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Supporting Information

Tuning the Guest-Binding Ability of a Helically Folded Capsule by In Situ Modification of the Aromatic Oligoamide Backbone

Guillaume Lautrette,[a] Christophe Aube,[b] Yann Ferrand,[a] Muriel Pipelier,[b] Virginie Blot,[b] Christine Thobie,[b] Brice Kauffmann,[c] Didier Dubreuil,*[b] and Ivan Huc*[a]

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Supporting Information

Tuning the guest binding ability of a helically folded capsule by *in situ* modification of its aromatic oligoamide backbone

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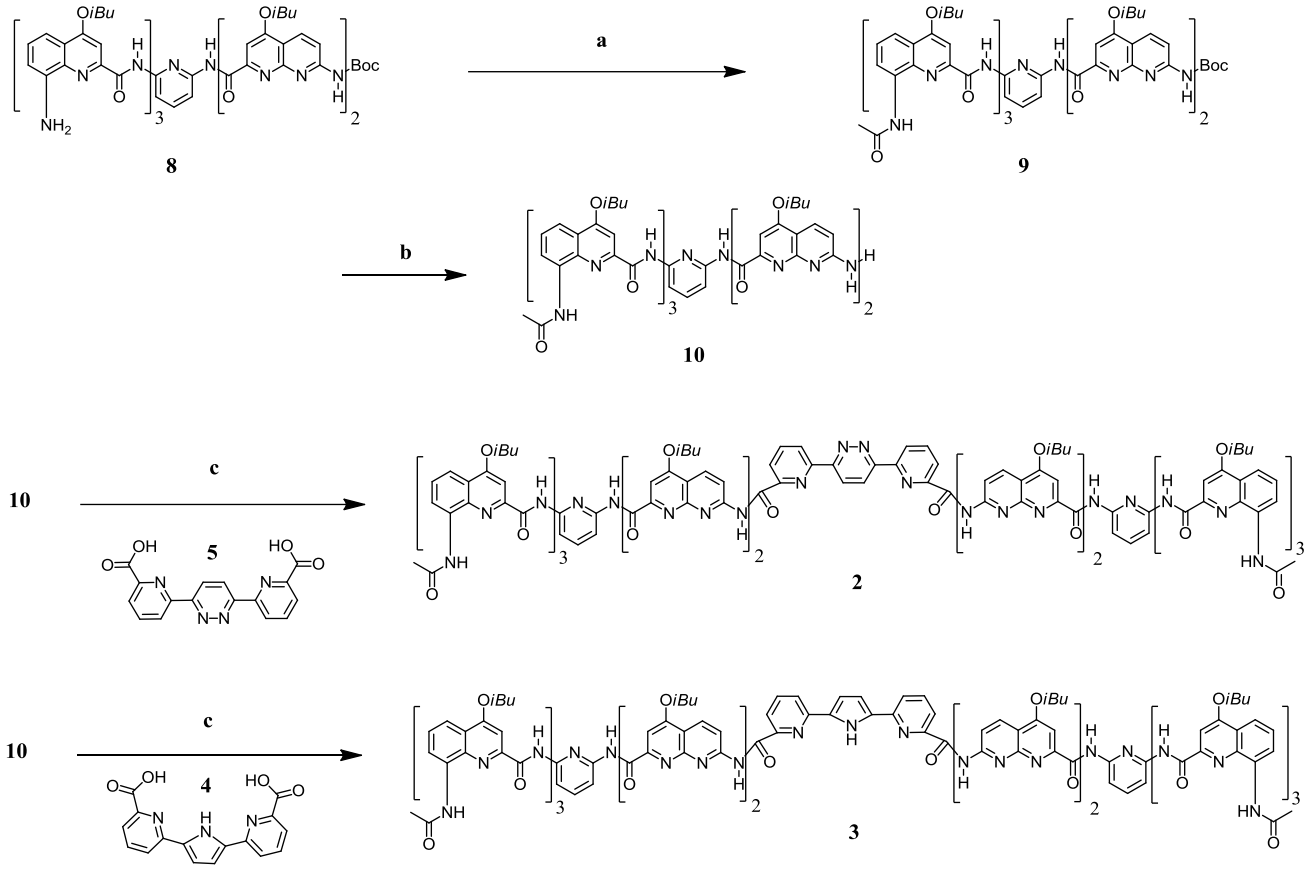
Synthetic schemes



Scheme S1. Synthesis of capsules **2** and **3** : (a) Acetic anhydride, $(i\text{Pr})_2\text{NEt}$, $CHCl_3$, 60°C ; (b) TFA, $CHCl_3$, rt ; (c) PyBop, $(i\text{Pr})_2\text{NEt}$, $CHCl_3$, 45°C.

Materials and methods

Nuclear Magnetic Resonance

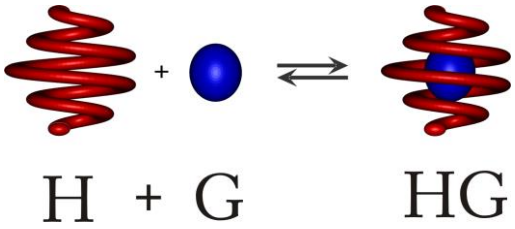
NMR spectra were recorded on 3 different NMR spectrometers: (1) an Avance II NMR spectrometer (Bruker Biospin) with a vertical 7.05T narrow-bore/ultrashield magnet operating at 300 MHz for ^{1}H observation, 282 MHz for ^{19}F observation and 75 MHz for ^{13}C observation by means of a 5-mm direct BBO H/X probe with Z gradient capabilities; (2) a DPX-400 NMR spectrometer (Bruker Biospin) with a vertical 9.4T narrow-bore/ultrashield magnet operating at 400 MHz for ^{1}H observation by means of a 5-mm direct QNP $^{1}H/^{13}C/^{31}P/^{19}F$ probe with gradient capabilities; (3) an Avance III NMR spectrometer (Bruker Biospin) with a vertical 16.45T 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. Chemical shifts are reported in parts per million (ppm, δ) relative to the ^{1}H residual signal of the deuterated solvent used. ^{1}H NMR splitting patterns with observed first-order coupling are designated as singlet (s), doublet (d), triplet (t), or quartet (q). Coupling constants (*J*) are reported in hertz. Samples were not degassed. Data processing was performed with Topspin 2.0 software.

Crystallography

Data collections were performed at the IECB X-ray facility (UMS 3033 CNRS) on a RIGAKU MM07 rotating anodes at the copper k_{α} wavelength at 213K (receptor **3**). The crystal was mounted on cryo-loops after quick soaking on Paratone—N oil from Hampton research and flash-frozen. Crystal structure was solved by the ab-initio method with dual-space recycling using the largest *E*-values implemented in SHELXD and refined using SHELXL. Full-matrix least-squares refinement was performed on F^2 for all unique reflections, minimizing $w(Fo^2- Fc^2)^2$, with anisotropic displacement parameters for non-hydrogen atoms. Hydrogen atoms were included in idealized positions and refined with a riding model, with Uiso constrained to 1.2 Ueq value of the parent atom (1.5 Ueq when CH_3). PLATON/SQUEEZE was used to treat two badly disordered dichloromethane molecules in the asymmetric unit. These were removed from the model. SQUEEZE reports that the volume of total potential solvent accessible void is 1087.2 $Å^3$ in the unit cell and the number of electrons within the void is reported to be 263 electrons/cell.

NMR Titrations

Determination of K_a through NMR integration:



For the equilibrium shown in Eq. 1, the association constant K_a of the receptor is given by Eq. 2.

$$H + G \rightleftharpoons HG \qquad (1)$$

$$K_a = \frac{[HG]}{[H][G]} \qquad (2)$$

where: [HG] = complex concentration; [H] = host concentration; [G] = guest concentration

Alternatively, $$K_a = \frac{n_{HG} \times V_T}{n_H \times n_G} \qquad (3)$$

where: V_T = total volume of the sample; n_H = number of moles of host (etc.)

From mass balance, $$n_{H_0} = n_H + n_{HG} \qquad (4)$$
$$n_{G_0} = n_G + n_{HG} \qquad (5)$$

where: n_{H0} = initial number of moles of host; n_{G0} = number of moles of guest added to the sample

Substituting equations (4) and (5) into (3), $$K_a = \frac{n_{HG} \times V_T}{(n_{H_0} - n_{HG}) \times (n_{G_0} - n_{HG})} \qquad (6)$$

From integration of the NMR spectrum it is possible to obtain the fraction of bound host molecules, x (Eq. 7).

$$x = \frac{n_{HG}}{n_{H_0}} \qquad (7)$$

Using Eq. 7 to eliminate n_{HG} from Eq. 6, $$K_a = \frac{x \times V_T}{n_{G_0} - (x \times n_{H_0}) - (x \times n_{G_0}) + (x^2 \times n_{H_0})} \qquad (8)$$

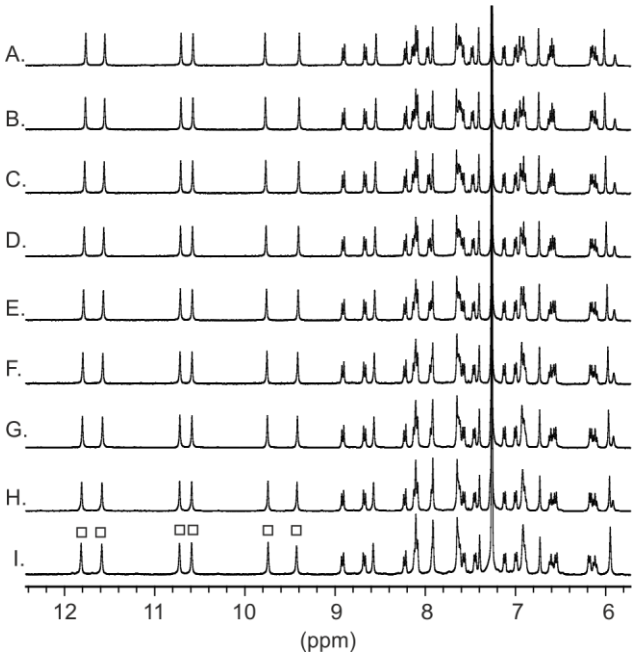
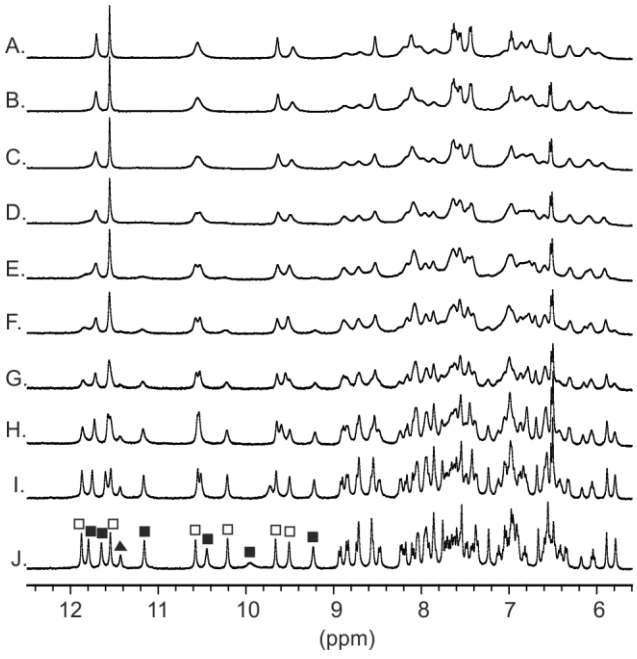


Figure S1. Part of the 400MHz ^{1}H NMR spectra of **2** (2mM) in $CDCl_3$ at: A. 303 K; B. 298 K; C. 293 K; D. 288 K; E. 283 K; F. 278 K; G. 273 K; H. 268 K; I. 263 K. Signals of the *anti-anti* capsule are marked with empty squares.



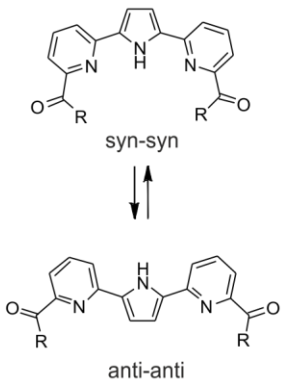


Figure S2. Part of the 400MHz ^{1}H NMR spectra of **3** (2mM) in CD_2Cl_2 at: A. 308 K; B. 303 K; C. 298 K; D. 293 K; E. 288 K; F. 283 K; G. 278 K; H. 273 K; I. 268 K; J. 263 K. Signals of the *anti-anti* and of the *syn-syn* capsule are marked with empty and black squares, respectively. The black triangle denotes the resonance of *syn-syn* N*H* of pyrrole.

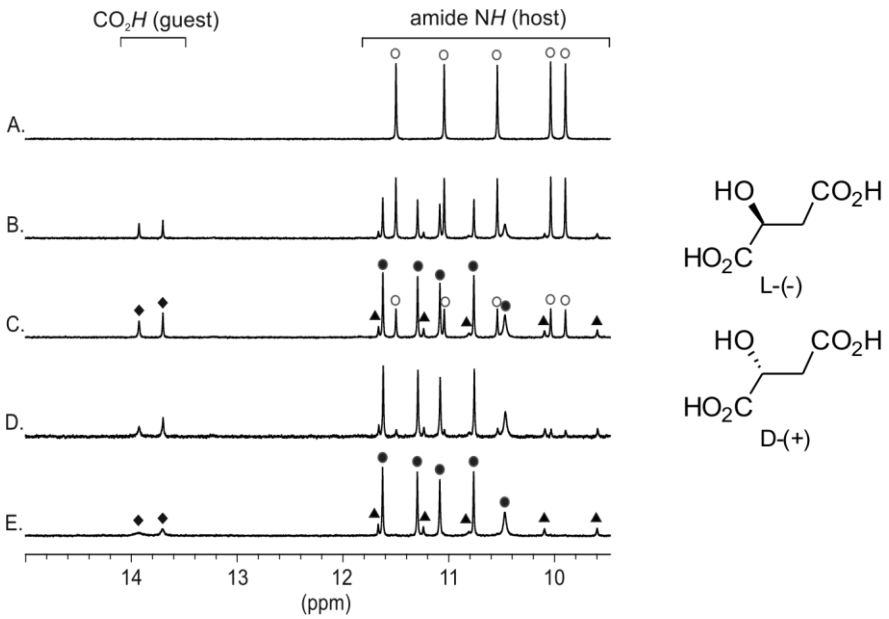


Figure S3. Representative 400 MHz NMR spectra of **1** (1 mM) in a mixture of $CDCl_3$:d_6-DMSO (99:1 vol/vol) at 298 K titrated with *D/L*-malic acid: A. 0 equiv., B. 0.5 equiv., C. 1 equiv., D. 2 equiv., E. 5 equiv.. Amide signals of the empty host are marked with empty white circles. Amide signals of the match host-guest complex and of the mismatch host-guest complex (i.e. diastereoisomer) are marked with black circles and black triangles, respectively. At low field (~ 14 ppm), one can see the two different carboxylic acid protons of malic acid (diamond). K_a = 9250 L.mol^{-1}

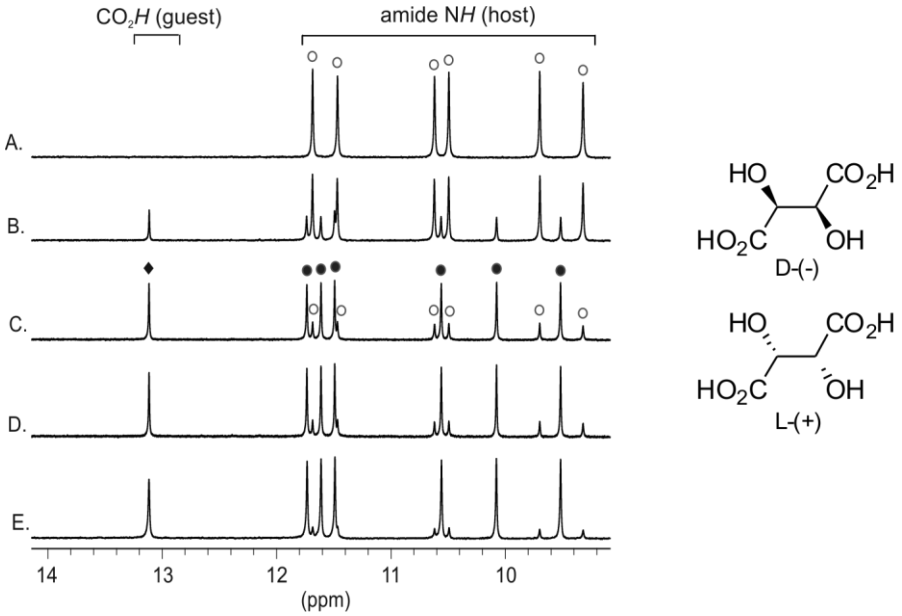


Figure S4. Representative 300 MHz NMR spectra of **3** (1 mM) in a mixture of $CDCl_3$:d_6-DMSO (99:1 vol/vol) at 298 K titrated with *D/L*-tartaric acid: A. 0 equiv., B. 0.25 equiv., C. 1 equiv., D. 1.5 equiv., E. 3 equiv.. Amide signals of the empty host and of the host–guest complex are marked with empty white and black circles, respectively. At low field (~ 13 ppm), one can see carboxylic acid protons of the bound tartaric acid (diamond). K_a = 16000 L.mol^{-1}

