

Supporting Information

Intramolecularly H-Bonded Aromatic Pentamers as Modularly Tunable Macrocyclic Receptors for Selective Recognition of Metal Ions

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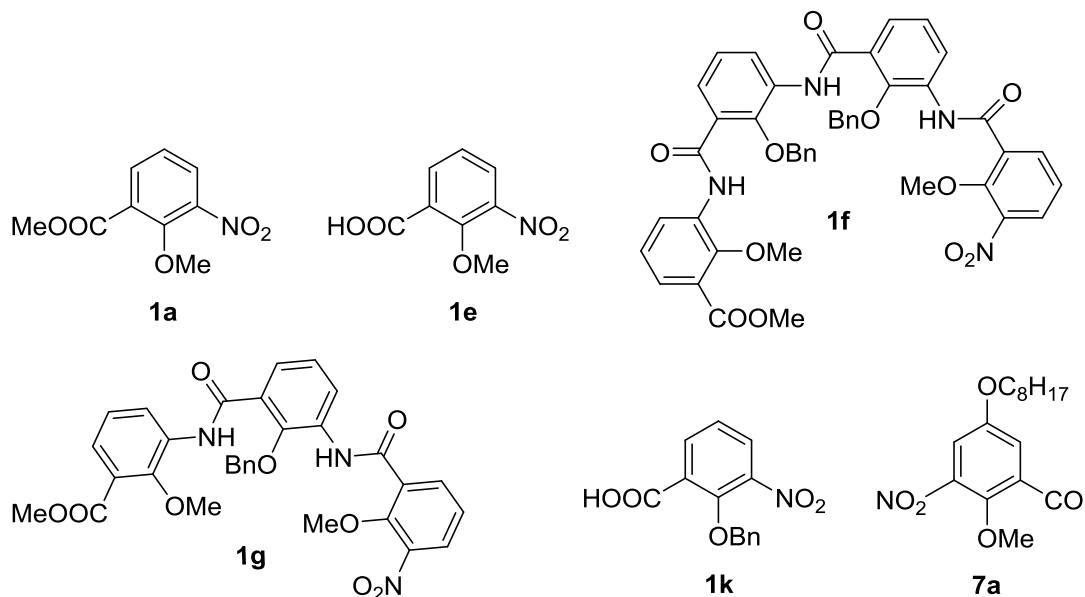
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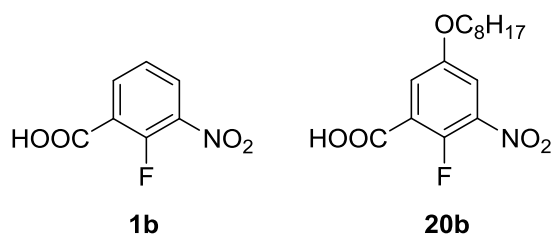
General remarks

All the reagents were obtained from commercial suppliers and used as received unless otherwise noted. Aqueous solutions were prepared from distilled water. The organic solutions from all liquid extractions were dried over anhydrous Na_2SO_4 for a minimum of 15 minutes before filtration. Reactions were monitored by thin-layer chromatography (TLC) on silica gel pre-coated glass plate (0.225 mm thickness, 60F-254, E. Merck). Flash column chromatography was performed using pre-coated 0.2 mm silica plates from Selecto Scientific. Chemical yields refer to pure isolated substances. Mass spectra were obtained using the Instrumentation includes Finnigan MAT95XL-T and Micromass VG7035. ^1H NMR spectra were recorded on Bruker ACF300 (300 MHz) and ACF500 (500 MHz) spectrometers. In addition, key compounds were characterized by X-ray Diffraction. The solvent signal of CDCl_3 was referenced at $\delta = 7.26$ ppm, and $\text{DMSO}-d_6$ at 2.50 ppm. Coupling constants (J values) are reported in Hertz (Hz). ^1H NMR data are recorded in the order: chemical shift value, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons that gave rise to the signal and coupling constant, where applicable. ^{13}C spectra were proton-decoupled and recorded on Bruker ACF300 (300 MHz) and ACF500 spectrometers (500 MHz). The solvent, CDCl_3 was referenced at 77 ppm and $\text{DMSO}-d_6$ at 39.5 ppm. CDCl_3 (99.8% deuterated) was purchased from Aldrich and used without further purification.

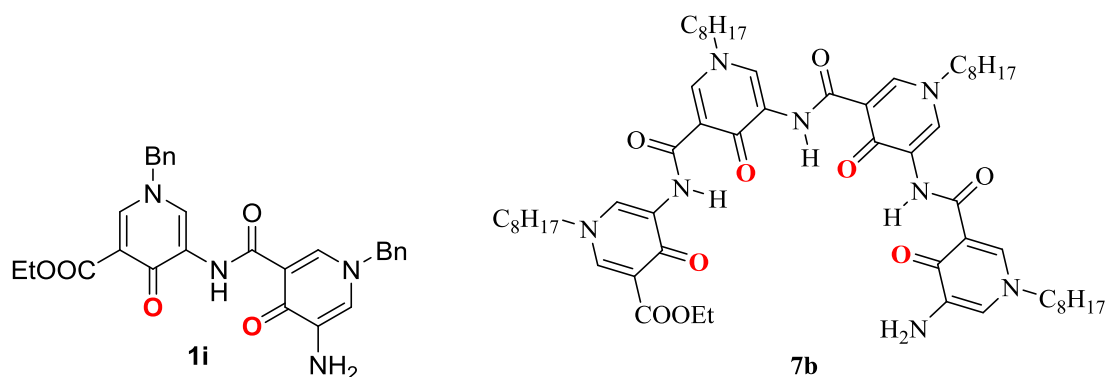
The synthetic procedures for compounds **1a**, **1e**, **1f**, **1g**, **1k** and **7a** can be found from our previous publication (Qin, B. *et al.* Persistently folded circular aromatic amide pentamers containing modularly tunable cation-binding cavities with high ion selectivity. *J. Am. Chem. Soc.* **2010**, *132*, 9564-9566).

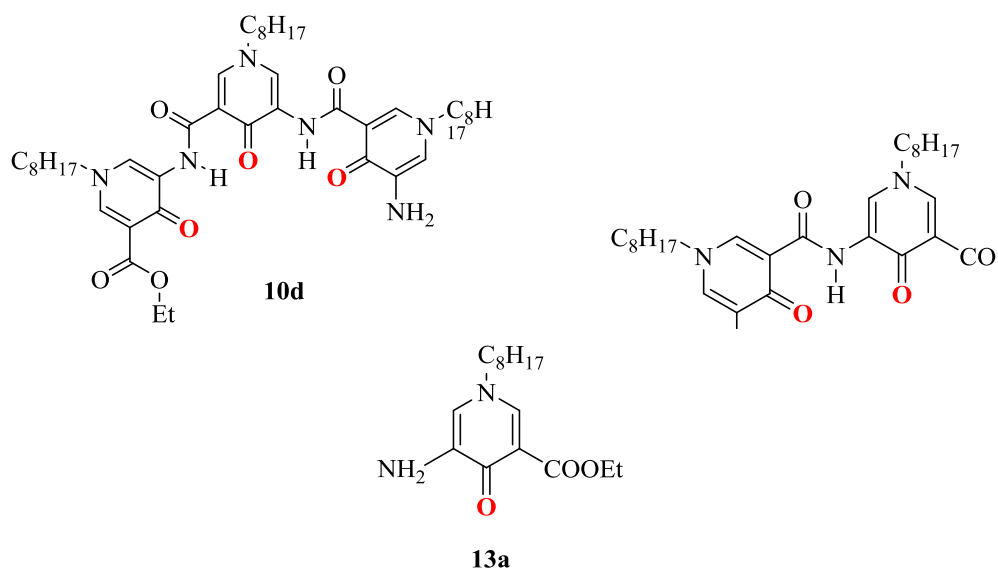


The synthetic procedures for **1b** and **20b** can be found from our previous publication (Ren, C. L. *et al.* Crystallographic realization of the mathematically predicted densest “All Pentamer” packing lattice by C5-symmetric “sticky” fluoropentamers. *Angew. Chem., Int. Ed.* **2011**, *50*, 10612-10615).

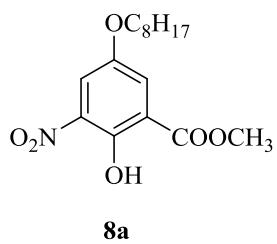


The synthetic procedures for **1i**, **7b**, **10d**, **11f** and **13a** can be found from our previous publication (Ren, C. L. *et al.* Fivefold-symmetric macrocyclic aromatic pentamers: High affinity cation recognition, ion-pair induced columnar stacking and nanofibrillation. *J. Am. Chem. Soc.* **2011**, *133*, 13930-13933).

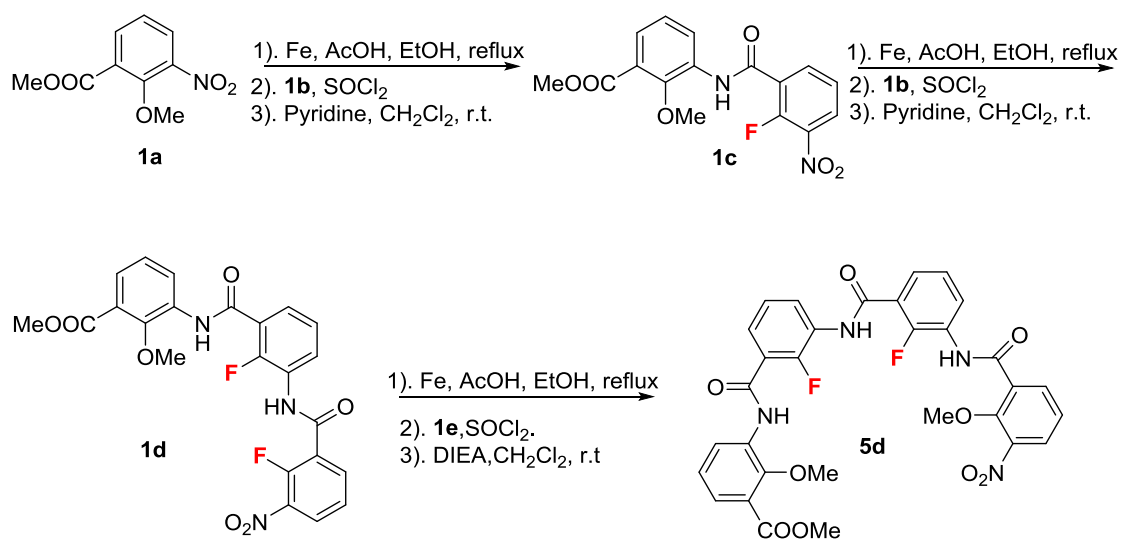




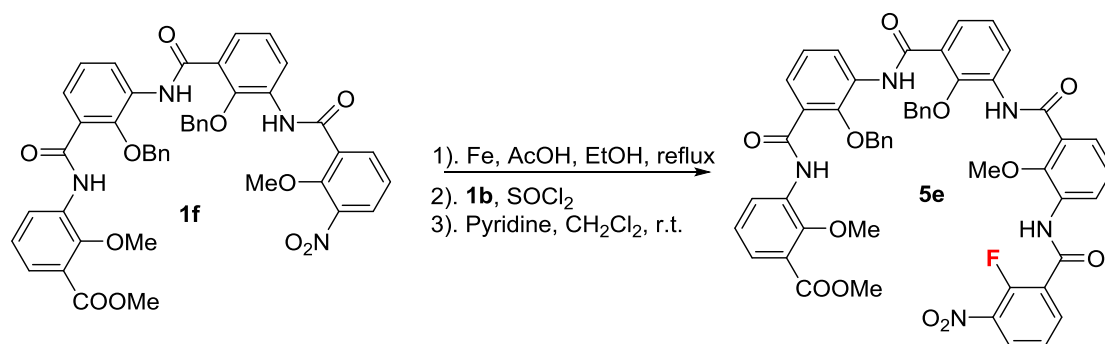
The synthetic procedure of **8a** can be found from our previous publication (Y. Yan et al. Helical Organization in Foldable Aromatic Oligoamides by a Continuous Hydrogen-Bonding Network. *Org. Lett.* **2009**, *11*, 1201-1204).



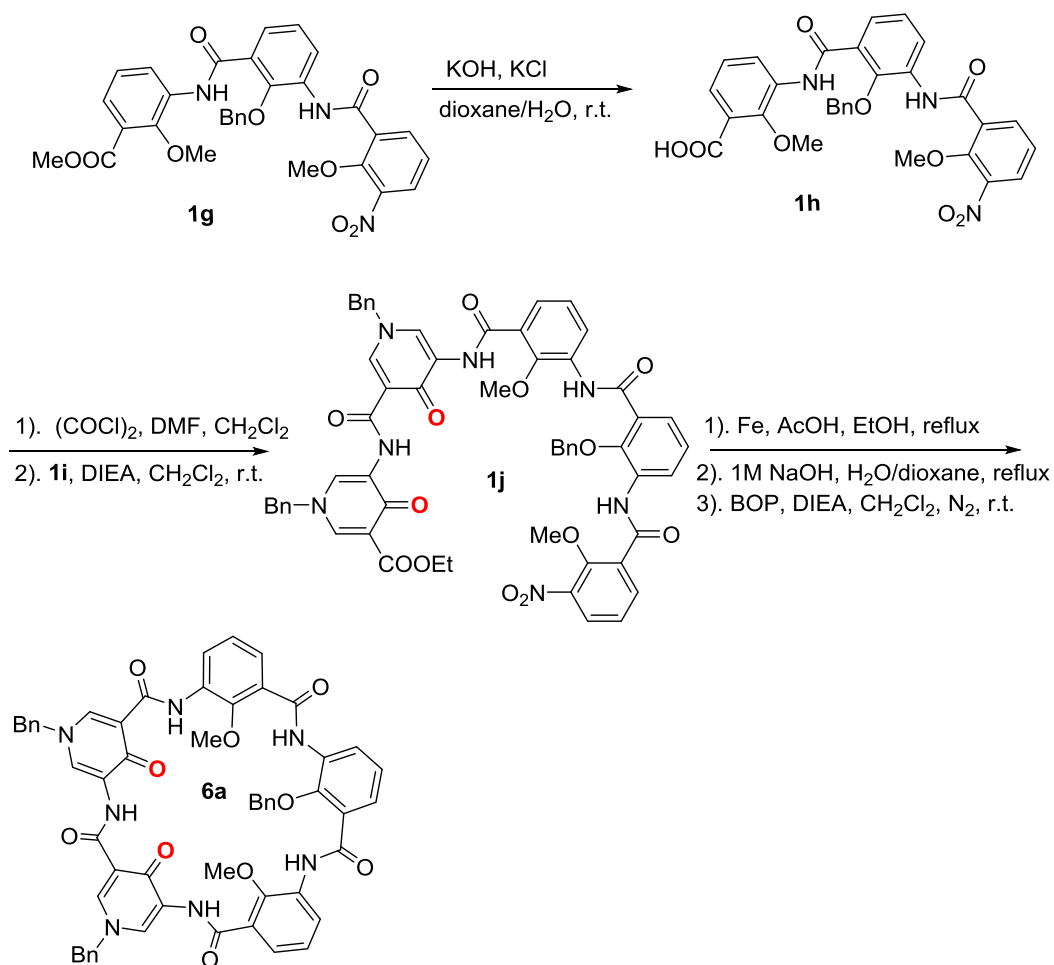
Scheme S1a: Synthesis of Compound 5d



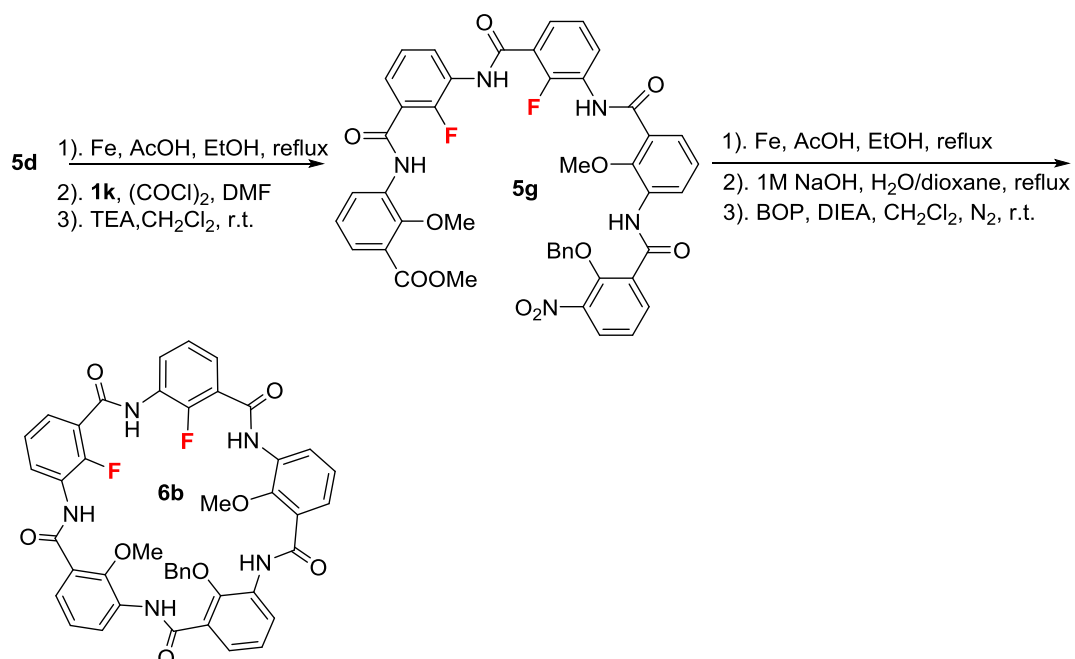
Scheme S1b: Synthesis of Compound 5e



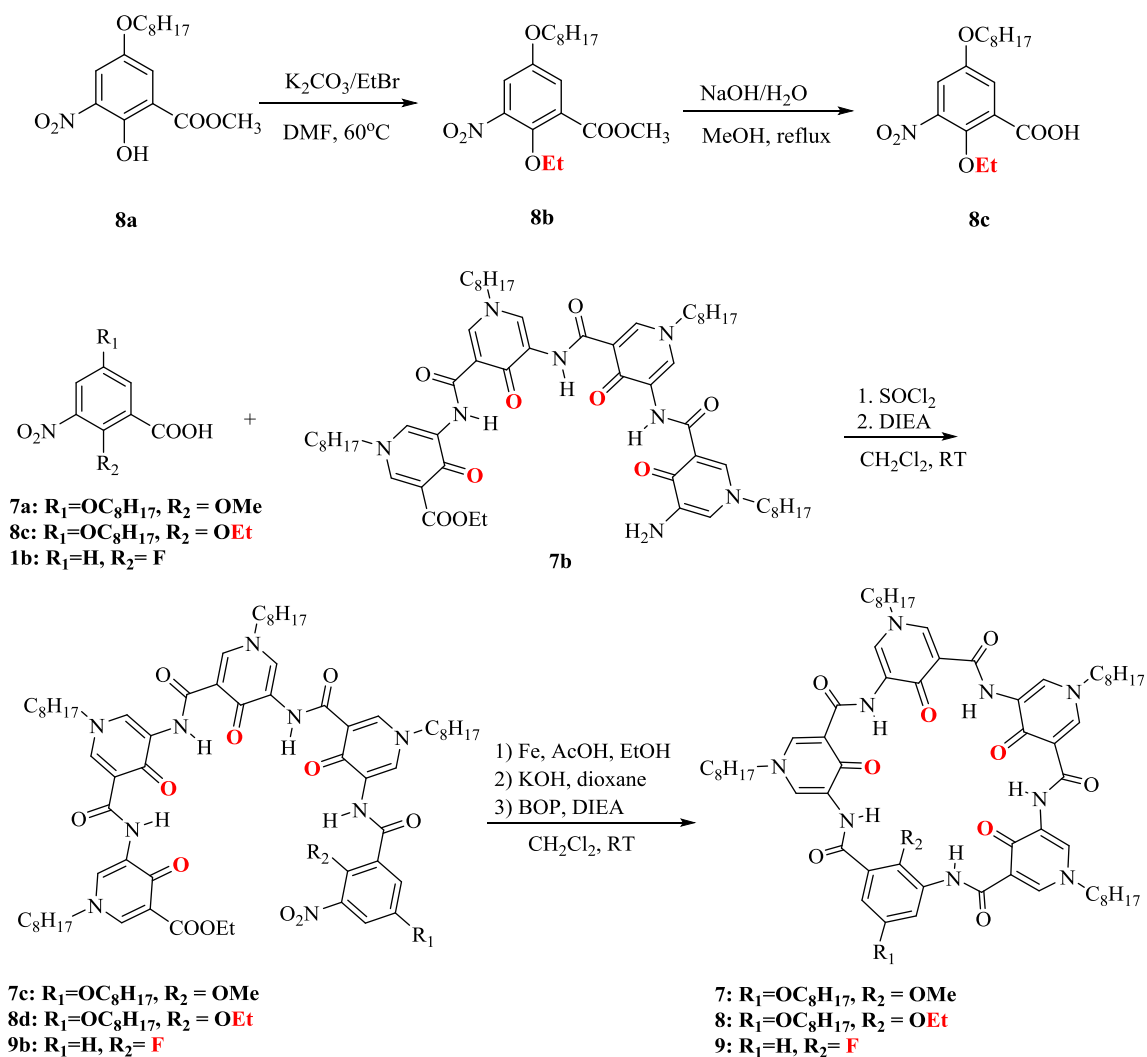
Scheme S1c: Synthesis of Compound 6a



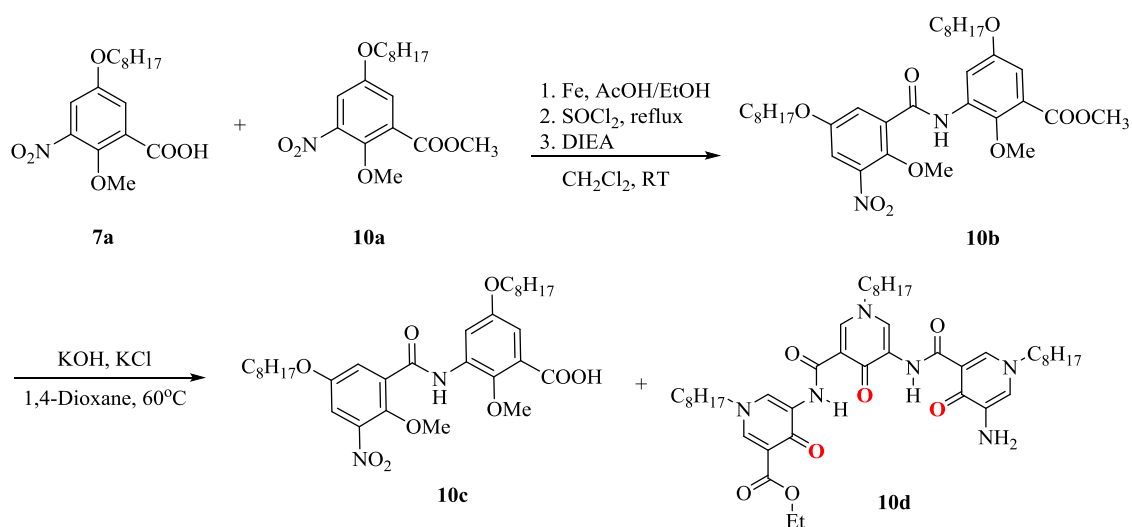
Scheme S1d: Synthesis of Compound 6b

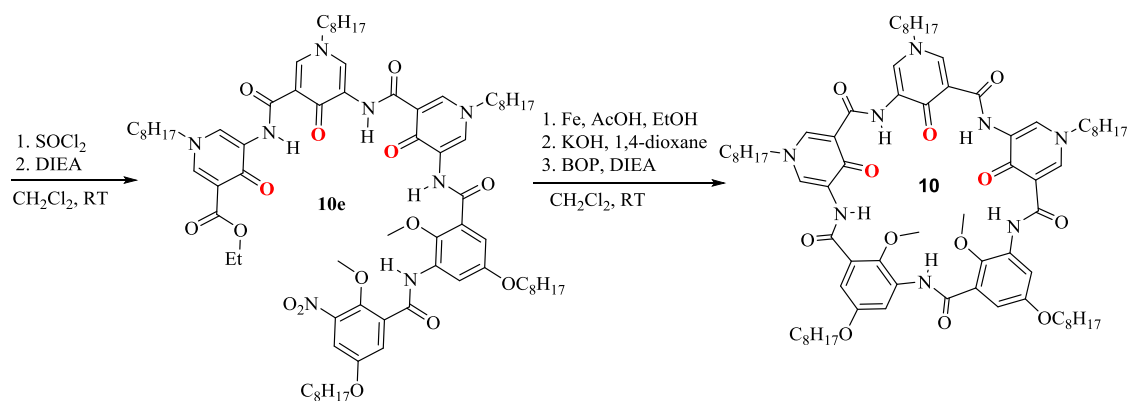


Scheme S1e: Synthesis of Compounds 7, 8 and 9

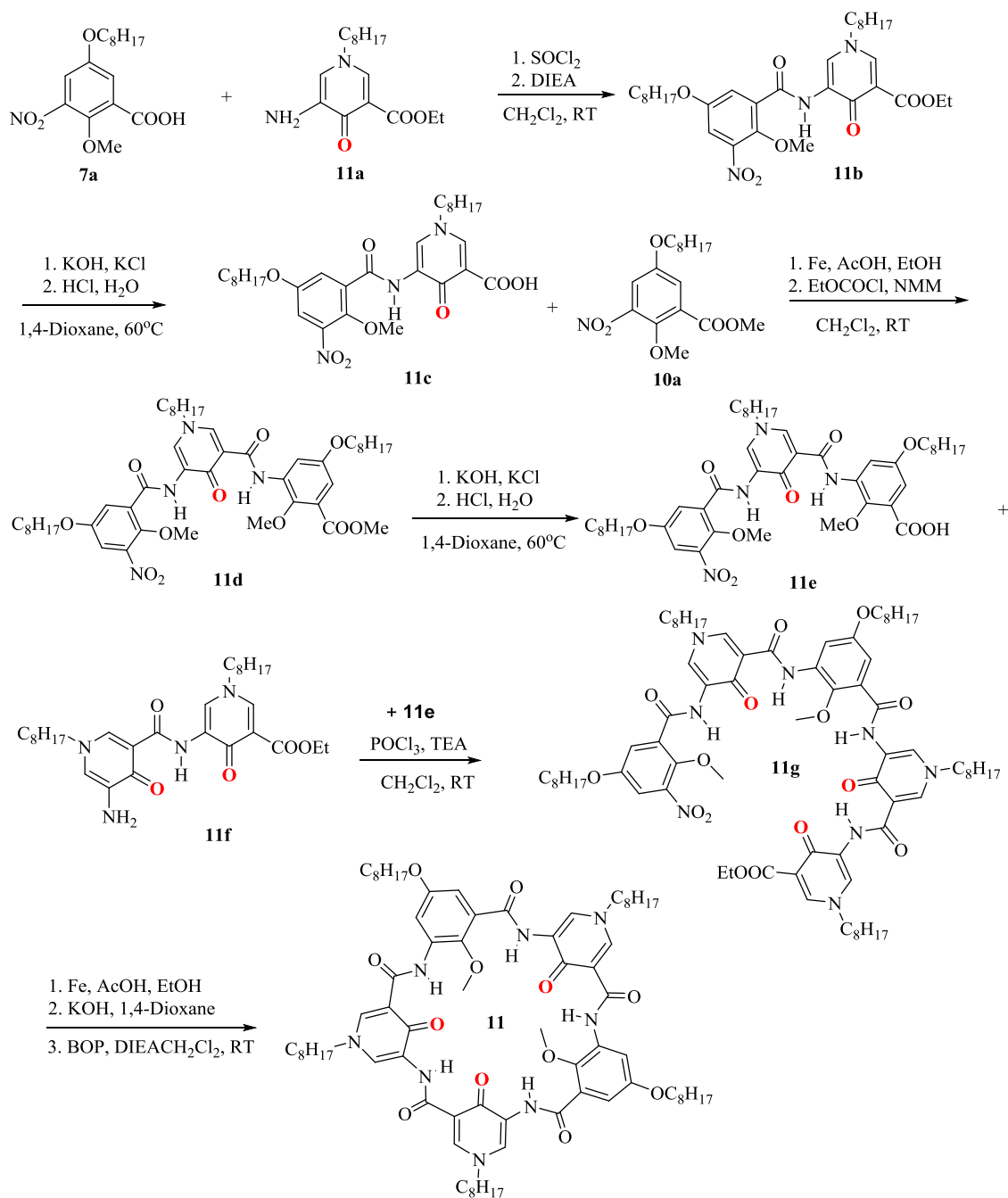


Scheme S1f: Synthesis of Compound 10

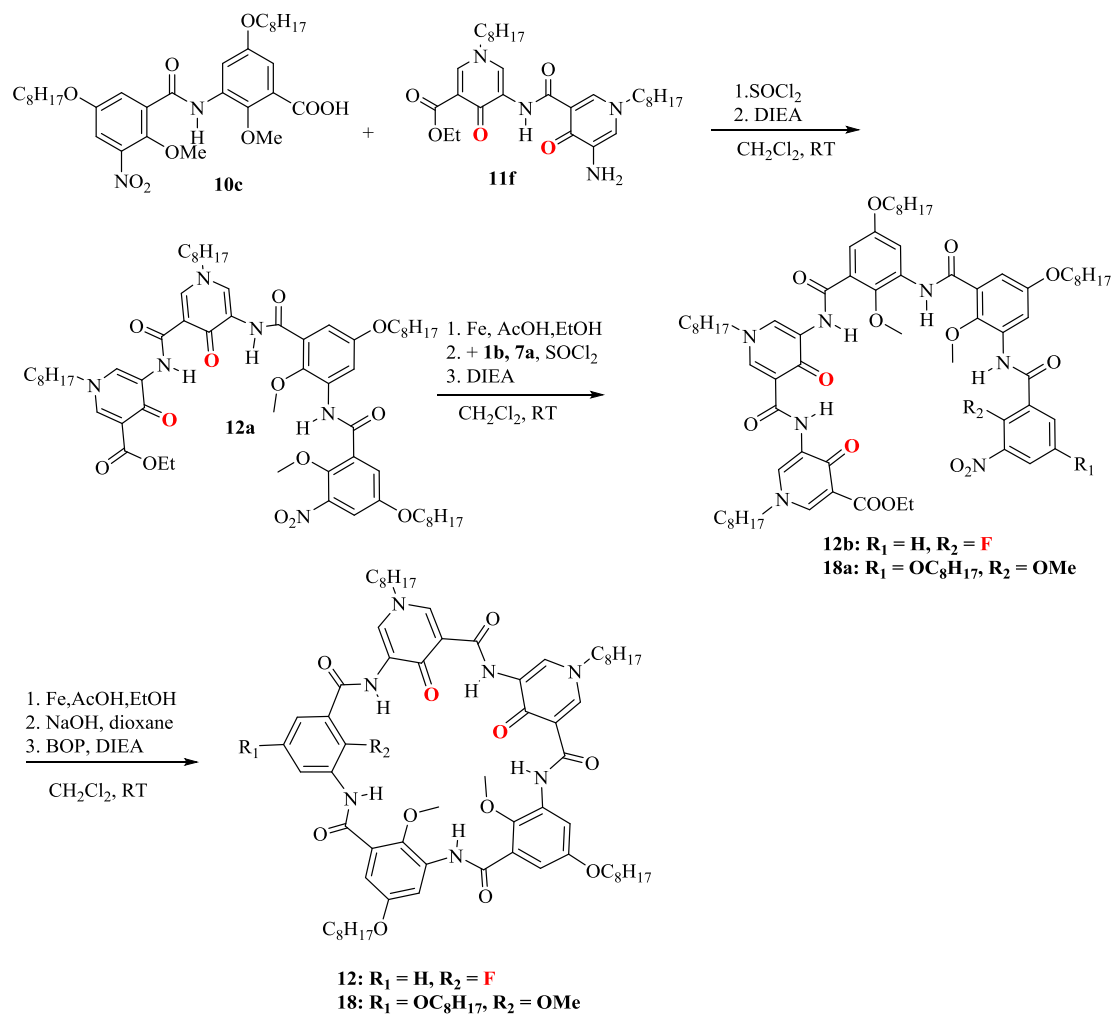




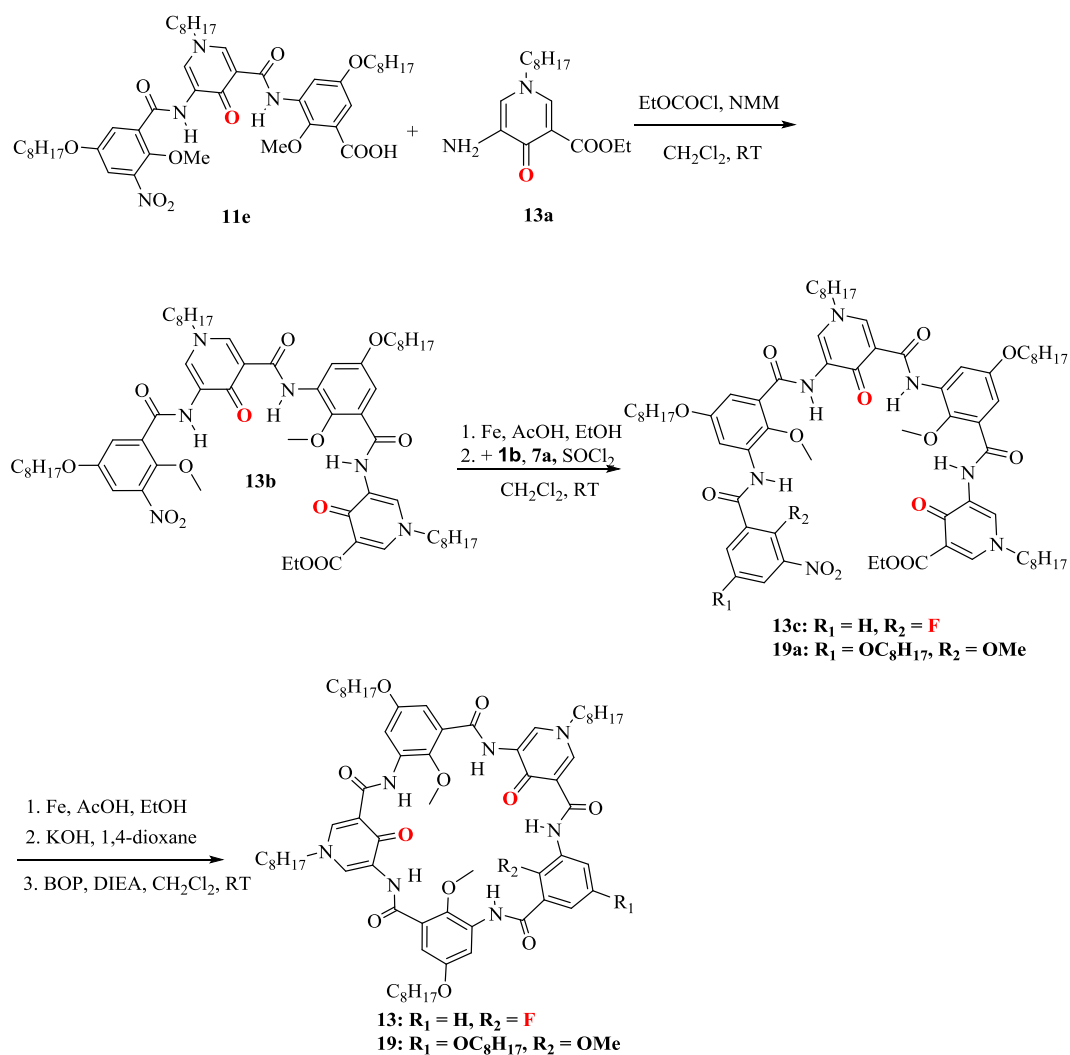
Scheme S1g: Synthesis of Compound 11



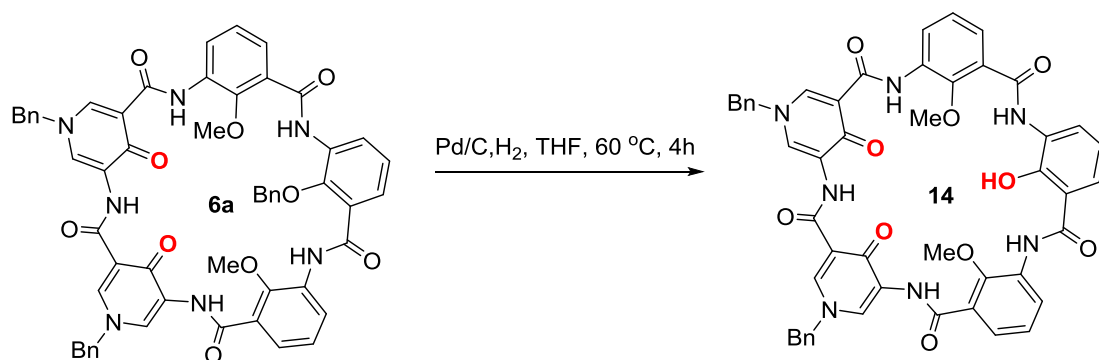
Scheme S1h: Synthetic Route that Affords Pentamers **12 & **18**.**



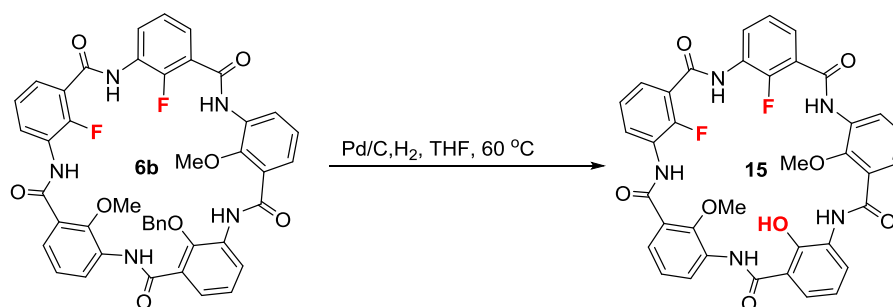
Scheme S1i: Synthetic Route that Affords Pentamers **13 & **19**.**



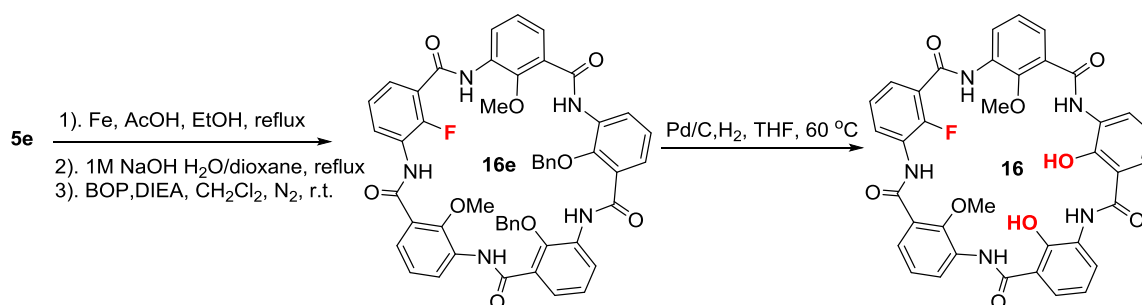
Scheme S1j: Synthetic Route that Affords Pentamer **14.**



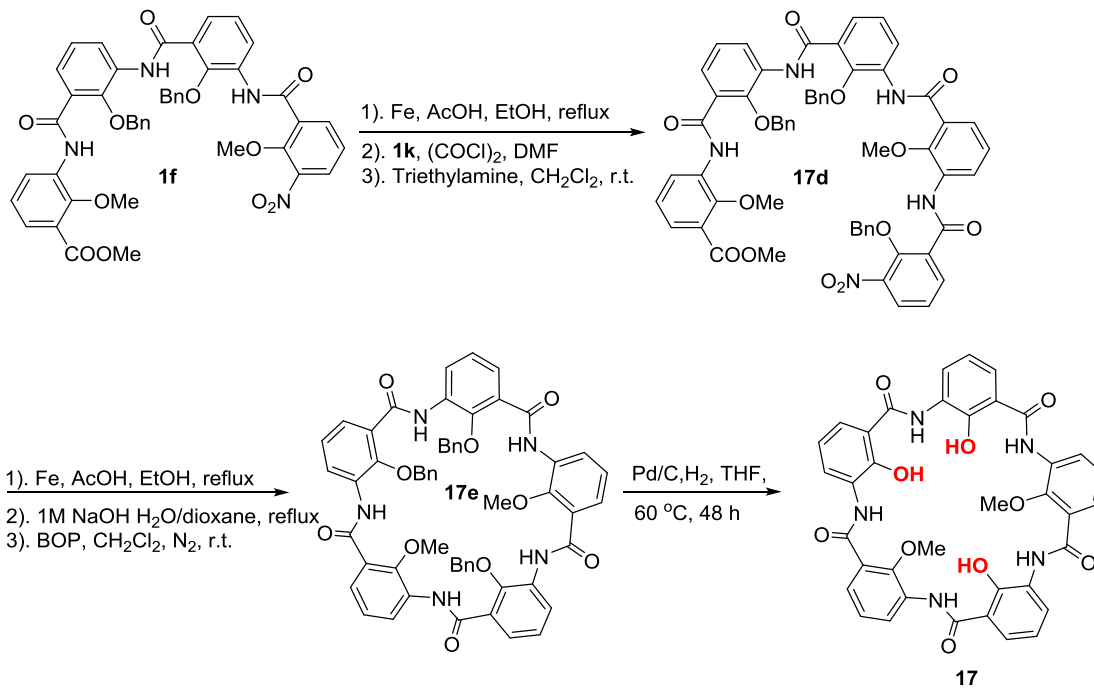
Scheme S1k: Synthetic Route that Affords Pentamer **15**.



