Supporting Information

Assessing Stabilization Through π-π Interactions in Aromatic Oligoamide β-Sheet Foldamers.

Laure Sebaoun,[†,¶] Brice Kauffmann,[‡,#,§] Thomas Delclos,[†,¶] Victor Maurizot,[†,¶] and Ivan Huc*[,†,¶]

† Univ. Bordeaux, CBMN (UMR 5248), Institut Européen de Chimie Biologie, 2 rue Escarpit 33600 Pessac, France

¶ CNRS, CBMN (UMR 5248), France

‡ Univ. Bordeaux, IECB (UMS 3033/US 001), 2 rue Escarpit, 33600 Pessac, France

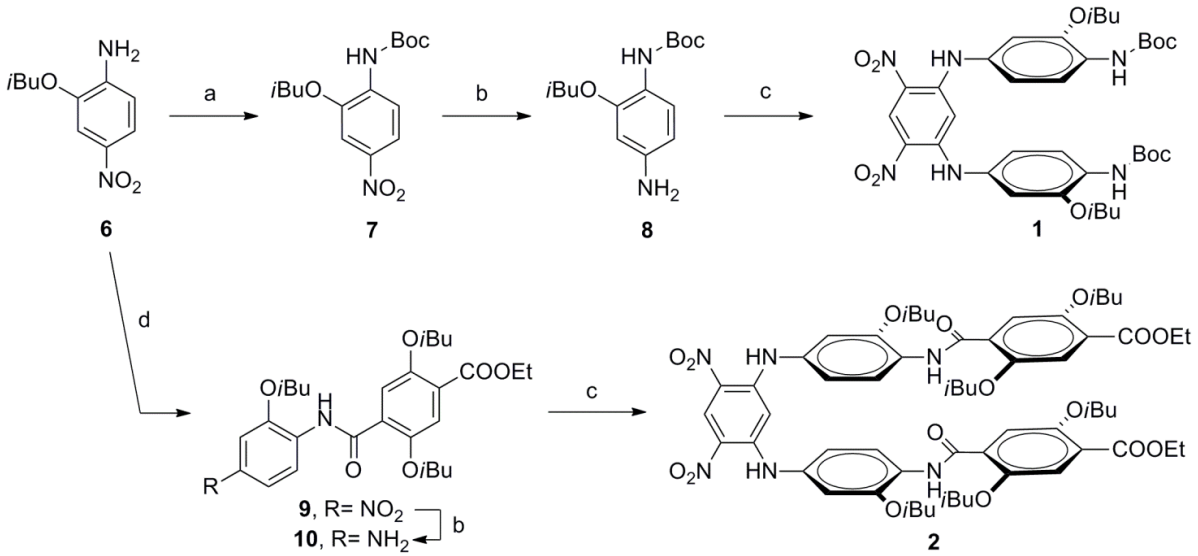
 # CNRS, IECB (UMS 3033), France

§ INSERM, IECB (US 001), France

Table of contents

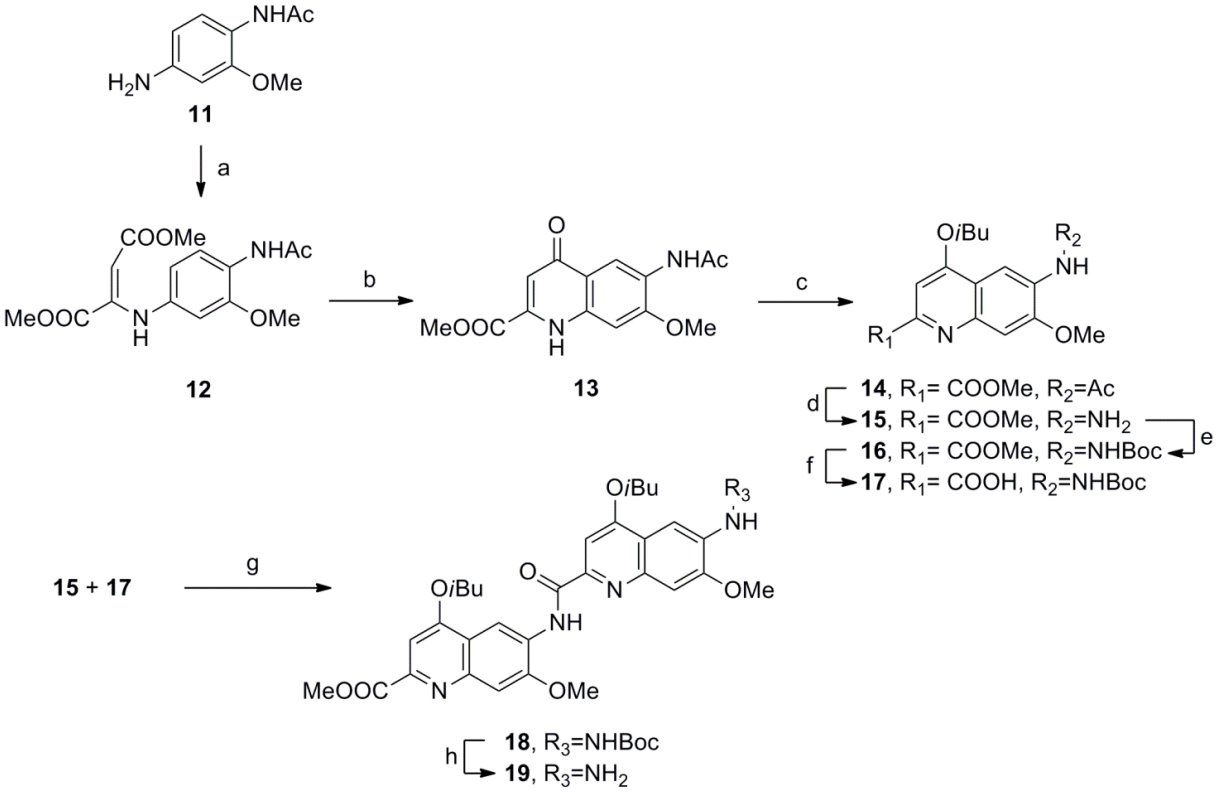
1. Synthetic schemes

Preparation of compounds 1 and 2



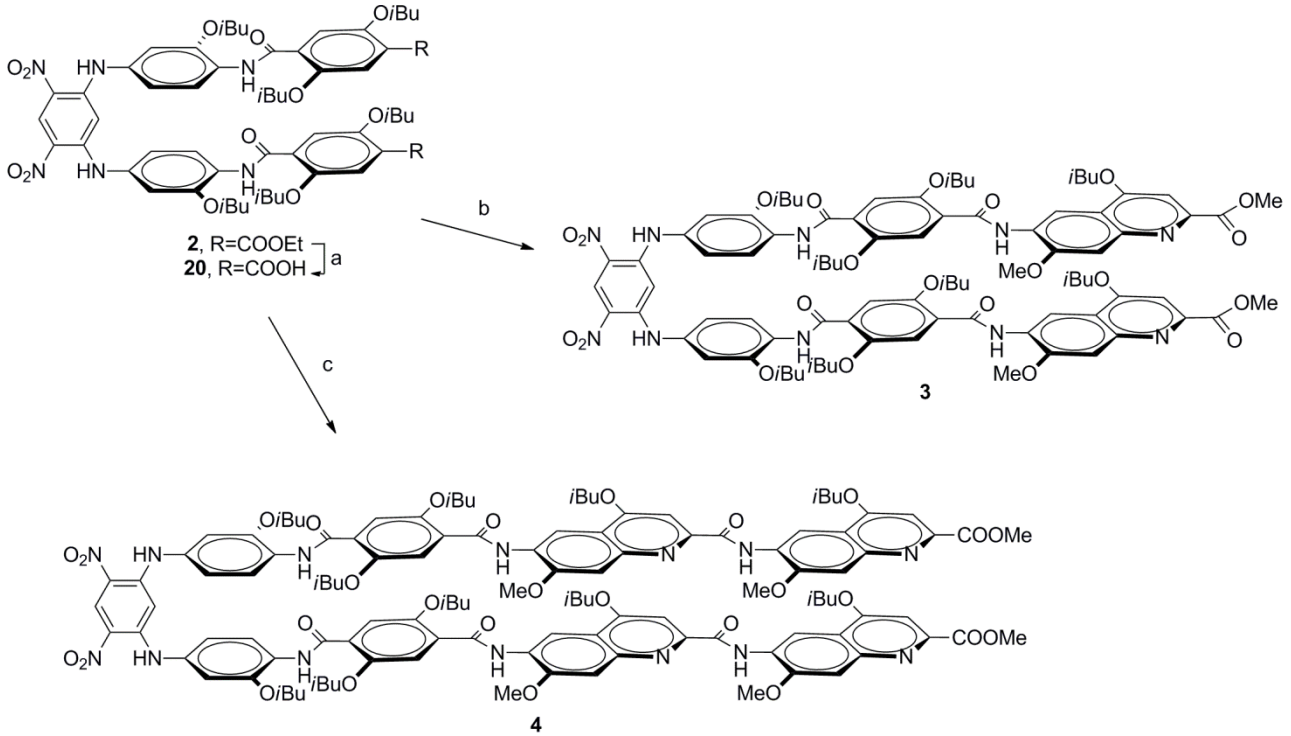
Reagents and conditions: a) 3 equiv. Boc_2O, THF, +70 °C, 8 days, 39%. b) H_2, 10% Pd/C, AcOEt, rt, 16h, 99% for **8**, 96% for **10**. c) 0.5 equiv. 1,5-difluoro-2,4-dinitrobenzene, DMSO, 4h, rt then 0.5 equiv. DIEA, DMSO, rt, 2 days, 86% for **1**, 72% for **2**. d) 0.9 equiv. 4-(ethoxycarbonyl)-2,5-diisobutoxybenzoic acid chloride, 1 equiv. DIEA, $CHCl_3$, 16h, rt, 71%.

Preparation of quinoline and quinoline dimers derivatives



Reagents and conditions: a) 1 equiv. dimethyl acetylenedicarboxylate, MeOH, rt, 3h then reflux, 1h, 90%. b) Ph_2O, 240-250 °C, 5 min, 91%. c) 1.5 equiv. K_2CO_3, DMF, 120 °C, 2h then 1.5 equiv. 1-iodo-2-methylpropane, 100 °C, 4h, 29%. d) 3 equiv. H_2SO_3, MeOH, rt, 16h, 49%. e) 3.5 equiv. Boc_2O, THF, +70 °C, 24h, 96%. f) 5 equiv. KOH, dioxane/H_2O 2.5:1, rt, 16h, 99%. g) 2 equiv. PyBOP, 3 equiv. DIEA, $CHCl_3$, +45 °C, 16h, 71%. h) 20% TFA/CH_2Cl_2, rt, 4h, 98%.

Preparation of compounds 3 and 4



Reagents and conditions: a) 5 equiv. KOH, dioxane/H_2O 7:1, rt, 24h, 96%. b) i. 10 equiv. $(COCl)_2$, $CHCl_3$, rt, 2h ii. 2 equiv. compound **15**, 2 equiv. NEt_3, $CHCl_3$, rt, 16h, 23%. c) 1.8 equiv. compound **19**, 8 eq. PyBOP, 11 eq. DIEA, +45 °C, $CHCl_3$, 24h, 16%.

2. NMR experiments

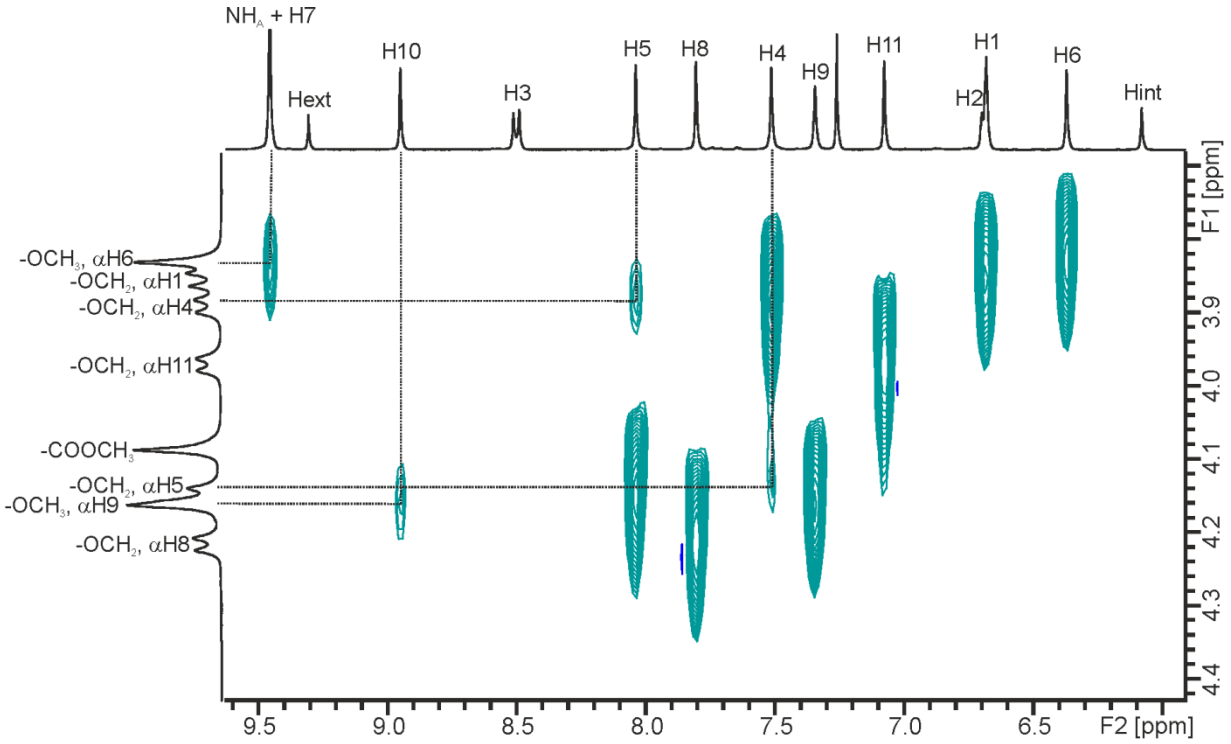


Figure S1. Excerpt of the 2D ROESY plot on 400MHz (τ_m = 300 ms) at +25 °C in $CDCl_3$ for nonamer **4**. Details on interstrand correlations.

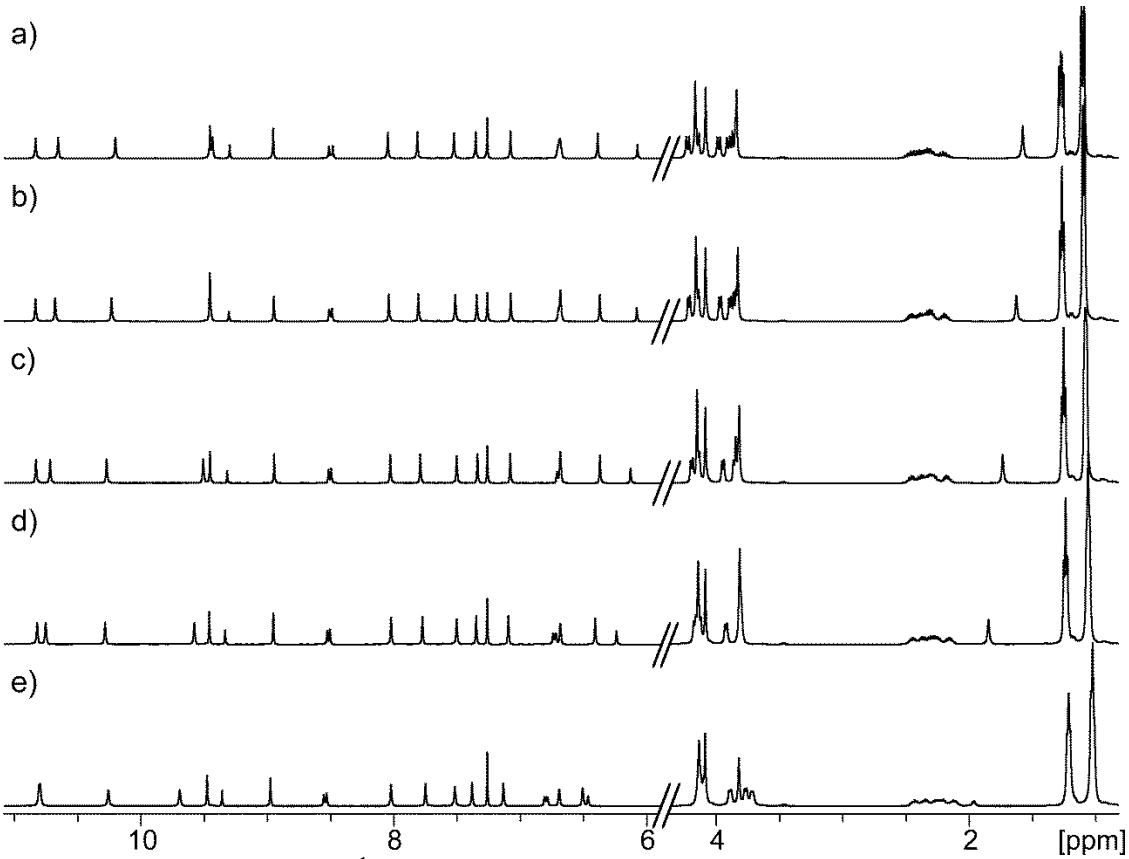


Figure S2. Parts of the 400 MHz ^{1}H NMR spectra in $CDCl_3$ of nonamer **4** a) at 313 K; b) at 298 K; c) at 273 K; d) at 248 K; and e) at 223 K.

