Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Porphyrin-templated synthetic G-quartet (PorphySQ): a second prototype of G-quartet–based G-quadruplex ligand

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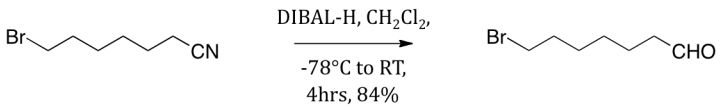
- Supporting Information -

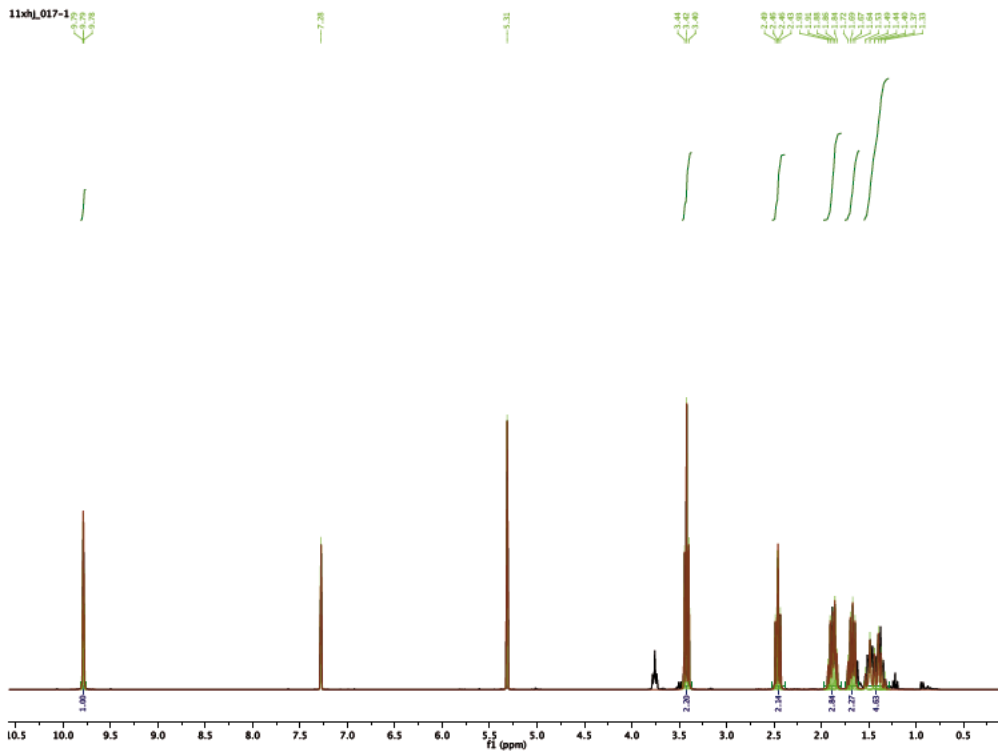
Instrumentation: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker DRX-300 AVANCE transform spectrometer at the "Pôle Chimie Moléculaire (Welience, UB-Filiale)". UV/Vis spectra were recorded with a Varian Cary 1 spectrophotometer. Mass spectra were obtained with a Bruker Daltonics Ultraflex II spectrometer in the MALDI-TOF reflectron mode using dithranol as a matrix or by ESI on a LTQ Orbitrap XL Thermo spectrometer. Accurate mass measurements (HRMS) were carried out under the same conditions as before.

Chemicals and Reagents: Unless otherwise noted, all chemicals and solvents were of analytical reagent grade and used as received. Absolute dichloromethane, chloroform and methanol were obtained from Carlo Erba. Silica gel (Merck; 70-120 μm) was used for column chromatography. Analytical thin-layer chromatography was performed with Merck 60 F254 silica gel (precoated sheets, 0.2 mm thick). Reactions were monitored by thin-layer chromatography, UV/Vis spectroscopy and MALDI/TOF mass spectrometry.

Step 1: **7-bromoheptanal (1)**

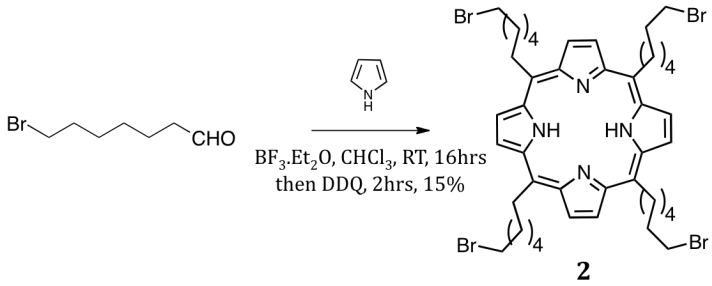


7-Bromoheptanenitrile (2.0g, 10.52mmol) was dissolved in 15mL of dry CH_2Cl_2 under argon. The solution was cooled to -78°C and 40mL of diisobutylaluminium hydride (1.0M in CH_2Cl_2) was added dropwise. The mixture was stirred for 1h at -78°C, then warmed to room temperature for 3h. The reaction was quenched with methanol (20mL) and 10mL HCl (10%) was added dropwise at -78°C. The product was extracted with ether (3x100mL) and washed with distilled water then brine. The solvent was removed by evaporation under reduced pressure to lead to compound **1** in 84% yield (1.7g, 8.80mmol). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.79 (s, 1H), 3.42 (t, 2H, $^{3}J_{HH}$ = 6.0Hz), 2.46 (m, 2H), 1.88 (m, 2H), 1.67 (m, 2H), 1.40 (m, 4H).



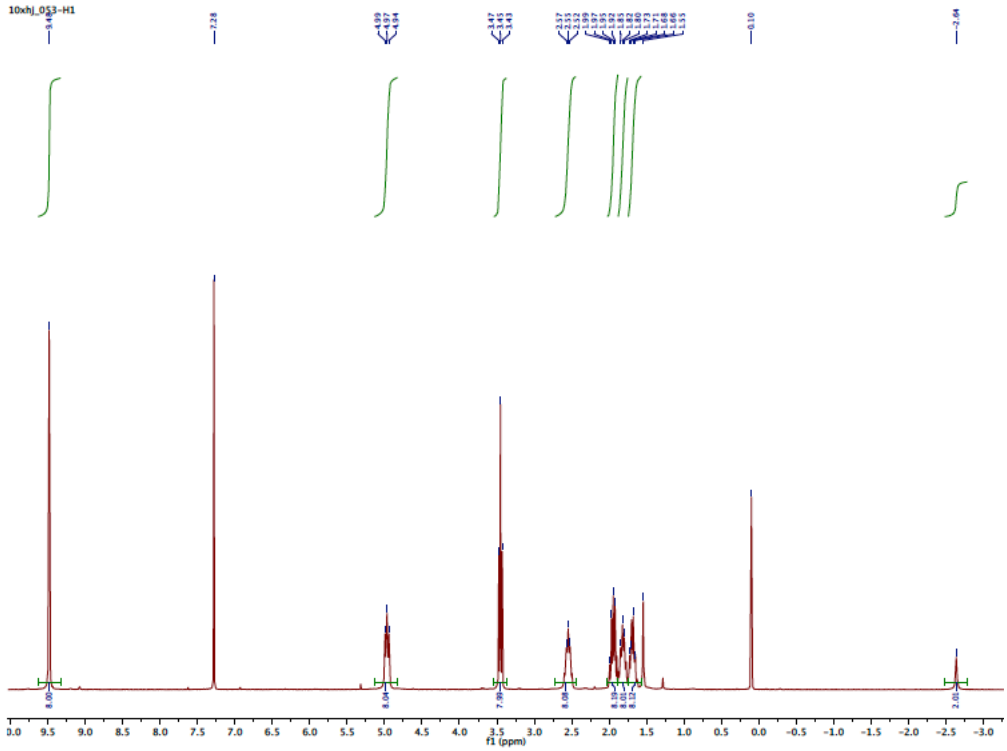
^{1}H NMR spectrum of **1** ($CDCl_3$, 298K).

Step 2: **Tetra(6-bromohexyl)porphyrin (2)**



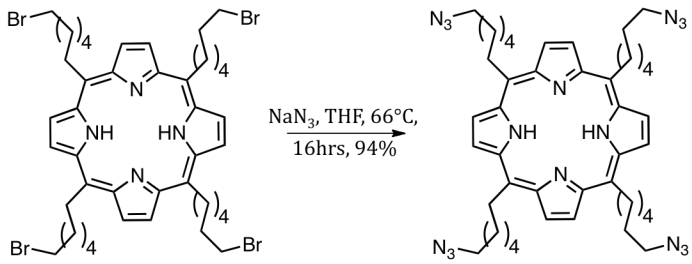
2

Under nitrogen, 3mmol of 7-bromoheptanal **1** (0.58g) and 3mmol of pyrrole (0.20g) were dissolved in 200mL of chloroform. The solution was purged by nitrogen for 2h. Still under nitrogen, 75µL of $BF_3 \cdot Et_2O$ were added to the solution at 20°C. The mixture was stirred overnight. DDQ (3mmol) was added and the mixture was again stirred for 2h, then two drops of triethylamine were added. The solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel using CH_2Cl_2 as eluent and recrystallized from $CHCl_3/CH_3OH$. Yield: 15.5% (112mg, 0.465 mmol). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.48 (s, 8H, H-pyrro), 4.97 (t, 8H, $^3J_{HH}$ = 6.0Hz, α-CH_2-), 3.45 (t, 8H, $^3J_{HH}$ = 6.0Hz, Br-CH_2-), 2.55 (m, 8H, β-CH_2-), 1.97 (m, 8H, γ-CH_2-), 1.82 (m, 8H, δ-CH_2), 1.68 (m, 8H, ε-CH_2-), -2.64 (s, 2H, N-H). ^{13}C NMR ($CDCl_3$) δ (ppm): 144.8, 128.6 (broad s), 118.1, 38.2, 35.3, 34.0, 32.9, 29.6, 28.2. MS (MALDI-TOF) m/z = 957.96 $[M]^{+\cdot}$, 958.14 calcd for $C_{44}H_{58}Br_4N_5$. UV-Vis (CH_2Cl_2): λ_{max} (nm) (ε x 10^{-3} L.mol^{-1}.cm^{-1}) = 416.9 (440.7), 519.0 (14.9), 554.0 (9.8), 600.1 (4.3), 658.1 (7.3).



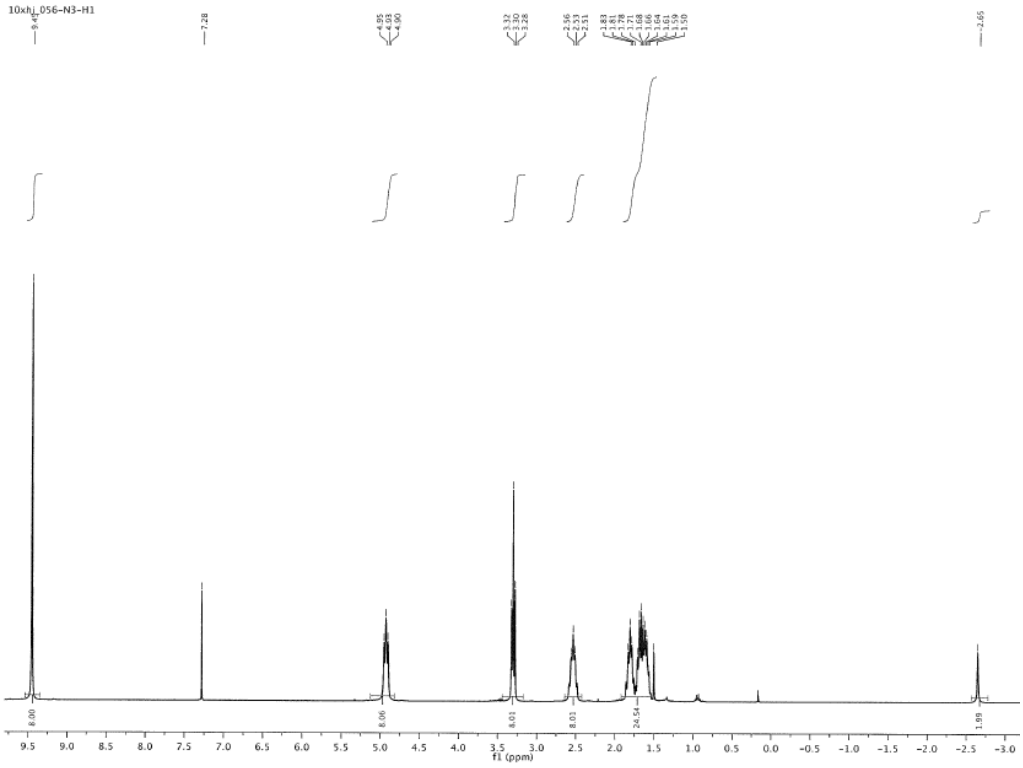
^{1}H NMR spectrum of **2** ($CDCl_3$, 298K).

Step 3: **Tetra(6-azidohexyl)porphyrin (3)**



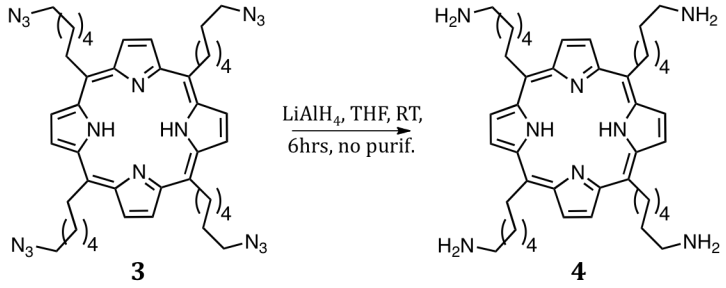
2 **3**

In 20mL of THF were dissolved 100mg (0.104mmol) of tetra(6-bromohexyl)porphyrin **2**, then 2mL of H_2O containing 56mg of NaN_3 were added to the solution. The mixture was heated to 66°C overnight. The solvent was removed under reduced pressure. The residue was dissolved in 100mL $CHCl_3$. The organic solution was washed with H_2O (3x10mL) and dried over $MgSO_4$. The organic solvent was then removed under reduced pressure. The product was purified by column chromatography on silica gel with CH_2Cl_2-heptane (8:2) as eluent then recrystallized from $CHCl_3/CH_3OH$. Yield: 94% (80mg, 0.098mmol). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.49 (s, 8H, H-pyrro), 4.93 (t, 8H, $^{3}J_{HH}$ = 9.0Hz, α-CH_2-), 3.30 (t, 8H, $^{3}J_{HH}$ = 6.0Hz, N_3-CH_2-), 2.53 (m, 8H, -CH_2-), 1.81 (m, 8H, -CH_2-), 1.65 (m, 16H, -CH_2-), -2.65 (s, 2H, N-H). ^{13}C NMR ($CDCl_3$) δ (ppm): 144.7, 128.3 (broad s), 118.1, 51.5, 38.3, 35.3, 29.9, 28.9, 26.8. MS (MALDI-TOF) m/z = 810.50 $[M]^{+\cdot}$, 810.50 calcd for $C_{44}H_{58}N_{16}$. UV-Vis (CH_2Cl_2): λ_{max} (nm) (ε x 10^{-3} $L.mol^{-1}.cm^{-1}$) = 416.0 (408.6), 519.0 (14.9), 554.0 (9.8), 601.0 (4.0), 658.9 (7.2).



^{1}H NMR spectrum of **3** ($CDCl_3$, 298K).

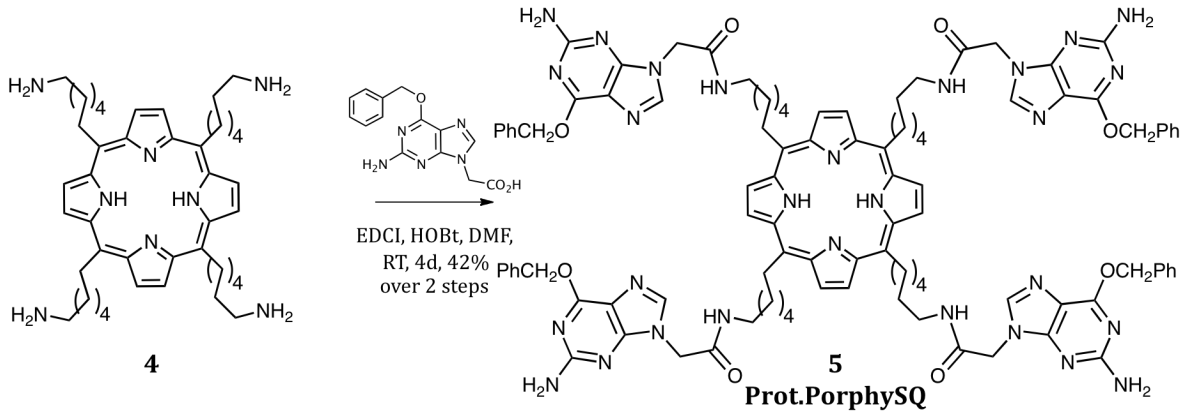
Step 4: **Tetra(6-aminohexyl)porphyrin (4)**



3 **4**

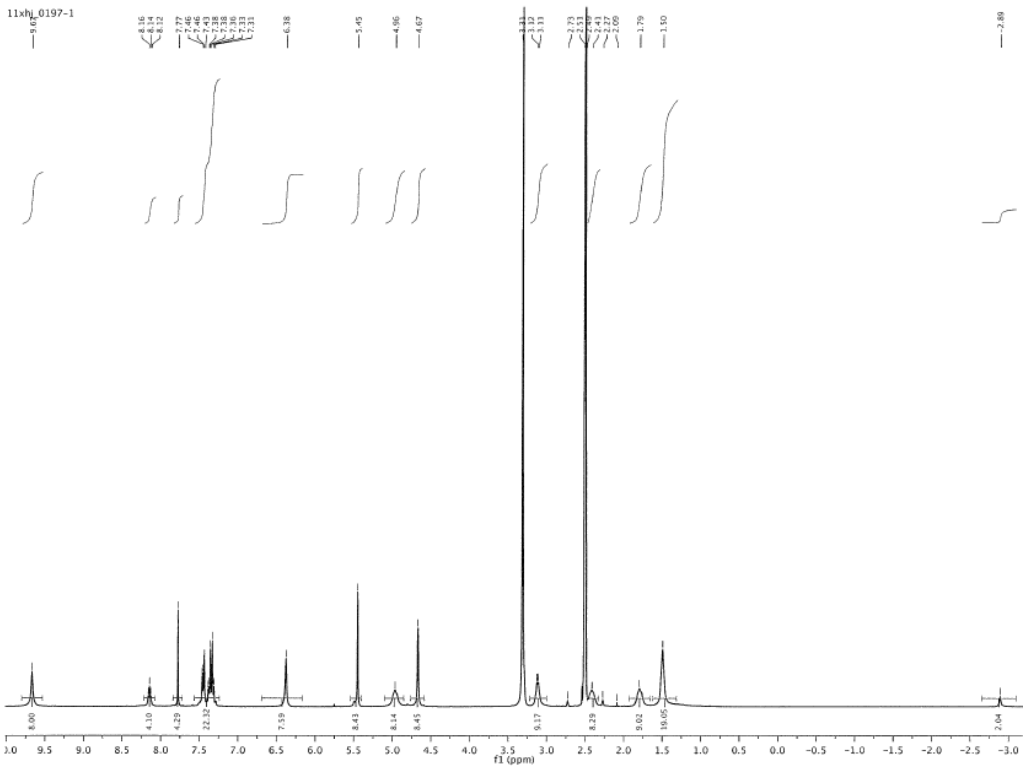
Under argon, 70mg (0.086mmol) of tetra(6-azidohexyl)porphyrin **3** was dissolved in 5mL of dry THF and cooled to 0°C. $LiAlH_4$ (30mg, 0.79mmol) in 3mL of dry THF was added slowly to the solution. The reaction mixture was heated to room temperature and stirred for 6h and 0.5mL of ethanol was added to quench the reaction. Then 50mL of water were added. The porphyrin was extracted with $CHCl_3$ (3x50mL). The collected organic solution was washed with H_2O, brine and dried over $MgSO_4$. The solution was concentrated to about 3mL and used directly in the next step without any further purification. ^{1}H NMR ($CDCl_3$) δ (ppm): 9.39 (s, 8H, H-pyrro), 4.87 (t, 8H, $^{3}J_{HH}$ = 8.1Hz, α-CH_2-), 2.64 (t, 8H, $^{3}J_{HH}$ = 6.6Hz, NH_2-CH_2-), 2.45 (m, 8H, -CH_2-), 1.74 (m, 8H, -CH_2-), 1.46 (m, 16H, -CH_2-), -2.70 (s, 2H, N-H). MS (MALDI-TOF) m/z = 706.36 $[M]^{+\cdot}$, 706.54 calcd for $C_{44}H_{66}N_8$.

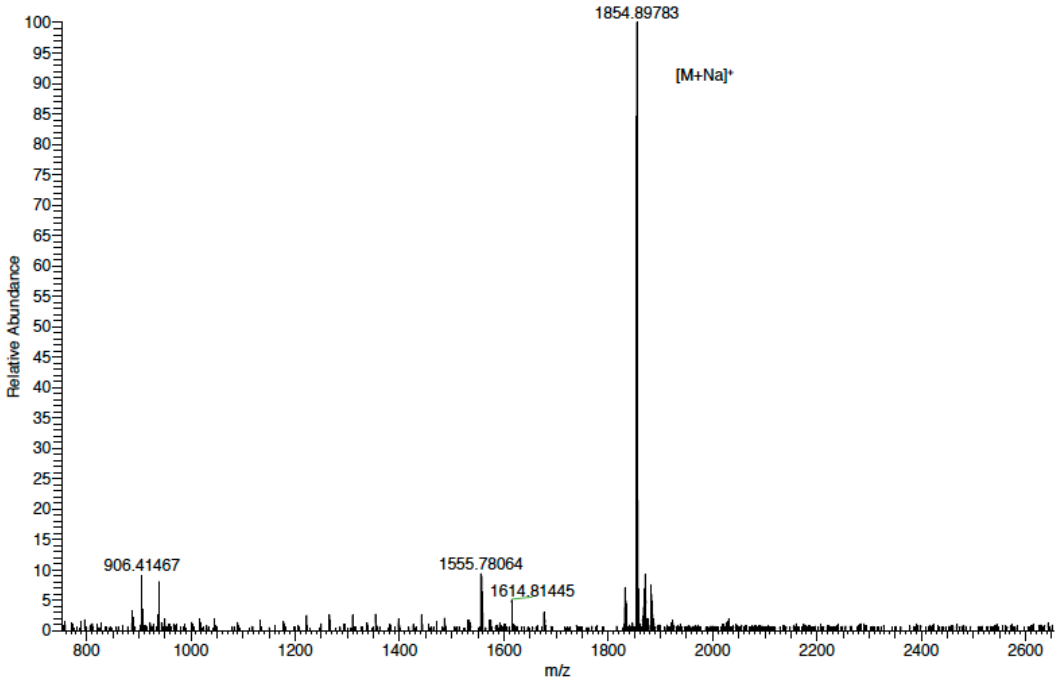
Step 5: **Prot.PorphySQ (5)**



4 **5** **Prot.PorphySQ**

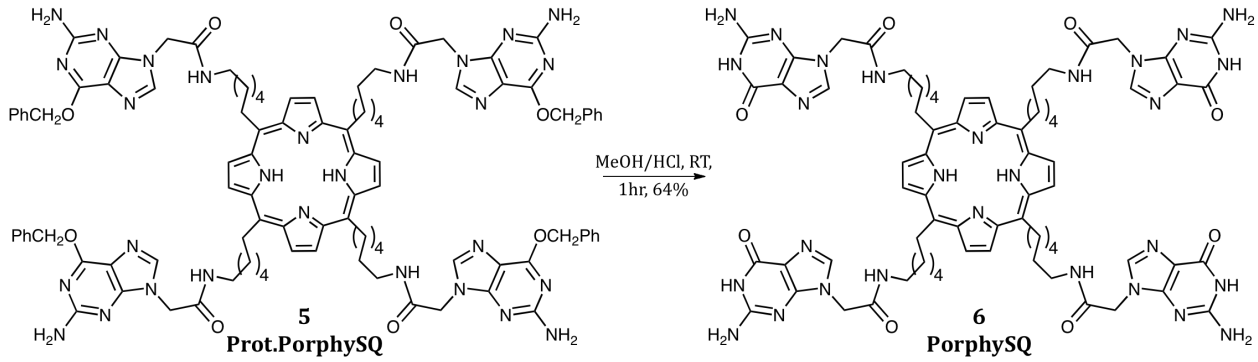
DMF (7mL) was added to the above solution of tetra(6-aminohexyl)porphyrin **4**. Then 2-(2-amino-6-(benzyloxy)-9H-purin-9-yl)acetic acid (110mg, 0.367mmol), N-hydroxybenzotriazole (HOBt) (56mg, 0.367mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) (70.5mg, 0.367mmol) were added. The resulting mixture was stirred at 20°C for 4d. After the solvent was removed under reduced pressure, the residue was washed with water, a saturated aqueous solution of $NaHCO_3$, CH_2Cl_2, ethyl acetate and methanol repeatedly to give compound **5** as a solid. Yield: 42% (65mg, 0.036mmol). ^1H NMR ($CDCl_3$) δ (ppm): 9.67 (s, 8H), 8.14 (t, 4H, $^3J_{HH}$ = 6.0Hz), 7.77 (s, 4H), 7.46-7.31 (m, 20H), 6.38 (s, 8H), 5.45 (s, 8H), 4.96 (m, 8H), 4.67 (s, 8H), 3.12 (d, 8H, J_{HH} = 3.0Hz), 2.41 (m, 8H), 1.77 (m, 8H), 1.50 (m, 16H), -2.89 (s, 2H). MS (MALDI-TOF) m/z = 1832.04 $[M]^{+\cdot}$, 1832.12 calcd for $C_{100}H_{110}N_{28}O_8$. HR-MS (ESI) m/z = 1853.8960 $[M+Na]^+$, 1853.8953 calcd for $C_{100}H_{110}N_{28}NaO_8$. UV-Vis (DMF): λ_{max} (nm) (ε x 10^{-3} $L.mol^{-1}.cm^{-1}$) = 416.0 (242.0), 519.0 (9.9), 552.0 (6.9), 600.9 (2.9), 658.9 (5.6).



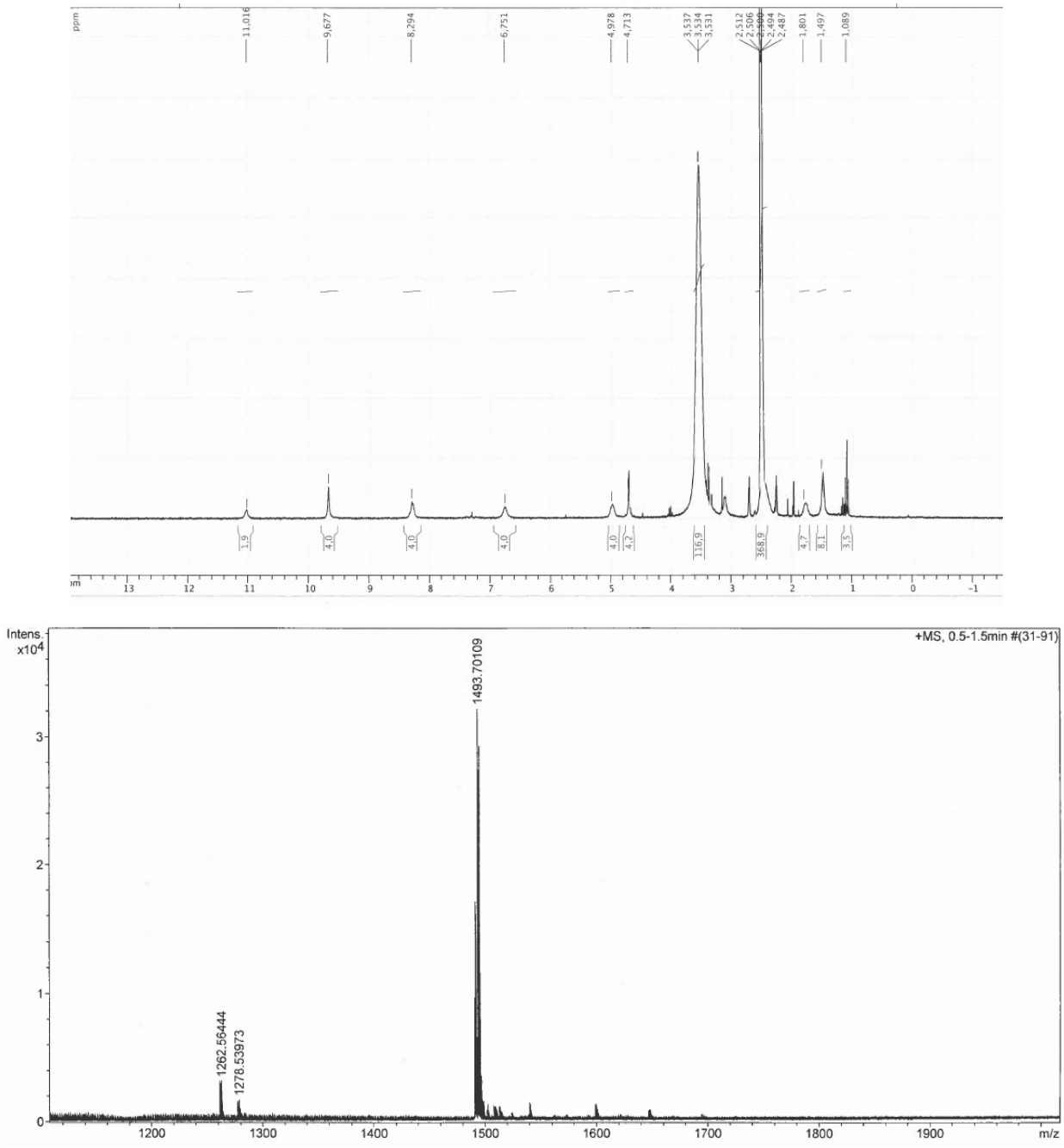


^{1}H NMR ($CDCl_3$, 298K) and HRMS-ESI mass spectra of Prot.PorphySQ (**5**)

Step 6: **PorphySQ (6)**



Protected porphyrin **5** (35.0mg, 0.019mmol) was taken up in a solution of MeOH saturated by HCl (20 mL). The mixture was stirred at 20°C for 1h. The final product was precipitated by addition of diethyl ether (80mL), and washed repeatedly with ether (20mL). Porphyrin **6** was obtained as a solid. Yield: 63% (18mg, 0.012mmol). ^{1}H NMR (DMSO) δ (ppm): 11.01 (s, 4H), 9.67 (s, 8H), 8.29 (s, 8H), 6.75 (s, 8H), 4.97 (s, 16H), 4.73 (s, 8H), 3.05 (s, 8H), 1.80 (s, 8H), 1.49 (s, 16H), -2.89 (s, 2H). ^{13}C NMR (DMSO) δ (ppm): 164.7, 152.2, 153.8, 150.1, 138.2, 128.9 (broad s), 108.5, 45.7, 34.6, 29.4, 28.9, 26.4. HR-MS (ESI) m/z = 1493.7011 $[M+Na]^+$, 1493.7076 calcd for $C_{72}H_{86}N_{28}NaO_8$. UV-Vis (DMSO): λ_{max} (nm) (ε x 10^{-3} L.mol^{-1}.cm^{-1}) = 418.0 (238.0), 519.0 (10.0), 554.0 (6.4), 600.0 (2.5), 659.0 (4.0).



^{1}H NMR ($CDCl_3$, 298K) and HRMS-ESI mass spectra of PorphySQ (**6**)