Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

A click chemistry approach for the synthesis of macrocycles from aryl amide-based precursors directed by hydrogen bonding

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Compound 21. A solution of **20** (15.0 g, 60.0 mmol) and sodium hydroxide (4.80 g, 0.12 mmol) in THF (30 mL), water (15 mL) and methanol (25 mL) was stirred for 1 h and then concentrated to 15 mL. Diluted hydrochloric acid was then added to pH = 3. The mixture was extracted with AcOEt (25 mL × 3). The organic phases were combined and washed with water (50 mL) and brine (50 mL) and dried over sodium sulfate. Upon removal the solvent under reduced pressure, the resulting residue was subject to flash chromatography (PE/EA 10:1) to give **21** as a pale yellow oil (13.5 g, 95%) ^{1}H NMR ($CDCl_3$): δ 9.96 (s, 1 H), 8.65 (d, J = 1.8 Hz, 1 H), 8.11 (d, J = 9.0 Hz, 1 H), 7.19 (d, J = 8.7 Hz, 1 H), 4.33 (t, J = 6.3 Hz, 2 H), 2.00−1.91 (m, 2 H), 1.54−1.38 (m, 4 H), 0.95 (t, J = 6.9 Hz, 3 H). MS (ESI): *m/z* 235.2 $[M - H]^-$.

Compound 22. To a solution of **21** (1.06 g, 4.48 mmol) and triethylamine (0.70 mL) in chloroform (15 mL), cooled in an ice-bath, was added isobutyl chloroformate (0.66 mL, 2.20 mmol) in 30 min. After stirring for another 30 min, a solution of **16** (0.57 g, 2.24 mmol) in chloroform (15 mL) was added slowly. The solution was stirred for 24 h and then washed with diluted hydrochloric acid (1 N, 10 mL), water (10 mL × 2) and brine (10 mL) and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the resulting residue was washed with cold methanol to give **22** as a white solid (1.41 g, 91%). ^{1}H NMR ($CDCl_3$): δ 9.97 (s, 2 H), 9.74 (s, 2 H), 9.32 (s, 1 H), 8.82 (d, J = 2.1 Hz, 2 H), 8.03 (d,d, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 2 H), 7.15 (d, J = 8.4 Hz, 2 H), 6.56 (s, 1 H), 4.31 (t, J = 7.2 Hz, 4 H), 3.82 (d, J = 6.9 Hz, 4 H), 2.12 (t t, J_1 = 6.9 Hz, J_2 = 6.6 Hz, 2 H), 1.94 (t,t, J_1 = 7.2 Hz, J_2 = 6.9 Hz, 4 H), 1.48–1.33 (m, 8 H), 1.02 (d, J = 6.6 Hz, 12 H), 0.89 (t, J = 7.2 Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 190.7, 161.8, 161.1, 146.5, 137.2, 132.0, 130.2, 123.2, 120.7, 117.7, 113.3, 98.3, 75.9, 70.2, 28.5, 28.3, 27.8, 22.3, 19.3, 13.9. MS (ESI): *m/z* 711.5 $[M + Na]^+$. HRMS (MALDI-FT): Calcd. for $C_{40}H_{52}N_2O_8Na$ $[M + Na]^+$: 711.3616. Found: 711.3613.

Compound 23. To a stirred solution of **22** (0.69 g, 1.00 mmol) in methanol (6 mL) and THF (12 mL) was added $NaBH_4$ (76 mg, 2.00 mmol). The mixture was stirred for 12 h and then concentrated with a rotavapor. The resulting residue was triturated with chloroform (30 mL) and the organic solution washed with water (20 mL × 3) and brine (20 mL) and dried over sodium sulfate. Upon removal of the solvent, the crude product was purified by flash chromatography (CH_2Cl_2/MeOH 30:1) to give **23** as a white solid (0.62 g, 90%). ^{1}H NMR ($CDCl_3$): δ 9.93 (s, 2 H), 9.27 (s, 1 H), 8.19 (d, J = 1.8 Hz, 2 H), 7.49 (d,d, J_1 = 8.1 Hz, J_2 = 2.4 Hz, 2 H), 6.98 (d, J = 8.7 Hz, 2 H), 6.54 (s, 1 H), 4.66 (s, 4 H), 4.16 (t, J = 6.9 Hz, 4 H), 3.78 (d, J = 6.6 Hz, 4 H), 3.04 (br, 2 H), 2.14–2.06 (m, 2 H), 1.88–1.80 (m, 4 H), 1.41–1.29 (m, 8 H), 1.00 (d, J = 6.9 Hz, 12 H), 0.86 (t, J = 6.9 Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 163.1, 156.1, 146.3, 134.3, 131.6, 131.2, 122.4, 121.0, 117.5, 113.2, 98.5, 75.9, 69.8, 64.3, 28.7, 28.3, 27.9, 22.4, 19.3, 13.9. MS (MALDI-TOF): *m/z* 715.6 $[M + Na]^+$. HRMS (MALDI-FT): Calcd. for $C_{40}H_{56}N_2O_8Na$ $[M + Na]^+$: 715.3929. Found: 715.3938.

Compound 24. To a stirred solution of **23** (0.17 g, 0.25 mmol) in CH_2Cl_2 (3 mL), cooled in an ice-bath, was added thionyl chloride (0.24 mL, 3.20 mmol) dropwise. The solution was stirred for 2 h and then concentrated with a rotavapor. The resulting residue was dissolved in chloroform (30 mL) and the solution washed with saturated sodium bicarbonate solution (15 mL), water (15 mL) and brine (15 mL) and dried over sodium sulfate. The solvent was removed and the crude product subjected to flash chromatography (CH_2Cl_2) to give **24** as a white solid (0.17 g, 95%). ^{1}H NMR ($CDCl_3$): δ 9.84 (s, 1 H), 9.26 (d, J = 1.8 Hz, 1 H), 8.32

(d, J = 2.4 Hz, 2 H), 7.49 (d d, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 2 H), 7.01 (d, J = 8.4 Hz, 2 H), 6.54 (s, 1 H), 4.61 (s, 4 H), 4.20 (t, J = 6.9 Hz, 4 H), 3.80 (d, J = 6.6 Hz, 4 H), 2.18–2.04 (m, 2 H), 1.94–1.84 (m, 4 H), 1.46–1.21 (m, 8 H), 1.01 (d, J = 6.9 Hz, 12 H), 0.88 (t, J = 7.2 Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 162.4, 156.7, 146.3, 133.1, 132.8, 130.4, 123.0, 120.9, 117.6, 113.3, 98.4, 75.9, 69.8, 45.7, 28.6, 28.3, 27.9, 22.3, 19.3, 13.9. MS (MALDI-TOF): *m/z* 767.5 [M + K]$^+$. Anal. Calcd. for $C_{40}H_{48}N_2O_6$: C, 65.83; H, 7.46, N, 3.84. Found: C, 65.83; H, 7.23; N, 3.64.

Compound 26. A solution of **25** (1.39 g, 7.13 mmol), iodine (3.62 g, 14.3 mmol) and silver sulfate (4.45 g, 14.3 mmol) in methanol (40 mL) was refluex for 20 h and cooled. The solid was filtrated off and the filtrate concentrated in vacuo. The resulting residue was triturated with AcOEt (40 mL) and the solution washed with saturated sodium bicarbonate solution (20 mL × 2), water (20 mL) and brine (20 mL) and dried over sodium sulfate. Upon removal of the solvent with a rotavapor, the crude product was purified by flash chromatography (CH_2Cl_2/EA 40:1) to give **26** as a pale yellow oil (2.16 g, 94%). ^{1}H NMR ($CDCl_3$): δ 8.08 (d, J = 2.4 Hz, 1 H), 7.76 (d,d, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1 H), 6.84 (d, J = 9.0 Hz, 1 H), 4.07 (t, J = 6.3 Hz, 2 H), 1.80 (m, J = 6.3 Hz, 2 H), 1.53–1.46 (m, 2 H), 0.96 (t, J = 7.5 Hz, 3 H). MS (EI): *m/z* 321 [M]$^+$.

Compound 27. To a solution of **26** (2.11 g, 6.56 mmol), $PdCl_2(PPh_3)_2$ (49 mg, 0.066 mmol), CuI (15 mg, 0.08 mmol) and NEt_3 (30 mL) in THF (30 mL) was added ethynyltrimethylsilane (1.10 mL, 7.32 mmol). The mixture was stirred for 12 h and then the solid filtrated off. The filtrate was concentrated and the resulting slurry triturated with AcOEt (30 mL). After workup, the crude product was purified by flash chromatography (PE/EA, 20:1） to afford **27** as a brown solid (1.91 g, 100%). ^{1}H NMR ($CDCl_3$): δ 7.91 (d, J = 1.8 Hz, 1 H), 7.57 (d,d, J_1 = 8.7 Hz, J_2 = 1.8 Hz, 1 H), 6.98 (d, J = 8.7 Hz, 1 H), 4.10 (t, J = 6.6 Hz, 2 H), 1.81 (m, J = 7.5 Hz, 2 H), 1.56–1.49 (m, 2 H), 0.97 (t, J = 7.5 Hz, 3 H), 0.24 (s, 9 H). ^{13}C NMR ($CDCl_3$): δ 151.3, 138.4, 136.2, 128.0, 114.3, 113.2, 101.3, 94.1, 68.5, 29.9, 18.0, 12.7, −1.2. MS (EI): *m/z* 291 [M]$^+$. Anal. Calcd. for $C_{15}H_{21}NO_3Si$: C, 62.60; H, 7.59, N, 4.64. Found: C, 62.43; H, 7.26; N, 4.81.

Compound 28. A solution of **27** (1.91 g, 6.56 mmol) and TBAF (1.72 g, 6.56 mmol) in THF (60 mL) was strried at 0 °C for 5 min and then concentrated. The resulting slurry was triturated with AcOEt (30 mL) and the solution washed with water (30 mL) and brine (30 mL) and dried over sodium sulfate. Upon removal of the solvent, **28** was obtained as a pale yellow solid (1.44 g, 100%). ^{1}H NMR ($CDCl_3$): δ 7.92 (s, 1 H), 7.60 (d, J = 9.0 Hz, 1 H), 7.01 (d, J = 9.0 Hz, 1 H), 4.11 (t, J = 6.3 Hz, 2 H), 3.07 (s, 1 H), 1.85–1.76 (m, 2 H), 1.54–1.44 (m, 2 H), 0.96 (t, J = 7.5 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 152.8, 139.7, 137.6, 129.3, 114.6, 114.4, 81.3, 78.1, 69.8, 31.1, 19.3, 13.9. MS (EI): *m/z* 219 [M]$^+$. Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98, N, 6.39. Found: C, 66.16; H, 6.04; N, 6.34.

Compound 29. A suspension of **28** (0.55 g, 2.50 mmol), NH_4Cl（0.14 g, 2.54 mmol）and iron powder (0.71 g, 12.7 mmol) in ethanol (20 mL) and water (15 mL) was refluxed for 6 h and then the solid filtrated off. The filtrate was concentrated and the resulting slurry triturated with CH_2Cl_2 (20 mL). After workup, the crude product was subject to flash chromatography (CH_2Cl_2/EA 15:1) to give **29** as a pale yellow solid (0.47 g, 100%). ^{1}H NMR ($CDCl_3$): δ 6.90–6.84 (m, 2 H), 6.69 (d, J = 8.1 Hz, 1 H), 3.99 (t, J = 6.6 Hz, 2 H), 3.72 (br, 2 H), 2.94 (s,

1 H), 1.84–1.75 (m, 2 H), 1.56–1.44 (m, 2 H), 0.98 (t, J = 7.5 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ

147.4, 136.0, 123.1, 118.1, 114.1, 110.9, 84.2, 75.0, 68.0, 31.3, 19.3, 13.9. MS (ESI): *m/z* 190.0 $[M + H]^+$. Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.16; H, 7.99, N, 7.40. Found: C, 76.51; H, 8.04; N, 7.41.

Compound 32. A suspension of **31** (9.55 g, 57 mmol), n-butyl bromide (12.3 mL, 0.11 mol), K_2CO_3 (39.5 g, 0.29 mmol) and KI (1.89 g, 11.0 mmol) in DMF (300 mL) was stirred at 80 ºC for 24 h. After workup, the crude product was purified by flash chromatography (PE/EA 8:1) to give **32** as a pale yellow oil (11.5 g, 90%). ^{1}H NMR ($CDCl_3$): δ 9.91 (s, 1 H), 8.31 (d, J = 1.8 Hz, 1 H), 8.04 (d d, J_1 = 8.7 Hz, J_2 = 1.8 Hz, 1 H), 7.21 (d, J = 8.7 Hz, 1 H), 4.20 (t, J = 6.3 Hz, 2 H), 1.88−1.79 (m, 2 H), 1.70−1.48 (m, 2 H), 0.97 (t, J = 7.5 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 188.8, 156.8, 140.0, 134.6, 128.7, 127.3, 114.5, 70.1, 30.7, 19.0, 13.7. MS (EI): *m/z* 223 $[M]^+$.

Compound 33. A suspension of **32** (0.67 g, 3.00 mmol) and $NaBH_4$ (0.11 g, 3.00 mmol) in MeOH (10 mL) and THF (20 mL) was stirred for 1 h and then concentrated. The resulting slurry was triturated with CH_2Cl_2 (20 mL). After workup, the crude product was purified by flash chromatography (PE/EA 4:1) to give **33** as a pale yellow oil (0.64 g, 95%). ^{1}H NMR ($CDCl_3$): δ 7.82 (d, J = 1.5 Hz, 1 H), 7.51 (J_1 = 8.4 Hz, J_2 = 1.5 Hz, 1 H), 7.05 (d, J = 8.4 Hz, 1 H), 4.68 (s, 2 H), 4.10 (J = 6.3 Hz, 2 H), 1.86−1.78 (m, 3 H), 1.55−1.47 (m, 2 H), 0.97 (t, J = 7.5 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 151.8, 139.6, 133.0, 132.5, 124.0, 114.6, 77.3, 69.5, 63.6, 31.0, 19.1, 13.7. MS (EI): *m/z* 225 $[M]^+$. Anal. Calcd. for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.33; H, 6.81; N, 6.18.

Compound 34. A suspension of **33** (0.57 g, 2.50 mmol), NH_4Cl (0.14 g, 2.54 mmol) and iron powder (0.71 g, 12.7 mmol) in EtOH (20 mL) and H_2O (15 mL) was refluxed for 6 h and then the solid filtrated off. The filtrate was concentrated and the resulting slurry triturated with CH_2Cl_2 (20 mL). After workup, the crude product was subjected to flash chromato-graphy (CH_2Cl_2/EA 5:1) to give **34** as a pale yellow solid (0.49 g, 100%). ^{1}H NMR ($CDCl_3$): δ 6.76–6.67 (m, 3 H), 4.52 (s, 2 H), 3.99 (t, J = 6.6 Hz, 2 H), 3.08 (br, 3 H), 1.84–1.74 (m, 2 H), 1.56–1.44 (m, 2 H), 0.98 (t, J = 7.5 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 147.3, 137.0, 134.4, 118.2, 115.0, 112.1, 68.9, 66.2, 32.2, 20.2, 14.7. MS (ESI): *m/z* 196.0 $[M + H]^+$. Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.76; H, 8.76; N, 7.14.

Compound 35. A solution of **30** (78 mg, 0.25 mmol) and HATU (0.19 g, 0.50 mmol) in DMF (2.5 mL) was stirred for 10 min. Then, a solution of **34** (98 mg, 0.50 mmol) and DIPEA (0.26 mL, 1.50 mmol) in DMF (2.5 mL) was added slowly. The solution was stirred for 24 h and then concentrated. The resulting slurry was triturated with CH_2Cl_2 (20 mL). After workup, the crude product was subjected to flash chromatography (CH_2Cl_2/MeOH 20:1) to afford **35** as a pale yellow solid (0.14 g, 85%). ^{1}H NMR ($CDCl_3$): δ 9.82 (s, 2 H), 9.00 (s, 1 H), 8.45 (s, 2 H), 7.07 (d, J = 7.5 Hz, 2 H), 6.89 (d, J = 7.8 Hz, 2 H), 6.60 (s, 1 H), 4.62 (s, 4 H), 4.08–4.04 (m, 8 H), 2.95 (s, 2 H), 2.29 (br, 2 H), 1.79–1.74 (m, 4 H), 1.47–1.38 (m, 4 H), 1.05 (d, J = 5.7 Hz, 12 H), 0.95 (t, J = 7.2 Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 162.6, 160.5, 147.6, 137.0, 130.6, 127.7, 124.1, 121.5, 115.7, 111.4, 97.5, 76.5, 68.5, 55.1, 31.1, 28.0, 18.5, 17.1, 13.8. MS (ESI): *m/z* 687.6 $[M + H]^+$. HRMS (MALDI-FT): Calcd. For $C_{38}H_{52}N_2O_8Na$ $[M + Na]^+$: 687.3616. Found: 687.3646.

Compound 36 was prepared as a white solid (95%) from the reaction of **35** and thionyl

chloride by using a procedure similar to that for **24**. ^{1}H NMR ($CDCl_3$): δ 9.74 (s, 2 H), 9.06 (s, 1 H), 8.66 (d, J = 1.8 Hz, 2 H), 7.10 (d d, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 2 H), 6.89 (d, J = 8.4 Hz, 2

H), 6.55 (s, 1 H), 4.62 (s, 4 H), 4.08 (t, J = 6.9 Hz, 4 H), 4.01 (d, J = 6.9 Hz, 4 H), 2.33–2.24 (m, 2 H), 1.84–1.74 (m, 4 H), 1.52–1.40 (m, 4 H), 1.06 (d, J = 6.3 Hz, 12 H), 0.96 (t, J = 7.5 Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 162.5, 160.1, 147.8, 137.4, 130.0, 128.5, 124.0, 121.6, 116.5, 111.3, 97.2, 76.3, 68.6, 46.7, 31.1, 28.0, 19.3, 19.0, 13.8. MS (MALDI-TOF): *m/z* 701.8 [M + H]$^+$. Anal. Calcd. for $C_{38}H_{50}Cl_2N_2O_6$: C, 65.04; H, 7.18; N, 3.99. Found: C, 64.77; H, 7.29; N, 3.89.

Compound 37. To a solution of **13** (5.80 g, 18.1 mmol) in THF (40 mL), cooled in an ice-bath, were added DMF (0.05 mL) and thionyl chloride (7.25 mL, 90.6 mmol). The solution was stirred for 2 h and then concentrated. The resulting slurry was dissolved in THF (50 mL) and the solution added to a stirred solution of **16** (20 mmol) and NEt_3 (3.70 mL, 27.2 mmol) in THF (50 mL) at 0 °C. Stirring was continued for another 1 h and then the solid filtrated off. The filtrate was concentrated with a rotavapor and dissolved in CH_2Cl_2 (50 mL). The solution was washed with diluted hydrochloric acid (0.5 N, 20 mL), water (20 mL) and brine (20 mL) and dried over sodium sulfate. Upon removal of the solvent, the crude product was subjected to flash chromatography (CH_2Cl_2/EA 5:1) to give **37** as a pale yellow solid (8.95 g, 89%). ^{1}H NMR ($CDCl_3$): δ 9.88 (s, 1 H), 8.50 (d, J = 2.1 Hz, 1 H), 8.00 (s, 1 H), 7.69 (d d, J_1 = 9 Hz, J_2 = 2.4 Hz, 1 H), 6.77 (d, J = 8.7 Hz, 1 H), 6.47 (s, 1 H), 4.16 (t, J = 6.9 Hz, 2 H), 3.73 (d, J = 6.9 Hz, 4 H), 3.40 (br, 2 H), 2.16–2.02 (m, 2 H), 1.89–1.80 (m, 2 H), 1.46–1.39 (m, 2 H), 1.05 (d, J = 6.6 Hz, 6 H), 0.99 (d, J = 6.6 Hz, 6 H), 0.92 (t, J = 7.5 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 161.4, 156.4, 143.0, 141.4, 141.0, 140.7, 129.8, 125.1, 121.8, 115.2, 109.2, 99.7, 83.6, 76.8, 75.3, 69.6, 30.7, 28.4, 28.3, 19.3, 19.3, 19.0, 13.7. MS (MALDI-TOF): *m/z* 554.7 [M + H]$^+$. Anal. Calcd. for $C_{25}H_{35}IN_2O_4$: C, 54.15; H, 6.36, N, 5.05. Found: C, 53.88; H, 6.45; N, 5.03.

