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Supporting Information

High-Affinity Hybridization of Complementary Aromatic Oligoamide Strands in Water

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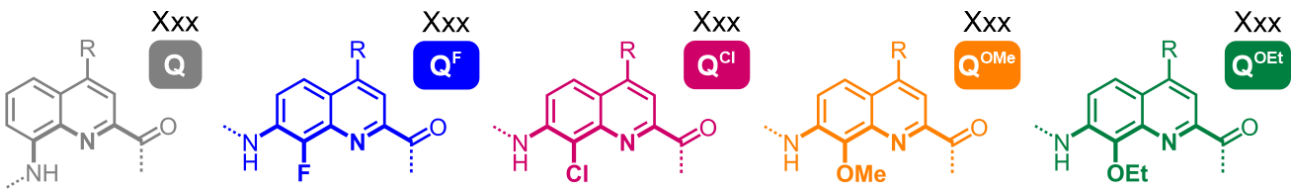
1. Abbreviations

Ala	alanine-like side chain: $-OCH_3$
Asp	aspartic acid-like side chain: $-OCH_2CO_2H$
br	broad
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DIAD	diisopropyl azodicarboxylate
DIPEA	*N*,*N*-diisopropylethylamine
ESI	electrospray ionization
HOESY	heteronuclear overhauser effect spectroscopy
HSQC	heteronuclear single quantum coherence
MMFFs	Merck molecular force field static
M.W.	microwave
NMP	*N*-methyl-2-pyrrolidone
Orn	ornithine-like side chain: $-O(CH_2)_3NH_2$
SPS	solid phase synthesis
Sul	sulfonic acid side chain: $-SO_3H$
TCAN	trichloroacetonitrile
TFE	2,2,2-trifluoroethanol
TIPS	triisopropyl silane
TSP-d_4	3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid sodium salt
wt.	weight

Q	8-amino-2-quinoline-carboxylic acid
Q^F	7-amino-8-fluoro-2-quinoline-carboxylic acid
Q^{Cl}	7-amino-8-chloro-2-quinoline-carboxylic acid
Q^{OMe}	7-amino-8-methoxy-2-quinoline-carboxylic acid
Q^{OEt}	7-amino-8-ethoxy-2-quinoline-carboxylic acid
R	water soluble side chain (Xxx = Ala, Asp, Orn or Sul)



2. Supplementary figures

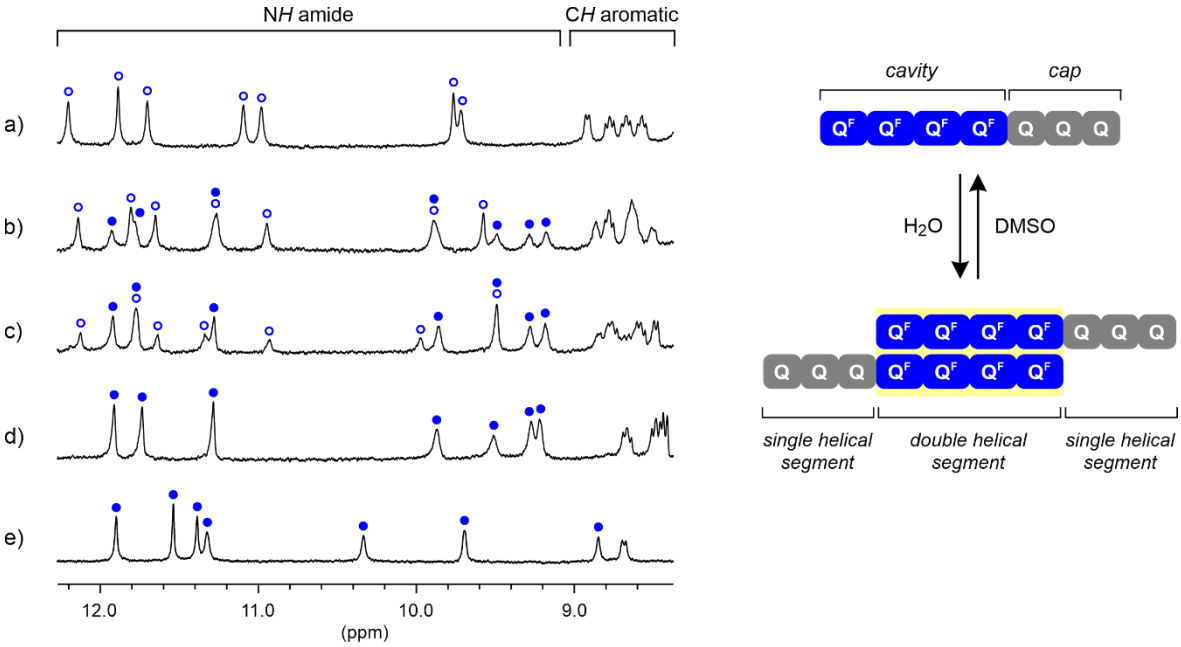


Figure S1. Part of the ^{1}H NMR spectra (300 MHz) of the amide region of **1** (1 mM) at 323 K in DMSO-d_6 / H_2O mixtures in the following vol/vol ratios: a) 100:0, b) 85:15, c) 80:20, d) 75:25 and e) H_2O / D_2O (95:5 vol/vol). Amide signals of the single helix are marked with empty blue circles whereas amide signals of the double helix are marked with full blue circles. Some aromatic resonances are represented. Spectra were calibrated with TSP-d_4 (internal NMR standard).

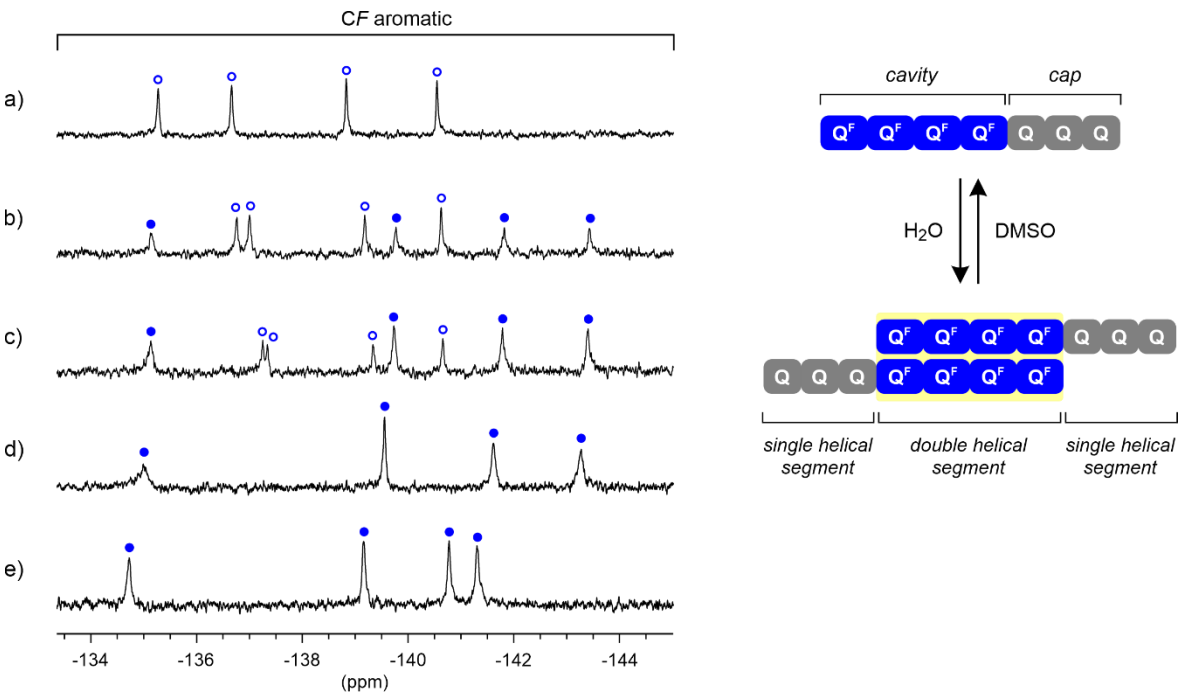


Figure S2. Part of the ^{19}F NMR spectra (282 MHz) of **1** (1 mM) at 323 K in DMSO-d_6 / H_2O mixtures in the following vol/vol ratios: a) 100:0, b) 85:15, c) 80:20, d) 75:25 and e) H_2O / D_2O (95:5 vol/vol). Fluorine signals of the single helix are marked with empty blue circles whereas fluorine signals of the double helix are marked with full blue circles. Spectra were calibrated with TFE (external NMR standard, insert tube).

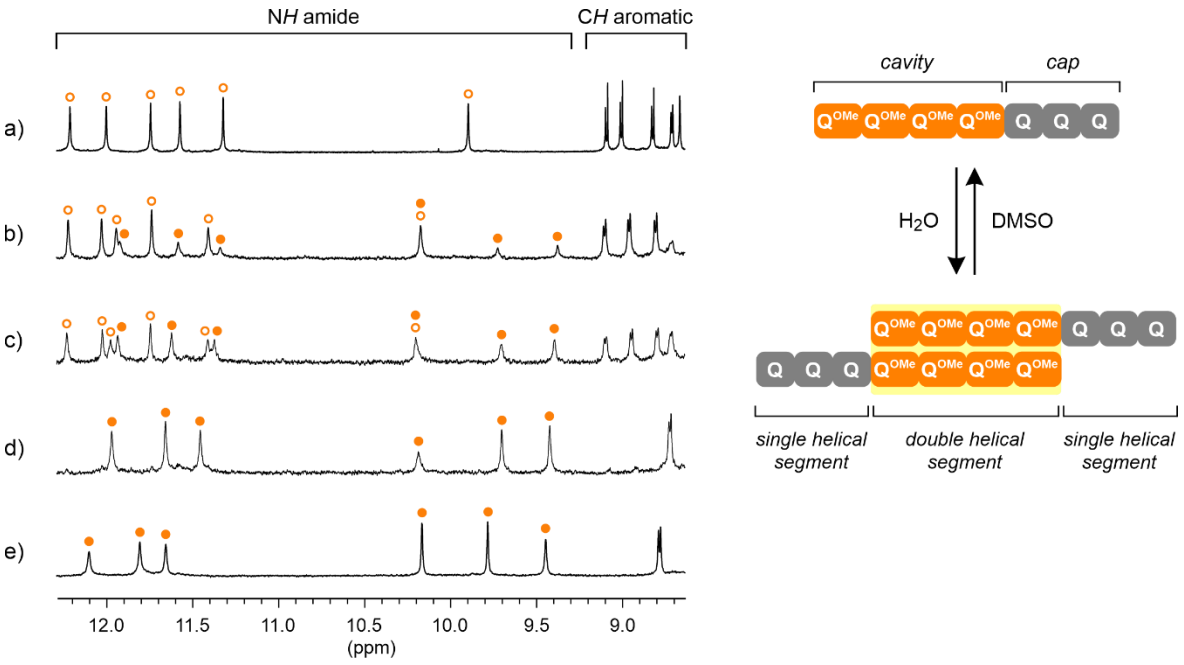


Figure S3. Part of the ^{1}H NMR spectra (300 MHz) of the amide region of **3** (1 mM) at 323 K in DMSO-d_6/H_2O mixtures in the following vol/vol ratios: a) 100:0, b) 65:35, c) 60:40, d) 55:45 and e) H_2O/D_2O (95:5 vol/vol). Amide signals of the single helix are marked with empty orange circles whereas amide signals of the double helix are marked with full orange circles. Some aromatic resonances are represented. Spectra were calibrated with TSP-d_4 (internal NMR standard).

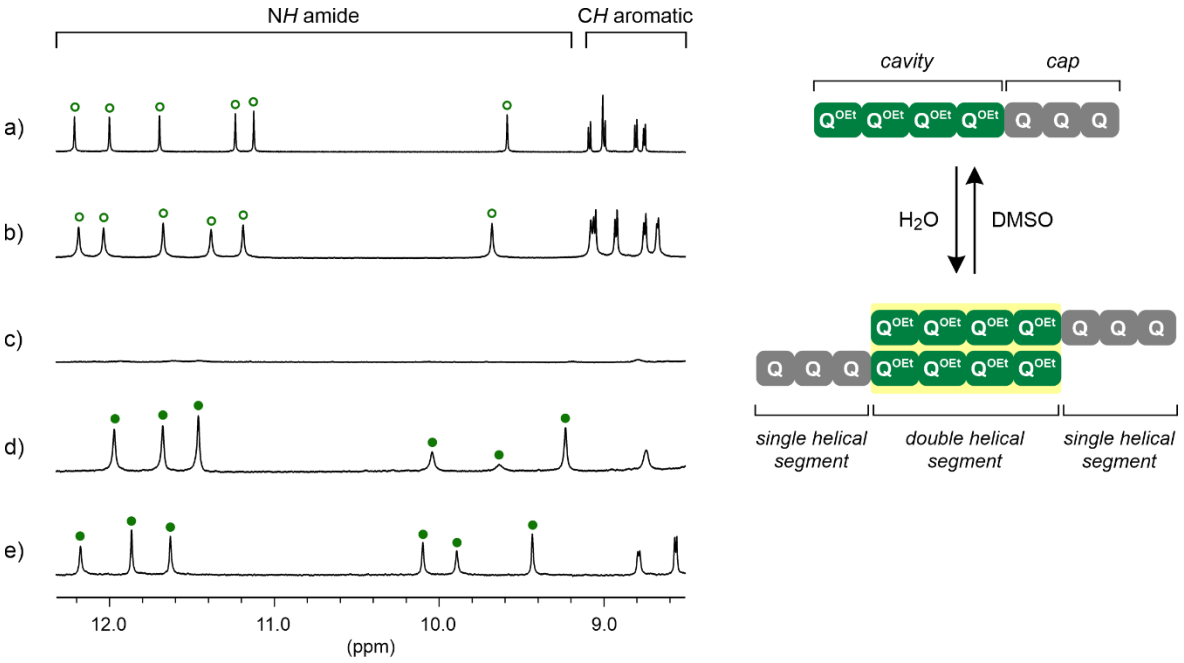


Figure S4. Part of the ^{1}H NMR spectra (700 MHz) of the amide region of **4** (1 mM) at 323 K in DMSO-d_6/H_2O mixtures in the following vol/vol ratios: a) 100:0, b) 60:40, c) 55:45, d) 50:50 and e) H_2O/D_2O (95:5 vol/vol). Amide signals of the single helix are marked with empty green circles whereas amide signals of the double helix are marked with full green circles. Some aromatic resonances are represented. Spectra were calibrated with TSP-d_4 (internal NMR standard).

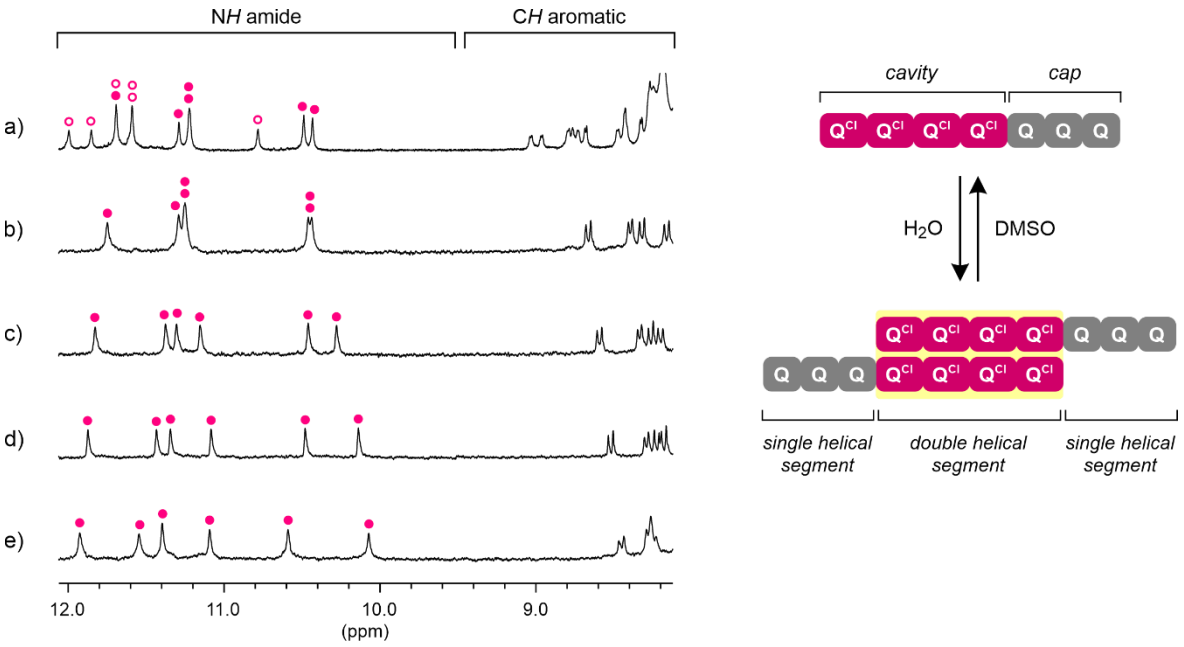


Figure S5. Part of the ^{1}H NMR spectra (300 MHz) of the amide region of **2** (1 mM) at 323 K in DMSO-d_6/H_2O mixtures in the following vol/vol ratios: a) 100:0, b) 90:10, c) 70:30, d) 40:60 and e) H_2O/D_2O (95:5 vol/vol). Amide signals of the single helix are marked with empty pink circles whereas amide signals of the double helix are marked with full pink circles. Some aromatic resonances are represented. Spectra were calibrated with TSP-d_4 (internal NMR standard).

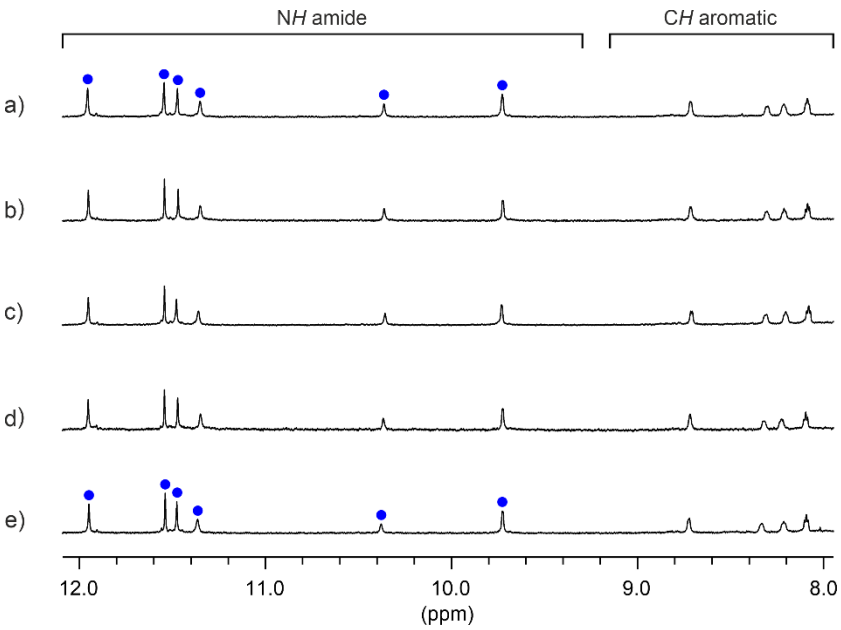


Figure S6. Part of the ^{1}H NMR spectra (700 MHz) of amide and aromatic regions at 323 K in H_2O/D_2O (95:5 vol/vol) of the oligomer **1** at a) 100 µM, b) 80 µM, c) 60 µM, d) 40 µM and e) 20 µM. Amide signals of the double helix **(1)**$_2$ are marked with blue circles. Spectra were calibrated with TSP-d_4. At 20 µM, only the double helix is detectable in solution so the dimerization constant of the oligomer **1** can be estimated $K_{dim} > 10^8$ L.mol^{-1} at 323 K.

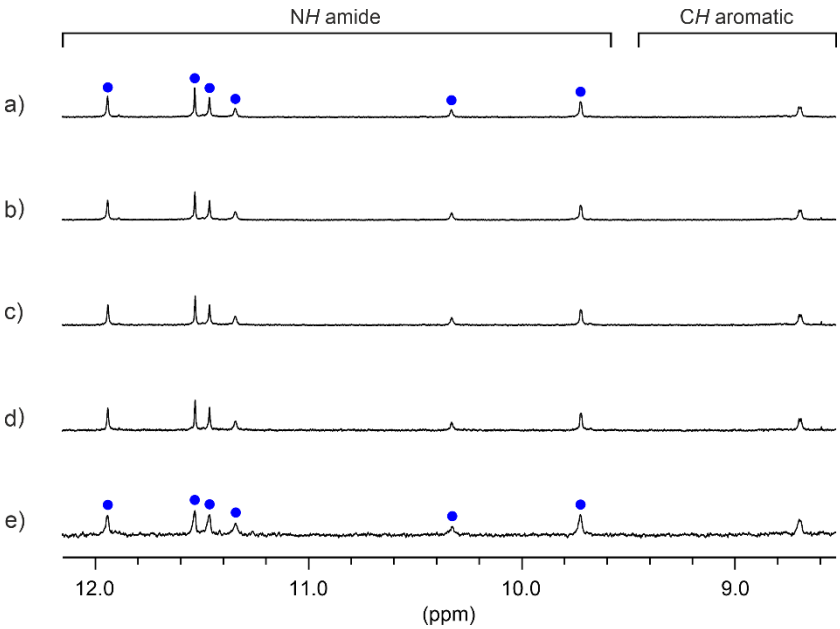


Figure S7. Part of the ^{1}H NMR spectra (700 MHz) of amide and aromatic regions at 323 K in 50 mM ammonium acetate aqueous buffer (NH_4OAc in H_2O/D_2O - 95:5 vol/vol at pH 6.8) of the oligomer **1** at a) 100 µM, b) 80 µM, c) 60 µM, d) 40 µM and e) 20 µM. Amide signals of the double helix **(1)**$_2$ are marked with blue circles. Spectra were calibrated with TSP-d_4.

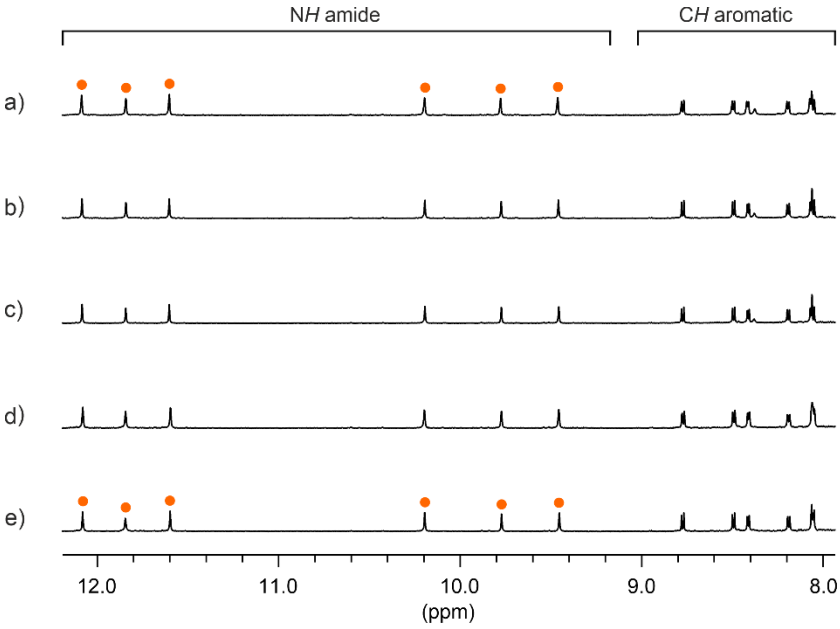


Figure S8. Part of the ^{1}H NMR spectra (700 MHz) of amide and aromatic regions at 323 K in H_2O/D_2O (95:5 vol/vol) of the oligomer **3** at a) 100 µM, b) 80 µM, c) 60 µM, d) 40 µM and e) 20 µM. Amide signals of the double helix **(3)**$_2$ are marked with orange circles. Spectra were calibrated with TSP-d_4.

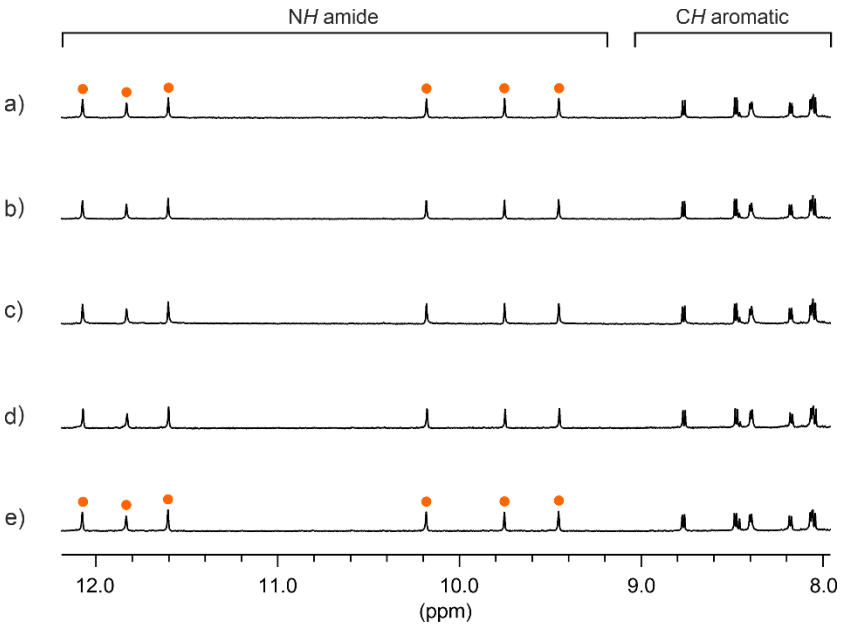


Figure S9. Part of the ^{1}H NMR spectra (700 MHz) of amide and aromatic regions at 323 K in 50 mM ammonium acetate aqueous buffer (NH_4OAc in H_2O/D_2O - 95:5 vol/vol at pH 6.8) of the oligomer **3** at a) 100 µM, b) 80 µM, c) 60 µM, d) 40 µM and e) 20 µM. Amide signals of the double helix **(3)**$_2$ are marked with orange circles. Spectra were calibrated with TSP-d_4.

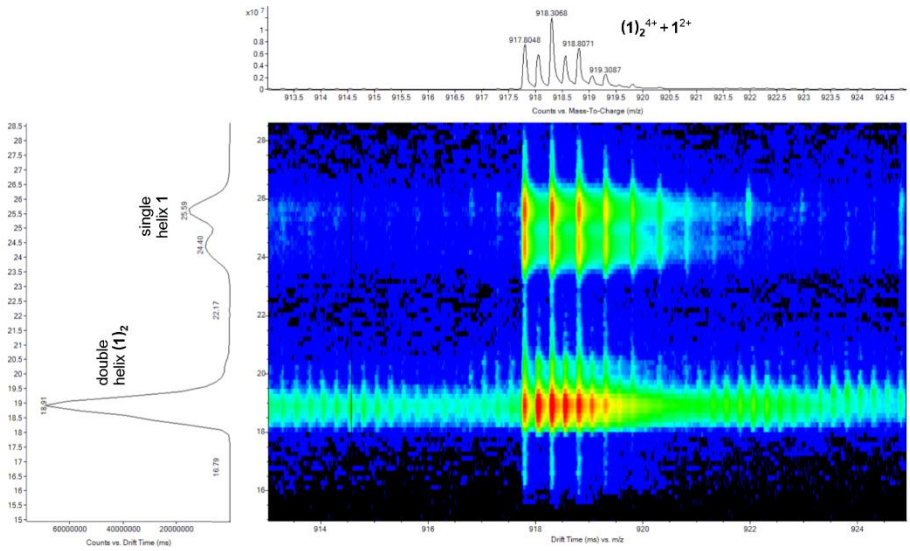


Figure S10. Ion-mobility mass spectra of the oligomer Ac-$Q^F{}_4Q_3$-OH **1** in 50 mM ammonium acetate aqueous buffer (53 µM, fragmentor at 320 V).

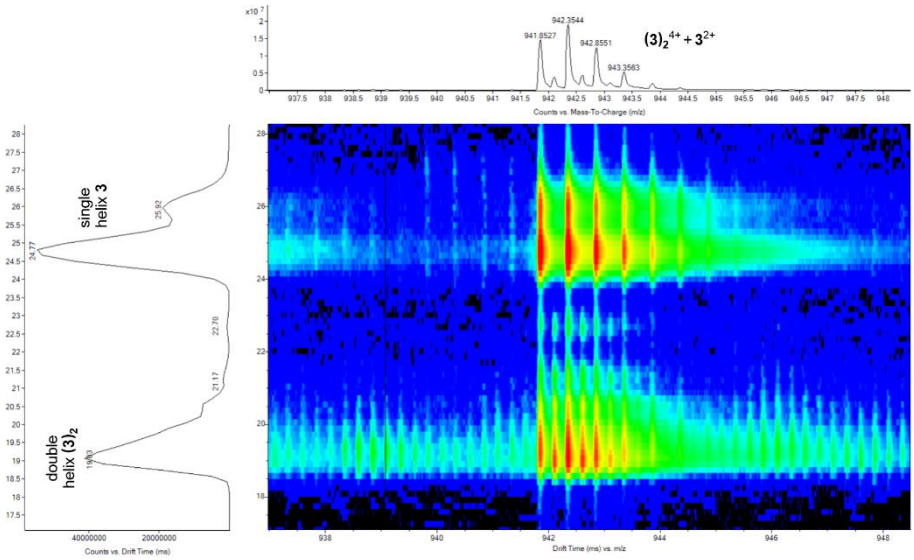


Figure S11. Ion-mobility mass spectra of the oligomer Ac-$Q^{OMe}{}_4Q_3$-OH **3** in 50 mM ammonium acetate aqueous buffer (53 µM, fragmentor at 320 V).

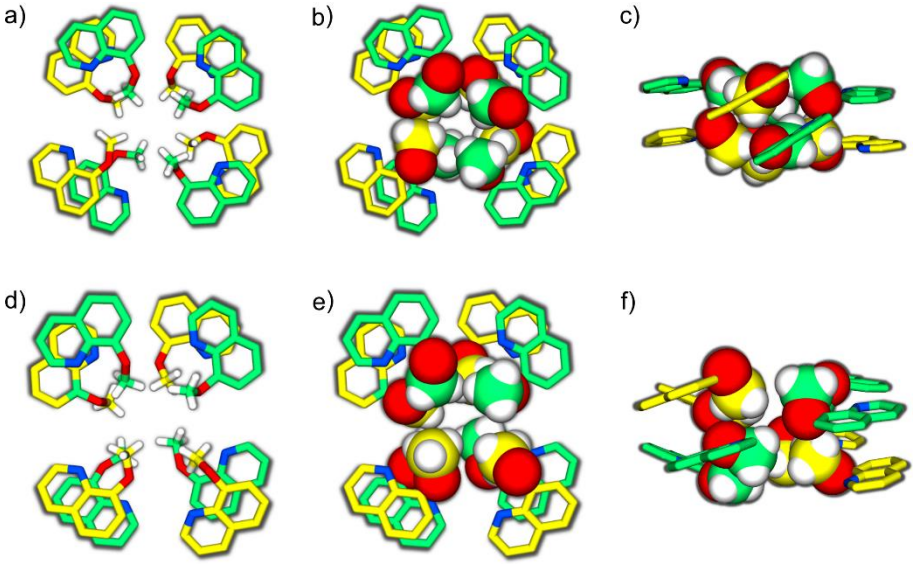


Figure S12. X-ray crystal structures of the cylindrical cavity of the homomeric double helix: a-c) **(5)**$_2$ and d-f) **(6)**$_2$. Carbon atoms of each helical molecular strands are represented with different colors (green and yellow). Water-soluble helix side chains and included solvent molecules have been removed for clarity.

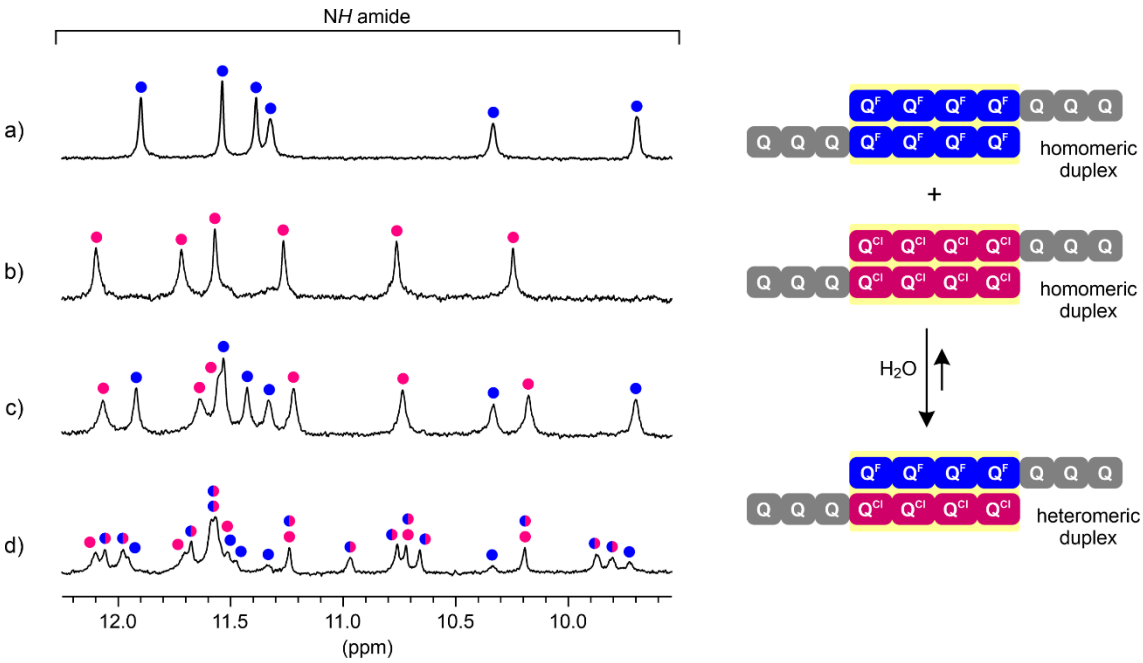


Figure S13. Part of the ^{1}H NMR spectra (H_2O/D_2O - 95:5 vol/vol, 300 MHz, 323 K, calibrated with TSP-d_4) of the amide region of a) the homomeric double helix **(1)**$_2$ (0.5 mM), b) the homomeric double helix **(2)**$_2$ (0.5 mM) and the mixture of both homomeric double helices after c) 12 h at 298 K and d) 12 h at 323 K (thermodynamic equilibrium). Amide signals of the homomeric double helix **(1)**$_2$, the homomeric double helix **(2)**$_2$ and the heteromeric double helix **(1·2)** are marked with blue, pink and blue/pink circles, respectively.

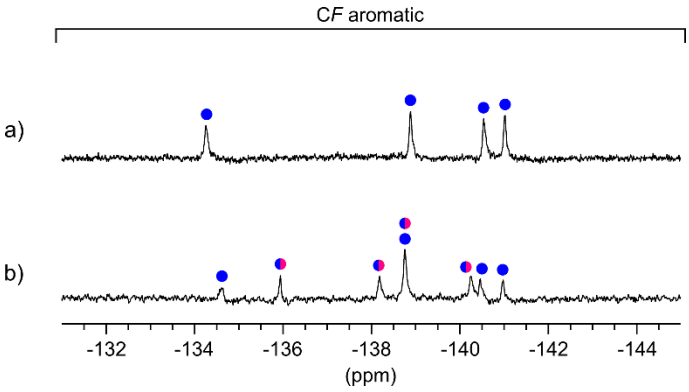


Figure S14. Part of the ^{19}F NMR spectra (H_2O/D_2O - 95:5 vol/vol, 376 MHz, 323 K, calibrated with TFE) of a) the homomeric double helix **(1)**$_2$ (0.5 mM) and b) the mixture of homomeric double helices **(1)**$_2$ (0.5 mM) and **(2)**$_2$ (0.5 mM) at the thermodynamic equilibrium. Fluorine signals of the homomeric double helix **(1)**$_2$ and the heteromeric double helix **(1·2)** are marked with blue and blue/pink circles, respectively.

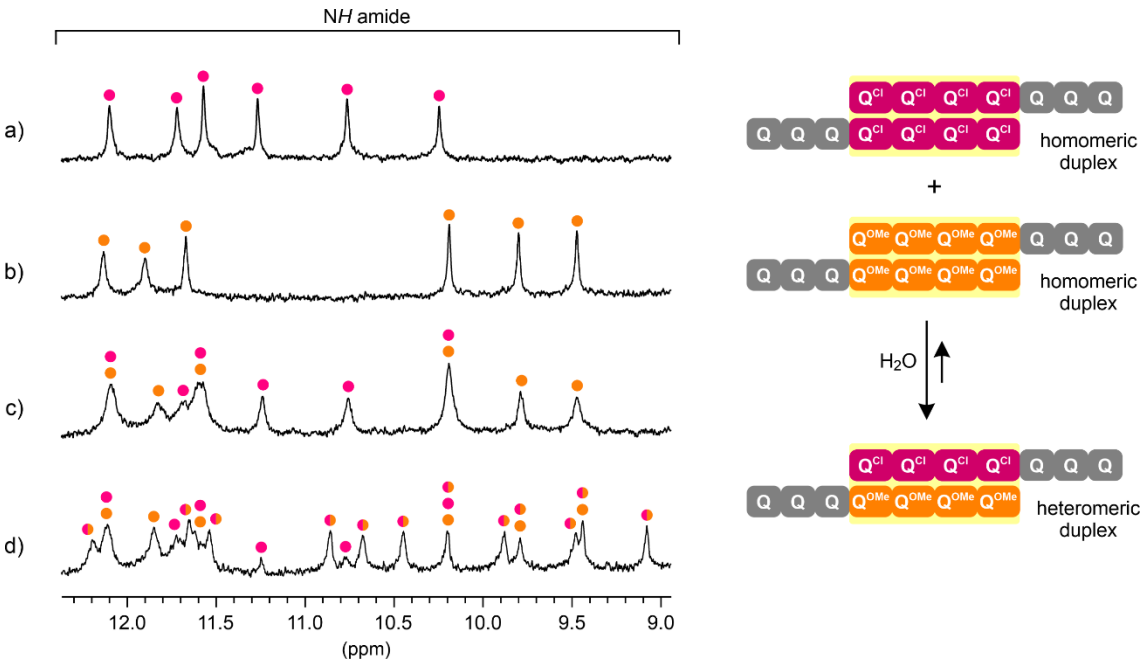


Figure S15. Part of the ^{1}H NMR spectra (H_2O/D_2O-95:5 vol/vol, 300 MHz, 323 K, calibrated with TSP-d_4) of the amide region of a) the homomeric double helix **(2)**$_2$ (0.5 mM), b) the homomeric double helix **(3)**$_2$ (0.5 mM) and the mixture of both homomeric double helices after c) 12 h at 298 K and d) 12 h at 323 K (thermodynamic equilibrium). Amide signals of the homomeric double helix **(2)**$_2$, the homomeric double helix **(3)**$_2$ and the heteromeric double helix **(2·3)** are marked with pink, orange and pink/orange circles, respectively.

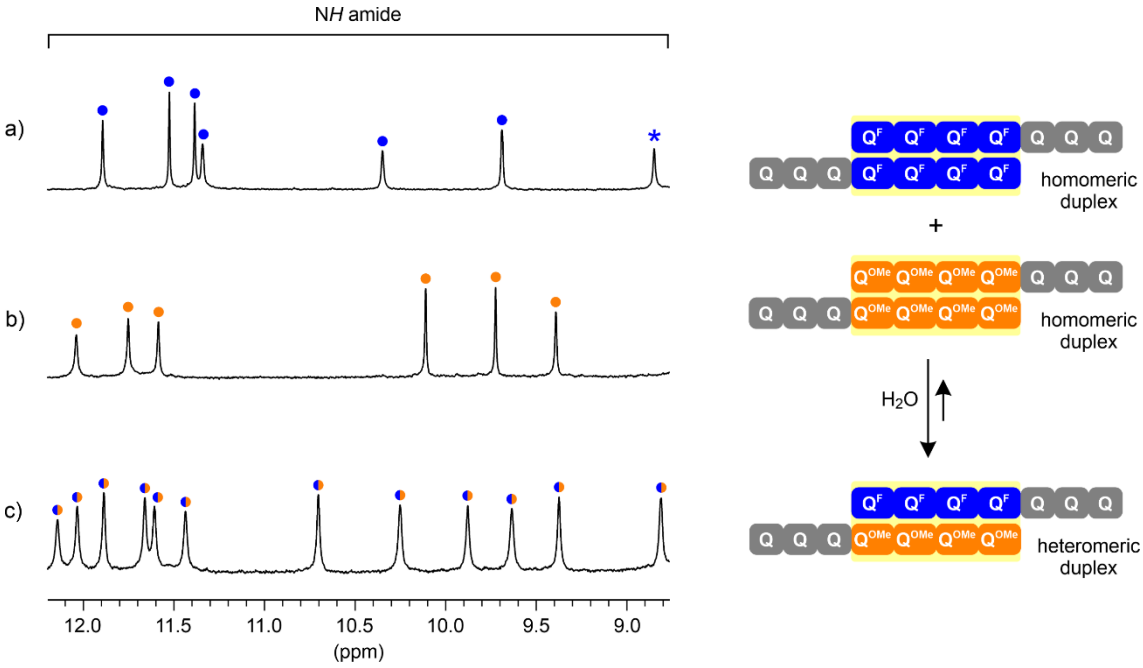


Figure S16. Part of the ^{1}H NMR spectra (700 MHz, calibrated with TSP-d_4) of the amide region at 323 K in H_2O/D_2O (95:5 vol/vol) of a) the homomeric double helix **(1)**$_2$ (0.5 mM), b) the homomeric double helix **(3)**$_2$ (0.5 mM) and c) the mixture of both homomeric double helices at the thermodynamic equilibrium (less than 5 min). Amide signals of the homomeric double helix **(1)**$_2$, the homomeric double helix **(3)**$_2$ and the heteromeric double helix **(1·3)** are marked with blue, orange and blue/orange circles, respectively. The star denotes the N*H*Ac amide signal of the homomeric double helix **(1)**$_2$.

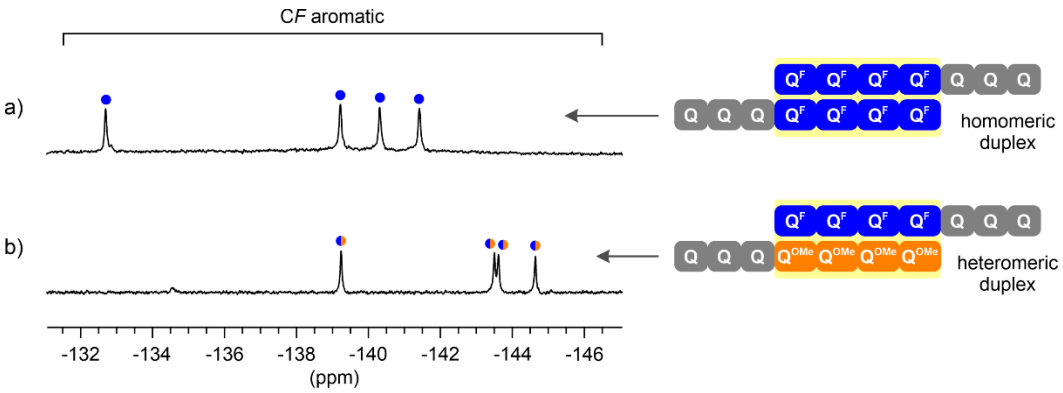


Figure S17. Part of the ^{19}F NMR spectra (376 MHz) at 323 K in H_2O/D_2O (95:5 vol/vol) of a) the homomeric double helix **(1)**$_2$ and b) the heteromeric double helix **(1·3)**. Fluorine signals of the homomeric double helix **(1)**$_2$ and the heteromeric double helix **(1·3)** are marked with blue and blue/orange circles, respectively. Spectra were calibrated with TFE (external standard, insert tube).

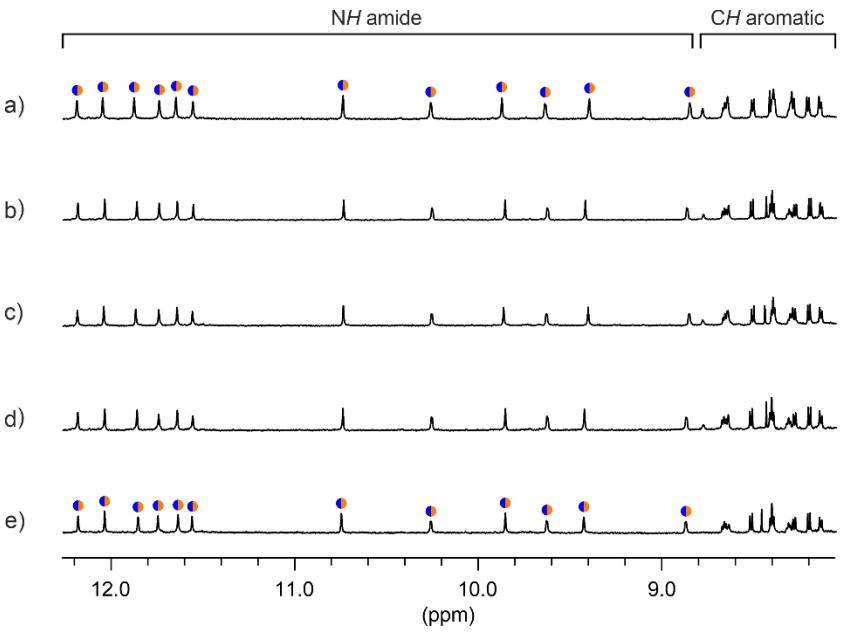


Figure S18. Part of the ^{1}H NMR spectra (700 MHz) of amide and aromatic regions at 323 K in H_2O/D_2O (95:5 vol/vol) of an equimolar mixture of oligomers **1** and **3** composed of a) 100 µM, b) 80 µM, c) 60 µM, d) 40 µM and e) 20 µM of each sequence. Amide signals of the heteromeric double helix **(1·3)** are marked with blue/orange circles. Spectra were calibrated with TSP-d_4.

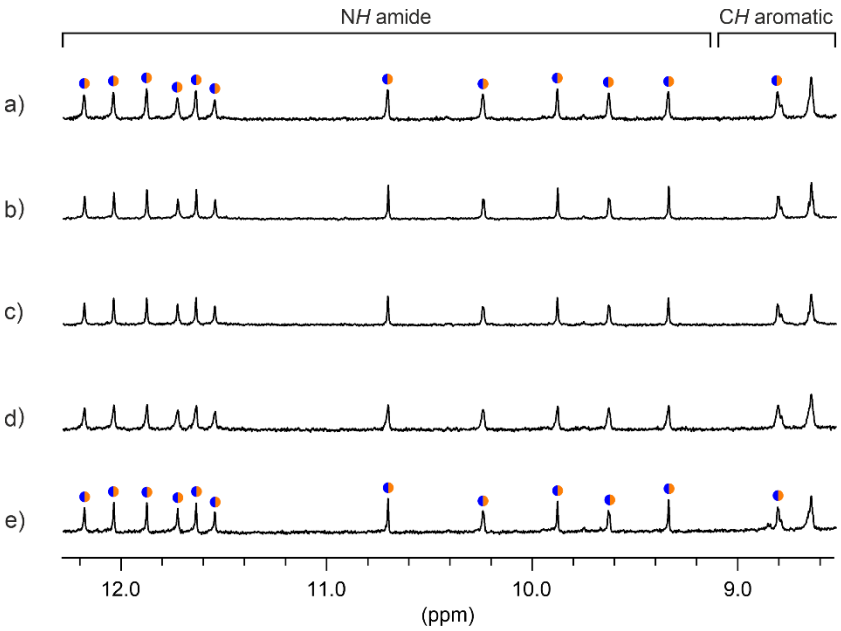


Figure S19. Part of the ^{1}H NMR spectra (700 MHz) of amide and aromatic regions at 323 K in 50 mM ammonium acetate aqueous buffer (NH_4OAc in H_2O/D_2O - 95:5 vol/vol at pH 6.8) of an equimolar mixture of oligomers **1** and **3** composed of a) 100 µM, b) 80 µM, c) 60 µM, d) 40 µM and e) 20 µM of each sequence. Amide signals of the heteromeric double helix **(1·3)** are marked with blue/orange circles. Spectra were calibrated with TSP-d_4.

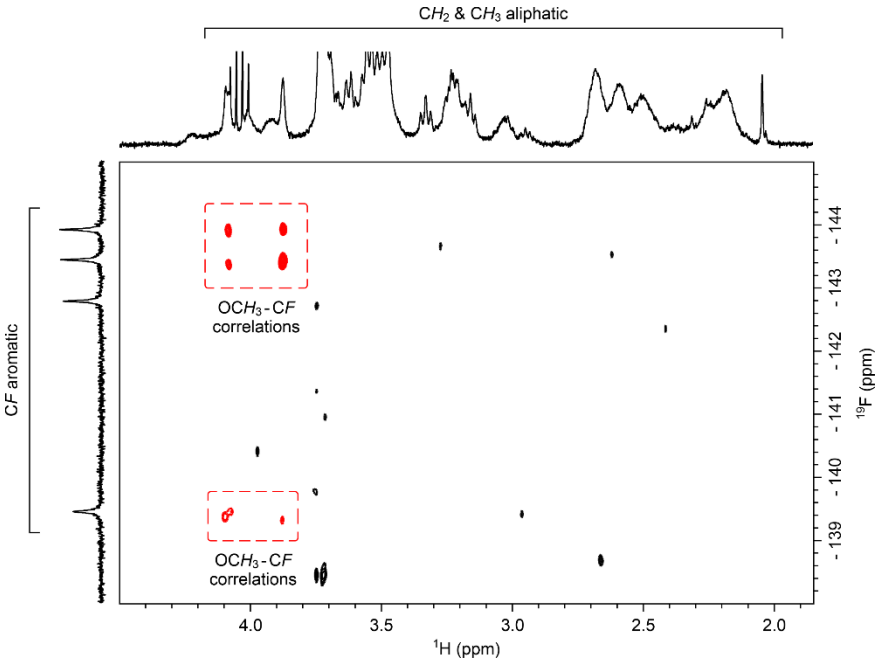


Figure S20. Zoom of the 2D ^{1}H - ^{19}F HOESY NMR spectrum (mixing time of 1 s) of the heteromeric double helix **(1·7)** at 2 mM (H_2O/D_2O - 95:5 vol/vol, 400 MHz, 323 K) showing correlations between fluorine atoms (located inside the cavity of the duplex) and methoxy substituents (also inside the cavity). The proton spectrum was calibrated with TSP-d_4 (internal standard) and the fluorine spectrum was calibrated with TFE (external standard, insert tube).

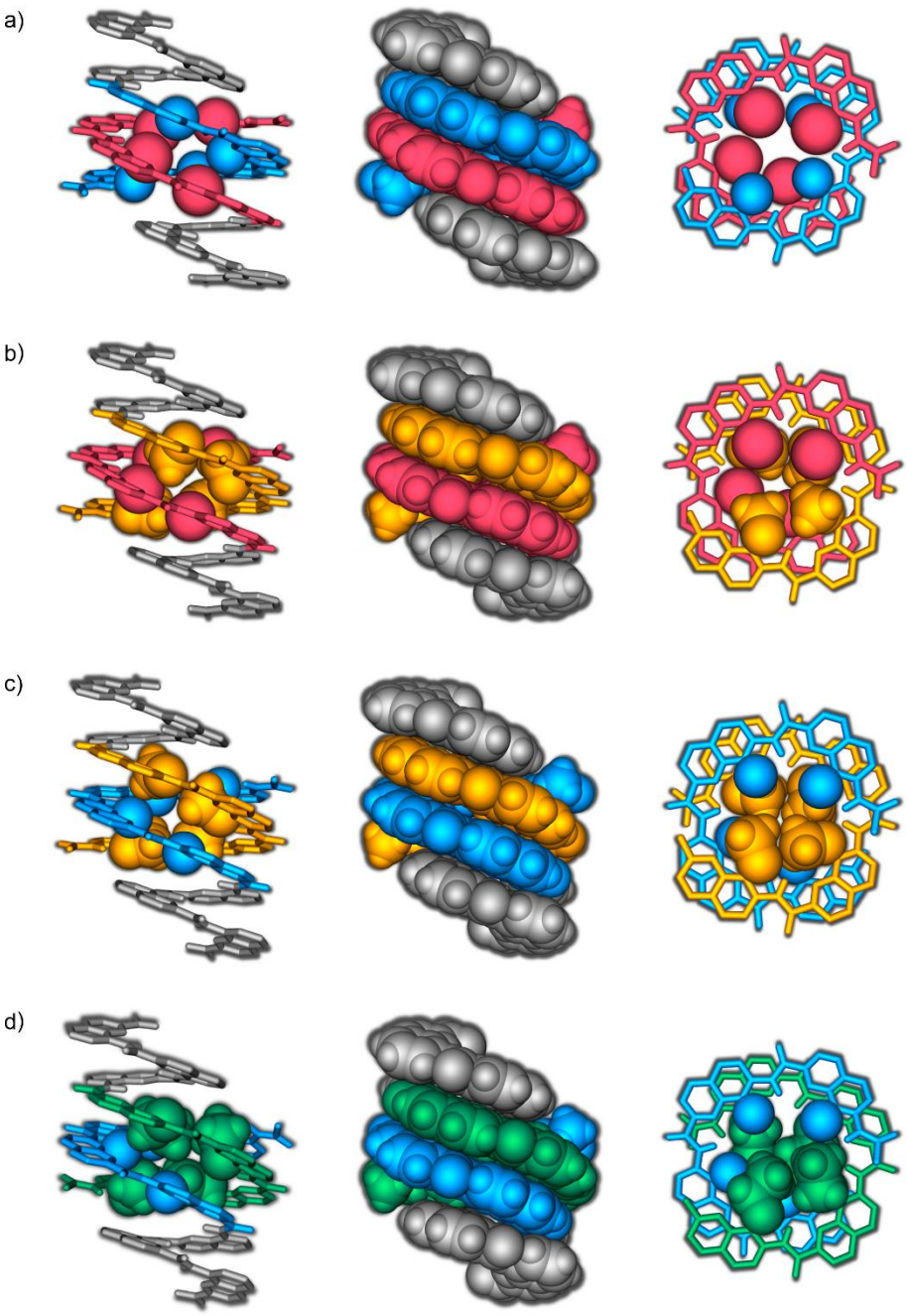


Figure S21. Side and top views of energy-minimized structures (MMFFs) in water of heteromeric double helices a) **(1·2)**, b) **(2·3)**, c) **(1·3)** and d) **(1·4)**. On the left, double helices are shown in tube representation without hydrogen atoms and all the substituents in position 8 of 8-substituted quinoline monomers are shown in CPK representation with hydrogen atoms. In the middle, double helices are shown in CPK representation with hydrogen atoms. And on the right, both Q_3 segments were removed for clarity and only the central cylindrical cavity of heteromeric double helices is shown in tube representation without hydrogen atoms whereas the substituents in position 8 of 8-substituted quinoline monomers are shown in CPK representation with hydrogen atoms. Lateral chains in position 4 of quinoline monomers were omitted for clarity. Q, Q^F, Q^{Cl}, Q^{OMe} and Q^{OEt} monomers are colored in grey, blue, pink, orange and green, respectively.