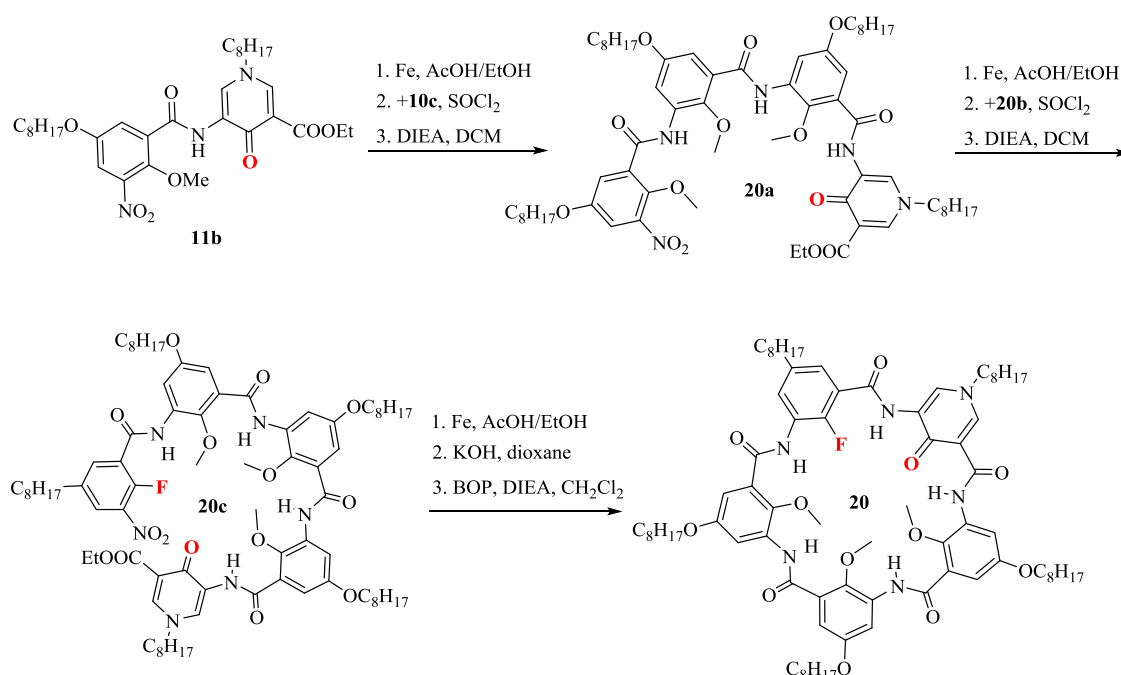
Scheme S1l: Synthetic Route that Affords Pentamer **16**.



Scheme S1m: Synthetic Route that Affords Pentamer **17**.

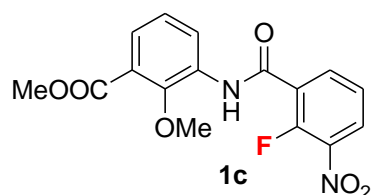


Scheme S1n: Synthetic Route that Affords Pentamer **20**.



Synthetic Procedures and Characterizations

Methyl 3-(2-fluoro-3-nitrobenzamido)-2-methoxybenzoate (**1c**)



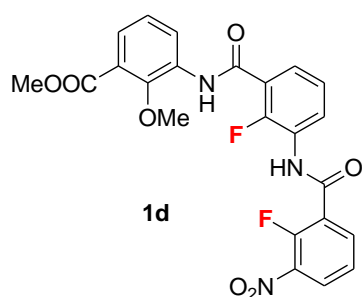
To a solution of **1a** (2.11 g, 10 mmol) and iron (2.24 g, 40 mmol) in EtOH (100 mL) was added acetate acid (10 mL).

The reaction was refluxed for 2 hours at room temperature.

After cooling, the solvent was removed and the residue was dissolved with CH₂Cl₂ and washed with water and Brine. The organic layer was dried over Na₂SO₄. Removal of the solvent gave the amine product used for the next step reaction without further purification. **1b** (2.04 g, 11.0mmol) was dissolved in SOCl₂ (5.5 mL) at room temperature. The reaction mixture was reflux for 2 hours at room temperature, then the excess SOCl₂ was removed in *vacuo* to produce the chloride compound. A solution of amine (1.81 g, 10 mmol) and pyridine (2.0 mL, 25 mmol) in CH₂Cl₂ (75 mL) was added. The reaction mixture was allowed to stir continuously overnight at room temperature. The reaction mixture was washed with 1 M HCl (50 mL), followed by saturated NaCl (100 mL). Drying over

Na₂SO₄ and removal of solvent in *vacuo* gave the crude product, which was recrystallized from methanol to give the pure product **1c** as a white solid. Yield: 2.96 g, 85%. ¹H NMR (500 MHz, CDCl₃): δ 9.25 (d, 1H, *J* = 12.7 Hz), 8.71 (d, 1H, *J* = 8.2 Hz), 8.45 (td, 1H, *J* = 9, 1.5 Hz), 8.22 (td, 1H, *J* = 9, 1.5 Hz), 7.65 (dd, 1H, *J* = 7.9, 1.5 Hz), 7.49 (t, 1H, *J* = 8.0 Hz), 7.22 (t, 1H, *J* = 8.1 Hz), 3.97 (s, 3H), 3.95 (s, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 165.70, 159.23, 154.25, 152.10, 149.42, 137.54, 132.22, 129.45, 127.00, 125.07, 125.01, 124.56, 124.32, 123.55, 62.63, 52.37. MS-ESI: calculated for [M]⁺ (C₁₆H₁₂FN₂O₆): *m/z* 347.0685, found: *m/z* 347.0680.

Methyl 3-(2-fluoro-3-(2-fluoro-3-nitrobenzamido)benzamido)-2-methoxybenzoate (1d)

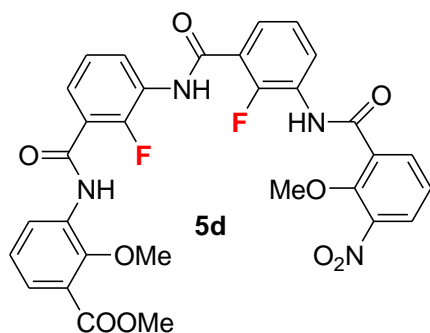


To a solution of **1c** (0.7 g, 2 mmol) and iron (0.45 g, 8 mmol) in EtOH (20 mL) was added acetate acid (2 mL). The reaction was refluxed for 2 hours at room temperature. After cooling, the solvent was removed and the residue was dissolved with CH₂Cl₂ and washed with water and Brine.

The organic layer was dried over Na₂SO₄. Removal of the solvent gave the amine product used for the next step reaction without further purification. **1b** (0.41 g, 2.2mmol) was dissolved in SOCl₂ (2 mL) at room temperature. The reaction mixture was reflux for 2 hours at room temperature, then the excess SOCl₂ was removed in *vacuo* to produce the chloride compound. A solution of amine (0.64 g, 2 mmol) and pyridine (0.4 mL, 5 mmol) in CH₂Cl₂ (20 mL) was added. The reaction mixture was allowed to stir continuously overnight at room temperature. The reaction mixture was washed with 1 M HCl (10 mL), followed by saturated NaCl (20 mL). Drying over Na₂SO₄ and removal of solvent in *vacuo* gave the crude product, which was recrystallized from methanol to give the pure product **1d** as a white solid. Yield: 0.65 g, 67%. ¹H NMR (500 MHz, CDCl₃): δ 9.20 (d, 1H, *J* = 13.1 Hz), 8.73 (dd, 1H, *J* = 8.1, 1.1 Hz), 8.69 (d, 1H, *J* = 12.6 Hz), 8.58 (t, 1H, *J* = 7.3 Hz), 8.50 – 8.40 (m, 1H), 8.31 – 8.20 (m, 1H), 7.93 (td, 1H, *J* = 7.8, 1.4 Hz), 7.62 (dd, 1H, *J* = 7.9, 1.5 Hz), 7.51 (t, 1H, *J* = 8.0 Hz), 7.38 (t, 1H, *J* = 8.0 Hz), 7.21 (t, 1H, *J* = 8.0 Hz), 3.95 (s, 3H), 3.94 (s, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 165.88, 160.64, 159.47, 154.22, 152.10, 149.16, 137.49,

132.43, 129.82, 127.46, 126.59, 126.39, 126.12, 125.35, 125.31, 125.23, 125.17, 124.62, 124.36, 123.79, 123.47, 62.55, 52.35. MS-ESI: calculated for $[M]^-$ ($C_{23}H_{16}F_2N_3O_7$): m/z 484.0950, found: m/z 484.0958.

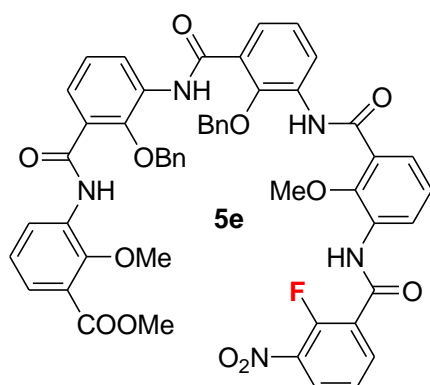
Methyl 3-(2-fluoro-3-(2-fluoro-3-(2-methoxy-3-nitrobenzamido)benzamido)benz amido)-2-methoxybenzoate (5d)



To a solution of **1d** (0.97 g, 2 mmol) and iron (0.45 g, 8 mmol) in EtOH/THF (20 mL/10 mL) was added acetate acid (2 mL). The reaction was refluxed for 2 hours at room temperature. After cooling, the solvent was removed and the residue was dissolved with CH_2Cl_2 and washed with water and Brine. The organic

layer was dried over Na_2SO_4 . Removal of the solvent gave the amine product used for the next step reaction without further purification. Compound **1e** (0.43 g, 2.2mmol) was dissolved in $SOCl_2$ (2 mL) at room temperature. The reaction mixture was reflux for 2 hours at room temperature, then the excess $SOCl_2$ was removed in *vacuo* to produce the chloride compound. A solution of amine (0.91 g, 2 mmol) and DIEA (0.81 mL, 5 mmol) in CH_2Cl_2 (20 mL) was added. The reaction mixture was allowed to stir continuously overnight at room temperature. The reaction mixture was washed with 1 M HCl (10 mL), followed by saturated NaCl (20 mL). Drying over Na_2SO_4 and removal of solvent in *vacuo* gave the crude product, which was recrystallized from methanol to give the pure product **5d** as a white solid. Yield: 0.89 g, 70%. 1H NMR (500 MHz, $CDCl_3$): δ 9.97 (s, 1H), 9.17 (d, 1H, $J = 12.8$ Hz), 8.74 (d, 1H, $J = 8.1$ Hz), 8.71 – 8.67 (m, 1H), 8.67 – 8.62 (m, 2H), 8.44 (dd, 1H, $J = 7.9, 1.7$ Hz), 8.03 (dd, 1H, $J = 8.0, 1.7$ Hz), 7.89 (t, 2H, $J = 7.4$ Hz), 7.62 (dd, 1H, $J = 7.9, 1.5$ Hz), 7.44 (t, 1H, $J = 8.0$ Hz), 7.38 (dt, 2H, $J = 10.9, 8.1$ Hz), 7.22 (t, 1H, $J = 8.0$ Hz), 4.14 (s, 3H), 3.94 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.81, 161.54, 161.06, 160.85, 151.41, 149.27, 144.31, 136.58, 132.59, 129.24, 128.51, 126.82, 126.74, 126.68, 126.60, 126.51, 126.24, 125.51, 125.48, 125.33, 125.29, 125.13, 124.74, 124.41, 123.52, 121.71, 121.62, 121.24, 121.15, 64.49, 62.50, 52.37. MS-ESI: calculated for $[M]^-$ ($C_{31}H_{23}F_2N_3O_9$): m/z 633.1439, found: m/z 633.1446.

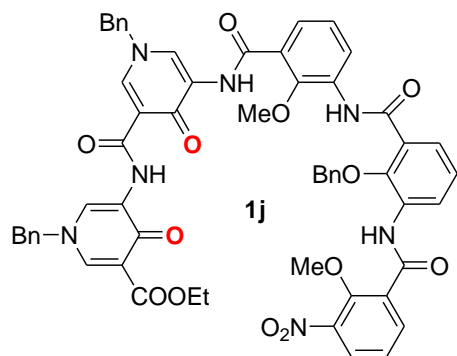
Methyl 3-(2-(benzyloxy)-3-(2-(benzyloxy)-3-(3-(2-fluoro-3-nitrobenzamido)-2-methoxybenzamido)benzamido)benzamido)-2-methoxybenzoate (5e)



To a solution of **1f** (1.62 g, 2 mmol) and iron (0.45 g, 8 mmol) in EtOH/THF (20 mL/10 mL) was added acetate acid (2 mL). The reaction was refluxed for 2 hours at room temperature. After cooling, the solvent was removed and the residue was dissolved in CH₂Cl₂ and washed with water and Brine. The organic layer was dried over Na₂SO₄. Removal of the solvent gave

the amine product used for the next step reaction without further purification. **1b** (0.41 g, 2.2mmol) was dissolved in SOCl₂ (2 mL) at room temperature. The reaction mixture was reflux for 2 hours at room temperature, then the excess SOCl₂ was removed in *vacuo* to produce the chloride compound. A solution of amine (0.64 g, 2 mmol) and pyridine (0.4 mL, 5 mmol) in CH₂Cl₂ (20 mL) was added. The reaction mixture was allowed to stir continuously overnight at room temperature. The reaction mixture was washed with 1 M HCl (10 mL), followed by saturated NaCl (20 mL). Drying over Na₂SO₄ and removal of solvent in *vacuo* gave the crude product, which was recrystallized from methanol to give the pure product **5e** as a white solid. Yield: 1.0 g, 54%. ¹H NMR (500 MHz, CDCl₃): δ 9.85 (s, 1H), 9.68 (s, 1H), 9.33 (s, 1H), 8.93 (d, 1H, *J* = 12.9 Hz), 8.78 (d, 1H, *J* = 8.1 Hz), 8.74 (d, 1H, *J* = 8.1 Hz), 8.67 (t, 2H, *J* = 7.2 Hz), 8.50 (t, 1H, *J* = 7.1 Hz), 8.25 (t, 1H, *J* = 7.5 Hz), 7.82 (t, 2H, *J* = 6.8 Hz), 7.63 (d, 1H, *J* = 7.8 Hz), 7.58 (d, 1H, *J* = 7.8 Hz), 7.54 (t, 1H, *J* = 8.0 Hz), 7.41 – 7.29 (m, 3H), 7.21 – 7.18 (m, 3H), 7.12 – 7.06 (m, 5H), 6.99 – 6.93 (m, 3H), 4.92 (s, 2H), 4.88 (s, 2H), 3.87 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 165.93, 163.56, 163.49, 162.96, 159.35, 154.15, 152.07, 149.38, 147.32, 146.06, 145.83, 138.25, 137.69, 134.80, 134.59, 132.80, 132.50, 132.45, 131.29, 129.71, 128.99, 128.94, 128.91, 128.67, 128.56, 128.41, 127.79, 127.57, 127.16, 126.72, 126.26, 125.94, 125.71, 125.68, 125.59, 125.36, 125.32, 125.11, 124.73, 124.61, 124.48, 124.20, 124.05, 123.38, 78.85, 78.79, 62.79, 62.19, 52.20. HRMS-ESI: calculated for [M]⁺ (C₅₂H₄₂FN₅O₁₂): *m/z* 946.2741, found: *m/z* 946.2711.

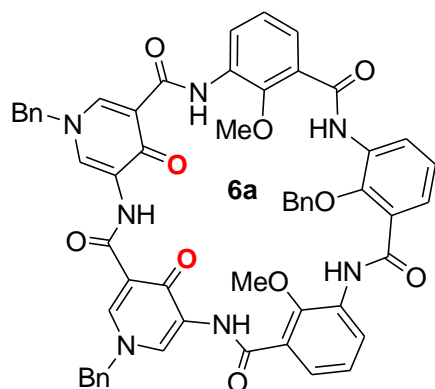
Ethyl 1-benzyl-5-(1-benzyl-5-(3-(2-(benzyloxy)-3-(2-methoxy-3-nitrobenzamido)benzamido)-2-methoxybenzamido)-4-oxo-1,4-dihydropyridine-3-carboxamido)-4-oxo-1,4-dihydropyridine-3-carboxylate (1j)



Compound **1g** (1.35 g, 2.3 mmol) was dissolved in dioxane and H₂O (100 mL, v/v 1/1) mixed solution to which 1 M KOH (4.6 mL) and KCl (3.4 g, 46 mmol) were added. The reaction was stirred at room temperature for 12 hours at room temperature, then 1 M HCl was added to neutralize the mixture to pH 3. The mixture was extracted with CH₂Cl₂ three times

(3 x 100 mL). The organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure to produce the acid product **1h**. The acid (131 mg, 0.23 mmol) was dissolved in SOCl₂ (2 mL) and stirred for 2 hours at room temperature, under reflux. Then the excess SOCl₂ was removed in *vacuo* to produce the chloride product. To the solution of chloride product in dry CH₂Cl₂ were added **1i** and DIEA (0.16 mL, 0.93 mmol). The reaction was allowed to proceed for 12 hours at room temperature. After washing with HCl solution, aqueous sat. NaHCO₃ and Brine, the organic layer was dried over Na₂SO₄. The residue was recrystallized from methanol to give the pure product **1j** as a white solid. Yield: 162 mg, 67%. ¹H NMR (500 MHz, CDCl₃): δ 12.70 (s, 1H), 10.88 (s, 1H), 10.11 (s, 1H), 9.45 (s, 1H), 9.08 (s, 1H), 8.95 (s, 1H), 8.74 (d, 1H, *J* = 7.8 Hz), 8.69 (d, 1H, *J* = 7.8 Hz), 8.43 (s, 1H), 8.28 (d, 1H, *J* = 7.6 Hz), 8.18 (s, 1H), 7.93 (d, 1H, *J* = 8.0 Hz), 7.79 (d, 1H, *J* = 7.8 Hz), 7.73 (d, *J* = 7.5 Hz, 1H), 7.45 – 6.98 (m, 18H), 5.12 (s, 2H), 5.07 (s, 2H), 5.02 (s, 2H), 4.23 (q, 2H, *J* = 6.8 Hz), 4.01 (s, 3H), 3.80 (s, 3H), 1.25 (t, 1H, *J* = 6.9 Hz). ¹³C NMR (126 MHz, CDCl₃): δ 168.83, 167.81, 164.94, 164.22, 163.43, 162.97, 161.61, 151.59, 148.05, 145.96, 144.21, 142.63, 141.23, 135.99, 134.52, 134.24, 133.96, 133.54, 132.65, 132.46, 132.35, 129.51, 129.40, 129.34, 129.13, 129.05, 128.58, 128.55, 128.43, 127.75, 127.51, 127.17, 127.04, 126.00, 125.80, 125.58, 125.35, 125.25, 125.16, 124.33, 115.78, 115.08, 79.10, 64.53, 62.90, 62.36, 61.77, 60.85, 14.34. HRMS-ESI: calculated for [M]⁺ (C₅₈H₅₀N₇O₁₃)⁺: *m/z* 1052.3461, found: *m/z* 1052.3507.

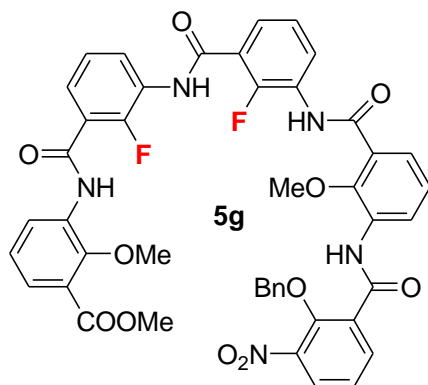
Pentamer 6a



To a solution of **1j** (523 mg, 0.50 mmol) and iron (112 mg, 2.0 mmol) in EtOH/THF (5 mL/2 mL) was added acetate acid (1.0 mL). The reaction was refluxed for 3 hours. After cooling, the solvent was removed and the residue was dissolved with CH₂Cl₂ and washed with water and Brine. The organic layer was dried over Na₂SO₄. After removal of the solvent, the residue was

not purified, but used directly in the next step. To the solution of residue in hot dioxane (1.5 mL) was added 1M KOH (1.0 mL). The reaction was heated under reflux for 4 hours. After quenching with water (15 mL), the aqueous layer was neutralized by addition of 1M HCl (1.5 mL). The mixture was extracted with CHCl₃ (3x15 mL). The organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. To the solution of the residue in dry CH₂Cl₂ (10 mL) was added BOP (0.55 g, 2.5 mmol) and DIEA (0.25 mL). The reaction was stirred in room temperature for 6 hours. The reaction was washed with HCl solution, aqueous sat. NaHCO₃ and Brine. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using CH₂Cl₂/ethyl acetate (20/1 v/v) as the eluent to give the product **6a**, three-step total yield: 170 mg, 35%. ¹H NMR (500 MHz, CDCl₃): δ 13.59 (s, 1H), 13.47 (s, 1H), 11.46 (s, 1H), 11.15 (s, 1H), 10.88 (s, 1H), 9.12 (d, 1H, *J* = 1.9 Hz), 9.09 (d, 1H, *J* = 1.7 Hz), 8.98 (d, 1H, *J* = 8.1 Hz), 8.88 (d, 1H, *J* = 8.0 Hz), 8.84 (d, 1H, *J* = 8.1 Hz), 8.62 (d, 1H, *J* = 2.1 Hz), 8.51 (d, 1H, *J* = 2.1 Hz), 7.94 (d, 1H, *J* = 7.9 Hz), 7.92 (d, 1H, *J* = 7.9 Hz), 7.85 (d, 1H, *J* = 7.8 Hz), 7.49 – 7.28 (m, 15H), 7.02 (t, 2H, *J* = 7.4 Hz), 6.92 (t, 1H, *J* = 7.3 Hz), 5.30 (d, 1H, *J* = 11.0 Hz), 5.19 (s, 2H), 5.18 (s, 2H), 5.11 (d, 1H, *J* = 11.0 Hz), 4.14 (s, 3H), 3.96 (s, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 169.86, 169.23, 163.16, 163.00, 162.79, 162.76, 162.68, 147.64, 147.43, 145.80, 141.16, 140.98, 134.06, 133.83, 133.68, 133.51, 133.15, 132.99, 132.64, 129.85, 129.61, 129.54, 129.49, 129.37, 128.82, 128.67, 127.81, 127.70, 127.30, 126.96, 126.70, 125.95, 125.63, 125.55, 125.29, 124.55, 124.45, 124.24, 123.87, 116.47, 115.53, 805, 62.54, 62.45, 62.24, 62.23. HRMS-ESI: calculated for [M+Na]⁺(C₅₆H₄₅O₁₀N₇Na)⁺: *m/z* 998.3120, found: *m/z* 998.3163.

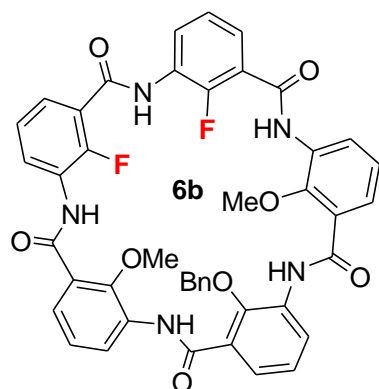
Methyl 3-(3-(3-(3-(2-(benzyloxy)-3-nitrobenzamido)-2-methoxybenzamido)-2-fluorobenzamido)-2-fluorobenzamido)-2-methoxybenzoate (5g)



To a solution of **5d** (1.27 g, 2 mmol) and iron (0.45 g, 8 mmol) in EtOH/THF (20 mL/10 mL) was added acetate acid (2 mL). The reaction was refluxed for 2 hours at room temperature. After cooling, the solvent was removed and the residue was dissolved with CH₂Cl₂ and washed with water and Brine. The organic layer was dried over Na₂SO₄. Removal of the solvent

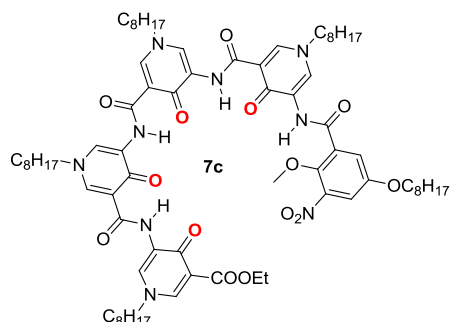
gave the amine product used for the next step reaction without further purification. Compound **1k** (0.6 g, 2.2mmol) was dissolved in CH₂Cl₂ (15 mL) to which DMF (40 μL), (COCl)₂ (0.4 mL, 3.3 mmol) was added at room temperature. The reaction mixture was stirred for 5 hours then the excess (COCl)₂ was removed in vacuo to produce the chloride compound. A solution of amine (1.21 g, 2 mmol) and TEA (0.4 mL, 5 mmol) in CH₂Cl₂ (20 mL) was added. The reaction mixture was allowed to stir continuously overnight at room temperature. The reaction mixture was washed with 1 M HCl (10 mL), followed by saturated NaCl (20 mL). Drying over Na₂SO₄ and removal of solvent in *vacuo* gave the crude product, which was recrystallized from methanol to give the pure product **5g** as a white solid. Yield: 0.93 g, 54%. ¹H NMR (500 MHz, CDCl₃): δ 9.76 (s, 1H), 9.67 (s, 1H), 9.14 (d, 1H, *J* = 11.7 Hz), 8.79 – 8.63 (m, 4H), 8.56 (d, 1H, *J* = 10.1 Hz), 8.38 (dd, 1H, *J* = 7.9, 1.8 Hz), 8.05 (dd, 1H, *J* = 8.1, 1.8 Hz), 7.95 – 7.85 (m, 3H), 7.64 (dd, 1H, *J* = 7.9, 1.6 Hz), 7.46 (t, 1H, *J* = 10.4 Hz), 7.42-7.36 (m, 3H), 7.33 – 7.29 (m, 2H), 7.23 (m, 2H), 7.20 – 7.17 (m, 2H), 5.18 (s, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.63 (s, 3H). MS-ESI: calculated for [M]⁺ (C₄₅H₃₄F₂N₅O₁₁): *m/z* 858.2228, found: *m/z* 858.2211.

Pentamer 6b



To a solution of **5g** (430 mg, 0.50 mmol) and iron (112 mg, 2.0 mmol) in EtOH/THF (5 mL/2 mL) was added acetate acid (1.0 mL). The reaction was refluxed for 3 hours. After cooling, the solvent was removed and the residue was dissolved with CH₂Cl₂ and washed with water and Brine. The organic layer was dried over Na₂SO₄. After removal of the solvent, the residue was not purified, but used directly in the next step. To the solution of residue in hot dioxane (1.5 mL) was added 1M KOH (1.0 mL). The reaction was heated under reflux for 4 hours. After quenching with water (15 mL), the aqueous layer was neutralized by addition 1M HCl (1.5 mL). The mixture was extracted with CHCl₃ (3x15 mL). The organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. To the solution of the residue in dry CH₂Cl₂ (10 mL) was added BOP (0.55 g, 2.5 mmol) and DIEA (0.25 mL). The reaction was stirred in room temperature for 6 hours. The reaction was washed with HCl solution, aqueous sat. NaHCO₃ and Brine. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using CH₂Cl₂/ethyl acetate (20/1 v/v) as the eluent to give the product **6b**, three-step total yield: 187 mg, 47%. ¹H NMR (500 MHz, CDCl₃): δ 10.91 (s, 1H), 10.87 (s, 1H), 10.35 (d, 1H, *J* = 4.0 Hz), 9.46 (d, 1H, *J* = 20 Hz), 9.28 (dd, 1H, *J* = 21.3, 4.7 Hz), 9.05 (dd, 2H, *J* = 13.2, 8.1 Hz), 9.00 (dd, 2H, *J* = 14.4, 6.8 Hz), 8.87 (d, 1H, *J* = 8.1 Hz), 8.11 (t, 1H, *J* = 7.4 Hz), 8.06-8.03 (m, 3H), 7.99 (dd, 1H, *J* = 7.9, 1.3 Hz), 7.55 – 7.39 (m, 7H), 7.17 (t, 2H, *J* = 7.4 Hz), 7.10 (t, 1H, *J* = 7.3 Hz), 5.05 (d, 2H, *J* = 2.3 Hz), 3.97 (s, 3H), 3.87 (s, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 162.60, 162.44, 162.23, 160.29, 1607, 151.42, 149.49, 146.66, 146.38, 145.84, 134.37, 133.29, 132.62, 132.03, 1305, 128.98, 128.53, 127.75, 127.65, 127.30, 127.27, 127.21, 127.20, 126.71, 126.63, 126.48, 126.46, 126.38, 126.13, 126.03, 125.69, 125.65, 125.37, 125.15, 124.77, 124.49, 124.07, 120.27, 120.23, 119.82, 119.79, 80.14, 62.35, 62.11. HRMS-ESI: calculated for [M]⁺(C₄₄H₃₂F₂O₈N₅): *m/z* 796.2236, found: *m/z* 796.2216.

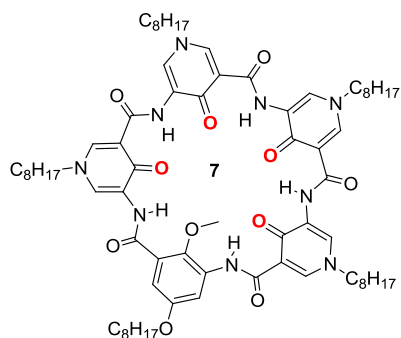
Ethyl 5-(5-(5-(5-(2-methoxy-3-nitro-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (7c)



A solution of **7a** (0.68 g, 2.00 mmol) in SOCl_2 (4.00 mL) was heated under reflux for 2 hours at room temperature. After removal of SOCl_2 , the **7b** (1.00 mmol) and DIEA (0.68 mL, 4.00 mmol) in dry CH_2Cl_2 (60 mL) were added to the residue.

The solution was allowed to proceed for 12 hours at room temperature. After washing with 1M HCl solution, the organic layer was dried over Na_2SO_4 . The residue was purified by column chromatography on silica gel using $\text{MeOH}/\text{CH}_2\text{Cl}_2$ as the eluent to give **7c** as a white solid. Yield: 0.97 g, 72%. ^1H NMR (500 MHz, $\text{CDCl}_3/\text{DMSO}-d_6 = 1/9$, 330K) δ 12.66 (s, 1H), 12.50 (s, 1H), 12.23 (s, 1H), 10.62 (s, 1H), 8.91 (s, 1H), 8.83 (s, 2H), 8.67 (s, 1H), 8.34 (s, 2H), 7.99 (s, 1H), 7.52 (s, 1H), 7.4 (s, 1H), 7.2 (s, 1H), 4.20 - 3.89 (m, 15H), 1.92 - 1.69 (m, 10H), 1.36-1.28 (m, 53H), 0.85 - 0.82 (s, 15H). ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6 = 1/9$, 330K) δ 168.4, 168.4, 168.2, 168.0, 162.1, 162.0, 162.0, 154.3, 153.8, 145.2, 145.1, 144.0, 141.9, 141.8, 141.2, 141.2, 141.1, 140.6, 140.4, 140.3, 132.7, 132.1, 131.4, 129.2, 127.5, 127.1, 126.4, 121.0, 120.8, 115.4, 115.3, 115.3, 115.2, 114.0, 111.8, 111.8, 68.9, 63.3, 58.9, 31.4, 31.3, 30.4, 30.3, 30.2, 28.9, 28.8, 28.7, 28.6, 28.6, 25.9, 25.8, 25.6, 25.5, 22.1, 22.1, 13.6. HRMS-ESI: calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{74}\text{H}_{108}\text{N}_9\text{O}_{14}$) : m/z 1346.8010, found: m/z 1346.7756.

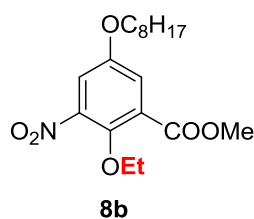
Compound 7



To a solution of **7c** (0.67 g, 0.50 mmol) and iron (0.14 g, 2.50 mmol) in EtOH (50 mL) and THF (50 mL) was added acetate acid (1.00 mL). The solution was refluxed for 5 hours. After cooling, the solvent was filtered and removed then the residue was dissolved in

CH₂Cl₂ (50 mL) and washed with water (3 × 100 mL). The organic layer was dried over Na₂SO₄. The solvent was removed and the residue was dissolved into dioxane (50 mL). 1M of KOH (1.00 mmol, 1.00 mL) was added to the solution and refluxed for 5 hours. After quenching with water (30 mL), the aqueous layer was neutralized by addition of 1M HCl (1.00 mL). The mixture was extracted with CH₂Cl₂. The organic extract was dried over Na₂SO₄ and concentrated under reduced pressure. To the solution of the residue in dry CH₂Cl₂ (20 mL) was added BOP (0.66 g, 1.50 mmol) and DIEA (0.26 mL, 2.00 mmol). The solution was stirred at room temperature for 12 hours at room temperature. The organic layer was washed with 1M HCl solution. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using MeOH/CH₂Cl₂ as the eluent to give the product **7**, three-step total yield: 220 mg, 35%. ¹H NMR (500 MHz, DMSO-*d*₆/CDCl₃ = 9/1, 370K) δ 12.42 (m, 4H), 10.89 (s, 1H), 8.38 – 8.22 (m, 3H), 8.09 (s, 1H), 7.84 (s, 1H), 7.78 (s, 2H), 7.70 (s, 1H), 7.58 (s, 1H), 6.54 (s, 1H), 3.93-3.89 (m, 9H), 3.23 (s, 4H), 1.95 – 1.72 (m, 10H), 1.56 – 1.33 (m, 50H), 0.98 – 0.91 (m, 15H). ¹³C NMR (125 MHz, DMSO-*d*₆/CDCl₃ = 9/1, 370K) δ 167.8, 167.5, 167.3, 167.2, 161.3, 161.2, 161.0, 160.9, 160.7, 160.7, 160.5, 154.4, 141.9, 139.5, 139.4, 139.3, 139.3, 133.2, 131.5, 131.4, 131.3, 131.1, 125.7, 125.5, 125.4, 125.3, 125.0, 124.9, 124.9, 124.9, 122.9, 122.9, 114.5, 114.3, 114.1, 113.8, 110.3, 107.6, 107.6, 67.6, 63.0, 58.1, 48.6, 31.3, 31.2, 29.9, 29.8, 29.2, 29.0, 28.8, 28.7, 28.7, 28.6, 28.6, 28.5, 25.9, 25.8, 25.8, 22.0, 21.9, 13.6, 13.5. MS-APCI: calculated for [M+Na]⁺ (C₇₂H₁₀₃N₉O₁₁Na): *m/z* 1292.7669, found: *m/z* 1292.7646.

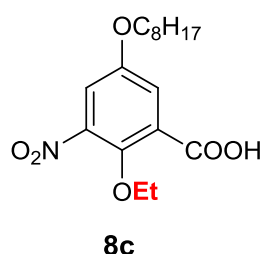
Methyl 2-ethoxy-3-nitro-5-(octyloxy)benzoate (**8b**)



Compound **8a** (3.25 g, 10 mmol) was dissolved in anhydrous DMF (30 mL), to which anhydrous K₂CO₃ (4.00 g, 25.0 mmol) and bromoethane (0.89 mL, 12.0 mmol) was added. The mixture was heated under 60 °C for 4 hours. CH₂Cl₂ (100 mL) was then added and the reaction mixture was filtered. The solvent was removed in *vacuo* and the concentrate was dissolved in CH₂Cl₂ (100 mL), washed with

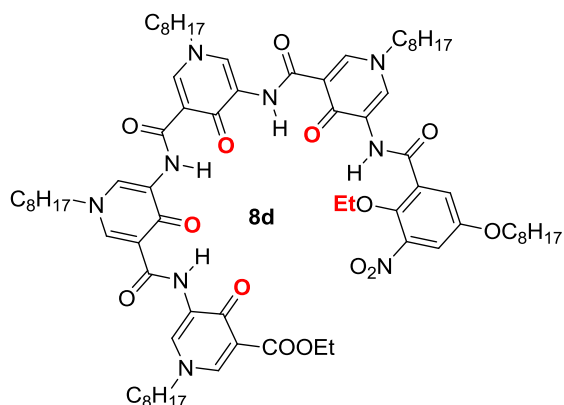
water (3 × 50 mL) and dried over anhydrous Na₂SO₄. Removal of CH₂Cl₂ gave the crude product, which was recrystallized from MeOH to give pure product **8b** as a yellow solid. Yield: 2.44 g, 72%. ¹H NMR (500 MHz, CDCl₃) δ 7.49 (d, *J* = 3.3 Hz, 1H), 7.37 (d, *J* = 3.2 Hz, 1H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.95 (t, *J* = 6.5 Hz, 2H), 3.90 (s, 3H), 1.78 – 1.72 (m, 2H), 1.45 – 1.38 (m, 2H), 1.30 (m, 11H), 0.85 (t, *J* = 6.9 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 164.76, 154.10, 145.73, 145.28, 128.03, 121.27, 113.78, 72.95, 69.06, 52.58, 31.67, 29.14, 29.09, 28.85, 25.79, 22.53, 15.18, 13.96. HRMS-ESI: calculated for [M]⁺ (C₁₈H₂₇O₆N₁): *m/z* 353.1838, found: *m/z* 353.1839.

2-ethoxy-3-nitro-5-(octyloxy)benzoic acid (**8c**)



Compound **8b** (2.81 g, 8.30 mmol) was dissolved in hot MeOH (30 mL), to which 1M NaOH (17.0 mL, 17.0 mmol) was added. The mixture was heated under reflux for 1 hour and then quenched with water (100 mL). The aqueous layer was neutralized by addition of 1M HCl (17.0 mL). The solution was removed under reduced pressure and the mixture was extracted with CH₂Cl₂. The organic extracts were dried over NaSO₄ and concentrated under reduced pressure to give a pure white solid **8c**. Yield: 2.30 g, 85%. ¹H NMR (500 MHz, CDCl₃) δ 7.80 (d, *J* = 3.3 Hz, 1H), 7.55 (d, *J* = 3.2 Hz, 1H), 4.19 (dd, *J* = 14.0, 7.0 Hz, 2H), 4.01 (t, *J* = 6.4 Hz, 2H), 1.84 – 1.75 (m, 2H), 1.51 – 1.39 (m, 5H), 1.30 (m, 8H), 0.89 (t, *J* = 6.7 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 166.69, 154.70, 145.39, 145.07, 125.99, 122.01, 116.00, 74.09, 69.34, 31.73, 29.19, 29.14, 28.87, 25.84, 22.60, 15.27, 14.04. HRMS-ESI: calculated for [M]⁺ (C₁₇H₂₄NO₆): *m/z* 338.1609, found: *m/z* 338.1595.

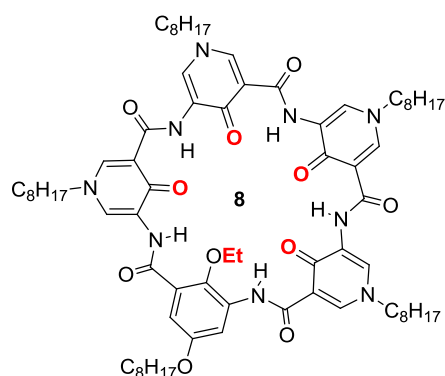
Ethyl 5-(5-(5-(5-(2-ethoxy-3-nitro-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (8d**)**



A solution of **8c** (0.68 g, 2.00 mmol) in SOCl₂ (4.00 mL) was heated under reflux for 2 hours at room temperature. After removal of the SOCl₂, **7b** (1.04 g, 1.0 mmol) and DIEA (0.68 mL, 4.00 mmol) in dry CH₂Cl₂ (60 mL) were added to the residue. The solution was allowed to

proceed for 12 hours at room temperature. After washing with 1M HCl solution, the organic layer was dried over Na₂SO₄. The residue was purified by column chromatography on silica gel using MeOH/CH₂Cl₂ as the eluent to give **8d** as a white solid. Yield: 0.91 g, 67%. ¹H NMR (500 MHz, CDCl₃/DMSO-*d*₆ = 1:9, 370K) δ 12.73 (s, 1H), 12.65 (s, 1H), 12.56 (s, 1H), 10.87 (s, 1H), 9.13 (s, 2H), 9.04 (s, 1H), 8.94 (s, 1H), 8.62 (s, 1H), 8.58 (s, 1H), 8.54 (s, 1H), 8.31 (s, 1H), 7.56 (d, *J* = 3.0 Hz, 1H), 7.50 (d, *J* = 3.0 Hz, 1H), 4.29 – 4.00 (m, 15H), 1.84 – 1.66 (m, 10H), 1.40 – 1.13 (m, 53H), 0.87 – 0.79 (m, 15H). ¹³C NMR (125 MHz, CDCl₃/DMSO-*d*₆ = 1:9, 330K) δ 168.56, 168.54, 168.52, 168.46, 168.23, 168.21, 168.20, 167.19, 167.17, 166.94, 164.50, 162.85, 162.81, 162.76, 162.53, 162.29, 154.15, 144.59, 144.55, 143.99, 143.31, 141.71, 141.69, 141.11, 140.49, 140.43, 140.41, 132.94, 132.30, 131.54, 130.39, 128.40, 127.15, 126.36, 120.59, 115.47, 114.19, 74.07, 69.18, 58.80, 58.66, 58.28, 53.64, 41.86, 31.28, 31.21, 30.17, 29.14, 28.80, 28.70, 28.65, 28.58, 28.52, 25.85, 25.51, 22.06, 22.02, 13.45, 13.43, 13.41. HRMS-ESI: calculated for [M+Na]⁺ (C₇₅H₁₀₉N₉NaO₁₄): *m/z* 1382.7986, found: *m/z* 1382.7949.

Compound 8

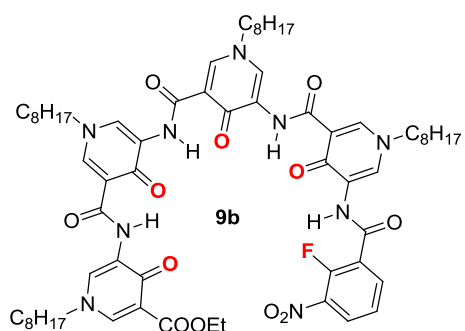


To a solution of **8d** (0.68 g, 0.50 mmol) and iron (0.14 g, 2.50 mmol) in EtOH (50 mL) and THF (50 mL) was added acetate acid (1.00 mL). The solution was refluxed for 5 hours. After cooling, the solvent was filtered and removed then the residue was dissolved in CH₂Cl₂ (50 mL) and

washed with water (3 × 100 mL). The organic layer was dried over Na₂SO₄. The solvent was removed and the residue was dissolved into dioxane (50 mL). 1M of KOH (1.00 mmol, 1.00 mL) was added to the solution and refluxed for 5 hours. After quenching with water (30 mL), the aqueous layer was neutralized by addition of 1M HCl (1.00 mL). The mixture was extracted with CH₂Cl₂. The organic extract was dried over Na₂SO₄ and concentrated under reduced pressure. To the solution of the residue in dry CH₂Cl₂ (20 mL) was added BOP (0.66 g, 1.50 mmol) and DIEA (0.26 mL, 2.00 mmol). The solution was stirred at room temperature for 12 hours at room temperature. The organic layer was washed with 1M HCl solution. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using MeOH/CH₂Cl₂ as the eluent to give the product **8**, three-step total yield: 269 mg, 42%. ¹H NMR (500 MHz, DMSO-*d*₆/CDCl₃ = 9/1, 370K) δ 13.11 (s, 1H), 13.08 (s, 1H), 13.06 (s, 1H), 13.03 (s, 1H), 11.24 (s, 1H), 8.82 – 8.57 (m, 4H), 8.23 – 8.16 (m, 5H), 7.03 (s, 1H), 4.14 – 4.10 (m, 10H), 3.80 (s, 2H), 1.98 – 1.85 (m, 8H), 1.62 – 1.56 (m, 4H), 1.47 – 1.25 (m, 51H), 0.93 – 0.88 (m, 15H). ¹³C NMR (125 MHz, DMSO-*d*₆/CDCl₃ = 9/1, 370K) δ 168.3, 168.2, 168.1, 167.8, 161.7, 161.6, 161.5, 161.4, 155.3, 140.6, 140.2, 134.0, 131.9, 131.8, 131.4, 131.0, 128.5, 126.2, 126.1, 124.7, 124.6, 115.0, 114.6, 114.5, 114.4, 111.0, 108.9, 104.6, 72.4, 68.2, 67.7, 64.8, 58.5, 58.4, 54.3, 31.3, 31.2, 31.2, 30.3, 30.2, 30.1, 30, 29.9, 29.1, 29.0, 28.9, 28.7, 28.6, 28.5, 25.9, 25.8, 22.1, 22.0, 14.5, 13.7, 13.6.