Compound 39 was prepared as a pale yellow solid (90%) from the reaction of **37** and **38** affording to a procedure similar to that for **17**. ^{1}H NMR ($CDCl_3$): δ 9.83 (s, 2 H), 9.46 (s, 2 H), 9.28 (s, 2 H), 8.60 (s, 2 H), 8.26 (d, J = 7.5 Hz, 2 H), 7.70 (d, J = 7.5 Hz, 2 H), 7.38 (t, J = 7.8 Hz, 1 H), 6.79 (d, J = 9.0 Hz, 2 H), 6.56 (s, 2 H), 4.19 (t, J = 6.9 Hz, 4 H), 4.06 (s, 3 H), 3.83–3.79 (m, 8 H), 2.17–2.08 (m, 4 H), 1.91–1.81 (m, 4 H), 1.49–1.42 (m, 4 H), 1.02 (d, J = 6.3 Hz, 24 H), 0.94 (t, J = 7.5 Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 162.5, 161.6, 156.5, 155.8, 146.4, 146.3, 141.1, 134.9, 128.3, 125.2, 124.7, 120.6, 120.2, 117.0, 115.1, 97.7, 83.6, 75.8, 75.5, 69.5, 64.3, 30.8, 28.2, 19.2, 19.0, 13.7. MS (MALDI-TOF): *m/z* 1291.8 [M + Na]$^+$. Anal. Calcd. for $C_{59}H_{74}I_2N_4O_{11}\cdot 1/2CH_2Cl_2$: C, 54.49; H, 5.76, N, 4.27. Found: C, 54.32; H, 5.91; N, 4.16.

Compound 40. To a stirred suspension of **39** (1.27 g, 1.00 mmol), $PdCl_2(PPh_3)_2$ (75 mg, 0.10 mmol), CuI (25 mg, 0.10 mmol) in THF (16 mL) and NEt_3 (4 mL) was added ethynyl-trimethylsilane (0.42 mL, 3 mmol). The mixture was stirred at 40 ºC for 12 h and then the solid filtrated off. The filtrate was concentrated and the resulting slurry triturated with CH_2Cl_2 (30 mL). The solution was washed successively with water (15 mL) and brine (15 mL) and dried over sodium sulfate. The solvent was then removed and the crude product subjected to flash chromatography (CH_2Cl_2/EA 10:1) to give **40** as a pale yellow solid (1.15 g, 95%). ^{1}H NMR ($CDCl_3$): δ 9.82 (s, 2 H), 9.46 (s, 2 H), 9.26 (s, 2 H), 8.45 (d, J = 2.1 Hz, 2

H), 8.26 (d, J = 7.5 Hz, 2 H), 7.52 (d,d, J_1 = 8.7 Hz, J_2 = 2.1 Hz, 2 H), 7.38 (t, J = 7.5 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 2 H), 6.56 (s, 2 H), 4.22 (t, J = 6.9 Hz, 4 H), 4.06 (s, 3 H), 3.83-3.79 (m, 8 H), 2.17–2.08 (m, 4 H), 1.92–1.82 (m, 4 H), 1.50–1.42 (m, 4 H), 1.02 (d, J = 6.6 Hz, 24 H), 0.95

(t, J = 7.5 Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 162.5, 162.2, 156.6, 155.8, 146.6, 146.4, 136.8, 135.7, 134.9, 128.4, 125.2, 122.8, 120.8, 120.3, 117.3, 116.3, 112.7, 104.2, 97.9, 93.4, 75.9, 75.6, 69.5, 64.3, 30.9, 28.3, 28.3, 19.2, 19.2, 19.0, 13.7. MS (MALDI-TOF): *m/z* 1231.3 [M + Na]$^+$. Anal. Calcd. for $C_{69}H_{92}N_4O_{11}Si_2$: C, 68.51; H, 7.67, N, 4.63. Found: C, 68.52; H, 7.80; N, 4.43.

Compound 43. A suspension of **41** (2.00 g, 11.0 mmol), n-butyl bromide (2.80 mL, 22.0 mmol), K_2CO_3 (4.50 g, 33 mmol) and KI (0.33 g, 2.00 mmol) in DMF (30 mL) was stirred at 80 °C for 5 h and then the solid filtrated off. The filtrate was concentrated with a rotavapor and the resulting slurry triturated with AcOEt (50 m). The solution was washed with water (20 mL) and brine (20 mL × 3) and dried over Na_2SO_4. Upon removal of the solvent, **42** was obtained as white solid (2.47 g, 95%), which was then added to a stirred solution of sodium hydroxide (0.83 g, 20.7 mmol) in THF/H_2O/MeOH (10 mL/5 mL/10 mL). The solution was stirred for 1 h and then concentrated to 10 mL. Diluted hydrochloric acid (0.5 N) was added to pH = 3. The mixture was then extracted with AcOEt (25 mL × 3). The organic phases were combined and washed with water (40 mL) and brine (40 mL) and dried over Na_2SO_4. Upon removal of the solvent, **43** was obtained as a pale yellow oil (2.15 g, 95%). ^{1}H NMR ($CDCl_3$): δ 9.96 (s, 1 H), 8.65 (d, J = 2.1 Hz, 1 H), 8.11 (d,d, J_1 = 8.7 Hz, J_2 = 2.1 Hz, 1 H), 7.19 (d, J = 8.7 Hz,), 4.34 (t, J = 6.6 Hz, 2 H), 1.98−1.89 (m, 2 H), 1.61−1.48 (m, 2 H), 1.02 (t, J = 7.5 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 190.8, 166.1, 162.9, 137.9, 135.5, 131.2, 119.2, 114.1, 71.4, 31.6, 19.9, 14.5. MS (ESI): *m/z* 220.9 [M − H]$^-$. Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.94; H, 6.66.

Compound 44 was prepared from **16** and **43** as pale yellow solid (55%) according to a procedure similar to that for **17**. ^{1}H NMR ($CDCl_3$): δ 9.54 (s, 2 H), 8.19 (d, J = 7.5 Hz, 2 H), 8.05 (s, 2 H), 7.38 (t, J = 7.5 Hz, 1 H), 6.48 (s, 2 H), 4.00 (s, 3 H), 3.75–3.72 (m, 8 H), 3.56 (br, 4 H), 2.16–2.04 (m, 4 H), 1.06 (d, J = 6.6 Hz, 12 H), 0.98 (d, J = 6.6 Hz, 12 H). MS (ESI): *m/z* 665.4 [M + H]$^+$.

Compound 45. To a stirred solution of **43** (0.64 g, 2.88 mmol) and NEt_3 (0.44 mL) in $CHCl_3$ (15 mL), cooled in an ice-bath, was added isopropyl chloroformate (0.42 mL, 3.17 mmol). The solution was stirred for 0.5 h and then a solution of **44** (0.96 g, 1.44 mmol) in $CHCl_3$ (15 mL) was added. Stirring was continued for 24 h and then the solvent was removed. The resulting slurry was dissolved in CH_2Cl_2 (40 mL) and the solution washed with diluted hydrochloric acid (0.5 N, 20 mL), saturated $NaHCO_3$ solution (20 mL), water (20 mL) and brine (20 mL) and dried over sodium sulfate. Upon removal of the solvent, the crude product was subjected to flash chromato-graphy (CH_2Cl_2/EA 3:1) to give **45** as a pale yellow solid (1.22 g, 79%). ^{1}H NMR ($CDCl_3$): δ 9.98 (s, 2 H), 9.76 (s, 2 H), 9.48 (s, 2 H), 9.31 (s, 2 H), 8.83 (d, J = 2.1 Hz, 2 H), 8.26 (d, J = 7.5 Hz, 2 H), 8.04 (d d, J_1 = 9.0 Hz, J_2 = 2.1 Hz, 2 H), 7.39 (t, J = 7.5 Hz, 1 H), 7.16 (d, J = 8.4 Hz, 2 H), 6.57 (s, 2 H), 4.33 (t, J = 6.6 Hz, 4 H), 4.07 (s, 3 H), 3.82 (t, J = 6.6 Hz, 8 H), 2.18–2.09 (m, 4 H), 1.97–1.87 (m, 4 H), 1.53–1.46 (m, 4 H), 1.02 (d, J = 6.3 Hz, 24 H), 0.97 (t, J = 7.5 Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 190.5, 162.5,

161.8, 161.1, 155.8, 146.4, 146.3, 136.8, 134.8, 132.1, 130.0, 128.4, 125.1, 123.0, 120.5, 120.3, 117.0, 113.2, 97.8, 75.8, 75.5, 69.8, 64.2, 30.7, 28.2, 28.2, 19.2, 18.9, 13.6. MS (MALDI-TOF): *m/z* 1095.8 $[M + Na]^+$. Anal. Calcd. for $C_{61}H_{76}N_4O_{13}$: C, 68.26; H, 7.14; N, 5.22. Found: C, 68.09; H, 7.32; N, 5.04.

Compound 46 was prepared as white solid (95%) form the reaction of **45** and $NaBH_4$

according to a procedure similar to that for **23**. ^1H NMR ($CDCl_3$): δ 9.95 (s, 2 H), 9.48 (s, 2 H), 9.28 (s, 2 H), 8.26-8.24 (m, 4 H), 7.51 (d,d, J_1 = 8.7 Hz, J_2 = 2.1 Hz, 2 H), 7.38 (J = 7.8 Hz, 1 H), 7.03 (d, J = 8.4 Hz, 2 H), 6.56 (s, 2 H), 4.69 (s, 4 H), 4.21 (t, J = 6.9 Hz, 4 H), 4.06 (s, 3 H), 3.83–3.79 (m, 8 H), 2.28 (br, 2 H), 2.17–2.08 (m, 4 H), 1.89–1.82 (m, 4 H), 1.50–1.43 (m, 4 H), 1.03–1.00 (m, 24 H), 0.95 (J = 7.5 Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 163.0, 162.5, 155.9, 155.7, 146.5, 146.2, 134.8, 134.1, 131.5, 131.0, 128.2, 125.1, 122.0, 120.7, 120.0, 117.0, 113.0, 97.7, 77.2, 75.7, 75.4, 69.3, 64.2, 64.1, 30.8, 28.1, 19.1, 19.1, 18.9, 13.7. MS (MALDI-FT): *m/z* 1099.6 $[M + Na]^+$. HRMS (MALDI-FT): Calcd. for $C_{61}H_{80}N_4O_{13}Na$ $[M + Na]^+$: 1099.5614. Found: 1099.5609.

Compound 47 was prepared quantitatively as a white solid from the reaction of **46** and thionyl chloride according to a procedure similar to that for **24**. ^1H NMR ($CDCl_3$): δ 9.91 (s, 2 H), 9.48 (s, 2 H), 9.30 (s, 2 H), 8.34 (d, J = 2.4 Hz, 2 H), 8.26 (d, J = 7.5 Hz, 2 H), 7.50 (d,d, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 2 H), 7.38 (t, J = 7.5 Hz, 1 H), 7.02 (d, J = 8.4 Hz, 2 H), 6.56 (s, 2 H), 4.61 (s, 4 H), 4.22 (t, J = 6.6 Hz, 4 H), 4.06 (s, 4 H), 3.83–3.79 (m, 8 H), 2.17–2.08 (m, 4 H), 1.92–1.83 (m, 4 H), 1.50–1.43 (m, 4 H), 1.02 (d, J = 6.6 Hz, 24 H), 0.95 (t, J = 7.2 Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 162.4, 162.3, 156.5, 155.7, 146.3, 146.1, 134.8, 132.9, 130.2, 128.2, 125.1, 122.5, 120.6, 120.0, 116.9, 113.1, 97.6, 77.2, 75.7, 75.3, 69.3, 64.2, 45.6, 30.7, 28.1, 28.1, 19.1, 19.1, 18.9, 13.6. MS (MALDI-FT): *m/z* 1135.5 $[M + Na]^+$. HRMS (MALDI-FT): Calcd. for $C_{61}H_{79}N_4O_{11}Cl_2$: 1113.5117. Found: 1113.5135.

Compound 48 was prepared as a white solid quantitatively form the hydrolysis of **47** in DMF in the presence of water and sodium azide according to a procedure similar to that for **6**. ^1H NMR ($CDCl_3$): δ 9.96 (s, 2 H), 9.37 (s, 2 H), 8.29 (d, J = 1.5 Hz, 2 H), 8.10 (s, 2 H), 7.42 (d, J = 7.5 Hz, 2 H), 7.06−7.03 (m, 3 H), 6.55 (s, 2 H), 4.34 (s, 4 H), 4.23 (t, J = 6.6 Hz, 4 H), 3.83−3.81 (m, 8 H), 2.21−2.09 (m, 4 H), 1.92−1.83 (m, 4 H), 1.50−1.40 (m, 4 H), 1.07 (d, J = 6.6 Hz, 12 H), 1.02 (d, J = 6.3 Hz, 12 H), 0.95 (t, J = 7.2 Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ 162.4, 160.3, 156.6, 146.3, 146.0, 132.7, 132.4, 128.1, 122.8, 122.8, 120.6, 118.7, 116.3, 113.2, 97.5, 75.7, 75.3, 69.4, 54.0, 30.8, 28.3, 28.2, 19.2, 19.2, 19.0, 13.7. MS (MALDI-FT): *m/z* 1135.6 $[M + Na]^+$. HRMS (MALDI-FT): Calcd. for $C_{60}H_{76}N_{10}O_{11}$: 1112.5690. Found: 1112.5687.

Compound 49. The reaction of **9** and **48** was performed in chloroform and MeCN according to a procedure similar to that for **4**. MALDI-FT mass showed that macrocycle **49** was formed, which could not be purified due to low yield. MS (MALDI-FT): *m/z* 2216.1 $[M + K]^+$. HRMS (MALDI-FT): Calcd. for $C_{123}H_{152}N_{14}O_{23}Na$ $[M + Na]^+$: 2200.1098. Found: 2200.1105.

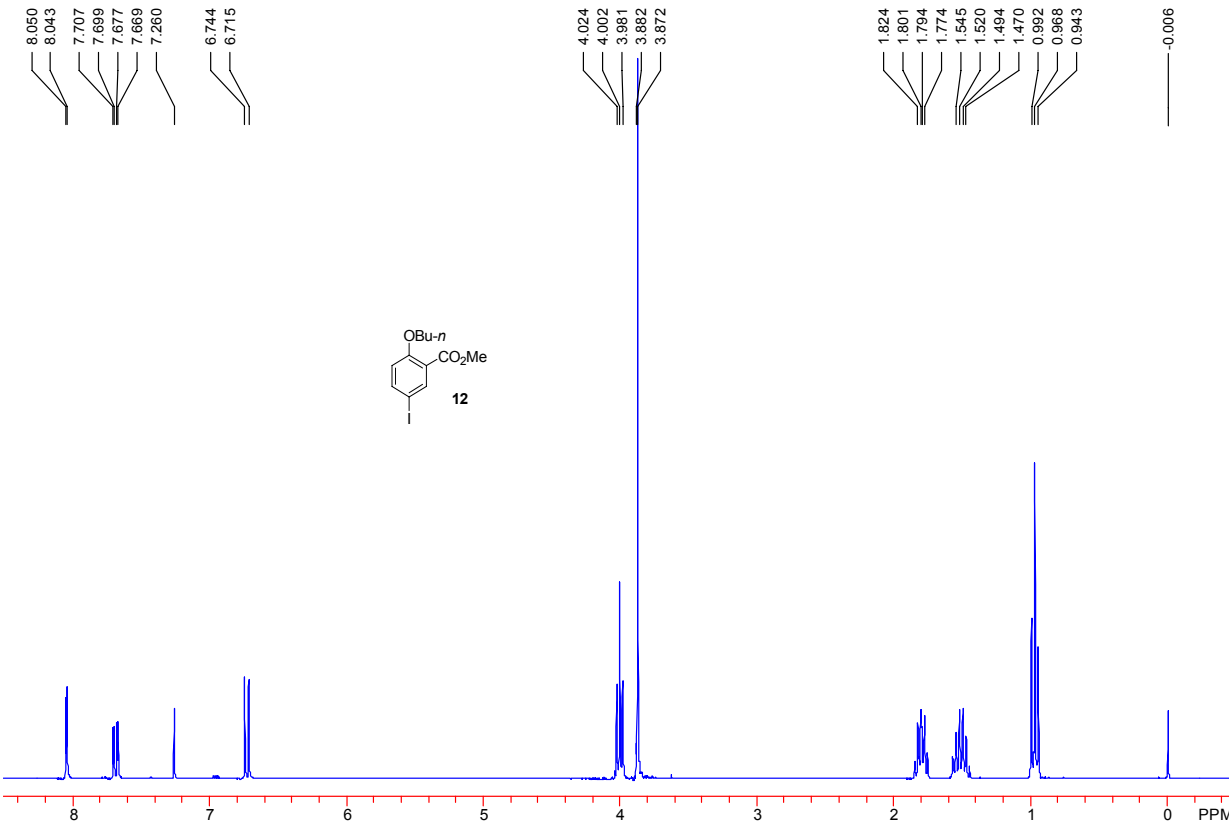

Figure S1. ^{1}H NMR spectrum of **12** (300 MHz) in $CDCl_3$ (10 mM).