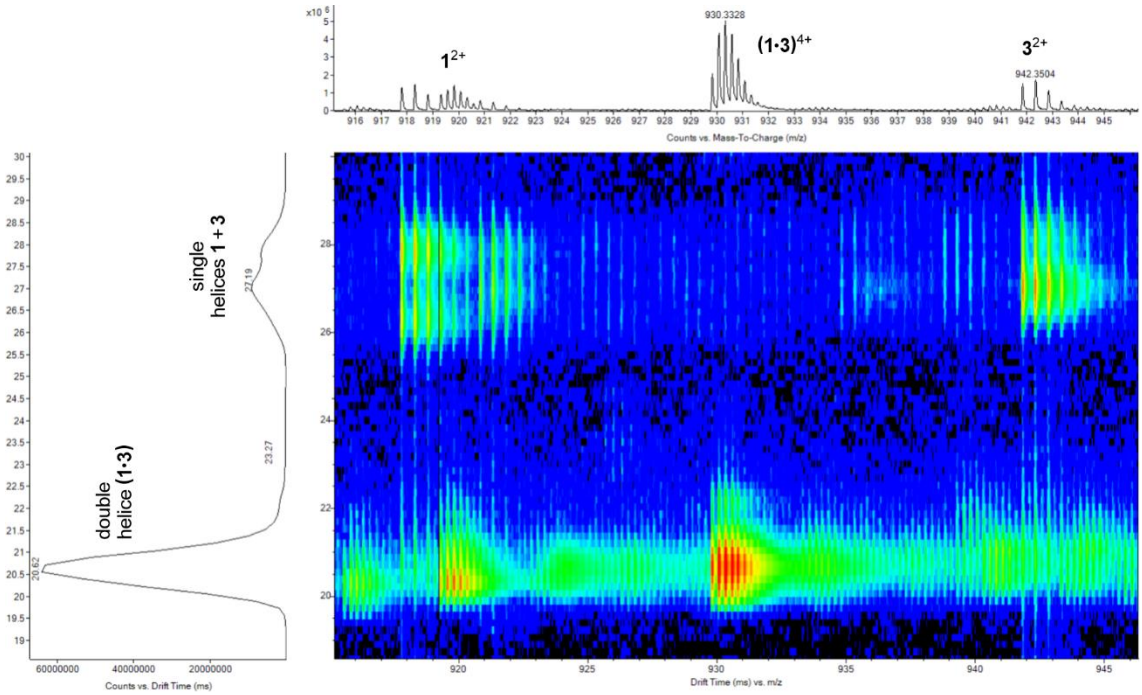


Figure S22. Ion-mobility mass spectra of an equimolar mixture of oligomers Ac-$Q^{F}{}_{4}Q_{3}$-OH **1** (53 µM) and Ac-$Q^{OMe}{}_{4}Q_{3}$-OH **3** (53 µM) in 50 mM ammonium acetate aqueous buffer (fragmentor at 320 V).

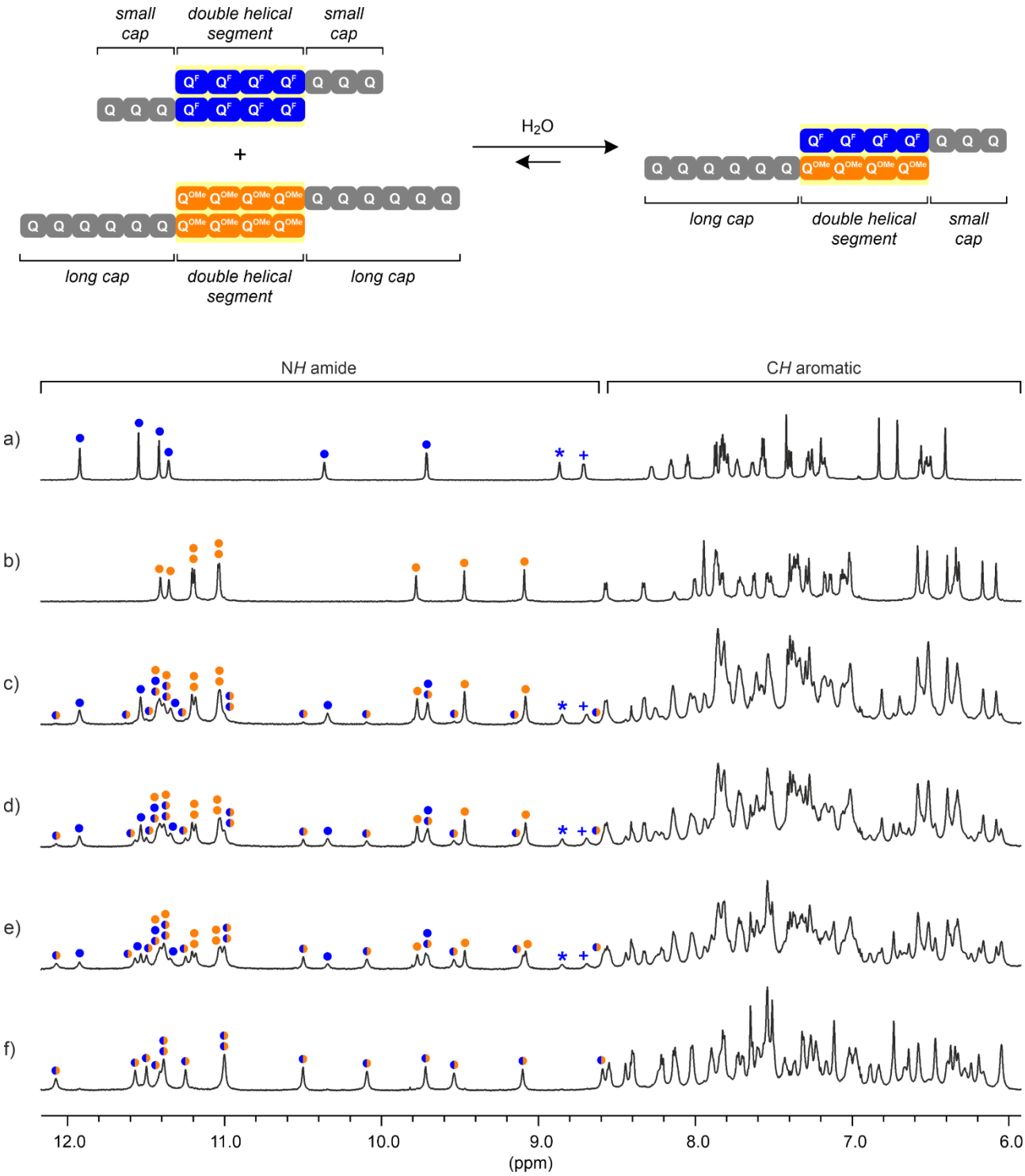


Figure S23. Part of the ^{1}H NMR spectra (700 MHz) of amide and aromatic regions at 323 K in H_2O/D_2O (95:5 vol/vol) of a) the homomeric double helix **(1)**$_2$ (0.5 mM), b) the homomeric double helix **(7)**$_2$ (0.5 mM) and a mixture of both homomeric double helices after c) 3 min, d) 20 min, e) 40 min and f) 1 h 30 min (thermodynamic equilibrium). Amide signals of the homomeric double helix **(1)**$_2$, the homomeric double helix **(7)**$_2$ and the heteromeric double helix **(1·7)** are marked with blue, orange and blue/orange circles, respectively. The star and the cross denote the N*H*Ac amide signal and one aromatic signal of the homomeric double helix **(1)**$_2$, respectively. Spectra were calibrated with TSP-d_4 (internal NMR standard).

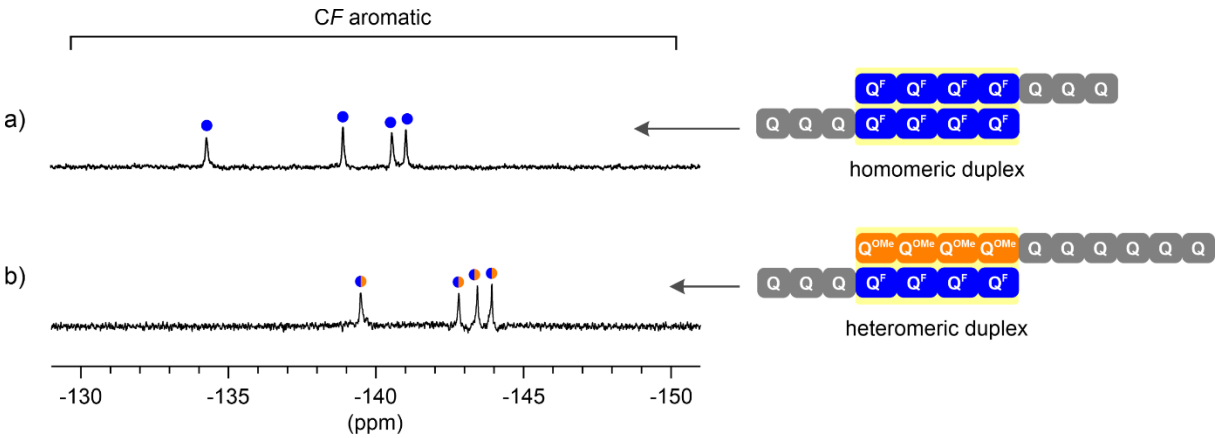


Figure S24. Part of the ^{19}F NMR spectra (376 MHz) at 323 K in H_2O/D_2O (95:5 vol/vol) of a) the homomeric double helix **(1)**$_2$ and b) the heteromeric double helix **(1·7)**. Fluorine signals of the homomeric double helix **(1)**$_2$ and the heteromeric double helix **(1·7)** are marked with blue and blue/orange circles, respectively. Spectra were calibrated with TFE (external NMR standard, insert tube).

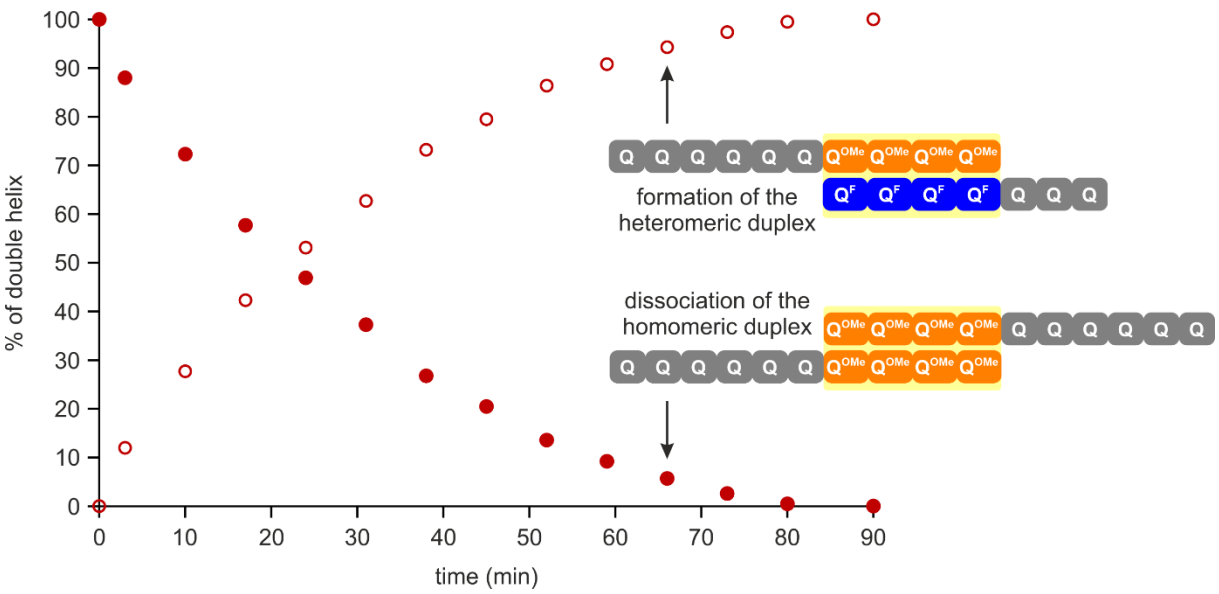


Figure S25. Time trace of heteroduplex cross-hybridization of a mixture between the homomeric double helix **(1)**$_2$ (0.5 mM) and the homomeric double helix **(7)**$_2$ (0.5 mM), monitored by ^{1}H NMR spectroscopy (700 MHz) at 323 K in H_2O/D_2O (95:5 vol/vol). Full red circles represente the dissociation of the homomeric duplex **(7)**$_2$ whereas empty red circles represente the formation of the heteromeric duplex **(1·7)**.

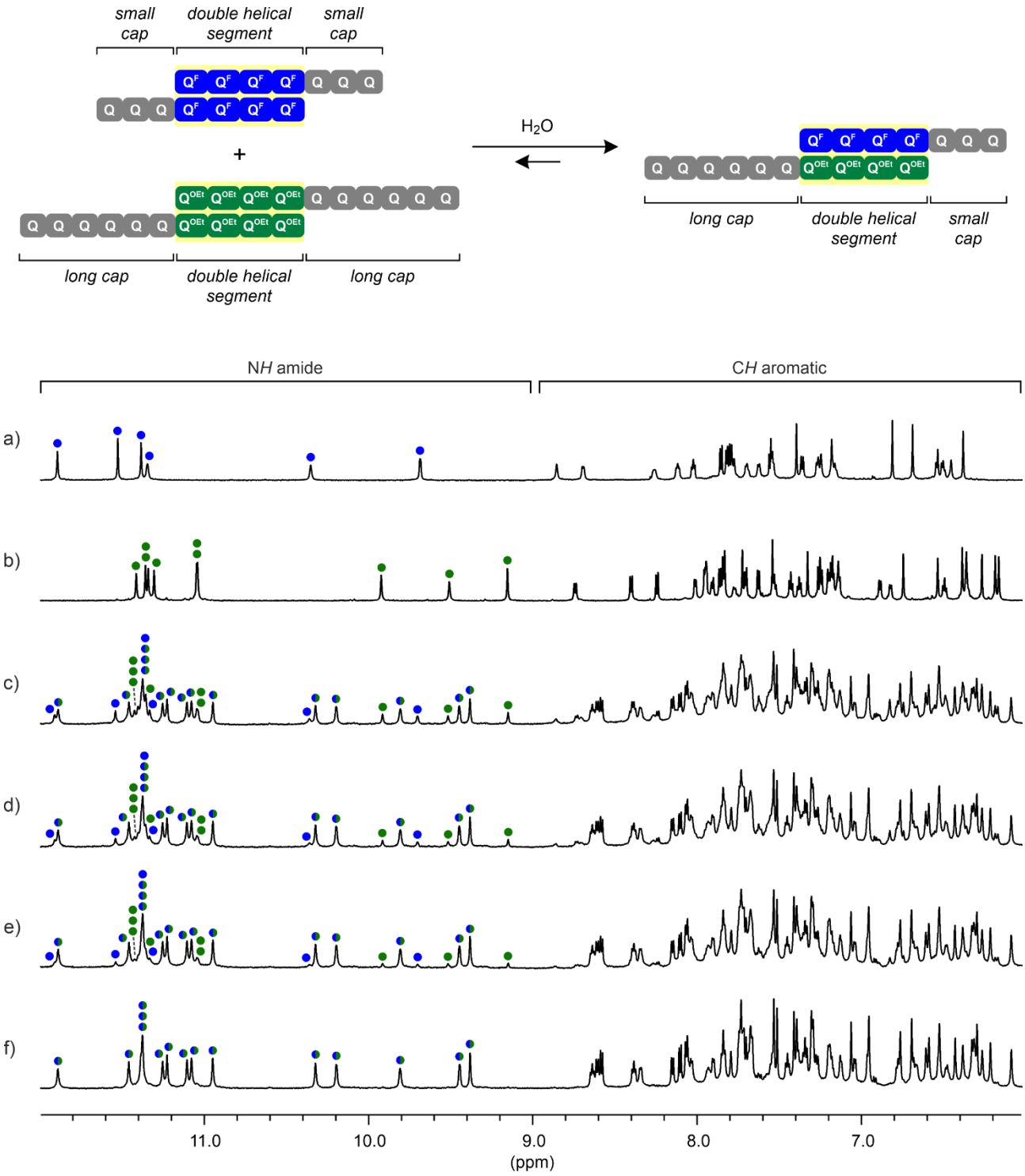


Figure S26. Part of the ^{1}H NMR spectra (700 MHz) of amide and aromatic regions at 323 K in H_2O/D_2O (95:5 vol/vol) of a) the homomeric double helix **(1)**$_2$ (0.5 mM), b) the homomeric double helix **(8)**$_2$ (0.5 mM) and a mixture of both homomeric double helices after c) 3 min, d) 6 min, e) 9 min and f) 15 min (thermodynamic equilibrium). Amide signals of the homomeric double helix **(1)**$_2$, the homomeric double helix **(8)**$_2$ and the heteromeric double helix **(1·8)** are marked with blue, green and blue/green circles, respectively. Spectra were calibrated with TSP-d_4 (internal NMR standard).

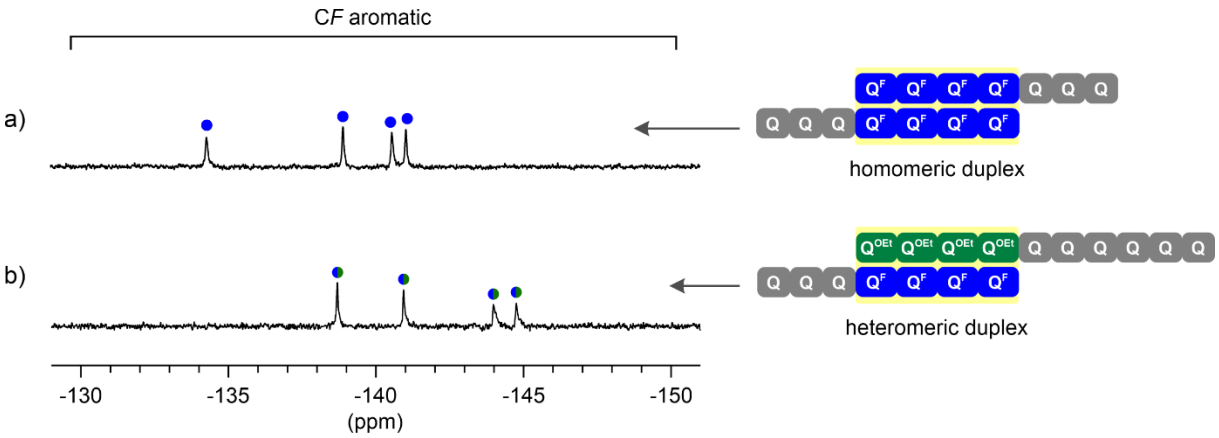


Figure S27. Part of the ^{19}F NMR spectra (376 MHz) at 323 K in H_2O/D_2O (95:5 vol/vol) of a) the homomeric double helix **(1)**$_2$ and b) the heteromeric double helix **(1·8)**. Fluorine signals of the homomeric double helix **(1)**$_2$ and the heteromeric double helix **(1·8)** are marked with blue and blue/green circles, respectively. Spectra were calibrated with TFE (external NMR standard, insert tube).

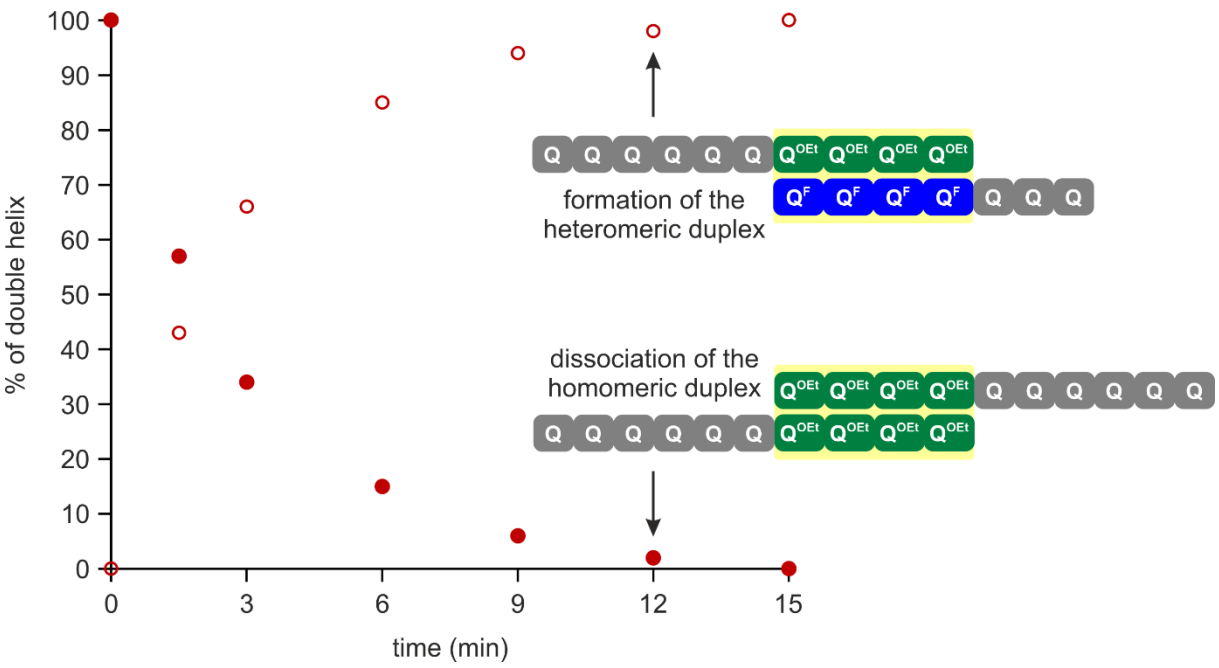


Figure S28. Time trace of heteroduplex cross-hybridization of a mixture between the homomeric double helix **(1)**$_2$ (0.5 mM) and the homomeric double helix **(8)**$_2$ (0.5 mM), monitored by ^{1}H NMR spectroscopy (700 MHz) at 323 K in H_2O/D_2O (95:5 vol/vol). Full red circles represente the dissociation of the homomeric duplex **(8)**$_2$ whereas empty red circles represente the formation of the heteromeric duplex **(1·8)**.

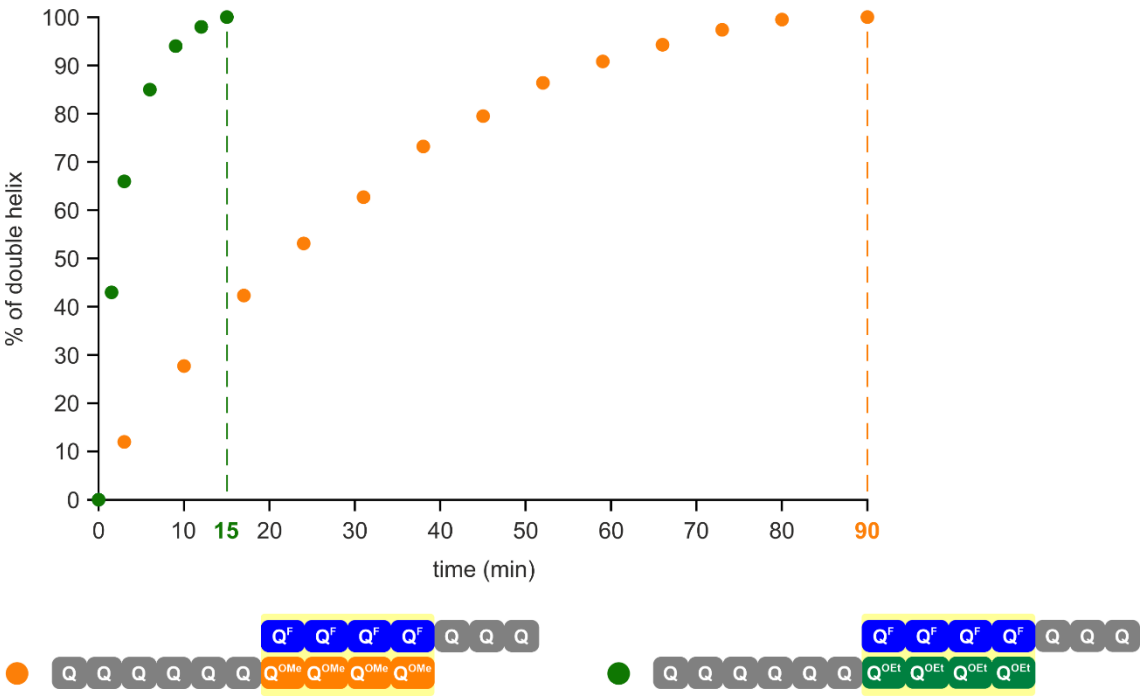


Figure S29. Time traces comparison of heteroduplex cross-hybridization of the heteromeric double helix **(1·7)** (orange circles) and the heteromeric double helix **(1·8)** (green circles), monitored by ^{1}H NMR spectroscopy (700 MHz) at 323 K in H_2O / D_2O (95:5 vol/vol). The heteromeric double helix **(1·7)** is quantitatively formed after 1 h 30 min whereas the heteromeric double helix **(1·8)** is quantitatively formed after 15 min, based on the integration of amide regions.

Table S1. Conditions and conversions for the hybridization of heteromeric duplex **(1·2)**, **(2·3)**, **(1·3)**, **(1·4)**, **(1·7)** and **(1·8)**. Conversions were measured by ^{1}H NMR spectroscopy based on the integration of amide signals.

Double helix	Concentration	Solvent	Temperature	Reaction time	NMR conditions	Conversion
(1·2)	1 mM	H_2O	338 K	12 h	300 MHz, 323 K	78 %
(2·3)	1 mM	H_2O	338 K	12 h	300 MHz, 323 K	87 %
(1·3)	1 mM	H_2O	298 K	< 5 min	700 MHz, 323 K	quant.
(1·4)	1 mM	H_2O	298 K	< 5 min	700 MHz, 323 K	quant.
(1·7)	1 mM	H_2O	298 K	1 h 30 min	700 MHz, 323 K	quant.
(1·8)	1 mM	H_2O	298 K	15 min	700 MHz, 323 K	quant.

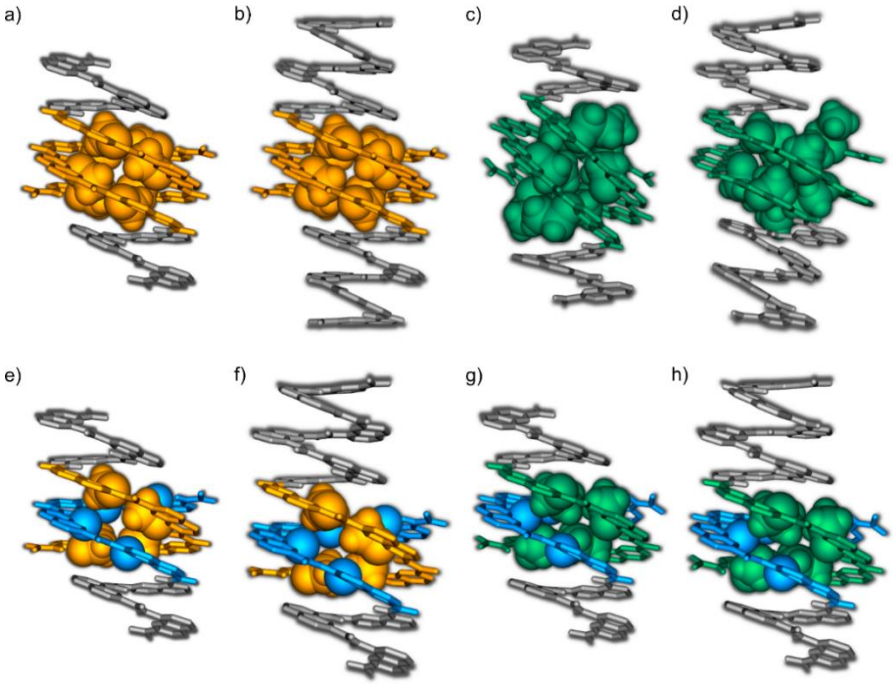


Figure S30. Energy-minimized structures (MMFFs) in water of double helices a) **(3)**$_2$, b) **(7)**$_2$, c) **(4)**$_2$, d) **(8)**$_2$, e) **(1·3)**, f) **(1·7)**, g) **(1·4)** and h) **(1·8)**. Double helices are shown in tube representation and all the substituents in position 8 of 8-substituted quinoline monomers are shown in CPK representation. Lateral chains in position 4 of quinoline monomers, which are outside the cylindrical cavity, were omitted for clarity. Only the hydrogen atoms of the substituents in position 8 of 8-substituted quinoline monomers are shown.

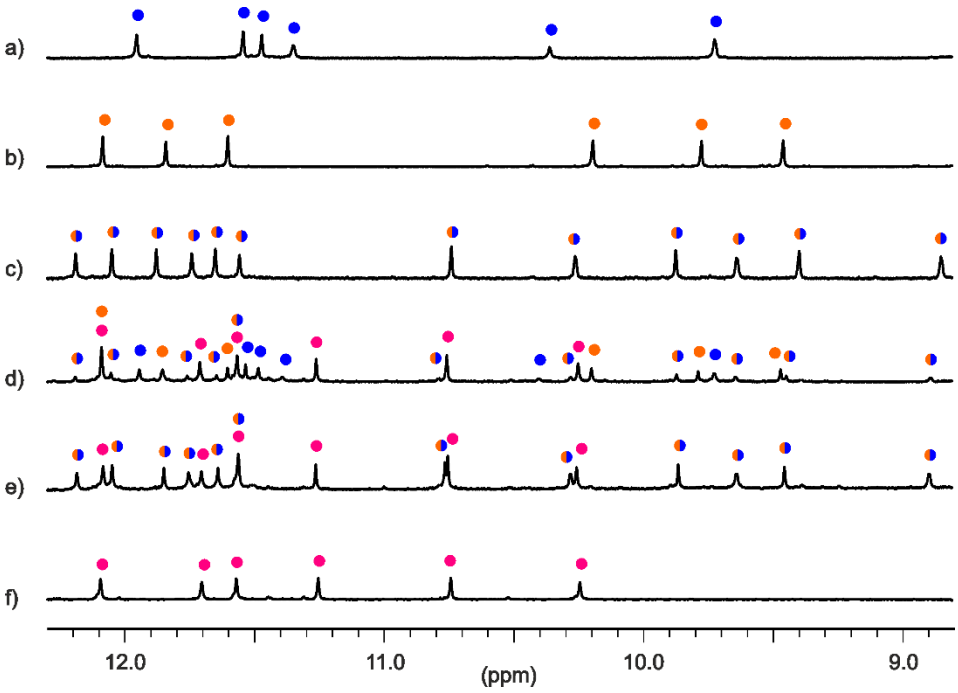


Figure S31. Part of the ^{1}H NMR spectra (700 MHz) of the amide region at 323 K in H_2O/D_2O (95:5 vol/vol) of a) the homomeric double helix **(1)**$_2$ (0.5 mM), b) the homomeric double helix **(3)**$_2$ (0.5 mM), c) the heteromeric double helix **(1.3)** (0.5 mM) and a mixture of the 3 homomeric double helices **(1)**$_2$, **(2)**$_2$ and **(3)**$_2$ after d) 30 min, e) 24 hours (at thermodynamic equilibrium). f) the homomeric double helix **(2)**$_2$ (0.5 mM) for comparison. Amide signals of **(1)**$_2$, **(2)**$_2$, **(3)**$_2$ and **(1·3)** are marked with blue, pink, orange, and orange/blue circles, respectively. Spectra were calibrated with TSP-d_4 (internal NMR standard).

3. Supplementary methods

3.1 Nuclear magnetic resonance spectroscopy

NMR spectra were recorded on 4 different NMR spectrometers: (1) an Avance II NMR spectrometer (Bruker BioSpin) with a vertical 7.05 T narrow-bore / ultrashield magnet operating at 300 MHz for ^{1}H observation, 282 MHz for ^{19}F observation and 75 MHz for ^{13}C observation by means of a 5-mm BBFO ^{15}N-^{31}P $^{19}F/^{1}H$ probe with Z gradient capabilities; (2) an Avance III HD 400 NMR spectrometer (Bruker BioSpin) with a vertical 9.4 T narrow-bore / ultrashield magnet operating at 400 MHz for ^{1}H observation, 376 MHz for ^{19}F observation and 100 MHz for ^{13}C observation by means of a 5-mm Smartprobe ^{109}Ag-^{31}P $^{19}F/^{1}H$ with gradient capabilities; (3) an Avance NEO NMR spectrometer (Bruker BioSpin) with a vertical 16.45 T narrow-bore / ultrashield magnet operating at 700 MHz for ^{1}H observation by means of a 5-mm TXI $^{1}H/^{13}C/^{15}N$ probe with Z gradient capabilities; (4) an Avance NEO NMR spectrometer (Bruker BioSpin) with a 18 T standard bore magnet operating at 800 MHz for ^{1}H observation by means of a 5-mm TCI $^{1}H/^{13}C/^{15}N$ cryoprobe with Z gradient capabilities. Chemical shifts are reported in parts per million (δ, ppm) relative to the ^{1}H residual signal of the deuterated solvent used or a NMR standard. ^{1}H NMR splitting patterns with observed first-order coupling are designated as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Coupling constants (*J*) are reported in hertz (Hz). Data processing was performed with Topspin 4.0 software (Bruker BioSpin).

3.2 Electrospray ionization mass spectrometry

Mass spectrometry experiments were carried out on a Thermo Scientific Exactive Orbitrap spectrometer equipped with a HESI electrospray source (Mass Spectrometry Laboratory, European Institute of Chemistry and Biology, UMS 3033, Pessac, France). The experiments were performed in positive ion mode using soft source conditions. The spray voltage was maintained at 3.7 kV, the capillary temperature was 140 °C, the skimmer voltage was 10 V, the gate lens inject was 6.2 V and the tube lens offset was 195 V. The samples were dissolved in ultrapure water and were injected in the HESI source using a 250 µL hamilton syringe at 6 $\mu L.min^{-1}$. In-source collisions induced partial homomeric and heteromeric duplex dissociation.

3.3 Native mass spectrometry

The foldamers are dissolved in ammonium acetate 50 mM using water from Biosolve (UPLC-MS grade). Foldamer solution were diluted at 13 µM, 26 µM and 50 µM in 50 mM NH_4OAc and heated to 80 °C for 5 min followed by a slow cooling down to ambient temperature (5 hours). Experiments were performed on an Agilent 6560 DTIMS-Q-TOF instrument (Agilent Technologies, Santa Clara, CA), with the dual-ESI source operated in the negative ion mode. A syringe pump flow rate of 190 µL/h was used. Capacitance diaphragm gauges are connected to the funnel vacuum chamber and to the drift tube. An in-house modification to the pumping system allows better equilibration of the pressures: a Edwards E2M40 vacuum pump (Edwards, UK) is connected to the source region with two Edwards SP16K diaphragm valves connected to the front pumping lines, while an Edwards nXR40i vacuum pump is connected to the Q-TOF region. The helium pressure in the drift tube was 3.89 ± 0.01 Torr, and the pressure in the trapping funnel was 3.79 ± 0.01 Torr. The pressure differential between the drift tube and the trapping funnel ensures only helium is present in the drift tube. The acquisition software version was B.09.00. All spectra were recorded using soft source conditions. The tuning parameters of the instrument (electrospray source, trapping region and post-IMS region (QTOF region)) are optimized as described elsewhere. The source temperature was set at 220 °C and the source fragmentor voltage was set to 320 V. The trapping time was 1000 µs and release time 200 µs. Trap entrance grid delta was set to 2 V.

3.4 High performance liquid chromatography

HPLC chromatograms were recorded on a Jasco LC-4000 analytical system, using RP-18 column (4.6*100 mm, 5 µm particle size). The elution method is H_2O + 0.1 % (vol/vol) TFA / CH_3CN + 0.1 % (vol/vol) TFA - 100:0 to 0:100 over a period of 7 min at 323 K. The wavelength of the UV detector is 254 nm.

3.5 X-ray crystallography

Aqueous solutions of **(5)$_2$** and **(6)$_2$** were prepared by dissolving the lyophilized powders in water to a final concentration of 3.5 mM and 5 mM respectively. Crystallization trials were carried with commercial sparse matrix screens using standard sitting drop vapor diffusion method at 293 K. X-ray quality crystals of **(5)$_2$** were obtained after three weeks by the addition of 0.8 µL of **(5)$_2$** and 0.8 µL of 35 % vol/vol 2-methyl-2,4-pentanediol (MPD), 20 mM BIS-TRIS buffer at pH 6.0, 50 mM sodium chloride, and 10 mM calcium chloride in the reservoir. X-ray quality crystals of **(6)$_2$** grew in 2 months by the addition of 0.8 µL of **(6)$_2$** and 0.8 µL of 9 % vol/vol 2-propanol, 50 mM imidazole buffer (pH 7.2), 15 mM magnesium acetate and 15 mM magnesium chloride in the reservoir. For low temperature diffraction measurement, crystals were fished using a micro-loop and plunged into liquid nitrogen. The mother liquor served as cryo-protectant for **(5)$_2$** while crystals of **(6)$_2$** were quickly soaked in 20 % weight/vol polyethylene glycol 8000 and 40 % vol/vol polyethylene glycol 400 for cryo-protection.

X-ray diffraction data for **(5)$_2$** was collected at the ID30B[1] beamline in European Synchrotron Radiation Facility (ESRF), Grenoble. Diffraction data was measured at T = 100.15 K, λ = 0.9184 Å. The crystal was exposed for 0.02 s and 0.2 ° oscillation per frame and a rotation pass of 360 ° was measured using a EIGER2 X 9M 450 µm Si sensor (Dectris) detector. Diffraction data was processed using the program *XDS*.[2] The crystal belonged to space group *C2/c* with unit cell parameters: a = 48.390 (10) Å, b = 21.957 (4) Å, c = 41.081 (10) Å, β = 109.840 (10) °; V = 41058 (12) Å^3 and two independent helices per asymmetric unit (Z = 16, Z' = 2). The structure was solved with *SHELXT*[3] structure solution program using Intrinsic Phasing and refined by full-matrix least-squares method on F^2 with *SHELXL*-2014[4] within *Olex2*.[5] The initial structure revealed all main-chain atoms of a homo-dimer. One of the aspartate side-chain was refined with two positions and partial occupancy. AFIX, SADI, DFIX and FLAT instructions were used to improve the geometry of molecules. All non-H atoms were refined with anisotropic displacement parameters. After several attempts to model the disordered side chains, the SQUEEZE[6] procedure was used to flatten the electron density map. Very disordered solvent molecules were removed. Calculated total potential solvent accessible void volume and electron count per cell are 10452.2 Å^3 and 3272, respectively. Hydrogen atoms for **(5)$_2$** were placed at idealized positions.

X-ray diffraction data for **(6)$_2$** was collected at P14 beamline operated by EMBL Hamburg, at the PETRA III storage ring (DESY, Hamburg) with an EIGER2 CdTe 16M detector. Diffraction data was measured at T = 100 K, λ = 0.9762 Å. The crystal was exposed for 0.08 s and 0.2 ° oscillation per frame and a rotation pass of 360 ° was collected. Diffraction data was processed using the program *XDS*.[2] The crystal belonged to space group *P1* with unit cell parameters: a = 27.592 (3) Å, b = 30.158 (8) Å, c = 36.417 (1) Å, α = 100.190 (3) °, β = 110.202 (1) °, γ = 106.600 (8) °; V = 25942 (19) Å^3 and 4 independent homo-dimers in the asymmetric unit ($Z = Z'$ = 4). The structure was solved with *SHELXD*[7] structure solution program using Dual Space method and refined by full-matrix least-squares method on F^2 with *SHELXL*-2014[4] within *Olex2*.[5] The data comprised of weak diffraction intensity and poor resolution (at best 1.26 Å). Only after several iterations of least-squares refinement, most of the main-chain trace could be improved to reveal eight helices forming 2 *P* and 2 *M* homo-dimers. AFIX, SADI, DFIX and FLAT instructions were used to improve the geometry of molecules. Majority of

the aspartate side chains were severely disordered and partially modelled. After several attempts to model the disordered side chains, the SQUEEZE[6] procedure was used to flatten the electron density map. Very disordered solvent molecules were removed. Calculated total potential solvent accessible void volume and electron count per cell are 12825.4 $Å^3$ and 3880, respectively. Hydrogen atoms for **(6)$_2$** were placed at idealized positions.

Statistics of data collection and refinement of **(5)$_2$** and **(6)$_2$** are described in tables S2 and S3. The final CIF files of **(5)$_2$** and **(6)$_2$** were examined in IUCr's *checkCIF* algorithm. Due to the large volume fractions of disordered solvent molecules, weak diffraction intensity and poor resolution, a number of A- and B- level alerts remain in the *checkCIF* file. These alerts are inherent to the data set and refinement procedures. They are listed below and were divided into two groups. The first group demonstrates weak quality of the data and refinement statistics when compared to those expected for small molecule structures from highly diffracting crystals. The second group is concerned to decisions made during refinement and explained below. Atomic coordinates and structure factors of **(5)$_2$** and **(6)$_2$** were deposited in the Cambridge Crystallographic Data Centre (CCDC) with accession code 2216832 and 2232111, respectively. The data is available free of charge upon request (www.ccdc.cam.ac.uk/).

CheckCIF validation of **(5)$_2$**:

Group 1 alerts (these illustrate weak quality of data and refinement statistics if compared to small molecule structures from highly diffracting crystals):

THETM01_ALERT_3_A the value of sine(theta_max)/wavelength is less than 0.550

Calculated sin(theta_max)/wavelength = 0.5204

PLAT029_ALERT_3_A _diffrn_measured_fraction_theta_full value low	0.934	
PLAT084_ALERT_3_B high wR2 value (i.e. > 0.25)	0.42	Report
PLAT241_ALERT_2_B high 'MainMol' Ueq as compared to neighbors of		Check
PLAT242_ALERT_2_B low 'MainMol' Ueq as compared to neighbors of		Check
PLAT260_ALERT_2_B large average Ueq of residue including O06X	0.351	Check
PLAT260_ALERT_2_B large average Ueq of residue including O075	0.326	Check
PLAT260_ALERT_2_B large average Ueq of residue including O20	0.413	Check
PLAT430_ALERT_2_B short inter D...A contact		Check
PLAT911_ALERT_3_B missing FCF Refl between Thmin & STh/L = 0.520	1385	Report
PLAT934_ALERT_3_A number of (Iobs-Icalc)/Sigma(W) > 10 outliers	21	Check

Group 2 alert (is connected with decision made during refinement and explained below):

PLAT306_ALERT_2_B isolated oxygen atom (H-atoms missing ?)	Check

Dummy O atom was introduced into refinement

CheckCIF validation of **(6)$_2$**:

Group 1 alerts (these illustrate weak quality of data and refinement statistics if compared to small molecule structures from highly diffracting crystals):

THETM01_ALERT_3_A the value of sine(theta_max)/wavelength is less than 0.550

Calculated sin(theta_max)/wavelength = 0.3968

PLAT029_ALERT_3_A _diffrn_measured_fraction_theta_full value low	0.868	
PLAT080_ALERT_2_A maximum shift/error	2.15	Report
PLAT082_ALERT_2_A high R1 value	0.21	Report

PLAT084_ALERT_3_A high wR2 value (i.e. > 0.25)	0.53	Report
PLAT201_ALERT_2_A isotropic non-H atoms in main residue(s)	128	Report
PLAT202_ALERT_3_A isotropic non-H atoms in anion/solvent	879	Check
PLAT241_ALERT_2_A high 'MainMol' Ueq as compared to neighbors of C12		Check
PLAT242_ALERT_2_A low 'MainMol' Ueq as compared to neighbors of C5D		Check
PLAT411_ALERT_2_A short inter H...H contact		
PLAT430_ALERT_2_B short inter D...A contact		
PLAT340_ALERT_3_B low bond precision on C-C bonds	0.04211	Ang

Group 2 alert (is connected with decision made during refinement and explained below):

ATOM007_ALERT_1_A _atom_site_aniso_label is missing. Unique label identifying the atom site. The molecules were not refined with anisotropic displacement parameters.

SHFSU01_ALERT_2_A the absolute value of parameter shift to su ratio > 0.20. Absolute value of the parameter shift to su ratio given 2.154. Additional refinement cycles did not improve this. This is due to weak diffraction data of a high solvent content and severely disordered side chains.

PLAT306_ALERT_2_B isolated oxygen atom (H-atoms missing ?)	O7RA	Check

Dummy O atom was introduced into refinement

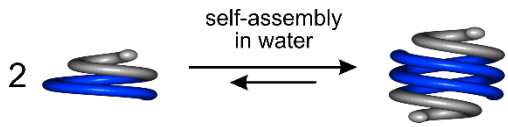
PLAT315_ALERT_2_B singly bonded carbon detected (H-atoms missing)	C34C	Check

This alert is due to partial modeling of severely disordered aspartate side chain

3.6 Molecular modeling

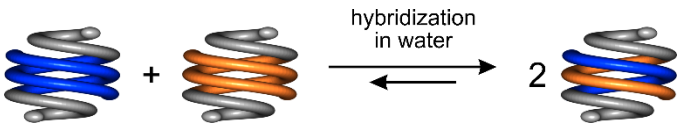
The crystal structure of the homomeric double helix **(6)**$_2$ was used to build its energy minimized molecular model. After the appropriate modifications of this model, models in water of homomeric doubles helices **(1)**$_2$-**(4)**$_2$, **(7)**$_2$-**(8)**$_2$ and heteromeric double helices **(1·2)**, **(2·3)**, **(1·3)**, **(1·4)**, **(1·7)** and **(1·8)** were obtained by minimization using the Merck Molecular Force Field static (MMFFs) implemented in MacroModel version 8.6 *via* Maestro version 6.5 (Schrödinger).

3.7 Formation of homomeric and heteromeric double helices



Homomeric double helices formation (self-assembly) in water:

Solutions of oligomers **1**-**4** and **7**-**8** (1 mM) in DMSO-d_6 / H_2O solvent mixtures (500 µL) were prepared in NMR tubes (5 mm diameter). After homogenization and equilibration, ^{1}H NMR spectra at 323 K were recorded on a 300 MHz spectrometer using a water suppression sequence (excitation sculpting). In the case of **1**, ^{19}F NMR spectra (proton decoupled) at 323 K were also recorded at 282.5 MHz. In DMSO (solvent known to disfavor the aggregation of aromatic oligoamide foldamers), oligomers **1**, **3**-**4** and **7**-**8** are folded as single helices whereas for **2** a mixture of the single helix **2** (minor species) and the double helix **(2)**$_2$ (major species) is observed. When the proportion of water increases, the quantitative self-assembly of single helices in antiparallel homomeric double helices is observed (slow exchange, at the NMR time scale). ^{1}H and ^{19}F NMR spectra were calibrated with TSP-d_4 (internal standard, chemical shifts are reported relative to the ^{1}H residual signal calibrated at δ = 0 ppm) and TFE (external standard, insert coaxial tube, chemical shifts are reported relative to the ^{19}F residual signal calibrated at δ = -76.76 ppm), respectively.

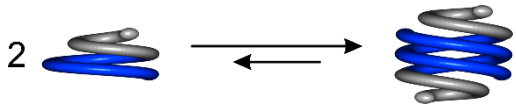


Heteromeric double helices formation (hybridization) in water:

Separately, solutions of two different oligomers (1 mM) in a H_2O/D_2O - 95:5 (vol/vol) solvent mixture (500 µL) containing TSP-*d4* (1 mM) as internal NMR standard were prepared in 5 mm NMR tubes. After homogenization and equilibration, ^{1}H NMR spectra were recorded at 323 K on a 700 MHz spectrometer using a water suppression sequence (excitation sculpting). The oligomer concentration of each NMR sample were adjusted, by integration using the singlet of the TSP-*d4* at δ = 0 ppm, to obtain excatly the same concentration of both sequences. The samples were freeze-dried and then mixed in a H_2O/D_2O - 95:5 (vol/vol) solvent mixture (500 µL). The dissociation of homomeric double helices and the subsequent hybridization in heteromeric double helix was followed by ^{1}H and ^{19}F NMR at 323 K using a 700 MHz spectrometer for ^{1}H observation and a 400 MHz spectrometer for ^{19}F observation. Heteromeric double helices were also studied by 2D ^{1}H - ^{19}F HOESY NMR to observe dipolar couplings between the groups (e.g. fluorine atoms and proton atoms of methoxyl groups) in the cylindrical cavity of the double helix. ^{1}H and ^{19}F NMR spectra were calibrated with TSP-*d4* (internal standard, chemical shifts are reported relative to the ^{1}H residual signal calibrated at δ = 0 ppm) and TFE (external standard, insert coaxial tube, chemical shifts are reported relative to the ^{19}F residual signal calibrated at δ = -76.76 ppm), respectively.

3.8 Determination of homodoubles helices K_{dim} and the stablization energy of heterodouble helices

➔ **Homodoubles helices K_{dim}**



For the equilibrium shown in equation (1), the dimerization constant of the oligomer is given by the equation (2):

(1) **2 SH ⇄ DH**

(2) $K_{dim} = [DH]/[SH]^2$

If x = [DH]/[SH] = I_{DH} / I_{SH}, the dimerization constant of the oligomer is given by the equation (4):

(3) $K_{dim} = x/[SH]$

(4) $K_{dim} = I_{DH}/(I_{SH}.[SH])$

Where: [SH] = concentration of the single helix (mol.L^{-1})

[DH] = concentration of the double helix (mol.L^{-1})

I_{SH} = integration of one amide proton of the single helix

I_{DH} = integration of one amide proton of the double helix

➔ **Stabilization of heterodimers:**

$A_2 + B_2 \Leftrightarrow 2AB$ $\qquad$ $K = [AB]^2/([A_2][B_2])$

This equilibrium requires two different species to form a new one. In the following, we consider $[A_{tot}] = [B_{tot}]$, and neglect the dissociation of the heterodimer into single helices [A] and [B] (the conditions of our experiments Kdim $> 10^8$ L mol^{-1}). We therefore have $[A_2] = [B_2]$.

The situation where K = 1 implies $[AB] = [A_2]$ does not correspond to a statistical distribution.

This means that half of A is in the homodimer and half in the heterodimer (NMR signals from A in both dimers have the same intensity).

A statistical distribution means that the interactions are the same in $A_2 + B_2$ and 2AB,

Each strand of A_2 has two choices among the strands of B_2 to produce AB.

K = 4 compensates for the statistical factor not being taken into account.

Formally, equilibrium must be defined with K' such that $4K' = [AB]^2/([A_2][B_2])$.

With K' = 1, we have a statistical distribution.

