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Chiral hydrogen-bonded frameworks featuring proline motifs as heterogeneous catalysts for the enantioselective synthesis of warfarin

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All solvents were purchased from commercial suppliers (Acros or Sigma-Aldrich). All other chemicals were purchased from Sigma-Aldrich Chemistry GmbH and used without further purification. Unless stated otherwise, column chromatography was performed with silica gel 60M from Macherey-Nagel. Proton and carbon nuclear magnetic resonance spectra were recorded on a Bruker Avance 400 NMR spectrometer (operating at 400 and 101 MHz, respectively, for ^{1}H and ^{13}C nuclei). Chemical shifts for ^{1}H and ^{13}C nuclei are reported in ppm relative to the residual solvent peak ($CDCl_3$: δ=7.26 ppm for ^{1}H NMR, δ=77.2 for ^{13}C NMR; DMSO-d_6: δ=2.50 ppm for ^{1}H-NMR, δ=39.5 for ^{13}C-NMR; D_2O: δ=4.79 ppm for ^{1}H-NMR). NMR data are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant, integration, and nucleus. No signals were present outside of the ppm range shown. Elemental analyses were carried out in the Laboratory of Microanalysis of A.N. Nesmeyanov Institute of Organoelement Compounds of the Russian Academy of Sciences. ATR FTIR spectra were recorded on a Vertex-70v Fourier spectrometer (Bruker) using an ATR accessory Pike with a diamond unit. HPLC analysis of warfarin was made on Prominence-i LC-2030C 3D Plus with Chiralcel OD-H column (250x4.6 mm, 5 μm), ethanol-heptane 1:1 mix as eluent used. (*S*)-Prolineamide of 4-methylaniline **MPA** [S1] and tetrakis(4-carboxyphenyl)silane **4** [S2] was prepared according to the known methodology.

Tetra-tert-butyl 2,2',2'',2'''-(((methanetetrayltetrakis(benzene-4,1-diyl))-tetrakis(azanediyl))tetrakis(carbonyl))(2S,2'S,2''S,2'''S)-tetrakis(pyrrolidine-1-carboxylate) (**Boc-TPA**). To a solution of 2.522 g (0.0117 mol) of Boc-(L)-proline in 25 mL of absolute CH_2Cl_2 was added a suspension of 2.522 g (0.0122 mol) of DCC in 25 mL of absolute CH_2Cl_2 under stirring. The mixture was cooled to 0°C, after which 1.115 g (0.0029 mol) of tetrakis(4-aminophenyl)methane was added under stirring. The mixture was left under stirring for 30 minutes at 0°C, after which it was warmed to room temperature and stirred for 12 hours. The precipitate was filtered off. The organic layer was washed three times successively with saturated aqueous $NaHCO_3$ solution (3x45 mL) and 0.1 M HCl (3x45 mL). The organic fraction was dried over Na_2SO_4. The precipitate was filtered (paper filter) and the filtrate was evaporated in vacuo. Yield 70%. Yellow solid. mp 201-205 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.10-9.94 (m, 4H), 7.59-7.42 (m, 8H), 7.11-6.93 (m, 8H), 4.30-4.11 (m, 4H), 3.47-3.24 (m, 8H), 2.25-2.04 (m, 4H), 1.94-1.68 (m, 12H), 1.39-1.28 (m, 36H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 171.9, 153.6, 141.8, 137.3, 131.1, 118.9, 78.9, 63.1, 60.7, 47.0, 31.5, 28.4, 23.7. FTIR (ν/cm^{-1}): 2974, 2930, 1693, 1666, 1603, 1511, 1390, 1366, 1159, 1123, 812. Elemental analysis calculated for $C_{65}H_{84}N_8O_{12}$: C, 66.76; H, 7.24; N, 9.58. Found: C, 66.84; H, 7.23; N, 9.67. $[\alpha]_D^{20}$= -96° (*c* = 0.5, $CHCl_3$).

