Hetero-Double Helices Formation by Cross Hybridization of Homo-Double Helices of 8-Halide Substituted Quinoline Oligoamides

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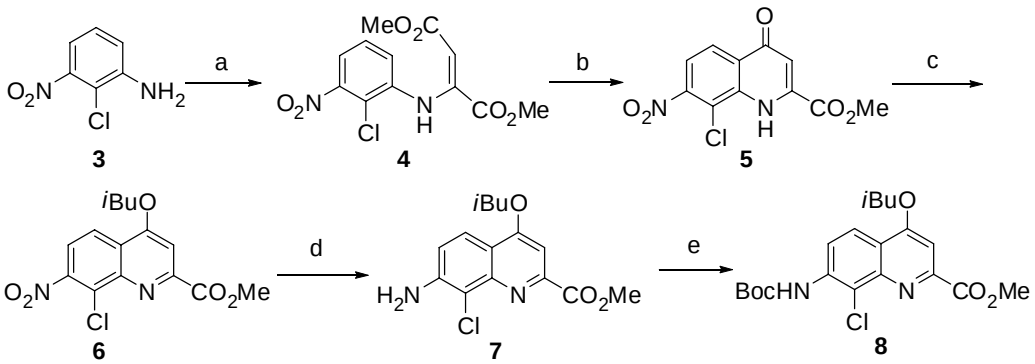
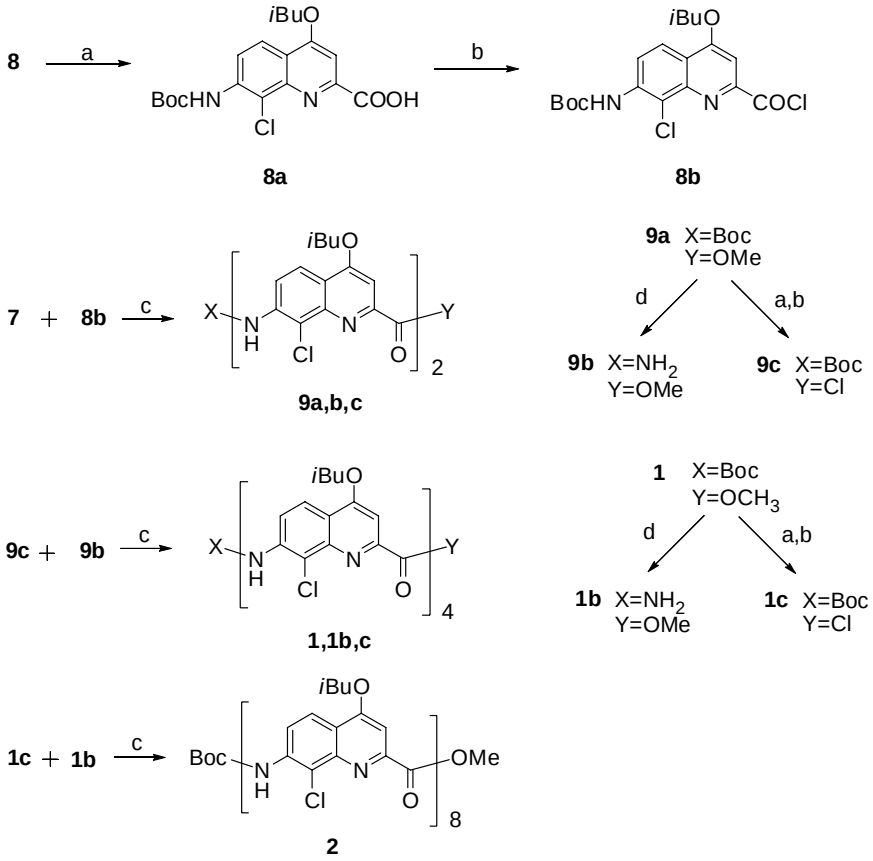
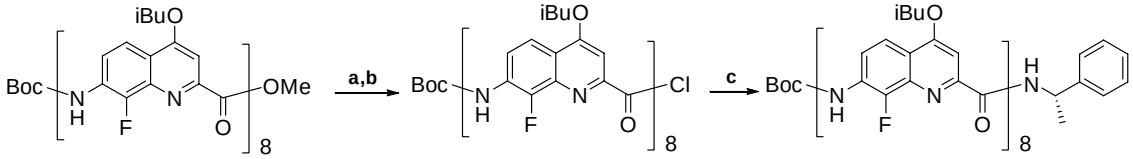


Scheme S1. Synthesis of fluoroquinoline monomer **8**: a) dimethylacetylene dicarboxylate, MeOH, Δ; b) diphenyl ether, reflux; c) *i*BuOH, DIAD, PPh_3, THF, r.t.; d) Fe, AcOH, 120°C; e) di-*tert*-butyl dicarbonate, dioxane, heating for 4 days.



Scheme S2. Synthesis of oligofluoroquinoline amides. a) NaOH, THF/water, rt; b) 1-chloro-N,N,2-trimethylpropenylamine, DCM, rt, 2h; c) DIEA, DCM; d) TFA/DCM, rt.



Scheme S3. Synthesis of Chiral octamer. a) KOH, THF/water, rt; b) 1-chloro-N,N,2-trimethylpropenylamine, DCM, rt, 2h; c) (*s*)-1-phenylethanamine, DCM.

NMR studies of aggregation

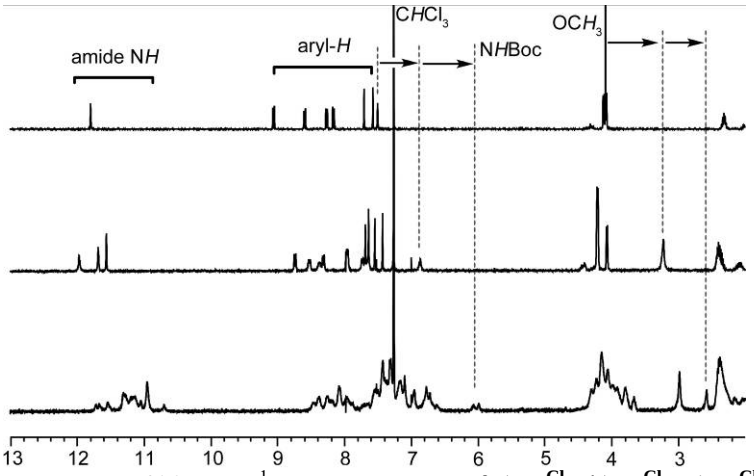


Figure S1: 400 MHz ^{1}H NMR spectra of a) $\mathbf{Q^{Cl}_2}$, b) $\mathbf{Q^{Cl}_4}$, c) $\mathbf{Q^{Cl}_8}$ in $CDCl_3$ (2mM) at 298K.

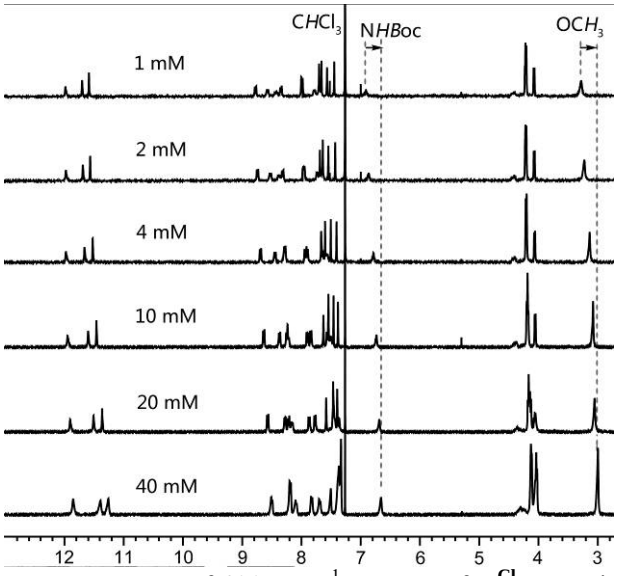


Figure S2 Part of 400MHz ^{1}H NMR of $\mathbf{Q^{Cl}_4}$ at various concentrations in $CDCl_3$ at 25°C.

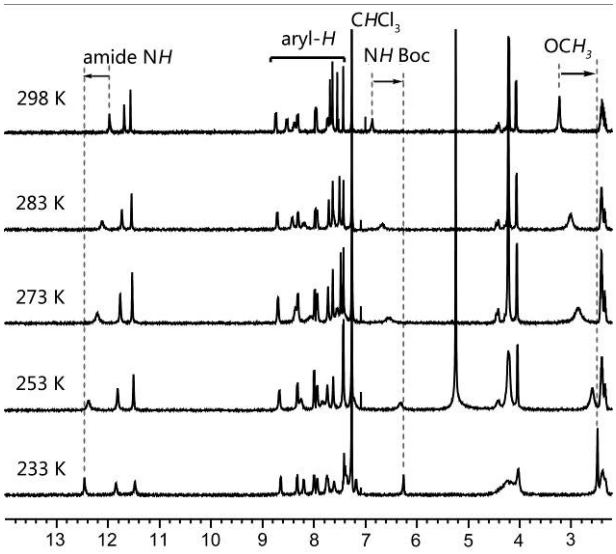


Figure S3 Temperature dependent ^{1}H NMR spectra (600 MHz) of $\mathbf{Q^{Cl}_4}$ (2 mM) in $CDCl_3$. The sharp signal at 5.4 ppm observed at 253K is not identified but likely associated with the solvent or water. It appears in the 243-253K range in the spectra of $\mathbf{Q^{Cl}_4}$.

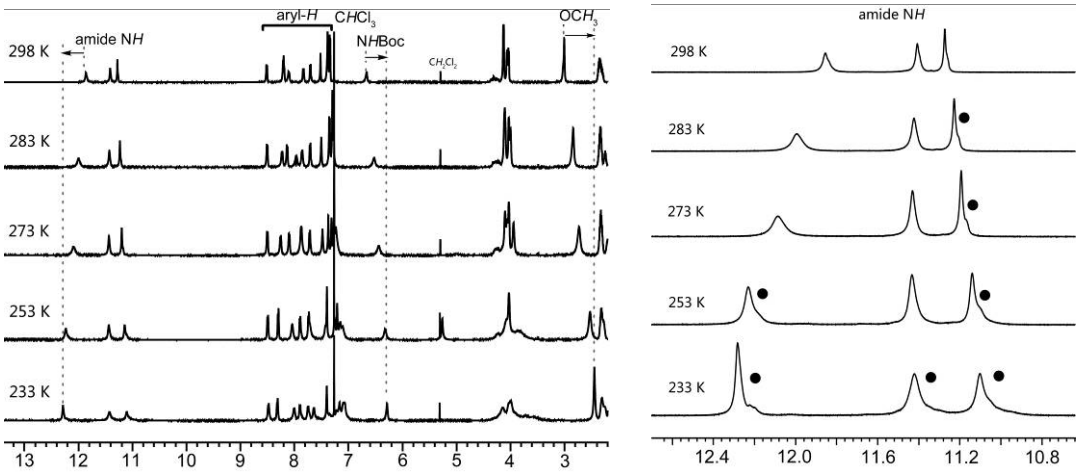


Figure S4 Temperature dependent ^{1}H NMR spectra (600 MHz) of $\mathbf{Q^{Cl}_4}$ (40 mM) in $CDCl_3$. The magnified spectra (right) of amide N*H* signal. The black circles indicate signals of a new species appearing at low temperature.

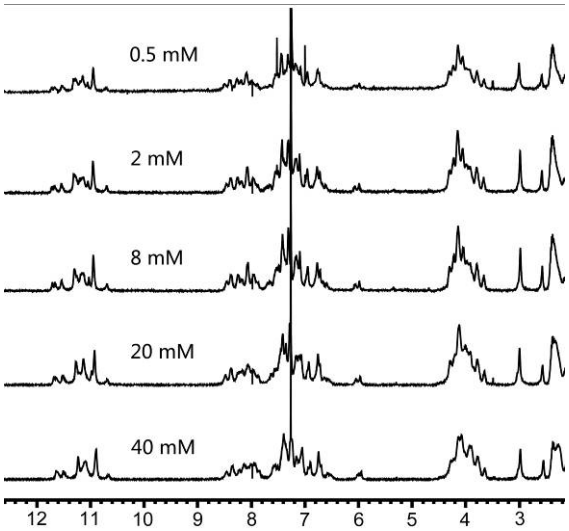


Figure S5 Part of 400MHz ^{1}H NMR of $\mathbf{Q^{Cl}_8}$ at various concentrations in $CDCl_3$ at 25°C.