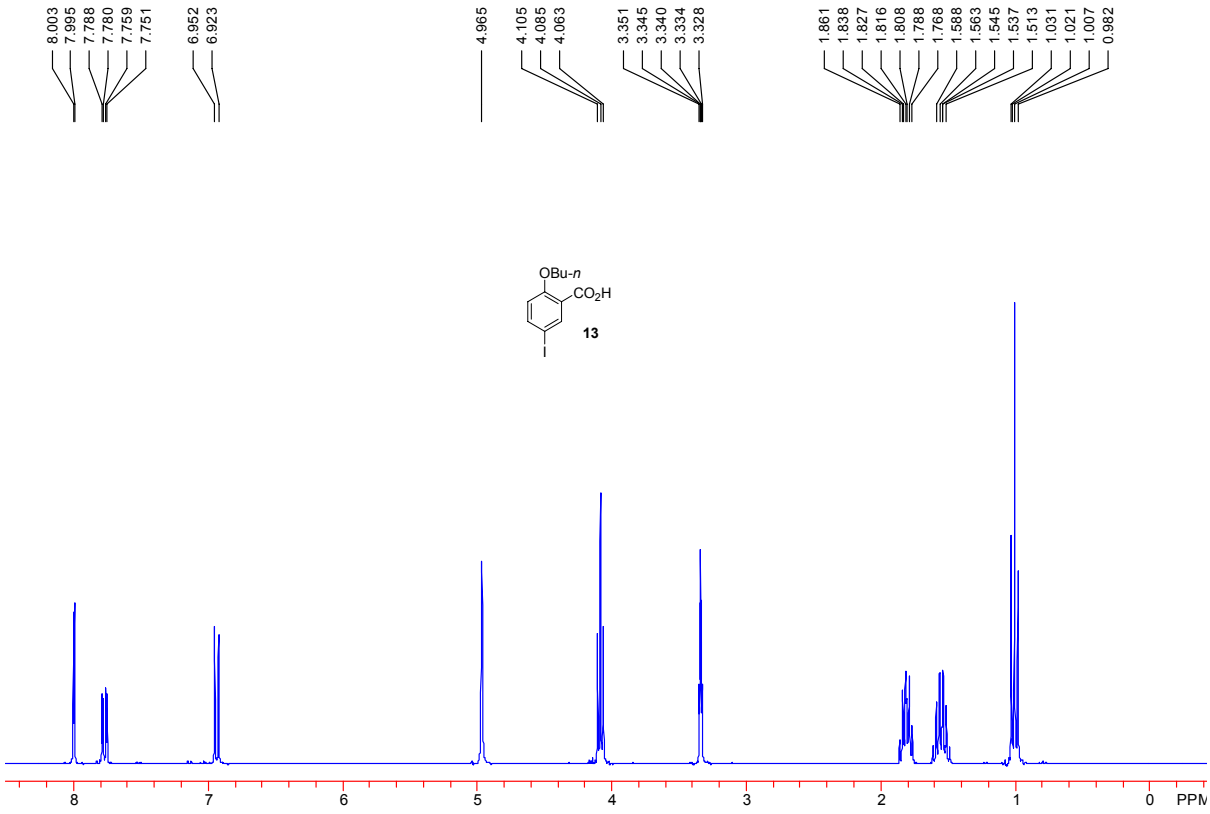

Figure S2. ^{1}H NMR spectrum of **13** (300 MHz) in CD_3OD (10 mM).

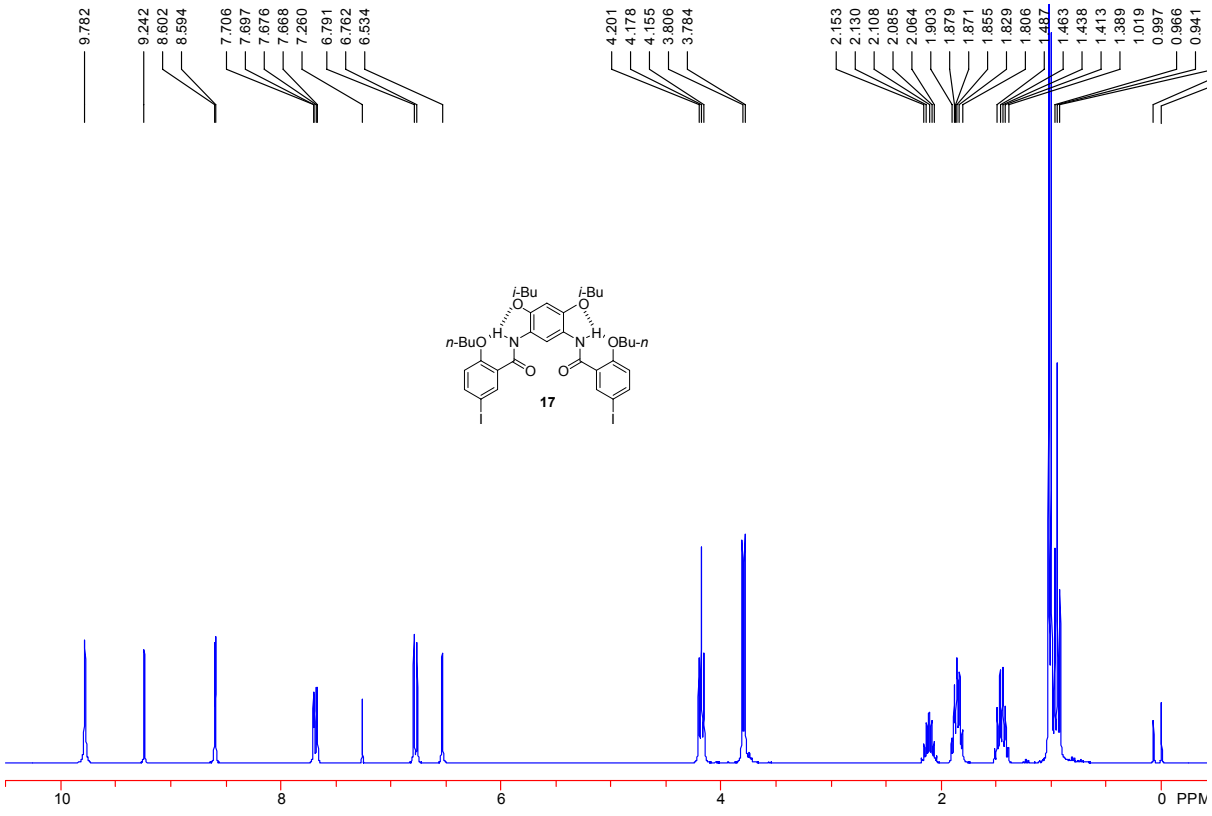

Figure S3. ^{1}H NMR spectrum of **17** (300 MHz) in $CDCl_3$ (10 mM).

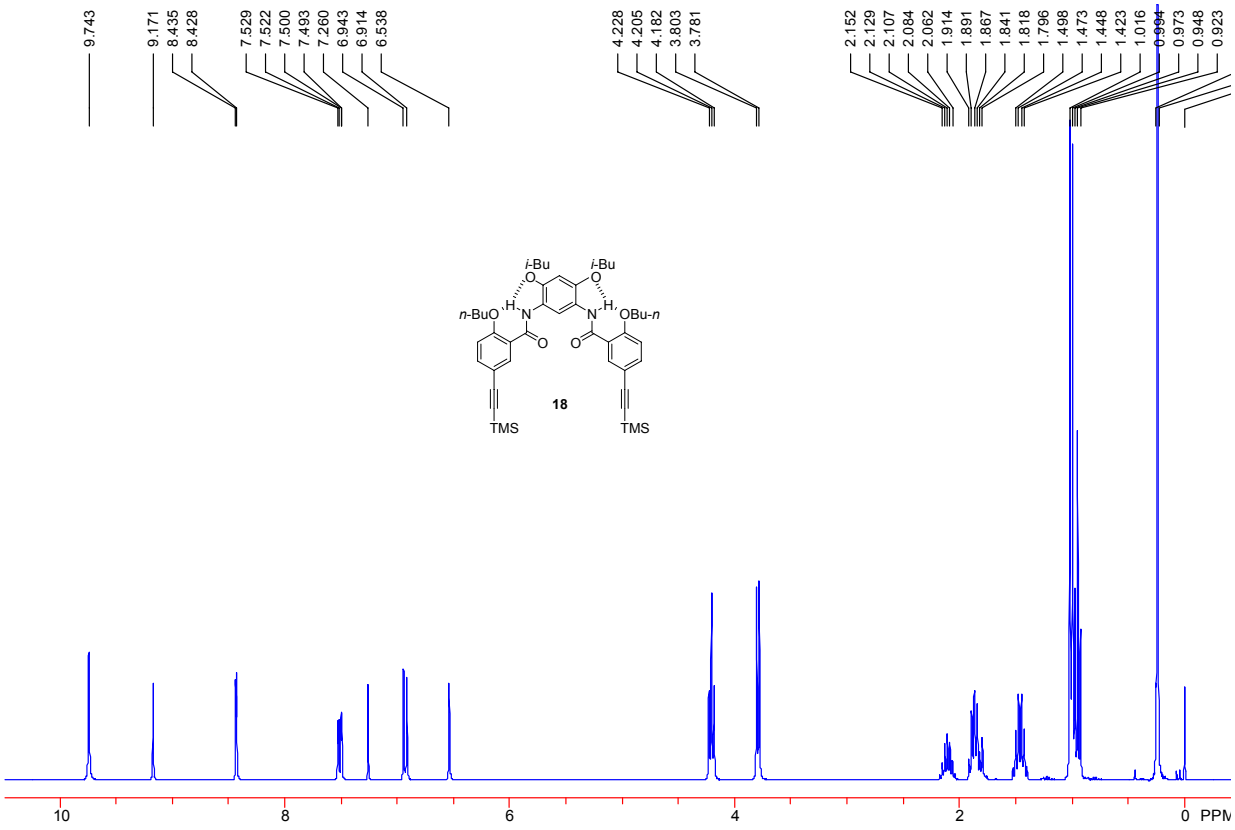

Figure S4. ^{1}H NMR spectrum of **18** (300 MHz) in $CDCl_3$ (10 mM).

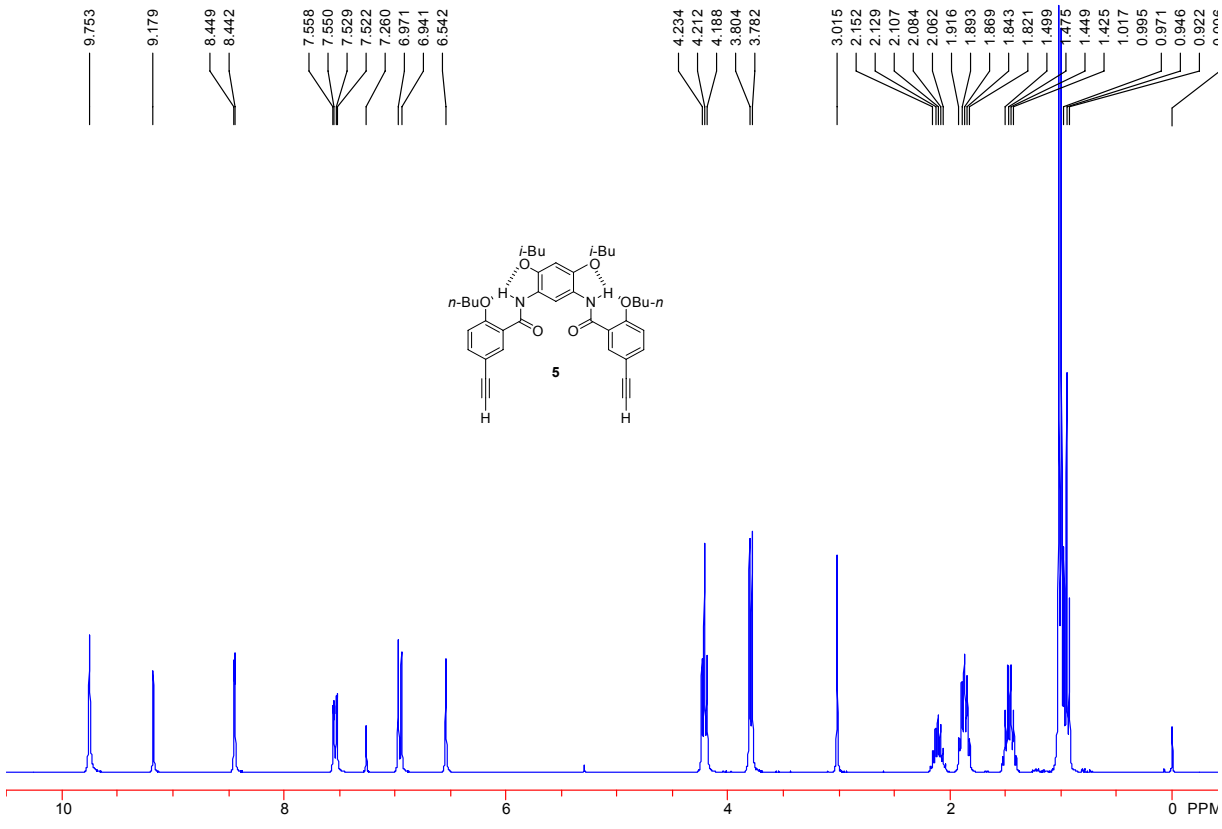

Figure S5. ^{1}H NMR spectrum of **5** (300 MHz) in $CDCl_3$ (10 mM).

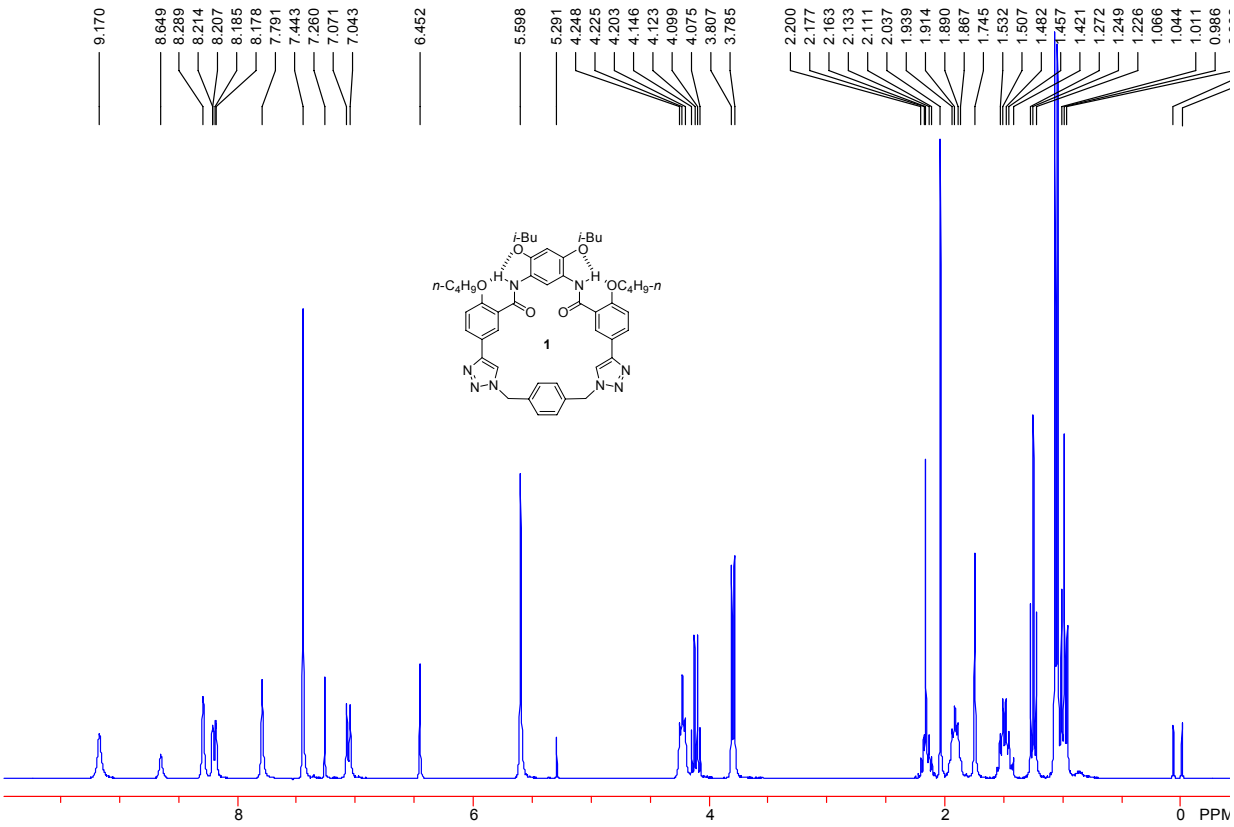

Figure S6. ^{1}H NMR spectrum of **1** (300 MHz) in $CDCl_3$ (5 mM).

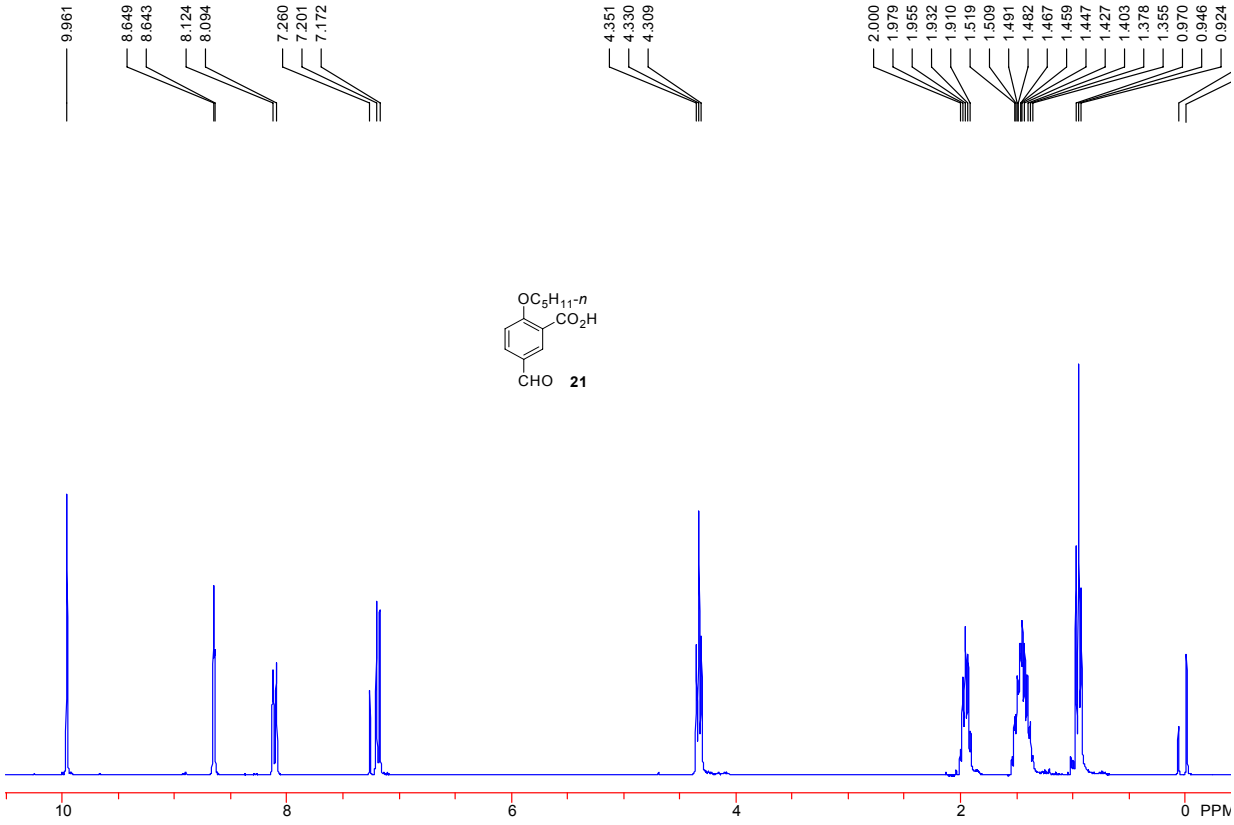

Figure S7. ^{1}H NMR spectrum of **21** (300 MHz) in $CDCl_3$ (10 mM).