Ethyl

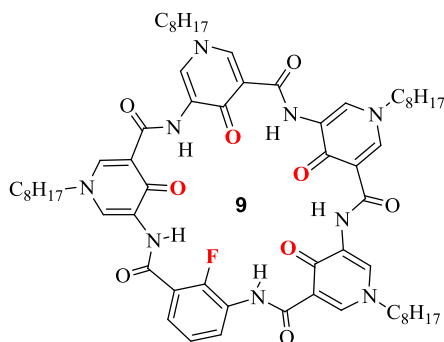
5-(5-(5-(5-(2-fluoro-3-nitrobenzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (9b)



A solution of **9a** (0.27 g, 2.00 mmol) in SOCl₂ (4.00 mL) was heated under reflux for 2 hours at room temperature. After removal of the SOCl₂, **7b** (1.04 g, 1.0 mmol) and DIEA (0.68 mL, 4.00 mmol) in dry CH₂Cl₂ (60 mL) were added to the residue. The

solution was allowed to proceed for 12 hours at room temperature. After washing with 1M HCl solution, the organic layer was dried over Na₂SO₄. The residue was purified by column chromatography on silica gel using MeOH/CH₂Cl₂ as the eluent to give **9b** as a white solid. Yield: 0.84 g, 71%. ¹H NMR (500 MHz, CDCl₃/DMSO-*d*₆ = 1:9, 370K) δ 12.60 (s, 1H), 12.49 (s, 1H), 12.41 (s, 1H), 10.50 (s, 1H), 9.07 (s, 2H), 8.97 (s, 1H), 8.91 (s, 1H), 8.52 (s, 1H), 8.46 (s, 1H), 8.44 (s, 1H), 8.21 – 8.19 (m, 2H), 8.07 (s, 1H), 7.54 (t, *J* = 7.3 Hz, 1H), 4.22 – 4.17 (m, 4H), 4.12 – 4.11 (m, 4H), 4.01 (t, *J* = 6.4 Hz, 2H), 1.94 – 1.76 (m, 8H), 1.35 – 1.27 (m, 43H), 0.87 – 0.85 (m, 12H). ¹³C NMR (500 MHz, CDCl₃/DMSO-*d*₆ = 1:9, 370K) δ 168.3, 168.2, 166.8, 166.7, 164.8, 164.3, 162.7, 162.5, 162.4, 161.3, 159.1, 153.5, 151.4, 142.0, 141.9, 141.2, 141.1, 137.6, 137.5, 135.4, 135.3, 132.5, 132.4, 131.9, 131.1, 131.0, 130.9, 129.6, 129.5, 129.4, 128.5, 128.4, 127.6, 127.5, 127.4, 126.7, 126.6, 126.5, 124.6, 124.5, 115.4, 115.2, 115.0, 114.2, 104.5, 59.7, 58.2, 58.1, 58.0, 57.5, 31.1, 30.1, 30, 29.9, 28.9, 28.9, 28.4, 25.6, 21.9, 14.0, 13.6. HRMS-APCI: calculated for [M+H]⁺ (C₆₅H₈₉O₁₂N₉F): *m/z* 1206.6609, found: *m/z* 1206.6567.

Compound 9

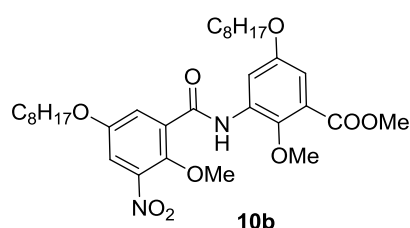


To a solution of **9b** (0.60 g, 0.50 mmol) and iron (0.14 g, 2.50 mmol) in EtOH (50 mL) and THF (50 mL) was added acetate acid (1.00 mL). The solution was refluxed for 5 hours. After cooling, the solvent was filtered and removed then the residue was dissolved in CH₂Cl₂ (50 mL) and washed with water (3 × 100 mL). The organic layer was dried over

Na₂SO₄. The solvent was removed and the residue was dissolve into dioxane (50 mL). 1M of KOH (1.00 mmol, 1.00 mL) was added to the solution and refluxed for 5 hours. After quenching with water (30 ml), the aqueous layer was neutralized by addition of 1M HCl (1.00 mL). The mixture was extracted with CH₂Cl₂. The organic extract was dried over NaSO₄ and concentrated under reduced pressure. To the solution of the residue in dry CH₂Cl₂ (20 mL) was added BOP (0.66 g, 1.50 mmol) and DIEA (0.26 mL, 2.00 mmol).

The solution was stirred at room temperature for 12 hours at room temperature. The organic layer was washed with 1M HCl solution. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using MeOH/CH₂Cl₂ as the eluent to give the product **9**, three-step total yield: 242 mg, 43%. HRMS-APCI: calculated for [M+H]⁺ (C₆₃H₈₅O₉N₉F) : m/z 1130.6449, found: m/z 1130.6451. HRMS-APCI: calculated for [M+H]⁺ (C₆₃H₈₅O₉N₉F) : m/z 1130.6449, found: m/z 1130.6451.

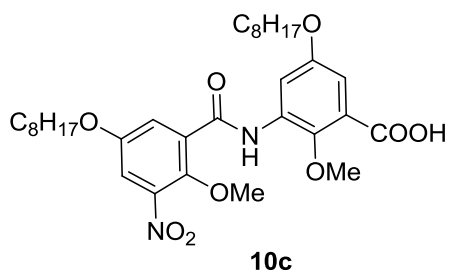
Methyl 2-methoxy-3-(2-methoxy-3-nitro-5-(octyloxy)benzamido)-5-(octyloxy)benzoate (10b)



To a solution of **10a** (0.56 g, 1.65 mmol) and iron (0.37 g, 6.60 mmol) in EtOH (20 mL) was added acetate acid (1.65 mL). The solution was refluxed for 2 hours at room temperature. After cooling, the solvent was removed and the residue was dissolved with CH₂Cl₂ and washed with water and Brine. The organic layer was dried over Na₂SO₄. Removal of the solvent gave the amine product, which was used for the next step reaction without further purification. A solution of **7a** (0.58 g, 1.80 mmol) in SOCl₂ (3.00 mL) was heated under reflux for 2 hours at room temperature. After removal of the SOCl₂, the amine product (1.65 mmol) and DIEA (0.61 mL, 3.60 mmol) in dry CH₂Cl₂ (20 mL) were added to the residue. The solution was allowed to proceed for 12 hours at room temperature. After washing with 1M HCl solution, the organic layer was dried over Na₂SO₄. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using hexane/ethyl acetate as the eluent to give the product **10b**. Yield: 0.88 g, 87%. ¹H NMR (500 MHz, CDCl₃) δ 10.48 (s, 1H), 8.46 (d, *J* = 3.1 Hz, 1H), 7.94 (d, *J* = 3.3 Hz, 1H), 7.49 (d, *J* = 3.3 Hz, 1H), 7.13 (d, *J* = 3.1 Hz, 1H), 4.01 (m, 7H), 3.93 (s, 3H), 3.88 (s, 3H), 1.85 – 1.74 (m, 4H), 1.51 – 1.40 (m, 4H), 1.30 (m, 16H), 0.89 (m, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 158.7, 154.2, 148.2, 148.1, 137.7, 137.6, 136.1, 126.3, 122.5, 116.7, 114.1, 108.1, 104.7, 104.1, 62.2, 61.6, 57.6, 55.6, 45.3, 24.8, 24.7, 22.3, 22.2, 22.2, 22.1, 22.1, 21.9, 19.0, 18.8, 15.7, 15.6, 7.1, 7.0. HRMS-ESI: calculated for [M+Na]⁺ (C₃₃H₄₈N₂O₉Na): *m/z*

639.3252, found: m/z 639.3268.

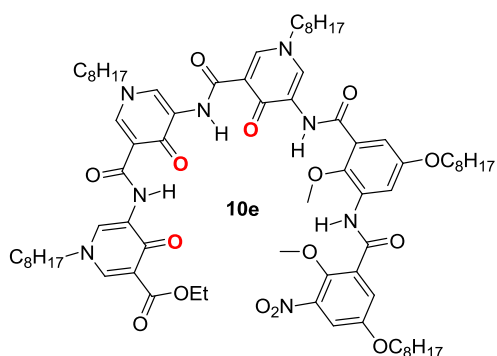
2-methoxy-3-(2-methoxy-3-nitro-5-(octyloxy)benzamido)-5-(octyloxy)benzoic acid (10c)



Compound **10b** (3.08 g, 5.0 mmol) was dissolved in hot 1,4-dioxane (20 mL) to which 1M KOH (10 mL, 10 mmol) and KCl (3.70g, 50 mmol) were added. The mixture was heated at 60 °C for 24 hours and then quenched with water (10 mL).

The aqueous layer was neutralized by addition of 1M HCl (10 mL). The solvent was removed at reduced pressure and the mixture was extracted with CH₂Cl₂. The organic extract was dried over NaSO₄ and concentrated under reduced pressure to give a pure white solid **10c**. Yield: 2.20 g, 73.0%, ¹H NMR (300 MHz, CDCl₃) δ 10.41 (s, 1H), 8.50 (d, J = 3.1 Hz, 1H), 7.95 (d, J = 3.3 Hz, 1H), 7.51 (d, J = 3.3 Hz, 1H), 7.32 (d, J = 3.2 Hz, 1H), 4.08 – 3.98 (m, 7H), 3.94 (s, 3H), 1.87 – 1.74 (m, 4H), 1.53 – 1.40 (m, 5H), 1.29 (dd, J = 12.2, 8.5 Hz, 18H), 0.89 (t, J = 6.8 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 168.5, 161.3, 155.6, 155.2, 144.7, 144.6, 143.4, 133.2, 129.3, 122.3, 121.2, 115.2, 112.7, 112.1, 69.3, 68.7, 64.6, 63.1, 31.8, 31.7, 29.3, 29.2, 29.2, 29.1, 28.9, 25.9, 25.8, 22.7, 22.6, 14.1, 14.0. HRMS-ESI: calculated for [M-H]⁻ (C₃₂H₄₅N₂O₉): m/z 601.3131, found: m/z 601.3147.

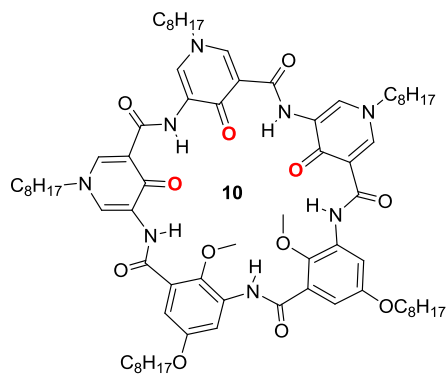
Ethyl 5-(5-(5-(2-methoxy-3-(2-methoxy-3-nitro-5-(octyloxy)benzamido)-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (10e)



A solution of **10c** (1.20 g, 2.00 mmol) in SOCl₂ (2.00 mL) was heated under reflux for 2 hours at room temperature. After removal of the SOCl₂, **10d** (0.79 g, 1.00 mmol) and DIEA (0.68 mL, 4.00 mmol) in dry CH₂Cl₂ (60 mL) were added to the residue. The solution was

allowed to proceed for 12 hours at room temperature. After washing with HCl solution, the organic layer was dried over Na₂SO₄. The residue was purified by column chromatography on silica gel using MeOH/CH₂Cl₂ as the eluent to give **10e** as a white solid. Yield: 1.04 g, 76%. ¹H NMR (500 MHz, CDCl₃/DMSO-*d*₆ = 1/4) δ 12.48 (s, 1H), 12.42 (s, 1H), 10.81 (s, 1H), 10.58 (s, 1H), 9.04 (s, 2H), 8.89 (s, 1H), 8.40 (s, 1H), 8.36 (s, 1H), 8.11 (s, 1H), 8.09 (s, 1H), 7.49 (s, 1H), 7.36 (s, 1H), 7.26 (s, 1H), 4.16 (s, 2H), 4.05 – 3.89 (m, 16H), 1.85 – 1.76 (m, 10H), 1.43 – 1.24 (m, 53H), 0.83 (s, 15H). ¹³C NMR (125 MHz, CDCl₃/DMSO-*d*₆ = 1/4) δ 168.4, 168.3, 167.0, 164.3, 163.3, 162.8, 162.8, 155.3, 154.3, 144.4, 144.0, 142.8, 142.0, 141.3, 140.8, 133.0, 132.9, 132.3, 131.9, 127.5, 126.8, 126.5, 126.0, 120.3, 115.4, 115.1, 114.3, 113.3, 113.2, 112.6, 112.6, 111.0, 110.9, 69.1, 68.4, 64.0, 62.7, 59.9, 58.7, 58.5, 58.0, 31.4, 31.3, 31.2, 30.3, 30.2, 30.2, 28.9, 28.8, 28.8, 28.7, 28.7, 28.6, 28.6, 25.8, 25.7, 25.5, 22.2, 22.1, 22.1, 14.1, 13.7, 13.6. MS-ESI: calculated for [M+H]⁺ (C₇₆H₁₁₁N₈NaO₁₅): *m/z* 1376.7312, found: *m/z* 1376.8.

Compound 10

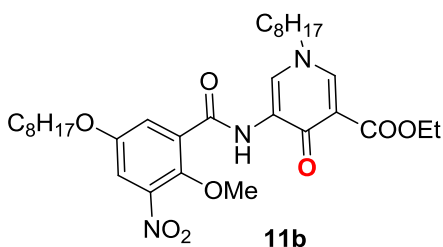


To a solution of **10e** (0.69 g, 0.50 mmol) and iron (0.14 g, 2.50 mmol) in EtOH (50 mL) and THF (50 mL) was added acetate acid (1.00 mL). The solution was refluxed for 5 hours. After cooling, the solvent was filtered and removed then the residue was dissolved in CH₂Cl₂ (50 mL) and washed with water (3 × 100 mL). The organic layer

was dried over Na₂SO₄. The solvent was removed and the amine product was dissolved into dioxane (50 mL). 1M of KOH (1.00 mmol, 1.00 mL) was added to the solution and refluxed for 5 hours. After quenching with water (30 ml), the aqueous layer was neutralized by addition 1M HCl (1.00 mL). The mixture was extracted with CH₂Cl₂. The organic extract was dried over NaSO₄ and concentrated under reduced pressure. To the solution of the residue in dry CH₂Cl₂ (20 mL) was added BOP (0.66 g, 1.50 mmol) and DIEA (0.26 mL, 2.00 mmol). The solution was stirred at room temperature for 12 hours at room

temperature. The solution was washed with HCl solution. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using MeOH/CH₂Cl₂ as the eluent to give the product **10**, three-step total yield: 292 mg, 45%. ¹H NMR (500 MHz, CDCl₃/DMSO-*d*₆ = 1/4) δ 13.10 (s, 1H), 13.02 (s, 1H), 12.96 (s, 1H), 11.42 (s, 1H), 11.13 (s, 1H), 8.77 (s, 1H), 8.75 (s, 1H), 8.62 (s, 1H), 8.24 (s, 1H), 8.20 (s, 1H), 8.14 (s, 1H), 8.10 (s, 1H), 8.08 (s, 1H), 7.14 (s, 1H), 7.01 (s, 1H), 4.12 – 4.00 (m, 16H), 2.02 – 1.89 (m, 6H), 1.87 – 1.80 (m, 4H), 1.56 – 1.51 (m, 4H), 1.48 – 1.23 (m, 46H), 0.90 – 0.83 (m, 15H). ¹³C NMR (125 MHz, CDCl₃/ DMSO-*d*₆ = 1/4) δ 168.6, 168.2, 162.6, 162.2, 162.1, 161.6, 161.4, 155.0, 154.9, 141.8, 141.7, 140.1, 139.9, 139.8, 133.6, 133.6, 132.3, 132.2, 131.7, 126.1, 126.0, 125.5, 124.4, 123.7, 115.2, 114.8, 114.6, 111.0, 110.4, 108.3, 67.9, 67.8, 63.9, 63.4, 58.8, 58.7, 58.7, 31.5, 31.5, 31.4, 31.3, 30.3, 30.2, 29.4, 29.3, 29.2, 29.0, 28.9, 28.8, 28.7, 28.7, 28.7, 28.6, 26.1, 26.0, 22.3, 22.2, 13.7, 13.6. HRMS-ESI: calculated for [M+Na]⁺ (C₇₄H₁₀₆O₁₂N₈Na) : *m/z* 1321.7822, found: *m/z* 1321.7762.

Ethyl 5-(2-methoxy-3-nitro-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (11b)

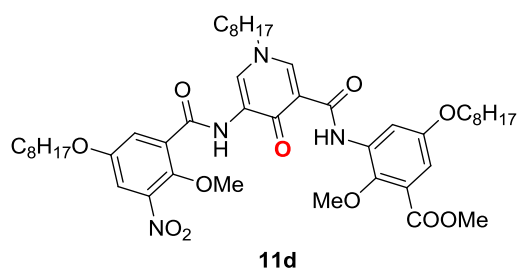


A solution of **7a** (3.25 g, 10 mmol) in SOCl₂ (5.00 mL) was heated under reflux for 2 hours at room temperature. After removal of the SOCl₂, **11a** (2.94 g, 10 mmol) and DIEA (3.40 mL, 20 mmol) in dry CH₂Cl₂ (30 mL) were added to the residue. The

solution was allowed to proceed for 12 hours at room temperature. After washing with 1M HCl solution, aqueous sat. NaHCO₃ and Brine, the organic layer was dried over Na₂SO₄. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate as the eluent to give **11b** as a white solid. Yield: 5.23 g, 87%. ¹H NMR (500 MHz, CDCl₃) δ 11.02 (s, 1H), 8.93 (d, *J* = 2.3 Hz, 1H), 8.17 (d, *J* = 2.3 Hz, 1H), 7.86 (d, *J* = 3.3 Hz, 1H), 7.47 (d, *J* = 3.3 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.06 (s, 3H), 4.01 (t, *J* = 6.5 Hz, 3H), 3.91 (t, *J* = 7.4 Hz, 2H), 1.93 – 1.84 (m, 2H), 1.83 – 1.75 (m, 2H), 1.49 – 1.22 (m, 22H), 0.91 – 0.85 (m, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 167.7, 165.8, 161.8, 154.8,

145.4, 144.8, 143.1, 133.0, 128.7, 126.6, 121.1, 115.1, 114.3, 105.0, 69.2, 64.4, 59.0, 52.4, 31.7, 31.6, 30.7, 29.2, 29.1, 29.0, 28.9, 28.9, 26.2, 25.9, 22.6, 22.5, 14.1, 14.0. HRMS-ESI: calculated for $[M+Na]^+$ ($C_{32}H_{47}O_8N_3Na$) : m/z 624.3255, found: m/z 627.3265.

Methyl 2-methoxy-3-(5-(2-methoxy-3-nitro-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-5-(octyloxy)benzoate (11d)

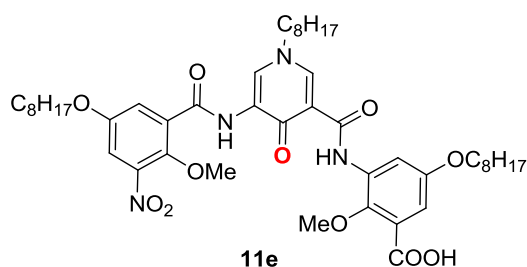


To a solution of **10a** (2.03 g, 6.00 mmol) and iron (1.68 g, 30 mmol) in EtOH (30 mL) was added acetate acid (6.00 mL). The solution was refluxed for 5 hours. After cooling, the reaction solvent was filtered and removed

then the residue was dissolved in CH_2Cl_2 (50 mL) and washed with water (3×100 mL). The organic layer was dried over Na_2SO_4 . Removal of the solvent gave the amine product, which was used for the next step reaction without further purification. Compound **11b** (6.01 g, 10 mmol) was dissolved in hot 1,4-dioxane (30 mL) to which 1M KOH (20 mL, 20 mmol) and KCl (3.70 g, 50 mmol) were added. The mixture was heated at 60 °C for 24 hours and then quenched with water (100 mL). The aqueous layer was neutralized by addition of 1M HCl (20 mL). The solvent was removed at reduced pressure and the mixture was extracted with CH_2Cl_2 . The organic extracts were dried over $NaSO_4$ and concentrated under reduced pressure to give a pure white solid **11c**. Yield: 5.16 g, 89.0%. Acid **11c** (2.86 g, 5.0 mmol) was dissolved in CH_2Cl_2 (20 mL) to which ethyl chloroformate (0.60 mL, 6.00 mmol) was added at 0 °C. The reaction mixture was stirred for at least 15 minutes after which a solution of amine and NMM (0.60 mL, 6.00 mmol) dissolved in CH_2Cl_2 (20 mL) were added. The reaction mixture was allowed to stir continuously for 12 hours at room temperature. The reaction mixture was washed with 1 M HCl and Brine. Drying over Na_2SO_4 and removal of solvent in *vacuo* to gave the crude product. It was purified by flash column chromatography on silica gel using hexane/ethyl acetate as the eluent to give the product **11d**. Yield: 2.72 g, 63%. 1H NMR (500 MHz,

CDCl₃) δ 12.72 (s, 1H), 11.04 (s, 1H), 8.96 (d, J = 2.2 Hz, 1H), 8.44 (d, J = 2.3 Hz, 1H), 8.43 (d, J = 3.1 Hz, 1H), 7.86 (d, J = 3.3 Hz, 1H), 7.47 (d, J = 3.3 Hz, 1H), 7.05 (d, J = 3.1 Hz, 1H), 4.08 (s, 3H), 4.02 – 3.95 (m, 6H), 3.94 (s, 3H), 3.92 (s, 3H), 1.93 – 1.85 (m, 2H), 1.82 – 1.72 (m, 4H), 1.47 – 1.39 (m, 4H), 1.28 – 1.32 (m, 26H), 0.89 – 0.84 (m, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 169.0, 166.1, 162.4, 161.5, 154.9, 154.8, 145.2, 144.7, 143.6, 141.2, 134.2, 131.6, 128.4, 127.3, 124.1, 121.0, 116.2, 115.1, 111.3, 110.8, 69.2, 68.4, 64.2, 62.3, 59.3, 52.2, 31.8, 31.7, 31.6, 30.7, 29.3, 29.2, 29.2, 29.1, 28.9, 28.8, 26.2, 25.9, 25.8, 22.6, 22.6, 22.5, 14.0, 13.9. HRMS-ESI: calculated for [M+Na]⁺ (C₄₇H₆₈O₁₁N₄Na) : m/z 887.4777, found: m/z 887.4736.

2-methoxy-3-(5-(2-methoxy-3-nitro-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydro pyridine-3-carboxamido)-5-(octyloxy)benzoic acid (11e)



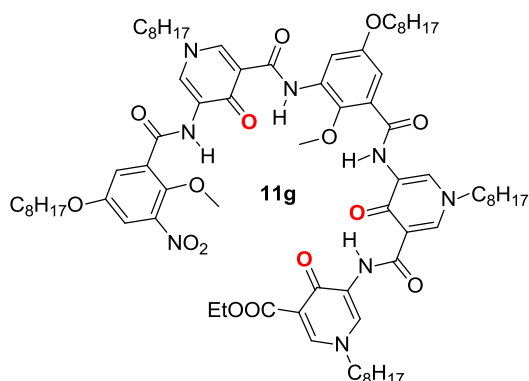
Compound **11d** (3.46 g, 4.00 mmol) was dissolved in hot 1,4-dioxane (10 mL) to which 1M KOH (8.00 mL, 8.00 mmol) and KCl (1.48 g, 20 mmol) were added. The mixture was heated at 60 °C for 24 hours

and then quenched with water (50 mL). The aqueous layer was neutralized by addition of 1M HCl (8.00 mL). The solution was removed under reduced pressure and the mixture was extracted with CH₂Cl₂. The organic extracts were dried over NaSO₄ and concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel using hexane/ethyl acetate as the eluent to give the product **11e**. Yield: 2.45 g, 72.0%.

¹H NMR (500 MHz, CDCl₃) δ 12.74 (s, 1H), 11.07 (s, 1H), 9.01 (d, J = 2.2 Hz, 1H), 8.49 (d, J = 2.2 Hz, 1H), 8.45 (d, J = 3.1 Hz, 1H), 7.89 (d, J = 3.3 Hz, 1H), 7.50 (d, J = 3.3 Hz, 1H), 7.08 (d, J = 3.1 Hz, 1H), 4.10 (s, 3H), 4.05 – 3.97 (m, 5H), 3.96 (s, 3H), 3.94 (s, 3H), 1.97 – 1.87 (m, 2H), 1.85 – 1.73 (m, 4H), 1.51 – 1.41 (m, 4H), 1.36 – 1.25 (m, 24H), 0.91 – 0.86 (m, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 169.1, 166.2, 162.5, 161.7, 155.0, 154.9, 145.2, 144.8, 143.7, 141.3, 134.3, 131.8, 128.6, 127.4, 124.2, 121.1, 116.4, 115.2, 111.5, 111.1, 69.3, 68.5, 64.3, 62.4, 59.4, 52.3, 31.8, 31.7, 31.6, 30.8, 29.7, 29.4, 29.3, 29.2, 29.0,

28.9, 26.2, 26.0, 25.9, 22.7, 22.6, 22.5, 14.1, 14.1, 14.0. HRMS-ESI: calculated for $[M+H]^+$ ($C_{46}H_{67}O_{11}N_4$) : m/z 851.4801, found: m/z 851.4815

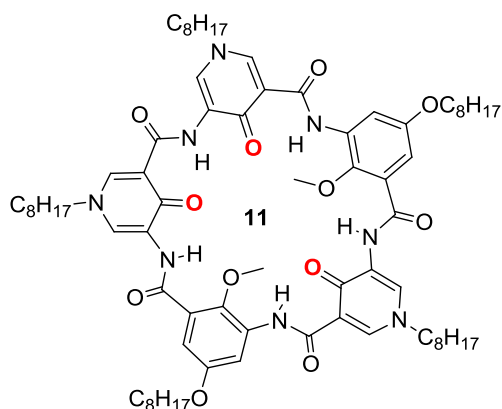
Ethyl 5-(5-(2-methoxy-3-(5-(2-methoxy-3-nitro-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (11g)



To a solution of **11e** (1.70 g, 2.0 mmol) and **11f** (1.08 g, 2.0 mmol) in CH_2Cl_2 (200 mL) was added $POCl_3$ (380 μ L, 4.0 mmol) at 40 °C. The solution was vigorously stirred. After 10 minutes, Et_3N (840 μ L, 6.0 mmol) was added into the reaction mixture. The solution was stirred for another 12 hours at

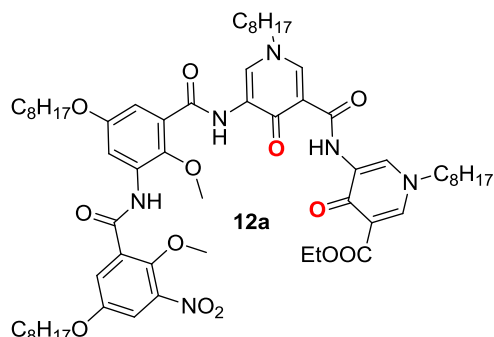
room temperature, which was then concentrated *in vacuo*. The residue was purified by flash column chromatography (MeOH/dichloromethane = 1/50) to produce **11g** as white solid. Yield: 1.74 g, 63%. 1H NMR (500 MHz, $CDCl_3/DMSO-d_6 = 4/1$) δ 12.67 (s, 1H), 12.52 (s, 1H), 10.92 (s, 1H), 10.89 (s, 1H), 8.91 (s, 1H), 8.89 (s, 1H), 8.82 (s, 1H), 8.43 (s, 1H), 8.32 (s, 1H), 8.23 (d, $J = 2.5$ Hz, 1H), 8.07 (s, 1H), 7.73 (d, $J = 2.9$ Hz, 1H), 7.37 (d, $J = 3.1$ Hz, 1H), 7.12 (d, $J = 2.5$ Hz, 1H), 4.12 – 3.86 (m, 14H), 1.90 – 1.69 (m, 10H), 1.42 – 1.10 (m, 53H), 0.84 – 0.78 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3/DMSO-d_6 = 4/1$) δ 168.7, 168.3, 167.5, 164.1, 164.0, 162.9, 162.7, 162.4, 161.3, 155.4, 154.3, 145.4, 144.0, 142.2, 142.0, 141.5, 141.1, 133.7, 133.0, 131.9, 131.4, 131.0, 129.5, 128.7, 128.7, 128.2, 127.6, 126.8, 126.4, 125.4, 121.0, 115.7, 115.1, 114.5, 113.6, 111.7, 109.2, 69.0, 68.2, 64.4, 62.6, 59.9, 59.0, 58.9, 58.4, 31.7, 31.6, 31.5, 30.7, 30.5, 29.4, 29.2, 29.1, 29.1, 29.0, 28.9, 28.8, 26.0, 25.9, 25.7, 22.5, 22.4, 22.4, 14.2, 14.1, 14.0. HRMS-ESI: calculated for $[M+Na]^+$ ($C_{76}H_{110}O_{15}N_8Na$) : m/z 1397.7983, found: m/z 1397.7931.

Compound 11



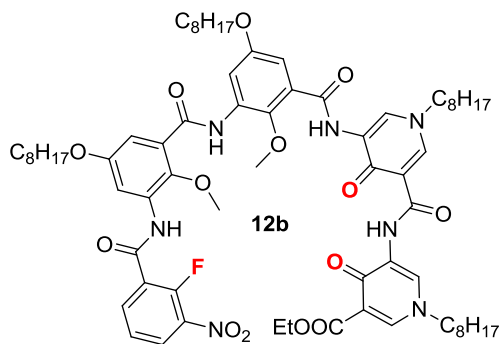
To a solution of **11g** (0.69 g, 0.50 mmol) and iron (0.14 g, 2.50 mmol) in EtOH (50 mL) and THF (50 mL) was added acetate acid (1.00 mL). The solution was refluxed for 5 hours. After cooling, the solvent was filtered and removed then the residue was dissolved in CH₂Cl₂ (50 mL) and washed with water (3 × 100 mL). The organic layer was dried over Na₂SO₄. The solvent was removed and the amine product was dissolved into dioxane (50 mL). 1M of KOH (1.00 mmol, 1.00 mL) was added to the solution and refluxed for 5 hours. After quenching with water (30 mL), the aqueous layer was neutralized by addition 1M HCl (1.00 mL). The mixture was extracted with CH₂Cl₂. The organic extract was dried over NaSO₄ and concentrated under reduced pressure. To the solution of the residue in dry CH₂Cl₂ (20 mL) was added BOP (0.66 g, 1.50 mmol) and DIEA (0.26 mL, 2.00 mmol). The solution was stirred at room temperature for 12 hours at room temperature. The solution was washed with HCl solution. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using MeOH/CH₂Cl₂ as the eluent to give the product **11**, three-step total yield: 253 mg, 39%. ¹H NMR (500 MHz, CDCl₃/DMSO-*d*₆ = 1/9, 350K) δ 13.21 (s, 1H), 13.10 (s, 1H), 12.99 (s, 1H), 11.47 (s, 1H), 11.41 (s, 1H), 8.85 (s, 1H), 8.73 (s, 1H), 8.71 (s, 1H), 8.39 (s, 1H), 8.32 (s, 2H), 8.26 (s, 1H), 8.22 (s, 1H), 7.11 (s, 2H), 4.15 – 4.14 (m, 6H), 4.01 – 4.05 (m, 10H), 1.82 – 1.93 (m, 10H), 1.54 – 1.50 (m, 4H), 1.49 – 1.23 (m, 46H), 0.94 – 0.81 (m, 15H). ¹³C NMR (125 MHz, CDCl₃/DMSO-*d*₆ = 1/9, 350K) δ 168.6, 168.2, 162.6, 162.2, 162.1, 161.6, 161.4, 155.0, 154.9, 141.8, 141.7, 140.1, 139.9, 139.8, 133.6, 133.6, 132.3, 132.2, 131.7, 126.1, 126.0, 125.5, 124.4, 123.7, 115.2, 114.8, 114.6, 111.0, 110.4, 108.3, 67.9, 67.8, 63.9, 63.4, 58.8, 58.7, 58.7, 31.5, 31.5, 31.4, 31.3, 30.3, 30.2, 29.4, 29.3, 29.2, 29.0, 28.9, 28.8, 28.7, 28.7, 28.6, 26.1, 26.0, 22.3, 22.2, 13.7, 13.6. HRMS-ESI: calculated for [M+Na]⁺ (C₇₄H₁₀₆O₁₂N₈Na) : *m/z* 1321.7822, found: *m/z* 1321.7886.

Ethyl 5-(5-(2-methoxy-3-(2-methoxy-3-nitro-5-(octyloxy)benzamido)-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (12a)



A solution of **10c** (1.80 g, 3.00 mmol) in SOCl_2 (6.00 mL) was heated under reflux for 2 hours at room temperature. After removal of SOCl_2 , **11f** (1.63g, 3.00 mmol) and DIEA (1.02 mL, 6.00 mmol) in dry CH_2Cl_2 (30 mL) were added to the residue. The solution was allowed to proceed for 12 hours at room temperature. After washing with 1M HCl solution, the organic layer was dried over Na_2SO_4 . The organic solvent was removed and the residue was purified by column chromatography on silica gel using $\text{MeOH}/\text{CH}_2\text{Cl}_2$ as the eluent to give **12a** as a white solid. Yield: 2.91 g, 86%. ^1H NMR (500 MHz, CDCl_3) δ 12.81 (s, 1H), 10.85 (s, 1H), 10.29 (s, 1H), 9.06 (d, $J = 2.0$ Hz, 1H), 8.93 (d, $J = 2.1$ Hz, 1H), 8.43 (d, $J = 3.0$ Hz, 1H), 8.38 (d, $J = 2.2$ Hz, 1H), 8.13 (d, $J = 2.2$ Hz, 1H), 7.91 (d, $J = 3.3$ Hz, 1H), 7.50 (d, $J = 3.2$ Hz, 1H), 7.33 (d, $J = 3.1$ Hz, 1H), 4.41 (q, $J = 7.1$ Hz, 2H), 4.13 (s, 3H), 4.04 (q, $J = 6.5$ Hz, 4H), 4.01 – 3.95 (m, 5H), 3.88 (t, $J = 7.3$ Hz, 2H), 1.97 – 1.75 (m, 8H), 1.52 – 1.19 (m, 43H), 0.90 – 0.85 (m, 12H). ^{13}C NMR (125 MHz, CDCl_3) δ 168.7, 167.8, 165.8, 163.5, 163.2, 161.7, 155.9, 155.0, 144.8, 144.7, 142.5, 141.7, 133.6, 132.9, 132.3, 129.7, 126.9, 126.6, 125.8, 120.9, 115.6, 115.1, 114.9, 111.9, 110.8, 69.2, 68.6, 64.8, 63.4, 61.2, 59.3, 58.7, 31.8, 31.7, 31.6, 30.7, 30.6, 29.3, 29.2, 29.2, 29.0, 28.9, 28.9, 26.2, 26.1, 25.9, 25.9, 22.6, 22.6, 22.6, 14.4, 14.1, 14.0, 14.0. HRMS-ESI: calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{62}\text{H}_{90}\text{N}_6\text{O}_{13}\text{Na}$): m/z 1149.6458, found: m/z 1149.6496.

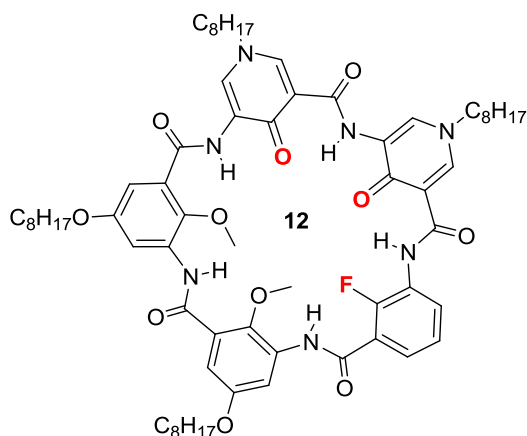
Ethyl-5-(5-(3-(3-(2-fluoro-3-nitrobenzamido)-2-methoxy-5-(octyloxy)benzamido)-2-methoxy-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (12b)



To a solution of **12a** (1.13 g, 1.00 mmol) and iron (0.37 g, 5.00 mmol) in EtOH (20 mL) was added acetate acid (1.00 mL). The solution was refluxed for 2 hours at room temperature. After cooling, the solvent was removed and the residue was dissolved with CH_2Cl_2 and washed with water and Brine. The

organic layer was dried over Na_2SO_4 . Removal of the solvent gave the amine product, which was used for the next step reaction without further purification. A solution of **1b** (0.37 g, 2.00 mmol) in SOCl_2 (4.00 mL) was heated under reflux for 2 hours at room temperature. After removal of SOCl_2 , the amine product and DIEA (0.68 mL, 4.00 mmol) in dry CH_2Cl_2 (20 mL) were added to the residue. The solution was allowed to proceed for 12 hours at room temperature. After washing with 1M HCl solution, the organic layer was dried over Na_2SO_4 . After removal of the solvent, the residue was purified by flash column chromatography on silica gel using MeOH/ CH_2Cl_2 as the eluent to give the product **12b**. Yield: 1.12 g, 89%. ^1H NMR (500 MHz, CDCl_3) δ 12.76 (s, 1H), 11.01 (s, 1H), 10.13 (s, 1H), 9.18 (d, J = 8.0 Hz, 1H), 9.06 (d, J = 2.1 Hz, 1H), 8.93 (d, J = 2.2 Hz, 1H), 8.48 (d, J = 3.1 Hz, 1H), 8.35 (dd, J = 9.0, 2.6 Hz, 3H), 8.19 (t, J = 8.3 Hz, 1H), 8.08 (d, J = 2.3 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.42 (d, J = 3.1 Hz, 1H), 7.35 (d, J = 3.1 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 4.04 (dd, J = 12.4, 6.3 Hz, 4H), 4.00 (s, 3H), 3.96 (s, 3H), 3.87 (t, J = 7.3 Hz, 2H), 2.03 (s, 4H), 1.94 – 1.76 (m, 8H), 1.52– 1.25 (m, 41H), 0.90 - 0.85 (m, 12H). ^{13}C NMR (125 MHz, CDCl_3) δ 168.8, 167.8, 165.0, 163.4, 163.3, 163.0, 160.1, 156.2, 156.0, 152.1, 142.3, 141.6, 141.3, 140.8, 138.1, 138.0, 136.9, 133.5, 133.2, 132.3, 132.1, 129.0, 126.8, 126.7, 126.6, 125.6, 125.5, 125.4, 124.9, 124.8, 115.5, 114.6, 112.2, 111.8, 111.2, 110.6, 68.7, 68.6, 63.4, 63.3, 60.7, 59.3, 58.8, 31.8, 31.6, 30.7, 30.6, 29.3, 29.2, 29.19, 29.2, 28.9, 28.9, 26.2, 26.1, 25.9, 22.6, 22.5, 14.3, 14.1, 14.0. HRMS-ESI: calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{69}\text{H}_{94}\text{FN}_7\text{NaO}_{14}$): m/z 1286.6735, found: m/z 1286.6750.

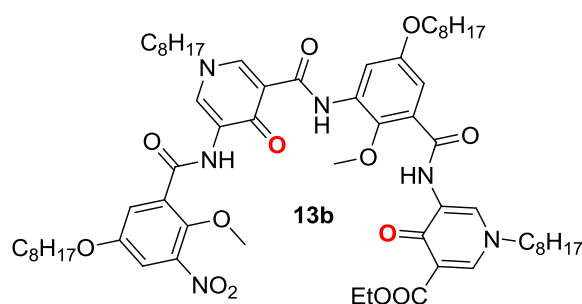
Compound 12



To a solution of **12b** (0.63 g, 0.50 mmol) and iron (0.14 g, 2.50 mmol) in EtOH (50 mL) and THF (50 mL) was added acetate acid (1.00 mL). The solution was refluxed for 5 hours. After cooling, the solvent was filtered and removed then the residue was dissolved in CH₂Cl₂ (50 mL) and washed with water (3 × 100 mL). The organic layer was dried over Na₂SO₄. Removal of the solvent gave the amine product, which was used for the next step reaction without further purification. To a solution of amine in 1,4-dioxane (50 mL), 1M of KOH (1.00 mmol, 1.00 mL) was added and refluxed for 5 hours. After quenching with water (30 mL), the aqueous layer was neutralized by addition 1M HCl (1.00 mL). The mixture was extracted with CH₂Cl₂ (3 × 50 mL). The organic extracts were dried over NaSO₄ and concentrated under reduced pressure. To the solution of the residue in dry CH₂Cl₂ (20 mL), BOP (0.66 g, 1.50 mmol) and DIEA (0.26 mL, 2.00 mmol) were added. The solution was stirred at room temperature for 12 hours at room temperature. The solution was washed with 1M HCl solution. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using MeOH/CH₂Cl₂ as the eluent to give the product **12**, three-step total yield: 0.28 g, 42%. ¹H NMR (500 MHz, CDCl₃/DMSO-*d*₆ = 4/1) δ 13.01 (s, 1H), 12.80 (s, 1H), 11.23 (s, 1H), 10.77 (s, 1H), 9.10 (d, *J* = 19.9 Hz, 1H), 8.77 (s, 1H), 8.61 (s, 1H), 8.49 (s, 1H), 8.22 (s, 1H), 8.02 (s, 1H), 7.93 (s, 1H), 7.62 (s, 1H), 7.09 (d, *J* = 21.6 Hz, 2H), 6.86 (s, 1H), 4.08 – 3.93 (m, 14), 1.93 (s, 4H), 1.86 – 1.77 (m, 4H), 1.53 – 1.51 (m, 4H), 1.44 – 1.20 (m, 37H), 0.89-0.82 (m, 12H). ¹³C NMR (125 MHz, CDCl₃/DMSO-*d*₆ = 4/1) δ 168.6, 168.0, 162.5, 162.4, 161.4, 160.9, 159.6, 155.3, 155.2, 151.3, 149.3, 141.1, 140.6, 140.2, 134.0, 139.9, 133.2, 132.4, 132.2, 131.6, 128.2, 128.1, 126.6, 125.9, 124.5, 124.4, 124.3, 124.2, 123.8, 123.7, 121.1, 119.4, 119.4, 115.2, 114.4, 110.8, 110.5, 109.3, 109.3, 109.2, 108.7, 108.6, 68.1, 67.9, 64.04, 63.4, 63.4, 59.2, 59.1, 37.5, 37.4, 31.8, 31.8, 31.6, 31.6, 30.5, 30.4, 29.5, 29.3, 29.3, 29.0, 26.3, 26.2,

26.1, 22.6, 22.5, 22.4, 14.1, 13.9. HRMS-ESI: calculated for $[M+Na]^+$ ($C_{67}H_{90}FN_7NaO_{11}$): m/z 1210.6575, found: m/z 1210.6573.