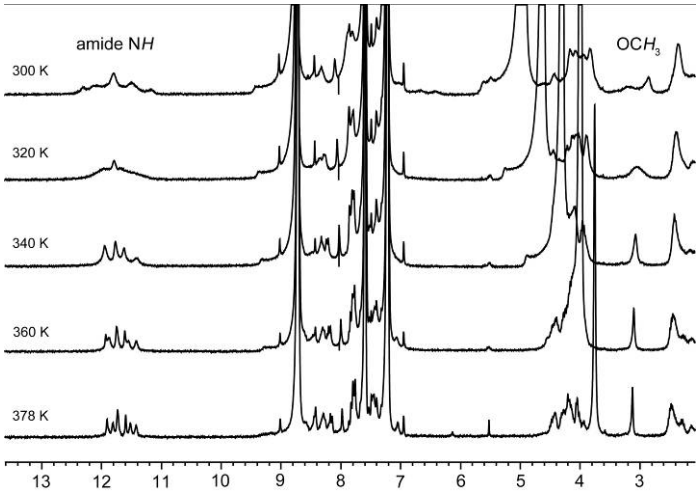


Figure S6. Partial ^{1}H NMR spectra (300 MHz) of $\mathbf{Q^{Cl}_8}$ (1mM) in pyridine-d_5 at various temperatures.

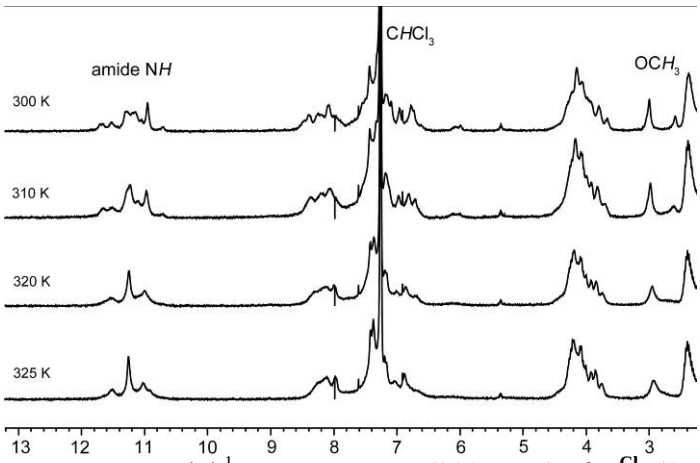


Figure S7. Partial ^{1}H NMR spectra (300 MHz) of $\mathbf{Q^{Cl}_8}$ (1mM) in $CDCl_3$ at various temperatures.

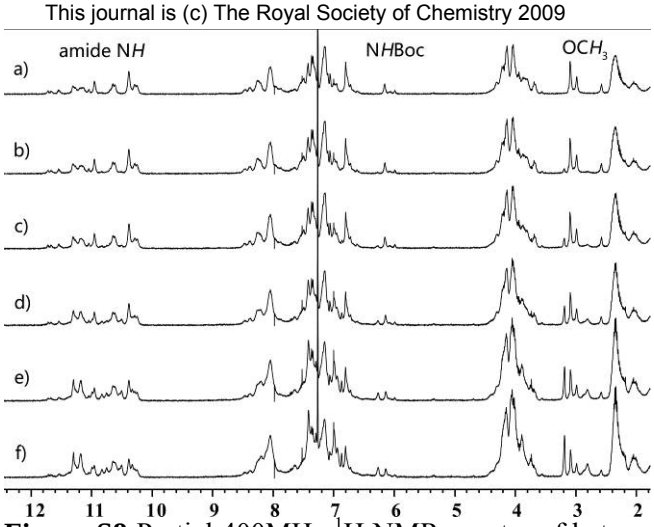


Figure S8 Partial 400MHz ^{1}H NMR spectra of hetero-hybridized process between $\mathbf{Q^{Cl}_8}$ and $\mathbf{Q^{F}_8}$ at 296 K (2 mM Each). a) 0h, b) 20h c) 46h, d) 96h, f) 155h, 202h.

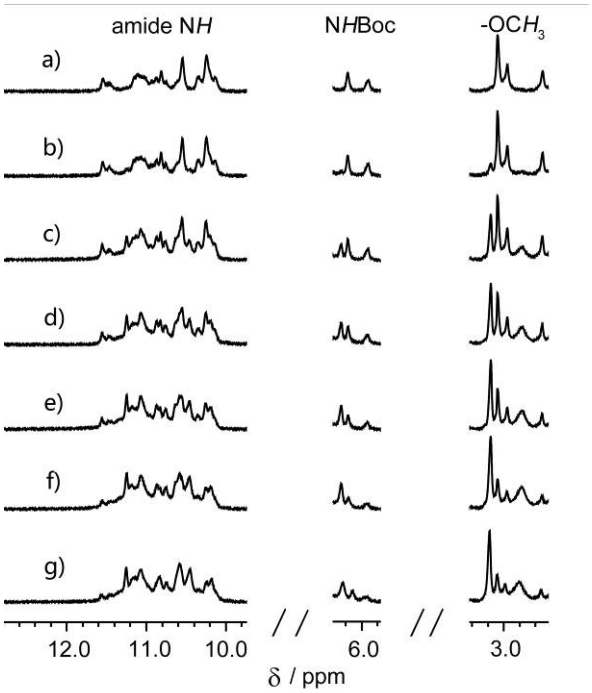


Figure S9 Partial 400MHz ^{1}H NMR spectra of hetero-hybridized process between $\mathbf{Q^{Cl}_8}$ and $\mathbf{Q^{F}_8}$ at 296 K (50 mM Each). a) 0h, b) 1h, c) 4h, d) 6h, e) 8h, f) 19h, g) after long time equilibrated.

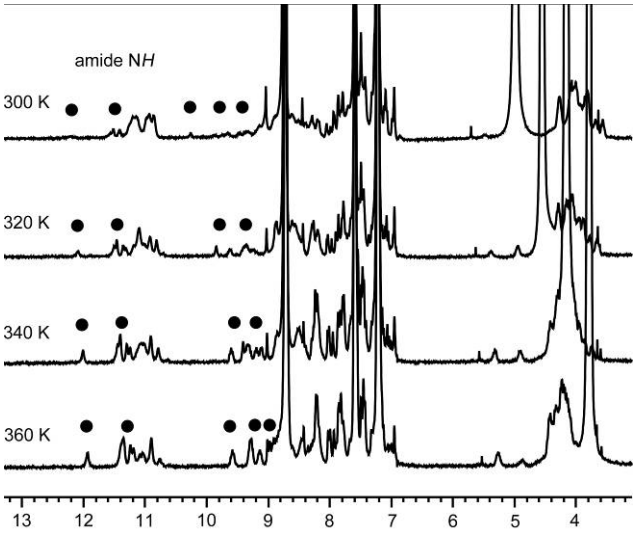


Figure S10 Partial ^{1}H NMR spectra (300 MHz) of **S-Q$^{F}_{8}$** (1mM) in pyridine-d$_5$ at various temperatures, showing a second set of signals appearing downfield (•).

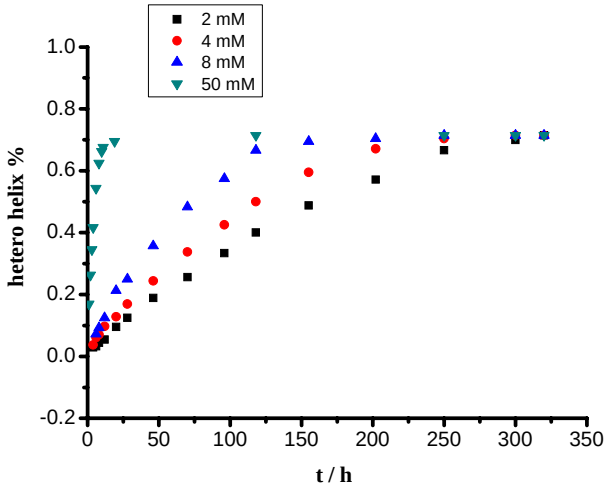


Figure S11 Kinetics of hetero-hybridized process monitored by ^{1}H NMR at 296 K in $CDCl_3$.

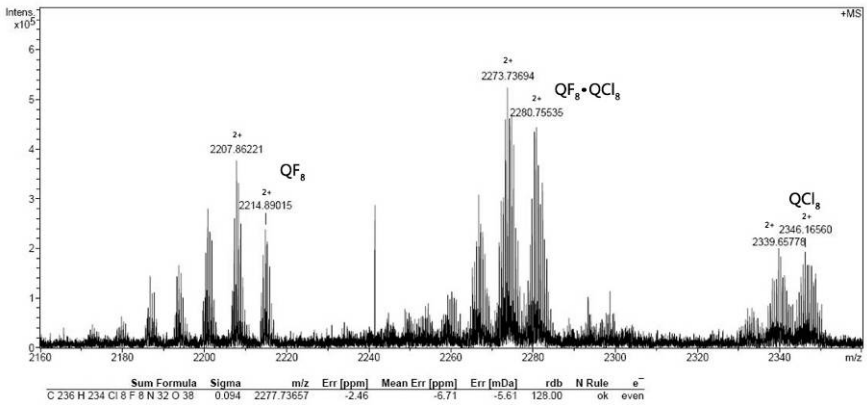


Figure S12 Experimental high resolution ESI mass spectrum of the equimolar mixture of **Q$^{Cl}_{8}$** and **Q$^{F}_{8}$**.

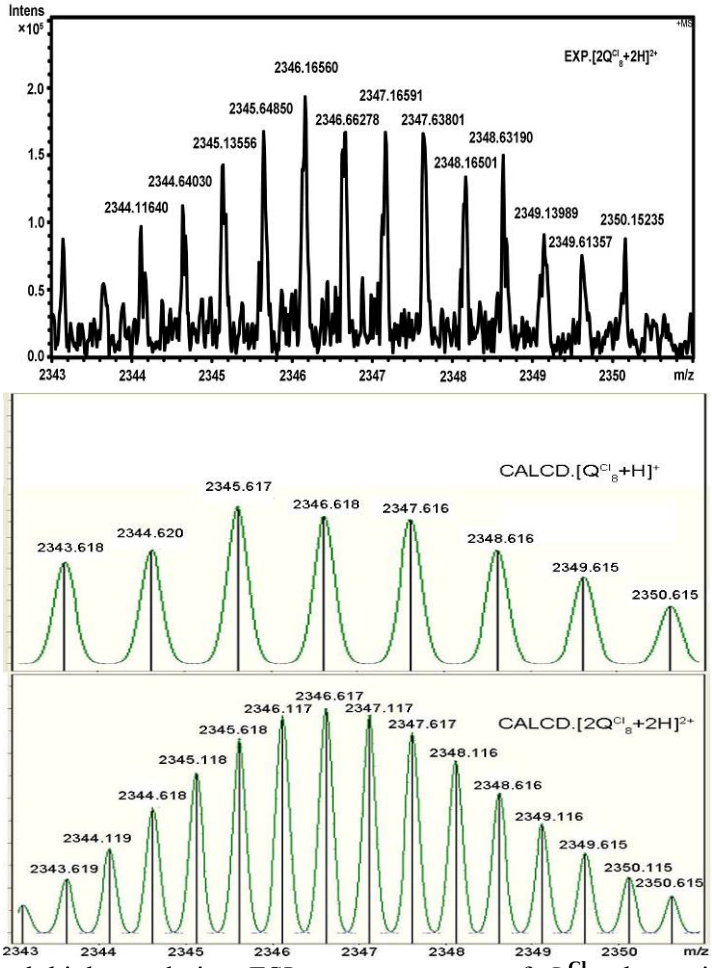


Figure S13 Experimental high resolution ESI mass spectrum of $\mathbf{Q^{Cl}_8}$ shows it forms double helices. 2346.66278 $[2M+2H]^{2+}$ (Top). The middle and bottom figures show the theoretical isotopic distributions of $[M+H]^+$ (middle) and $[2M+2H]^{2+}$ (bottom), respectively.