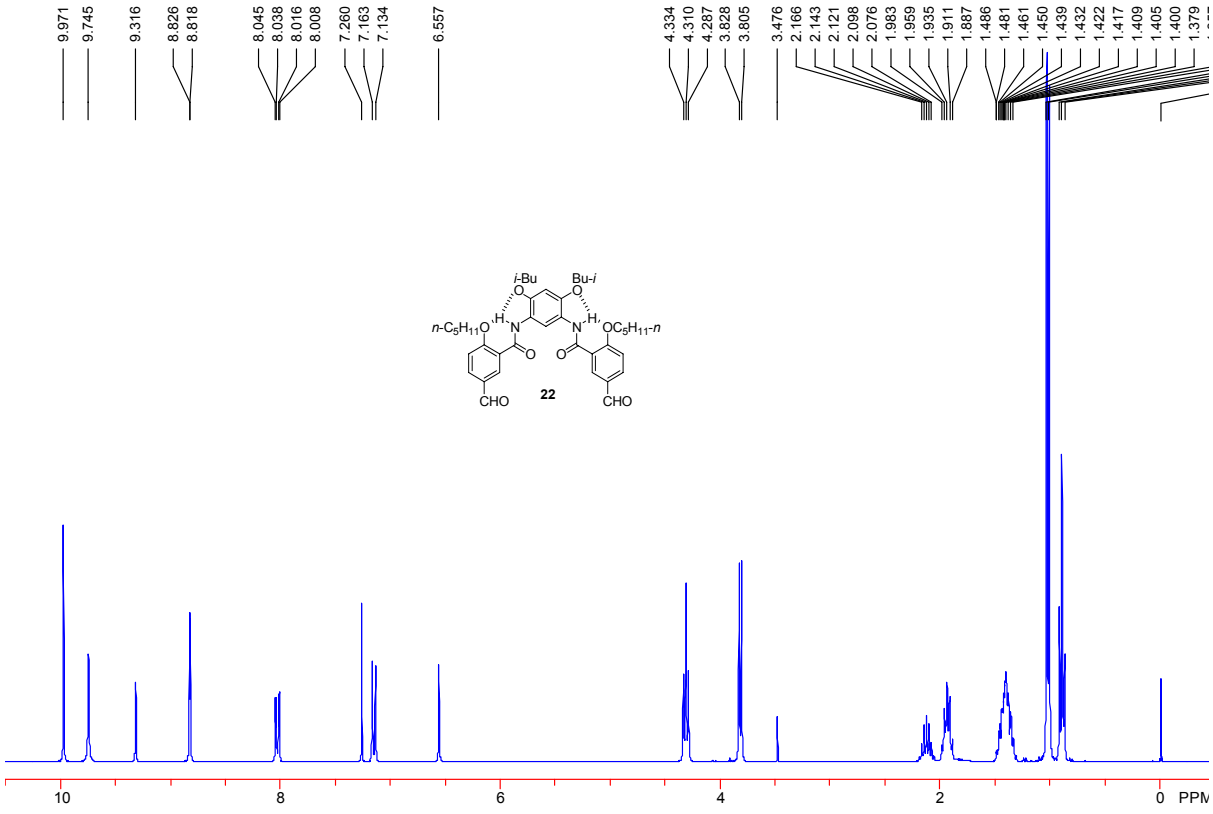

Figure S8. ^{1}H NMR spectrum of **22** (300 MHz) in $CDCl_3$ (10 mM).

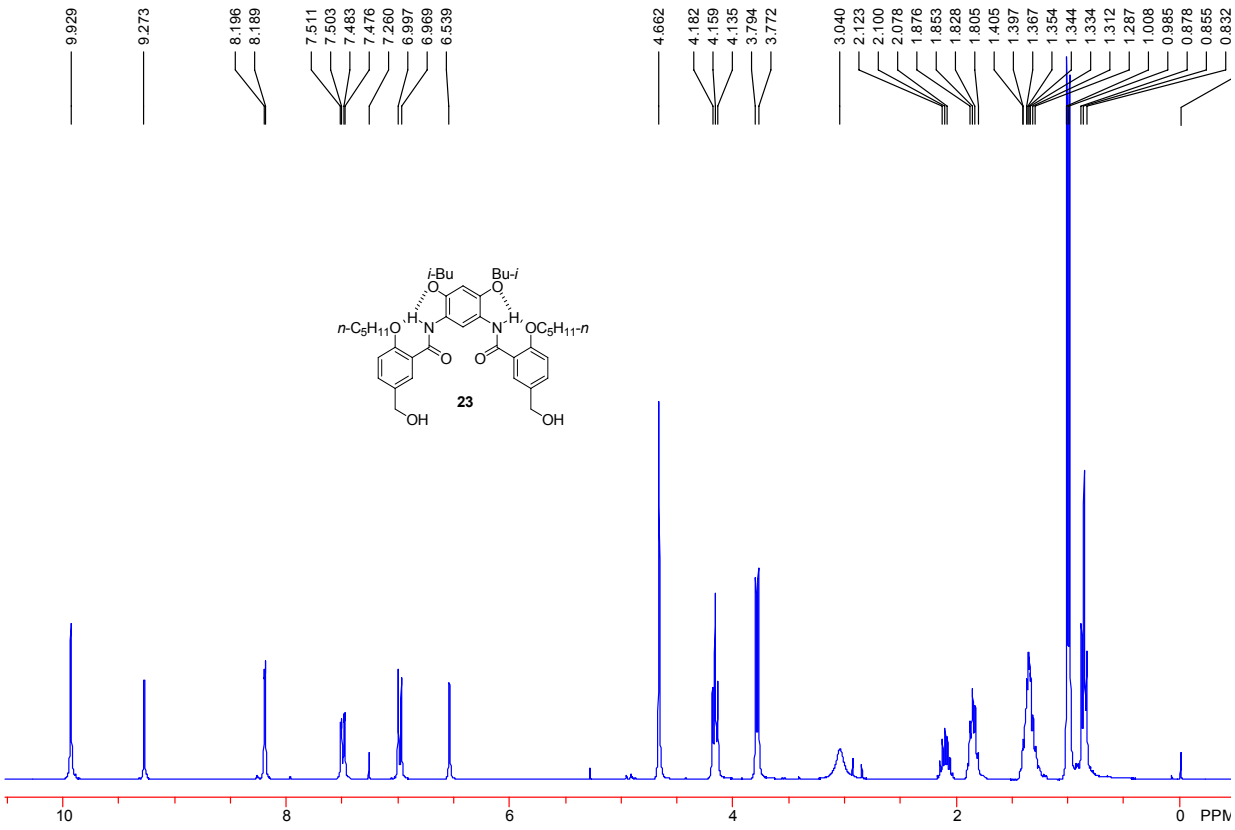

Figure S9. ^{1}H NMR spectrum of **23** (300 MHz) in $CDCl_3$ (10 mM).

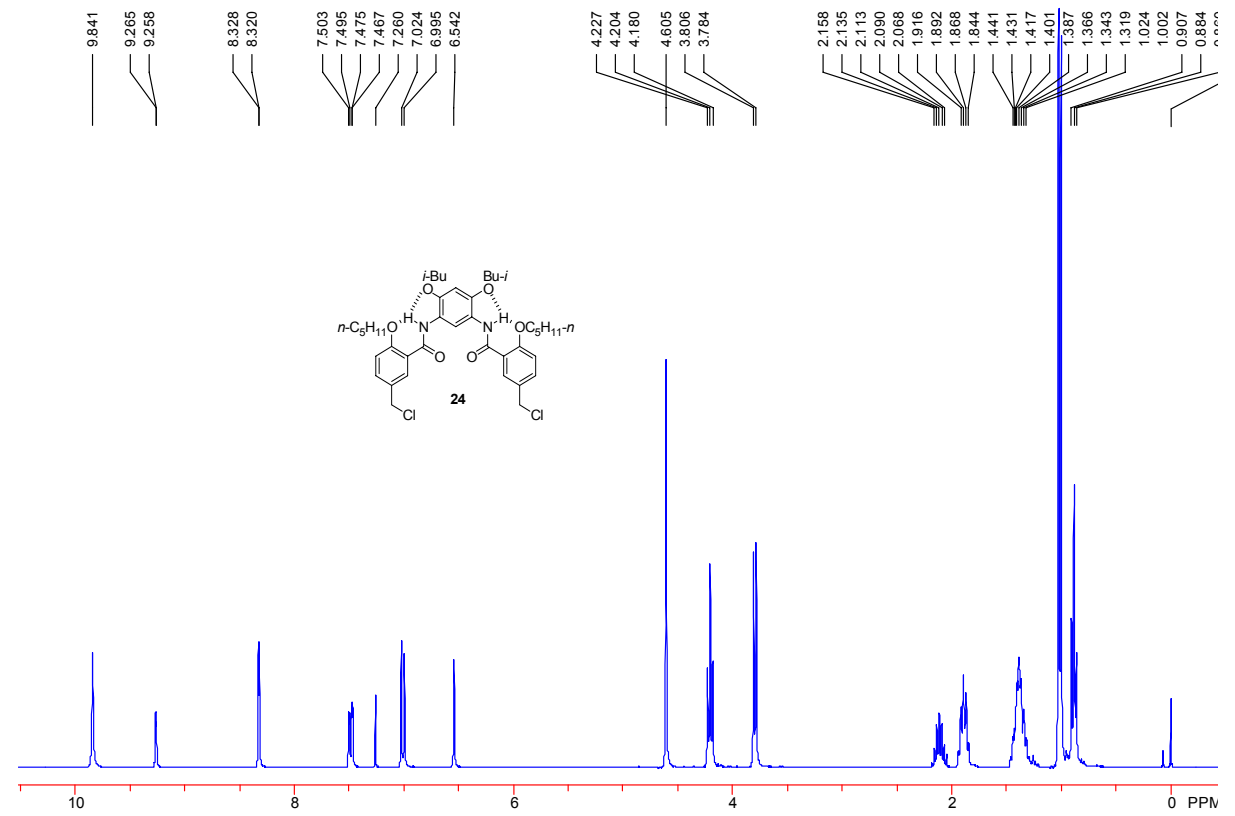

Figure S10. ^{1}H NMR spectrum of **24** (300 MHz) in $CDCl_3$ (10 mM).

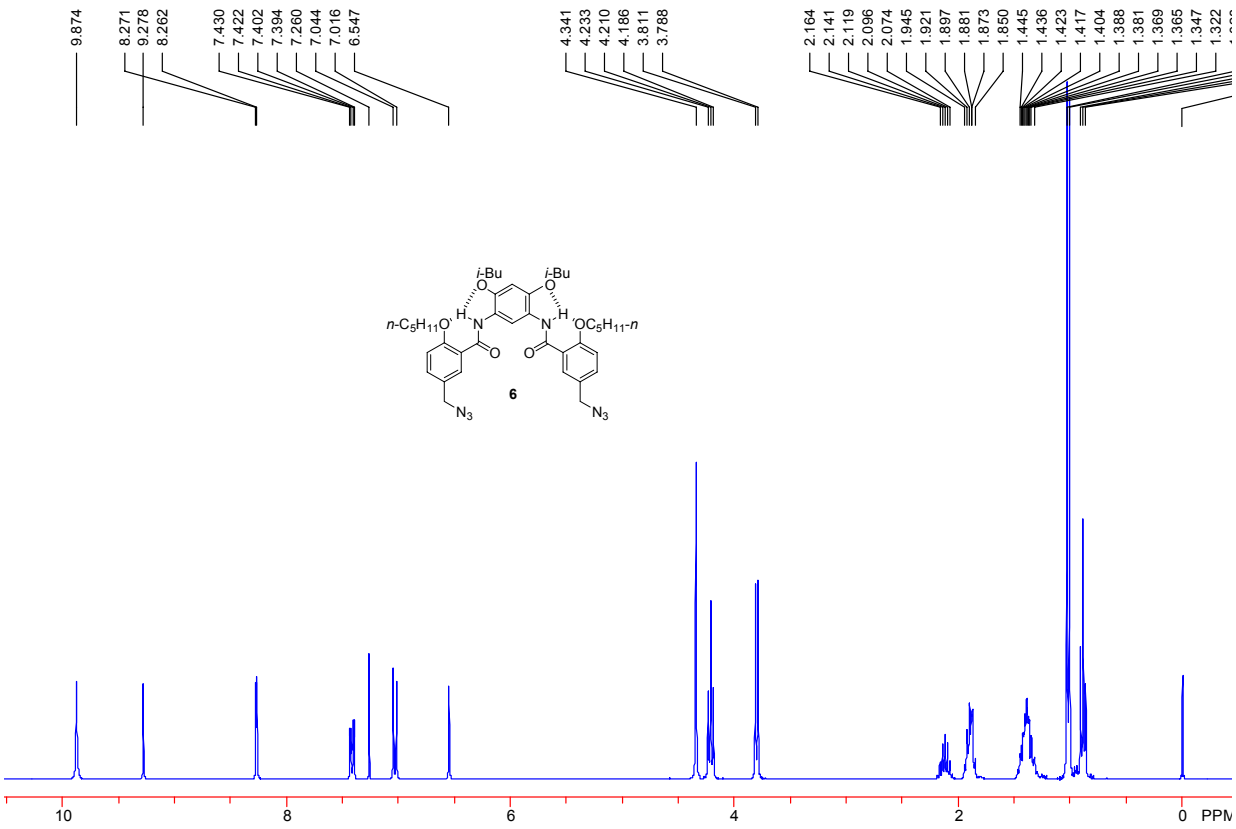

Figure S11. ^{1}H NMR spectrum of **6** (300 MHz) in $CDCl_3$ (10 mM).

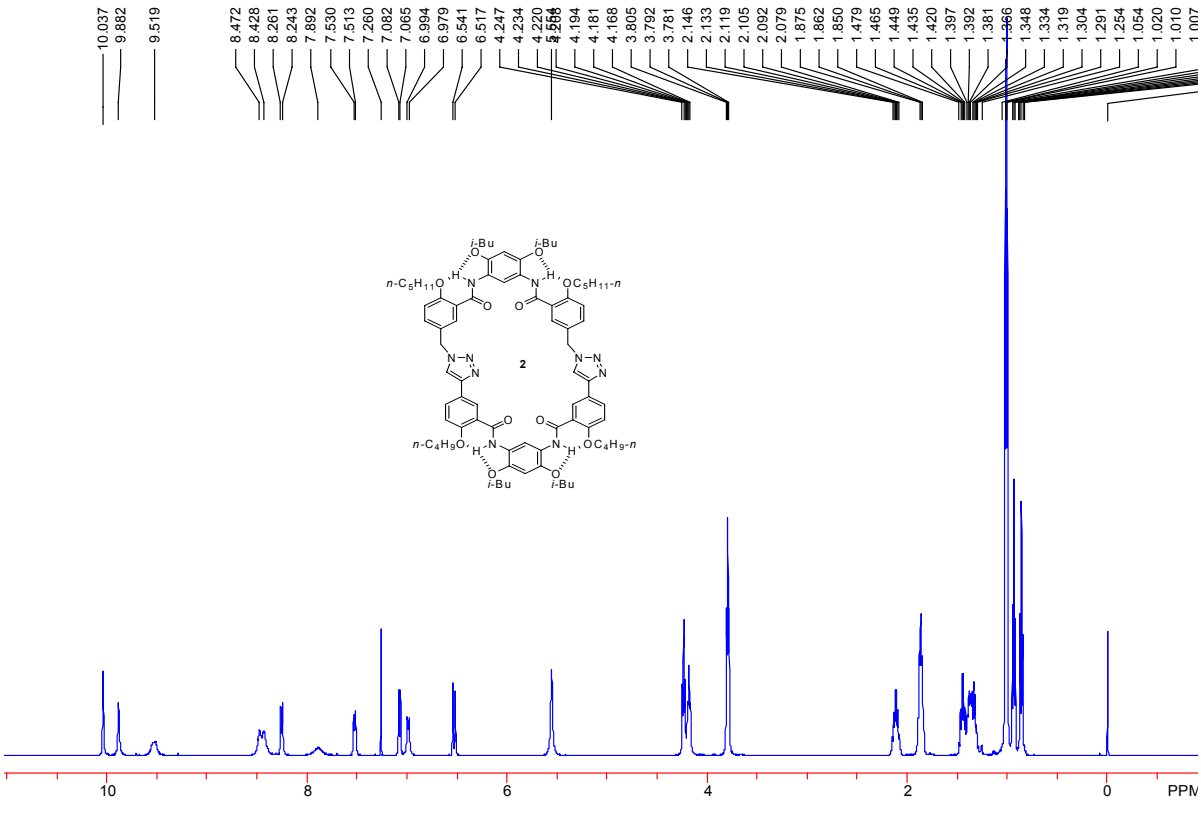

Figure S12. ^{1}H NMR spectrum of **2** (500 MHz) in $CDCl_3$ (10 mM).

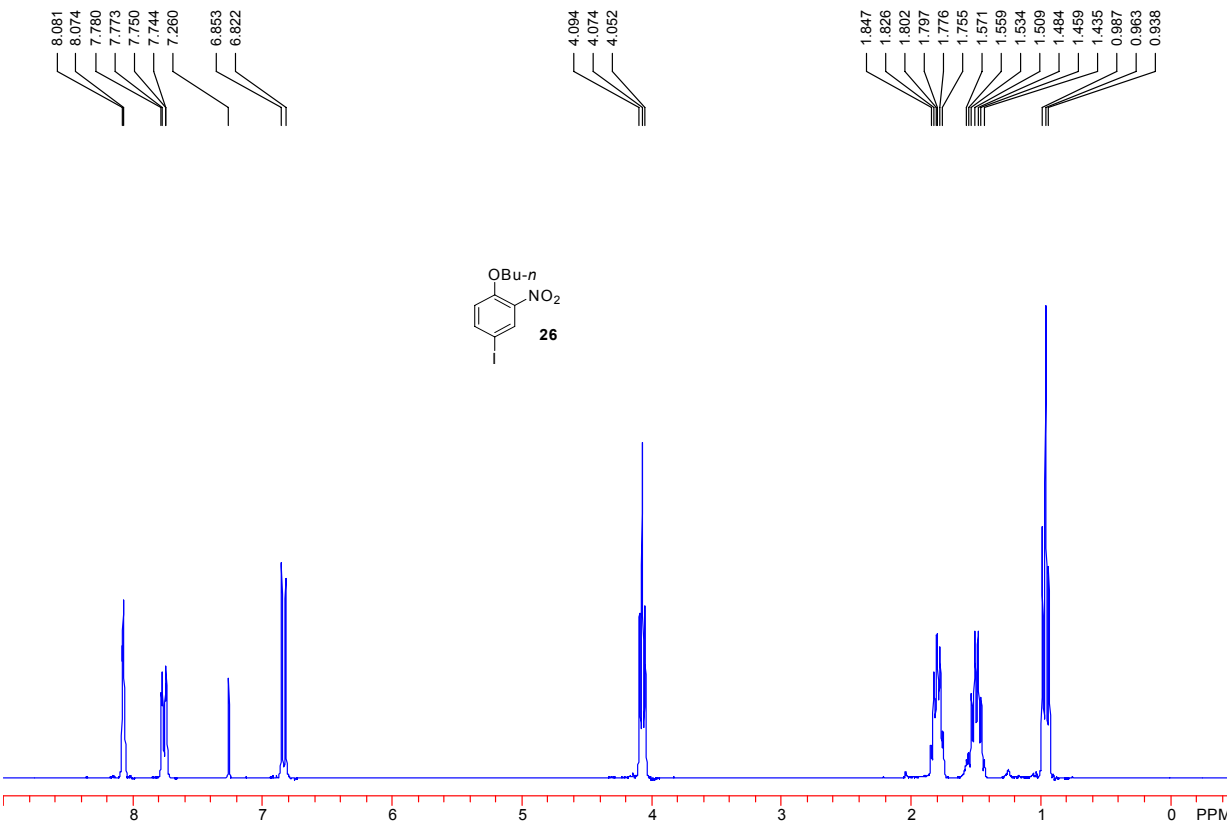

Figure S13. ^{1}H NMR spectrum of **26** (300 MHz) in $CDCl_3$ (10 mM).