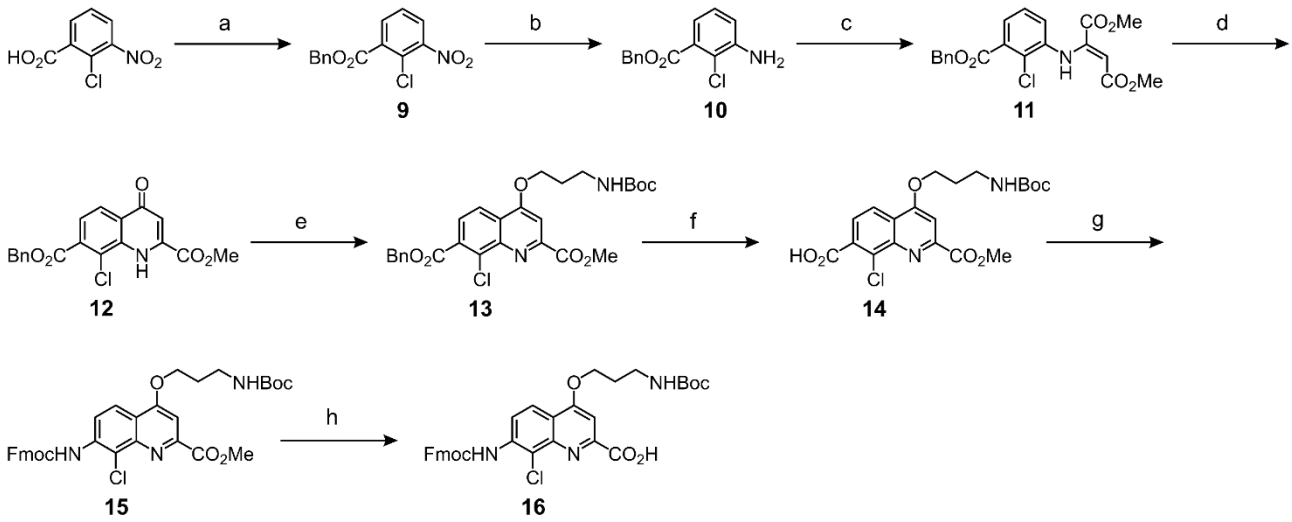
The NMR observation that $[AB] > 100\ [A_2]$ (no A_2 observed) implies that $4K' = [AB]^2/([A_2][B_2]) > 10000$, *i.e.* $K' > 2500$.

➔ Thus, the hetero double helix stabilisation can be estimated as: $\Delta G = - RT.\ln(2500) < -19.4$ kJ/mol

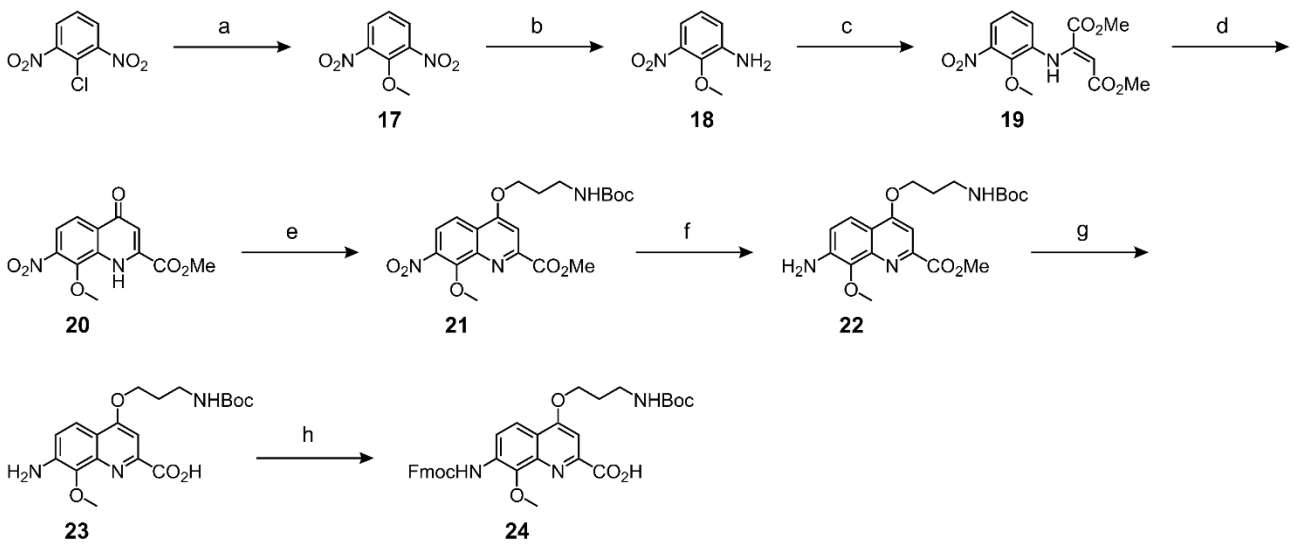
4. Synthetic schemes

Reactions were carried out under a dry inert atmosphere unless otherwise specified. Commercial reagents were purchased from Sigma-Aldrich, Fisher Scientific or TCI Chemicals and were used without further purification. Tetrahydrofurane (THF) and dichloromethane (CH_2Cl_2) were dried over alumina columns (MBRAUN SPS-800 solvent purification system); chloroform ($CHCl_3$) was dried over oven dried potassium carbonate (K_2CO_3) then filtered and distilled from phosphorus pentoxide (P_2O_5); triethylamine (NEt_3) and diisopropylethylamine (DIPEA) were distilled over calcium hydride (CaH_2). Reactions were monitored by thin layer chromatography 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). New synthetic compounds were characterized by ^1H / ^{13}C NMR and ESI mass spectrometry. Fmoc-acid monomers Q(Orn), Q^F(Orn), Q(Asp), Q(Ala) and Q(Sul) were prepared as described in the litterature.[8-11]

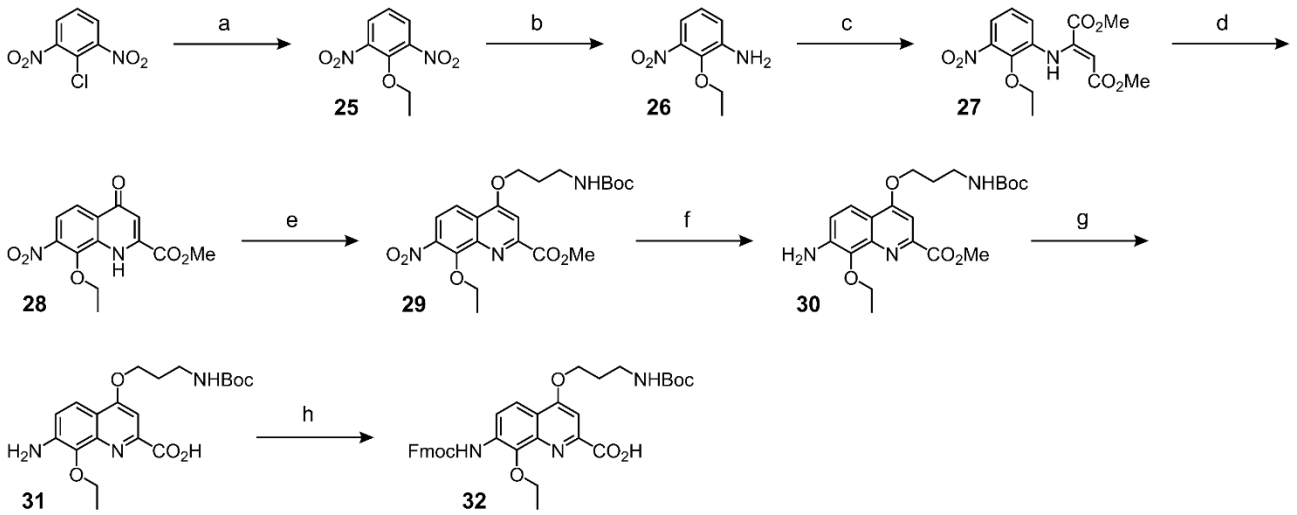
4.1 Monomers synthesis



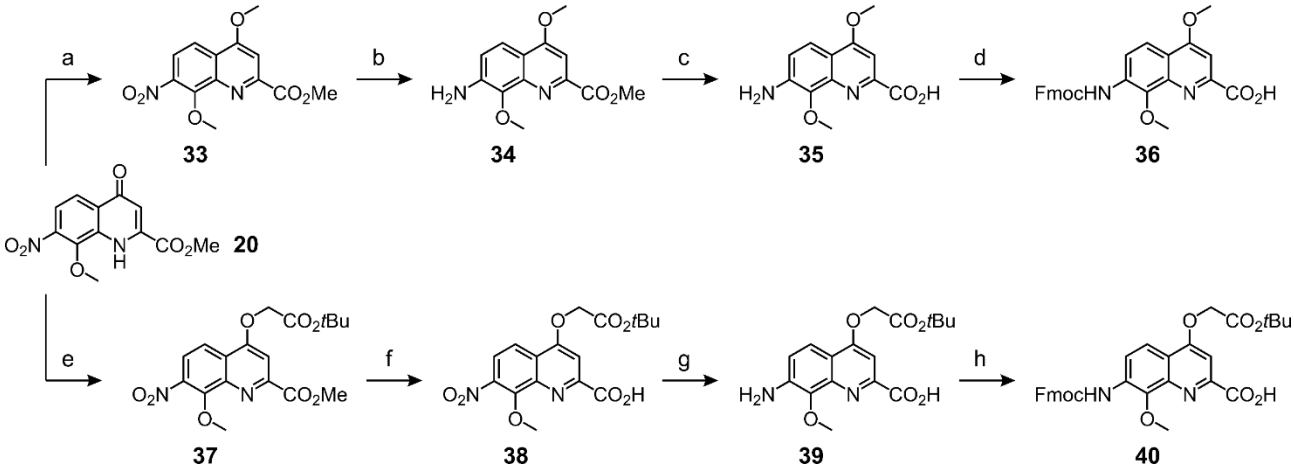
Scheme S1. Synthesis of the Fmoc-Q^{Cl}-OH monomer **16**: a) $SOCl_2$, 80 °C, 2 h then benzyl alcohol, DIPEA, THF, 0 °C then room temperature, overnight, 89 % yield. b) $CuSO_4.5H_2O$, $NaBH_4$, CH_2Cl_2/MeOH, 0 °C, 30 min, 79 % yield. c) dimethylacetylene dicarboxylate, MeOH, room temperature, overnight, 65 % yield. d) diphenyl ether, 260 °C, 10 min, 83 % yield. e) *N*-Boc-protected propanolamine, PPh_3, DIAD, THF, 0 °C then room temperature, 3 h, 99 % yield. f) H_2, Pd/C, DMF, room temperature, 15 min, 95 % yield. g) 9-fluorenemethanol, diphenylphosphoryl azide, DIPEA, toluene, 85 °C, 5 h, 93 % yield. h) LiI, EtOAc, 85 °C, overnight, 84 % yield.



Scheme S2. Synthesis of the Fmoc-Q^{OMe}-OH monomer **24**: a) NaOMe, MeOH, 0 °C then 40 °C, 30 min, 97 % yield. b) Fe, MeOH/AcOH, 90 °C, 30 min, 73 % yield. c) dimethylacetylene dicarboxylate, MeOH, room temperature, 12 h, 75 % yield. d) diphenyl ether, 260 °C, 10 min, 72 % yield. e) *N*-Boc-protected propanolamine, PPh_3, DIAD, THF, 0 °C then room temperature, 12 h, 72 % yield. f) H_2, Pd/C, EtOAc, room temperature, 12 h, 92 % yield. g) KOH, THF/MeOH/H_2O, room temperature, 1 h 30 min, quant. h) Fmoc-Cl, $NaHCO_3$, dioxane/H_2O, 0 °C then room temperature, 12 h, 61 % yield.

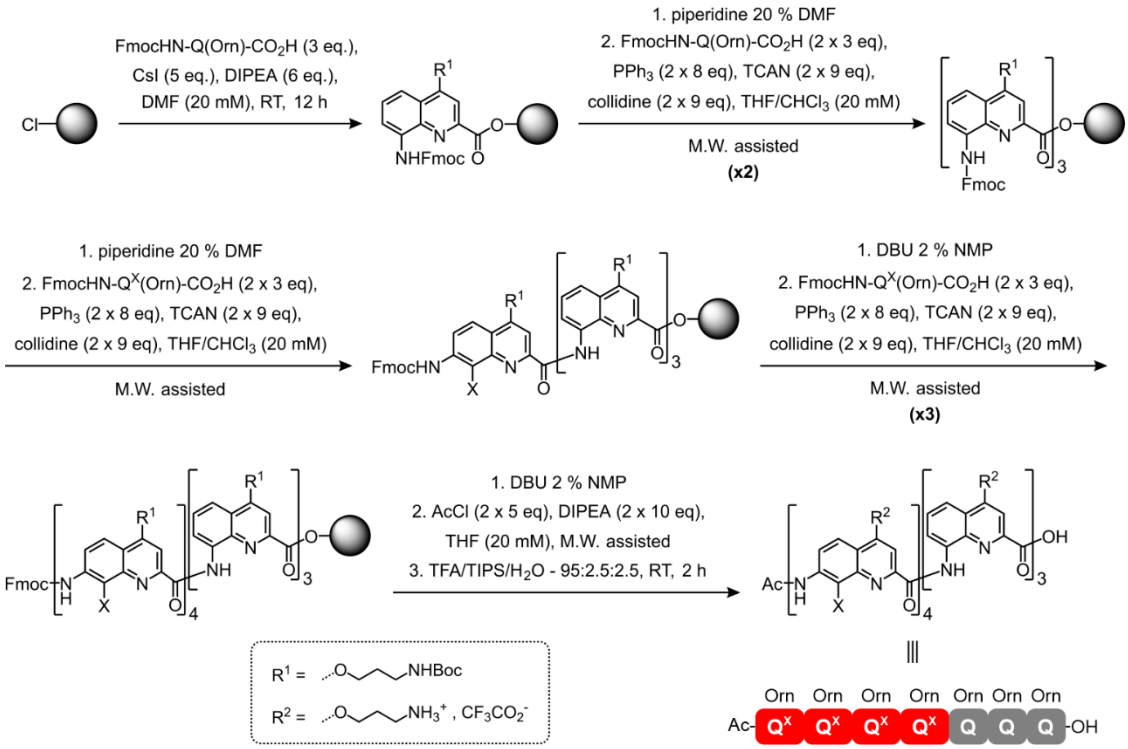


Scheme S3. Synthesis of the Fmoc-Q^{OEt}-OH monomer **32**: a) NaOEt, EtOH, 0 °C then 40 °C, 30 min, 86 % yield. b) Fe, MeOH / AcOH, 100 °C, 30 min, 81 % yield. c) dimethylacetylene dicarboxylate, MeOH, room temperature, 24 h, 70 % yield. d) diphenyl ether, 260 °C, 10 min, 82 % yield. e) *N*-Boc-protected propanolamine, PPh_3, DIAD, THF, 0 °C then room temperature, 12 h, 65 % yield. f) H_2, Pd/C, EtOAc / MeOH, room temperature, 12 h, 89 % yield. g) KOH, THF / MeOH / H_2O, room temperature, 1 h 30 min, 81 % yield. h) Fmoc-Cl, $NaHCO_3$, dioxane / H_2O, 0 °C then room temperature, 12 h, 79 % yield.

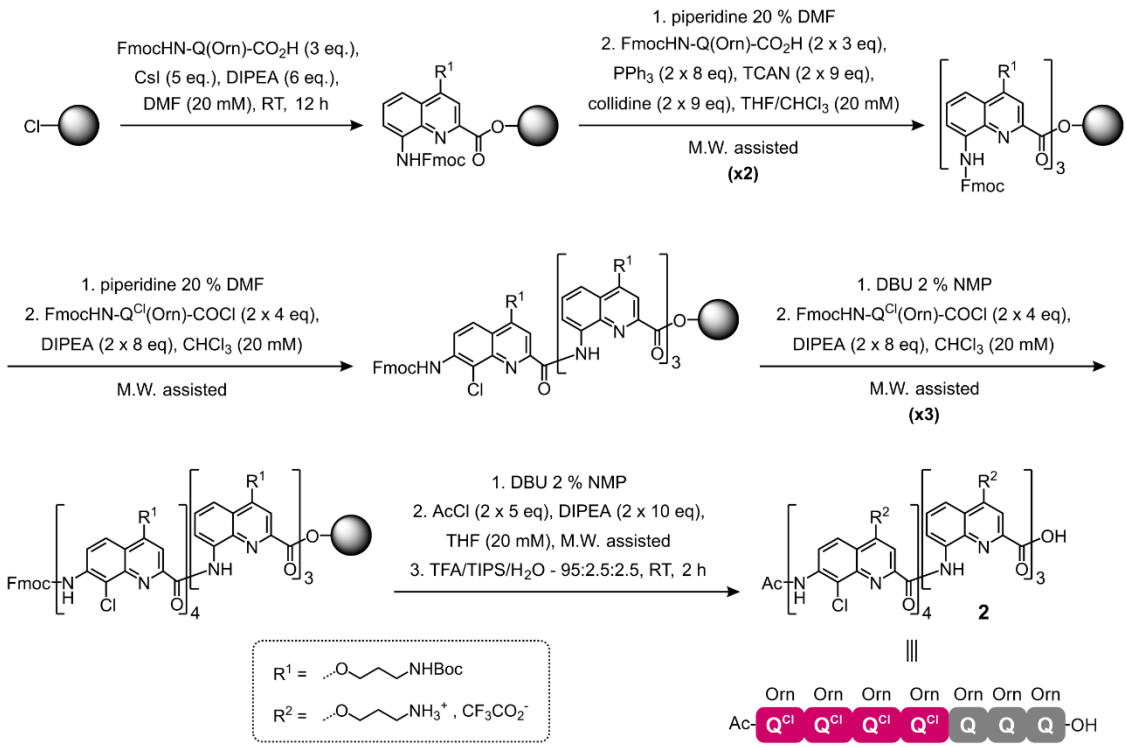


Scheme S4. Synthesis of Fmoc-Q^{OMe}(Ala)-OH **36** and Fmoc-Q^{OMe}(Asp)-OH **40** monomers: a) MeOH, PPh_3, DIAD, THF, 0 °C then room temperature, 12 h, 82 % yield. b) H_2, Pd/C, THF, room temperature, 12 h, 93 % yield. c) KOH, THF / MeOH / H_2O, room temperature, 1 h, 70 % yield. d) Fmoc-Cl, $NaHCO_3$, dioxane / H_2O, 0 °C then room temperature, 12 h, 63 % yield. e) *tert*-butyl bromoacetate, NaI, Na_2CO_3, DMF/acetone, 70 °C, 12 h, 76 % yield. f) LiOH, THF/H_2O, 0 °C, 30 min, 74 % yield. g) H_2, Pd/C, DMF, room temperature, 12 h, 84 % yield. h) Fmoc-Cl, $NaHCO_3$, dioxane / H_2O, 0 °C then room temperature, 12 h, 54 % yield.

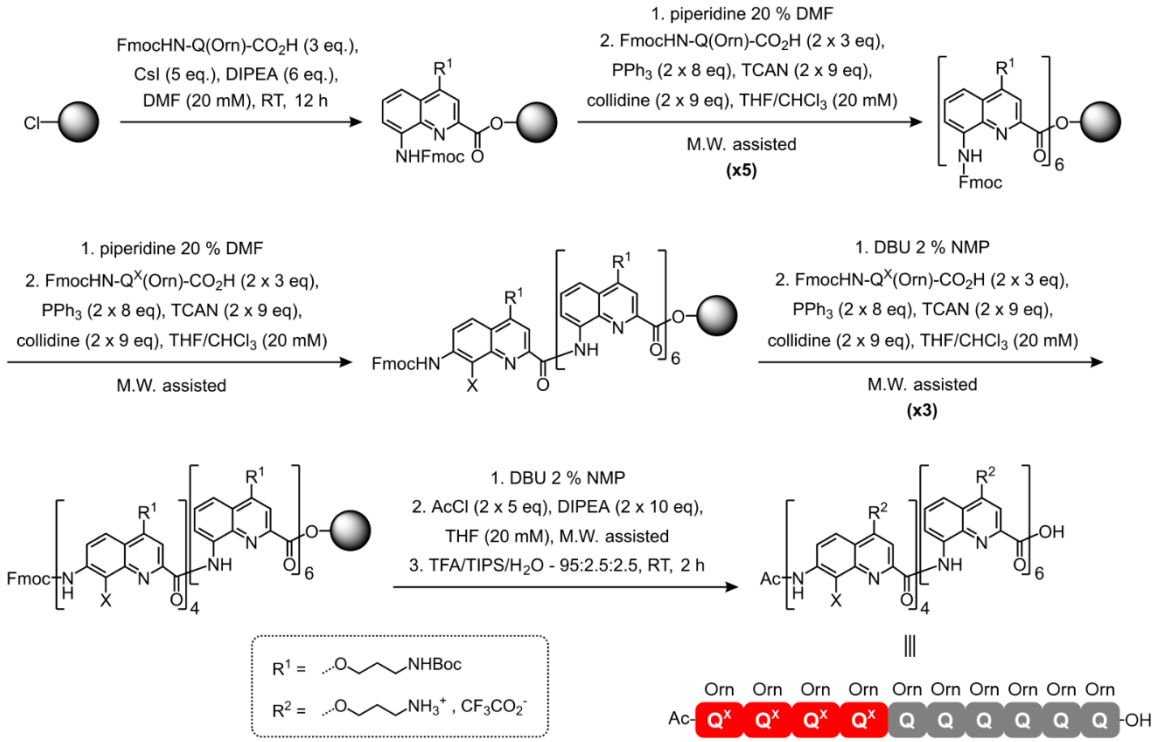
4.2 Solid phase synthesis of aromatic oligoamide foldamers 1-8



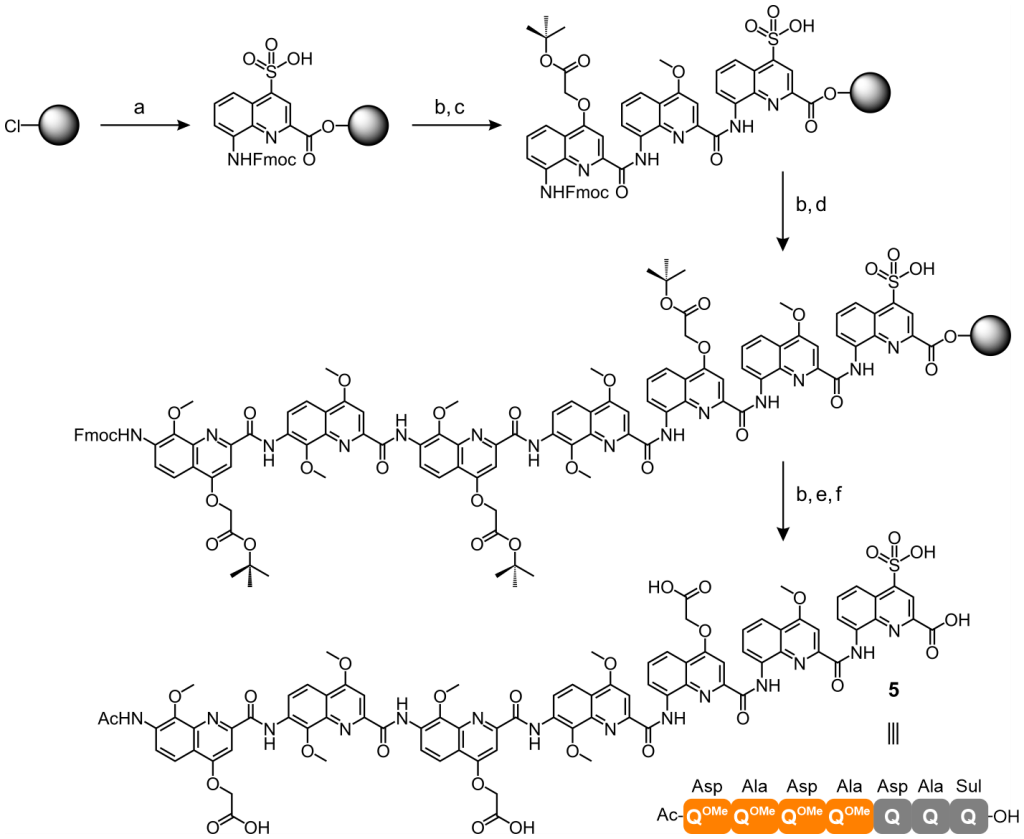
Scheme S5. Solid phase synthesis of oligomers Ac-Q$^X_4$Q$_3$-OH (X = F, OMe or OEt) using the Cl-MPA ProTide resin. Micro-waves conditions for coupling reactions: 50 °C, 50 W, 15 min and the final acetylation: 50 °C, 50 W, 5 min.



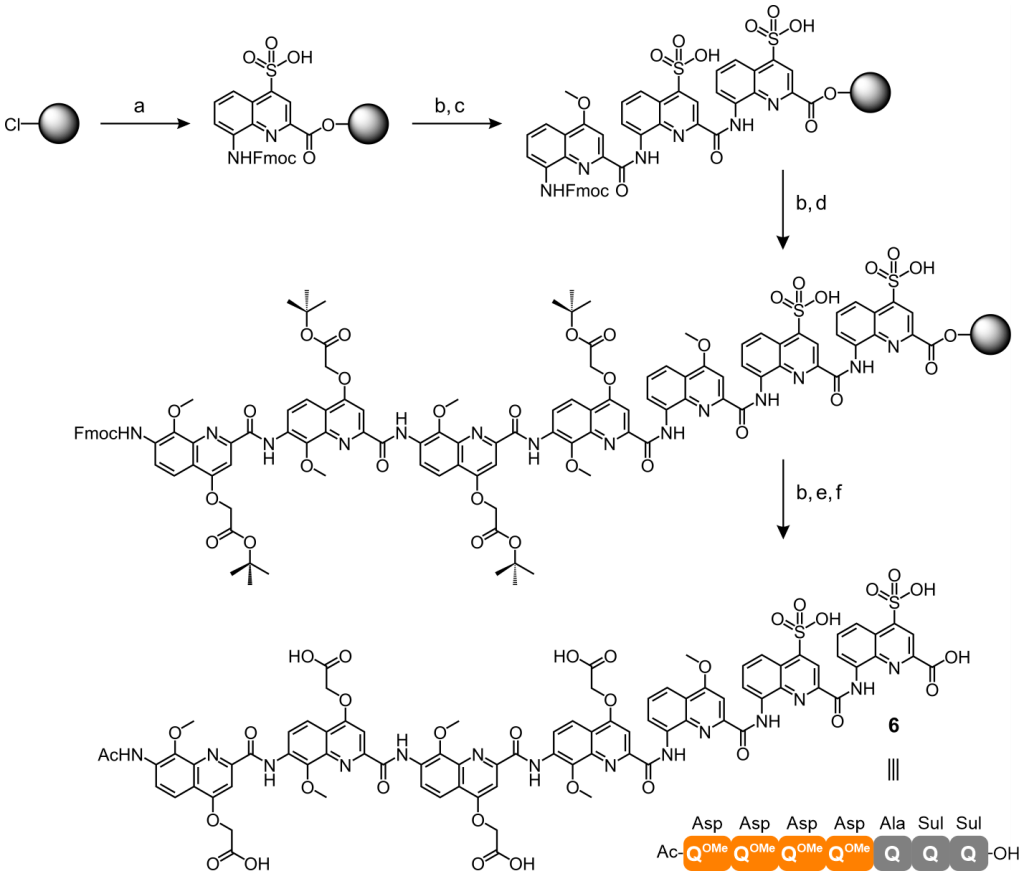
Scheme S6. Solid phase synthesis of the oligomer Ac-$Q^{Cl}{}_4Q_3$-OH **2** using the Cl-MPA ProTide resin. Micro-waves conditions for coupling reactions: 50 °C, 50 W, 15 min and the final acetylation: 50 °C, 50 W, 5 min.



Scheme S7. Solid phase synthesis of oligomers Ac-$Q^X{}_4Q_6$-OH (X = OMe or OEt) using the Cl-MPA ProTide resin. Micro-waves conditions for coupling reactions: 50 °C, 50 W, 15 min and the final acetylation: 50 °C, 50 W, 5 min.



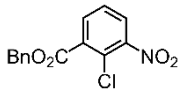
Scheme S8. Solid phase synthesis of the oligomer Ac-$Q^{OMe}{}_4Q_3$-OH **5** using the Cl-MPA ProTide resin: a) FmocHN-Q(SO_3H)-CO_2H (3 eq.), CsI (5 eq.), DIPEA (6 eq.), DMF (20 mM), RT, 12 h. b) DBU 2 % NMP. c) FmocHN-Q(Xxx)-CO_2H (3 eq.), PPh_3 (8 eq.), TCAN (9 eq.), collidine (9 eq.), THF/$CHCl_3$ (20 mM), 50 °C, 50 W, 2 x 15 min. d) FmocHN-Q^{OMe}(Xxx)-CO_2H (3 eq.), PPh_3 (8 eq.), TCAN (9 eq.), collidine (9 eq.), THF/$CHCl_3$ (20 mM), 50 °C, 50 W, 2 x 15 min. e) AcCl (5 eq.), DIPEA (10 eq.), THF (20 mM), 50 °C, 50 W, 2 x 5 min. f) TFA/TIPS/H_2O - 95:2.5:2.5, RT, 2 h.



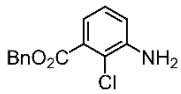
Scheme S9. Solid phase synthesis of the oligomer Ac-$Q^{OMe}{}_4Q_3$-OH **6** using the Cl-MPA ProTide resin: a) FmocHN-Q(SO_3H)-CO_2H (3 eq.), CsI (5 eq.), DIPEA (6 eq.), DMF (20 mM), RT, 12 h. b) DBU 2 % NMP. c) FmocHN-Q(Xxx)-CO_2H (3 eq.), PPh_3 (8 eq.), TCAN (9 eq.), collidine (9 eq.), THF/$CHCl_3$ (20 mM), 50 °C, 50 W, 2 x 15 min. d) FmocHN-Q^{OMe}(Xxx)-CO_2H (3 eq.), PPh_3 (8 eq.), TCAN (9 eq.), collidine (9 eq.), THF/$CHCl_3$ (20 mM), 50 °C, 50 W, 2 x 15 min. e) AcCl (5 eq.), DIPEA (10 eq.), THF (20 mM), 50 °C, 50 W, 2 x 5 min. f) TFA/TIPS/H_2O - 95:2.5:2.5, RT, 2 h.

5. Experimental procedures for monomers synthesis

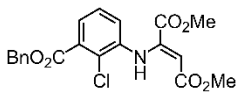
5.1 Synthesis of Fmoc-Q^{Cl}(Orn)-OH monomer 16



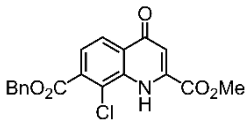
Compound 9. To 2-chloro-3-nitrobenzoic acid (24 g, 0.12 mol) was added thionyl chloride (87 mL, 1.2 mol) and the resulting suspension was heated at 80 °C during 2 h to give the corresponding acid chloride. The solution was evaporated to dryness and a mixture of benzyl alcohol (14.6 mL, 0.14 mol) and DIPEA (40.8 mL, 0.24 mol) in THF (60 mL) was added dropwise at 0 °C. After 1 h, the solution was allowed to proceed at room temperature overnight. Then the mixture was washed with a saturated solution of NH_4Cl (3 x 200 mL) and H_2O (3 x 200 mL). The resulting organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude compound was purified by flash chromatography (SiO_2) eluting with cyclohexane/ethyl acetate - 95:5 to 90:10 to give the pure product **9** (31.3 g, 89 %). ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 7.96 (dd, 1H), 7.84 (dd, 1H), 7.51-7.35 (m, 6H), 5.41 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 164.13, 150.01, 134.92, 133.80, 133.24, 128.77, 128.75, 128.59, 127.42, 127.23, 125.72, 68.13. HRMS (ESI): *m/z* calcd for $C_{14}H_{11}ClNO_4^+$ $[M+H]^+$ 292.0371 found 292.0376.



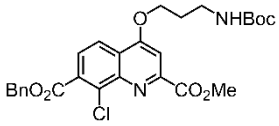
Compound 10. A solution of compound **9** (31.2 g, 0.11 mol) in CH_2Cl_2 (30 mL) was cooled down at 0 °C and $NaBH_4$ (20.8 g, 0.55 mol) was added by portions over a period of 30 min. Then MeOH (60 mL) was added slowly to the colorless solution and finally $CuSO_4.5H_2O$ (69.9 g, 0.28 mol) was added by portions over a period of 30 min. During the addition, the solution became a blue suspension then a black suspension. The mixture was evaporated at 30 °C and the crude was purified by flash chromatography (SiO_2) eluting with CH_2Cl_2 to give the compound **10** (22.1 g, 77 %). ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 7.49-7.30 (m, 5H), 7.19 (dd, 1H), 7.09 (t, 1H), 6.88 (dd, 1H), 5.36 (s, 2H), 4.19 (br, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 166.18, 144.21, 135.83, 131.05, 128.72, 128.49, 128.45, 127.04, 120.68, 118.63, 117.95, 67.28. HRMS (ESI): *m/z* calcd for $C_{14}H_{13}ClNO_2^+$ $[M+H]^+$ 262.0629 found 262.0633.



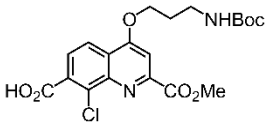
Compound 11. To a solution of compound **10** (22 g, 0.08 mol) in MeOH (230 mL) was added dropwise dimethyl acetylenedicarboxylate (11 mL, 0.09 mol) and the solution was stirred at room temperature overnight. The crude mixture was concentrated (≃ 80 mL) then the precipitate was filtered and washed with cold MeOH (3 x 20 mL) to give the fumarate **11** (20.5 g, 63 %) as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 9.87 (br, 1H), 7.53-7.30 (m, 6H), 7.18 (t, 1H), 6.87 (dd, 1H), 5.62 (s, 1H), 5.38 (s, 2H), 3.76 (s, 3H), 3.70 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 169.43, 165.53, 164.27, 145.98, 138.81, 135.50, 131.70, 128.71, 128.50, 128.47, 126.54, 125.84, 124.63, 123.31, 97.40, 67.54, 53.00, 51.62. HRMS (ESI): *m/z* calcd for $C_{20}H_{19}ClNO_6^+$ $[M+H]^+$ 404.0895 found 404.0901.



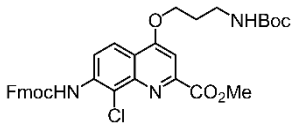
Compound 12. A mixture of compound **11** (20 g, 0.05 mol) and diphenyl ether (120 mL) was heated at 260 °C during 10 min. After cooling at room temperature, the product began to precipitate. The mixture was diluted with cyclohexane (300 mL) to complete the precipitation. The solid was filtered and then triturated in cyclohexane (3 x 300 mL) and diethyl ether (300 mL) to afford the pure compound **12** (15.3 g, 82 %). ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 9.57 (br, 1H), 8.28 (d, 1H), 7.78 (d, 1H), 7.52-7.35 (m, 5H), 7.02 (d, 1H), 5.43 (s, 2H), 4.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 178.64, 164.50, 162.68, 136.93, 136.28, 135.00, 133.22, 128.77, 128.71, 128.58, 128.48, 125.09, 124.85, 122.82, 112.49, 68.01, 54.19. HRMS (ESI): *m/z* calcd for $C_{19}H_{15}ClNO_5^+$ $[M+H]^+$ 372.0633 found 372.0647.



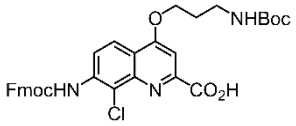
Compound 13. A mixture of compound **12** (5 g, 13.4 mmol), triphenylphosphine (4.6 g, 17.4 mmol) and *N*-Boc-protected propanolamine (3.0 g, 17.4 mmol) in anhydrous THF (70 mL) was cooled to 0 °C under argon atmosphere. Diisopropyl azodicarboxylate (3.4 mL, 17.4 mmol) was added dropwise and after the addition, the mixture was allowed to proceed at room temperature during 3 h. The obtained precipitate was filtered and washed with cold THF (3 x 30 mL) to give the compound **13** (5.6 g, 79 %). ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 8.18 (d, 1H), 7.86 (d, 1H), 7.67 (s, 1H), 7.54-7.31 (m, 5H), 5.47 (s, 2H), 4.71 (br, 1H), 4.37 (t, 2H), 4.08 (s, 3H), 3.42 (q, 2H), 2.18 (quin, 2H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 165.94, 165.91, 162.80, 156.06, 150.45, 145.30, 135.43, 134.81, 132.71, 128.77, 128.59, 128.45, 127.60, 124.68, 120.64, 102.62, 79.68, 67.89, 67.34, 53.59, 37.78, 29.51, 28.51. HRMS (ESI): *m/z* calcd for $C_{27}H_{30}ClN_2O_7^+$ $[M+H]^+$ 529.1736 found 529.1754.



Compound 14. Compound **13** (3 g, 5.7 mmol) was dissolved in DMF (60 mL) and Pd/C (10 %, 300 mg) was added to the solution. The mixture was stirred under H_2 atmosphere at room temperature during 30 min. Then the reaction mixture was immediately filtered through celite, eluted with CH_2Cl_2/MeOH - 90:10 (250 mL) and solvents were evaporated under reduced pressure. The resulting oily crude mixture was dissolved in EtOAc (150 mL) and washed with water (5 x 150 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness to give the carboxylic acid **14** (2.2 g, 88 %) which was used directly without further purification. ^{1}H NMR (DMSO-d_6, 300 MHz, 298 K): δ (ppm) = 13.88 (br, 1H), 8.23 (d, 1H), 7.88 (d, 1H), 7.65 (s, 1H), 6.97 (br, 1H), 4.39 (t, 2H), 3.98 (s, 3H), 3.20 (q, 2H), 2.01 (quin, 2H), 1.34 (s, 9H). ^{13}C NMR (DMSO-d_6, 75 MHz, 298 K): δ (ppm) = 167.18, 165.16, 162.39, 155.66, 150.23, 144.06, 134.69, 131.40, 126.80, 123.45, 120.92, 102.52, 77.54, 67.26, 52.90, 36.75, 28.79, 28.19. HRMS (ESI): *m/z* calcd for $C_{20}H_{24}ClN_2O_7^+$ $[M+H]^+$ 439.1267 found 439.1272.

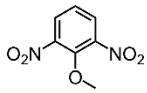


Compound 15. Compound **14** (1.5 g, 3.4 mmol) and 9-fluorenemethanol (4.0 g, 20.4 mmol) was dissolved in dry toluene (40 mL) and then DIPEA (1.2 mL, 6.8 mmol) and diphenylphosphoryl azide (1.5 mL, 6.8 mmol) was added. The mixture was stirred at 80 °C during 24 h and was then evaporated under reduced pressure. The crude mixture was purified by flash chromatography (SiO_2) eluting with cyclohexane/ethyl acetate - 100:0 to 70:30 to give the pure product **15** (1.9 g, 88 %). ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 8.53 (br, 1H), 8.15 (d, 1H), 7.84-7.76 (m, 2H), 7.71-7.62 (m, 3H), 7.57 (s, 1H), 7.49-7.31 (m, 4H), 4.73 (br, 1H), 4.59 (d, 2H), 4.41-4.29 (m, 3H), 4.07 (s, 3H), 3.43 (q, 2H), 2.18 (quin, 2H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 166.03, 162.80, 156.05, 153.08, 150.17, 145.13, 143.58, 141.44, 137.24, 128.01, 127.30, 125.10, 121.04, 120.23, 120.13, 119.24, 118.98, 100.82, 79.58, 67.85, 67.07, 53.44, 47.07, 37.81, 29.47, 28.48. HRMS (ESI): *m/z* calcd for $C_{34}H_{35}ClN_3O_7^+$ $[M+H]^+$ 632.2158 found 632.2177.

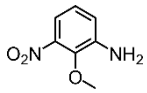


Compound 16. Compound **15** (1.8 g, 2.8 mmol) was dissolved in degassed EtOAc (160 mL) and then LiI (1.1 g, 8.4 mmol) was added. The solution was stirred at 85 ºC under inert atmosphere overnight. After cooling to room temperature, the mixture was acidified with a 5 % solution of citric acid until pH 4. The organic phase was extracted, washed with water (3 x 100 mL), dried over Na_2SO_4, filtered and evaporated to give the compound **16** (1.6 g, 92 %). ^{1}H NMR (DMSO-d_6, 300 MHz, 298 K): δ (ppm) = 13.45 (br, 1H), 9.66 (s, 1H), 8.10 (d, 1H), 7.95-7.88 (m, 2H), 7.87-7.75 (m, 3H), 7.55 (s, 1H), 7.48-7.30 (m, 4H), 6.98 (br, 1H), 4.50 (d, 2H), 4.40-4.30 (m, 3H), 3.20 (q, 2H), 2.00 (quin, 2H), 1.35 (s, 9H). ^{13}C NMR (DMSO-d_6, 75 MHz, 298 K): δ (ppm) = 166.35, 162.29, 155.67, 153.84, 150.99, 144.61, 143.67, 140.79, 137.38, 127.72, 127.12, 125.32, 124.76, 124.16, 120.21, 120.14, 119.53, 101.15, 77.53, 66.92, 66.45, 46.56, 36.79, 28.85, 28.20. HRMS (ESI): *m/z* calcd for $C_{33}H_{33}ClN_3O_7^+$ $[M+H]^+$ 618.2002 found 618.2021.

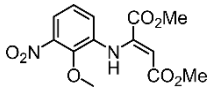
5.2 Synthesis of Fmoc-Q^{OMe}(Orn)-OH monomer 24



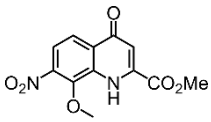
Compound 17. To a solution of 2-chloro-1,3-dinitrobenzene (32 g, 0.16 mol) in distilled MeOH (80 mL) was added dropwise a sodium methoxide solution (30 wt. % in MeOH, 44.4 mL, 0.24 mol) at 0 °C under argon atmosphere. After the addition, the yellow suspension was heated at 40 °C during 30 min and finally the suspension turned purple. The reaction mixture was poured into ice and vigorously stirred during 15 min. Then the precipitate was filtered and wash with water (3 x 300 mL) to give, after drying in vacuum oven, the compound **17** (30.4 g, 97 %), which was used directly without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 8.05 (d, 2H), 7.37 (t, 1H), 4.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 147.71, 145.42, 129.28, 124.15, 64.85. HRMS (ESI): *m/z* calcd for $C_7H_7N_2O_5^+$ $[M+H]^+$ 199.0349 found 199.0353.



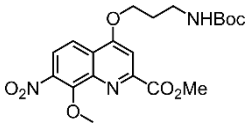
Compound 18. A solution of 2-methoxy-1,3-dinitrobenzene **17** (30 g, 0.15 mol) in AcOH (300 mL) and MeOH (300 mL) was heated to 90 °C. Reduced iron powder (25.1 g, 0.45 mol) was added in portions over a period of 15 min and then the mixture was heated to reflux for 15 min. The hot reaction mixture was filtered through celite and eluted with CH_2Cl_2 (≃ 1.5 L). The filtrate was neutralized with a sodium hydroxide solution (4 M) until pH 8, extracted with CH_2Cl_2 (3 x 500 mL), dried over Na_2SO_4, filtered and evaporated to dryness. Then the crude compound was purified by flash chromatography (SiO_2) eluting with cyclohexane/ethyl acetate - 85:15 to give the pure product **18** (18.5 g, 73 %). ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 7.23-7.16 (m, 1H), 7.04-6.90 (m, 2H), 4.07 (br, 2H), 3.91 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 144.16, 142.35, 140.20, 124,40, 119.88, 114,07, 61.01. HRMS (ESI): *m/z* calcd for $C_7H_9N_2O_3^+$ $[M+H]^+$ 169.0608 found 169.0606.



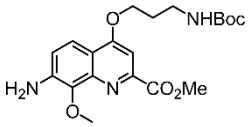
Compound 19. To a solution of compound **18** (18 g, 0.11 mol) in MeOH (650 mL) was added dropwise dimethyl acetylenedicarboxylate (14.8 mL, 0.12 mol) and the solution was stirred at room temperature overnight. The crude mixture was concentrated (≃ 500 mL) then the precipitate was filtered and washed with cold MeOH (3 x 50 mL) to give the fumarate **19** (24.8 g, 75 %) as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 9.68 (br, 1H), 7.56-7.48 (m, 1H), 7.16-7.01 (m, 2H), 5.64 (s, 1H), 3.89 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 169.69, 163.89, 146.43, 145.09, 144.63, 136.45, 125.37, 124.06, 119.89, 96.36, 62.17, 53.05, 51.60. HRMS (ESI): *m/z* calcd for $C_{13}H_{15}N_2O_7^+$ $[M+H]^+$ 311.0874 found 311.0868.



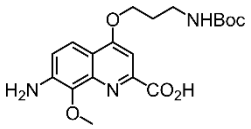
Compound 20. A mixture of compound **19** (24 g, 0.08 mol) and diphenyl ether (350 mL) was heated at 260 °C during 10 min. After cooling at room temperature, the product began to precipitate. The mixture was diluted with cyclohexane (700 mL) to complete the precipitation. The solid was filtered and then triturated in cyclohexane (3 x 700 mL) and diethyl ether (700 mL) to afford the pure compound **20** (15.6 g, 72 %). ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 9.41 (br, 1H), 8.12 (d, 1H), 7.74 (d, 1H), 7.03 (d, 1H), 4.14 (s, 3H), 4.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 178.49, 162.84, 143.80, 143.00, 137.09, 134.58, 129.11, 121.53, 119.33, 113.23, 63.31, 54.27. HRMS (ESI): *m/z* calcd for $C_{12}H_{11}N_2O_6^+$ $[M+H]^+$ 279.0612 found 279.0627.



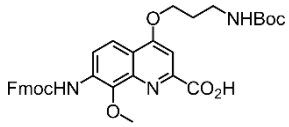
Compound 21. A mixture of compound **20** (5 g, 18.0 mmol), triphenylphosphine (6.1 g, 23.4 mmol) and *N*-Boc-protected propanolamine (4.1 g, 23.4 mmol) in anhydrous THF (70 mL) was cooled to 0 °C under argon atmosphere. Diisopropyl azodicarboxylate (4.6 mL, 23.4 mmol) was added dropwise and after the addition, the mixture was allowed to proceed at room temperature overnight. The solvent was evaporated and the crude mixture was purified by flash chromatography (SiO_2) eluting with cyclohexane/ethyl acetate - 90:10 to 60:40 to give the pure product **21** (5.6 g, 72 %). ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 8.00 (d, 1H), 7.85 (d, 1H), 7.65 (s, 1H), 4.69 (br, 1H), 4.45 (s, 3H), 4.37 (t, 2H), 4.06 (s, 3H), 3.43 (q, 2H), 2.19 (quin, 2H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 165.68, 162.77, 156.09, 151.08, 149.66, 143.69, 143.33, 125.48, 122.03, 117.11, 102.82, 79.63, 67.29, 64.59, 53.35, 37.73, 29.49, 28.48. HRMS (ESI): *m/z* calcd for $C_{20}H_{26}N_3O_8^+$ $[M+H]^+$ 436.1714 found 436.1737.



Compound 22. Compound **21** (5.5 g, 12.6 mmol) was dissolved in ethyl acetate (150 mL) and Pd/C (10 %, 550 mg) was added to the solution. The mixture was stirred under H_2 atmosphere at room temperature overnigh. Then the reaction mixture was filtered through celite and eluted with CH_2Cl_2/MeOH - 90:10 (500 mL) to give the pure amine **22** (4.7 g, 92 %), which was used directly without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 7.80 (d, 1H), 7.35 (s, 1H), 7.09 (d, 1H), 4.74 (br, 1H), 4.30 (t, 2H), 4.26 (br, 2H), 4.17 (s, 3H), 4.02 (s, 3H), 3.41 (q, 2H), 2.14 (quin, 2H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 166.76, 162.56, 156.06, 148.46, 143.71, 140.47, 139.65, 119.37, 117.54, 116.15, 98.24, 79.40, 66.47, 61.32, 52.91, 37.96, 29.40, 28.47. HRMS (ESI): *m/z* calcd for $C_{20}H_{28}N_3O_6^+$ $[M+H]^+$ 406.1973 found 406.1995.

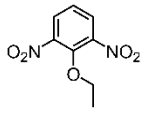


Compound 23. Compound **22** (4.5 g, 11.1 mmol) was dissolved in a mixture of THF (36 mL), MeOH (18 mL) and H_2O (6 mL). To this solution was added KOH (1.9 g, 33.3 mmol) and the reaction mixture was stirred at room temperature. After 1 h 30 min, the reaction was neutralized with acetic acid (1.9 mL, 33.3 mmol), organic solvents were removed under reduced pressure and the compound precipated out of water. This precipitate was filtered and washed with water (3 x 100 mL) to give, after drying in vacuum oven, the amino acid **23** (4.3 g, quantitative), which was used directly without further purification. ^{1}H NMR (DMSO-d_6, 300 MHz, 298 K): δ (ppm) = 7.71 (d, 1H), 7.24 (s, 1H), 7.18 (d, 1H), 6.95 (br, 1H), 5.77 (br, 2H), 4.29 (t, 2H), 3.93 (s, 3H), 3.16 (q, 2H), 1.96 (quin, 2H), 1.36 (s, 9H). ^{13}C NMR (DMSO-d_6, 75 MHz, 298 K): δ (ppm) = 165.51, 163.19, 155.66, 149.15, 142.84, 141.43, 136.11, 119.49, 117.53, 113.52, 97.14, 77.53, 66.56, 60.23, 36.87, 28.92, 28.22. HRMS (ESI): *m/z* calcd for $C_{19}H_{26}N_3O_6^+$ $[M+H]^+$ 392.1816 found 392.1832.

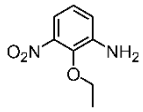


Compound 24. Compound **23** (4 g, 10.2 mmol) was dissolved in dioxane (120 mL) and a solution of 10 % $NaHCO_3$ in H_2O was added (300 mL). Then, a solution of 9-fluorenylmethyl chloroformate (2.9 g, 11.2 mmol) in dioxane (30 mL) was added dropwise at 0 °C over a period of 1 h. After 12 h at room temperature, the mixture was neutralized with citric acid 5 % until pH 4. The aqueous phase was extracted with CH_2Cl_2 (3 x 300 mL), dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography (SiO_2) eluting with CH_2Cl_2/MeOH - 100:0 to 90:10 and then by preparative HPLC (C18) eluting with H_2O/CH_3CN - 100:0 to 0:100 over a period of 45 min, to give the pure compound **24** (3.8 g, 61 %). ^{1}H NMR (DMSO-d_6, 300 MHz, 298 K): δ (ppm) = 9.37 (br, 1H), 8.04-7.75 (m, 6H), 7.50-7.30 (m, 5H), 6.97 (br, 1H), 4.48 (d, 2H), 4.40-4.27 (m, 3H), 4.14 (s, 3H), 3.19 (q, 2H), 1.99 (quin, 2H), 1.36 (s, 9H). ^{13}C NMR (DMSO-d_6, 75 MHz, 298 K): δ (ppm) = 166.58, 162.20, 155.68, 153.96, 149.13, 145.21, 143.76, 142.31, 140.79, 131.61, 127.72, 127.13, 125.36, 122.69, 120.14, 119.05, 116.19, 99.89, 77.54, 66.57, 66.30, 62.15, 46.61, 36.87, 28.91, 28.21. HRMS (ESI): *m/z* calcd for $C_{34}H_{36}N_3O_8^+$ $[M+H]^+$ 614.2497 found 614.2530.

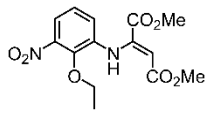
5.3 Synthesis of Fmoc-Q^{OEt}(Orn)-OH monomer 32



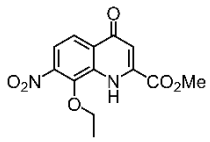
Compound 25. To a solution of 2-chloro-1,3-dinitrobenzene (10 g, 49.4 mmol) in distilled EtOH (25 mL) was added dropwise a sodium ethoxide solution (21 wt. % in EtOH, 24.0 mL, 74.1 mmol) at 0 °C under argon atmosphere. After the addition, the yellow suspension was heated at 40 °C during 30 min and finally the suspension turned purple. The reaction mixture was poured into ice and vigorously stirred during 15 min. Then the precipitate was filtered and wash with water (3 x 150 mL) to give, after drying in vacuum oven, the compound **25** (9 g, 86 %), which was used directly without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 8.03 (d, 2H), 7.35 (t, 1H), 4.25 (q, 2H), 1.45 (t, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 146.76, 145.71, 129.12, 123.91, 74.24, 15.42. HRMS (ESI): *m/z* calcd for $C_8H_9N_2O_5^+$ $[M+H]^+$ 213.0506 found 213.0504.