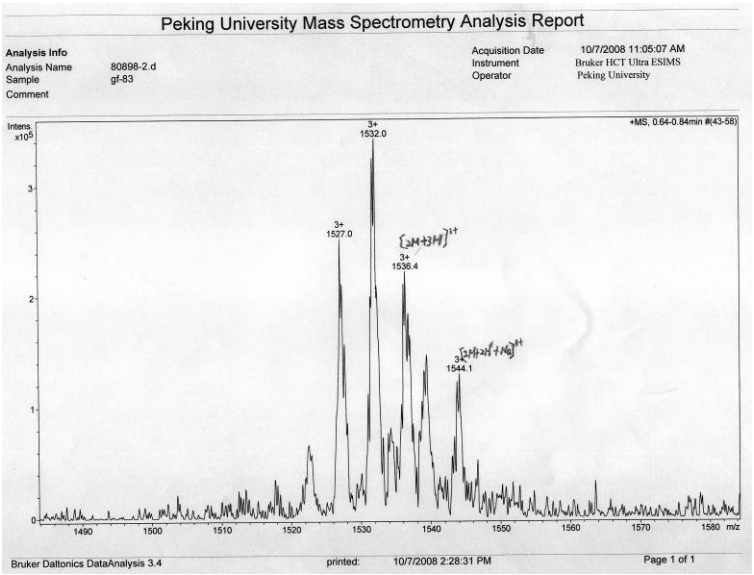


Figure S14 Experimental high resolution ESI mass spectrum of $\mathbf{S\text{-}Q^F_8}$ shows it forms double helices. 1536.4 $[2M+3H]^{3+}$, 1544.1 $[2M+2H+Na]^{3+}$.

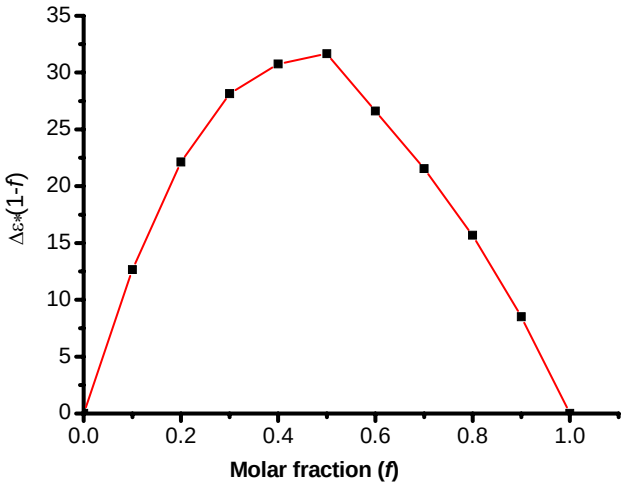


Figure S15 Job plot showing the 1:1 hybridization of **S-Q$^{F}_{8}$** and **Q$^{Cl}_{8}$.** The total concentration of **S-Q$^{F}_{8}$** and **Q$^{Cl}_{8}$** is 1x10^{-5} M in $CHCl_3$. The solutions were equilibrated at 23°C for 5 d before measurements.

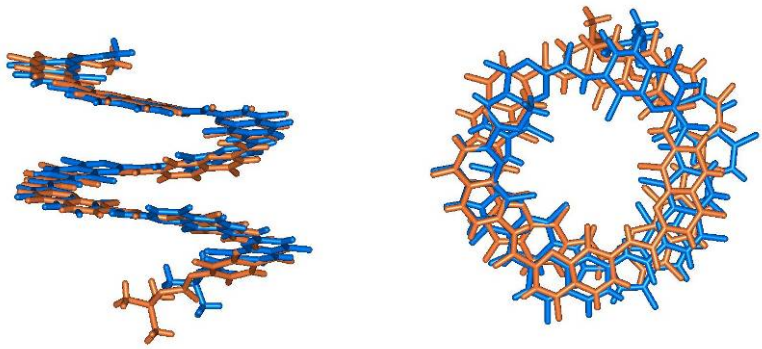


Figure S16 The superimposed structure of Q^{F}_{8} (Blue) and Q^{Cl}_{8} (Golden).

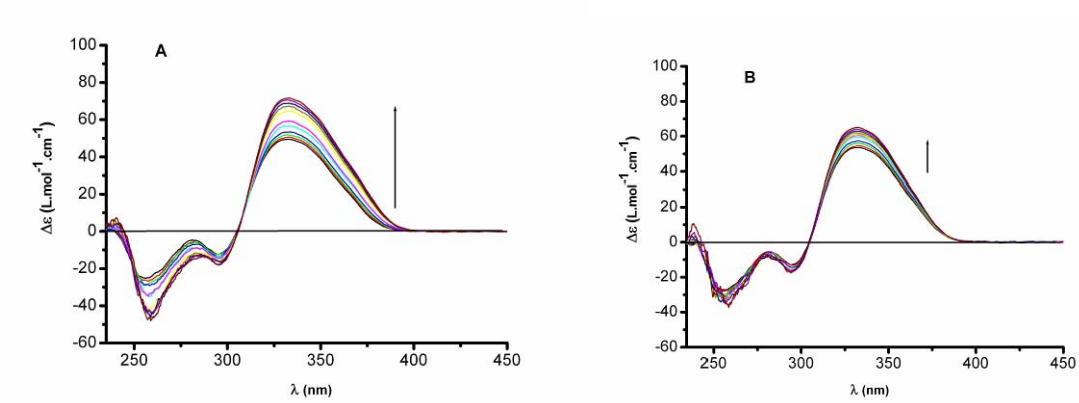


Figure S17 the CD spectra of the mixtures of ***s*-Q$^{F}_{8}$** (5×10^{-6} M) with variable concentration of **Q$^{Cl}_{8}$** (A) and **Q$^{F}_{8}$** (B) in $CHCl_3$, respectively. The concentrations of **Q$^{Cl}_{8}$** and **Q$^{F}_{8}$** vary from 0 to 1×10^{-5} M. All solutions were equilibrated at 23°C for 5 days before measurements.

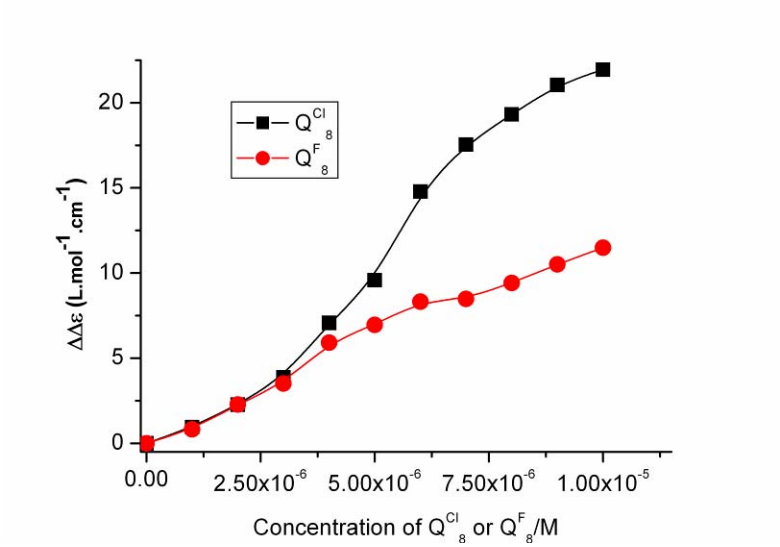


Figure S18 the change of CD Intensity at 331nm for the mixtures of ***s*-$\mathbf{Q^F_8}$** (5×10^{-6} M) with variable concentration of $\mathbf{Q^{Cl}_8}$ and $\mathbf{Q^F_8}$ in $CHCl_3$, respectively. The concentrations of $\mathbf{Q^{Cl}_8}$ and $\mathbf{Q^F_8}$ vary from 0 to 1×10^{-5} M. All solutions were equilibrated at 23°C for 5 days before measurements.

Crystal data were collected on a Bruker AXS X8Proteum Cu Kα rotating anode equipped with a high flux Helios optic. The data collection was performed using Proteum2 suite. Cell refinement and data reduction were performed using SAINT (Siemens, 1996). The positions of non-H atoms were determined by the program SUPERFLIP. Crystal data for $(QCl_8)_2$: $(C_{118}H_{114}Cl_8N_{16}O_{19})_2$, Mr = 4687.72, T = 173(2) K, monoclinic space group C2/c, a = 31.428(6), b = 36.642(7), c = 24.101(5) Å , β= 114.01(3)°, V = 25353(9) $Å^3$, ρcalc = 1.228 $g.cm^{-3}$, Z = 8, 56066 reflections collected, 9628 independent reflections (Rint = 0.063), final R indices [I>2σ(I)]: R1 = 0.1389, wR2 = 0.3449, R indices (all data) R1 = 0.2104, wR2 = 0.3872. Crystals grew as long needles that are not single crystals. The poor crystal quality combined with a highly disordered solvent content explains the low quality of the refined structure. The structure was solved in the monoclinic space group using the charge fliping method with the program superflip. The squeeze module of the platon suite was used to attenuate the disordered solvent effect. CCDC: 745835. For crystallographic data in cif or other formats, see DOI XXXXX.

(1) L. Palatinus and G. Chapuis, J. Appl. Cryst., 2007, 40, 786-790
(2) G. M. Sheldrick, Acta Cryst., 2008, A64 112-122.
(3) A.L.Spek, J.Appl.Cryst. 2003, 36, 7-13

Experimental section

General. All reactions were carried out under a dry nitrogen atmosphere. NMR spectra were recorded on Bruker AVANCE 600 (600 MHz), Bruker AVANCE 400 (400 MHz) and Bruker DMX 300 (300 MHz) spectrometers. 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). EI, ESI, MALDI-TOF and high resolution ESI mass spectra were obtained on GCT， LC-MS 2010, Autotlex Ⅲ and Bruker Apex Ⅳ FTMS spectrometers, respectively. Circular Dichroism (CD) spectra were measured in a 10-mm quartz cell on a Biflex spectrometer.

2-Chloro-3-nitroaniline 3 To glacial acetic acid (80 mL) was added 2- **Chloro**-1,3-dinitrobenzene (9.0 g, 44.4 mmol). The mixture was heated to 120°C. Reduced iron powder (7.2 g, 2.9 equiv.) was added in portions over a period of 40 min and the mixture was heated to reflux for 2.5 h. The hot reaction mixture was poured into cold water and extracted with ether (3×50 mL). The combined organic fractions were washed with brine (5×40 mL), dried over Na_2SO_4, filtered and evaporated to dryness to give 4.33 g (56.5% yield) of

the crude product as a yellow solid, which was used without further purification. ^{1}H NMR ($CDCl_3$): δ 7.19-7.16 (m, 2H), 6.95-6.93 (m, 1H), 4.41 (s, 2H). ^{13}C NMR (CDCl3): δ 145.1, 134.3, 127.5, 118.6, 114.4, 110.7.

Dimethyl N-(2-Chloro-3-nitro-phenyl)-amino-fumarate 4 To a solution of **3** (2.2 g, 12.8 mmol) in MeOH (20 mL) was added dimethyl acetylenedicarboxylate (1.72 mL, 14.0 mol). After 18 h of stirring, the mixture was heated to reflux for 6 h and cooled. The resulting yellow prisms were collected by filtration to yield 3.0 g (75%) of the product. ^{1}H NMR ($CDCl_3$): δ 9.87 (s, 1H), 7.49-7.46 (m, 1H), 7.27 (t, *J*=8.1 Hz, 1H), 6.92 (d, *J*=8.2 Hz, 1H), 5.73 (s, 1H), 3.77 (s, 3H), 3.76 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 169.3, 163.8, 149.4, 145.1, 139.9, 127.1, 123.4, 119.4, 117.8, 99.6, 53.2, 51.9. MS (ESI) : 315.1 $[M+H]^+$, 327.2 $[M+Na]^+$.

Methyl 8-chloro-7-nitro-4-(*1H*)-quinolone-2-carboxylate 5 A mixture of **4** (3.00 g, 9.5 mmol) and diphenyl ether (30.00 g) was heated with stirring at 240-250°C for 10 min. The product began to precipitate in the hot reaction medium. After cooling, the mixture was diluted with 100 ml of light petroleum ether to complete the precipitation. The solid was filtered off, washed well with hexane, and recrystallized from methanol in which it is sparingly soluble yield to give 2.57 g (94%) of the product. ^{1}H NMR ($CDCl_3$): δ 9.50 (br, 1H), 8.40 (d, *J*=8.8 Hz, 1H), 7.77 (d, *J*=8.8 Hz, 1H), 7.05 (s, 3H), 4.09 (s, 3H). MS (ESI) : 304.9 $[M+Na]^+$, 320.9 $[M+K]^+$.

Methyl 8-chloro-4-isobutoxy-7-nitro-2-quinolinecarboxylate 6 A mixture of **5** (2.57 g, 9.1 mmol) and triphenylphosphine (2.53 g, 1.05 equiv.), and 2-methyl-1-propanol (0.93 mL, 1.1 equiv.) in anhydrous THF (40 mL) was cooled to 0°C under nitrogen. Diisopropyl azodicarboxylate (1.9 mL, 1.05 equiv.) was added dropwise and the mixture was stirred at 0°C for 30 min, then at room temperature for 2 h. The solvent was evaporated. The product was purified by flash chromatography (SiO_2) eluting with CH_2Cl_2 to yield 2.40 g (78%) of a white solid. ^{1}H NMR ($CDCl_3$): δ 8.29 (d, *J*=9.1 Hz, 1H), 7.86 (d, *J*=9.1 Hz, 1H), 7.68 (s, 1H), 4.10 (d, *J*=8.8 Hz, 2H), 4.08 (s, 3H), 2.36-2.26 (m, 1H), 1.15 (d, *J*=6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 165.6, 163.3, 151.8, 149.6, 145.2, 128.0, 124.7, 122.0, 121.8, 103.4, 76.1, 53.7, 28.2, 19.3. MS (ESI) : 339.1 $[M+H]^+$, 361.1 $[M+Na]^+$.

