)
Multiplicity	4.3 (4.1)
Completeness (%)	94.53 (81.28)
Mean I/sigma (I)	15.98 (5.02)
Wilson B-factor	14.79
R-merge	0.06324 (0.234)
R-meas	0.07193 (0.2674)
R-pim	0.03343 (0.1265)
CC1/2	0.998 (0.984)
CC*	0.999 (0.996)
Reflections used in refinement	4748 (395)
Reflections used for R-free	245 (15)
R-work	0.3479 (0.2287)
R-free	0.3821 (0.5667)
CC (work)	0.530 (0.572)
CC (free)	0.606 (0.519)
Number of non-hydrogen atoms	609
RMS (bonds)	0.029
RMS (angles)	5.63
Clash score	18.06
Average B-factor	19.74

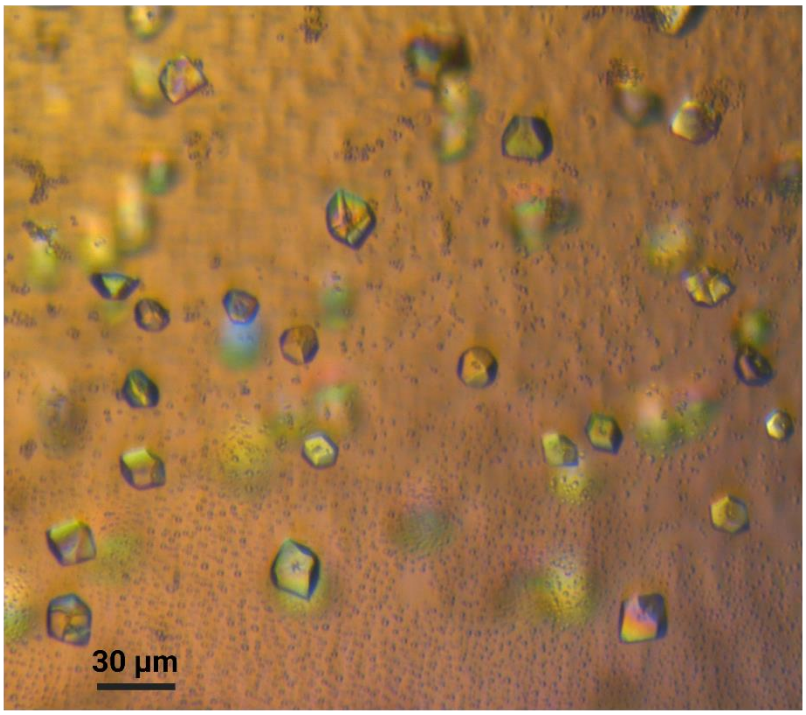


Figure S40. Crystals of compound **13** observed under crossed polarizing microscope.

6. References

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