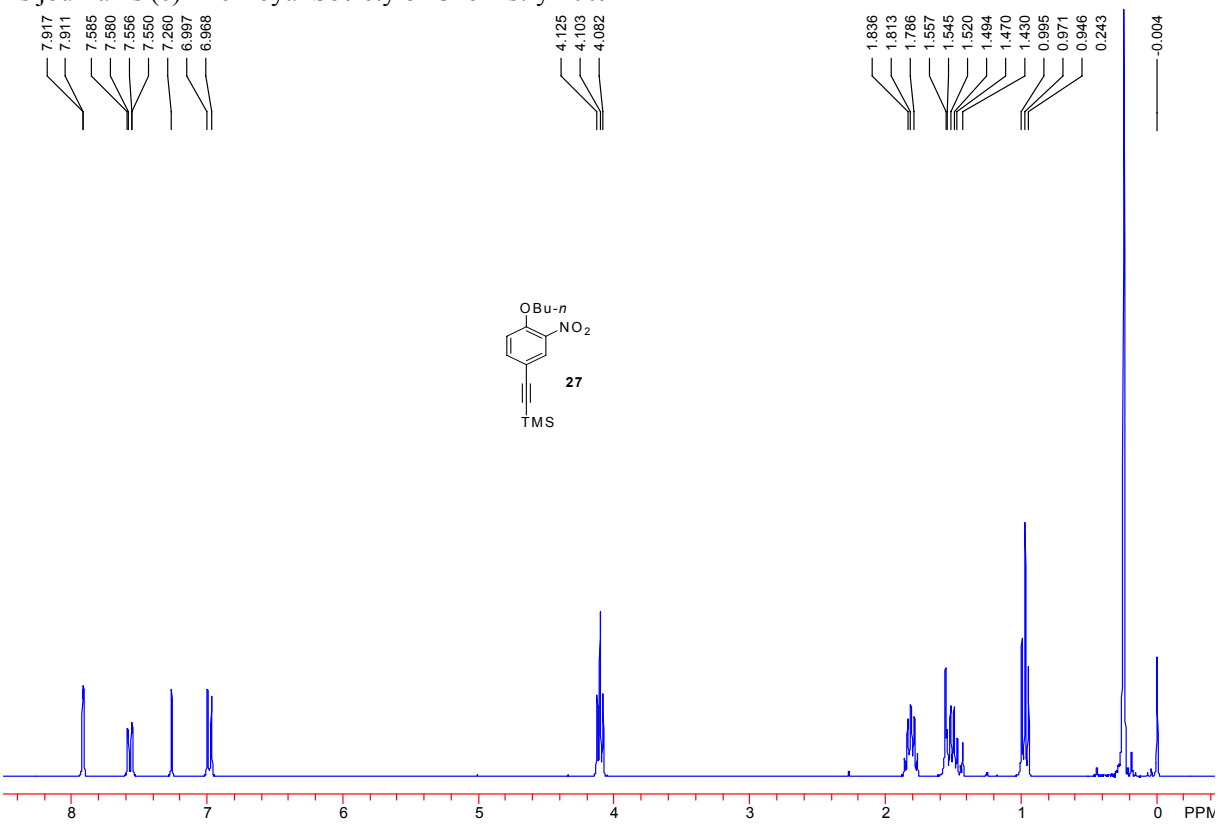

Figure S14. ^{1}H NMR spectrum of **27** (300 MHz) in $CDCl_3$ (10 mM).

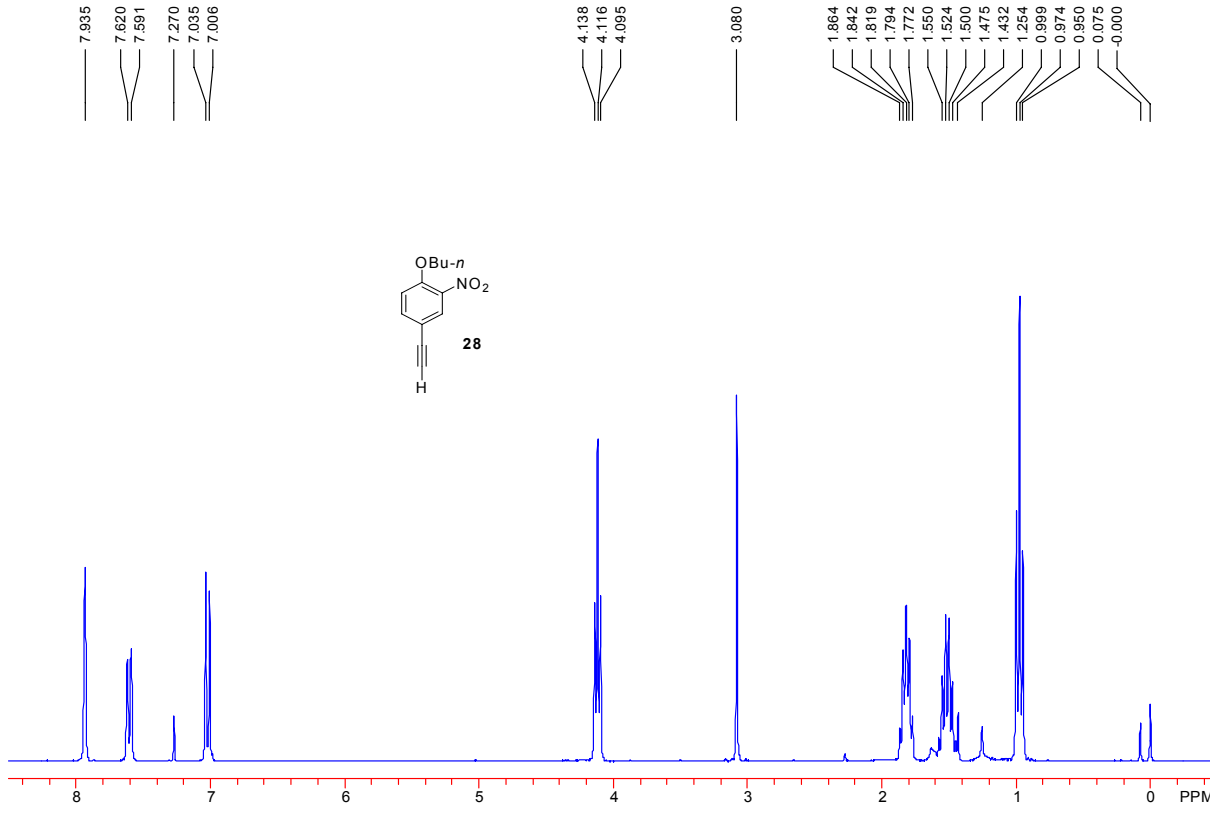

Figure S15. ^{1}H NMR spectrum of **28** (300 MHz) in $CDCl_3$ (20 mM).

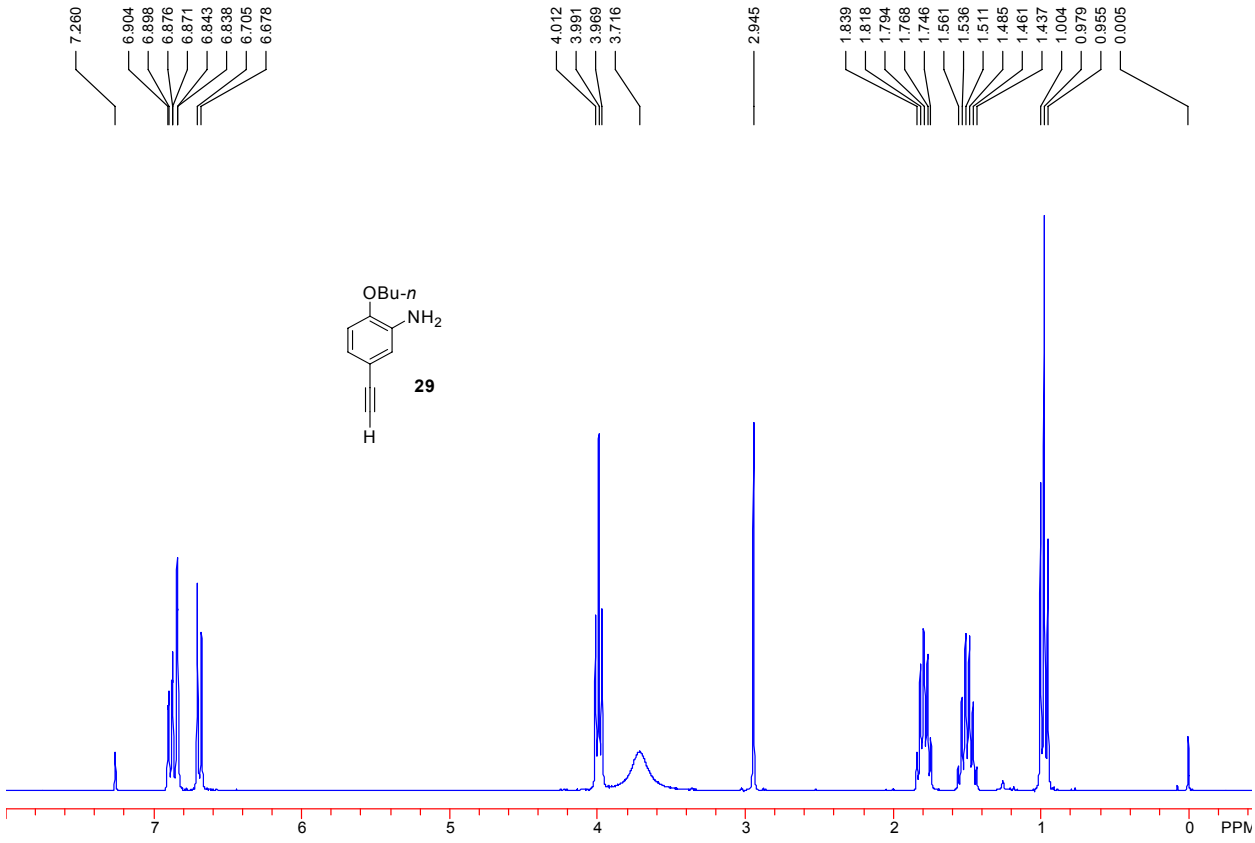

Figure S16. ^{1}H NMR spectrum of **29** (300 MHz) in $CDCl_3$ (20 mM).

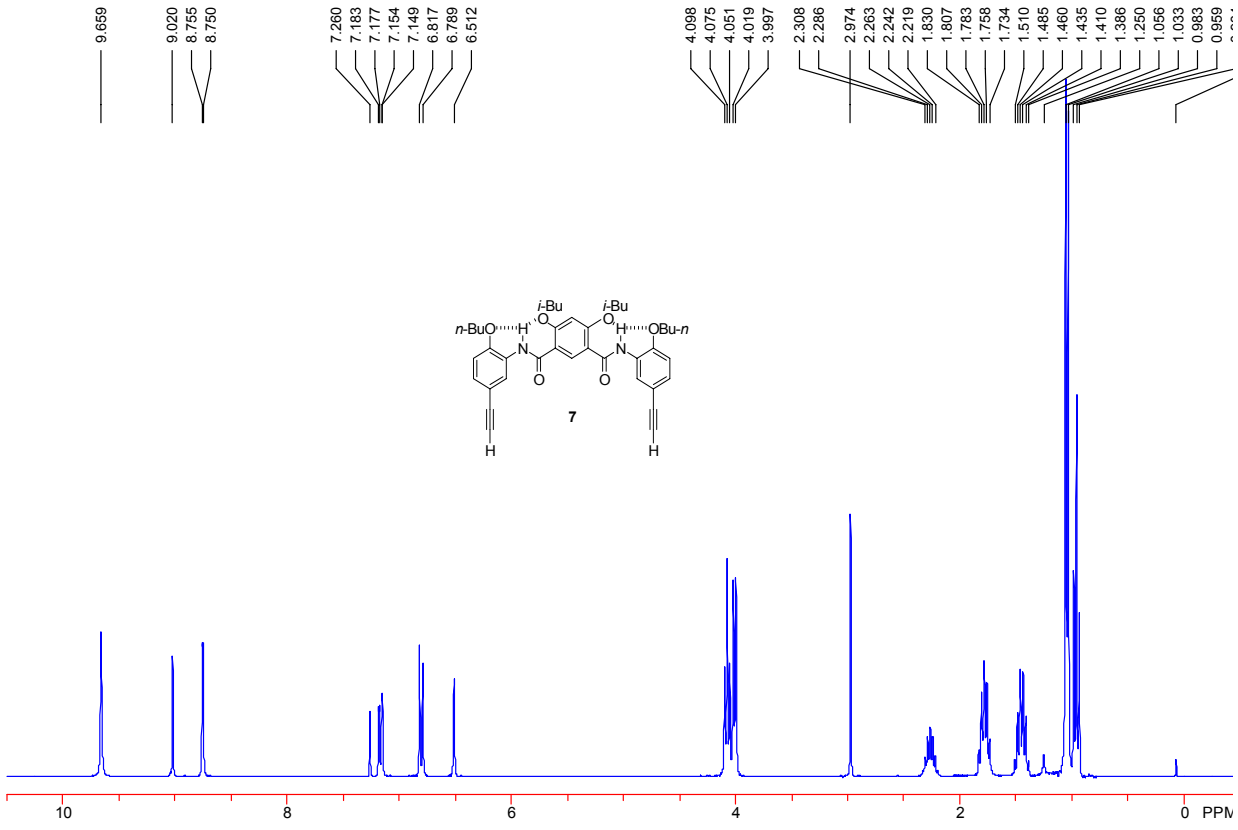

Figure S17. ^{1}H NMR spectrum of **7** (300 MHz) in $CDCl_3$ (10 mM).

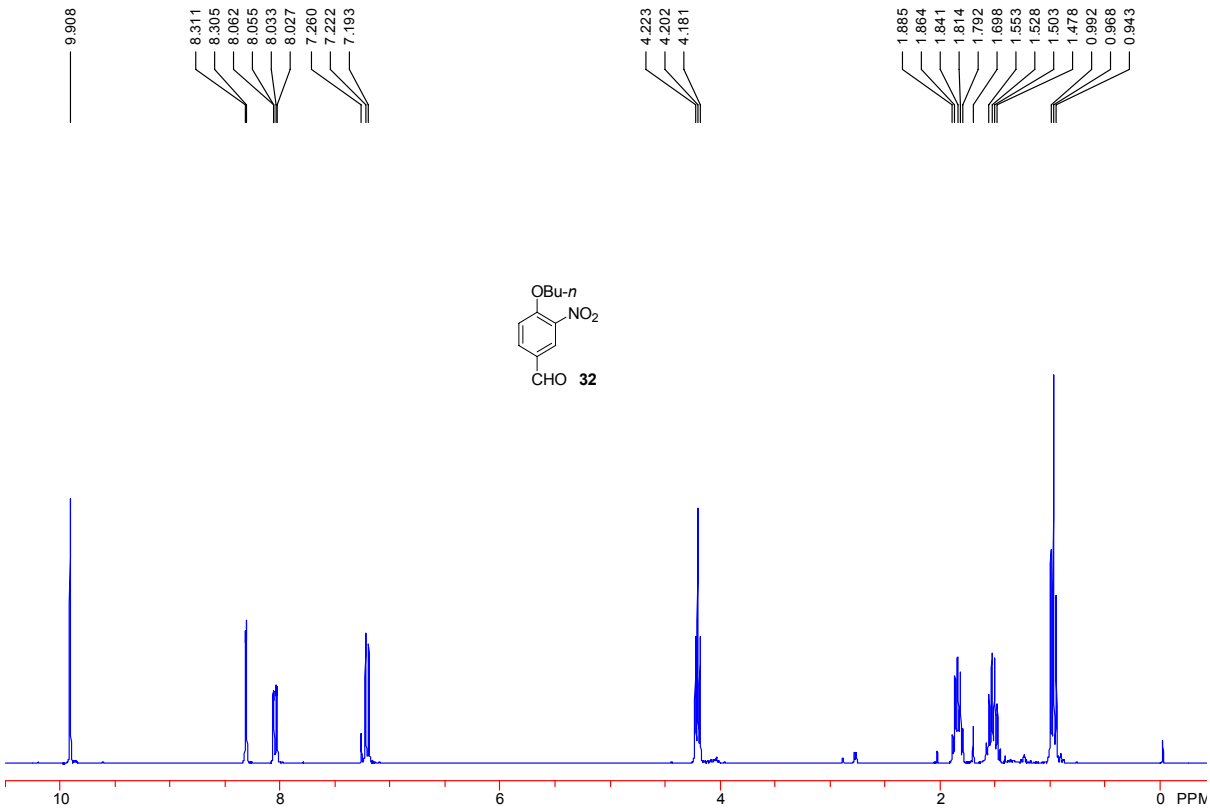

Figure S18. ^{1}H NMR spectrum of **32** (300 MHz) in $CDCl_3$ (20 mM).

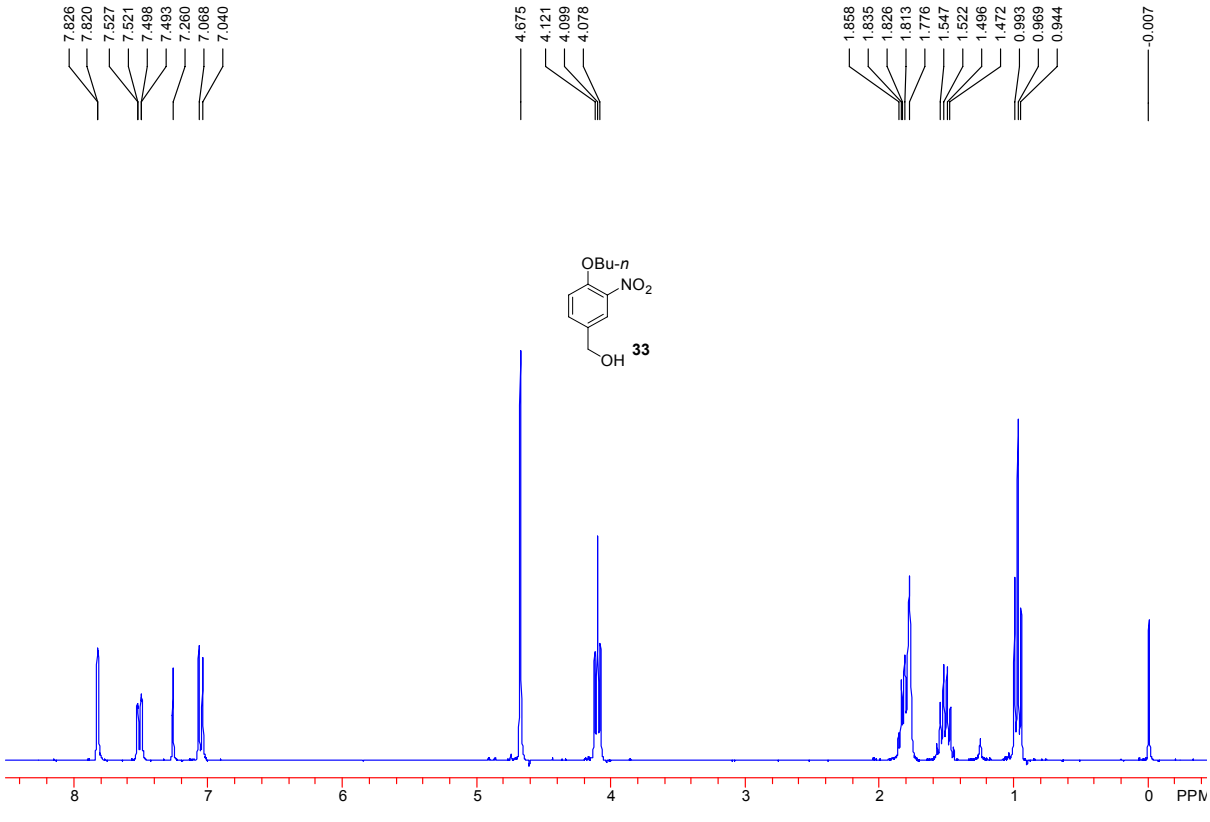

Figure S19. ^{1}H NMR spectrum of **33** (300 MHz) in $CDCl_3$ (10 mM).