Methyl 7-amino-8-chloro-4-isobutoxy-2-quinolinecarboxylate 7 The nitro quinoline **6** (1.32 g, 3.9 mmol) was dissolved in glacial acetic acid (20 mL) and the solution was heated to 120°C Reduced iron powder (0.63 g, 2.9 equiv.) was added in one portion and the mixture was stirred at 120°C for 2 h. The hot mixture was poured into water, and the precipitate was filtered off and washed with cold water to give 1.14 g (95%) of the product as a yellow solid which was used without additional purification. ^{1}H NMR ($CDCl_3$): δ 7.99 (d, *J*=9.0 Hz, 1H), 7.42 (s, 1H), 7.09 (t, *J*=9.0 Hz, 1H), 4.60 (br, 2H), 4.03 (s, 3H), 4.01 (d, *J*=6.5 Hz, 2H), 2.26-2.21 (m, 1H) 2.53-2.27 (m, 1H), 1.11 (d, *J*=6.7 Hz, 6H). ^{13}C NMR (CDCl3): δ 166.6, 163.1, 149.9, 146.4, 145.0, 121.1, 118.6, 116.5, 112.9, 99.4, 75.2, 53.3, 28.3, 19.3. MS (ESI) : 309.1 $[M+H]^+$, 331.1 $[M+Na]^+$.

Methyl 7-(*tert*-butoxycarbonylamino)-8-chloro-4-isobutoxy-2-quinolinecarboxylate 8 A solution of **7** (1.45 g, 4.7 mmol) in dioxane (30 mL) containing di-*tert*-butyl-dicarbonate (6.14 g, 28.2 mmol) was heated at 80°C for 4 days. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel eluting with CH_2Cl_2 to afford the pure product (1.76 g, 92%). ^{1}H NMR ($CDCl_3$): δ 8.60 (d, *J*=9.3 Hz, 1H), 8.15 (d, *J*=9.3 Hz, 1H), 7.52 (s, 1H), 7.50 (s, 1H), 4.05 (s, 3H), 4.05 (d, *J*=8.3 Hz, 2H), 2.30-2.26 (m, 1H), 1.57 (s, 9H), 1.13 (d, *J*=6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 166.3, 163.2, 152.3, 150.1, 145.3, 137.9, 121.0, 119.9, 119.1, 118.1, 100.7, 81.8, 75.5, 53.4, 28.4, 28.3, 19.3. MS (ESI) : 409.2 $[M+H]^+$, 431.2 $[M+Na]^+$.

Dimer 9a. Monomer **8** (0.82 g, 2.0 mmol) was dissolved in a mixture of THF (60 mL) and H_2O (6 mL). To this solution was added NaOH (0.2 g, 2.5 equiv.). The solution was stirred at room temperature for 5 h. Then solution was neutralized with 1N HCl to pH = 4~5, and concentrated under reduced pressure to remove THF. H_2O (30 mL) was added to the residue. The aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried over Na_2SO_4, filtered, then evaporated to give monomer acid **8a** as a white solid. It was dried in vacuo, and then dissolved in CH_2Cl_2 (40 mL). 1-chloro-*N*,*N*,2-trimethyl-propenylamine (0.32 mL, 1.2 equiv.) was added. The reaction mixture was stirred at RT for 2 h resulting in a homogeneous solution, and then evaporated to provide the corresponding acid chloride **8c**. To a solution of the monomer amine **7** (0.56 g, 1.8 mmol) in CH_2Cl_2 (20 mL) containing DIEA (1.4 mL, 8.0 mmol) was added a solution of acid chloride **8c** in CH_2Cl_2 (20 mL) via cannula. The reaction mixture was stirred at RT overnight. The solution was evaporated and the product was purified by flash chromatography (SiO_2) eluting with CH_2Cl_2. Yield 1.10 g (89%) of a white solid. ^{1}H NMR ($CDCl_3$): δ 11.80 (s, 1H), 9.07 (d, *J*=9.2 Hz, 1H), 8.60 (d, *J*=9.3 Hz, 1H), 8.28 (d, *J*=9.3 Hz, 1H), 8.17 ((d, *J*=9.3 Hz, 1H), 7.70 (s, 1H), 7.57 (s, 1H), 7.50 (s, 1H), 4.13-4.07 (m, 7H), 2.37-2.27 (m, 2H), 1.59 (m, 9H), 1.17-1.14 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 166.3, 163.9, 163.1, 162.6, 152.3, 151.2, 150.1, 145.2, 143.9, 138.0, 137.4, 121.0, 121.0, 120.5, 120.3, 119.8, 119.6,

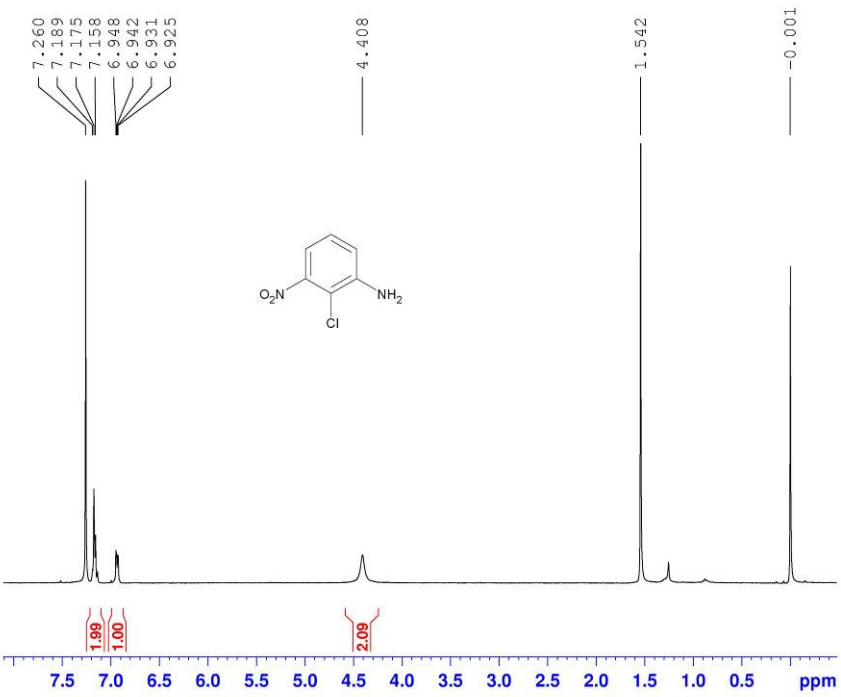
119.0, 117.7, 100.8, 97.8, 81.9, 75.7, 75.5, 53.4, 28.4, 28.3, 28.3, 19.4, 19.4. MS (MALDI-TOF): 685.4 $[M+H]^+$, 707.4 $[M+Na]^+$, 723.4 $[M+K]^+$.

Tetramer 1 Dimer **9a** (0.61 g 0.9 mmol) was dissolved in CH_2Cl_2 (10 mL), and excess TFA (5 mL) was added. The mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (20 mL), washed with saturated $NaHCO_3$, dried over Na_2SO_4 and then evaporated to give dimer amine **9b** as a yelllow solid. It was dried in vacuo, and used without further purification. Separately, dimer **9a** (0.68 g, 1.0 mmol) was dissolved in a mixture of THF (50 mL) and H_2O (5 mL). NaOH (0.1 g, 2.5 mmol) was added, and the solution was stirred at room temperature for 5h. The solution was neutralized with 1N HCl to pH = 4~5, then concentrated under reduced pressure to remove THF. H_2O (30 mL) was added to the residue. The aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried over Na_2SO_4 and then evaporated to give the corresponding dimer acid as a white solid. It was dried in vacuo, and then dissolved in CH_2Cl_2 (40 mL). To this solution was added 1-chloro-*N*,*N*,2-trimethylpropenylamine (0.16 mL, 1.2 equiv.). The reaction mixture was stirred at RT for 2 h resulting in a homogeneous solution, then evaporated to provide the corresponding acid chloride **9c**. To a solution of the dimer amine **9b** in CH_2Cl_2 (20 mL) containing DIEA (0.7 mL, 4.0 mmol) was added a solution of acid chloride **9c** in CH_2Cl_2 (20 mL) via cannula. The reaction mixture was stirred at RT overnight. The solution was evaporated and the product was purified by flash chromatography (SiO_2) eluting with CH_2Cl_2/EtOAc, 20:1. Yield 0.86 g (78%) of a white solid. ^{1}H NMR (2mM, $CDCl_3$): δ 11.97 (s, 1H), 11.69 (s, 1H), 11.58 (s, 1H), 8.77 (d, *J*=9.3 Hz, 1H), 8.56 (d, *J*=9.3 Hz, 1H), 8.41 (d, *J*=9.3 Hz, 1H), 8.34 (d, *J*=9.3 Hz, 1H), 7.99 (d, *J*=9.3 Hz, 1H), 7.77 (d, *J*=9.3 Hz, 1H), 7.69 (s, 1H), 7.65 (s, 1H), 7.56 (s, 1H), 7.44 (s, 1H), 6.89 (br, 1H), 4.21-4.06 (m, 8H), 3.25 (s, 3H), 2.44-2.31 (m, 4H), 1.35 (s, 9H), 1.30-1.22 (m, 24H). ^{13}C NMR ($CDCl_3$): δ 166.4, 163.3, 163.0, 163.0, 162.2, 162.1, 161.9, 151.8, 150.8, 150.5, 150.5, 149.5, 145.0, 143.2, 143.1, 142.9, 137.1, 136.9, 136.6, 136.5, 121.4, 120.3, 119.7, 118.9, 118.4, 100.2, 97.9, 97.5, 97.4, 81.2, 75.5, 75.4, 75.2, 75.1, 52.4, 28.5, 28.4, 28.4, 28.4, 28.0, 19.5, 19.5, 19.4, 19.4. MS (MALDI-TOF) : 1261.2 $[M+Na]^+$, 1277.2 $[M+K]^+$.

Octamer 2 was prepared from tetramer 1 via saponification on one hand and TFA treatment on the other hand to get the tetramer acid and tetramer amine, respectively. The synthetic procedures are the same as used for the synthesis of **1**. Yield > 70%. ^{1}H NMR (4 mM, $CDCl_3$): δ 11.68-10.68 (br, 7H), 8.49-7.86 (br, 7H), 7.63-7.28 (br, 9H), 7.16-6.56 (br, 8H), 6.04-5.97 (br, 1H), 4.28-3.65 (m, 16H), 2.99-2.56 (br, 3H), 2.40-2.33 (m, 8H), 1.39-0.81 (m, 57H). ^{13}C NMR ($CDCl_3$): δ 166.1, 165.6, 162.5, 162.3, 162.1, 162.0, 161.8, 161.6, 161.1, 160.8, 151.5, 150.4, 150.1, 149.5, 148.6, 142.9, 142.8, 142.5, 142.2, 142.1, 141.7, 141.7, 141.5, 141.3, 136.7, 136.3, 136.2, 136.0, 135.6, 135.5, 135.0, 121.3, 120.5, 120.3, 120.2, 120.0, 119.9, 119.6, 119.5, 119.2, 118.8, 118.7, 118.6, 118.1, 118.0, 117.5, 117.3, 117.2, 116.8, 116.4, 116.2, 99.4, 99.2, 97.8, 97.4, 97.3, 97.0, 96.0, 80.8, 75.3, 75.1, 74.6, 74.4, 52.5, 51.8, 28.6, 28.5, 28.2, 27.8, 27.4, 19.6, 19.3, 19.1. MS (MALDI-TOF) : 2367.6 $[M+Na]^+$. ESI: 2346.66278 $[2M+2H]^{2+}$.