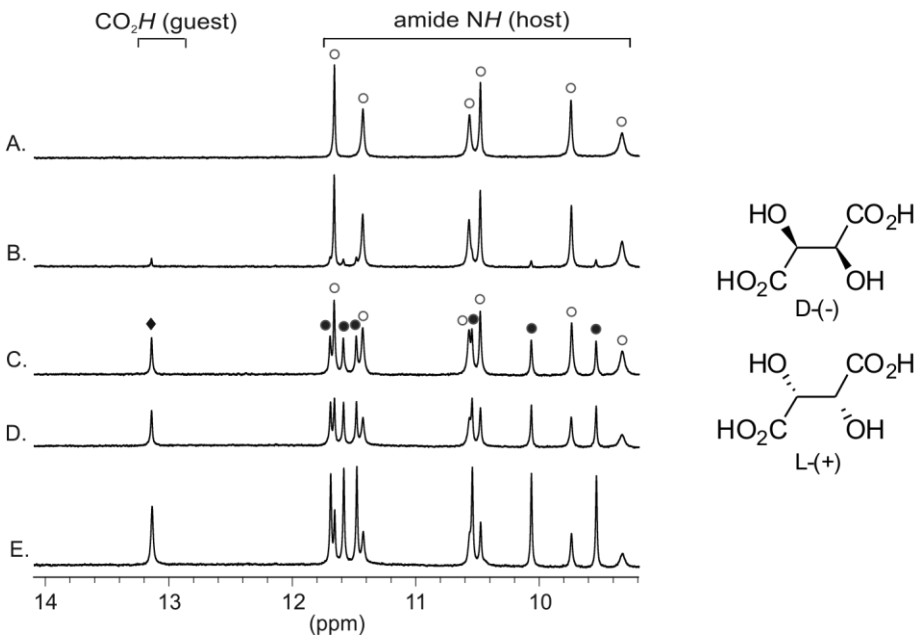


Figure S5. Representative 300 MHz NMR spectra of **3** (1 mM) in a mixture of $CDCl_3$:d_6-DMSO (90:10 vol/vol) at 298 K titrated with *D/L*-tartaric acid: A. 0 equiv., B. 1 equiv., C. 4 equiv., D. 8 equiv., E. 16 equiv.. Amide signals of the empty host and of the host–guest complex are marked with empty white and black circles, respectively. At low field (~ 13ppm), one can see carboxylic acid protons of the bound tartaric acid (diamond). K_a = 110 L.mol^{-1}

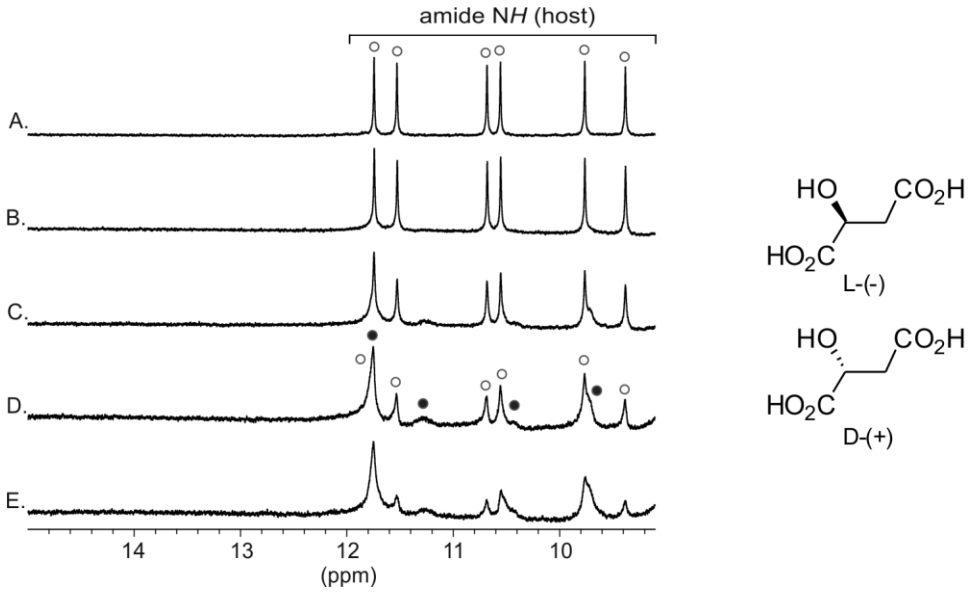


Figure S6. Representative 400 MHz NMR spectra of **3** (1 mM) in a mixture of $CDCl_3$:d_6-DMSO (99:1 vol/vol) at 298 K titrated with *D/L*-malic acid: A. 0 equiv., B. 2 equiv., C. 8 equiv., D. 16 equiv., E. 32 equiv.. Amide signals of the empty host and of the host–guest complex are marked with empty white and black circles, respectively. K_a = 100 L.mol^{-1}

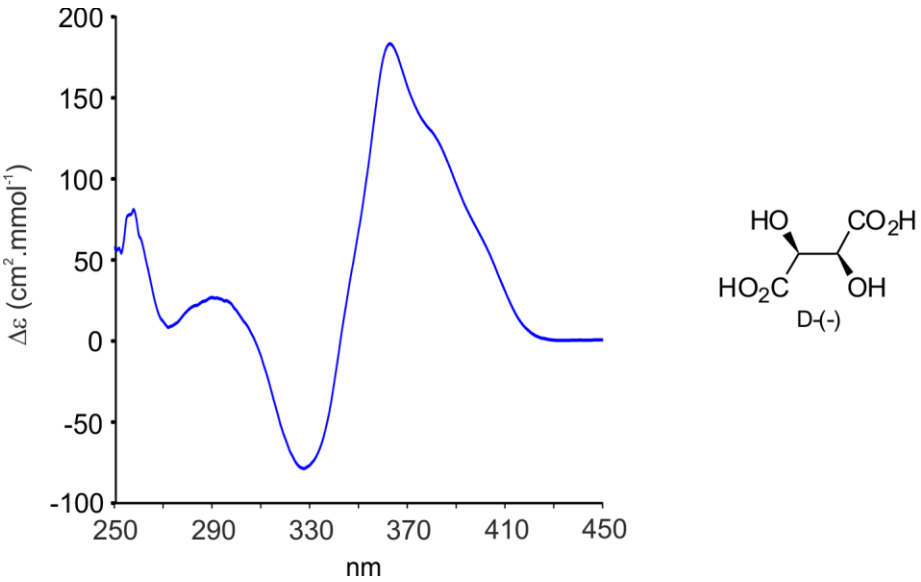


Figure S7. CD spectra of **3** (200 μM in $CHCl_3$:d_6-DMSO 99:1 vol/vol) at 298 K titrated with 10 equiv. of *D*-tartaric acid.

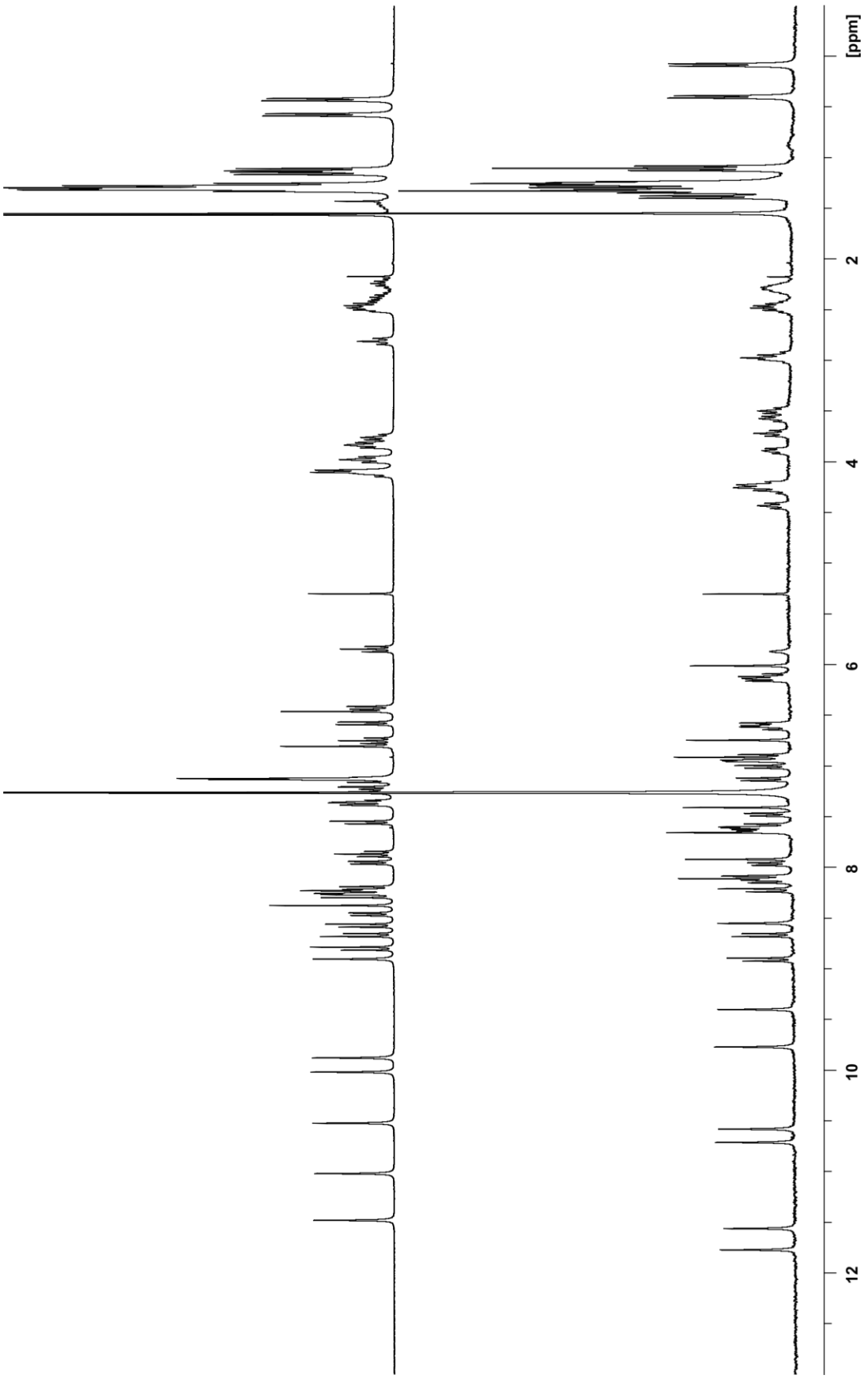


Figure S8. ^{1}H NMR spectrum (300 MHz) of **1** (left) and **3** (right) in $CDCl_3$ at 298 K.

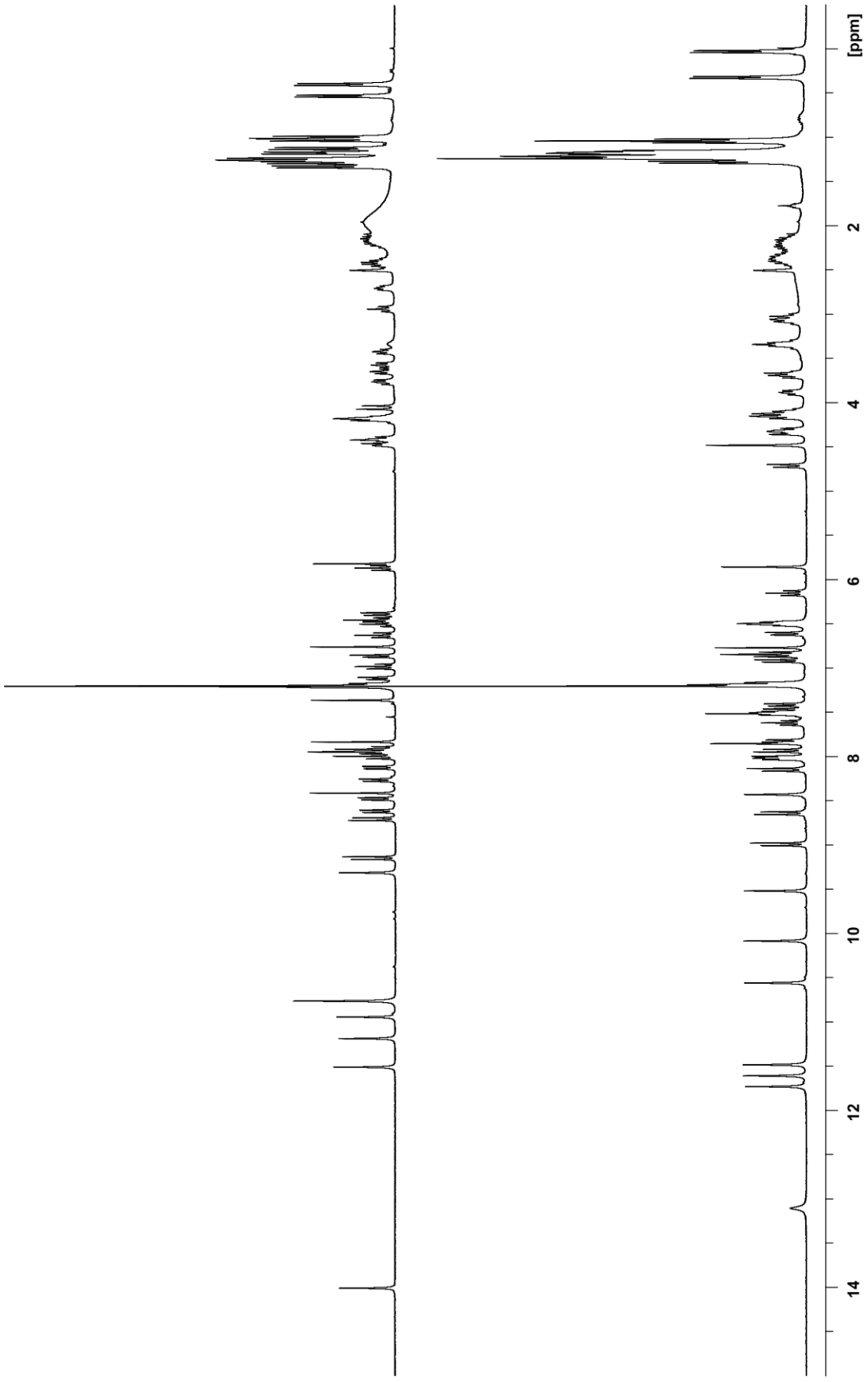


Figure S9. ^{1}H NMR spectrum (300 MHz) of **1** ⊃ *D/L*-tartaric acid (left) in $CDCl_3$/d_6-DMSO (99/1 vol/vol) at 298 K. ^{1}H NMR spectrum (300 MHz) of **3** ⊃ *D/L*-tartaric acid (right) in $CDCl_3$/d_6-DMSO (99/1 vol/vol) at 298 K.

Determination of the structures of **3** and **3** ⊃ *D*/*L*-tartaric in solution by 1D and 2D NMR:

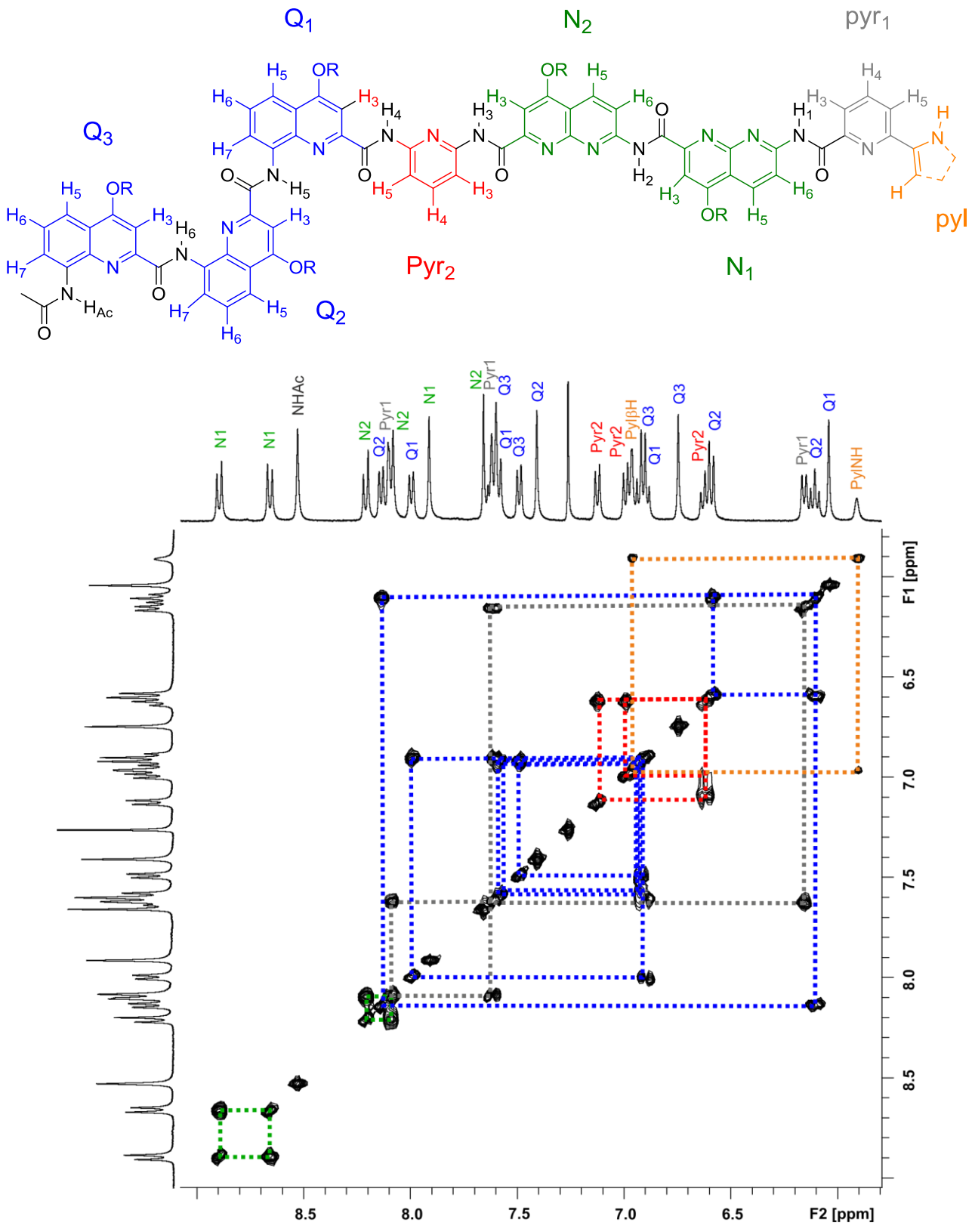


Figure S10. Part of the 400 MHz COSY plot of **3** in $CDCl_3$ at 298 K. The spin systems of pyridine rings from pyr-pyl-pyr (pyr1, grey), pyrrole rings (Pyl, orange), diaminopyridine rings (pyr2, red), naphthyridine rings (N, green) and quinoline rings (Q, blue) are connected by color coded full lines.