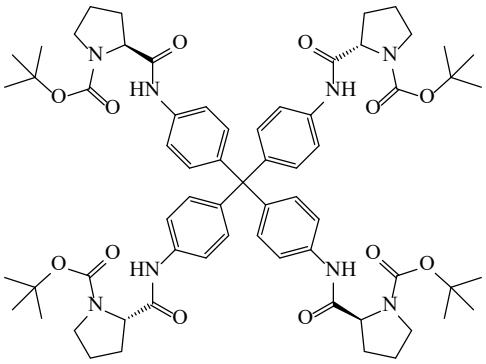

Figure S1. Structure of **Boc-TPA**

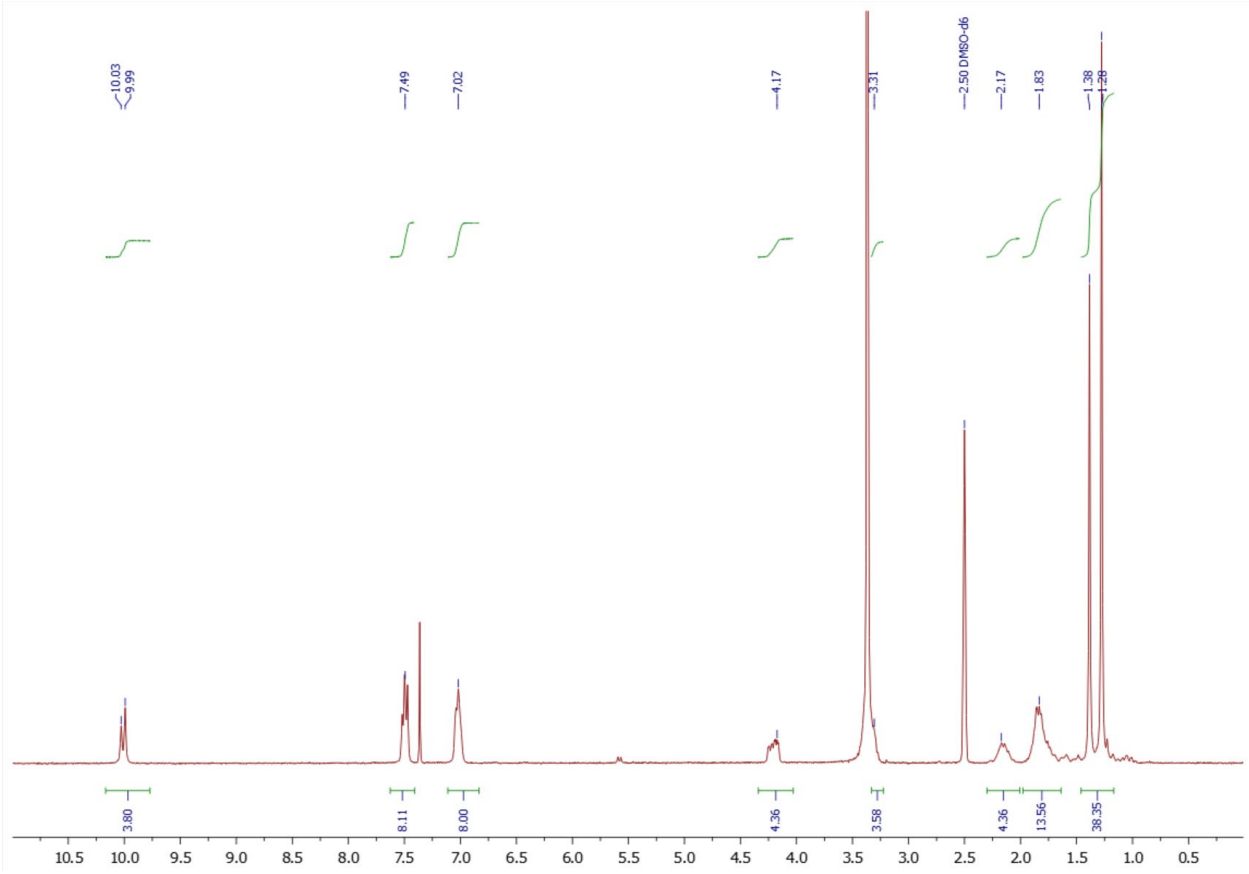

Figure S2. ^{1}H-NMR spectrum of **Boc-TPA**

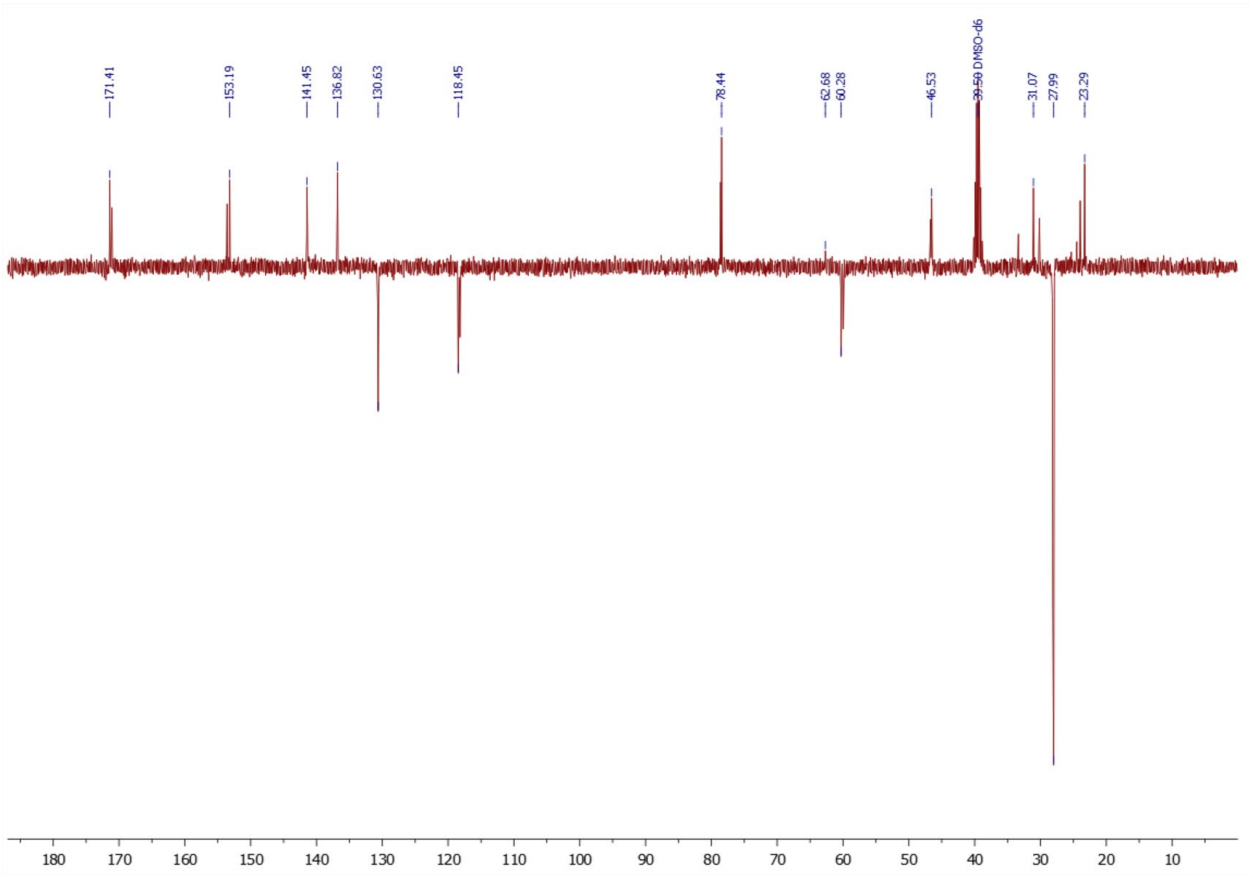

Figure S3. ^{13}C-NMR spectrum (J-mode) of **Boc-TPA**

(2S,2'S,2''S,2'''S)-(((Methanetetrayltetrakis(benzene-4,1-diyl))tetrakis(azanediyl)) tetrakis(carbonyl))tetrakis(1l5-pyrrolidine-2,1-diyl) tetrakis(2,2,2-trifluoroacetate) (**TPA·4TFA**). To a solution of 2.004 g (0.0017 mol) **Boc-TPA** in 14.5 mL CH_2Cl_2 was added 14.5 mL trifluoroacetic acid. The reaction mixture was left under stirring for 3 days at room temperature. The resulting solution was evaporated in vacuo. Yield 99%. Brown solid. ^{1}H-NMR (400 MHz, D_2O) δ: 7.36-6.78 (m, 16H), 4.41-4.20 (m, 4H), 3.41-3.16 (m, 8H), 2.45-2.17 (m, 4H), 2.01-1.72 (m, 12H). ^{13}C-NMR (101 MHz, D_2O) δ: 167.5, 163.2-152.5 (m), 143.2, 134.4, 131.1, 120.5, 116.19 (q, J = 291.6 Hz), 63.1, 60.1, 46.5, 29.9, 23.7. FTIR (ν/cm^{-1}): 3253, 2937, 2868, 1663, 1604, 1506, 1405, 1315, 1186, 1103, 816. Elemental analysis calculated for $C_{35}H_{56}F_{12}N_8O_{18}$: C, 51.96; H, 4.61; F, 18.61; N, 9.15. Found: C, 51.57; H, 4.55; F, 18.87; N, 9.04. $[\alpha]_D^{20}$= -66° (c = 0.5, H_2O).