3. Solution structure determination

Multi-dimentionnal NMR experiences (HSQC, HMBC, TOCSY et ROESY) allow complete structural assignment of three oligomers.[1]

- *Experimental conditions:*

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 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.

TOCSY. Total Correlation Spectroscopy (TOCSY) experiments were recorded at 400 MHz or at 700 MHz. They were used to identify protons of oligomer that belong to the same whole spin system regardless of the exact topology with the following acquisition parameters: the acquisition was performed with 2048(t_2) × 256(t_1) data points, relaxation delay of 2 s, and 32 scans per increment. Processing was done after a sine-bell multiplication in both dimensions and Fourier transformation in 1K x 1K real points.

HSQC. Heteronuclear Single-Quantum Correlation spectroscopy (HSQC) experiments were recorded at 400 MHz or at 700 MHz. They were used to observe correlations between nuclei of two different types which are separated by one bond with the following acquisition parameters: the acquisition was performed with 2048(t_2) × 256(t_1) data points, relaxation delay of 2 s, and 64 scans per increment. Processing was done after a sine-bell multiplication in both dimensions and Fourier transformation in 1K x 1K real points.

HMBC. Heteronuclear Multiple Bond Correlation spectroscopy (HMBC) experiments were recorded at 400 MHz or 700 MHz. They were used to detect heteronuclear correlations over longer ranges of about 2–4 bonds with the following acquisition parameters: the acquisition was performed with 2048(t_2) × 256(t_1) data points, relaxation delay of 2 s, and 64 scans per increment. Processing was done after a sine-bell multiplication in both dimensions and Fourier transformation in 1K x 1K real points.

ROESY. Rotating-frame Overhauser Spectroscopy (ROESY) experiments were recorded at 400 or 700 MHz and were used to observe dipolar interactions between protons with the following acquisition parameters: the acquisition was performed with 2048(t_2) × 256(t_1) data points, in States-TPPI mode with CW-spinlock for mixing, relaxation delay of 1.5 s, and 90 scans per increment, mixing time of 300 ms. Processing was done after a sine-bell multiplication in both dimensions and Fourier transformation in 1K x 1K real points.

- *Nonamer, **4** :*

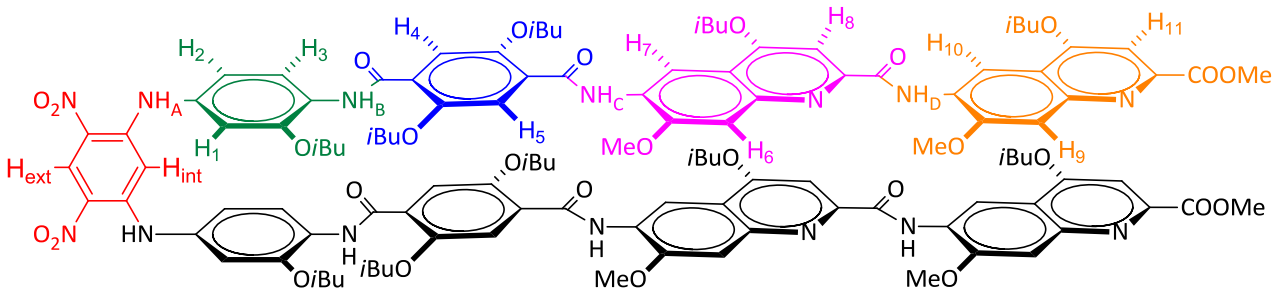


Table S1 : ^{1}H and ^{13}C chemical shifts for nonamer **4** in $CDCl_3$, 400 MHz, +25°C.

Proton	^{1}H Chemical Shift (ppm)	^{13}C Chemical Shift (ppm)
H_{ext}	9.31	129.11
H_{int}	6.08	96.85
NH_A	9.45	
H1	6.69	110.26
H2	6.69	118.85
H3	8.50	121.51
OiBu αH1 CH_2	3.85	75.92
OiBu αH1 CH	2.52-2.12	28.16
OiBu αH1 CH_3	1.10	19.42
$NHCO_B$	10.23	
H4	7.51	116.17
OiBu αH4 CH_2	3.89	76.61
OiBu αH4 CH	2.52-2.12	27.64
OiBu αH4 CH_3	1.27	19.66
H5	8.04	117.28
OiBu αH5 CH_2	4.15	77.25
OiBu αH5 CH	2.52-2.12	28.13
OiBu αH5 CH_3	1.09	19.55
$NHCO_C$	10.68	
OMe	3.83	55.59
H6	6.37	105.93
H7	9.45	110.75
H8	7.81	97.30
OiBu αH8 CH_2	4.22	75.45
OiBu αH8 CH	2.52-2.12	28.47
OiBu αH8 CH_3	1.27	19.66
$NHCO_D$	10.83	
OMe	4.16	56.54
H9	7.34	107.54
H10	8.95	108.82
H11	7.08	99.81
OiBu αH11 CH_2	3.97	74.80
OiBu αH11 CH	2.52-2.12	28.38
OiBu αH11 CH_3	1.27	19.71
COOMe	4.09	53.03

Table S2: HSQC and HMBC correlation for nonamer **4** in $CDCl_3$, 400 MHz, +25°C.

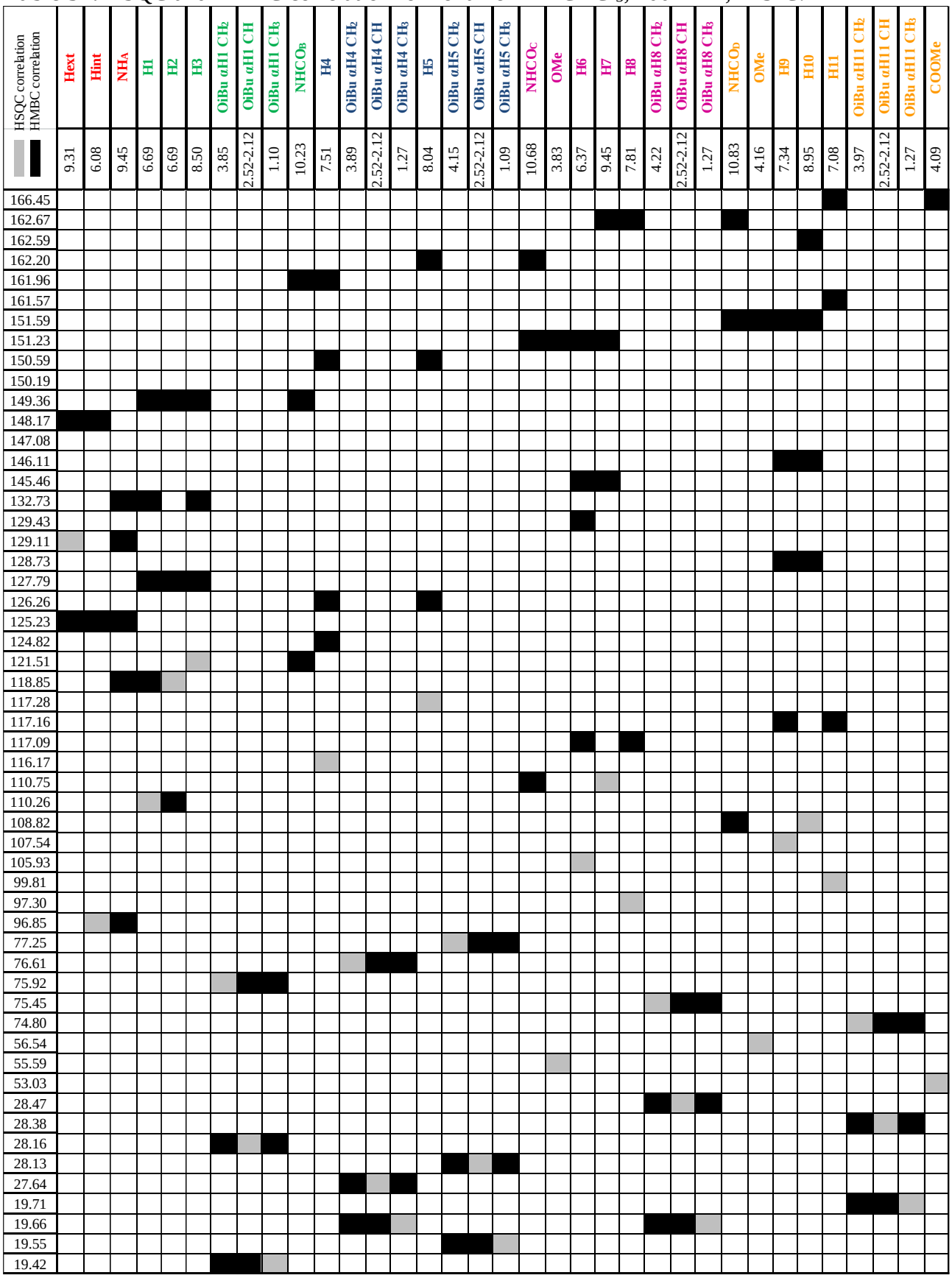
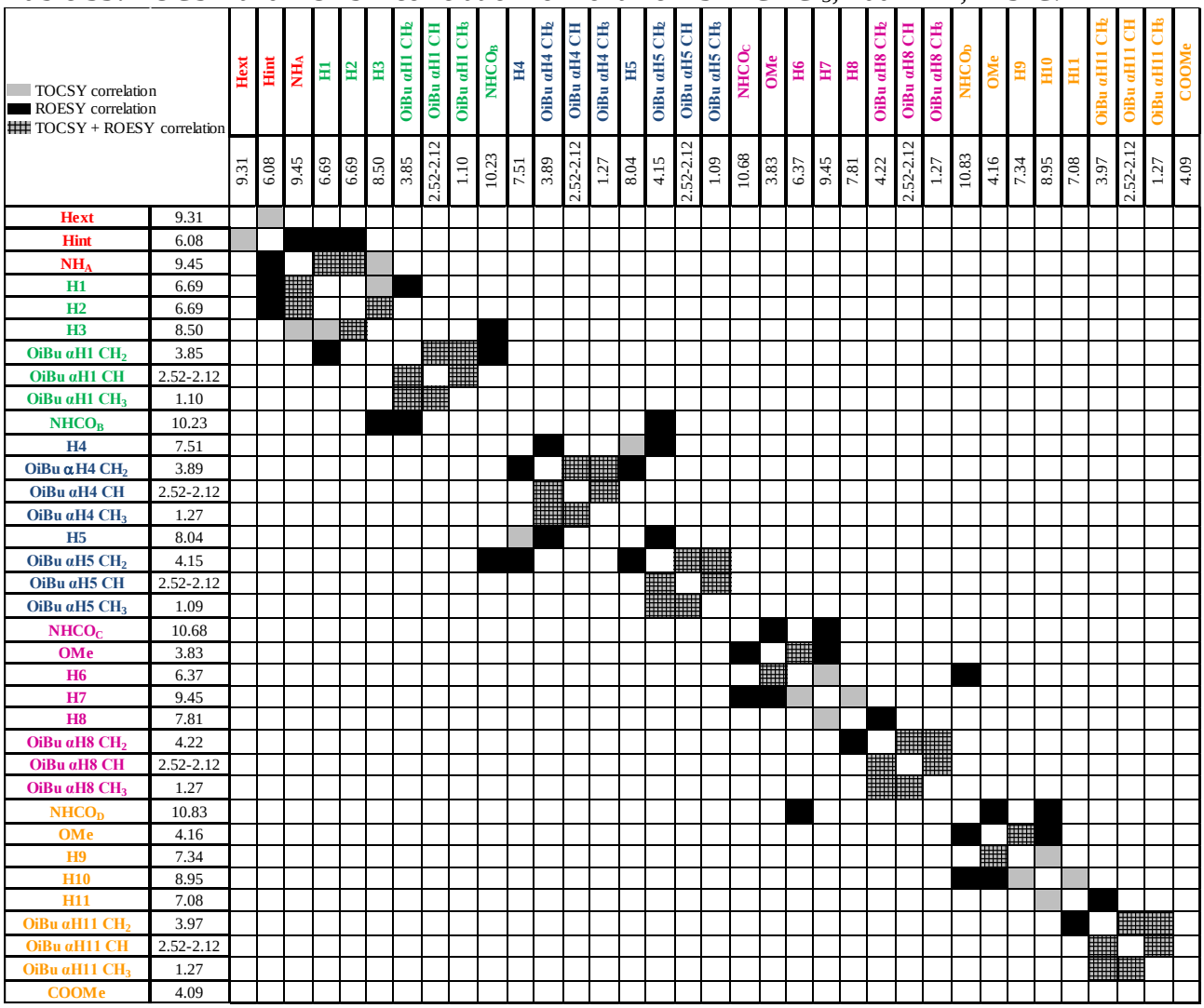


Table S3: TOCSY and ROESY correlation for nonamer **13** in $CDCl_3$, 400 MHz, +25°C.



4. Crystallography

4.1 Methods for X-ray crystallography

X-ray analyses were carried out at the IECB X-ray facility (UMS 3033 CNRS) on a R-Axis Rapid Rigaku MSC with a Cu Kα rotating anode and an image plate as detector at the copper K_α wavelength. Both crystals were collected at 213K and mounted on cryo-loops after quick soaking on Paratone—N oil from Hampton research before to be flash-frozen. The data were processed using the CrystalClear© suite[2]. Both structures were solved by direct methods using SHELXD or and refined using Shelxl2013[3] in the integrated WinGX system.[4] The positions of the H atoms were deduced from coordinates of the non-H atoms and confirmed by Fourier synthesis. The non-H atoms were mostly refined with anisotropic temperature parameters. Due to the modest quality of the data (low resolution and then low ratio parameters/data) some atoms on both structures were kept with isotropic U factors. H atoms were included for structure factor calculations but not refined. The BYPASS SQUEEZE procedure was tested to take into account the electron density in the potential disordered solvent area for the crystal structure of both compounds but no improvement was observed.[5] Finally, the non-modified structure factors were used to push the refinement as far as possible. Data statistics are shown in table S4.

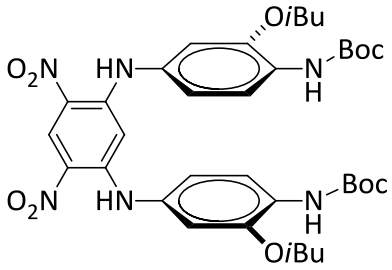
4.2 Summary of X-Ray crystallographic data

Table S4: X-ray crystallographic data.