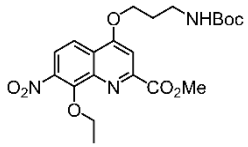
Compound 26. A solution of 2-ethoxy-1,3-dinitrobenzene **25** (8.8 g, 41.5 mmol) in AcOH (90 mL) and MeOH (90 mL) was heated to 100 °C. Reduced iron powder (6.7 g, 0.12 mol) was added in portions over a period of 10 min and then the mixture was heated to reflux for 20 min. The hot reaction mixture was filtered through celite and eluted with CH_2Cl_2 (≃ 500 mL). The filtrate was neutralized with a sodium hydroxide solution (4 M) until pH 8, extracted with CH_2Cl_2 (3 x 250 mL), dried over Na_2SO_4, filtered and evaporated to dryness. Then the crude compound was purified by flash chromatography (SiO_2) eluting with cyclohexane/ethyl acetate - 85:15 to give the pure product **26** (6.1 g, 81 %). ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 7.19 (dd, 1H), 7.03-6.89 (m, 2H), 4.15-3.98 (m, 4H), 1.43 (t, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 144.30, 142.57, 139.34, 124.18, 119.71, 114.01, 69.73, 15.66. HRMS (ESI): *m/z* calcd for $C_8H_{11}N_2O_3^+$ $[M+H]^+$ 183.0764 found 183.0765.



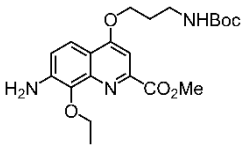
Compound 27. To a solution of compound **26** (5.9 g, 32.4 mmol) in MeOH (100 mL) was added dropwise dimethyl acetylenedicarboxylate (4.4 mL, 35.6 mmol) and the solution was stirred at room temperature during 24 h. The crude was concentrated (≃ 50 mL) then the precipitate was filtered and washed with cold MeOH (3 x 25 mL) to give the fumarate **27** (7.4 g, 70 %) as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 9.71 (s, 1H), 7.51 (dd, 1H), 7.14-7.00 (m, 2H), 5.62 (s, 1H), 4.06 (q, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 1.39 (t, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 169.65, 163.88, 146.51, 144.82, 144.15, 136.60, 125.15, 123.87, 119.85, 95.91, 71.15, 53.00, 51.56, 15.21. HRMS (ESI): *m/z* calcd for $C_{14}H_{17}N_2O_7^+$ $[M+H]^+$ 325.1030 found 325.1031.



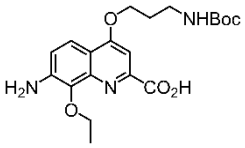
Compound 28. A mixture of compound **27** (7.2 g, 22.2 mmol) and diphenyl ether (80 mL) was heated at 260 °C during 10 min. After cooling at room temperature, the product began to precipitate. The mixture was diluted with cyclohexane (200 mL) to complete the precipitation. The solid was filtered and then triturated in cyclohexane (3 x 200 mL) and diethyl ether (200 mL) to afford the pure compound **28** (5.3 g, 82 %). ^{1}H NMR (DMSO-d_6, 300 MHz, 298 K): δ (ppm) = 12.42 (br, 1H), 8.06-7.86 (m, 2H), 7.59 (br, 1H), 4.68 (br, 2H), 3.95 (s, 3H), 1.40 (t, 3H). Limited solubility of the compound **28** prevented the characterization by ^{13}C NMR spectroscopy. HRMS (ESI): *m/z* calcd for $C_{13}H_{13}N_2O_6^+$ $[M+H]^+$ 293.0768 found 293.0768.



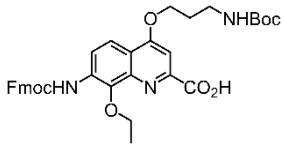
Compound 29. A mixture of compound **28** (5 g, 17.1 mmol), triphenylphosphine (5.8 g, 22.2 mmol) and *N*-Boc-protected propanolamine (3.9 g, 22.2 mmol) in anhydrous THF (70 mL) was cooled to 0 °C under argon atmosphere. Diisopropyl azodicarboxylate (4.4 mL, 22.2 mmol) was added dropwise and after the addition, the mixture was allowed to proceed at room temperature overnight. The solvent was evaporated and the crude was purified by flash chromatography (SiO_2) eluting with cyclohexane/ethyl acetate - 90:10 to 60:40 to give the product **29** (5 g, 65 %). ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 7.98 (d, 1H), 7.84 (d, 1H), 7.64 (s, 1H), 4.81-4.68 (m, 3H), 4.36 (t, 2H), 4.05 (s, 3H), 3.43 (q, 2H), 2.18 (quin, 2H), 1.58 (t, 3H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 165.60, 162.67, 156.07, 150.40, 149.41, 143.76, 143.53, 125.30, 121.90, 116.82, 102.67, 79.51, 73.58, 67.21, 53.21, 37.67, 29.42, 28.43, 15.68. HRMS (ESI): *m/z* calcd for $C_{21}H_{28}N_3O_8^+$ $[M+H]^+$ 450.1871 found 450.1874.



Compound 30. Compound **29** (4.8 g, 10.7 mmol) was dissolved in ethyl acetate (108 mL) and MeOH (12 mL) then Pd/C (10 %, 480 mg) was added to the solution. The mixture was stirred under H_2 atmosphere at room temperature overnigh. Then the reaction mixture was filtered through celite and eluted with CH_2Cl_2/MeOH - 90:10 (300 mL) to give the amine **30** (4 g, 89 %), which was used directly without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 7.78 (d, 1H), 7.34 (s, 1H), 7.09 (d, 1H), 4.76 (br, 1H), 4.49 (q, 2H), 4.30 (t, 2H), 4.25 (br, 2H), 4.01 (s, 3H), 3.41 (q, 2H), 2.13 (quin, 2H), 1.49 (t, 3H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 166.76, 162.56, 156.05, 148.27, 143.83, 140.84, 138.89, 119.31, 117.30, 116.19, 98.18, 79.43, 69.83, 66.49, 52.88, 38.00, 29.40, 28.48, 16.03. HRMS (ESI): *m/z* calcd for $C_{21}H_{30}N_3O_6^+$ $[M+H]^+$ 420.2129 found 420.2127.

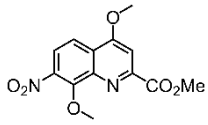


Compound 31. Compound **30** (3.8 g, 9.1 mmol) was dissolved in a mixture of THF (30 mL), MeOH (15 mL) and H_2O (5 mL). To this solution was added KOH (1.5 g, 27.3 mmol) and the reaction mixture was stirred at room temperature. After 1 h 30 min, the reaction was neutralized with acetic acid (1.6 mL, 27.3 mmol), organic solvents were removed under reduced pressure and the compound precipated out of water. This precipitate was filtered and washed with water (3 x 70 mL) to give, after drying in vacuum oven, the amino acid **31** (3 g, 81 %), which was used directly without further purification. ^{1}H NMR (DMSO-d_6, 300 MHz, 298 K): δ (ppm) = 7.71 (d, 1H), 7.25 (s, 1H), 7.19 (d, 1H), 6.96 (br, 1H), 5.77 (br, 2H), 4.30 (t, 2H), 4.23 (q, 2H), 3.16 (q, 2H), 1.96 (quin, 2H), 1.42-1.29 (m, 12H). ^{13}C NMR (DMSO-d_6, 75 MHz, 298 K): δ (ppm) = 164.99, 163.66, 155.71, 149.14, 143.46, 140.92, 134.44, 119.49, 117.60, 113.42, 97.14, 77.60, 68.24, 66.75, 36.89, 28.93, 28.25, 15.61. HRMS (ESI): *m/z* calcd for $C_{20}H_{28}N_3O_6^+$ $[M+H]^+$ 406.1973 found 406.1970.

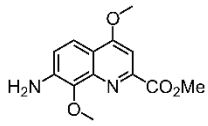


Compound 32. Compound **31** (2.8 g, 6.9 mmol) was dissolved in dioxane (70 mL) and a solution of 10 % $NaHCO_3$ in H_2O was added (160 mL). Then, a solution of 9-fluorenylmethyl chloroformate (2 g, 7.6 mmol) in dioxane (10 mL) was added dropwise at 0 °C over a period of 1 h. After 12 h at room temperature, the mixture was neutralized with citric acid 5 % until pH 4. The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL), dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography (SiO_2) eluting with CH_2Cl_2/MeOH - 100:0 to 90:10 and then by preparative HPLC (C18) eluting with H_2O/CH_3CN - 100:0 to 0:100 over a period of 45 min, to give the pure compound **32** (3.4 g, 79 %). ^{1}H NMR (DMSO-d_6, 300 MHz, 298 K): δ (ppm) = 9.20 (br, 1H), 8.00-7.75 (m, 6H), 7.49-7.29 (m, 5H), 6.98 (br, 1H), 4.54-4.43 (m, 4H), 4.39-4.28 (m, 3H), 3.19 (q, 2H), 1.99 (quin, 2H), 1.41-1.30 (m, 12H). ^{13}C NMR (DMSO-d_6, 75 MHz, 298 K): δ (ppm) = 166.59, 162.23, 155.69, 153.90, 149.08, 144.28, 143.75, 142.41, 140.81, 131.95, 127.72, 127.10, 125.33, 122.82, 120.15, 119.12, 116.06, 99.92, 77.53, 70.02, 66.58, 66.28, 46.60, 36.88, 28.92, 28.22, 15.50. HRMS (ESI): *m/z* calcd for $C_{35}H_{38}N_3O_8^+$ $[M+H]^+$ 628.2653 found 628.2654.

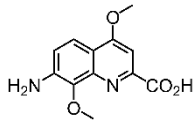
5.4 Synthesis of Fmoc-Q^{OMe}(Ala)-OH monomer 36



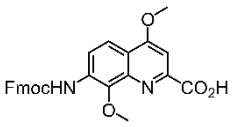
Compound 33. Compound **20** (3 g, 10.8 mmol) and triphenylphosphine (3.7 g, 14.0 mmol) were dissolved in anhydrous THF (30 mL) and anhydrous MeOH (567 µL, 14.0 mmol) was added. The mixture was cooled to 0 °C under argon atmosphere and diisopropyl azodicarboxylate (2.8 mL, 14.0 mmol) was added dropwise. After the addition, the mixture was allowed to proceed at room temperature overnight. The solvent was evaporated and the crude mixture was purified by precipitation in CH_2Cl_2/MeOH. The yellow precipitate was washed with cold MeOH (2 x 10 mL) and was used without further purification (2.6 g, 82 %). ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 8.01 (d, 1H), 7.86 (d, 1H), 7.67 (s, 1H), 4.45 (s, 3H), 4.15 (s, 3H), 4.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 165.82, 163.69, 151.11, 149.74, 143.71, 143.38, 125.58, 122.10, 117.18, 102.31, 64.61, 56.68, 53.41. HRMS (ESI): *m/z* calcd for $C_{13}H_{13}N_2O_6^+$ $[M+H]^+$ 293.0768 found 293.0787.



Compound 34. Compound **33** (2.5 g, 8.6 mmol) was dissolved in THF (85 mL) and Pd/C (10 %, 250 mg) was added to the solution. The mixture was stirred under H_2 atmosphere at room temperature overnigh. Then the reaction mixture was filtered through celite and eluted with CH_2Cl_2 (200 mL) to give the pure amine **34** (2.1 g, 93 %), which was used directly without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ (ppm) = 7.80 (d, 1H), 7.37 (s, 1H), 7.10 (d, 1H), 4.25 (br, 2H), 4.17 (s, 3H), 4.07 (s, 3H), 4.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ (ppm) = 166.86, 163.55, 148.54, 143.69, 140.43, 139.66, 119.37, 117.59, 116.24, 97.73, 61.32, 55.95, 52.94. HRMS (ESI): *m/z* calcd for $C_{13}H_{15}N_2O_4^+$ $[M+H]^+$ 263.1026 found 263.1034.

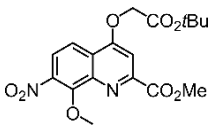


Compound 35. Compound **34** (2.0 g, 7.6 mmol) was dissolved in a mixture of THF (19.5 mL), MeOH (6.5 mL) and H_2O (2.5 mL). To this solution was added KOH (1.3 g, 22.8 mmol) and the reaction mixture was stirred at room temperature. After 5 min, the reaction was neutralized with HCl (1 M), organic solvents were removed under reduced pressure and the compound precipated out of water. This precipitate was filtered and washed with water (3 x 10 mL) to give, after drying in vacuum oven, the product **35** (1.3 g, 70 %), which was used directly without further purification. ^{1}H NMR (DMSO-d_6, 300 MHz, 298 K): δ (ppm) = 7.69 (d, 1H), 7.27 (s, 1H), 7.16 (d, 1H), 5.74 (br, 1H), 4.75 (br, 2H), 4.06 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz, 298 K): δ (ppm) = 165.71, 163.74, 149.11, 142.77, 141.68, 136.34, 119.59, 117.32, 113.45, 96.64, 60.26, 56.26. HRMS (ESI): *m/z* calcd for $C_{12}H_{13}N_2O_4^+$ $[M+H]^+$ 249.0870 found 249.0866.

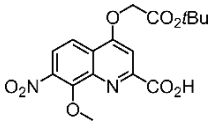


Compound 36. Compound **35** (1.2 g, 4.8 mmol) was dissolved in dioxane (20 mL) and a solution of 10 % $NaHCO_3$ in H_2O was added (63 mL). Then, a solution of 9-fluorenylmethyl chloroformate (1.6 g, 5.8 mmol) in dioxane (16 mL) was added dropwise at 0 °C over a period of 1 h. After 12 h at room temperature, the mixture was neutralized with citric acid 5 % until pH 4. The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL), dried over Na_2SO_4, filtered and evaporated. The crude was purified by flash chromatography (SiO_2) eluting with CH_2Cl_2/MeOH - 100:0 to 90:10 and then by preparative HPLC (C18) eluting with H_2O/CH_3CN - 100:0 to 0:100 over a period of 45 min, to give the compound **36** (1.4 g, 63 %). ^{1}H NMR (DMSO-d_6, 300 MHz, 298 K): δ (ppm) = 9.39 (br, 1H), 8.07-7.77 (m, 6H), 7.52-7.31 (m, 5H), 4.48 (d, 2H), 4.35 (t, 1H), 4.15 (s, 3H), 4.10 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz, 298 K): δ (ppm) = 166.54, 163.08, 154.00, 149.19, 145.06, 143.79, 142.17, 140.83, 131.79, 127.76, 127.17, 125.40, 122.75, 120.18, 118.91, 116.13, 99.47, 66.36, 62.19, 56.40, 54.94, 46.64. HRMS (ESI): *m/z* calcd for $C_{27}H_{23}N_2O_6^+$ $[M+H]^+$ 471.1551 found 471.1576.

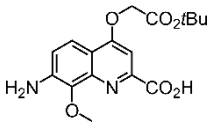
5.5 Synthesis of Fmoc-Q^{OMe}(Asp)-OH monomer 40



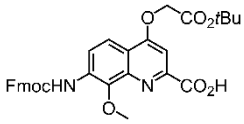
Compound 37. Compound **20** (1 g, 3.6 mmol), sodium iodide (108 mg, 0.7 mmol) and sodium carbonate (580 mg, 5.4 mmol) were dissolved in a mixture of acetone (88 mL) and DMF (16 mL). The suspension was cooled to 0 °C under argon atmosphere and *tert*-butyl bromoacetate (800 µL, 5.4 mmol) was added dropwise. After the addition, the mixture was allowed to proceed at 70 °C overnight. Solvents were evaporated under reduced pressure and the mixture was dissolved in CH_2Cl_2 (50 mL) and the salts were removed by filtration. The obtained crude was finally purified by flash chromatography (SiO_2) eluting with CH_2Cl_2 to give the pure product **37** (1.4 g, 53 %). ^{1}H NMR (DMSO-d_6, 300 MHz, 298 K): δ (ppm) = 8.08-7.99 (m, 2H), 7.60 (s, 1H), 5.16 (s, 2H), 4.33 (s, 3H), 3.98 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (DMSO-d_6, 75 MHz, 298 K): δ (ppm) = 166.52, 164.72, 161.60, 149.61, 149.08, 143.07, 142.61, 124.59, 122.12, 117.20, 103.60, 82.27, 65.97, 64.09, 53.04, 27.63. HRMS (ESI): *m/z* calcd for $C_{18}H_{21}N_2O_8^+$ $[M+H]^+$ 393.1292 found 393.1320.



Compound 38. Compound **37** (710 mg, 1.8 mmol) was dissolved in THF (100 mL) and a solution of LiOH (114 mg, 2.7 mmol) in H_2O (25 mL) was added dropwise at 0 °C. After 15 min, the reaction was neutralized with citric acid 5 % until pH 4. The organic phase was extracted with CH_2Cl_2/MeOH - 9:1 (20 mL), washed with water (20 mL), dried over Na_2SO_4, filtered and evaporated to give the compound **38** (500 mg, 73 %), which was used directly without further purification. ^{1}H NMR (DMSO-d_6, 300 MHz, 298 K): δ (ppm) = 13.64 (br, 1H), 8.08-8.01 (m, 2H), 7.60 (s, 1H), 5.16 (s, 2H), 4.35 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (DMSO-d_6, 75 MHz, 298 K): δ (ppm) = 167.11, 166.30, 162.01, 150.99, 150.10, 143.54, 143.11, 125.04, 122.35, 117.68, 104.05, 82.73, 66.39, 64.60, 28.13. HRMS (ESI): *m/z* calcd for $C_{17}H_{19}N_2O_8^+$ $[M+H]^+$ 379.1136 found 379.1163.



Compound 39. Compound **38** (480 mg, 1.3 mmol) was dissolved in DMF (12 mL) and Pd/C (20 %, 96 mg) was added to the solution. The mixture was stirred under H_2 atmosphere at room temperature overnigh. Then the reaction mixture was filtered through celite and eluted with CH_2Cl_2/MeOH - 95:5 (100 mL) to give, after evaporation of solvents, the pure amino acid **39** (410 mg, 93 %), which was used directly without further purification and characterisation.



Compound 40. Compound **39** (513 mg, 1.5 mmol) was dissolved in dioxane (15 mL) and a solution of 10 % $NaHCO_3$ in H_2O was added (50 mL). Then, a solution of 9-fluorenylmethyl chloroformate (776 mg, 3 mmol) in dioxane (10 mL) was added dropwise at 0 °C in four batches (4 x 194 mg in 2 mL of dioxane) with a stirring time of 30 min between each addition. After 12 h at room temperature, the mixture was neutralized with citric acid 5 % until pH 4. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), dried over Na_2SO_4, filtered and evaporated. The crude was purified by flash chromatography (SiO_2) eluting with CH_2Cl_2/MeOH - 100:0 to 90:10 and then by preparative HPLC (C18) eluting with H_2O/CH_3CN - 100:0 to 0:100 over a period of 45 min, to give the compound **40** (400 mg, 47 %). ^{1}H NMR (DMSO-d_6, 300 MHz, 298 K): δ (ppm) = 9.41 (br, 1H), 8.11-7.76 (m, 6H), 7.48-7.30 (m, 5H), 5.08 (s, 2H), 4.48 (d, 2H), 4.35 (t, 1H), 4.15 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (DMSO-d_6, 75 MHz, 298 K): δ (ppm) = 166.91, 166.35, 161.32, 153.96, 148.90, 145.22, 143.74, 142.48, 140.77, 131.73, 127.72, 127.13, 125.36, 123.04, 120.15, 118.80, 116.09, 100.38, 82.06, 66.31, 65.58, 62.17, 46.58, 27.65. HRMS (ESI): *m/z* calcd for $C_{32}H_{31}N_2O_8^+$ $[M+H]^+$ 571.2075 found 571.2136.

6. Experimental procedures for solid phase synthesis of aromatic oligoamide foldamers

6.1 General procedure for solid phase synthesis

Solid phase synthesizer: The microwave-assisted solid phase synthesis of aromatic oligoamide foldamers **1**-**4** and **7**-**8** was carried out on a Discover Bio CEM® microwave oven in a closed vessel mode. The temperature of the reaction mixture within the reactor vessel was monitored with an optical fiber probe. Cl-MPA ProTide® resin was purchased from CEM Corporation. Peptide grade DMF and NMP was used. Foldamers **1**-**4** and **7**-**8** were characterized by ^{1}H NMR spectroscopy (700 MHz, 323 K) in DMSO-d_6 and H_2O/D_2O - 95:5 vol/vol and RP-LCMS equiped with a C18 column Kinetex® and a TOF-MS detector (H_2O + 0.1 % vol/vol acid formic and acetonitrile + 0.1 % vol/vol acid formic). Sequences **5** and **6** was prepared using an automated solid phase synthesizer: Gyros Protein Technologies PurePep Chorus synthesizer with induction heating.

Loading of the first monomer on the resin: Cl-MPA ProTide® resin (0.16 mmol/g, 200 mg, 0.032 mmol), monomer Fmoc-Q-CO_2H (0.096 mmol, 3 equiv.) and CsI (0.16 mmol, 5 equiv.) were mixed in dry DMF (20 mM) followed by the addition of dry DIPEA (0.192 mmol, 6 equiv.). The resulting mixture was shaken overnight at room temperature. Then the resin was washed carrefully with DMF (3 x 3 mL), MeOH (3 x 3 mL) and CH_2Cl_2 (3 x 3 mL).

Fmoc deprotection: Fmoc protecting groups of quinoline monomers **Q**, grafted on the resin, were removed by the addition of 20 % (vol/vol) solution of piperidine in DMF (3 mL) and the resin was gently stirred at room temperature during 5 min. The resin was washed briefly with DMF (2 x 3 mL) and the same process was repeated during 10 min. Then the resin was washed carrefully with DMF (3 x 3 mL) and dry THF (3 x 3 mL). Fmoc protecting groups of 8-substituted quinoline monomers (**Q**$^{\mathbf{F}}$, **Q**$^{\mathbf{Cl}}$, **Q**$^{\mathbf{OMe}}$ and **Q**$^{\mathbf{OEt}}$), grafted on the resin, were removed by the addition of 2 % (vol/vol) solution of DBU in NMP (3 mL) and the resin was gently stirred at room temperature during 5 min. The resin was washed briefly with NMP (2 x 3 mL) and the same process was repeated during 10 min. Then the resin was washed carrefully with NMP (3 x 3 mL) and dry THF (3 x 3 mL).

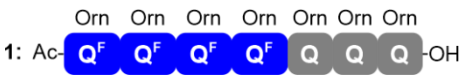
Coupling with freshly prepared acid chloride (Q$^{\mathbf{Cl}}$ monomers): In a round bottom flask, monomer acid (3 equiv.) was dissolved in dry CH_2Cl_2 (1 mL) under Ar atmosphere and Ghosez's reagent (1-chloro-*N*,*N*,2-trimethyl-1-propenylamine, 3.6 equiv.) was added. The resulting mixture was stirred during 1 h under Ar atmosphere at room temperature and the corresponding freshly prepared acid chloride was dried using a high vacuum line during approximately 1 h. Monomer acid chloride (3 equiv.) was then redissolved in dry $CHCl_3$ (500 µL) and added on the resin, previously covered by dry $CHCl_3$ (500 µL) and containing DIPEA (6 equiv.). The resulting mixture was treated with microwaves (50 W, 50 °C, 15 min) and the resin was washed briefly with dry $CHCl_3$ (2 x 3 mL). The same process was repeated and finally the resin was washed carrefully with $CHCl_3$ (3 x 3 mL) and DMF (3 x 3 mL).

In situ coupling (Q, **Q**$^{\mathbf{F}}$, **Q**$^{\mathbf{OMe}}$ **and Q**$^{\mathbf{OEt}}$ **monomers):** Monomer acid (3 equiv.) and PPh_3 (8 equiv.) was dissolved in dry $CHCl_3$ (500 µL) followed by the addition of trichloroacetonitrile (9 equiv.) and the corresponding in situ prepared acid chloride was added on the resin, previously covered by dry THF (500 µL) and containing collidine (9 equiv.). The resulting mixture was treated with microwaves (50 W, 50 °C, 15 min). The resin was washed briefly with $CHCl_3$ (2 x 3 mL) and dry THF (2 x 3 mL). The same process was repeated and finally the resin was washed carrefully with $CHCl_3$ (3 x 3 mL), THF (3 x 3 mL) and DMF (3 x 3 mL).

Final acetylation: At the end of the solid phase synthesis of the target oligomer, the *N*-terminus of the sequence was acetylated. The last Fmoc protecting group of the 8-substituted quinoline (**Q^F**, **Q^{Cl}**, **Q^{OMe}** or **Q^{OEt}**) was removed by the addition of 2 % (vol/vol) solution of DBU in NMP (3 mL) and the resin was gently stirred at room temperature during 5 min. The resin was washed briefly with NMP (2 x 3 mL) and the same process was repeated during 10 min. The resin was washed carrefully with NMP (3 x 3 mL) and dry THF (3 x 3 mL). Then dry THF (1 mL) was added on the resin followed by DIPEA (10 equiv.) and AcCl (5 equiv.). The resulting mixture was treated with microwaves (50 W, 50 °C, 5 min) and the resin was washed briefly with dry THF (2 x 3 mL). The same process was repeated and finally the resin was washed carrefully with THF (3 x 3 mL) and DMF (3 x 3 mL).

Resin cleavage: The resin was washed carrefully with DMF (3 x 5 mL), MeOH (3 x 5 mL) and CH_2Cl_2 (3 x 5 mL) then stirred in a mixture of TFA / TIPS / H_2O (95 : 2.5 : 2.5 vol/vol/vol, 4 mL) during 6 h at room temperature. The resin was removed by filtration, washed with CH_2Cl_2 (2 mL) and the yellow filtrate was evaporated under reduced pressure. The resulting oily solid was triturated with Et_2O and centrifugated to give the target foldamer.

6.2 Synthesis of aromatic oligoamide foldamers 1-8



Prepared on a 13.9 µmol scale (100 mg of ProTide resin, 0.139 mmol/g) using the general procedure reported above, the oligomer **1** was obtained as a yellow solid and was used without further purification (30 mg, 82 %). ^{1}H NMR (H_2O/D_2O - 95:5, 700 MHz, 323 K, calibrated with TSP-d_4): δ (ppm) = 11.89 (s, 1H), 11.53 (s, 1H), 11.39 (s, 1H), 11.34 (s, 1H), 10.35 (s, 1H), 9.69 (s, 1H), 8.85 (s, 1H), 8.69 (d, 1H), 8.26 (d, 1H), 8.12 (t, 1H), 8.02 (t, 1H), 7.86 (d, 1H), 7.83 (d, 1H), 7.81-7.76 (m, 2H), 7.73-7.68 (m, 1H), 7.63-7.58 (m, 1H), 7.58-7.52 (m, 2H), 7.40 (s, 1H), 7.37 (d, 1H), 7.30-7.22 (m, 2H), 7.20-7.12 (m, 2H), 6.82 (s, 1H), 6.69 (s, 1H), 6.55 (d, 1H), 6.52-6.46 (m, 2H), 6.38 (s, 1H). ^{19}F NMR (H_2O/D_2O - 95:5, 400 MHz, 323 K, calibrated with TFE): δ (ppm) = -134.7, -139.2, -140.8, -141.3.

Prepared on a 14.4 µmol scale (100 mg of ProTide resin, 0.144 mmol/g) using the general procedure reported above, the oligomer **2** was obtained as a orange solid and was used without further purification (35 mg, 90 %). ^{1}H NMR (H_2O/D_2O - 95:5, 700 MHz, 323 K, calibrated with TSP-d_4): δ (ppm) = 12.10 (s, 1H), 11.72 (s, 1H), 11.57 (s, 1H), 11.27 (s, 1H), 10.76 (s, 1H), 10.25 (s, 1H), 8.63 (d, 1H), 8.45 (d, 1H), 8.42 (d, 1H), 8.28-8.19 (m, 2H), 7.96 (d, 1H), 7.77-7.60 (m, 8H), 7.45 (t, 1H), 7.00 (d, 1H), 6.98 (s, 1H), 6.81 (t, 1H), 6.78 (d, 1H), 6.73 (d, 1H), 6.62 (s, 1H), 6.60 (s, 1H), 6.55 (d, 1H), 6.52 (s, 1H), 6.29 (s, 1H).

Prepared on a 13.6 µmol scale (100 mg of ProTide resin, 0.136 mmol/g) using the general procedure reported above, the oligomer **3** was obtained as a yellow solid and was used without further purification (32 mg, 88 %). ^{1}H NMR (H_2O/D_2O - 95:5, 700 MHz, 323 K, calibrated with TSP-d_4): δ (ppm) = 12.06 (s, 1H), 11.68 (s, 1H), 11.61 (s, 1H), 10.17 (s, 1H), 9.78 (s, 1H), 9.45 (s, 1H), 8.75 (d, 1H), 8.46 (d, 1H), 8.39 (d, 1H), 8.33 (s, 1H), 8.19 (d, 1H), 8.11 (d, 1H), 8.02 (d, 1H), 7.88 (d, 1H), 7.85 (d, 1H), 7.82 (d, 1H), 7.65-7.57 (m, 2H), 7.48 (s, 1H), 7.42-7.36 (m, 2H), 7.32 (s, 1H), 7.27-7.21 (m, 2H), 7.18 (d, 1H), 6.81 (t, 1H), 6.75-6.65 (m, 3H), 6.60 (s, 1H), 6.39 (s, 1H).

4: 

Prepared on a 13.6 µmol scale (100 mg of ProTide resin, 0.136 mmol/g) using the general procedure reported above, the oligomer **4** was obtained as a yellow solid and was used without further purification (35 mg, 94 %). ^{1}H NMR (H_2O/D_2O - 95:5, 700 MHz, 323 K, calibrated with TSP-d_4): δ (ppm) = 12.18 (s, 1H), 11.87 (s, 1H), 11.63 (s, 1H), 10.10 (s, 1H), 9.89 (s, 1H), 9.44 (s, 1H), 8.79 (d, 1H), 8.56 (d, 1H), 8.46-8.37 (m, 2H), 8.16 (d, 1H), 8.04 (d, 1H), 7.97-7.92 (m, 2H), 7.91-7.85 (m, 2H), 7.78 (s, 1H), 7.66 (t, 1H), 7.59 (s, 1H), 7.50-7.43 (m, 3H), 7.36-7.28 (m, 2H), 7.11-7.01 (m, 2H), 6.92 (t, 1H), 6.63-6.51 (m, 3H), 6.48 (s, 1H).

5: 

Prepared on a 27.2 µmol scale (200 mg of ProTide resin, 0.136 mmol/g) using the general procedure reported above, the oligomer **5** was obtained as a yellow solid and was used without further purification (44 mg, 92 %). The ^{1}H NMR spectrum of the oligomer **5** in H_2O/D_2O - 95:5 is too broad to be characterized. However, the X-ray crystal sructure of this sequence **5** show an antiparallel homomeric double helix **(5)**$_2$ arrangement in water.

6: 

Prepared on a 27.2 µmol scale (200 mg of ProTide resin, 0.136 mmol/g) using the general procedure reported above, the oligomer **6** was obtained as a yellow solid and was used without further purification (49 mg, 97 %). The ^{1}H NMR spectrum of the oligomer **6** in H_2O/D_2O - 95:5 is too broad to be characterized. However, the X-ray crystal sructure of this sequence **6** show an antiparallel homomeric double helix **(6)**$_2$ arrangement in water.

7: 

Prepared on a 14.1 µmol scale (100 mg of ProTide resin, 0.141 mmol/g) using the general procedure reported above, the oligomer **7** was obtained as a yellow solid and was used without further purification (49 mg, 93 %). ^{1}H NMR (H_2O/D_2O - 95:5, 700 MHz, 323 K, calibrated with TSP-d_4): δ (ppm) = 11.40 (s, 1H), 11.34 (s, 1H), 11.20 (s, 1H), 11.18 (s, 1H), 11.03 (s, 1H), 11.02 (s, 1H), 9.77 (s, 1H), 9.46 (s, 1H), 9.08 (s, 1H), 8.56 (d, 1H), 8.32 (d, 1H), 8.12 (s, 1H), 8.00 (d, 1H), 7.96-7.90 (m, 2H), 7.89-7.84 (m, 2H), 7.82 (d, 1H), 7.74-7.67 (m, 2H), 7.62 (d, 1H), 7.53 (d, 1H), 7.51 (t, 1H), 7.39 (s, 1H), 7.38-7.32 (m, 4H), 7.29 (s, 1H), 7.27 (s, 1H), 7.16 (d, 1H), 7.13 (d, 1H), 7.07-7.02 (m, 2H), 7.02-6.99 (m, 2H), 6.59-6.55 (m, 2H), 6.54-6.50 (m, 2H), 6.39 (s, 1H), 6.36-6.32 (m, 2H), 6.31 (s, 1H), 6.16 (s,1H), 6.07 (s, 1H).

8: 

Prepared on a 14.1 µmol scale (100 mg of ProTide resin, 0.141 mmol/g) using the general procedure reported above, the oligomer **8** was obtained as a yellow solid and was used without further purification (51 mg, 95 %). ^{1}H NMR (H_2O/D_2O - 95:5, 700 MHz, 323 K, calibrated with TSP-d_4): δ (ppm) = 11.41 (s, 1H), 11.37 (s, 1H), 11.35 (s, 1H), 11.28 (s, 1H), 11.05 (m, 2H), 9.93 (s, 1H), 9.52 (s, 1H), 9.16 (s, 1H), 8.75 (d, 1H), 8.41 (d, 1H), 8.26 (d, 1H), 8.02 (br, 1H), 7.99-7.94 (m, 2H), 7.92 (d, 1H), 7.89-7.83 (m, 3H), 7.78 (d, 1H), 7.75-7.70 (m, 2H), 7.64 (d, 1H), 7.57-7.52 (m, 2H), 7.46 (t, 1H), 7.39 (t, 1H), 7.34 (s, 1H), 7.29-7.24 (m, 2H), 7.23-7.18 (m, 3H), 7.17-7.13 (m, 2H), 6.90 (d, 1H), 6.84 (d, 1H), 6.76 (s, 1H), 6.55 (s, 1H), 6.51 (t, 1H), 6.41 (s, 1H), 6.39-6.35 (m, 2H), 6.28 (s, 1H), 6.20 (s, 1H), 6.17 (s, 1H).

7. Solution state studies: Nuclear magnetic resonance

7.1 Self-assembly of homomeric double helices $(7)_2$ and $(8)_2$

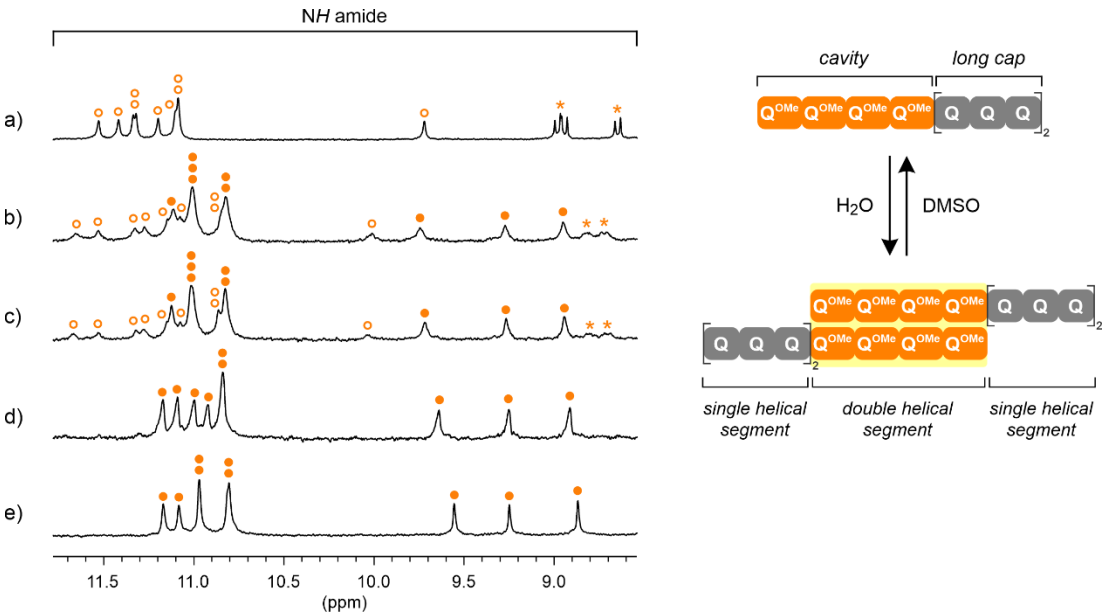


Figure S32. Part of the ^{1}H NMR spectra (300 MHz) of the amide region of **7** (1 mM) at 323 K in DMSO-d_6/H_2O mixtures in the following vol/vol ratios: a) 100:0, b) 50:50, c) 45:55, d) 40:60 and e) H_2O/D_2O (95:5 vol/vol). Amide signals of the single helix are marked with empty orange circles whereas amide signals of the double helix are marked with full orange circles. Some aromatic signals of the single helix are denoted with stars. Spectra were calibrated with TSP-d_4 (internal NMR standard).

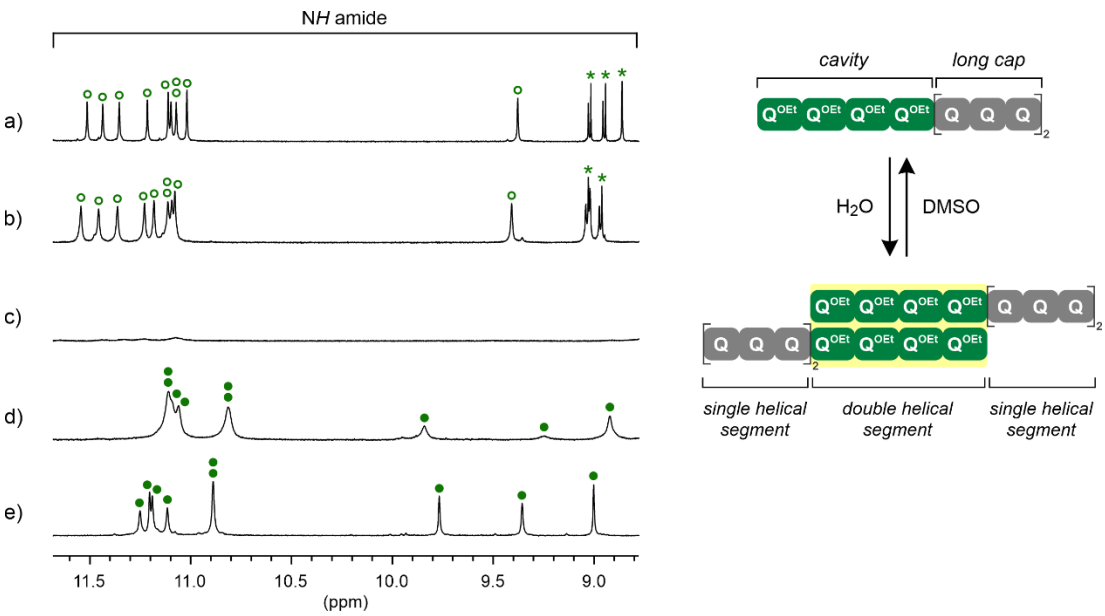


Figure S33. Part of the ^{1}H NMR spectra (700 MHz) of the amide region of **8** (1 mM) at 323 K in DMSO-d_6/H_2O mixtures in the following vol/vol ratios: a) 100:0, b) 60:40, c) 50:50, d) 40:60 and e) H_2O/D_2O (95:5 vol/vol). Amide signals of the single helix are marked with empty green circles whereas amide signals of the double helix are marked with full green circles. Some aromatic signals of the single helix are denoted with stars. Spectra were calibrated with TSP-d_4 (internal NMR standard).

7.2 Hybridization of the heteromeric double helix (1·4)

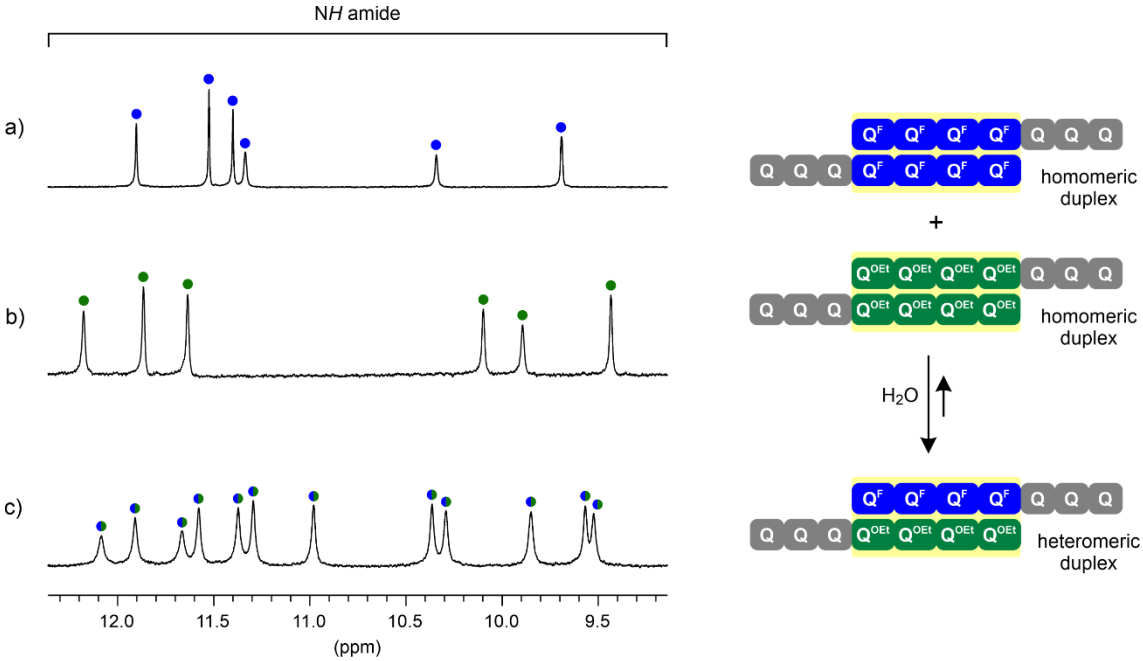


Figure S34. Part of the ^{1}H NMR spectra (700 MHz, calibrated with TSP-d_4) of the amide region at 323 K in H_2O/D_2O (95:5 vol/vol) of a) the homomeric double helix **(1)**$_2$ (0.5 mM), b) the homomeric double helix **(4)**$_2$ (0.5 mM) and c) the mixture of both homomeric double helices at the thermodynamic equilibrium (less than 5 min). Amide signals of the homomeric double helix **(1)**$_2$, the homomeric double helix **(4)**$_2$ and the heteromeric double helix **(1·4)** are marked with blue, green and blue/green circles, respectively.

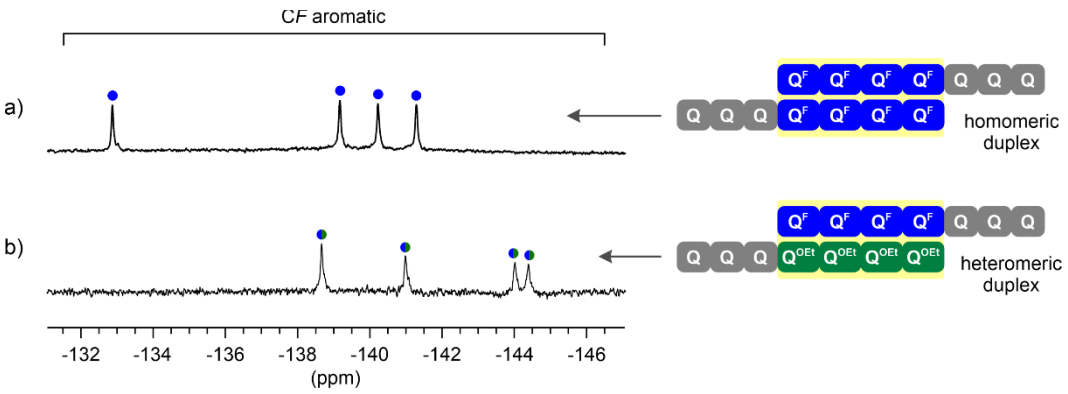


Figure S35. Part of the ^{19}F NMR spectra (376 MHz) at 323 K in H_2O/D_2O (95:5 vol/vol) of a) the homomeric double helix **(1)**$_2$ and b) the heteromeric double helix **(1·4)**. Fluorine signals of the homomeric double helix **(1)**$_2$ and the heteromeric double helix **(1·4)** are marked with blue and blue/green circles, respectively. Spectra were calibrated with TFE (external standard, insert tube).

7.3 2D ^{1}H - ^{19}F HOESY NMR of the heteromeric double helix (1·8)

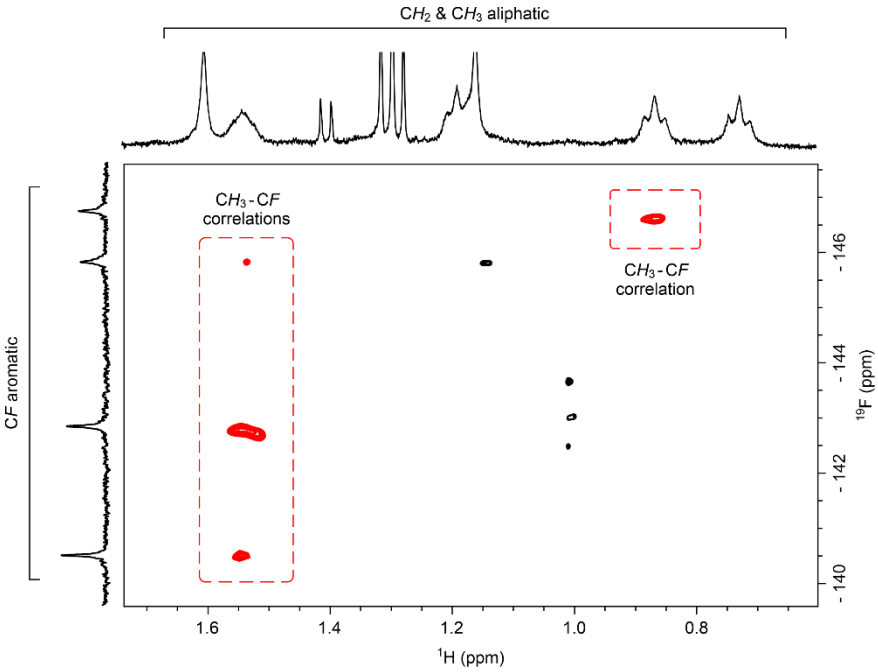


Figure S36. a) Zoom of the 2D ^{1}H - ^{19}F HOESY NMR spectrum (mixing time of 0.5 s) of the heteromeric double helix **(1·8)** at 2 mM (H_2O / D_2O - 95:5 vol/vol, 400 MHz, 323 K) showing correlations between fluorine atoms (located inside the cavity of the duplex) and ethoxy substituents (also inside the cavity). The proton spectrum was calibrated with TSP-d_4 (internal standard) and the fluorine spectrum was calibrated with TFE (external standard, insert tube).

8. Solid state studies: X-ray crystallography and molecular modeling

8.1 Crystal structures and X-ray data of homomeric double helices $(5)_2$ and $(6)_2$

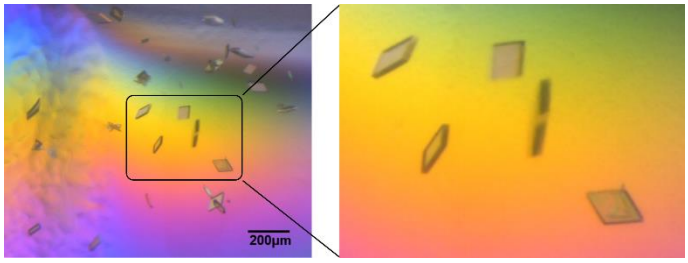


Figure S37. Crystals of the homomeric double helix $(5)_2$ observed under crossed polarizing microscope. Crystals were obtained after three weeks by mixing 0.8 µL of a 3.5 M solution of $(5)_2$ in water, 0.8 µL of 35 % vol/vol 2-methyl-2,4-pentanediol (MPD), 20 mM BIS-TRIS buffer at pH 6.0, 50 mM sodium chloride and 10 mM calcium chloride.

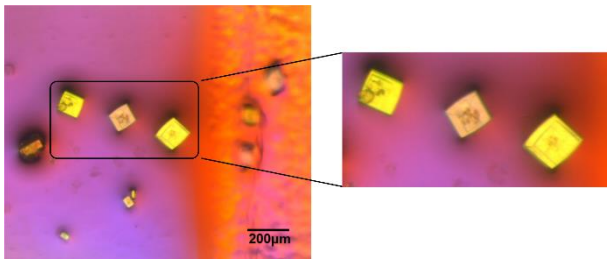


Figure S38. Crystals of the homomeric double helix **(6)**$_2$ observed under crossed polarizing microscope. Crystals were obtained after two months by mixing 0.8 µL of a 3.5 M solution of **(6)**$_2$ in water, 0.8 µL of 9 % vol/vol 2-propanol, 50 mM imidazole buffer at pH 7.2, 15 mM magnesium acetate and 15 mM magnesium chloride.

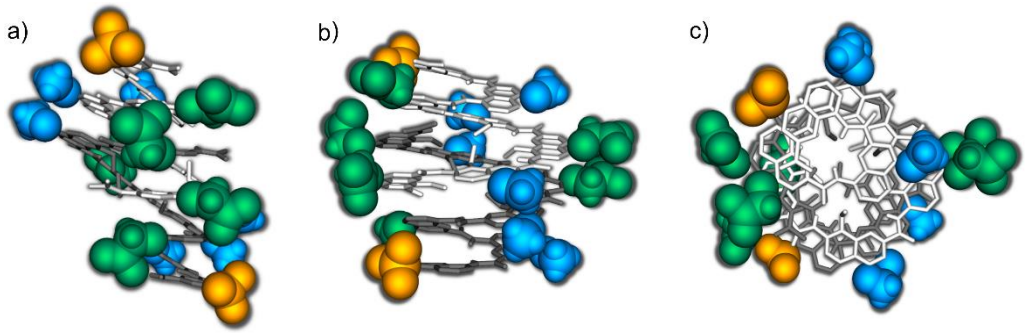


Figure S39. a,b) Side views and c) top view of the double helix **(5)**$_2$ with water-soluble helix side chains in CPK representation. Sulfonic acid (Sul), aspartate-like (Asp) and alanine-like (Ala) side chains are colored in orange, green and blue, respectively. Included solvent molecules have been removed for clarity.

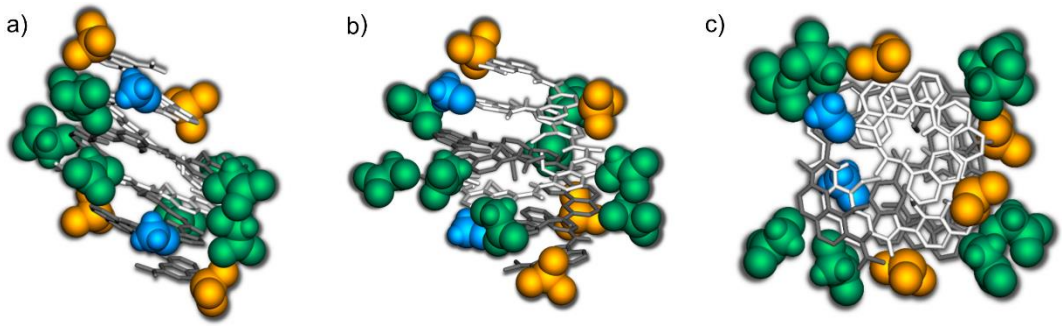


Figure S40. a,b) Side views and c) top view of the double helix **(6)**$_2$ with water-soluble helix side chains in CPK representation. Sulfonic acid (Sul), aspartate-like (Asp) and alanine-like (Ala) side chains are colored in orange, green and blue, respectively. Included solvent molecules have been removed for clarity.

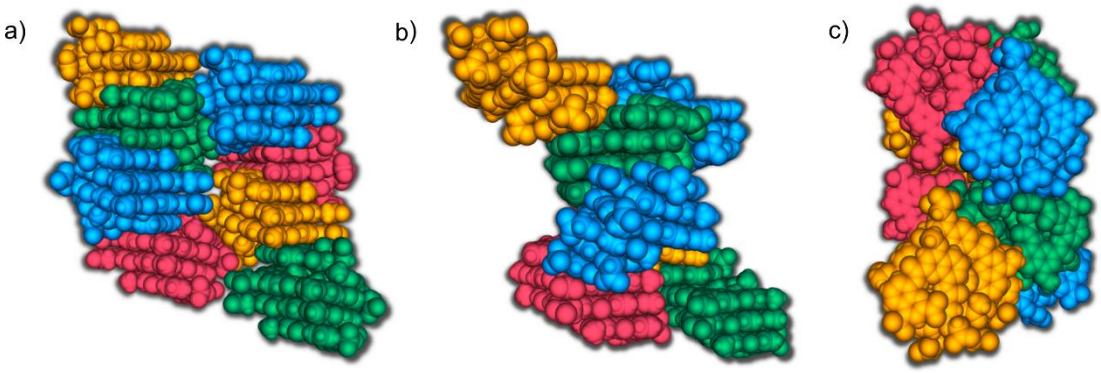


Figure S41. Packing of **(5)**$_2$ in the crystal viewed down a) the b-axis, b) the a-axis and c) the c-axis. Eight antiparallel homomeric double helices **(5)**$_2$ are in the same unit cell and are represented with different colors for clarity.