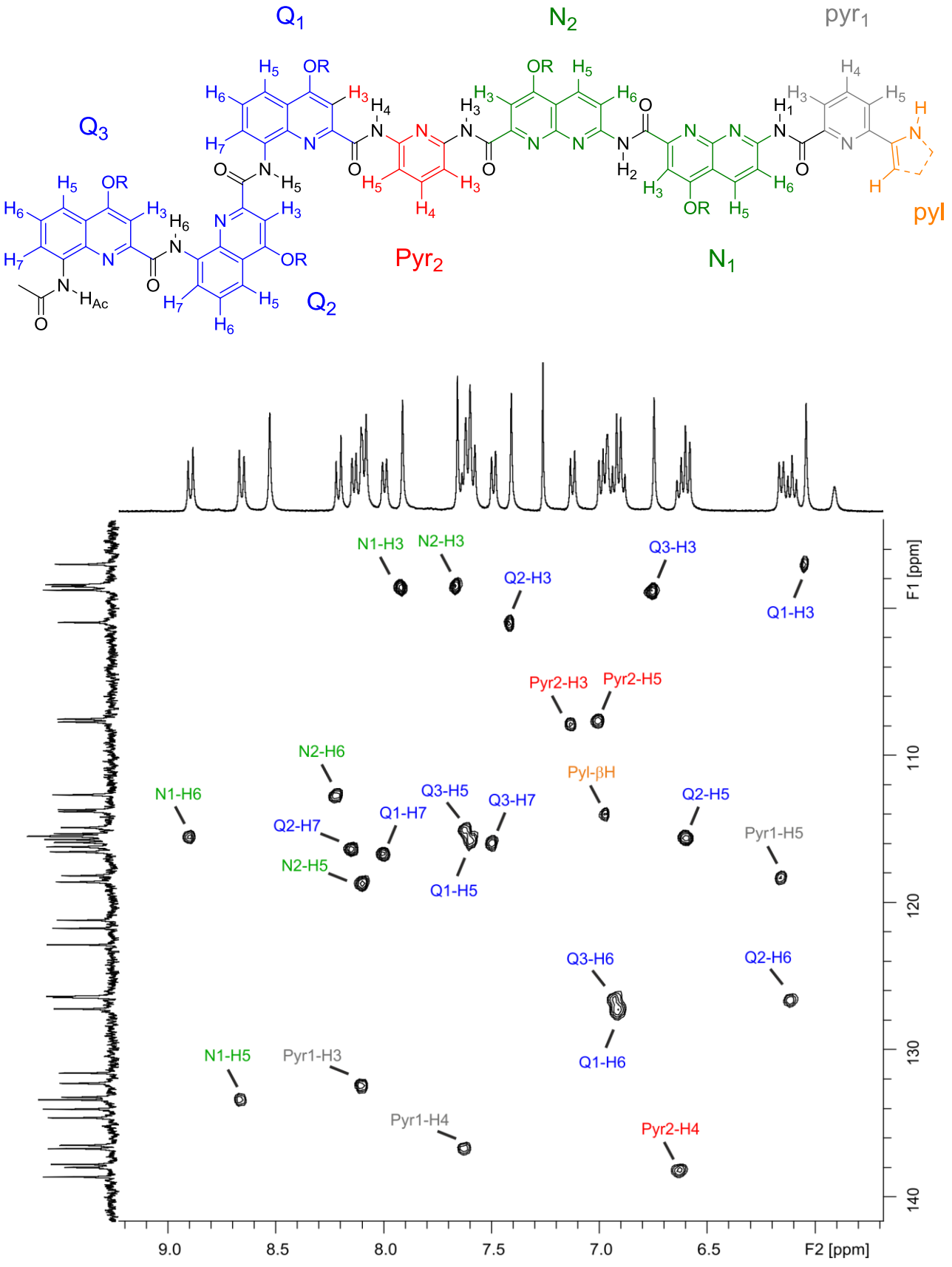


Figure S11. Parts of the 400 MHz HSQC plot of **3** in $CDCl_3$ at 298 K, showing cross-peaks between directly bonded hydrogen and carbons. The horizontal scale is that of proton resonances and the vertical scale is that of carbon resonances.

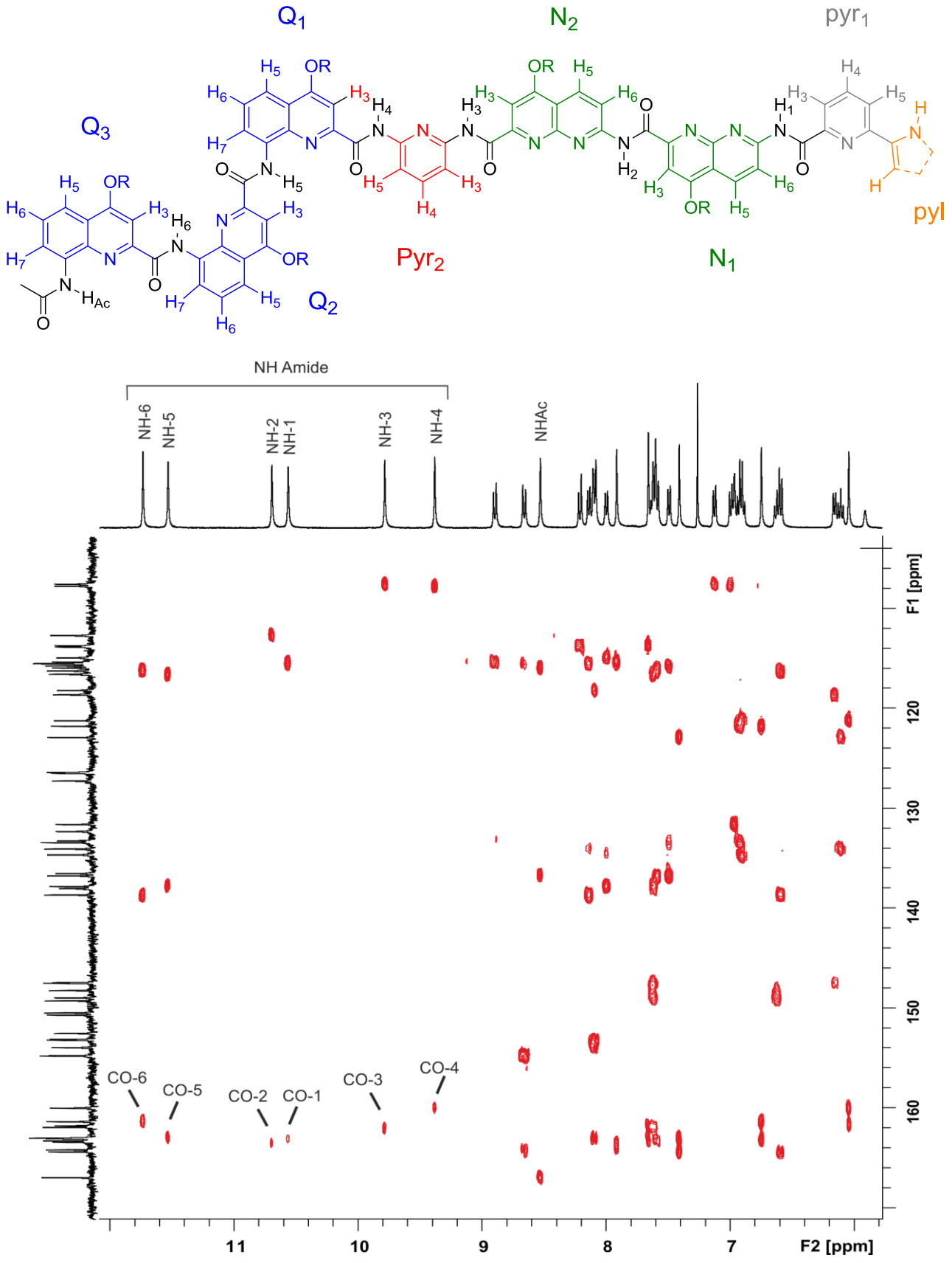


Figure S12. Parts of the 400 MHz HMBC plot of **3** in $CDCl_3$ at 298 K. The horizontal scale is that of proton resonances and the vertical scale is that of carbon resonances.

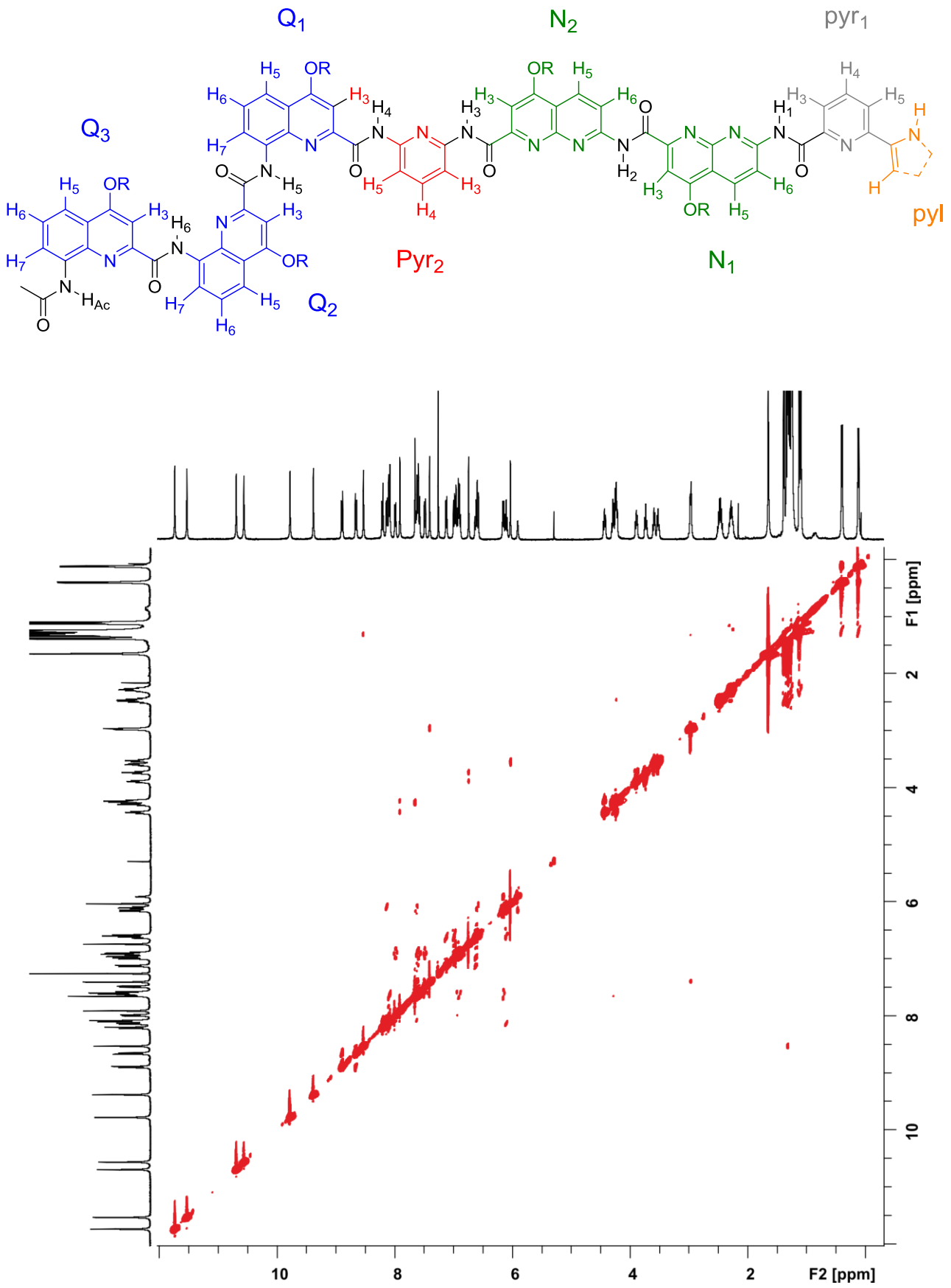


Figure S13. 2D ROESY spectrum (400 MHz) of **3** in $CDCl_3$ at 298 K showing through-space correlations (intramolecular NOE contacts).

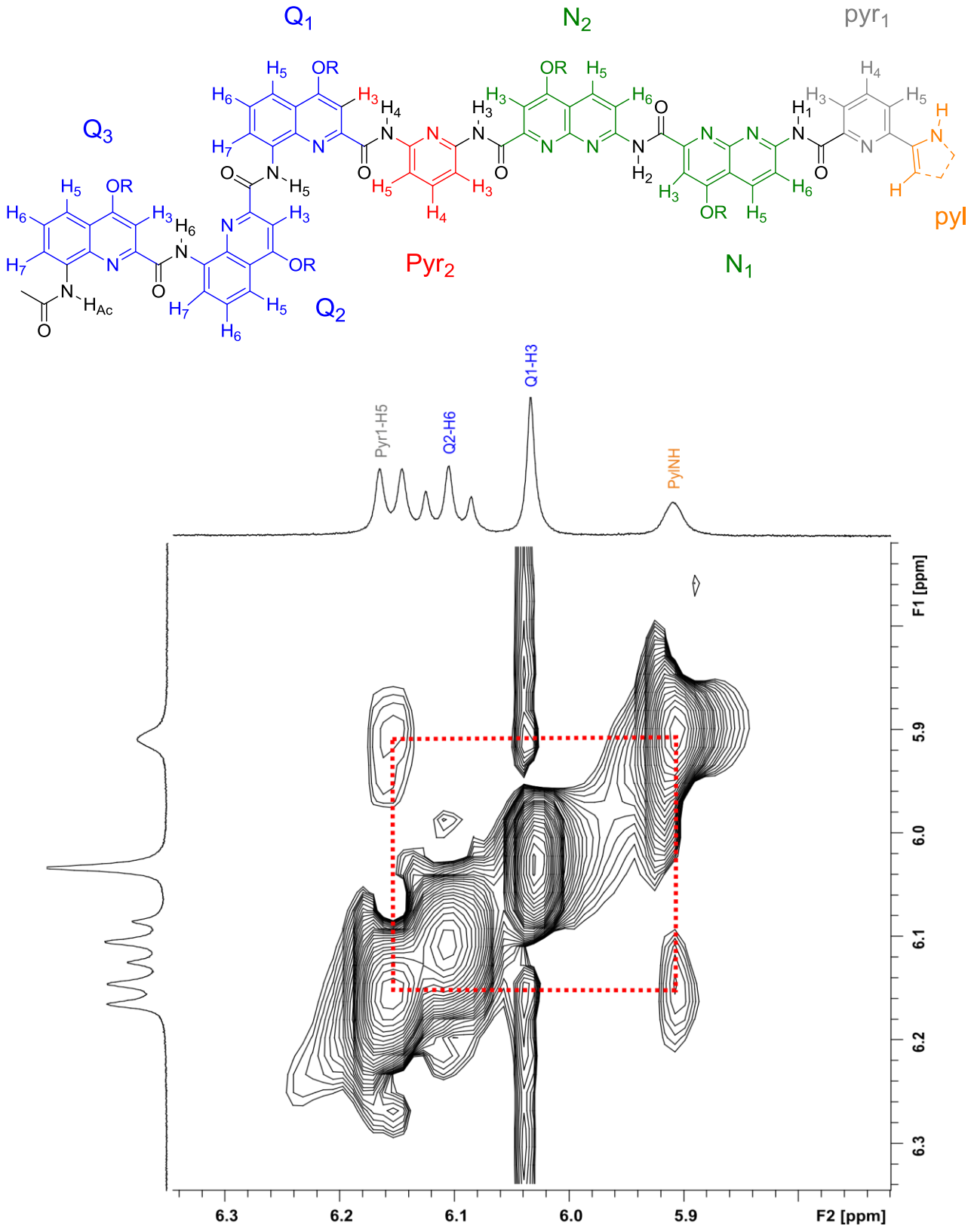


Figure S14. Zoom of 2D NOESY spectrum (400 MHz) of **3** in $CDCl_3$ at 298 K showing intramolecular correlations (NOE contacts) between the amine group of the pyrrole and the *ortho* position of the neighbouring pyridine (pyr1).