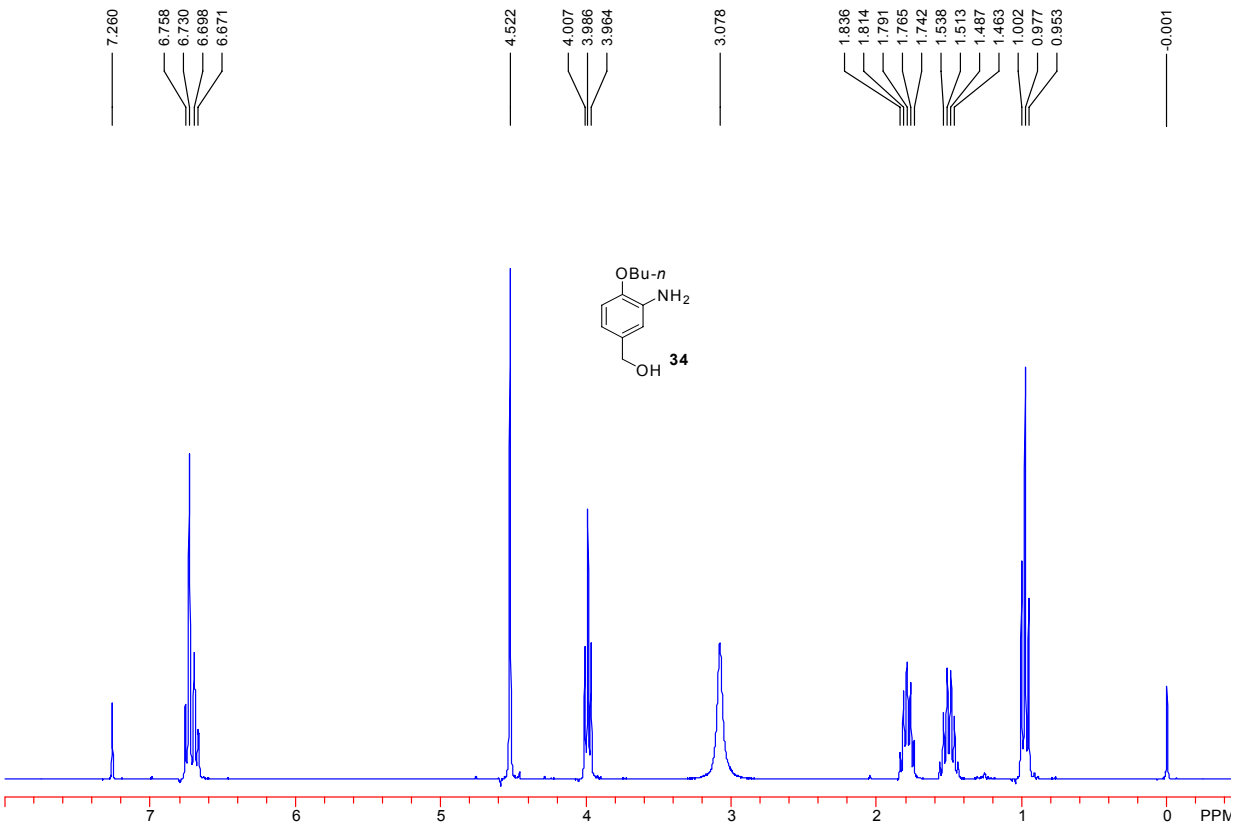

Figure S20. ^{1}H NMR spectrum of **34** (300 MHz) in $CDCl_3$ (20 mM).

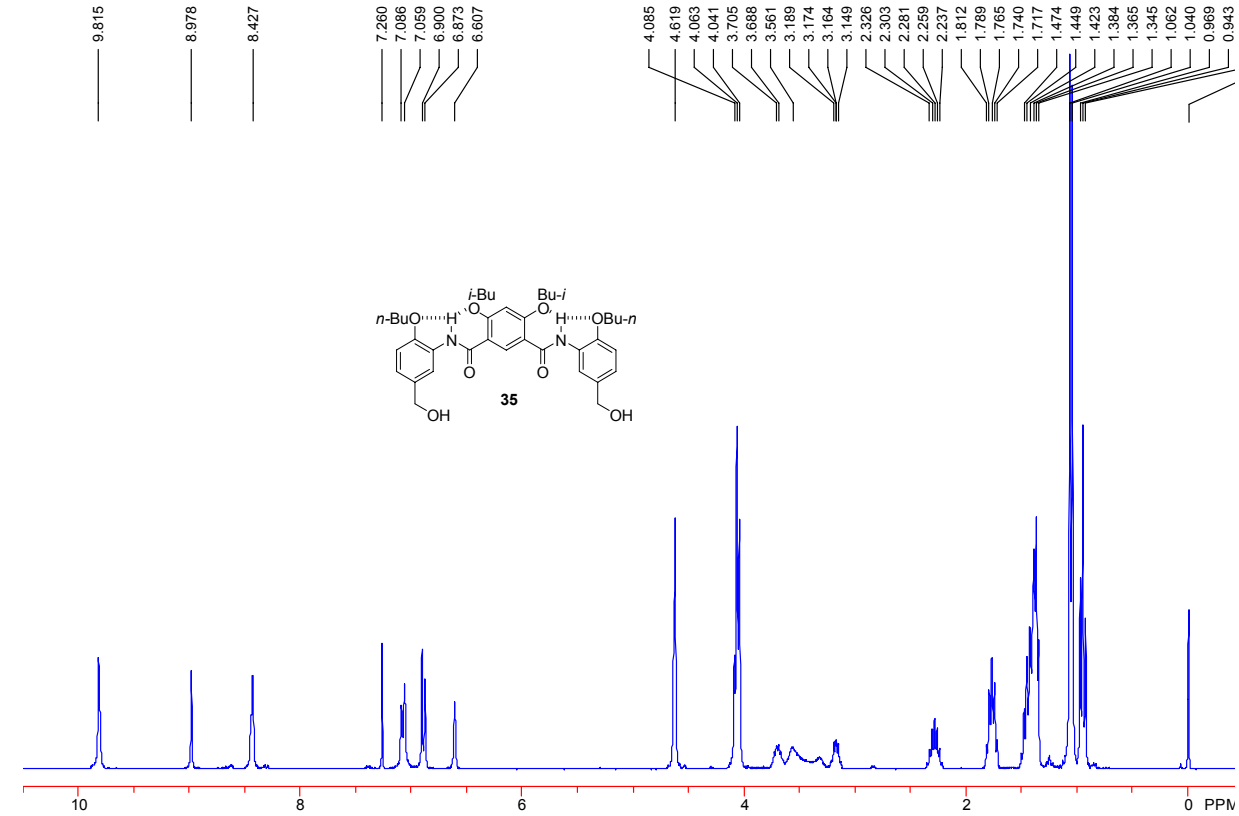

Figure S21. ^{1}H NMR spectrum of **35** (300 MHz) in $CDCl_3$ (10 mM).

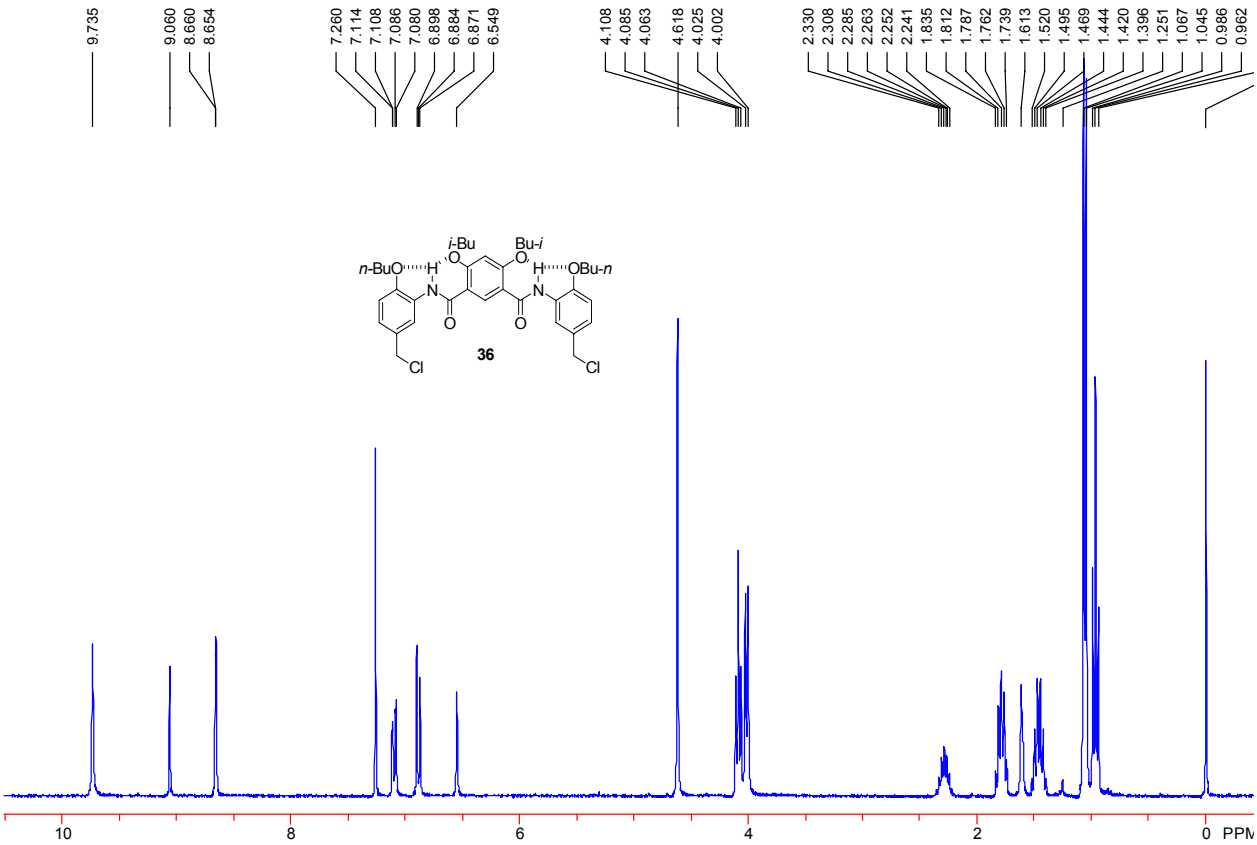

Figure S22. ^{1}H NMR spectrum of **36** (300 MHz) in $CDCl_3$ (5 mM).

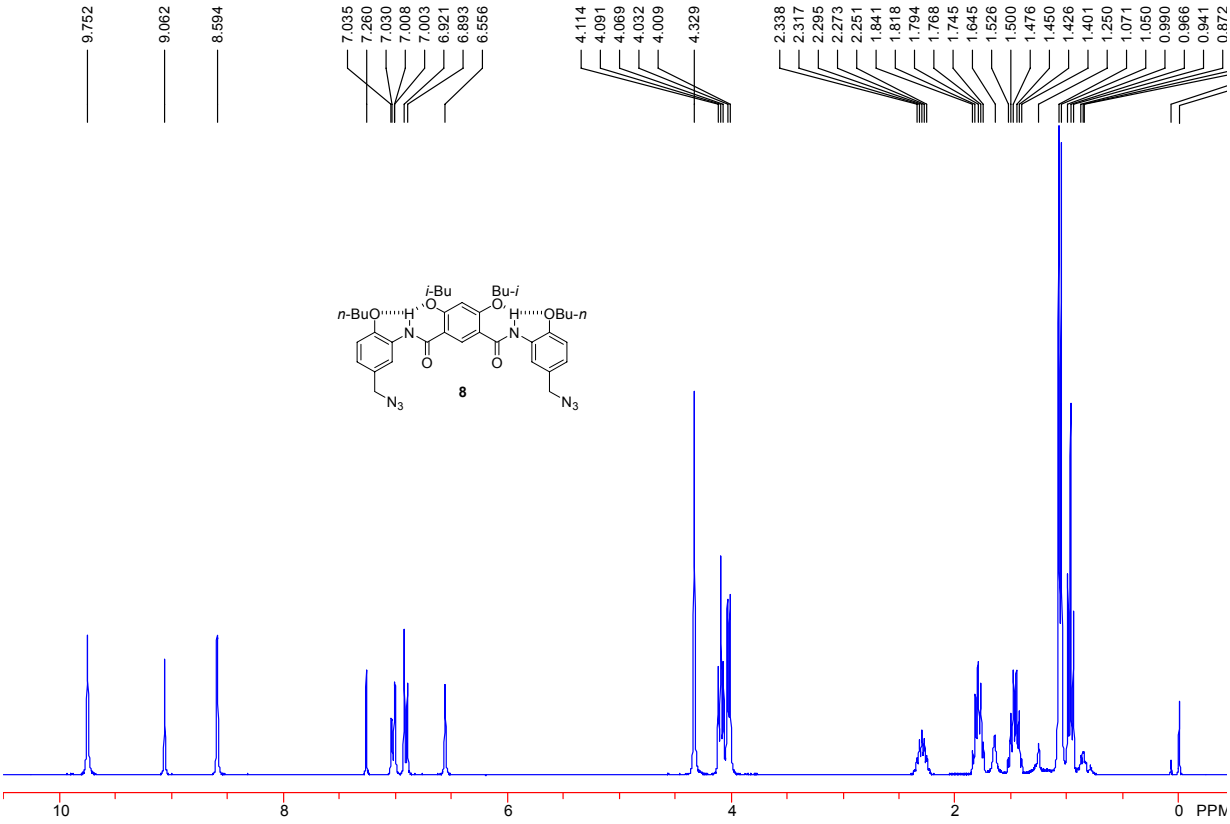

Figure S23. ^{1}H NMR spectrum of **8** (300 MHz) in $CDCl_3$ (10 mM).

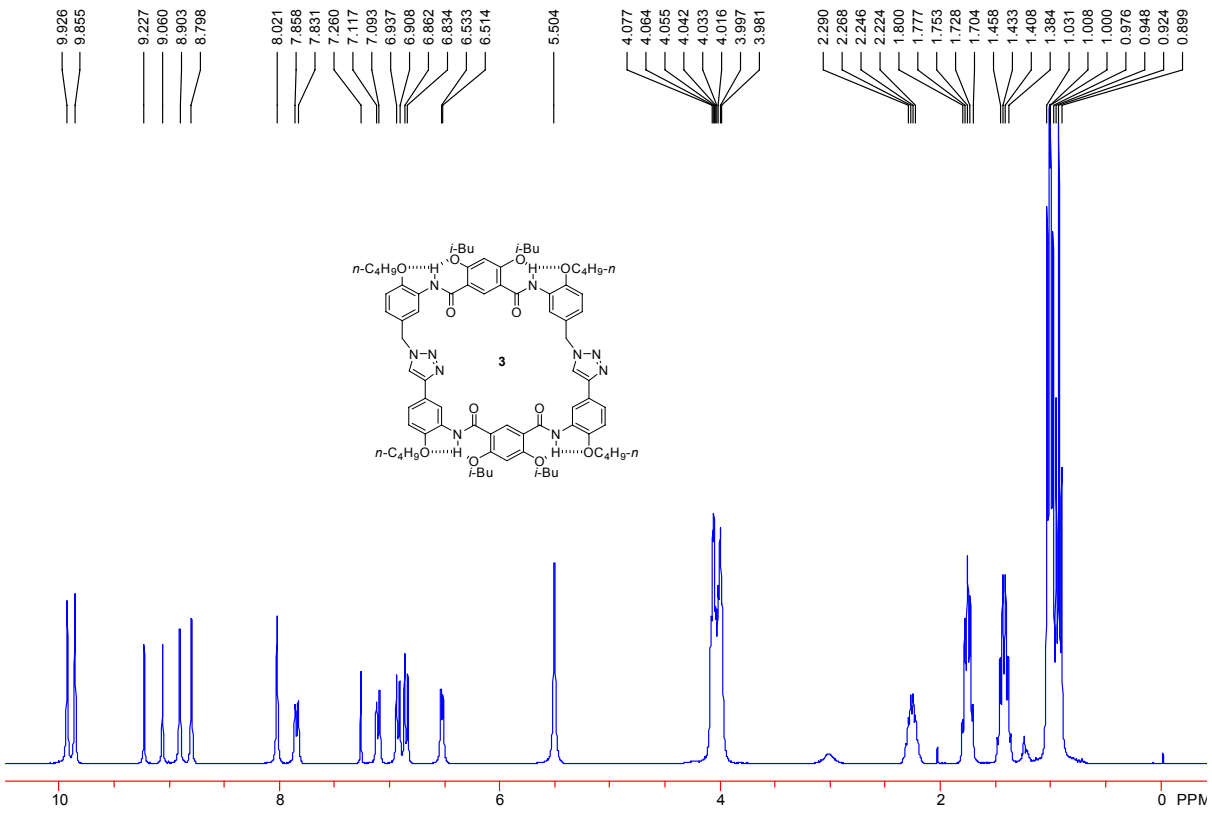

Figure S24. ^{1}H NMR spectrum of **3** (300 MHz) in $CDCl_3$ (10 mM).

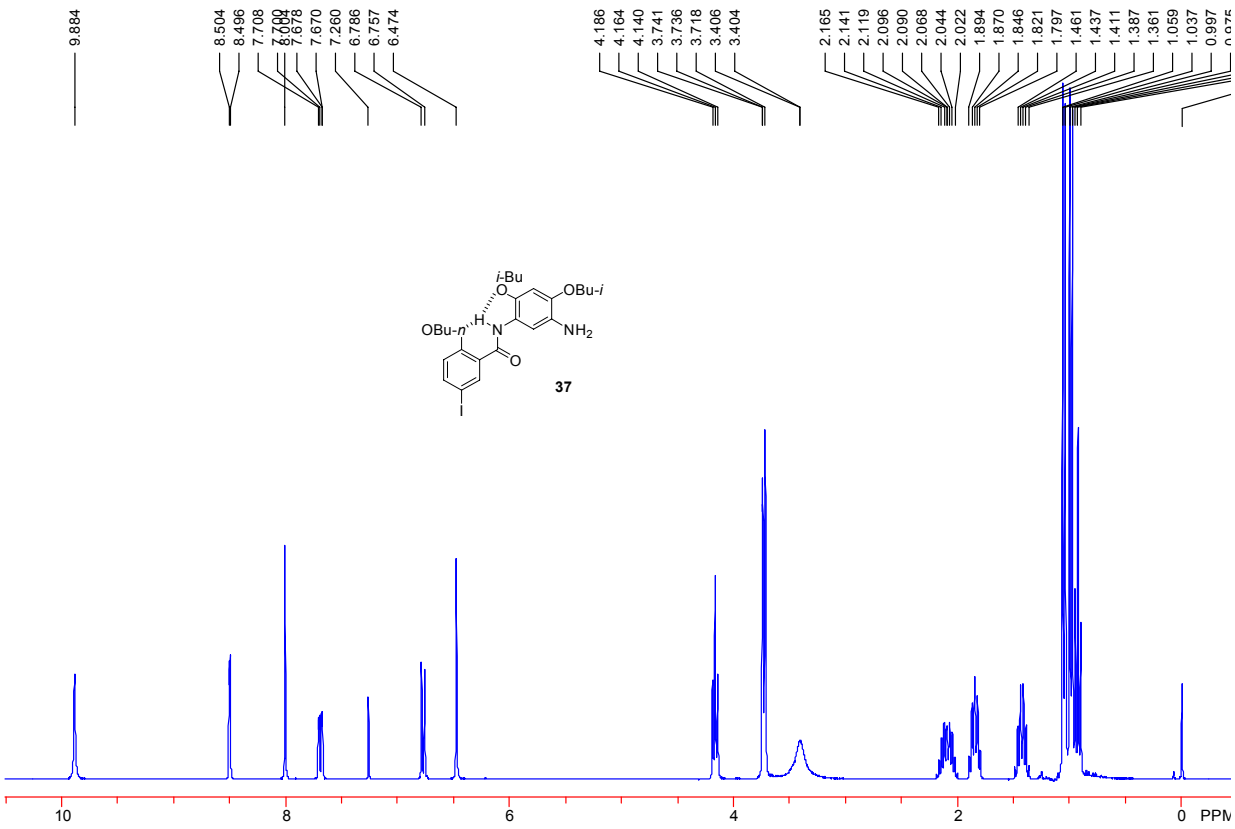

Figure S25. ^{1}H NMR spectrum of **37** (300 MHz) in $CDCl_3$ (10 mM).