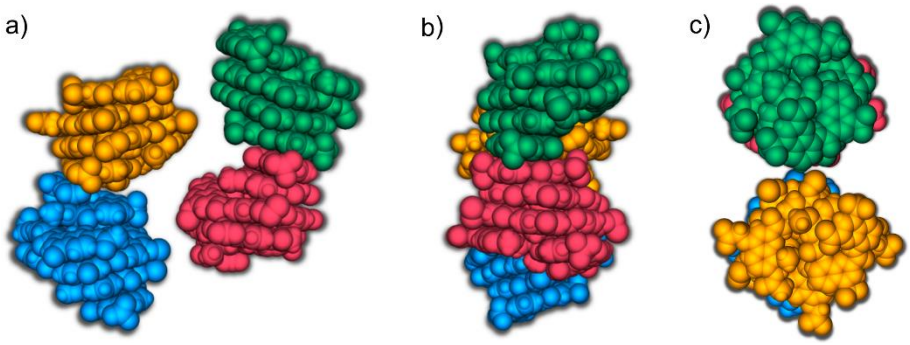


Figure S42. Packing of **(6)**$_2$ in the crystal viewed down a) the b-axis, b) the a-axis and c) the c-axis. Four antiparallel homomeric double helices **(6)**$_2$ are in the same unit cell and are represented with different colors for clarity.

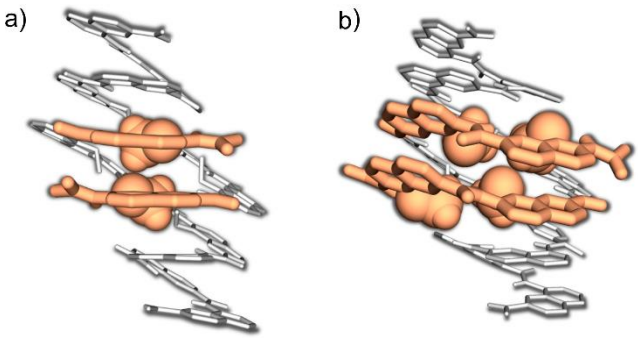


Figure S43. Comparison between crystal structures in water of homomeric double helices a) **(5)**$_2$ and b) **(6)**$_2$ showing a different screwing pattern. In the duplex **(5)**$_2$, one methoxy-quinoline monomer of one strand is stacked with one methoxy-quinoline monomer of the other strand (highlighted in beige) whereas in the duplex **(6)**$_2$, two methoxy-quinoline monomers of one strand is stacked with two methoxy-quinoline monomers of the other strand (highlighted in beige).

Table S2. Crystallographic data and refinement details for the double helix **(5)$_2$**.

Identification code	**(5)$_2$**
Emperical formula	$C_{85}H_{61}Ca_{0.5}N_{14}O_{33.75}S_1$
Formula weight	1870.57
Temperature	100.15 K
Wavelength	0.9184 Å
Crystal system	Monoclinic
Space group	*C2/c*
Unit cell dimensions	a = 48.390 (10) Å b = 21.957 (4) Å c = 41.081 (10) Å α = 90 ° β = 109.840 (10) ° γ = 90 °
Volume	41058 (12) Å^3
Z	16 helices
Density (calculated)	1.210 g/cm^3
Absorption coefficient	0.253 µ/mm^{-1}
Colour and shape	Pale yellow, block
Crystal size	0.200 x 0.08 x 0.005 mm
Index ranges	$-47 \leq h \leq 47$ $-22 \leq k \leq 22$ $-40 \leq l \leq 40$
Reflections collected	128613
R_{int}	0.0434
Data/restraints/parameters	22650/15/2338
Goodness-of-fit on F^2	1.887
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.1268 wR_2 = 0.3946
Final R indexes [all data]	R_1 = 0.1431 wR_2 = 0.4216
Largest diff. peak and hole	1.40/-1.06
CCDC number	2216832

Table S3. Crystallographic data and refinement details for the double helix **(6)$_2$**.

Identification code	**(6)$_2$**
Emperical formula	C_{82} $H_{53.13}$ $N_{14.75}$ $O_{27.25}$ S_2
Formula weight	1745.13
Temperature	100.15 K
Wavelength	0.9762 Å
Crystal system	Triclinic
Space group	*P1*
Unit cell dimensions	a = 27.592 (3) Å b = 30.158 (8) Å c = 36.417 (1) Å α = 100.190 (3) ° β = 110.202 (1) ° γ = 106.600 (8) °
Volume	25942 (13) Å^3
Z	8 helices
Density (calculated)	0.894 g/cm^3
Absorption coefficient	0.234 µ/mm^{-1}
Colour and shape	Yellow, block
Crystal size	0.200 x 0.180 x 0.005 mm
Index ranges	$-21 \leq h \leq 21$ $-23 \leq k \leq 23$ $-27 \leq l \leq 28$
Reflections collected	91996
R_{int}	0.0463
Data/restraints/parameters	46604/1084/2492
Goodness-of-fit on F^2	1.877
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.2118 wR_2 = 0.4488
Final R indexes [all data]	R_1 = 0.2796 wR_2 = 0.5259
Largest diff. peak and hole	1.25/-0.80
CCDC number	2232111

8.2 Molecular modeling of homomeric double helices $(1)_2$-$(4)_2$

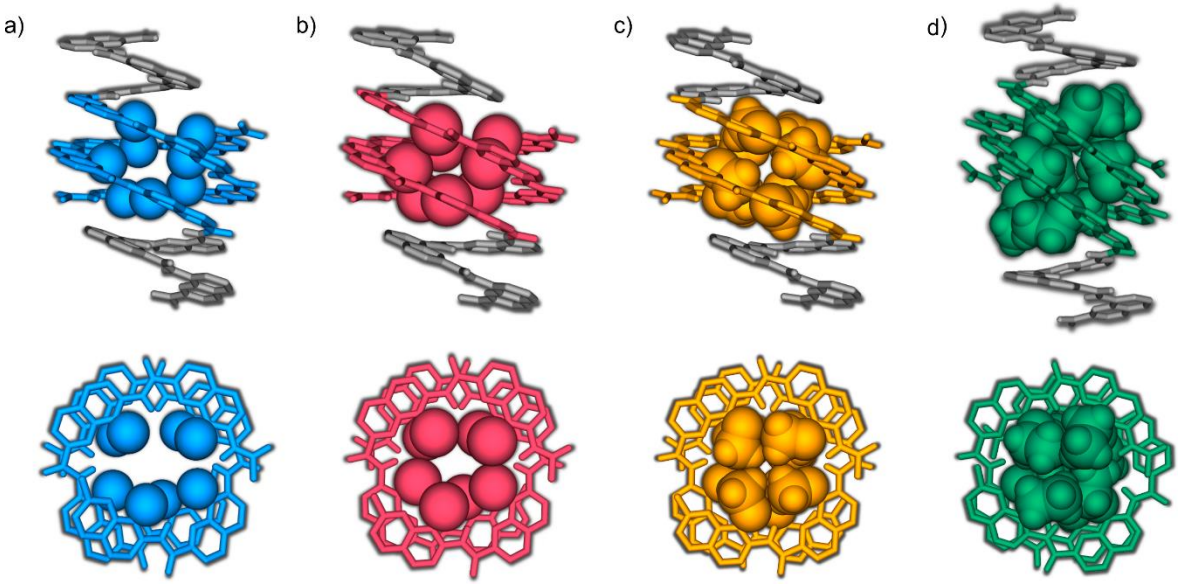


Figure S44. Side and top views of energy-minimized structures (MMFFs) in water of homomeric double helices a) $(\mathbf{1})_2$, b) $(\mathbf{2})_2$, c) $(\mathbf{3})_2$ and d) $(\mathbf{4})_2$. Double helices are shown in tube representation and all the substituents in position 8 of 8-substituted quinoline monomers are shown in CPK representation. Lateral chains in position 4 of quinoline monomers, which are outside the cylindrical cavity, were omitted for clarity. In top views, both Q_3 segments were removed. Only the hydrogen atoms of the substituents in position 8 of 8-substituted quinoline monomers are shown.

8.3 Molecular modeling of heteromeric double helices (1·7) and (1·8)

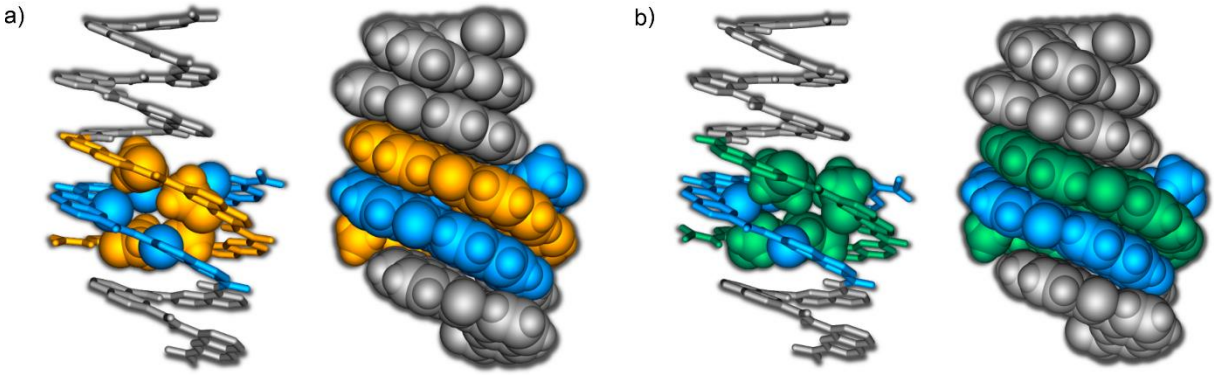


Figure S45. Side views of energy-minimized structures (MMFFs) in water of heteromeric double helices a) **(1·7)** and b) **(1·8)**. On the left, double helices are shown in tube representation without hydrogen atoms and all the substituents in position 8 of 8-substituted quinoline monomers are shown in CPK representation with hydrogen atoms. On the right, double helices are shown in CPK representation with hydrogen atoms. Lateral chains in position 4 of quinoline monomers were omitted for clarity. Q, Q^F, Q^{OMe} and Q^{OEt} monomers are colored in grey, blue, orange and green, respectively.

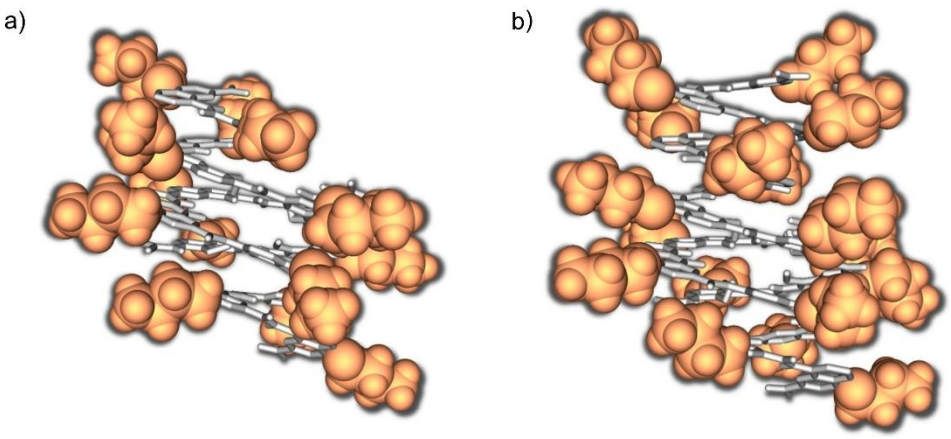


Figure S46. Side views of energy-minimized structures (MMFFs) in water of heteromeric double helices a) **(1·3)** and b) **(1·7)**. Double helices are shown in white tube representation without hydrogen atoms whereas water-soluble lateral chains (ornithine-like side chain $-O(CH_2)_3NH_3^+$) in position 4 of quinoline monomers, which are outside the cylindrical cavity, are shown in beige CPK representation with hydrogen atoms.

9. References

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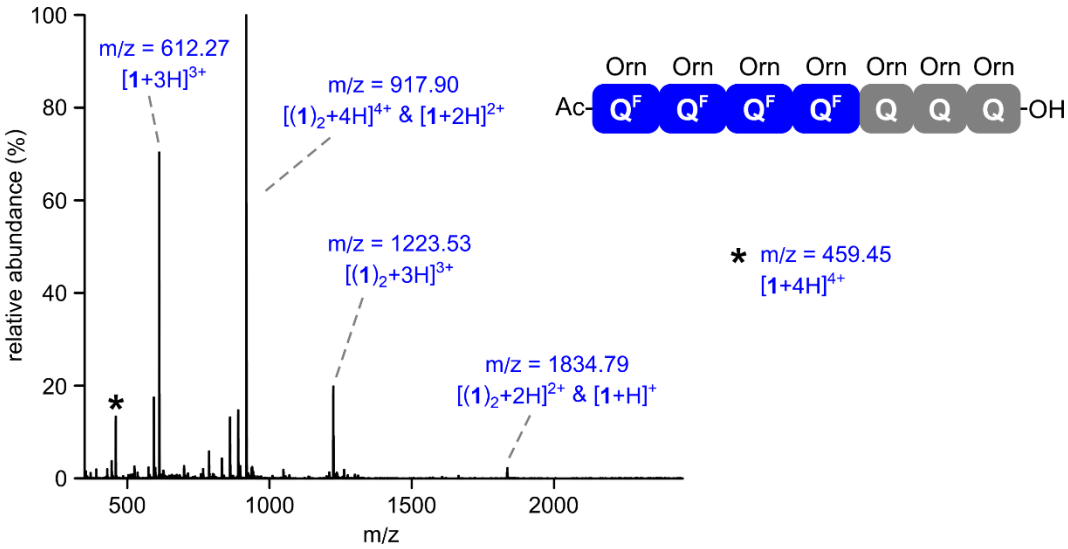
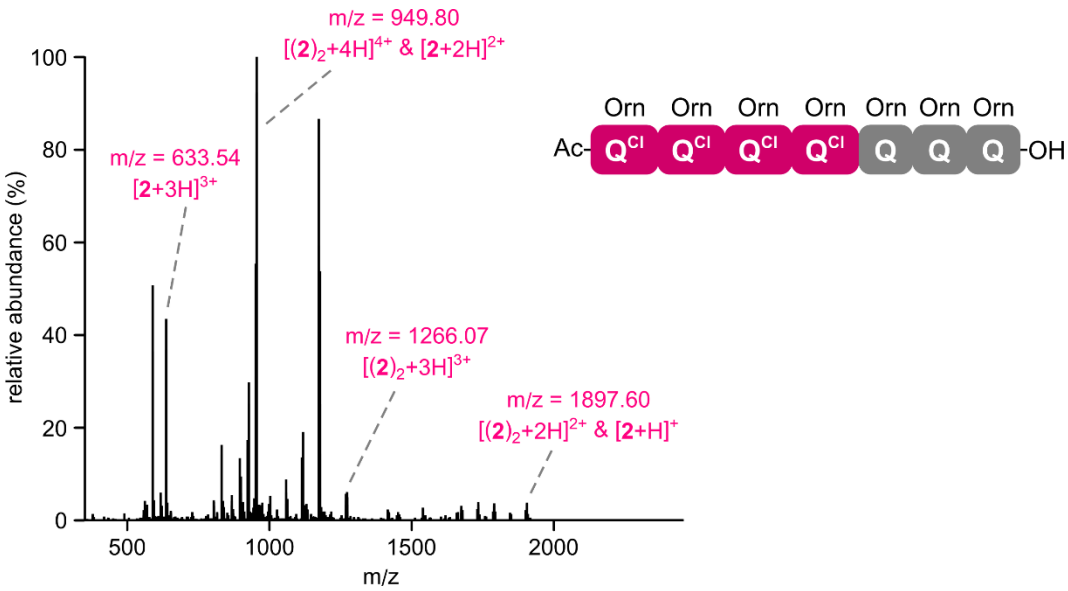
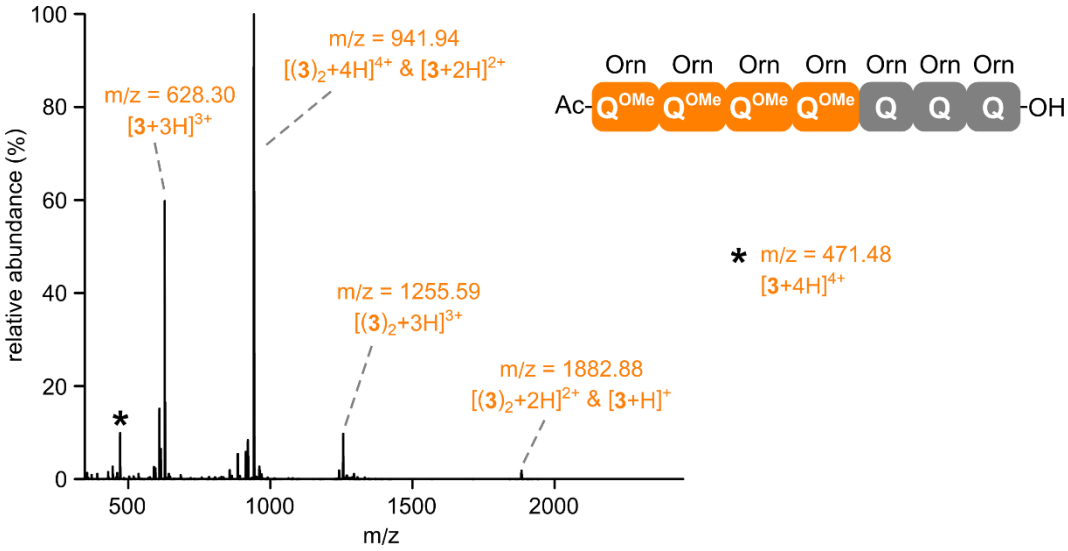
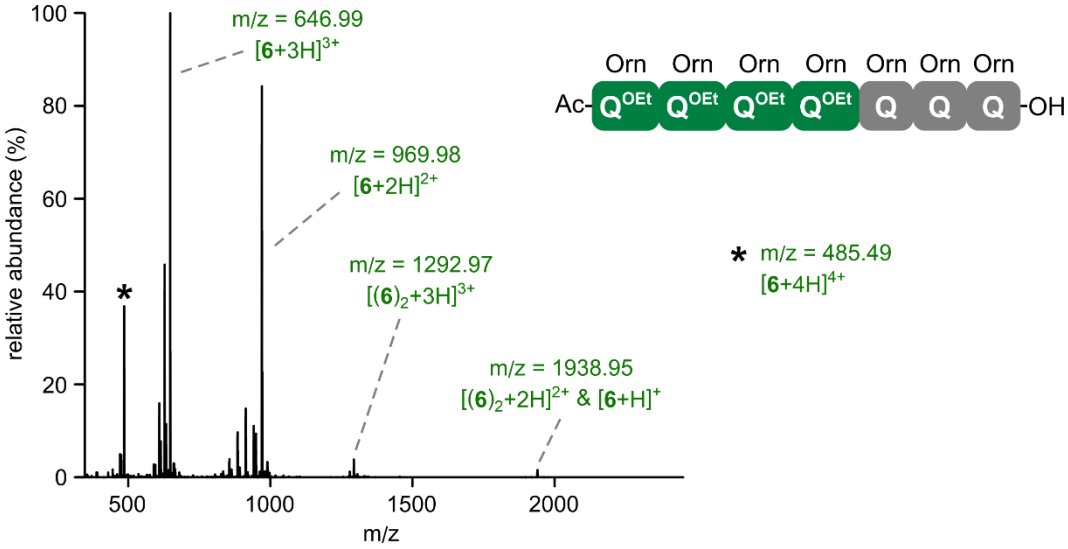
10. Characterizations of new synthetic compounds

10.1 ESI mass spectra of homomeric and heteromeric double helices





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m/z = 969.98
[6+2H]2+
m/z = 1292.97
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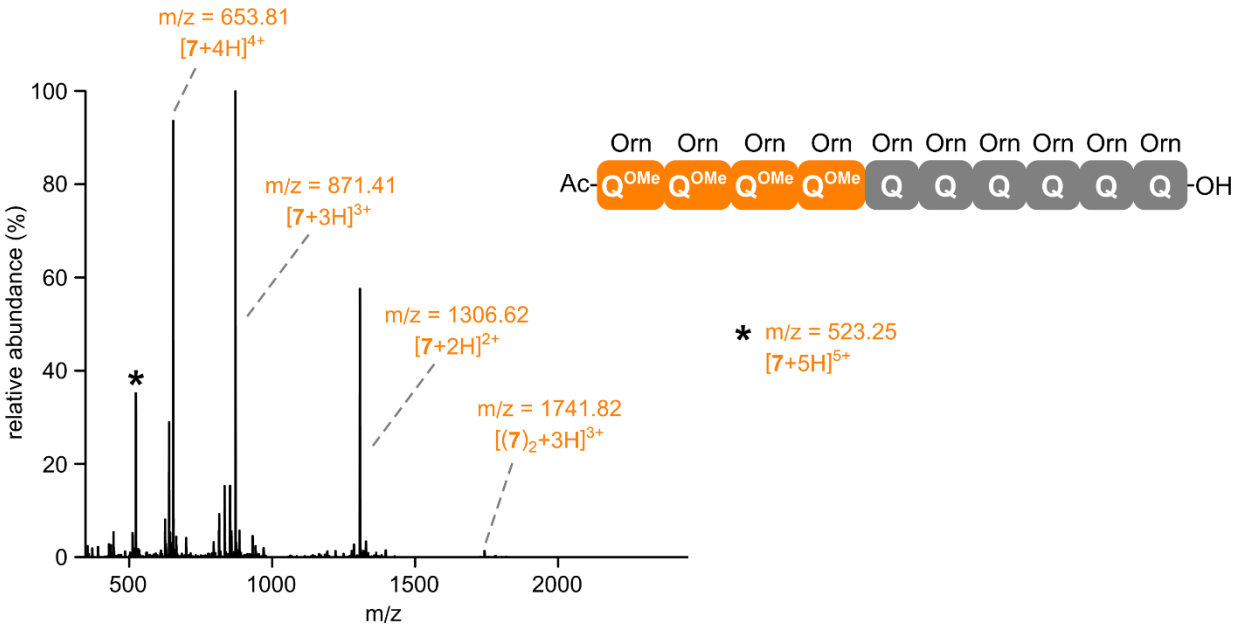
m/z = 1938.95
[(6)2+2H]2+ & [6+H]+
* m/z = 485.49
[6+4H]4+
relative abundance (%)
m/z
Orn Orn Orn Orn Orn Orn Orn
Ac- QOEt QOEt QOEt QOEt Q Q Q -OH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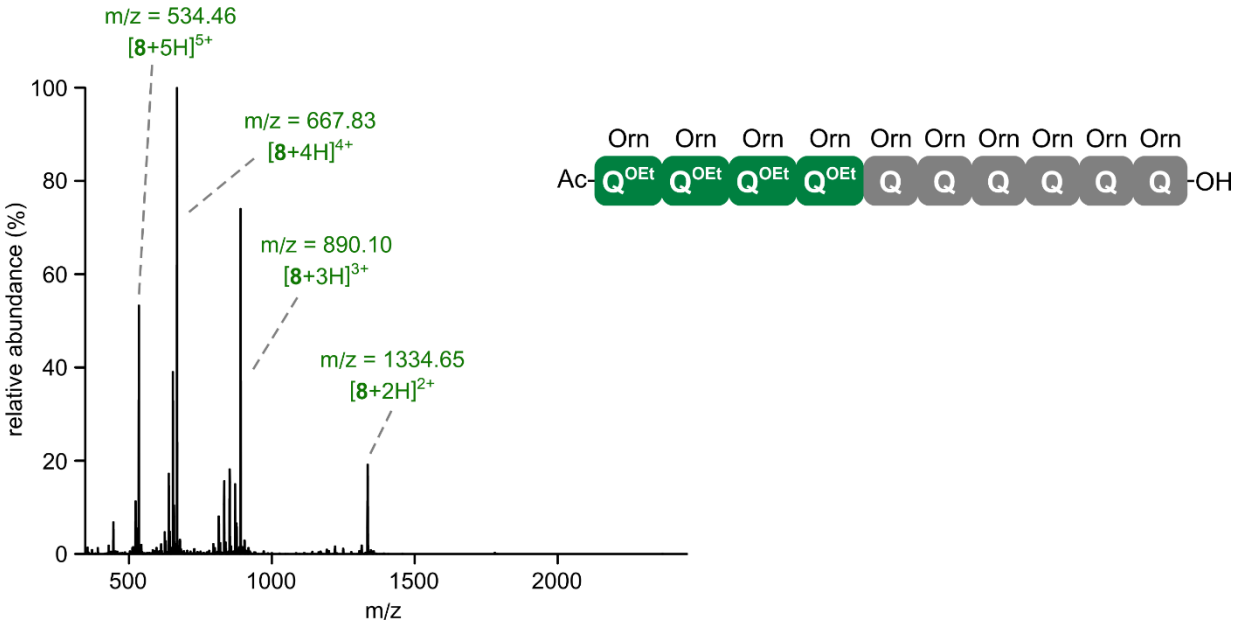
* m/z = 523.25
[7+5H]5+
relative abundance (%)
m/z
Orn Orn Orn Orn Orn Orn Orn Orn Orn Orn
Ac- QOMe QOMe QOMe QOMe Q Q Q Q Q Q -OH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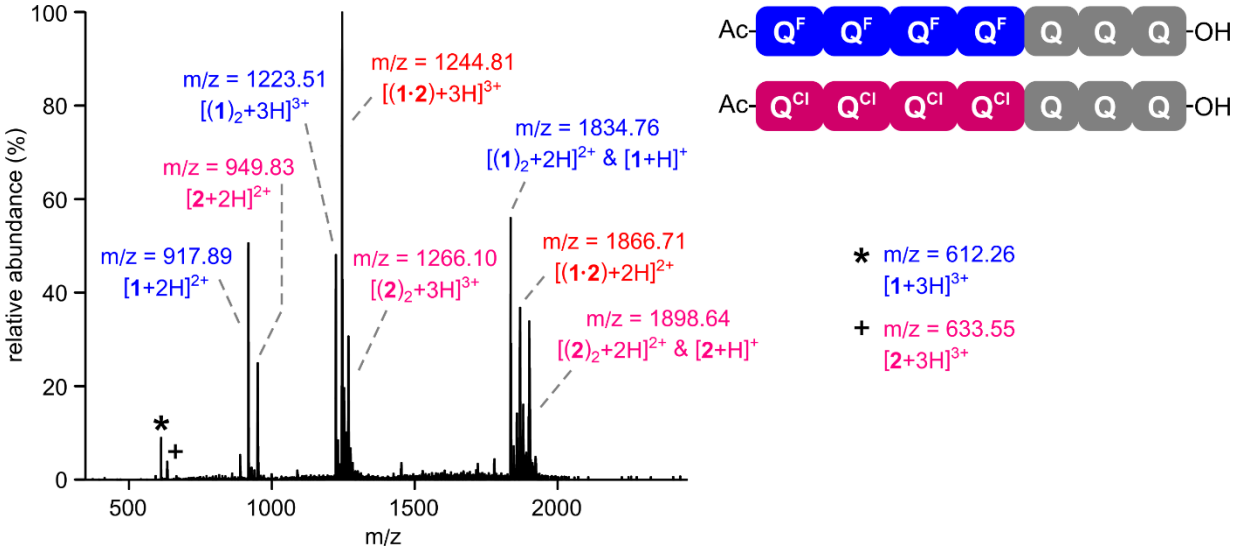
m/z = 1334.65
[8+2H]2+
relative abundance (%)
m/z
Orn Orn Orn Orn Orn Orn Orn Orn Orn Orn
Ac- QOEt QOEt QOEt QOEt Q Q Q Q Q Q -OH


relative abundance (%)
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m/z = 917.89
[1+2H]2+
m/z = 1266.10
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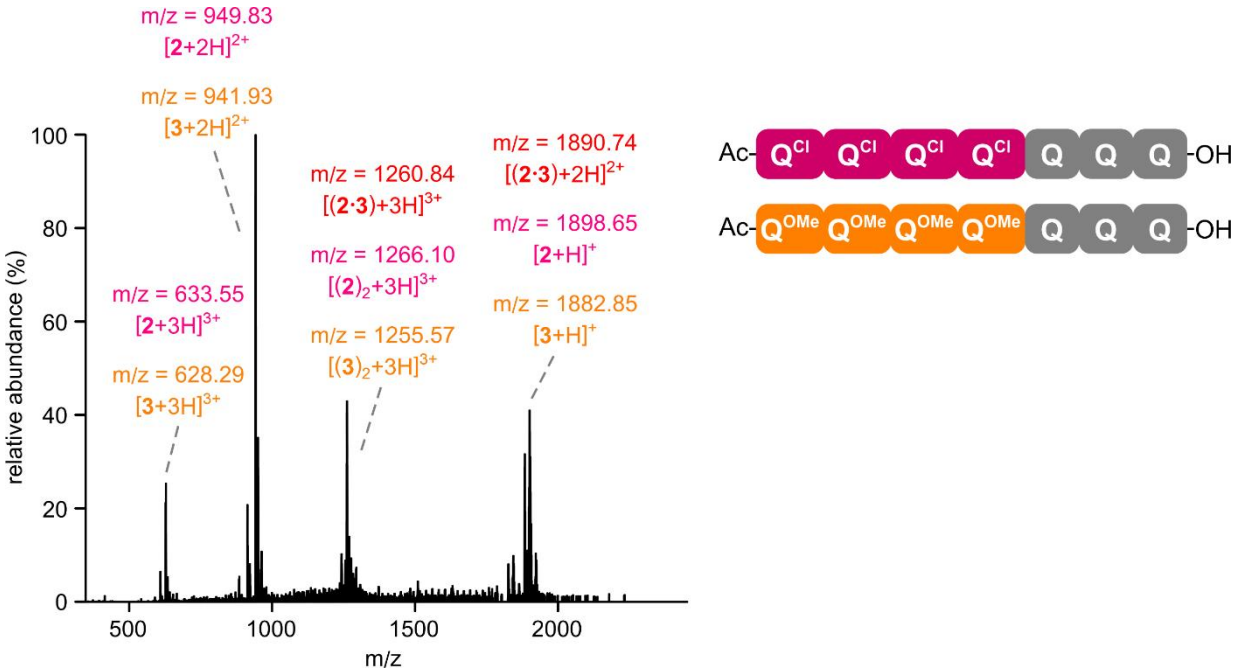
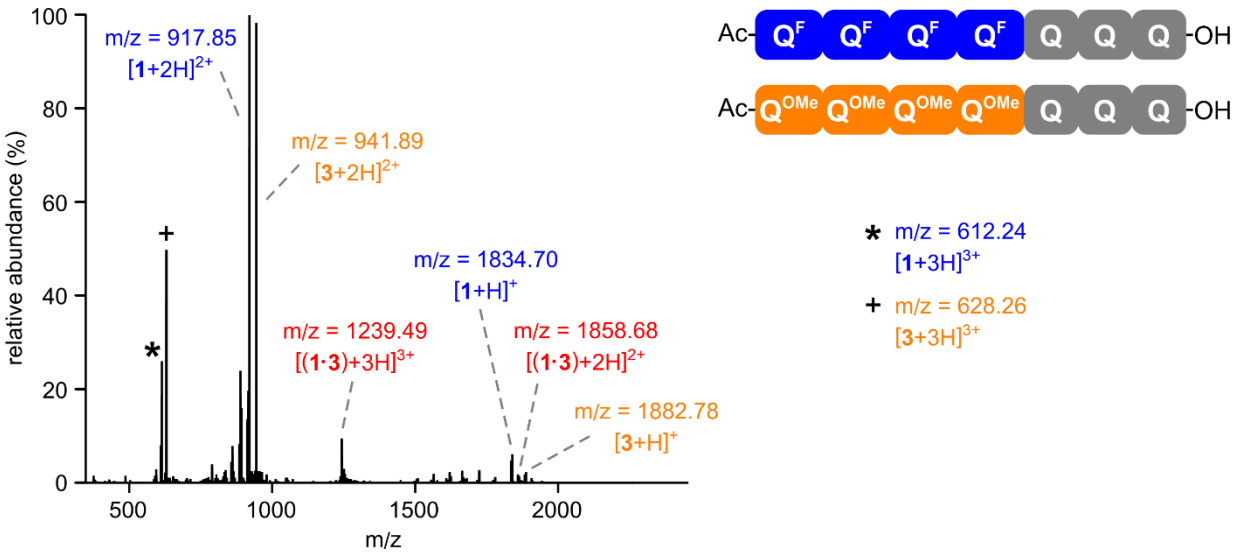
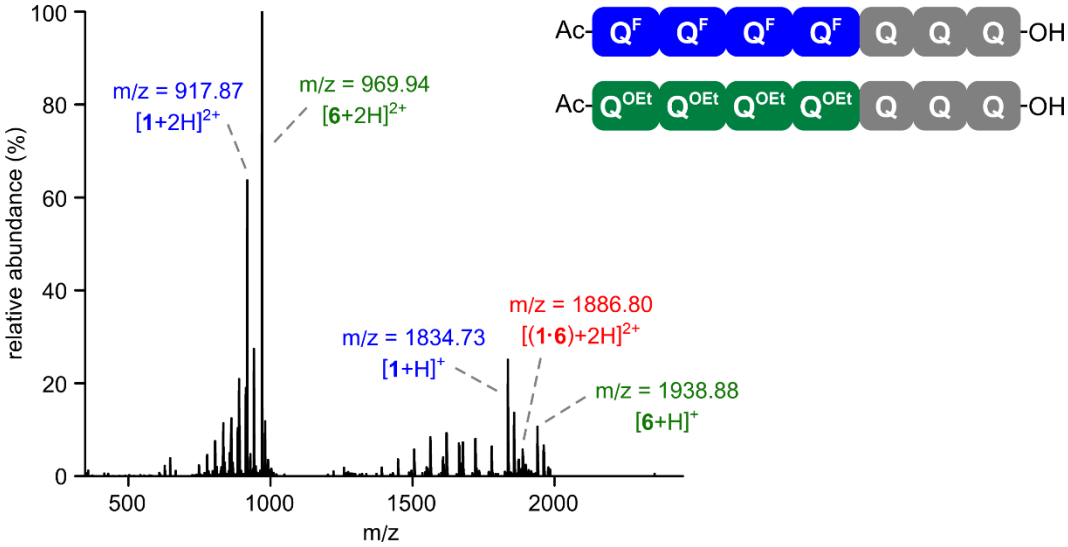
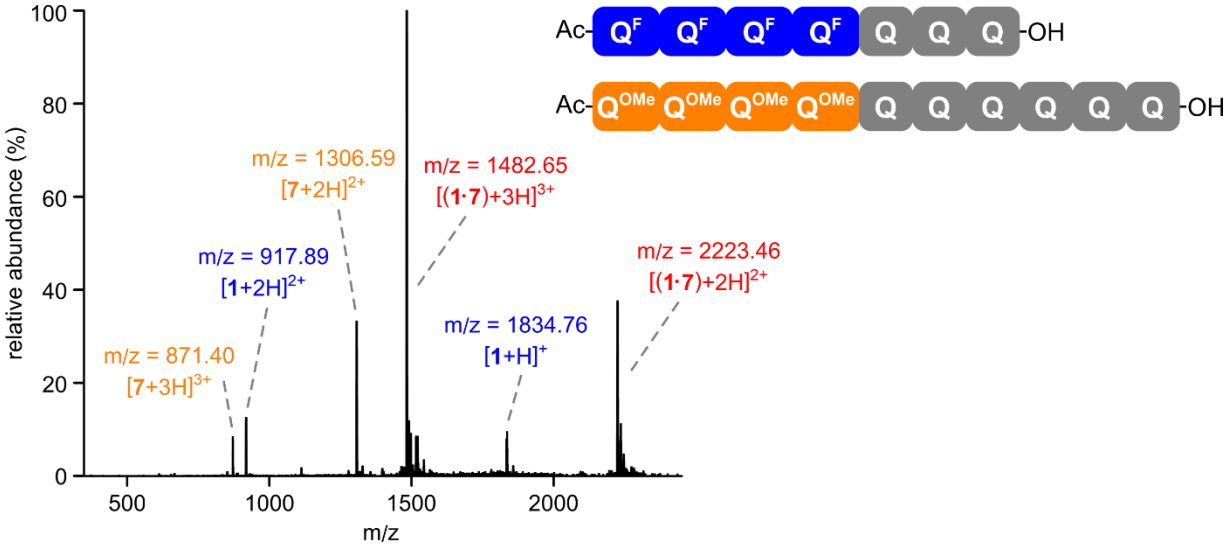
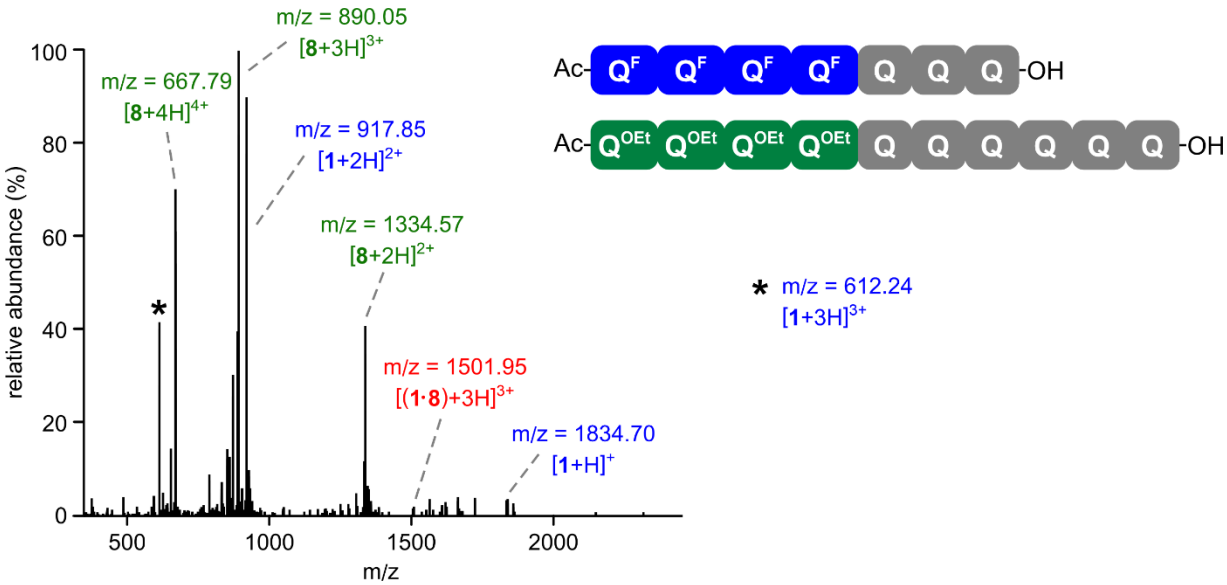
m/z = 1866.71
[(1·2)+2H]2+
m/z = 1898.64
[(2)2+2H]2+ & [2+H]+
* m/z = 612.26
[1+3H]3+
+ m/z = 633.55
[2+3H]3+
Ac-QF QF QF QF Q Q Q-OH
Ac-QCl QCl QCl QCl Q Q Q-OH


relative abundance (%)
m/z
m/z = 949.83
[2+2H]2+
m/z = 941.93
[3+2H]2+
m/z = 1890.74
[(2·3)+2H]2+
m/z = 1260.84
[(2·3)+3H]3+
m/z = 1898.65
[2+H]+
m/z = 1266.10
[(2)2+3H]3+
m/z = 633.55
[2+3H]3+
m/z = 1882.85
[3+H]+
m/z = 1255.57
[(3)2+3H]3+
m/z = 628.29
[3+3H]3+
Ac-QCl QCl QCl QCl Q Q Q-OH
Ac-QOMe QOMe QOMe QOMe Q Q Q-OH

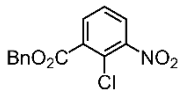

relative abundance (%)
m/z
m/z = 917.85
[1+2H]2+
m/z = 941.89
[3+2H]2+
m/z = 1834.70
[1+H]+
m/z = 1239.49
[(1·3)+3H]3+
m/z = 1858.68
[(1·3)+2H]2+
m/z = 1882.78
[3+H]+
* m/z = 612.24
[1+3H]3+
+ m/z = 628.26
[3+3H]3+
Ac-QF QF QF QF Q Q Q-OH
Ac-QOMe QOMe QOMe QOMe Q Q Q-OH


relative abundance (%)
m/z
m/z = 917.87
[1+2H]2+
m/z = 969.94
[6+2H]2+
m/z = 1834.73
[1+H]+
m/z = 1886.80
[(1·6)+2H]2+
m/z = 1938.88
[6+H]+
Ac- QF QF QF QF Q Q Q -OH
Ac- QOEt QOEt QOEt QOEt Q Q Q -OH

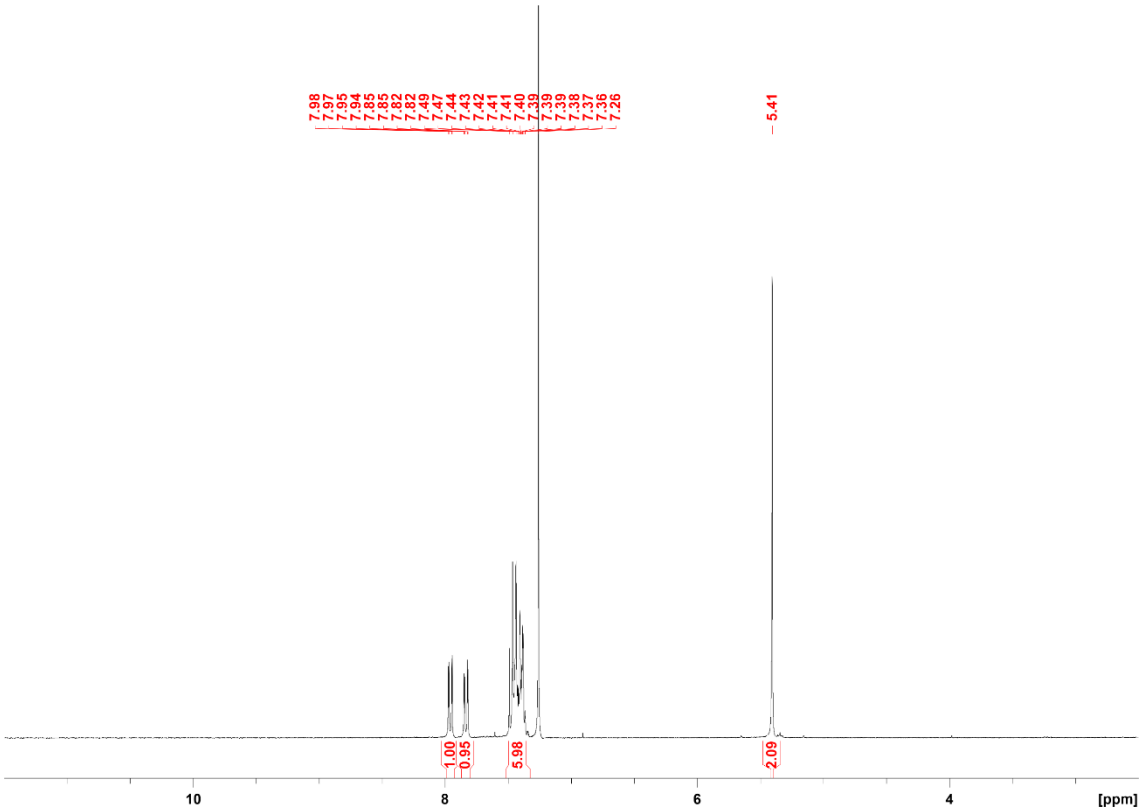

relative abundance (%)
m/z
m/z = 871.40
[7+3H]3+
m/z = 917.89
[1+2H]2+
m/z = 1306.59
[7+2H]2+
m/z = 1482.65
[(1·7)+3H]3+
m/z = 1834.76
[1+H]+
m/z = 2223.46
[(1·7)+2H]2+
Ac- QF QF QF QF Q Q Q -OH
Ac- QOMe QOMe QOMe QOMe Q Q Q Q Q Q -OH

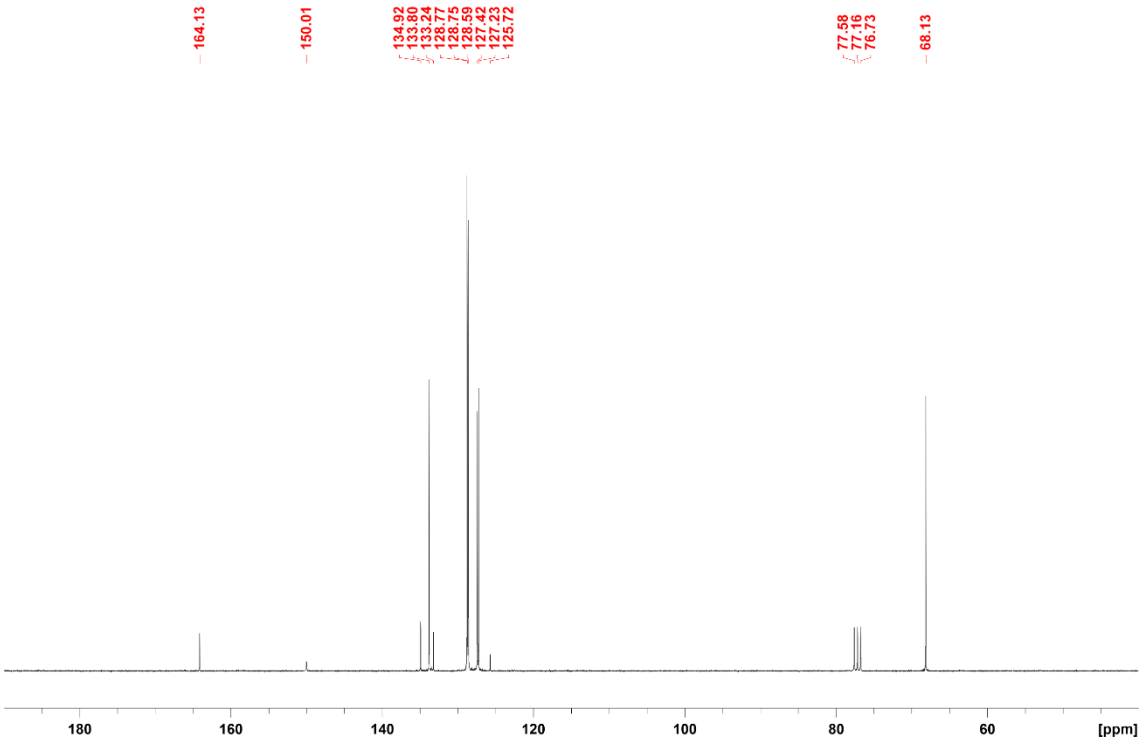

relative abundance (%)
m/z
m/z = 667.79
[8+4H]4+
m/z = 890.05
[8+3H]3+
m/z = 917.85
[1+2H]2+
m/z = 1334.57
[8+2H]2+
m/z = 1501.95
[(1·8)+3H]3+
m/z = 1834.70
[1+H]+
* m/z = 612.24
[1+3H]3+
Ac- QF QF QF QF Q Q Q -OH
Ac- QOEt QOEt QOEt QOEt Q Q Q Q Q Q -OH

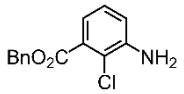
10.2 ^{1}H and ^{13}C NMR spectra of monomers and intermediates