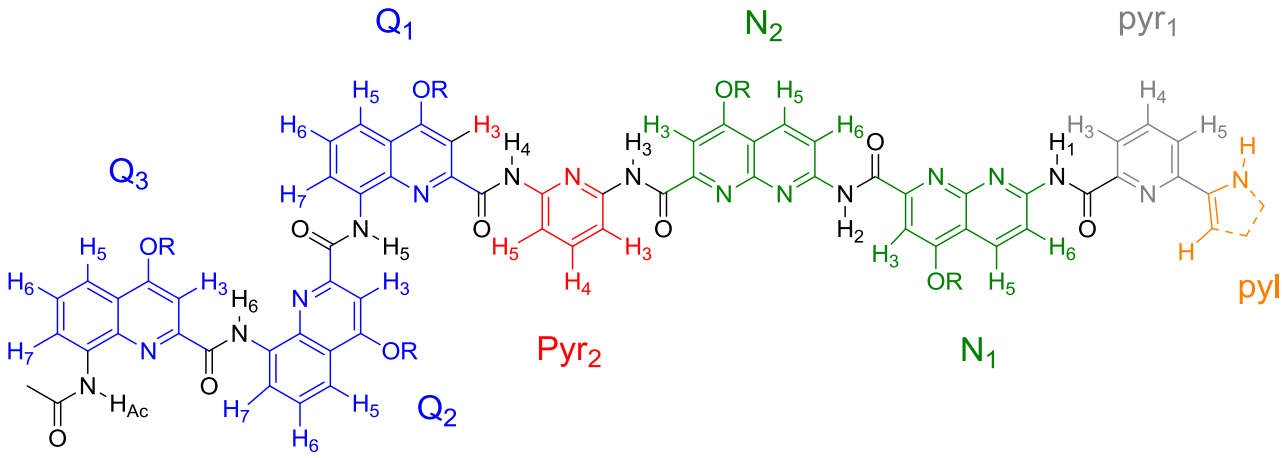


Table S1. ^{1}H and ^{13}C chemical shifts for **3** in $CDCl_3$.

	^{1}H	^{13}C		^{1}H	^{13}C
pyl-Hβ	6.96	113.8	**Q2-H3**	7.41	100.9
pyr1-H3	8.09	132.3	**Q2-H5**	6.59	115.5
pyr1-H4	7.62	136.7	**Q2-H6**	6.10	126.5
pyr1-H5	6.16	118.2	**Q2-H7**	8.14	116.2
N1-H3	7.91	98.5	**Q3-H3**	6.74	98.7
N1-H5	8.66	133.4	**Q3-H5**	7.61	114.9
N1-H6	8.89	115.5	**Q3-H6**	6.92	126.4
N2-H3	7.66	98.4	**Q3-H7**	7.49	115.9
N2-H5	8.09	118.6	**NH-1**	10.56	
N2-H6	8.21	112.6	**NH-2**	10.69	
pyr2-H3	7.12	107.7	**NH-3**	9.78	
pyr2-H4	6.63	138.0	**NH-4**	9.38	
pyr2-H5	6.99	107.5	**NH-5**	11.53	
Q1-H3	6.04	97.0	**NH-6**	11.73	
Q1-H5	7.59	115.7	**NH-Ac**	8.53	
Q1-H6	6.90	127.2	**CH_3Ac**	1.32	23.9
Q1-H7	7.99	116.5	**NH-Pyl**	5.91	

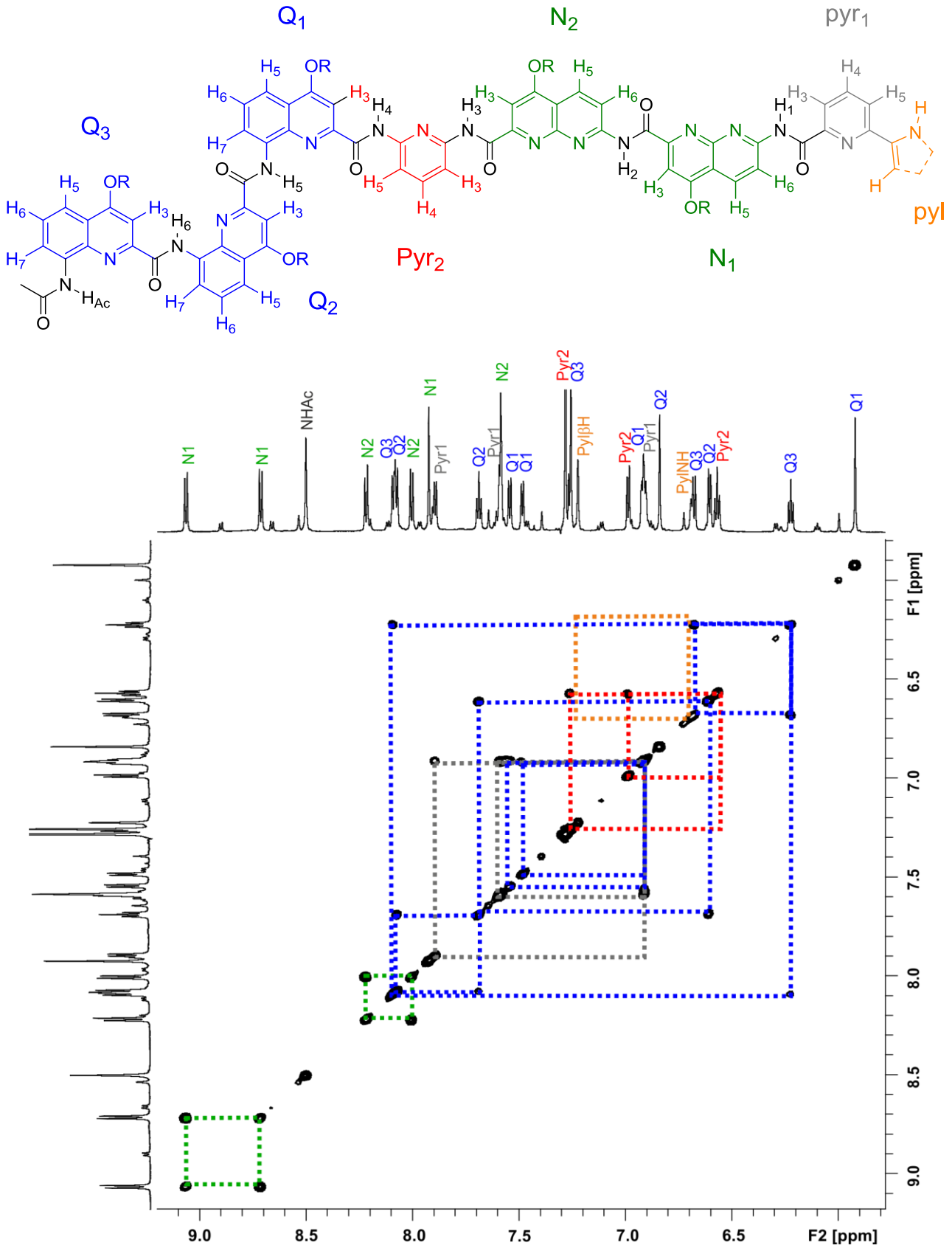


Figure S15. Part of the 700 MHz COSY plot of **3** ⊃ *D/L*-tartaric acid in $CDCl_3$:d_6-DMSO (99:1 vol/vol) at 298 K. The spin systems of pyridine rings from pyr-pyl-pyr (pyr1, grey), pyrole rings (Pyl, orange), diaminopyridine rings (pyr2, red), naphthyridine rings (N, green) and quinoline rings (Q, blue) are connected by color coded full lines.

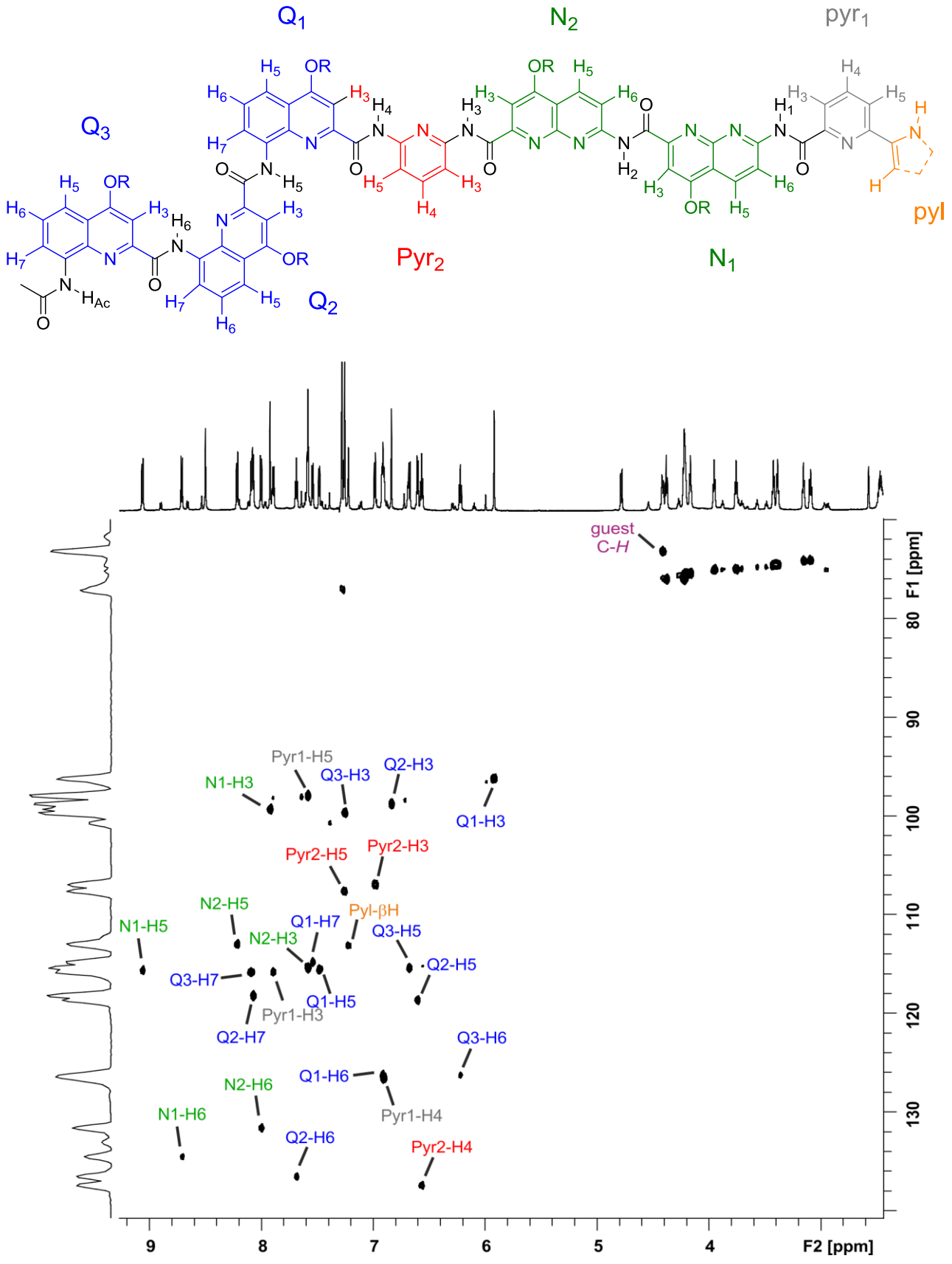


Figure S16. Parts of the 700 MHz HSQC plot of **3** ⊃ *D*/*L*-tartaric acid in $CDCl_3$:d_6-DMSO (99:1 vol/vol) at 298 K, showing cross-peaks between directly bonded hydrogen and carbons. The horizontal scale is that of proton resonances and the vertical scale is that of carbon resonances.

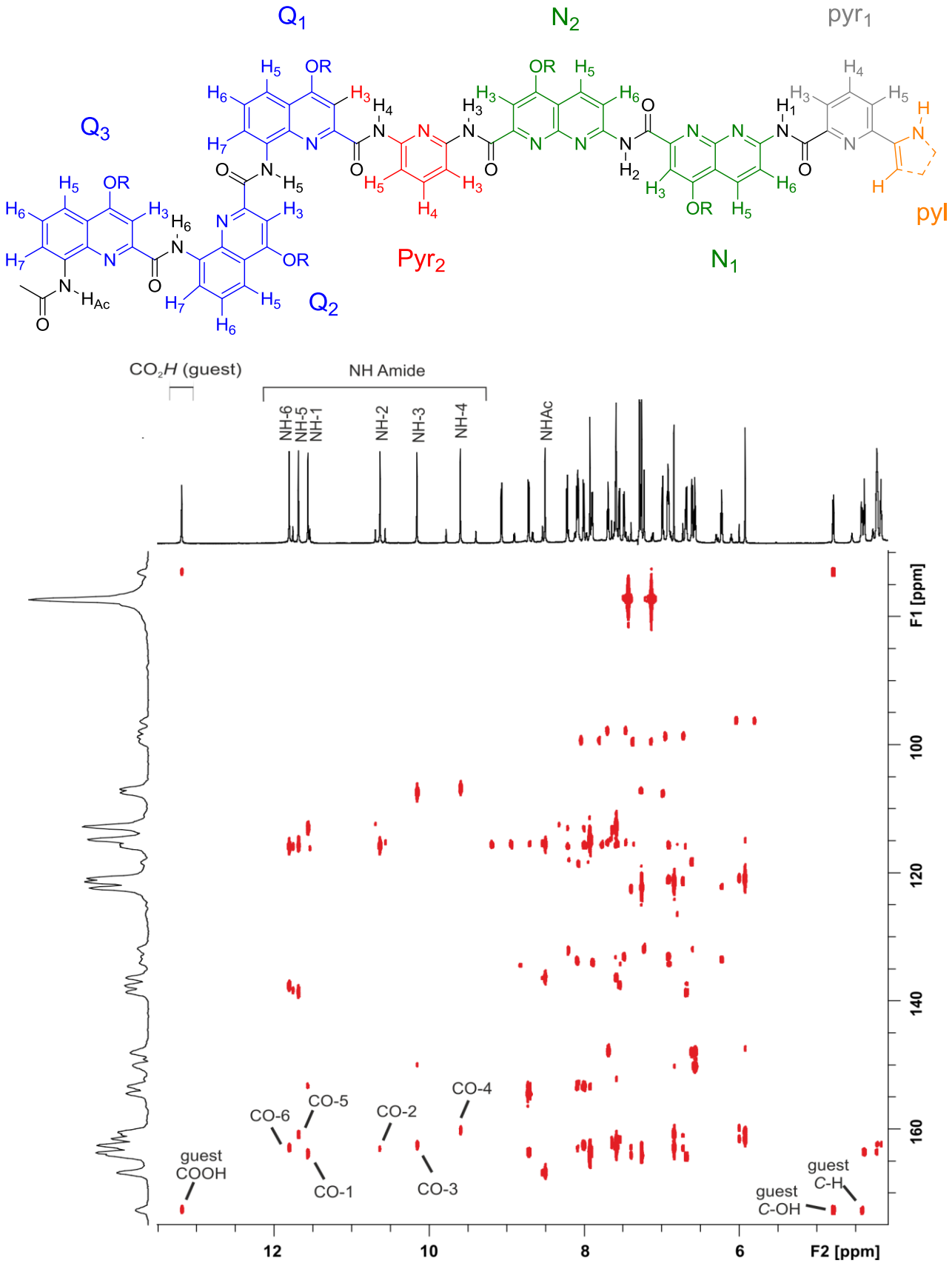


Figure S17. Parts of the 700 MHz HMBC plot of **3** ⊃ *D/L*-tartaric acid in $CDCl_3$:d_6-DMSO (99:1 vol/vol) at 298 K. The horizontal scale is that of proton resonances and the vertical scale is that of carbon resonances.