Name	Pentamer, **2**	Nonamer, **4**
Formula	$C_{61.25}$ $H_{74.5}$ N_6 O_{16}	C_{121} H_{141} Cl_3 N_{14} O_{28}
M	1150.76	2345.82
Crystal system	P_{-1}	P_{-1}
Space group	Triclinic	Triclinic
***a*/Å**	10.604(2)	14.837(6)
***b*/Å**	23.472(5)	18.674(8)
***c*/Å**	27.553(6)	25.801(11)
α/o	77.89(3)	76.16(3)
β/o	83.86(3)	89.61(3)
γ/o	80.29(3)	72.57(3)
U/Å^3	6591(2)	6606(5)
T /*K*	213(2)	213(2)
Z	2	2
ρ/g cm^{-1}	1.160	1.179
Size (mm)	0.1x0.05x0.01	0.2 x 0.05 x 0.05
λ/ Å	1.54178	1.54178
μ/mm^{-1}	0.695	1.230
Unique data	20949	13278
Parameters / Restraints	59/1341	7 / 1376
Final R indices [I>2sigma(I)]	R1 = 0.22, wR2 = 0.4951	R1 = 0.1772, wR2 = 0.4005
Goodness of fit	1.498	1.128

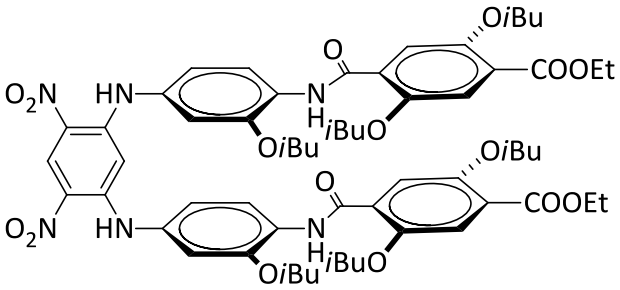
5. Experimental section

General. All reactions were carried out under a dry nitrogen atmosphere. Commercial reagents were purchased from Sigma-Aldrich, TCI Chemicals or Alfa-Aesar and were used without further purification unless otherwise specified. Tetrahydrofurane (THF) and dichloromethane (DCM) were dried over alumina columns; chloroform, triethylamine (Et_3N) and diisopropylethylamine (DIEA) were distilled over 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 chromatography purifications were carried out on Merck GEDURAN Si60 (40-63 µm). Circular chromatography purifications were carried out on Chromatotron® with silica gel, Merck grade 7749, TLC grade with binder and fluorescent indicator. NMR spectra were recorded on Bruker 300 Avance II, Bruker 400 DPX or Bruker Avance III 700 NB US. Chemical shifts are expressed in parts per million (ppm, δ) using residual solvent protons as internal standards (chloroform: δ 7.26 ppm; DMSO: δ 2.50 ppm). Coupling constants are expressed in Hertz. ESI and MALDI mass spectra were obtained on a Waters LCT Premier and a Bruker Reflex III spectrometers respectively, from the Mass Spectrometry Laboratory at the European Institute of Chemistry and Biology (UMS 3033 - IECB), Pessac, France and a Voyager DE-STR mass spectrometer from AB Sciex, Les Ulis, France. Melting points were obtained on a Büchi B-540 at the European Institute of Chemistry and Biology (UMS 3033 - IECB), Pessac, France.



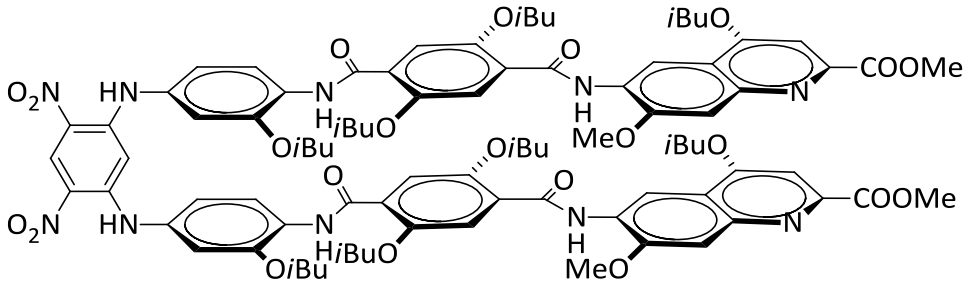
Hairpin turn trimer, 1. To compound **7** (0.46 g, 1.64 mmol) dissolved in DMSO (15 mL) was added 1,5-difluoro-2,4-dinitrobenzene (0.17 g, 0.82 mmol). After stirring for 4h at room temperature, distilled DIEA (143 µL, 0.82 mmol) was added. Then the reaction mixture was allowed to proceed at room temperature for 48h. After addition of water (30 mL), the mixture was filtered. The precipitate was solubilized in AcOEt and washed with H_2O. After evaporation, the residue was purified by chromatography (SiO_2) eluting with CH_2Cl_2/toluene (5:5, vol/vol) to obtain the product **1** as a yellowish solid (0.5 g, 86% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.70 (s, 2H), 9.32 (s, 1H), 8.04 (d, *J* = 8.5 Hz, 2H), 6.99 (s, 2H), 6.72 (dd, *J* = 8.6, 2.2 Hz, 2H), 6.68 (s, 1H), 6.60 (d, *J* = 2.2 Hz, 2H), 3.56 (d, *J* = 6.6 Hz, 4H), 2.09 (dt, *J* = 13.3, 6.7 Hz, 2H), 1.54 (s, 18H), 1.01 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.68, 147.78, 147.36, 131.36, 129.61, 127.20, 125.27, 118.74, 117.17, 108.28, 94.64, 80.75, 75.34, 28.49, 28.19, 19.35. HRMS (ES^+): m/z calcd for $C_{36}H_{49}N_6O_{10}$ $[M+H]^+$ 725.35047 found 725.35020, mp 194-195 °C.



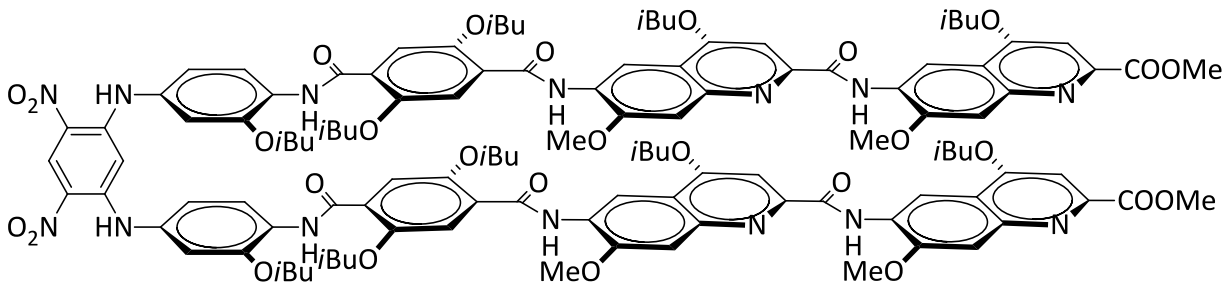
Hairpin turn pentamer, 2. To compound **9** (0.480 g, 0.96 mmol) dissolved in DMSO (10 mL) was added 1,5-difluoro-2,4-dinitrobenzene (0.098 g, 0.48 mmol). After stirring for 4h at room temperature, distilled DIEA (80 µL, 0.48 mmol) was added. Then the reaction mixture was allowed to proceed at room temperature for 48h. After addition of water (20 mL), the precipitate was filtered off, solubilized in AcOEt and washed with H_2O. After drying with $MgSO_4$ and evaporation, the residue was purified by chromatography (SiO_2) eluting with Cyclohexane/Ethyl acetate (9:1, vol/vol) to obtain the product **2** as a yellowish solid (0.404 g, 72% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.18 (s, 2H), 9.89 (s, 2H), 9.38 (s, 1H), 8.58 (d, *J* = 8.6 Hz, 2H), 7.77 (s, 2H), 7.40 (s, 2H), 6.93 (s, 1H), 6.85 (dd, *J* = 8.7, 2.1 Hz, 2H), 6.74 (d, *J* = 2.2 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 4H), 3.90 (d, *J* = 7.0 Hz, 4H), 3.81 (d, *J* = 6.4 Hz, 4H), 3.66 (d, *J* = 6.9 Hz, 4H), 2.18 – 1.88 (m, 6H), 1.40 (t, *J* = 7.2 Hz, 6H), 1.03 (d, *J* = 6.7 Hz, 12H), 0.94 (d, *J* = 6.7 Hz, 12H), 0.88 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz) : δ 166.35, 162.63, 152.77, 149.89, 149.12, 146.86, 133.03, 129.82, 126.87, 126.45, 125.51, 124.31, 122.03, 117.01, 116.63, 116.39, 107.98, 94.65, 75.87, 75.67, 61.55, 30.30, 29.84, 28.53, 28.03, 27.88, 27.03, 19.32, 19.24, 19.21, 14.45. HRMS (ES^-): *m/z* calcd for $C_{62}H_{79}N_6O_{16}$ $[M-H]^-$ 1163.5553 Found 1163.5559, mp 95-97 °C.



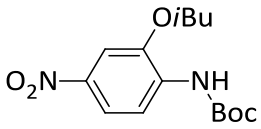
Hairpin turn heptamer, 3. Compound **19** (0.029 g, 0.026 mmol) was suspended in anhydrous $CHCl_3$ (0.5 mL). Oxalyl chloride (20 μL, 0.26 mmol) was added and the reaction was allowed to stir at room temperature for 2h. The solvent and excess reagents were removed under vacuum and the residue was dried under vacuum for at least 2h to yield acid chloride as a white solid. To a solution of compound **14** (0.017 g, 0.057 mmol) and distilled NEt_3 (8 μL, 0.057 mmol) in anhydrous $CHCl_3$ (1 mL) was added dropwise a solution of the freshly prepared diacid chloride in anhydrous $CHCl_3$ (1 mL) via a syringe. The reaction was allowed to proceed at room temperature for 16h. The solution was washed with H_2O, dried over Na_2SO_4, filtered, and then concentrated. The residue was purified by chromatography (SiO_2) eluting with DCM to obtain the product **3** as a yellowish solid (0.010 g, 23% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.71 (s, 2H), 10.20 (s, 2H), 9.82 (s, 2H), 9.37 (s, 1H), 9.36 (s, 2H), 8.55 (d, *J* = 8.6 Hz, 2H), 7.99 (s, 2H), 7.81 (s, 2H), 7.46 (s, 2H), 7.45 (s, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.80 (s, 1H), 6.75 (s, 2H), 4.06 (s, 6H), 4.06-4.04 (m, 8H), 3.99 (s, 6H), 3.98 (d, *J* = 8.7 Hz, 4H), 3.73 (d, *J* = 6.9 Hz, 4H), 2.34 – 2.19 (m, 4H), 1.14 (d, *J* = 6.7 Hz, 12H), 1.05 (d, *J* = 6.6 Hz, 12H), 0.99 (d, *J* = 6.6 Hz, 12H), 0.95 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.60, 162.42, 152.01, 150.95, 150.79, 149.39, 147.13, 133.17, 129.81, 129.79, 129.75, 129.64, 126.89, 126.49, 125.49, 125.38, 122.20, 117.72, 117.44, 116.86, 116.52, 110.93, 108.53, 100.56, 95.44, 75.72, 75.36, 56.29, 53.35, 28.26, 28.12, 28.05, 19.53, 19.46, 19.35, 19.31. MS(MALDI-TOF): *m/z* calcd for $C_{90}H_{109}N_{10}O_{22}$ $[M+H]^+$ 1681.769 Found 1681.76, mp 247-249 °C.



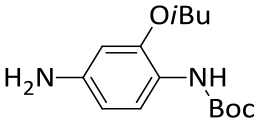
Hairpin turn nonamer, 4. Compound **19** (0.100 g, 0.09 mmol) and compound **18** (0.095 g, 0.16 mmol) were dissolved in $CHCl_3$ (1 mL), then distilled DIEA (172 µL, 0.99 mmol) and PyBOP (0.343 g, 0.66 mmol) were added. The reaction mixture was allowed to reach +45 °C and stirred for 24h. Then the solution was washed with H_2O and evaporated. The residue was precipitated in methanol and purified by flash chromatography (SiO_2) eluting with CH_2Cl_2/MeOH (95:5, vol/vol), and circular chromatography (SiO_2) eluting with CH_2Cl_2 to obtain product **4** as a yellowish solid (0.030 g, 16% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.83 (s, 2H), 10.68 (s, 2H), 10.23 (s, 2H), 9.45 (s, 4H), 9.31 (s, 1H), 8.95 (s, 2H), 8.50 (d, *J* = 9.1 Hz, 2H), 8.04 (s, 2H), 7.81 (s, 2H), 7.51 (s, 2H), 7.34 (s, 2H), 7.08 (s, 2H), 6.69 (m, 4H), 6.37 (s, 2H), 6.08 (s, 1H), 4.22 (d, *J* = 6.7 Hz, 4H), 4.16 (s, 6H), 4.15 (d, *J* = 9.1 Hz, 4H), 4.09 (s, 6H), 3.97 (d, *J* = 6.6 Hz, 4H), 3.89 (d, *J* = 6.9 Hz, 4H), 3.85 (d, *J* = 7.1 Hz, 4H), 3.83 (s, 6H), 2.52 – 2.12 (m, 10H), 1.27 (m, 36H), 1.10 (s br, 12H), 1.09 (s br, 12H).^{13}C NMR ($CDCl_3$, 75 MHz) : δ 166.45, 162.67, 162.59, 162.20, 161.96, 161.57, 151.59, 151.23, 150.59, 150.19, 149.36, 148.17, 147.08, 146.11, 145.46, 132.73, 129.43, 129.11, 128.73, 127.79, 126.26, 125.23, 124.82, 121.51, 118.85, 117.28, 117.16, 117.09, 116.17, 110.75, 110.26, 108.82, 107.54, 105.93, 99.81, 97.30, 96.85, 77.25, 76.61, 75.92, 75.45, 74.80, 56.54, 55.59, 53.03, 28.47, 28.38, 28.16, 28.13, 27.64, 19.71, 19.66, 19.55, 19.42. MS(MALDI-TOF): m/z calcd for $C_{120}H_{141}N_{14}O_{28}$ $[M+H]^+$ 2226.00 Found 2225.96, degradation at 326-327 °C.



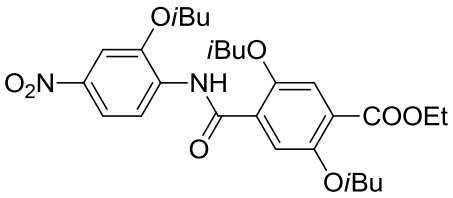
***tert*-butyl 2-isobutoxy-4-nitrophenylcarbamate, 7.** To 2-isobutoxy-4-nitrobenzenamine **6**[6] (7.688 g, 36.6 mmol) dissolved in THF (150 mL) was added di-*tert*-butyl dicarbonate (24 g, 110 mmol). After heating for 8 days at +70 °C, the reaction mixture was evaporated. The residue was purified by chromatography (SiO_2) eluting with toluene, and precipitated in MeOH to obtain the product **7** as a yellowish solid (4.444 g, 39% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.26 (d, *J* = 9.0 Hz, 1H), 7.89 (dd, *J* = 8.9, 1.8 Hz, 1H), 7.70 (d, *J* = 1.7 Hz, 1H), 7.29 (s, 1H), 3.89 (d, *J* = 6.6 Hz, 2H), 2.20 (dt, *J* = 13.2, 6.6 Hz, 1H), 1.55 (s, 9H), 1.08 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) : δ 152.16, 146.37, 142.26, 134.87, 117.80, 116.51, 106.18, 81.89, 75.77, 28.38, 28.18, 19.40. HRMS (ES^-): m/z calcd for $C_{15}H_{21}N_2O_5$ $[M-H]^-$ 309.14450 Found 309.14529, mp 98-99 °C.



***tert*-butyl 4-amino-2-isobutoxyphenylcarbamate, 8.** To compound **7** (4.444 g, 14 mmol) dissolved in AcOEt (100 mL) was added 10% Pd/C (0.44 g). The reaction mixture was stirred for 16h under hydrogen at atmospheric pressure. After filtration through celite and concentration, the product **8** was obtained as purple oil (4 g, 99% yield) and used without further purification.

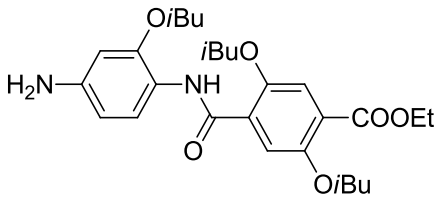
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.73 (s, 1H), 6.70 (s, 1H), 6.29-6.23 (m, 2H), 3.71 (d, *J* = 6.6 Hz, 2H), 3.49 (br, 2H), 2.12 (dt, *J* = 13.3, 6.7 Hz, 1H), 1.51 (s, 9H), 1.03 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.04, 148.55, 142.56, 120.08, 119.13, 106.72, 99.56, 79.45, 74.54, 28.18, 27.92, 19.04. HRMS (ES^+): m/z calcd for $C_{15}H_{25}N_2O_3$ $[M+H]^+$ 281.1860 Found 281.1873.



Dimer-NO_2 alkoxyl-terephtalate, 9. 4-(ethoxycarbonyl)-2,5-diisobutoxybenzoic acid (4.390 g, 13 mmol) was suspended in anhydrous $CHCl_3$ (5 mL). Oxalyl chloride (5.6 mL, 65 mmol) was added and the reaction was allowed to stir at room temperature for 2h. The solvent and excess reagents were removed under vacuum and the residue was dried under vacuum for at least 2h to yield acid chloride as a white solid. To a solution of 2-isobutoxy-4-nitrobenzenamine **6**[6] (3 g, 14.3 mmol) and distilled DIEA (2 mL, 14.3 mmol) in anhydrous $CHCl_3$ (13 mL) was added dropwise a solution of the freshly prepared diacid chloride in anhydrous $CHCl_3$ (2 mL) via a syringe. The reaction was allowed to proceed at room temperature for 16h. The solution was washed with H_2O, dried over Na_2SO_4, filtered, and then concentrated. The residue was purified by chromatography (SiO_2) eluting with DCM to obtain the product **9** as a yellowish solid (4.882 g, 71% yield).

