*Supplementary Information*

# Polar solvent effects on tartaric acid binding by aromatic oligoamide foldamer capsules

Nagula Chandramouli,[a,b] Mohammed Farrag El-Behairy,[a,b,c] Guillaume Lautrette,[a,b] Yann Ferrand[a,b] and Ivan Huc[a,b]

[a] Univ. Bordeaux, CBMN, UMR 5248, Institut Européen de Chimie Biologie, 2 rue Robert Escarpit 33607 Pessac, France.
[b] CNRS, CBMN, UMR 5248, 33607 Pessac, France.
[c] Medicinal and Pharmaceutical Chemistry Department, Pharmaceutical and Drug Industries Research Division, National Research Centre,12622 Dokki, Giza, Egypt.

**Table of contents**

| | |
|---|---|
| 1. Materials and methods | Page S2 |
| 2. Synthetic schemes | Page S3 |
| 3. Experimental section | Page S4 |
| 4. NMR studies | Page S15 |
| 5. $^{1}$H NMR and $^{13}$C NMR spectra | Page S17 |
| 6. References | Page S33 |

## 1. Materials and methods

All reactions were carried out under a dry nitrogen atmosphere. Triethylamine and *N,N*-diisopropylethylamine (DIEA) was distilled over calcium hydride. Reactions requiring anhydrous conditions were performed under argon. 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). Analytical grade organic solvents were used for solid phase synthesis. Anhydrous THF and $CH_2Cl_2$ were dispensed from an MBRAUN SPS-800 solvent purification system. ESI mass spectra were obtained from the mass spectrometry service at the IECB (UMS3033 & US01). Preparative recycling GPC (gel permeation chromatography) were performed on JAIGEL 20*600 mm columns (Japan Analytical Industry) at a flow rate of 7 mL $min^{-1}$ with a mobile phase composed of 1% (vol/vol) $Et_3N$ in chloroform. Monitoring by UV detection was carried out at 254 nm, 280 nm, 300 nm and 360 nm.

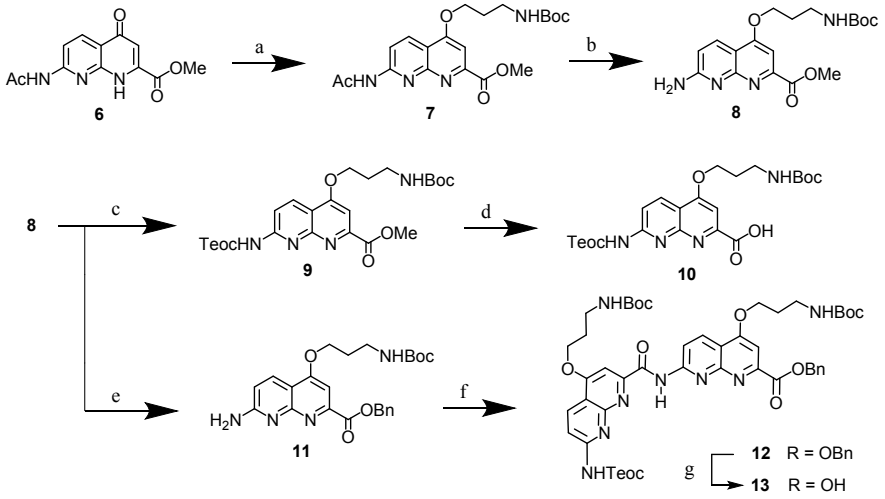
*Nuclear Magnetic Resonance*

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 and 75 MHz for $^{13}C$ observation by means of a 5-mm direct BBO H/X probe with Z gradient capabilities; (2) a Avance 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 1H observation by means of a 5-mm TXI 1H/13C/15N probe with Z gradient capabilities. $^{1}H$-NMR spectra were measured at 300, 400 or 700 MHz and $^{13}C$-NMR spectra were measured at 75 MHz. Chemical shifts are reported in ppm and are calibrated against residual solvent signals of $CDCl_3$ (δ 7.26, 77.2), $d_6$-DMSO (δ 2.50), $CD_3OH$ (δ 3.31), $d_6$-acetone (2.05). All coupling constants are reported in hertz (Hz). Signals were abbreviated as s, singlet; brs, broad singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet, dd, doublet of doublets. Data processing was performed with Topspin 2.0 software.

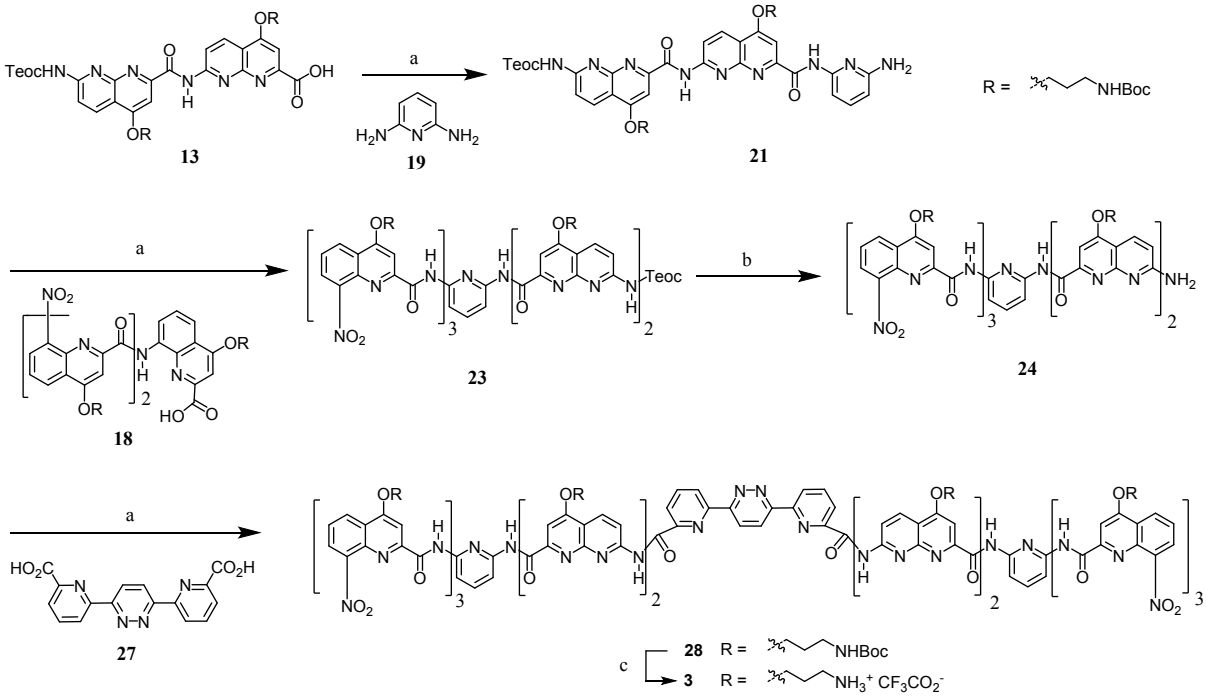
*Isothermal Titration Calorimetry (ITC)*

Isothermal Titration Microcalorimetry (ITC) experiments were performed on an ITC200 microcalorimeter at 298K (MicroCal, Inc., Northampton, MA). Each exothermic heat pulse corresponds to the injection of 5 μL of the guest [**5**] into a cell (volume = 0.2032 mL) containing either capsule **3** (0.5 mM) or capsule **4** (1.5 mM). Guest concentration in the syringe was changed according to the affinity of each receptor: [**5**] = 25 mM or [**5**] = 54 mM for the titration of capsule **3** and **4**, respectively. Data were fitted using the Origin 7 software using a 1:1 binding model after subtracting a blank experiment.

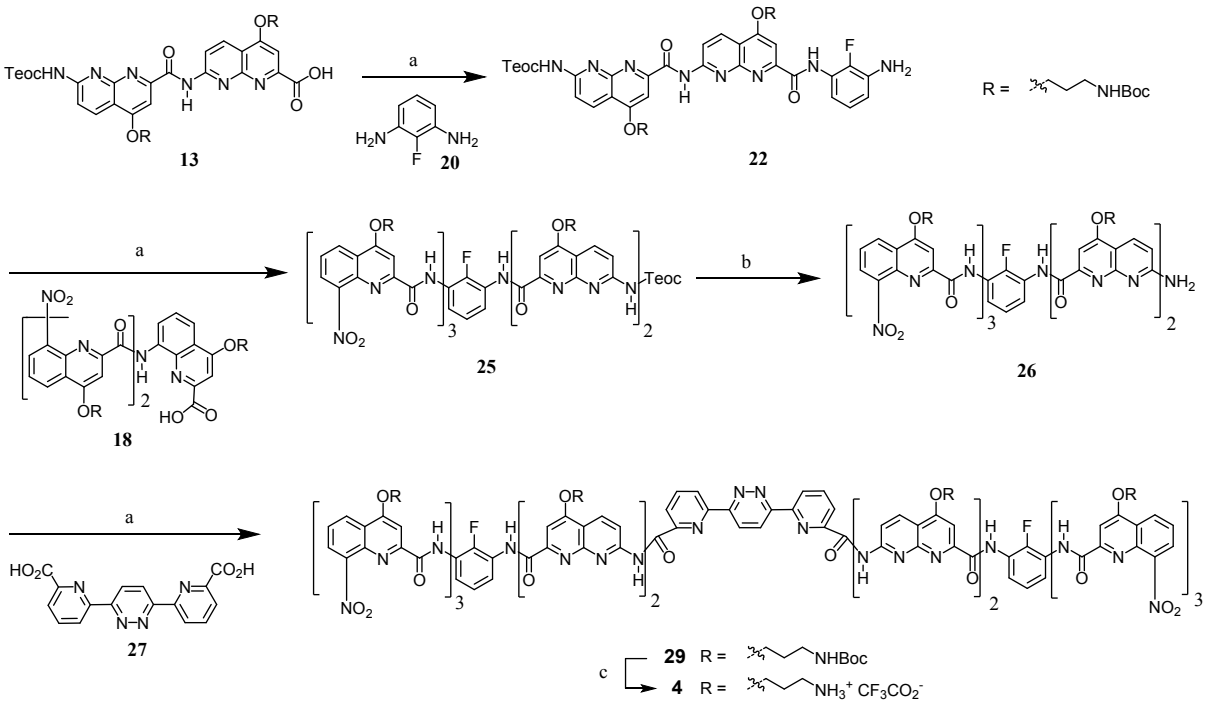
## 2. Synthetic schemes



**Scheme S1**. Synthesis of capsule naphthyridine dimer **13** acid: (a) $PPh_3$, diisopropylazodicarboxylate, N-(tert-butoxycarbonyl)-3-aminopropanol (65%); (b) $H_2SO_4$, MeOH (66%); (c) 4-Nitrophenyl 2-(trimethylsilyl)ethyl carbonate, Δ (90%); (d) NaOH (99%); (e) BnOH, $Et_3N$ (80%); (f) **10**, PyBOP, DIEA (86%); (g) Pd/C, $H_2$ (98%).

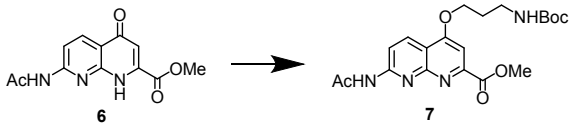


**Scheme S2**. Synthesis of capsule **3**: (a) PyBOP, DIEA; (b) TBAF; (c) TFA.



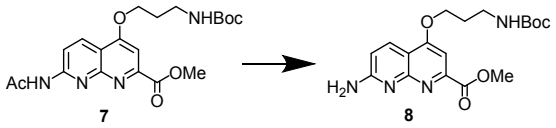

**Scheme S3**. Synthesis of capsule **4**: (a) PyBOP, DIEA; (b) TBAF; (c) TFA.

## 3. Experimental section

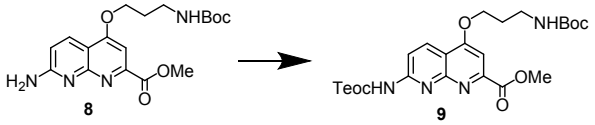



**Acetamido naphthyridine 7**. In a dry round-bottom-flask placed under inert atmosphere, 300 mL anhydrous THF was added to naphthyridone[1] **6** (76.6 mmol, 20 g), *N*-(t-butoxycarbonyl)-3-aminopropanol (92.0 mmol, 16.1 mL) and triphenylphosphine (114.9 mmol, 30.1 g) (note that **6** is not soluble in THF before the addition of diisopropyl azodicarboxylate). Diisopropyl azodicarboxylate (114.9 mmol, 22.6 mL) was added at 0°C over a period of 30 min., then the reaction mixture was stirred at RT for 24 h. Solvents were evaporated, and the residue was recrystallised from methanol. Product was dried under reduced pressure to give naphthyridine **7** (white powder, 65%, 21 g). mp 200-201°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ ppm = 10.80 (s, 1H); 8.44 (d, *J* = 8.85, 1H); 8.10 (d, *J* = 8.85, 1H); 6.86 (bs, 1H); 6.39 (s, 1H); 4.37 (t, *J* = 7.25, 2H); 3.95 (s, 3H); 3.00 (m, 2H); 2.21 (s, 3H); 1.84 (m, 2H); 1.37 (s, 9H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ ppm = 175.7, 170.0, 163.4, 155.6, 154.1, 148.9, 144.1, 137.5, 117.6, 111.6,

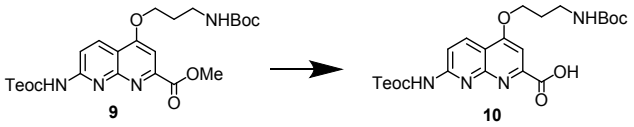
110.8, 77.5, 53.6, 44.5, 40.3, 38.7, 37.5, 29.7, 28.2, 24.3. HRMS (ESI$^+$): *m/z* calcd for $C_{40}H_{53}N_8O_{12}$ $[2M+H]^+$ 837.3777 found 837.3792.



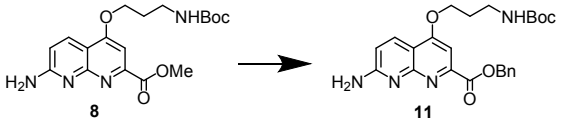

**Naphthyridine amine 8**. Naphthyridine derivative **7** (23.9 mmol, 10 g) was dissolved in 200 mL methanol. Reaction mixture was cooled to 0°C, then $H_2SO_4$ (11.9 mmol, 0.64 mL) was added dropwise. The resulting mixture was then heated at reflux. After 3 hours, the reaction mixture was cooled and half of the solvent was evaporated. The mixture was neutralised with a saturated $NaHCO_3$ solution and extracted with dichloromethane. Organic layers were washed twice with distilled water and dried over $MgSO_4$. Solvents were evaporated under reduced pressure, then the resulting solid was dissolved in a minimum of dichloromethane and precipitated with methanol to give **8** as a white powder (66%, 6.0 g). mp 139-141°C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm = 8.13 (d, *J* = 9.04, 1H); 7.26 (s, 1H); 6.96-6.83 (m, 4H); 5.75 (s, 1H); 4.24 (t, *J* = 6.05, 2H); 3.89 (s, 3H); 3.15 (m, 2H); 1.94 (m, 2H); 1.35 (s, 9H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ ppm = 165.8, 162.3, 161.3, 157.2, 155.7, 149.9, 131.3, 113.7, 109.5, 99.0, 77.5, 66.5, 52.5, 40.3, 38.7, 36.8, 28.9, 28.2. HRMS (ESI$^+$): *m/z* calcd for $C_{18}H_{25}N_4O_5$ $[M+H]^+$ 377.1819 found 377.1827.