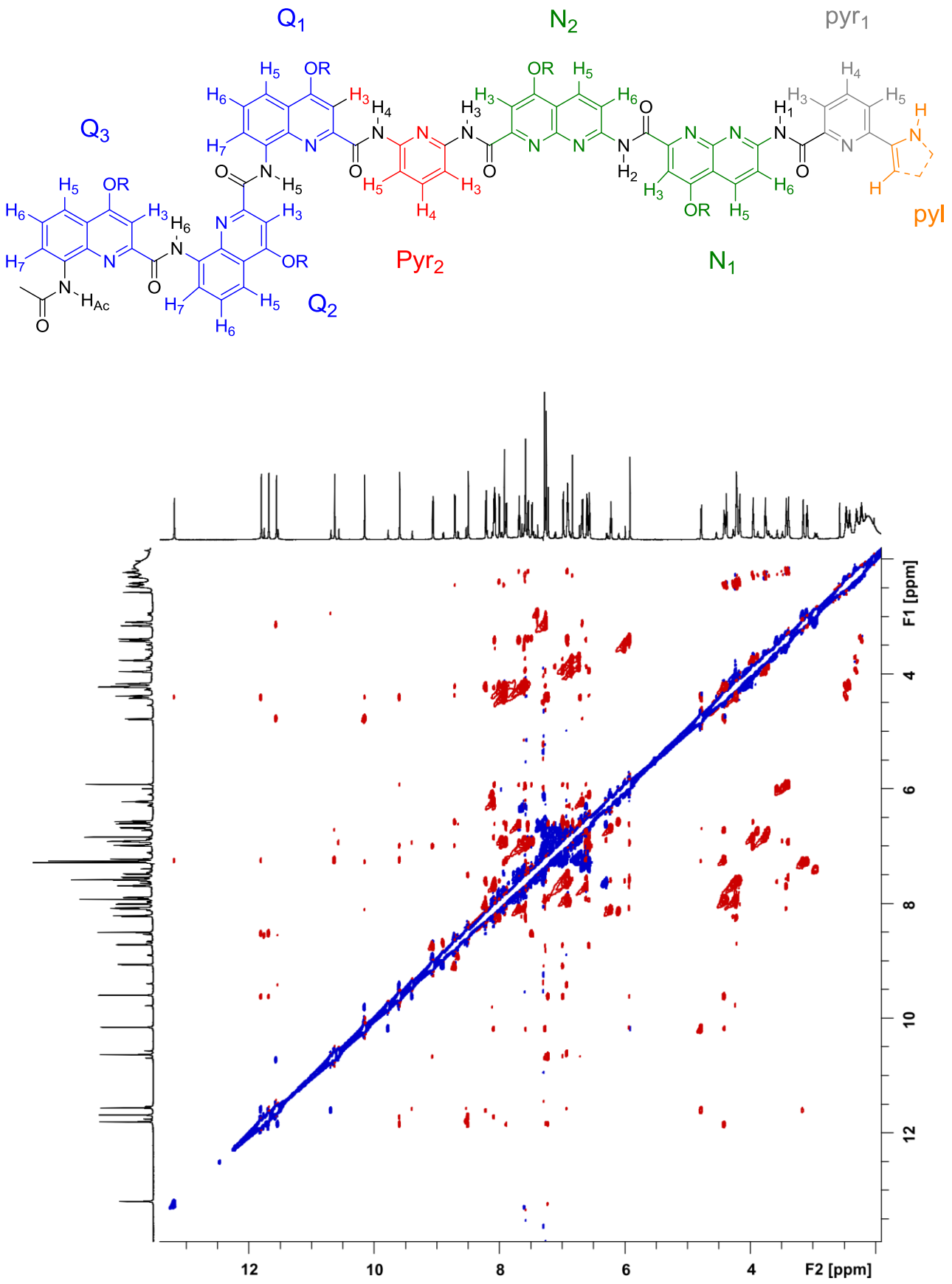


Figure S18. 2D ROESY spectrum (700 MHz) of **3** ⊃ *D/L*-tartaric acid in $CDCl_3$:d_6-DMSO (99:1 vol/vol) at 298 K showing through-space correlations (intra and intermolecular NOE contacts).

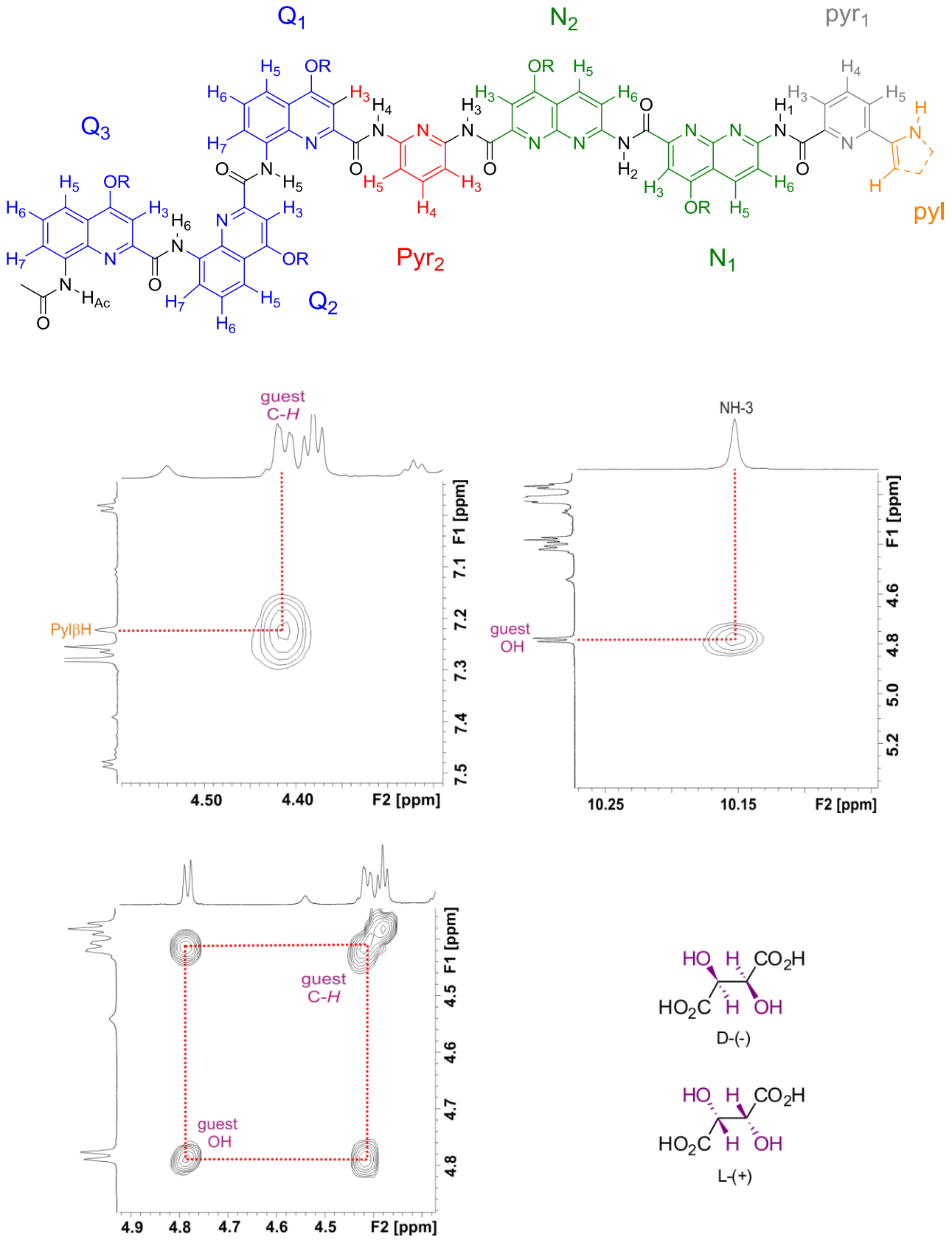


Figure S19. Zoom of 2D ROESY (700MHz) spectrum (top) and of COSY (700MHz) spectrum (bottom) of **3** ⊃ *D/L*-tartaric acid in $CDCl_3$:d_6-DMSO (99:1 vol/vol) at 298 K showing intramolecular correlations (NOE contacts) and assignment of tartaric acid in the complex, respectively.

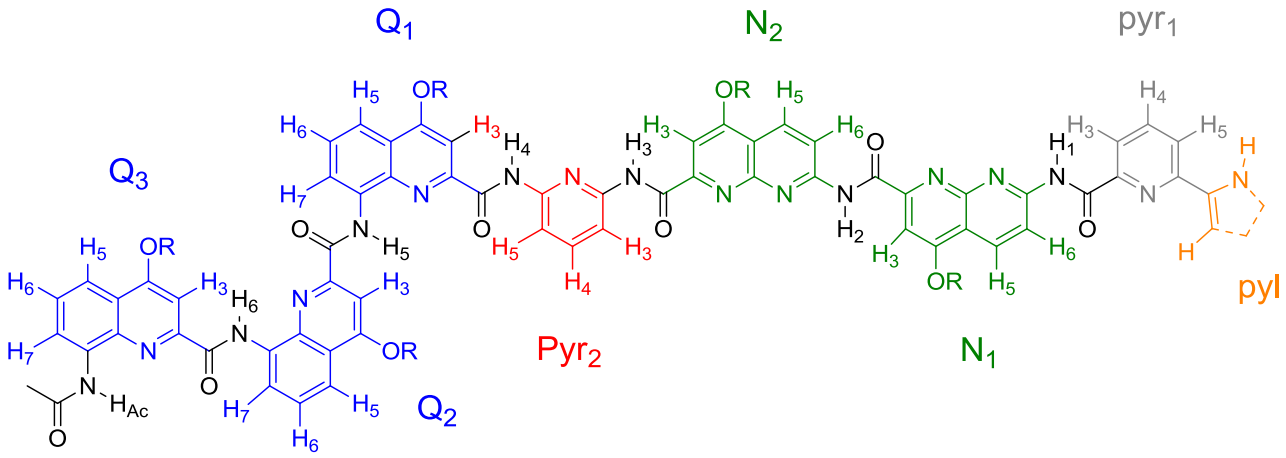


Table S2. ^{1}H and ^{13}C chemical shifts for **3** ⊃ D/L tartaric acid in $CDCl_3$:d_6-DMSO (99:1 vol/vol).

	^{1}H	**^{13}C**		**^{1}H**	**^{13}C**
Pyl-Hβ	7.22	113.1	**Q2-H5**	6.60	118.6
Pyr1-H3	7.89	115.8	**Q2-H6**	7.69	136.5
Pyr1-H4	6.91	126.6	**Q2-H7**	8.08	118.2
Pyr1-H5	7.59	97.9	**Q3-H3**	7.25	99.7
N1-H3	7.92	99.3	**Q3-H5**	6.68	115.4
N1-H5	9.06	115.6	**Q3-H6**	6.22	126.3
N1-H6	8.71	134.5	**Q3-H7**	8.09	115.7
N2-H3	7.58	115.4	**NH-1**	11.56	
N2-H5	8.22	112.9	**NH-2**	10.63	
N2-H6	8.00	131.6	**NH-3**	10.15	
Pyr2-H3	6.99	106.9	**NH-4**	9.59	
Pyr2-H4	6.56	137.4	**NH-5**	11.68	
Pyr2-H5	7.26	107.6	**NH-6**	11.80	
Q1-H3	5.92	96.2	**NH-Ac**	8.53	
Q1-H5	7.48	115.5	**NH-Pyl**	6.69	
Q1-H6	6.91	126.4	**COOH**	13.20	
Q1-H7	7.54	112.8	**C*H*OH**	4.41	73.7
Q2-H3	6.84	98.7	**CHO*H***	4.80	

Crystallography

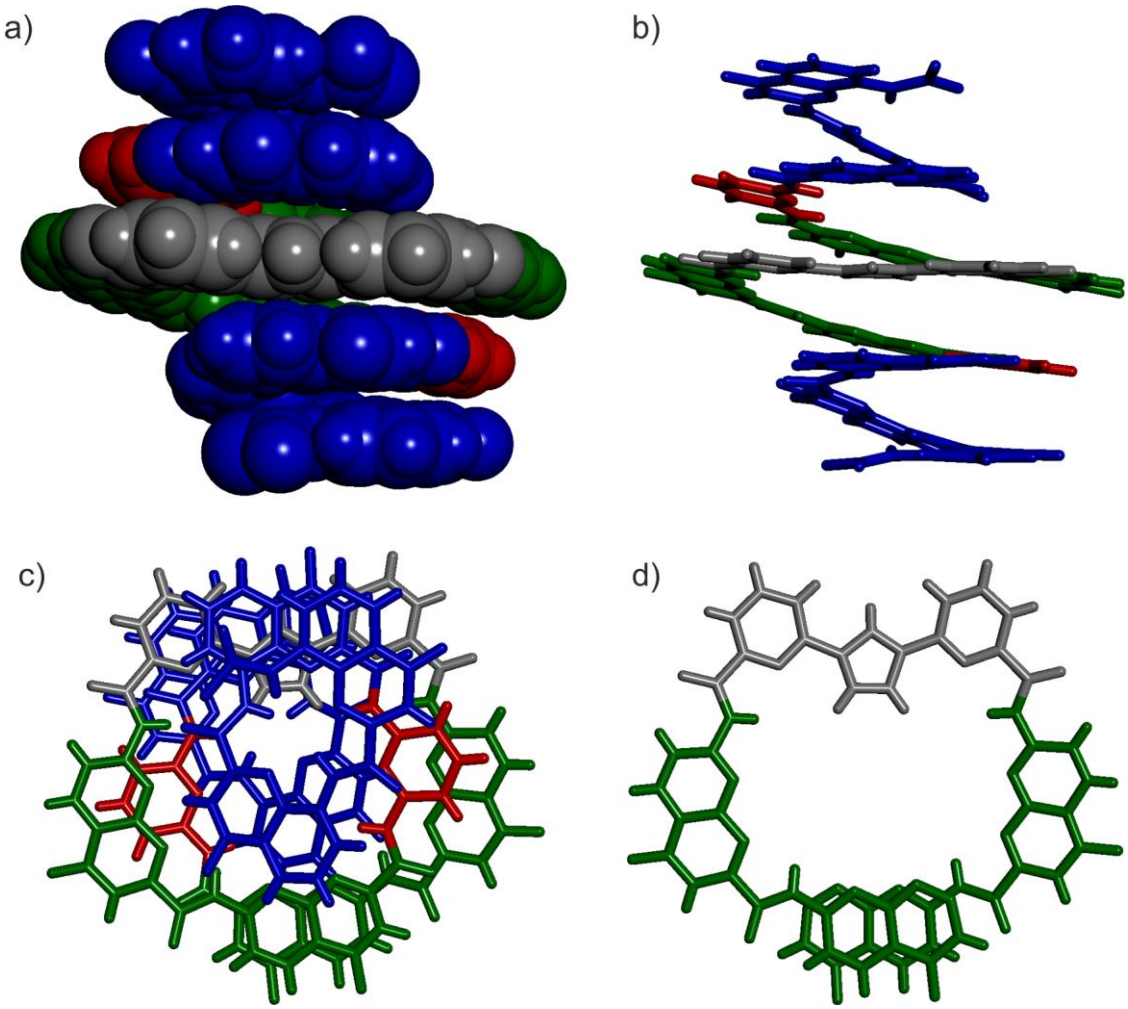


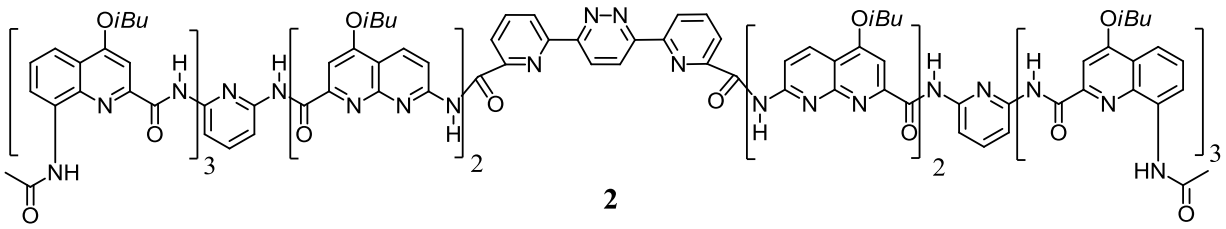
Figure S20. Side view of the crystal structure of **3**: a) in CPK representation; b) in tube representation. Tube representations of the solid-state structures of **3**: c) top view and d) slice of the capsule showing the N_2-pyr-pyl-pyr-N_2 segment from above of the *P*-helix of **3** (Q_3PN_2-pyr-pyl-pyr-N_2PQ_3 with an *anti-anti* conformation of the pyrrole). Isobutyl side chains and included solvent molecules have been removed for clarity.

Table S3: Crystal data and structure refinement for capsule **3**

Name	Receptor **3**
Formula	C176 H181 Cl19.50 N33 O25
M	3849.80
Crystal system	triclinic
Space group	P-1
a/Å	18.261(6)
b/Å	24.751(9)
c/Å	25.506(7)
α/°	114.19(3)
β/°	97.69(3)
γ/°	102.08(3)
U/Å^3	9967(6)
T /K	213(2)
Z	2
ρ/g cm^{-1}	1.283
Shape and color	Colorless needles
size (mm)	0.1x0.1x0.05
λ/ Å	1.54178
μ/mm^{-1}	3.028
Total reflections	74035
Unique data	16832
R_{int}	0.0808
parameters/restraints	2290/3
*R*1, *wR*2	0.1654/ 0.4267
goodness of fit	1.586
CCDC #	964832

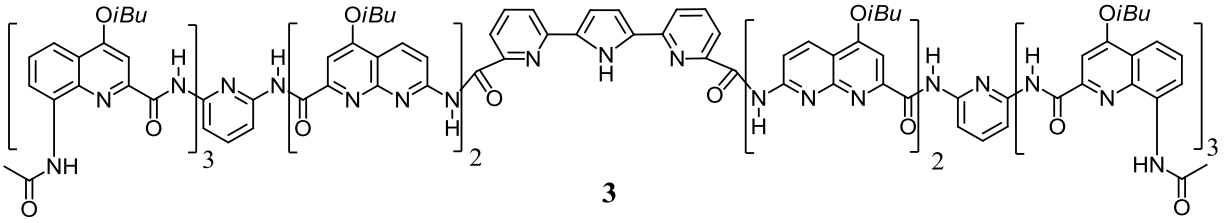
Experimental section.