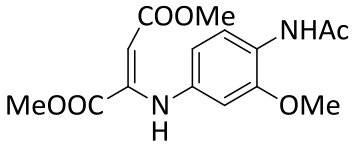
^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.44 (s, 1H), 8.77 (d, *J* = 9.0 Hz, 1H), 7.95 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.78 (d, *J* = 2.5 Hz, 1H), 7.77 (s, 1H), 7.46 (s, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.99 (d, *J* = 7.0 Hz, 2H), 3.95 (d, *J* = 7.0 Hz, 2H), 3.85 (d, *J* = 6.4 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 12H), 0.98 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.30, 163.38, 152.86, 150.01, 147.83, 143.46, 134.42, 126.05, 125.00, 119.97, 117.58, 117.28, 116.62, 106.70, 76.09, 75.93, 61.64, 31.05, 28.54, 28.09, 28.02, 19.29, 14.45. HRMS (ES^+): m/z calcd for $C_{28}H_{39}N_2O_8$ $[M+H]^+$

531.2696 Found 531.2711, mp 111-112 °C.



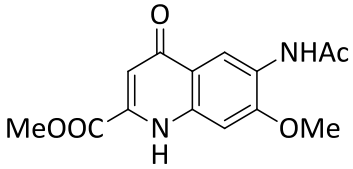
Dimer-NH_2 alkoxyl-terephtalate, 10. To compound **9** (6.557 g, 12 mmol) dissolved in AcOEt (130 mL) was added 10% Pd/C (0.66 g). The reaction mixture was stirred for 16h under hydrogen at atmospheric pressure. After filtration through celite and concentration, the product **10** was obtained as yellowish solid (5.95 g, 96% yield) and used without further purification.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.94 (s, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 7.83 (s, 1H), 7.43 (s, 1H), 6.33 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.29 (d, *J* = 2.3 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.93 (d, *J* = 6.9 Hz, 2H), 3.85 (d, *J* = 6.5 Hz, 2H), 3.76 (d, *J* = 6.9 Hz, 2H), 3.61 (s, 2H), 2.26 – 2.03 (m, 3H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 6H), 0.98 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR (CDCl3, 75 MHz): δ 166.38, 161.95, 152.72, 149.87, 149.83, 143.85, 127.17, 123.51, 122.97, 119.50, 116.84, 116.56, 106.92, 99.75, 77.11, 75.73, 75.13, 61.30, 28.41, 28.08, 27.98, 19.24, 19.21, 19.19, 14.34. HRMS (ES^-): m/z calcd for $C_{28}H_{39}N_2O_6$ $[M-H]^-$ 499.2798 Found 499.2705, mp 113-114 °C.



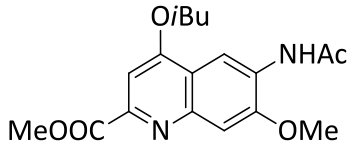
Dimethyl 2-(4-acetamido-3-methoxyphenylamino)fumarate, 12. In a 500 mL round-bottom flask, dimethyl acetylenedicarboxylate (15.8 mL, 0.12 mol) and N-(4-amino-2-methoxyphenyl)acetamide **11** (21.3 g, 0.12 mol) were dissolved in 65 mL of methanol. The reaction mixture was stirred at room temperature for 3h then heated at reflux for 1h. After cooling, the product started to precipitate. The product **12** was purified by precipitation in a minimum volume of cooled methanol and obtained with a yield of 90%.

^{1}H NMR (DMSO, 300 MHz): δ 9.62 (s, 1H), 9.12 (s, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 6.76 (d, *J* = 2.3 Hz, 1H), 6.43 (dd, *J* = 8.6, 2.3 Hz, 1H), 5.25 (s, 1H), 3.81 (s, 3H), 3.70 (s, 3H), 3.68 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (DMSO, 75 MHz) : δ 168.52, 168.33, 164.53, 150.21, 147.60, 136.59, 123.71, 122.57, 111.51, 104.21, 92.40, 55.65, 53.04, 51.05, 23.72. HRMS (ES^+): *m/z* calcd for $C_{15}H_{18}N_2O_6Na$ $[M+Na]^+$ 345.1047 Found 345.1069, mp 138-139°C.



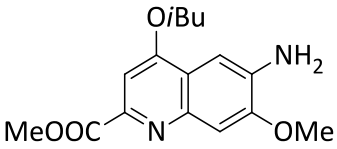
Quinolinone monomer, 13. In a 500 mL round-bottom flask, compound **12** (5 g, 15 mmol) was dissolved in 80 mL of diphenyl ether and heated with stirring at 240-250 °C for 5 minutes. After cooling, the mixture was poured into 100 mL of light petroleum ether to complete the precipitation. 5.04 g of solid was filtered off with a yield of 91% and used as product **13** without any further purification.

^{1}H NMR (DMSO, 300 MHz): δ 11.87 (s, 1H), 9.31 (s, 1H), 8.65 (s, 1H), 7.48 (s, 1H), 6.54 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (DMSO, 75 MHz) : δ 176.53, 168.66, 162.74, 153.71, 137.65, 136.60, 125.75, 120.18, 116.07, 109.78, 99.31, 56.00, 53.44, 23.95. HRMS (ES^+): m/z calcd for $C_{14}H_{15}N_2O_5$ $[M+H]^+$ 291.0975 Found 291.0985 and $C_{14}H_{14}N_2O_5Na$ $[M+Na]^+$ 313.0975 Found 313.0806, mp 293-294 °C.



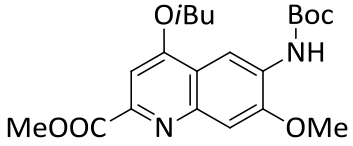
Quinoline-NHAc monomer, 14. In a 500 mL round-bottom flask, compound **13** (5 g, 17 mmol) and potassium carbonate (3.6 g, 26 mmol) were dissolved in 50 mL of DMF and heated with stirring at +120 °C for 2h. The reaction mixture was cooled to +100 °C and 1-iodo-2-methylpropane (3 mL, 26 mmol) was added. The reaction mixture was stirred for 4h at +100°C. After cooling, the mixture was filtered. The filtrate was extracted by $CHCl_3$ (3x100 mL), washed with H_2O and evaporated. Both precipitate and residue from extraction were recrystallized in hot methanol and compound **14** was obtained (1.7 g, 29%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.19 (s, 1H), 8.05 (s, 1H), 7.54 (s, 1H), 7.47 (s, 1H), 4.05 (s, 3H), 4.02 (s, 3H), 4.02 (d, *J* = 6.4 Hz, 2H), 2.27 (s, 3H), 1.14 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) : δ 168.60, 166.57, 162.46, 151.11, 148.07, 146.41, 129.21, 117.91, 110.03, 107.84, 100.47, 75.13, 56.35, 28.31, 25.18, 19.42. HRMS (ES^+): *m/z* calcd for $C_{18}H_{23}N_2O_5$ $[M+H]^+$ 347.1601 Found 347.1611, mp 206-208 °C.



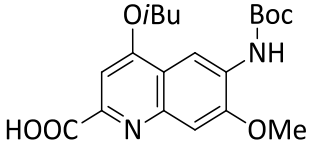
Quinoline-NH_2 monomer, 15. In a 100 mL round-bottom flask, compound **14** (1.7 g, 5 mmol) was dissolved in 75 mL of methanol and stirred until solubilization. Sulfuric acid (0.8 mL, 15 mmol) was added and the reaction mixture was stirred at room temperature for 16h. A saturated solution of sodium bicarbonate was added slowly to stop the reaction and precipitation occured. Solid was filtrered off and washed with H_2O. After drying, the product **15** was obtained (0.7 g, 49%) and used without any further purification.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.47 (s, 1H), 7.43 (s, 1H), 7.29 (s, 1H), 4.36 (s, 2H), 4.04 (s, 3H), 3.99 (d, J = 6.5 Hz, 2H), 3.99 (s, 3H), 2.30 – 2.18 (m, 1H), 1.12 (d, J = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) : δ 166.90, 160.45, 151.69, 145.25, 144.66, 138.69, 118.76, 108.05, 101.14, 100.16, 74.83, 56.03, 31.09, 28.38, 19.46. HRMS (ES^+): m/z calcd for $C_{16}H_{21}N_2O_4$ $[M+H]^+$ 305.1496 Found 305.1518, mp 234-236 °C.



Quinoline-NHBoc monomer, 16. Compound **15** (0.346 g, 1.1 mmol) and di-tert-butyl dicarbonate (0.744 g, 3.8 mmol) were dissolved in THF (4 mL). The mixture reaction was heated for 24h at +70 °C then evaporated. The product **16** was precipitated in Et_2O and purified by chromatography (SiO_2) eluting with Cyclohexane/Ethyl Acetate (7:3, vol/vol) to obtain as a solid (0.441 g, 96% yield).

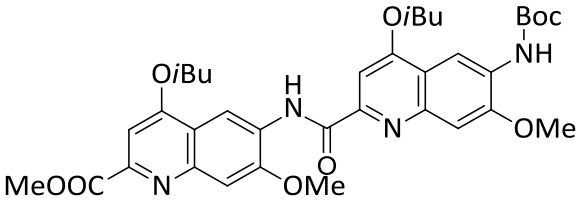
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.81 (s, 1H), 7.56 (s, 1H), 7.52 (s, 1H), 7.41 (s, 1H), 4.09 (s, 3H), 4.06 (d, J = 6.8 Hz, 2H), 4.05 (s, 3H), 2.35-2.26 (m, 1H), 1.61 (s, 9H), 1.17 (d, J = 6.7 Hz, 6H). HRMS (ES^+): m/z calcd for $C_{21}H_{29}N_2O_6$ $[M+H]^+$ 405.2018 Found 405.2020.



Quinoline-COOH monomer, 17. Compound **16** (2.7 g, 6.7 mmol) and potassium hydroxyde (1.9 g, 33 mmol) were dissolved in a mixture dioxane/H_2O (2.5:1). The reaction mixture was allowed to proceed at room temperature for 16h. The dioxane was evaporated and the solution acidified by a

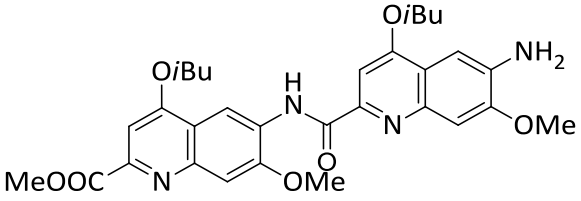
5% citric acid solution. Compound **17** was filtered off, washed with H_2O, dried and used without any further purification (2.5 g, 99%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.89 (s, 1H), 8.40 (s, 1H), 7.73 (s, 1H), 7.46 (s, 1H), 4.26 (s, 3H), 4.20 (d, *J* = 6.8 Hz, 2H), 2.42-2.33 (m, 1H), 1.60 (s, 9H), 1.16 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) : δ 166.85, 161.91, 153.72, 152.19, 149.52, 137.20, 130.83, 116.51, 107.43, 101.52, 100.32, 81.57, 57.52, 28.37, 28.04, 19.22. HRMS (ES^+): m/z calcd for $C_{20}H_{27}N_2O_6$ $[M+H]^+$ 391.1864 Found 391.18778, mp 207-208 °C.



Quinoline dimer, 18. Compound **17** (0.107 g, 0.27 mmol) and compound **15** (0.076 g, 0.25 mmol) were dissolved in $CHCl_3$ (1 mL), then distilled DIEA (130 μL, 0.75 mmol) and PyBOP (0.260 g, 0.5 mmol) were added. The reaction mixture was allowed to reach +45 °C and stirred for 16h. Then the solution was washed with H_2O and evaporated. The residue was purified by precipitation in methanol and the quinoline dimer **18** was obtained as a solid (0.120 g, 71% yield).

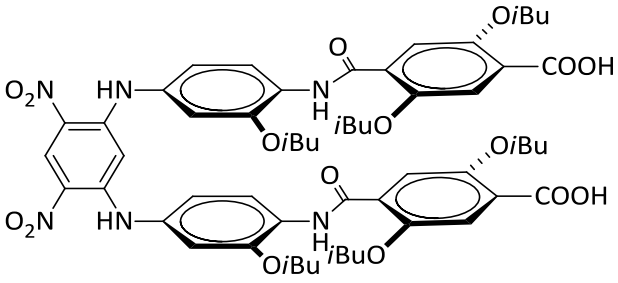
^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.07 (s, 1H), 9.44 (s, 1H), 8.83 (s, 1H), 7.71 (s, 1H), 7.66 (s, 1H), 7.52 (s, 1H), 7.40 (s, 1H), 7.36 (s, 1H), 4.17 (s, 3H), 4.11 (d, *J* = 10.1 Hz, 4H), 4.10 (s, 3H), 4.08 (s, 3H), 2.42 – 2.30 (m, 2H), 1.59 (s, 9H), 1.19 (d, *J* = 6.7 Hz, 6H), 1.16 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) : δ163.48, 162.88, 152.54, 151.41, 150.01, 145.09, 129.81, 129.63, 118.12, 110.11, 108.29, 107.94, 107.06, 100.57, 98.10, 81.17, 75.39, 56.67, 56.28, 53.21, 29.87, 28.56, 28.40, 28.33, 19.59, 19.51. HRMS (ES^+): m/z calcd for $C_{36}H_{45}N_4O_9$ $[M+H]^+$ 699.3175 Found 677.3184, mp 242-243 °C.



Quinoline-NH_2 dimer, 19. Compound **18** (0.109 g, 0.16 mmol) was dissolved in a solution 20% TFA/CH_2Cl_2 (5 mL) and stirred for 4h at room temperature. Then toluene (10 mL) was added to the

solution and evaporated. The residue was dissolved in CH_2Cl_2 (20 mL), and washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered and then concentrated to give compound **19** (0.091 g, 98% yield) that was used without further purification.

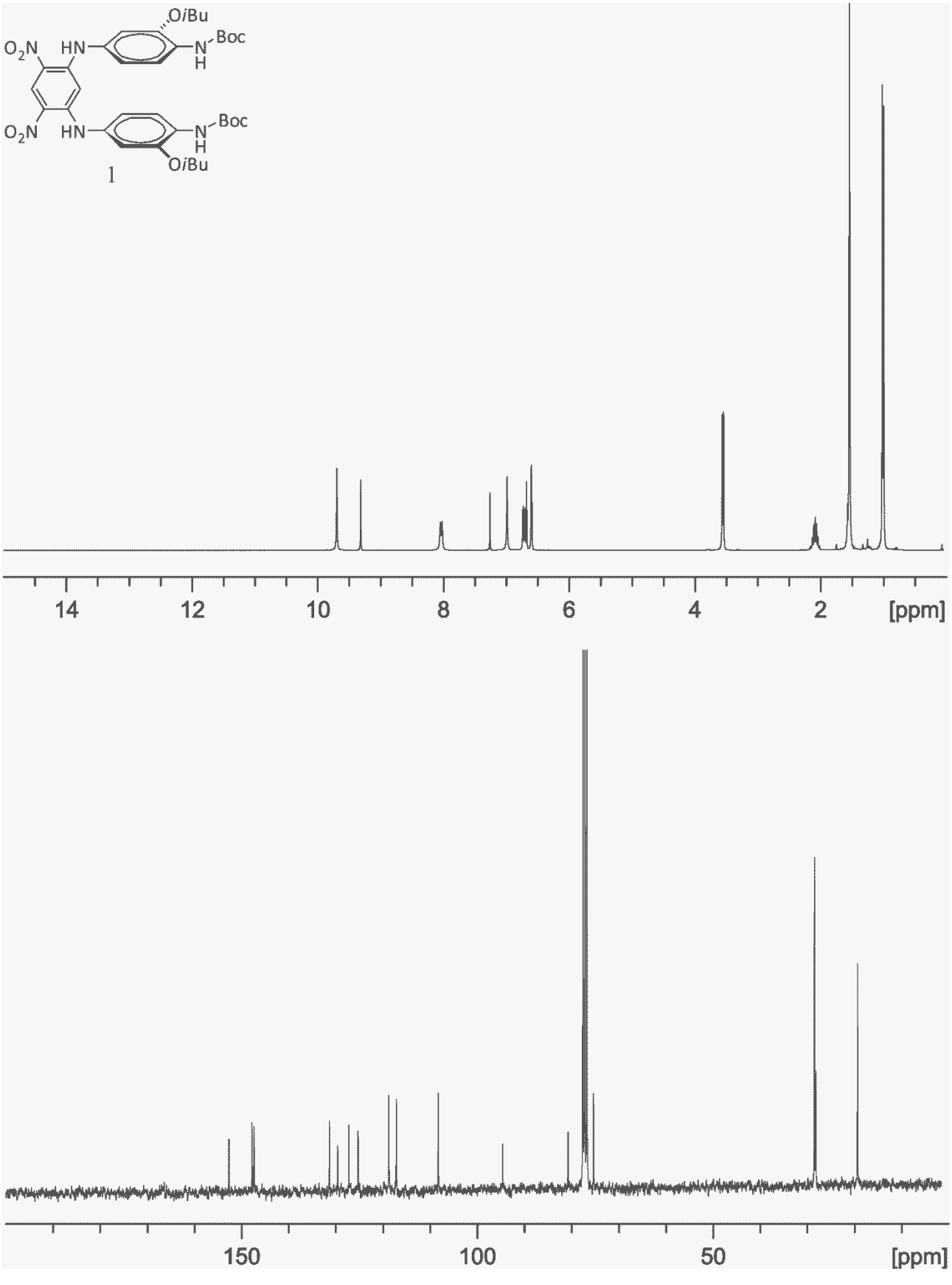
^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.09 (s, 1H), 9.44 (s, 1H), 7.66 (s, 1H), 7.65 (s, 1H), 7.52 (s, 1H), 7.35 (s, 1H), 7.34 (s, 1H), 4.17 (s, 3H), 4.08-4.08 (m, 8H), 4.06 (d, *J* = 3.4 Hz, 2H), 2.41-2.23 (m, 2H), 1.18 (d, *J* = 6.7 Hz, 6H), 1.13 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) : δ 166.50, 163.66, 162.47, 161.00, 152.34, 151.74, 147.58, 146.42, 143.52, 138.30, 129.62, 118.54, 117.97, 109.63, 107.69, 106.98, 101.57, 100.37, 97.57, 75.20, 74.94, 56.55, 55.92, 53.23, 28.32, 28.26, 19.54, 19.40. HRMS (ES^+): m/z calcd for $C_{31}H_{37}N_4O_7$ $[M+H]^+$ 577.2674 Found 577.2674, mp 265-266 °C.