Ethyl 5-(2-methoxy-3-(5-(2-methoxy-3-nitro-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (13b)

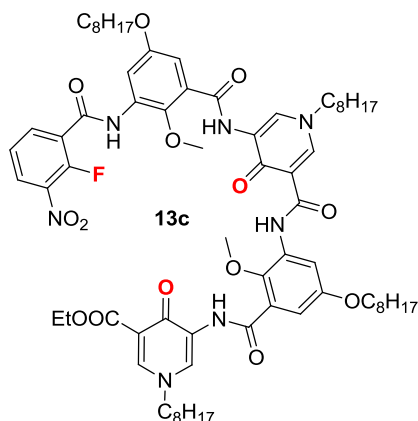


Compound **11e** (2.55 g, 3.00 mmol) was dissolved in CH_2Cl_2 (20 mL) to which ethyl chloroformate (0.33 mL, 3.30 mmol) was added at 0 °C. The reaction mixture was stirred for at least 15 mins after which a solution of **13a**

(1.18 g, 4.00 mmol) and NMM (0.33 mL, 3.30 mmol) in CH_2Cl_2 (20 mL) were added. The reaction mixture was allowed to stir continuously for 12 hours at room temperature. The reaction mixture was washed with 1 M HCl and Brine. Drying over Na_2SO_4 and removal of solvent in *vacuo* gave the crude product and it was purified by flash column chromatography on silica gel using MeOH/ CH_2Cl_2 as the eluent to give the product **13b**. Yield: 2.20 g, 65.0%. 1H NMR (500 MHz, $CDCl_3$) δ 12.58 (s, 1H), 11.16 (s, 1H), 10.91 (s, 1H), 9.06 (d, $J = 2.1$ Hz, 1H), 9.01 (d, $J = 2.2$ Hz, 1H), 8.50 (d, $J = 2.2$ Hz, 1H), 8.39 (d, $J = 3.1$ Hz, 1H), 8.17 (d, $J = 2.2$ Hz, 1H), 7.85 (d, $J = 3.2$ Hz, 1H), 7.49 (d, $J = 3.3$ Hz, 1H), 7.35 (d, $J = 3.1$ Hz, 1H), 4.42 (q, $J = 7.1$ Hz, 2H), 4.13 (s, 3H), 4.06 – 3.98 (m, 9H), 3.90 (t, $J = 7.3$ Hz, 2H), 1.83 (m, 10H), 1.50 – 1.16 (m, 41H), 0.91– 0.86 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 167.9, 165.4, 163.7, 162.6, 162.0, 155.6, 154.8, 145.2, 144.9, 142.7, 142.6, 141.4, 133.6, 133.4, 131.7, 128.8, 127.4, 126.2, 125.5, 120.9, 116.2, 115.0, 114.4, 112.5, 110.2, 69.2, 68.6, 64.6, 62.7, 62.6, 61.2, 59.3, 58.9, 31.8, 31.7, 31.6, 30.8, 30.7, 29.7, 29.3, 29.2, 29.1, 29.0, 28.9, 28.9, 26.2, 25.9, 25.8, 22.6, 22.6, 22.5, 14.4, 14.1, 14.0, 14.0.

Ethyl 5-(3-(5-(3-(2-fluoro-3-nitrobenzamido)-2-methoxy-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-2-methoxy-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (13c)

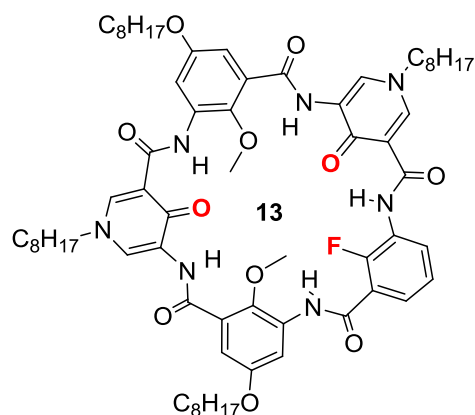
1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**13c**)



To a solution of **13b** (2.25 g, 2.00 mmol) and iron (0.56 g, 10 mmol) in EtOH (100 mL) was added acetate acid (2.00 mL). The solution was refluxed for 2 hours at room temperature. After cooling, the solvent was removed and the residue was dissolved with CH₂Cl₂ and washed with water and Brine. The organic layer was dried over Na₂SO₄. Removal of the solvent gave the amine product, which was used

for the next step reaction without further purification. A solution of **1b** (0.55 g, 3.00 mmol) in SOCl₂ (3.00 mL) was heated under reflux for 2 hours at room temperature. After removal of SOCl₂, the amine product and DIEA (1.00 mL, 6.00 mmol) in dry CH₂Cl₂ (20 mL) were added into the residue. The solution was allowed to proceed for 12 hours at room temperature. After washing with 1M HCl solution, the organic layer was dried over Na₂SO₄. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using MeOH/CH₂Cl₂ as the eluent to give the product **13c**. Yield: 2.07 g, 82%. ¹H NMR (300 MHz, CDCl₃) δ 12.62 (s, 1H), 10.99 (s, 1H), 10.92 (s, 1H), 9.58 (s, 1H), 8.99 – 8.91 (m, 2H), 8.39 (s, 1H), 8.34 (d, *J* = 3.2 Hz, 1H), 8.21 (t, *J* = 6.7 Hz, 1H), 8.13 – 7.97 (m, 3H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 2.9 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.04 – 3.85 (m, 14H), 1.93 – 1.71 (m, 8H), 1.46 – 1.22 (m, 43H), 0.89 – 0.82 (m, 12H). ¹³C NMR (125 MHz, CDCl₃) δ 168.8, 168.7, 167.6, 163.7, 163.6, 163.0, 162.9, 162.8, 162.7, 162.5, 160.8, 143.1, 143.0, 142.4, 142.3, 142.1, 140.7, 137.5, 137.4, 137.4, 136.4, 133.6, 132.8, 132.7, 132.1, 131.8, 128.0, 126.8, 126.3, 126.2, 126.1, 125.3, 125.2, 124.8, 124.7, 124.6, 124.5, 115.6, 115.5, 113.7, 113.4, 113.3, 112.2, 111.4, 109.6, 109.6, 68.4, 68.3, 62.7, 62.7, 62.4, 60.3, 59.2, 58.8, 31.7, 31.5, 30.6, 30.5, 29.2, 29.1, 29.1, 28.8, 26.1, 26.0, 25.9, 25.8, 22.0, 22.4, 14.1, 13.9, 13.8. HRMS-ESI: calculated for [M+Na]⁺ (C₆₉H₉₄FN₇NaO₁₄): *m/z* 1286.6735, found: *m/z* 1286.6728.

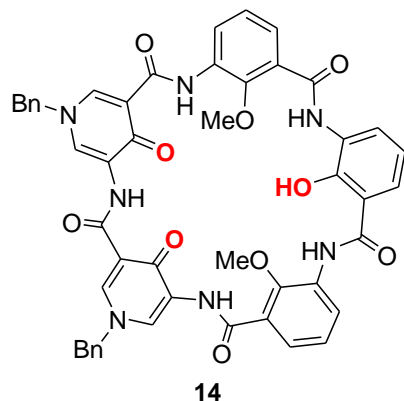
Compound 13



To a solution of **13c** (0.63 g, 0.50 mmol) and iron (0.14 g, 2.50 mmol) in EtOH (50 mL) and THF (50 mL) was added acetate acid (1.00 mL). The solution was refluxed for 5 hours. After cooling, the solvent was filtered and removed then the residue was dissolved in CH₂Cl₂ (50 mL) and washed with water (3 × 100 mL). The organic layer was dried over Na₂SO₄. Removal of the solvent gave the amine product, which was used for the next step reaction without further purification. To a solution of amine in dioxane (50 mL), 1M of KOH (1.00 mmol, 1.00 mL) was added and refluxed for 5 hours. After quenching with water (30 ml), the aqueous layer was neutralized by addition of 1M HCl (1.00 mL). The mixture was extracted with CH₂Cl₂. The organic extracts were dried over NaSO₄ and concentrated under reduced pressure. To the solution of the residue in dry CH₂Cl₂ (20 mL), BOP (0.66 g, 1.50 mmol) and DIEA (0.26 mL, 2.00 mmol) were added. The solution was stirred at room temperature for 12 hours at room temperature. The solution was washed with 1M HCl solution. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using MeOH/CH₂Cl₂ as the eluent to give the product **13**, three-step total yield: 243 mg, 41%. ¹H NMR (500 MHz, CDCl₃) δ 13.15 (s, 1H), 13.10 (s, 1H), 11.40 (s, 1H), 11.31 (s, 1H), 9.37 (d, *J* = 21.6 Hz, 1H), 8.69 (s, 2H), 8.54 (s, 1H), 8.19 (s, 1H), 8.15 (s, 1H), 8.10 (s, 1H), 8.08 (s, 1H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.21 – 7.16 (m, 2H), 7.13 (s, 1H), 4.12 (s, 6H), 4.03 – 3.96 (m, 4H), 3.96 – 3.86 (m, 4H), 1.92 - 1.91 (m, 4H), 1.88 - 1.82 (m, 4H), 1.47 – 1.24 (m, 40H), 0.96 - 0.89 (m, 12H). ¹³C NMR (125 MHz, CDCl₃) δ 168.6, 168.5, 162.3, 162.1, 161.9, 161.5, 159.7, 155.4, 155.2, 151.4, 149.4, 142.0, 141.3, 139.8, 139.7, 134.0, 132.8, 131.9, 131.4, 131.4, 128.3, 128.2, 126.1, 126.0, 126.0, 124.5, 124.2, 124.1, 123.9, 123.8, 119.4, 119.3, 114.9, 110.9, 110.7, 108.9, 108.3, 68.0, 62.7, 62.4, 59.2, 59.1, 31.8, 31.6, 31.6, 30.6, 30.1, 29.5, 29.4, 29.3, 29.2, 29.2, 29.1, 29.0, 26.4, 26.3, 26.1, 26.04 22.6, 22.5, 22.5, 22.4, 14.0, 13.9. HRMS-ESI: calculated for

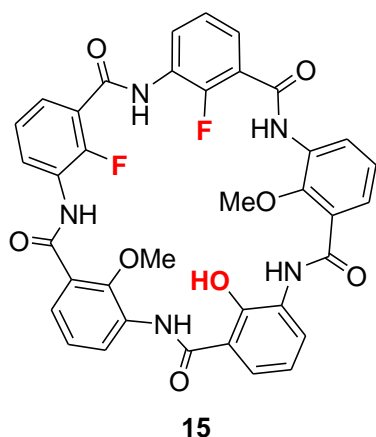
$[M+Na]^+$ ($C_{67}H_{90}FN_7NaO_{11}$): m/z 1210.6575, found: m/z 1210.6573.

Pentamer 14



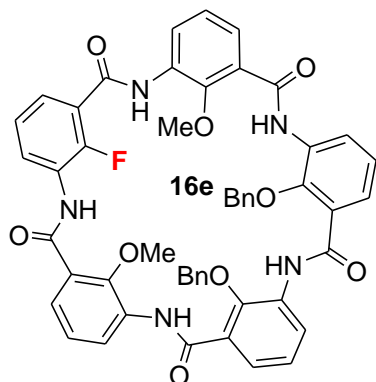
Pentamer **6a** (293 mg, 0.3mmol) was reduced by catalytic hydrogenation in THF (90 mL) at 60 °C, using 10% Pd/C (30 mg, 10%) as the catalyst for 4 hours. The reaction mixture was then filtered and the solvent removed in *vacuo* and washed with ether to give the green solid pentamer **14**. Yield: 159 mg, 60%. HRMS-ESI: calculated for $[M]^-$ ($C_{49}H_{39}N_7O_{10}$): m/z 884.2686, found: m/z 884.2691.

Pentamer 15



Pentamer **6b** (80 mg, 0.1 mmol) was reduced by catalytic hydrogenation in THF (30 mL) at 60 °C, using 10% Pd/C (8 mg, 10%) as the catalyst for 48 hours. The reaction mixture was then filtered and the solvent removed in *vacuo* and washed with ether to give the green solid pentamer **15**. Yield: 42 mg, 60%. HRMS-ESI: calculated for $[M]^-$ ($C_{37}H_{26}F_2N_5O_8$): m/z 706.1755, found: m/z 706.1765.

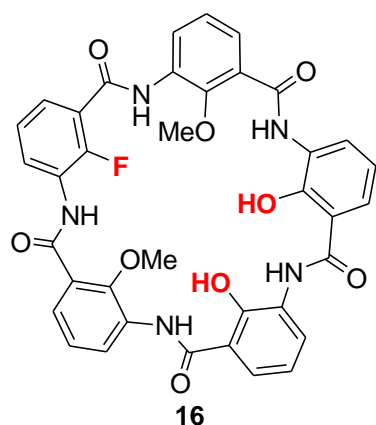
Pentamer 16e



To a solution of **5e** (473 mg, 0.50 mmol) and iron (112 mg, 2.0 mmol) in EtOH/THF (5 mL/2 mL) was added acetate acid (1.0 mL). The reaction was refluxed for 3 hours. After cooling, the solvent was removed and the residue was dissolved with CH_2Cl_2 and washed with water and Brine. The organic layer was dried over Na_2SO_4 . After removal of the solvent, the residue was not purified, but used directly in the next step. To the solution of residue in hot dioxane (1.5 mL) was added 1M KOH (1.0

mL). The reaction was heated under reflux for 4 hours. After quenching with water (15 mL), the aqueous layer was neutralized by addition 1M HCl (1.5 mL). The mixture was extracted with CHCl₃ (3x15 mL). The organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. To the solution of the residue in dry CH₂Cl₂ (10 mL) was added BOP (0.55 g, 2.5 mmol) and DIEA (0.25 mL). The reaction was stirred in room temperature for 6 hours. The reaction was washed with HCl solution, aqueous sat. NaHCO₃ and Brine. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using CH₂Cl₂/ethyl acetate (20/1 v/v) as the eluent to give the product **16e**, three-step total yield: 230 mg, 52%. ¹H NMR (500 MHz, CDCl₃): δ 10.53 (d, 1H, *J* = 4.1 Hz), 10.42 (s, 1H), 10.36 (s, 1H), 10.20 (s, 1H), 9.52 (d, 1H, *J* = 19.3 Hz), 8.98 (td, 1H, *J* = 8.0, 1.5 Hz), 8.91 (ddd, 2H, *J* = 11.2, 8.1, 1.6 Hz), 8.84 (dd, 1H, *J* = 8.1, 1.5 Hz), 8.82 (dd, 1H, *J* = 8.1, 1.6 Hz), 8.05 (td, 1H, *J* = 7.9, 1.6 Hz), 7.95 (ddd, 2H, *J* = 10.9, 7.9, 1.6 Hz), 7.89 (dd, 1H, *J* = 7.9, 1.6 Hz), 7.82 (dd, 1H, *J* = 7.9, 1.6 Hz), 7.48 (t, 1H, *J* = 8.0 Hz), 7.45 – 7.37 (m, 4H), 7.18 – 7.07 (m, 4H), 7.06 – 6.90 (m, 6H), 5.08 (d, 1H, *J* = 11.2 Hz), 5.02 (q, 2H, *J* = 11.2 Hz), 4.91 (d, 1H, *J* = 11.2 Hz), 3.86 (s, 3H), 3.80 (s, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 162.82, 162.58, 162.41, 162.09, 160.24, 151.58, 149.74, 146.54, 146.44, 145.21, 145.19, 133.74, 133.71, 133.16, 133.14, 132.56, 132.13, 129.51, 129.43, 129.36, 129.21, 128.49, 127.74, 127.64, 127.19, 126.90, 126.46, 126.36, 126.33, 126.22, 126.16, 126.01, 125.95, 125.90, 125.47, 125.09, 124.42, 124.28, 123.79, 123.69, 120.37, 79.94, 79.90, 62.75, 62.64. HRMS-ESI: calculated for [M]⁺(C₅₁H₄₀FO₉N₅)⁺: *m/z* 884.2737, found: *m/z* 884.2698.

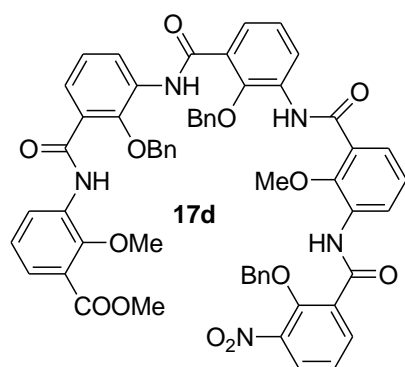
Pentamer 16



Pentamer **16e** (265 mg, 0.3mmol) was reduced by catalytic hydrogenation in THF (90 mL) at 60 °C, using 10% Pd/C (53 mg, 20%) as the catalyst for 12 hours at room temperature. The reaction mixture was then filtered and the solvent removed in *vacuo* and washed with ether to give the green solid pentamer **16**. Yield: 90 mg, 42%. ¹H NMR (500 MHz, DMSO-*d*₆:CDCl₃): δ 11.71 (s, 1H), 11.01

(s, 1H), 10.92 (s, 1H), 10.74 (s, 1H), 10.31 (bs, 1H), 9.63 (d, 1H, $J = 17.9$ Hz), 8.81 (d, 1H, $J = 7.9$ Hz), 8.73 (t, 1H, $J = 7.2$ Hz), 8.66 – 8.57 (m, 2H), 8.55 (d, 1H, $J = 7.3$ Hz), 8.02 – 7.69 (m, 5H), 7.67 (d, 1H, $J = 7.5$ Hz), 7.33–7.26 (m, 3H), 7.11 (q, 2H, $J = 8.0$ Hz), 4.07 (s, 6H). ^{13}C NMR (126 MHz, DMSO- d_6 :CDCl $_3$): δ 163.72, 163.42, 162.42, 161.99, 160.30, 151.93, 149.99, 147.56, 147.15, 144.52, 143.81, 133.45, 132.33, 132.30, 132.01, 127.84, 127.74, 126.39, 126.34, 125.83, 125.64, 125.61, 125.52, 125.48, 125.28, 125.18, 125.13, 124.94, 124.80, 124.53, 124.32, 124.19, 123.19, 122.65, 122.61, 63.30, 63.14. HRMS-ESI: calculated for $[\text{M}]^-$ (C $_{51}$ H $_{27}$ FN $_5$ O $_9$) $^-$: m/z 704.1798, found: m/z 704.1803.

Methyl 3-(2-(benzyloxy)-3-(2-(benzyloxy)-3-(2-(methoxy)-3(2-(benzyloxy)-3-nitrobenzamido)benzamido)benzamido)benzamido)-2- methoxybenzoate (17d)

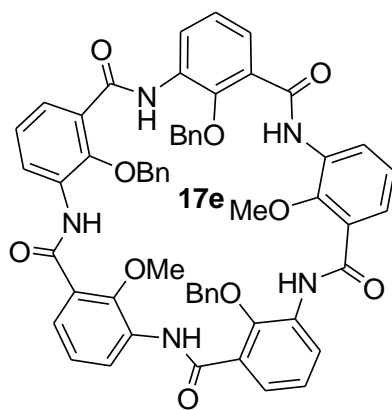


To a solution of **1f** (1.5 g, 1.9 mmol) and iron (410 mg, 7.4 mmol) in EtOH (20 mL) was added acetate acid (2 mL). The reaction was refluxed for 2 hours at room temperature. After cooling, the solvent was removed and the residue was dissolved with CH $_2$ Cl $_2$ and washed with water and Brine. The organic layer was dried over Na $_2$ SO $_4$. Removal of the solvent gave the amine product

used for the next step reaction without further purification. Acid **1k** (628 mg, 2.3 mmol) was dissolved in CH $_2$ Cl $_2$ (20 mL) to which DMF (0.06 mL), (COCl) $_2$ (0.6 mL, 4.6 mmol) was added at room temperature. The reaction mixture was stirred for 5 hours then the excess (COCl) $_2$ was removed in vacuo to produce the chloride compound. The amine product (1.53 g, 1.9 mmol) and TEA (0.4 mL, 6.9 mmol) in dry CH $_2$ Cl $_2$ (60 mL) were added to the residue. The reaction was allowed to proceed for 4 h. After washing with HCl solution, aqueous sat. NaHCO $_3$ and Brine, the organic layer was dried over Na $_2$ SO $_4$. The residue was recrystallized from methanol to give the pure product **17d** as a white solid. Yield: 1.05 g, 55%. ^1H NMR (500 MHz, CDCl $_3$): δ 9.81 (s, 1H), 9.67 (s, 1H), 9.33 (s, 1H), 9.20 (s, 1H), 8.79 - 8.76 (m, 2H), 8.70 (d, 2H, $J = 8.2$ Hz), 8.35 (dd, 1H, $J = 8.2, 1.9$ Hz), 8.06 (dd, 1H, $J = 8.2, 1.9$ Hz), 7.86 - 7.82 (m, 2H), 7.62 - 7.58 (m, 2H), 7.5 (t, 1H, $J = 8.2$ Hz), 7.39 - 7.32 (m, 3H), 7.21 - 7.13 (m,

6H), 7.12 - 7.01 (m, 7H), 6.95 - 6.89 (m, 3H), 5.11 (s, 2H), 4.83 (s, 2H), 4.79 (s, 2H), 3.90 (s, 3H), 3.60 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.8, 163.5, 163.3, 162.9, 161.9, 149.4, 149.2, 147.2, 146.0, 145.6, 144.9, 136.0, 134.5, 133.9, 132.8, 132.4, 131.4, 131.1, 130.8, 129.5, 129.3, 128.9, 128.9, 128.8, 128.8, 128.6, 128.5, 128.4, 128.4, 128.0, 127.5, 126.8, 126.4, 126.2, 126.1, 125.8, 125.6, 125.5, 125.4, 125.4, 124.8, 124.6, 124.5, 124.4, 124.1, 123.4, 80.3, 78.8, 78.6, 65.8, 62.4, 62.0; MS-ESI: calculated for $[\text{M}]^-(\text{C}_{59}\text{H}_{48}\text{N}_5\text{O}_{13})$: m/z 1034.3254, found: m/z 1034.3219.

Pentamer **17e**

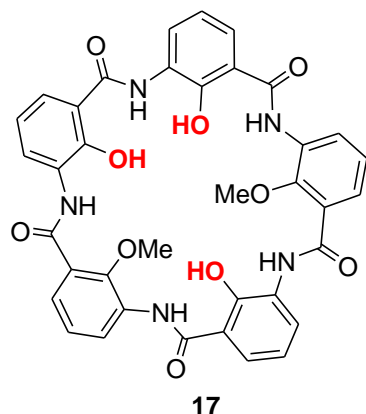


To a solution of **17d** (600 mg, 0.58 mmol) and iron (130 mg, 2.32 mmol) in EtOH (6 mL) was added acetate acid (0.6 mL). The reaction was refluxed for 2 hours at room temperature. The reaction was dissolved with CH_2Cl_2 and washed with water and Brine. The organic layer was dried over Na_2SO_4 . After removal of the solvent, the residue was not purified, but used directly in the next step.

To the solution of residue in hot methanol (10 mL) was added 1M NaOH (1.2 mL). The reaction was heated under reflux for 2 hours at room temperature. After quenching with water (10 mL), the aqueous layer was neutralized by addition 1M HCl (1.2 mL). The mixture was extracted with CH_2Cl_2 . The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. To the solution of the residue in dry CH_2Cl_2 (25 mL) was added BOP (774 mg, 1.8 mmol) and DIEA (0.41 mL, 2.4 mmol). The reaction was stirred in room temperature for 6 hours. The reaction was washed with HCl solution, aqueous sat. NaHCO_3 and brine. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using ethyl acetate / CH_2Cl_2 (1/10 v/v) as the eluent to give the product **17e**, three-step total yield: 104 mg, 18%. ^{13}C NMR (125 MHz, CDCl_3) δ 163.3, 162.9, 162.8, 162.6, 162.5, 162.4, 162.4, 162.3, 162.2, 162.2, 146.5, 146.3, 146.2, 146.1, 145.1, 144.9, 144.9, 144.5, 144.5, 144.3, 134.1, 133.7, 133.6, 133.4, 133.4, 133.3, 133.1, 133.1, 133.1, 133.0, 132.8, 132.8, 132.7, 132.7, 132.4, 132.4, 130.1, 129.7, 129.6, 129.4, 129.3, 129.2,

129.2, 129.1, 128.6, 128.5, 128.5, 128.2, 127.9, 127.9, 127.6, 127.5, 126.7, 126.4, 126.2, 126.2, 126.2, 126.1, 126.1, 126.1, 126.0, 125.9, 125.9, 125.8, 125.8, 125.7, 125.6, 124.1, 124.0, 123.8, 123.6, 123.5, 123.4, 79.9, 79.7, 79.7, 79.7, 79.7, 79.4, 63.6, 63.4, 62.5, 62.4; MS-ESI: calculated for $[M]^{-}(\text{C}_{58}\text{H}_{46}\text{N}_5\text{O}_{10}^{-})$: m/z 972.3250, found: m/z 972.3217.

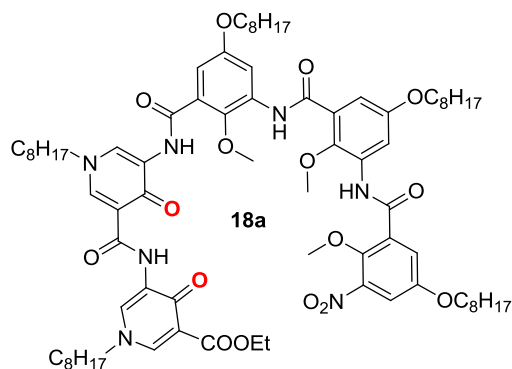
Pentamer 17



Compound **17e** (130 mg, 0.13 mmol) was reduced by catalytic hydrogenation in THF (25 mL) at 60 °C, using 10% Pd-C (39 mg, 30%) as the catalyst for 48 hours. The reaction mixture was then filtered and the solvent removed in *vacuo* and washed with ether to give the green solid pentamer **17**. Yield: 66%. ^1H NMR (500 MHz, d_6 -DMSO:CDCl₃ = 10:1): δ 11.86 (b, 1H), 11.23 (b, 1H), 11.07 (s, 3H), 8.86 – 8.84 (m, 2H), 8.70 – 8.66 (m, 3H), 7.88 – 7.75 (m, 5H), 7.42 (t, 2H, J

= 7.6 Hz), 7.22 – 7.21 (m, 3H); ^{13}C NMR (125 MHz, d_6 -DMSO:CDCl₃ = 10:1): δ 163.1, 162.9, 161.6, 161.5, 147.0, 146.8, 133.2, 132.4, 132.2, 132.0, 126.0, 125.9, 125.5, 125.5, 124.8, 124.8, 124.7, 124.6, 124.5, 124.3, 123.7, 123.3, 123.2, 123.1, 122.8, 122.3, 122.1, 63.1, 63.0; HRMS-ESI: calculated for $[M+\text{Na}]^{+}(\text{C}_{37}\text{H}_{29}\text{N}_5\text{O}_{10}+\text{Na}^{+})$: 726.1812 m/z , found: 726.1839 m/z .

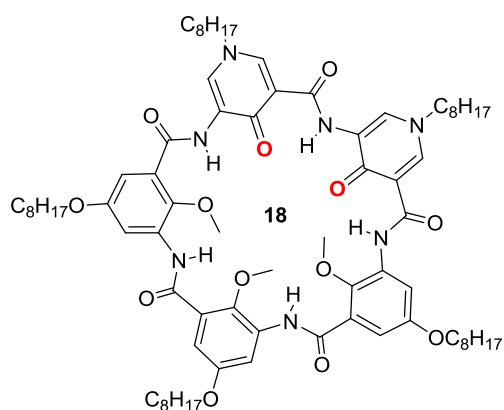
5-(5-(2-methoxy-3-(2-methoxy-3-(2-methoxy-3-nitro-5-(octyloxy)benzamido)-5-(octyloxy)benzamido)-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (18a)



To a solution of **12a** (1.27 g, 1.00 mmol) and iron (0.28 g, 5.00 mmol) in EtOH (20 mL) was added acetate acid (1.00 mL). The solution was refluxed for 2 hours at room temperature. After cooling, the solvent was removed and the residue was dissolved with CH₂Cl₂ and washed with water and Brine.

The organic layer was dried over Na₂SO₄. Removal of the solvent gave the amine product, which was used for the next step reaction without further purification. Acid **7a** (0.65g, 2.00 mmol) in SOCl₂ (2.00 mL) was heated under reflux for 2 hours at room temperature. After removal of SOCl₂, the amine product and DIEA (0.68 mL, 4.00 mmol) in dry CH₂Cl₂ (60 mL) were added to the residue. The solution was allowed to proceed for 12 hours at room temperature. After washing with 1M HCl solution, the organic layer was dried over Na₂SO₄. The residue was purified by column chromatography on silica gel using MeOH/CH₂Cl₂ as the eluent to give **18a** as a white solid. Yield: 0.77 g, 74%. ¹H NMR (500 MHz, CDCl₃) δ 12.78 (s, 1H), 10.93 (s, 1H), 10.32 (s, 1H), 10.11 (s, 1H), 9.05 (d, *J* = 2.3 Hz, 1H), 8.92 (d, *J* = 2.2 Hz, 1H), 8.46 (d, *J* = 3.1 Hz, 1H), 8.43 (d, *J* = 3.1 Hz, 1H), 8.37 (d, *J* = 2.3 Hz, 1H), 8.11 (d, *J* = 2.3 Hz, 1H), 7.93 (d, *J* = 3.2 Hz, 1H), 7.49 (d, *J* = 3.3 Hz, 1H), 7.39 (d, *J* = 3.1 Hz, 1H), 7.32 (d, *J* = 3.1 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.16 (s, 3H), 4.07 – 4.02 (m, 6H), 3.99 (s, 3H), 3.96 (s, 3H), 3.88 – 3.85 (m, 2H), 1.95 – 1.77 (m, 8H), 1.51 – 1.42 (m, 4H), 1.35 – 1.23 (m, 53H), 0.91 – 0.84 (m, 15H). ¹³C NMR (125 MHz, CDCl₃) δ 168.7, 167.7, 165.2, 163.5, 163.2, 163.1, 161.7, 156.2, 156.0, 154.9, 145.0, 144.4, 142.4, 141.6, 141.3, 140.8, 133.5, 133.3, 132.7, 132.3, 129.8, 126.8, 126.8, 126.6, 125.7, 121.0, 115.6, 115.1, 114.6, 111.8, 111.7, 110.7, 110.5, 69.2, 68.6, 68.6, 64.8, 63.6, 63.2, 60.7, 59.7, 58.7, 31.8, 31.7, 31.6, 30.7, 30.6, 29.6, 29.3, 29.2, 29.2, 29.1, 29.0, 28.9, 26.2, 25.9, 25.8, 22.7, 22.6, 22.5, 14.3, 14.1, 14.0, 13.9. HRMS-ESI: calculated for [M+Na]⁺ (C₇₈H₁₁₃FN₇NaO₁₆): *m/z* 1326.8136, found: *m/z* 1326.8073.

Compound 18

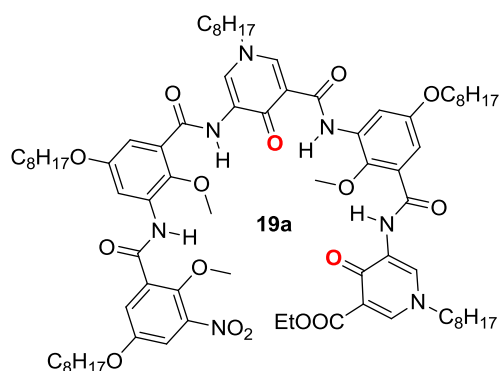


To a solution of **18a** (0.70 g, 0.50 mmol) and iron (0.14 g, 2.50 mmol) in EtOH (50 mL) and THF (50 mL) was added acetate acid (1.00 mL). The solution was refluxed for 5 hours. After cooling, the solvent was filtered and removed then the residue was dissolved with CH₂Cl₂ (50 mL) and washed with water

(3 × 100 mL). The organic layer was dried over Na₂SO₄. Removal of the solvent gave the

amine product, which was used for the next step reaction without further purification. To a solution of amine in dioxane (50 mL), 1M of KOH (1.00 mmol, 1.00 mL) was added and refluxed for 5 hours. After quenching with water (30 mL), the aqueous layer was neutralized by addition of 1M HCl (1.00 mL). The mixture was extracted with CH₂Cl₂. The organic extract was dried over NaSO₄ and concentrated under reduced pressure. To the solution of the residue in dry CH₂Cl₂ (20 mL) was added BOP (0.66 g, 1.50 mmol) and DIEA (0.26 mL, 2.00 mmol). The solution was stirred at room temperature for 12 hours at room temperature. The solution was washed with 1M HCl solution. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using MeOH/CH₂Cl₂ as eluent to give the product **18**. Yield: 0.30 g, 45%. ¹H NMR (500 MHz, CDCl₃) δ 13.14 (s, 1H), 13.10 (s, 1H), 11.39 (s, 1H), 11.23 (s, 1H), 11.14 (s, 1H), 8.88 (d, *J* = 1.4 Hz, 1H), 8.86 (d, *J* = 1.4 Hz, 1H), 8.36 (d, *J* = 1.8 Hz, 1H), 8.34 (d, *J* = 2.3 Hz, 1H), 8.31 (s, 1H), 8.29 (s, 2H), 7.31 (d, *J* = 2.8 Hz, 1H), 7.25 (d, *J* = 2.3 Hz, 1H), 7.23 (d, *J* = 2.6 Hz, 1H), 4.25 (s, 3H), 4.16 – 4.05 (m, 10H), 4.01 (s, 3H), 3.92 (s, 3H), 2.03 – 1.98 (m, 4H), 1.92 – 1.83 (m, 6H), 1.55 – 1.50 (m, 6H), 1.48 – 1.25 (m, 44H), 0.91 (m, 15H). ¹³C NMR (125 MHz, CDCl₃) δ 168.9, 168.6, 162.7, 162.4, 162.1, 161.8, 161.4, 155.9, 155.8, 155.6, 141.1, 140.8, 140.6, 140.6, 140.5, 133.5, 133.4, 132.2, 131.9, 127.0, 126.7, 124.6, 124.3, 124.2, 115.7, 115.0, 111.3, 110.7, 109.6, 109.2, 68.4, 68.3, 63.9, 62.9, 62.7, 59.4, 59.2, 31.8, 31.7, 30.7, 30.6, 29.6, 29.5, 29.5, 29.4, 29.3, 29.1, 29.1, 29.0, 26.4, 26.3, 26.2, 26.1, 22.7, 22.6, 14.1, 14.0. HRMS-ESI: calculated for [M+H]⁺ (C₇₆H₁₁₀N₇NaO₁₃): *m/z* 1328.7178, found: *m/z* 1328.8095.

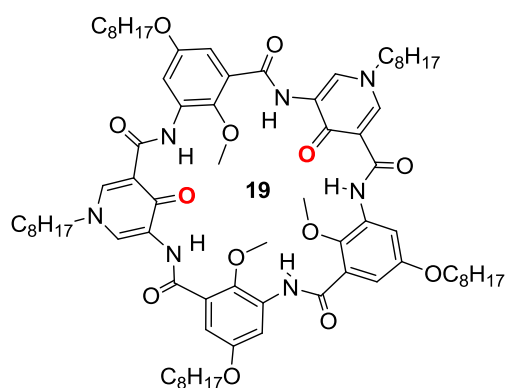
Ethyl 5-(2-methoxy-3-(5-(2-methoxy-3-(2-methoxy-3-nitro-5-(octyloxy)benzamido)-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxamido)-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (19a)



To a solution of **13b** (2.25 g, 2.00 mmol) and iron (0.56 g, 10 mmol) in EtOH (100 mL) was added acetate acid (2.00 mL). The solution was refluxed for 2 hours at room

temperature. After cooling, the solvent was removed and the residue was dissolved with CH_2Cl_2 and washed with water and Brine. The organic layer was dried over Na_2SO_4 . Removal of the solvent gave the amine product, which was used for the next step reaction without further purification. A solution of **7a** (0.97 g, 3.00 mmol) in SOCl_2 (3.00 mL) was heated under reflux for 2 hours at room temperature. After removal of SOCl_2 , the amine product and DIEA (1.00 mL, 6.00 mmol) in dry CH_2Cl_2 (20 mL) were added to the residue. The solution was allowed to proceed for 12 hours at room temperature. After washing with 1M HCl solution, the organic layer was dried over Na_2SO_4 . After removal of the solvent, the residue was purified by flash column chromatography on silica gel using $\text{MeOH}/\text{CH}_2\text{Cl}_2$ as eluent to give the product **19a**. Yield: 2.08 g, 74%. ^1H NMR (500 MHz, CDCl_3) δ 12.73 (s, 1H), 11.13 (s, 1H), 10.90 (s, 1H), 10.41 (s, 1H), 9.07 (s, 1H), 9.00 (d, $J = 2.1$ Hz, 1H), 8.48 (d, $J = 2.0$ Hz, 1H), 8.41 (d, $J = 2.9$ Hz, 1H), 8.37 (d, $J = 3.1$ Hz, 1H), 8.15 (d, $J = 2.2$ Hz, 1H), 7.92 (d, $J = 3.2$ Hz, 1H), 7.48 (d, $J = 3.2$ Hz, 1H), 7.36 – 7.33 (m, 2H), 4.23 (q, $J = 7.1$ Hz, 2H), 4.16 (s, 3H), 4.05 – 4.00 (m, 12H), 3.98 (s, 3H), 3.90 (t, $J = 7.3$ Hz, 2H), 1.96 – 1.85 (m, 4H), 1.85 – 1.74 (m, 8H), 1.50 – 1.41 (m, 4H), 1.39 – 1.22 (m, 45H), 0.90 – 0.86 (m, 15H). ^{13}C NMR (125 MHz, CDCl_3) δ 168.9, 167.6, 164.6, 163.4, 163.2, 162.6, 161.5, 155.9, 155.5, 154.6, 145.2, 144.0, 142.5, 142.4, 141.7, 140.9, 133.6, 133.1, 132.9, 131.9, 129.6, 128.9, 128.1, 128.0, 126.9, 126.0, 125.7, 125.4, 125.1, 120.9, 115.9, 115.1, 113.9, 112.3, 111.8, 110.6, 109.9, 77.0, 69.1, 68.5, 68.4, 67.8, 64.7, 63.2, 62.5, 60.6, 59.2, 58.9, 31.7, 31.6, 31.5, 29.3, 29.1, 29.0, 28.9, 26.1, 26.1, 25.9, 25.8, 22.5, 22.5, 22.4, 14.2, 14.0, 13.9, 13.8. HRMS-ESI: calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{78}\text{H}_{113}\text{N}_7\text{NaO}_{16}$): m/z 1426.8136, found: m/z 1426.8130.

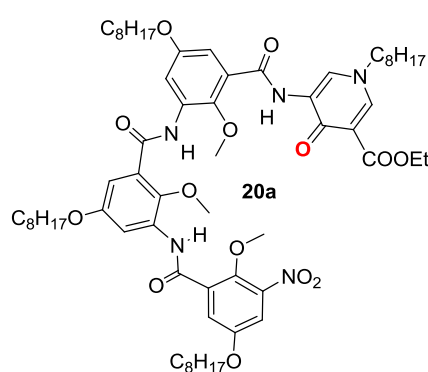
Compound 19



To a solution of **19a** (0.70 g, 0.50 mmol) and iron (0.14 g, 2.50 mmol) in EtOH (50 mL) and THF (50 mL) was added acetate acid (1.00 mL). The solution was refluxed for 5 hours. After cooling, the solvent was filtered

and removed then the residue was dissolved in CH₂Cl₂ (50 mL) and washed with water (3 × 100 mL). The organic layer was dried over Na₂SO₄. Removal of the solvent gave the amine product, which was used for the next step reaction without further purification. To a solution of amine in dioxane (50 mL), 1M of KOH (1.00 mmol, 1.00 mL) was added and refluxed for 5 hours. After quenching with water (30 mL), the aqueous layer was neutralized by addition of 1M HCl (1.00 mL). The mixture was extracted with CH₂Cl₂. The organic extract was dried over Na₂SO₄ and concentrated under reduced pressure. To the solution of the residue in dry CH₂Cl₂ (20 mL), BOP (0.66 g, 1.50 mmol) and DIEA (0.26 mL, 2.00 mmol) were added. The solution was stirred at room temperature for 12 hours at room temperature. The solution was washed with 1M HCl solution. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using MeOH/CH₂Cl₂ as eluent to give the product **19**, three-step total yield: 0.21 mg, 35%. ¹H NMR (500 MHz, CDCl₃) δ 13.06 (s, 1H), 13.02 (s, 1H), 11.33 (s, 1H), 11.23 (s, 1H), 11.00 (s, 1H), 8.71 (s, 1H), 8.60 (s, 1H), 8.32 (s, 1H), 8.22 (s, 1H), 8.15 (s, 1H), 8.06 (s, 1H), 8.00 (s, 1H), 7.21 (s, 1H), 7.09 (s, 1H), 6.96 (s, 1H), 4.05 – 3.80 (m, 19H), 1.89-1.80 (m, 10H), 1.51 – 1.16 (m, 50H), 0.87 – 0.81 (m, 15H). ¹³C NMR (125 MHz, CDCl₃) δ 168.9, 168.8, 162.4, 162.2, 162.1, 161.9, 161.8, 155.6, 155.5, 141.9, 141.6, 141.3, 140.3, 134.2, 133.6, 133.6, 131.9, 131.8, 126.4, 126.2, 124.8, 124.3, 124.2, 115.5, 115.2, 111.3, 111.2, 110.3, 109.3, 108.8, 108.4, 108.3, 68.3, 68.1, 68.0, 63.9, 63.2, 63.1, 62.0, 59.2, 31.8, 31.7, 31.6, 30.7, 30.6, 29.5, 29.4, 29.3, 29.3, 29.2, 29.2, 28.9, 28.8, 26.2, 26.2, 26.1, 26.0, 22.6, 22.5, 14.1, 13.9. MS-ESI: calculated for [M+H]⁺ (C₇₆H₁₁₀N₇NaO₁₃): *m/z* 1328.7178, found: *m/z* 1328.7.