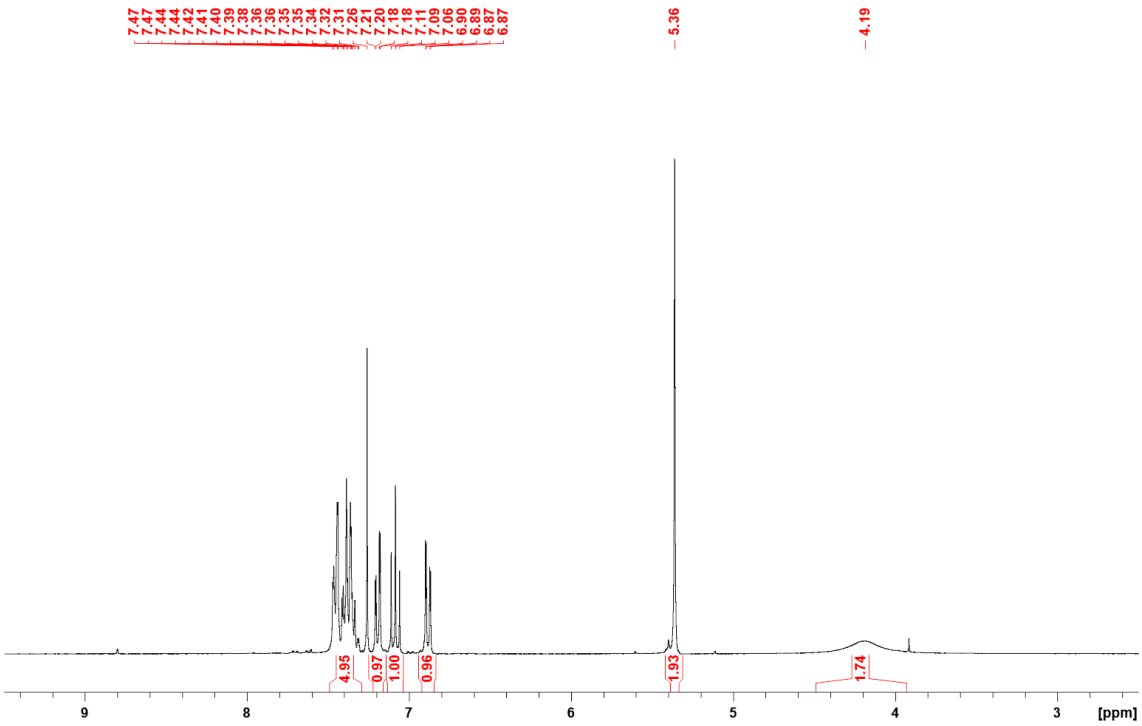
Compound **9**, $CDCl_3$, 300 MHz

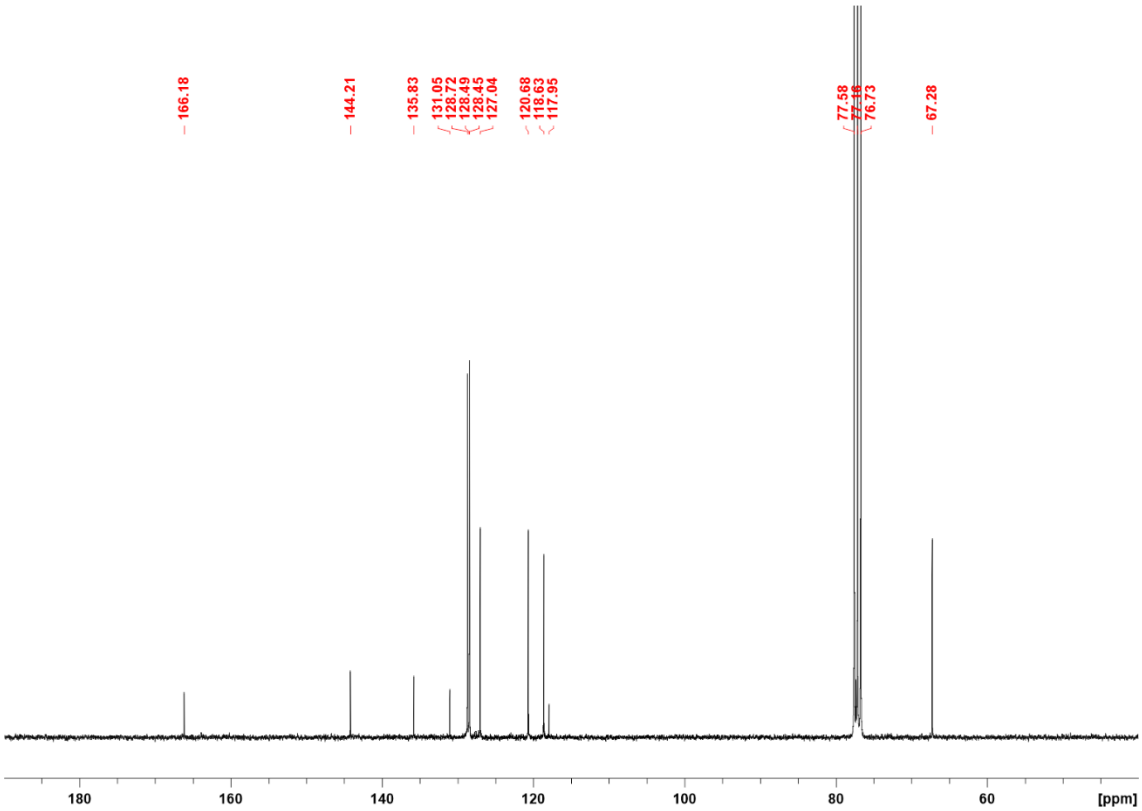


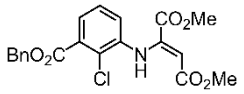




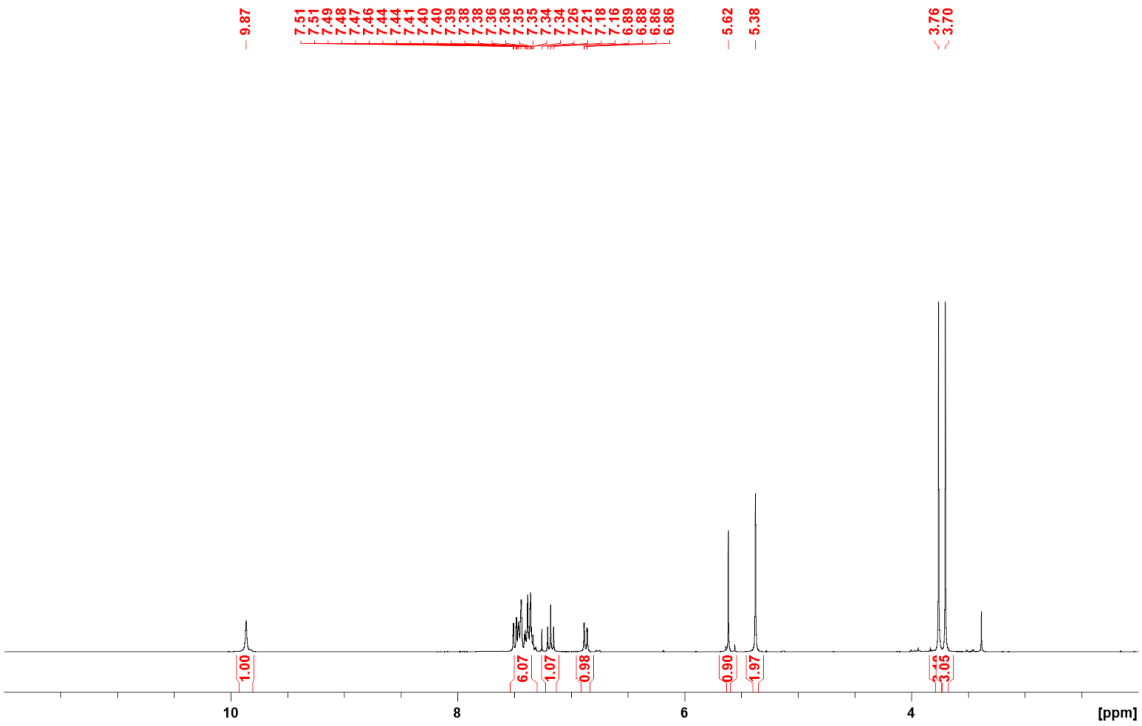
Compound **10**, $CDCl_3$, 300 MHz

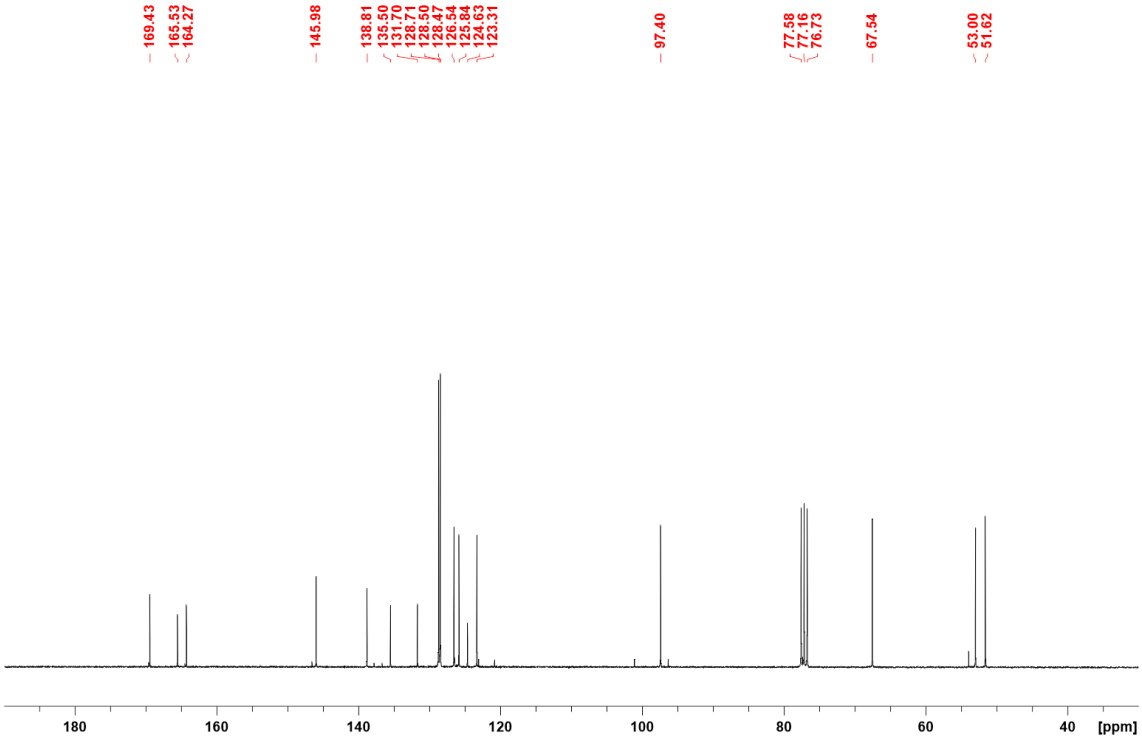


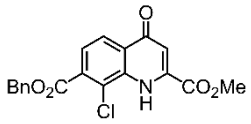




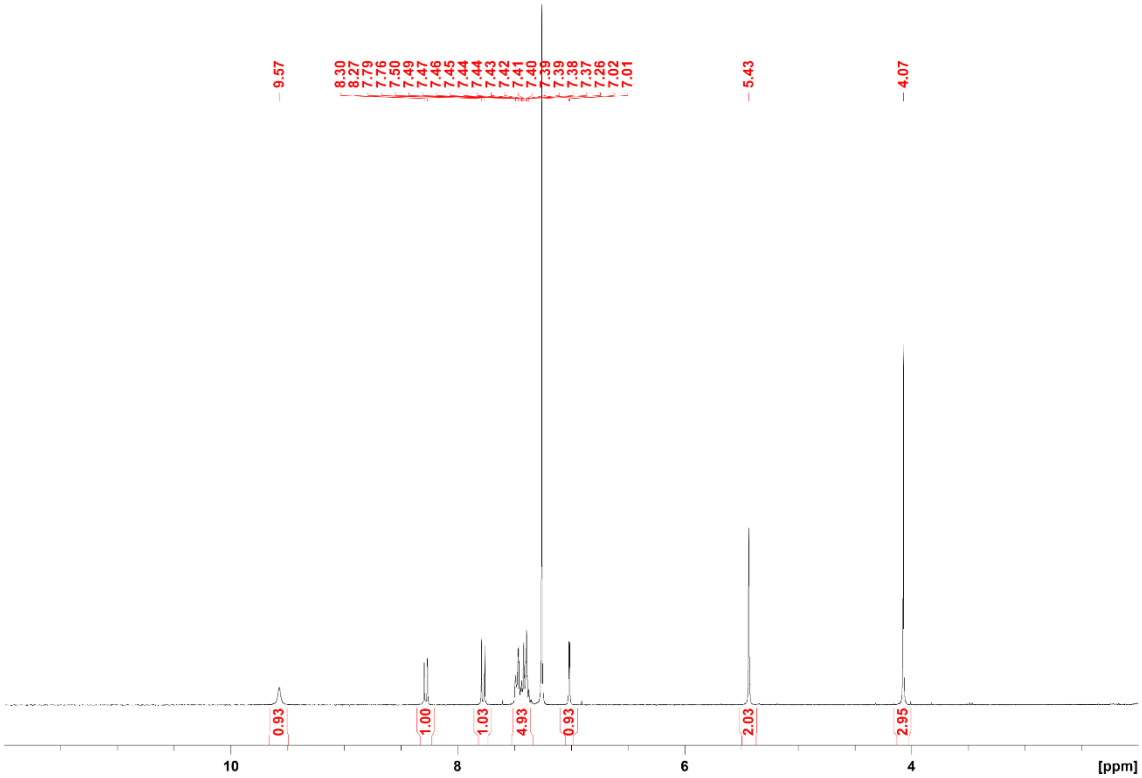
Compound **11**, $CDCl_3$, 300 MHz

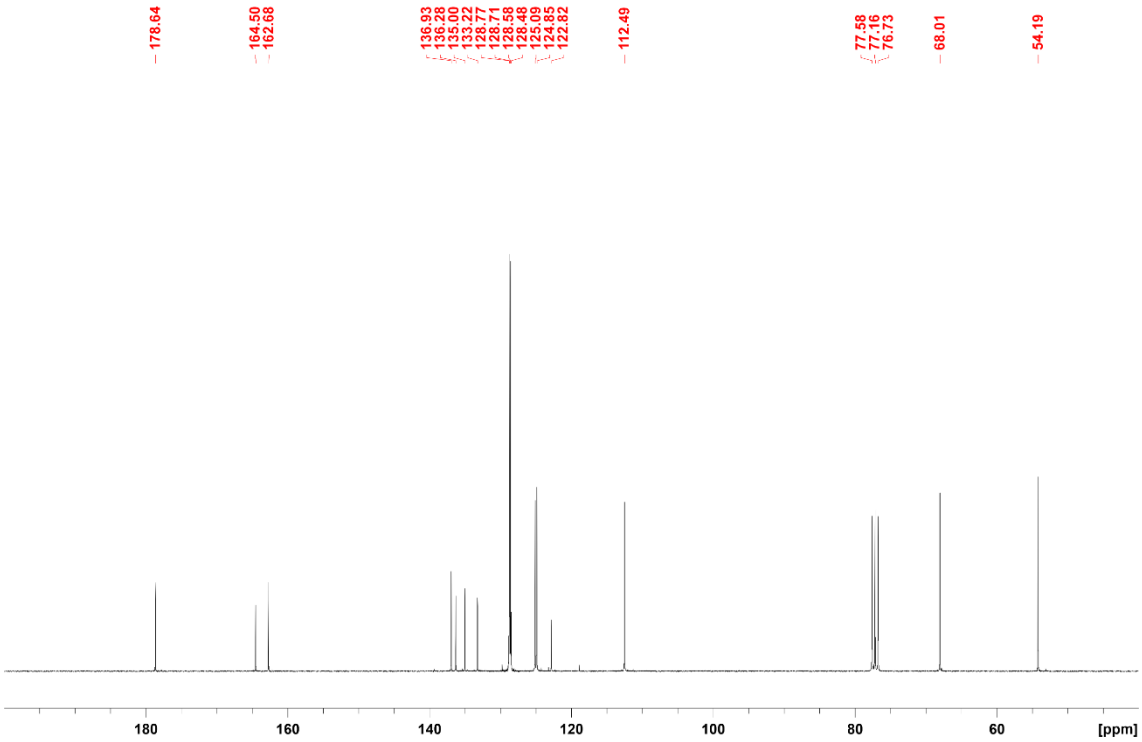


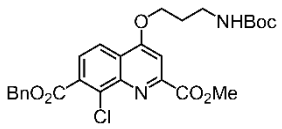




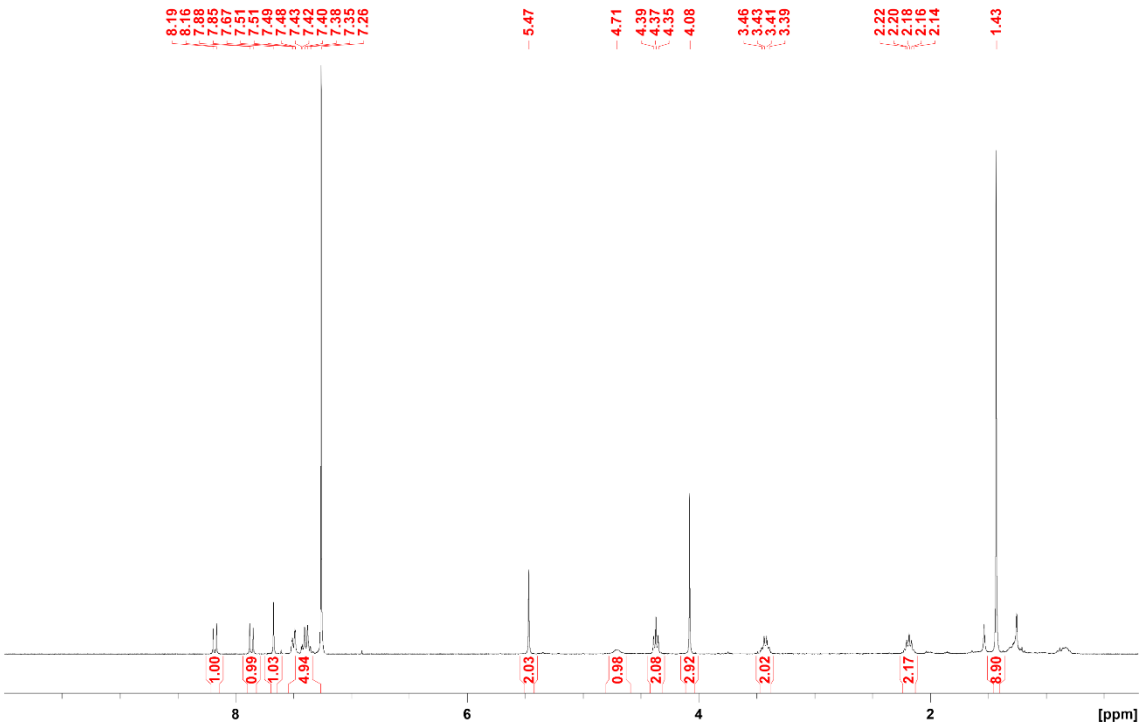
Compound **12**, $CDCl_3$, 300 MHz

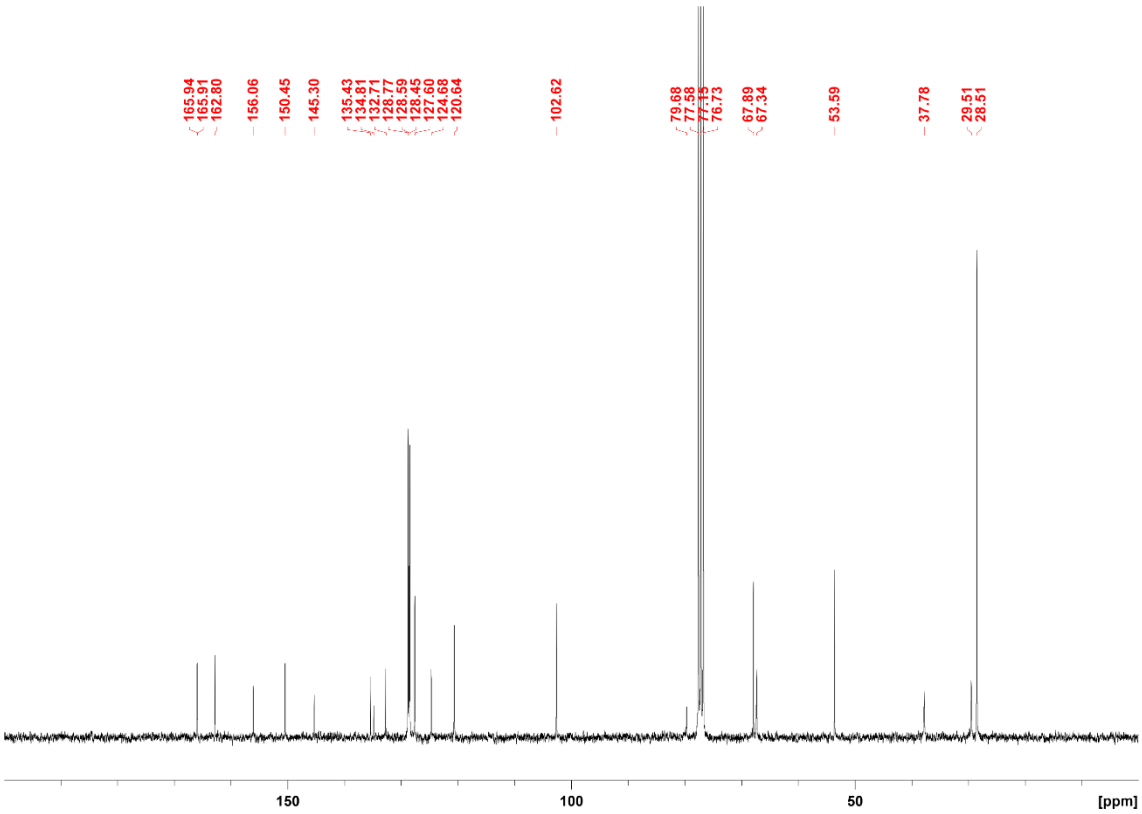


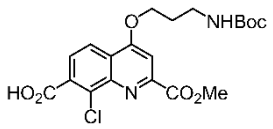




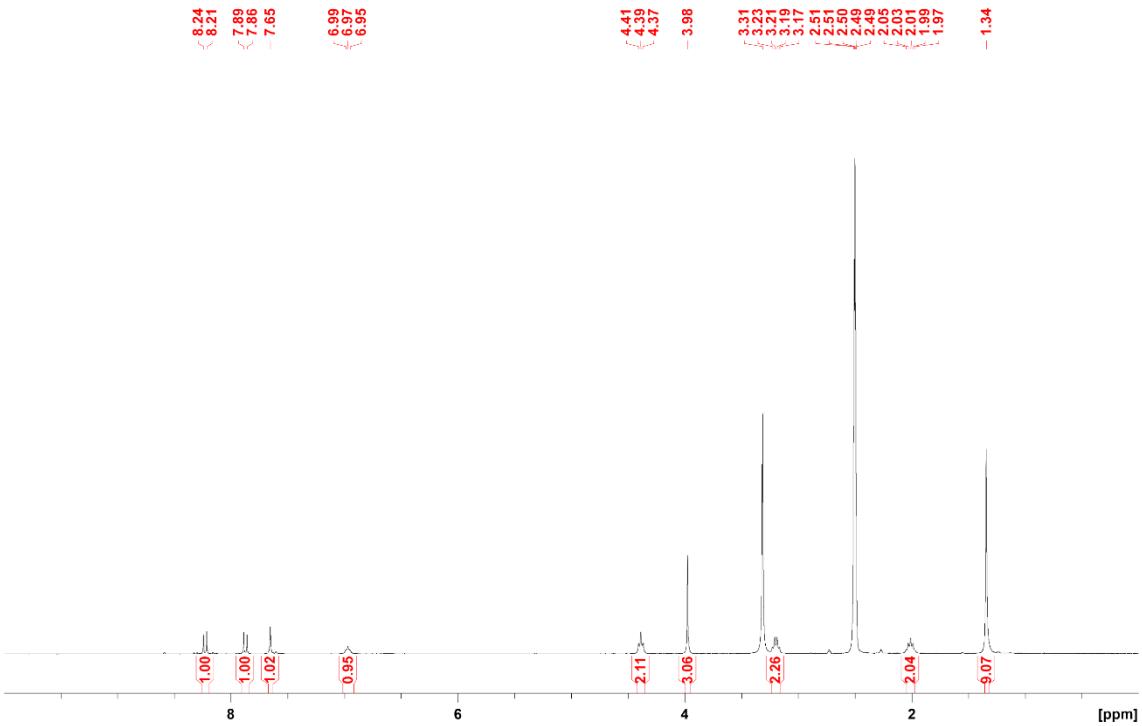
Compound **13**, $CDCl_3$, 300 MHz

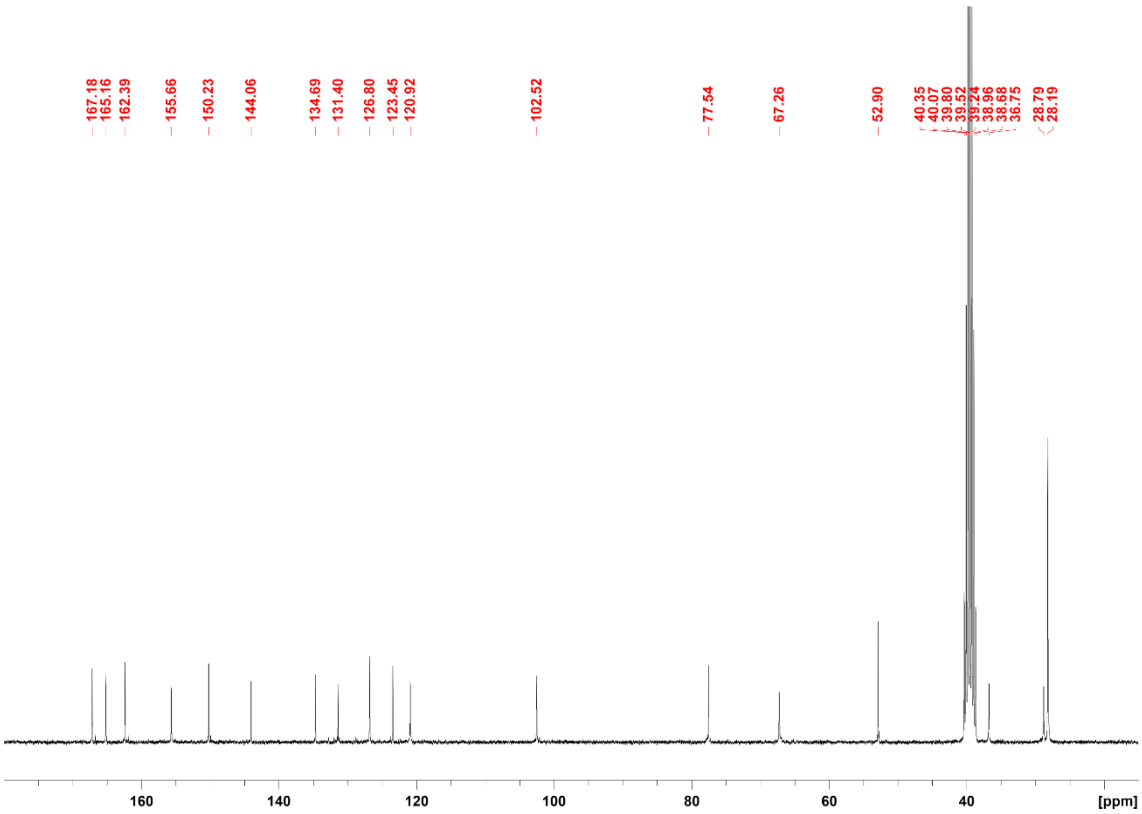


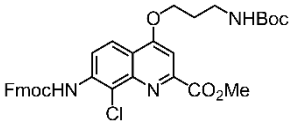




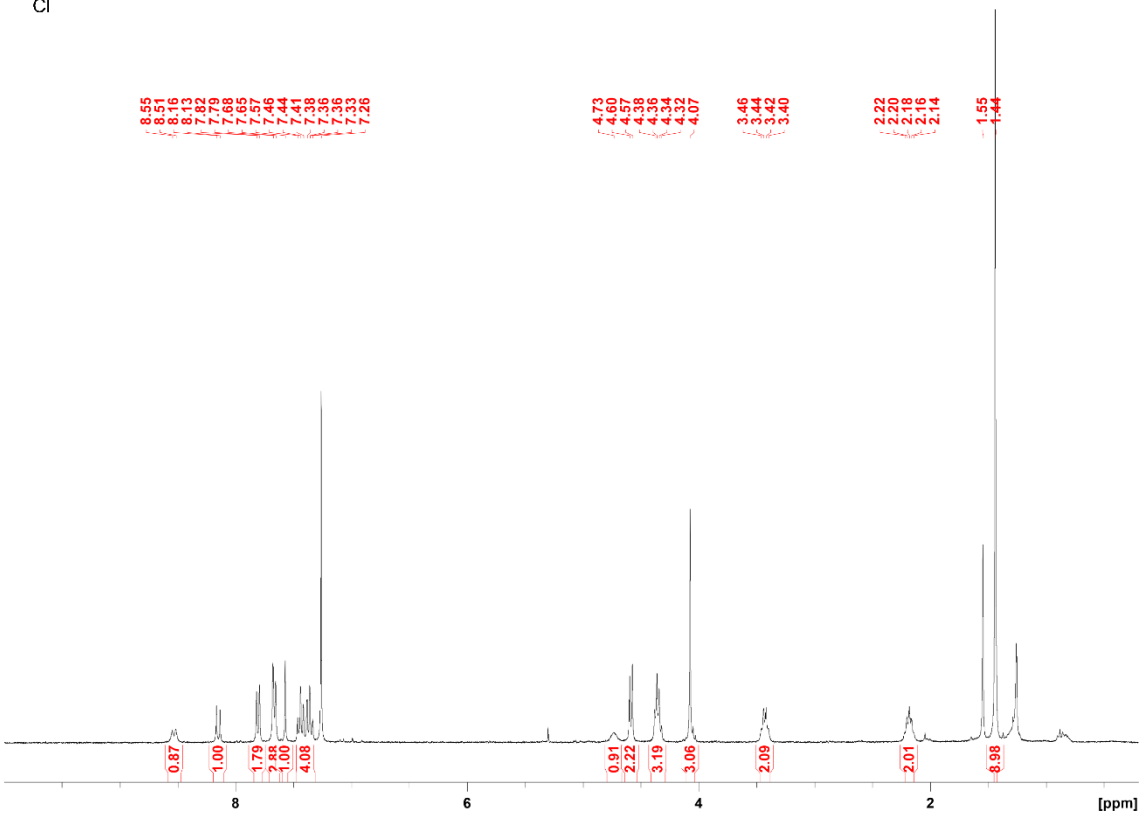
Compound **14**, DMSO-d_6, 300 MHz

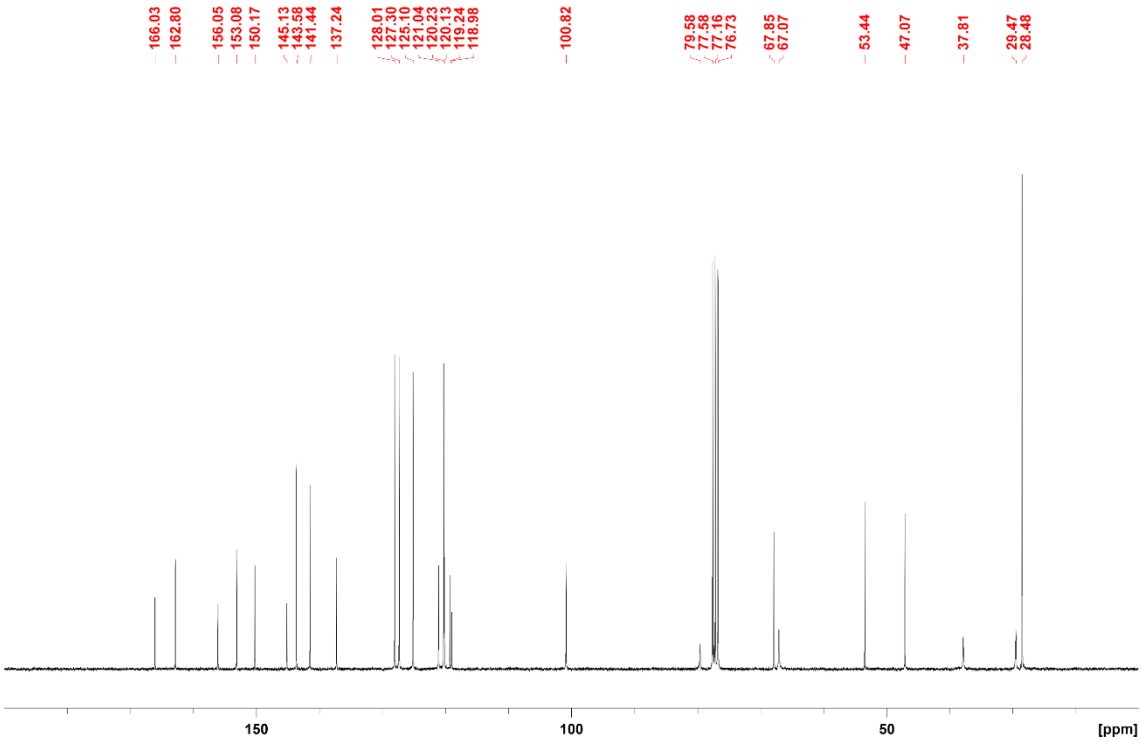


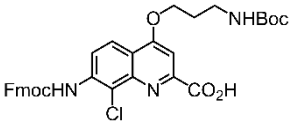




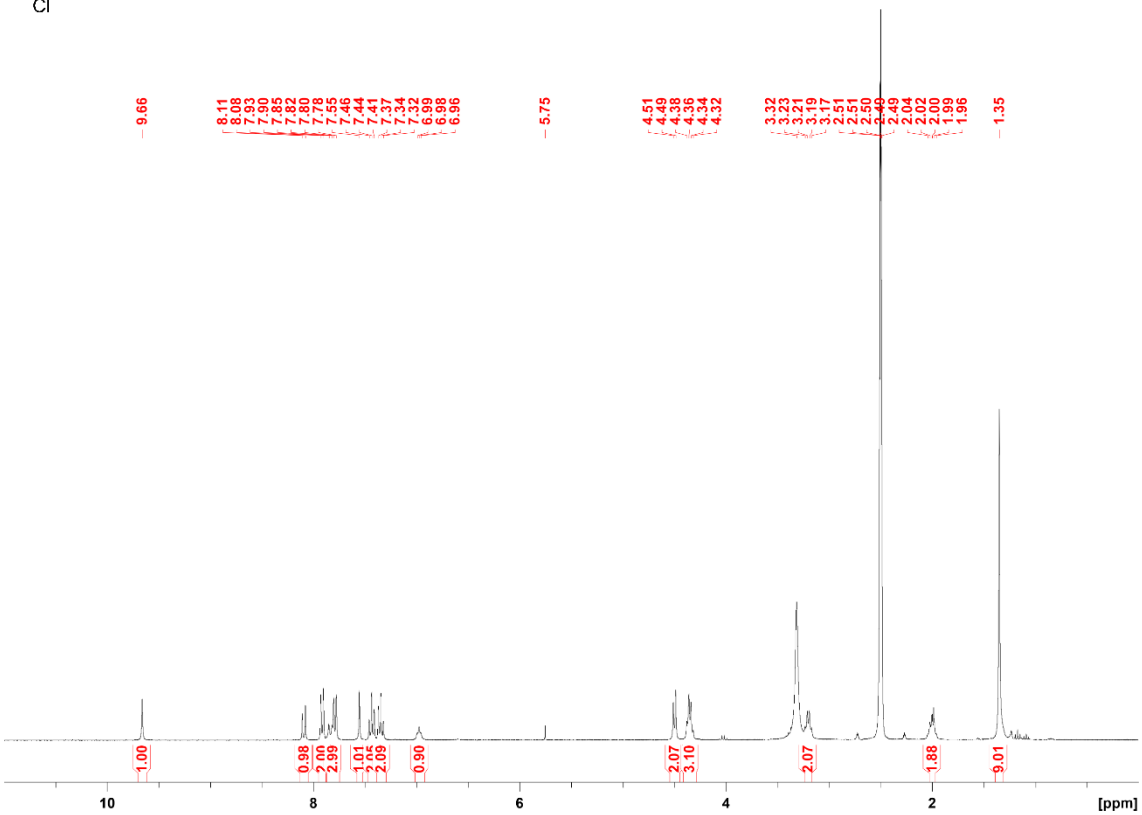
Compound **15**, $CDCl_3$, 300 MHz

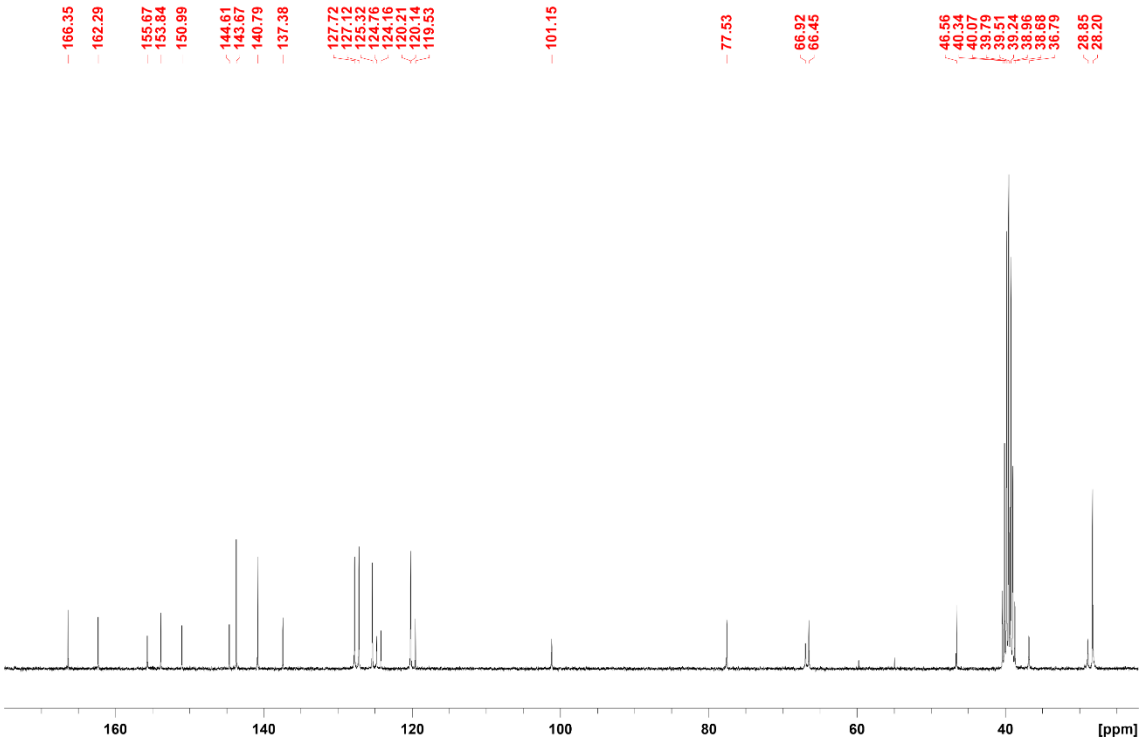


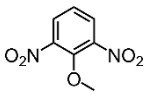




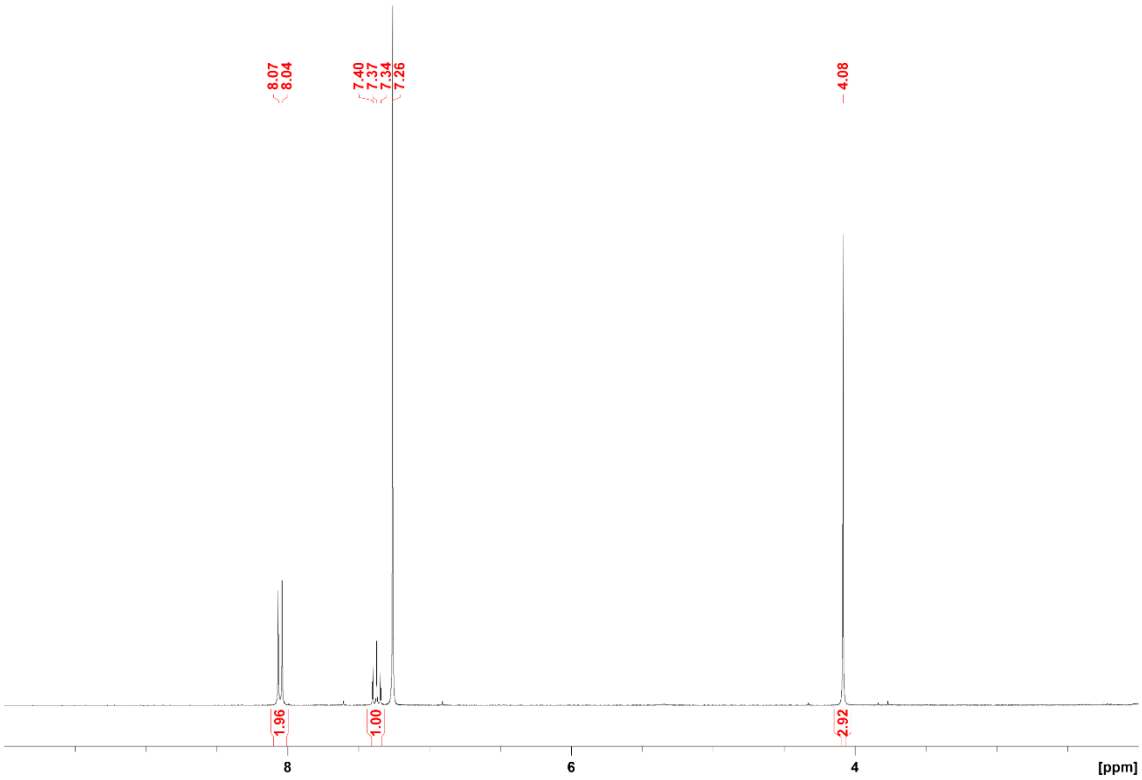
Compound **16**, DMSO-d_6, 300 MHz

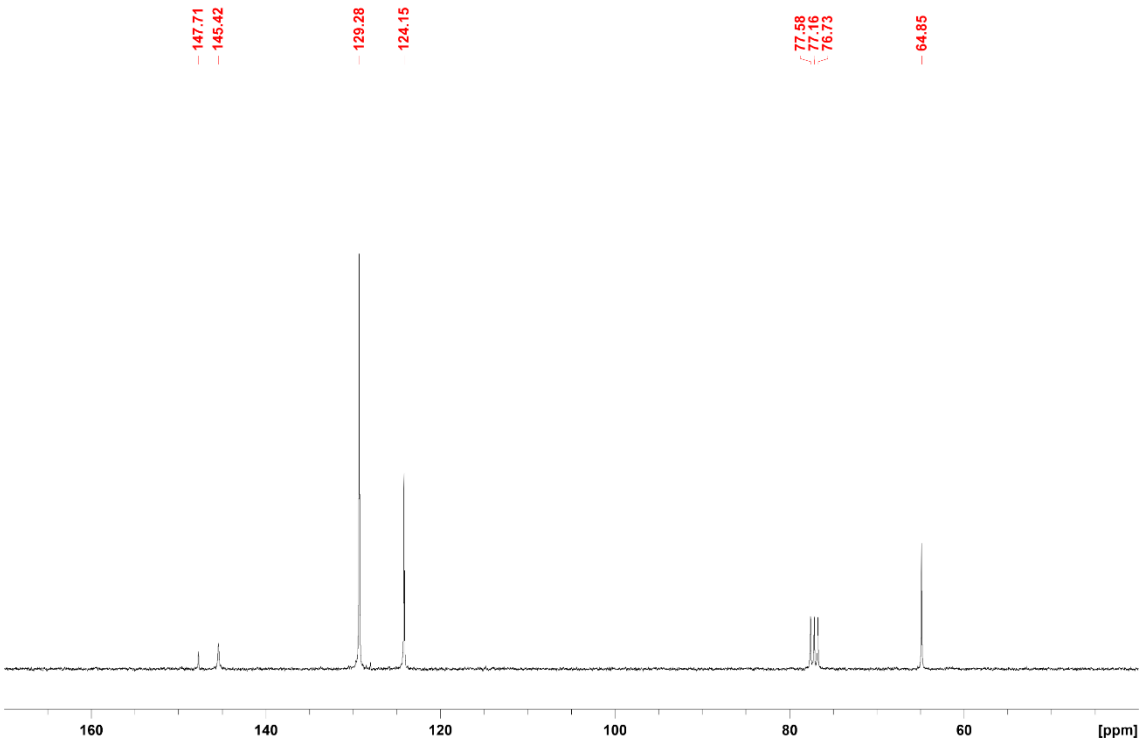


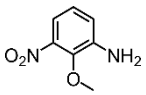




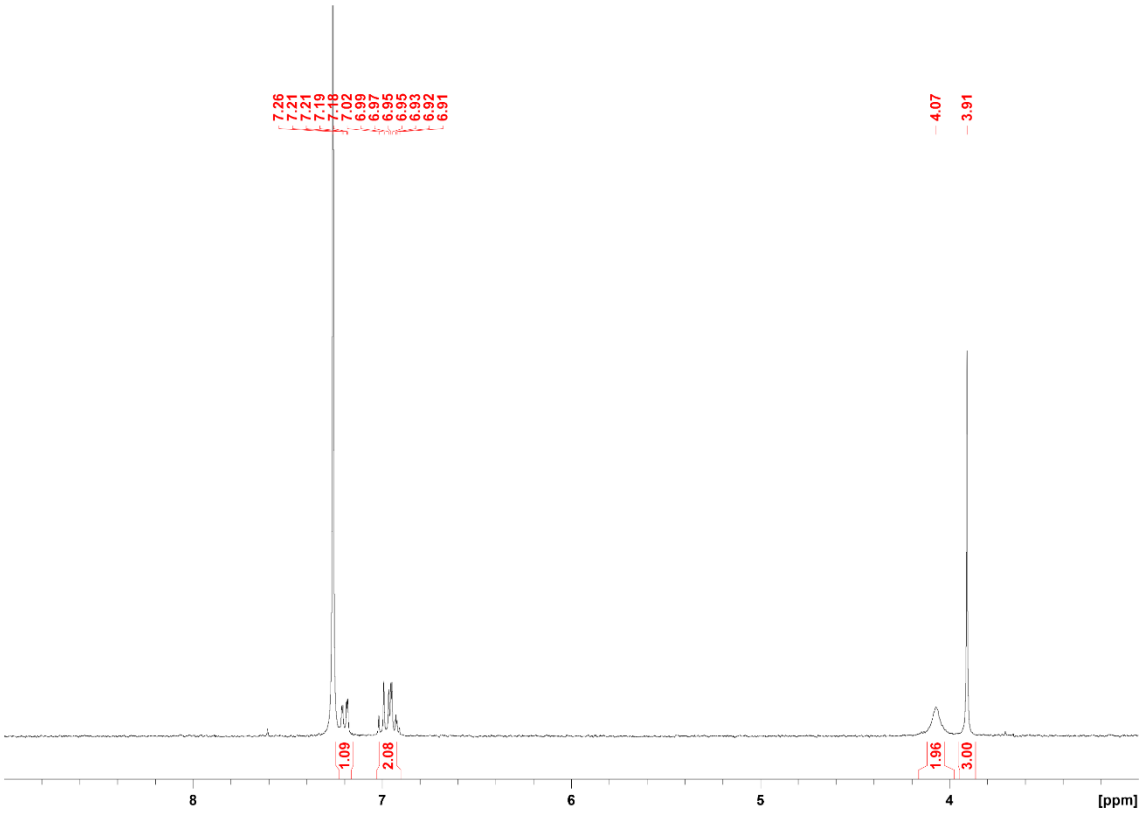
Compound **17**, $CDCl_3$, 300 MHz

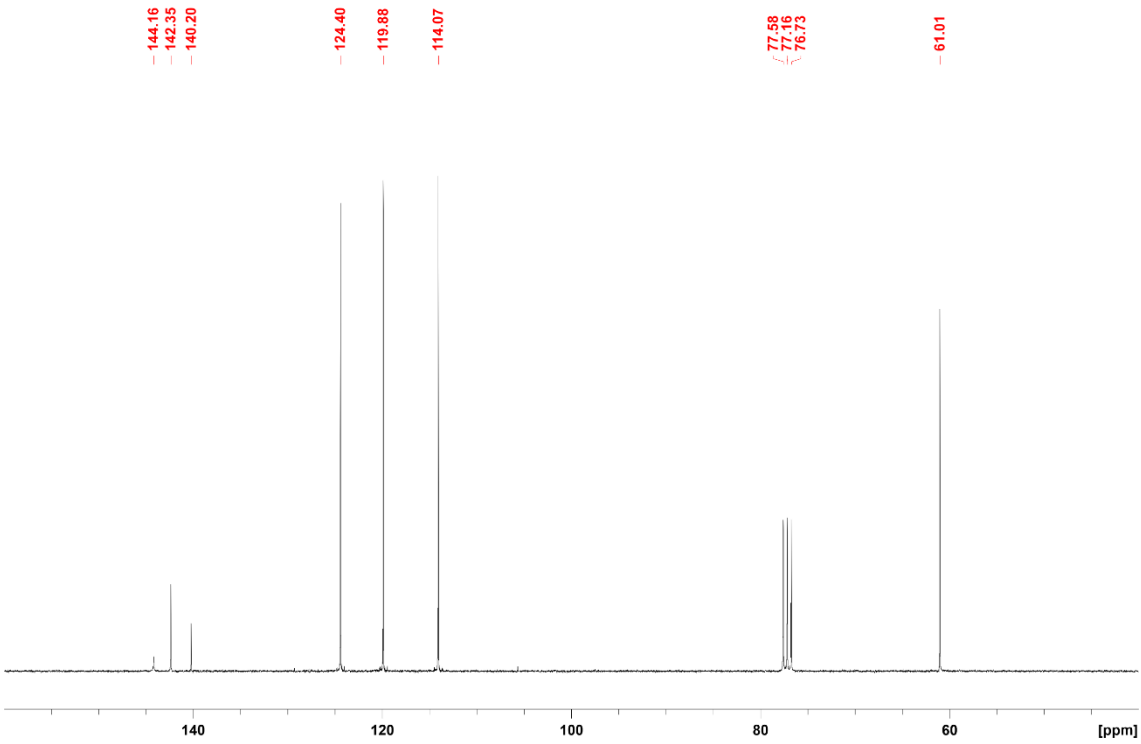


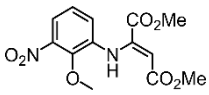




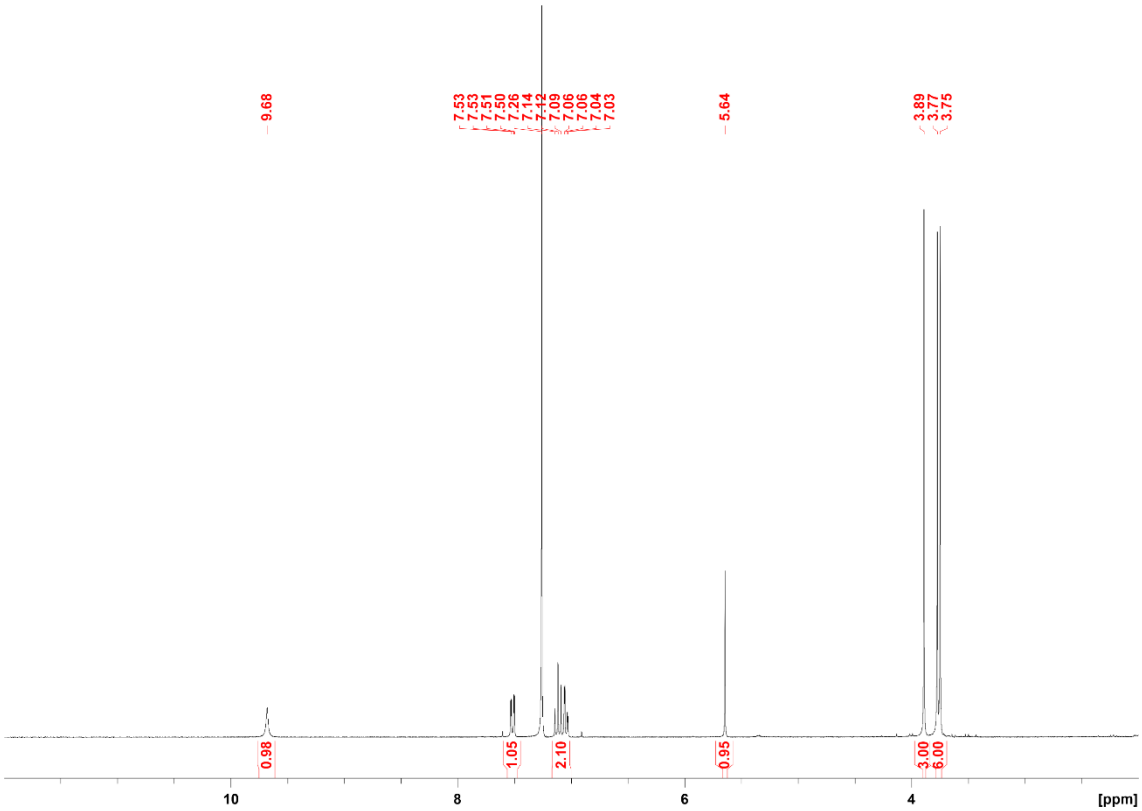
Compound **18**, $CDCl_3$, 300 MHz

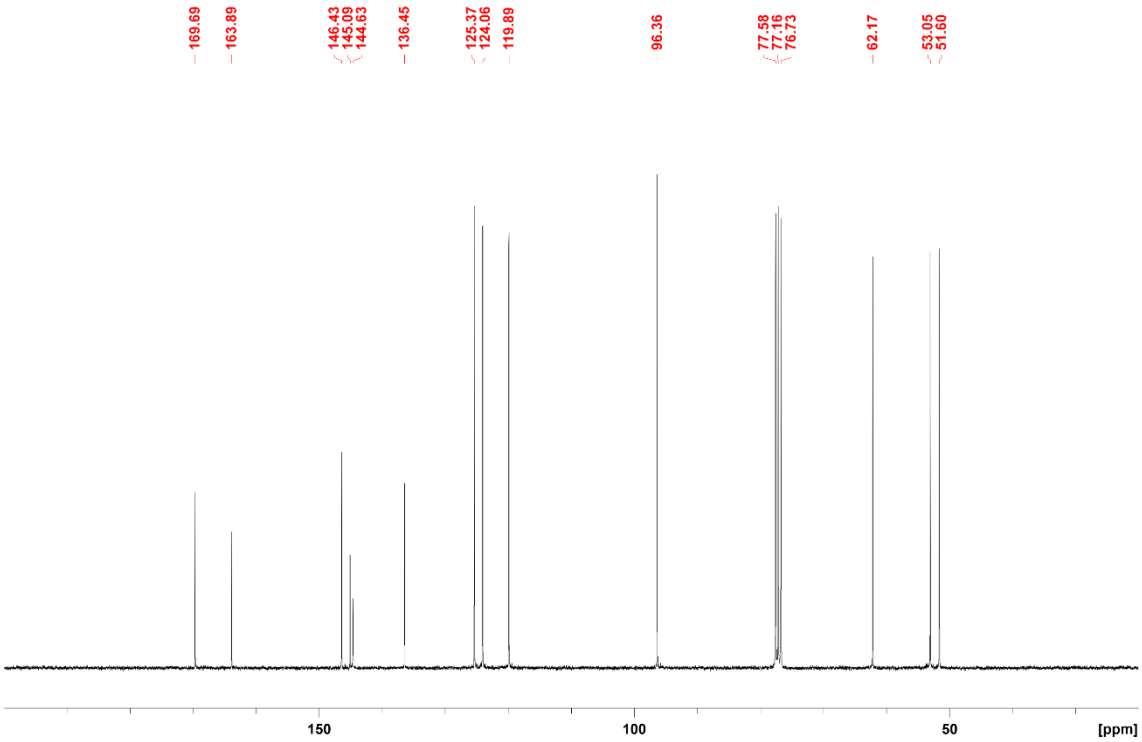


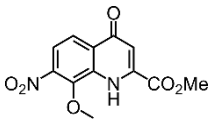




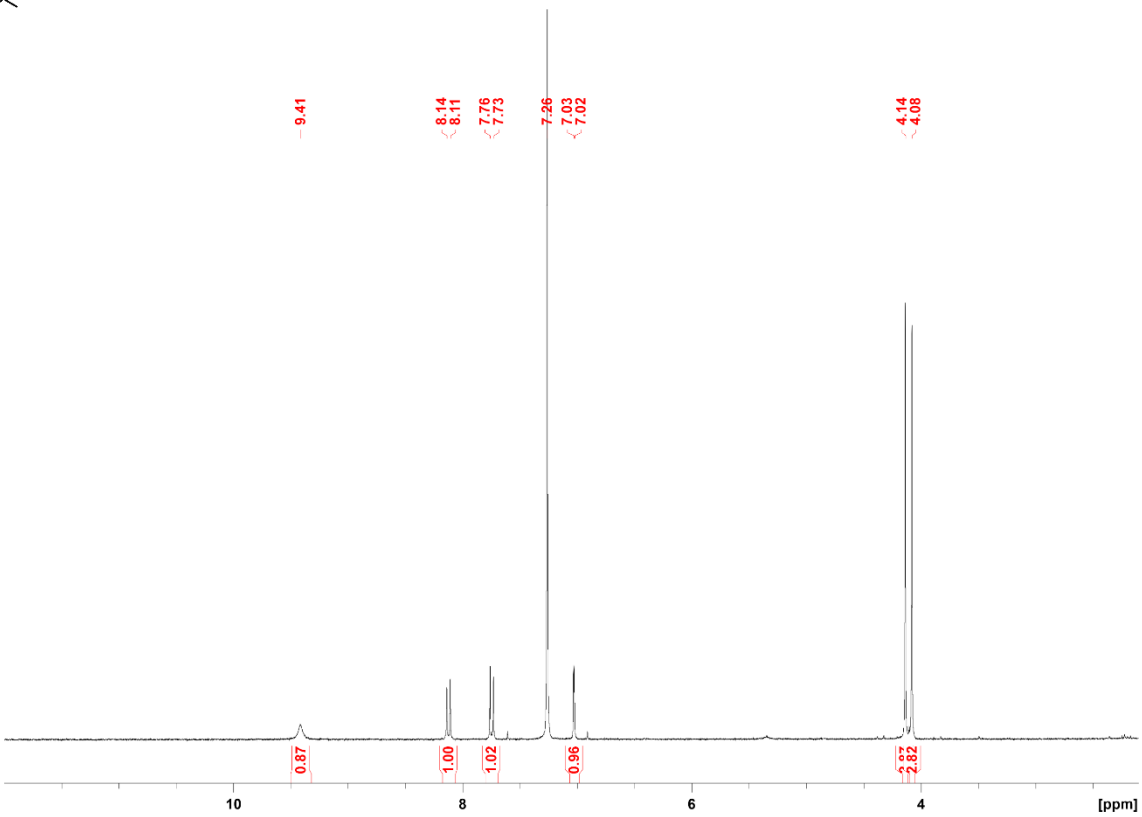