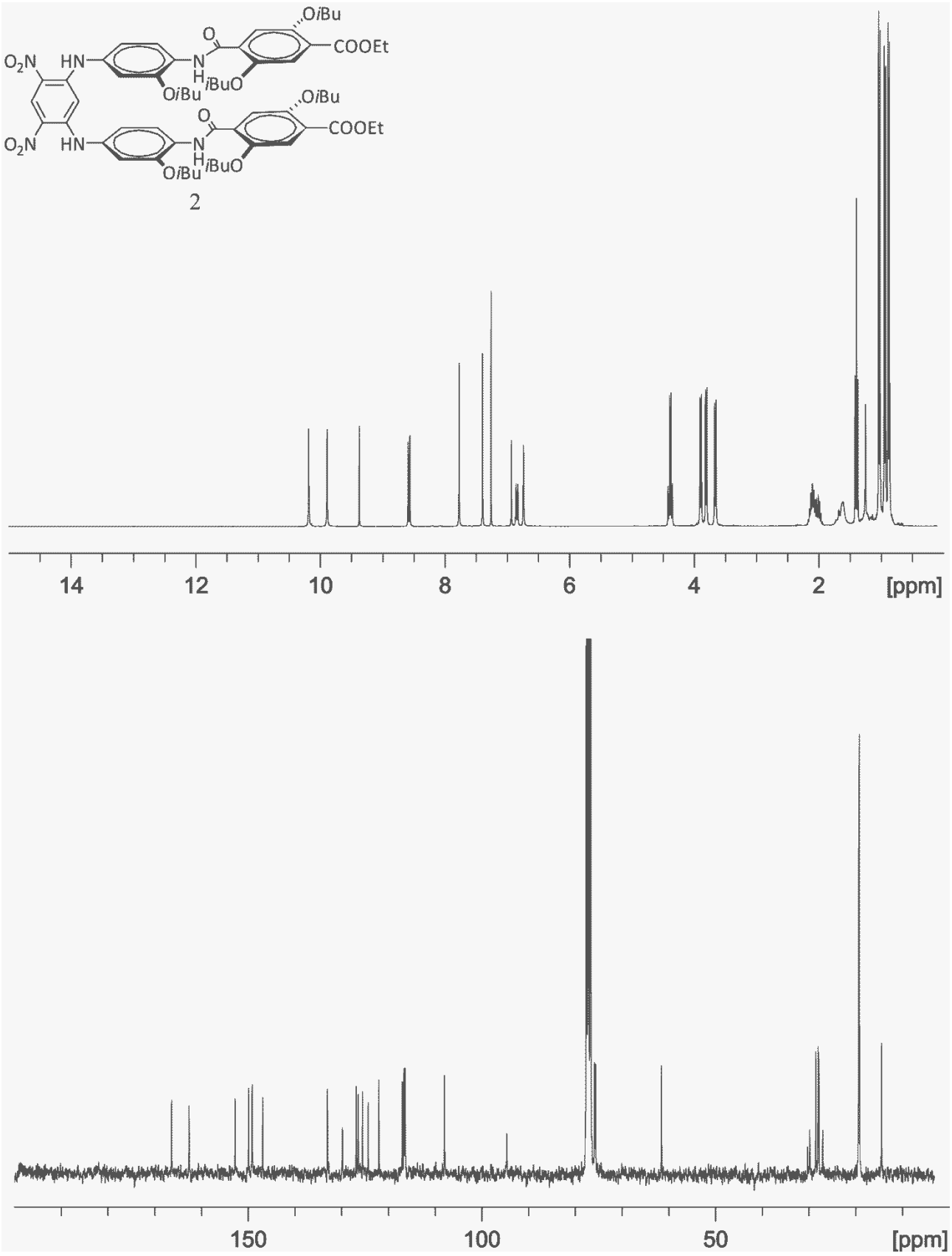


Hairpin turn pentamer-COOH, 20. Compound **2** (0.319 g, 0.27 mmol) and potassium hydroxyde (0.077 g, 1.37 mmol) were dissolved in a mixture dioxane/H_2O (7:1). The reaction mixture was allowed to proceed at room temperature for 24h. The dioxane was evaporated and the solution acidified to pH=1 by a HCl 1N solution. Compound **20** was filtered off, washed with H_2O, dried and used without any further purification (0.292 g, 96%).

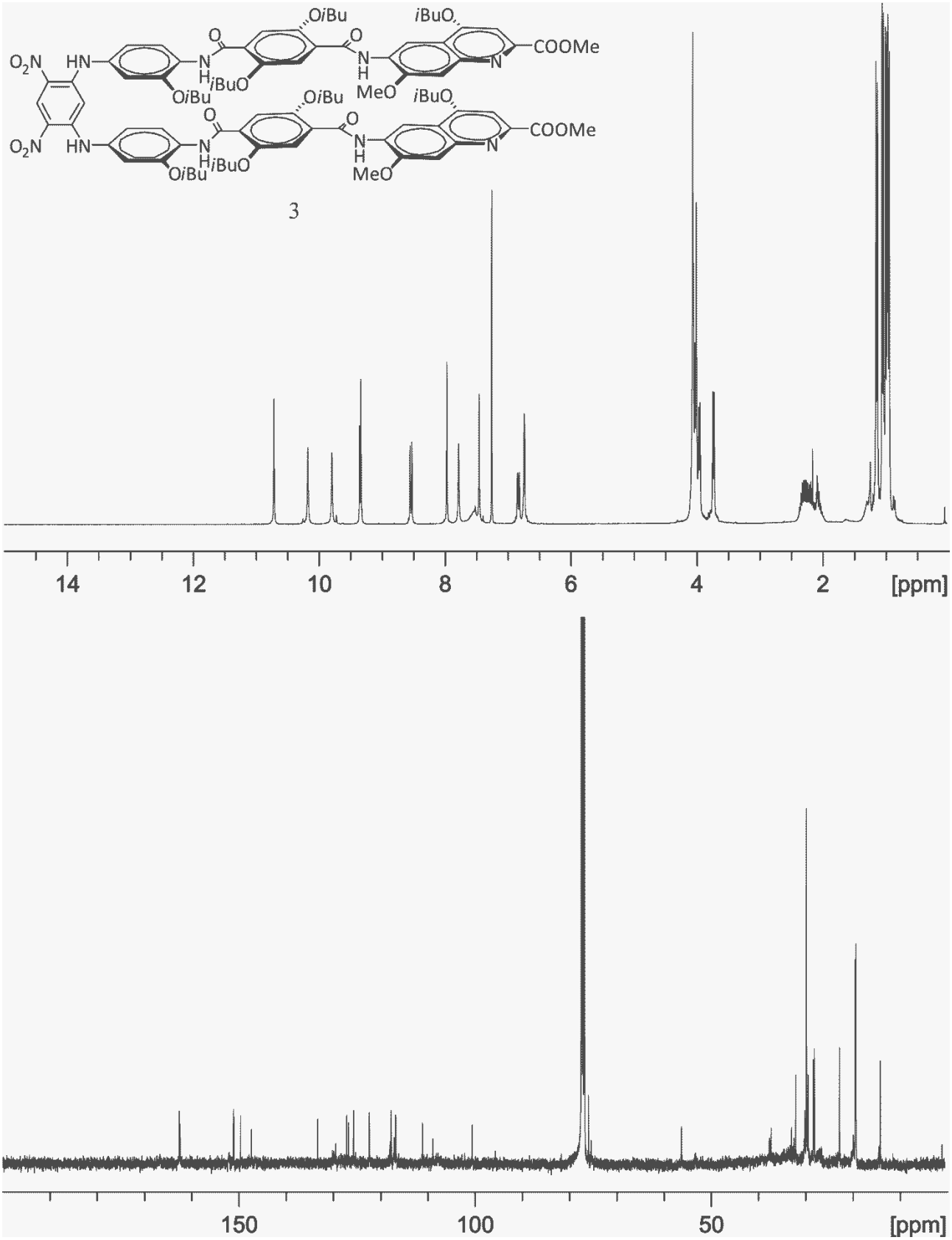
^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.09 (s, 2H), 10.19 (s, 2H), 9.89 (s, 2H), 9.38 (s, 1H), 8.53 (d, *J* = 8.6 Hz, 2H), 7.88 (s, 2H), 7.81 (s, 2H), 6.89 (s, 1H), 6.86 (dd, *J* = 8.7, 2.2 Hz, 2H), 6.75 (d, *J* = 2.2 Hz, 2H), 4.04 (d, *J* = 6.5 Hz, 4H), 3.98 (d, *J* = 7.1 Hz, 4H), 3.72 (d, *J* = 7.0 Hz, 4H), 2.27 – 1.99 (m, 6H), 1.07 (d, *J* = 6.7 Hz, 12H), 0.96 (d, *J* = 6.7 Hz, 12H), 0.92 (d, *J* = 6.7 Hz, 12H). HRMS (ES^+): *m/z* calcd for $C_{58}H_{73}N_6O_{16}$ $[M+H]^+$ 1109.50776 Found 1109.50859, mp 260-261°C.

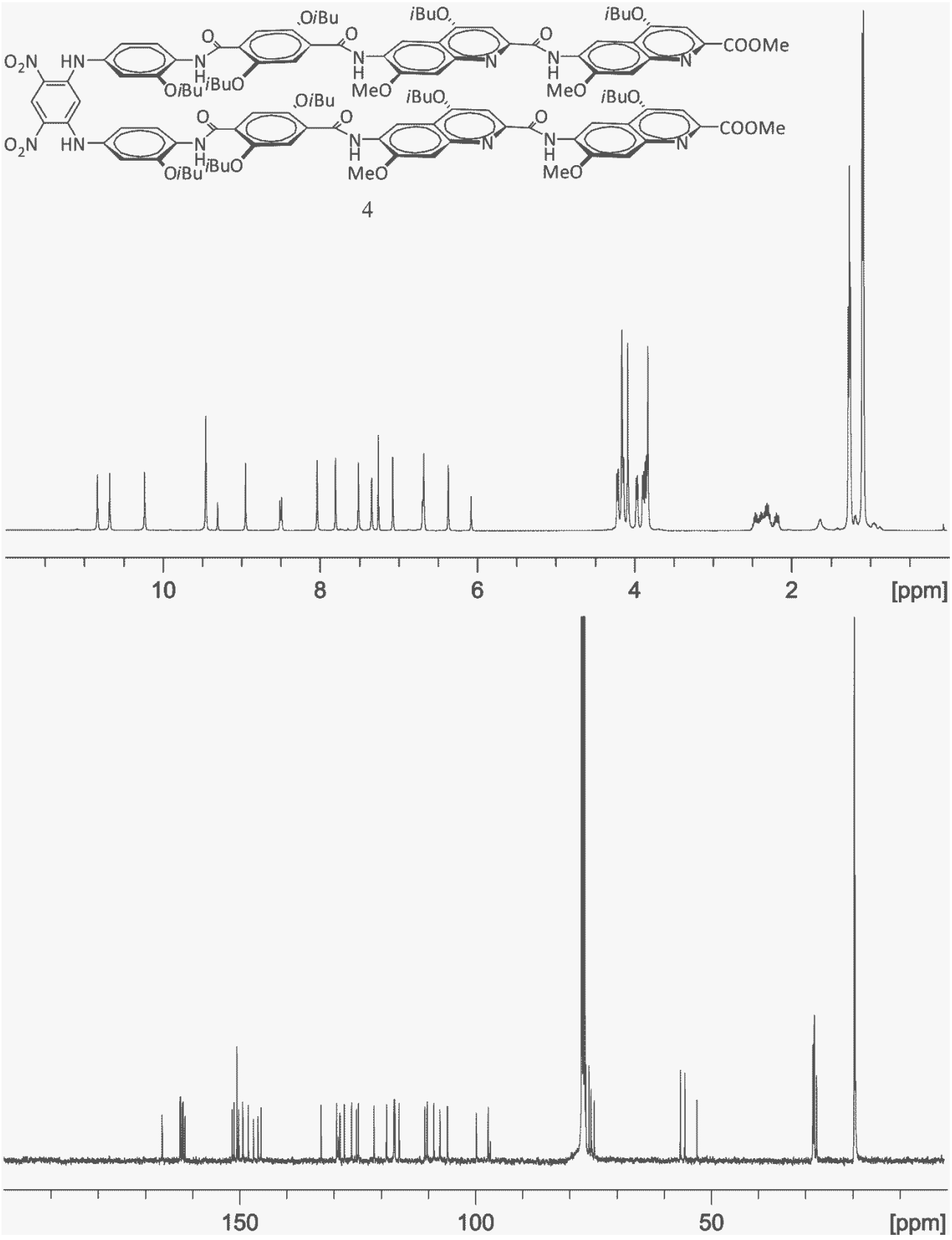
6. ^{1}H NMR spectra of all relevant synthetic intermediates and title compounds.