General. All reactions were carried out under a dry nitrogen atmosphere. Commercial reagents were purchased from Sigma-Aldrich or Alfa-Aesar and were used without further purification unless otherwise specified. Chloroform, diisopropylethylamine (DIPEA) were distilled from calcium hydride (CaH_2) prior to use. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60-F254 plates and observed under UV light. Column chromatographies were carried out on Merck GEDURAN Si60 (40-63 μm). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in deuterated solvents on 300 and 400 MHz spectrometers. Chemical shifts are reported in parts per million (ppm, δ) relative to the signal of the NMR solvent used. ^{1}H NMR splitting patterns with observed first-order coupling are designated as singlet (s), doublet (d), triplet (t), or quartet (q). Coupling constants (J) are reported in hertz. Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m) or broad (br). ^{13}C NMR spectra were recorded on 300 or 400 MHz spectrometers. Chemical shifts are reported in ppm (δ) relative to carbon resonances of the NMR solvent. Mass spectra (MS) were obtained using matrix-assisted laser desorption/ionization (MALDI) or were measured on a DSQ Thermoelectron apparatus by electronic impact (70eV). High Resolution Mass Spectra (HRMS) were measured by electronic impact or by chemical ionisation on quadripolar spectrometers KRATOS MS 80RF or Micromasse Q T of 1. They were equally measured by MALDI-TOF in positive ionization mode on spectrometer Autoflex III of Bruker in the service "Biopolymères, Interactions, Biologie Structurale" of INRA (Institut National de la Recherche Agronomique). The used matrices were DHB (2,5-DiHydroxyBenzoic acid) or DCTB (T-2-(3-(4-*t*-Butylphenyl)-2-methyl-2-propenylidene)malononitrile). Melting points were measured on a RCH microscope (C. Reichert) with a heating plate KOFLER or by a Tottoli microscope (Büchi) with the aid of capillaries. FT-IR spectra were measured on a Bruker Vector 22 FT-IR spectrometer between 500 and 4000 cm^{-1} by KBr pellets. Cyclic voltammetry experiments and preparative electrolysis were performed using a potentiostat-galvanostat SP 300 (Biologic) controlled by the EC-Lab software. In cyclic voltammetry, a conventional three-electrode system was used with a glassy carbon working electrode, a saturated calomel reference electrode (SCE) and a platinum wire counter electrode. Preparative electrolysis were carried out under cathodic potential (E_t) in a concentric cylindrical cell with two compartments separated by a glass frit. A mercury pool electrode (diameter 4.7 cm) or reticulated vitreous carbon (HF 1077-BAS) was used as the cathode, calomel saturated electrode as reference and platinum plate as the anode. In the cathodic compartment, the solution is deoxygenated before electrochemical measures.



2

Capsule 2. Diacid **5** (0.036 mmol, 0.012 g) and hexamer amine **10** (0.072 mmol, 0.099 g) were dissolved in dry chloroform (2 mL). Then, DIPEA (0.18 mmol, 0.032 mL) and PyBop (0.18 mmol, 0.094 g) were added at RT and the reaction mixture was heated at 45°C for 12 hours. Then, the solvents were removed under reduced pressure and the residue was purified by flash chromatography (SiO_2) eluting with EtOAc:cyclohexane (20:80 vol/vol) and by precipitation from minimum amount of MeOH to obtain **2** as a light yellow solid (70 %, 0.075 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm = 11.56 (s, 2H); 11.36 (s, 2H); 10.64 (s, 2H); 9.92 (s, 2H); 9.87 (s, 2H); 8.89 (s, 2H); 8.82 (d, ^3J = 9.0, 2H); 8.68 (d, ^3J = 8.9, 2H); 8.59 (d, ^3J = 8.8, 2H); 8.45 (s,2H); 8.37 (s, 2H); 8.27 (m, 8H); 8.18 (d, ^3J = 9.0, 2H); 7.99 (d, ^3J = 8.7, 2H); 7.87 (t, ^3J = 7.8, 2H); 7.57 (m, 6H); 7.40 (m, 8H); 7.19 (m, 4H); 6.93 (t, ^3J = 8.0, 2H); 6.72 (m, 8H); 6.3 (m, 4H); 6.01 (t, ^{3}J = 7.9, 2H); 4.13 (m, 8H); 3.99 (t, ^3J = 7.3, 2H); 3.86 (m, 5H); 3.72 (m, 5H); 2.82 (m, 3H); 2.36 (m, 7H); 1.28 (m, 36H); 1.10 (m, 12H); 0.57 (d, ^3J = 6.6, 6H); 0.44 (d, ^3J = 6.8, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 166.8; 164.0; 163.4; 163.2; 163.1; 163.0; 162.3; 161.5; 161.4; 160.5; 159.2; 154.9; 154.7; 153.7; 153.6; 153.1; 152.0; 151.5; 151.1; 150.7; 150.1; 148.9; 148.2; 148.1; 146.8; 139.7; 138.4; 137.6; 137.1; 136.5; 134.2; 134.1; 133.6; 133.1; 126.8; 126.5; 125.9; 124.6; 123.9; 123.7; 122.4; 121.6; 121.4; 116.7; 116.6; 116.2; 116.0; 115.6; 114.6; 114.4; 114.1; 113.7; 108.8; 107.7; 100.7; 98.4; 98.1; 96.9; 76.0; 75.8; 75.2; 75.2; 28.5; 28.4; 28.2; 28.1; 27.6; 23.8; 19.6; 19.5; 19.5; 19.4; 19.1; 18.5. MS (MALDI): *m/z* calcd for $C_{166}H_{160}N_{34}O_{24}$ $[M+H]^+$: 3015.2457 found 3015.10.



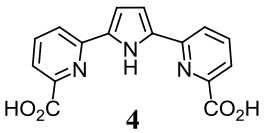
3

Capsule 3. Diacid **4** (0.083 mmol, 0.026 g) and hexamer amine **10** (0.150 mmol, 0.202 g) were dissolved in dry chloroform (4 mL). Then, DIPEA (0.30 mmol, 0.05 mL) and PyBop (0.23 mmol, 0.120 g) were added at RT and the reaction mixture was heated at 45°C for 24 hours. Then, the solvents were removed under reduced pressure and the residue was purified by flash chromatography (SiO_2) eluting with EtOAc:DCM (10:90 vol/vol) and by precipitation from minimum amount of MeOH to obtain **3** as a yellow solid (44 %, 0.098 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 11.73 (s, 2H); 11.53 (s, 2H); 10.69 (s, 2H); 10.56 (s, 2H); 9.78 (s, 2H); 9.38 (s,2H); 8.89 (d, ^3J = 8.8, 2H); 8.66 (d, ^3J = 8.8, 2H); 8.53 (s,2H); 8.21 (d, ^3J = 8.8, 2H); 8.11 (m, 6H); 7.99 (d, ^3J = 7.4, 2H); 7.91 (s, 2H); 7.62 (m, 8H); 7.49 (d, ^3J = 7.4, 2H); 7.41 (s, 2H); 7.12 (d, ^3J = 7.7, 2H); 6.94 (m, 10H); 6.63 (t, ^{3}J = 7.8, 2H); 6.59 (d, ^3J = 8.2, 2H); 6.16 (d, ^3J = 7.7, 2H); 6.10 (t, ^3J = 7.8, 2H); 6.04 (s, 2H); 5.91 (br, 1H); 4.44 (t, ^3J = 8.0, 2H); 4.27 (m, 6H); 3.89 (t, ^3J = 6.1, 2H);

3.74 (t, ^3J = 8.0, 2H); 3.60 (t, ^3J = 6.6, 2H); 3.53 (t, ^3J = 7.9, 2H); 2.99 (m, 4H); 2.46 (m, 5H); 2.28 (m, 5H); 1.31 (m, 36H); 1.11 (m, 18H); 0.60 (d, ^3J = 6.4, 6H); 0.13 (d, ^3J = 6.5, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 166.9; 164.3; 164.1; 163.4; 163.2; 163.0; 163.0; 162.9; 161.9; 161.7; 161.3; 159.9; 157.7; 154.7; 153.9; 153.1; 152.5; 150.6; 150.4; 149.2; 148.9; 148.2; 147.4; 147.4; 138.6; 138.0; 137.8; 136.7; 136.5; 134.6; 134.0; 133.4; 133.2; 132.3; 131.6; 127.2; 126.5; 126.4; 122.8; 121.7; 121.2; 118.6; 118.2; 116.5; 116.2; 115.9; 115.7; 115.5; 115.3; 114.9; 113.8; 113.7; 112.6; 107.7; 107.5; 100.9; 98.7; 98.5; 98.4; 97.0; 76.1; 76.8; 75.3; 75.2; 75.1; 28.6; 28.5; 28.4; 28.2; 27.4; 23.9; 19.6; 19.5; 19.4; 19.4; 19.0; 18.1. MS (MALDI): *m/z* calcd for $C_{166}H_{161}N_{34}O_{24}$ $[M+H]^+$: 3002.2504 found 3002.05.

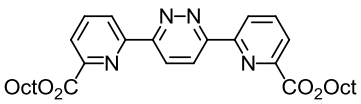
In situ chemical reduction of pyridazine casule **2** to give pyrrole capsule **3** :

To a solution of capsule pyridazine **2** (4.98 mmol, 0.015 g,) in glacial acetic acid (1 mL) heated at reflux was added activated zinc (99 mmol, 0.0065 g) the reaction was stirred at this temperature for 4 hours. After cooling to R.T., the mixture was filtered through a pad of celite which was washed with MeOH (10 mL) and concentrated. After flash chromatography (SiO_2) eluting with PE:EtOAc:DCM 60:30:10 (vol/vol), the capsule **3** was obtained as a yellow powder (50 %, 0.007 g).



4

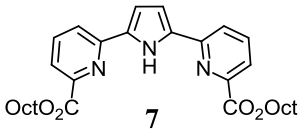
Compound 4. Dioctyl 6,6'-(1*H*-pyrrol-2,5-diyl)bis-2-pyridinecarboxylate **7** (0.11 mmol, 0.06 g) was dissolved in MeOH (5 mL) and H_2O (1 mL) and was added a solution of KOH (0.45 mmol, 0.025 g) dissolved in H_2O (0.5 mL per mmol of starting material). After 4 hours at reflux, the crude was concentrated and the residue was treated with H_2O and aqueous 2N HCl solution until a pH value of 3 was obtained. After addition of MeOH, a precipitate was formed. The solid was washed consecutively with MeOH, H_2O and Et_2O and dried under vacuum. The compound **4** was obtained as a yellow powder (85%, 0.029 g). m.p. 301°C; ^{1}H NMR (300 MHZ, DMSO-d_6) δ = 13.08 (br, 2H, OH); 11.90 (br, 1H, NH); 8.11 (d, ^3J = 7.8, 2H); 8.01 (t, ^3J = 7.8, 2H); 7.87 (d, ^3J = 7.8, 2H); 7.07 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.8; 149.7; 147.1; 138.5; 132.2; 122.3; 121.5; 111.3; IR: ν = 3415 cm^{-1} (NH), 1732 cm^{-1} (C=O); MS (EI, 70eV): m/z (%): 309 (40) [M^+], 265 (41) [M^+ - (2OH)], 221 (100) [M^+ - ($2CO_2H$)], HRMS (ESI+): calcd. for $C_{16}H_{12}N_3O_4$ $[M + H]^+$ 309.0750; found 309.0751.



6

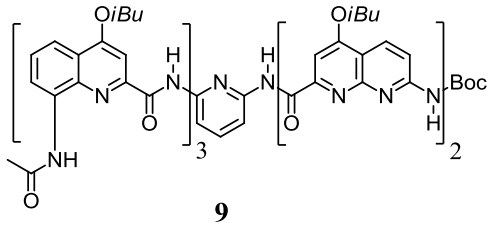
Compound 6. 6,6'-(pyridazin-3,6-diyl)bis-2-pyridylcarboxylic acid **5**[1] (2.79 mmol, 0.90 g) was dissolved in $SOCl_2$ (8 mL) and the mixture was refluxed during 18 hours. After elimination of thionyl chloride by distillation under vacuum, the obtained dipicolinyl chloride was dissolved in DCM (5 mL). After

cooling to 0 °C, triethylamine (16.77 mmol, 2.3 mL) and the desired alcohol (8.38 mmol, 1.3 mL) were successively added and the mixture was stirred at R.T. under inert atmosphere until total consumption of the corresponding dipicolinyl chloride. The mixture was diluted in DCM, washed with water, dried over Na_2SO_4 and concentrated. After flash chromatography (SiO_2) eluting with DCM:MeOH (95:5 vol/vol), the compound **6** was obtained as a white powder (88%, 1.3 g). m.p. 89°C; ^{1}H NMR (300 MHZ, $CDCl_3$) δ ppm = 8.94 (d, ^3J = 7.8, 2H); 8.85 (s, 2H); 8.20 (d, ^3J = 7.8, 2H); 8.05 (t, ^3J = 7.8, 2H); 4.44 (t, ^3J = 6.8, 4H, CH_2); 1.89 - 1.77 (m, 4H, CH_2); 1.51 - 1.29 (m, 20H, CH_2); 0.87 (t, ^3J = 6.6, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm =165.1; 157.9; 153.7; 148.4; 138.3; 126.1; 125.8; 124.7; 66.3; 31.9; 29.5; 29.4; 28.8; 26.1; 22.8; 14.2; IR: ν = 1716 cm^{-1} (C=O); MS (EI, 70eV): m/z (%): 546 (100) [M$^+$], 433(20) [M$^+$ - (C_8H_{17})], 232 (58) [M$^+$ - ($2C_9H_{17}O_2$)], HRMS (ESI+): calcd. for $C_{32}H_{42}N_4NaO_4$ [M + Na]$^+$ 569.3098; found 569.3096.



7

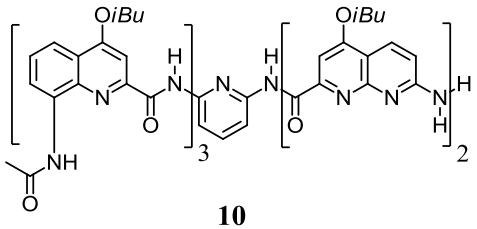
Compound 7. A solution of dioctyl 6,6'-(pyridazin-3,6-diyl)bis-2-pyridinecarboxylate **6** (0.44 mmol, 0.242 g) was dissolved in THF/acetate buffer/CH_3CN (5/4/1, 100 mL), introduced into the cathodic compartment of the electrochemical cell and reduced at E_w = -1.15 V/SCE. Prior to and during electrolysis at E_w, the catholyte was deaerated with argon and stirred magnetically. The course of the reaction was followed by cyclic voltammetry in the cathodic compartment and the electrolysis was stopped when the consumption of the starting substrate was completed. Then the solvents were partially evaporated, the aqueous phase was neutralized by addition of aqueous saturated Na_2CO_3 solution and extracted with DCM. The combined organic layers were dried (Na_2SO_4) and concentrated. After flash chromatography (SiO_2) eluting with PE:EtOAc (75:25 vol/vol), the compound **7** was obtained as a yellow powder (51%, 0.120 g). m.p. 68°C; ^{1}H NMR (300 MHZ, $CDCl_3$**)** δ ppm = 12.12 (br, 1H, NH); 7.85 (dd, J = 7.8 and 1.9, 2H); 7.79 (t, J = 7.8, 2H); 7.73 (dd, J = 7.8 and 1.9, 2H); 6.81 (d, J = 2.5, 2H); 4.42 (t, J = 6.8, 4H, CH_2); 1.90 - 1.80 (m, 4H, CH_2), 1.49 - 1.25 (m, 20H, CH_2); 0.87 (t, J = 6.6, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm = 165.6; 150.9; 147.7; 137.3; 133.7; 122.1; 121.9; 110.1; 66.3; 31.9; 29.5; 29.4; 28.8; 26.1; 22.8; 14.2; IR: ν = 3431 cm^{-1} (NH), 1728 cm^{-1} (C=O); MS (EI, 70eV): m/z (%): 533 (100) [M$^+$], 420 (7) [M$^+$ - (C_8H_{17})], 219 (33) [M$^+$ - ($2C_9H_{17}O_2$)], HRMS (ESI+): calcd. for $C_{32}H_{44}N_3O_4$ [M + H]$^+$ 534.3326; found 534.3321.



9

AcNH-Q$_3$PN$_2$-NHBoc (9). To a solution of H_2N-Q$_3$PN$_2$-NHBoc **8**[2] (0.23 mmol, 0.33 g) in dioxane (12 mL) was added acetic anhydride (2.3 mmol, 0.2 mL) and (2.3 mmol, 0.4 mL). After 12 hours at 60°C, the reaction mixture was let at RT. The volatiles were removed under reduced pressure to give a solid which

was dissolved in dichloromethane and washed with a saturated solution of $NaHCO_3$, distilled water and then with brine. The organic layers were dry over Na_2SO_4 then the volatiles were removed under reduce pressure to give **9** as a pale yellow solid (96%, 0.33 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm = 12.41 (s, 1H); 12.25 (s, 1H); 11.03 (s, 1H); 10.36 (s, 1H); 9.91 (s, 1H); 9.84 (s,1H); 9.45 (d, ^3J = 7, 1H); 9.11 (s, 1H); 8.96 (s, 1H); 8.76 (m, 2H); 8.62 (m, 3H); 8.18 (d, ^3J = 7.8, 1H); 8.09 (d, ^3J = 7.6, 1H); 7.87 (m, 3H); 7.74 (m, 4H); 7.31 (s, H); 7.21 (t, ^3J = 8.2, 1H); 6.98 (d, ^3J = 7.4, 1H); 6.87 (s,1H); 6.81 (t, ^3J = 7.9, 1H); 4.14 (m, 7H); 3.87 (m, 3H); 2.39 (m, 5H); 1.91 (m, 3H); 1.83 (s, 9H); 1.19 (m, 24H); 0.71 (d, ^3J = 6.5, 3H); 0.52 (d, ^3J = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm = 167.1; 164.7; 164.2; 164.0; 163.9; 163.6; 163.3; 161.7; 161.5; 160.2; 156.9; 155.0; 154.3; 153.9; 153.6; 153.1; 152.1; 151.3; 150.5; 149.3; 148.4; 147.9; 140.2; 138.6; 138.3; 136.9; 134.3; 134.3; 134.1; 133.5; 133.4; 127.7; 126.8; 123.0; 122.2; 122.0; 117.7; 117.4; 116.7; 116.2; 115.9; 115.9; 114.8; 114.8; 114.2; 109.4; 108.6; 102.7; 99.1; 98.4; 98.2; 98.0; 81.7; 77.3; 75.8; 75.7; 75.5; 75.3; 28.7; 28.3; 28.2; 28.0; 24.5; 19.5; 19.4; 19.3; 19.3; 19.2; 18.6. HRMS (MALDI): *m/z* calcd for $C_{80}H_{85}N_{15}O_{13}$ $[M+Na]^+$ 1486.63490 found 1486.63151.