Compound **19**, $CDCl_3$, 300 MHz

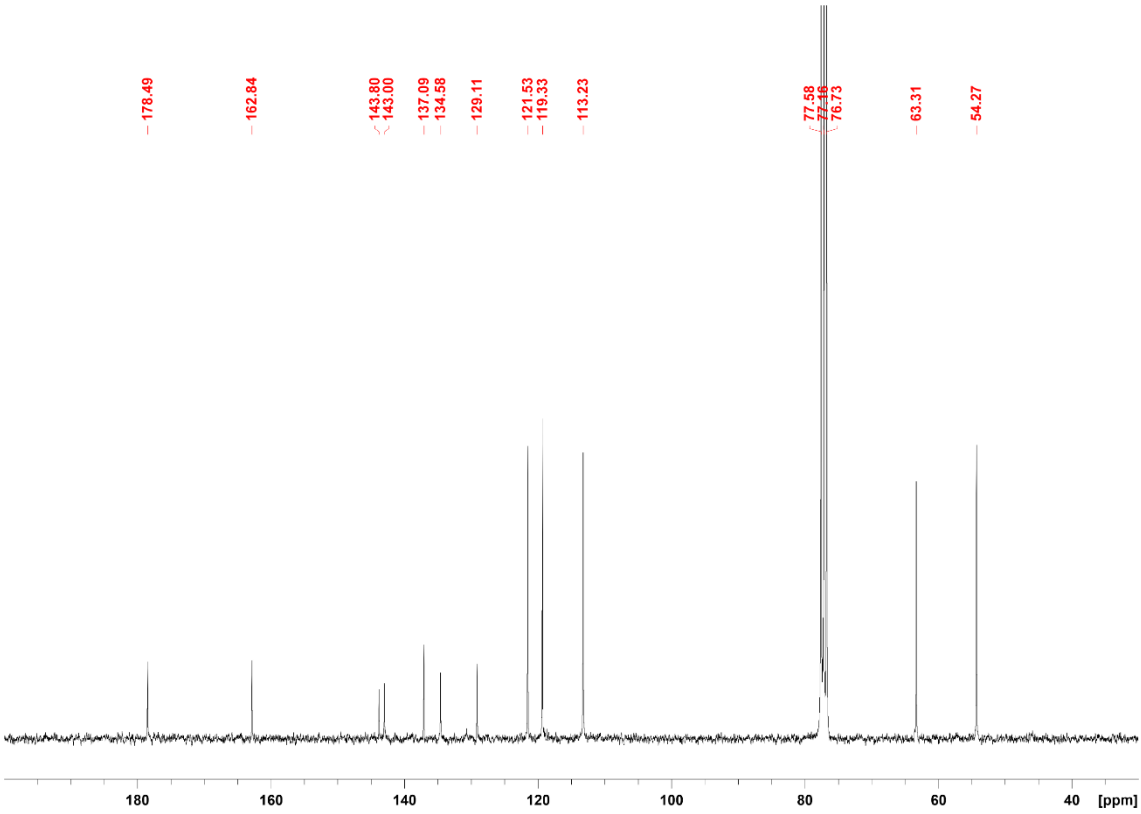


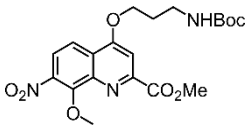




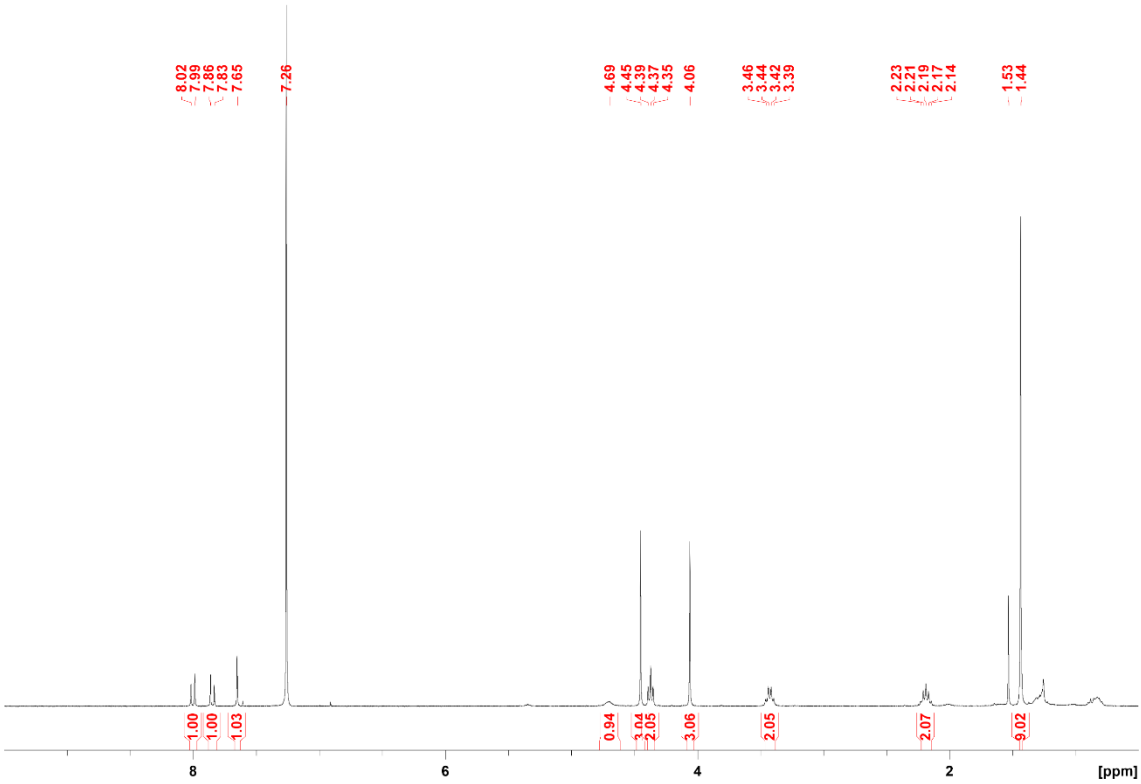
Compound **20**, $CDCl_3$, 300 MHz

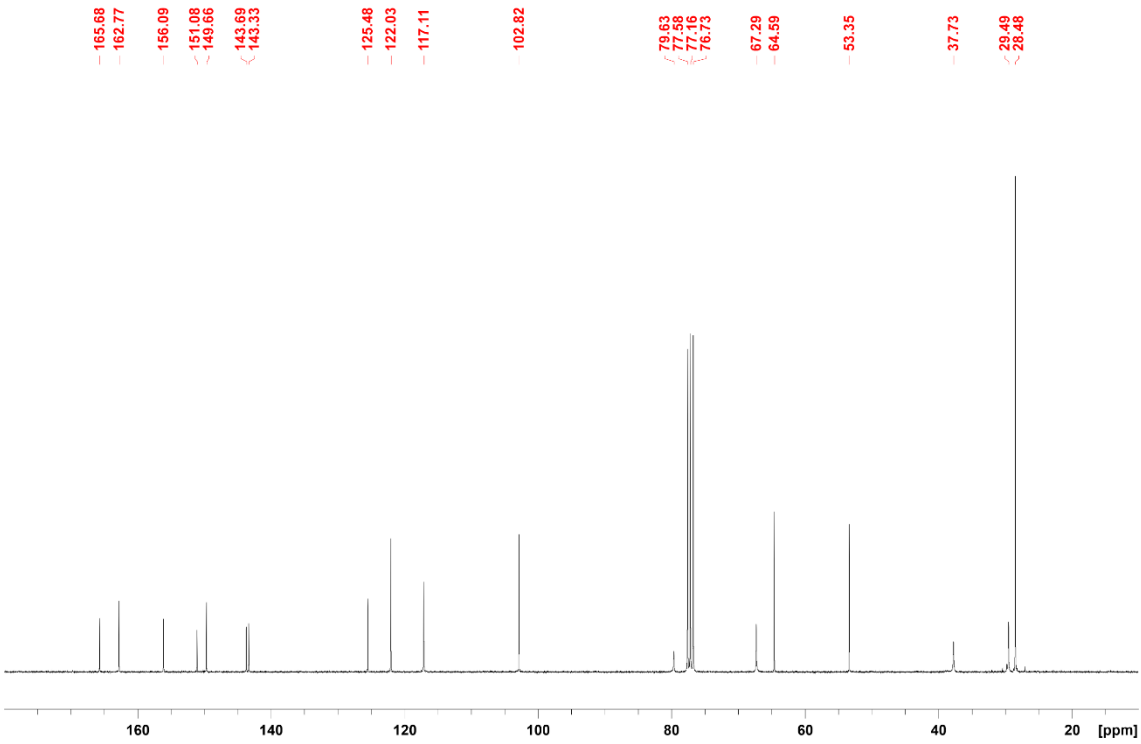


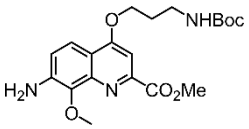




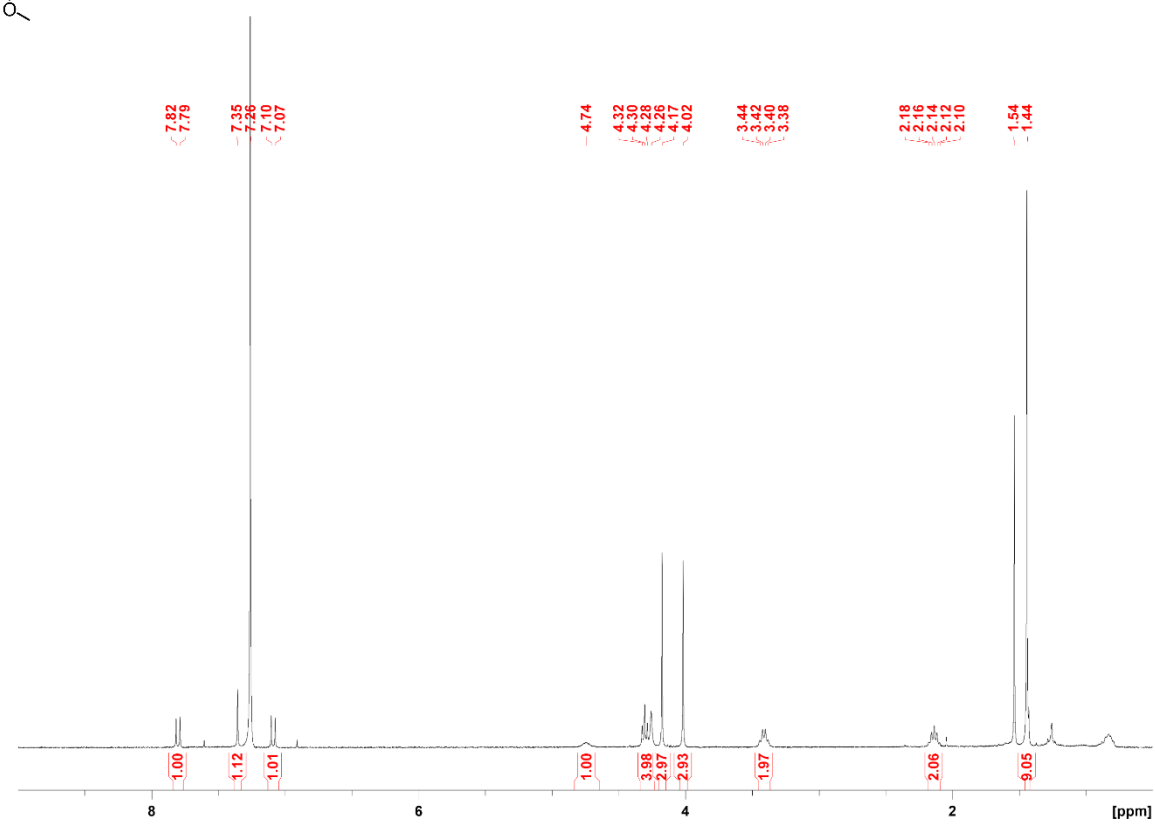
Compound **21**, $CDCl_3$, 300 MHz

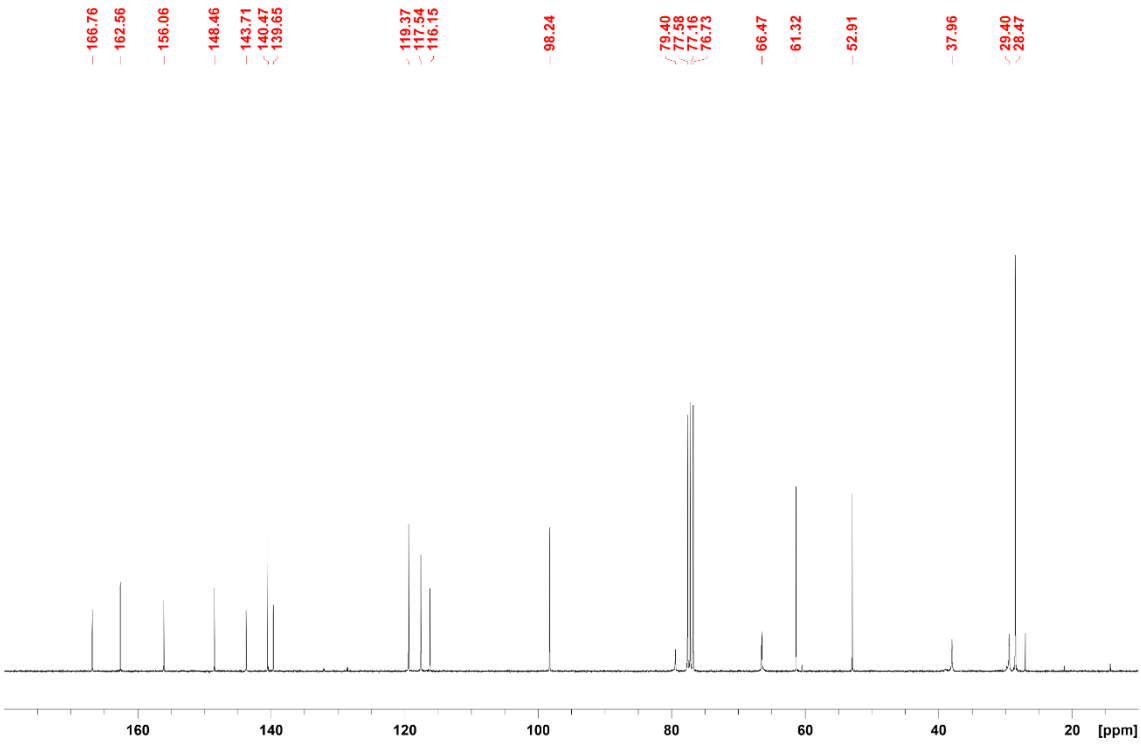


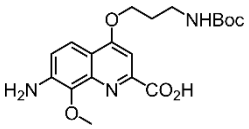




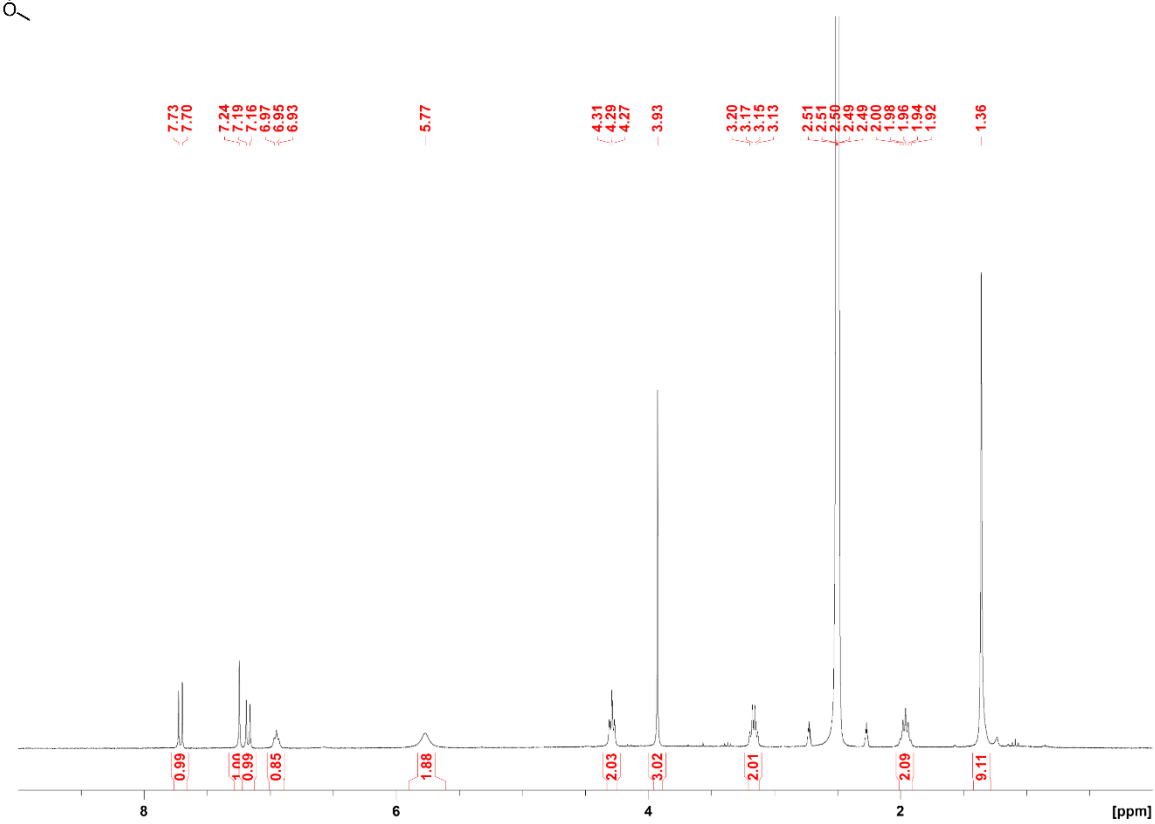
Compound **22**, $CDCl_3$, 300 MHz

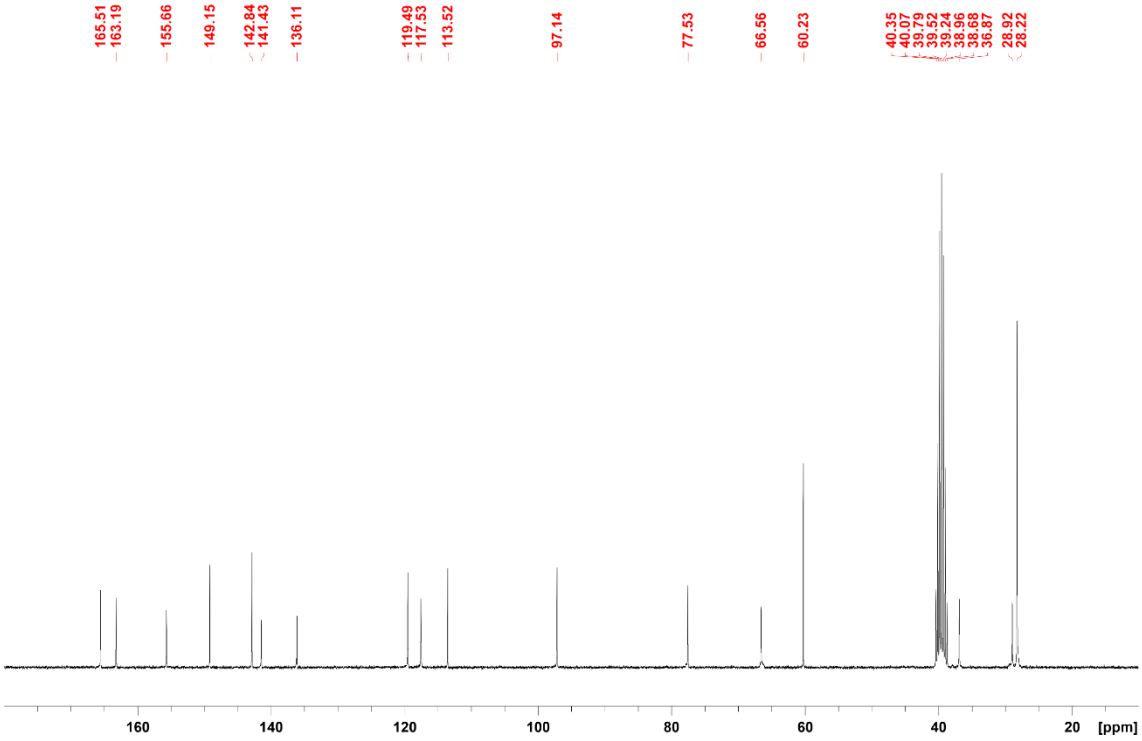


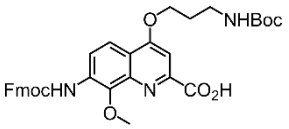




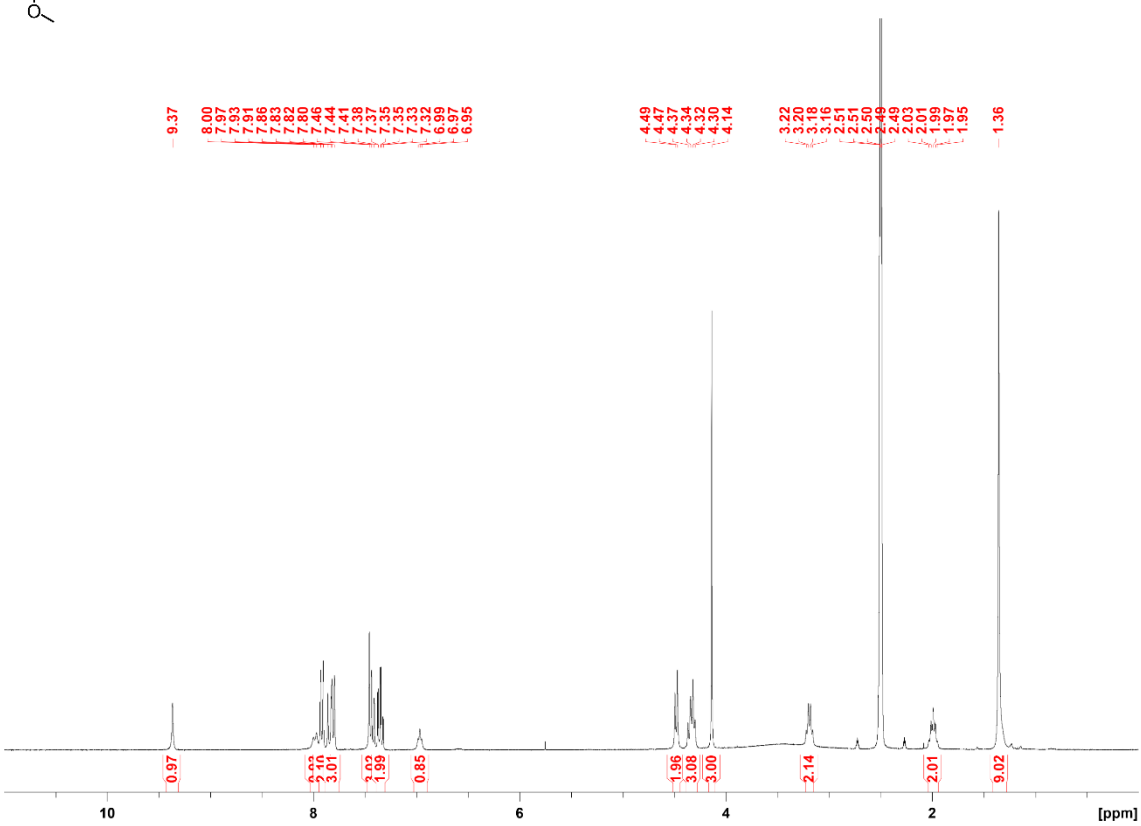
Compound **23**, DMSO-d_6, 300 MHz

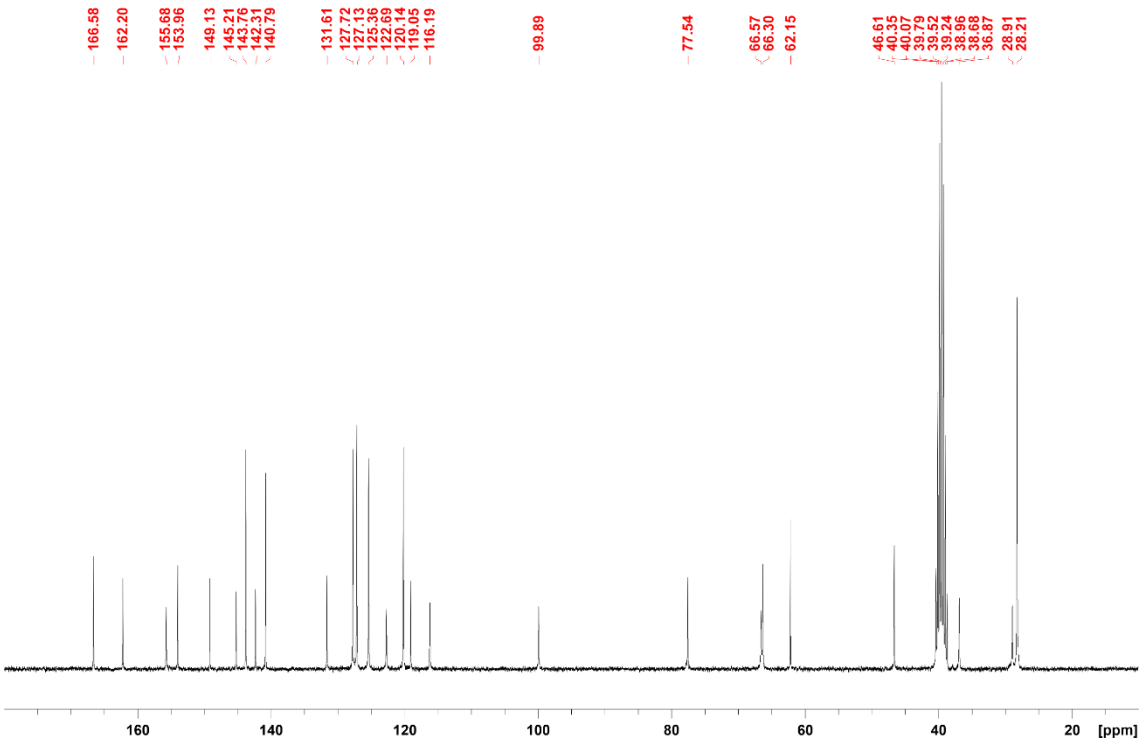


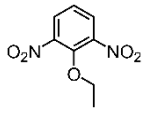




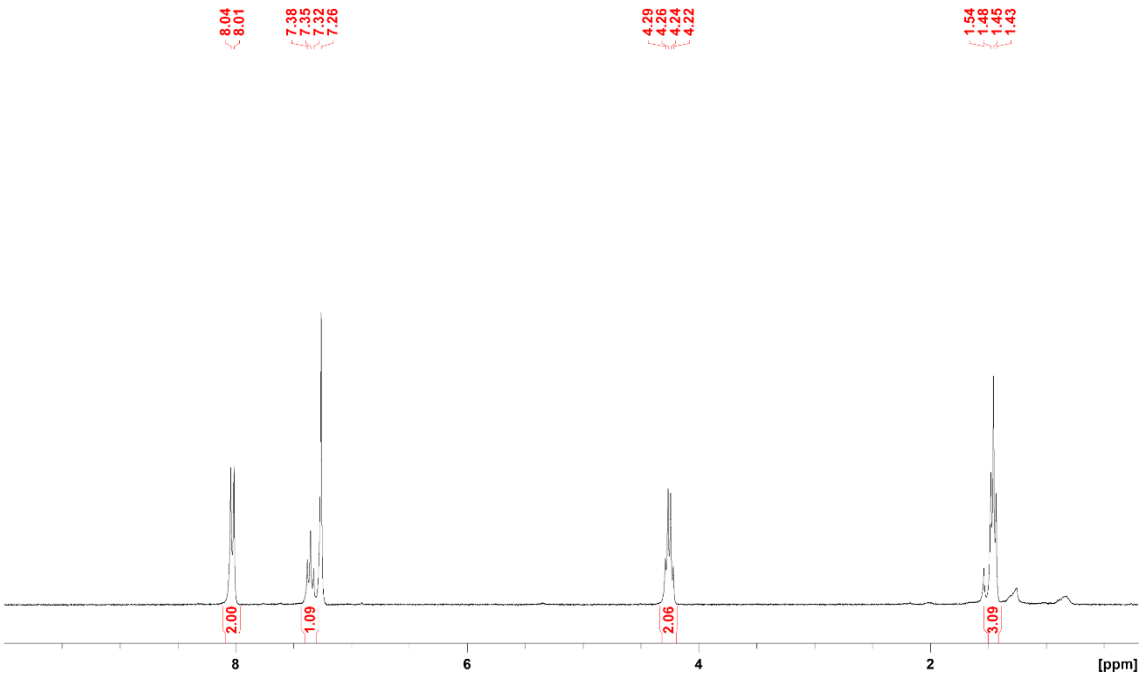
Compound **24**, DMSO-d_6, 300 MHz

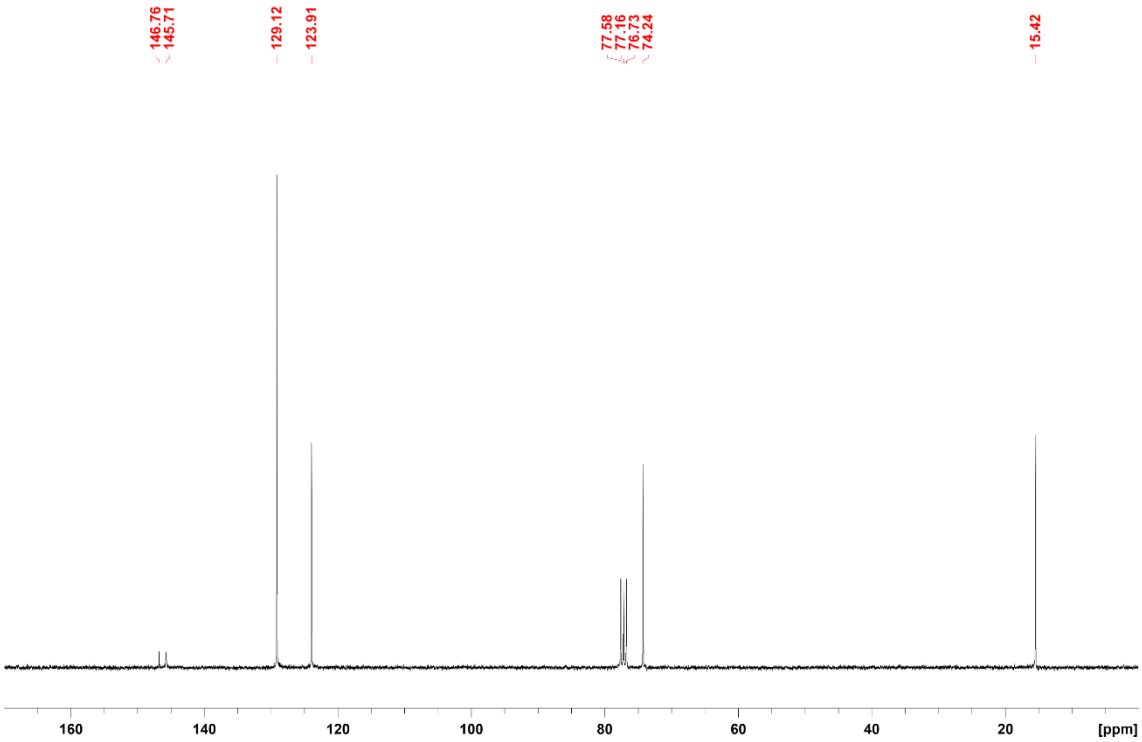


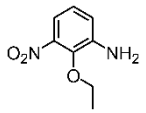




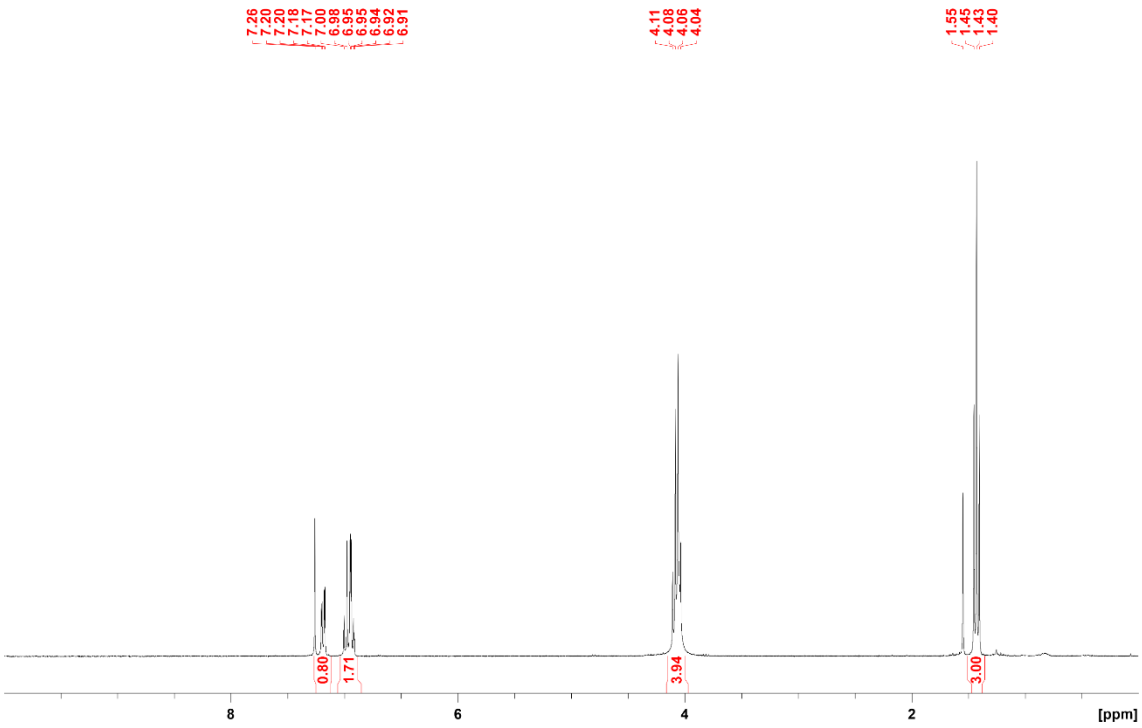
Compound **25**, $CDCl_3$, 300 MHz

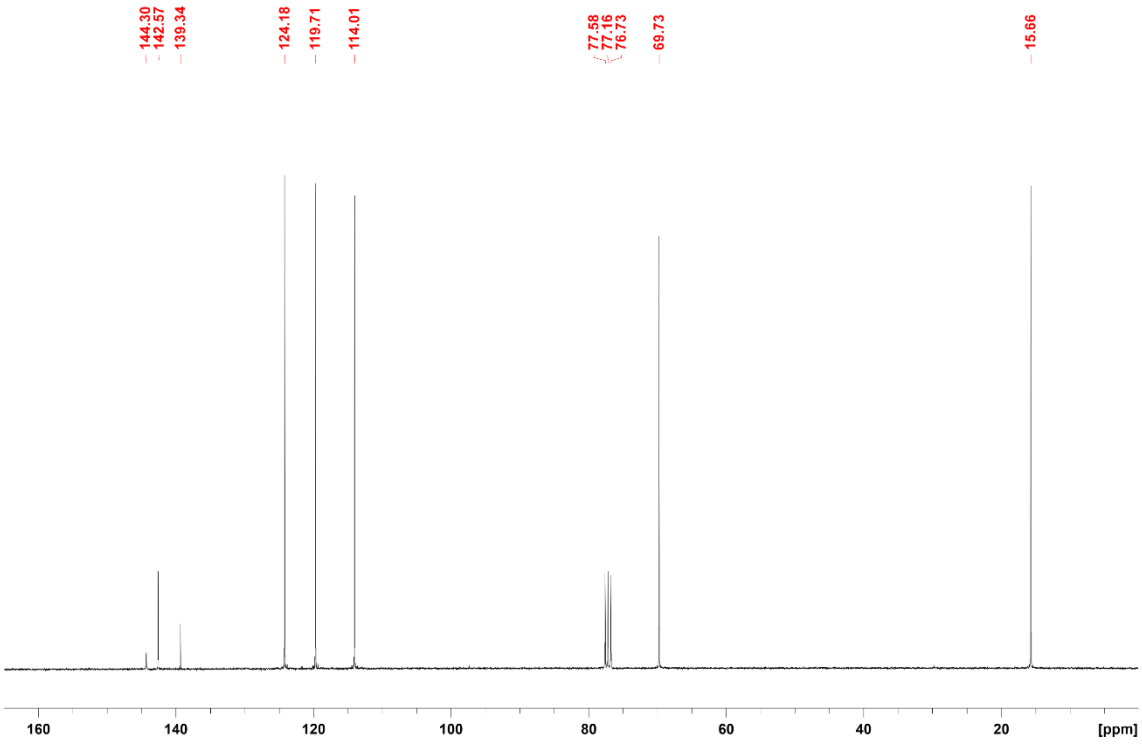


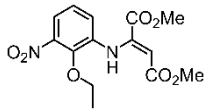




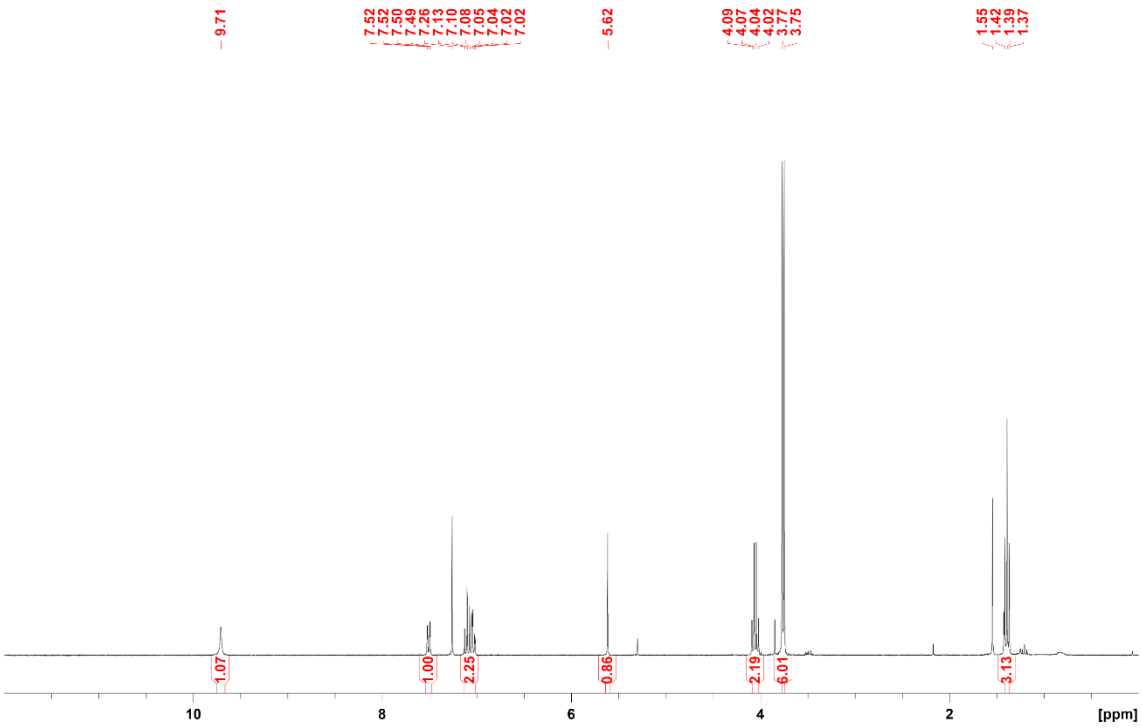
Compound **26**, $CDCl_3$, 300 MHz

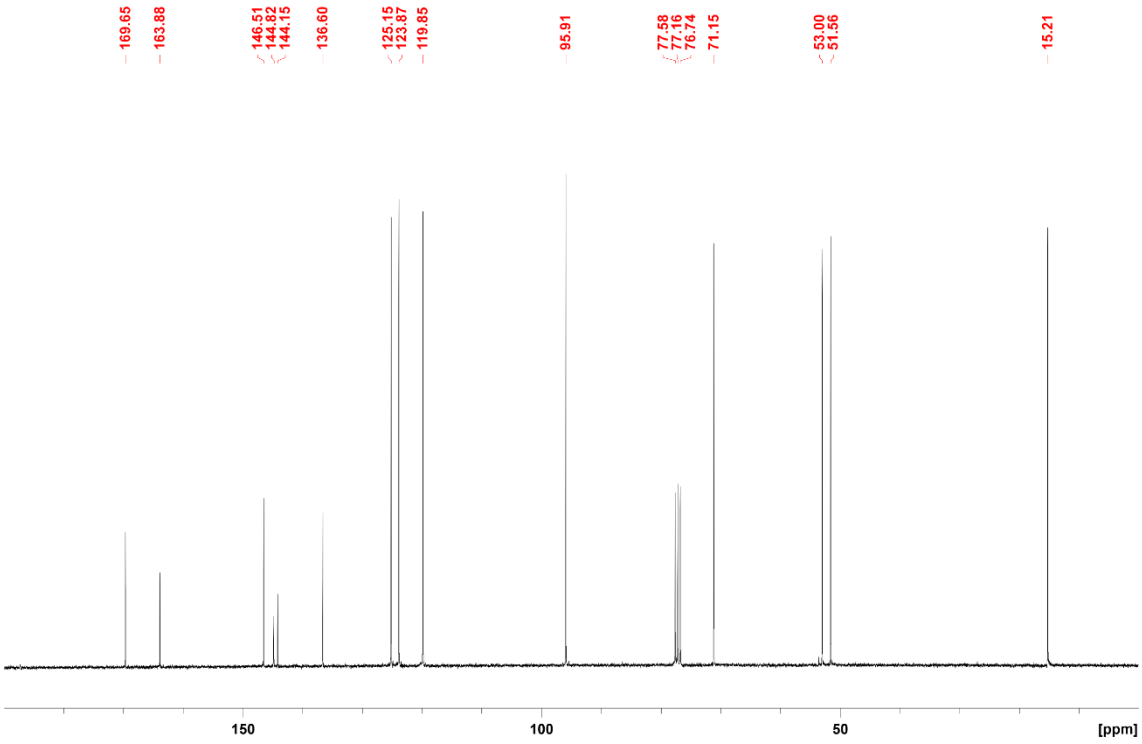


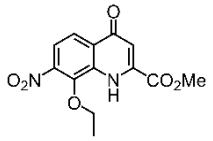




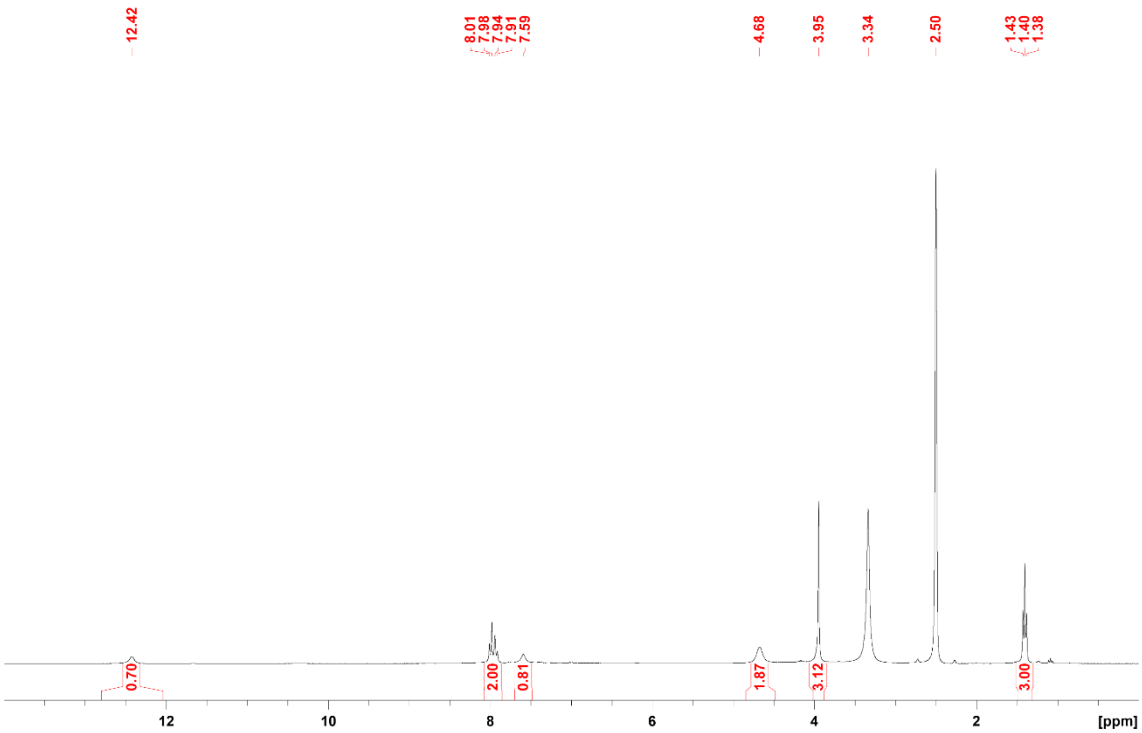
Compound **27**, $CDCl_3$, 300 MHz



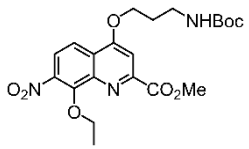




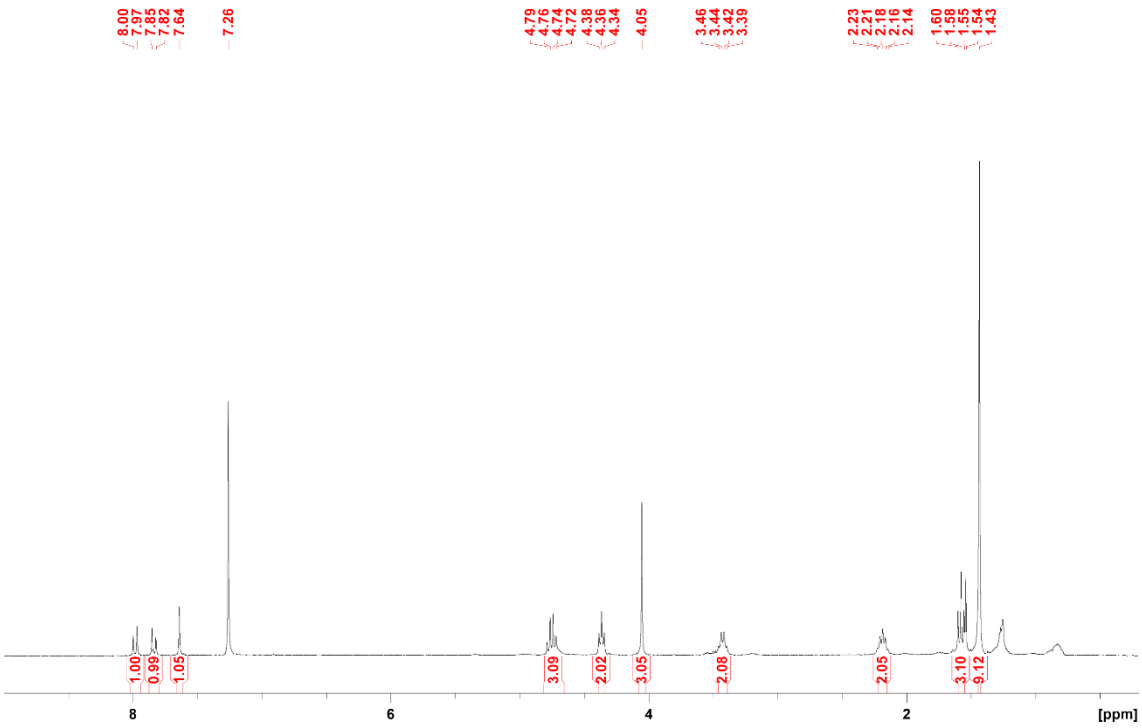
Compound **28**, DMSO-d_6, 300 MHz

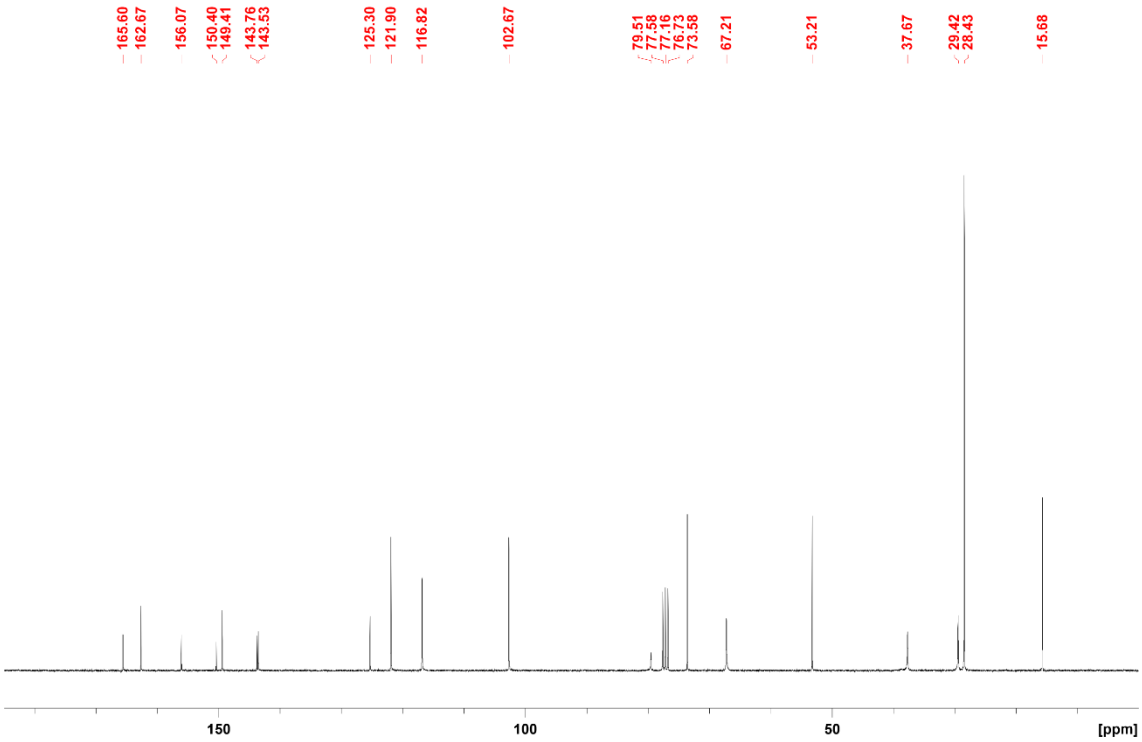


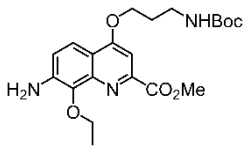
Limited solubility of the compound **28** prevented the characterization by ^{13}C NMR spectroscopy.