Chiral octamer 8-fluoroquinoline octamer (0.1 g, 0.045 mmol) was dissolved in a mixture of THF (10 mL) and H_2O (2 mL). To this solution was added KOH (12.0 mg, 5.0 equiv.). The solution was was heated to reflux for 4 h and cooled. Then solution was neutralized with 1N HCl to pH = 4~5, and concentrated under reduced pressure to remove THF. H_2O (10 mL) was added to the residue. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried over Na_2SO_4, filtered, then evaporated to give octamer acid as a white solid. It was dried in vacuo, and then dissolved in CH_2Cl_2 (10 mL). 1-chloro-*N*,*N*,2-trimethyl-propenylamine (0.012 mL, 2.0 equiv.) was added. The reaction mixture was stirred at RT for 2 h resulting in a homogeneous solution, and then evaporated to provide the corresponding acid chloride. To a solution of (*s*)-1-phenylethanamine (0.023 mL, 0.18 mmol) in CH_2Cl_2 (10 mL) was added a solution of octamer acid chloride in CH_2Cl_2 (10 mL) via cannula. The reaction mixture was stirred at RT overnight. The solution was evaporated and the product was purified by flash chromatography (SiO_2) eluting with CH_2Cl_2/EtOAc, 20:1. Yield 0.095 g (91%) of a white solid. ^{1}H NMR (4 mM, $CDCl_3$): δ 10.50-10.29 (br, 7H), 8.34-7.88 (br, 8H), 7.45-7.35 (br, 4H), 7.15-6.85 (br, 17H), 6.15 (br, 1H), 4.40-3.67 (m, 17H), 2.38-2.12 (m, 8H), 1.35-0.75 (m, 60H). ^{13}C NMR ($CDCl_3$): δ 162.8, 162.2, 162.1, 161.8, 161.7, 161.5, 161.4, 151.5, 150.8, 150.6, 150.4, 149.7, 149.6, 149.5, 147.3, 146.6, 146.5, 146.4, 145.5, 144.8, 144.3, 144.0, 143.9, 143.8, 143.8, 143.6, 142.9, 136.7, 136.6, 136.4, 136.3, 136.2, 136.1, 136.0, 135.9, 128.2, 128.1, 126.7, 126.5, 126.2, 126.0, 125.9, 125.9, 125.6, 119.6, 119.2, 119.2, 118.5, 118.3, 118.0, 117.8, 117.7, 117.4, 116.6, 116.1, 116.0, 115.8, 115.5, 98.0, 97.6, 97.3, 97.1, 96.9, 96.5, 80.9, 75.1, 49.5, 28.5, 28.4, 28.3, 28.2, 27.4, 19.7, 19.6, 19.6, 19.5, 19.4, 19.3, 19.2. MS (ESI) : 1536.4 $[2M+3H]^{3+}$, 1544.1 $[2M+2H+Na]^{3+}$.

^{1}H and ^{13}C NMR spectra of all relevant synthetic intermediates and title compounds.

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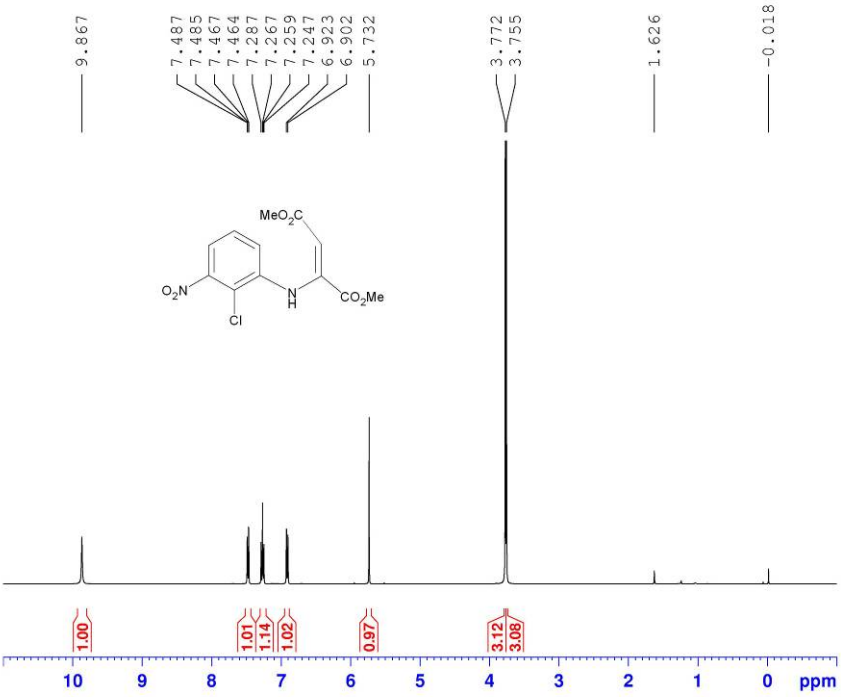


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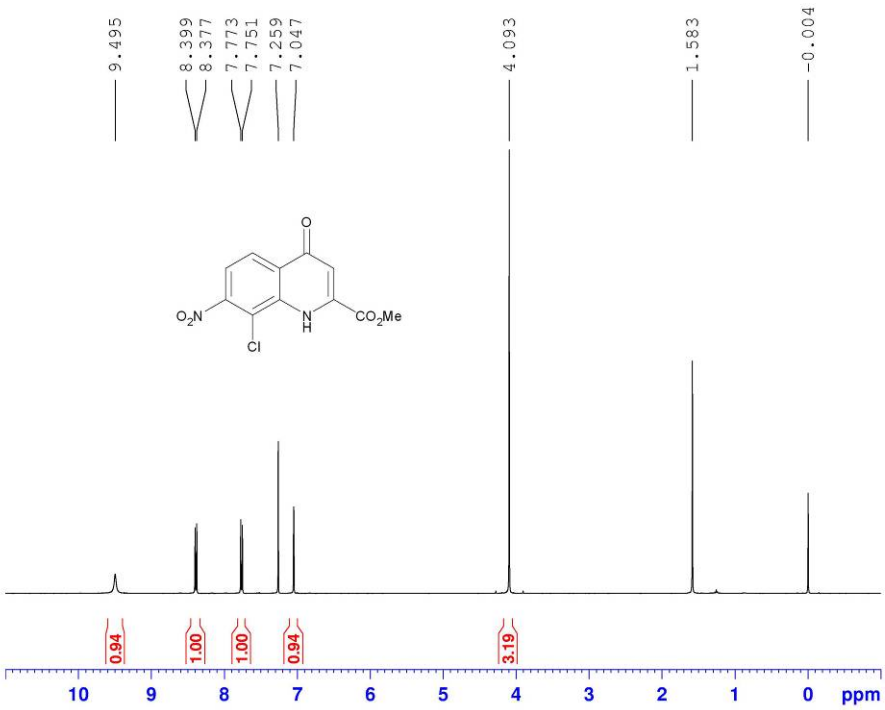


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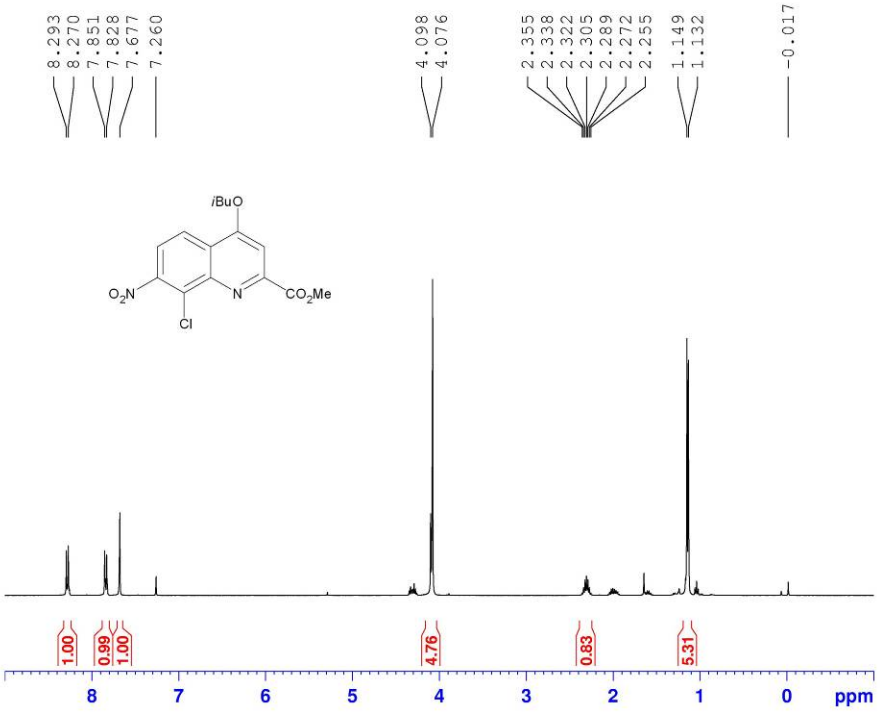


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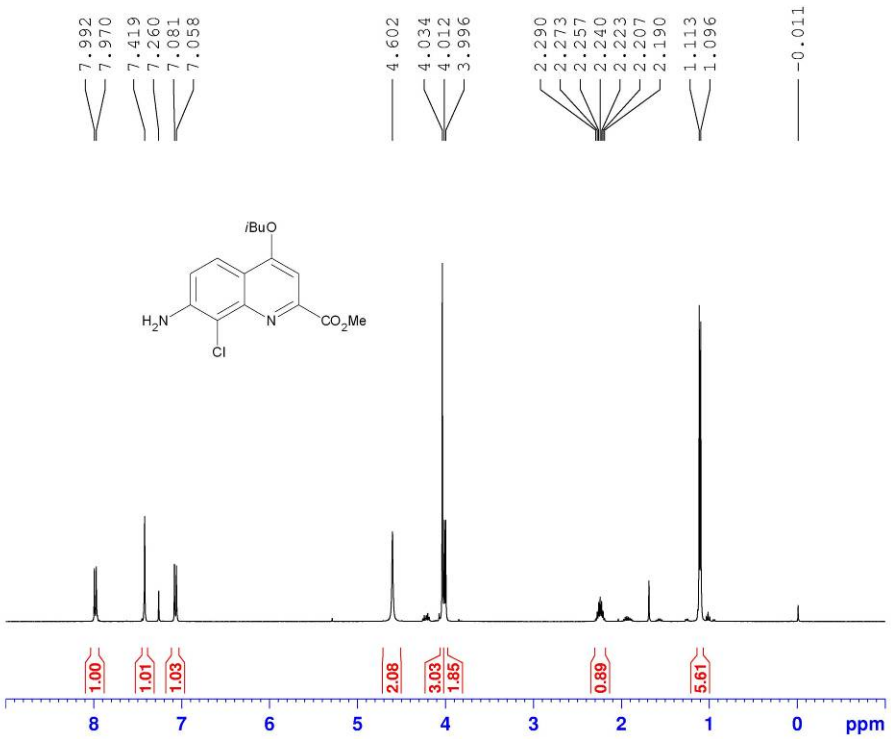


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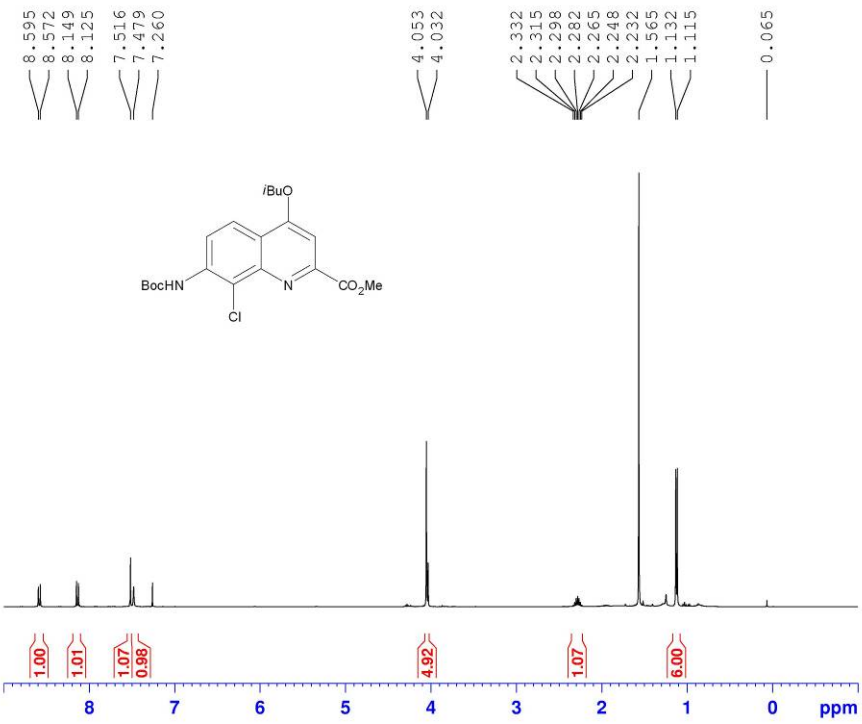