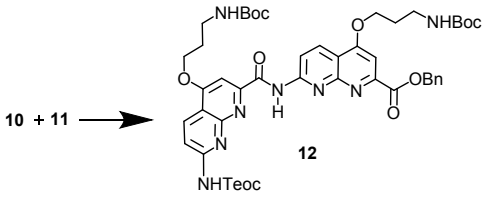

**Naphthyridine 9**. To a solution of dioxane (10 mL) containing amino naphthyridine derivative **8** (1.06 mmol, 0.4 g) and 2-(Trimethylsilyl)ethyl 4-nitrophenyl carbonate (1.59 mmol, 0.45 g) was added DIEA (2.12 mmol, 0.37 mL) and a catalytic amount of DMAP. The reaction mixture was let to stir at 95°C for 40 hours. Dioxane was removed under reduced pressure and the residue was purified by column chromatography on silica to give **9** as a white powder (90 %, 0.4 g). mp 199-201°C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm = 10.73 (s, 1H); 8.55 (d, *J* = 9.26, 1H); 8.24 (d, *J* = 9.26, 1H); 7.47 (s, 1H); 6.97 (t, *J* = 5.15, 1H); 4.36-4.24 (m, 4H); 3.95 (s, 3H); 3.20 (m, 2H); 2.00 (m, 2H); 1.36 (s, 9H); 1.07 (m, 2H); 0.05 (s, 9H). $^{13}$C NMR (75 MHz, DMSO-d6) δ ppm = 165.4, 162.7, 155.6, 155.4, 155.1, 153.7, 151.2, 133.5, 114.2, 112.9, 100.7, 77.5, 67.0, 62.9, 52.7, 40.3, 38.7, 36.7, 28.7, 28.2, 17.3, -1.4. HRMS (ESI$^+$): *m/z* calcd for $C_{24}H_{37}N_4O_7Si$ $[M+H]^+$ 521.2426 found 521.2428.



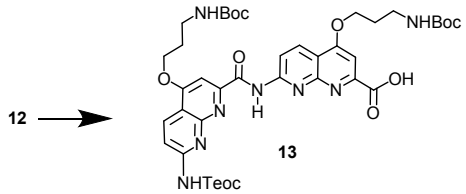

**Naphthyridine acid 10**. An aqueous solution (2mL) of NaOH (17.3 mmol, 0.07 g) was added to **9** (5.76 mmol, 0.3 g) which was previously dissolved a THF and methanol solution (20 mL, 8:2 vol/vol). The resulting mixture was stirred at RT for 3h. The reaction was then quenched with a solution of citric acid (5%) and extracted with dichloromethane. The organic layers were washed twice with distilled water, dried over $MgSO_4$ and the solvents were removed under reduced pressure. The naphthyridine derivative **10** was obtained as a white powder (99%, 0.29 g). mp 201-202°C; $^1$H NMR (300 MHz, $CDCl_3$) δ ppm = 8.59 (d, *J* = 9.09, 1H); 8.43 (d, *J* = 9.29, 1H); 7.80 (s, 1H); 7.62 (s, 1H); 4.76 (s, 1H); 4.37 (m, 4H); 3.42 (m, 2H); 2.18 (m, 2H); 1.44 (s, 9H); 1.10 (t, *J* = 8.47, 2H); 0.09 (s, 9H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ ppm = 166.5, 162.7, 155.6, 155.0, 153.7, 133.4, 128.5, 128.2, 113.9, 112.7, 100.5, 77.5, 66.9, 62.9, 36.8, 28.8, 28.2, 17.3, -1.5. HRMS (ESI$^+$): *m/z* calcd for $C_{23}H_{35}N_4O_7Si$ $[M+H]^+$ 507.2270 found 507.2273.



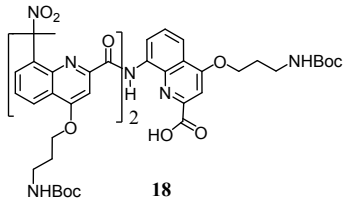

**Naphthyridine amine 11**. The amino naphthyridine derivative **8** (7.97 mmol, 3 g) and triethylamine (39.8 mmol, 5.5 mL) were added to dry benzyl alcohol (0.2 mol, 21 mL). The resulting mixture was let to stir at 60°C for at least 48 hours. The reaction was monitored by TLC and stopped accordingly. The solvents were removed under high vacuum and the residue was purified by chromatography. The benzyl ester derivative **11** was obtained as a white solid (80 %, 2.1 g). mp 173-175°C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm = 8.12 (d, *J* = 9.03, 1H); 7.51-7.36 (m, 5H); 7.28 (s, 1H); 6.96-6.83 (m, 4H); 5.39 (s, 2H); 4.24 (t, *J* = 5.70, 2H); 3.16 (q, *J* = 12.36, 2H); 1.94 (m, 2H); 1.34 (s, 9H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ ppm = 165.3, 162.3, 161.3, 157.2, 155.6, 149.9, 135.9, 131.3, 128.5, 128.1, 128.1, 113.7, 109.5, 99.0, 77.5, 66.6, 66.4, 36.8, 28.8, 28.2. HRMS (ESI$^+$): *m/z* calcd for $C_{24}H_{29}N_4O_5$ $[M+H]^+$ 453.2132 found 453.2135.




**Naphthyridine dimer 12.**The naphthyridine acid derivative **10** (4.30 mmol, 2.21 g), the amino derivative **11** (4.30 mmol, 1.94 g) and PyBOP (8.60 mmol, 4.48 g) were dissolved in 80 mL of dry dichloromethane. Then, triethylamine (17.3 mmol, 2.4 mL) was added and the reaction mixture was let to stir at room temperature for 24 hours. The solvents were removed under reduced pressure and the residue was purified by column chromatography on silica. The dimer **12** was obtained as a white solid (86 %, 3.6 g). $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ ppm = 11.01 (s, 1H); 10.77 (s, 1H); 8.70-8.53 (m, 3H); 8.26 (d, *J* = 9.08, 1H); 7.63-7.40 (m, 7H); 7.02 (m, 2H); 5.46 (s, 2H); 4.42-4.15 (m, 6H); 3.23 (m, 4H); 2.03 (m, 4H); 1.37 (s, 16H); 1.09 (t, *J* = 8.80, 2H); 0.10 (s, 9H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ ppm = 164.7, 163.4, 162.4, 161.8, 155.7, 155.5, 154.6, 153.6, 153.5, 153.0, 151.4, 151.3, 135.7, 134.1, 133.3, 128.5, 128.2, 113.8, 112.9, 100.7, 97.7, 77.5, 66.9, 62.9, 40.3, 40.0, 39.8, 39.5, 39.2, 38.9, 38.7, 36.8, 28.8, 28.2, 17.3, -1.5. HRMS (ESI$^+$): *m/z* calcd for $C_{47}H_{61}N_8O_{11}Si$ $[M+H]^+$ 941.4224 found 941.4234.

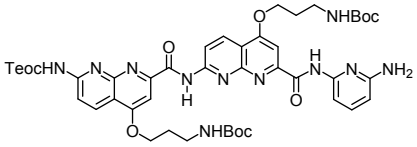



**Naphthyridine dimer acid 13**. To a solution of dimer **12** (0.9 g, 0.009 mmol) in DMF (20 ml) was added Pd/C (10%) (150 mg). The flask was first placed under vacuum then filled with hydrogen gas. The reaction mixture was stirred vigorously for 12h at room temperature. The Pd catalyst was removed by filtration over celite (celite was washed carefully with dichloromethane) and the filtrate was evaporated under reduced pressure to give **13** as a white solid (98%, 0.8 g). $^{1}$H NMR (300 MHz, $CDCl_3$) δ ppm = 11.24 (s, 1H); 8.83 (d, *J* = 8.98, 1H); 8.70 (d, *J* = 9.15, 1H); 8.59 (d, *J* = 8.98, 1H); 8.59 (d, *J* = 9.15, 1H); 7.78-7.68 (m, 3H); 4.73 (bs, 2H); 4.44-4.34 (m, 6H); 4.19 (s, 1H); 3.44 (m, 4H); 2.20 (m, 4H); 1.44 (s, 18H); 1.25 (s, 2H); 1.14 (m, 2H); 0.10 (s, 9H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ ppm = 166.2, 163.6, 162.7, 162.2, 155.7, 154.6, 153.9, 153.6, 153.2, 152.8, 151.7, 134.5, 133.6, 114.1, 113.2, 100.8, 98.1, 77.5, 67.3, 63.0, 36.8, 28.8, 28.2, 17.3, -1.5. HRMS (ESI$^+$): *m/z* calcd for $C_{40}H_{55}N_8O_{11}Si$ $[M+H]^+$ 851.3754 found 851.3770.



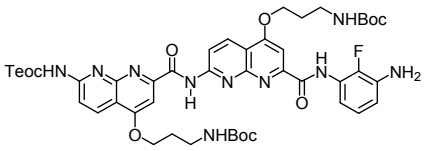
18

**Quinoline trimer acid 18.** The trimer acid was synthesized as previously described for dimeric and tetrameric oligomers.[3] $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ ppm = 12.13 (s, 1H); 11.90 (s, 1H); 8.91 (d, *J* = 7.6, 1H); 8.54 (d, *J* = 7.6, 1H); 8.43 (d, *J* = 8.1, 1H); 8.10-7.47 (m, 7H); 7.03 (s, 3H); 6.70 (s, 1H); 4.65-4.42 (m, 6H); 3.05-3.22 (m, 6H); 2.23-1.96 (m, 6H); 1.41 (s, 27H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm = 164.9, 163.6, 163.4, 163.0, 162.6161.7, 156.2, 154.5, 150.9, 145.8, 139.4, 138.5, 138.1, 135.4, 134.7, 128.3, 127.5, 125.7, 123.4, 122.0, 121.3, 117.5, 116.5, 116.0, 100.9, 99.7, 78.1, 67.8, 67.5, 66.8, 37.4, 37.3, 29.4, 29.3, 28.7. HRMS (ESI$^+$): *m/z* calcd for $C_{54}H_{64}N_9O_{15}$ $[M+H]^+$ 1078.4516, found 1078.4513.



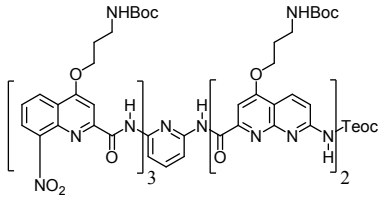
21

**Trimer amine 21**. Naphthyridine dimer acid **13** (0.490 mmol, 0.4 g), 2,6-diaminopyridine **19** (4.9 mmol, 0.51 g) and PyBOP (0.94 mmol, 4.89 g) were dissolved in 20 mL of distilled chloroform. Then, triethylamine (1.41 mmol, 0.19 mL) was added and the reaction mixture was let to stir at RT. After 24 hours the solvents were removed under reduced pressure and the residue was dissolved in the minimum of dichloromethane and precipitate from a minimum amount of methanol to give **21** as a pale yellow solid (95%, 0.42 g). $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ ppm = 11.12 (s, 1H); 10.75 (s, 1H); 10.27 (s, 1H); 8.71 (d, *J* = 8.92, 1H); 8.55 (m, 2H); 8.24 (d, *J* = 8.92, 1H); 7.69-7.41 (m, 4H); 7.00 (t, *J* = 5.54, 2H); 6.30 (d, *J* = 7.80, 1H); 6.03 (bs, 2H); 4.41 (m, 4H); 4.29-4.19 (m, 3H); 3.22 (m, 4H); 2.03 (m, 4H); 1.36 (s, 18H); 1.07 (m, 2H); 0.08 (s, 9H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ ppm = 163.1, 161.5, 160.8, 158.9, 155.8, 155.3, 153.4, 152.9, 152.5, 150.9, 148.8, 139.1, 133.9, 132.9, 113.6, 113.3, 112.6, 104.4, 100.2, 97.7, 97.2, 77.7, 67.1, 63.0, 40.3, 40.0, 39.8, 39.5, 39.2, 38.9, 38.7, 36.9, 29.7, 28.9, 28.3, 26.4, 17.3, -1.4. HRMS (ESI$^+$): *m/z* calcd for $C_{45}H_{60}N_{11}O_{10}Si$ $[M+H]^+$ 942.4288 found 942.4318.




**22**

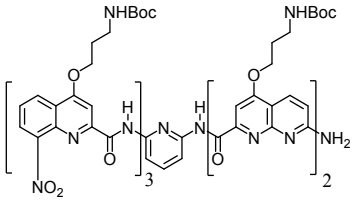
**Trimer amine 22**. Naphthyridine dimer acid **13** (0.44 mmol, 0.375 g), 2,6-diaminofluorobenzene[2] **20** (4.4 mmol, 0.55 g) and PyBOP (1.1 mmol, 0.572 g) were dissolved in distilled chloroform (20 mL). Then DIEA (1.43 mmol, 0.25 mL) was added at RT and the reaction mixture was let to stir at 40°C under nitrogen. After 24 hours, the solvents were removed under reduced pressure. The residue was dissolved in dichloromethane, washed with solutions of $NH_4Cl$, $NaHCO_3$ and distilled water then dried over MgSO4. The organic phases were evaporated and the residue was purified by flash chromatography ($SiO_2$) eluting with EtOAc:dichloromethane (30:70 vol/vol) to afford 160 mg (40%) of trimer **22** as a white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11.21 (s, 1H), 10.89 (s, 1H), 10.52 (s, 1H), 8.81 (d, *J* = 9.0 Hz, 1H), 8.64 (dd, *J* = 9.0, 4.3 Hz, 2H), 8.31 (d, *J* = 9.1 Hz, 1H), 7.72 (d, *J* = 3.1 Hz, 2H), 7.54 (t, J = 6.9 Hz, 1H), 7.05 – 6.89 (m, 3H), 6.65 (t, *J* = 8.1 Hz, 1H), 5.31 (s, 2H), 4.46 (t, *J* = 6.0 Hz, 4H), 4.35 – 4.23 (m, 2H), 3.25 (m, 4H), 2.06 (t, *J* = 6.2 Hz, 4H), 1.38 (s, 18H), 1.10 (m, 2H), 0.10 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.8, 167.7, 160.7, 159.4, 156.2, 138.6, 137.9, 128.2, 118.6, 118.1, 117.2, 114.8, 102.7, 102.5, 83.4, 81.4, 71.2, 68.2, 53.5, 53.2, 52.9, 52.6, 52.3, 52.0, 51.7, 41.2, 33.0, 32.2, 21.5, 2.1. HRMS (ESI$^+$): *m/z* calcd for $C_{46}H_{60}FN_{10}O_{10}Si$ [M+H]+: 959.4242 found 959.4258.




**23**

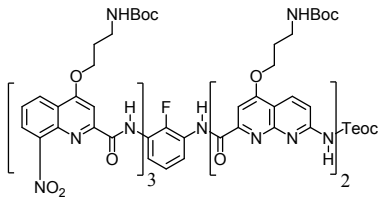
**Hexamer 23**. Trimer amine **21** (0.499 mmol, 0.47 g), quinoline trimer acid[3] **18** (0.499 mmol, 0.54 g) and PyBOP (1.49 mmol, 0.78 g) were dissolved in 30 mL of distilled chloroform. Then, DIEA (1.49 mmol, 0.23 mL) was added and the reaction mixture was let to stir at RT for 24 hours. The solvents were removed under reduced pressure and the residue was purified by column chromatography on silica to give **23** as a pale yellow solid (81%, 0.8 g). $^1$H NMR (300 MHz, $CDCl_3$) δ ppm = 12.35 (s, 1H); 12.08 (s, 1H); 11.14 (s, 1H), 10.56 (s, 1H); 10.00 (s, 1H); 9.73 (s, 1H); 9.41 (d, *J* = 7.65, 1H); 8.87 (s, 1H); 8.77 (m, 2H); 8.67-8.58 (m, 3H); 8.49 (d, *J* = 8.37, 1H); 8.21 (d, *J* = 7.89, 1H); 7.96 (d, *J* = 8.37, 1H); 7.87-7.67 (m, 6H); 7.53 (d, *J* = 7.17, 1H); 7.40 (m, 2H); 6.89 (m, 2H); 6.71 (t, *J* = 8.13, 1H); 5.41 (bs, 1H); 4.99-4.08 (m, 20H); 3.48 (m, 9H); 2.96 (m, 2H); 2.24 (m, 9H); 2.04 (s, 2H); 1.57-1.23 (m, 66H); 0.20 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ ppm = 164.1, 163.9, 163.6, 163.0, 162.8, 161.9, 161.1, 160.8, 156.8, 156.1,

155.7, 154.8, 154.5, 153.9, 153.3, 152.0, 150.9, 149.7, 148.4, 145.5, 140.2, 139.0, 138.8, 135.3, 134.5, 133.7, 128.3, 127.6, 126.5, 125.7, 124.6, 123.5, 122.8, 121.9, 117.5, 116.0, 114.8, 114.3, 110.0, 108.5, 102.4, 99.9, 98.5, 98.2, 97.6, 79.6, 79.2, 77.6, 77.3, 77.1, 76.7, 67.8, 67.3, 64.4, 53.5, 37.8, 30.3, 29.4, 29.1, 28.5, 28.4, 27.0, 18.6, -1.2. HRMS ($ESI^+$): *m/z* calcd for $C_{99}H_{121}N_{20}O_{24}Si$ $[M+H]^+$ 2002.8660 found 2002.8706.