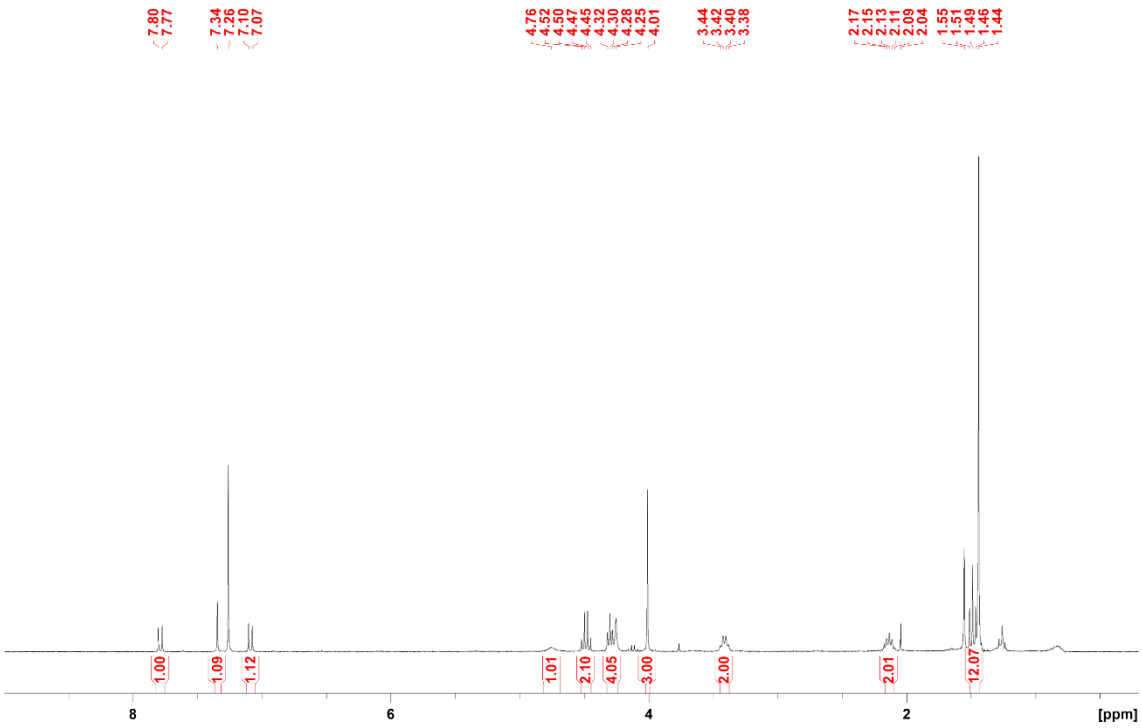
Compound **29**, $CDCl_3$, 300 MHz

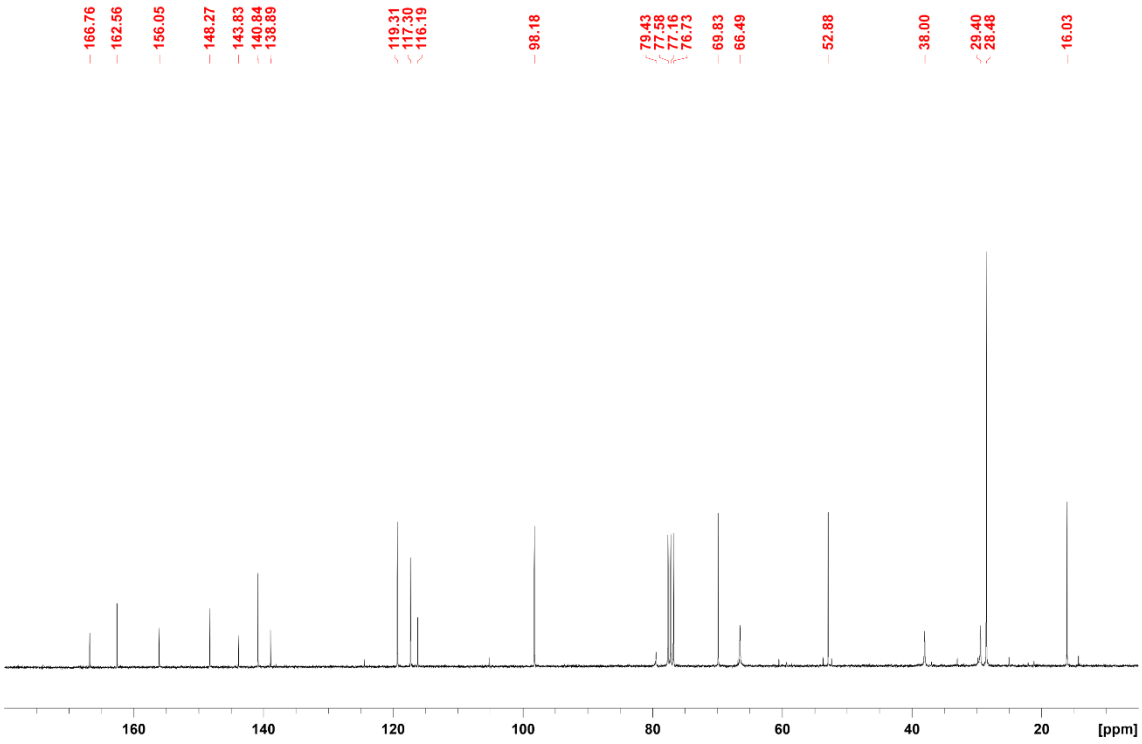


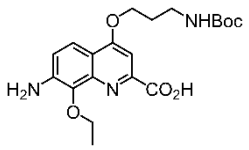




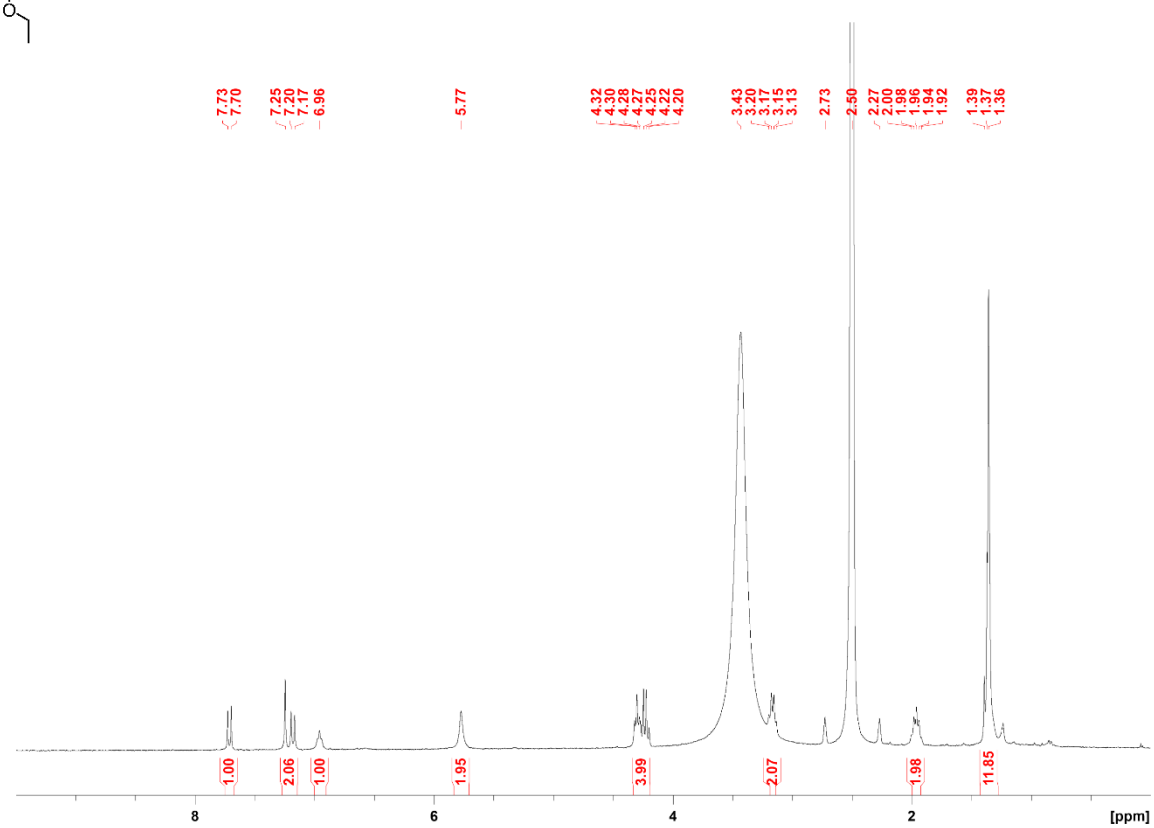
Compound **30**, $CDCl_3$, 300 MHz

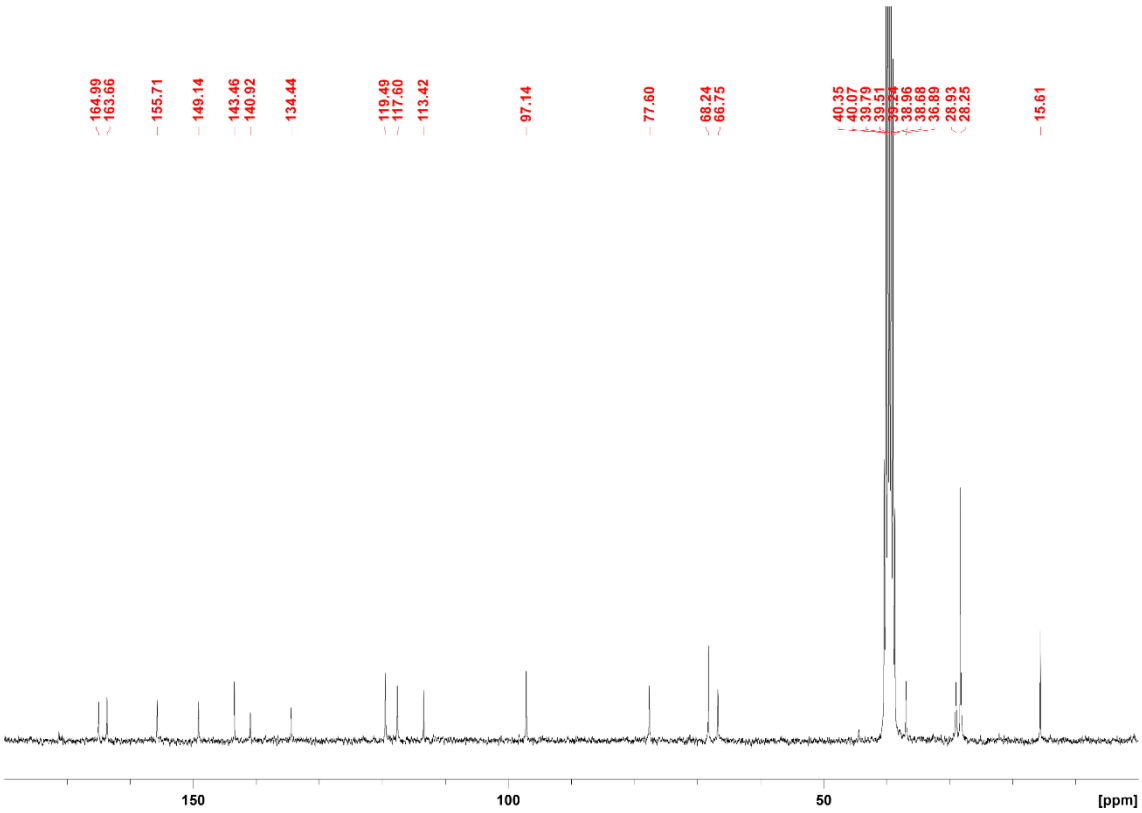


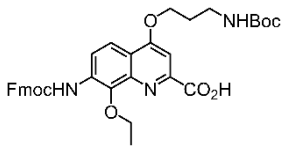




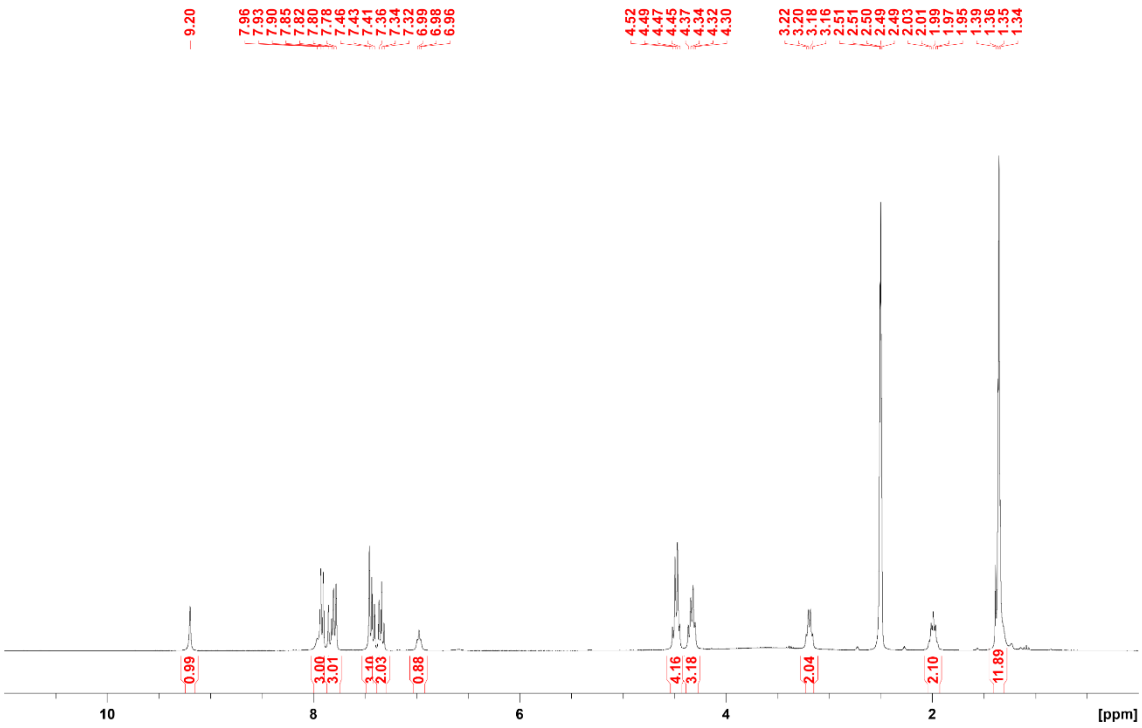
Compound **31**, DMSO-d_6, 300 MHz

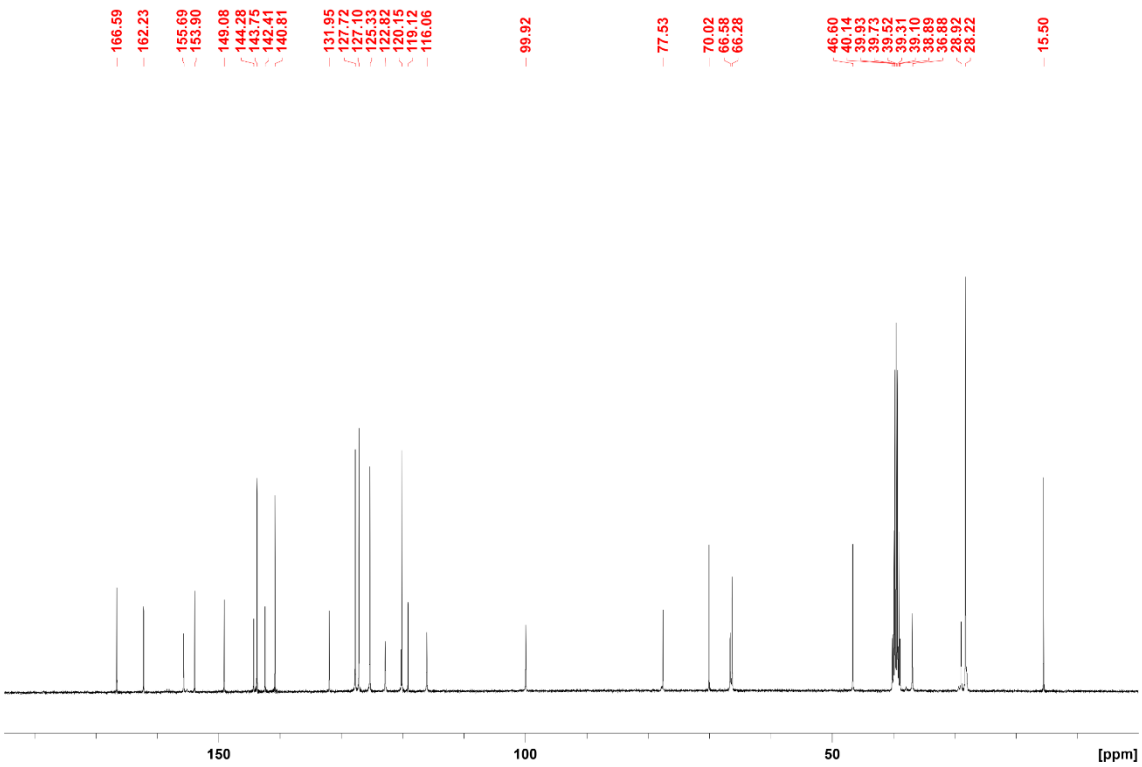


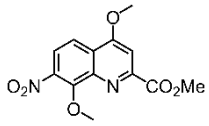




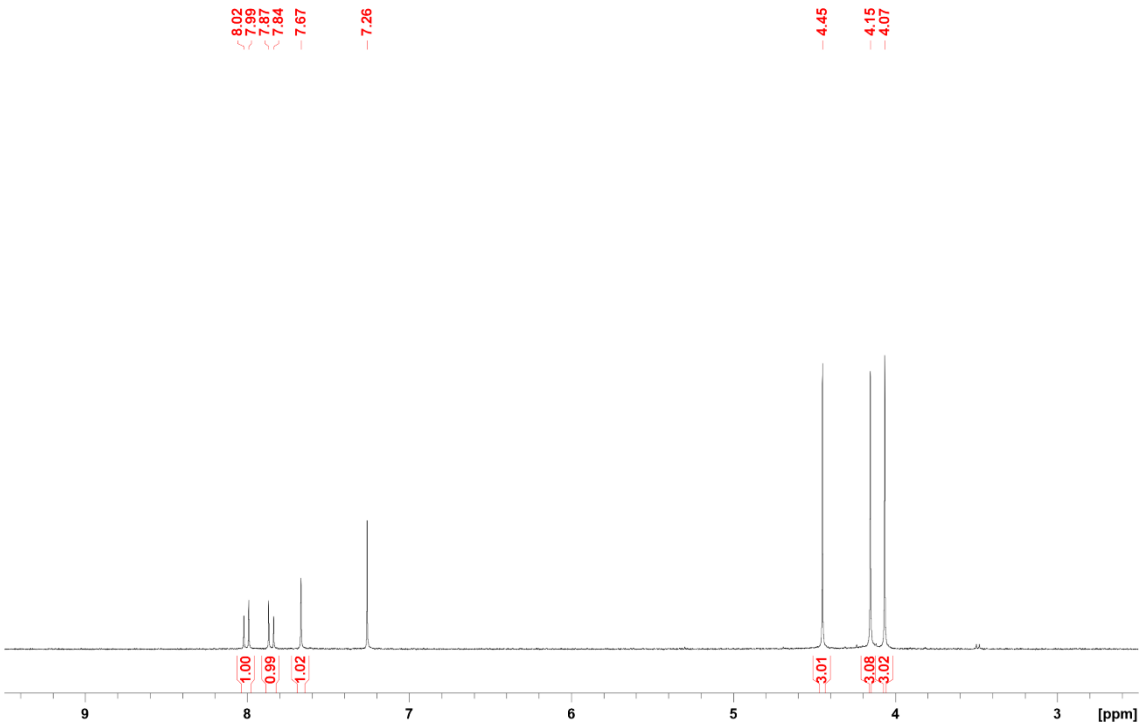
Compound **32**, DMSO-d_6, 300 MHz

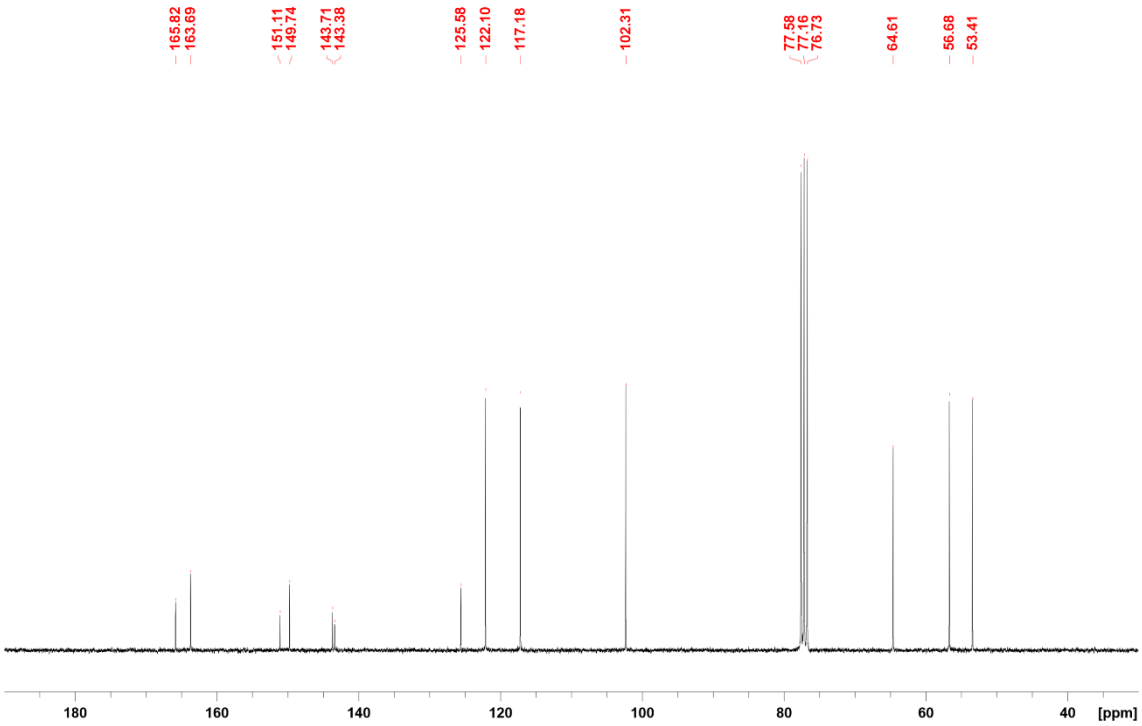


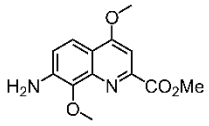




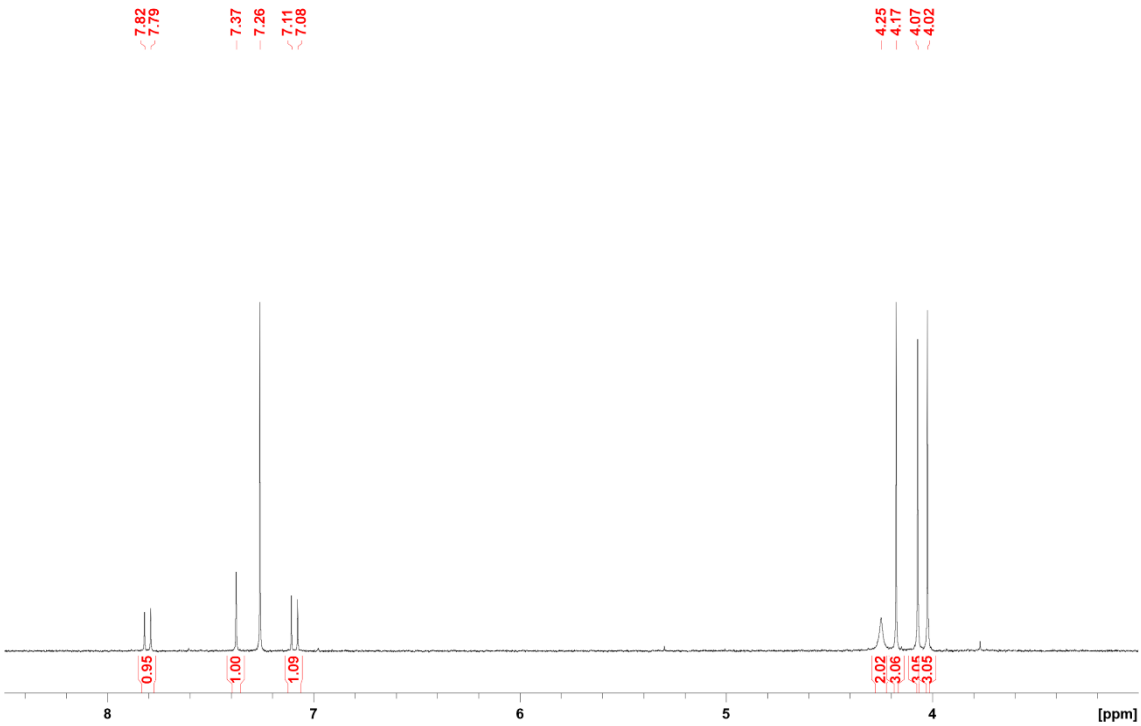
Compound **33**, $CDCl_3$, 300 MHz

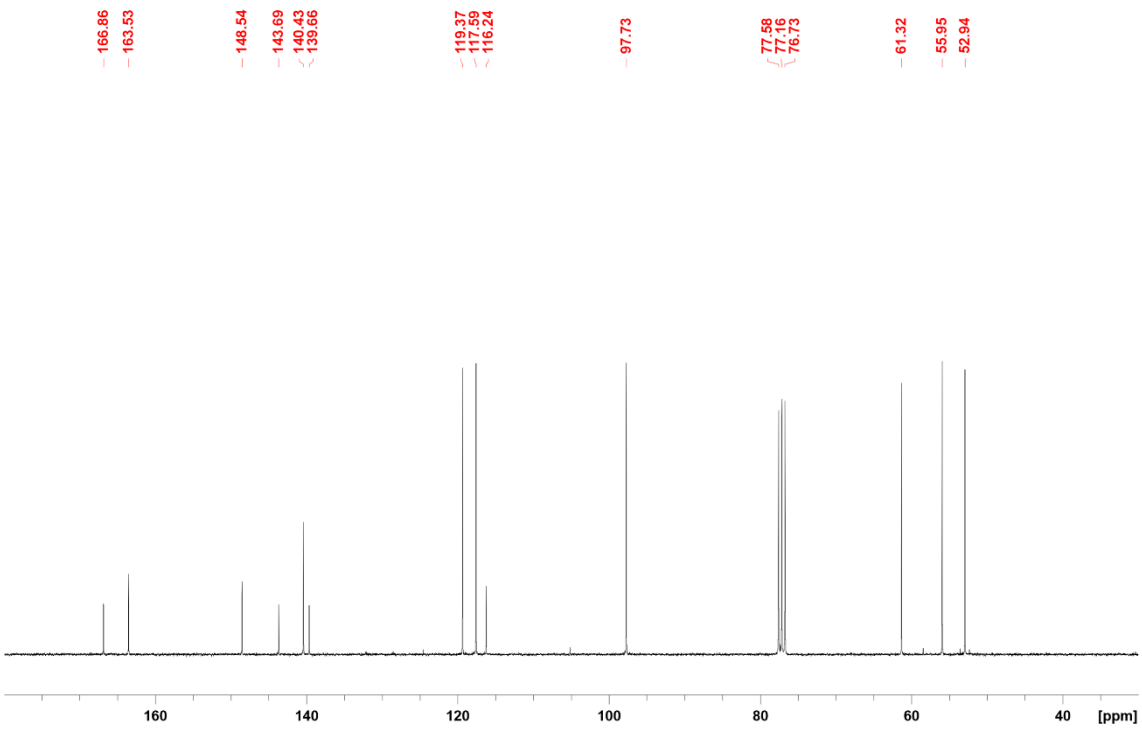


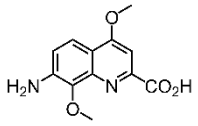




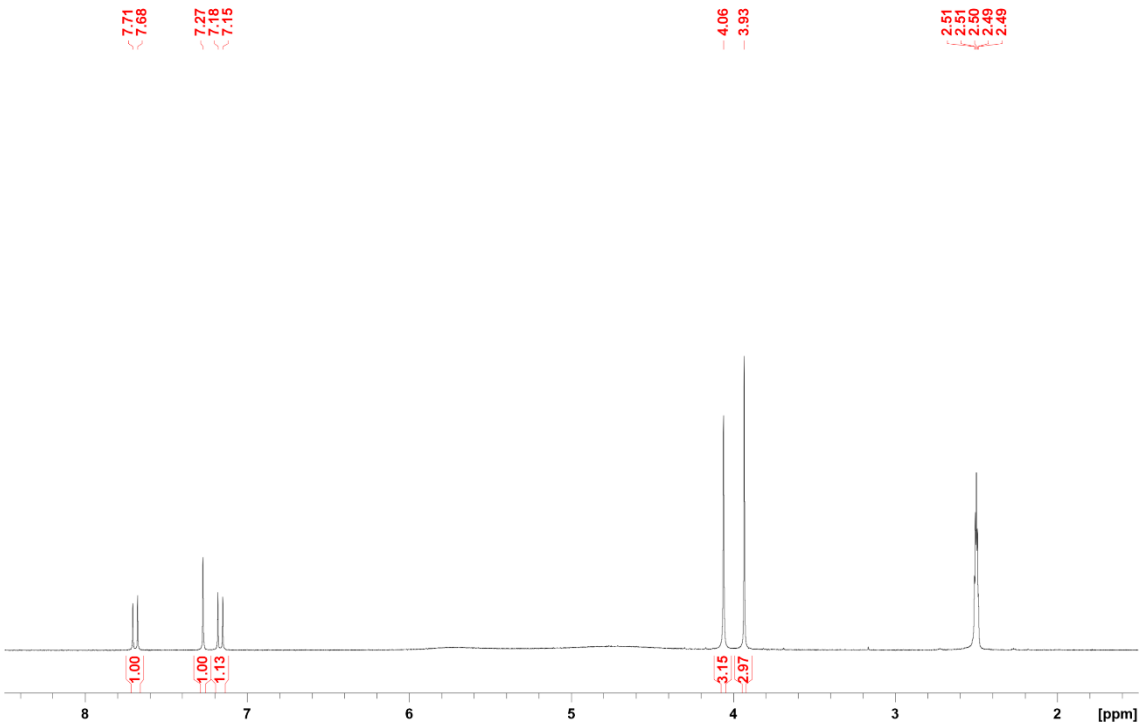
Compound **34**, $CDCl_3$, 300 MHz

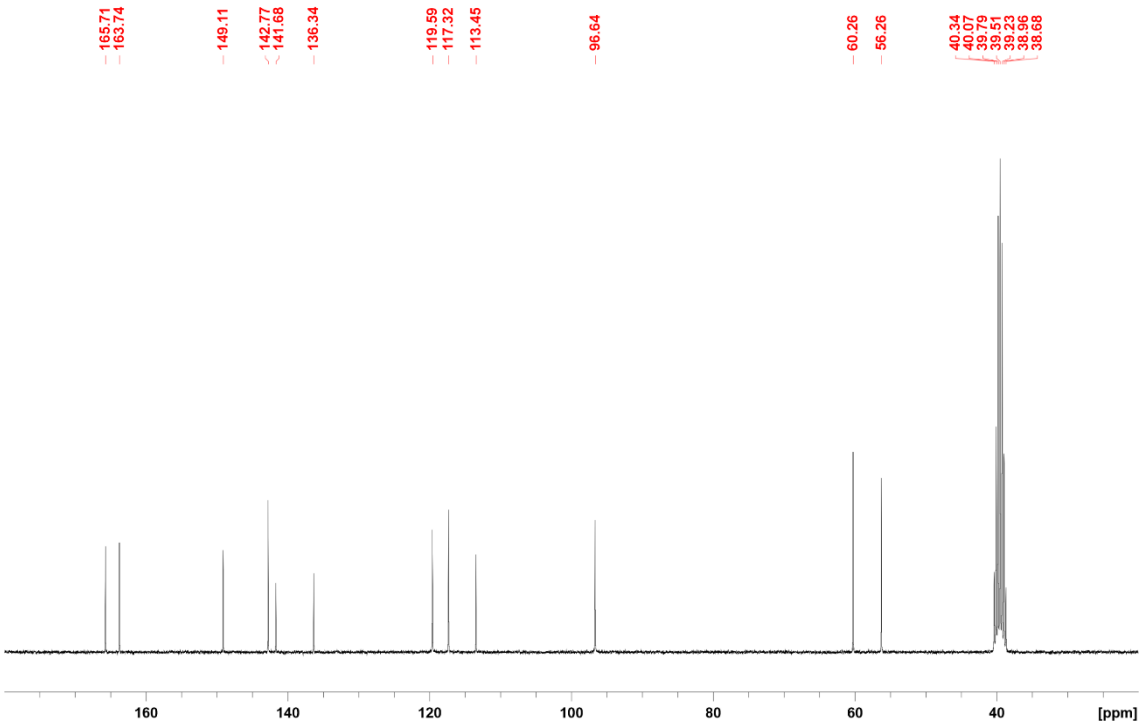


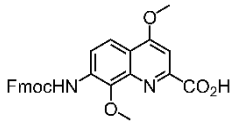




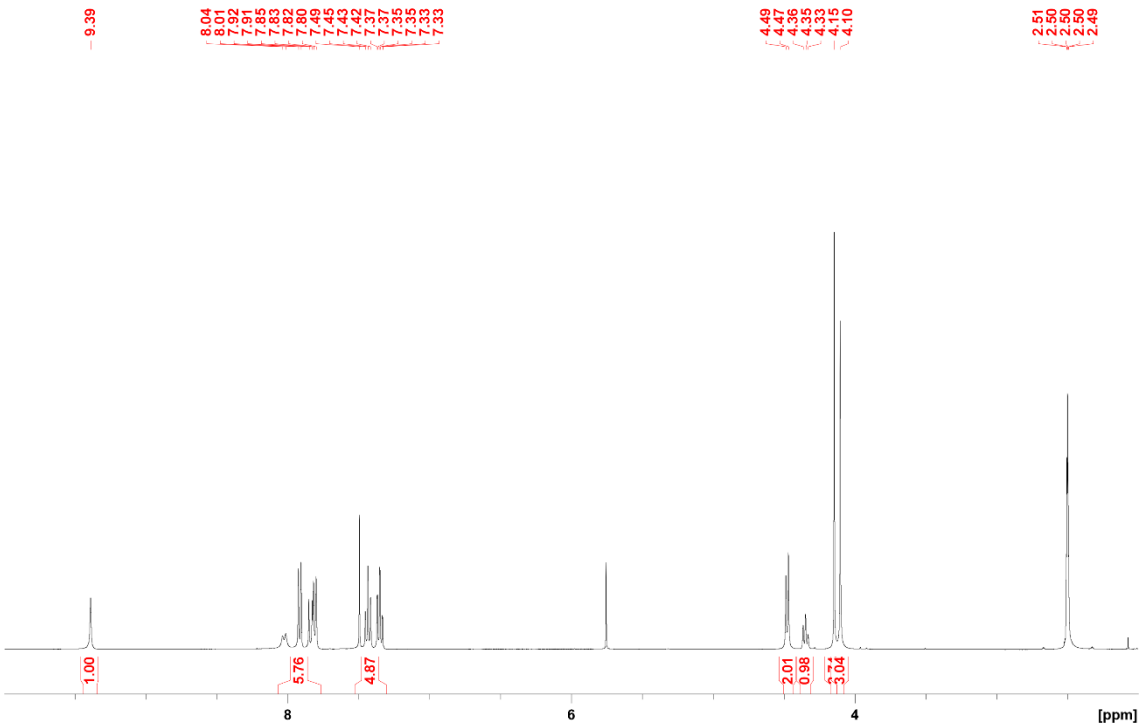
Compound **35**, DMSO-d_6, 300 MHz

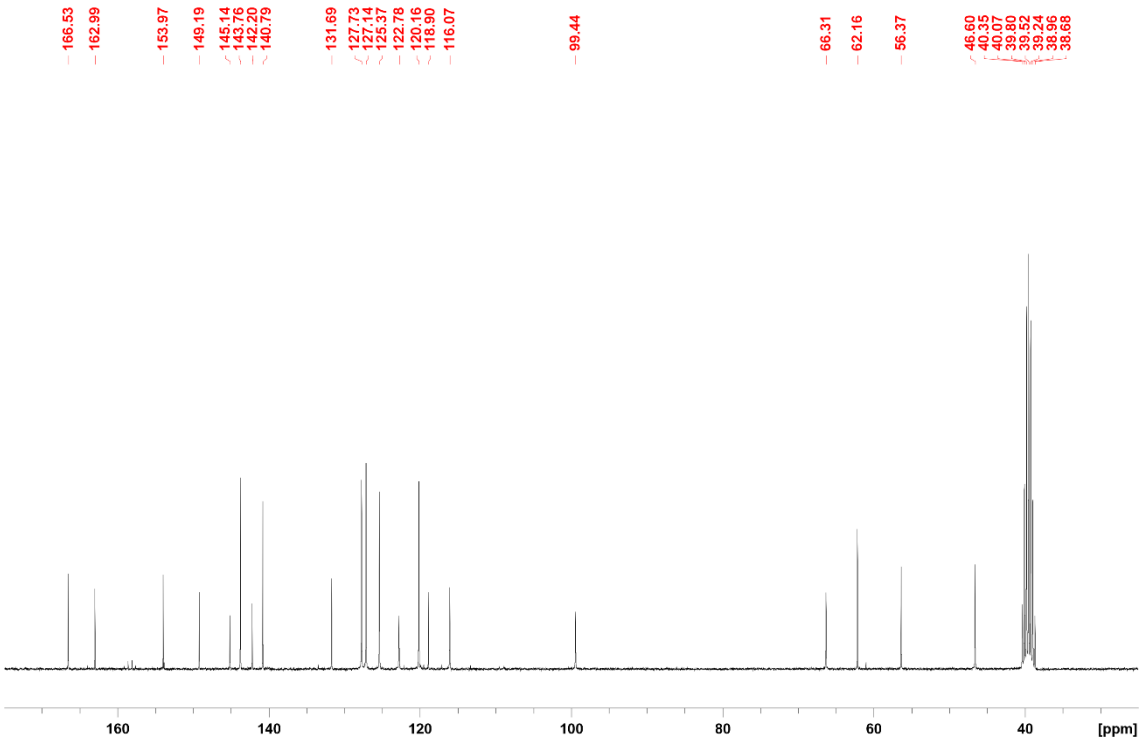


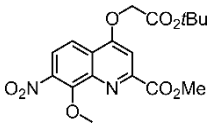




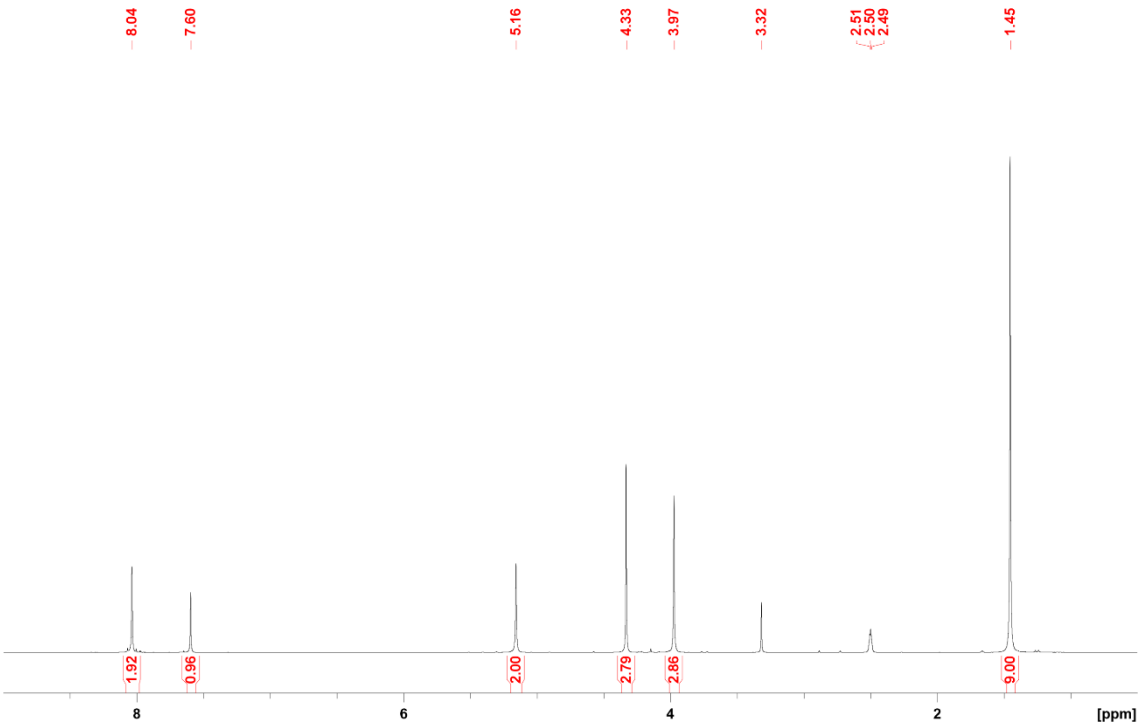
Compound **36**, DMSO-d_6, 300 MHz

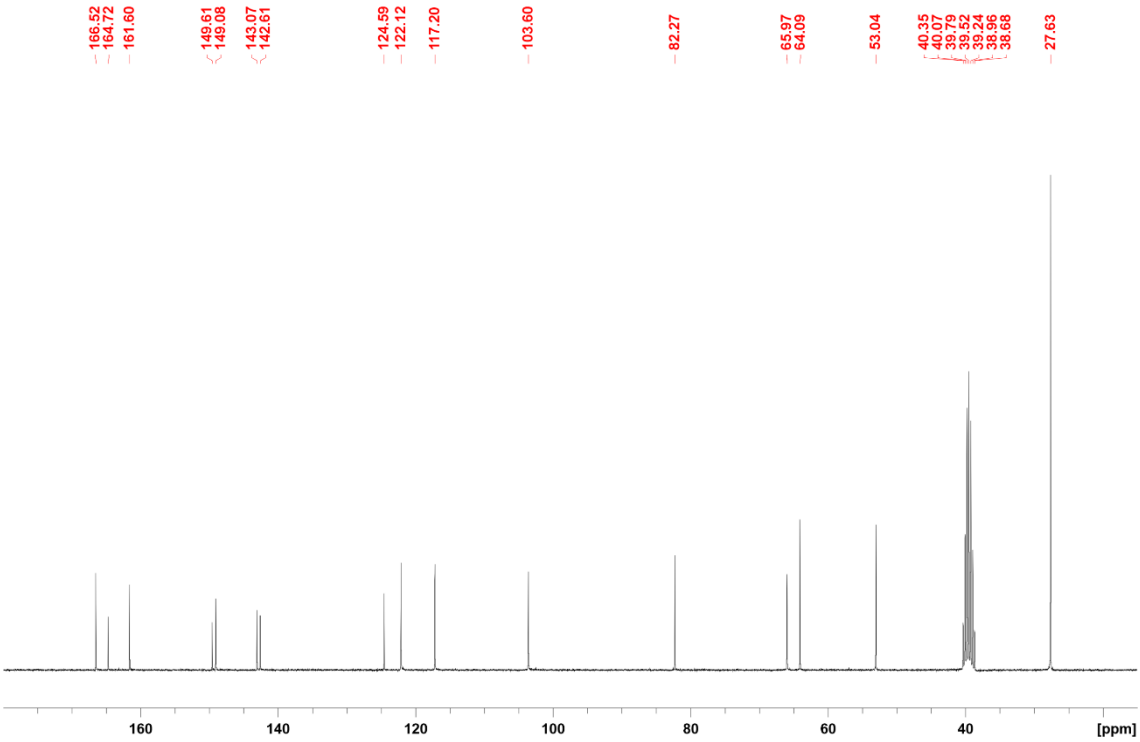


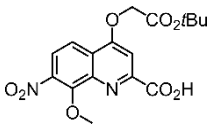




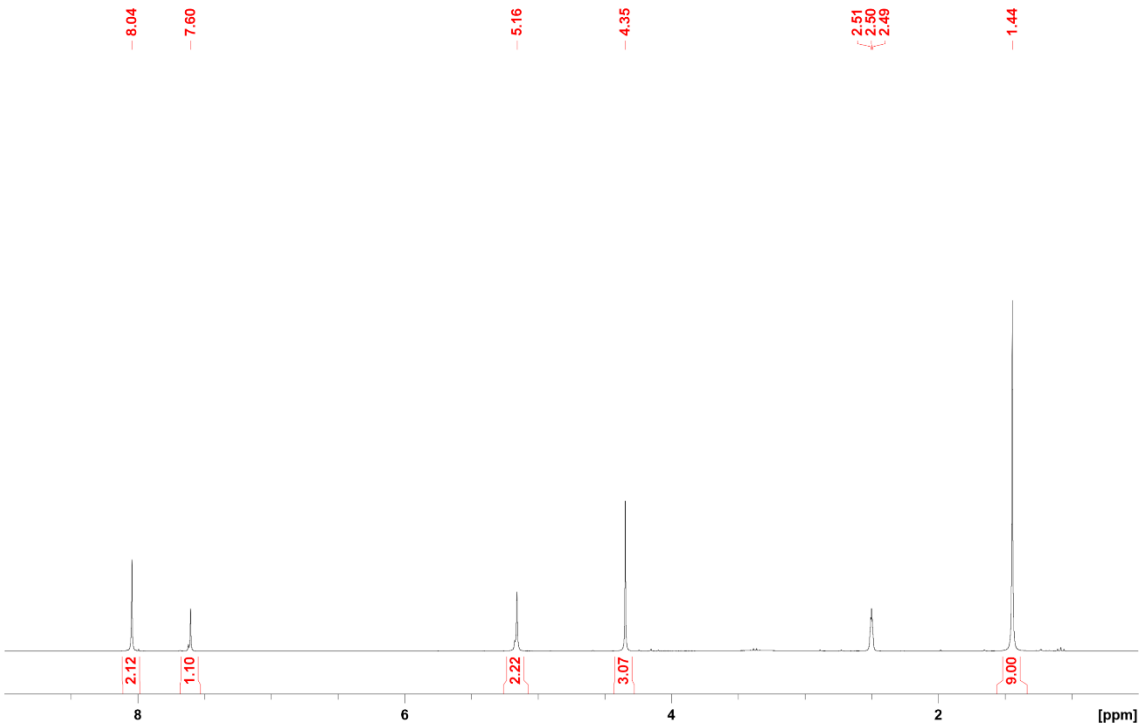
Compound **37**, DMSO-d_6, 300 MHz

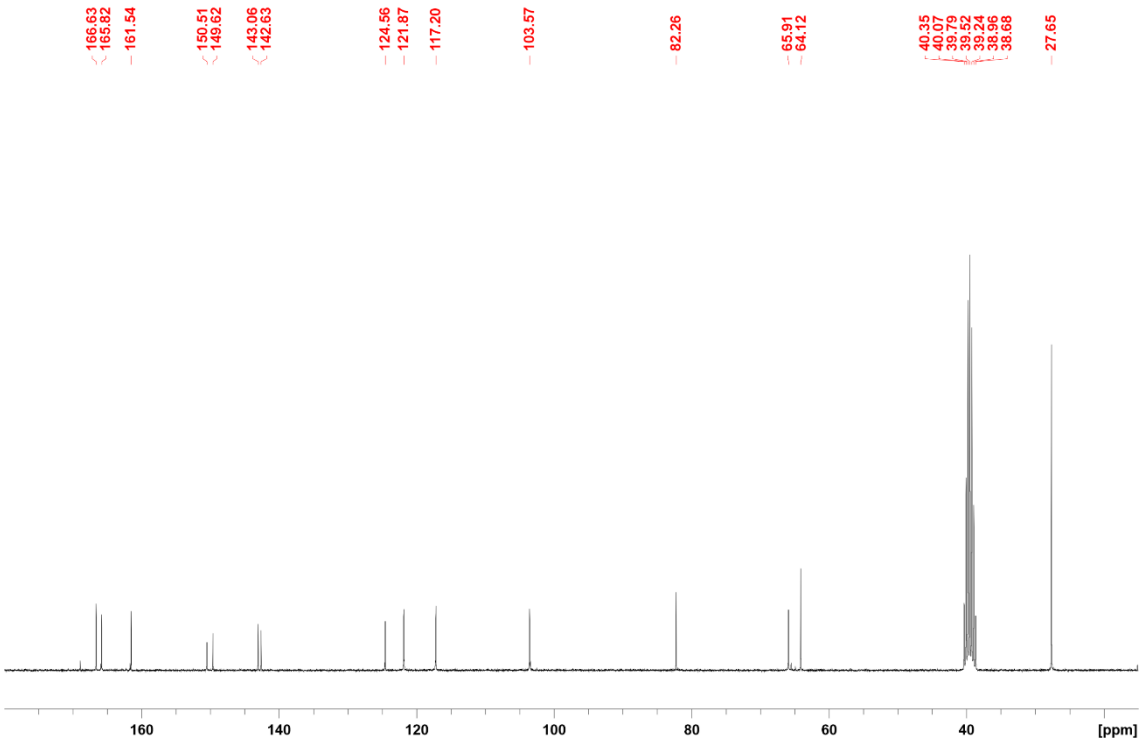


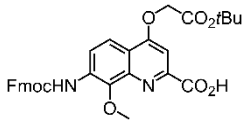




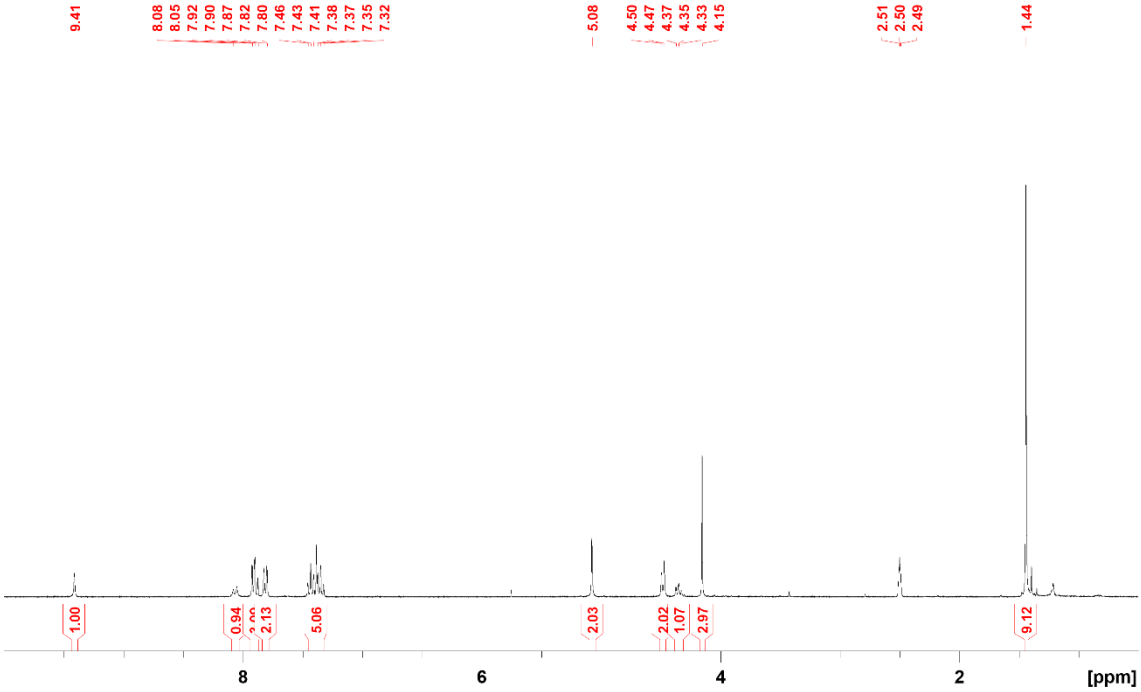
Compound **38**, DMSO-d_6, 300 MHz

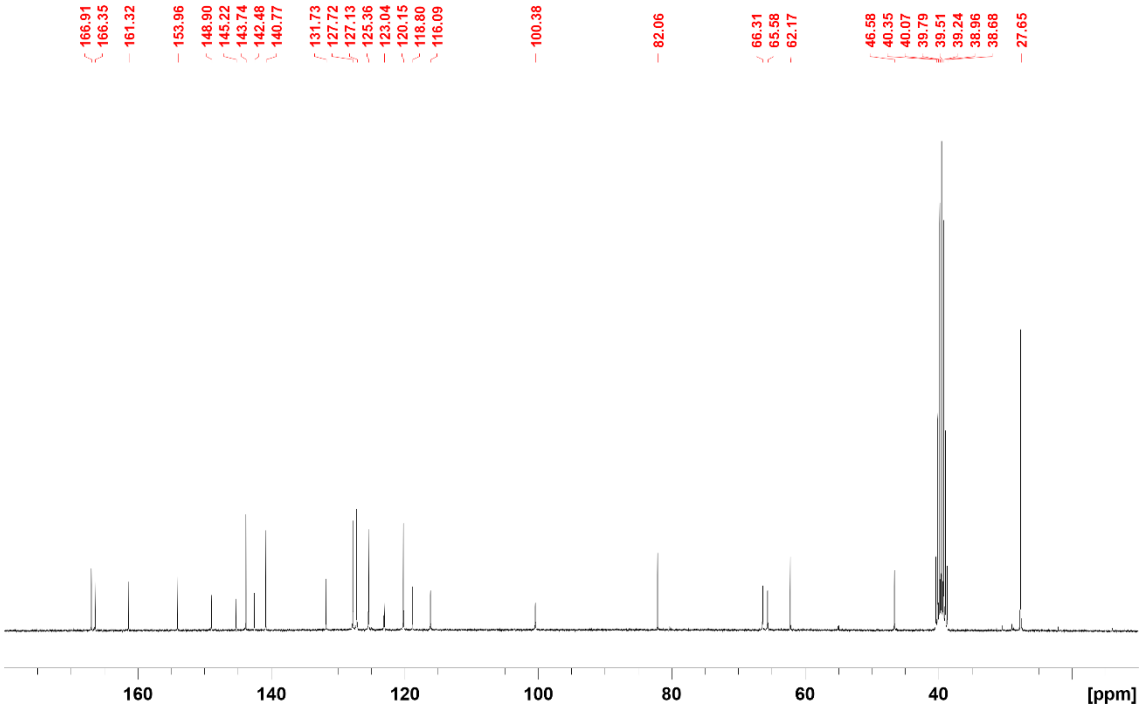






Compound **40**, DMSO-d_6, 300 MHz





10.3 HPLC chromatograms of Fmoc-acid monomers