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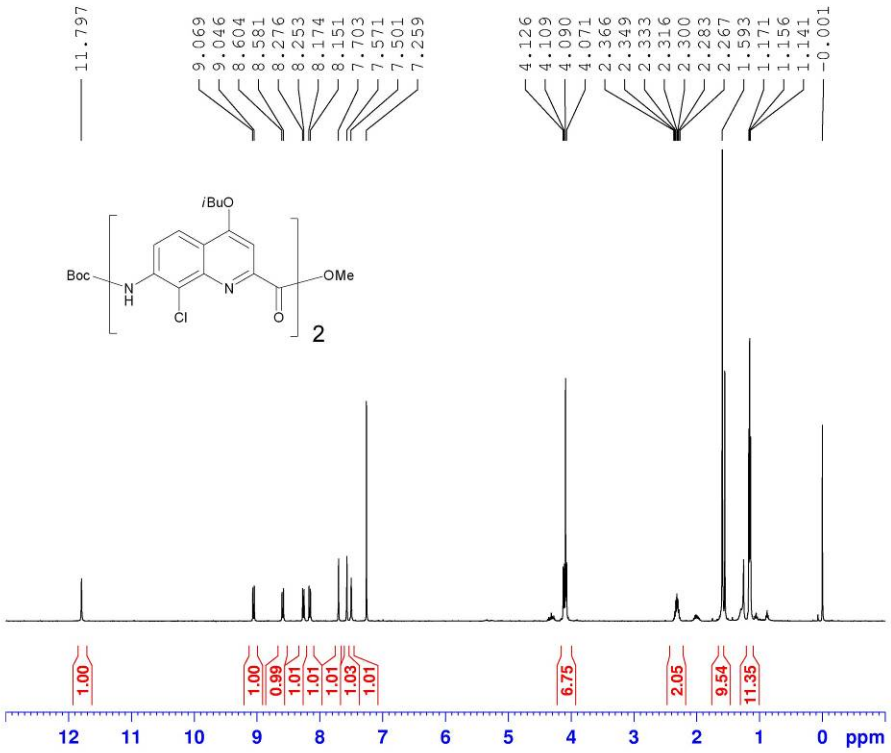


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F2 - Processing parameters
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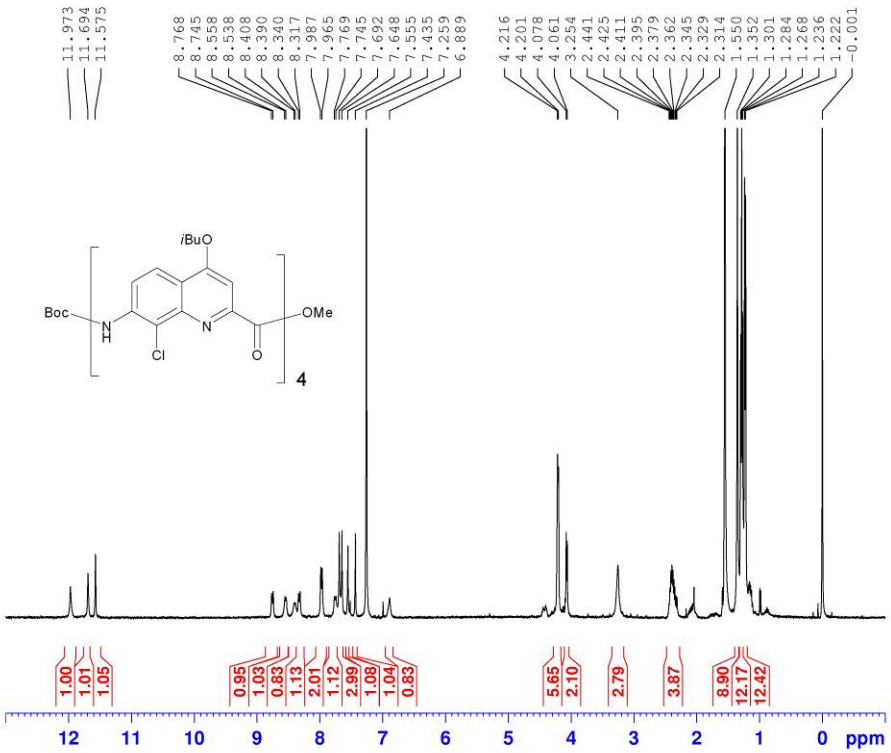


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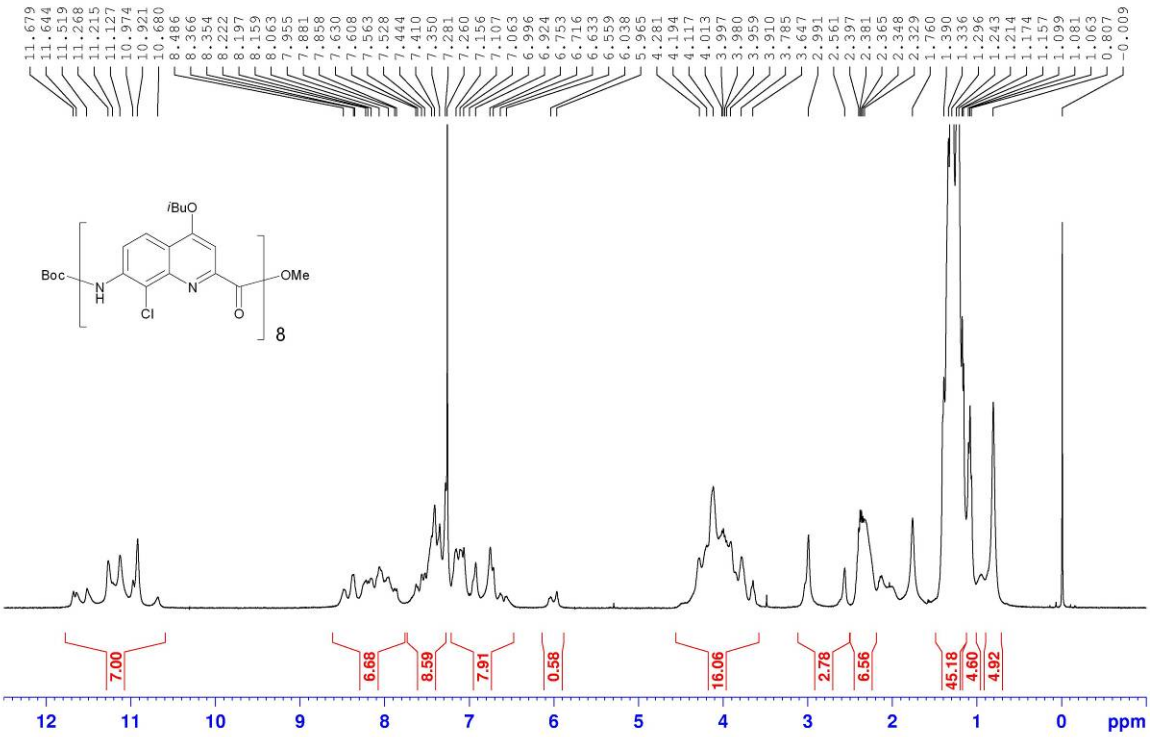
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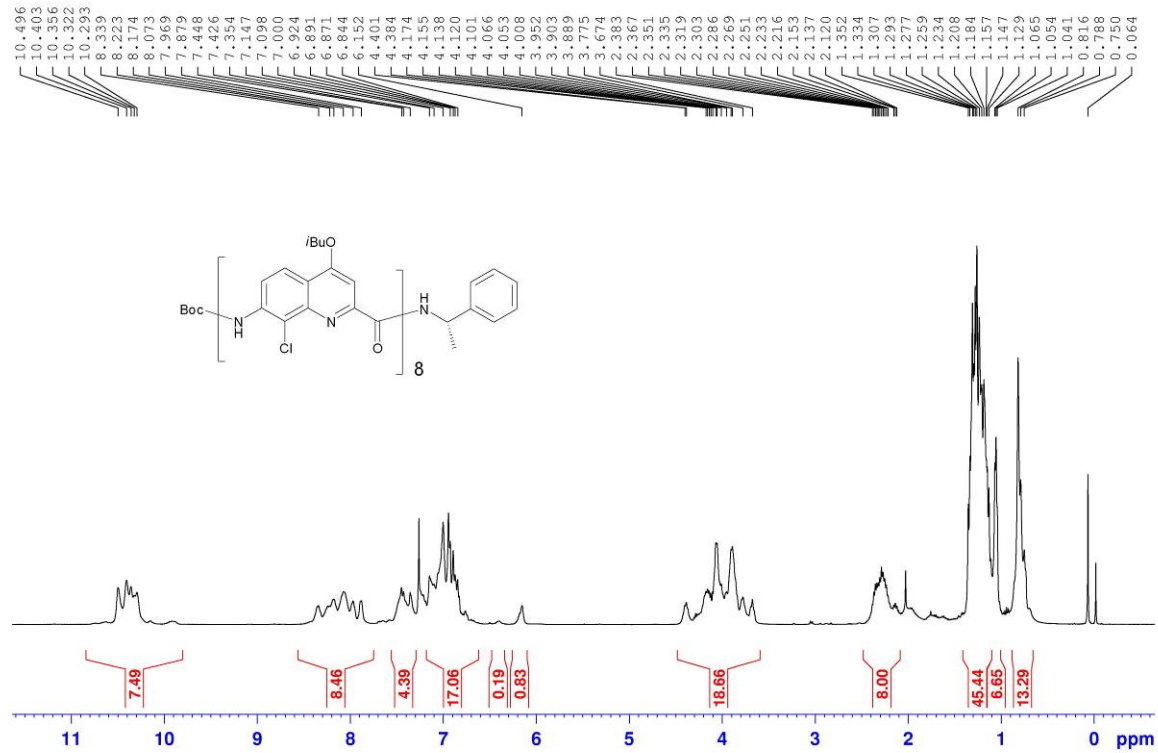
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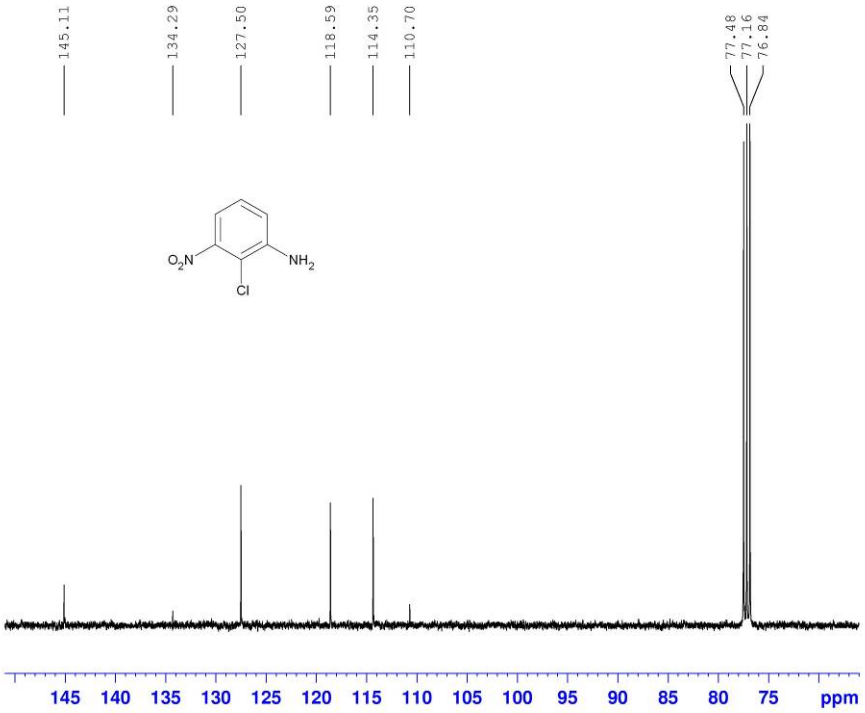
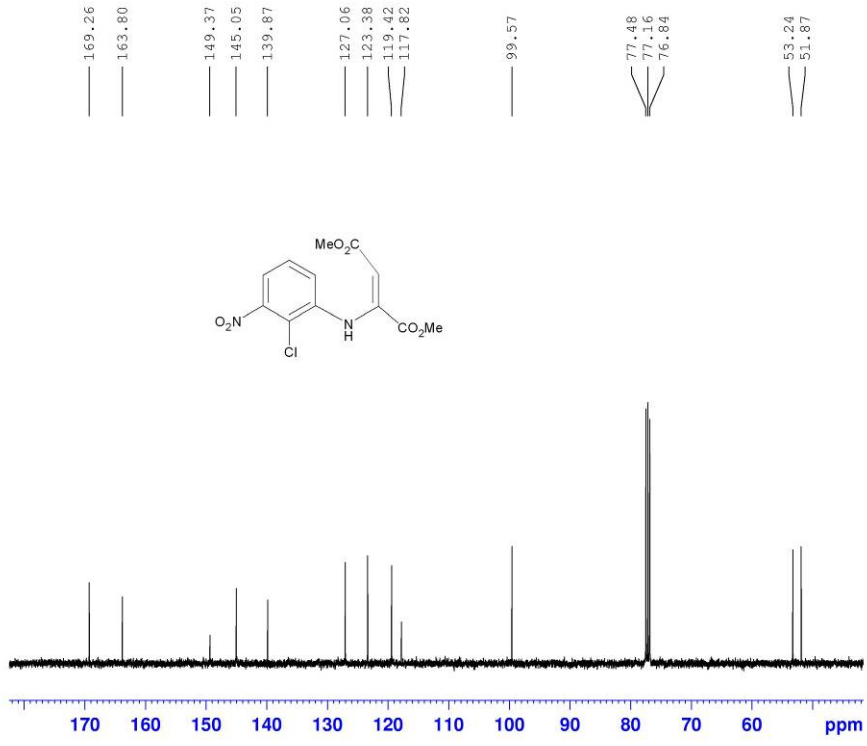
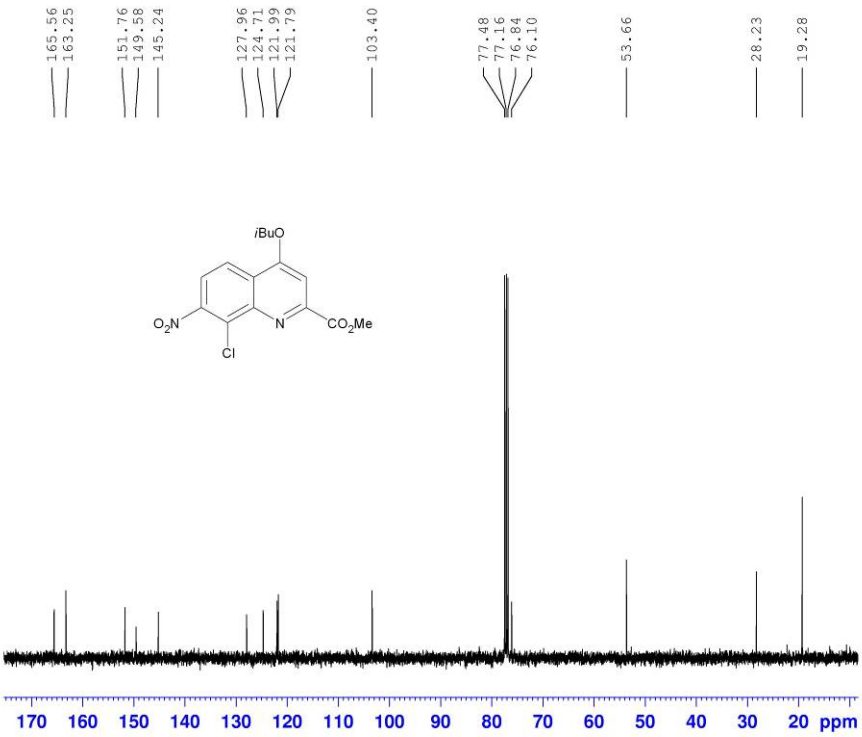
0
ppm