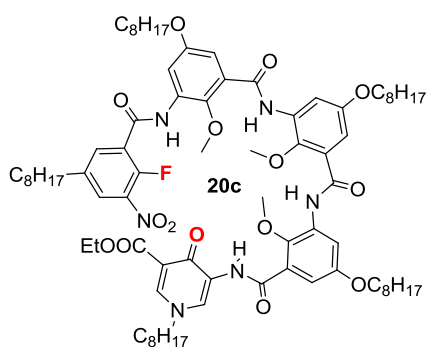
Ethyl 5-(2-methoxy-3-(2-methoxy-3-(2-methoxy-3-nitro-5-(octyloxy)benzamido)-5-(octyloxy)benzamido)-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (20a)



To a solution of **11b** (1.20 g, 2.00 mmol) and iron (0.56 g, 100 mmol) in EtOH (40 mL) was added acetate acid (2.00 mL). The solution was refluxed for

2 hours at room temperature. After cooling, the solvent was removed and the residue was dissolved with CH₂Cl₂ and washed with water and Brine. The organic layer was dried over Na₂SO₄. Removal of the solvent gave the amine product, which was used for the next step reaction without further purification. A solution of **10c** (1.32 g, 2.20 mmol) in SOCl₂ (6.00 mL) was heated under reflux for 2 hours at room temperature. After removal of the SOCl₂, the amine product (2.00 mmol) and DIEA (0.82 mL, 4.80 mmol) in dry CH₂Cl₂ (40 mL) were added to the residue. The solution was allowed to proceed for 12 hours at room temperature. After washing with 1M HCl solution, the organic layer was dried over Na₂SO₄. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using hexane/ethyl acetate as the eluent to give the product **20a**. Yield: 1.73 g, 75%. ¹H NMR (300 MHz, CDCl₃) δ 10.98 (s, 1H), 10.18 (s, 2H), 9.01 (d, *J* = 2.4 Hz, 1H), 8.47 (d, *J* = 3.0 Hz, 1H), 8.43 (d, *J* = 3.0 Hz, 1H), 8.17 (d, *J* = 2.4 Hz, 1H), 7.92 (d, *J* = 3.2 Hz, 1H), 7.53 (d, *J* = 3.2 Hz, 1H), 7.42 (d, *J* = 3.1 Hz, 1H), 7.35 (d, *J* = 3.1 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.09 – 4.03 (m, 9H), 3.94 – 3.88 (m, 8H), 1.89 – 1.78 (m, 8H), 1.64–1.29 (m, 43H), 0.94 – 0.81 (m, 12H). MS-ESI: calculated for [M+Na]⁺ (C₆₄H₉₃N₅O₁₄Na): *m/z* 1178.67 found: *m/z* : 1178.66

Ethyl 5-(3-(3-(3-(2-fluoro-3-nitro-5-octylbenzamido)-2-methoxy-5-(octyloxy)benzamido)-2-methoxy-5-(octyloxy)benzamido)-2-methoxy-5-(octyloxy)benzamido)-1-octyl-4-oxo-1,4-dihydropyridine-3-carboxylate (20c)

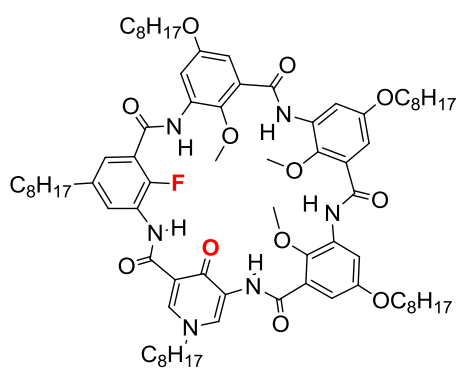


To a solution of **20a** (1.73 g, 1.50 mmol) and iron (0.42 g, 7.50 mmol) in EtOH (30 mL) was added acetate acid (1.50 mL). The solution was refluxed for 2 hours at room temperature. After cooling, the solvent was removed and the residue was dissolved with CH₂Cl₂ and washed with water and Brine. The

organic layer was dried over Na₂SO₄. Removal of the solvent gave the amine product, which was used for the next step reaction without further purification. A solution of **20b** (0.59 g, 2.00 mmol) in SOCl₂ (6.00 mL) was heated under reflux for 2 hours at room

temperature. After removal of the SOCl_2 , the amine product (1.50 mmol) and DIEA (0.82 mL, 4.80 mmol) in dry CH_2Cl_2 (40 mL) were added to the residue. The solution was allowed to proceed for 12 hours at room temperature. After washing with 1M HCl solution, the organic layer was dried over Na_2SO_4 . After removal of the solvent, the residue was purified by flash column chromatography on silica gel using hexane/ethyl acetate as the eluent to give the product **20c**. Yield: 1.58g, 75%. ^1H NMR (500 MHz, CDCl_3) δ 10.98 (s, 1H), 10.35 (s, 1H), 9.97 (s, 1H), 9.10 (d, $J = 10.8$ Hz, 1H), 9.00 (d, $J = 2.0$ Hz, 1H), 8.47 (d, $J = 3.1$ Hz, 1H), 8.46 (d, $J = 3.1$ Hz, 1H), 8.37 (d, $J = 3.0$ Hz, 1H), 8.20 (dd, $J = 5.7, 1.9$ Hz, 1H), 8.13 (d, $J = 2.1$ Hz, 1H), 7.98 (dd, $J = 5.7, 1.9$ Hz, 1H), 7.42 (d, $J = 3.2$ Hz, 1H), 7.41 (d, $J = 3.1$ Hz, 1H), 7.33 (d, $J = 3.1$ Hz, 1H), 4.27 (q, $J = 7.1$ Hz, 2H), 4.06 – 4.01 (m, 6H), 3.97 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H), 3.90 – 3.89 (m, 2H), 2.72 (t, $J = 7.5$, 2H), 1.89 – 1.85 (m, 2H), 1.84 – 1.75 (m, 6H), 1.66 (dt, $J = 15.4, 7.6$ Hz, 2H), 1.48 – 1.44 (m, 6H), 1.38 – 1.23 (m, 47H), 0.90 – 0.85 (m, 15H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.9, 164.5, 163.3, 162.9, 162.8, 159.9, 156.2, 156.2, 156.0, 152.4, 150.3, 142.4, 141.5, 141.0, 140.9, 140.5, 140.4, 137.7, 137.6, 137.0, 133.3, 133.1, 132.9, 132.2, 128.8, 126.8, 126.2, 125.5, 124.4, 124.3, 114.1, 111.9, 111.8, 111.6, 111.2, 110.8, 110.5, 68.6, 68.5, 68.5, 63.4, 63.3, 63.1, 60.8, 58.9, 34.8, 31.8, 31.6, 30.8, 30.6, 29.3, 29.2, 29.2, 29.1, 29.1, 29.1, 29.0, 28.9, 28.9, 26.1, 25.9, 22.6, 22.5, 22.5, 14.3, 14.1, 14.0, 13.9. MS-ESI: calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{79}\text{H}_{113}\text{FN}_6\text{O}_{15}\text{Na}$): m/z 1427.81 found: m/z : 1427.81.

Compound 20



To a solution of **20c** (0.70 g, 0.50 mmol) and iron (0.14 g, 2.50 mmol) in EtOH (50 mL) and THF (50 mL) was added acetate acid (1.00 mL). The solution was refluxed for 5 hours. After cooling, the solvent was filtered and removed then the residue was dissolved in CH_2Cl_2 (50 mL) and washed with water (3×100 mL). The organic

layer was dried over Na_2SO_4 . The solvent was removed and the residue was dissolve into

dioxane (50 mL). 1M of KOH (1.00 mmol, 1.00 mL) was added to the solution and refluxed for 5 hours. After quenching with water (30 ml), the aqueous layer was neutralized by addition of 1M HCl (1.00 mL). The mixture was extracted with CH₂Cl₂. The organic extract was dried over NaSO₄ and concentrated under reduced pressure. To the solution of the residue in dry CH₂Cl₂ (20 mL) was added BOP (0.66 g, 1.50 mmol) and DIEA (0.26 mL, 2.00 mmol). The solution was stirred at room temperature for 12 hours at room temperature. The organic layer was washed with 1M HCl solution. After removal of the solvent, the residue was purified by flash column chromatography on silica gel using MeOH/CH₂Cl₂ as the eluent to give the product **20**, three-step total yield: 260 mg, 39%. ¹H NMR (500 MHz, CDCl₃) δ 13.14 (s, 1H), 11.44 (s, 1H), 11.00 (s, 2H), 9.49 (s, 1H), 8.99 (s, 1H), 8.71 (s, 1H), 8.43 (s, 2H), 8.34 (s, 2H), 7.70 (s, 1H), 7.41 (s, 1H), 7.33 (s, 2H), 4.12 – 3.95 (m, 17H), 2.70 – 2.67 (t, *J* = 7.5 Hz, 2H), 1.98 – 1.95 (m, 2H), 1.85 – 1.81 (m, 6H), 1.69 (dt, *J* = 15.3, 7.7 Hz, 2H), 1.50 – 1.49 (m, 6H), 1.38 – 1.24 (m, 44H), 0.92 – 0.87 (m, 15H). ¹³C NMR (125MHz, CDCl₃) δ 169.1, 162.5, 161.8, 161.6, 160.6, 156.4, 156.4, 150.1, 148.2, 140.7, 140.6, 140.5, 140.4, 140.3, 133.6, 133.3, 132.7, 132.1, 127.9, 127.8, 126.9, 125.3, 125.2, 125.1, 125.0, 124.9, 124.9, 124.7, 124.4 119.2 119.1, 115.5, 111.6, 111.0, 110.7, 110.4, 110.2 110, 68.6 68.5, 63.7, 63.1, 62.9, 59.5, 35.8 31.8, 31.8, 31.6, 31.2, 30.7 29.6, 29.4, 29.4 29.3, 29.2, 29.0, 26.2, 26.0, 22.7 22.6, 22.5, 14.1, 14.0.

X-ray Crystal Data Sheet for 2, 5, 6 and 14

Identification code	2b	
Empirical formula	C50 H60 N10 O10	
Formula weight	961.08	
Temperature	153(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 23.3719(6) Å	$\alpha = 90^\circ$.
	b = 10.7207(3) Å	$\beta = 114.4100(10)^\circ$.
	c = 26.6334(7) Å	$\gamma = 90 (3)^\circ$.
Volume	6076.8(3) Å ³	
Z	4	
Density (calculated)	1.050 Mg/m ³	
Absorption coefficient	0.612 mm ⁻¹	
F(000)	2040	
Crystal size	0.20 x 0.10 x 0.08 mm ³	
Theta range for data collection	2.12 to 63.67°.	
Index ranges	-26<=h<=27, -12<=k<=12, -30<=l<=28	
Reflections collected	37443	
Independent reflections	9823 [R(int) = 0.0676]	
Completeness to theta = 27.48°	98.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9526 and 0.8873	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	9823 / 265 / 581	
Goodness-of-fit on F ²	1.087	
Final R indices [I>2sigma(I)]	R1 = 0.1641, wR2 = 0.3507	
R indices (all data)	R1 = 0.1793, wR2 = 0.3594	
Largest diff. peak and hole	1.459 and -1.137 e.Å ⁻³	

Identification code	5b	
Empirical formula	C ₃₄ H ₄₆ N ₆ O ₉	
Formula weight	682.77	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 12.1129(9) Å	α = 69.583(2)°.
	b = 12.7793(10) Å	β = 68.112(2)°.
	c = 13.0678(10) Å	γ = 75.921(2)°.
Volume	1744.1(2) Å ³	
Z	2	
Density (calculated)	1.300 Mg/m ³	
Absorption coefficient	0.095 mm ⁻¹	
F(000)	728	
Crystal size	0.10 x 0.08 x 0.04 mm ³	
Theta range for data collection	1.71 to 26.37 °.	
Index ranges	-15 ≤ h ≤ 15, -15 ≤ k ≤ 15, -16 ≤ l ≤ 16	
Reflections collected	53798	
Independent reflections	7139 [R(int) = 0.0794]	
Completeness to theta = 27.48°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9962 and 0.9905	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	7139 / 130 / 538	
Goodness-of-fit on F ²	1.016	
Final R indices [I > 2σ(I)]	R1 = 0.0642, wR2 = 0.1561	
R indices (all data)	R1 = 0.1344, wR2 = 0.1967	
Largest diff. peak and hole	0.255 and -0.222 e.Å ⁻³	

Identification code	5c	
Empirical formula	C42 H30 F3 N7 O8	
Formula weight	817.73	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 12.6347(15) Å	$\alpha = 94.470(3)^\circ$.
	b = 12.8579(16) Å	$\beta = 117.546(2)^\circ$.
	c = 13.3997(17) Å	$\gamma = 101.859(3)^\circ$.
Volume	1851.0(4) Å ³	
Z	2	
Density (calculated)	1.467 Mg/m ³	
Absorption coefficient	0.114 mm ⁻¹	
F(000)	844	
Crystal size	0.40 x 0.24 x 0.20 mm ³	
Theta range for data collection	1.84 to 27.48°.	
Index ranges	-16 ≤ h ≤ 16, -16 ≤ k ≤ 16, -17 ≤ l ≤ 17	
Reflections collected	24267	
Independent reflections	8473 [R(int) = 0.0270]	
Completeness to theta = 27.48°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9776 and 0.9559	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	8473 / 0 / 562	
Goodness-of-fit on F ²	1.051	
Final R indices [I > 2σ(I)]	R1 = 0.0411, wR2 = 0.1078	
R indices (all data)	R1 = 0.0492, wR2 = 0.1129	
Largest diff. peak and hole	0.348 and -0.250 e.Å ⁻³	

Identification code	5d	
Empirical formula	C31 H24 F2 N4 O9	
Formula weight	634.54	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.6353(8) Å	$\alpha = 65.420(2)^\circ$.
	b = 13.1566(13) Å	$\beta = 79.934(2)^\circ$.
	c = 15.6352(16) Å	$\gamma = 74.621(2)^\circ$.
Volume	1373.4(2) Å ³	
Z	2	
Density (calculated)	1.534 Mg/m ³	
Absorption coefficient	0.123 mm ⁻¹	
F(000)	656	
Crystal size	0.60 x 0.44 x 0.44 mm ³	
Theta range for data collection	1.74 to 27.50°.	
Index ranges	-9 ≤ h ≤ 9, -17 ≤ k ≤ 17, -20 ≤ l ≤ 20	
Reflections collected	17991	
Independent reflections	6288 [R(int) = 0.0317]	
Completeness to theta = 27.50°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9478 and 0.9298	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	6288 / 0 / 430	
Goodness-of-fit on F ²	1.031	
Final R indices [I > 2σ(I)]	R1 = 0.0432, wR2 = 0.1064	
R indices (all data)	R1 = 0.0483, wR2 = 0.1099	
Largest diff. peak and hole	0.316 and -0.400 e.Å ⁻³	

Identification code	5e	
Empirical formula	C ₅₂ H ₄₂ F N ₅ O ₁₂	
Formula weight	947.91	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 14.2003(11) Å	α = 90°.
	b = 19.8416(15) Å	β = 111.9200(10)°.
	c = 16.9153(13) Å	γ = 90°.
Volume	4421.4(6) Å ³	
Z	4	
Density (calculated)	1.424 Mg/m ³	
Absorption coefficient	0.105 mm ⁻¹	
F(000)	1976	
Crystal size	0.60 x 0.20 x 0.16 mm ³	
Theta range for data collection	2.05 to 27.50°.	
Index ranges	-18 ≤ h ≤ 15, -25 ≤ k ≤ 25, -13 ≤ l ≤ 21	
Reflections collected	31302	
Independent reflections	10157 [R(int) = 0.0352]	
Completeness to theta = 27.50°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9834 and 0.9395	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	10157 / 4 / 646	
Goodness-of-fit on F ²	1.052	
Final R indices [I > 2σ(I)]	R1 = 0.0482, wR2 = 0.1078	
R indices (all data)	R1 = 0.0586, wR2 = 0.1132	
Largest diff. peak and hole	0.331 and -0.301 e.Å ⁻³	

Identification code	5f	
Empirical formula	C38 H35 N3 O7	
Formula weight	645.69	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 8.8451(8) Å	α = 90°.
	b = 23.553(2) Å	β = 99.906(2)°.
	c = 15.8186(13) Å	γ = 90°.
Volume	3246.4(5) Å ³	
Z	4	
Density (calculated)	1.321 Mg/m ³	
Absorption coefficient	0.092 mm ⁻¹	
F(000)	1360	
Crystal size	0.40 x 0.30 x 0.26 mm ³	
Theta range for data collection	1.57 to 27.50°.	
Index ranges	-11 ≤ h ≤ 11, -18 ≤ k ≤ 30, -19 ≤ l ≤ 20	
Reflections collected	22969	
Independent reflections	7453 [R(int) = 0.0392]	
Completeness to theta = 27.50°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8621 and 0.6748	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	7453 / 45 / 469	
Goodness-of-fit on F ²	1.105	
Final R indices [I > 2σ(I)]	R1 = 0.0803, wR2 = 0.1846	
R indices (all data)	R1 = 0.1024, wR2 = 0.1977	
Largest diff. peak and hole	0.961 and -0.526 e.Å ⁻³	

Identification code	6a	
Empirical formula	C57.50 H49 Cl2 N7 O10.50	
Formula weight	1076.94	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 18.507(2) Å	$\alpha = 90^\circ$.
	b = 11.2044(13) Å	$\beta = 93.092(3)^\circ$.
	c = 24.538(3) Å	$\gamma = 90^\circ$.
Volume	5080.8(10) Å ³	
Z	4	
Density (calculated)	1.408 Mg/m ³	
Absorption coefficient	0.199 mm ⁻¹	
F(000)	2244	
Crystal size	0.48 x 0.24 x 0.06 mm ³	
Theta range for data collection	1.42 to 25.00°.	
Index ranges	-21 ≤ h ≤ 22, -13 ≤ k ≤ 13, -29 ≤ l ≤ 21	
Reflections collected	28869	
Independent reflections	8939 [R(int) = 0.0783]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7456 and 0.5630	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	8939 / 188 / 731	
Goodness-of-fit on F ²	1.049	
Final R indices [I > 2σ(I)]	R1 = 0.0850, wR2 = 0.2099	
R indices (all data)	R1 = 0.1360, wR2 = 0.2371	
Largest diff. peak and hole	1.004 and -0.680 e.Å ⁻³	

Identification code	6b	
Empirical formula	C44 H33 F2 N5 O8	
Formula weight	797.75	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 13.3567(11) Å	$\alpha = 90^\circ$.
	b = 22.8181(18) Å	$\beta = 90^\circ$.
	c = 23.430(2) Å	$\gamma = 90^\circ$.
Volume	7140.7(10) Å ³	
Z	8	
Density (calculated)	1.484 Mg/m ³	
Absorption coefficient	0.111 mm ⁻¹	
F(000)	3312	
Crystal size	0.29 x 0.28 x 0.23 mm ³	
Theta range for data collection	1.99 to 25.00°.	
Index ranges	-15 ≤ h ≤ 13, -25 ≤ k ≤ 27, -24 ≤ l ≤ 27	
Reflections collected	40113	
Independent reflections	6272 [R(int) = 0.0822]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9750 and 0.9686	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	6272 / 0 / 534	
Goodness-of-fit on F ²	1.037	
Final R indices [I > 2σ(I)]	R1 = 0.0983, wR2 = 0.2467	
R indices (all data)	R1 = 0.1307, wR2 = 0.2689	
Largest diff. peak and hole	1.366 and -0.581 e.Å ⁻³	

Identification code	14	
Empirical formula	C100 H82 Cl4 K N14 O20	
Formula weight	1980.70	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 18.6302(16) Å	α = 90°.
	b = 20.0894(19) Å	β = 98.302(2)°.
	c = 23.762(2) Å	γ = 90°.
Volume	8800.3(14) Å ³	
Z	4	
Density (calculated)	1.495 Mg/m ³	
Absorption coefficient	0.268 mm ⁻¹	
F(000)	4108	
Crystal size	0.46 x 0.37 x 0.27 mm ³	
Theta range for data collection	1.81 to 25.00°.	
Index ranges	-14 ≤ h ≤ 22, -23 ≤ k ≤ 22, -28 ≤ l ≤ 28	
Reflections collected	25457	
Independent reflections	7741 [R(int) = 0.0475]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7457 and 0.6085	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	7741 / 218 / 664	
Goodness-of-fit on F ²	1.956	
Final R indices [I > 2σ(I)]	R1 = 0.1587, wR2 = 0.4501	
R indices (all data)	R1 = 0.1893, wR2 = 0.4789	
Largest diff. peak and hole	1.956 and -1.308 e.Å ⁻³	

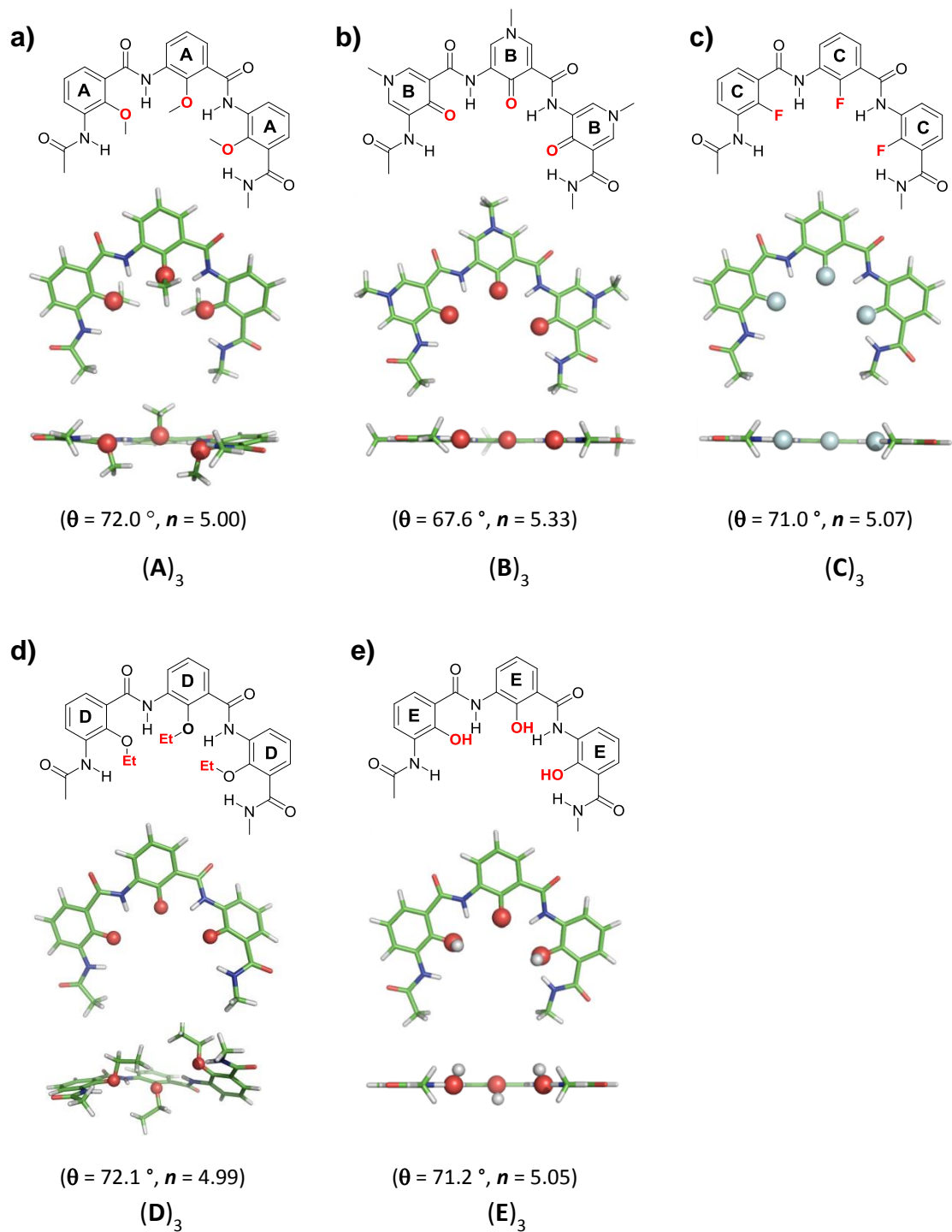


Figure S1. Computationally determined structures of trimers **(A)₃**-**(E)₃** and the corresponding θ values and the number of residues (n) required for A-E to form a regular pentagon.

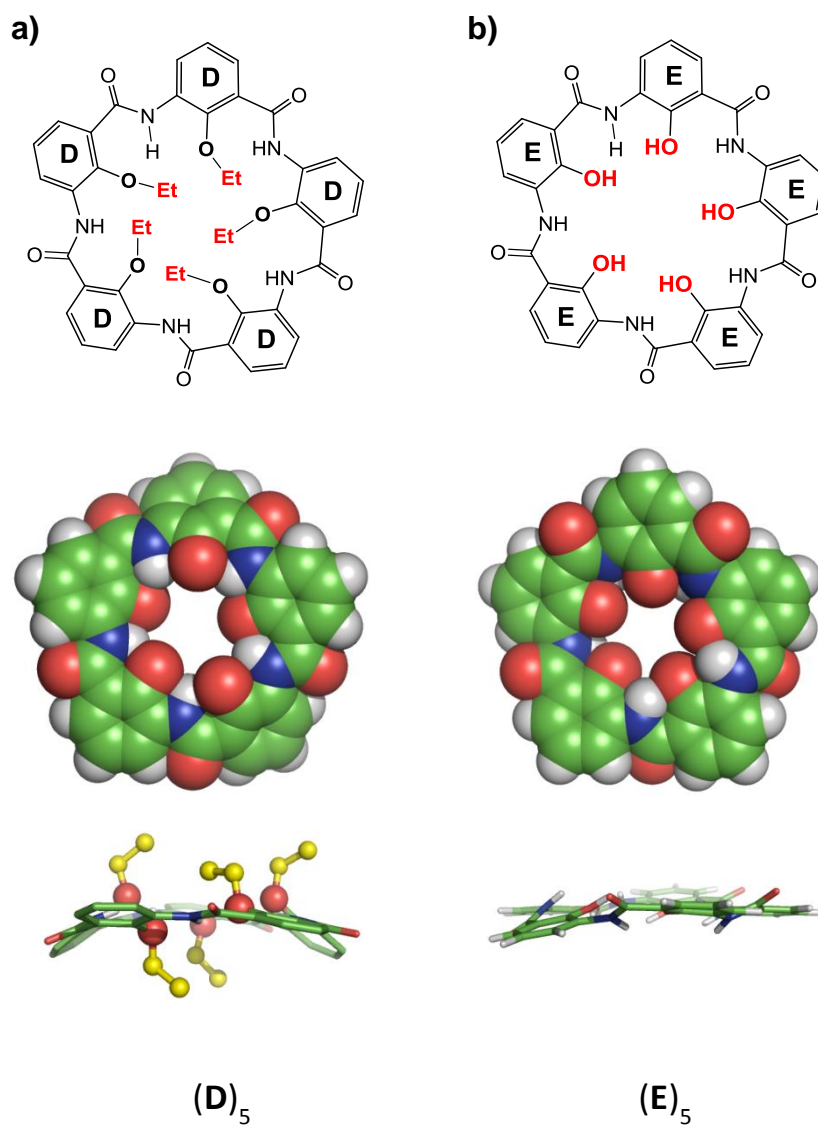


Figure S2. Computationally determined structures of circular pentamers (**D**)₅ and (**E**)₅. While the larger ethyl groups in **D** significantly distorts the pentameric backbone of (**D**)₅, a roughly planar backbone is still maintained in (**E**)₅.

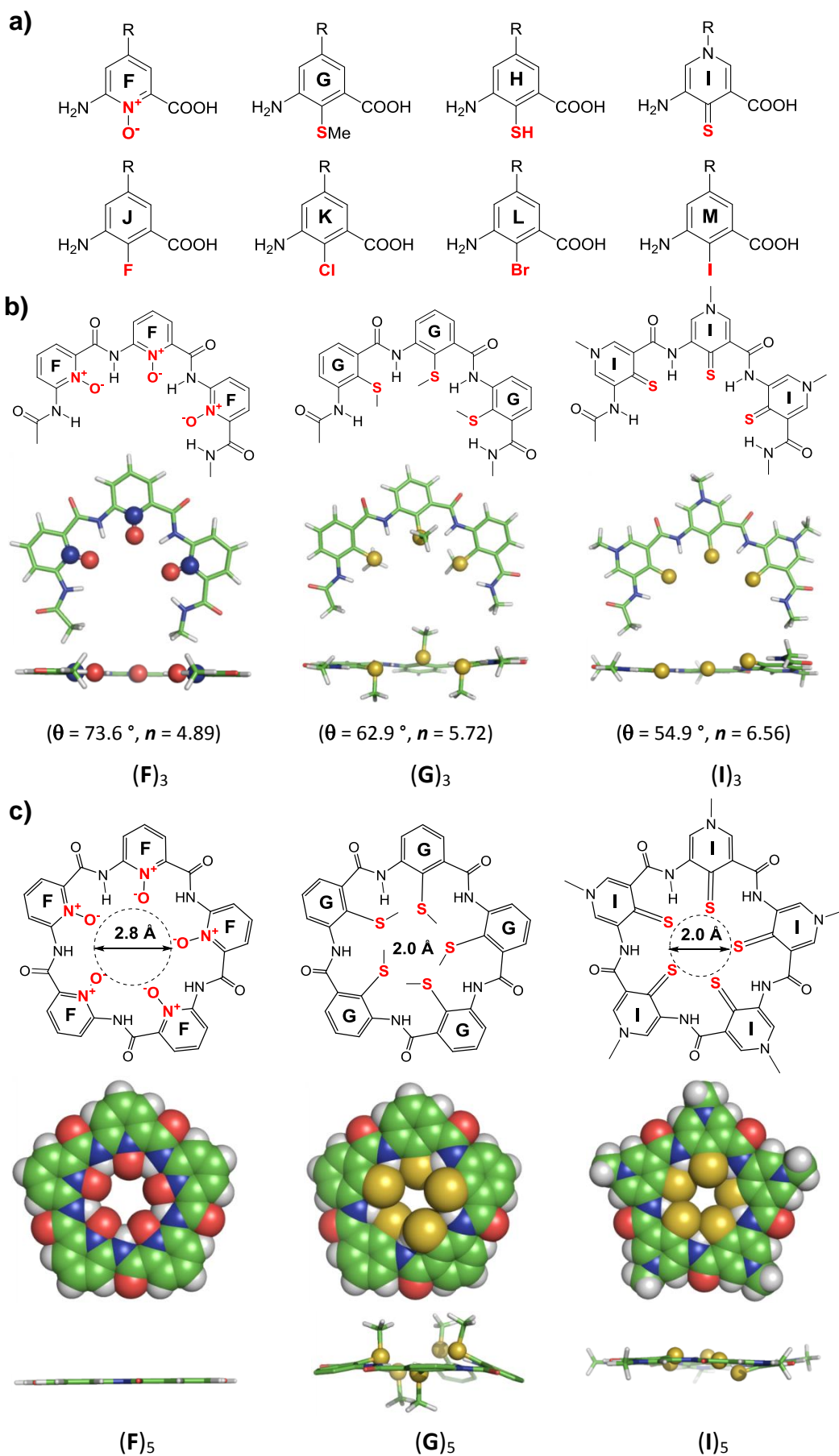
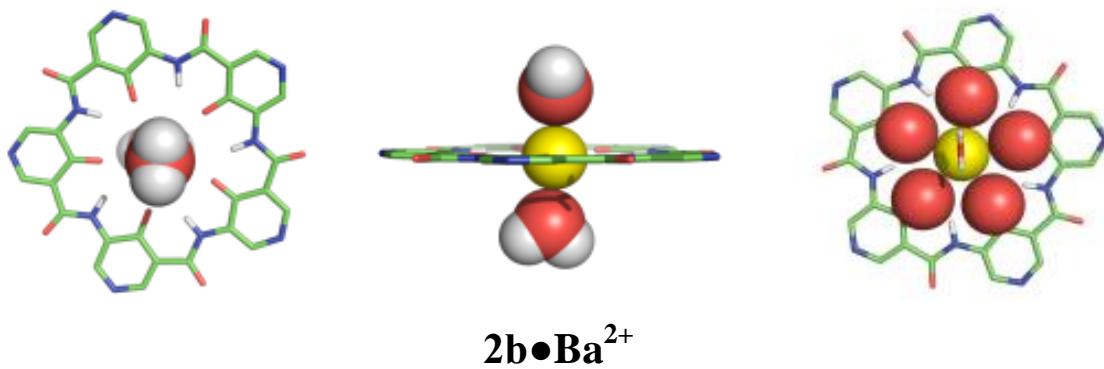


Figure S3. Possible functional groups for incorporation into the pentameric framework for augmenting ion-binding potential and selectivity.

a)



b)

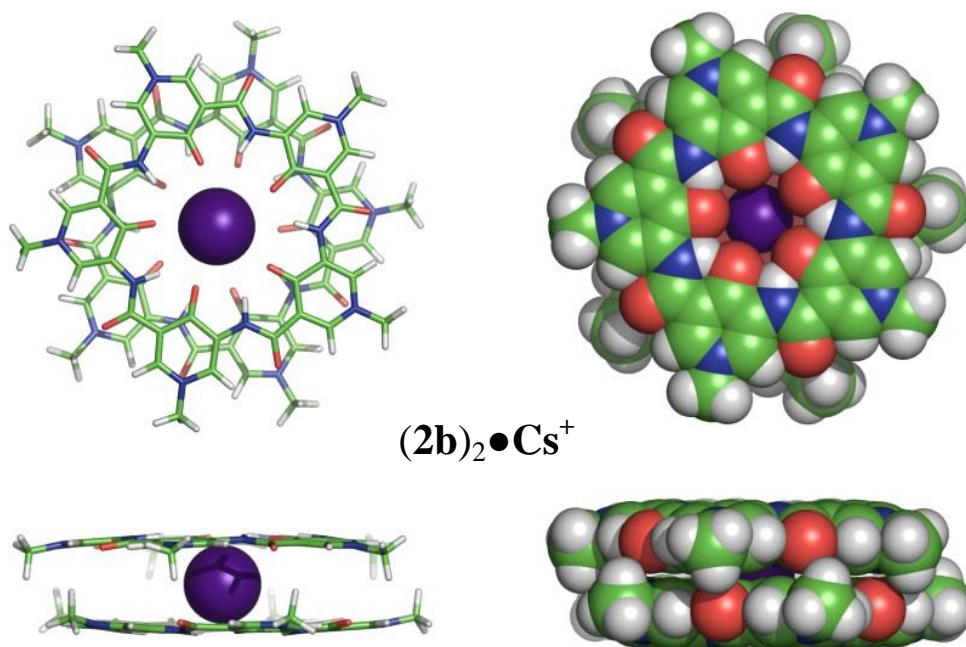


Figure S4. (a) Computationally determined structure of (a) the partially hydrated metal complex **2b•Ba²⁺** containing two water molecules and (b) sandwiched metal complex **(2b)₂•Cs⁺**. From (b), an inter-planar distance of 3.8 Å between the two pentamers can be obtained.

Table S1. Extraction efficiencies (%) of 20 metal ions in their nitrate salts by macrocyclic hosts **2b** and **6-23** as determined by inductively coupled plasma mass spectrometry (ICP) with [total metal ions] = 0.60 mM and that of host variable from 0.30, 0.60 and 1.20 mM.^a

	2b			7			8			9			10			11			12		
	0.30 mM	0.60 mM	1.20 mM	0.30 mM	0.60 mM	1.20 mM	0.30 mM	0.60 mM	1.20 mM	0.30 mM	0.60 mM	1.20 mM	0.30 mM	0.60 mM	1.20 mM	0.30 mM	0.60 mM	1.20 mM	0.30 mM	0.60 mM	1.20 mM
Na⁺	42	78	95	32	66	92	27	66	94	24	47	91	26	53	86	31	67	93	17	41	87
K⁺	57	92	98	45	79	94	34	71	95	27	57	95	41	80	92	46	82	94	39	77	95
Rb⁺	69	>99	>99	70	98	>99	67	>99	>99	65	98	>99									
Cs⁺	98	>99	>99	95	>99	>99	95	>99	>99	97	>99	>99			11		13	35			
Ca²⁺	14	43	90	16	36	72	12	33	67	10	18	32	13	38	79	17	33	72	24	43	90
Ag⁺	40	78	>99	37	86	>99	34	82	>99	43	83	>99	57	91	96	19	37	74	10	30	67
Tl⁺	85	>99	>99	83	>99	>99	72	>99	>99	35	65	93						7			
Pb²⁺	27	82	>99	14	20	47				6	17	45									
	13			14			15			16			17			18			19		
	0.30 mM	0.60 mM	1.20 mM	0.30 mM	0.60 mM	1.20 mM	0.30 mM	0.60 mM	1.20 mM	0.30 mM	0.60 mM	1.20 mM	0.30 mM	0.60 mM	1.20 mM	0.30 mM	0.60 mM	1.20 mM	0.30 mM	0.60 mM	1.20 mM
Na⁺	18	47	89	23	53	90	24	56	91	16	52	86	31	70	94	21	50	88	29	58	93
K⁺	20	59	93	32	77	97	28	67	95	40	80	95	38	74	96	23	61	94	30	64	95
Rb⁺																					
Cs⁺																					
Ca²⁺		19	30	13	23	56	24	41	87	23	44	89	20	47	82	7	15	27	15	25	42
Ag⁺	15	27	70	13	37	75	77	98	>99	47	93	>99	95	98	>99	15	35	81	18	37	87
Tl⁺																					
Pb²⁺																14	25	33			
	20			6a			6b			21			22			23					
	0.30 mM	0.60 mM	1.20 mM	0.30 mM	0.60 mM	1.20 mM	0.30 mM	0.60 mM	1.20 mM	0.30 mM	0.60 mM	1.20 mM	0.30 mM	0.60 mM	1.20 mM	0.30 mM	0.60 mM	1.20 mM			
Na⁺	16	51	85		6	16	15	49	78	87	95	97			10	73	93	94			
K⁺	22	56	93	6	42	70	24	63	94	92	95	98			9	78	94	97			
Rb⁺																					
Cs⁺													11	21							
Ca²⁺	8	21	33	7	39	69	23	52	85	66	91	94			9	38	67	91			
Ag⁺	41	85	95			7			15		8	15					7	20			
Tl⁺																		7			
Pb²⁺	9										19				6			8			

^a The concentration of each metal ion is set at 0.03 mM with a total concentration for 20 metal ions being 0.60 mM in H₂O containing 1% HNO₃, and that of the organic macrocyclic hosts ranges from 0.30 mM to 0.6 mM and to 1.20 mM in CHCl₃. Extractions were carried out in a biphasic system using equal volumes of H₂O containing metal ions and CHCl₃ containing organic host at 25 °C. All the reported data are averaged values over six runs with relative errors within 3%, and only extraction efficiencies of ≥ 6% are listed. Except for additional extractions of Ba²⁺ and Cu²⁺ by **2b** and Mg²⁺ by **23** (please see Table S2), extractions of other metal ions including Li⁺, Mg²⁺, Ba²⁺, Al³⁺, Cr³⁺, Mn²⁺, Fe³⁺, Co²⁺, Ni²⁺, Cu²⁺, Zn²⁺ and Cd²⁺ by the macrocyclic hosts remain experimentally undetectable. The most extractable Ions and those ions whose extractability lies within 80% of the most extractable ions are highlighted in gray to illustrate the ion-binding selectivity by the varying hosts. The numbers highlighted in yellow were used to calculate the ion-binding selectivity by **10-16**, **18-20** and **22** as presented in Figure 6b-c, and for similar calculations for **2b**, **2-9**, **21** and **23**, see Table S2. ^b Total extraction is the sum of all the measurable extraction efficiencies for the ions, and extraction values for Ba²⁺ and Cu²⁺ by **2b** and Mg²⁺ by **23** as shown in Table S2 were also included in the calculation.