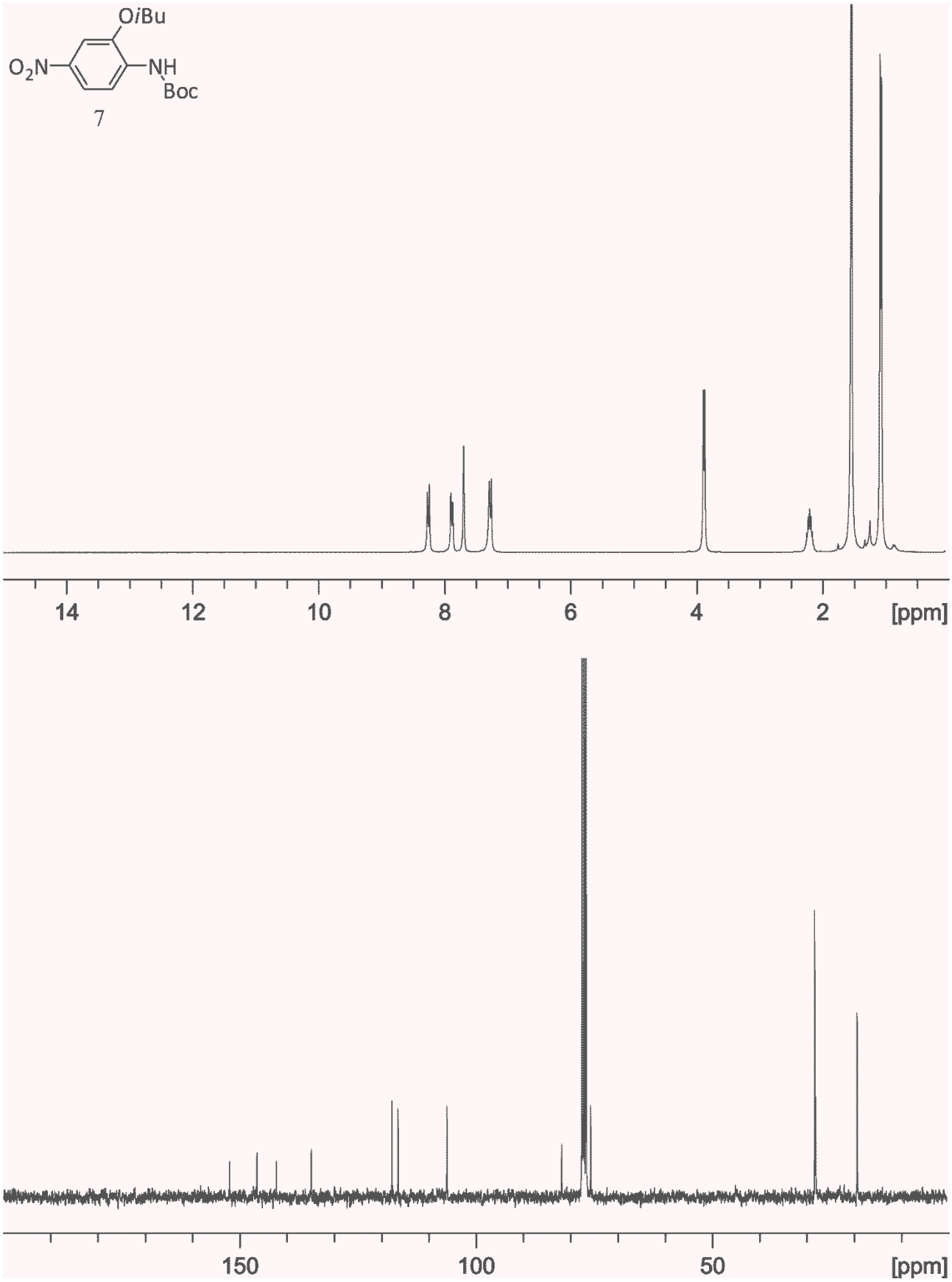


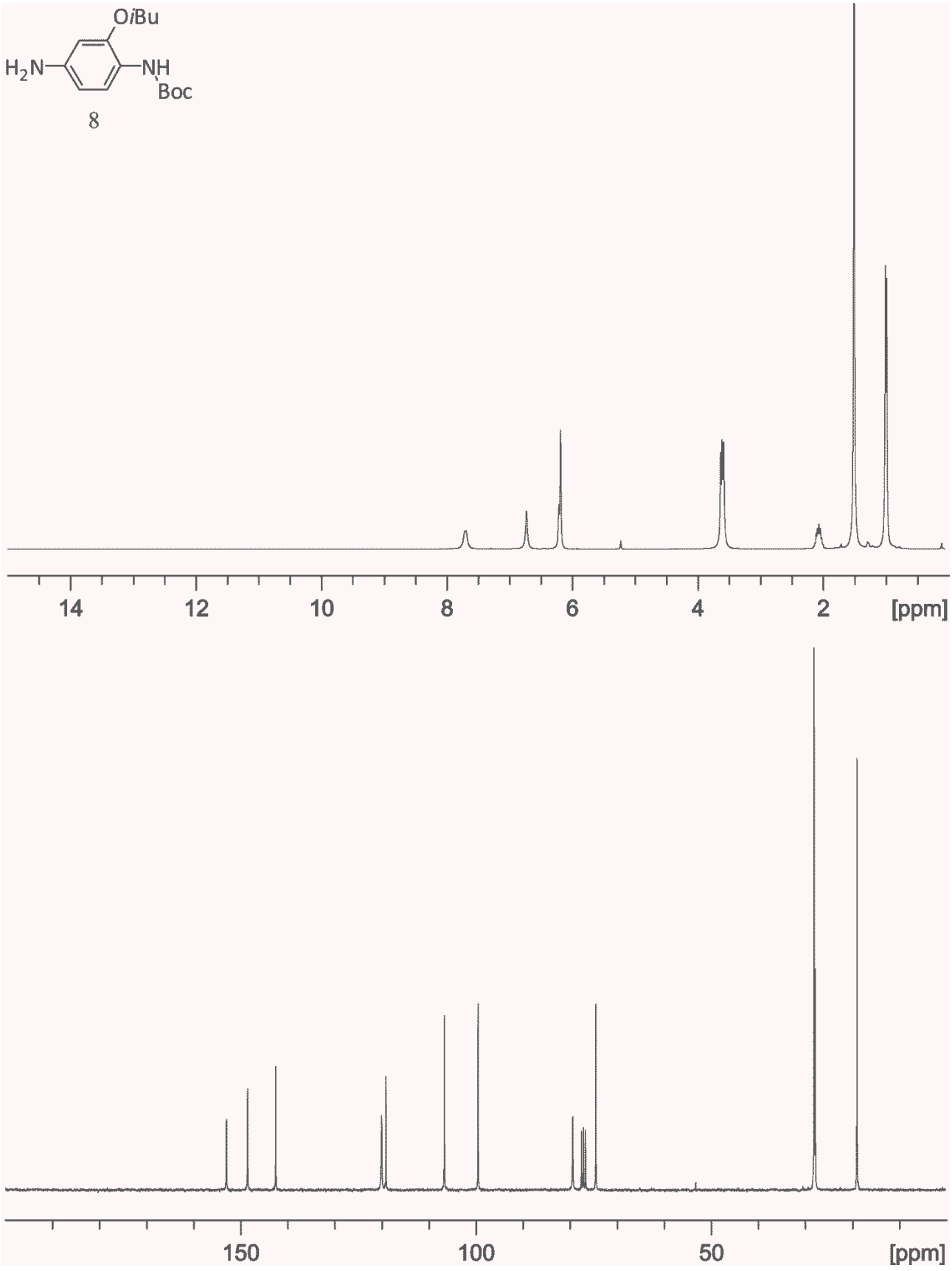
2

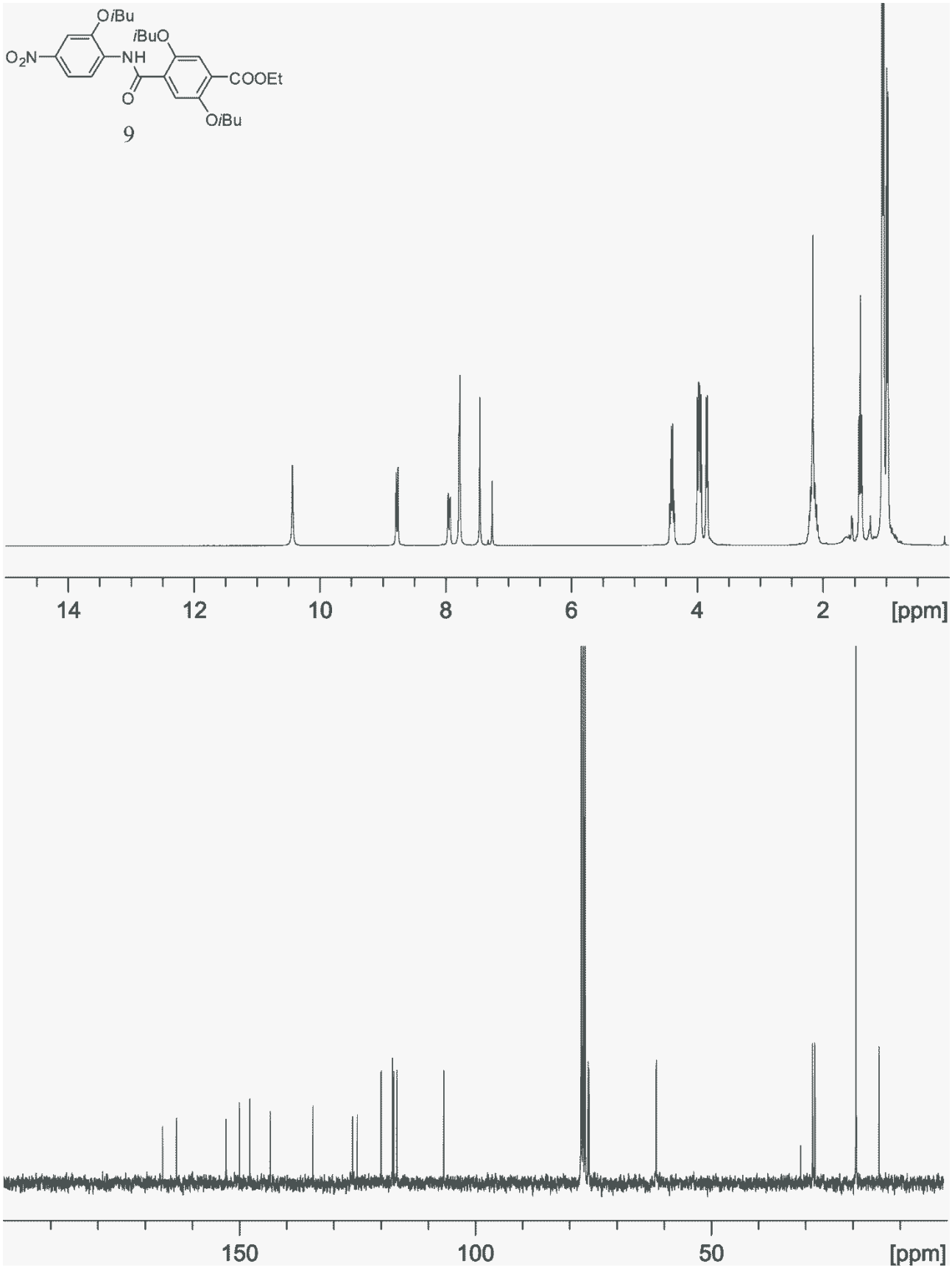

OiBu
iBuO
COOMe
O2N
HN
N
H
iBuO
OiBu
MeO
3
14
12
10
8
6
4
2
[ppm]
150
100
50
[ppm]

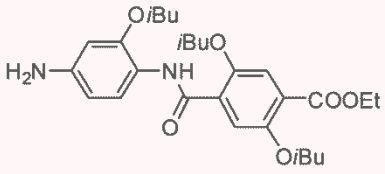


4

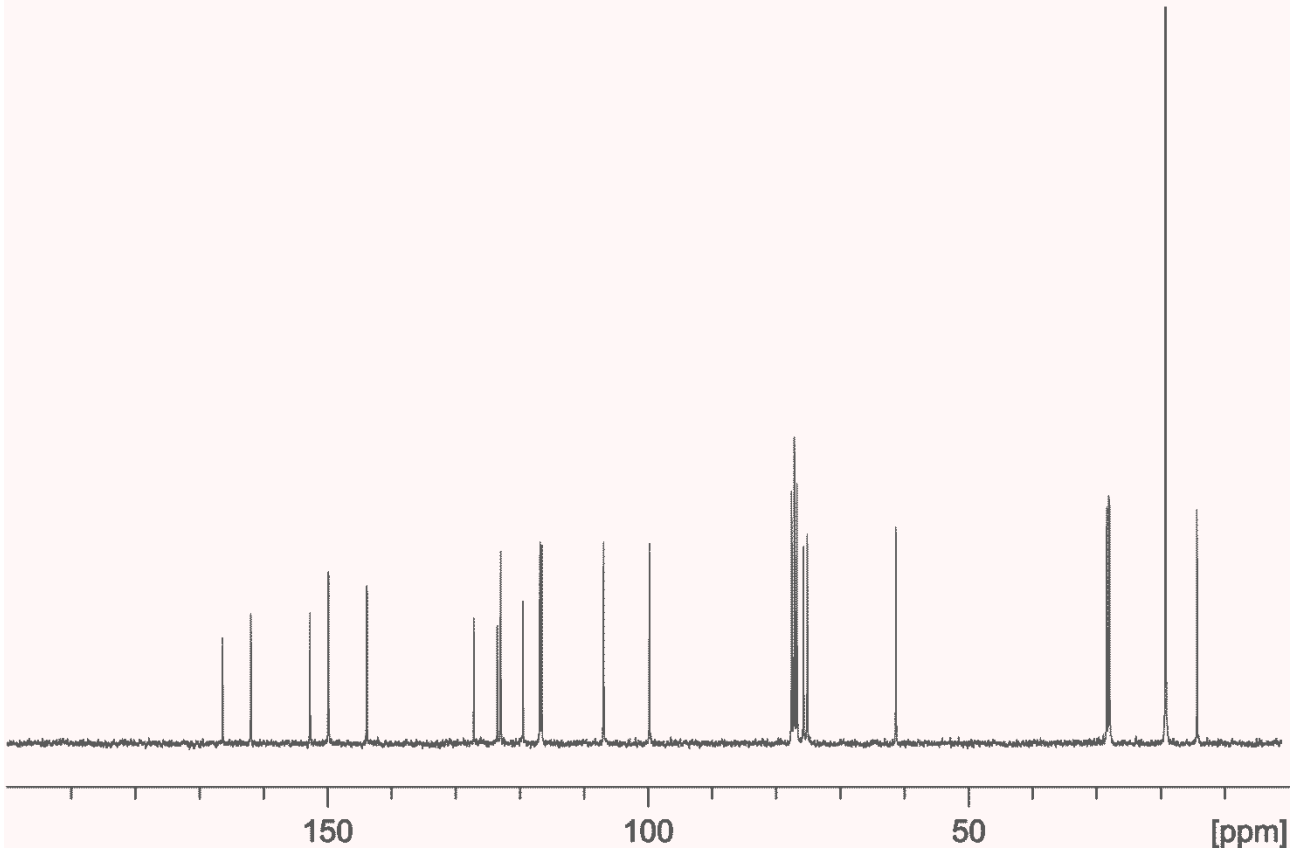

OiBu
O2N
NH
Boc
7
14
12
10
8
6
4
2
[ppm]
150
100
50
[ppm]

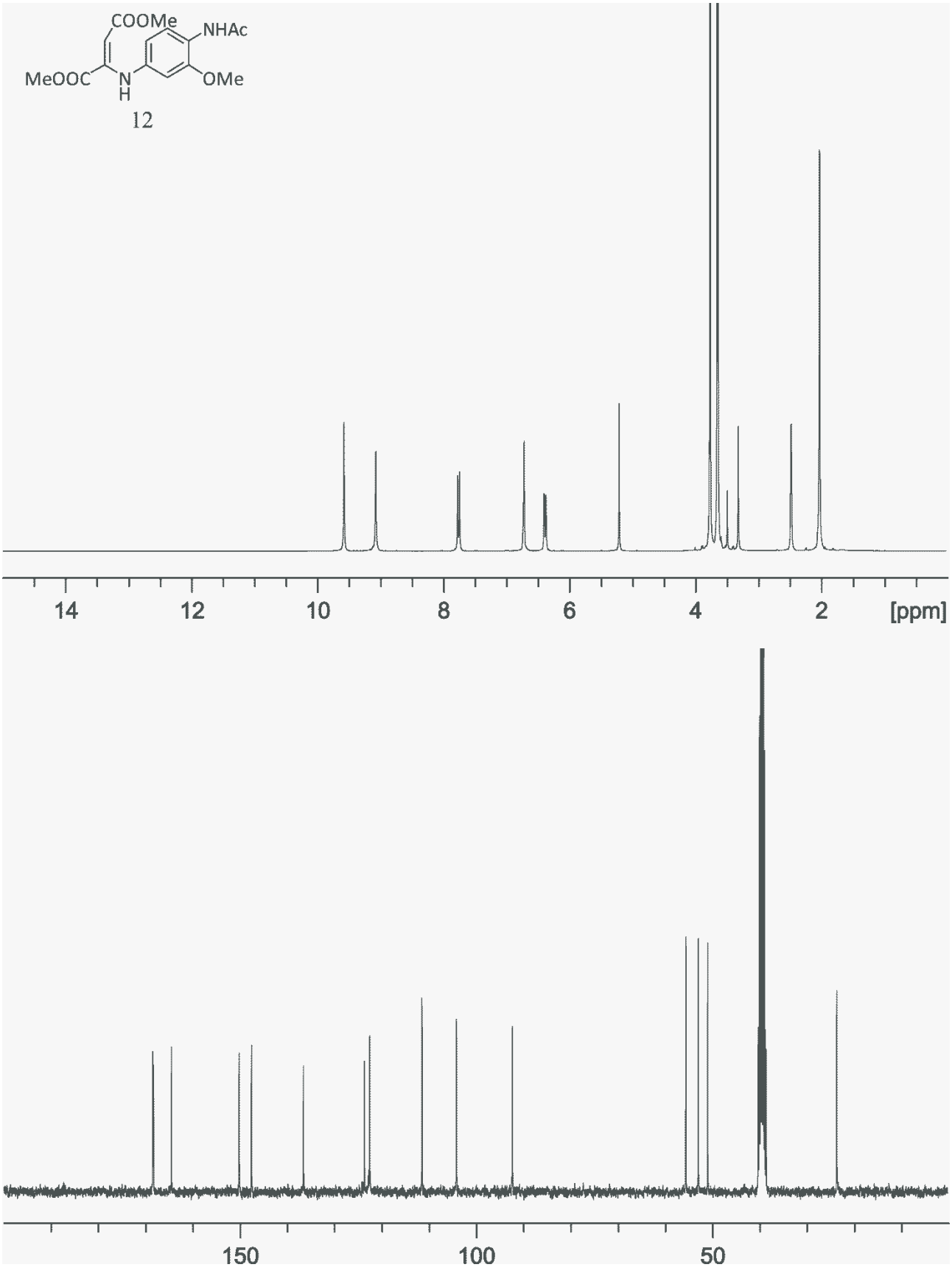

OiBu
H2N
NH
Boc
8
14
12
10
8
6
4
2
[ppm]
150
100
50
[ppm]