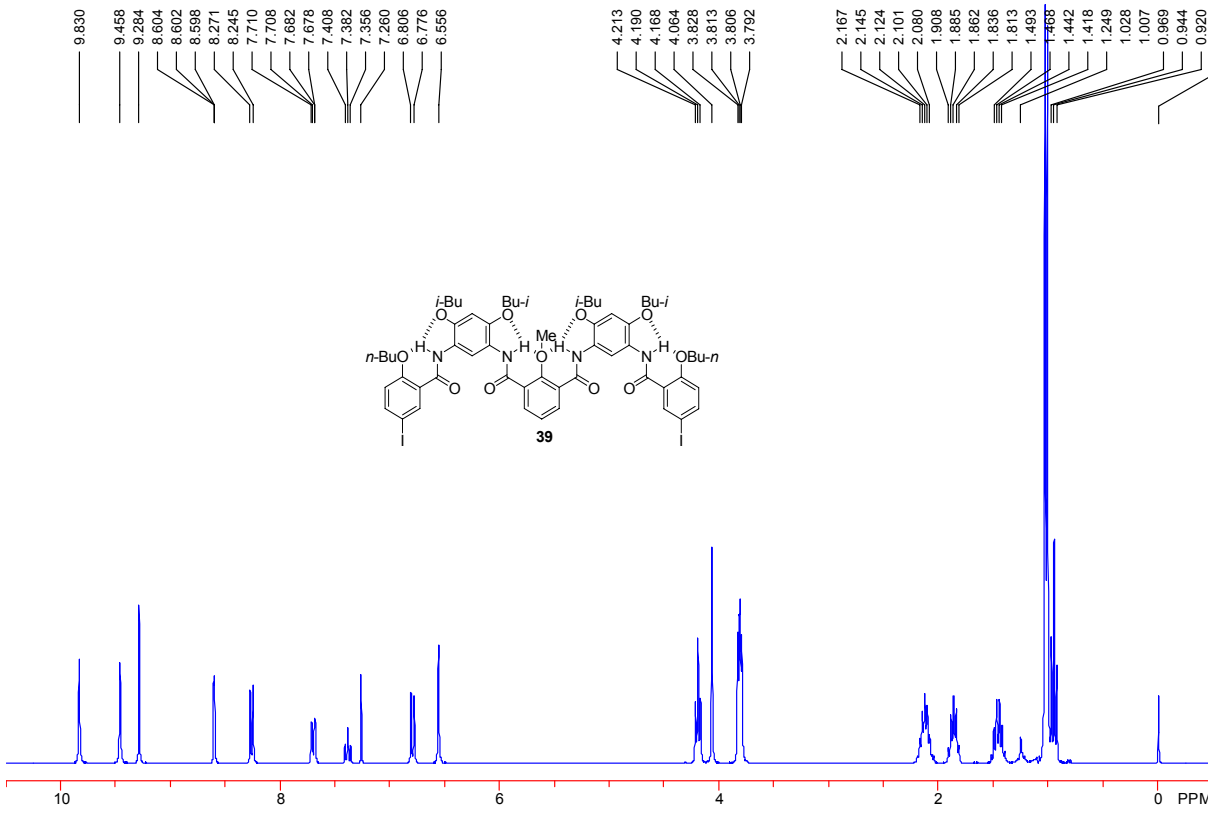

Figure S26. ^{1}H NMR spectrum of **39** (300 MHz) in $CDCl_3$ (10 mM).

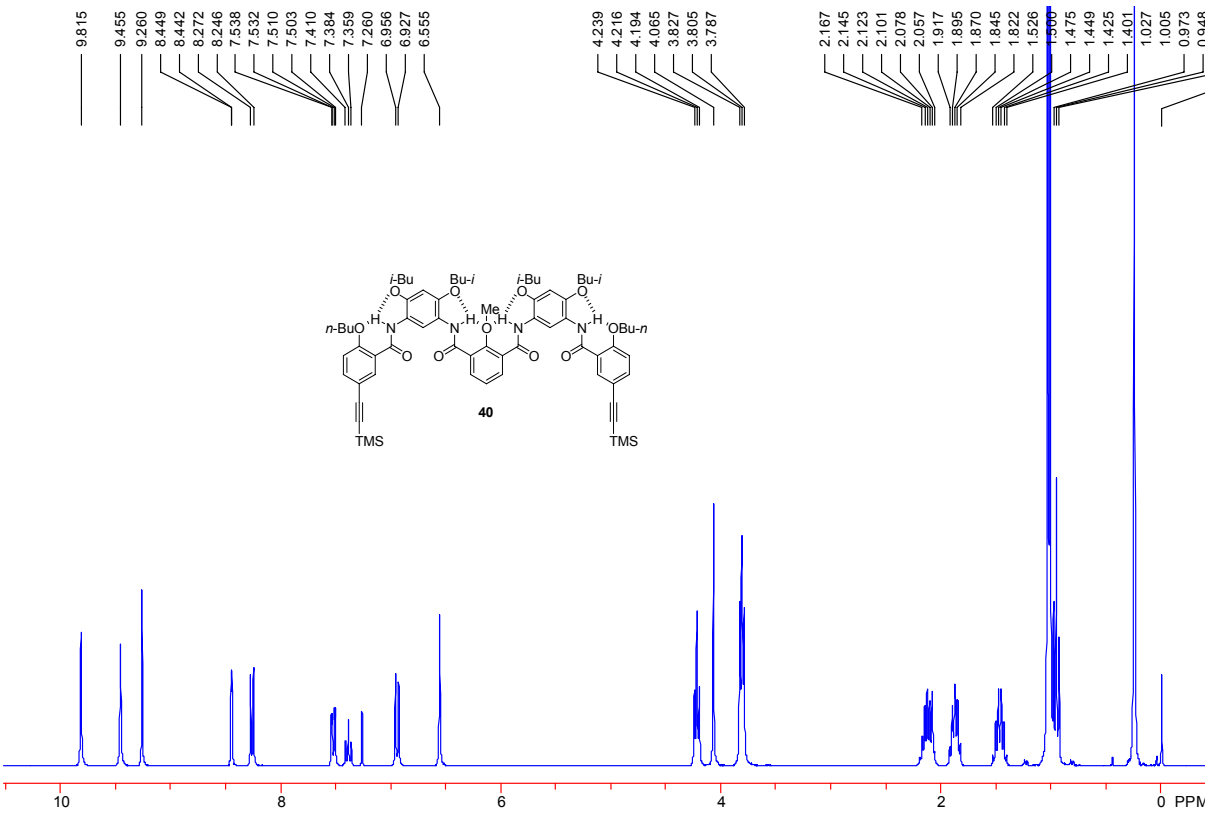

Figure S27. ^{1}H NMR spectrum of **40** (300 MHz) in $CDCl_3$ (10 mM).

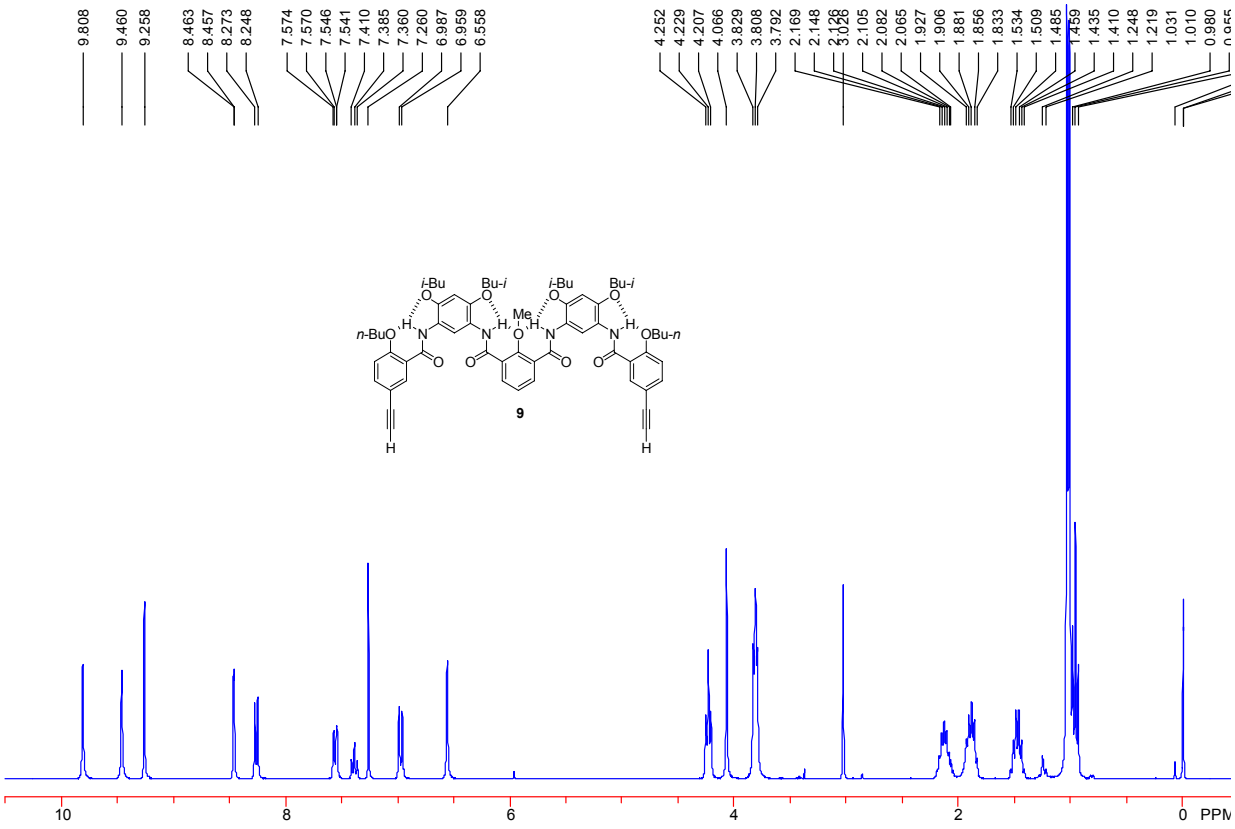

Figure S28. ^{1}H NMR spectrum of **9** (300 MHz) in $CDCl_3$ (10 mM).

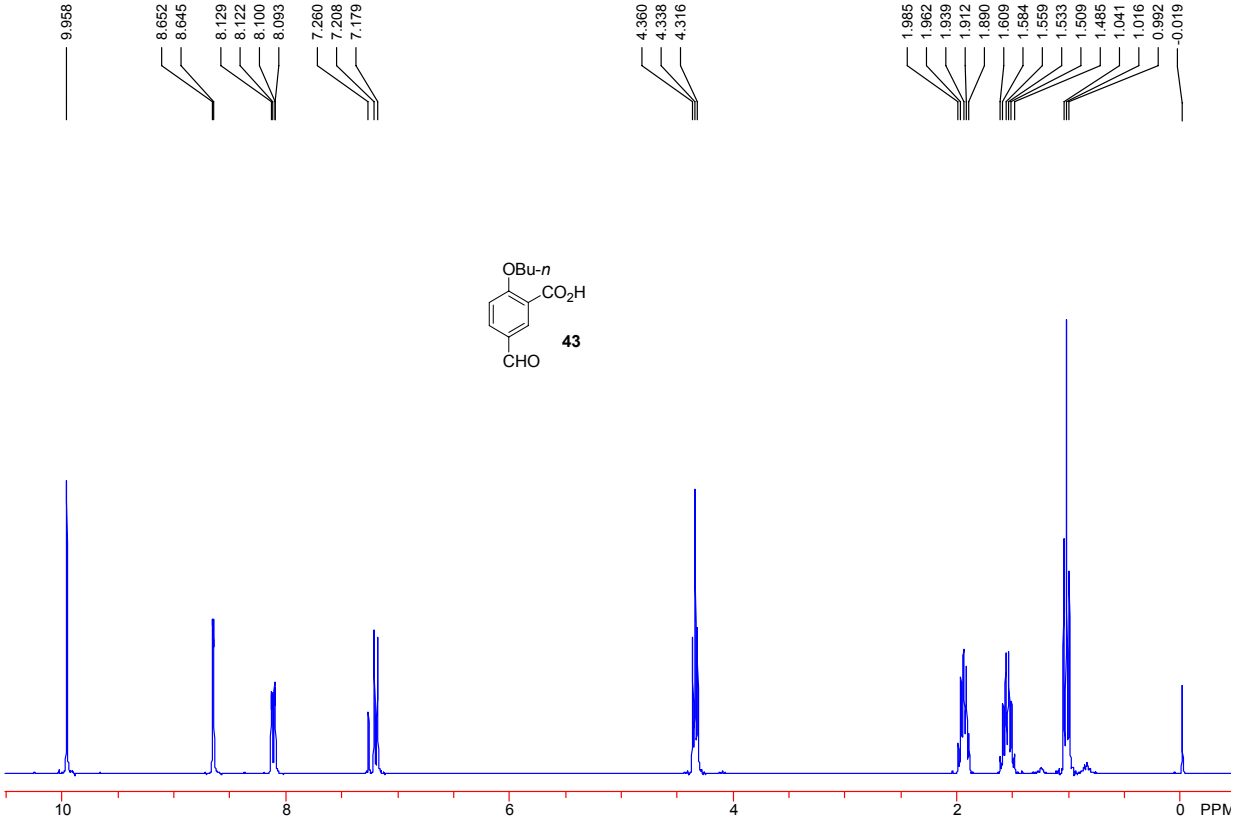

Figure S29. ^{1}H NMR spectrum of **43** (300 MHz) in $CDCl_3$ (15 mM).

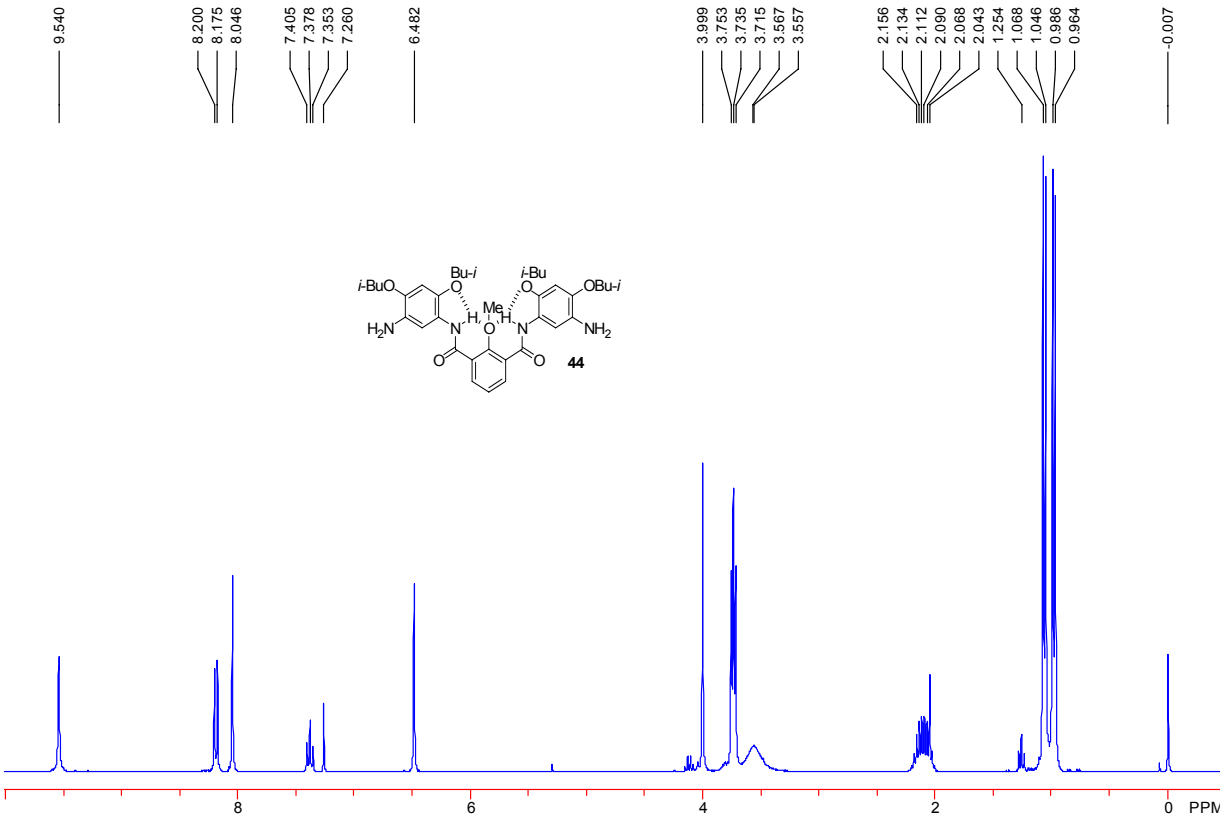

Figure S30. ^{1}H NMR spectrum of **44** (300 MHz) in $CDCl_3$ (15 mM).