Table S2. Extraction efficiencies (%) of 20 metal ions in their nitrate salts by macrocyclic hosts **2b** and **7-9** as determined by inductively coupled plasma mass spectrometry (ICP) with [total metal ions] = 0.60 mM and that of host variable from 0.10, 0.15, 0.30, 0.60 and 1.20 mM.^a

	2b					7					8					9				
	0.10 mM	0.15 mM	0.30 mM	0.60 mM	1.20 mM	0.10 mM	0.15 mM	0.30 mM	0.60 mM	1.20 mM	0.10 mM	0.15 mM	0.30 mM	0.60 mM	1.20 mM	0.10 mM	0.15 mM	0.30 mM	0.60 mM	1.20 mM
Na⁺		13	42	78	93	9	15	32	66	92		9	27	66	94		9	24	47	91
K⁺	13	25	57	92	94	13	21	45	79	94	10	15	34	71	95		11	27	57	95
Rb⁺	17	28	69	>99	>99	20	37	70	98	>99	18	30	67	>99	>99	18	31	65	98	>99
Cs⁺	62	89	98	>99	>99	65	87	95	>99	>99	63	85	95	>99	>99	63	90	97	>99	>99
Ca²⁺		7	14	41	88			16	36	72			12	33	67			10	18	32
Ag⁺		15	43	78	>99	9	21	37	86	>99	5	15	34	82	>99	15	25	43	83	>99
Tl⁺	21	39	85	>99	>99	23	45	83	>99	>99	18	31	72	>99	>99	9	16	35	65	93
Pb²⁺		8	27	82	>99			14	20	47								6	17	45
Ba²⁺	26	64	99	>99	>99			10	31										8	26
Cu²⁺			12	43	95				10					19				7		21
	17					21					23									
	0.10 mM	0.15 mM	0.30 mM	0.60 mM	1.20 mM	0.10 mM	0.15 mM	0.30 mM	0.60 mM	1.20 mM	0.10 mM	0.15 mM	0.30 mM	0.60 mM	1.20 mM					
Na⁺		9	31	70	94	23	39	87	95	97	19	30	73	93	94					
K⁺	8	15	38	74	96	28	45	92	95	98	23	36	78	94	97					
Rb⁺																				
Cs⁺																				
Ca²⁺		7	20	47	82	12	26	66	91	94	10	13	38	67	91					
Ag⁺	55	83	95	98	>99				8	15				7	20					
Tl⁺															7					
Pb²⁺									13						8					
Ba²⁺																				
Cu²⁺																				
Mg²⁺											7	23	33	71						

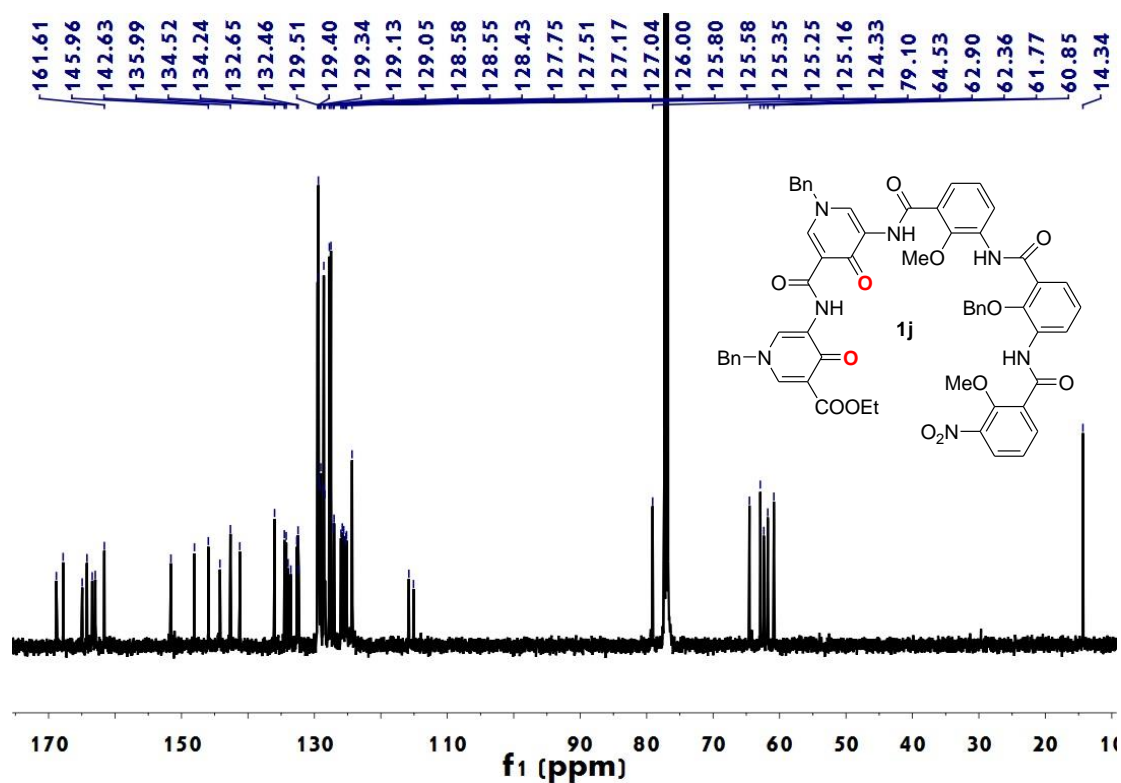
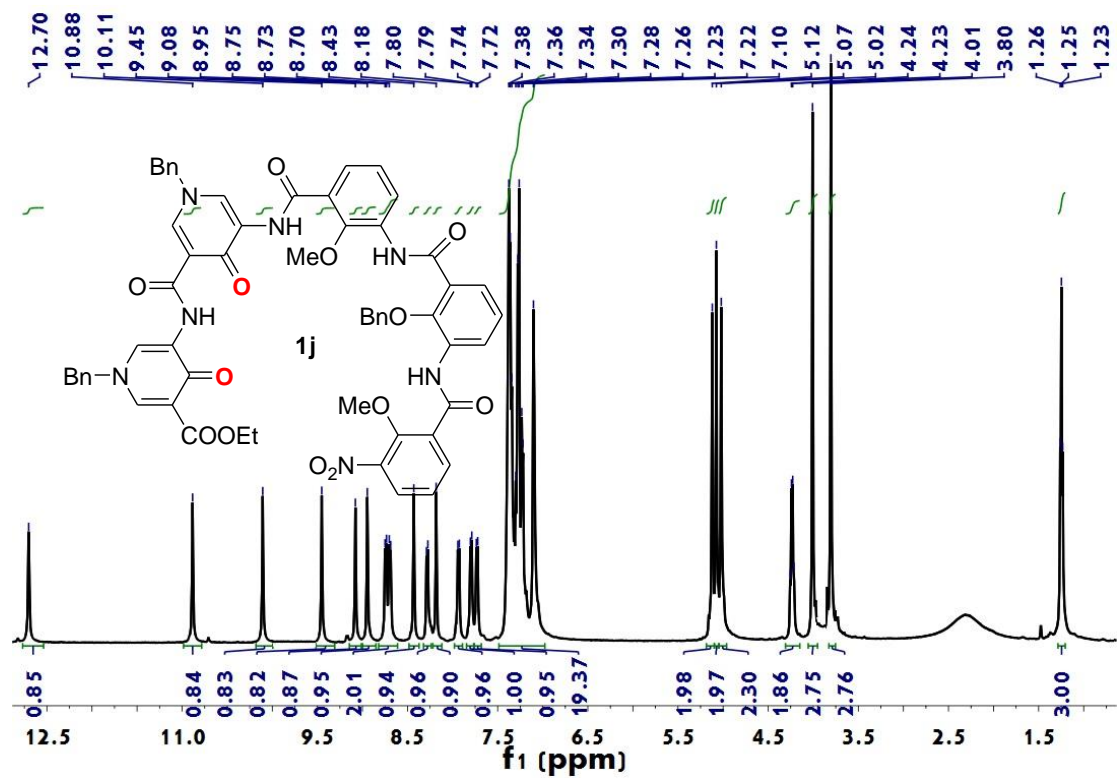
^a The concentration of each metal ion is set at 0.03 mM with a total concentration for 20 metal ions being 0.60 mM in H₂O containing 1% HNO₃, and that of the organic macrocyclic hosts ranges from 0.10 mM to 1.20 mM in CHCl₃. Extractions were carried out in a biphasic system using equal volumes of H₂O containing metal ions and CHCl₃ containing organic host at 25 °C. All the reported data are averaged values over six runs with relative errors within 3%, and only extraction efficiencies of ≥ 6% are listed. Except for additional extractions of Ba²⁺ and Cu²⁺ by **2b** and Mg²⁺ by **23**, extractions of other metal ions including Li⁺, Mg²⁺, Ba²⁺, Al³⁺, Cr³⁺, Mn²⁺, Fe³⁺, Co²⁺, Ni²⁺, Cu²⁺, Zn²⁺ and Cd²⁺ by the macrocyclic hosts remain experimentally undetectable. The most extractable Ions and those ions whose extractability lies within 80% of the most extractable ions are highlighted in gray to illustrate the ion-binding selectivity by the varying hosts. The numbers highlighted in yellow were used to calculate the ion-binding selectivity for **2b**, **2-9**, **21** and **23** as presented in Figure 6b-c.

Picrate Extraction Experiment for Determination of Binding Constants

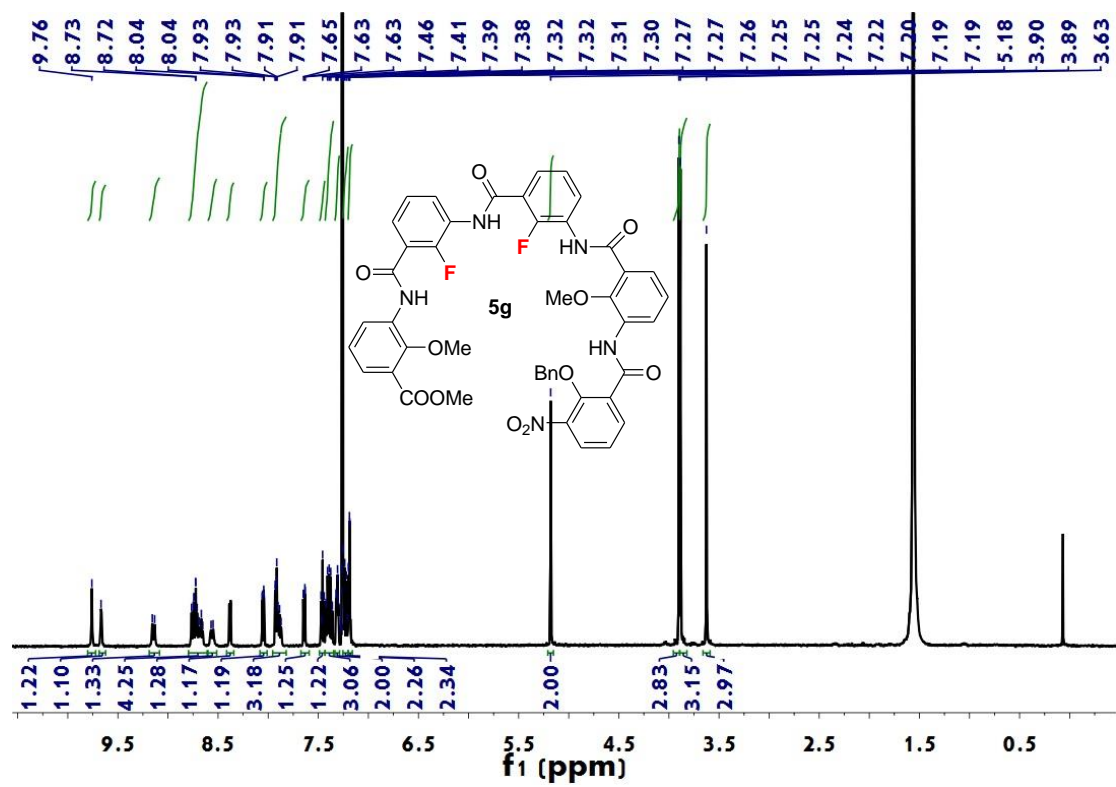
Preparation of Alkali metal Picrates: The alkali metal picrates (Li^+ , Na^+ , K^+ , Rb^+ and Cs^+) were prepared by dissolving picric acid in a minimum amount of distilled boiling water to which a stoichiometric amount of the alkali metal hydroxide was slowly added. The alkali metal picrate solution was then cooled to room temperature and placed in an ice bath to facilitate crystallization. The precipitate was filtered and recrystallized from distilled water. After filtration and extensive air drying, the salt was carefully heated to dryness in a vacuum oven at 75°C for overnight and cooled to room temperature under N_2 protection. The anhydrous metal picrates were stored in a desiccator.

Procedure for Picrate Extraction Experiment: Extractions of alkali metal picrates (Li^+ , Na^+ , K^+ , Rb^+ and Cs^+) with hosts were performed by placing 1.0 mL of a 10 mM solution of the metal picrate in deionized water and 1.0 mL of a 10 mM solution of the hosts in chloroform into a 4-mL sample vial and mixing the solutions on a vortex mixer for 60 seconds. The sample was then allowed to stand for overnight to ensure a complete separation of the layers and extraction of ions into chloroform layer. Aliquot was taken from the aqueous phase of the sample, and its concentration of metal picrate was determined by UV-Visible spectroscopy with a scanning from 250 nm to 500 nm to obtain the concentration of metal picrate (C) in chloroform layer. The control extraction experiments using chloroform containing no ligands were carried out in the same way, and the concentration of metal picrate extracted into chloroform layer was deducted from concentration C to derive the actual concentration of metal picrate extracted into chloroform layer by ligands. The extraction constants (K_{ex}) and association constants (K_a) were calculated according to method previously described (Moore, S. S.; Tarnowski, T. L.; Newcomb, M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, 99, 6398-6405). Three samples were prepared for each picrate extraction experiment. Standard deviations from the analysis of the three samples were less than 10% in terms of both K_{ex} and K_a values.

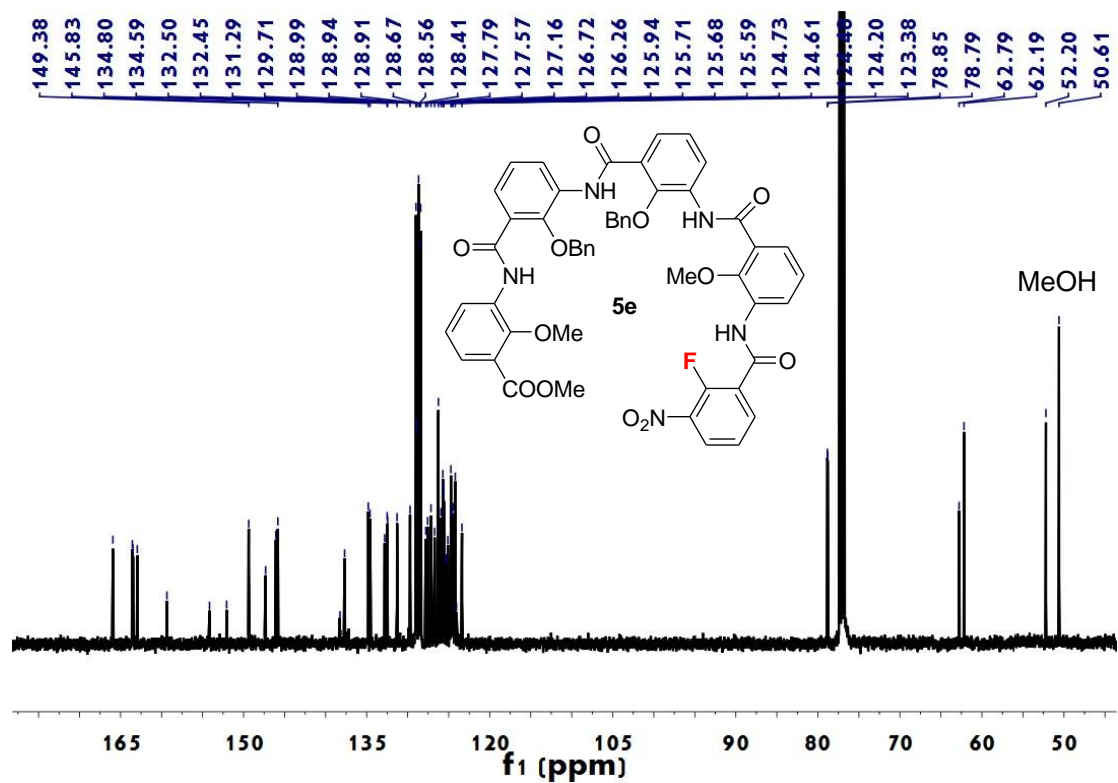
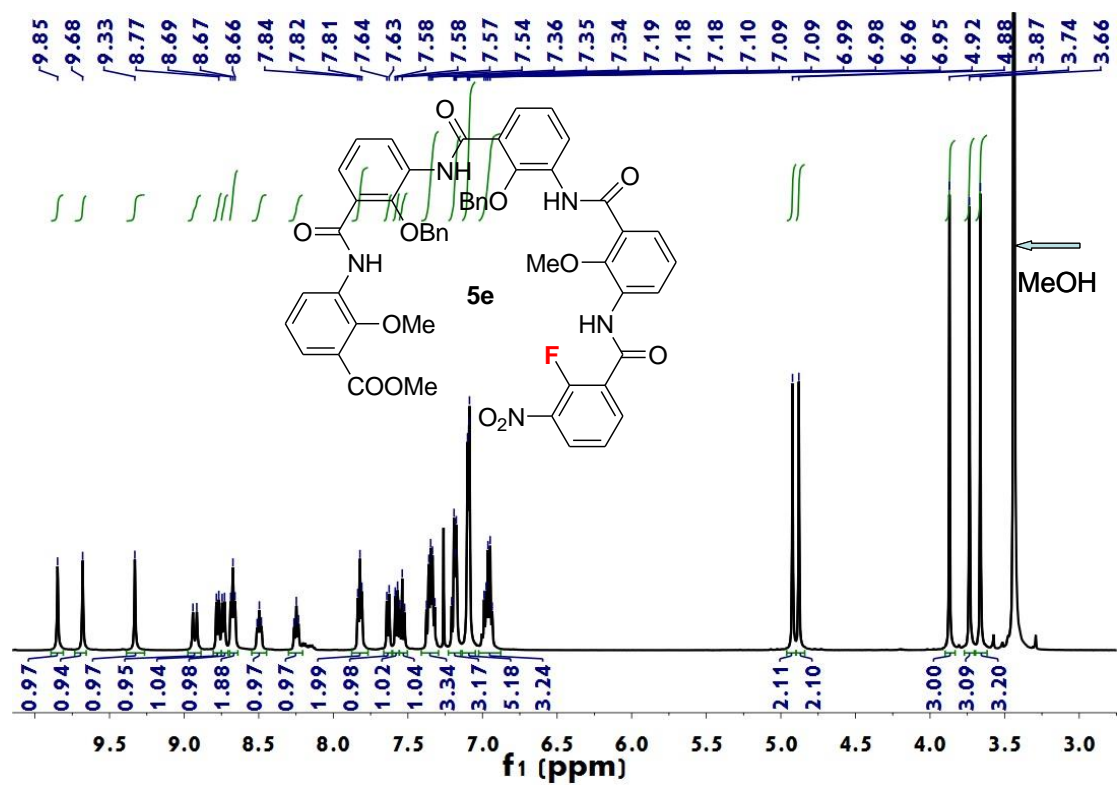
^1H and ^{13}C NMR spectra of 1j



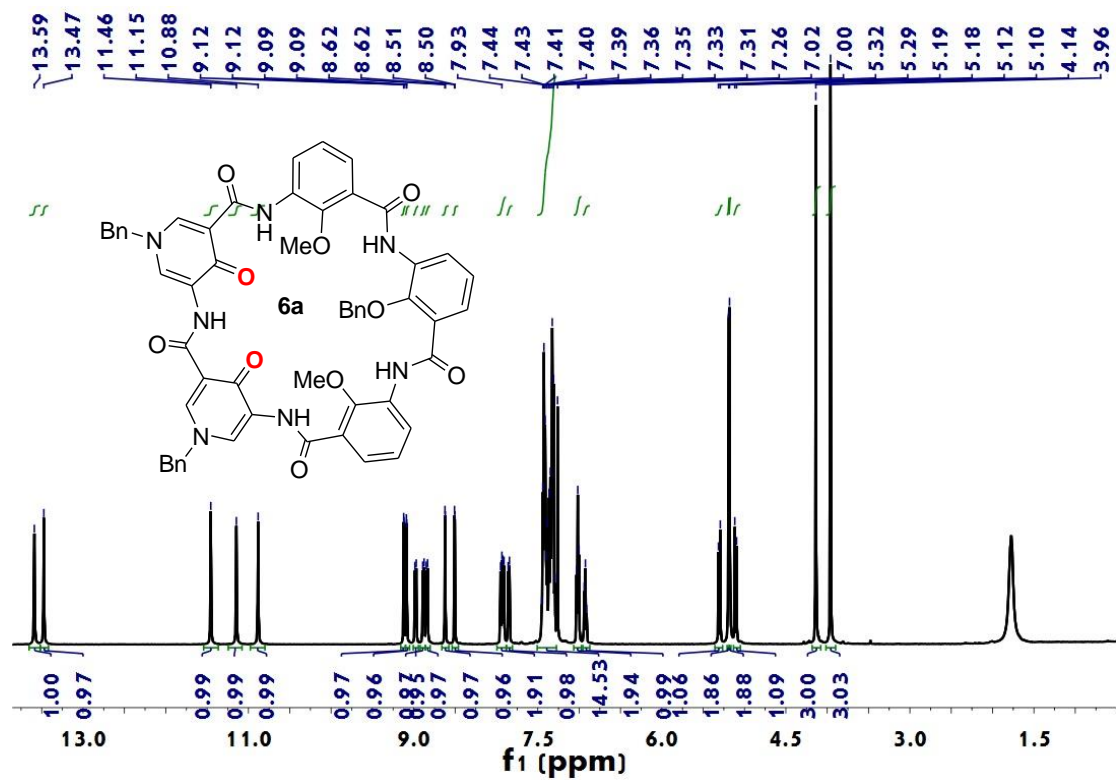
^1H spectrum of 5g

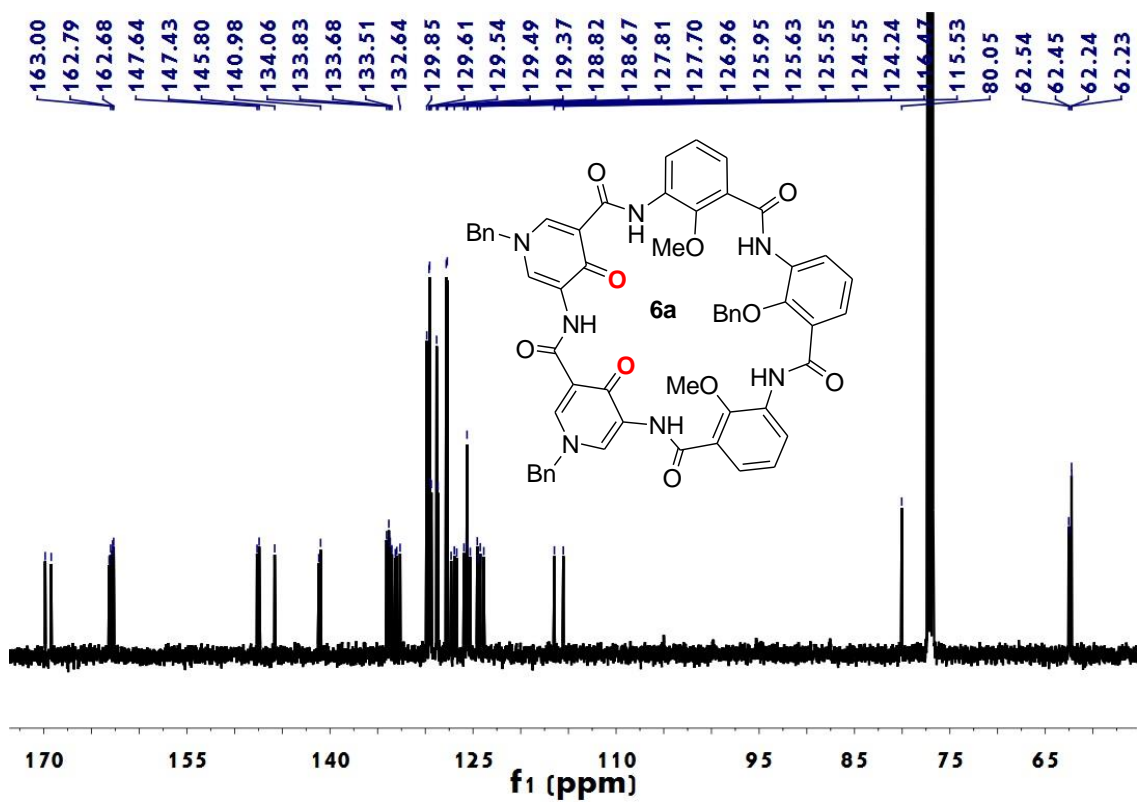


^1H and ^{13}C NMR spectra of **5e**

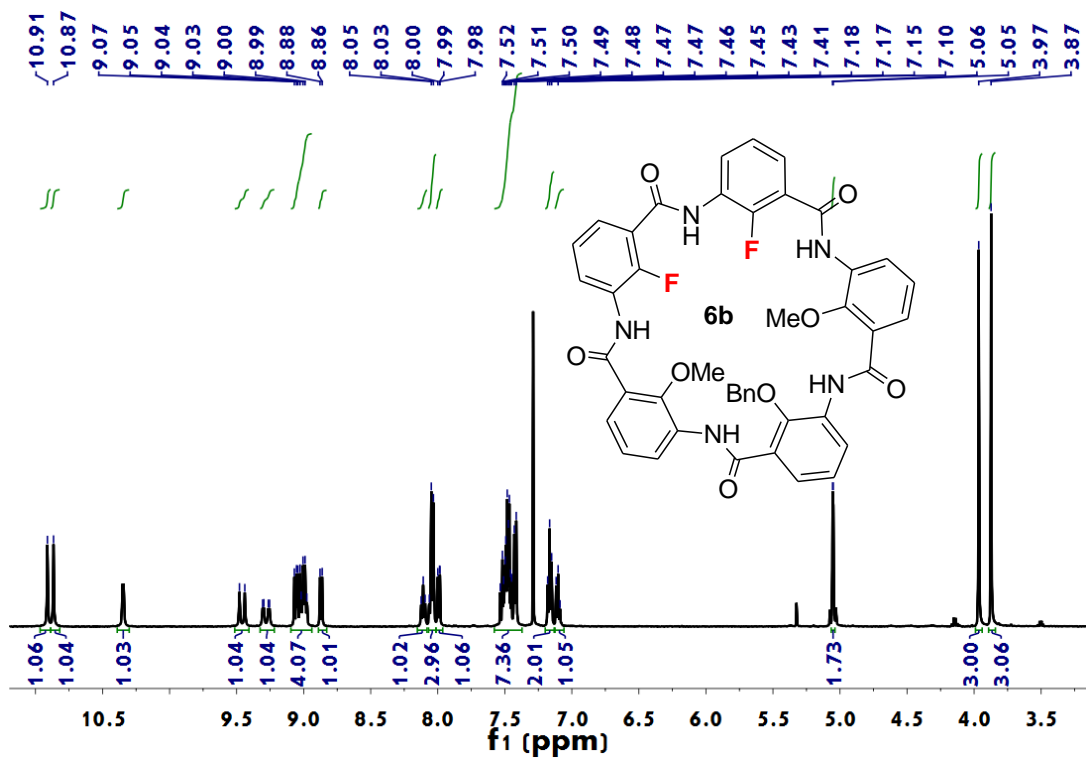


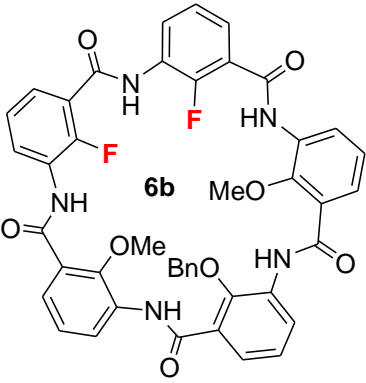
^1H and ^{13}C NMR spectra of 6a





¹H and ¹³C NMR spectra of 6b

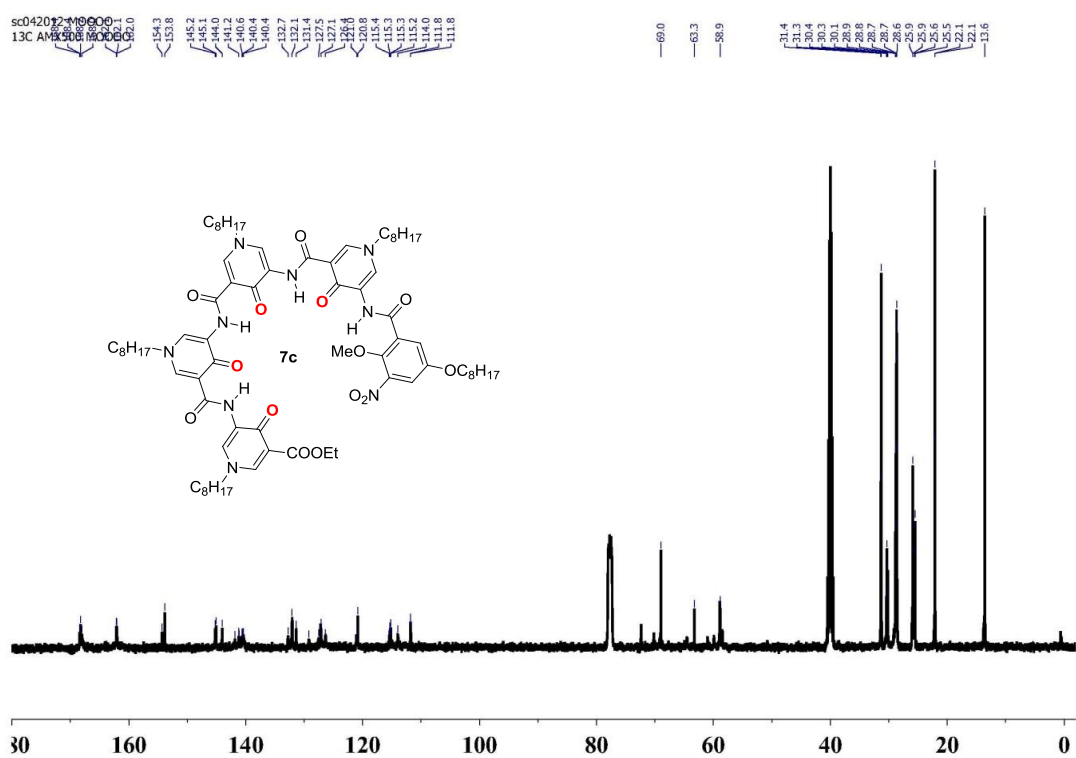




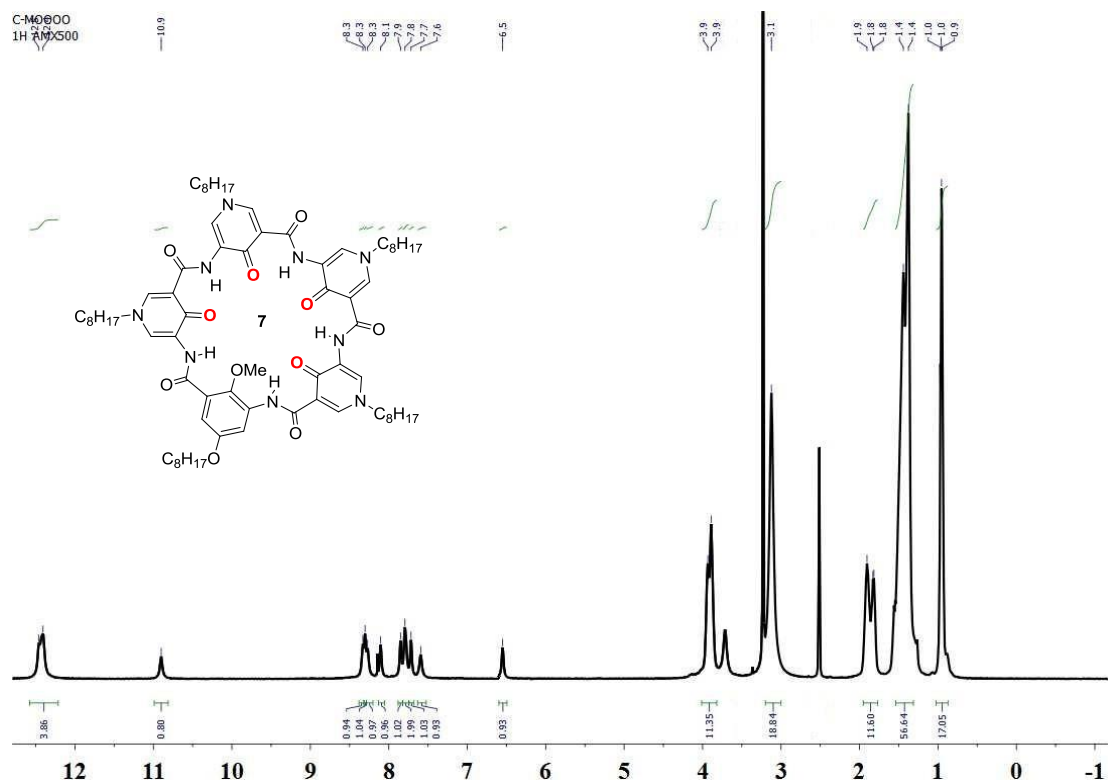
Chemical structure of compound **7c** is shown, featuring a central amide linkage connecting two pyridine rings. The structure includes various substituents: a long alkyl chain (C_8H_{17}), a methoxy group (MeO), a nitro group (O_2N), and an ethyl ester group ($COOEt$).

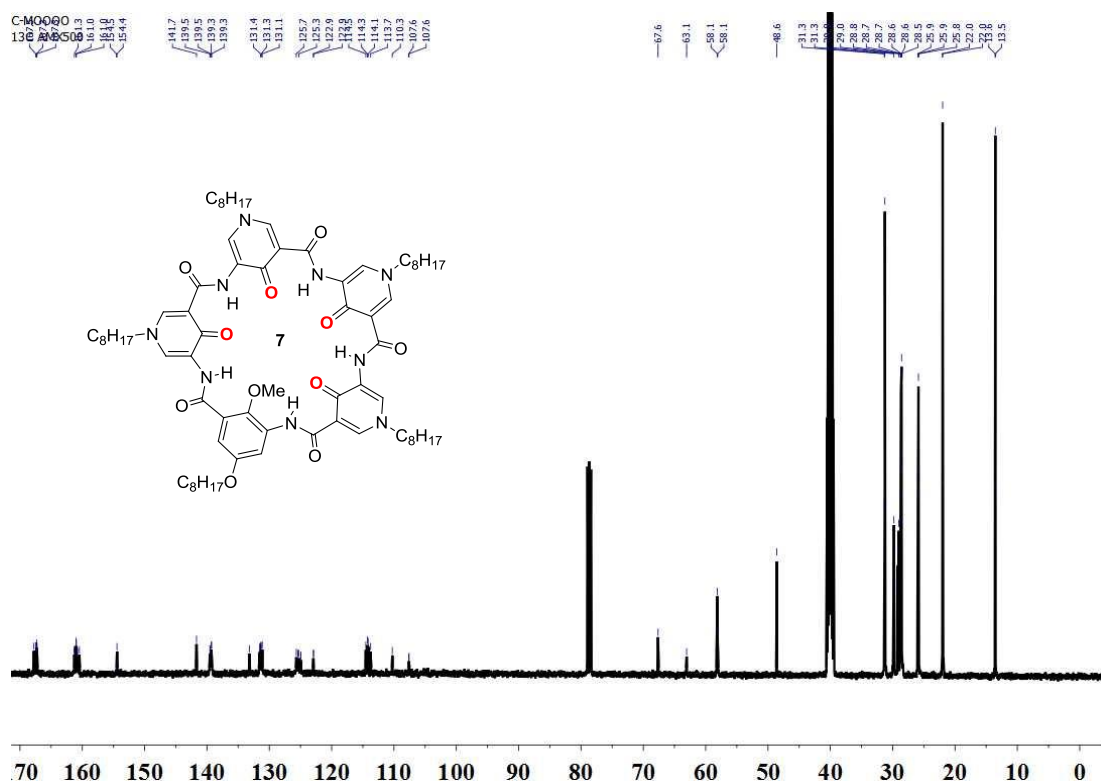
The 1H NMR spectrum (CDCl₃) shows peaks corresponding to the structure. Integration values are provided for several peak regions:

- 0.86, 0.96, 0.98 (triplet, CH_3 of $COOEt$)
- 0.75 (singlet, CH of $COOEt$)
- 1.18, 1.07, 1.00, 1.08, 1.22, 1.00 (multiplet, CH_2 of $COOEt$)
- 0.93, 0.91 (multiplet, CH of $COOEt$)
- 1.455 (multiplet, CH_2 of $COOEt$)
- 12.62, 5.730, 15.79 (aromatic and amide protons)