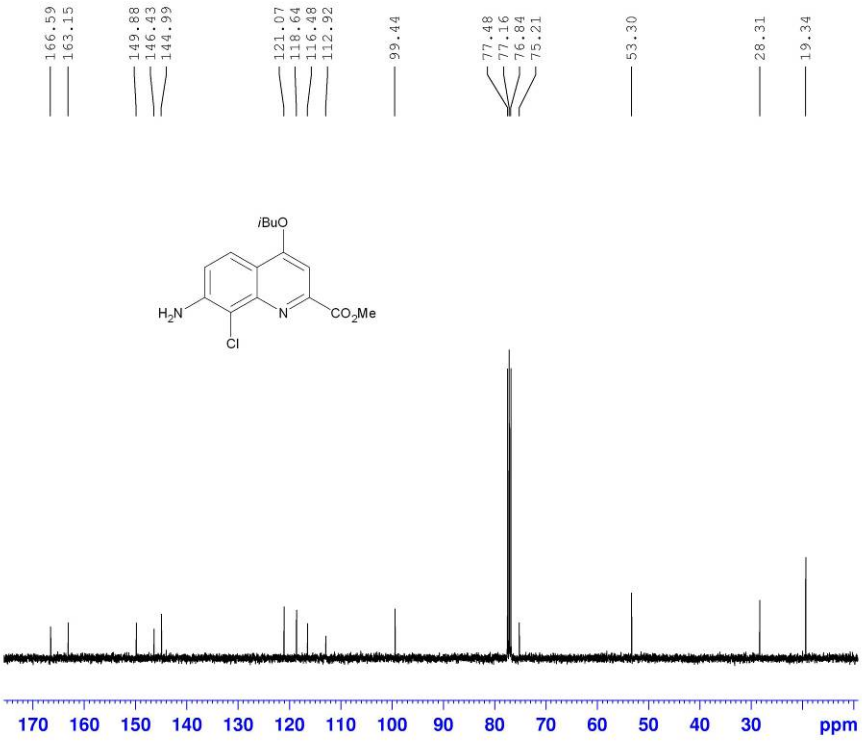

```
Current Data Parameters
NAME                  13c 200806
EXPNO                        100
PROCNO                         1

F2 - Acquisition Parameters
Date_                  20080514
Time                      20.41
INSTRUM                   AV400
PROBHD  5 mm PABBO BB-
PULPROG                 zgig30
TD                       65536
SOLVENT                  CDCl3
NS                         409
DS                           0
SWH                  24154.590 Hz
FIDRES                0.368570 Hz
AQ                    1.3566452 se
RG                      14596.5
DW                       20.700 us
DE                        6.00 us
TE                       297.8 K
D1                    2.00000000 se
d11                   0.03000000 se
MCREST                0.00000000 se
MCWRK                 0.01500000 se

======== CHANNEL f1 ========
NUC1                        13C
P1                         9.60 us
PL1                       -3.00 dB
SFO1                100.6228298 MH

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                        1H
PCPD2                     80.00 us
PL2                       -1.00 dB
PL12                      14.46 dB
SFO2                400.1327813 MH

F2 - Processing parameters
SI                         32768
SF                  100.6127560 MH
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```



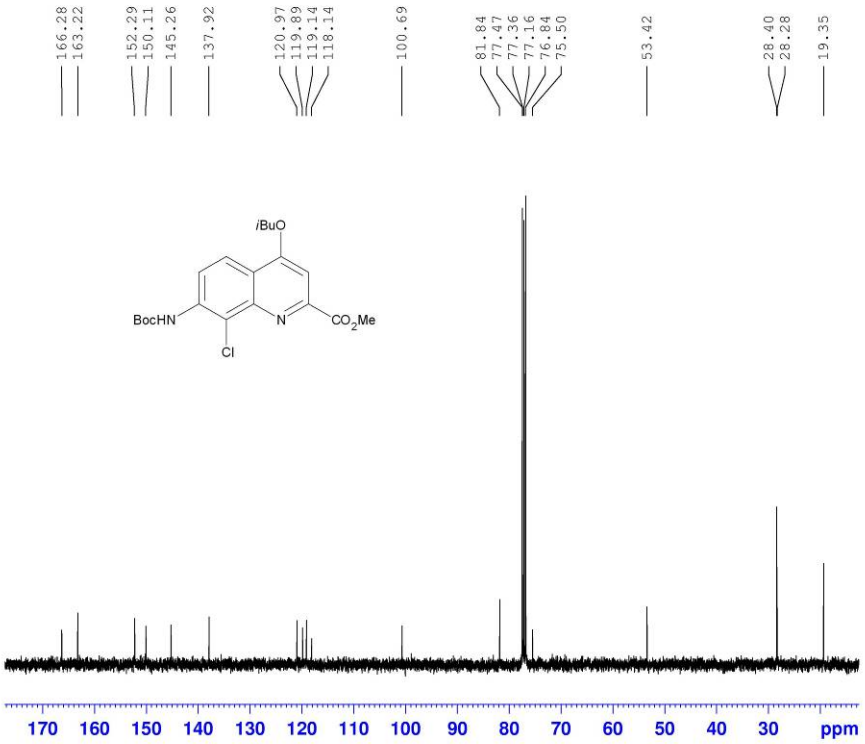

```
Current Data Parameters
NAME                  13c 200806
EXPNO                         99
PROCNO                         1

F2 - Acquisition Parameters
Date_                  20080514
Time                      20.29
INSTRUM                   AV400
PROBHD  5 mm PABBO BB-
PULPROG                 zgig30
TD                       65536
SOLVENT                  CDCl3
NS                          54
DS                           0
SWH                  24154.590 Hz
FIDRES                0.368570 Hz
AQ                    1.3566452 sec
RG                      14596.5
DW                       20.700 use
DE                        6.00 use
TE                       297.3 K
D1                    2.00000000 sec
d11                   0.03000000 sec
MCREST                0.00000000 sec
MCWRK                 0.01500000 sec

======== CHANNEL f1 ========
NUC1                        13C
P1                         9.60 use
PL1                       -3.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                        1H
PCPD2                     80.00 use
PL2                       -1.00 dB
PL12                      14.46 dB
SFO2                400.1327813 MHz

F2 - Processing parameters
SI                         32768
SF                  100.6127589 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```



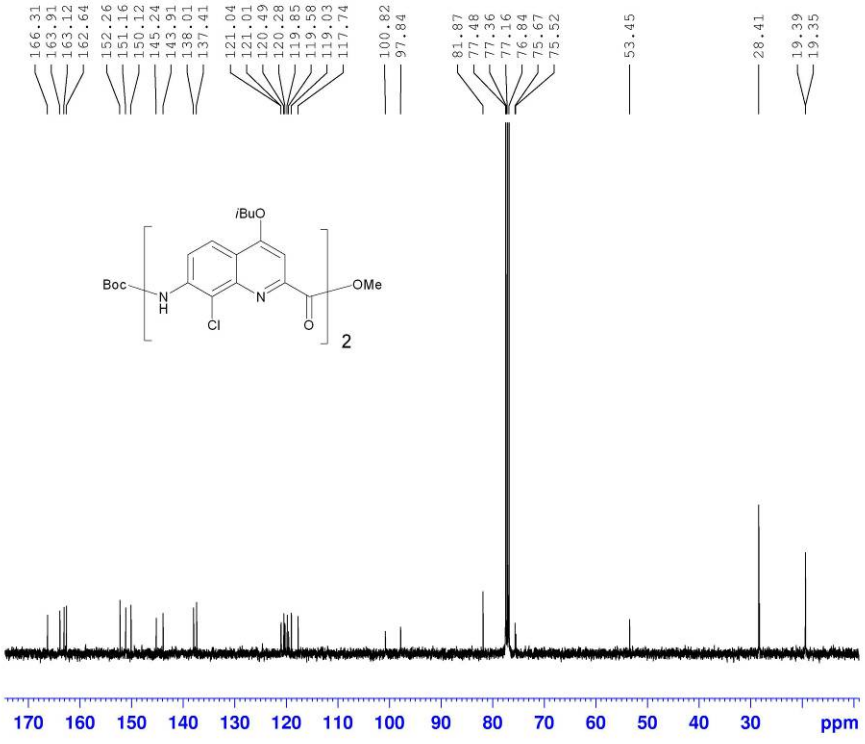

```
Current Data Parameters
NAME                  13c 200806
EXPNO                         60
PROCNO                         1

F2 - Acquisition Parameters
Date_                  20080418
Time                      23.17
INSTRUM                   AV400
PROBHD          5 mm PABBO BB-
PULPROG                 zgig30
TD                       65536
SOLVENT                   DMSO
NS                           80
DS                            0
SWH                 24154.590 Hz
FIDRES               0.368570 Hz
AQ                  1.3566452 sec
RG                      9195.2
DW                      20.700 use
DE                       6.00 use
TE                      299.9 K
D1                  2.00000000 sec
d11                 0.03000000 sec
MCREST              0.00000000 sec
MCWRK               0.01500000 sec

======== CHANNEL f1 ========
NUC1                       13C
P1                        9.60 use
PL1                      -3.00 dB
SFO1           100.6238364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                    80.00 use
PL2                      -1.00 dB
PL12                     14.46 dB
SFO2           400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF             100.6127571 MHz
WDW                           EM
SSB                            0
LB                        1.00 Hz
GB                             0
PC                        1.40
```