**24**

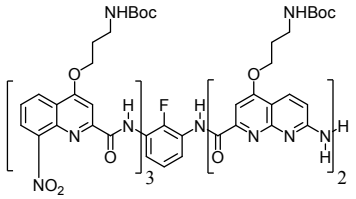
**Hexamer amine 24**. TBAF (0.80 mL) was added drop wise to a solution of **23** (0.199 mmol, 0.4 g) in 5 mL of dry THF under nitrogen at 0°C. Then, the resultant mixture was stirred at RT for 5 h. The solvents were removed under reduced pressure to give a solid which was dissolved in dichloromethane, washed twice with a 5% citric acid solution, distilled water and then with brine. The organic layers were dried over $MgSO_4$, the solvents evaporated and the resulting solid purified by column chromatography to give hexamer **24** as pale yellow solid (96%, 355 mg). $^1H$ NMR (300 MHz, $CDCl_3$) δ ppm = 12.03 (s, 2H); 11.29 (s, 1H); 9.41 (d, *J* = 12.59, 2H); 9.09 (d, *J* = 7.23, 1H); 8.75 (s, 2H); 8.54-7.34 (m, 14H); 6.87 (m, 3H); 6.64 (bs, 2H); 5.35-3.97 (m, 15H); 3.65-3.36 (m, 8H); 2.93 (s, 2H); 2.37-2.04 (m, 8H); 1.68-1.26 (m, 48H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ ppm = 163.5, 162.9, 162.7, 162.2, 161.3, 160.7, 156.6, 156.1, 154.3, 153.7, 153.1, 150.8, 149.4, 148.3, 147.0, 145.0, 140.2, 138.6, 134.8, 134.1, 132.3, 128.2, 127.8, 126.2, 125.8, 124.7, 123.2, 122.2, 121.7, 117.2, 115.9, 114.7, 114.4, 113.7, 110.6, 110.1, 108.7, 100.9, 99.4, 98.4, 97.3, 79.4, 67.2, 66.9, 49.7, 49.4, 49.1, 48.8, 48.5, 48.3, 47.9, 46.2, 46.1, 37.2, 28.9, 28.2, 28.1, 26.3, 26.2. HRMS ($ESI^+$): *m/z* calcd for $C_{93}H_{109}N_{20}O_{22}$ $[M+H]^+$ 1858.8056 found 1858.8091.




**25**

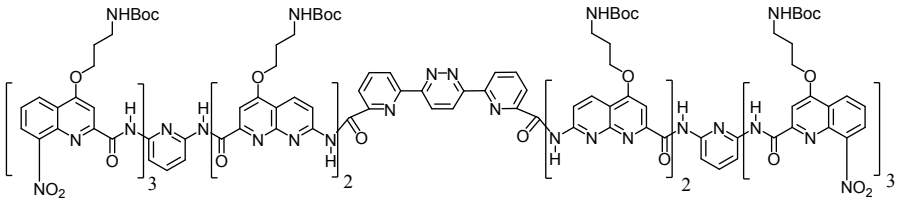
**Hexamer 25.** Trimer amine **22** (0.166 mmol, 0.16 g), quinoline trimer acid **18** (0.166 mmol, 0.18 g) and PyBOP (0.417 mmol, 0.217 g) were dissolved in distilled chloroform (20 mL). Then, DIEA (0.667 mmol, 100 μL) was added and the reaction mixture was let to stir at 40°C under inert atmosphere for 48 hours. The solution mixture was washed with solutions of $NH_4Cl$, $NaHCO_3$, distilled water and dried over MgSO4. The organic phases were evaporated and the residue was purified by flash chromatography ($SiO_2$) eluting with EtOAc:dichloromethane

(50:50 vol/vol) to afford 350 mg of material which was further purified by recycling preparative GPC (chloroform) to afford 185 mg of hexamer **25** as yellow solid (53%). $^1$H NMR (300 MHz, $CDCl_3$) δ 12.31 (s, 1H), 12.04 (s, 1H), 11.04 (s, 1H), 10.35 (s, 2H), 10.04 (s, 1H), 9.31 (d, J = 7.6 Hz, 1H), 8.84 – 8.71 (m, 3H), 8.64 (m, 3H), 8.52 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.37 (t, *J* = 7.7 Hz, 1H), 8.00-7.93 (m, 3H), 7.81 (s, 1H), 7.76 (s, 1H), 7.70 (t, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.48 (s, 1H), 7.40 (m, 2H), 7.30 (s, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.88 (s, 1H), 6.78 (t, *J* = 8.0 Hz, 1H), 5.51 (s, 1H), 4.98 (s, 4H), 4.61 (t, *J* = 8.6 Hz, 2H), 4.49 (s, 6H), 4.24 (s, 2H), 3.50 (q, *J* = 7.0 Hz, 4H), 3.05 – 2.89 (m, 2H), 2.25 (m, 6H), 1.55-1.48 (m, 36H), 1.35 (s, 9H), 1.23 (t, *J* = 7.0 Hz, 4H), 0.87 (m, 4H), 0.20 (s, 9H). HRMS (ESI$^+$): *m/z* calcd for $C_{100}H_{121}FN_{19}O_{24}Si$ $[M+H]^+$: 2019.8619 found 2019.8778.



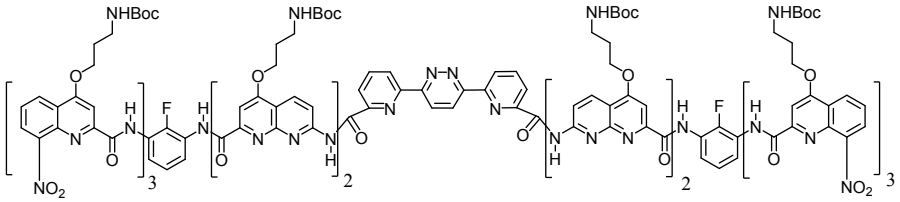

**26**

**Hexamer amine 26**. TBAF (0.28 mmol, 72.5 mg, 277.33 μL of 1.0 mol in THF) was added drop wise to a solution of **25** (140 mg, 0.07 mmol) in 5 mL of dry THF under nitrogen at 0°C. Then, the resultant mixture was stirred at RT for 4 h. The solvents were removed under reduced pressure to give a solid which was dissolved in dichloromethane, washed with solutions of $NH_4Cl$, $NaHCO_3$, distilled water and the organic phases was dried over MgSO4. The organic phases were evaporated and the residue was purified by flash chromatography to afford 120 mg of a yellow solid which was further purified by preparative GPC (chloroform) to afford 40 mg (35%) of hexamer **26**. $^1$H NMR (300 MHz,$CDCl_3$) δ 12.19 (s, 1H), 12.07 (s, 1H), 11.30 (s, 1H), 10.15 (s, 1H), 10.00 (s, 1H), 9.04 (d, *J* = 7.6 Hz, 1H), 8.78 (q, 2H), 8.63 (d, *J* = 7.6 Hz, 1H), 8.52 (d, *J* = 4.8 Hz, 1H), 8.48 (s, 1H), 8.41 (t, *J* = 7.6 Hz, 1H), 8.33 (d, *J* = 8.9 Hz, 1H), 8.07 (s, 1H), 7.92 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.79 (s, 1H), 7.70 (t, *J* = 8.1 Hz, 1H), 7.64 (s, 1H), 7.53 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.49 (s, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.30 (s, 4H), 7.19 (dd, *J* = 8.4, 1.3 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.79 (t, *J* = 8.0 Hz, 1H), 6.40 (s, 2H), 5.52 (s, 1H), 5.02 (d, *J* = 6.9 Hz, 1H), 4.87 (s, 2H), 4.53 (d, *J* = 6.0 Hz, 1H), 4.25 (s, 3H), 3.83 - 3.74 (m, 1H), 3.65 (s, 3H), 3.50 (m, 4H), 3.40 – 3.30 (m, 2H), 3.00 (s, 2H), 2.26 (m, 8H), 1.67-1.49 (m, 45H), 1.04 (t, *J* = 7.3 Hz, 4H). HRMS (ESI$^+$): *m/z* calcd for $C_{94}H_{109}FN_{19}O_{22}$ $[M+H]^+$: 1875.8007 found 1875.8128.



**28**

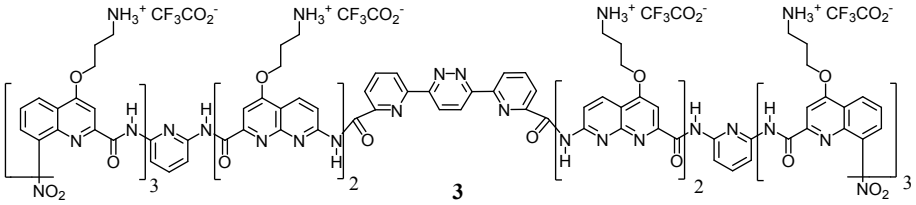
**Capsule 28**. Hexamer amine **24** (0.027 mmol, 50 mg), **pyr-pyz-pyr** diacid[4] **27** (0.0135 mmol, 4.33 mg) and PyBOP (0.067 mmol, 35 mg) were dissolved in distilled $CHCl_3$ (4 mL). Then, DIEA (0.067 mmol, 0.01 mL) was added and the reaction mixture was stirred at 40°C. After 24 hours the solvents were removed under reduced pressure and the residue was purified by column chromatography on silica to give capsule **28** as a pale yellow solid (84%, 45 mg). $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm = 11.39 (s, 2H); 11.23 (s, 2H); 9.90 (s, 2H), 9.82 (s, 2H); 9.62 (s, 2H), 9.56 (s, 2H); 8.76 (m, 4H); 8.49 (d, *J* = 8.48, 2H); 8.35 (m, 4H); 8.19 (m, 6H); 7.92-7.82 (m, 6H); 7.49 (m, 4H); 7.34-7.00 (m, 22H); 6.75 (d, *J* = 7.00, 2H); 6.60-6.46 (m, 6H); 6.25 (d, *J* = 8.11, 2H); 6.02 (s, 2H); 5.94 (t, *J* = 7.74, 2H); 4.66-3.99 (m, 22H); 3.44 (m, 10H); 3.30-3.13 (m, 18H); 2.32-1.99 (m, 24H); 1.71-0.83 (m, 184H). $^{13}$C NMR (75 MHz, DMSO-$d_6$:$CDCl_3$, 10/90, vol/vol) δ ppm = 164.0, 163.4, 162.4, 161.9, 161.5, 160.8, 160.3, 159.1, 156.8, 156.5, 156.0, 154.3, 154.1, 153.8, 153.4, 153.0, 151.7, 150.8, 150.2, 148.2, 147.5, 146.1, 144.2, 139.7, 138.3, 137.9, 137.4, 134.0, 133.7, 127.8, 127.3, 126.8, 126.1, 125.7, 125.4, 124.3, 122.8, 121.9, 120.8, 117.4, 116.3, 115.6, 114.8, 114.2, 113.4, 109.1, 107.5, 100.3, 98.8, 97.1, 79.5, 79.3, 78.9, 66.9, 66.6, 66.2, 49.4, 49.1, 48.8, 48.5, 48.3, 47.9, 47.7, 37.2, 36.8, 31.7, 29.4, 29.1, 28.8, 28.3, 28.1, 27.9, 22.4, 13.7. HRMS (ESI$^+$): *m/z* calcd for $C_{202}H_{224}N_{44}O_{46}$ $[M+2H]^{2+}$ 2001.8299 found 2001.8334.



**29**

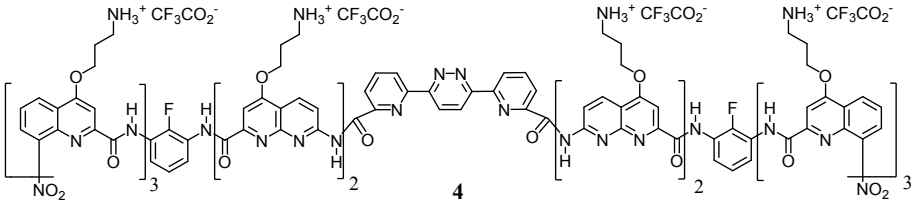
**Capsule 29**. Hexamer amine **26** (0.016 mmol, 30 mg), **pyr-pyz-pyr** diacid **27** (0.008 mmol, 2.57 mg) and PyBOP (0.04 mmol, 0.02 g) were dissolved in distilled $CHCl_3$ (5 mL). Then, DIEA (0.032 mmol, 5 μL) was added and the reaction mixture was stirred at 40°C. After 24 hours the solvents were removed under reduced pressure to give a solid which was dissolved in dichloromethane, washed with solutions of $NH_4Cl$, $NaHCO_3$ and distilled water then dried over MgSO4. The organic phases were evaporated and the residue was purified by flash chromatography ($SiO_2$) eluting with EtOAc:dichloromethane (50:50 vol/vol) to afford 30 mg

of material which was further purified by preparative recycling GPC (chloroform) to afford 10 mg (15%) of capsule **29**. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11.31 (s, 2H), 11.00 (s, 2H), 10.65 (s, 2H), 10.31 (s, 2H), 9.72 (s, 2H), 9.15 (s, 2H), 8.58 (m, 10H), 8.25 (dd, *J* = 16.5, 7.7 Hz, 4H), 8.06 (d, *J* = 7.9 Hz, 4H), 7.89 (d, *J* = 7.6 Hz, 6H), 7.68 (s, 2H), 7.55-7.19 (m, 10H), 7.13 (s, 10H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.76 (s, 2H), 6.69 (s, 2H), 6.47 (s, 4H), 6.19 (s, 2H), 6.06 (t, *J* = 8.0 Hz, 2H), 4.50 (s, 12H), 4.24 (s, 8H), 2.34-2.20 (m, 10H), 2.12 (s, 10H), 1.60-1.40 (m, 90H), 1.21 (s, 20H). HRMS (ESI$^+$): *m/z* calcd for $C_{204}H_{224}F_2N_{42}O_{46}$ $[M+2H]^{2+}$ 2018.8252 found 2018.8307



**3**

**Water soluble capsule 3**. Trifluoroacetic acid (1 mL) was added dropwise to a solution of **28** (45 mg, 0.011 mmol) in 1 mL of $CHCl_3$ under nitrogen at 0 °C and let to stir at RT for 2 h. The solvents were removed under reduced pressure to give a solid (99%, 46 mg) which was purified by HPLC to give **3** (28 mg) as a yellow solid. $^1$H NMR (300 MHz, $H_2O$:$D_2O$, 9/1, vol/vol) δ ppm = 11.63 (s, 2H); 11.16 (s, 2H); 10.39 (s, 2H), 10.37 (s, 2H); 9.94 (s, 2H), 9.29 (s, 2H); 8.76 (m, 4H); 8.64 (d, *J* = 9.08, 2H); 8.51 (s, 2H); 8.30-8.17 (m, 8H); 8.06-7.72 (m, 18H); 7.55 (t, *J* = 8.00, 2H); 7.34-7.24 (m, 10H); 7.18 (s, 2H); 6.92 (s, 2H); 6.83 (t, *J* = 8.10, 2H); 6.70 (s, 2H); 6.42 (d, *J* = 8.10, 2H); 6.26 (d, *J* = 8.27, 2H); 6.19 (s, 2H); 6.05 (t, *J* = 8.10, 2H); 3.49-3.17 (m, 16H); 2.95 (m, 2H); 2.77-2.22 (m, 40H); 1.56 (m, 10H). HRMS (ESI$^+$): *m/z* calcd for $C_{153}H_{146}KN_{44}O_{27}$ $[M+CH_3OH+K]^+$ 3071.1069 found 3072.0825.



**4**

**Water soluble capsule 4**. Trifluoroacetic acid (0.2 μL) was added to a solution of **29** (10 mg, 0.011 mmol) in $CH_2Cl_2$ (1 mL) under nitrogen at 0 °C and let to stir at RT for 5 h. The solvents were removed under reduced pressure and the residue was purified by preparative HPLC then lyophilized to afford 7 mg of capsule **4** as a yellow solid. $^1$H NMR (700 MHz, $H_2O$:$D_2O$, 9/1,

vol/vol) δ ppm = 11.50 (s, 2H); 10.95 (s, 2H); 10.78 (s, 2H), 10.61 (s, 2H); 9.88 (s, 2H), 9.23 (s, 2H); 8.95 (s, 2H); 8.79 (d, *J* = 8.0, 2H); 8.74 (d, *J* = 8.5, 2H); 8.60 (d, *J* = 8.5, 2H); 7.96 (d, *J* = 6.8, 2H); 7.90 (t, *J* = 7.0, 2H); 7.81 (d, *J* = 6.8, 2H); 7.66-7.60 (m, 4H); 7.52 (d, *J* = 7.4, 2H); 7.38 (d, *J* = 7.3, 2H); 7.34 (d, *J* = 7.3, 2H); 7.27 (s, 2H); 7.23 (s, 2H); 7.16 (s, 1H); 6.94 (t, *J* = 7.6, 2H); 6.86 (t, *J* = 7.9, 2H); 6.82 (s, 2H); 6.77 (t, *J* = 6.5, 2H); 6.30 (s, 2H); 6.27 (d, *J* = 7.9, 2H); 6.05 (t, *J* = 8.5, 2H); 3.48-3.33 (m, 10H); 3.27 (t, *J* = 8.0, 4H); 3.12 (s, 1H); 2.66-2.25 (m, 40H); 1.50-1.33 (m; 10H). HRMS (ESI$^+$): *m/z* calcd for $C_{154}H_{142}F_2N_{42}O_{26}$ $[M+2H]^{2+}$: 1517.5597 found 1518.0675.

## 4. NMR studies

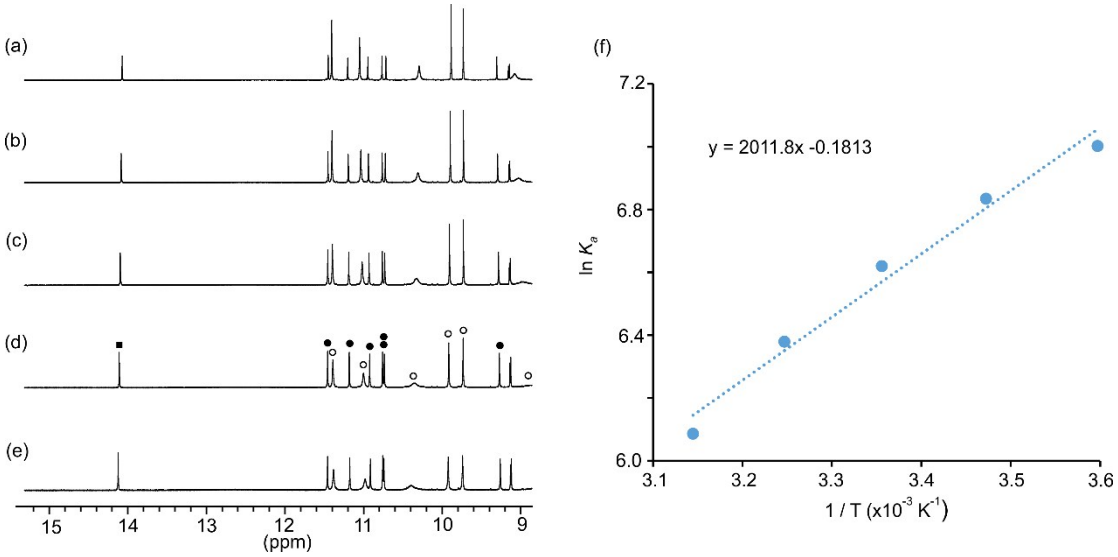



**Figure S1.** Excerpts of the 700 MHz $^1$H NMR spectra of capsule **1** (1 mM, $CDCl_3$:[$D_6$]-DMSO 80:20 vol/vol) in the presence of 0.5 equiv. of D/L-**5** at: (a) 318 K; (b) 308 K; (c) 298 K; (d) 288 K and (e) 278 K. (f) Van't Hoff plot of the encapsulation of D/L-**5** in capsule **1** in a $CDCl_3$:[$D_6$]-DMSO mixture (80:20 vol/vol). Experimental data were fitted to the Van't Hoff equation using linear regression analysis (blue line, $R^2$=0.9802). ΔH and TΔS were extracted to be -16.73 and -0.45 kJ.mol$^{-1}$, respectively.

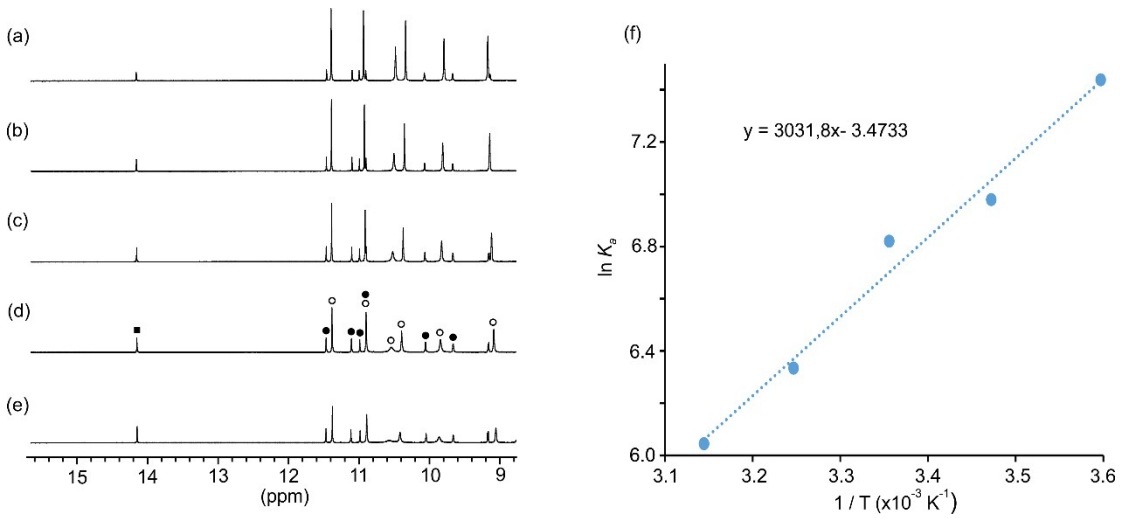



**Figure S2.** Excerpts of the 700 MHz $^1$H NMR spectra of capsule **2** (1 mM, $CDCl_3$:[$D_6$]-DMSO 80:20 vol/vol) in the presence of 0.5 equiv. of D/L-**5** at: (a) 318 K; (b) 308 K; (c) 298 K; (d) 288 K and (e) 278 K. (f) Van't Hoff plot of the encapsulation of D/L-**5** in capsule **2** in a $CDCl_3$:[$D_6$]-DMSO mixture (80:20 vol/vol). Experimental data were fitted to the Van't Hoff equation using linear regression analysis (blue line, $R^2$=0.9822). ΔH and TΔS were extracted to be -25.21 and -8.61 kJ.mol$^{-1}$, respectively.

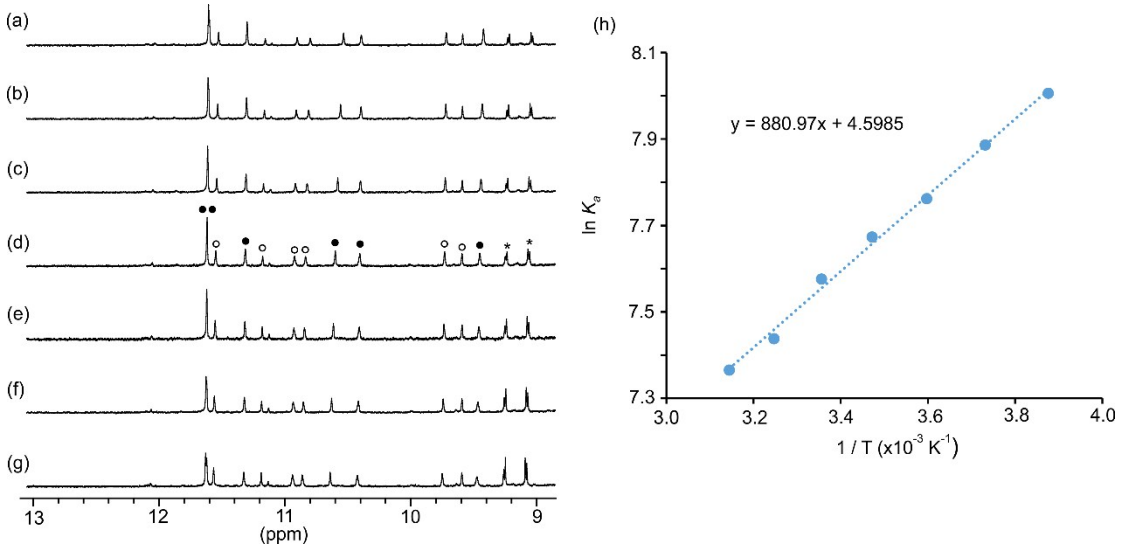



**Figure S3.** Excerpts of the 700 MHz $^1$H NMR spectra of capsule **3** (0.25 mM, $CD_3OH$) in the presence of 2 equiv. of D/L-**5** at: (a) 318 K; (b) 308 K; (c) 298 K; (d) 288 K; (e) 278 K; (f) 268 K and (g) 258K. (h) Van't Hoff plot of the encapsulation of D/L-**5** in capsule **3** in $CD_3OH$. Experimental data were fitted to the Van't Hoff equation using linear regression analysis (blue line, $R^2$=0.9962). ΔH and TΔS were extracted to be -7.3 and 11.4 kJ.mol$^{-1}$, respectively.

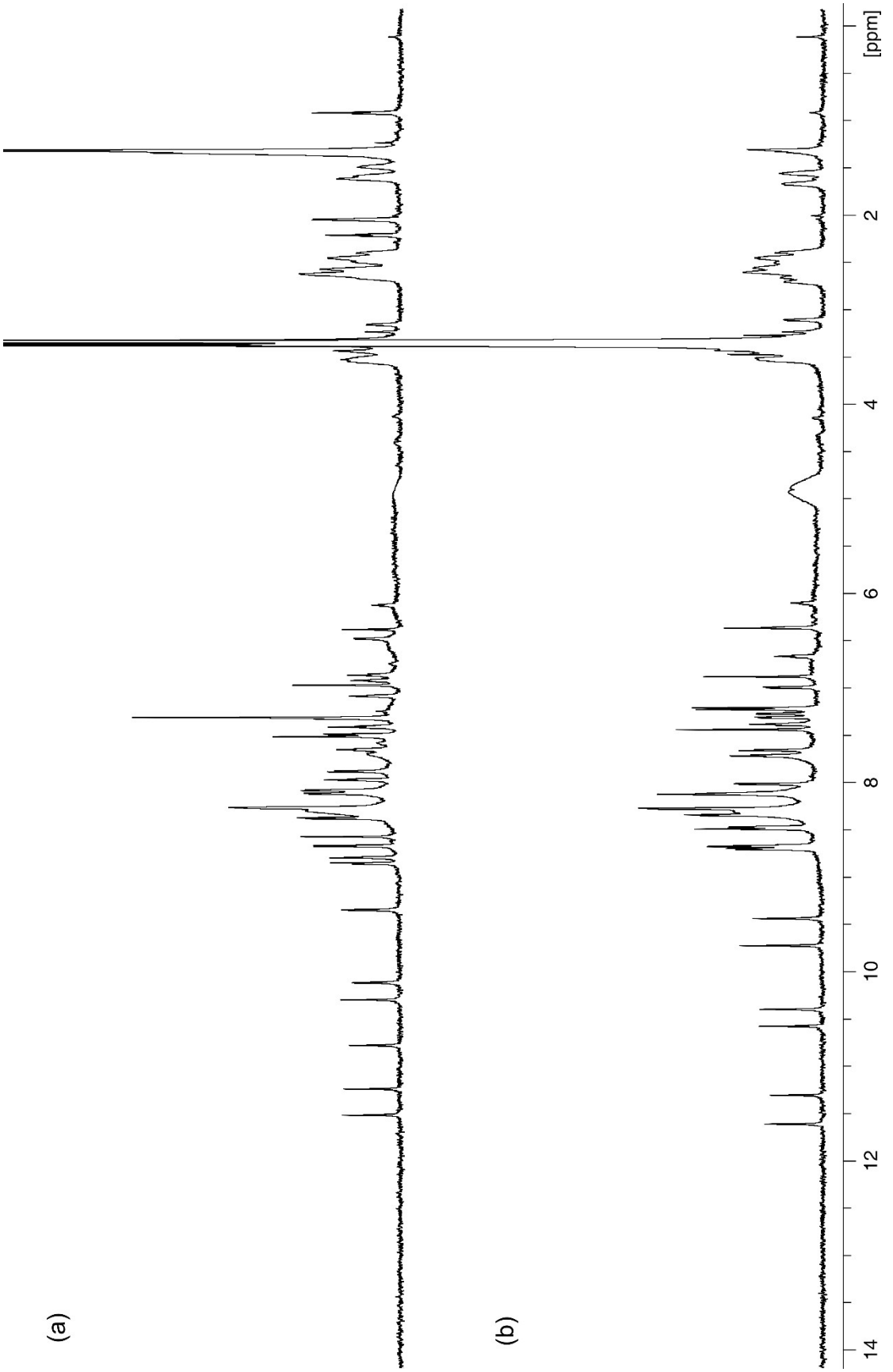
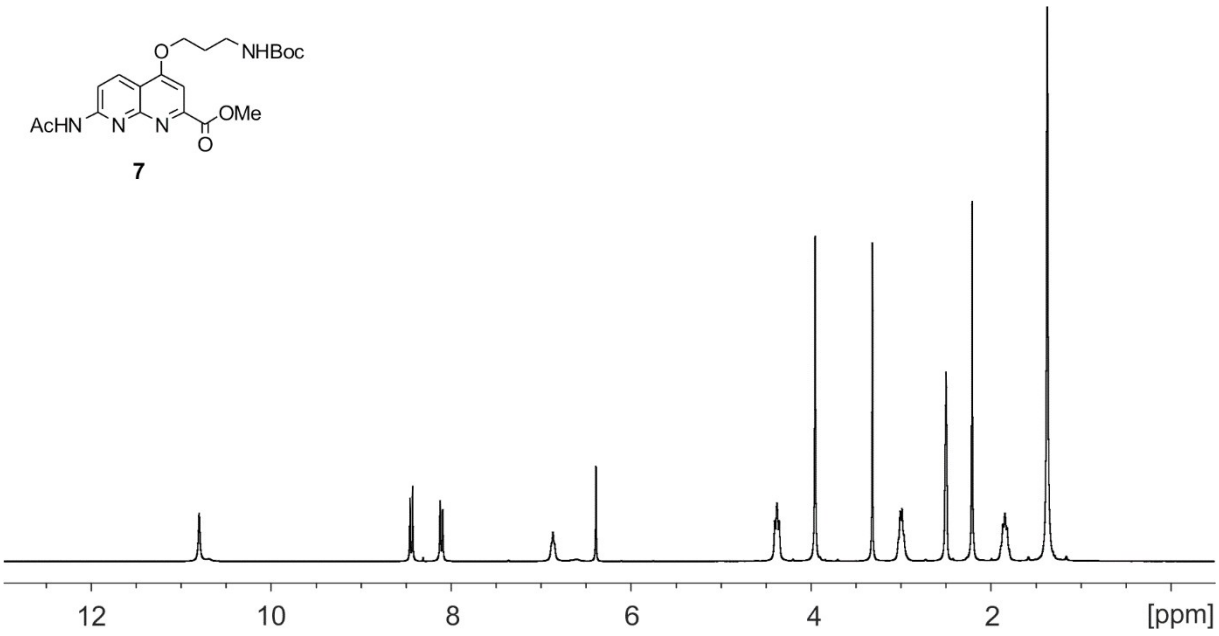
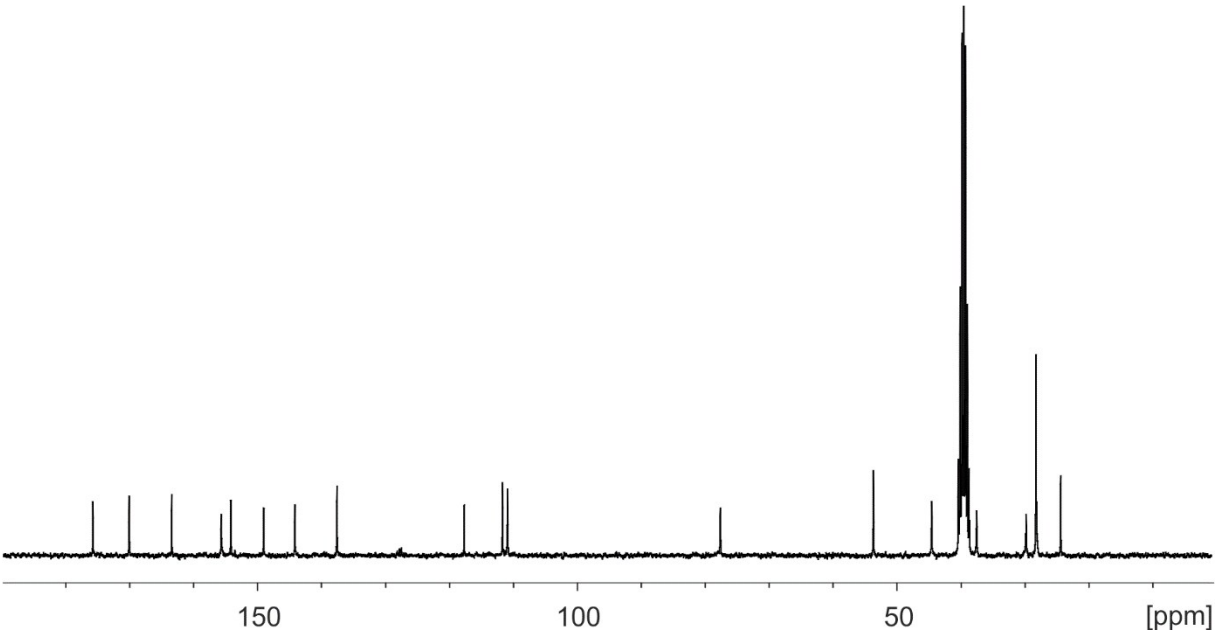


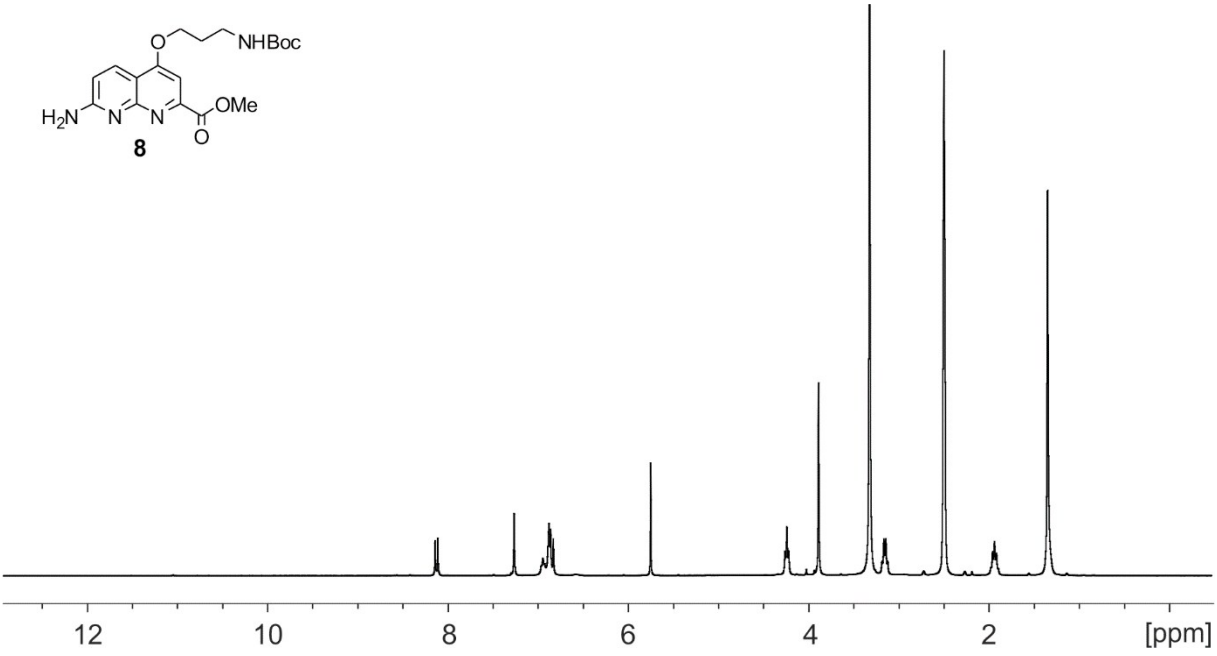

**Figure S4.** $^{1}H$ NMR spectra in $CD_3OH$ at 700 MHz (298K) of: (a) capsule **4** and (b) capsule **3**.

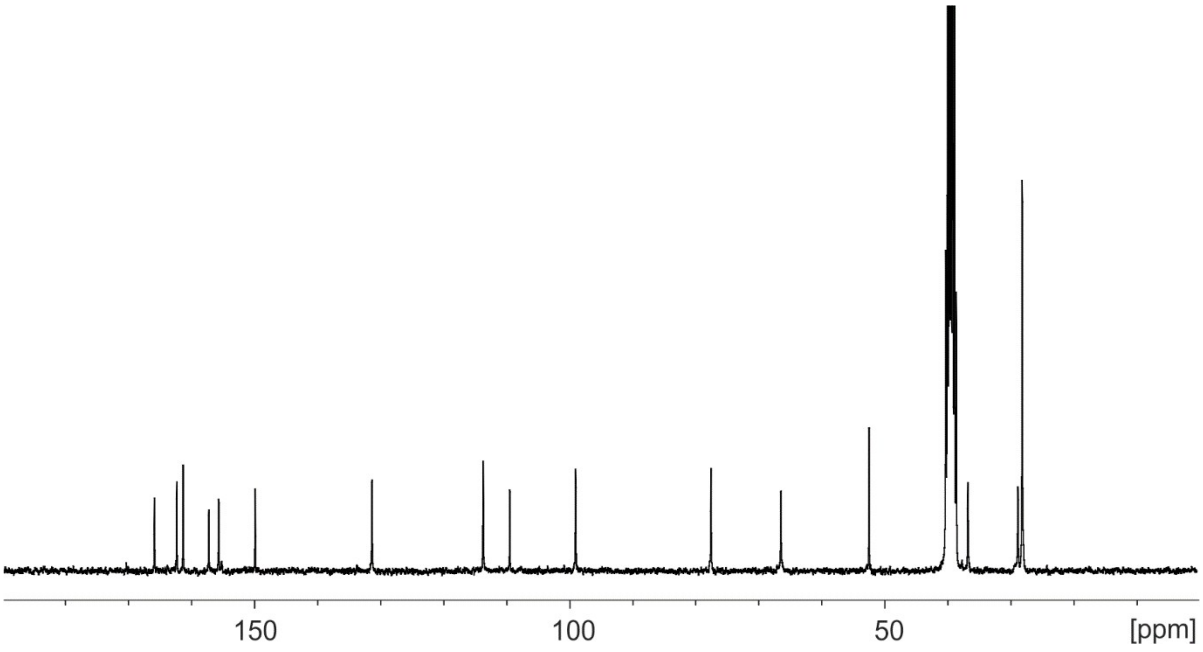
**5. $^{1}$H NMR and $^{13}$C NMR spectra of all relevant synthetic intermediates and title compounds.**

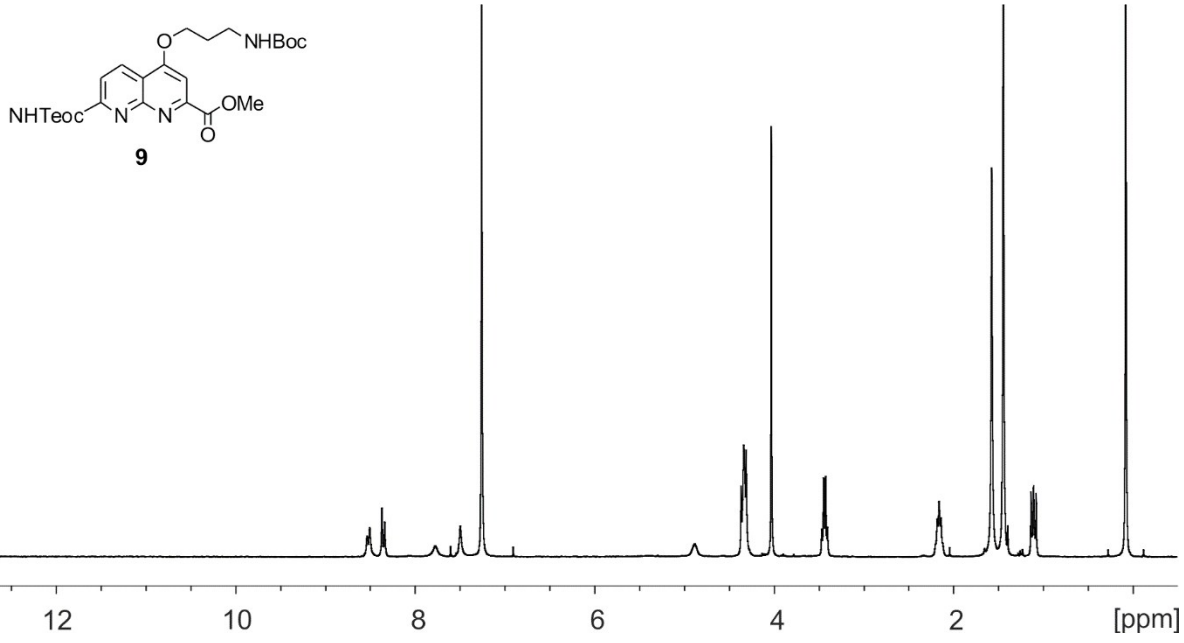



**7**

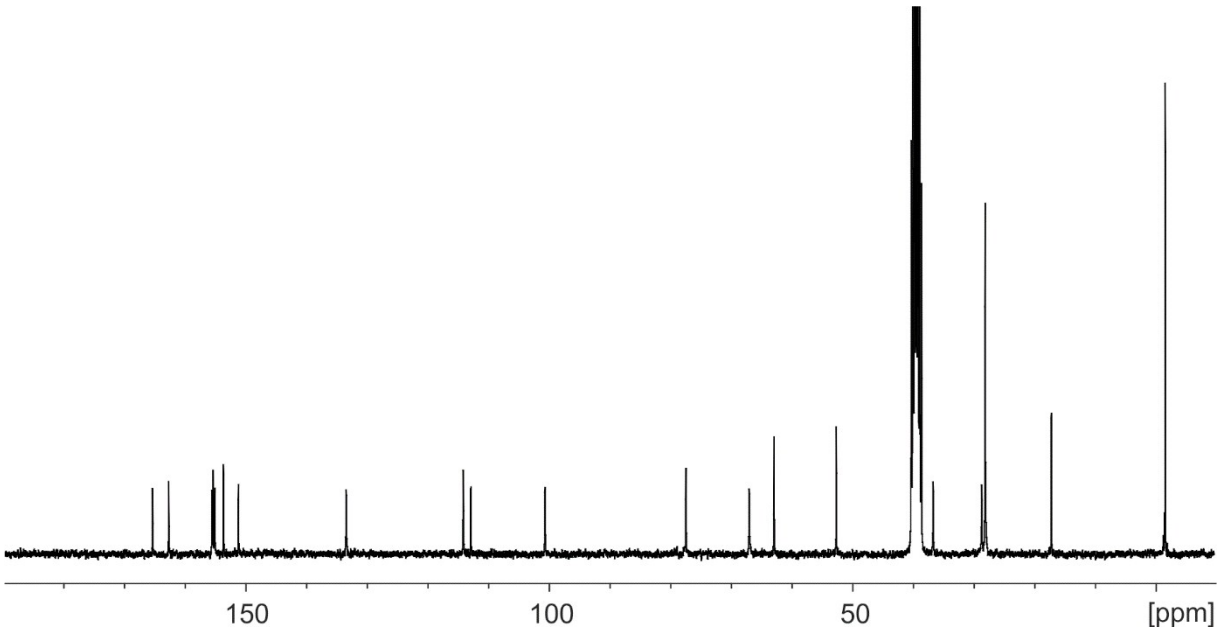


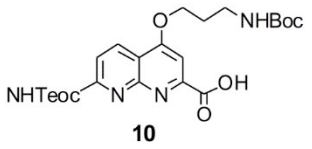

NHBoc
O
H2N
N
N
OMe
O
8
12
10
8
6
4
2
[ppm]


150
100
50
[ppm]



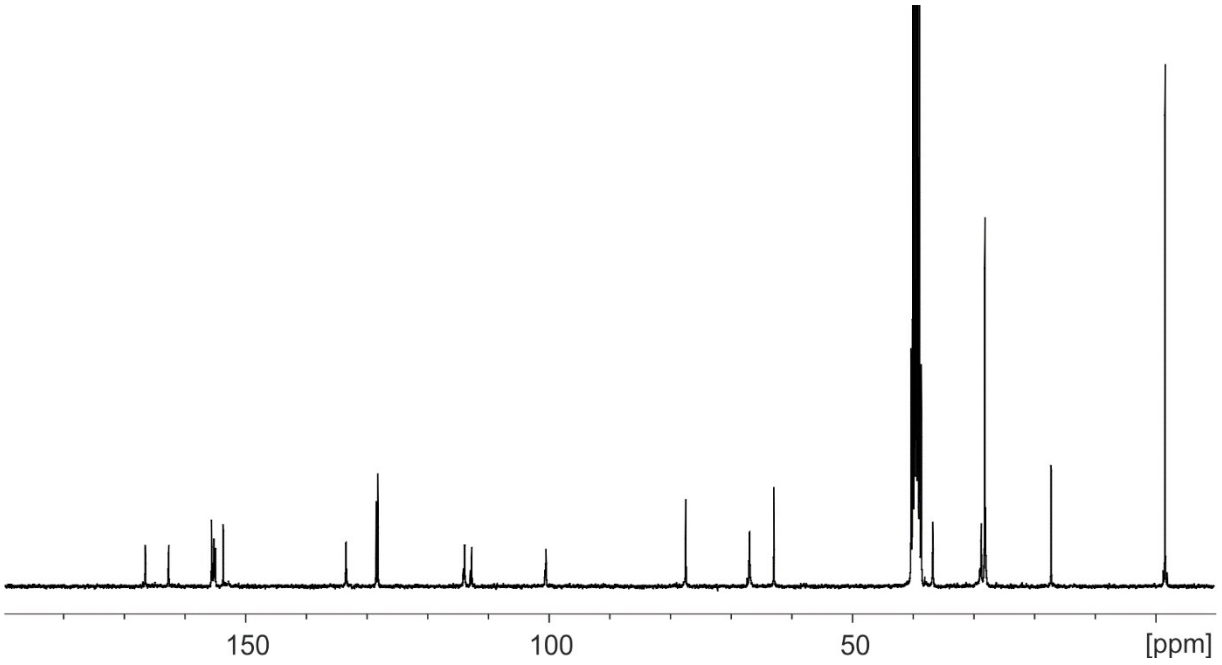

**9**

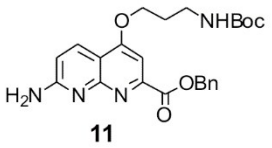





**10**

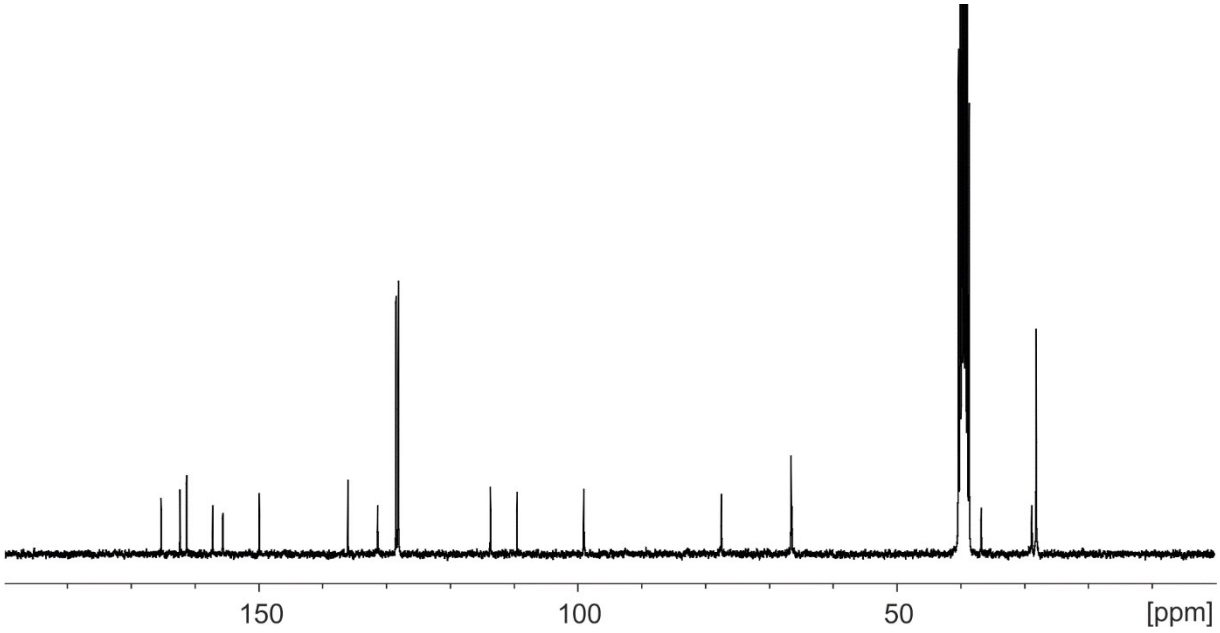


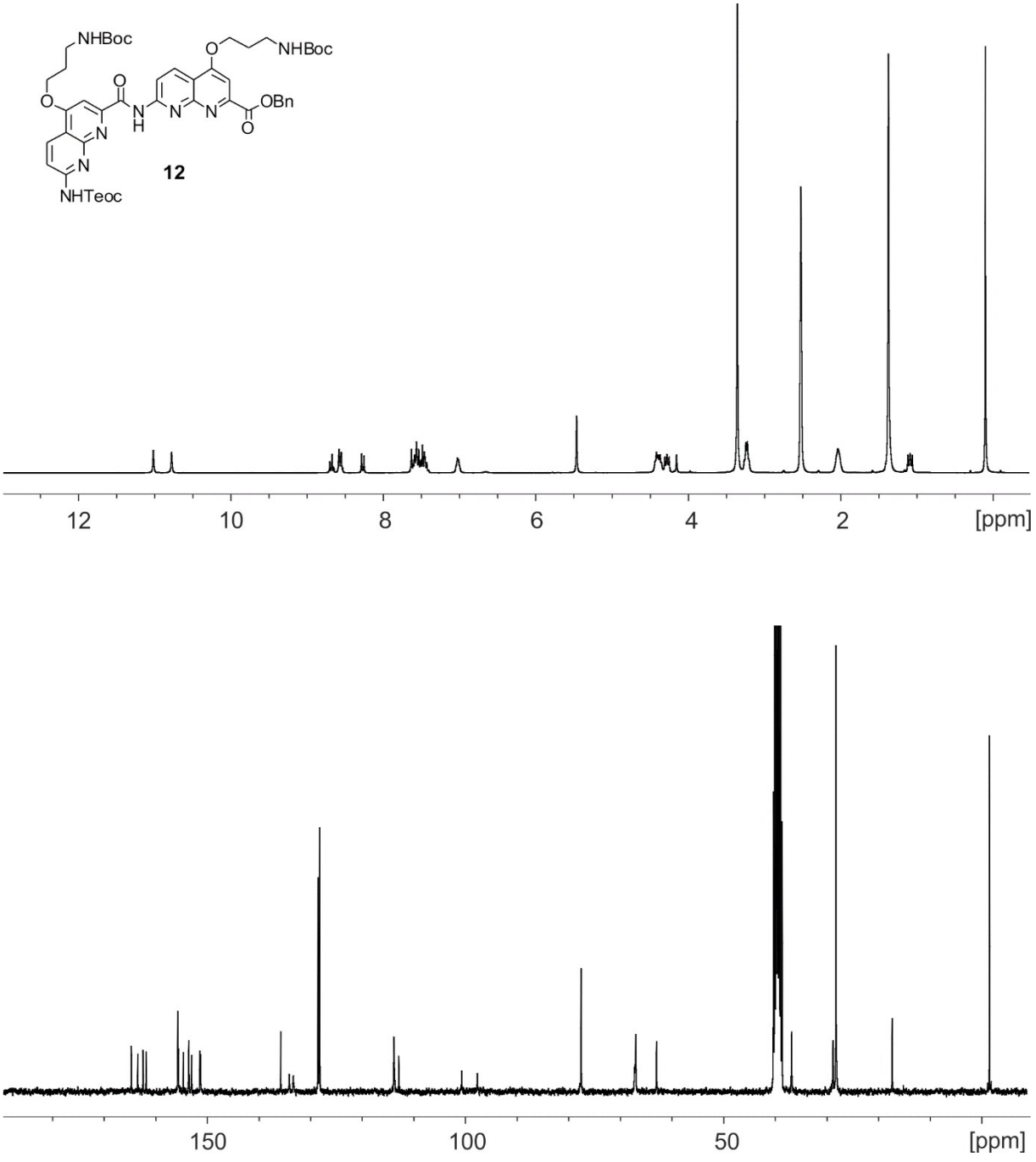



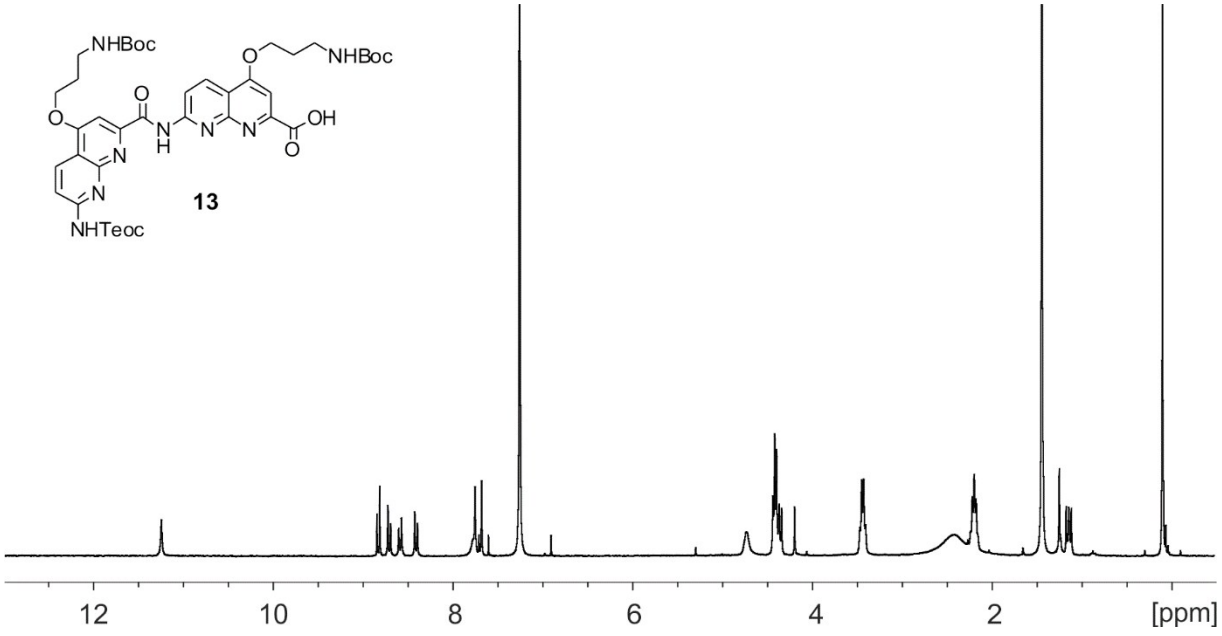


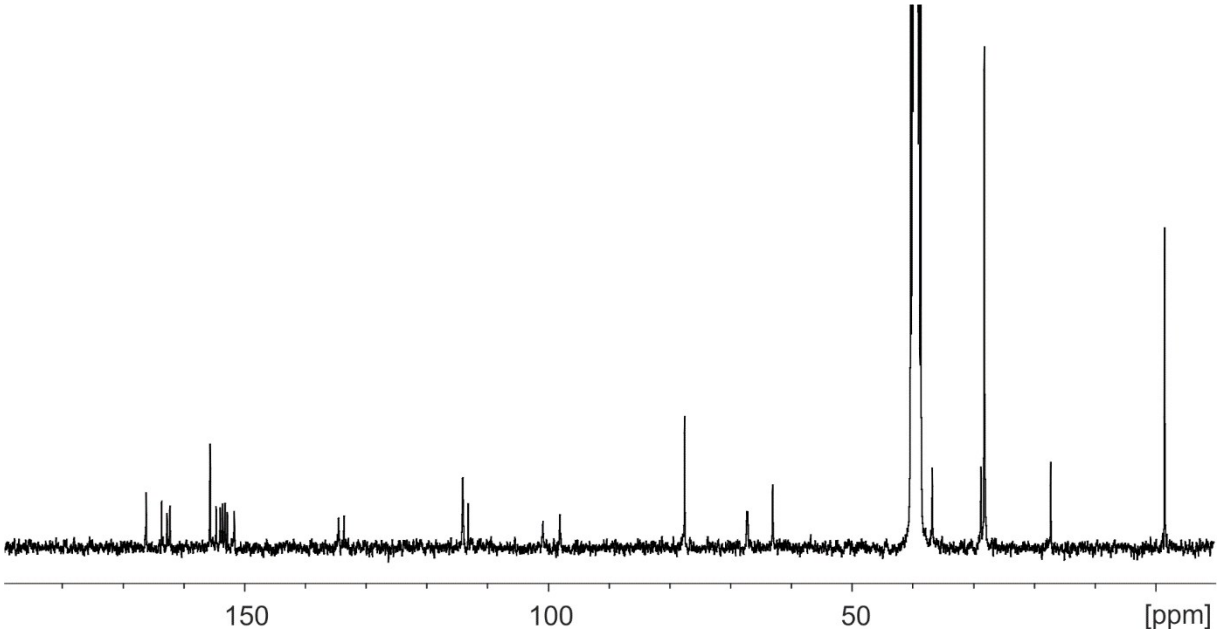

**11**

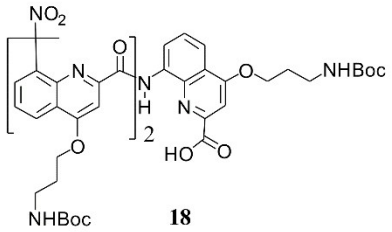



NHBoc
NHBoc
OBn
NHTeoc
12
12
10
8
6
4
2
[ppm]
150
100
50
[ppm]

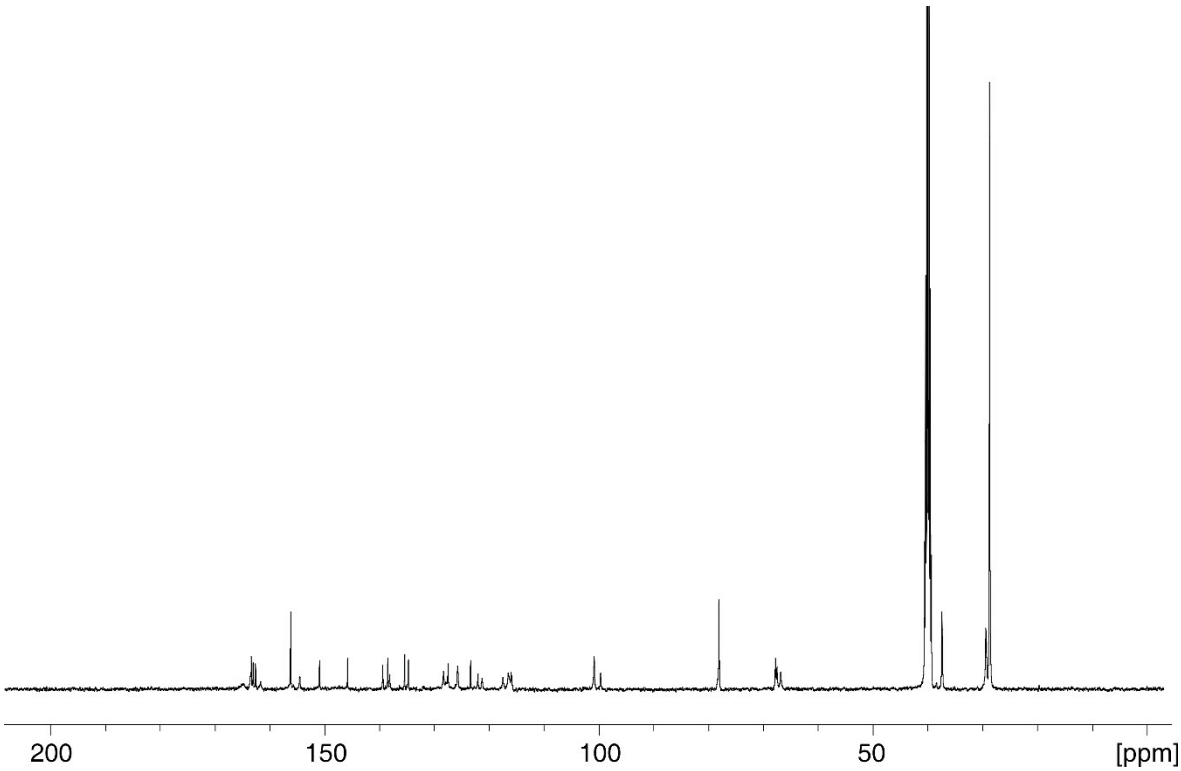

NHBoc
NHBoc
O
O
N
H
N
N
N
N
OH
O
O
N
NHTeoc
13
12
10
8
6
4
2
[ppm]

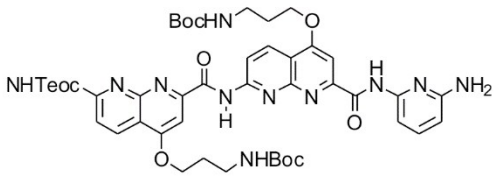

150
100
50
[ppm]


NO2
O
N
N
H
2
O
NHBoc
N
HO
O
O
NHBoc

**18**

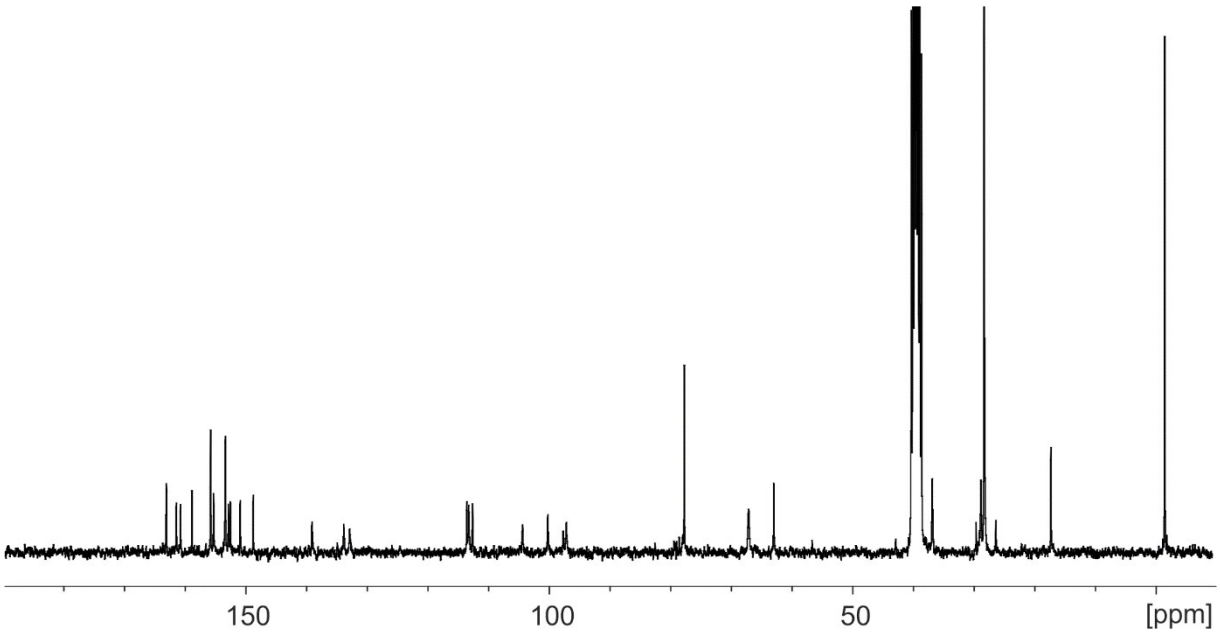

12
10
8
6
4
2
0 [ppm]

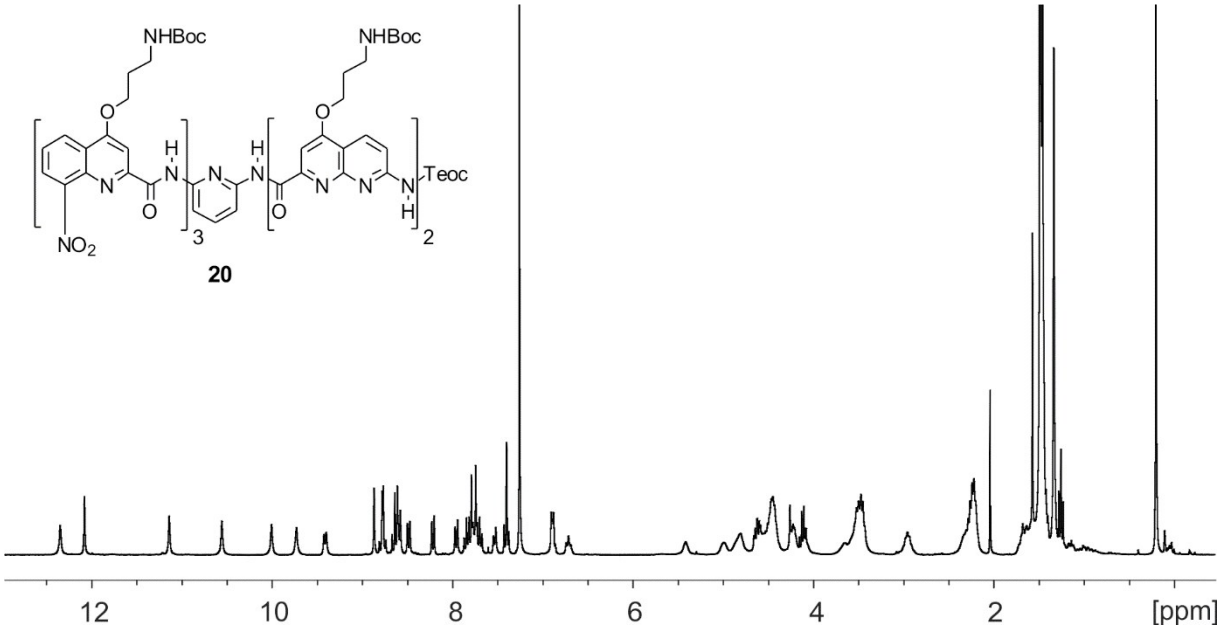

200
150
100
50
[ppm]


BocHN
O
NHTeoc
N
N
O
N
H
H
N
N
N
O
N
NH2
O
NHBoc

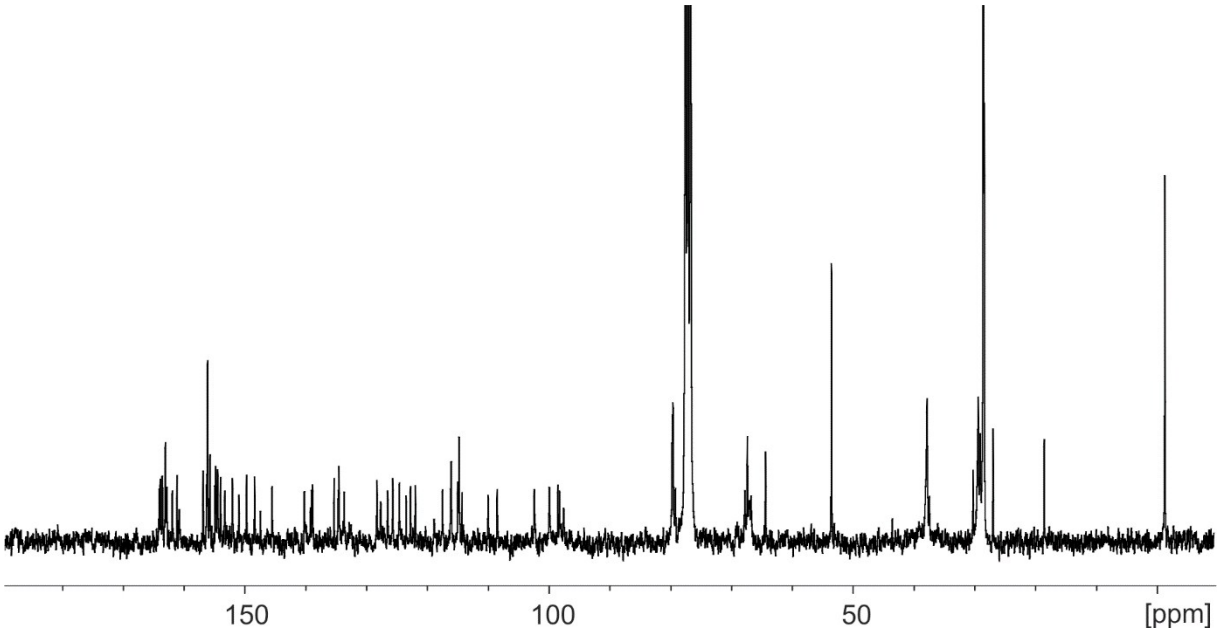
**19**

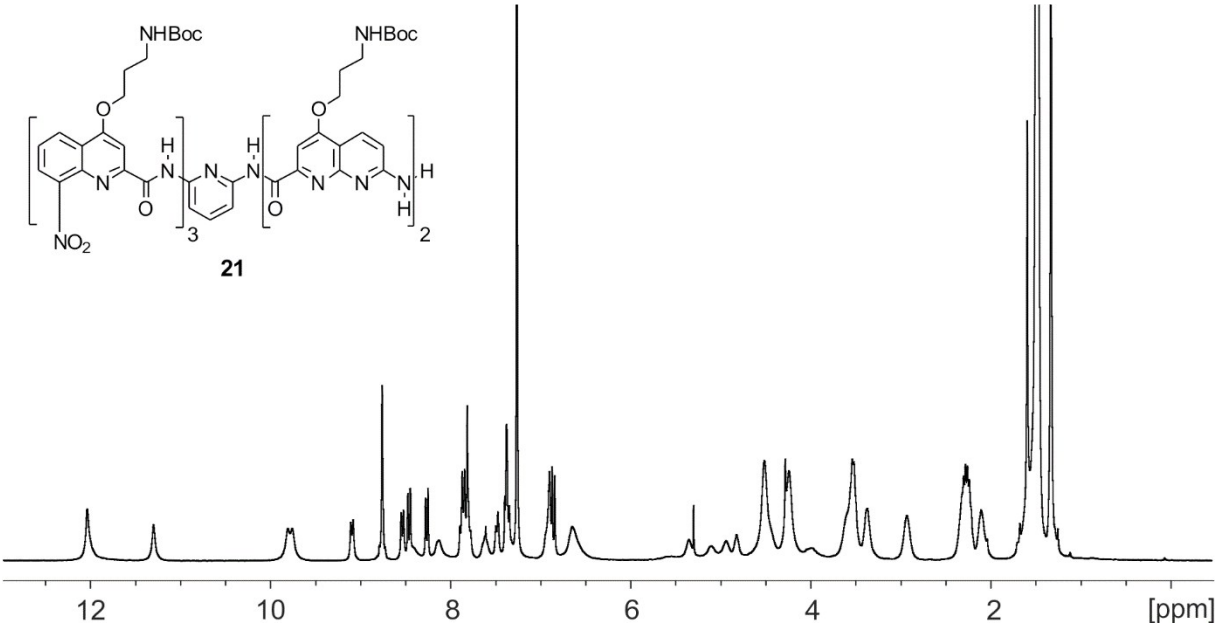

12
10
8
6
4
2
[ppm]


150
100
50
[ppm]

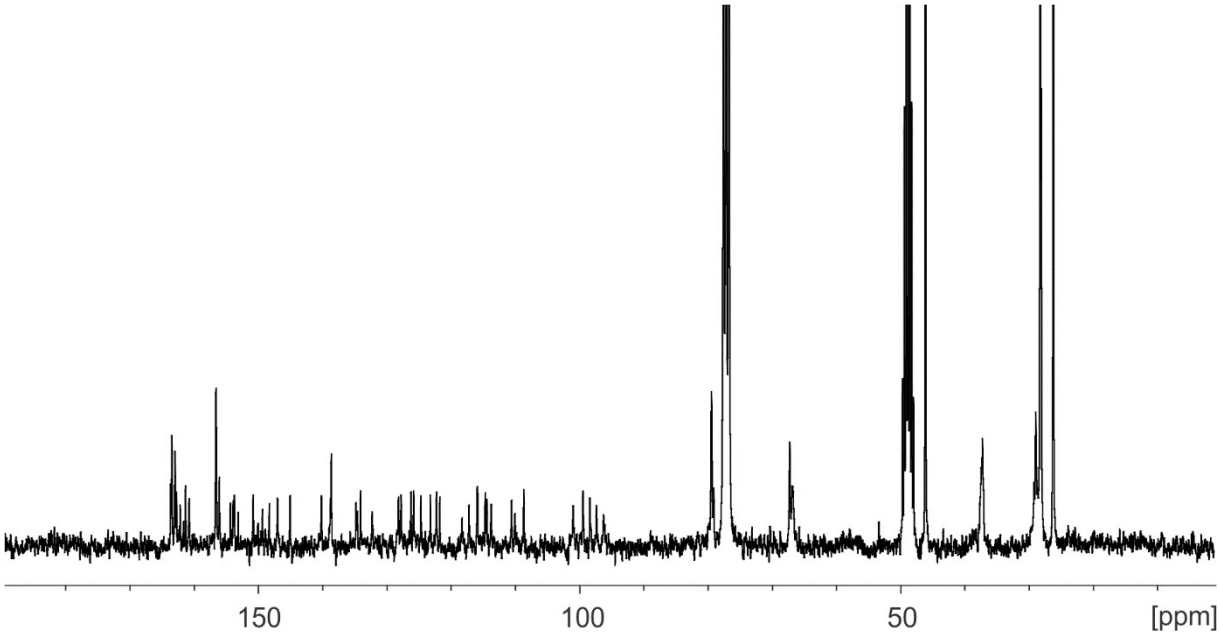

NHBoc
NHBoc
O
O
H
N
N
N
O
N
N
N
H
Teoc
NO2
3
2
12
10
8
6
4
2
[ppm]

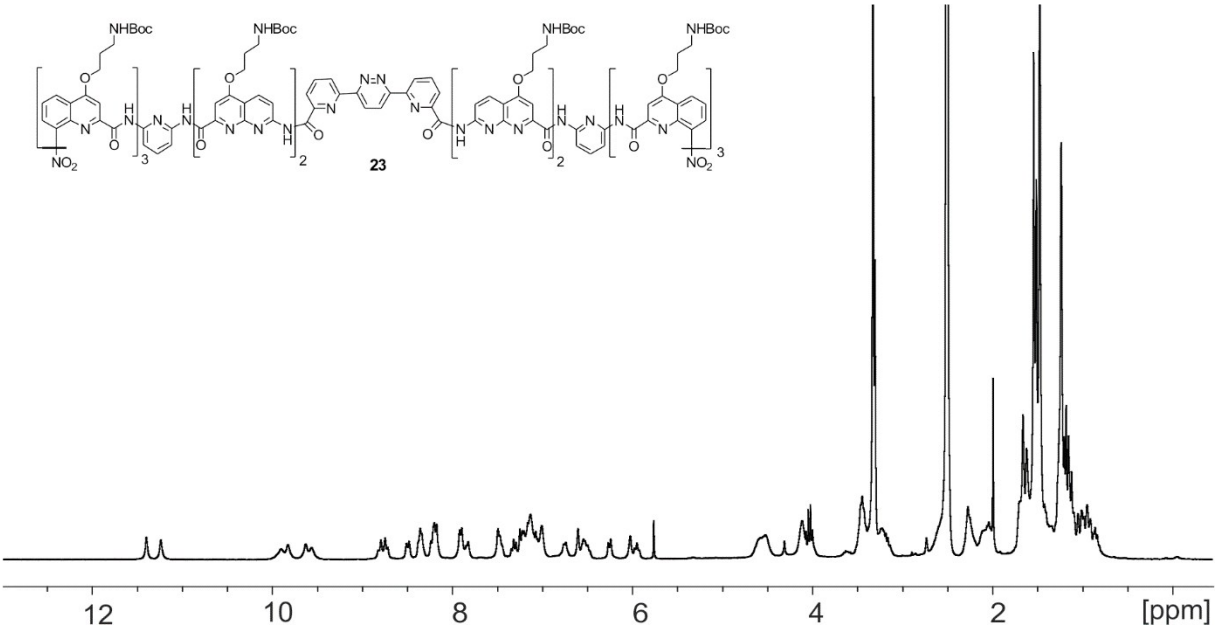
**20**

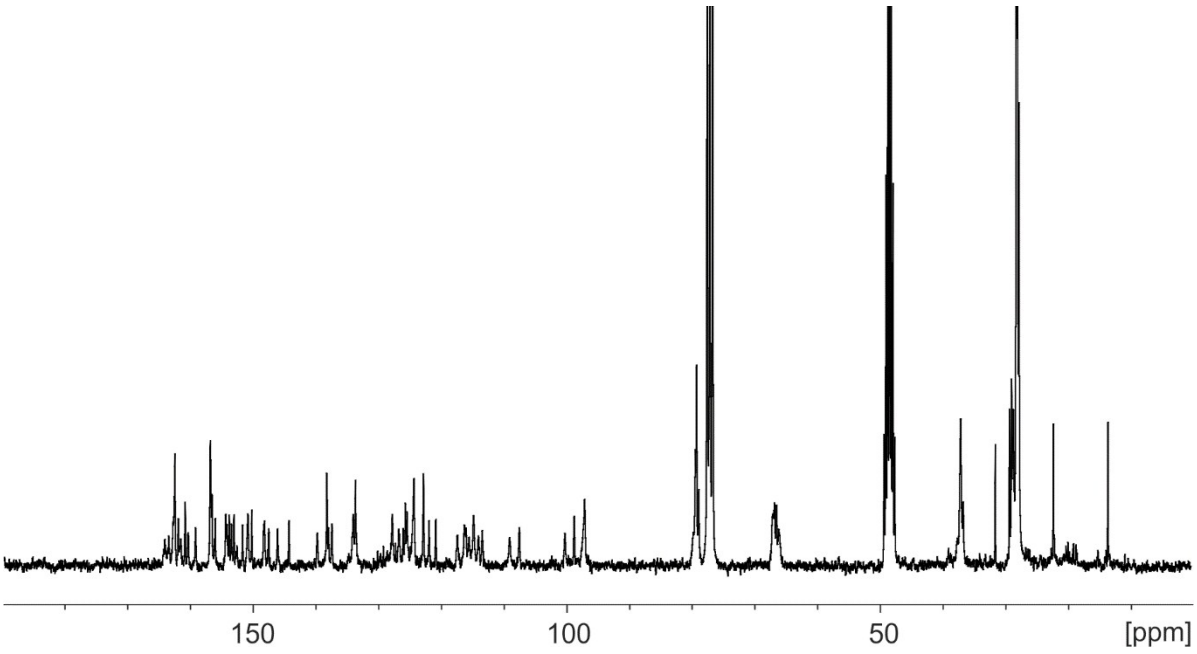

150
100
50
[ppm]

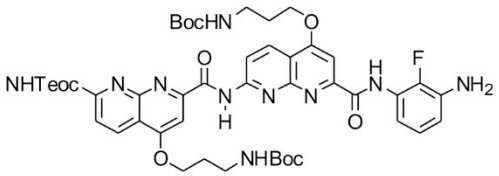

NHBoc
NHBoc
O
O
H
N
N
N
N
N
N
O
O
H
N
H
NO2
3
2
12
10
8
6
4
2
[ppm]

**21**


150
100
50
[ppm]

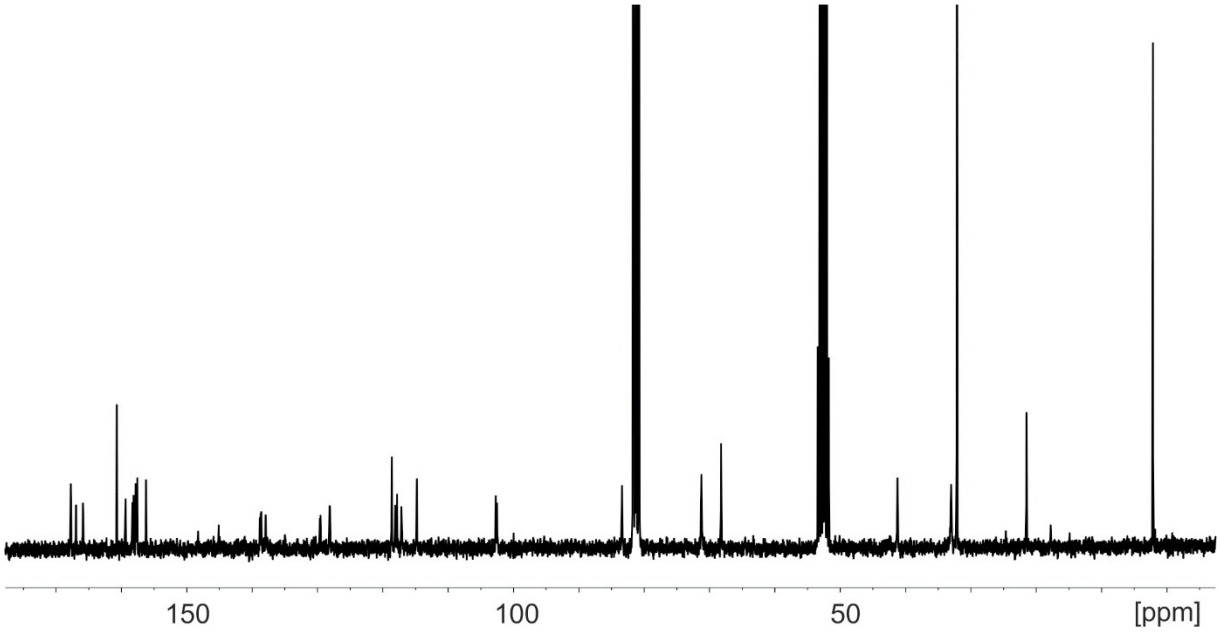

NHBoc
NHBoc
NHBoc
NHBoc
NO2
NO2
23
12
10
8
6
4
2
[ppm]

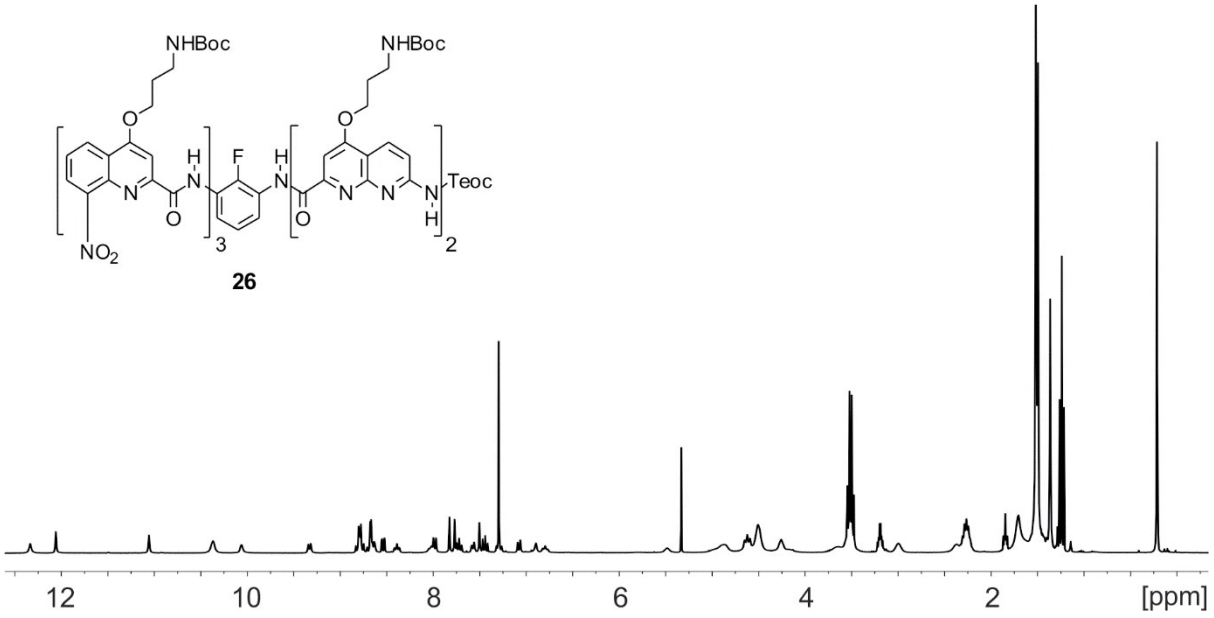

150
100
50
[ppm]


BocHN
O
NHTeoc
N
N
O
N
H
N
N
H
N
N
F
NH2
O
NHBoc

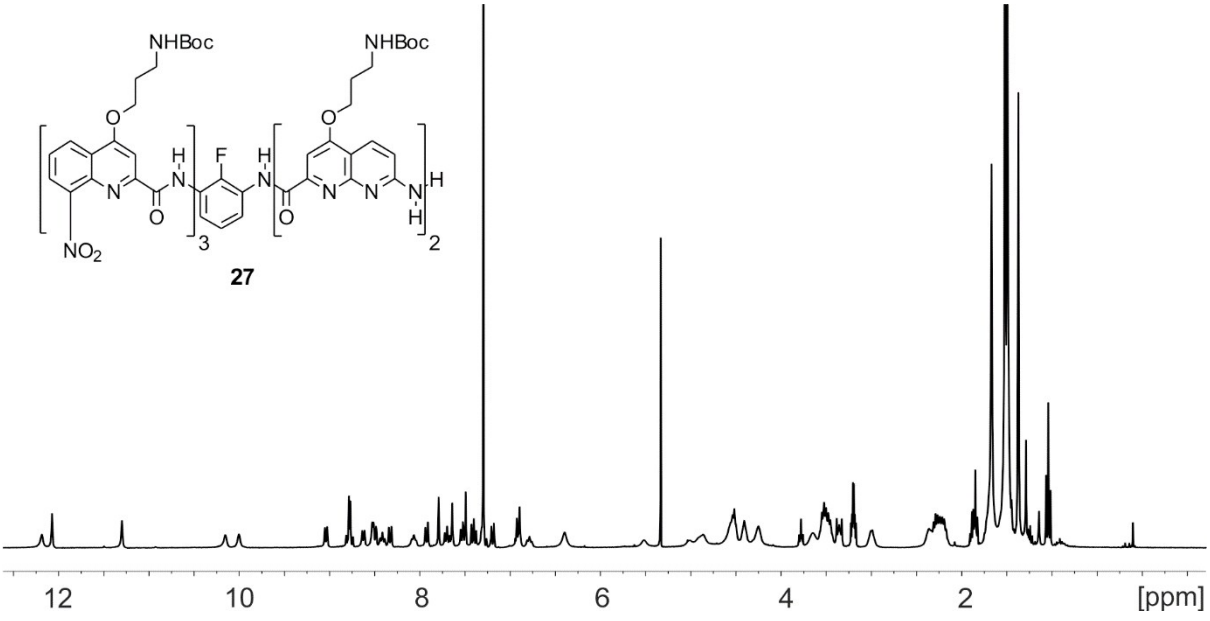
**25**

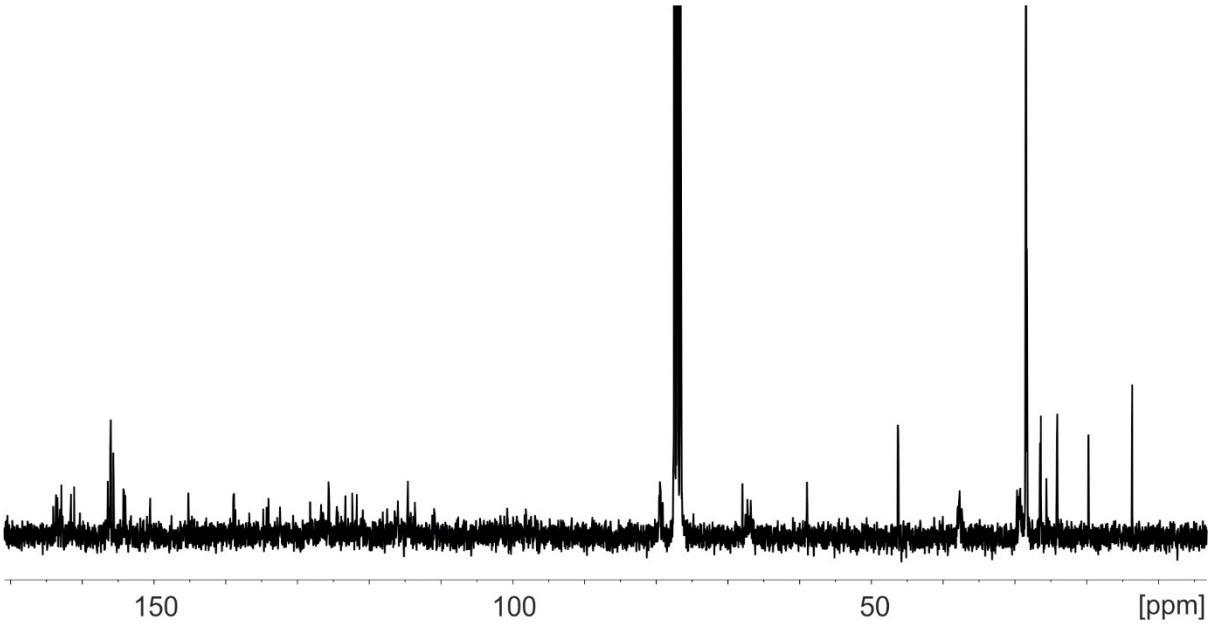

10
8
6
4
2
[ppm]

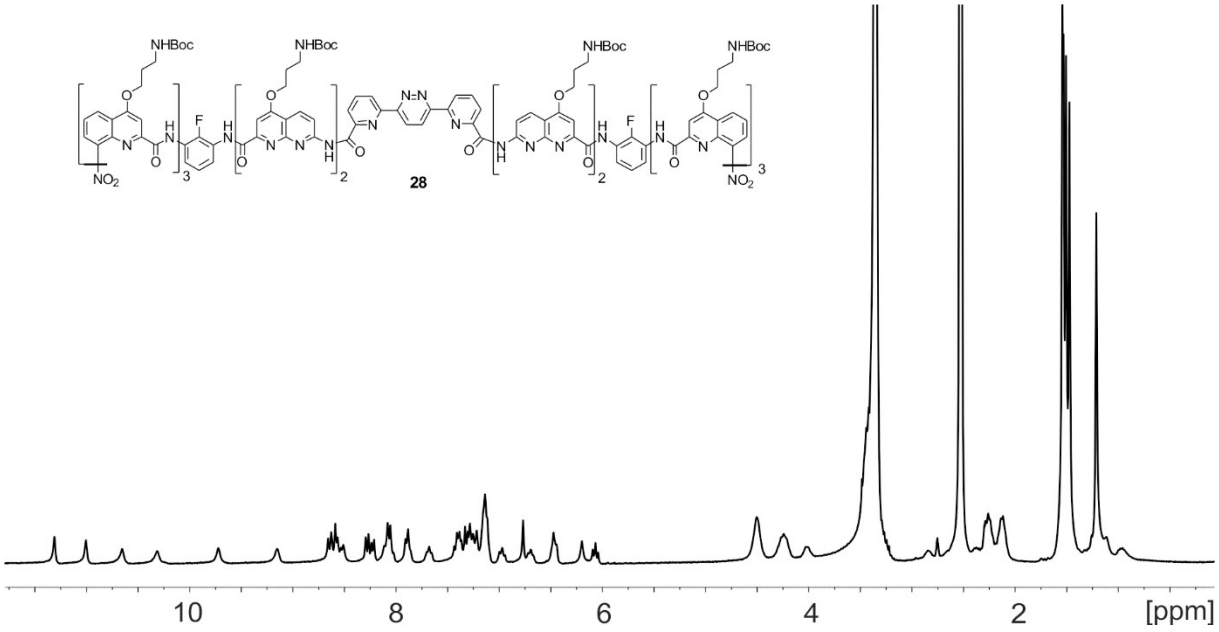

150
100
50
[ppm]




**26**


NHBoc
NHBoc
O
O
H
N
F
H
N
N
N
N
H
O
O
3
2
NO2
27
12
10
8
6
4
2
[ppm]


150
100
50
[ppm]


NHBoc
NHBoc
NHBoc
NHBoc
F
F
N=N
NO2
NO2
3
2
2
3
28
10
8
6
4
2
[ppm]

## 6. References


1. Y. Ferrand, A. M. Kendhale, J. Garric, B. Kauffmann, I. Huc, *Angew. Chem. Int. Ed.* 2010, **49**, 1778.

2. Q. Gan, C. Bao, B. Kauffmann, A. Grélard, J. Xiang, S. Liu, I. Huc, H. Jiang, *Angew. Chem. Int. Ed.* 2008, **47**, 1715

3. E. Gillies, F. Deiss, C. Staedel, J.-M. Schmitter, I. Huc, *Angew. Chem. Int. Ed.* 2007, **46**, 4081.

4. Y. Ferrand, A. M. Kendhale, B. Kauffmann, A. Grélard, C. Marie, V. Blot, M. Pipelier, D. Dubreuil, I. Huc, *J. Am. Chem. Soc.* 2010, **132**, 7858.