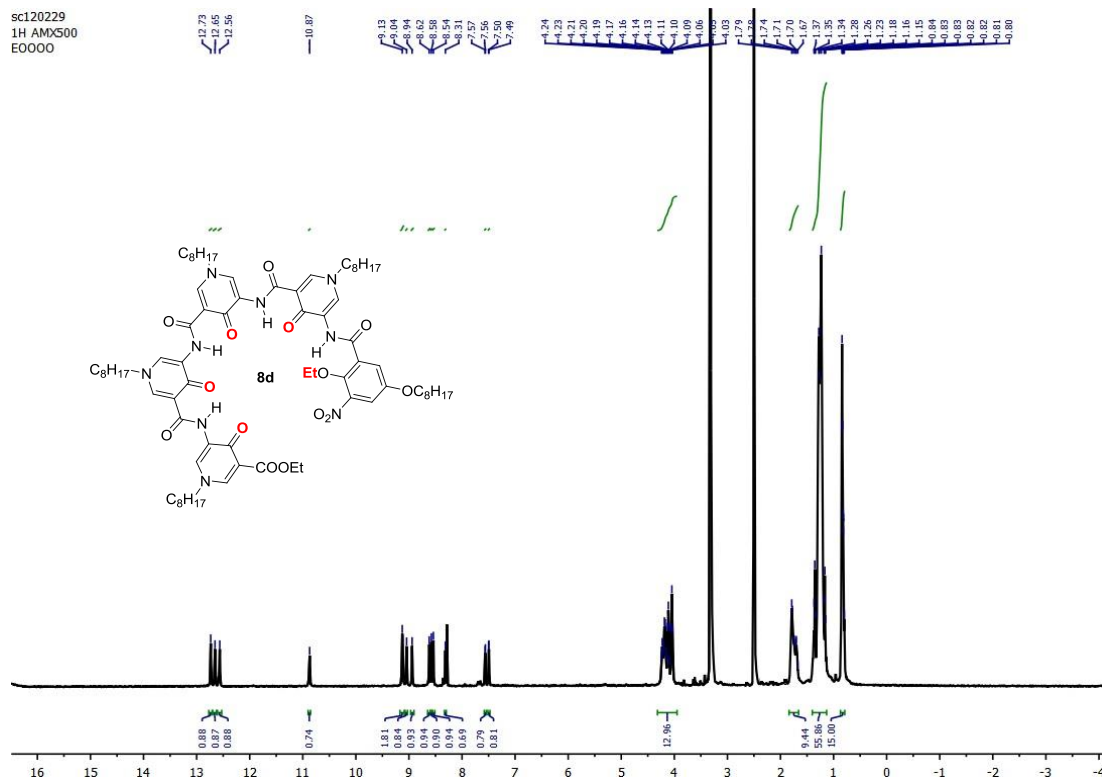


¹H and ¹³C NMR spectra of 7



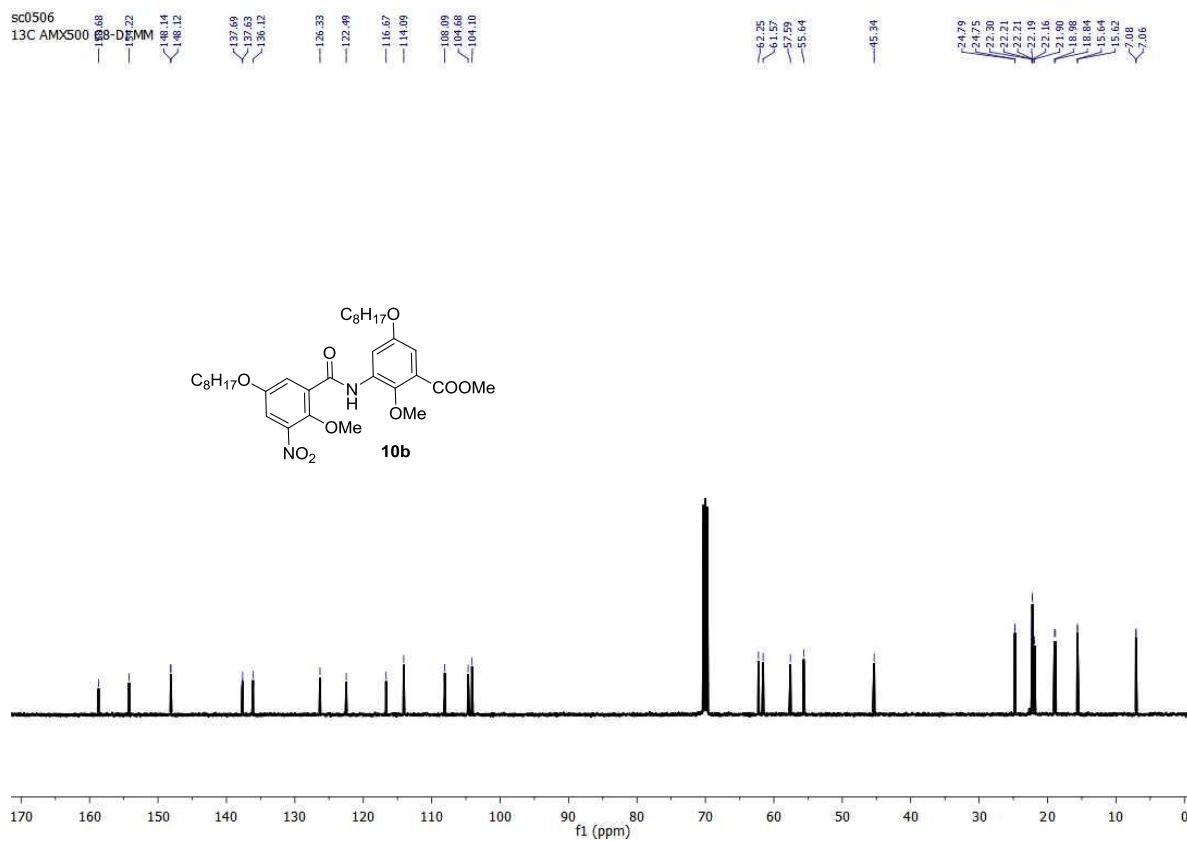


¹H and ¹³C NMR spectra of 8d

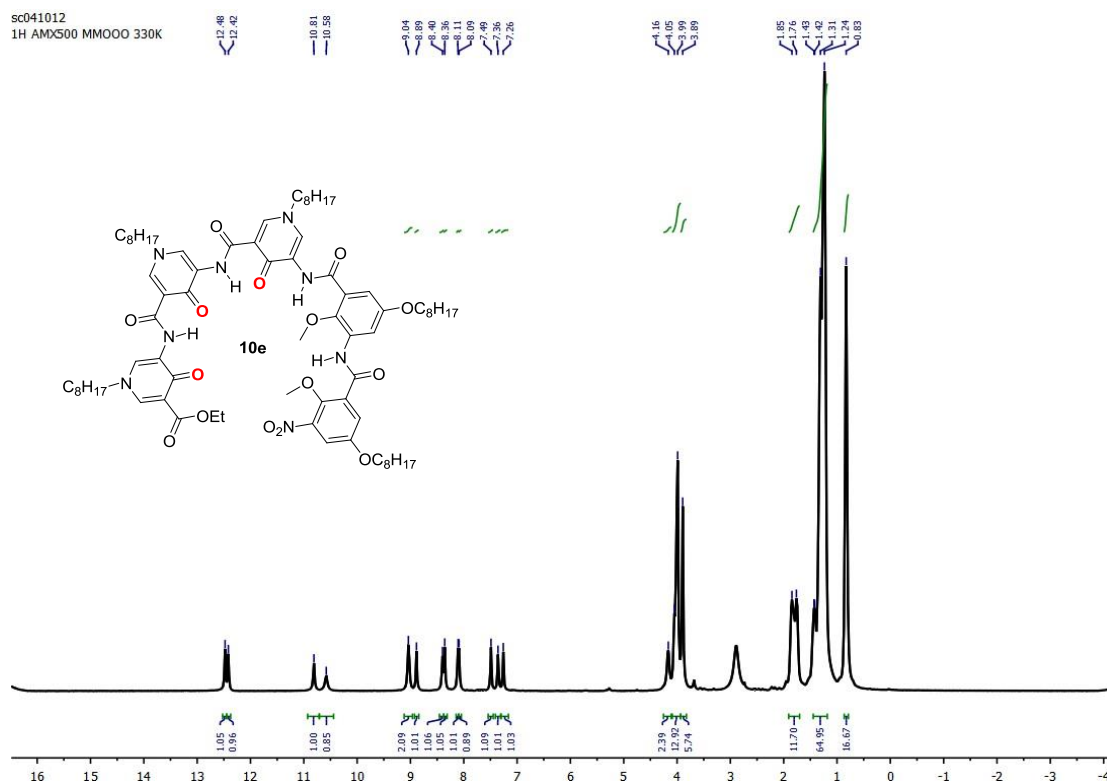


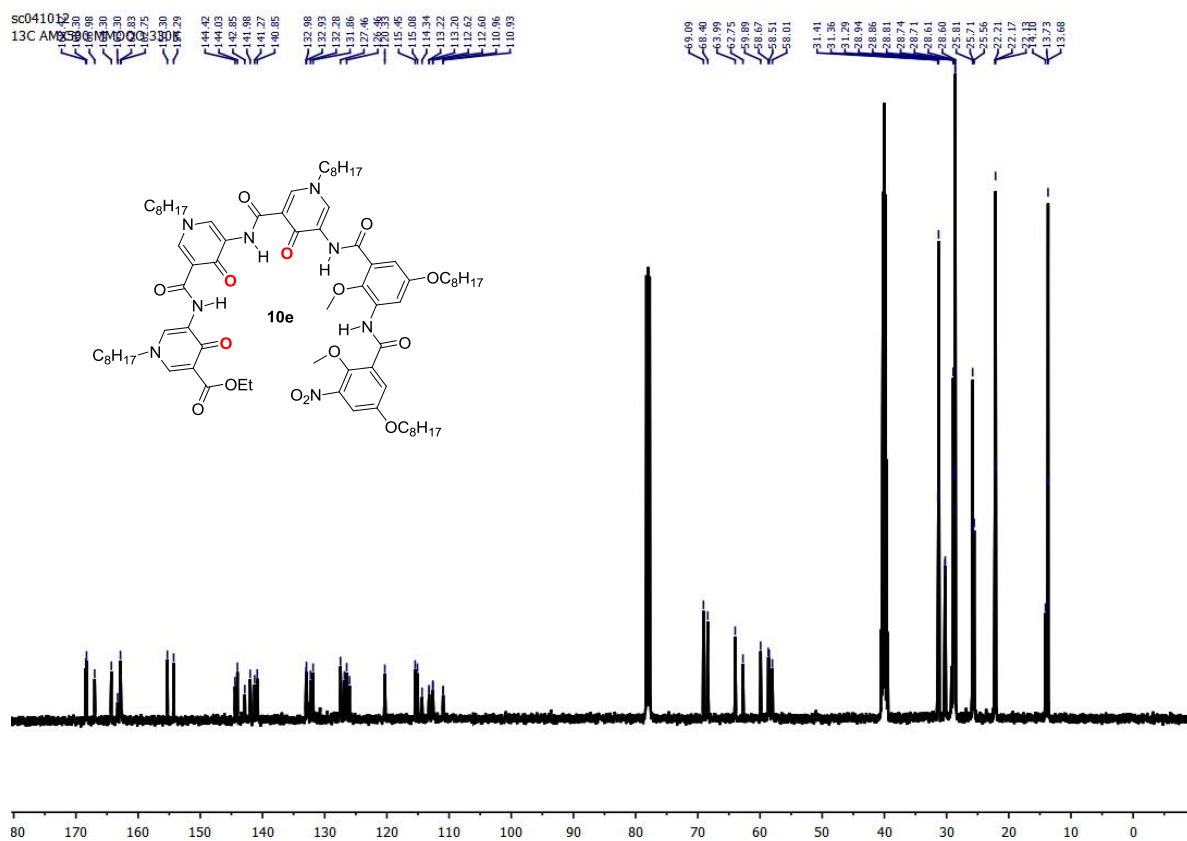




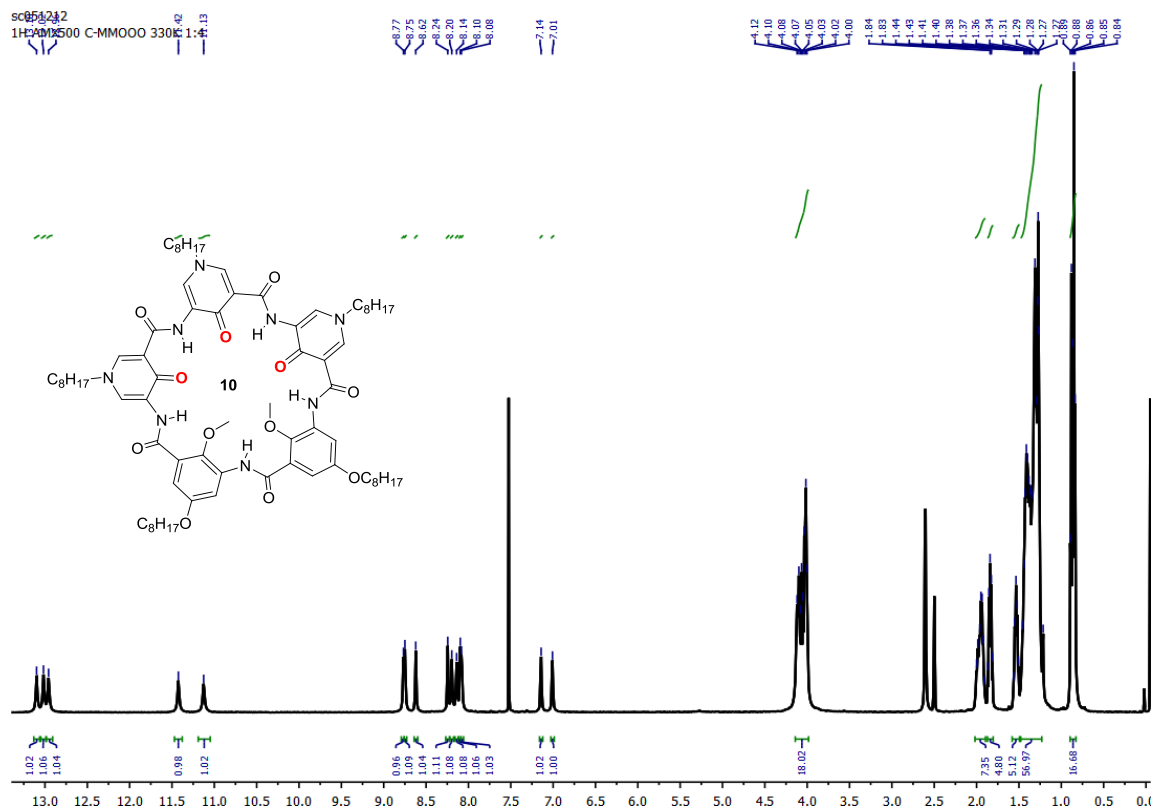


^1H and ^{13}C NMR spectra of **10e**





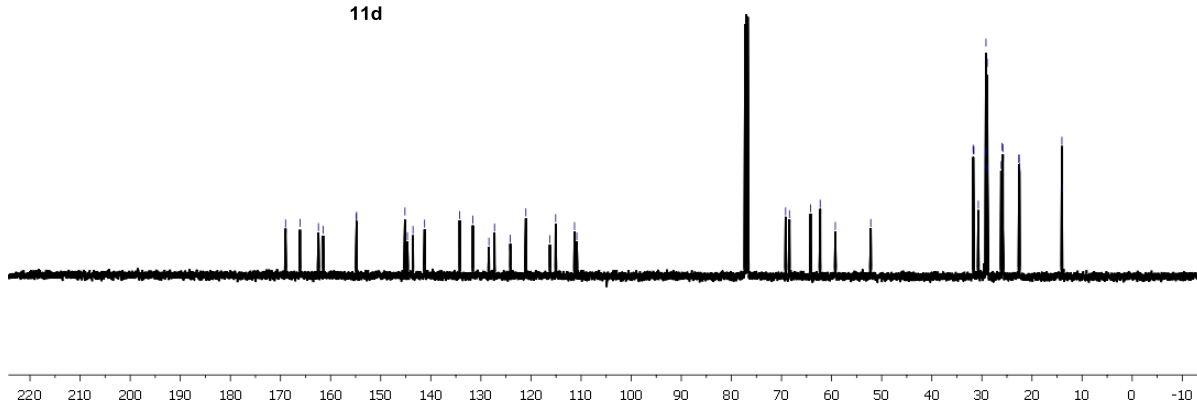
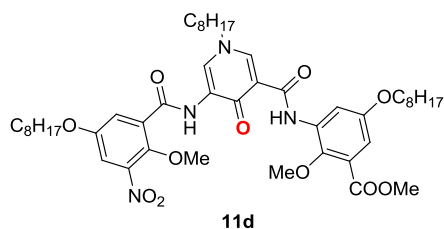
¹H and ¹³C NMR spectra of 10



sc0308
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161.49
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143.55
141.23
134.24
131.61
128.59
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121.03
116.24
115.07
111.31
110.85

69.49
68.42
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59.26
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13.96



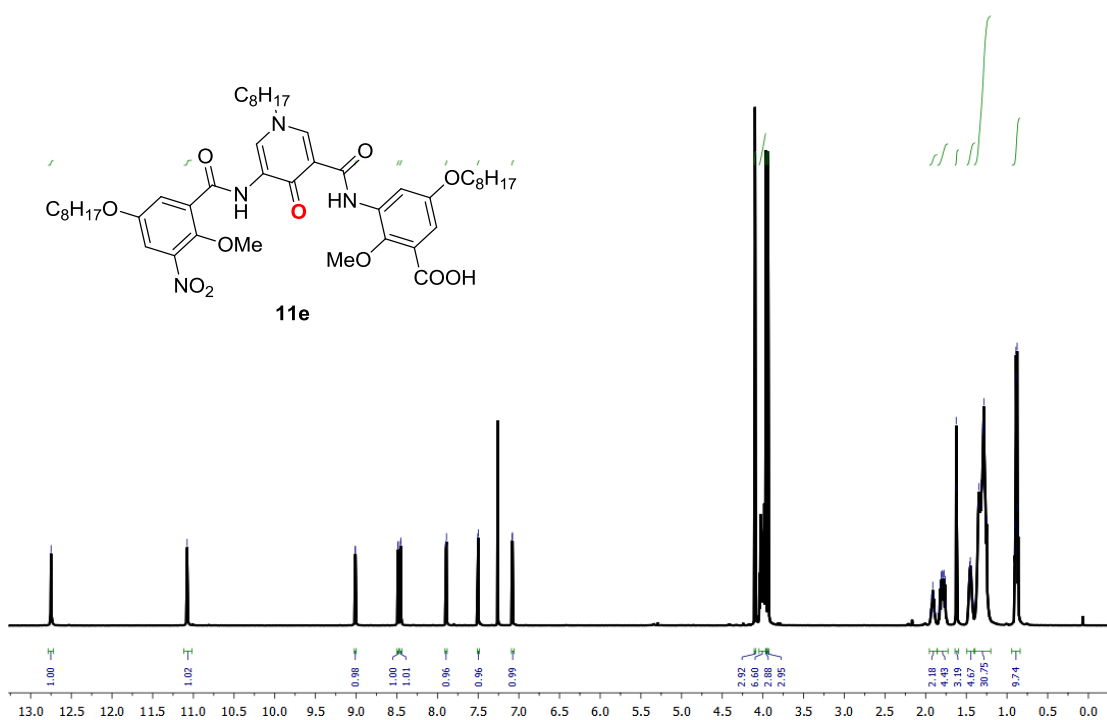
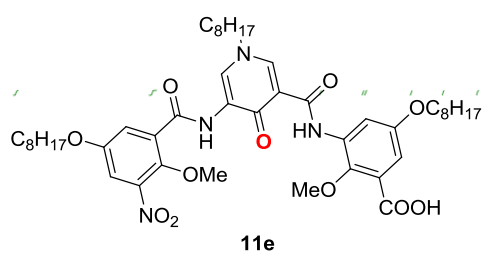
¹H and ¹³C NMR spectra of 11e

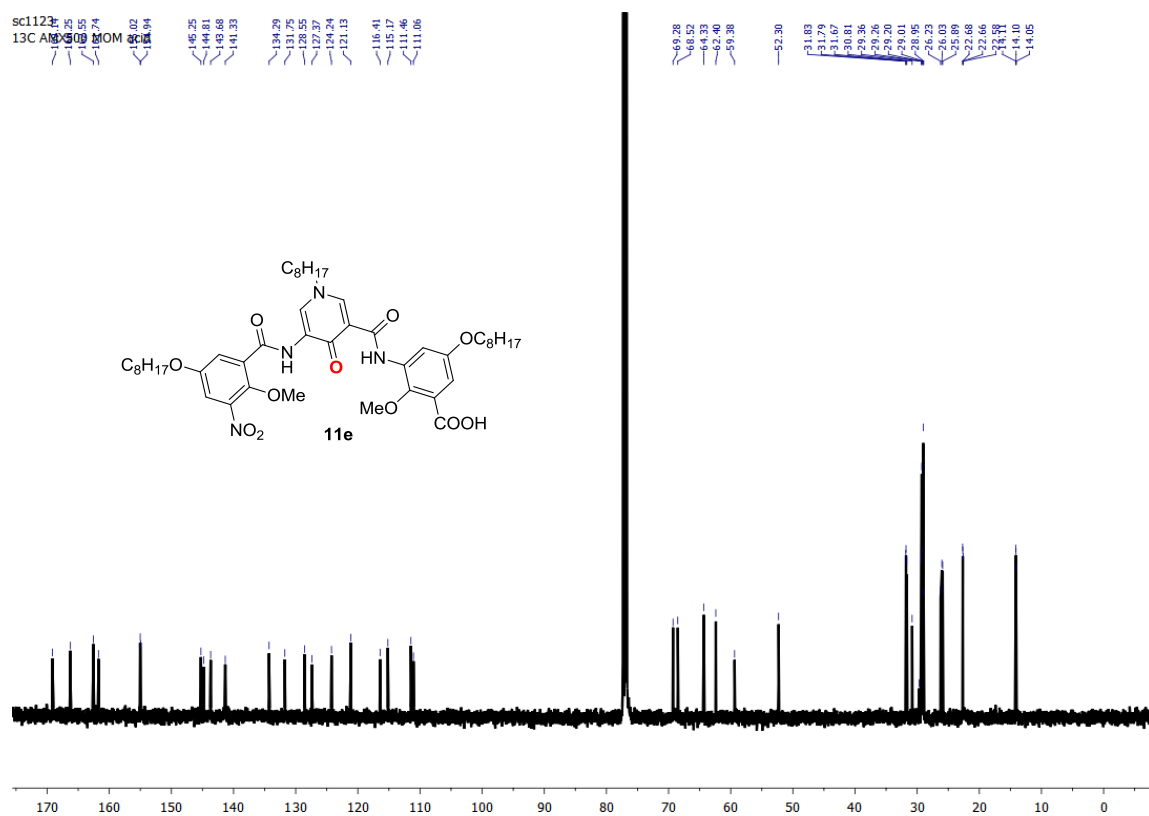
sc1123
1H AMX500 MOM acid

11.08

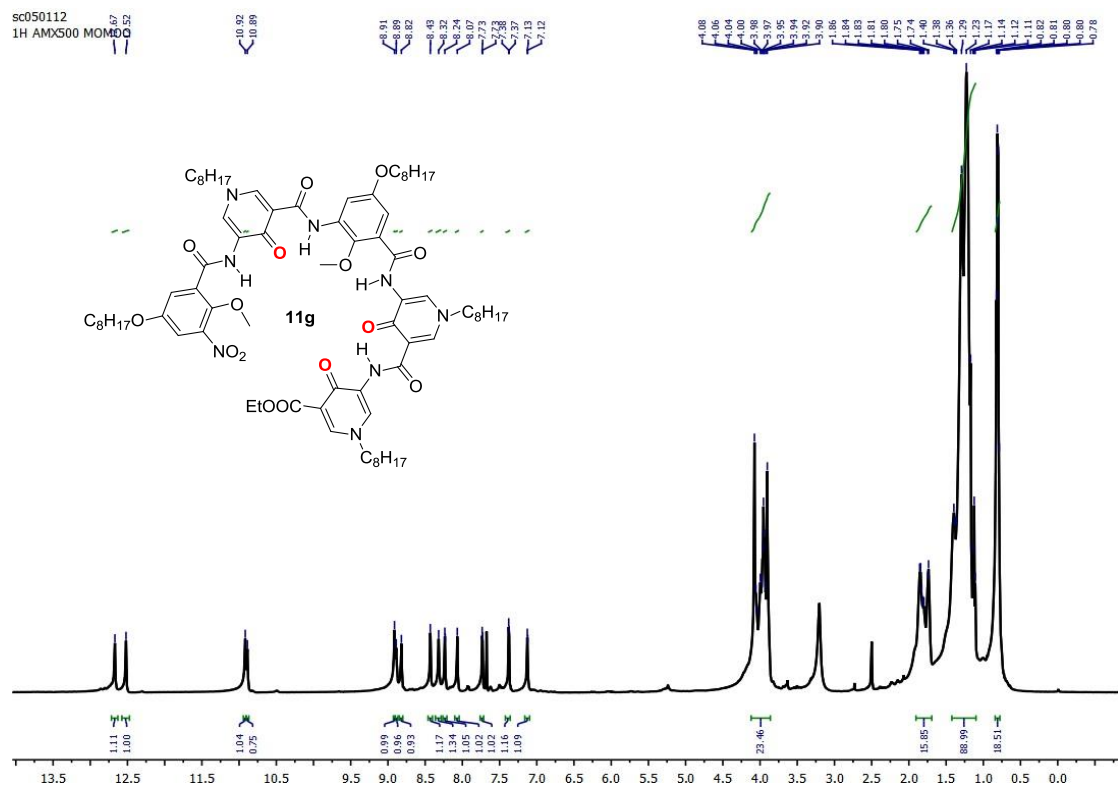
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8.46
8.45
7.90
7.50
7.50
7.08
7.08

1.94
1.93
1.91
1.90
1.88
1.84
1.82
1.81
1.79
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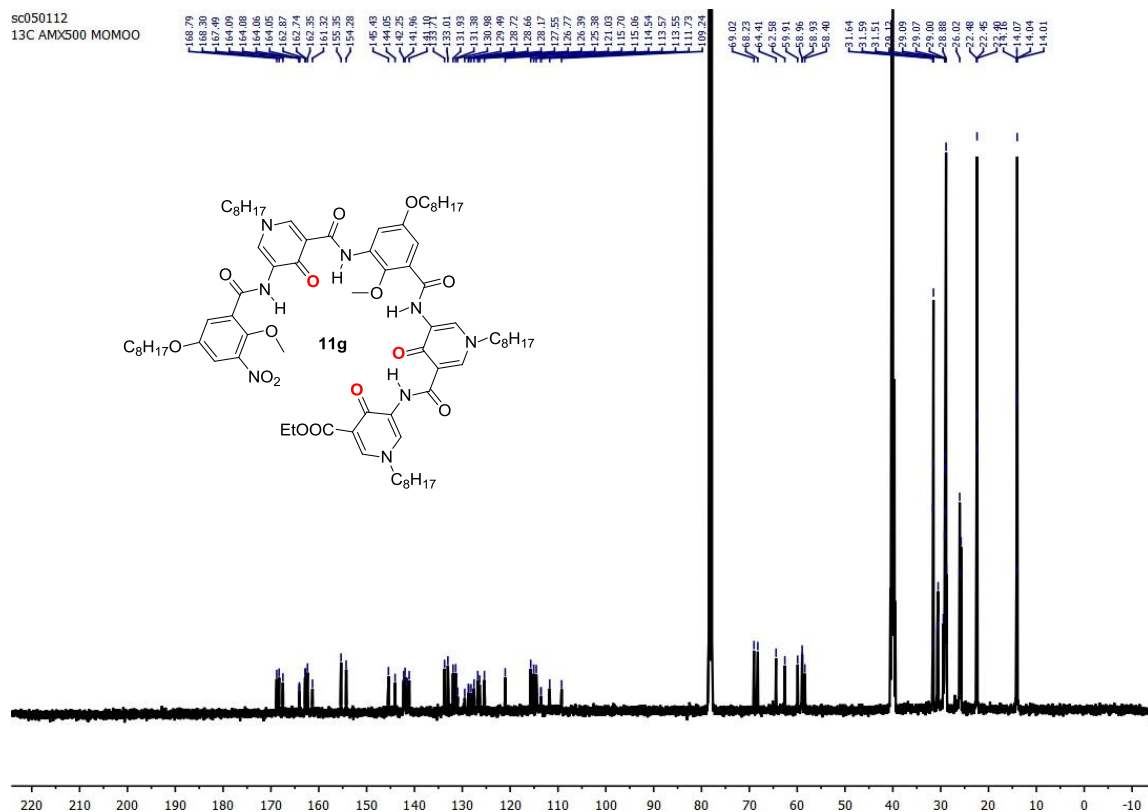




^1H and ^{13}C NMR spectra of 11g

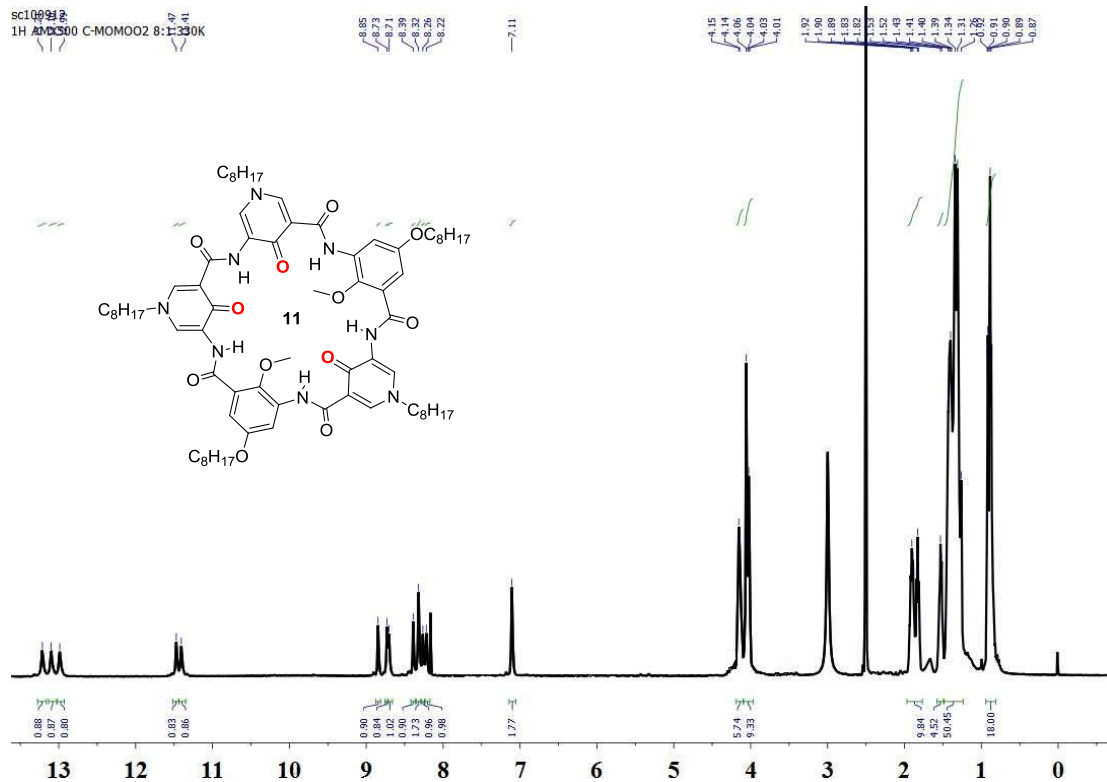


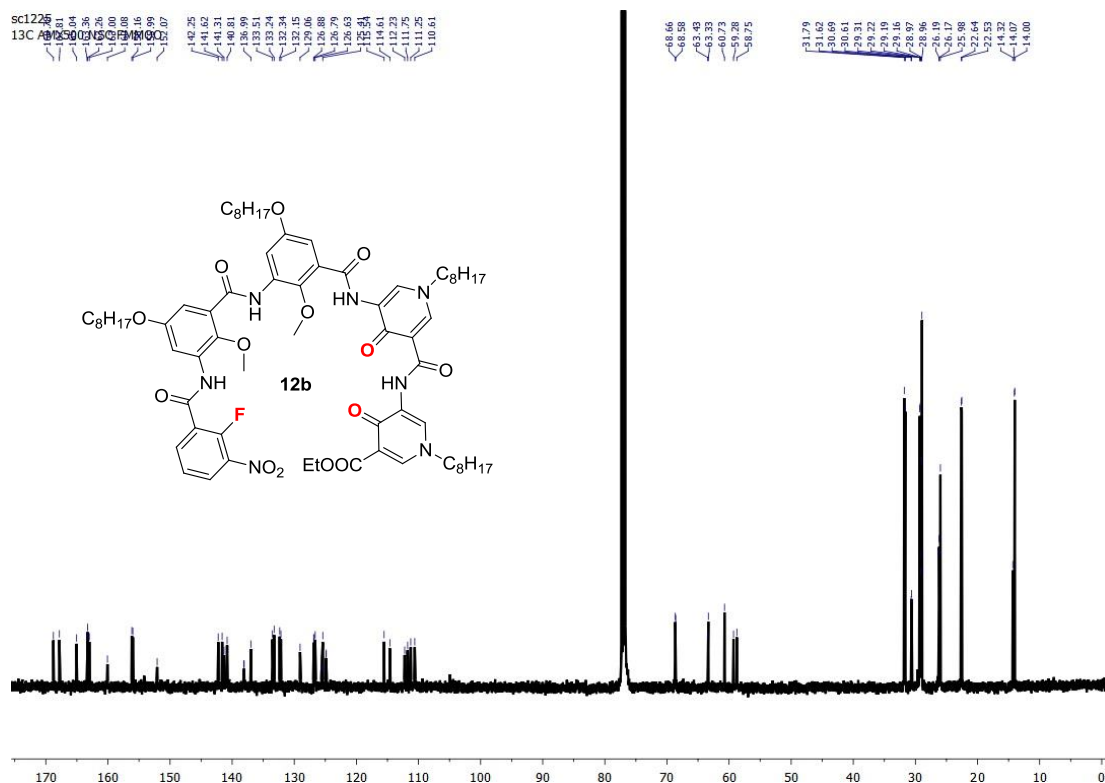
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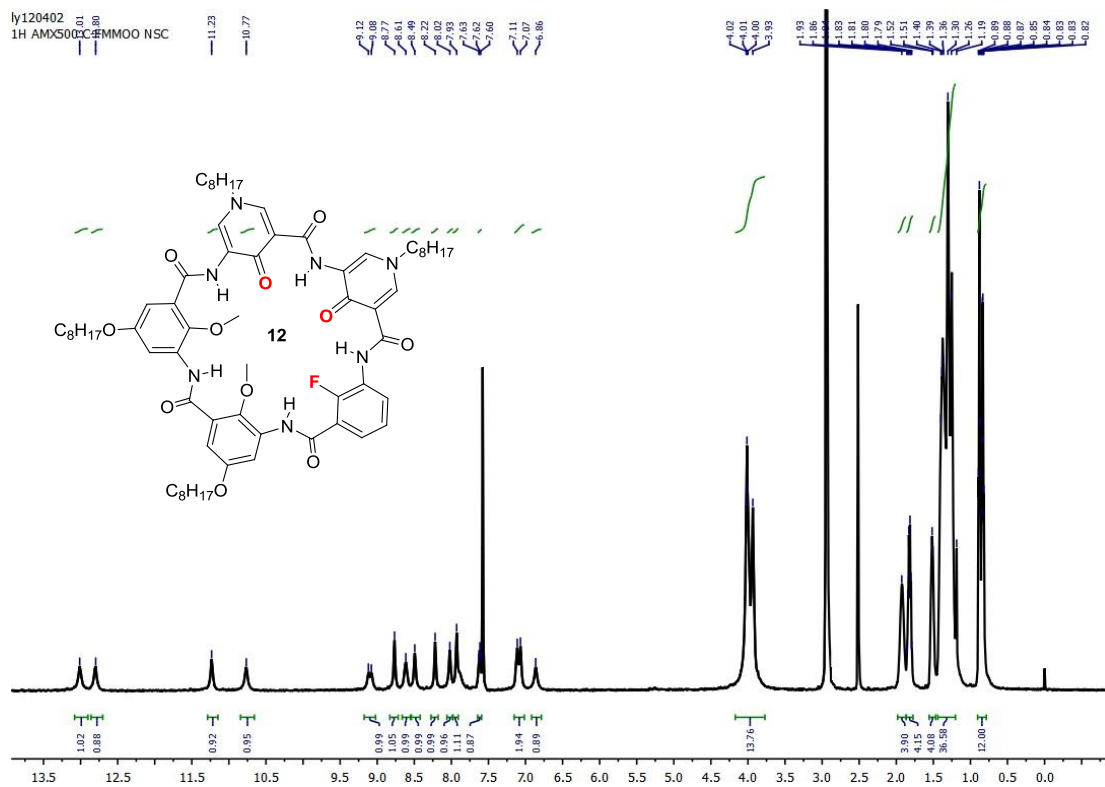
¹H and ¹³C NMR spectra of 11

sc109992
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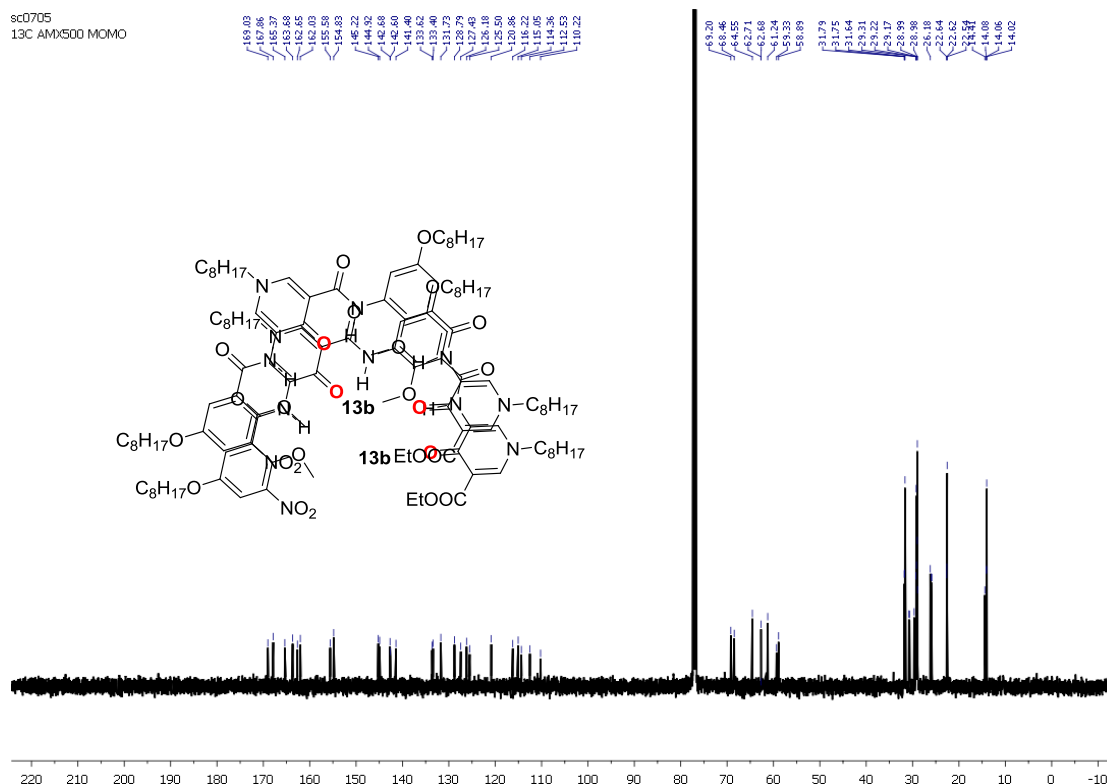




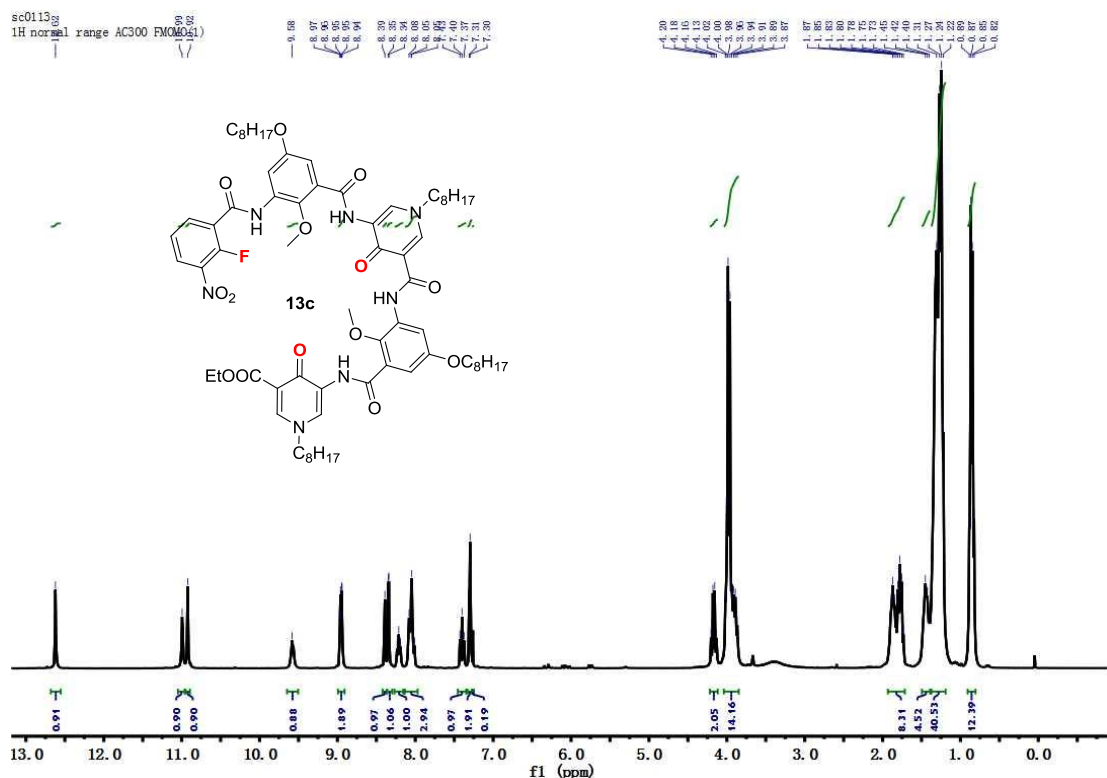
¹H and ¹³C NMR spectra of **12**

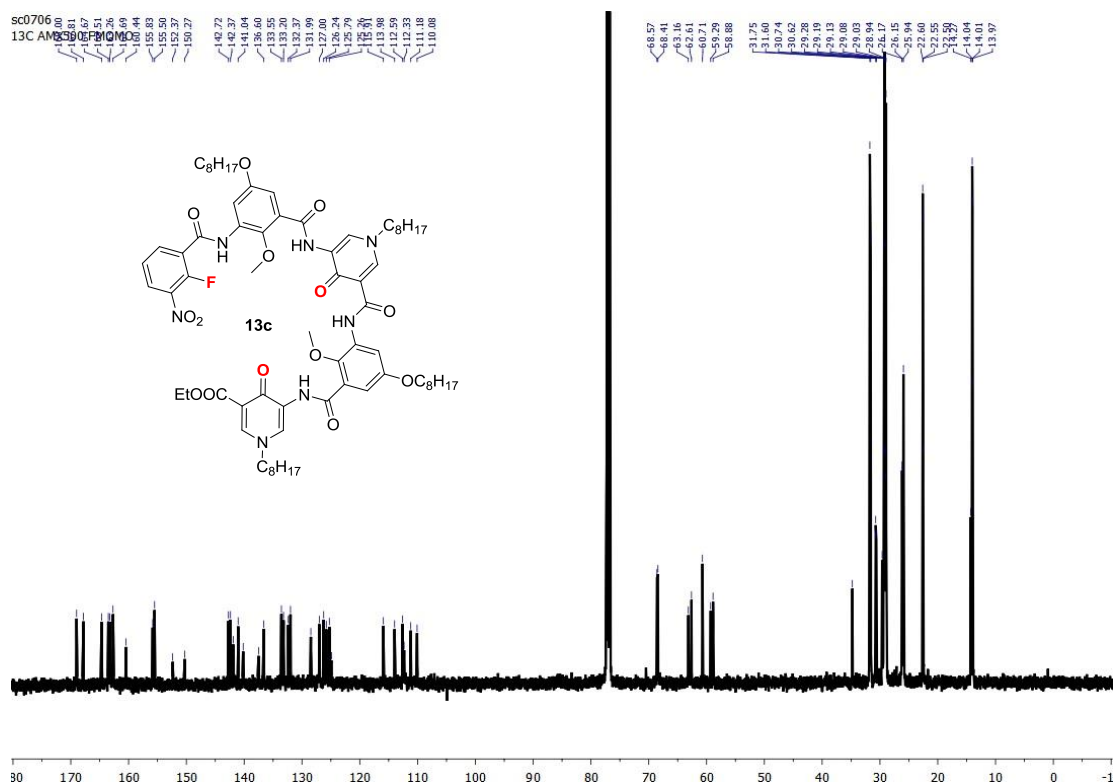


sc0705
13C AMX500 MOMO

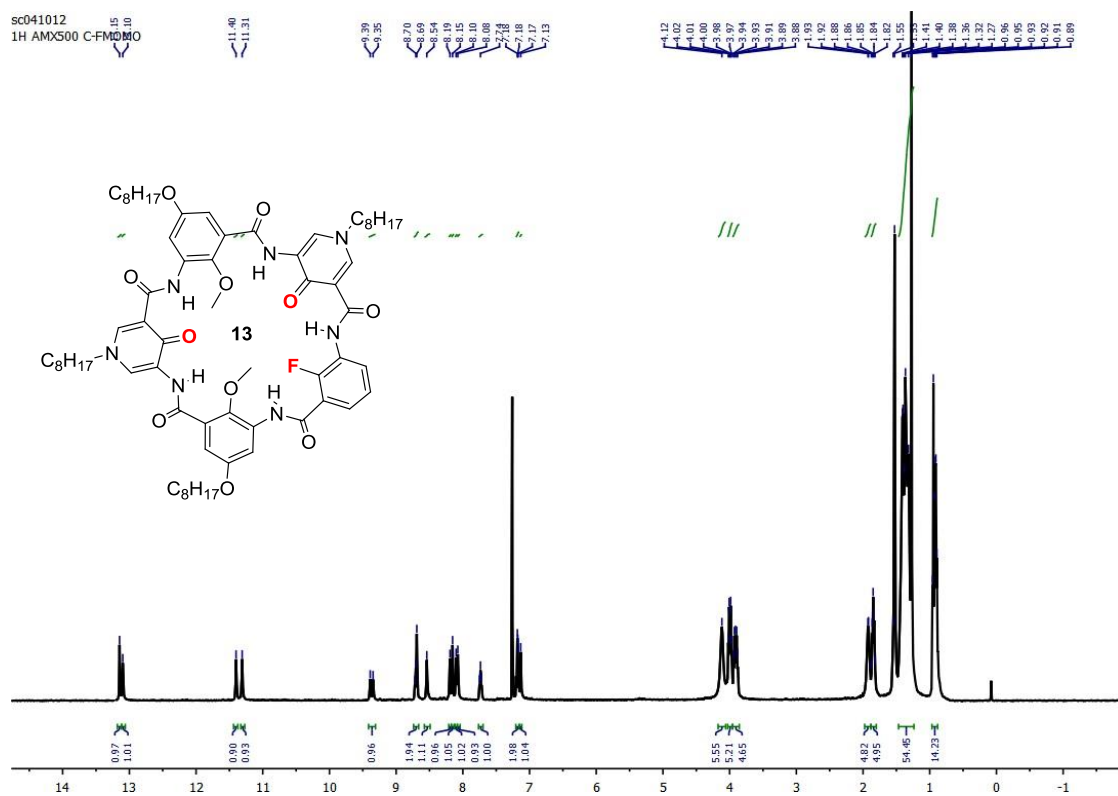


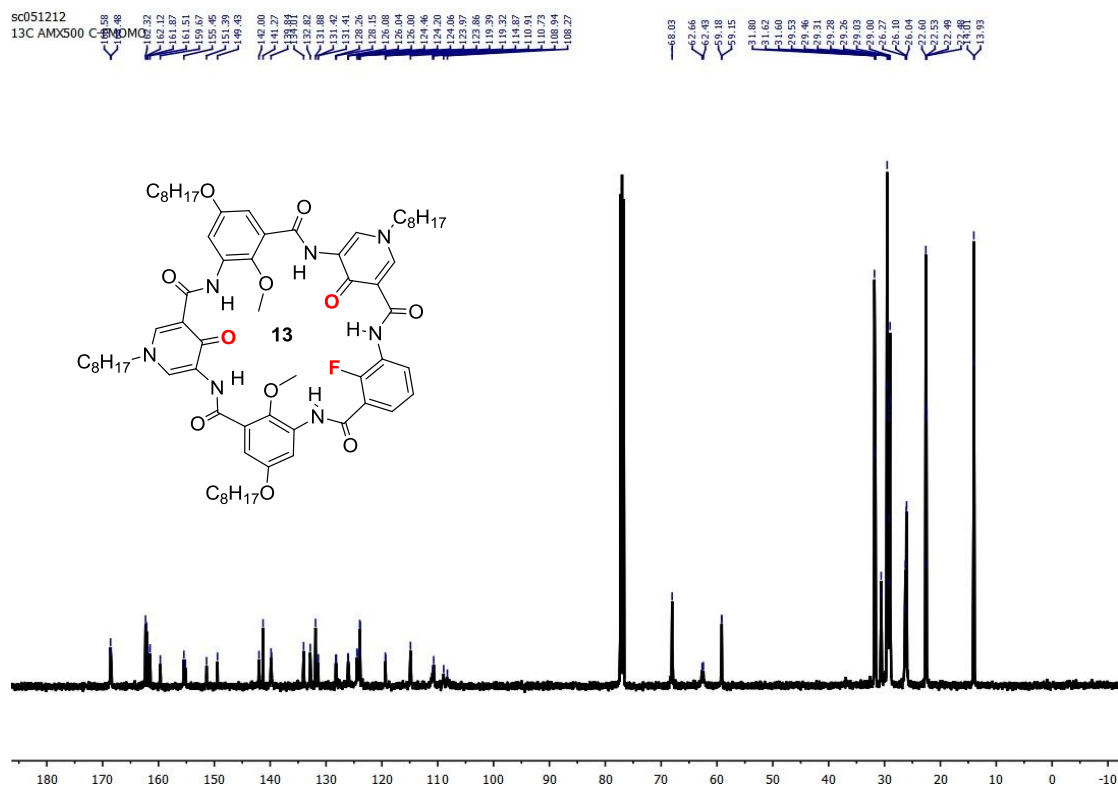
¹H and ¹³C NMR spectra of 13c



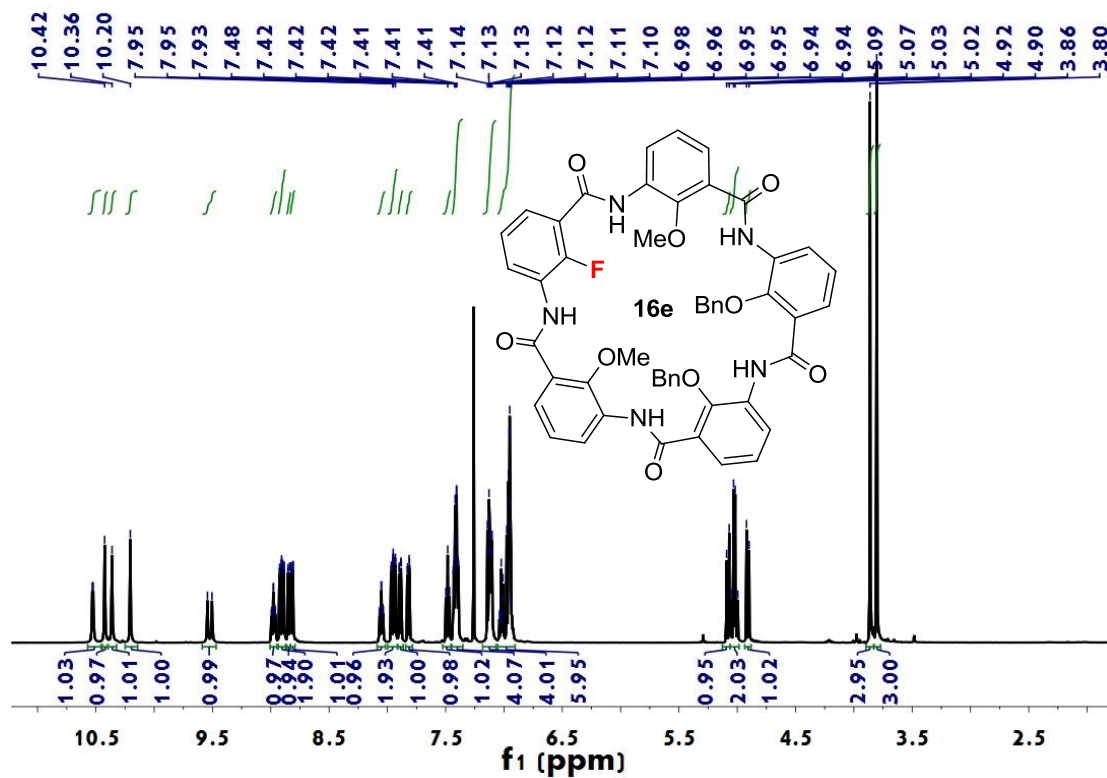


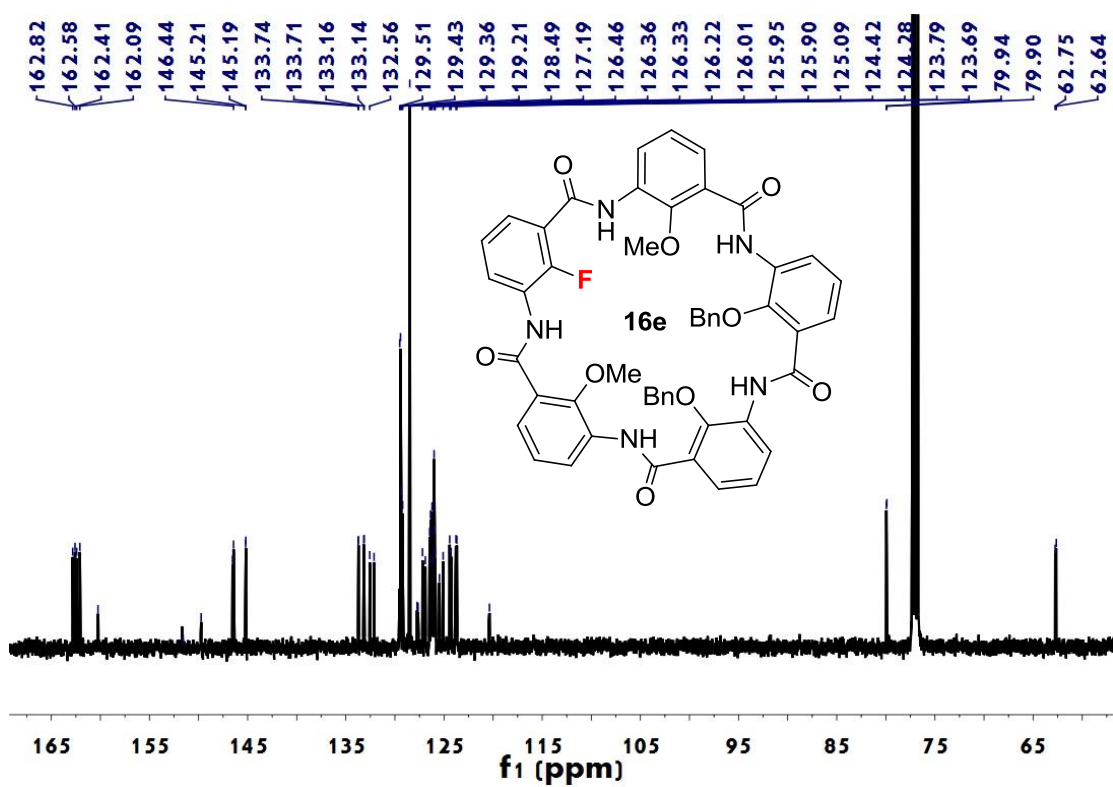
¹H and ¹³C NMR spectra of 13



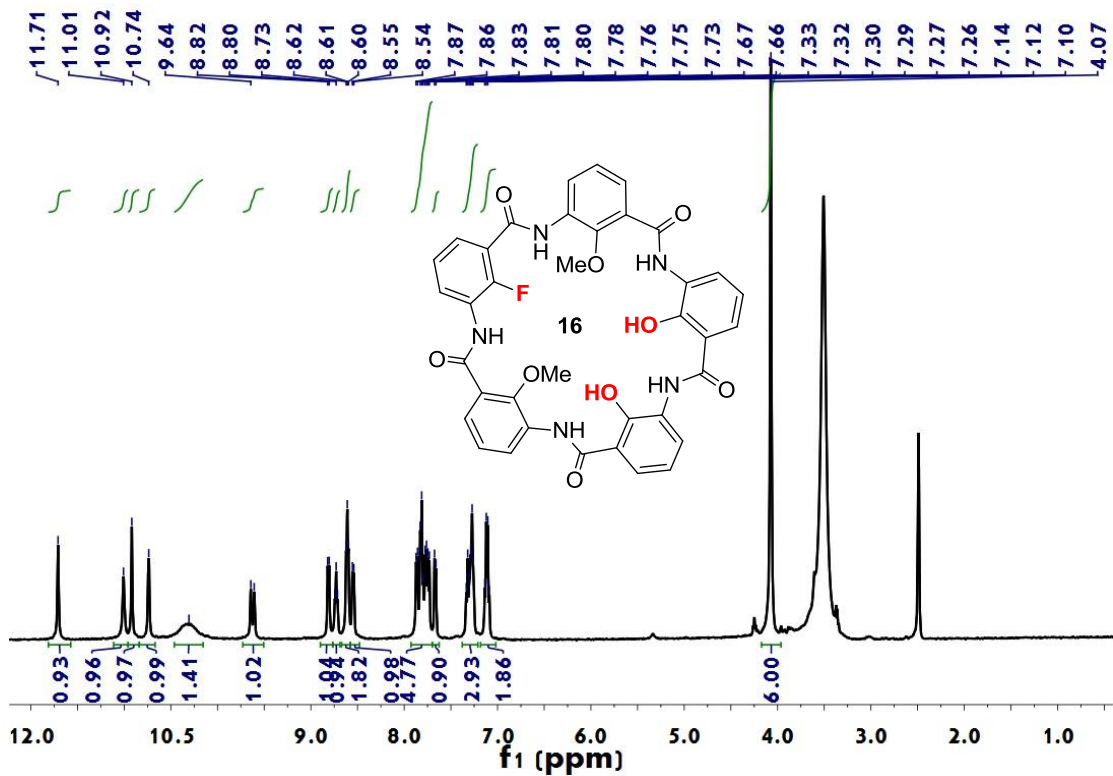


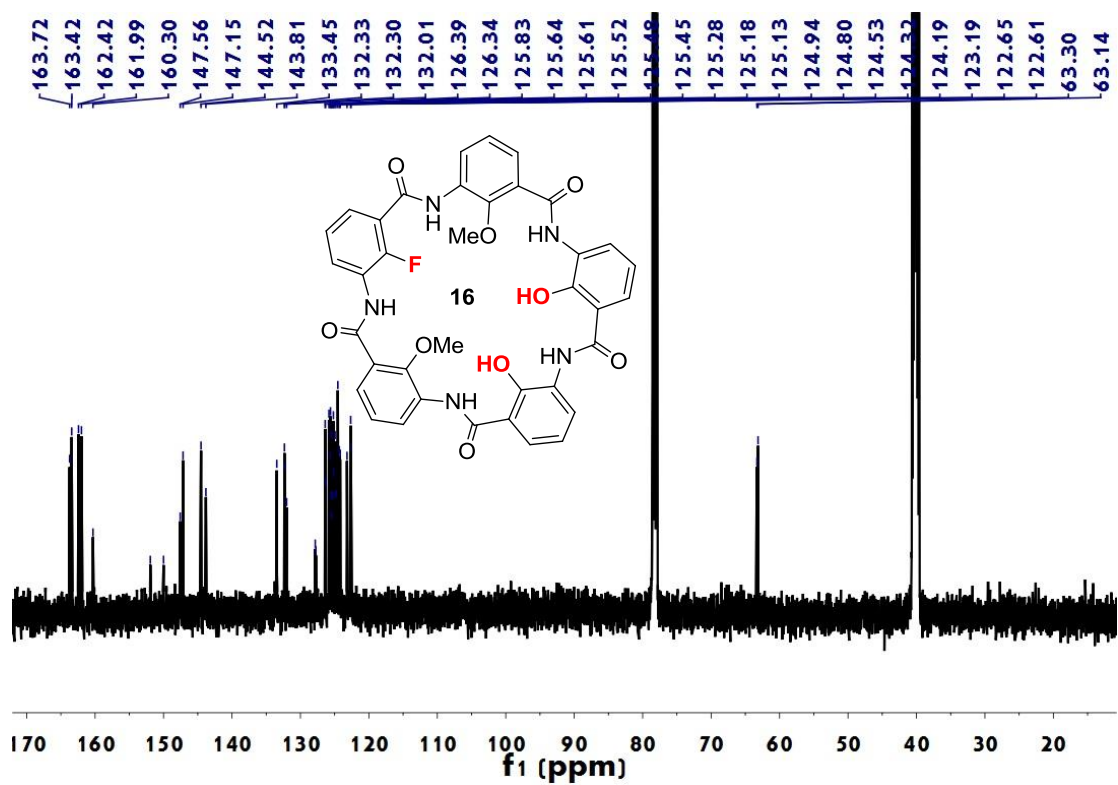
^1H and ^{13}C NMR spectra of 16e



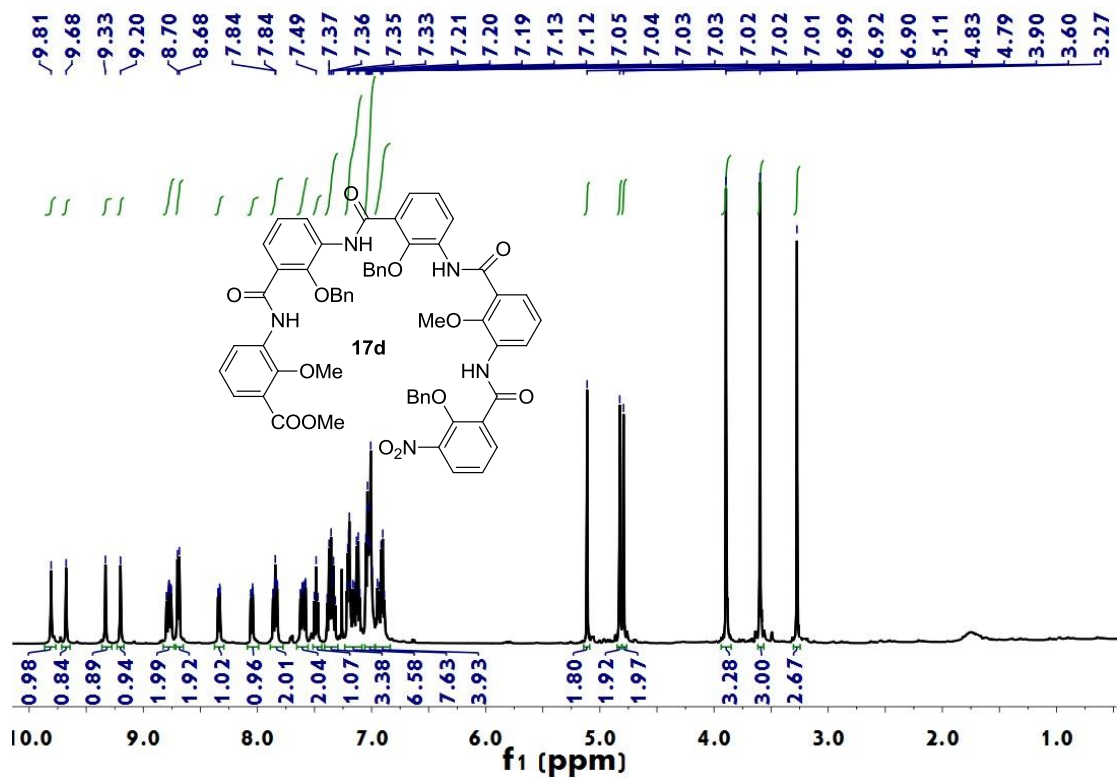


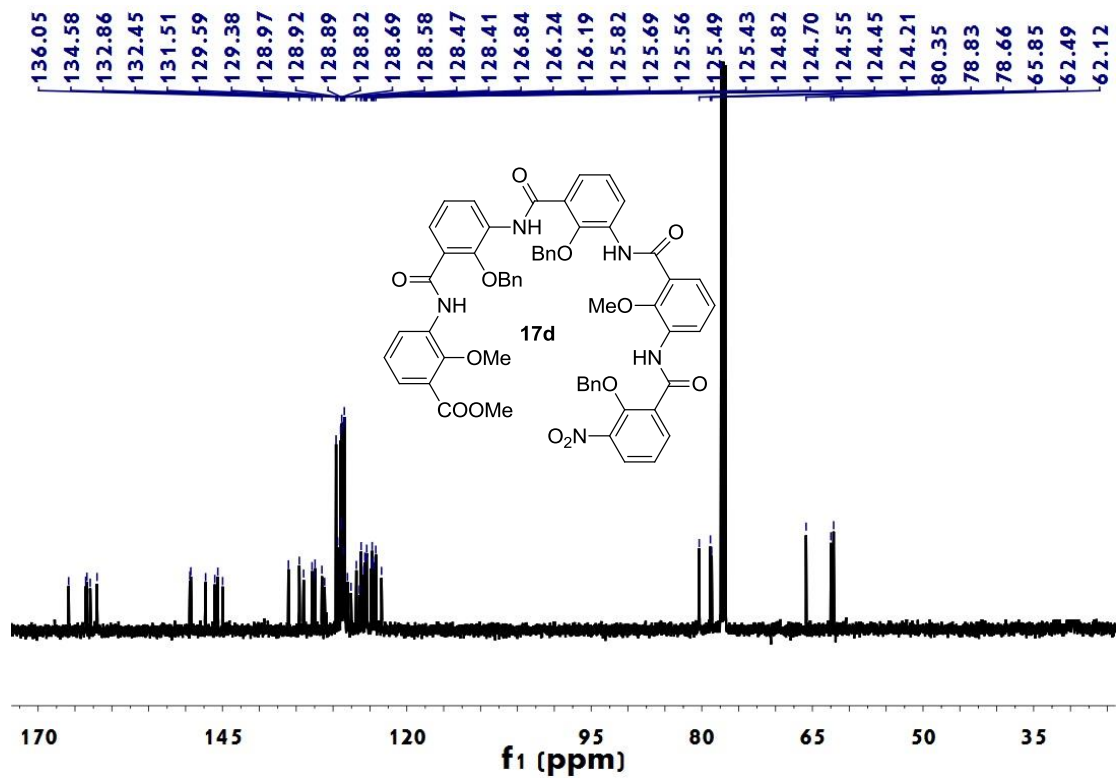
¹H and ¹³C NMR spectra of 16



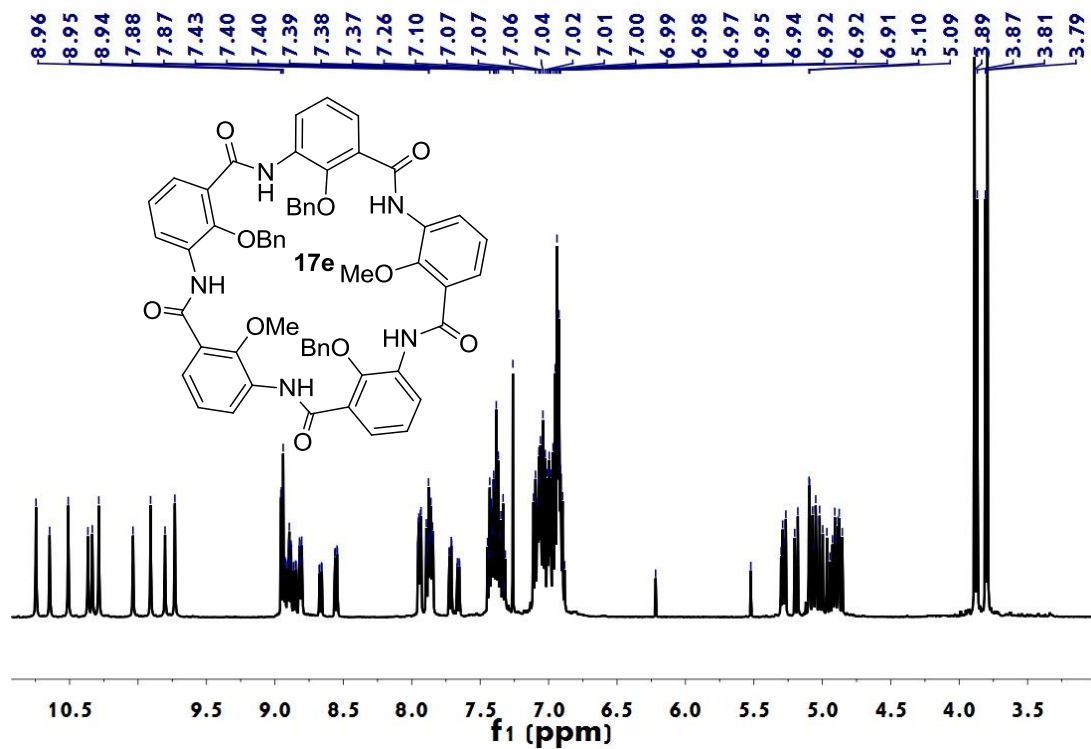


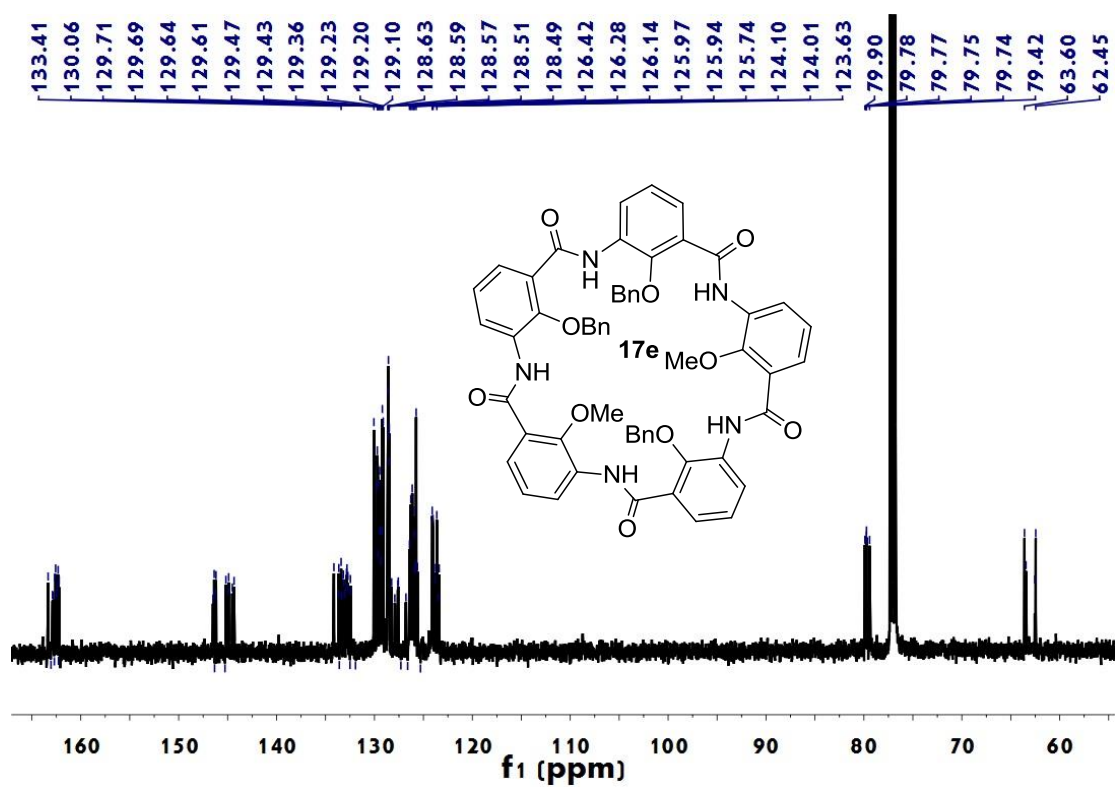
¹H and ¹³C NMR spectra of 17d



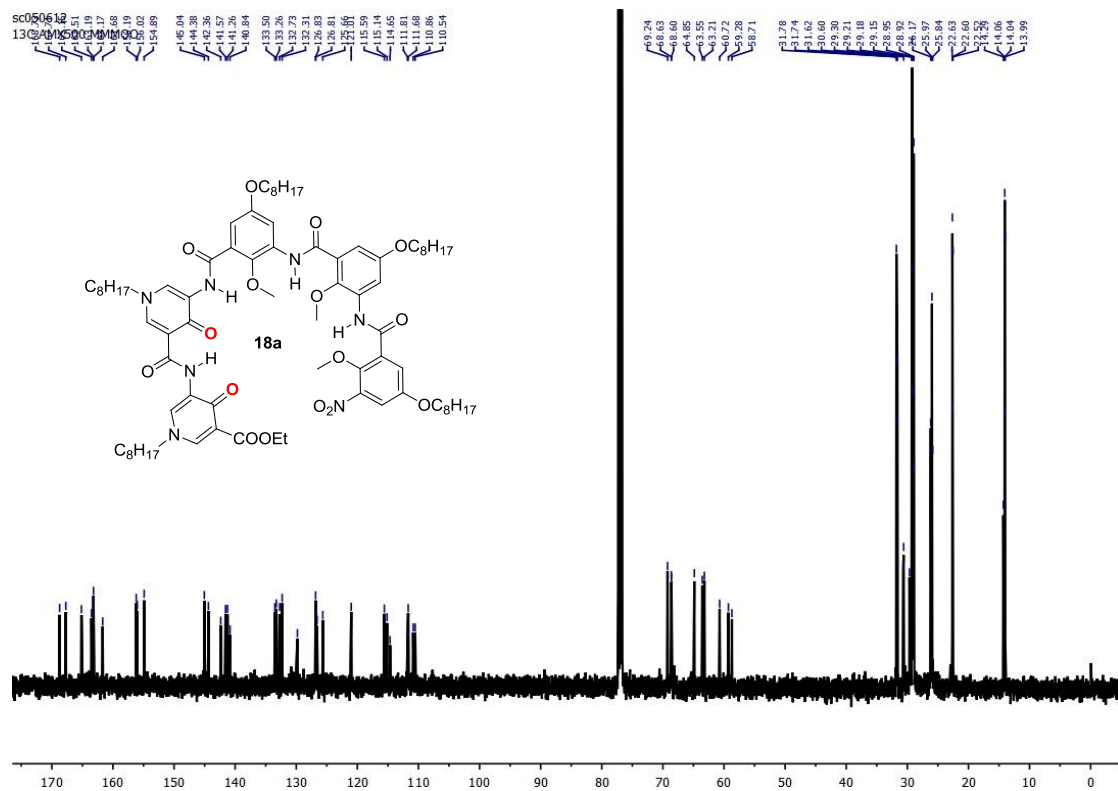
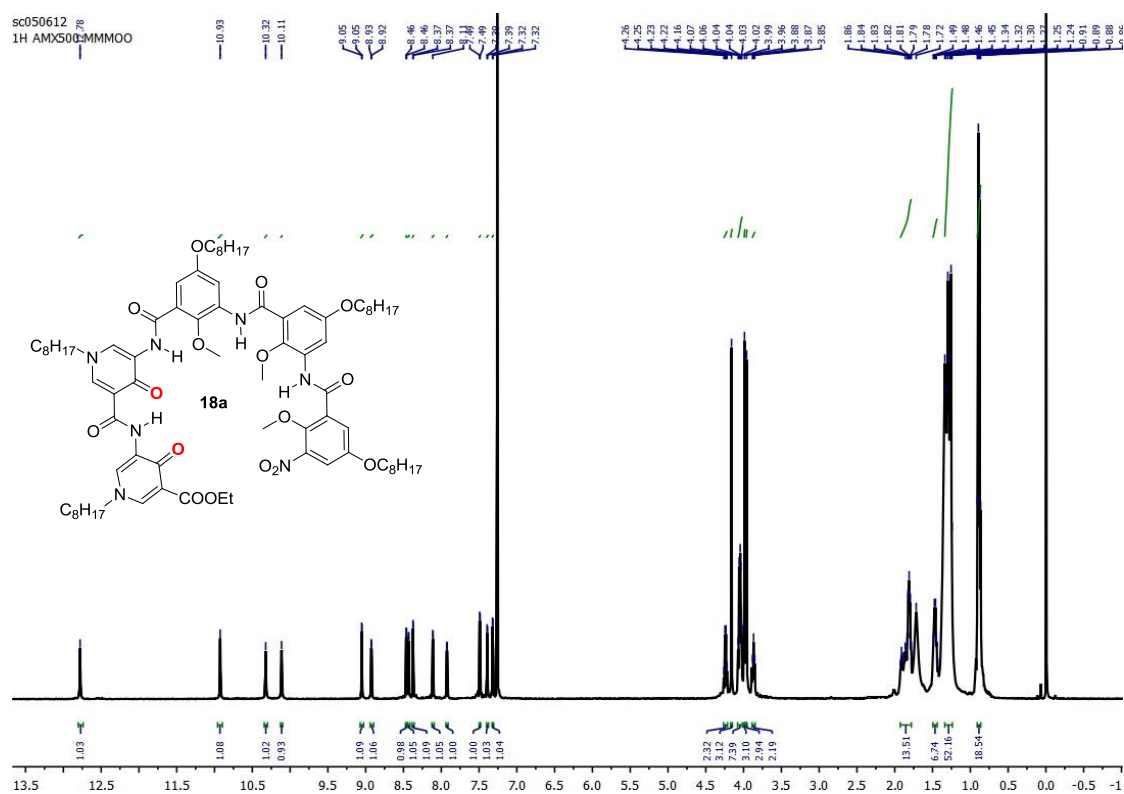


¹H and ¹³C NMR spectra of 17e

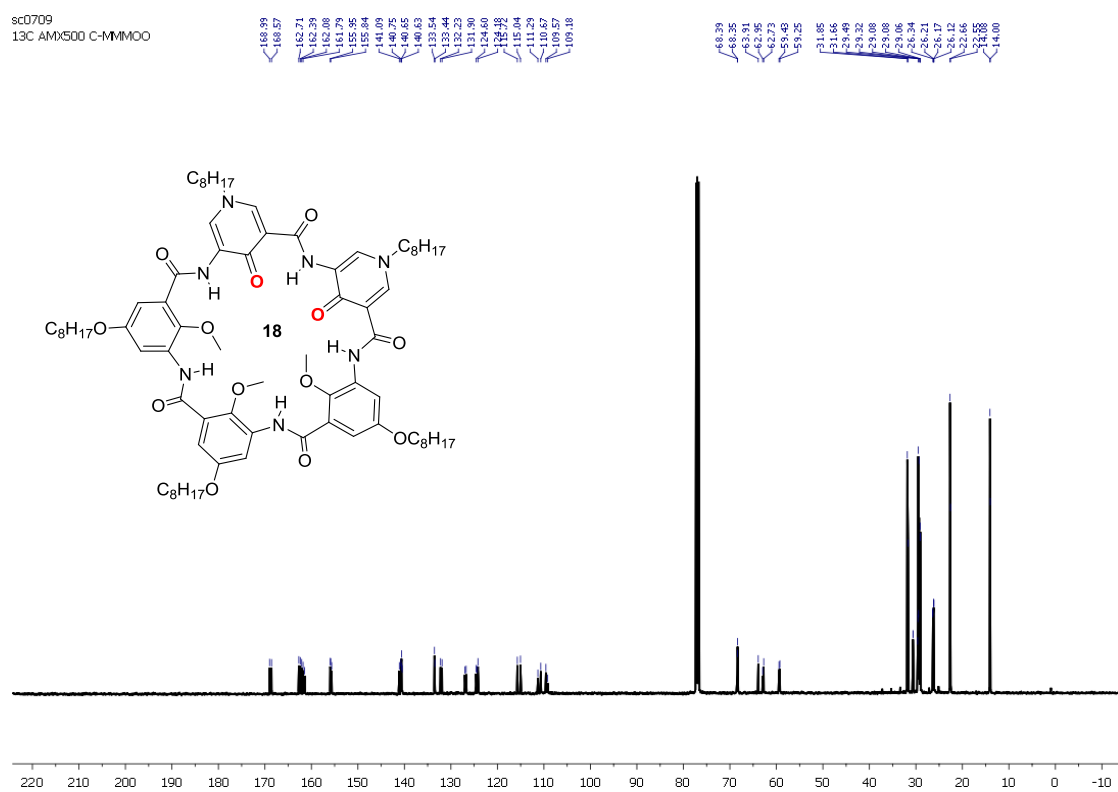
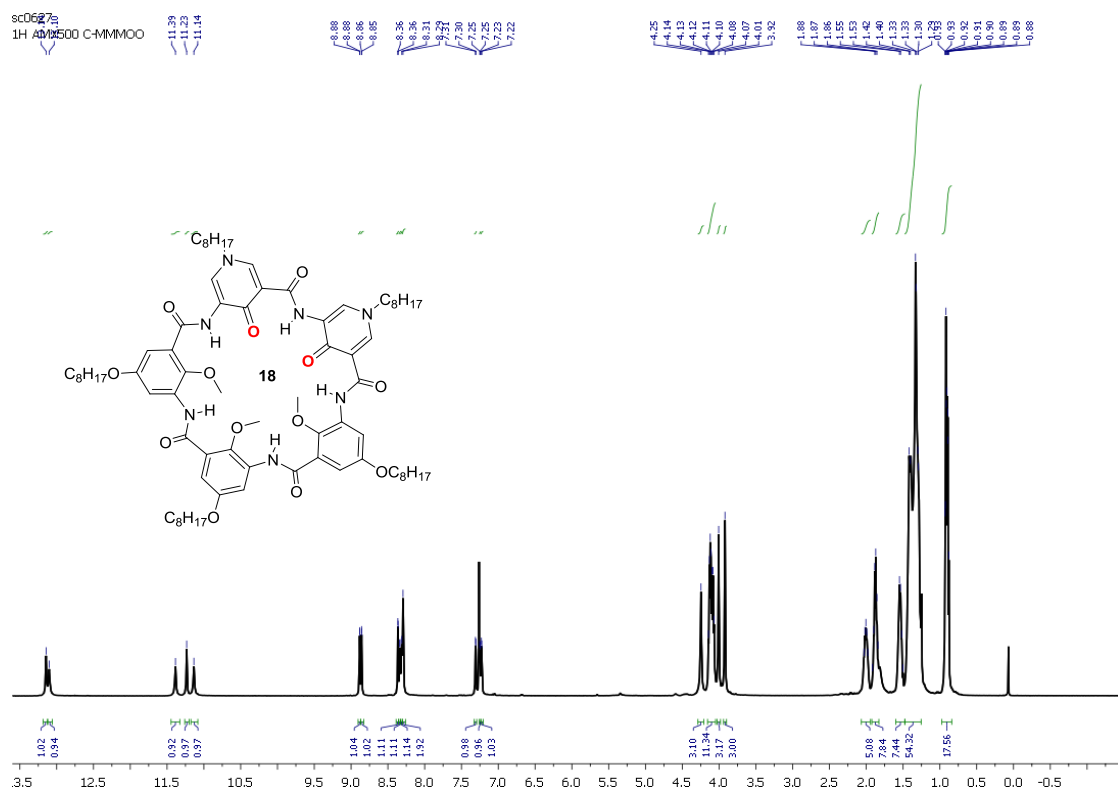




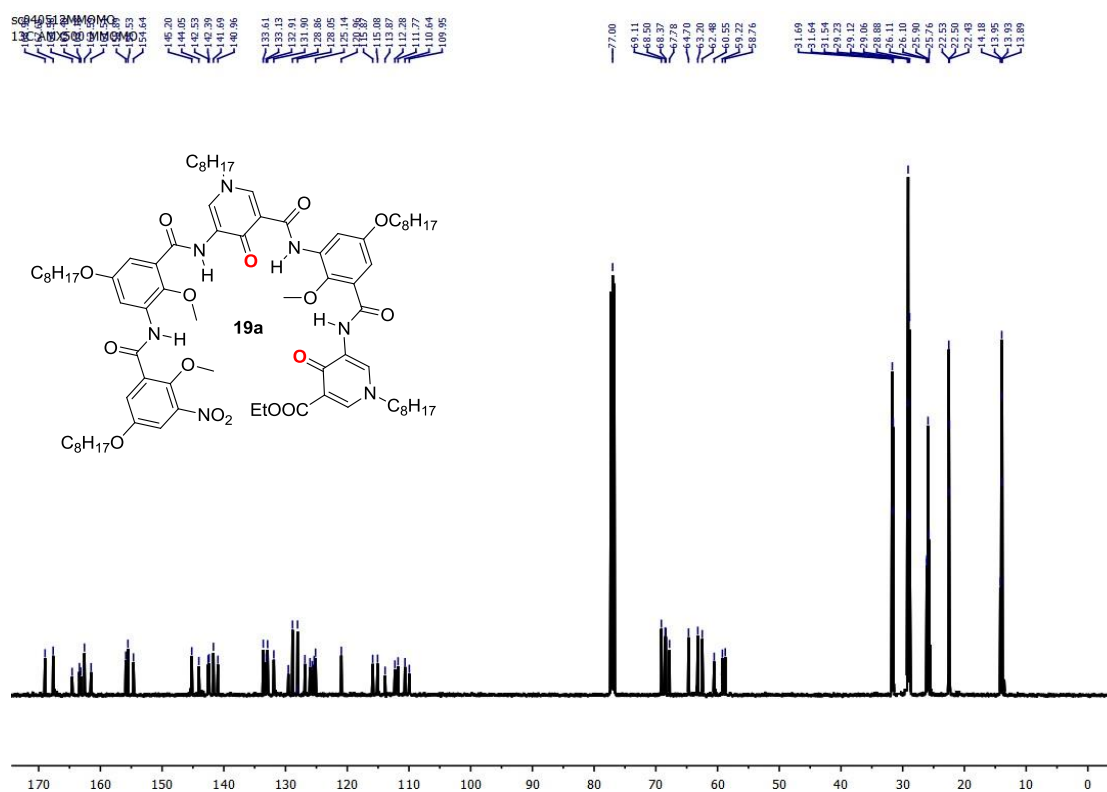
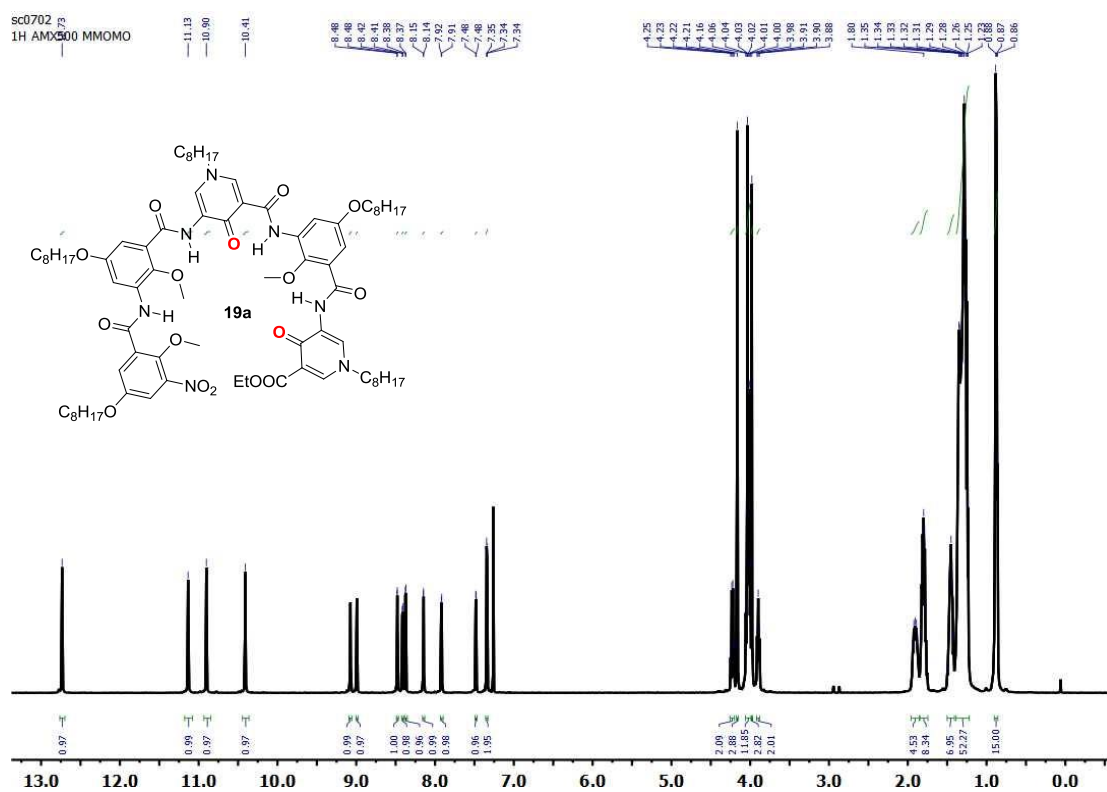
^1H spectrum of 17

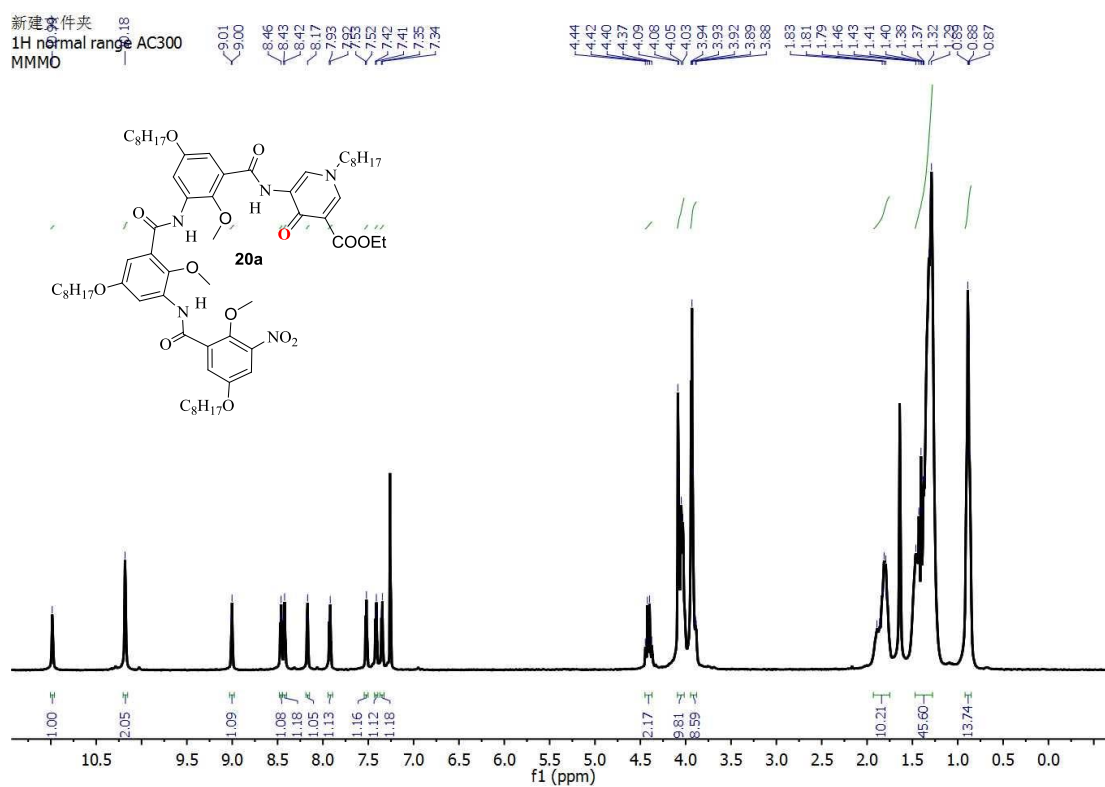


¹H and ¹³C NMR spectra of **18**



H and ¹³C NMR spectra of 19a





¹H and ¹³C NMR spectra of 20c