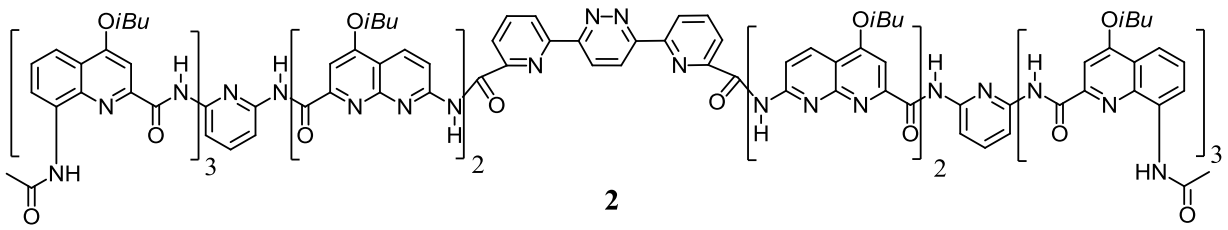
10

AcNH-Q$_3$PN$_2$-NH$_2$ (10). Trifluoroacetic acid (0.2 mL) was added drop wise to a solution of **9** (0.07 mmol, 0.1 g) in 1 mL of chloroform under nitrogen at RT. Then, the resultant mixture was stirred at RT for 4 hours. The volatiles were removed under reduced pressure to give a solid which was dissolved in dichloromethane and washed with a saturated solution of $NaHCO_3$, distilled water and then with brine. The organic layers were dry over Na_2SO_4 then the volatiles were removed under reduce pressure to give the amine derivative **10** as pale yellow solid (97%, 0.093 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm = 12.35 (s, 1H); 12.22 (s, 1H); 11.36 (s, 1H); 9.79 (s, 1H); 9.78 (s, 1H); 9.14 (d, ^3J = 7.3, 1H); 9.08 (s, 1H); 8.77 (m, 2H); 8.64 (s, 1H); 8.60 (d, ^3J = 7.4, 1H); 8.30 (d, ^3J = 8.9, 1H); 8.24 (d, ^3J = 7.6, 1H); 7.84 (m, 5H); 7.71 (t, ^3J = 8.0, 1H); 7.54 (s, 1H); 7.28 (m, 2H); 7.21 (t, ^3J = 8.1, 1H); 7.03 (d, ^3J = 8.2, 1H); 6.89 (m,2H); 6.75 (t, ^3J = 8.1, 1H); 6.31 (br, 2H); 4.59 (br, 1H); 4.20 (m, 3H); 4.05 (m, 3H); 3.91 (d, ^3J = 6.4, 2H); 3.77 (t, ^3J = 8.5, 1H); 2.36 (m, 5H); 1.87 (s, 3H); 1.19 (m, 24H); 0.70 (d, ^3J = 6.1, 3H); 0.48 (d, ^3J = 6.3, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm = 167.4; 164.6; 164.1; 164.0; 163.8; 163.6; 163.3; 162.5; 161.8; 160.6; 156.5; 154.8; 154.2; 153.5; 151.2; 150.7; 150.6; 149.7; 148.9; 147.9; 140.4; 138.7; 138.2; 137.1; 134.5; 134.4; 134.2; 133.7; 132.6; 128.0; 127.0; 126.8; 123.0; 122.2; 122.1; 117.7; 117.2; 116.7; 116.4; 116.0; 116.0; 115.0; 114.6; 113.8; 111.0; 109.9; 109.0; 102.1; 99.1; 98.7; 98.1; 77.4; 76.0; 75.6; 75.4; 28.5; 28.4; 28.2; 27.9; 24.5; 19.6; 19.5; 19.4; 19.3; 18.6. HRMS (ES$^+$): *m/z* calcd for $C_{75}H_{77}N_{15}O_{11}$ $[M+H]^+$: 1364.60052 found 1365.59850.

References

1. Y. Ferrand, A. M. Kendhale, B. Kauffmann, A. Grélard, C. Marie, V. Blot, M. Pipelier, D. Dubreuil, I. Huc, *J. Am. Chem. Soc.* **2010**, 23, 7858.
2. Y. Ferrand, C. Nagula, A. M. Kendhale, C. Aube, B. Kauffmann, A. Grélard, M. Laguerre, D. Dubreuil, I. Huc, *J. Am. Chem. Soc*. **2012**, 134, 11282-11288.

^{1}H NMR spectra of all relevant synthetic intermediates and title compounds.



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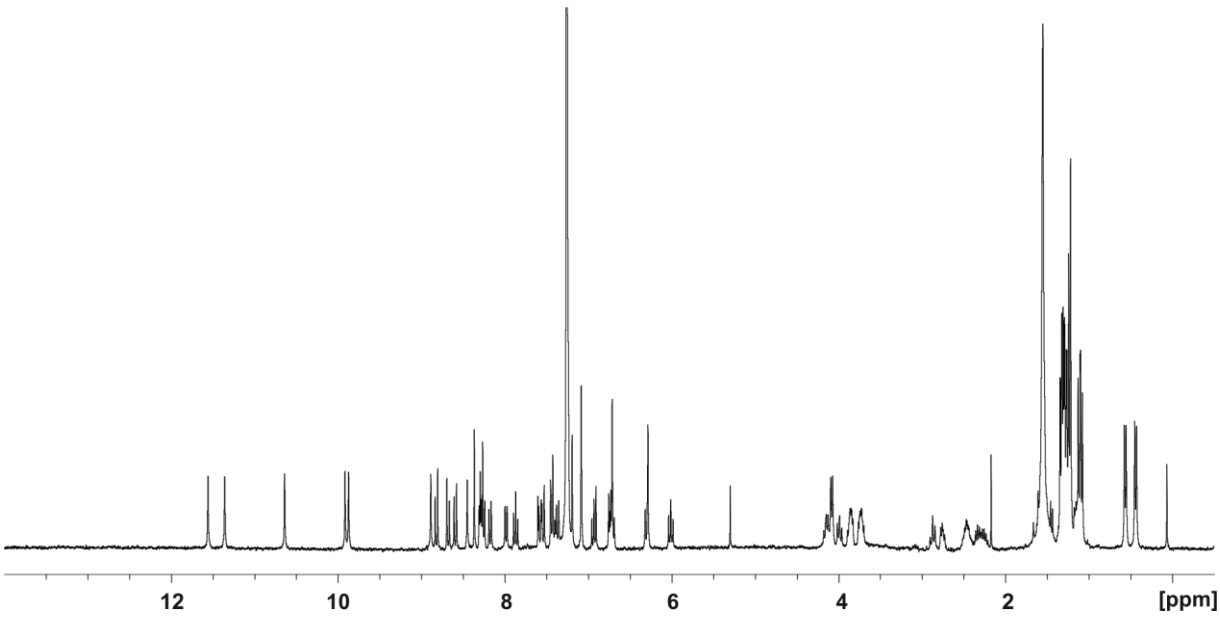

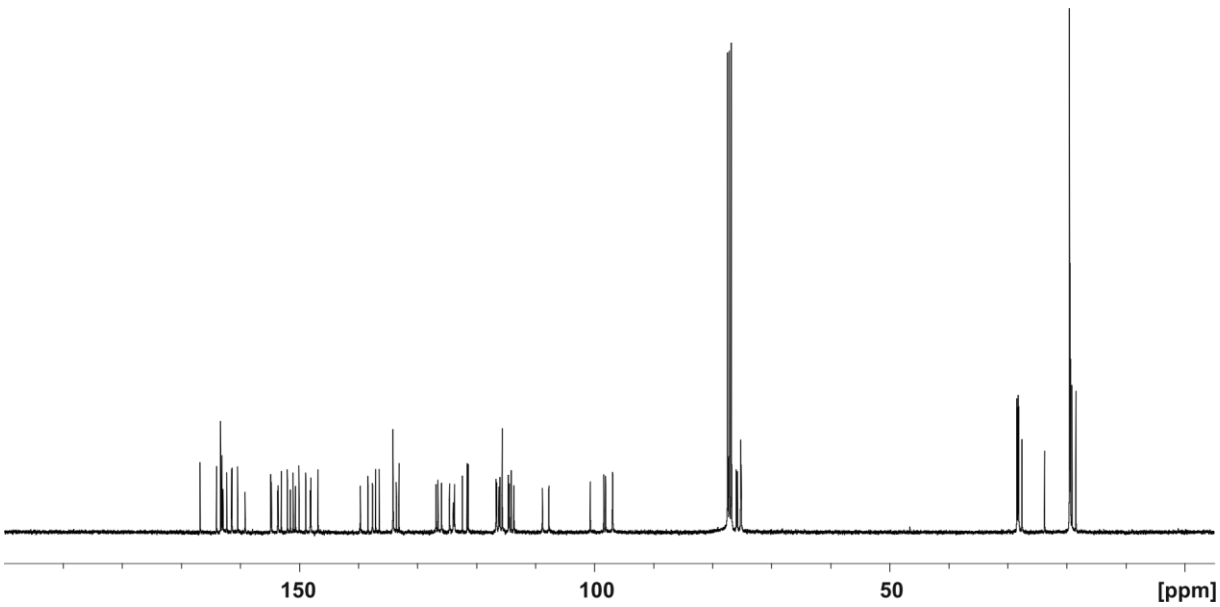

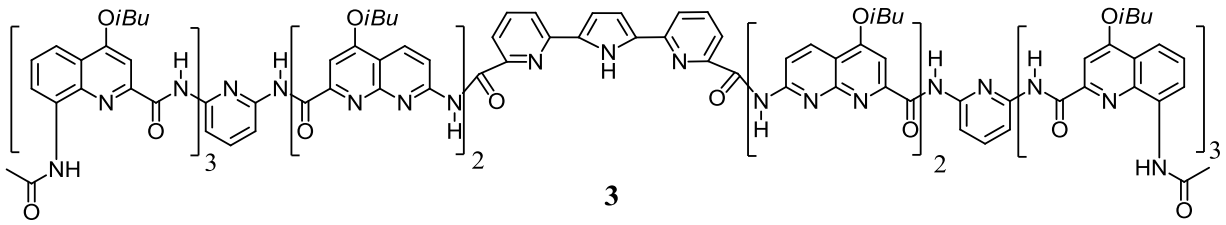

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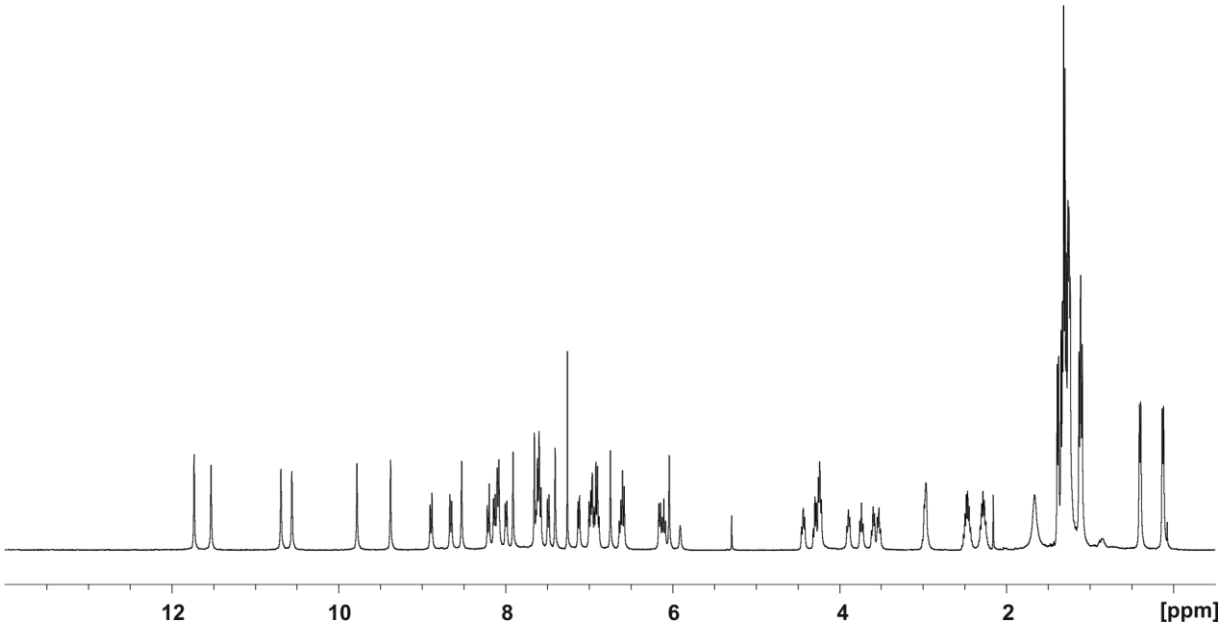
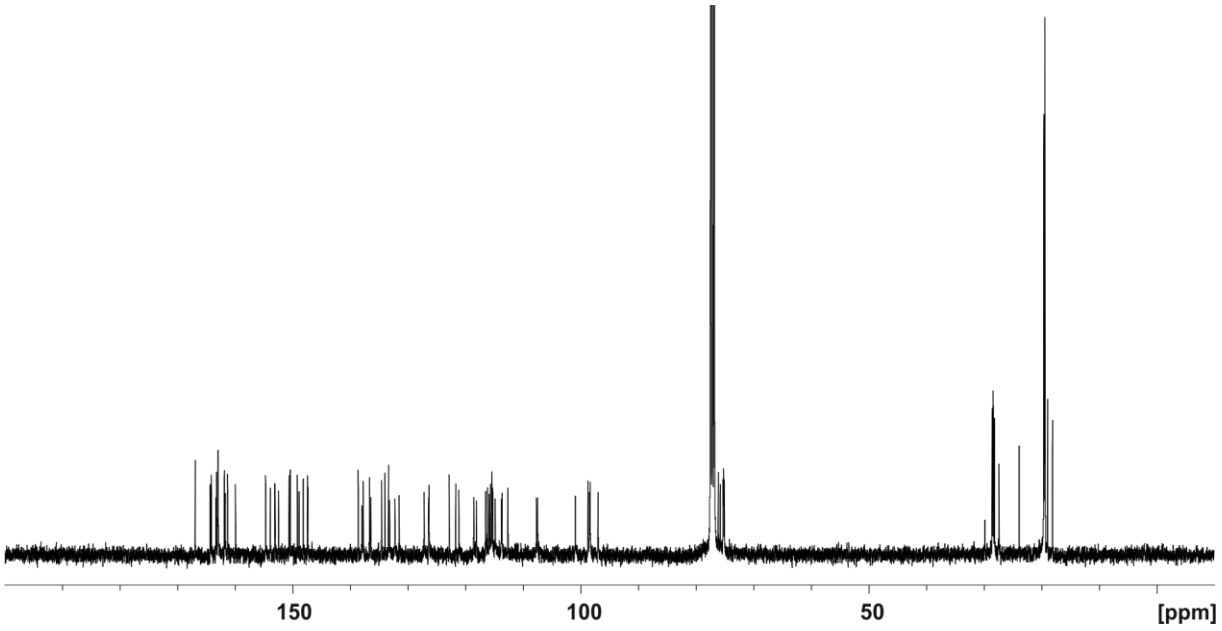
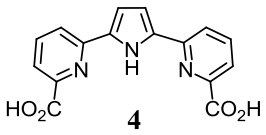
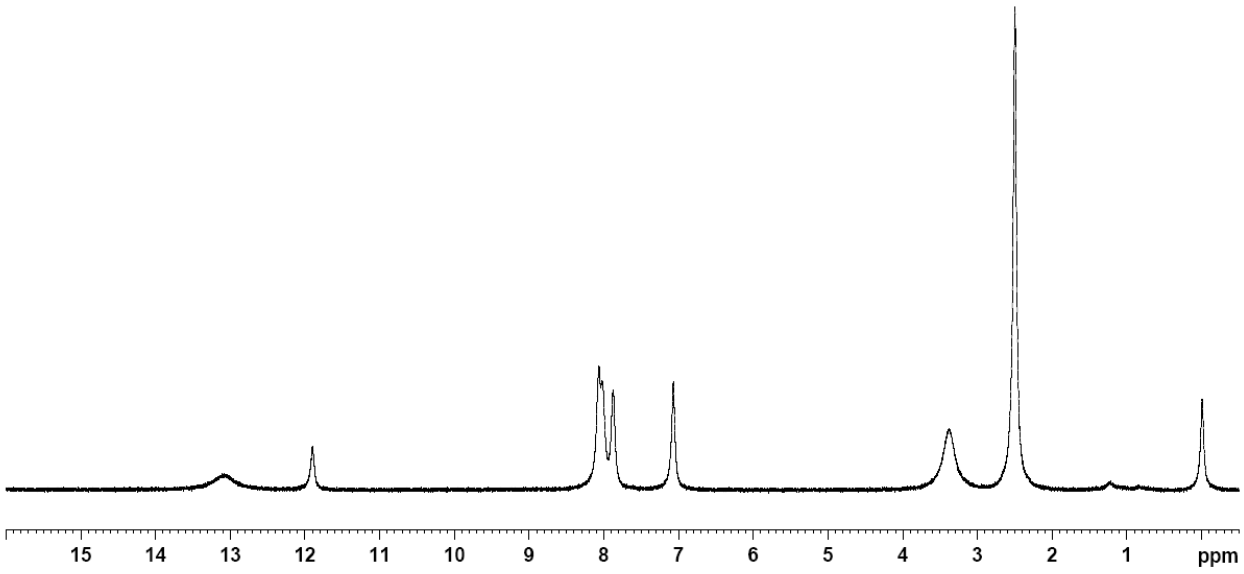
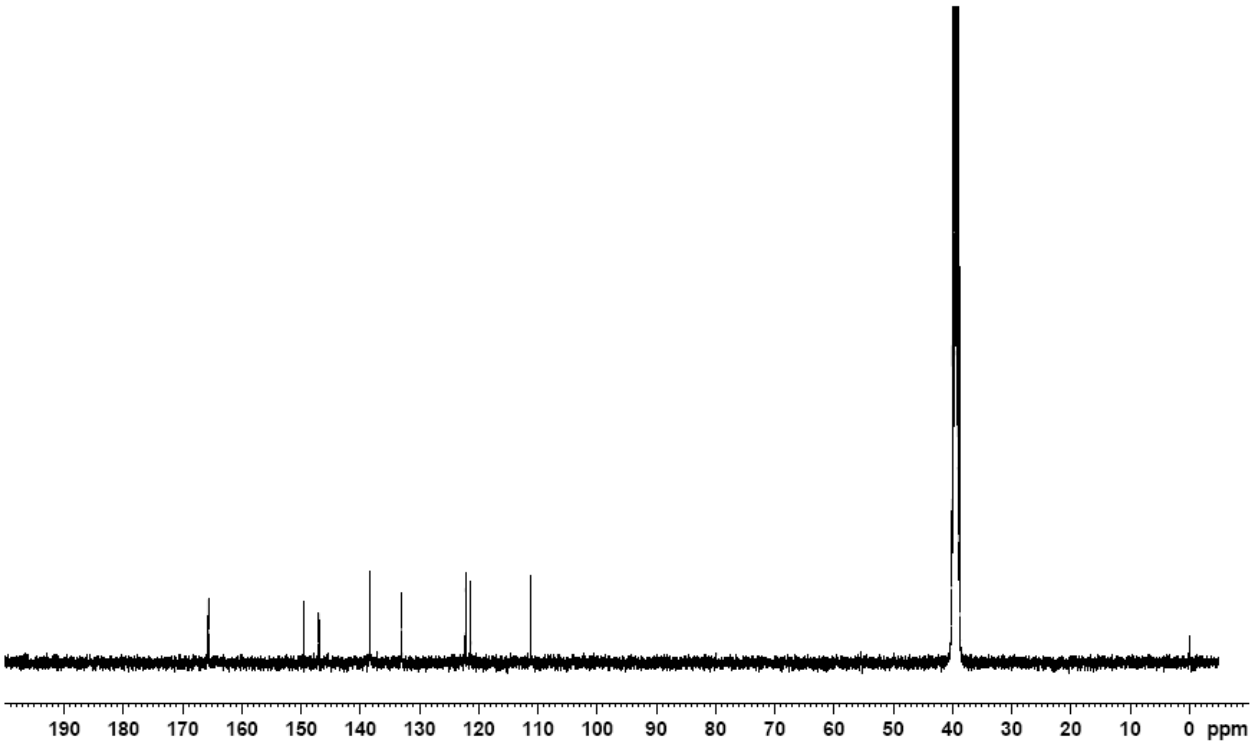