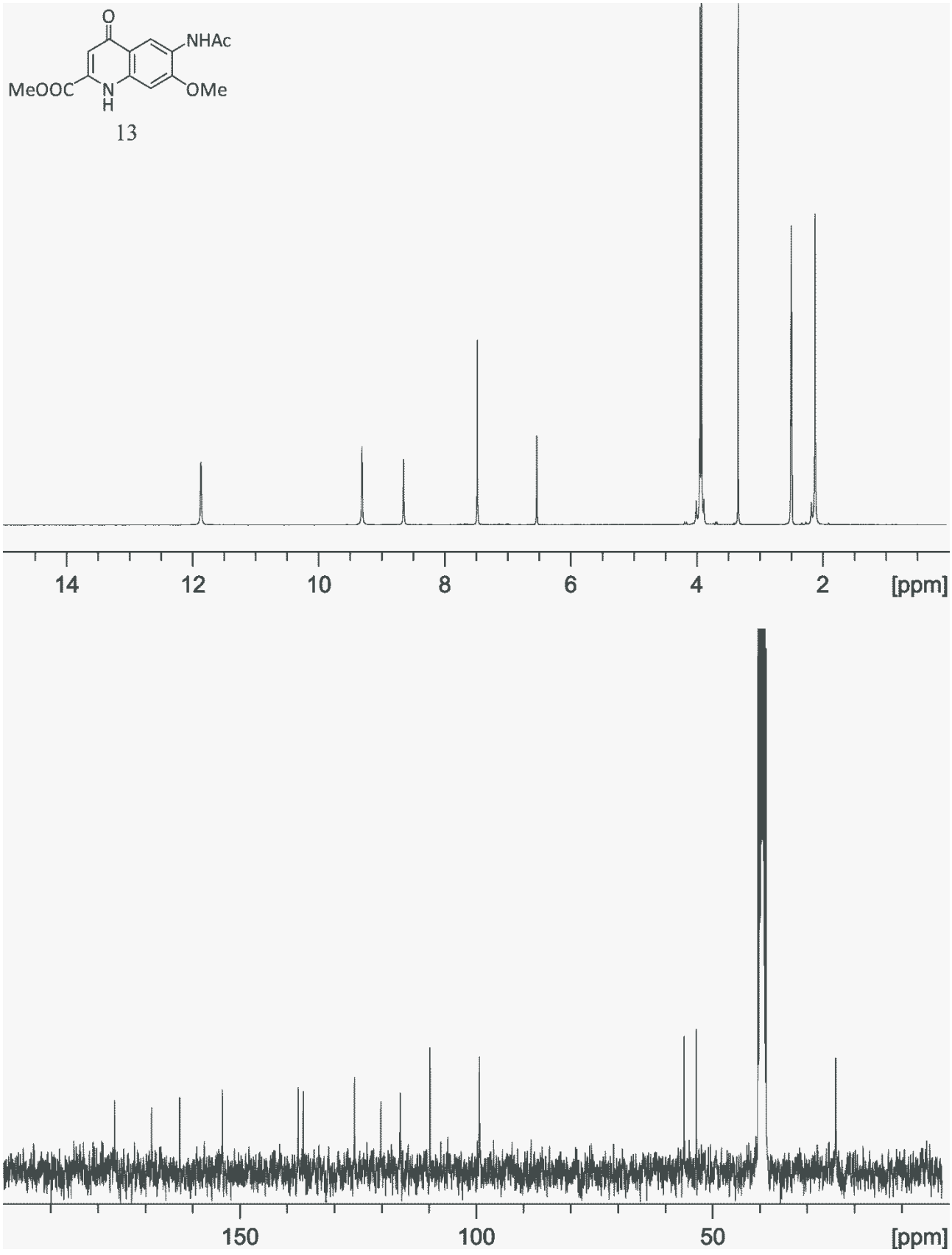

OiBu
iBuO
O_2N
NH
O
COOEt
OiBu
9
14
12
10
8
6
4
2
[ppm]
150
100
50
[ppm]