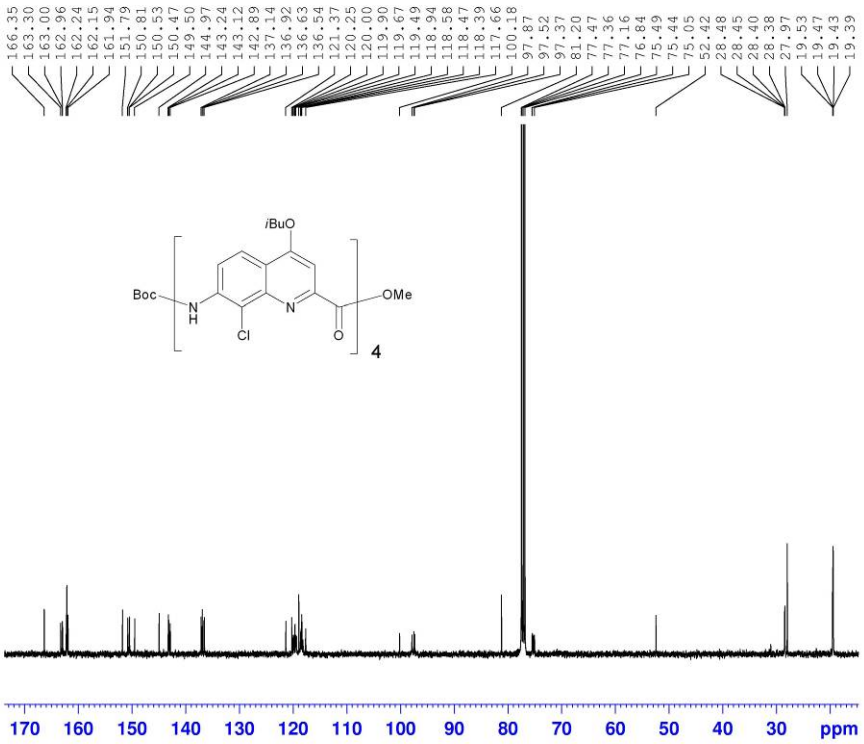

```
Current Data Parameters
NAME                  13c 200806
EXPNO                         73
PROCNO                         1

F2 - Acquisition Parameters
Date_                  20080430
Time                      20.52
INSTRUM                   AV400
PROBHD          5 mm PABBO BB-
PULPROG                 zgig30
TD                       65536
SOLVENT                   CDCl3
NS                          108
DS                            0
SWH                 24154.590 Hz
FIDRES               0.368570 Hz
AQ                  1.3566452 sec
RG                      14596.5
DW                      20.700 usec
DE                       6.00 usec
TE                      299.0 K
D1                  2.00000000 sec
d11                 0.03000000 sec
MCREST              0.00000000 sec
MCWRK               0.01500000 sec

======== CHANNEL f1 ========
NUC1                       13C
P1                        9.60 usec
PL1                      -3.00 dB
SFO1           100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                    80.00 usec
PL2                      -1.00 dB
PL12                     14.46 dB
SFO2           400.1327813 MHz

F2 - Processing parameters
SI                         32768
SF             100.6127574 MHz
WDW                           EM
SSB                            0
LB                        1.00 Hz
GB                             0
PC                        1.40
```



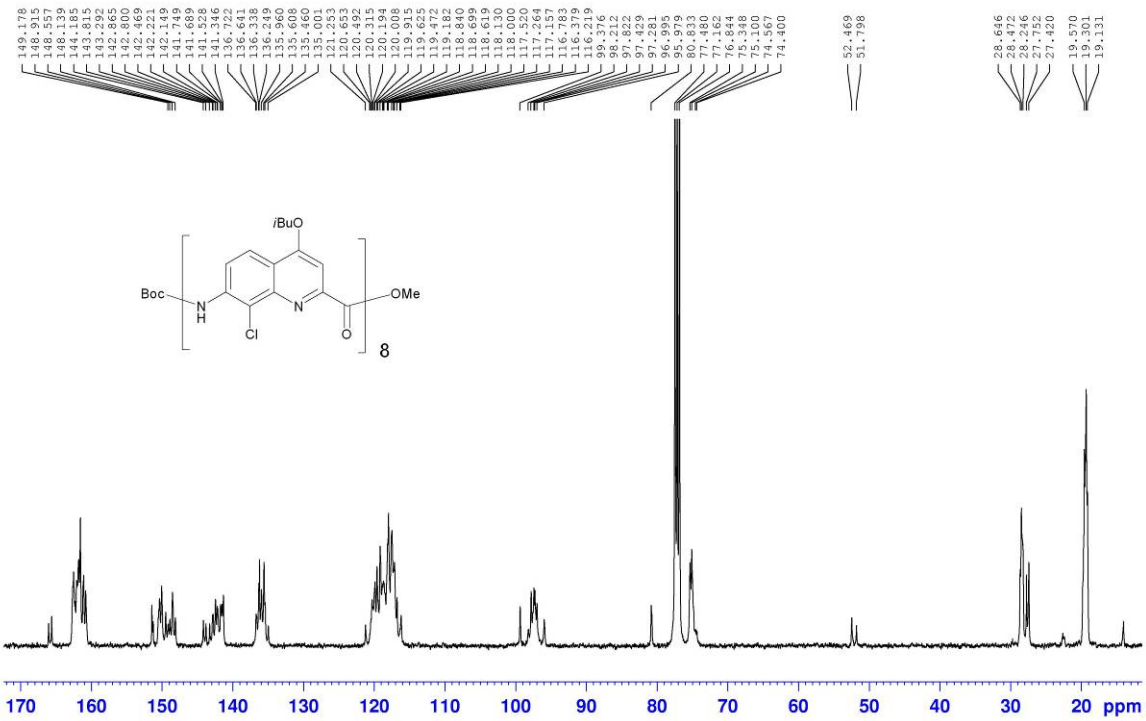

```
Current Data Parameters
NAME                  13c 2008-11-04
EXPNO                              5
PROCNO                             1

F2 - Acquisition Parameters
Date_                       20080627
Time                           21.28
INSTRUM                        AV400
PROBHD           5 mm BBO BB-1H
PULPROG                     zgig30
TD                             65536
SOLVENT                        CDCl3
NS                               144
DS                                 0
SWH                    25125.629 Hz
FIDRES                  0.383387 Hz
AQ                     1.3042164 sec
RG                             13004
DW                        19.900 use
DE                         6.00 use
TE                           300.1 K
D1                    2.00000000 sec
d11                   0.03000000 sec
MCREST                0.00000000 sec
MCWRK                 0.01500000 sec

======== CHANNEL f1 ========
NUC1                           13C
P1                           12.20 use
PL1                          -1.00 dB
SFO1                 100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                   waltz16
NUC2                           1H
PCPD2                        80.00 use
PL2                           0.00 dB
PL12                         17.30 dB
SFO2                 400.1327813 MHz

F2 - Processing parameters
SI                             32768
SF                   100.6127558 MHz
WDW                               EM
SSB                                0
LB                            1.00 Hz
GB                                 0
PC                              0.20
```

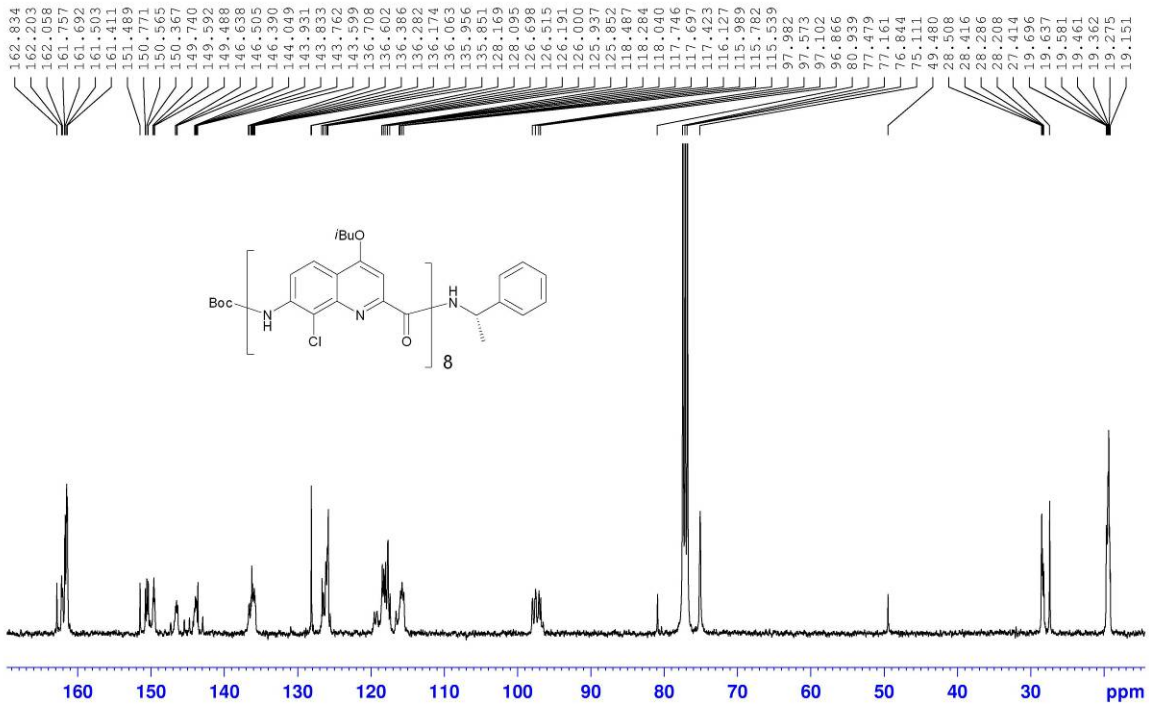



```
Current Data Parameters
NAME                  13c 2008-11-04
EXPNO                              3
PROCNO                             1

F2 - Acquisition Parameters
Date_                       20080621
Time                           14.58
INSTRUM                        AV400
PROBHD           5 mm BBO BB-1H
PULPROG                     zgig30
TD                             65536
SOLVENT                        CDCl3
NS                               481
DS                                 0
SWH                    25125.629 Hz
FIDRES                  0.383387 Hz
AQ                     1.3042164 sec
RG                            14596.5
DW                        19.900 use
DE                         6.00 use
TE                           300.6 K
D1                    2.00000000 sec
d11                   0.03000000 sec
MCREST                0.00000000 sec
MCWRK                 0.01500000 sec

======== CHANNEL f1 ========
NUC1                           13C
P1                           12.20 use
PL1                          -1.00 dB
SFO1                 100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                   waltz16
NUC2                           1H
PCPD2                        80.00 use
PL2                           0.00 dB
PL12                         17.30 dB
SFO2                 400.1327813 MHz

F2 - Processing parameters
SI                             32768
SF                   100.6127559 MHz
WDW                               EM
SSB                                0
LB                            1.00 Hz
GB                                 0
PC                              0.20
```




```
Current Data Parameters
NAME                  13c 2008-11-04
EXPNO                              4
PROCNO                             1

F2 - Acquisition Parameters
Date_                       20080621
Time                           15.44
INSTRUM                       AV400
PROBHD             5 mm BBO BB-1H
PULPROG                     zgig30
TD                           65536
SOLVENT                      CDCl3
NS                            2958
DS                               0
SWH                      25125.629 Hz
FIDRES                    0.383387 Hz
AQ                       1.3042164 sec
RG                         14596.5
DW                          19.900 use
DE                           6.00 use
TE                          300.6 K
D1                     2.00000000 sec
d11                    0.03000000 sec
MCREST                 0.00000000 sec
MCWRK                  0.01500000 sec

======== CHANNEL f1 ========
NUC1                           13C
P1                           12.20 use
PL1                          -1.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                    waltz16
NUC2                           1H
PCPD2                        80.00 use
PL2                           0.00 dB
PL12                         17.30 dB
SFO2                400.1327813 MHz

F2 - Processing parameters
SI                            32768
SF                  100.6127558 MHz
WDW                              EM
SSB                               0
LB                            1.00 Hz
GB                                0
PC                             0.20
```

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161.692
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150.565
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149.488
146.638
146.505
146.390
144.049
143.931
143.833
143.762
143.599
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136.602
136.386
136.282
136.174
136.063
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128.095
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126.515
126.191
126.000
125.937
125.852
118.487
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117.697
117.423
116.127
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115.539
97.982
97.573
97.102
96.866
80.939
77.479
77.161
76.844
75.111
49.480
28.508
28.416
28.286
28.208
27.414
19.696
19.637
19.581
19.461
19.362
19.275
19.151
/BuO
Boc
N
H
Cl
N
O
H
N
8
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm