Foldamer-based K^+ Channels with Ion Selectivity Surpassing the KcsA Channel

Ze Lin, Zhaocheng Xu, Jun Tian, Chenyang Zhang, Chuqiao Sheng and Zeyuan Dong*

Z. Lin, Z. C. Xu, J. Tian, Dr. C. Y. Zhang, C. Q. Sheng, Prof. Z. Y. Dong,
State Key Laboratory of Supramolecular Structure and Materials, and Center for Supramolecular Chemical Biology,
College of Chemistry, Jilin University, Changchun 130012, China
E-mail: zdong@jlu.edu.cn

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1. General Remarks

All the reagents were obtained from commercial suppliers and used as received unless otherwise noted. N, N-dimethylformamide (DMF), triethylamine (TEA), and chloroform ($CHCl_3$) were distilled from CaH_2 before use. The aqueous solution was prepared from MilliQ water. All the reactions were monitored by thin-layer chromatography (TLC) and observed with ultraviolet light (UV), while column chromatography purifications were carried out via silica gel. ^1H and ^{13}C NMR spectra were recorded on the WNMR-I 400 or Bruker AVANCEIII500. The solvent signals of $CDCl_3$ and DMSO-d_6 (Dimethyl sulfoxide-d_6) for ^1H NMR spectrum were referenced at δ = 7.26 and 2.50 ppm, respectively. ^1H NMR data are recorded in the order: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), and number of protons. The solvent signals of $CDCl_3$ and DMSO-d_6 for ^{13}C NMR spectrum were referenced at δ = 77.16 and 39.52 ppm, respectively. The mass spectra were obtained on an HP1100EMD (electrospray ionization mass spectrometry, ES MS).

2. Synthesis and characterization of M1-M5

The synthesis and characterization of **M2** and **M4** are referred to the previous literature.[S1] The synthesis and characterization of **M0** are detailed in the reference literature.[S3]

To provide a clearer representation of the structures of molecules **M1**-**M5**, the flat diagram showing the extended side chains is as follows:

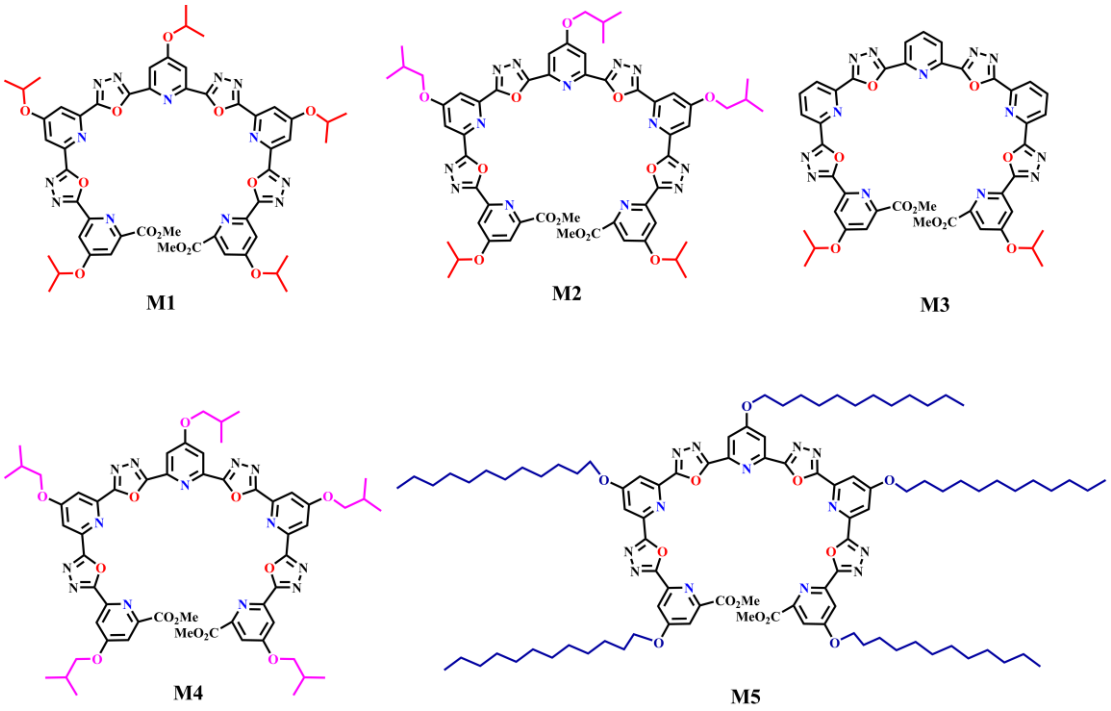
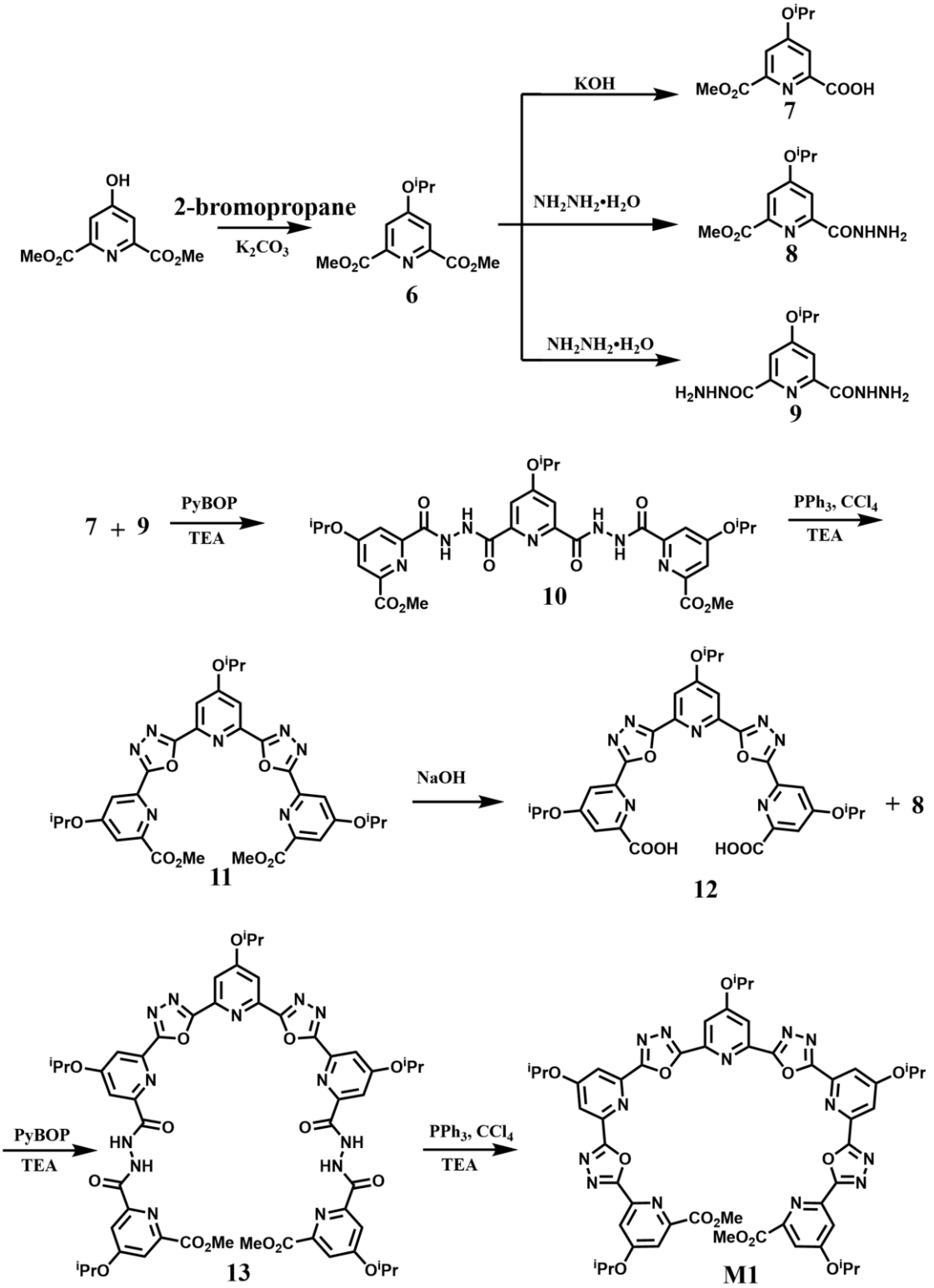
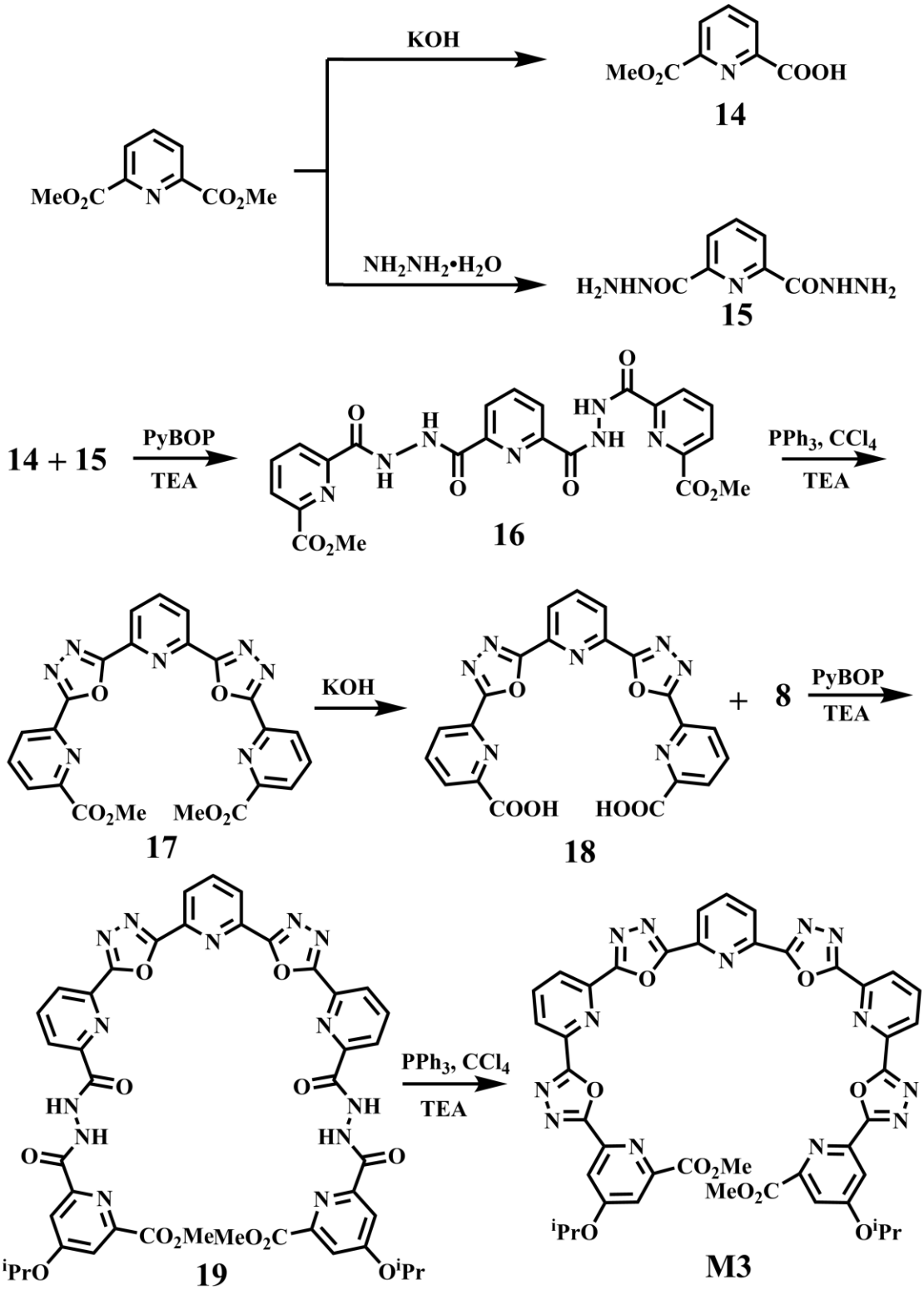


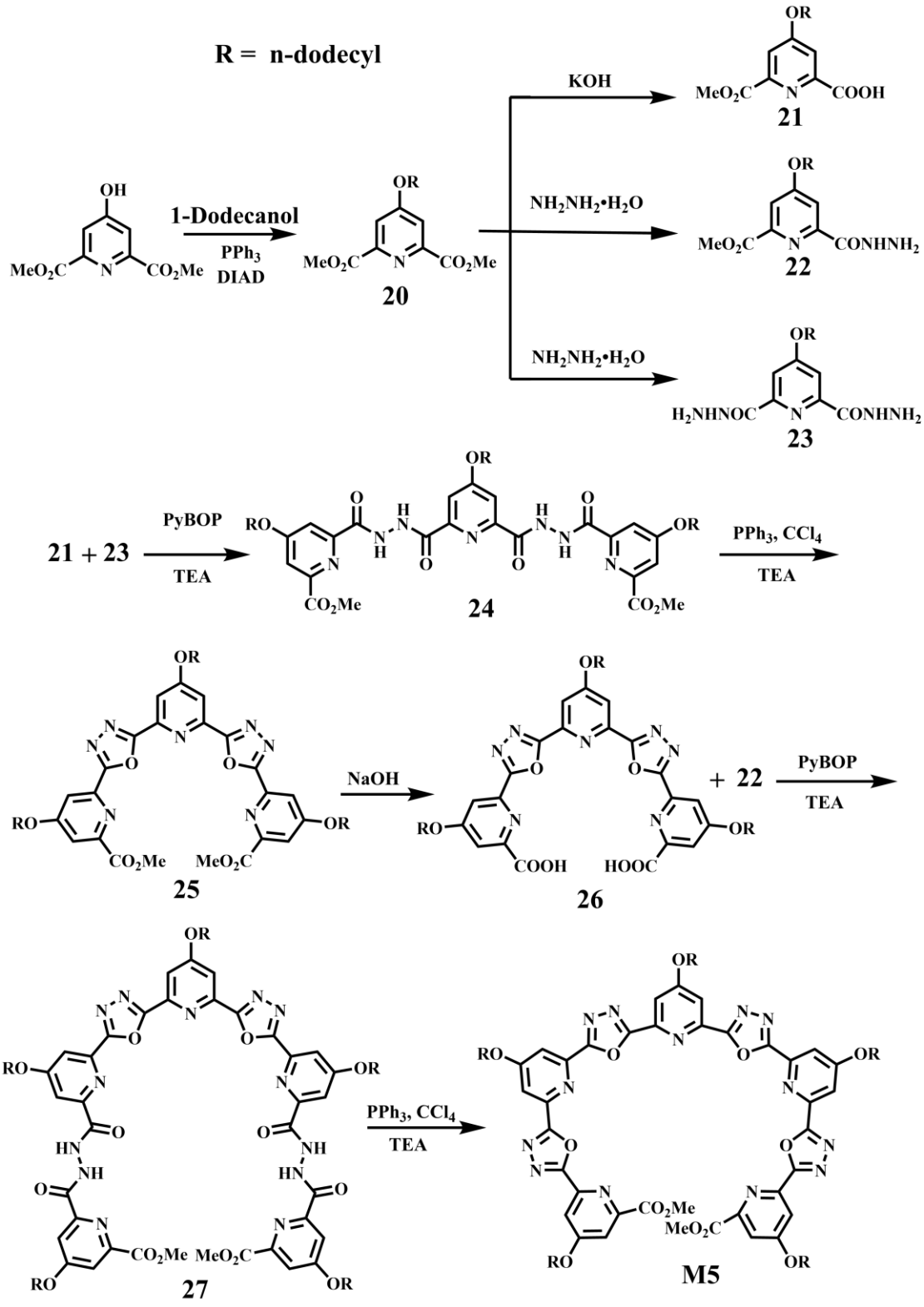
Figure S1. Chemical structures of foldamers **M1**-**M5**.



Scheme S1. Synthesis route of **M1**.



Scheme S2. Synthesis route of **M3**.

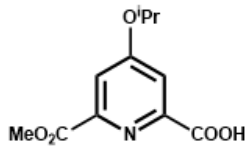


Scheme S3. Synthesis route of **M5**.

Synthesis of 6, 8 and 9

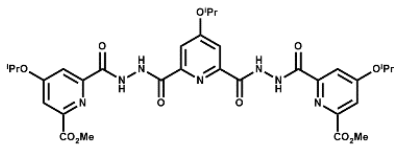
6, **8,** and **9** were synthesized according to the previously reported methods.[S1,S2]

Compound 7



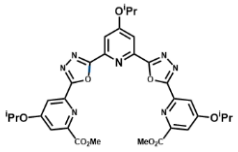
Compound **6** (10.0 g, 39.5 mmol) was dissolved in 100 mL methanol and then added with NaOH (1.6 g, 39.5 mmol) and 1 mL water under stirring at room temperature. After 5 hours, the excess solvent was removed under reduced pressure and the product was dispersed in water. The suspension was then neutralized with 0.1 M HCl and filtered with pure water. The filter residue was then completely dried under vacuum at 50°C for two days and was collected as a crude product. The crude product was purified by silica gel column chromatography using dichloromethane/methanol (150: 1, vol/vol) to obtain **7** (6.6 g, yield 70%). ^{1}H NMR (400 MHz, DMSO) δ 7.64 (d, *J* = 9.2 Hz, 2H), 5.19 – 4.63 (m, 1H), 3.89 (s, 3H), 1.31 (d, *J* = 5.5 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 166.76, 166.25, 165.83, 152.23, 150.23, 115.26, 115.21, 71.97, 53.58, 22.28. ESI m/z: calculated for $[M+H]^+$ $C_{11}H_{14}NO_5$ 240.08; Found 240.08.

Compound 10



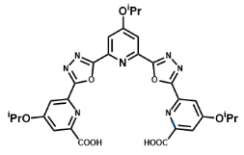
To a solution of **7** (4.0 g, 16.7 mmol) and **9** (2.1 g, 8.4 mmol) in dry DMF (100 mL) was added benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) (17.4 g, 33.4 mmol) and TEA (8.4 g, 83.5 mmol), and the solution was refluxed at 75°C for 24 hours. The solution was evaporated under vacuum and the resulting solid was purified by silica gel column chromatography using dichloromethane and methanol as eluent to obtain **10** (3.8 g, yield 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.82 (s, 2H), 10.22 (s,2H), 7.61 (d, *J* = 2.3 Hz, 2H), 7.51 (s, 2H), 7.45 (d, *J* = 2.3 Hz, 2H), 4.79 – 4.55 (m, 3H), 3.96 (s, 6H), 1.36 (d, *J* = 6.0 Hz, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.40, 165.92, 164.70, 163.45, 162.50, 150.06, 149.16, 148.02, 115.26, 111.73, 111.45, 71.41, 71.38, 52.93, 21.66, 21.63. ESI m/z: calculated for $[M+H]^+$ $C_{32}H_{38}N_7O_{11}$ 696.26; Found 696.26.

Compound 11



To a solution of **10** (3.0 g, 4.3 mmol) in dry $CHCl_3$ (30 mL) was added triphenylphosphine (PPh_3) (2.5 g, 9.5 mmol), CCl_4 (1.5 g, 9.5 mmol) and TEA (4.4 g, 43.0 mmol), and the resulting solution was refluxed at 80°C for 24 hours. The solution was evaporated and the solid left was purified by silica gel column chromatography using dichloromethane and methanol (50: 1, vol/vol) as eluent for two times to obtain **11** (1.3 g, yield 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 2.2 Hz, 2H), 8.01 (s, 2H), 7.78 (d, *J* = 2.3 Hz, 2H), 4.90 (dt, *J* = 12.3, 6.3 Hz, 3H), 4.05 (s, 6H), 1.48 (d, *J* = 6.1 Hz, 6H), 1.45 (d, *J* = 6.1 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.03, 165.80, 165.19, 164.39, 164.29, 150.52, 145.43, 144.74, 114.55, 113.56, 113.08, 71.89, 71.69, 53.14, 21.74, 21.68. ESI m/z: calculated for $[M+H]^+$ $C_{32}H_{34}N_7O_9$ 660.23; Found 660.24.

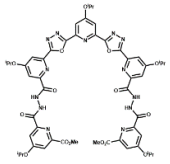
Compound 12



Compound **11** (1.2 g, 1.8 mmol) was dissolved in 15 mL methanol and then added with NaOH (0.7 g, 18 mmol) and 1 mL water under stirring at room temperature. After 24 hours, the excess solvent was removed under reduced pressure and the product was dispersed in water. The suspension was then

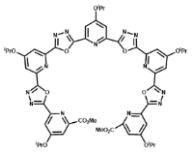
neutralized with 0.1 M HCl and filtered with pure water. The filter residue was then completely dried under vacuum at 50℃ for two days and was collected as product to obtain **12** (1.1 g, yield 95%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 41.0 Hz, 3H), 7.66 (s, 3H), 5.01 – 4.87 (m, 1H), 4.88 – 4.74 (m, 2H), 1.50 (d, *J* = 6.0 Hz, 4H), 1.44 (t, *J* = 4.9 Hz, 12H), 1.38 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.13, 165.49, 165.29, 164.29, 164.49, 150.79, 145.53, 144.83, 114.65, 113.66, 113.19, 71.99, 71.24, 53.24, 21.84, 21.78. ESI m/z: calculated for $[M+H]^+$ $C_{30}H_{30}N_7O_9$ 632.20; Found 632.21.

Compound 13



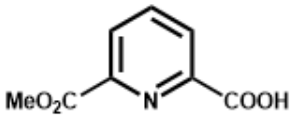
To a solution of **8** (936.5 mg, 3.7 mmol) and **12** (1.1 g, 1.7 mmol) in dry DMF (50 mL) was added benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) (3.5 g, 6.8 mmol) and TEA (1.7 g, 17.0 mmol), and the solution was refluxed at 75℃ for 48 hours. The solution was evaporated under vacuum and the resulting solid was purified by silica gel column chromatography using dichloromethane and methanol as eluent to obtain **13** (748.9 mg, yield 40%)^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 1.8 Hz, 2H), 8.05 (s, 2H), 7.97 (s, 2H), 7.96 – 7.91 (m, 4H), 5.08 (dt, *J* = 12.0, 6.0 Hz, 2H), 5.01 (dt, *J* = 12.1, 6.0 Hz, 1H), 4.95 (dt, *J* = 12.1, 6.0 Hz, 2H), 4.17 (s, 6H), 1.52 (t, *J* = 5.3 Hz, 18H), 1.49 (d, *J* = 6.0 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.35, 167.13, 166.83, 165.63, 164.49, 164.23, 163.46, 163.12, 159.41, 159.08, 158.75, 158.41, 150.61, 149.74, 148.09, 144.90, 142.88, 116.72, 116.14, 114.45, 113.94, 112.66, 72.95, 72.60, 72.46, 53.81, 21.90, 21.81. ESI m/z: calculated for $[M+H]^+$ $C_{52}H_{56}N_{13}O_{15}$ 1102.39; Found 1102.39.

Compound M1



To a solution of **13** (660.8 mg, 0.6 mmol) in dry $CHCl_3$ (10 mL) was added triphenylphosphine (PPh_3) (346.2 mg, 1.3 mmol), CCl_4 (203.0 mg, 1.3 mmol) and TEA (607.2 mg, 6.0 mmol), and the resulting solution was refluxed at 80℃ for 24 hours. The solution was evaporated and the solid left was purified by silica gel column chromatography using dichloromethane and methanol as eluent two times to obtain **M1** (223.7 mg, yield 35%)^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 2H), 8.02 (d, *J* = 2.3 Hz, 2H), 8.00 (d, *J* = 2.4 Hz, 2H), 7.98 (d, *J* = 2.2 Hz, 2H), 7.78 (d, *J* = 2.3 Hz, 2H), 4.99 (dd, *J* = 12.2, 6.1 Hz, 1H), 4.93 (dd, *J* = 12.2, 6.1 Hz, 2H), 4.88 (dt, *J* = 12.1, 6.1 Hz,2H), 4.05 (s, 6H), 1.51 (d, *J* = 6.1 Hz, 6H), 1.49 (d, *J* = 6.1 Hz, 12H), 1.46 (d, *J* = 6.1 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.08, 165.93, 165.13, 164.41, 164.31, 164.24, 150.38, 145.41, 145.37, 144.68, 114.81, 113.46, 113.19, 113.14, 113.04, 71.98, 71.76, 53.19, 21.78, 21.75, 21.70. ESI m/z: calculated for $[M+H]^+$ $C_{52}H_{52}N_{13}O_{13}$ 1066.37; Found 1066.37, calculated for $[2M+H]^+$ $C_{104}H_{104}N_{26}O_{26}$ 2130.76; Found 2130.76.

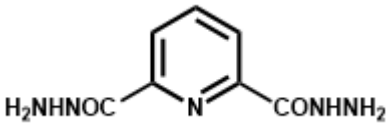
Compound 14



Dimethyl 2,6-pyridinedicarboxylate (5.0 g, 25.6 mmol) was dissolved in 50 mL methanol and then added with KOH (1.4 g, 25.6 mmol) and 1 mL water under stirring at room temperature. After 24 hours, the excess solvent was removed under reduced pressure and the product was dispersed in water. The suspension was then

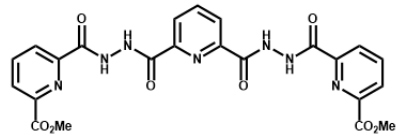
neutralized with 0.1 M HCl and filtered with pure water. The filter residue was completely dried under vacuum at 50°C for two days and then purified by silica gel column chromatography using dichloromethane and methanol as eluent to obtain **14** (2.8g, yield 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 7.8, 1.0 Hz, 1H), 8.35 (dd, *J* = 7.8, 1.0 Hz, 1H), 8.12 (t, *J* = 7.8 Hz, 1H), 4.02 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.29, 163.79, 146.75, 146.61, 139.59, 128.72, 127.01, 53.21. ESI m/z: calculated for $[M+H]^+$ $C_8H_8NO_4$ 182.04; Found 182.05.

Compound 15



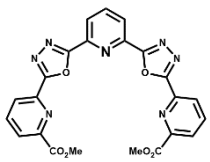
To a solution of Dimethyl 2,6-pyridinedicarboxylate (5.0 g, 25.6 mmol) in tetrahydrofuran/methanol (1: 1, vol: vol) was added a solution of hydrazine hydrate (7.7 g, 153.6 mmol) in methanol and the mixture was stirred overnight. The solvent was removed followed by the addition of 40 mL of methanol and storage at 4°C for an hour. The product **15** was obtained by collecting precipitation (4.5 g, yield 90%). ^{1}H NMR (500 MHz, DMSO) δ 10.64 (t, *J* = 4.0 Hz, 2H), 8.14 (s, 3H), 4.63 (d, *J* = 4.5 Hz, 4H). ^{13}C NMR (126 MHz, DMSO) δ 162.85, 149.36, 140.26, 124.62. ESI m/z: calculated for $[M+H]^+$ $C_7H_{10}N_5O_2$ 196.08; Found 196.08.

Compound 16



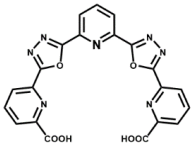
To a solution of **14** (1.9 g, 10.26 mmol) and **15** (1.0 g, 5.13 mmol) in dry DMF (30 mL) was added benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) (10.6 g, 20.4 mmol) and TEA (5.2 g, 51.0 mmol), and the solution was refluxed at 75°C for 24 hours. The solution was evaporated under vacuum and the resulting solid was purified by silica gel column chromatography using dichloromethane and methanol as eluent to obtain **16** (1.7 g, yield 65%)^{1}H NMR (400 MHz, DMSO) δ 11.36 (s, 2H), 10.80 (s, 2H), 8.32 (t, *J* = 5.4 Hz, 3H), 8.27 (d, *J* = 11.5 Hz, 6H), 3.95 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 165.14, 163.52, 162.48, 150.08, 148.23, 147.41, 140.56, 140.07, 128.24, 126.34, 125.72, 53.26. ESI m/z: calculated for $[M+H]^+$ $C_{23}H_{20}N_7O_8$ 522.13; Found 522.14.

Compound 17



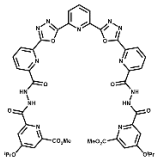
To a solution of **16** (1.0 g, 1.9 mmol) in dry $CHCl_3$ (15 mL) was added triphenylphosphine (PPh_3) (1.1g, 4.2mmol), CCl_4 (642.9 mg,4.2 mmol) and TEA (1.9 g, 19.0 mmol), and the resulting solution was refluxed at 80°C for 24 hours. The solution was evaporated and the solid left was purified by silica gel column chromatography using dichloromethane and methanol as eluent to obtain **17** (368.7 mg, yield 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 7.6 Hz, 2H), 8.56 (d, *J* = 7.8 Hz, 2H), 8.34 (d, *J* = 7.7 Hz, 2H), 8.19 (d, *J* = 7.9 Hz, 1H), 8.13 (t, *J* = 7.8 Hz, 2H), 4.08 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.94, 164.30, 164.10, 148.93, 144.02, 143.36, 138.79, 138.70, 127.34, 126.80, 125.92, 53.24. ESI m/z: calculated for $[M+H]^+$ $C_{23}H_{16}N_7O_6$ 486.11; Found 486.14.

Compound 18



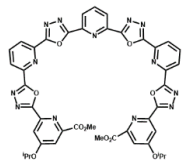
Compound **17** (360.0 mg, 0.7 mmol) was dissolved in 10 mL methanol and then added with NaOH (180.0 mg, 4.5 mmol) and 0.5 mL water under stirring at room temperature. After 24 hours, the excess solvent was removed under reduced pressure and the product was dispersed in water. The suspension was then neutralized with 0.1 M HCl and filtered with pure water. The filter residue was then completely dried under vacuum at 50℃ for two days and was collected as the product to obtain **18** (321.3 mg, yield 95%) ^{1}H NMR (400 MHz, MeOD) δ 8.60 (s, 2H), 8.39 (s, 4H), 8.34 – 8.17 (m, 3H). ^{13}C NMR (101 MHz, DMSO) δ 164.22, 164.18, 164.12, 143.89, 142.65, 140.69, 140.37, 127.68, 125.94. ESI m/z: calculated for $[M+H]^+$ $C_{21}H_{12}N_7O_6$ 458.08; Found 458.08.

Compound 19



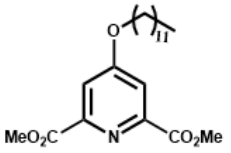
To a solution of **8** (274.2 mg, 0.6 mmol) and **18** (303.7 mg, 1.2 mmol) in dry DMF (10 mL) was added benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) (1.2 g, 2.4 mmol) and TEA (607.2 mg, 6.0 mmol), and the solution was refluxed at 75℃ for 48 hours. The solution was evaporated under vacuum and the resulting solid was purified by silica gel column chromatography using dichloromethane and methanol as eluent to obtain **19** (194.7 mg, yield 35%) ^{1}H NMR (400 MHz, DMSO) δ 10.78 (s, 4H), 8.65 (d, *J* = 7.9 Hz, 2H), 8.58 (d, *J* = 7.7 Hz, 2H), 8.43 (t, *J* = 7.8 Hz, 1H), 8.34 (t, *J* = 7.7 Hz, 2H), 8.23 (d, *J* = 7.9 Hz, 2H), 7.70 (d, *J* = 6.2 Hz, 4H), 4.97 (d, *J* = 6.0 Hz, 2H), 3.89 (s, 6H), 1.32 (d, *J* = 5.8 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.26, 165.12, 164.33, 163.97, 161.87, 160.76, 150.81, 149.56, 148.37, 143.89, 141.75, 139.05, 138.69, 126.10, 125.94, 124.93, 115.53, 111.75, 71.38, 53.03, 21.66. ESI m/z: calculated for $[M+H]^+$ $C_{43}H_{38}N_{13}O_{12}$ 928.27; Found 928.26; Calculated for $[2M+H]^+$ $C_{86}H_{76}N_{26}O_{24}$ 1856.54; Found 1856.50.

Compound M3



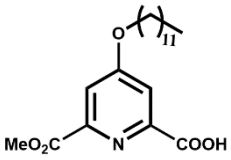
To a solution of **19** (185.5 mg, 0.2 mmol) in dry $CHCl_3$ (8 mL) was added triphenylphosphine (PPh_3) (104.9 mg, 0.4 mmol), CCl_4 (61.5 mg, 0.4 mmol) and TEA (202.4 mg, 2.0 mmol), and the resulting solution was refluxed at 80℃ for 24 hours. The solution was evaporated and the solid left was purified by silica gel column chromatography using dichloromethane and methanol as eluent to obtain **M3** (53.5 mg, yield 30%) ^{1}H NMR (400 MHz, DMSO) δ 8.62 (d, *J* = 7.7 Hz, 2H), 8.56 (d, *J* = 7.3 Hz, 2H), 8.45 (d, *J* = 7.8 Hz, 1H), 8.39 (d, *J* = 7.4 Hz, 2H), 8.33 (t, *J* = 7.7 Hz, 2H), 7.81 (s, 2H), 7.57 (s, 2H), 4.98 (s, 2H), 3.71 (s, 6H), 1.38 (d, *J* = 5.8 Hz, 12H). ^{13}C NMR (101 MHz, DMSO) δ 166.12, 165.07, 164.89, 164.84, 164.73, 164.58, 150.64, 145.01, 144.23, 144.15, 144.03, 140.93, 140.73, 126.81, 115.24, 113.98, 72.46, 55.86, 53.48, 22.27. ESI m/z: calculated for $[M+H]^+$ $C_{43}H_{34}N_{13}O_{10}$ 892.25; Found 892.25.

Compound 20



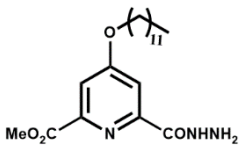
To a mixed solution of triphenylphosphine (12.4 g, 47.4 mmol), 1-dodecanol (6.6 g, 35.5 mmol), and dimethyl 2,6-pyridinedicarboxylate (5.0 g, 23.7 mmol) in dry tetrahydrofuran (300 ml) under N2 atmosphere and ice bath condition was added diisopropyl azodiformate (4.8 g, 23.7 mmol). The reaction was stirred overnight at room temperature, and the solvent was removed in vacuo. The crude mixture was purified by recrystallization in methanol to provide the desired product **20** (7.8 g, yield 87%.) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 2H), 4.11 (t, *J* = 6.5 Hz, 2H), 3.98 (s, 6H), 1.89 – 1.71 (m, 2H), 1.44 (dt, *J* = 15.0, 6.8 Hz, 2H), 1.37 – 1.18 (m, 16H), 0.85 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.16, 165.24, 149.69, 114.57, 69.14, 53.25, 31.92, 29.65, 29.63, 29.57, 29.52, 29.35, 29.26, 28.73, 25.84, 22.70, 14.14. ESI m/z: calculated for $[M+H]^+$ $C_{21}H_{34}NO_5$ 380.24; Found 380.24.

Compound 21



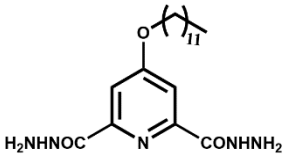
Compound **20** (5.0 g, 13.2 mmol) was dissolved in 50 mL methanol and then added with KOH (740.5 mg, 13.2 mmol) and 1 mL water under stirring at room temperature. After 24 hours, the excess solvent was removed under reduced pressure and the product was dispersed in water. The suspension was then neutralized with 0.1 M HCl and filtered with pure water. The filter residue was then completely dried under vacuum at 50℃ for two days and then purified by silica gel column chromatography using dichloromethane and methanol as eluent to obtain **21** (2.3 g, yield 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 2.4 Hz, 1H), 7.84 (d, *J* = 2.4 Hz, 1H), 4.19 (t, *J* = 6.5 Hz, 2H), 4.04 (s, 3H), 1.94 – 1.80 (m, 2H), 1.59 – 1.43 (m, 2H), 1.44 – 1.22 (m, 16H), 0.91 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.20, 164.33, 163.76, 148.09, 148.04, 116.05, 112.09, 69.57, 53.17, 31.94, 29.66, 29.58, 29.53, 29.38, 29.25, 28.68, 25.81, 22.72, 14.16. ESI m/z: calculated for $[M+H]^+$ $C_{20}H_{32}NO_5$ 366.22; Found 366.23.

Compound 22



To a solution of compound **20** (5.0 g, 13.2 mmol) in tetrahydrofuran/methanol (1: 1, vol: vol) was added a solution of hydrazine hydrate (660.7 mg, 13.2 mmol) in methanol and the mixture was stirred overnight. The solution was evaporated and the solid left was purified by silica gel column chromatography using dichloromethane and methanol as eluent to obtain **22** (2.7 g, yield 54%) ^{1}H NMR (400 MHz, DMSO) δ 9.61 (s, 1H), 7.65 (s, 2H), 4.69 (s, 2H), 4.21 (s, 2H), 3.92 (s, 3H), 1.76 (s, 2H), 1.42 (s, 2H), 1.25 (s, 16H), 0.86 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 167.50, 165.36, 163.73, 151.28, 147.71, 114.75, 111.17, 69.15, 53.14, 31.90, 29.61, 29.55, 29.50, 29.33, 29.24, 28.71, 25.81, 22.67, 14.07. ESI m/z: calculated for $[M+H]^+$ $C_{20}H_{34}N_3O_4$ 380.25; Found 380.25.

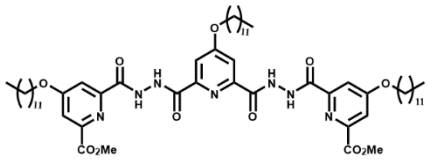
Compound 23



To a solution of compound **20** (4.0 g, 10.5 mmol) in tetrahydrofuran/methanol (1: 1, vol: vol) was added a solution of hydrazine hydrate (3.2 g, 63.3 mmol) in methanol and the mixture was stirred overnight. The solvent was removed followed by the

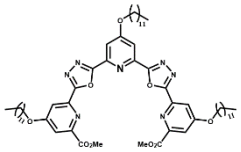
addition of 50 mL of methanol and storage at 4°C for an hour. The product **23** was obtained by collecting precipitation (3.7 g, yield 93%).^{1}H NMR (500 MHz, DMSO) δ 10.61 (s, 2H), 7.55 (s, 2H), 4.62 (s, 4H), 4.17 (t, *J* = 6.5 Hz, 2H), 1.77 – 1.67 (m, 2H), 1.39 (dd, *J* = 14.9, 7.3 Hz, 2H), 1.34 – 1.27 (m, 2H), 1.24 (d, *J* = 21.3 Hz, 14H). ^{13}C NMR (101 MHz, DMSO) δ 167.49, 162.16, 150.95, 110.03, 68.93, 39.33, 39.07, 38.86, 38.66, 38.45, 38.24, 31.77, 29.48, 29.43, 29.18, 28.70, 25.74, 22.57, 14.43. ESI m/z: calculated for $[M+H]^+$ $C_{19}H_{34}N_5O_3$ 380.26; Found 380.26.

Compound 24



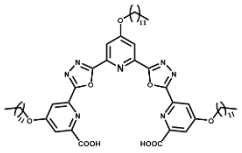
To a solution of **21** (2.3 g, 6.3 mmol) and **23** (1.2 g, 3.1 mmol) in dry DMF (40 mL) was added benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) (6.5 g, 12.4 mmol) and TEA (3.1 g, 31.0mmol), and the solution was refluxed at 75°C for 24 hours. The solution was evaporated under vacuum and the resulting solid was purified by silica gel column chromatography using dichloromethane and methanol as eluent to obtain **24** (1.6 g, yield 48%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.33 (s, 4H), 8.01 (s, 1H), 7.88 (d, *J* = 2.4 Hz, 2H), 7.83 (s, 1H), 7.78 (d, *J* = 2.3 Hz, 2H), 4.21 (t, *J* = 6.3 Hz, 2H), 4.16 (t, *J* = 6.5 Hz, 4H), 4.03 (s, 6H), 1.86 (ddd, *J* = 20.3, 13.5, 6.7 Hz, 12H), 1.48 (dd, *J* = 14.2, 6.4 Hz, 6H), 1.31 (d, *J* = 15.4 Hz, 42H), 0.90 (t, *J* = 6.9 Hz,9H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.46, 167.06, 165.10, 165.01, 164.31, 160.76, 150.39, 150.26, 148.54, 144.65, 114.94, 114.23, 112.67, 111.38, 69.36, 69.19, 53.18, 52.92, 31.91, 29.62, 29.55, 29.51, 29.33, 29.25, 28.74, 25.83, 22.68, 14.10. ESI m/z: calculated for $[M+H]^+$ $C_{59}H_{92}N_7O_{11}$1074.68; Found 1074.68.

Compound 25



To a solution of **24** (1.6 g, 1.5 mmol) in dry $CHCl_3$ (15 mL) was added triphenylphosphine (PPh_3) (865.6 mg, 3.3 mmol), CCl_4 (507.5 mg, 3.3 mmol) and TEA (1.5 g, 15.0 mmol), and the resulting solution was refluxed at 80°C for 24 hours. The solution was evaporated and the solid left was purified by silica gel column chromatography using dichloromethane and methanol as eluent to obtain **25** (669.2 mg, yield 43%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 2.3 Hz, 3H), 7.80 (d, *J* = 2.3 Hz, 3H), 4.18 (t, *J* = 6.4 Hz, 6H), 4.04 (s, 6H), 1.86 (s, 6H), 1.52 – 1.45 (m, 6H), 1.37 (d, *J* = 8.0 Hz, 6H), 1.28 (d, *J* = 13.8 Hz, 42H), 0.88 (t, *J* = 6.8 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.31, 165.41, 164.56, 150.63, 144.90, 114.49, 112.99, 69.61, 53.48, 32.20, 29.93, 29.91, 29.85, 29.81, 29.63, 29.53, 29.03, 26.11, 22.97, 14.41. ESI m/z: calculated for $[M+H]^+$ $C_{59}H_{88}N_7O_9$ 1038.66; Found 1038.65.

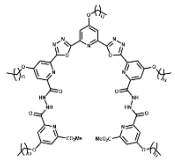
Compound 26



Compound **25** (622.6 mg, 0.6 mmol) was dissolved in 10 mL methanol and then added with NaOH (240.0 mg, 6.0 mmol) and 1 mL water under stirring at room temperature. After 24 hours, the excess solvent was removed under reduced pressure and the product was dispersed in water. The suspension was then neutralized with 0.1 M HCl and filtered with pure water. The filter residue was then completely dried under vacuum at 50°C for two days and was collected as the product to obtain **26** (581.5 mg, yield 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 2H), 8.09 (s, 1H), 8.01 (s, 3H), 4.34

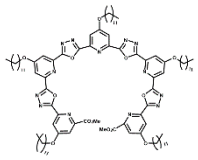
(s, 6H), 1.94 (s, 6H), 1.52 (s, 6H), 1.40 (s, 6H), 1.28 (s, 42H), 0.88 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.02, 165.12, 164.28, 150.34, 144.61, 114.20, 112.70, 69.33, 31.91, 29.64, 29.62, 29.56, 29.52, 29.34, 29.25, 28.74, 25.82, 22.69, 14.13. ESI m/z: calculated for $[M+H]^+$ $C_{57}H_{84}N_7O_9$ 1010.63; Found 1010.63.

Compound 27



To a solution of **26** (504.8 mg, 0.5 mmol) and **22** (379.3 mg, 1.0 mmol) in dry DMF (10 mL) was added benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) (1.0 g, 2.0 mmol) and TEA (506.0 mg, 5.0 mmol), and the solution was refluxed at 75℃ for 48 hours. The solution was evaporated under vacuum and the resulting solid was purified by silica gel column chromatography using dichloromethane and methanol as eluent to obtain **27** (329.1 mg, yield 38%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 4H), 7.97 (d, J = 14.9 Hz, 6H), 4.41 (s, 3H), 4.29 (s, 3H), 4.20 (d, J = 17.3 Hz, 10H), 1.97 (d, J = 29.9 Hz, 10H), 1.49 (d, J = 27.0 Hz, 10H), 1.31 (s, 80H), 0.91 (d, J = 6.6 Hz, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.38, 165.14, 164.54, 161.95, 151.45, 150.73, 150.09, 148.76, 148.49, 143.73, 130.95, 126.50, 121.17, 115.05, 112.93, 111.56, 111.07, 108.17, 69.66, 69.46, 53.10, 48.75, 48.72, 32.23, 29.96, 29.88, 29.67, 29.12, 26.45, 26.38, 26.17, 23.00, 14.42. ESI m/z: calculated for $[M+H]^+$ $C_{97}H_{146}N_{13}O_{15}$ 1733.10; Found 1733.10.

Compound M5



To a solution of **27** (173.2 mg, 0.1 mmol) in dry $CHCl_3$ (8 mL) was added triphenylphosphine (PPh_3) (52.4 mg, 0.2 mmol), CCl_4 (33.8 mg, 0.2 mmol) and TEA (101.2 mg, 1.0 mmol), and the resulting solution was refluxed at 80℃ for 24 hours. The solution was evaporated and the solid left was purified by silica gel column chromatography using dichloromethane and methanol as eluent to obtain **M5** (39.0 mg, yield 23%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 2H), 8.07 (dd, J = 29.6, 20.4 Hz, 6H), 7.78 (s, 2H), 4.30 (s, 5H), 4.19 (s, 5H), 4.05 (s, 6H), 1.85 (s, 10H), 1.50 (s, 10H), 1.28 (s,80H), 0.89 (s, 15H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.36, 165.28, 164.65, 164.52, 164.47, 150.56, 145.54, 144.87, 114.65, 114.53, 112.98, 112.83, 112.72, 69.92, 69.66, 53.42, 32.19, 29.91, 29.85, 29.63, 29.57, 29.08, 29.03, 26.13, 22.96, 14.39. ESI m/z: calculated for $[M+H]^+$ $C_{97}H_{142}N_{13}O_{13}$ 1697.08; Found 1697.08.

3. Characteristic spectra of compounds.

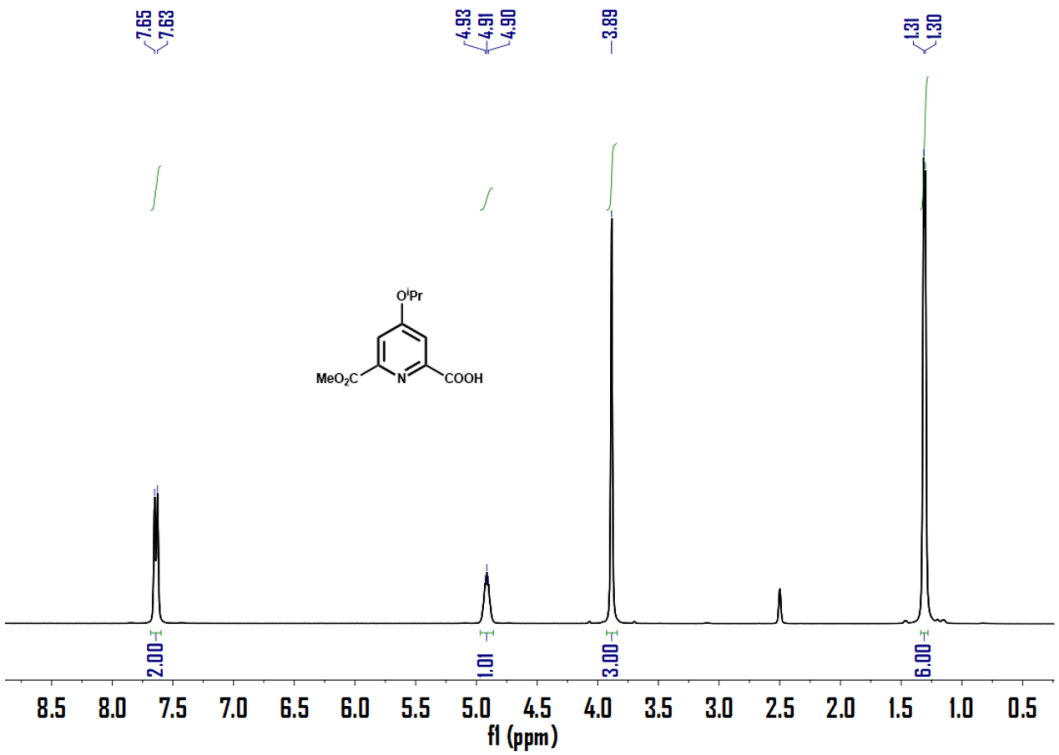


Figure S2. ^{1}H NMR spectrum of **7** in DMSO.

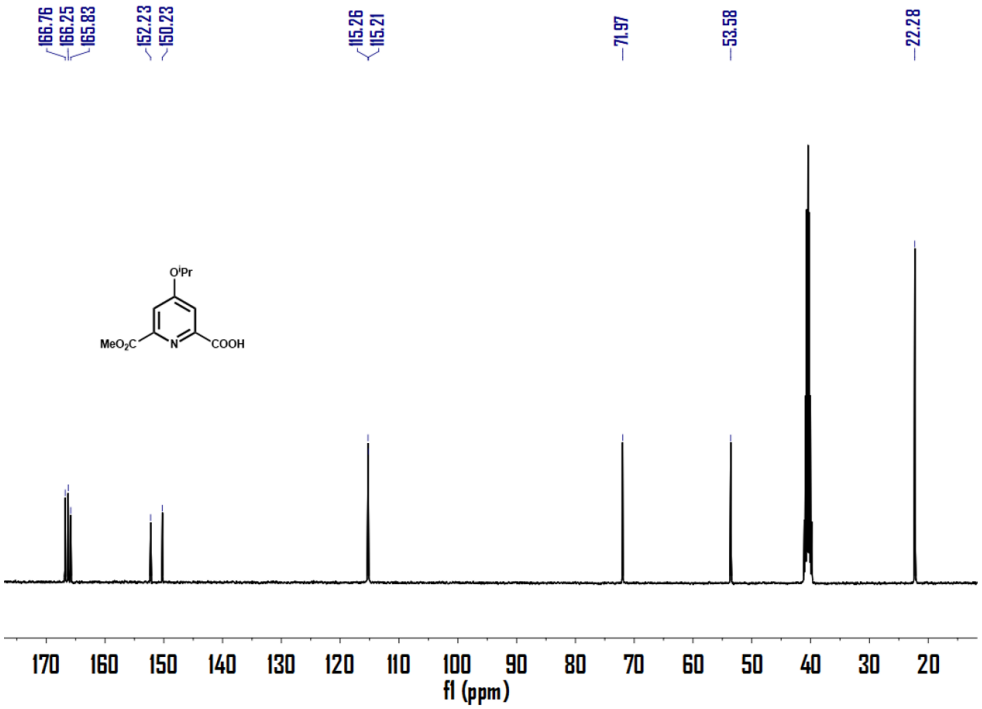


Figure S3. ^{13}C NMR spectrum of **7** in DMSO.

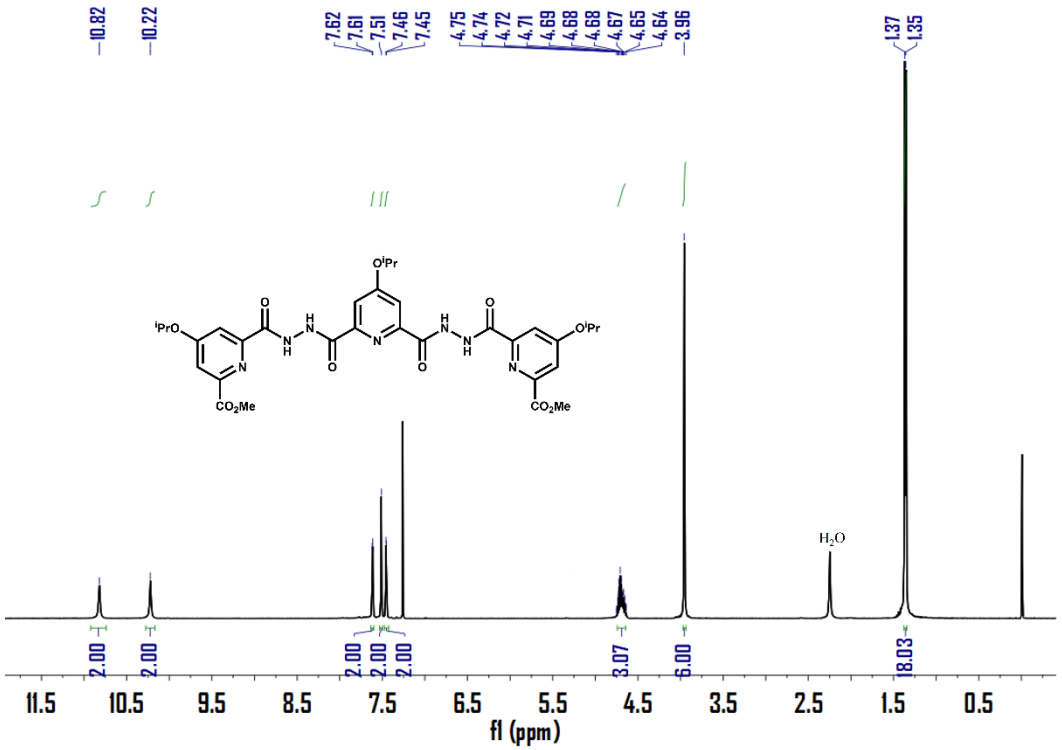


Figure S4. ^{1}H NMR spectrum of **10** in $CDCl_3$.

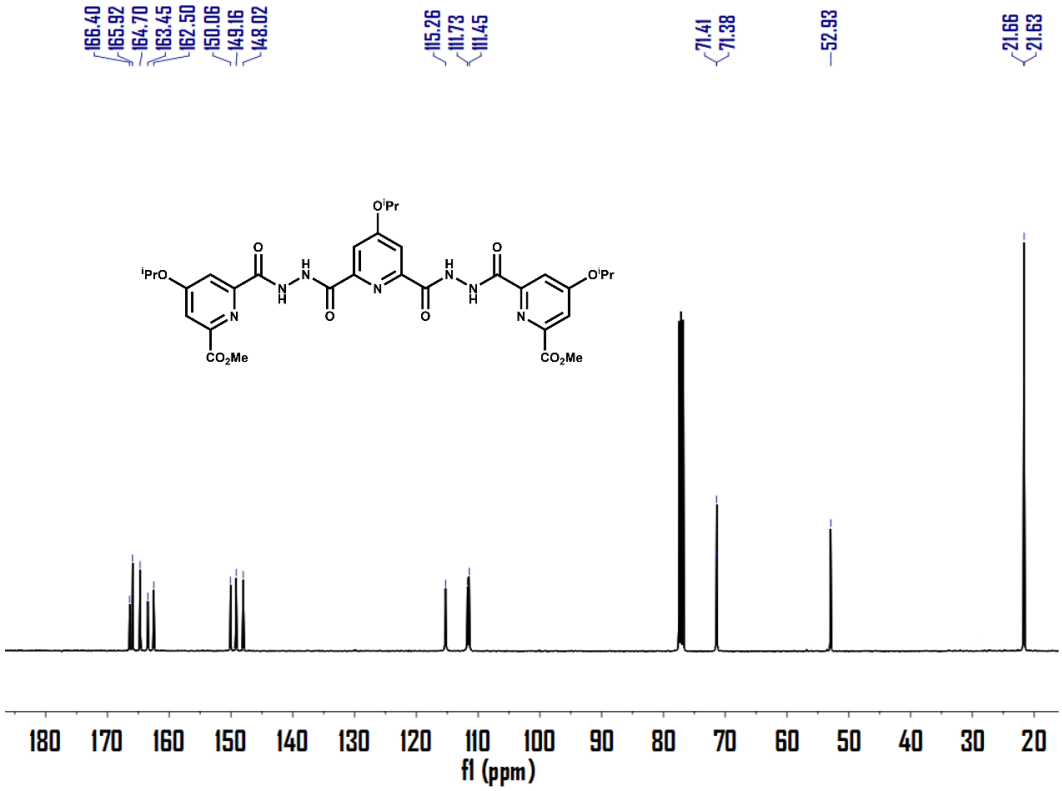


Figure S5. ^{13}C NMR spectrum of **10** in $CDCl_3$.

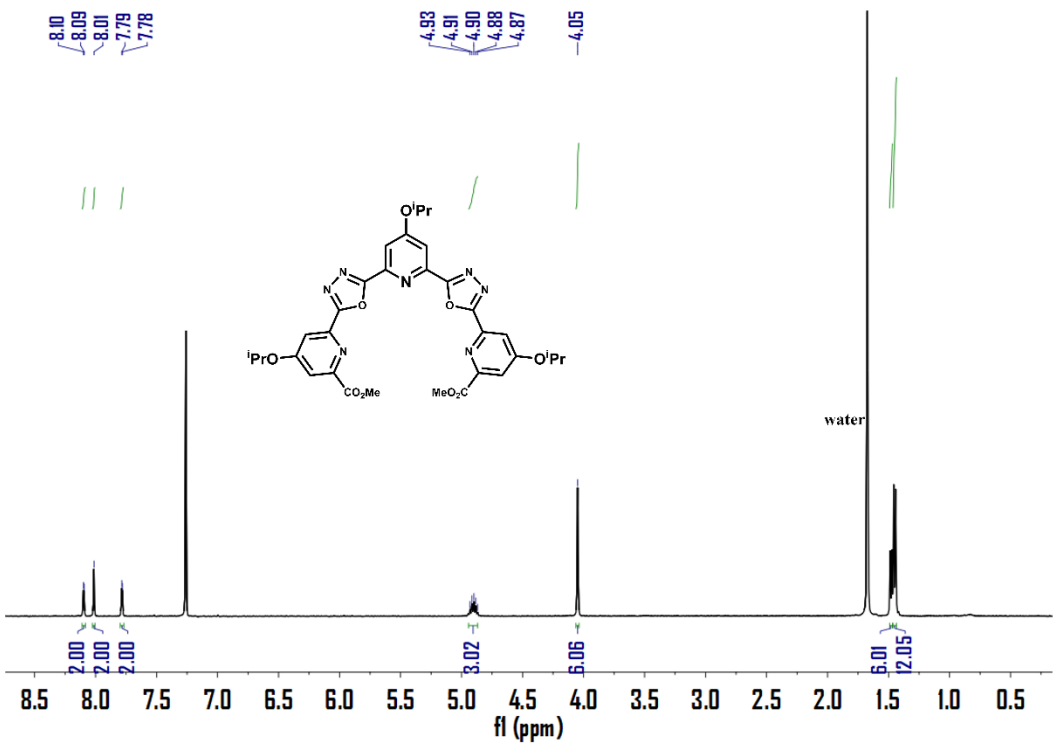


Figure S6. ^{1}H NMR spectrum of **11** in $CDCl_3$.

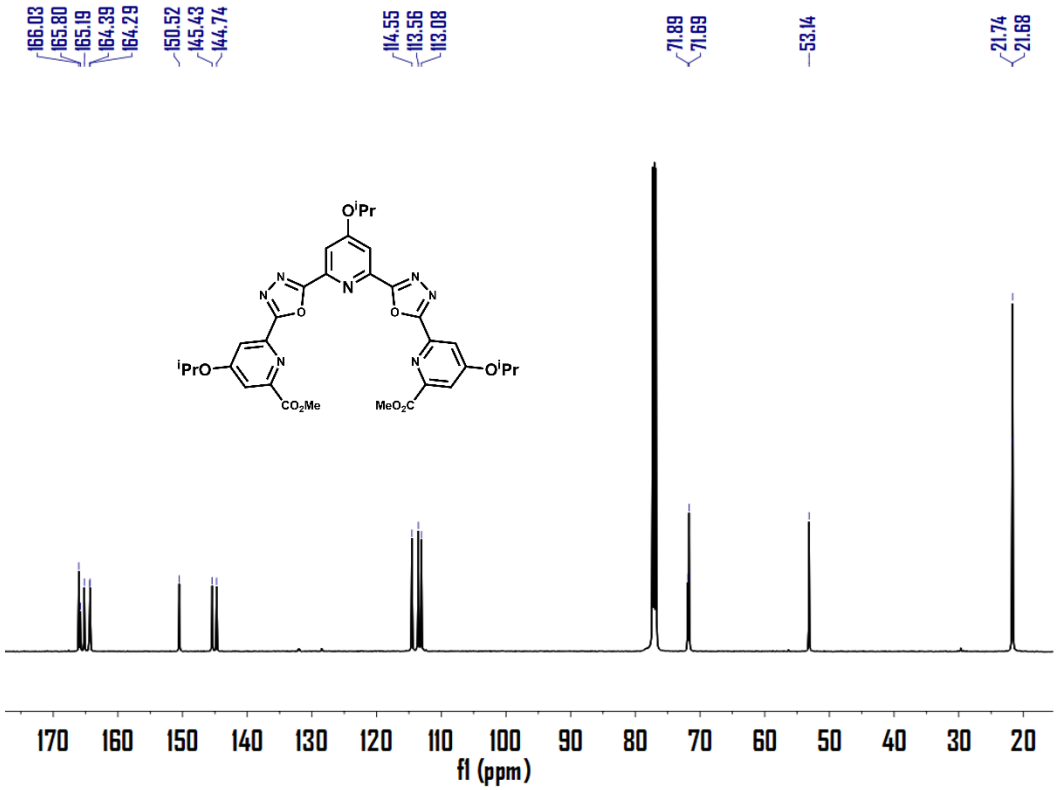


Figure S7. ^{13}C NMR spectrum of **11** in $CDCl_3$.

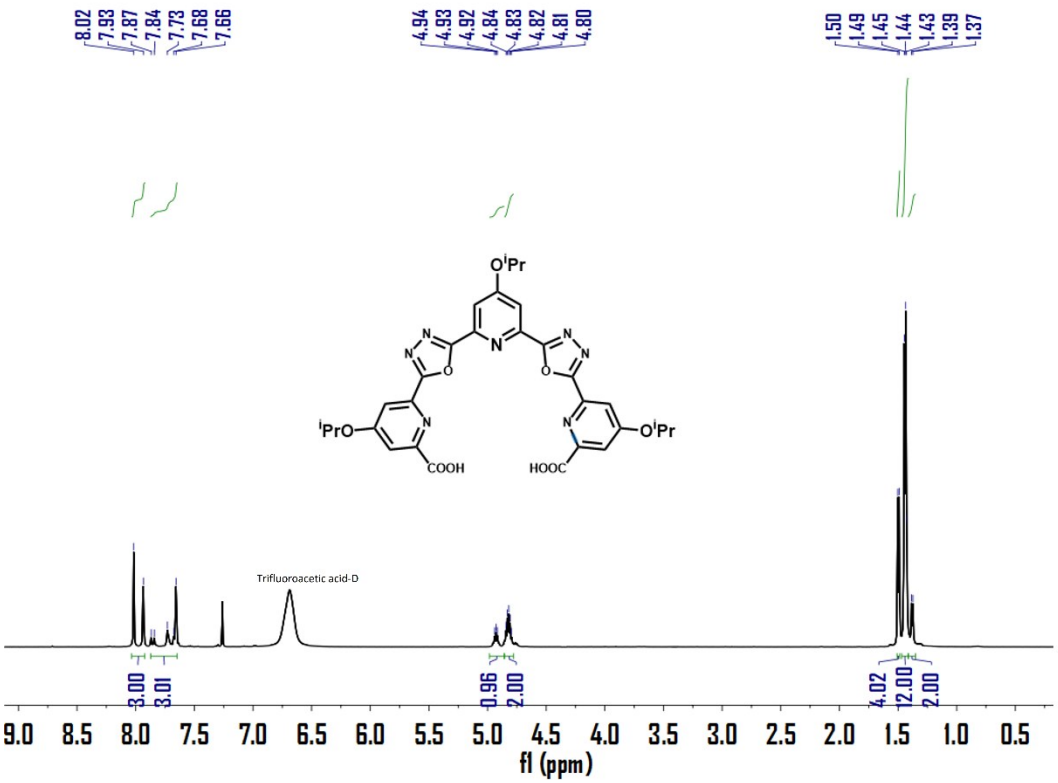


Figure S8. ^{1}H NMR spectrum of **12** in $CDCl_3$($CDCl_3$/Trifluoroacetic acid-D 30:1).

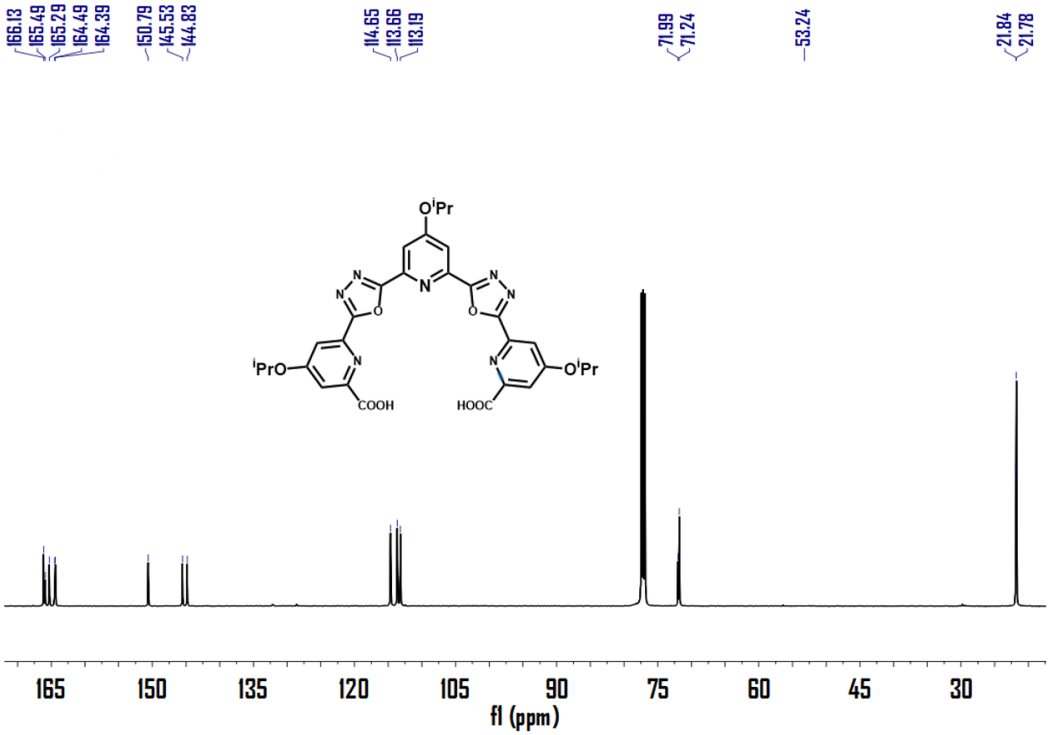


Figure S9. ^{13}C NMR spectrum of **12** in $CDCl_3$.

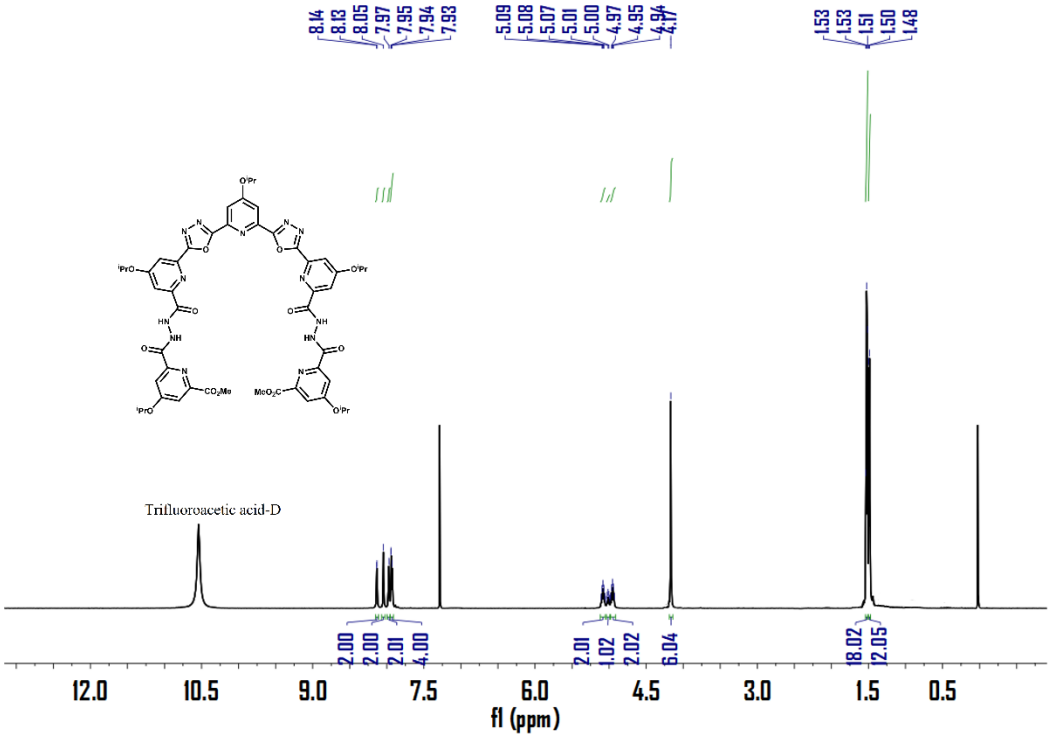


Figure S10. ^{1}H NMR spectrum of **13** in $CDCl_3$.

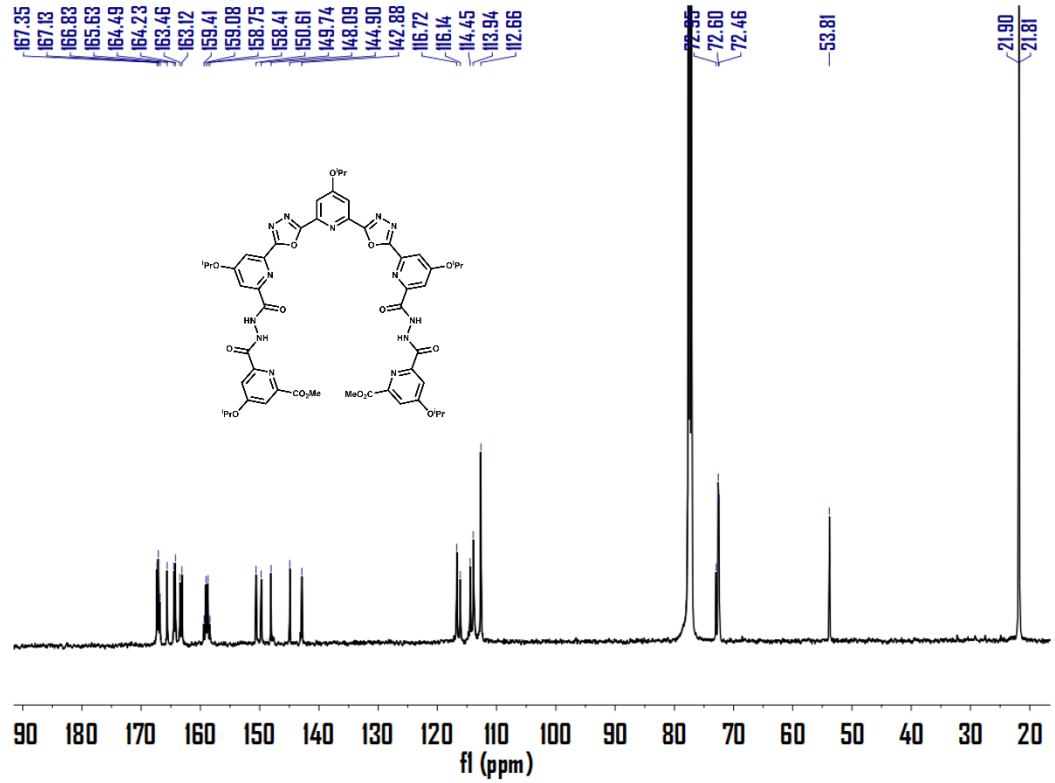


Figure S11. ^{13}C NMR spectrum of **13** in $CDCl_3$.

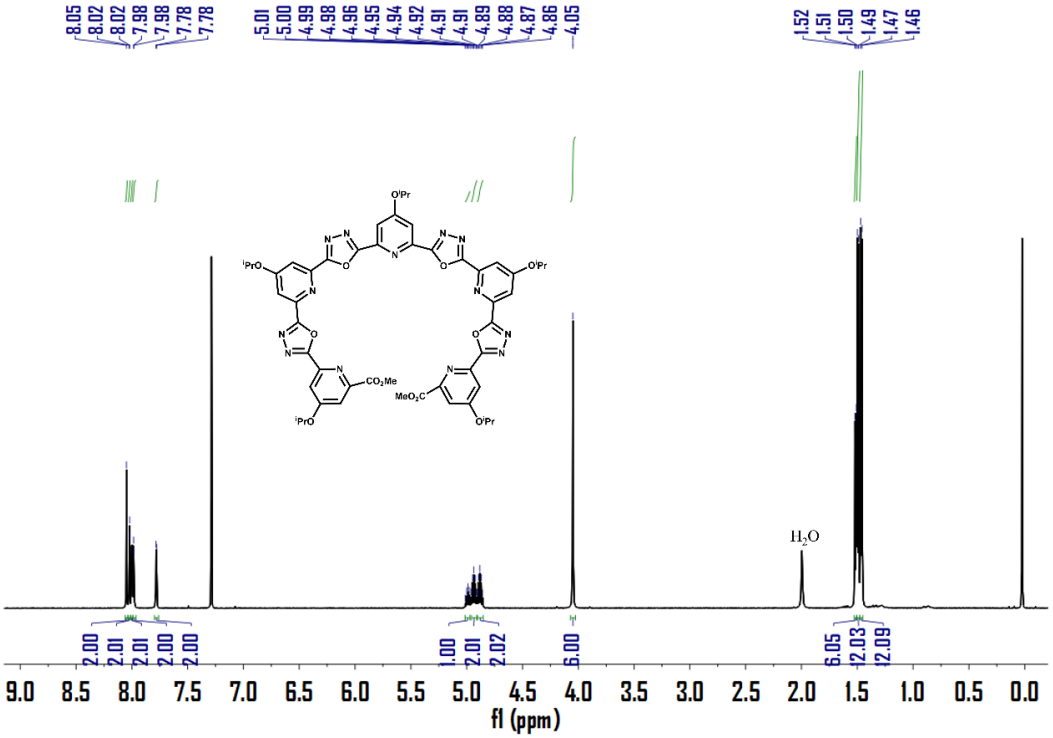


Figure S12. ^{1}H NMR spectrum of **M1** in $CDCl_3$.

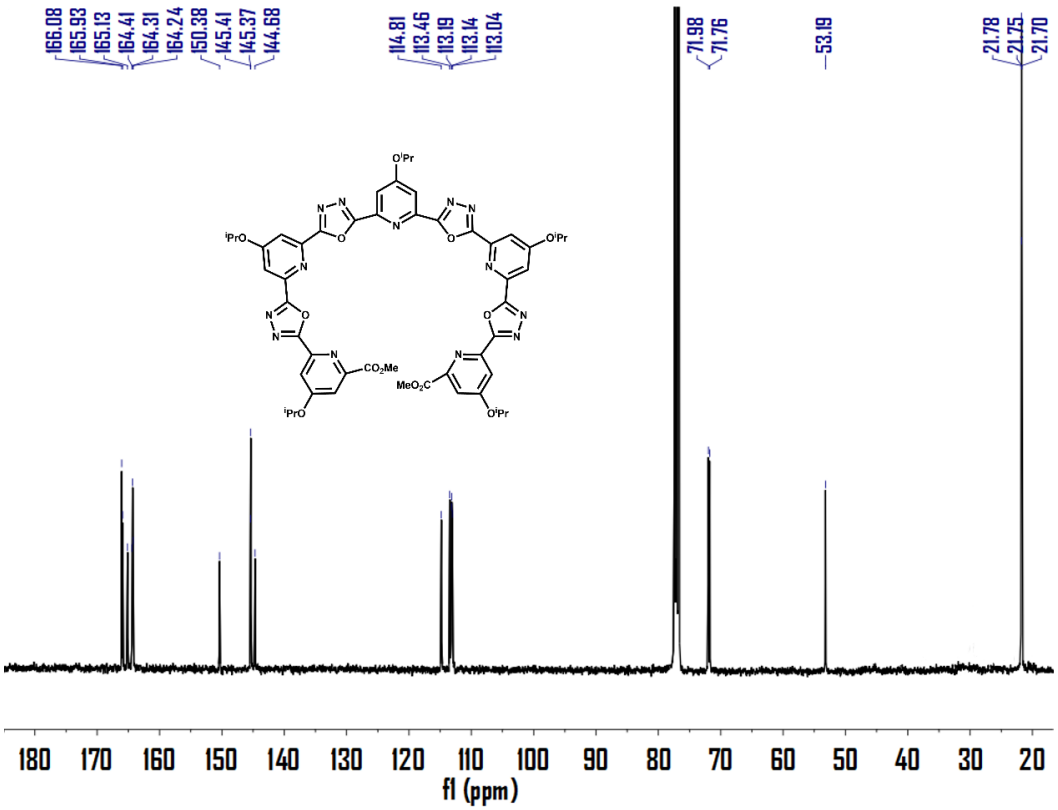


Figure S13. ^{13}C NMR spectrum of **M1** in $CDCl_3$.

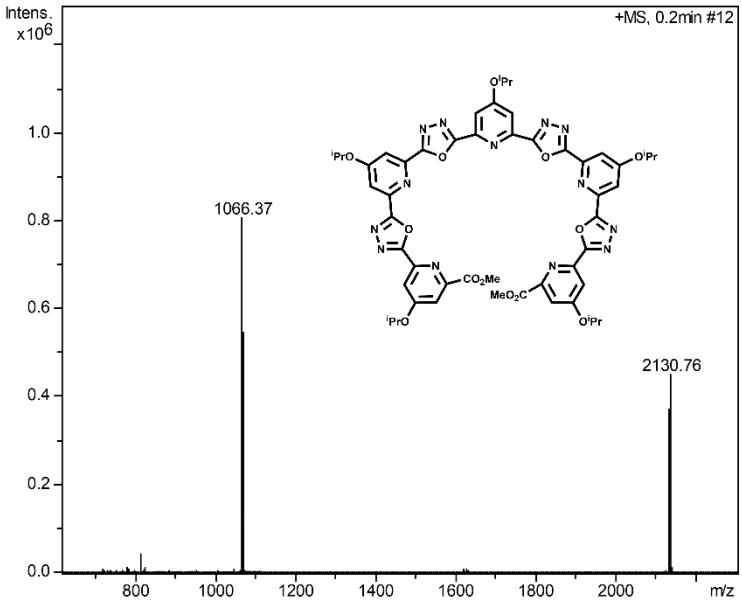


Figure S14. ESI MS spectrum of **M1**.

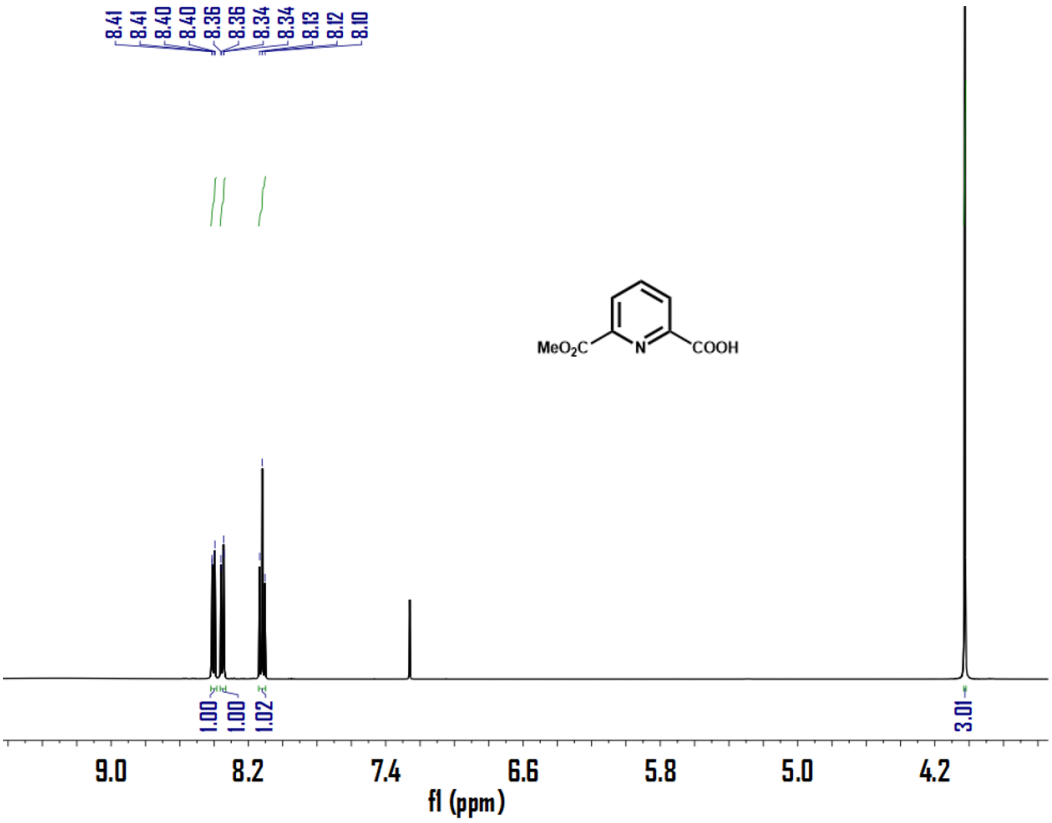


Figure S15. ^{1}H NMR spectrum of **14** in $CDCl_3$.

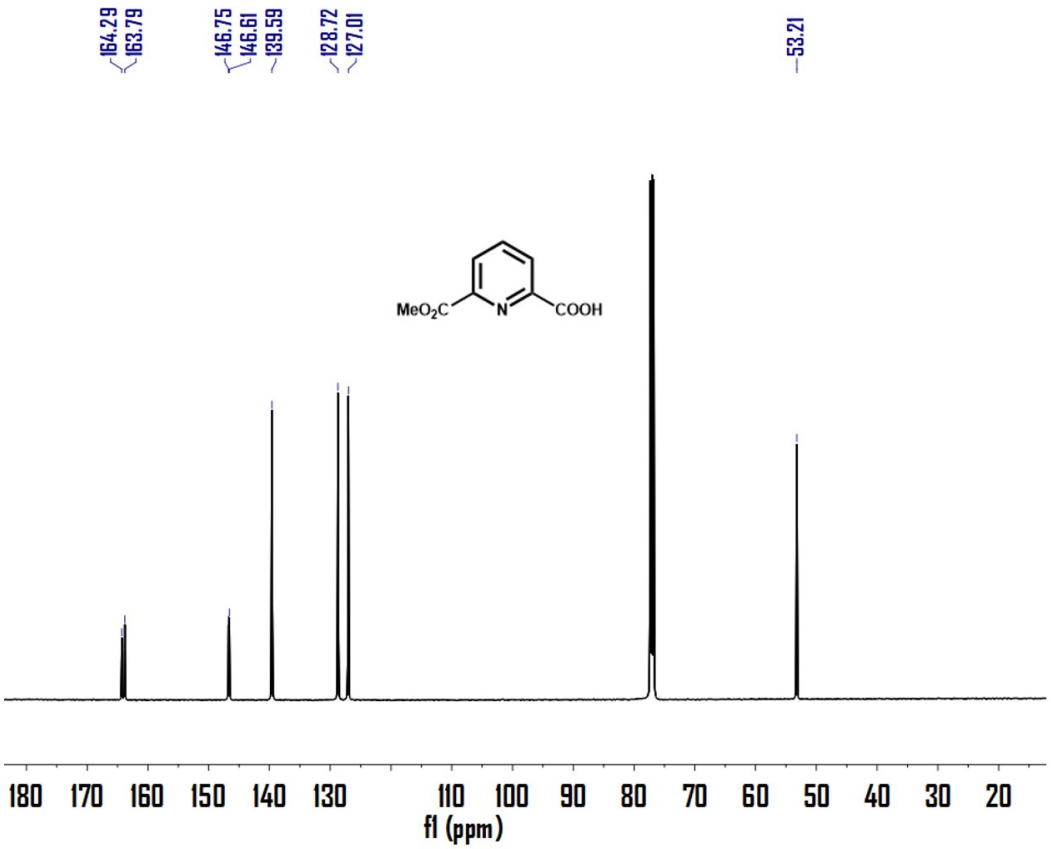


Figure S16. ^{13}C NMR spectrum of **14** in $CDCl_3$.

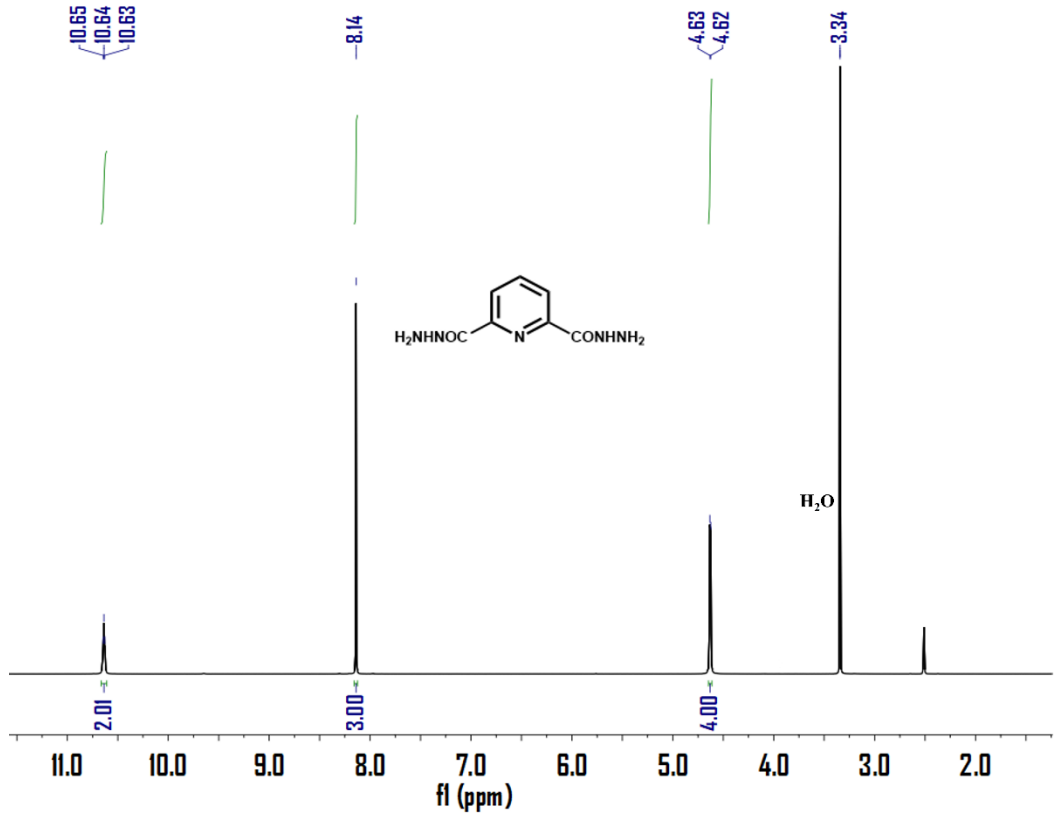


Figure S17. ^{1}H NMR spectrum of **15** in DMSO.

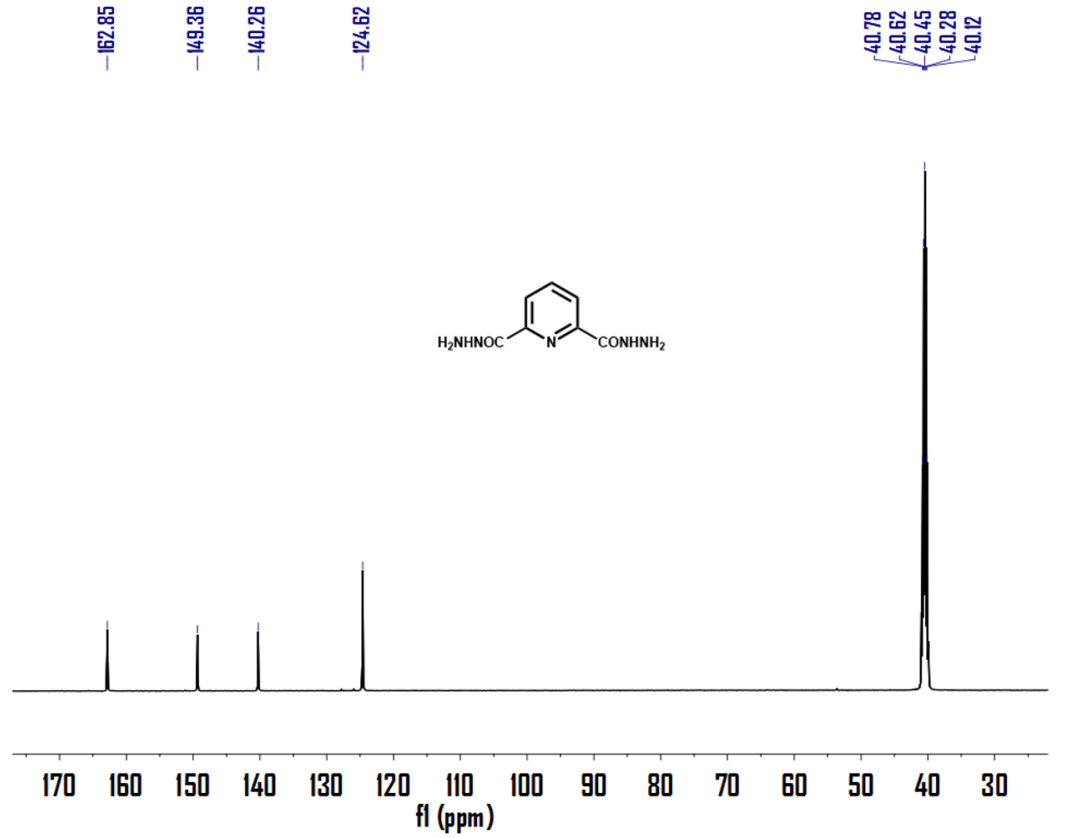


Figure S18. ^{13}C NMR spectrum of **15** in DMSO.

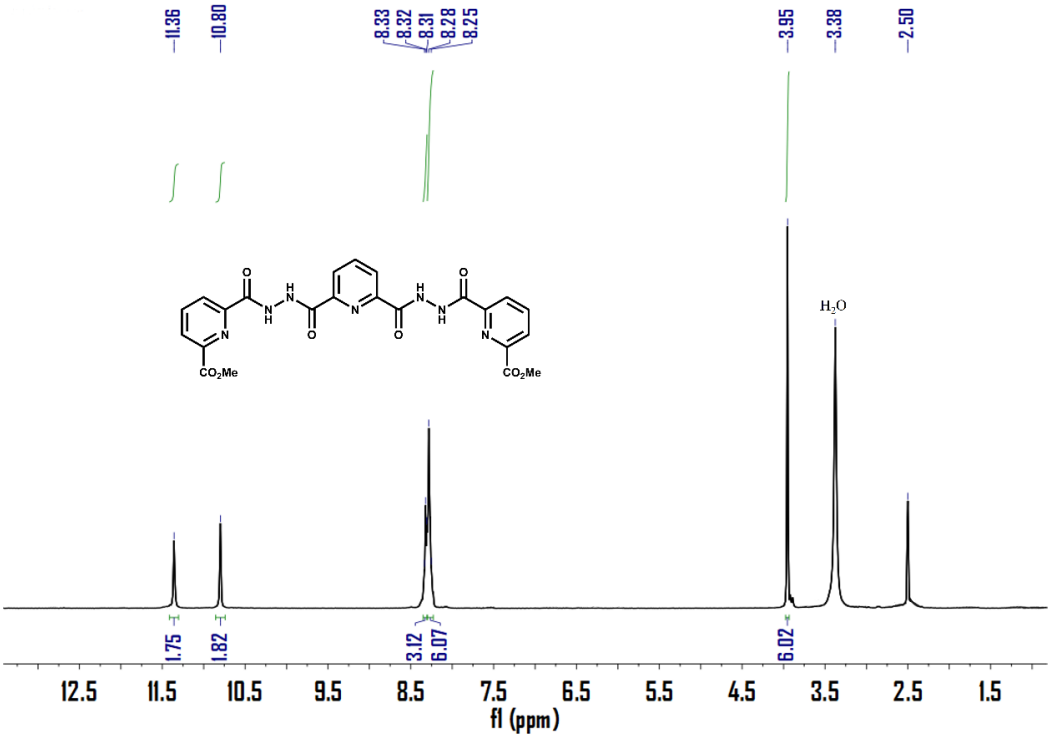


Figure S19. ^{1}H NMR spectrum of **16** in DMSO.

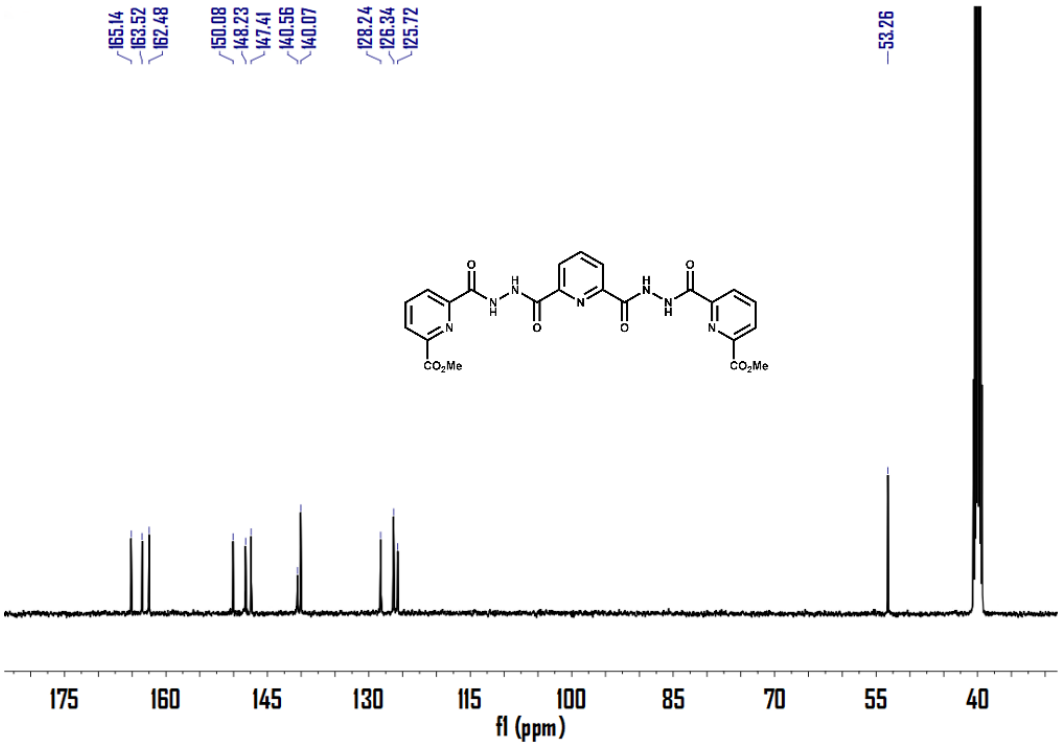


Figure S20. ^{13}C NMR spectrum of **16** in DMSO.

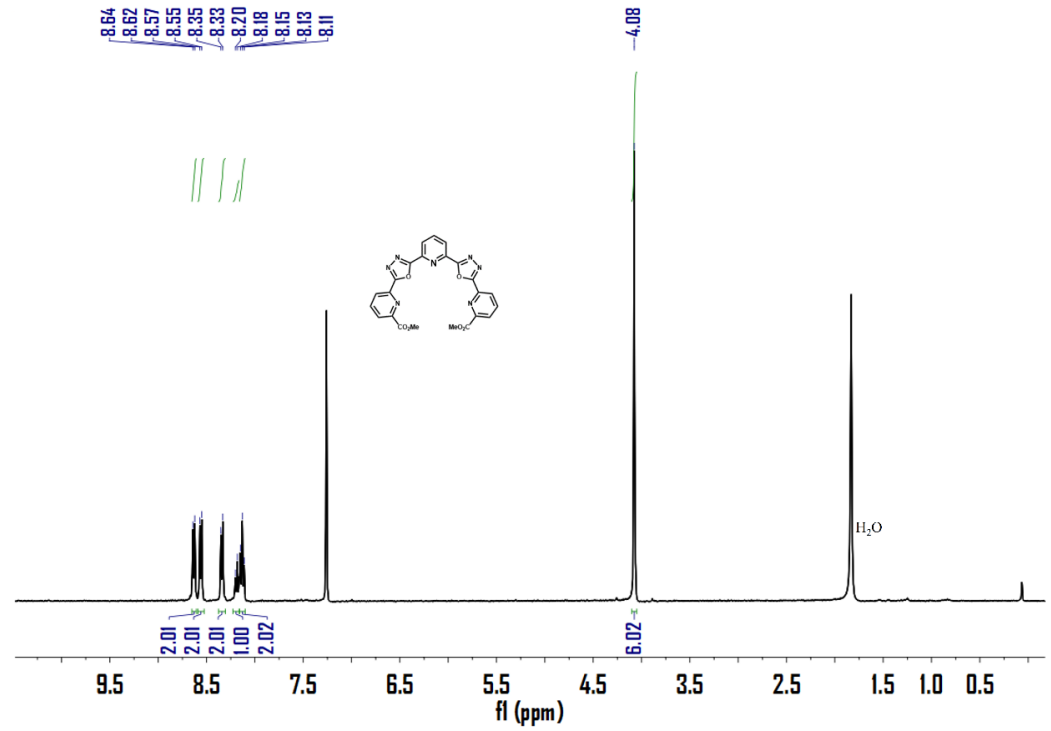


Figure S21. ^{1}H NMR spectrum of **17** in $CDCl_3$.

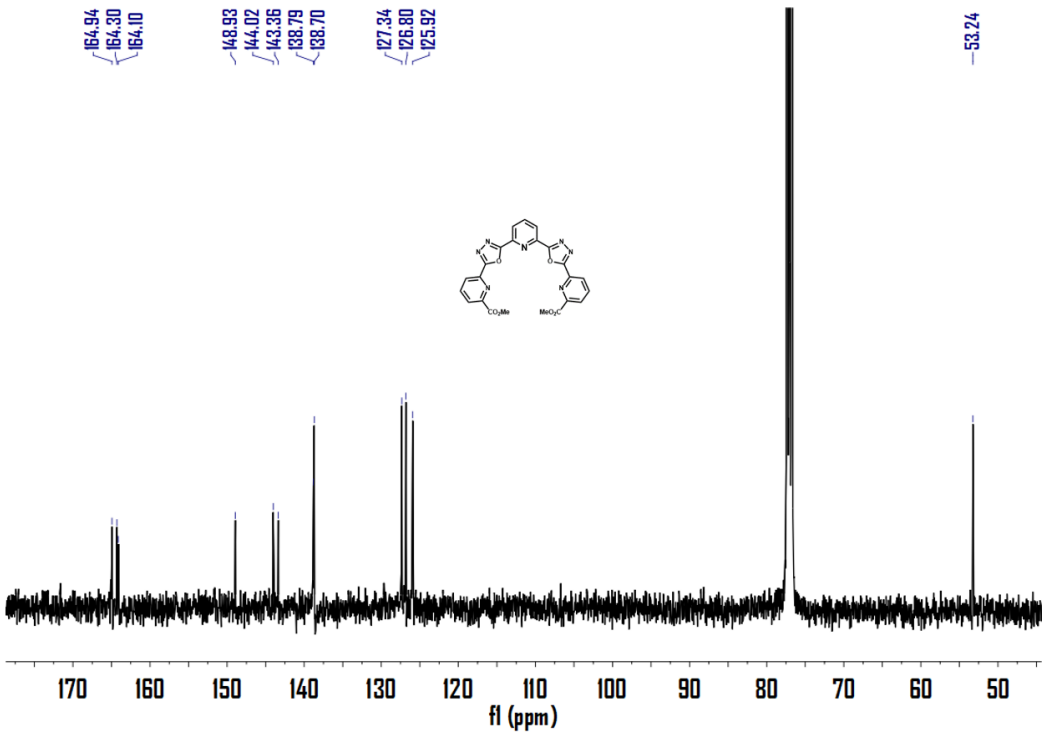


Figure S22. ^{13}C NMR spectrum of **17** in $CDCl_3$.

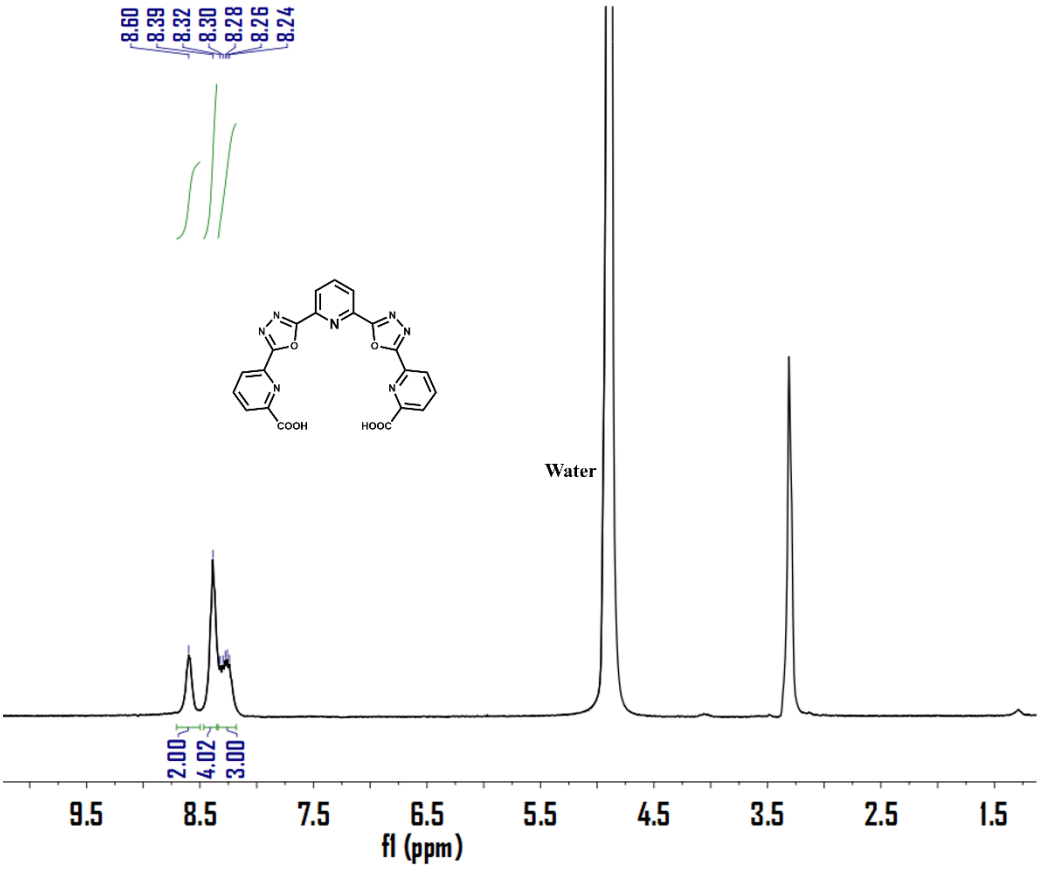


Figure S23. ^{1}H NMR spectrum of **18** in CD_3OD.

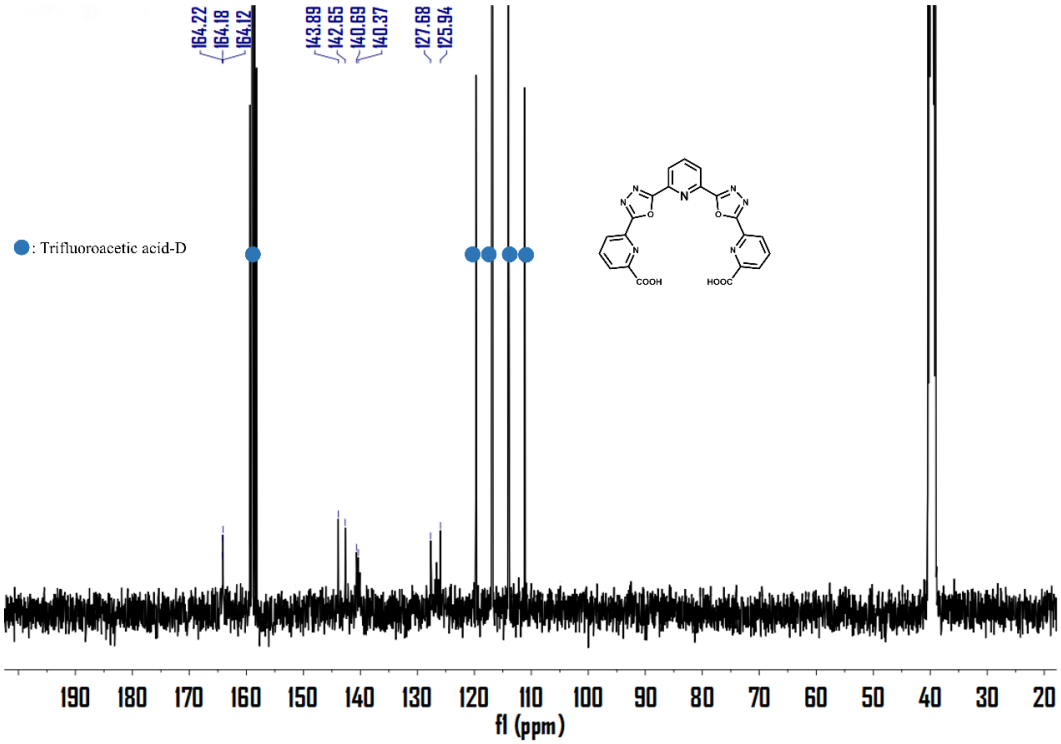


Figure S24. ^{13}C NMR spectrum of **18** in DMSO (DMSO/Trifluoroacetic acid-D 20:1).

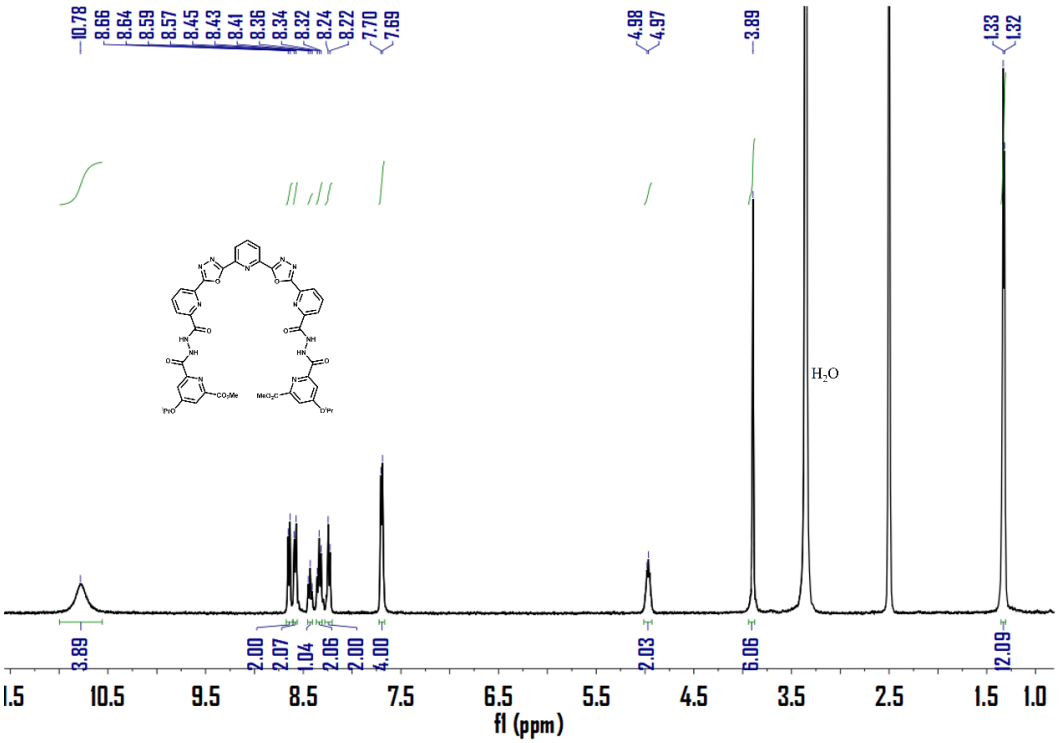


Figure S25. ^{1}H NMR spectrum of **19** in DMSO.

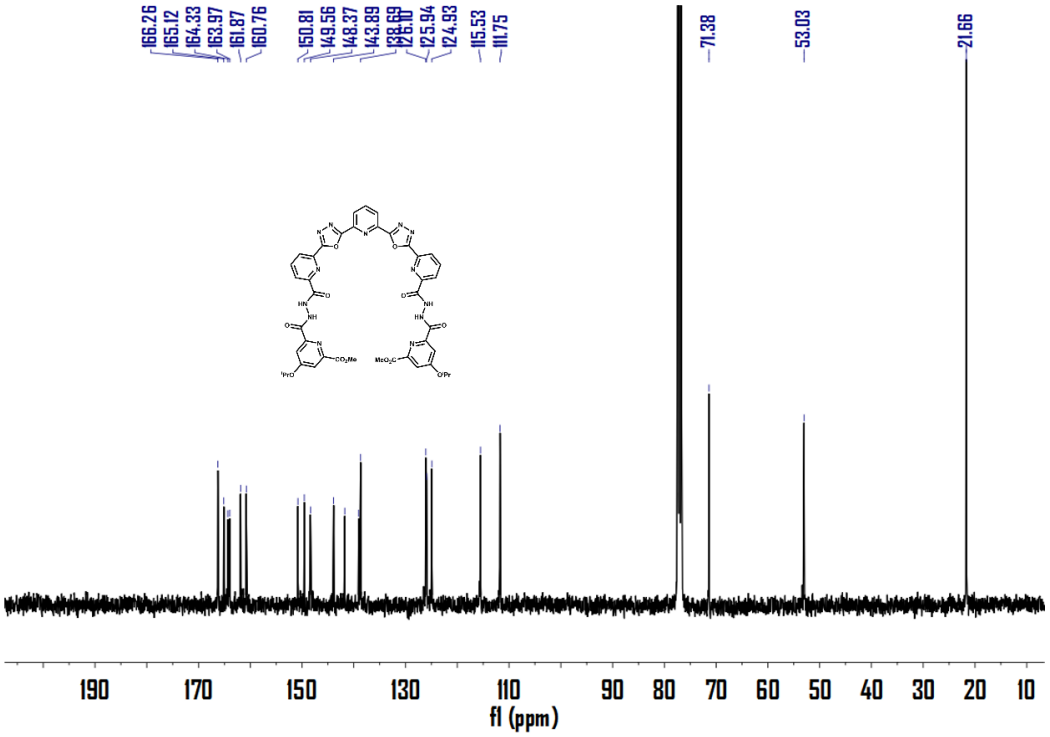


Figure S26. ^{13}C NMR spectrum of **19** in $CDCl_3$.

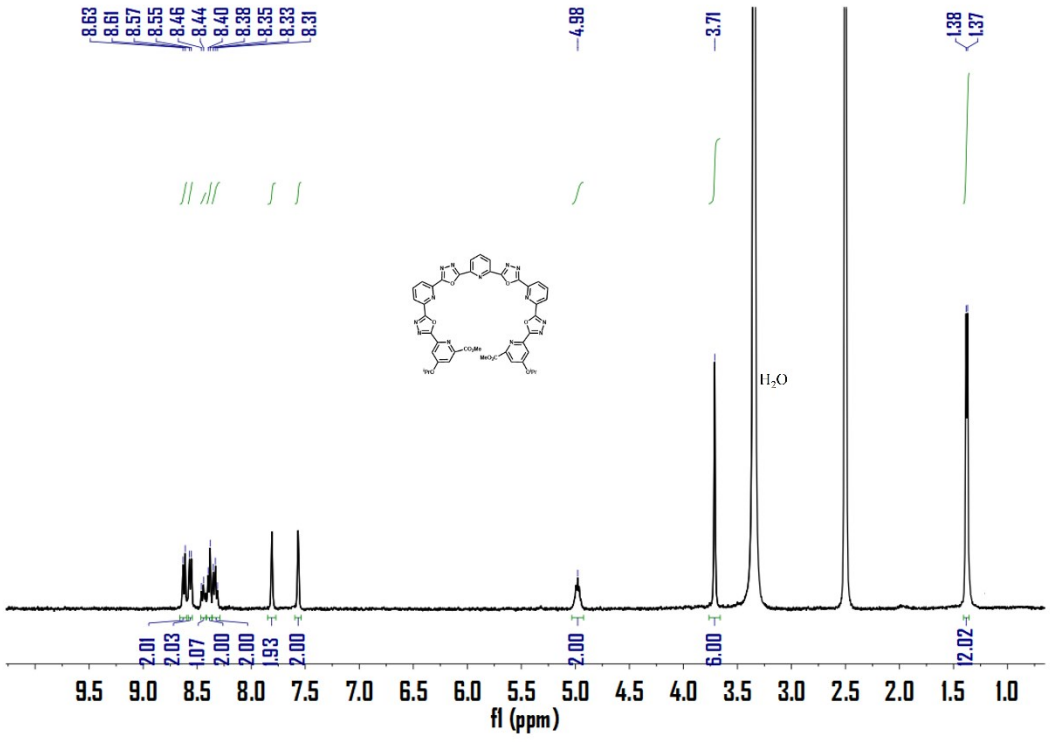


Figure S27. ^{1}H NMR spectrum of **M3** in DMSO.

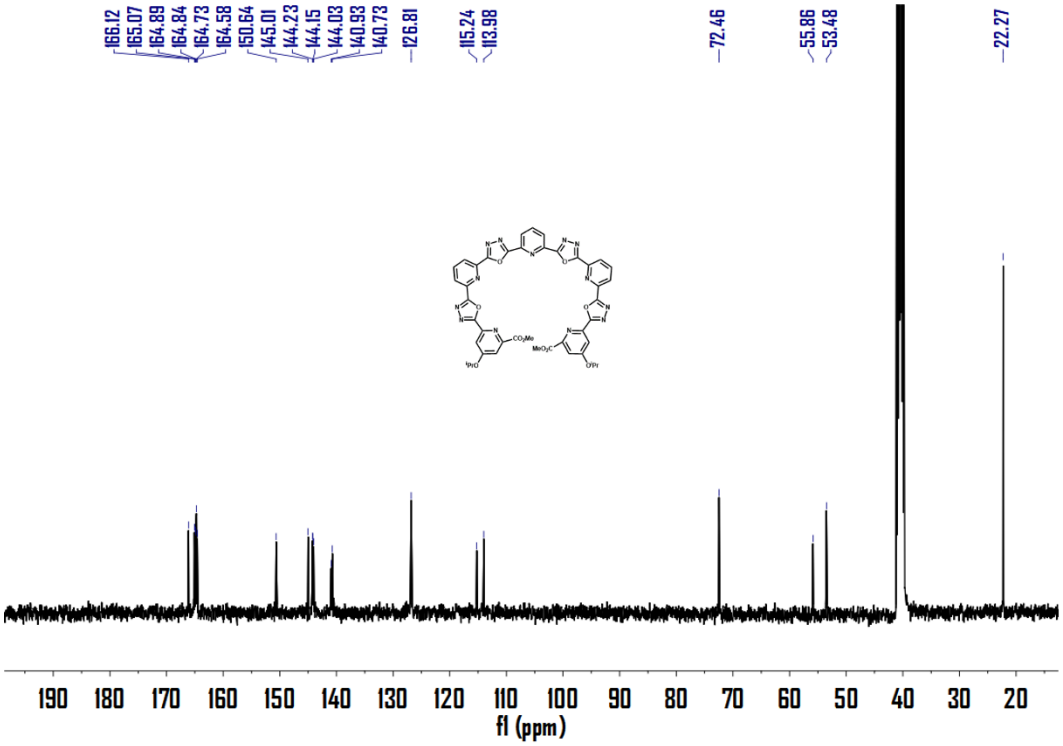


Figure S28. ^{13}C NMR spectrum of **M3** in DMSO.

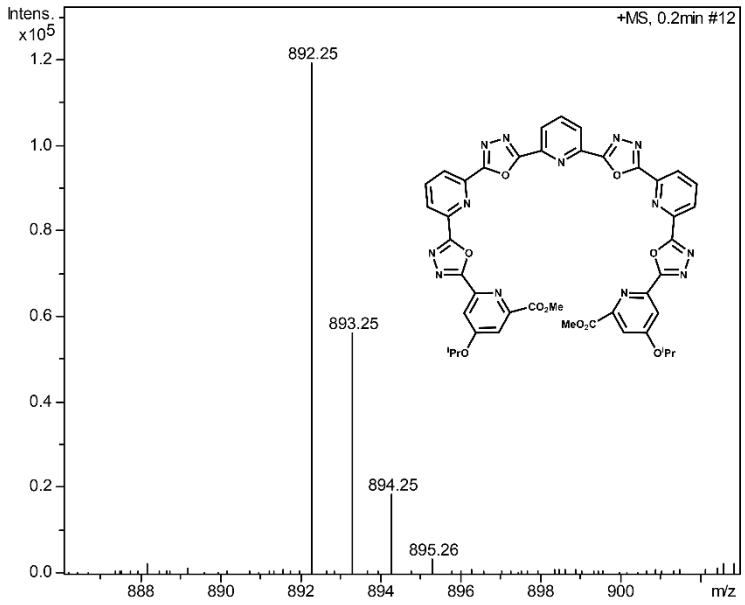


Figure S29. ESI MS spectrum of **M3**.

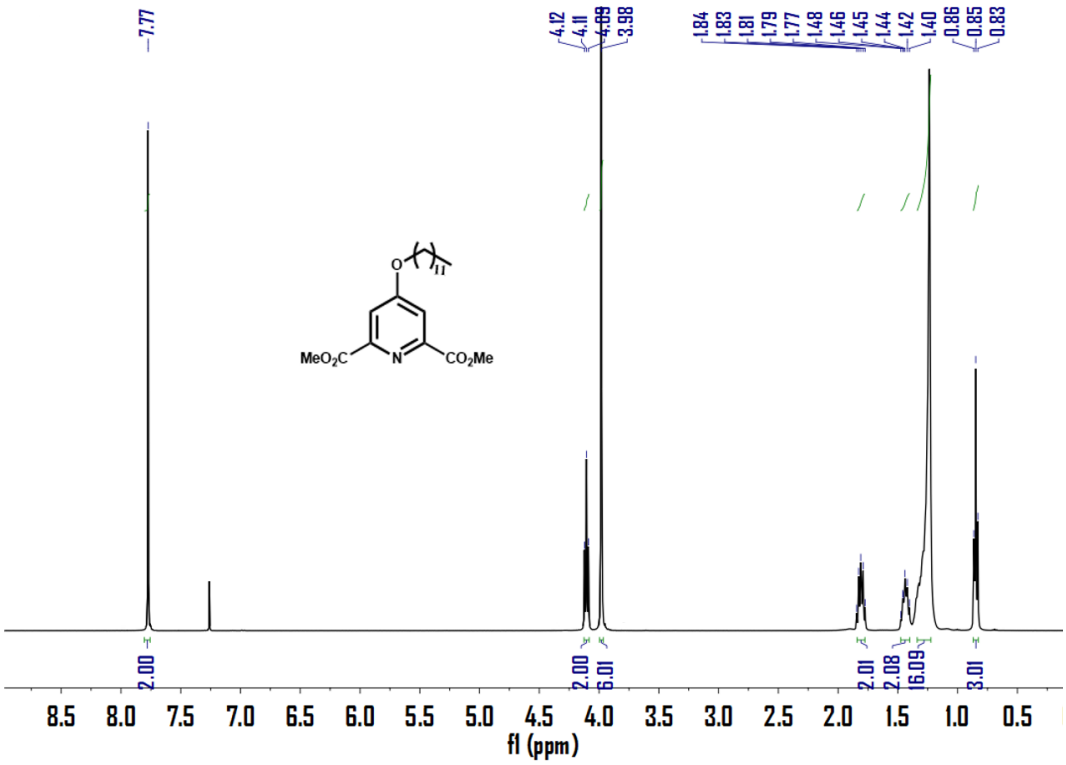


Figure S30. ^{1}H NMR spectrum of **20** in $CDCl_3$.

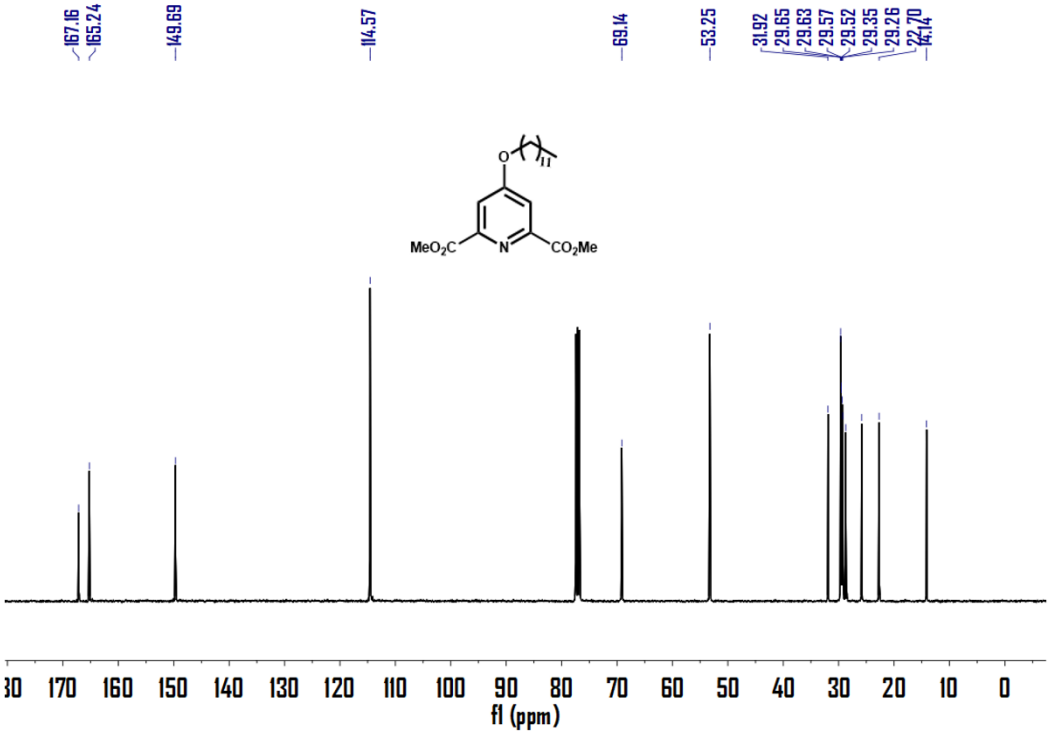


Figure S31. ^{13}C NMR spectrum of **20** in $CDCl_3$.

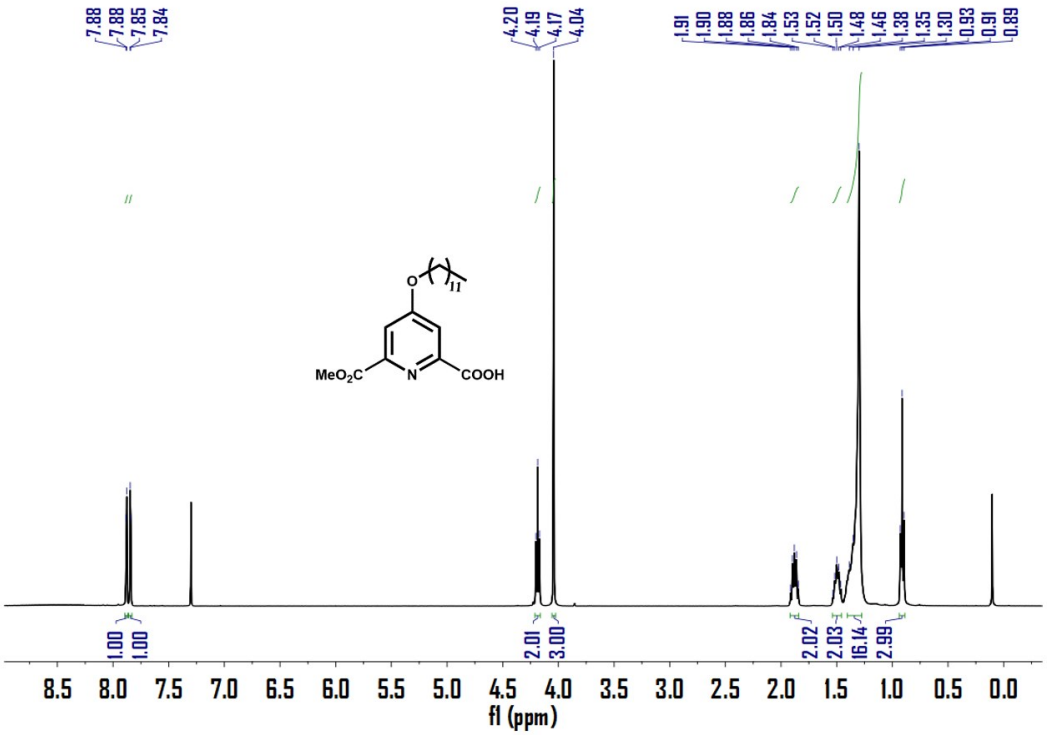


Figure S32. ^{1}H NMR spectrum of **21** in $CDCl_3$.

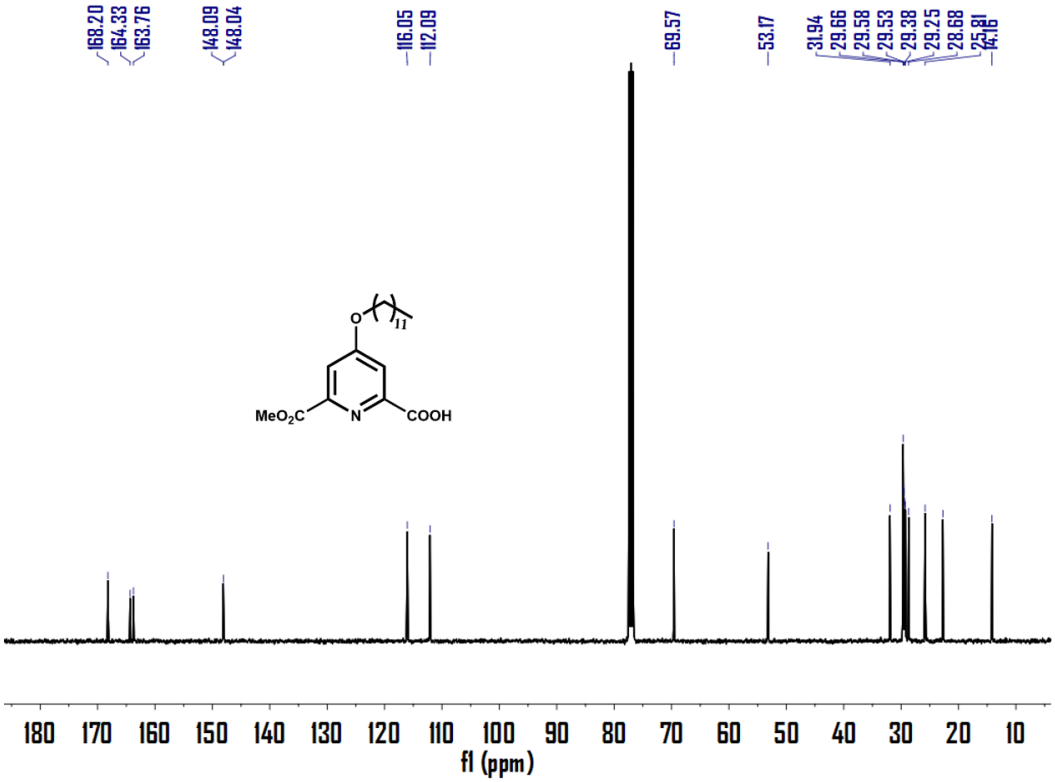


Figure S33. ^{13}C NMR spectrum of **21** in $CDCl_3$.

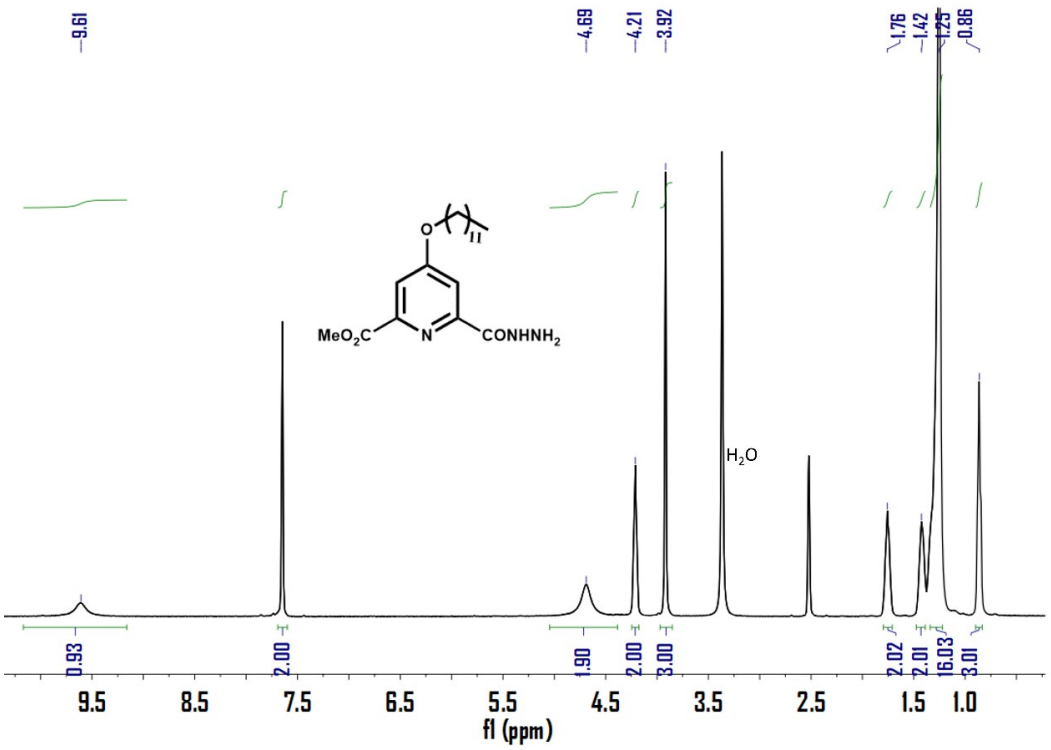


Figure S34. ^{1}H NMR spectrum of **22** in DMSO.

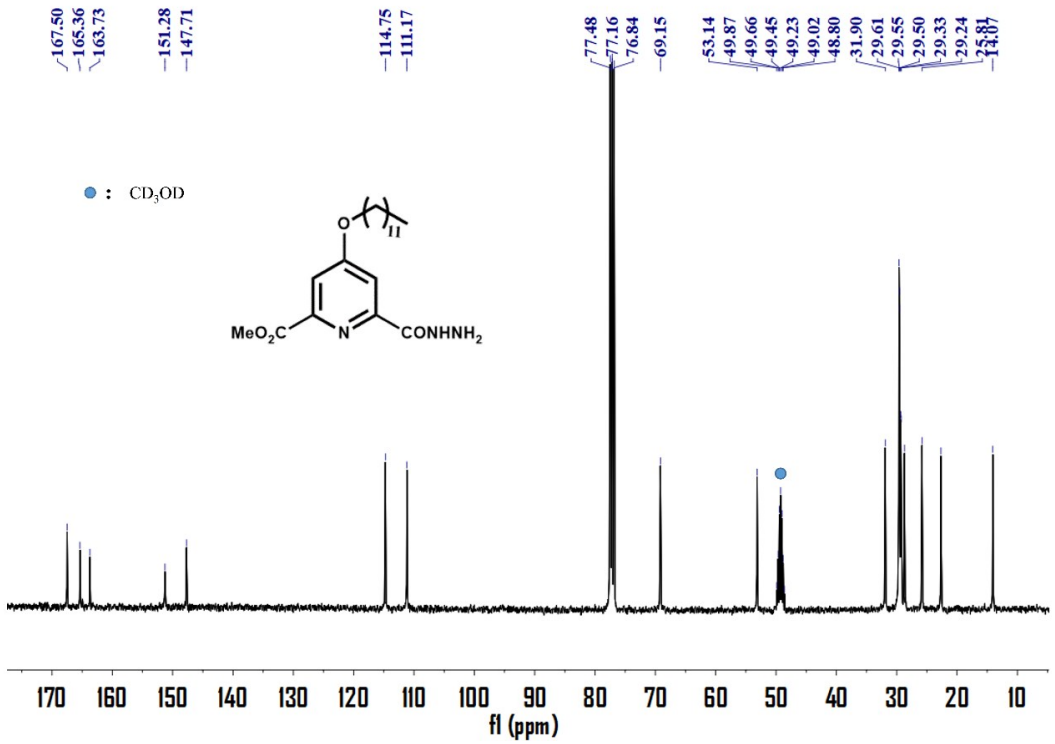


Figure S35. ^{13}C NMR spectrum of **22** in CDCl3 (CDCl3/CD_3OD 10:1).

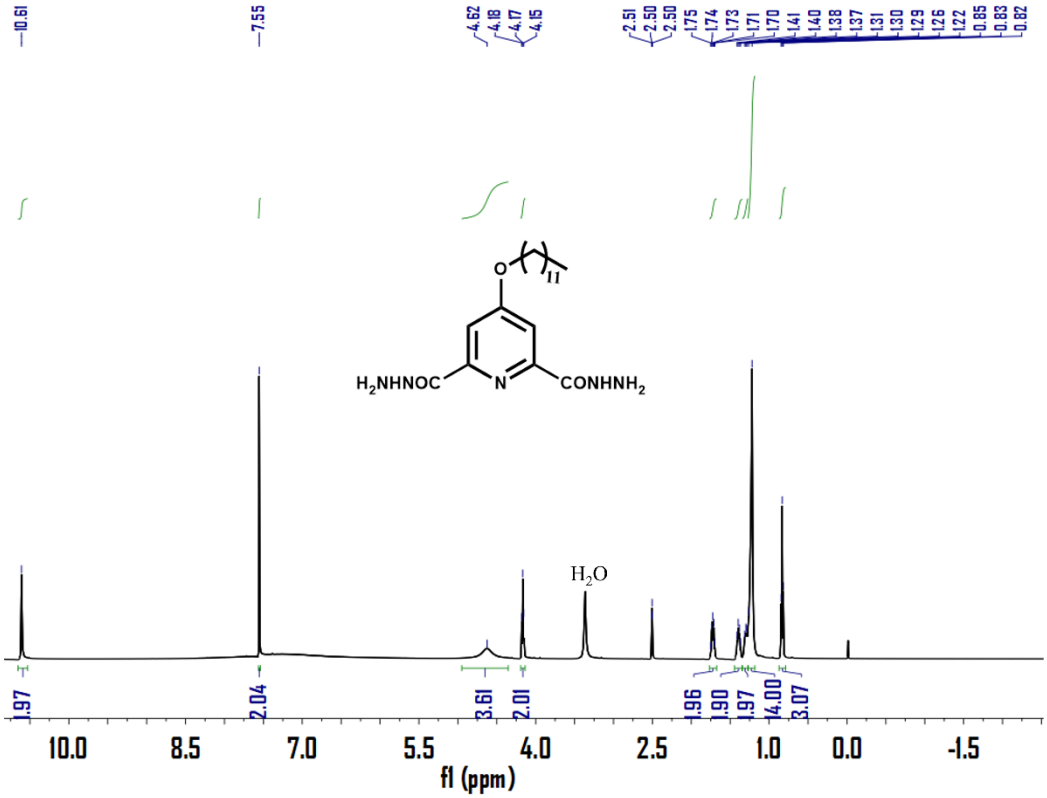


Figure S36. [1]H NMR spectrum of **23** in DMSO.

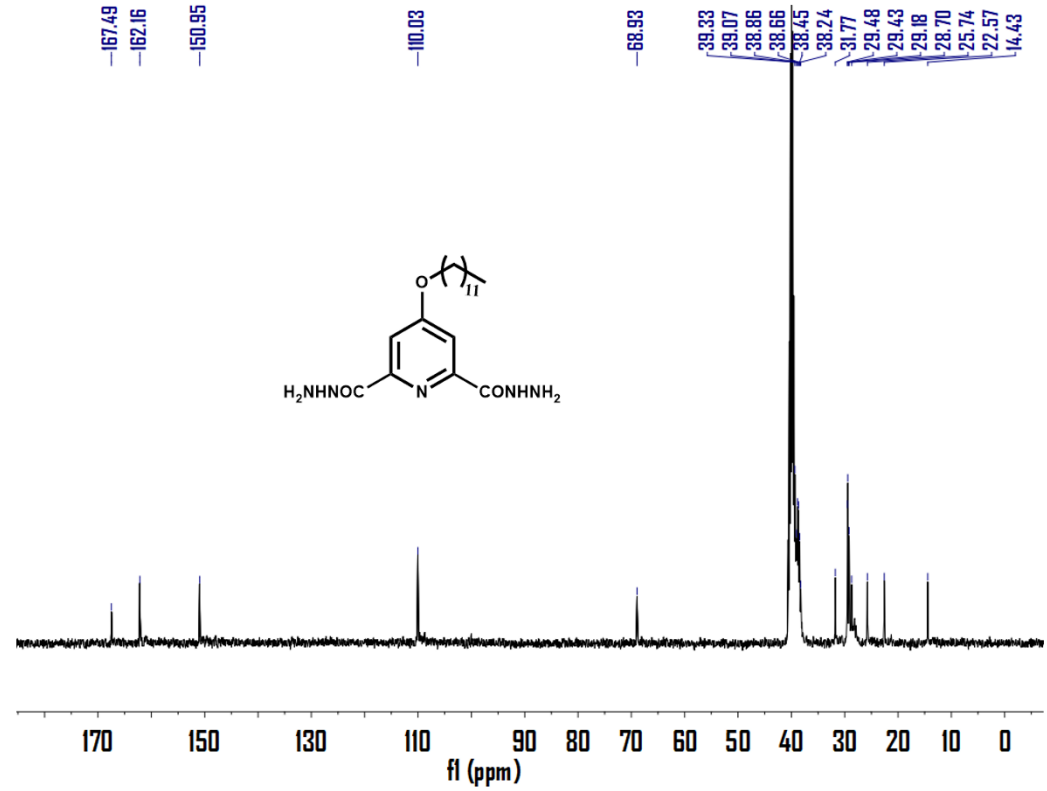


Figure S37. [13]C NMR spectrum of **23** in DMSO.

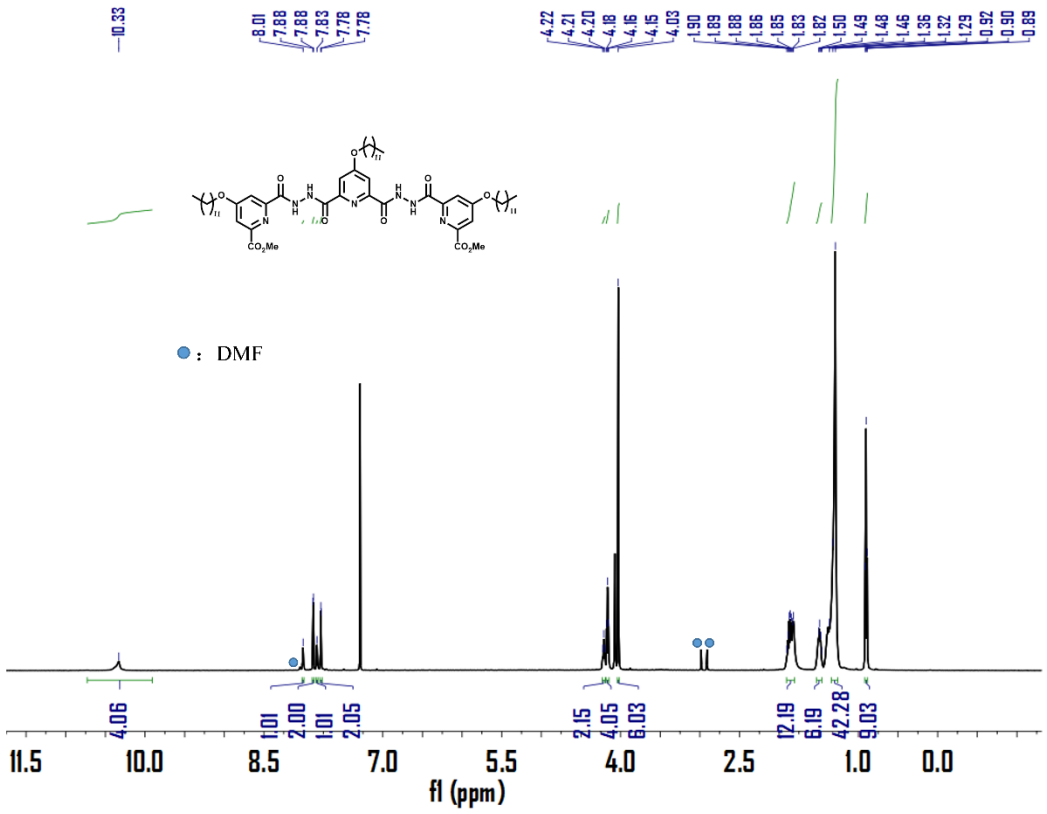


Figure S38. ^{1}H NMR spectrum of **24** in $CDCl_3$.

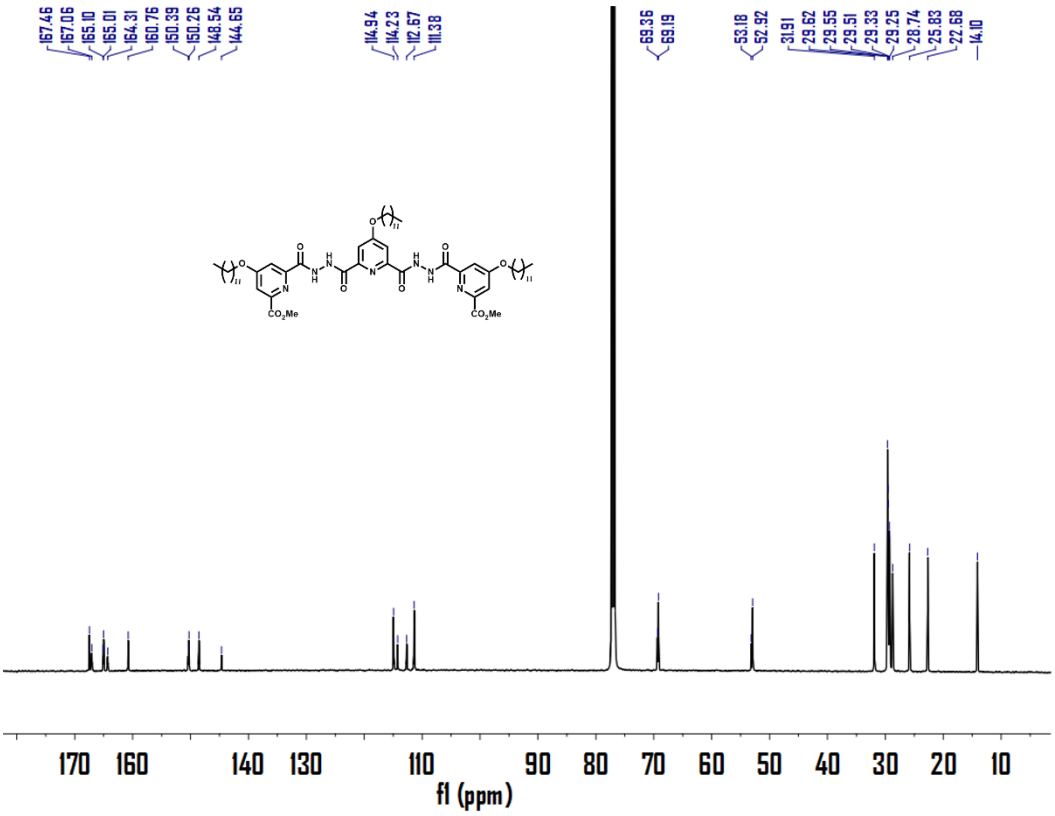


Figure S39. ^{13}C NMR spectrum of **24** in $CDCl_3$.

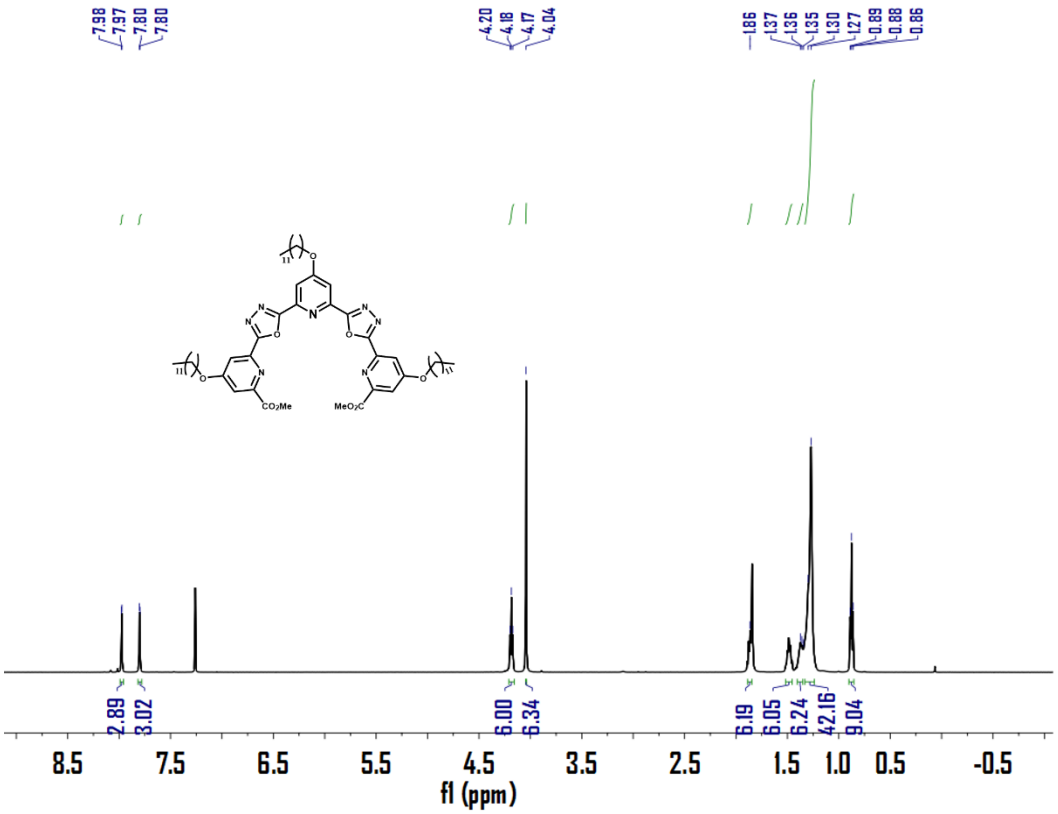


Figure S40. ^{1}H NMR spectrum of **25** in $CDCl_3$.

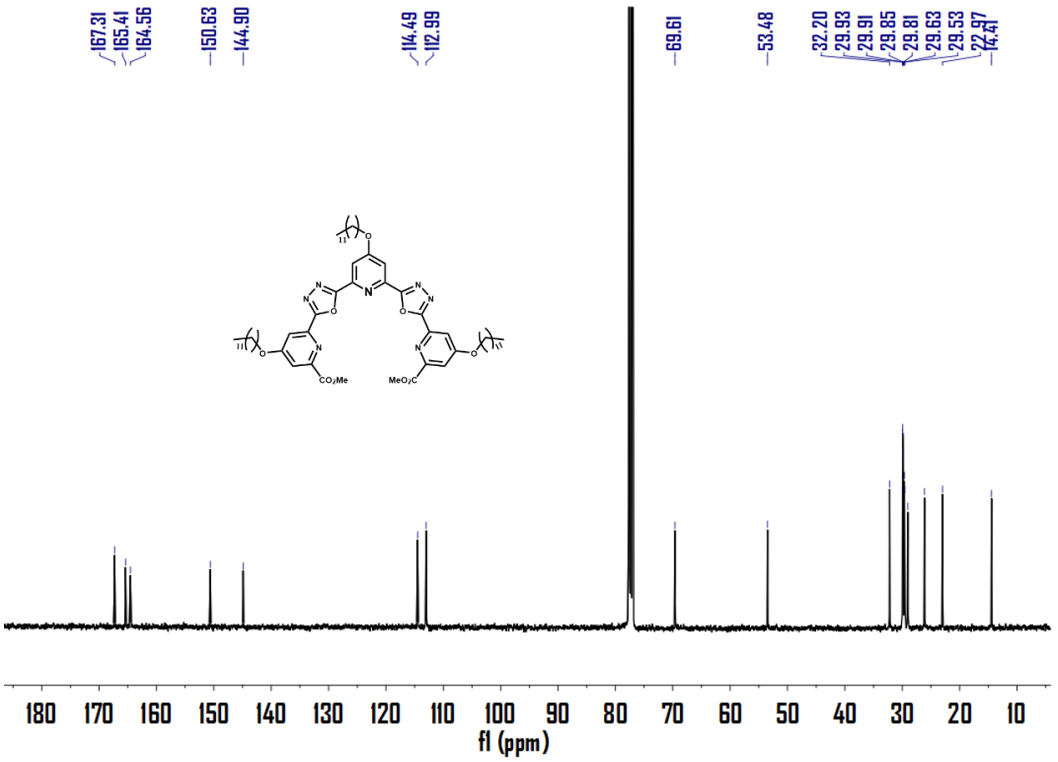


Figure S41. ^{13}C NMR spectrum of **25** in $CDCl_3$.

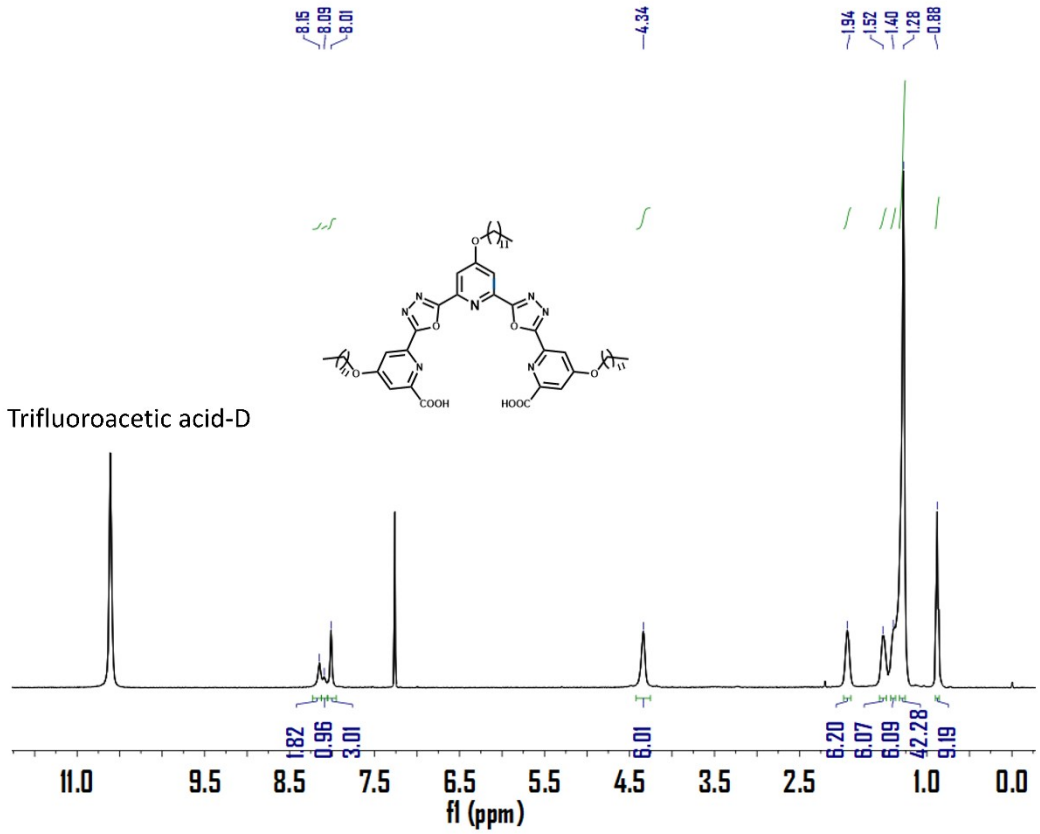


Figure S42. [1]H NMR spectrum of **26** in CDCl3 (CDCl3/Trifluoroacetic acid-D 20:1).

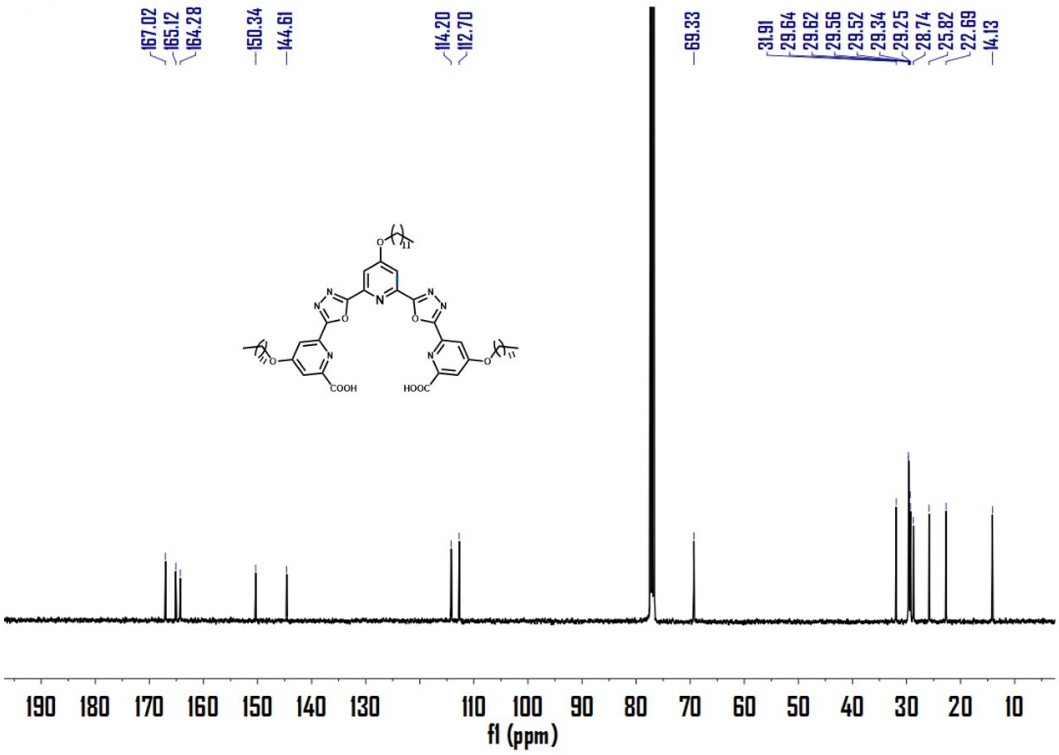


Figure S43. [13]C NMR spectrum of **26** in CDCl3.

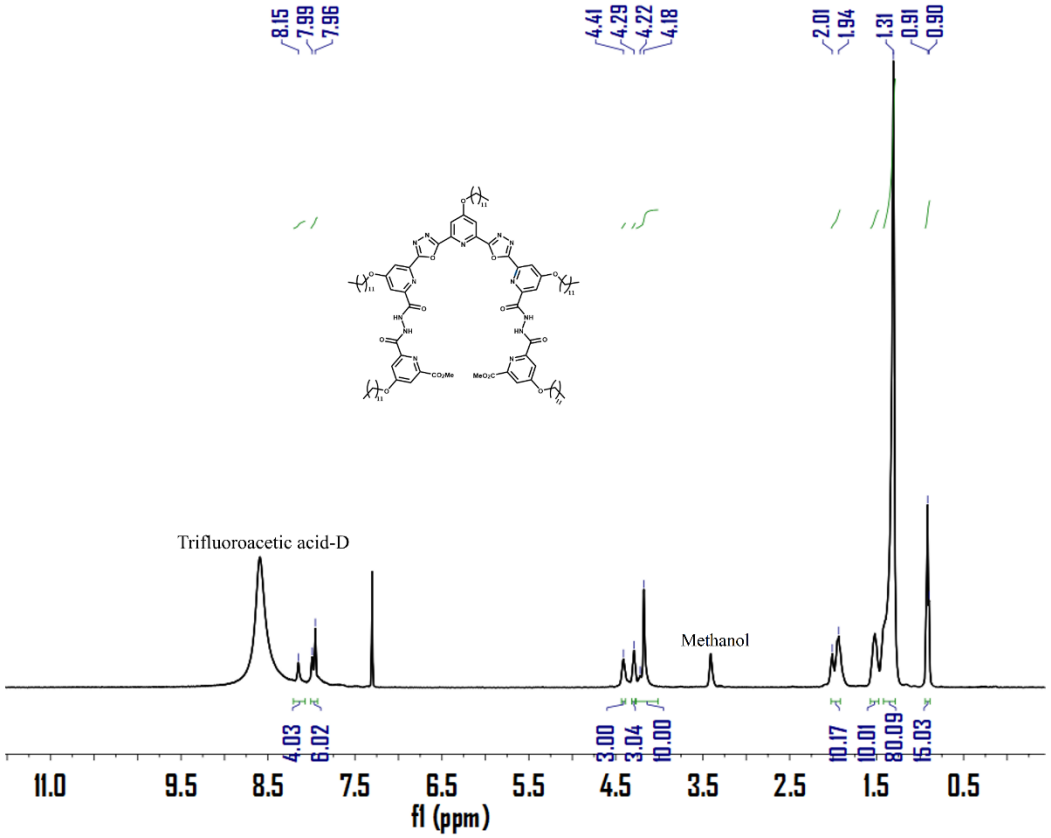


Figure S44. ^{1}H NMR spectrum of **27** in $CDCl_3$.

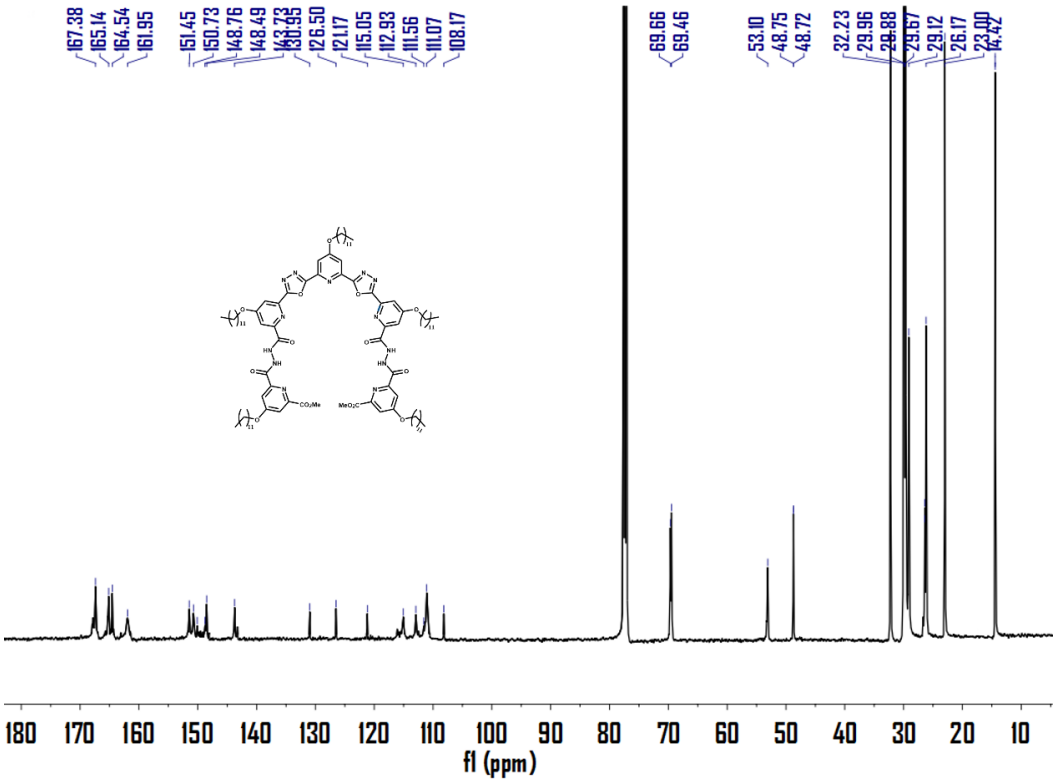


Figure S45. ^{13}C NMR spectrum of **27** in $CDCl_3$.

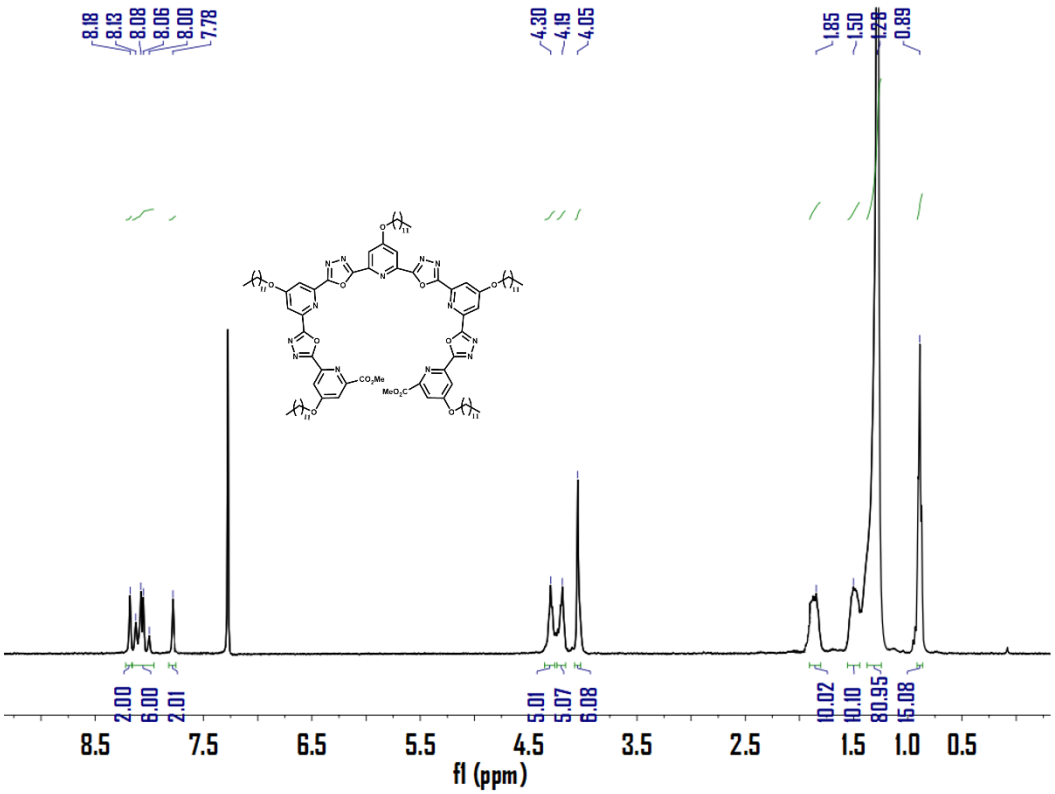


Figure S46. ^{1}H NMR spectrum of **M5** in CDCl3.

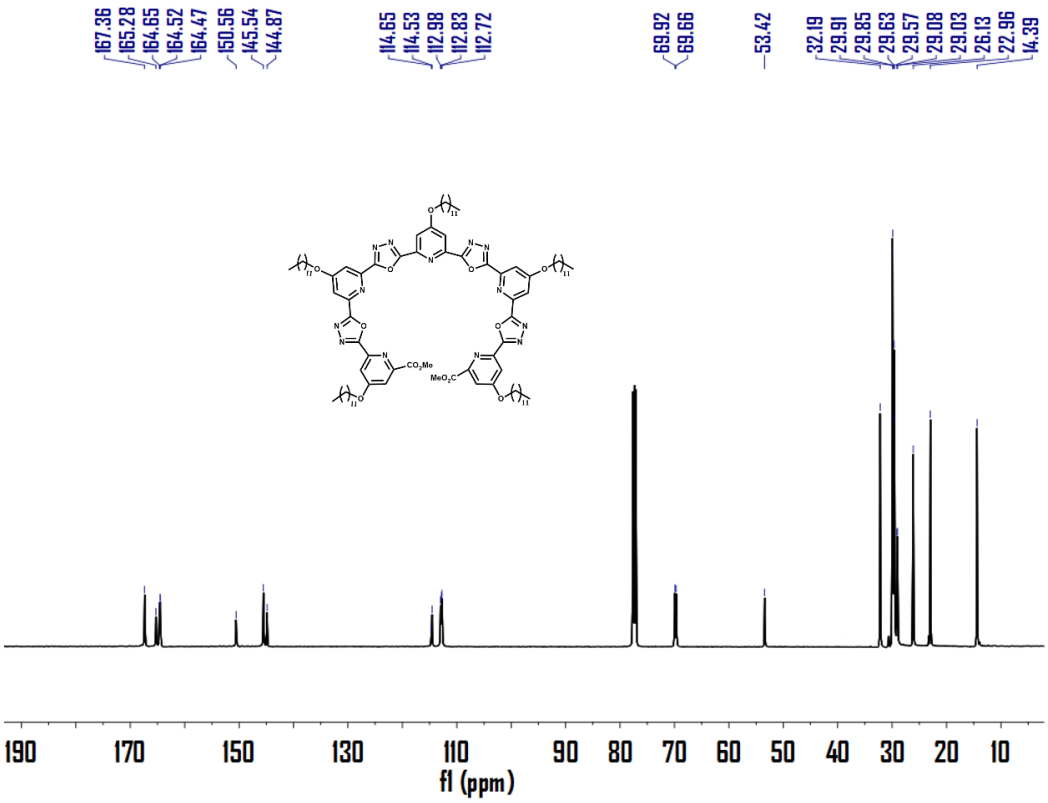


Figure S47. ^{13}C NMR spectrum of **M5** in $CDCl_3$.

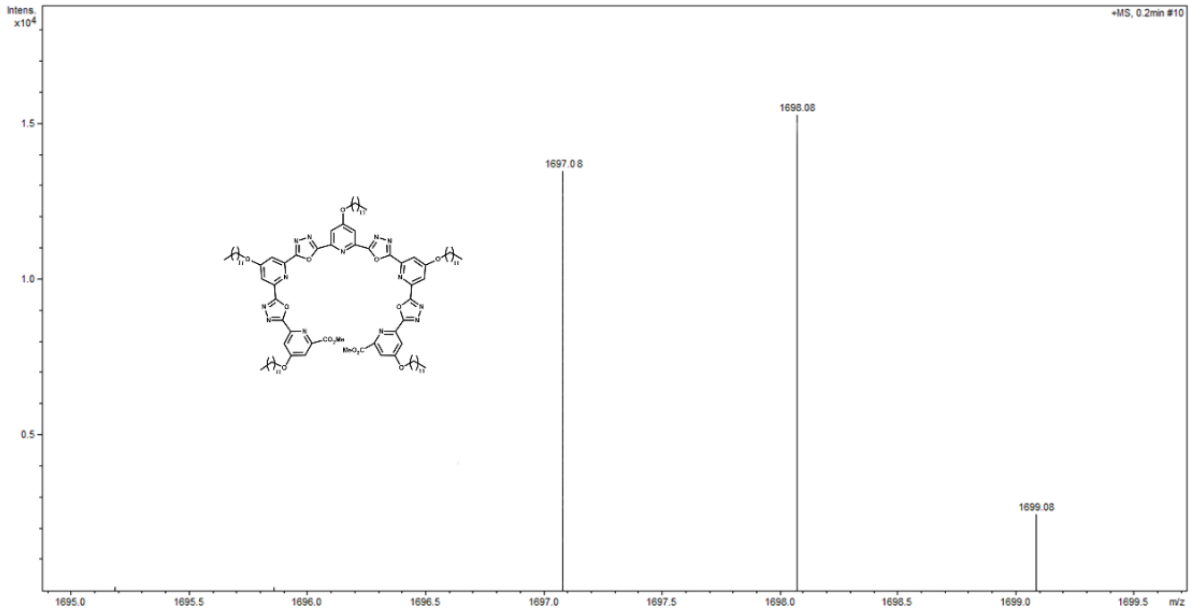


Figure S48. ESI MS spectrum of compound **M5**.

4. X-Ray crystal data of M0.

The block like single crystal was obtained by vapour diffusion, in which **M0** was dissolved in dry trichloromethane while methanol as antisolvent.

CCDC 2467629 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

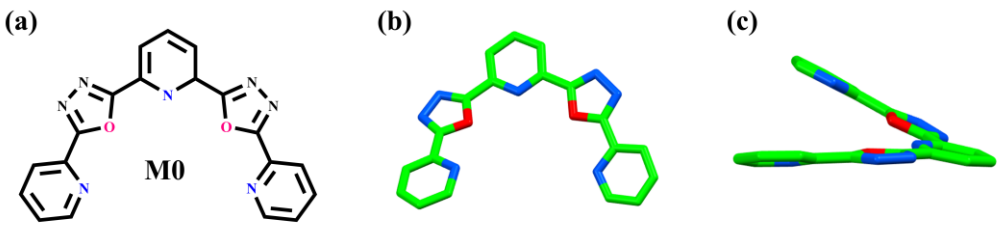


Figure S49. (a) Chemical structure of foldamer **M0**. The front view (b) and side view (c) of the crystal structure of **M0** (hydrogens omitted for clarity).

Table S1. Crystallographic data for **M0**.

CCDC number	
Empirical formula	$C_{19}H_{11}N_7O_2$
Formula weight	369.35
Temperature [K]	298.00
Crystal system	monoclinic
Space group (number)	$P2_1/n$ (14)
a [Å]	4.3394(5)
b [Å]	36.940(5)
c [Å]	11.2673(14)
α [°]	90
β [°]	92.790(5)
γ [°]	90
Volume [Å^3]	1804.0(4)
Z	4
ρ_{calc} [gcm^{-3}]	1.360
μ [mm^{-1}]	0.095
F(000)	760
Crystal size [m**m**^{3}]	0.13×0.12×0.11
Crystal colour	clear light colourless
Crystal shape	block
Radiation	MoK_α (λ=0.71073 Å)
2θ range [°]	5.71 to 50.05 (0.84 Å)
Index ranges	−5 ≤ h ≤ 5
	−43 ≤ k ≤ 43
	−13 ≤ l ≤ 13
Reflections collected	45194
Independent reflections	3087
	R_{int} = 0.0570
	R_{sigma} = 0.0212
Completeness to θ = 25.027°	97.3 %
Data / Restraints / Parameters	3087/0/253
Absorption correction	?/?
T_{min}/T_{max} (method)	(none)
Goodness-of-fit on F^2	1.122
Final *R* indexes	R_1 = 0.0804
[$I \geq 2\sigma(I)$]	wR_2 = 0.2090
Final *R* indexes	R_1 = 0.1126
[all data]	wR_2 = 0.2657
Largest peak/hole [eÅ^{-3}]	0.28/−0.27

5. Concentration-dependent fluorescence titrations

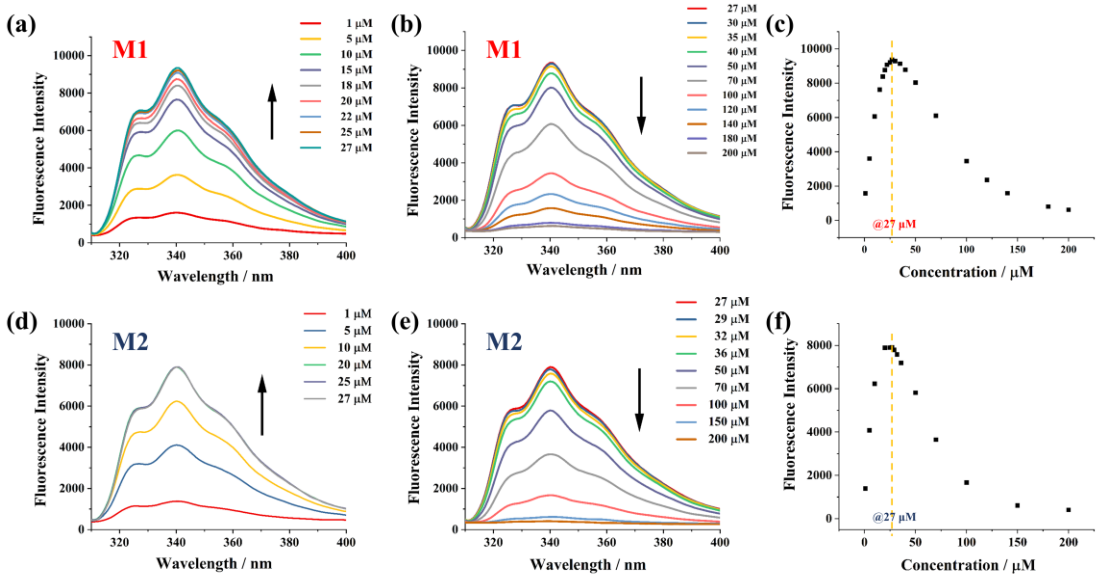


Figure S50. Concentration-dependent fluorescence titrations of **M1** (a, b) and **M2** (d, e) in the mixture solvent acetonitrile / water (9:1) from 1 μM to 200 μM. The fluorescence intensity at 340 nm for molecules **M1** (c) and **M2** (f) at different concentrations (1 ~ 200 μM). EX= 290 nm.

6. Ion-induced fluorescence titrations of foldamers M1 and M2.

Potassium and sodium ion concentration-dependent fluorescence titration was performed on the foldamers **M1** and **M2** with a SHIMADZU RF-5301PC Spectro fluorophotometer to ascertain the ion preference of the helical foldamers. In the acetonitrile/water (9: 1, vol/vol) mixture, NaCl and KCl were gradually added to the foldamers (20 μM). Fluorescence intensity and absorption wavelength were monitored at room temperature.

7. Liposome-based assays for validating the H^+/K^+ antiport mechanism

(1) Chloride transport experiment with lucigenin assay

Preparation of LUVs: The typical procedure of preparation of lucigenin entrapped in large unilamellar vesicles (LUVs) was as follows: 10 mg of egg yolk L-α-phosphatidylcholine (EYPC) was dissolved in dry $CDCl_3$ (2 mL) and the solution was dried with N_2 flow. The thin film of EYPC was dried under vacuum for 3 hours to remove the solvent completely, then the lipid was hydrated with 1 mL of buffer solution (HEPES, 10 mM, pH = 7.0) containing 100 mM of K_2SO_4 and 1 mM

of chloride sensitive dye lucigenin for 3 hours at 37℃. The suspension was carried out 10 times freeze-thaw cycles with liquid nitrogen and thermostat water bath and was extruded 10 times using 200 μm polycarbonate membrane, and then was purified by Sephadex G-50 to remove the dye outside the vesicles (mobile phase: HEPES buffer (10 mM, pH = 6.5) with 100 mM KCl). The ultimate solution was kept under 4℃ and used within one week.

Fluorescent experiments: In a 1.5 mL cuvette, 50 μL LUVs suspensions were mixed with 950 μL 100 mM KCl with pH=6.5 and in HEPES buffer. Fluorescence intensity (Et) was continuously monitored at 505 nm (Excitation wavelength: 455 nm). After 50s, 10 μL channel M1 solution in DMSO was added into the suspension under stirring and 10 μL 40% Triton X-100 solution was added at 300s to stop this test. The data was continuously measured until the fluorescence intensity (E_∞) did not change. The collected time course data E_t was normalized according to the equation:

$$\mathbf{R_f = (E_t - E_0)/(E_\infty - E_0)}$$

Where R_f is the normalized fluorescence intensity, E_0 is the initial emission intensity, E_∞ is the final emission intensity.

(2) Proton transport experiment with HPTS assay in the presence of FCCP

The method for vesicle preparation is similar to the one described above, except that the internal buffer solution contains KCl at pH 7.0, and the internal pH indicator is HPTS at a concentration of 1 mM. The external buffer solution is KCl at pH 7.6. The remaining steps for vesicle preparation are consistent with what was mentioned above.

The testing method is similar to the one described above, except that the excitation wavelength is 460 nm, and the emission wavelength detection occurs at 510 nm. Additionally, during the testing, channel M1 (0.5 nM) is added first, followed by FCCP (10 nM). The calculation method is the same as described above.

(3) Proton transport experiment with HPTS assay in the presence of Valinomycin

The method for vesicle preparation is consistent with that in Experiment 2, titled "Proton transport experiment with HPTS assay in the presence of FCCP."

The testing method is consistent with that in Experiment 2, titled "Proton transport experiment with HPTS assay in the presence of FCCP." Additionally, during the testing, valinomycin (VA, 10 nM) is added first, followed by the introduction of channel M1 (0.5 nM). The calculation method is the same as described above.

During the testing process, the concentration of M1 in these three experiments is consistently 0.5 nM.

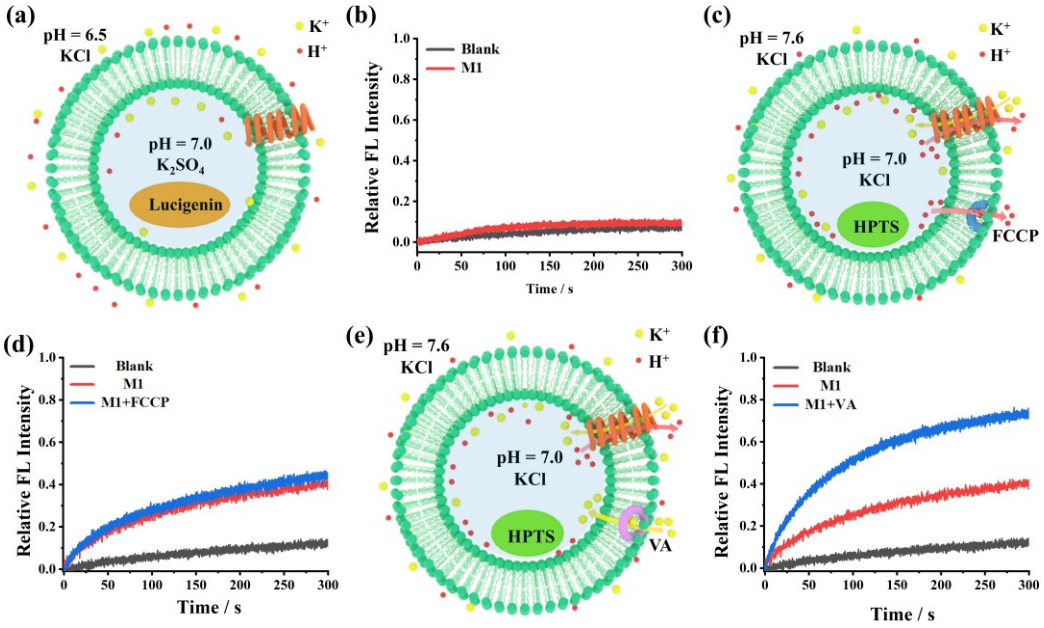


Figure S51. a) and b) Chloride ion transport assay monitored with the chloride-sensitive dye lucigenin. c) and d) Liposome transport assay in the presence of the protonophore FCCP. e) and f) Liposome transport assay in the presence of the potassium ionophore valinomycin (VA).

8. Ion transport experiment of foldamers M1-M5 with HPTS assay

The typical procedure of preparation of HPTS entrapped in large unilamellar vesicles (LUVs) was as follows: 10 mg of egg yolk L-α-phosphatidylcholine (EYPC) was dissolved in dry $CDCl_3$ (2 mL) and the solution was dried with N_2 flow. The thin film of EYPC was dried under vacuum for 3 hours to remove the solvent completely, then the lipid was hydrated with 1 mL of buffer solution (HEPES, 10 mM, pH = 7.0) containing 100 mM of NaCl and 1 mM of pH sensitive dye HPTS for 3 hours at 37°C. The suspension was carried out 10 times freeze-thaw cycles with liquid nitrogen and thermostat water bath and was extruded for 10 times using 200 μm polycarbonate membrane, and then was purified by Sephadex G-50 to remove the dye outside the vesicles (mobile phase: HEPES buffer (10 mM, pH = 7.0) with 100 mM NaCl). The ultimate solution was kept under 4°C and used within one week.

EYPC assay: To 950 μL 100 mM MCl or 50 mM NCl_2(M = Li^+, Na^+, K^+, Rb^+, Cs^+ and N = Ca^{2+}, Mg^{2+}) buffer solution (HEPES, 10 mM, pH = 7.6) in a quartz fluorimetric cell was added 50 μL of LUVs containing HPTS. The addition of 50 μL LUVs resulted in a phospholipid concentration of 0.09 mM in the system. The emission of HPTS at 510 nm was monitored at excitation 460 nm, and then 10 μL of channel in DMSO was added. Finally, the monitoring was stopped by lysing the vesicles with detergent (10 μL of 20% aqueous Triton X-100). The injection part of the spectrum was subtracted for clarity. The collected time course data Et was normalized according to the equation:

$$\mathbf{R_f = (E_t - E_0)/(E_\infty - E_0)}$$

Where R_f is the normalized fluorescence intensity, E_0 is the initial emission intensity, E_∞ is the

final emission intensity.

The logistic function of helical concentration (C) and fractional activity (Y) can be fitted by Hill equation:

$Y = 1/(1+(EC_{50}/[C])^{n})$

providing the EC_{50} and Hill coefficient *n*.

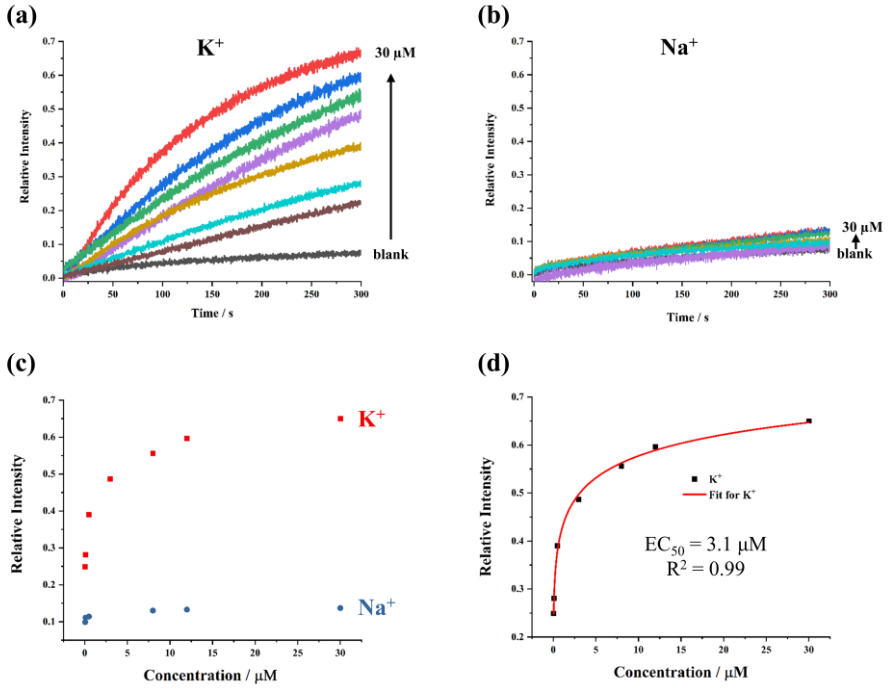


Figure S52. Normalized a) K^+ and b) Na^+ transport activity of **M2** at different concentrations. c) Job's plot of ion transport activity experiments of **M2** at 300 s. d) Hill plot for K^+ transport by **M2.**

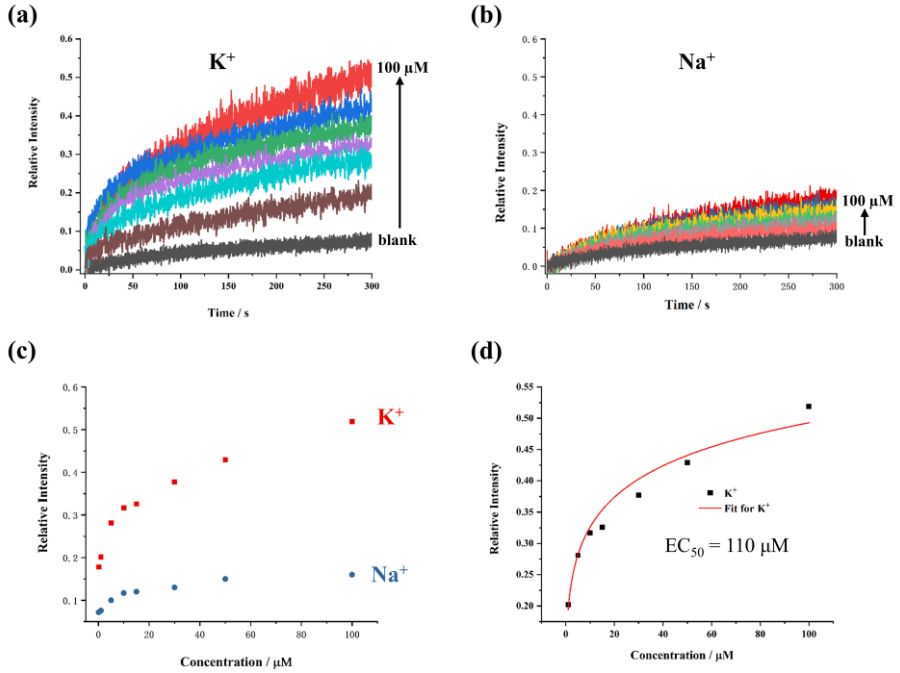


Figure S53. Normalized a) K^+ and b) Na^+ transport activity of **M3** at different concentrations. c) Job's plot of ion transport activity experiments of **M3** at 300s. d) Hill plot for K^+ transport by **M3**.

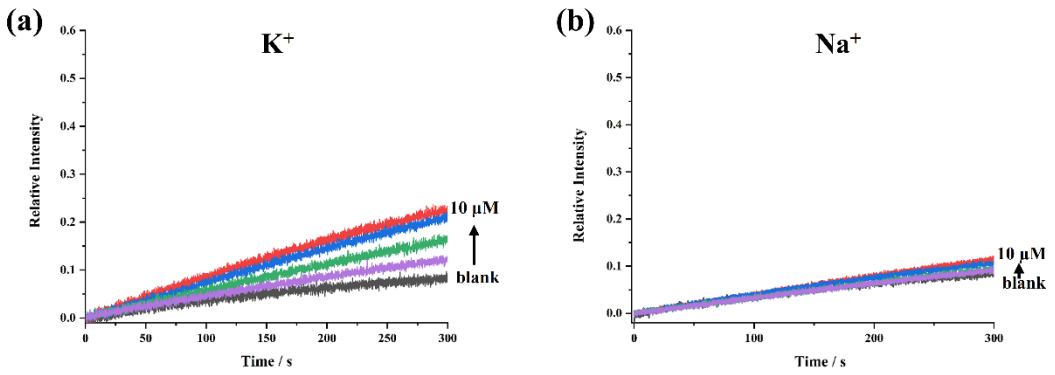


Figure S54. Normalized a) K^+ and b) Na^+ transport activity of **M4** at different concentrations.

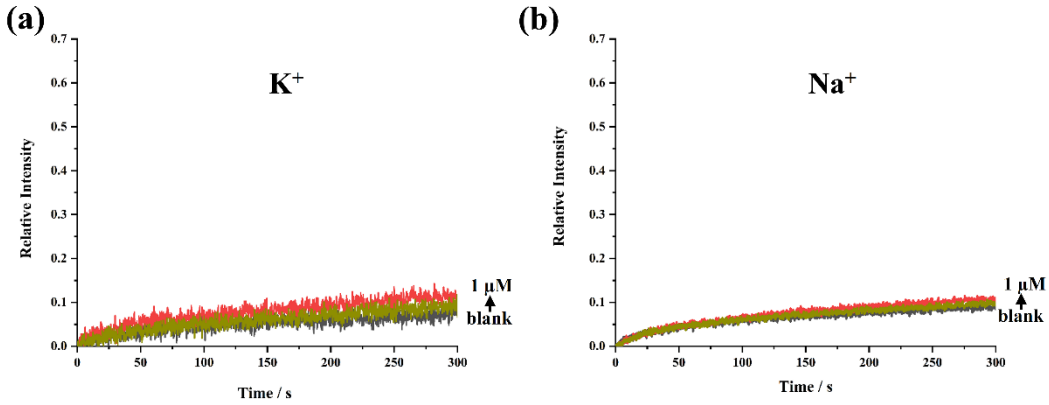
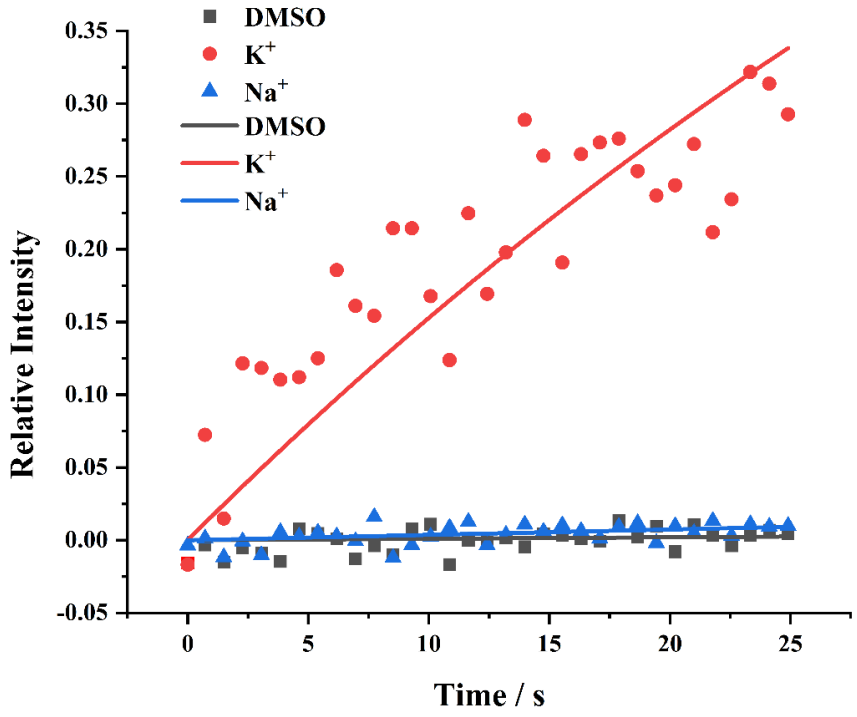


Figure S55. Normalized a) K^+ and b) Na^+ transport activity of **M5** at different concentrations.

The normalized fluorescence intensity can be reasonably fitted by the following equation:

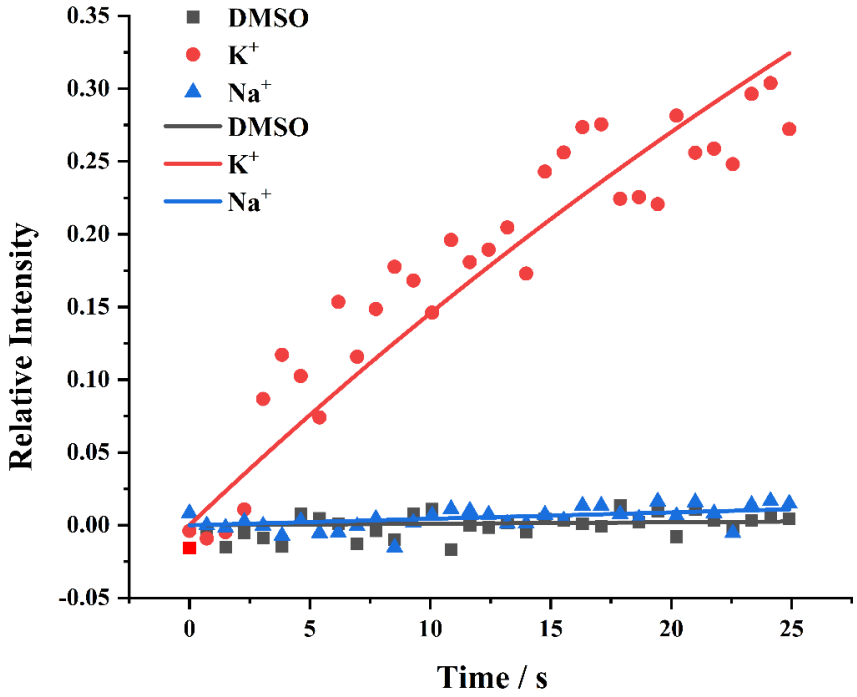
y = 1-e^(-k*x)

The selectivities of channels are estimated using the ratio of the first-order rate constants calculated from the equation.



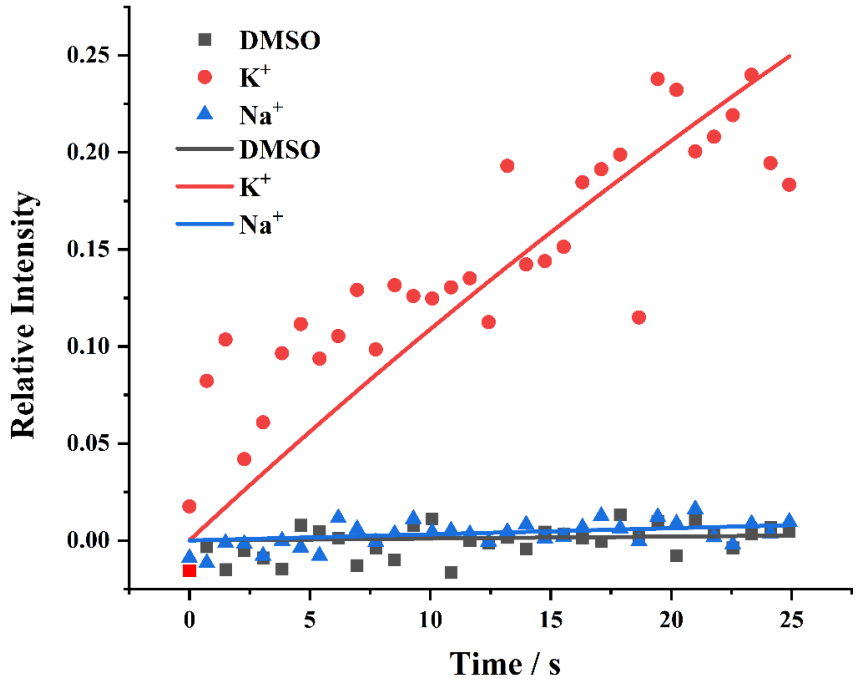
	K	Na	DMSO
k	$1.657*10^{-2}$	$3.698*10^{-4}$	$1.012*10^{-4}$
Standard Error	$8.287*10^{-5}$	$7.443*10^{-5}$	$9.507*10^{-5}$

Figure S56. Fitting of normalized fluorescence intensity of **M1** at a final concentration of 15 nM ($S_{K/Na}$ = 61.3 ± 3.9).