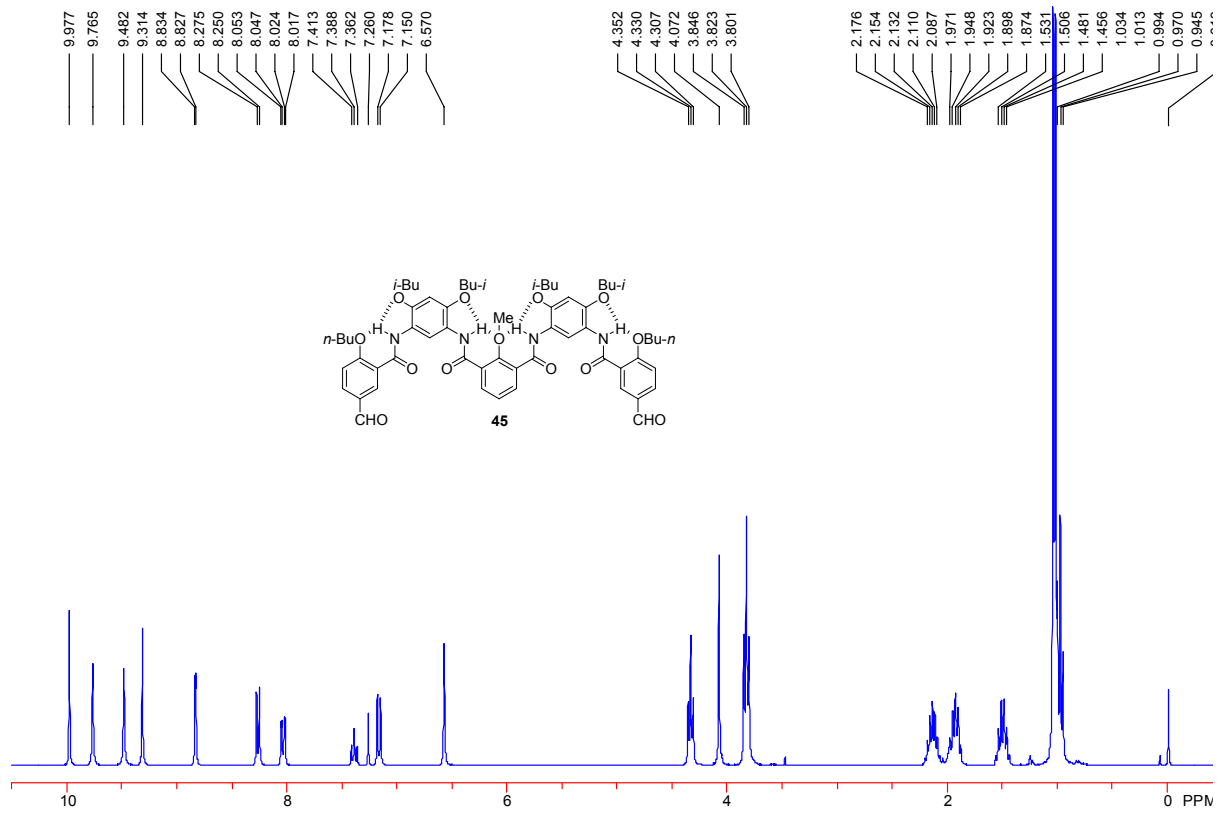

Figure S31. ^{1}H NMR spectrum of **45** (300 MHz) in $CDCl_3$ (15 mM).

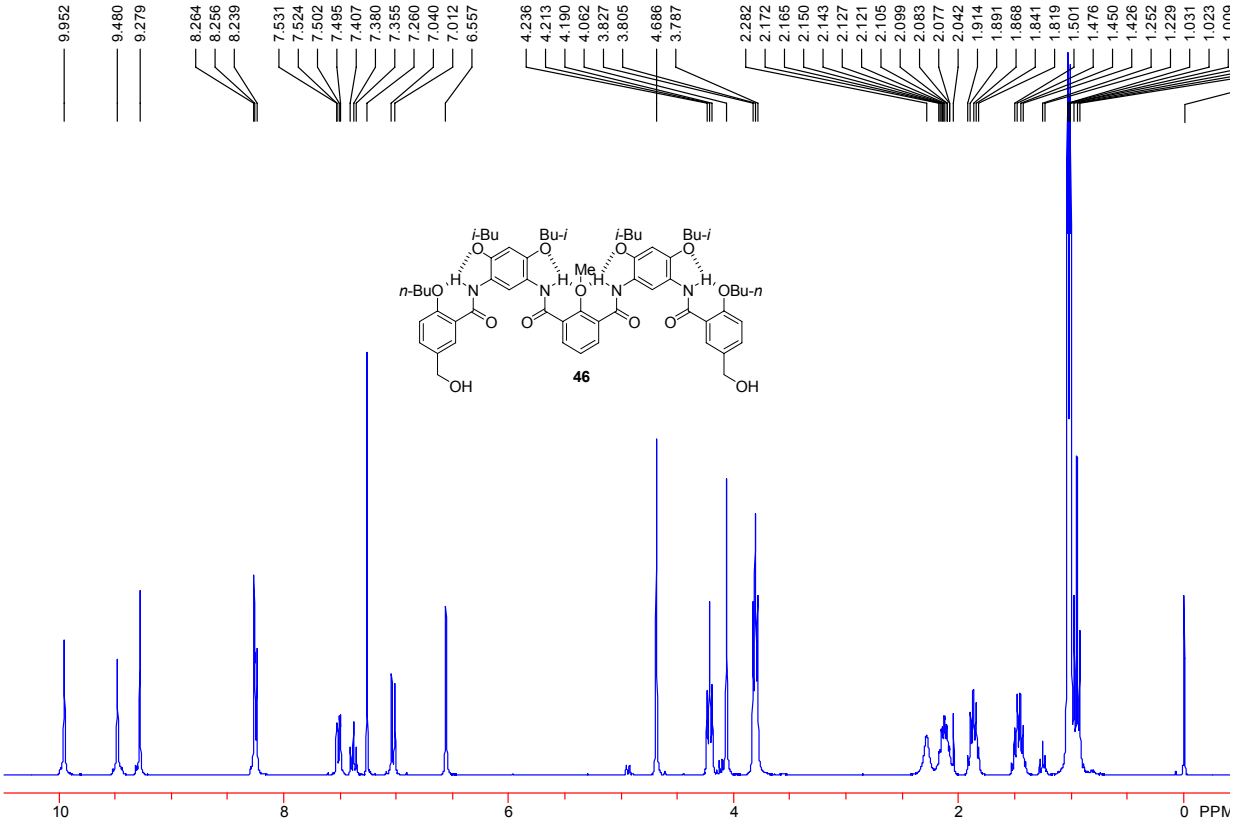

Figure S32. ^{1}H NMR spectrum of **46** (300 MHz) in $CDCl_3$ (5 mM).

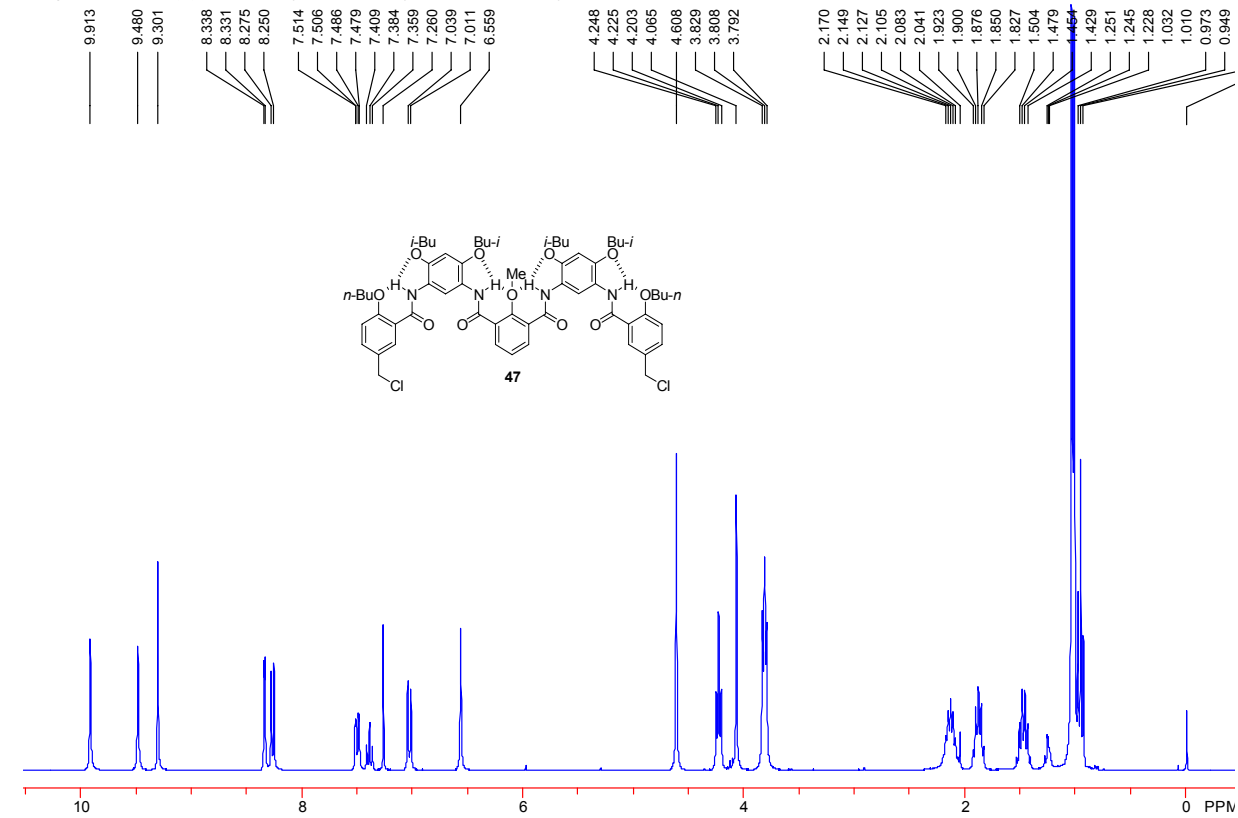

Figure S33. ^{1}H NMR spectrum of **47** (300 MHz) in $CDCl_3$ (10 mM).

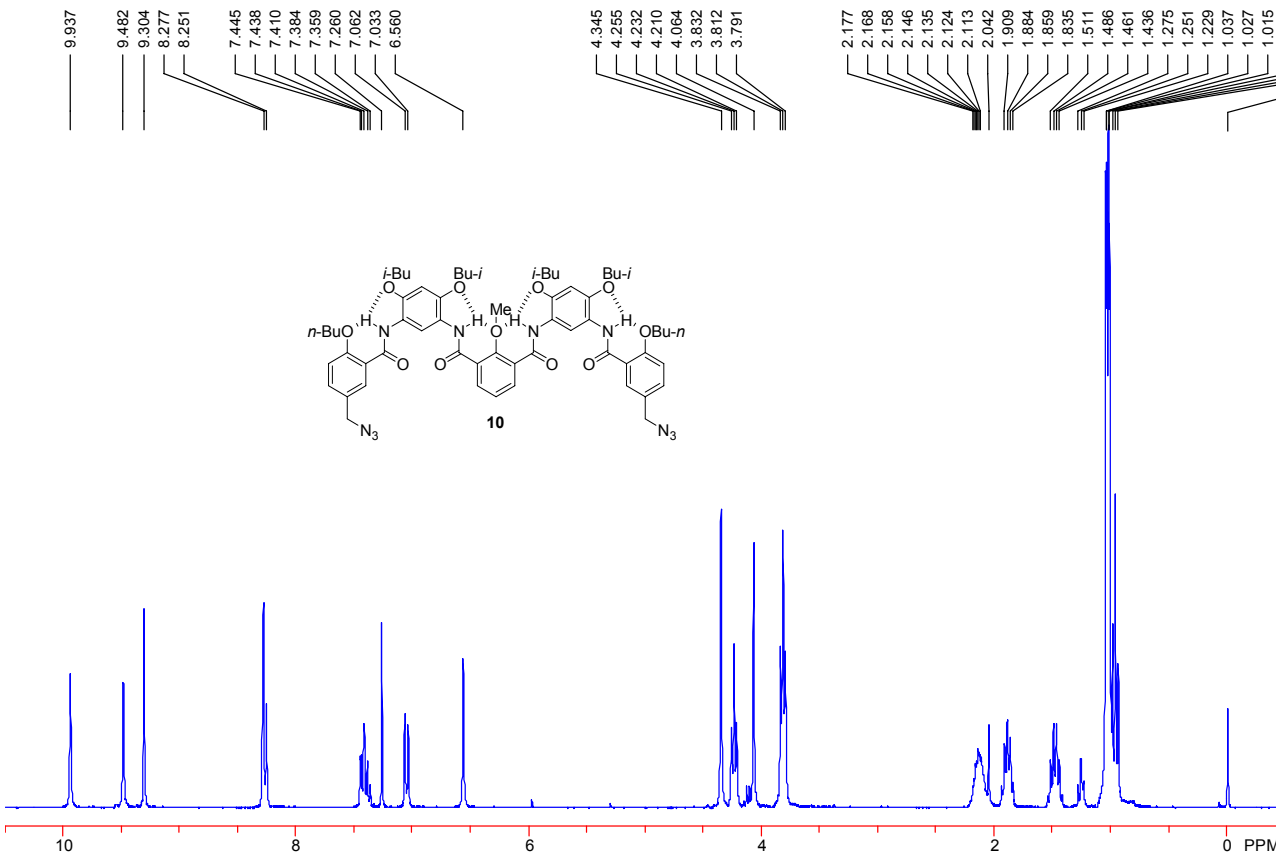

Figure S34. ^{1}H NMR spectrum of **10** (300 MHz) in $CDCl_3$ (10 mM).

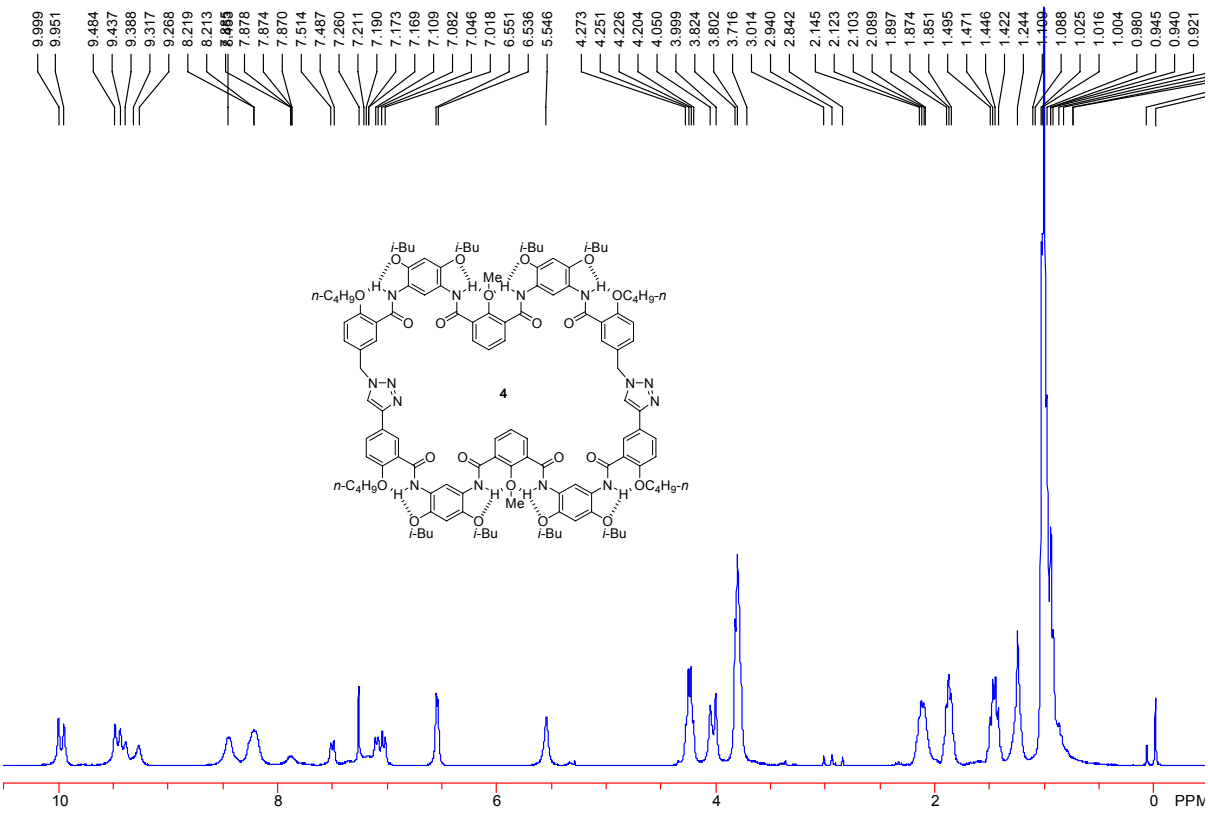

Figure S35. ^{1}H NMR spectrum of **4** (300 MHz) in $CDCl_3$ (10 mM).

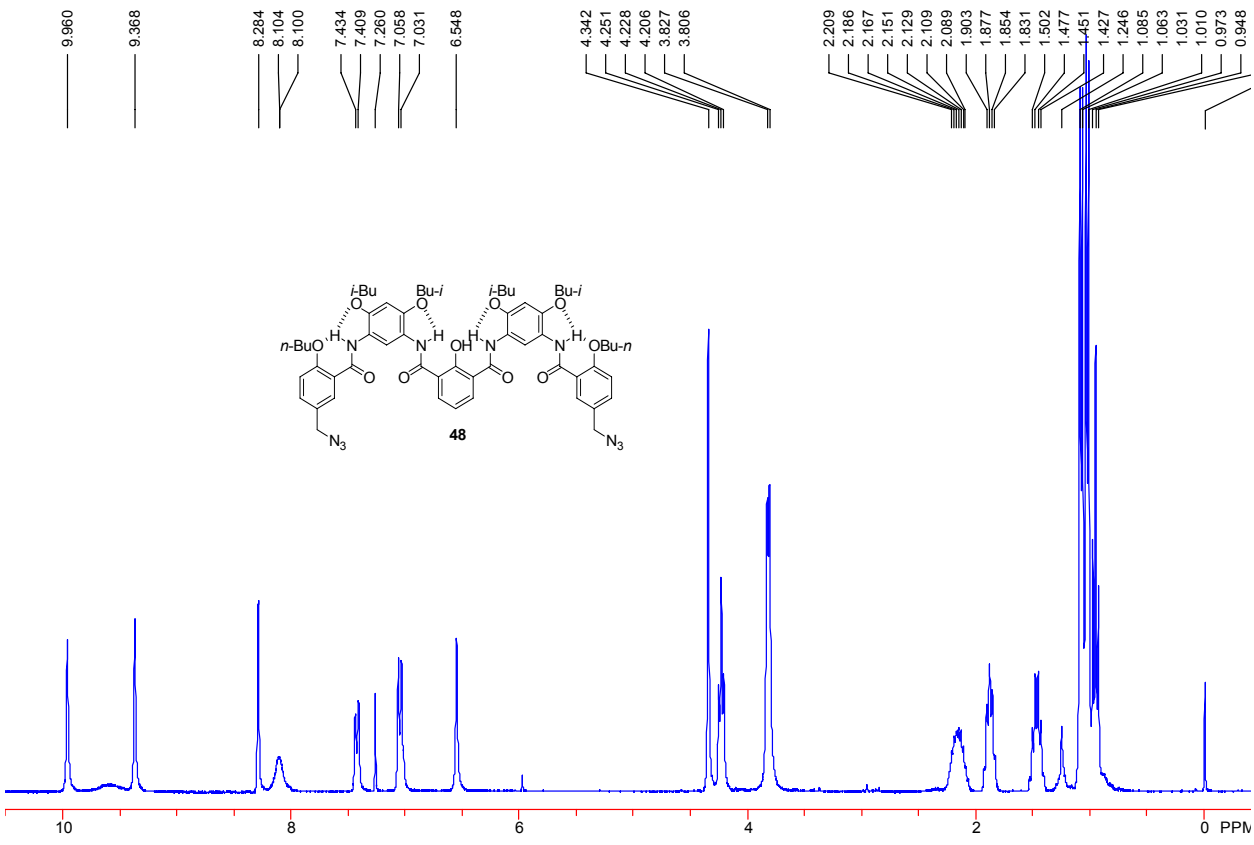

Figure S36. ^{1}H NMR spectrum of **48** (300 MHz) in $CDCl_3$ (10 mM).