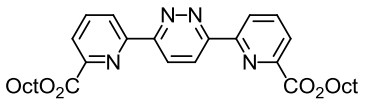



N
H
N
HO2C
CO2H

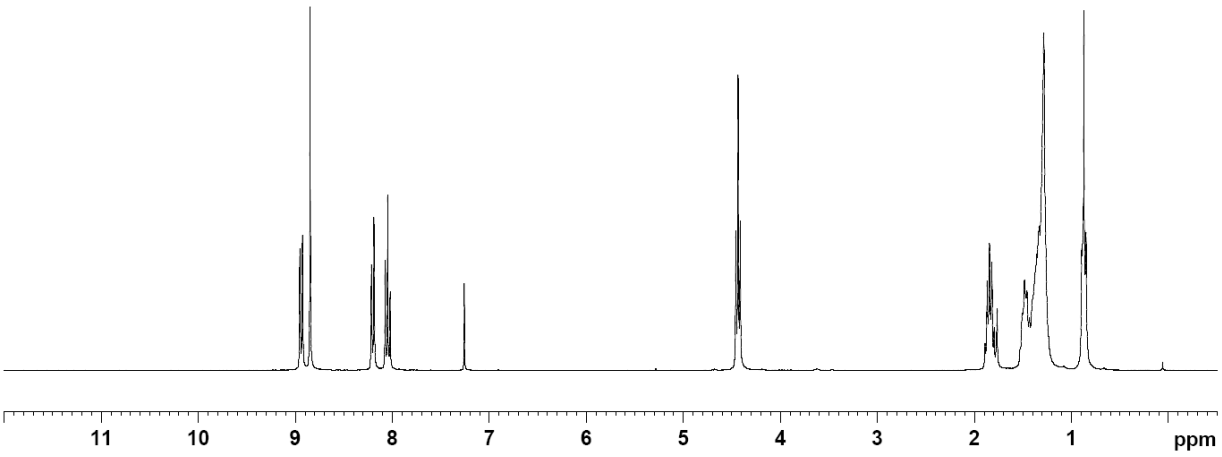
4

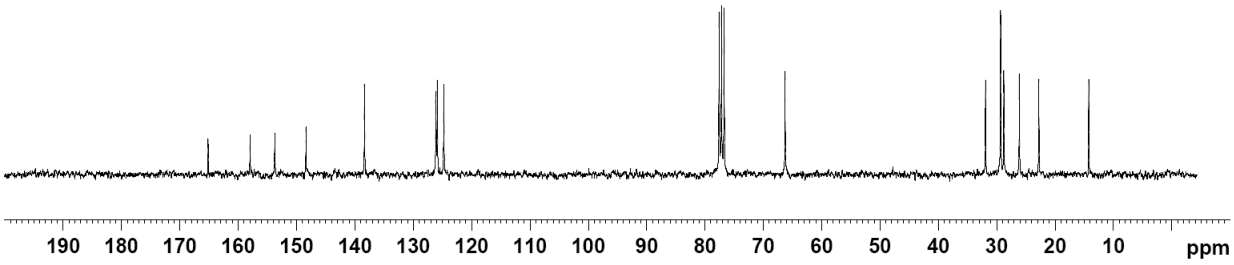

15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm


N–N
N
N
OctO2C
CO2Oct

6


11
10
9
8
7
6
5
4
3
2
1
ppm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180
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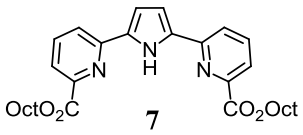
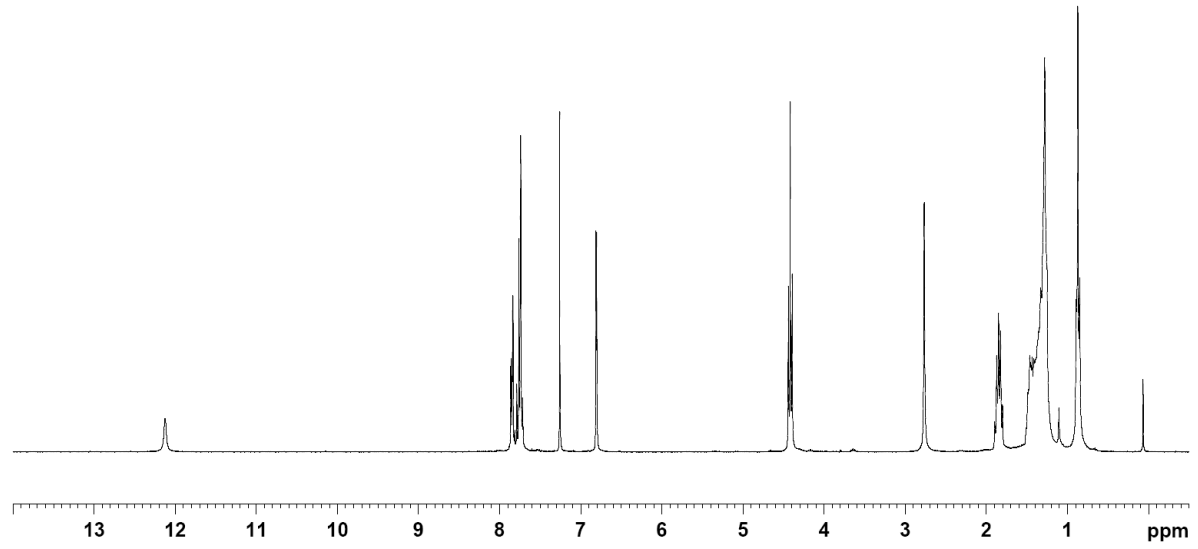
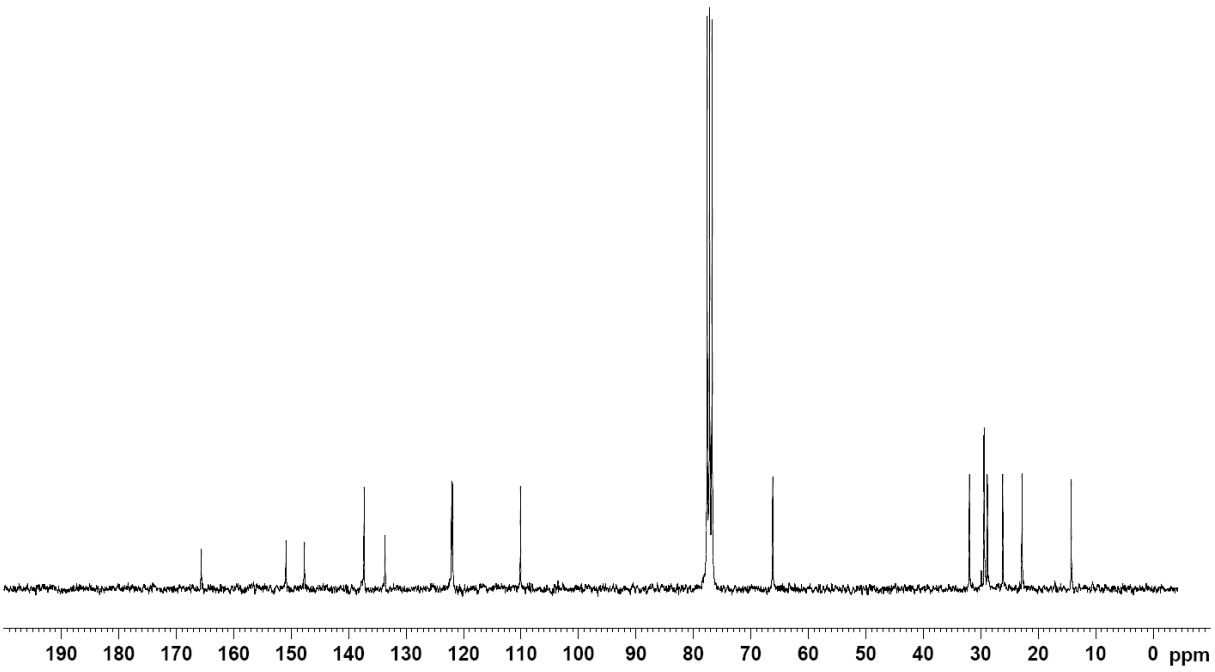
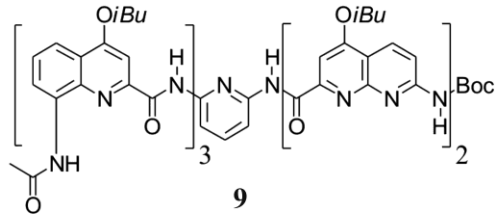
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


N
H
N
OctO2C
CO2Oct

7

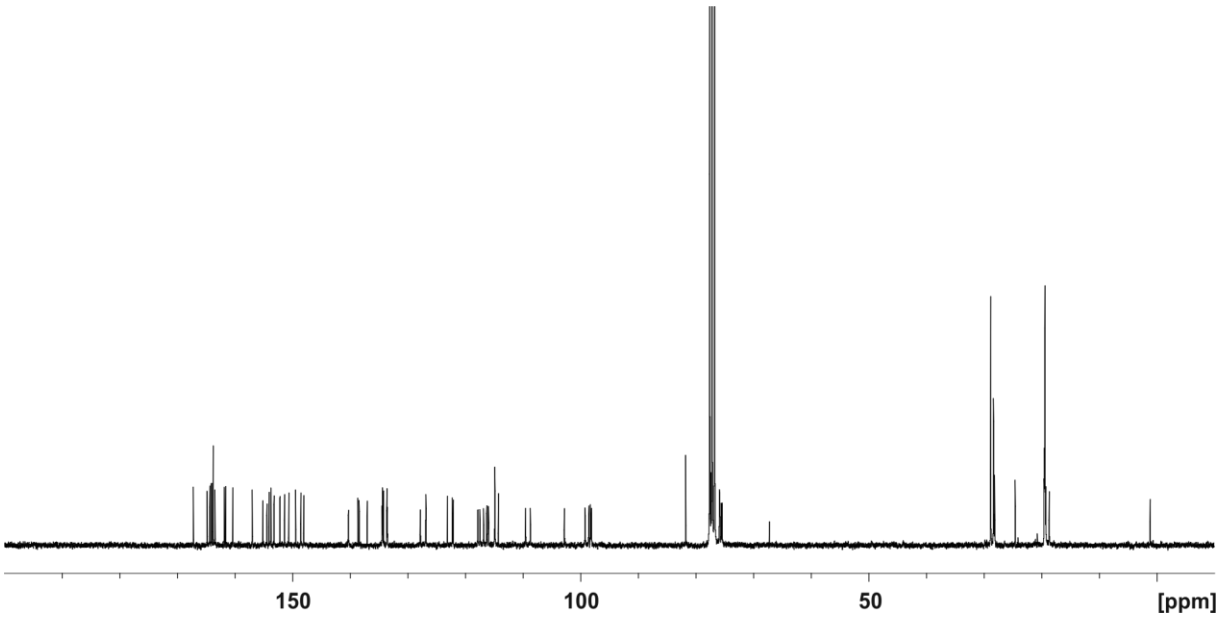

13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

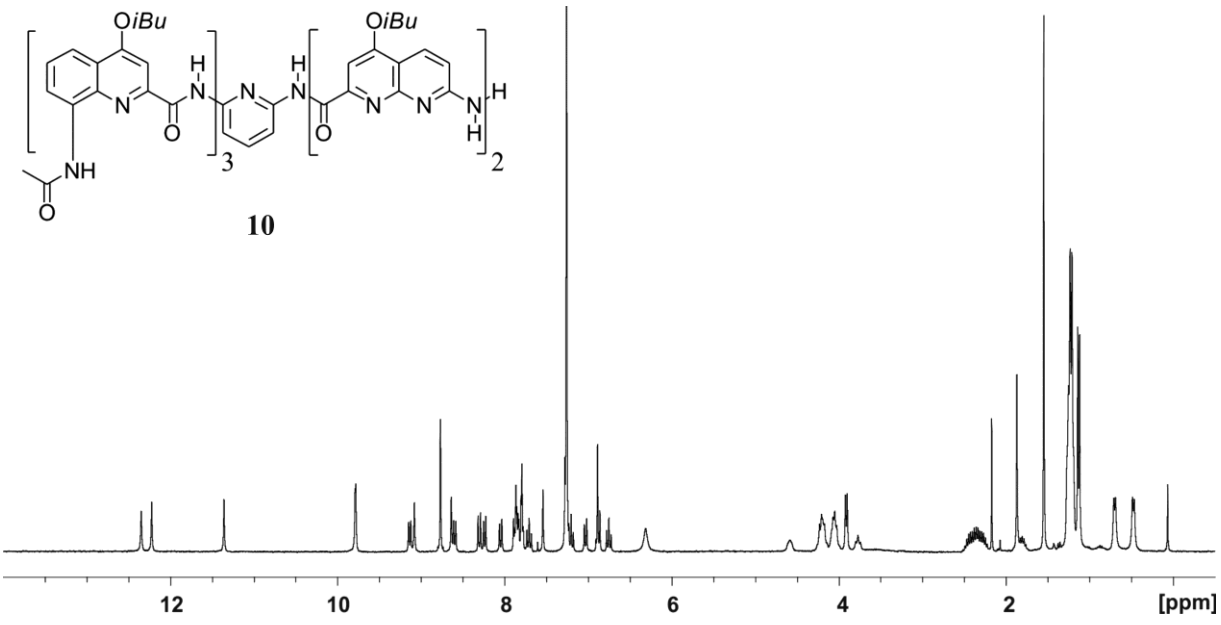

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm


OiBu
OiBu
H
N
N
H
N
N
N
N
N
Boc
H
O
O
NH
O
3
2

9

12
10
8
6
4
2
[ppm]


150
100
50
[ppm]



10