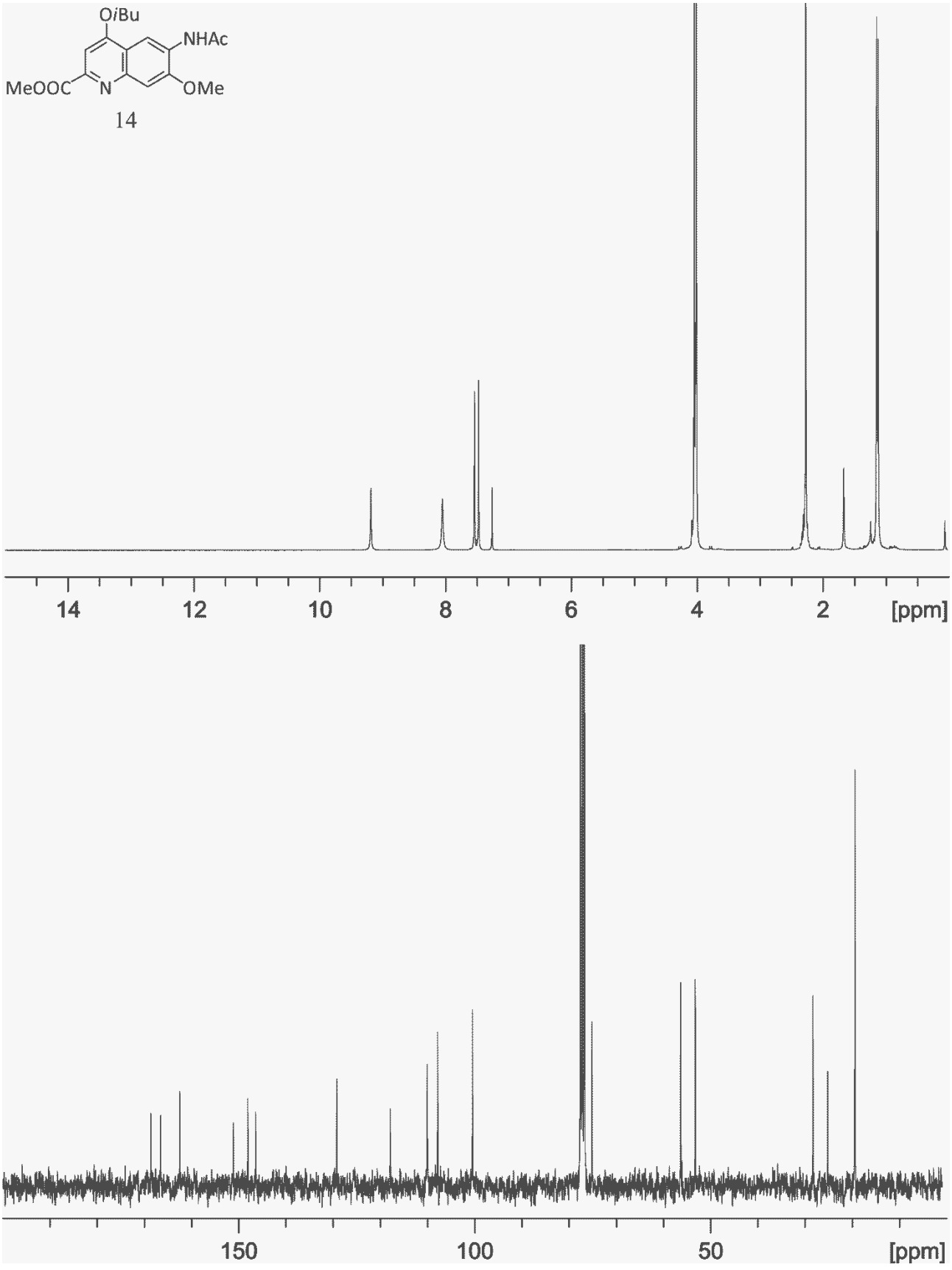


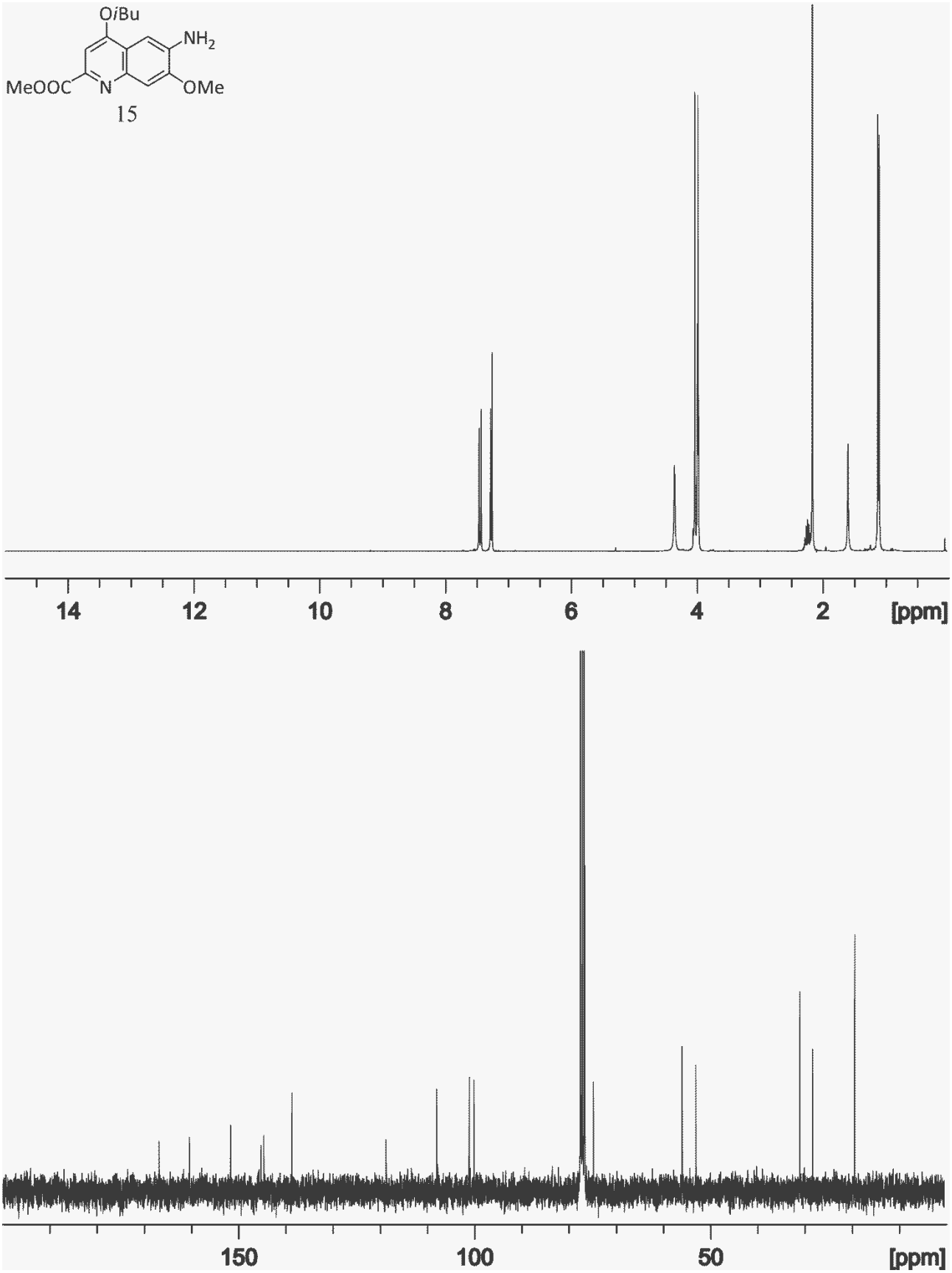
10

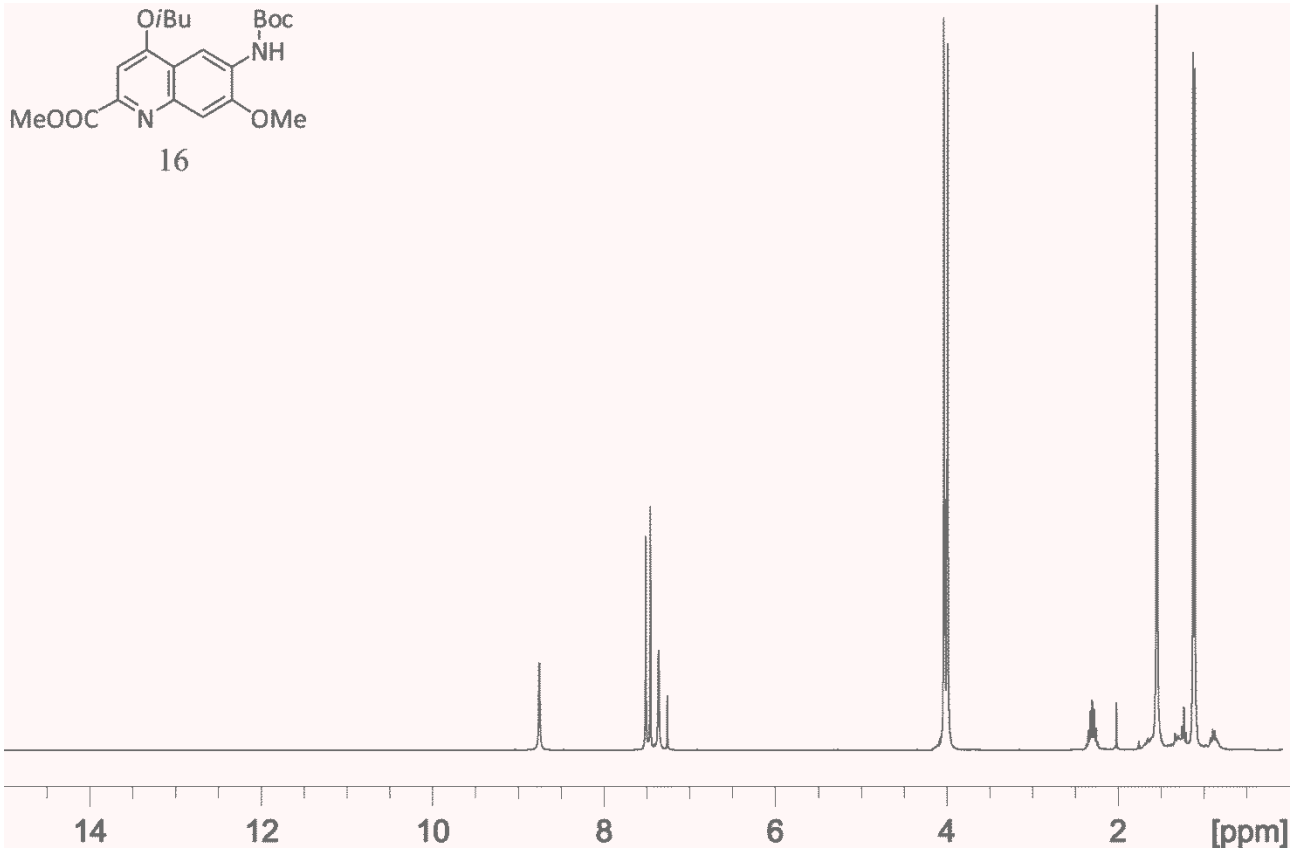


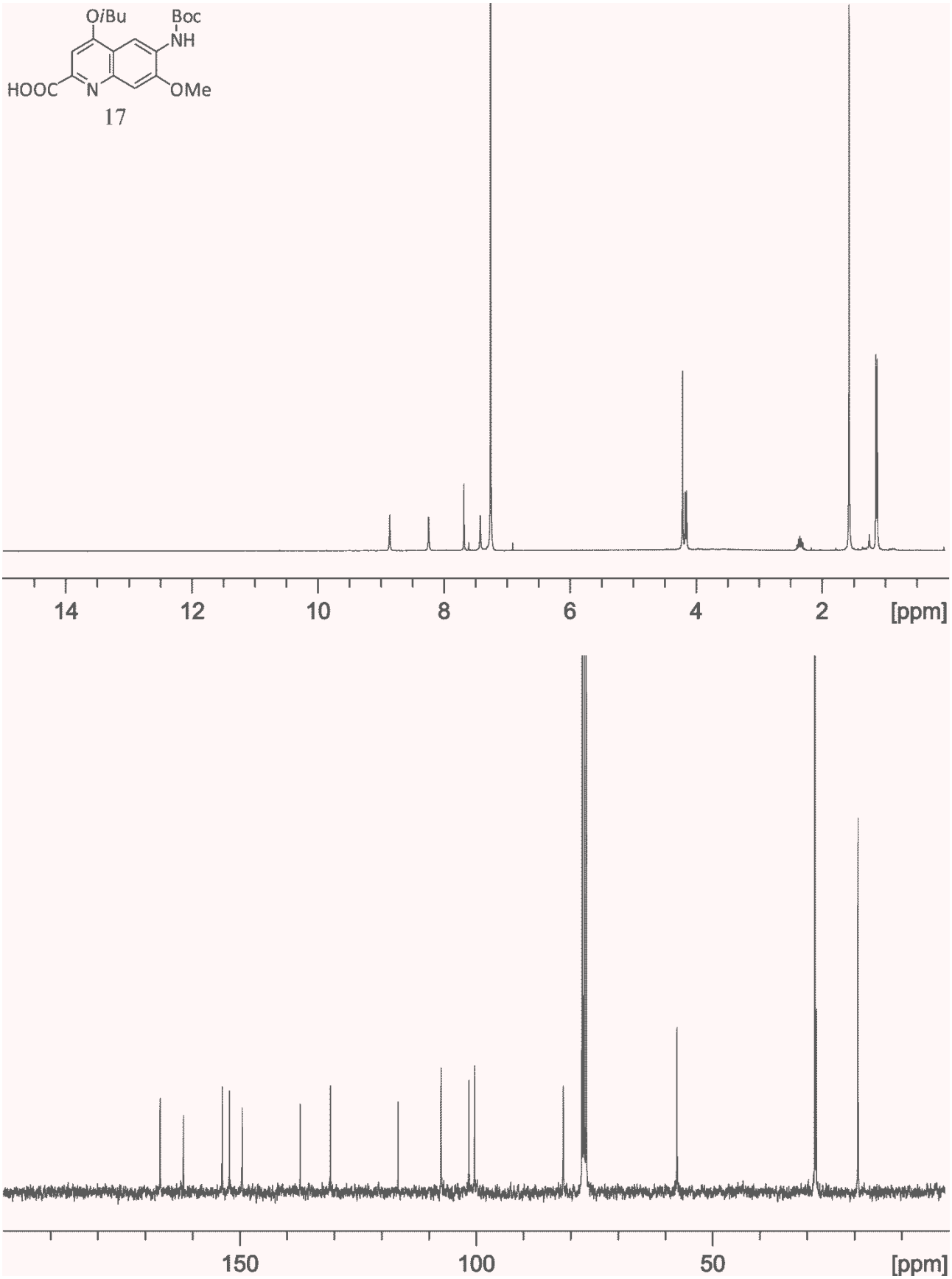

COOMe
NHAc
MeOOC
N
H
OMe
12
14
12
10
8
6
4
2
[ppm]
150
100
50

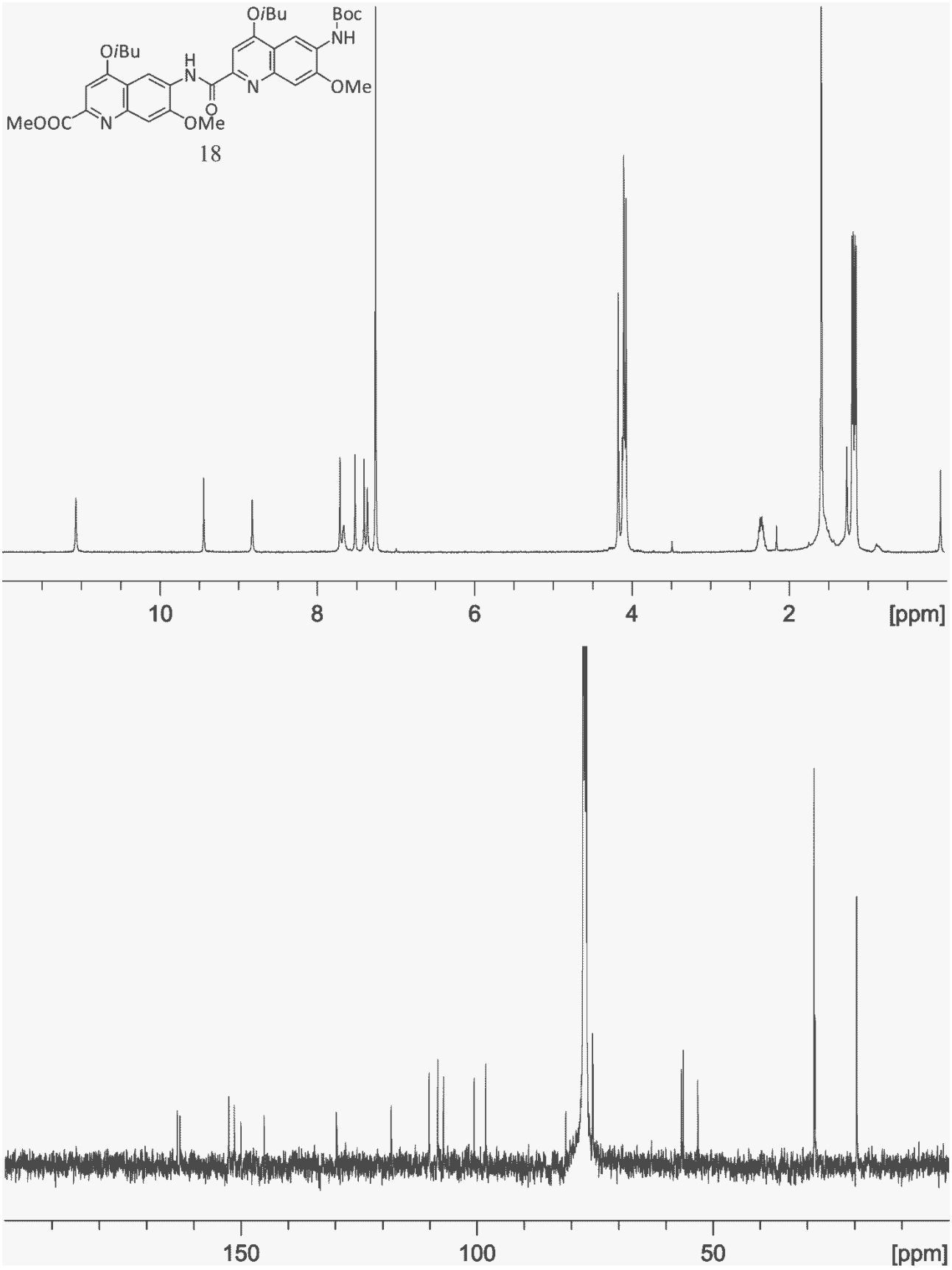

O
NHAc
MeOOC
N
H
OMe
13
14
12
10
8
6
4
2
[ppm]
150
100
50
[ppm]


OiBu
NHAc
MeOOC
N
OMe
14
14
12
10
8
6
4
2
[ppm]
150
100
50
[ppm]

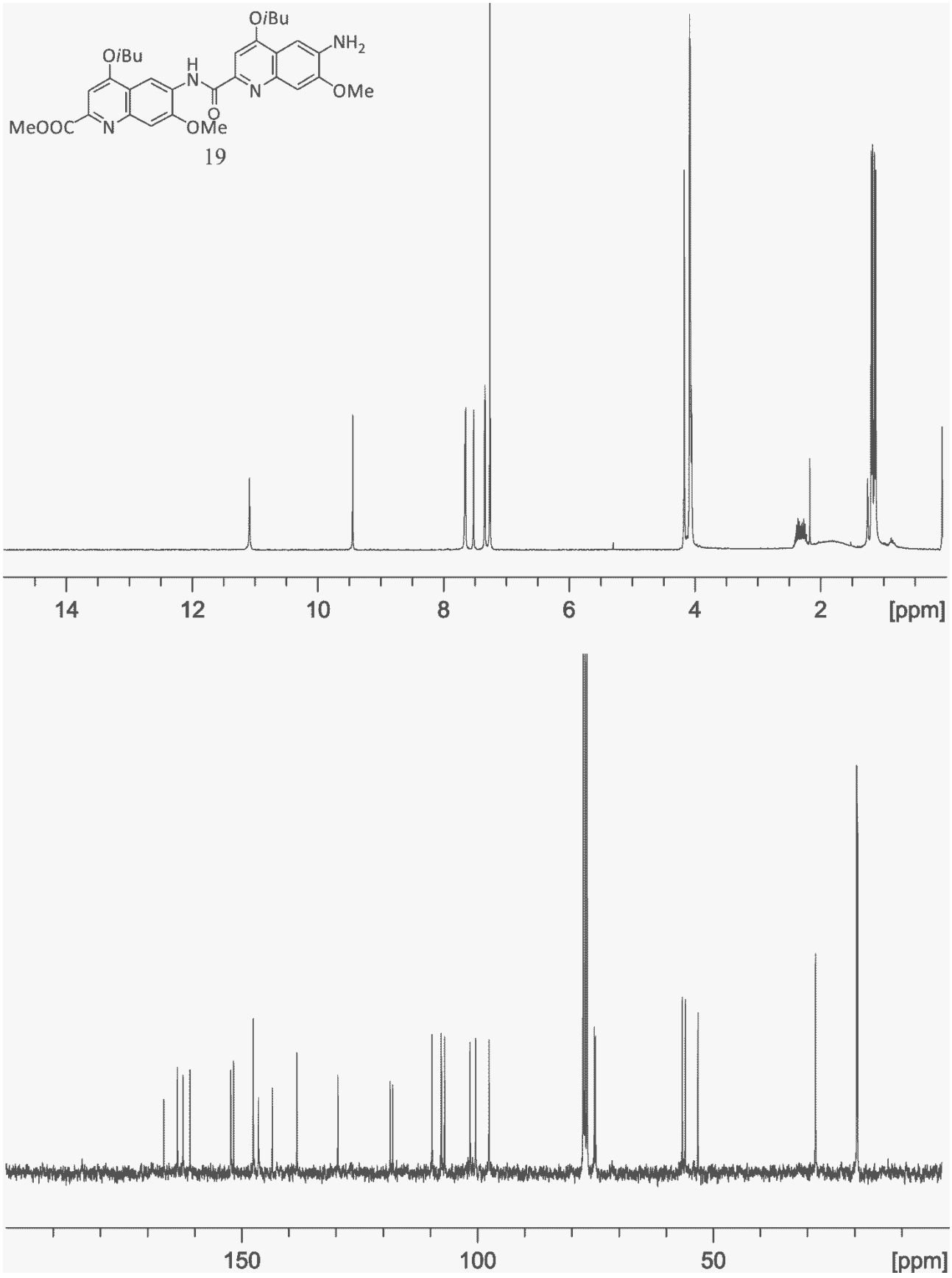

O*i*Bu
NH2
MeOOC
N
OMe
15
14
12
10
8
6
4
2
[ppm]
150
100
50
[ppm]

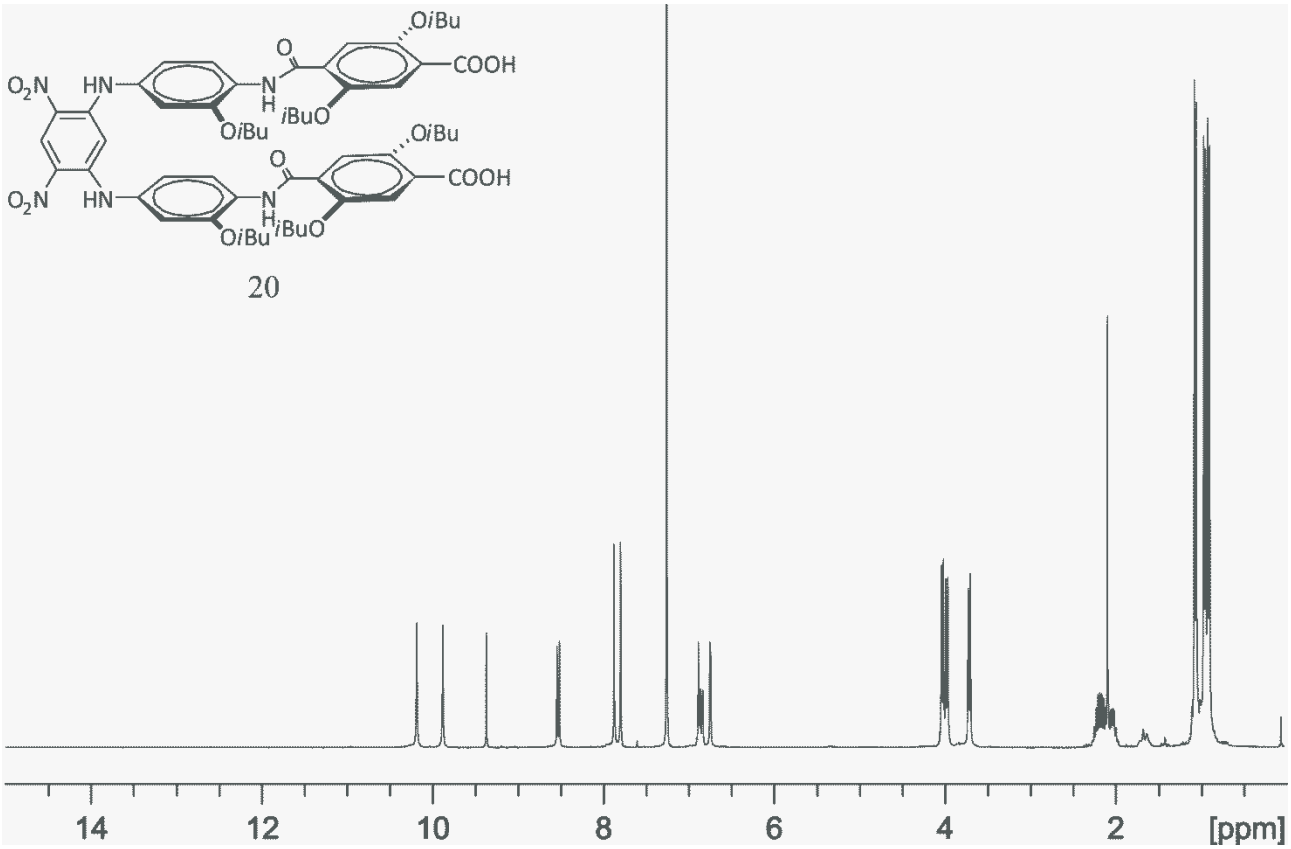

OiBu
Boc
NH
MeOOC
N
OMe
16
14
12
10
8
6
4
2
[ppm]


O*i*Bu
Boc
NH
HOOC
N
OMe
17
14
12
10
8
6
4
2
[ppm]
150
100
50
[ppm]



18


OiBu
NH2
OiBu
H
N
N
OMe
O
MeOOC
N
OMe
19
14
12
10
8
6
4
2
[ppm]
150
100
50
[ppm]


OiBu
COOH
O2N
HN
N
H
O
iBuO
OiBu
OiBu
COOH
O2N
HN
N
H
O
iBuO
OiBu
14
12
10
8
6
4
2
[ppm]

20

7. References

[1] For methods, see C. Dolain, A. Grélard, M. Laguerre, H. Jiang, V. Maurizot, I. Huc. *Chem. Eur. J.* **2005**, *11*, 6135-6144.
[2] *CrystalClear* (Version 1.36). MSC, The Woodlands, Texas, USA.
[3] SHELXLD G. M. Sheldrick *Acta Cryst.* (2008). A**64**, 112-122.
[4] WINGX L. J. Farrugia, *J. Appl. Cryst.* (2012),**45**, 849-854.
[5] SQUEEZE/PLATON v.d. Sluis & A.L. Spek, Acta Cryst. A46, (1990), 194).
[6] K. J. Divakar, B. V. Gaikwad, N. F. Tampal, S. Rajappa. *J. Chem. Res.* Synopses, **1986**, *5*, 161.