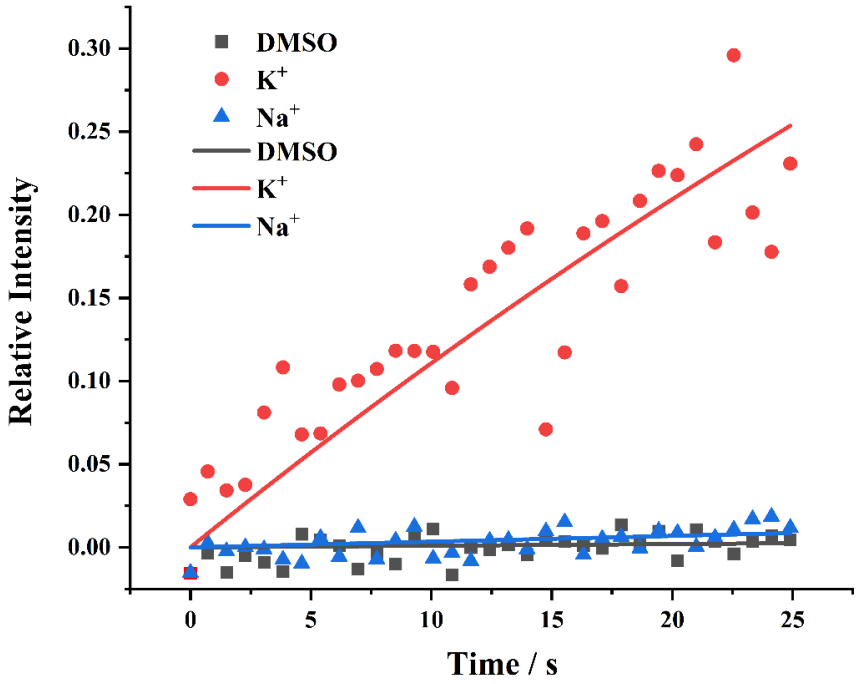
	K	Na	DMSO
k	$1.574*10^{-2}$	$3.814*10^{-4}$	$1.012*10^{-4}$
Standard Error	$5.433*10^{-5}$	$7.706*10^{-5}$	$9.507*10^{-5}$

Figure S57. Fitting of normalized fluorescence intensity of **M1** at a final concentration of 12 nM ($S_{K/Na}$ = 55.8 ± 3.1).



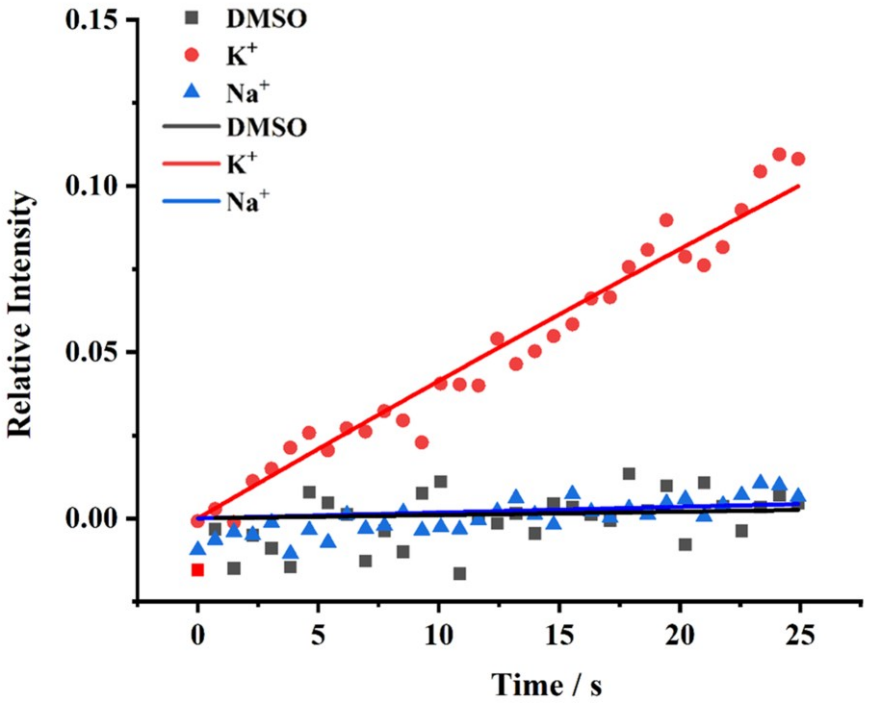
	K	Na	DMSO
k	$1.152*10^{-2}$	$3.169*10^{-4}$	$1.012*10^{-4}$
Standard Error	$5.764*10^{-5}$	$6.864*10^{-5}$	$9.507*10^{-5}$

Figure S58. Fitting of normalized fluorescence intensity of **M1** at a final concentration of 10 nM ($S_{K/Na}$ = 52.9 ± 3.4).



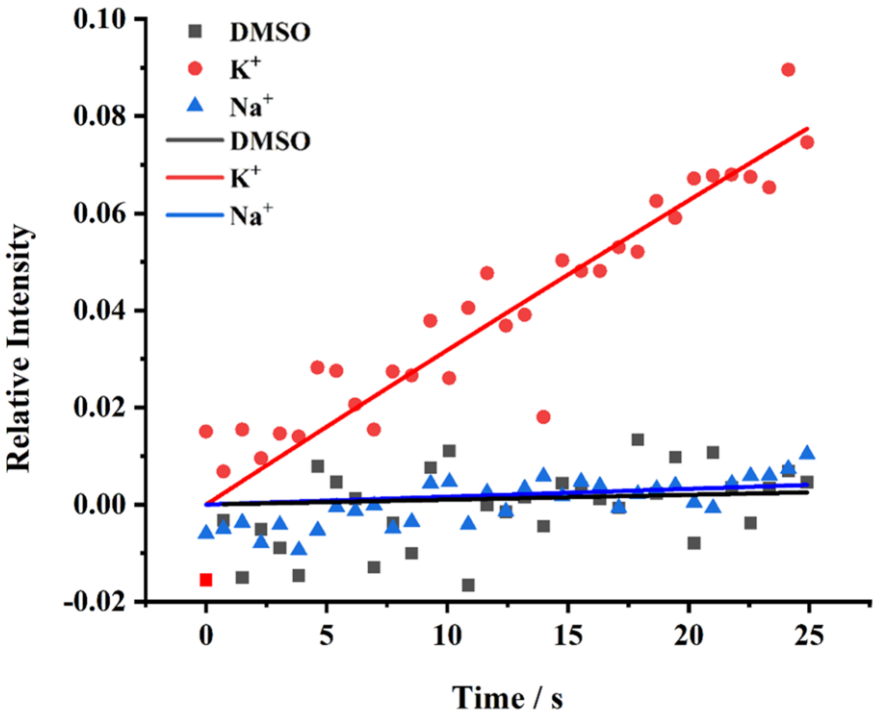
	K	Na	DMSO
k	$1.174*10^{-2}$	$3.335*10^{-4}$	$1.012*10^{-4}$
Standard Error	$5.470*10^{-5}$	$8.714*10^{-5}$	$9.507*10^{-5}$

Figure S59. Fitting of normalized fluorescence intensity of **M1** at a final concentration of 5 nM ($S_{K/Na}$ = 50.1 ± 3.7).



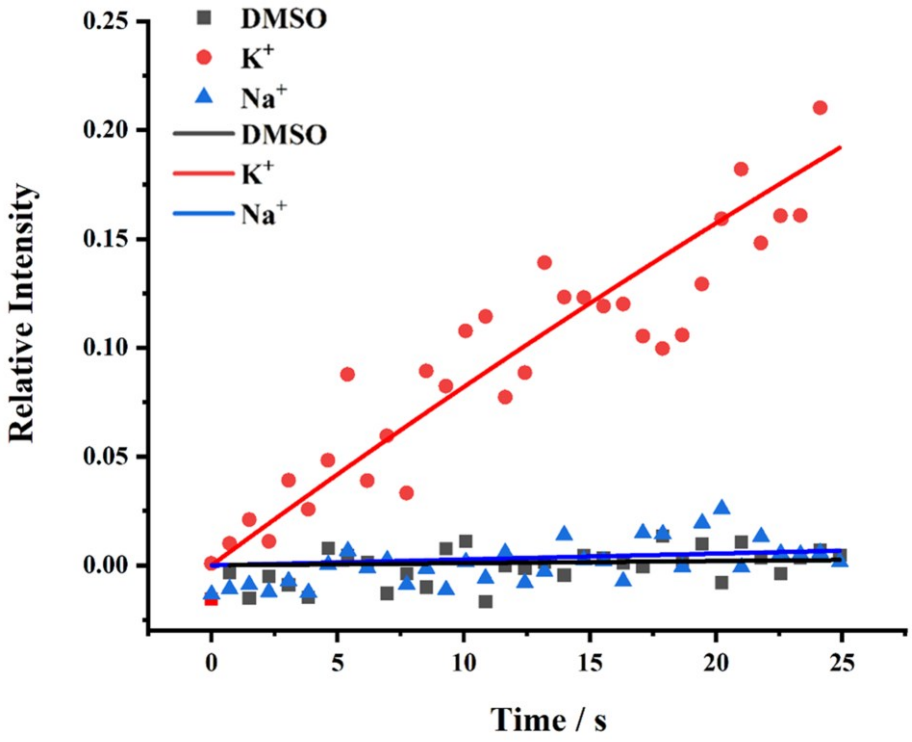
	K	Na	DMSO
k	$4.220*10^{-3}$	$1.743*10^{-4}$	$1.012*10^{-4}$
Standard Error	$8.364*10^{-5}$	$5.583*10^{-5}$	$9.507*10^{-5}$

Figure S60. Fitting of normalized fluorescence intensity of **M2** at a final concentration of 12 μM ($S_{K/Na}$ = 56.4 ± 5.7).



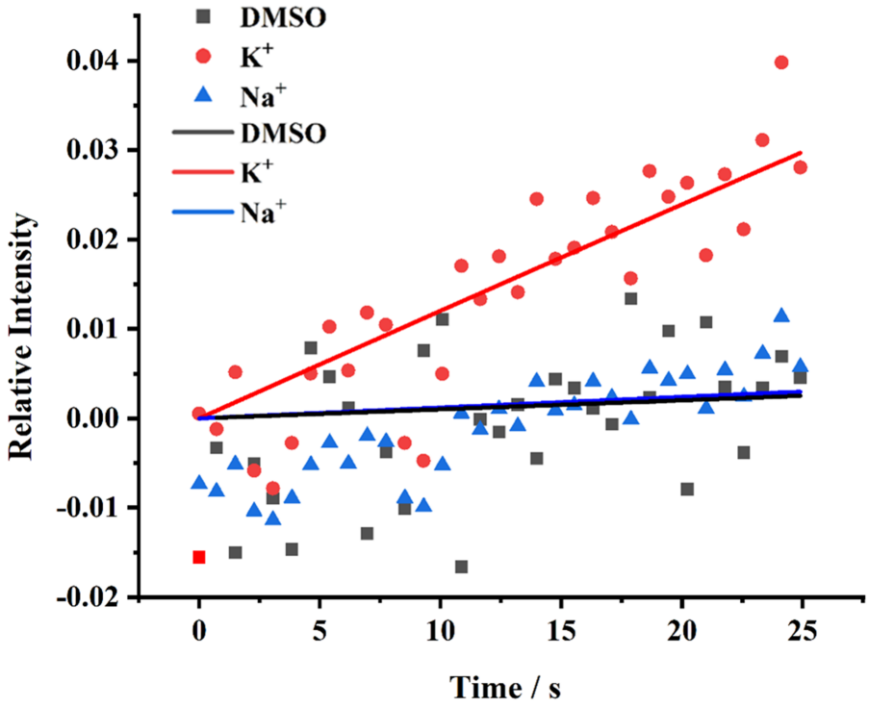
	K	Na	DMSO
k	$3.230*10^{-3}$	$1.627*10^{-4}$	$1.012*10^{-4}$
Standard Error	$1.021*10^{-4}$	$5.047*10^{-5}$	$9.507*10^{-5}$

Figure S61. Fitting of normalized fluorescence intensity of **M2** at a final concentration of 8 μM ($S_{K/Na}$ = 50.9 ± 2.1).



	K	Na	DMSO
k	$8.550*10^{-3}$	$2.721*10^{-4}$	$1.012*10^{-4}$
Standard Error	$3.656*10^{-4}$	$1.097*10^{-4}$	$9.507*10^{-5}$

Figure S62. Fitting of normalized fluorescence intensity of **M3** at a final concentration of 15 μM ($S_{K/Na}$ = 49.4 ± 8.5).



	K	Na	DMSO
k	$1.210*10^{-3}$	$1.201*10^{-4}$	$1.012*10^{-4}$
Standard Error	$7.484*10^{-5}$	$6.767*10^{-5}$	$9.507*10^{-5}$

Figure S63. Fitting of normalized fluorescence intensity of **M4** at a final concentration of 10.0 μM ($S_{K/Na}$ = 58.7 ± 7.4).

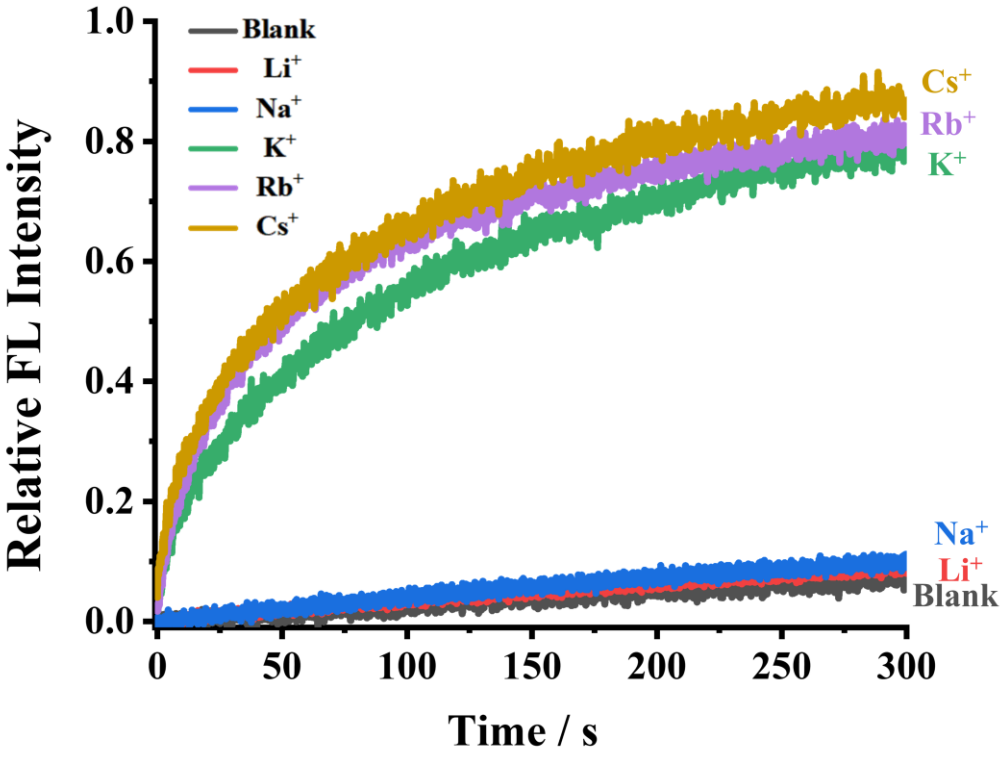


Figure S64. Normalized Li^+, Na^+, K^+, Na^+, Rb^+ and Cs^+ transport activity of **M1** at 10 nM.

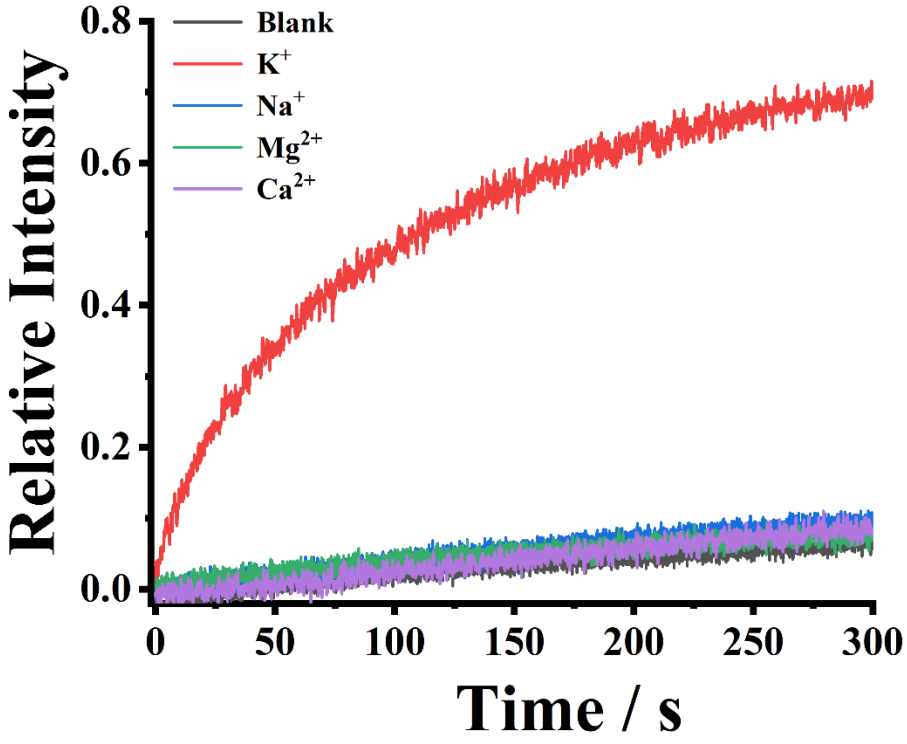


Figure S65. Normalized K^+, Na^+, Ca^{2+} and Mg^{2+} transport activity of **M1** at 10 nM.

9. Procedures for the confocal laser scanning microscopy experiment

(a) Cell culture: Human Umbilical Vein Endothelial Cell (HUVEC) was obtained from Shanghai Biowang Applied Biotechnology Co. TED (Shanghai, CN). Leukocyte was separated from human peripheral venous blood. The cells were cultured in complete 10% FBS/DMEM and incubated in a standard humidified incubator with 5% CO_2 at 37 °C.

(b) General procedures: Cells were seeded in 96-well plates at a density of 1×105 cells per well in 100 μL of HUVEC cell line, and cultured in 5% CO_2 at 37 °C for 24 h. Then, the prepared suspension of **M1** (5 μM) was added to the corresponding wells with broth as control, and the samples were incubated for 24 h. The cell survival rate was determined by 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) assay. The optical density (OD) values at a wavelength of 490 nm were measured using an enzyme standard instrument.

(c) Fluorescence microscopy imaging experiments and confocal laser scanning microscopy (CLSM) imaging experiments: Above HUVEC and leukocyte cells were firstly incubated in the medium containing the commercial fluorescent membrane tracer 1,1-dioctadecyl-3,3,3,3-tetramethylindocarbocyanine perchlorate (Dil, 5 μM) for 0.5 h and washed with phosphate-buffered saline (PBS) buffer for three times to remove free Dil. The cells were then incubated with **M1** (5 μM) for 1 h. After washed with PBS buffer three times to remove free **M1**, the cells were subjected to fluorescence microscopy imaging and CLSM imaging. The fluorescence of Dil was excited by a 549 nm laser and the emission was collected 565 nm.

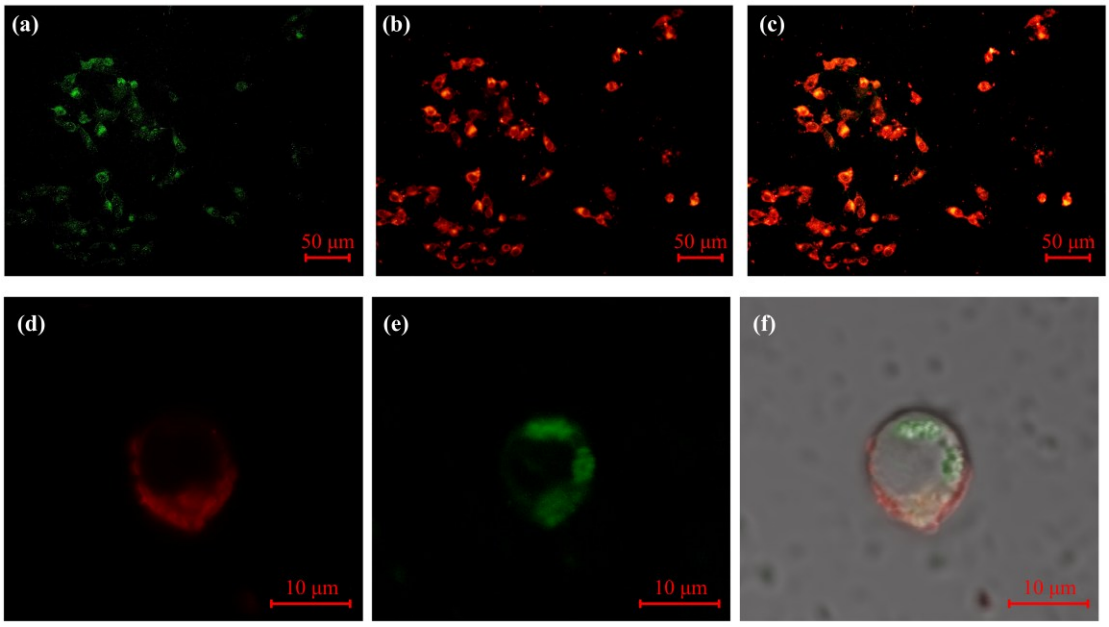


Figure S66. Fluorescence microscopy images of HUVEC after incubation with (a) 1,1-dioctadecyl-3,3,3,3-tetramethylindocarbocyanine perchlorate (Dil) and (b) **M1**. (c) Image showing the merge of (a) and (b). Confocal laser scanning microscopy (CLSM) images of single white blood cell (WBC) from human after incubation with (d) Dil and (e) **M1**. (f) Image showing the merge of (d) and (e).

10. Schematic illustration of the introduction of the channel into the system.

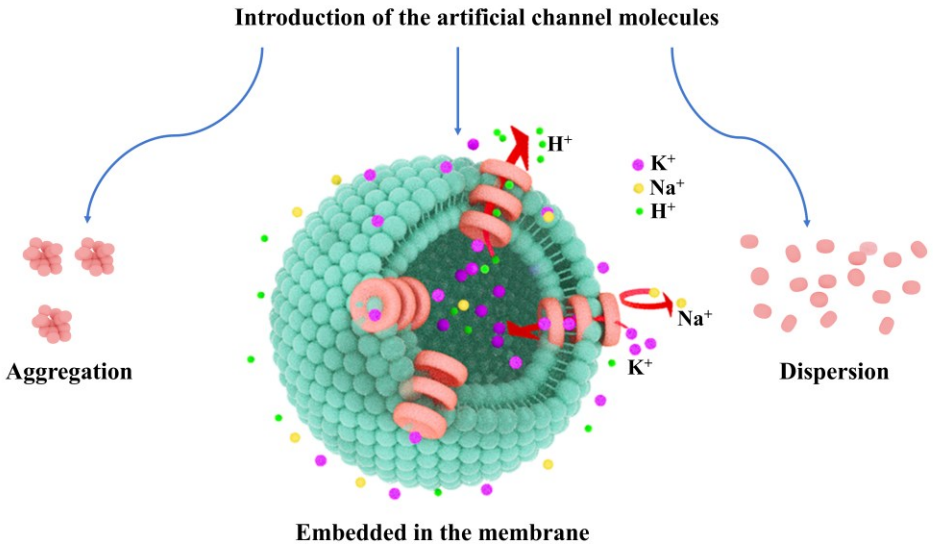


Figure S67. The diagram illustrates the three states of artificial channel molecules with different amphiphilic properties after being added to the system.

If the water solubility of the channel molecules is too poor, they fail to disperse in water and aggregate, preventing dissolution and diffusion (left). Excessively hydrophilic channel molecules diffuse freely in the solution, which hinders their assembly and membrane embedding (right). Only assemblies with appropriate amphiphilicity can effectively embed into the membrane and facilitate ion transport. The coordination sites and cavity size within the channels further determine their ion selectivity. This process emphasizes the importance of balancing hydrophilicity and lipophilicity for effective channel formation and membrane integration.

11. Simulation of lipid-water partition coefficients (logP) using ALOGPS 2.1

The logP values of **M1**-**M5**, as well as cereulide and valinomycin, were predicted using ALOGP 2.1. The principles behind this method can be found in the references,[S4] and the specific prediction website is https://vcclab.org/.

12. Electrophysiological Properties of the Channels

A chloroform solution of DiPhytanoyl Phosphatidylcholine (DIPHYC) was dried using nitrogen gas to form a thin film and then dissolved in n-decane (25 mg/mL). 0.5 μL of the n-decane

solution was precoated on the aperture (diameter = 200 μm) of the Delrin® cup, followed by removing the solvent with nitrogen gas. Both the cup (reference electrode) and chamber (input electrode) on the two sides of the aperture were filled with 1.0 mL of KCl or NaCl (1.0 M). Ag-AgCl electrodes were applied directly to the two solutions. Planar lipid bilayer was formed by painting 0.3 μL of the lipid solution around the pretreated aperture and judged by the capacitance (80-120 pF). The solution of channels in DMSO (0.5 μL, 0.05 mM) was added into the cup and stirred for 3 minutes. The currents were obtained by a Warner BC-535 bilayer clamp amplifier and collected using the ML846 data acquisition system. All data was filtered at 1 KHz with 8-pole Bessel filter.

For the single-channel conductance measurement of **M1**, two chambers at both sides of the bilayer were charged with KCl (1 M, 1 mL). The solution of **M1** in DMSO was added into the trans compartment and the solution was stirred for 3 minutes.

For the measurement of the transport selectivity of K^+ over Na^+ for **M1** and **M2**, the trans chamber was charged with NaCl (1 M, 1 mL), and the *cis* one was charged with KCl (1 M, 1 mL). The solution of **M1** or **M2** (0.05 mM, 0.5 μL) in DMSO was added into the cup and stirred for 3 minutes.

For the measurement of the transport selectivity of K^+ over Na^+ at high concentrations for **M1**, the trans chamber was charged with NaCl (2 M, 1 mL), and the cis one was charged with KCl (2 M, 1 mL). The solution of **M1** (0.05 mM, 0.5 μL) in DMSO was added into the cup and stirred for 3 minutes.

For the measurement of the transport selectivity of K^+ over Na^+ under conditions close to physiological ion concentrations for **M1**, the trans chamber was charged with NaCl (150 mM, 1 mL), and the cis one was charged with KCl (150 mM, 1 mL). The solution of **M1** (0.05 mM, 0.5 μL) in DMSO was added into the cup and stirred for 3 minutes.

13. References

(S1) Lang, C.; Deng, X.; Yang, F.; Yang, B.; Wang, W.; Qi, S.; Zhang, X.; Zhang, C.; Dong, Z.; Liu, J. Highly Selective Artificial Potassium Ion Channels Constructed from Pore-Containing Helical Oligomers. *Angew. Chem. Int. Ed.* **2017**, (41), 12668-12671.

(S2) Qi, S. W.; Zhang, C. Y.; Yu, H.; Zhang, J.; Yan, T. F.; Lin, Z.; Yang, B.; Dong, Z. Y. Foldamer-based Potassium Channels with High Ion Selectivity and Transport Activity. *J. Am. Chem. Soc.* **2021**, (9), 3284-3288.

(S3) Yao, C.; Xu, Z.; Tian, J.; Lin, Z.; Zhang, C.; Ge, Y.; Zhang, L.; Wang, S.; Dong, Z. Alkali-Cation-Selective Arylation Promoted by Ion Recognition of Foldamers. *Org. Lett.* **2025**, (1), 129-133.

(S4) Tetko, I. V. Computing Chemistry on the Web. *Drug Discov. Today* **2005**, (22), 1497-1500.