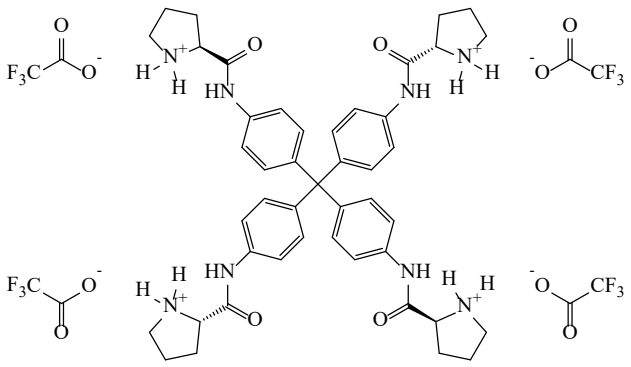

Figure S4. Structure of **TPA·4TFA**

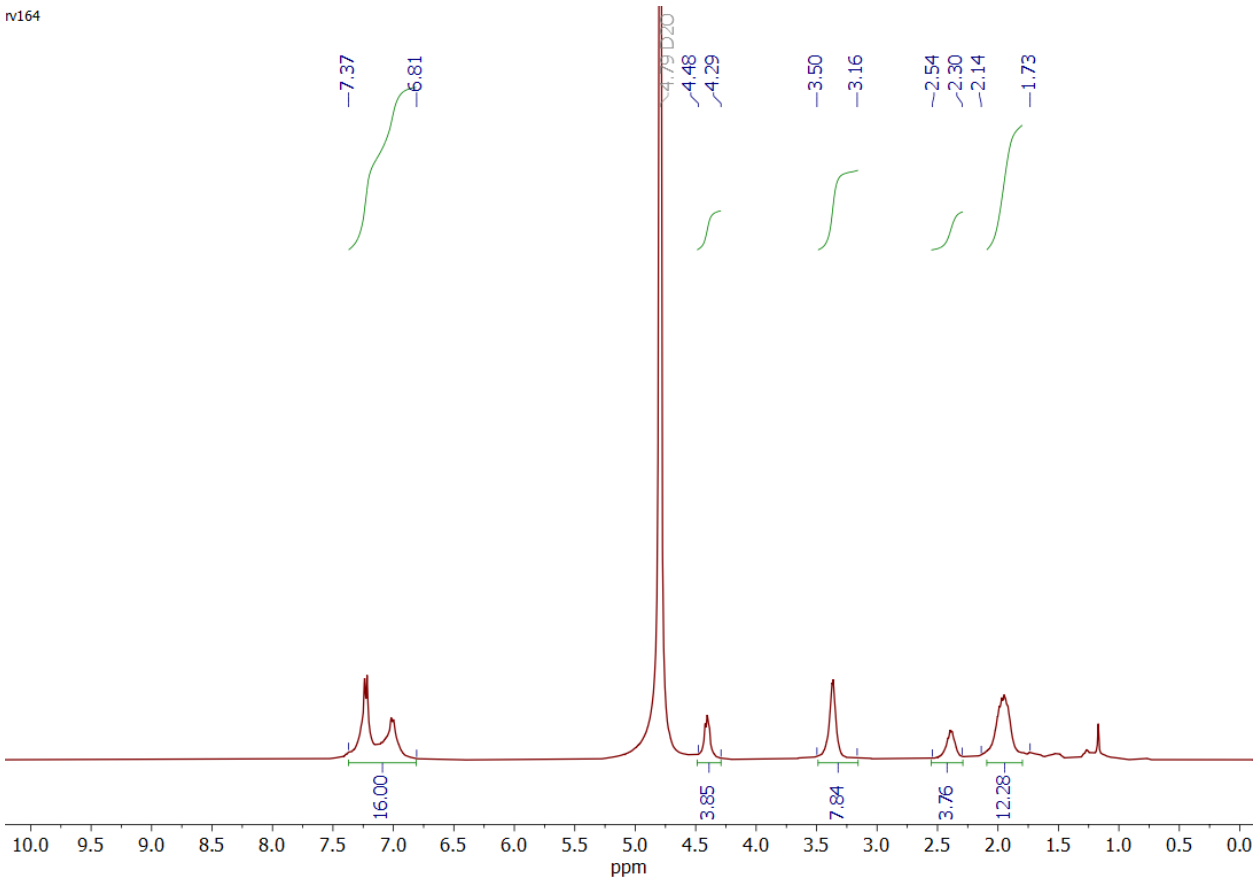

Figure S5. ^{1}H-NMR spectrum of **TPA·4TFA**

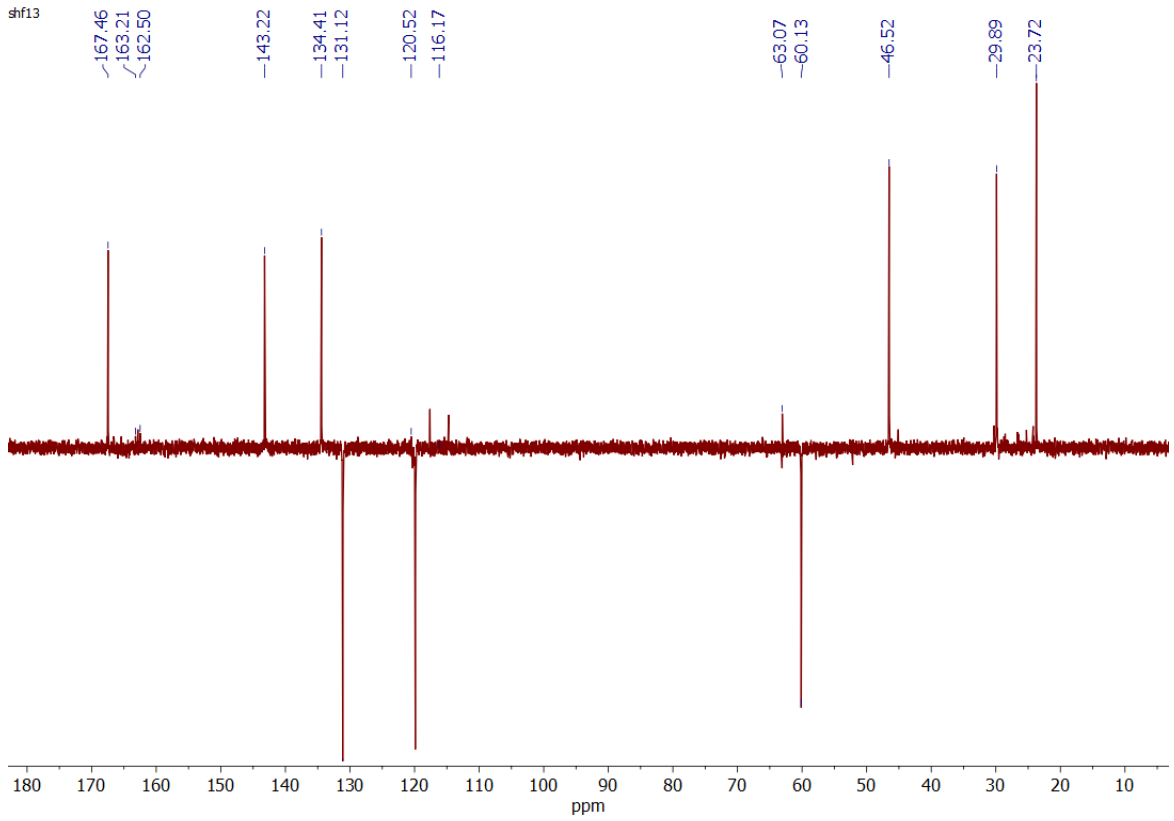

Figure S6. ^{13}C-NMR spectrum (J-mode) of **TPA·4TFA**

*(2S,2'S,2''S,2'''S)-N,N',N'',N'''-(Methanetetrayltetrakis(benzene-4,1-diyl))tetrakis (pyrrolidine-2-carboxamide) (**TPA**)*. To a solution of 0.637 g (0.742 mmol) of **TPA·4TFA** in 10 mL water was added 15 mL of 1M NaOH solution, and precipitation was observed. The resulting mixture is extracted twice in 40 mL ethyl acetate, the organic layer is dried with anhydrous Na_2SO_4, filtered and evaporated at a rotary evaporator. Yield 86%. Off-white solid, mp 285-288 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 9.95 (s, 4H), 7.55 (d, J = 8.5 Hz, 8H), 7.02 (d, J = 8.5 Hz, 8H), 3.68-3.64 (m, 4H), 3.44-3.36 (m, 4H), 2.88-2.85 (m, 8H), 2.05-1.98 (m, 4H), 2.09-2.02 (m, 4H), 1.66-1.61 (m, 8H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 174.2, 125.6, 124.0, 61.1, 47.4, 30.9, 26.3. FTIR (ν/cm^{-1}): 3221, 2928, 2852, 1698, 1509, 1407, 1375. $C_{45}H_{52}N_8O_4 \times 2CO_2 \times 3H_2O$: C, 61.96; H, 6.42; N, 12.30; Found: C, 62.18; H, 6.09; N, 12.19. $[\alpha]_D^{20}$= -46° (c = 0.5, DMSO).

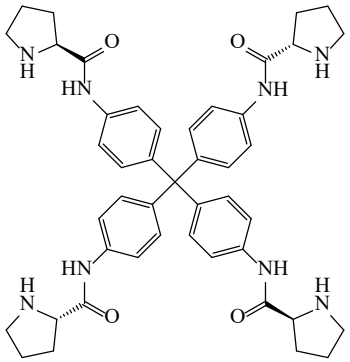

Figure S7. Structure of **TPA**

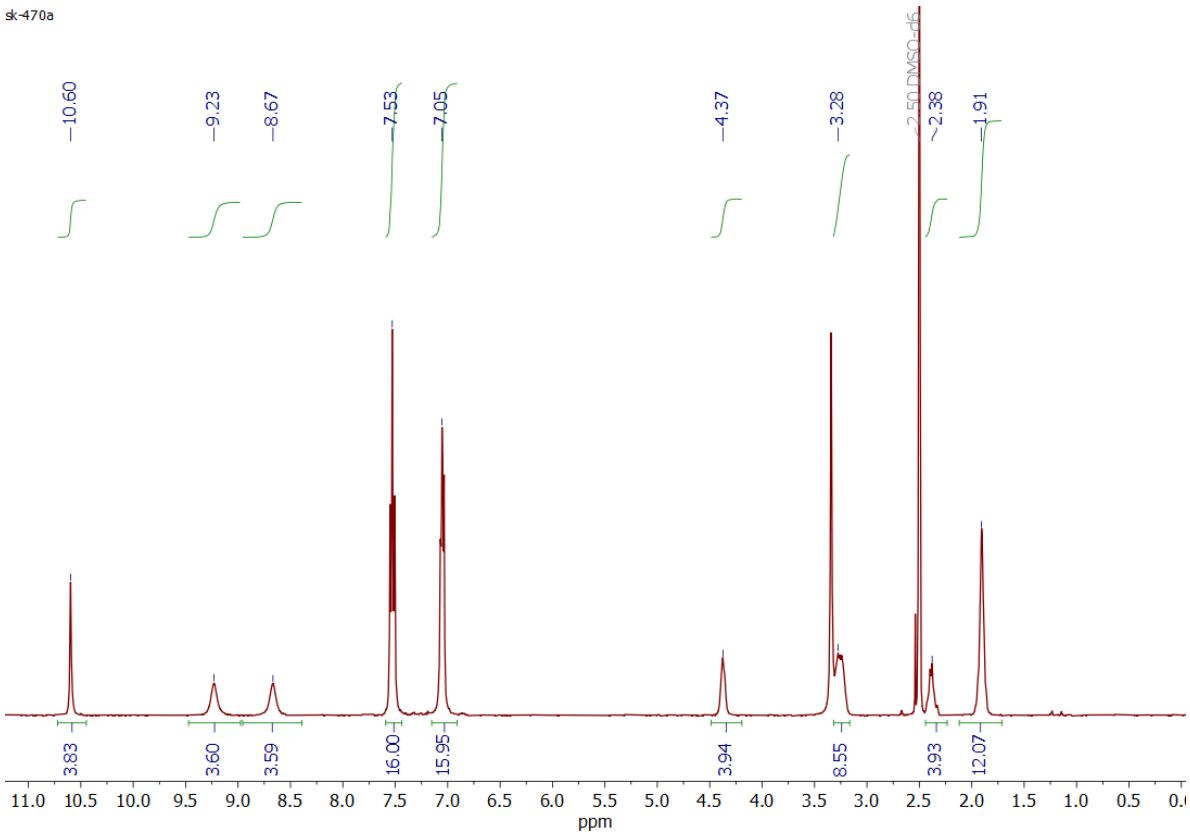

Figure S8. ^{1}H-NMR spectrum of **TPA**

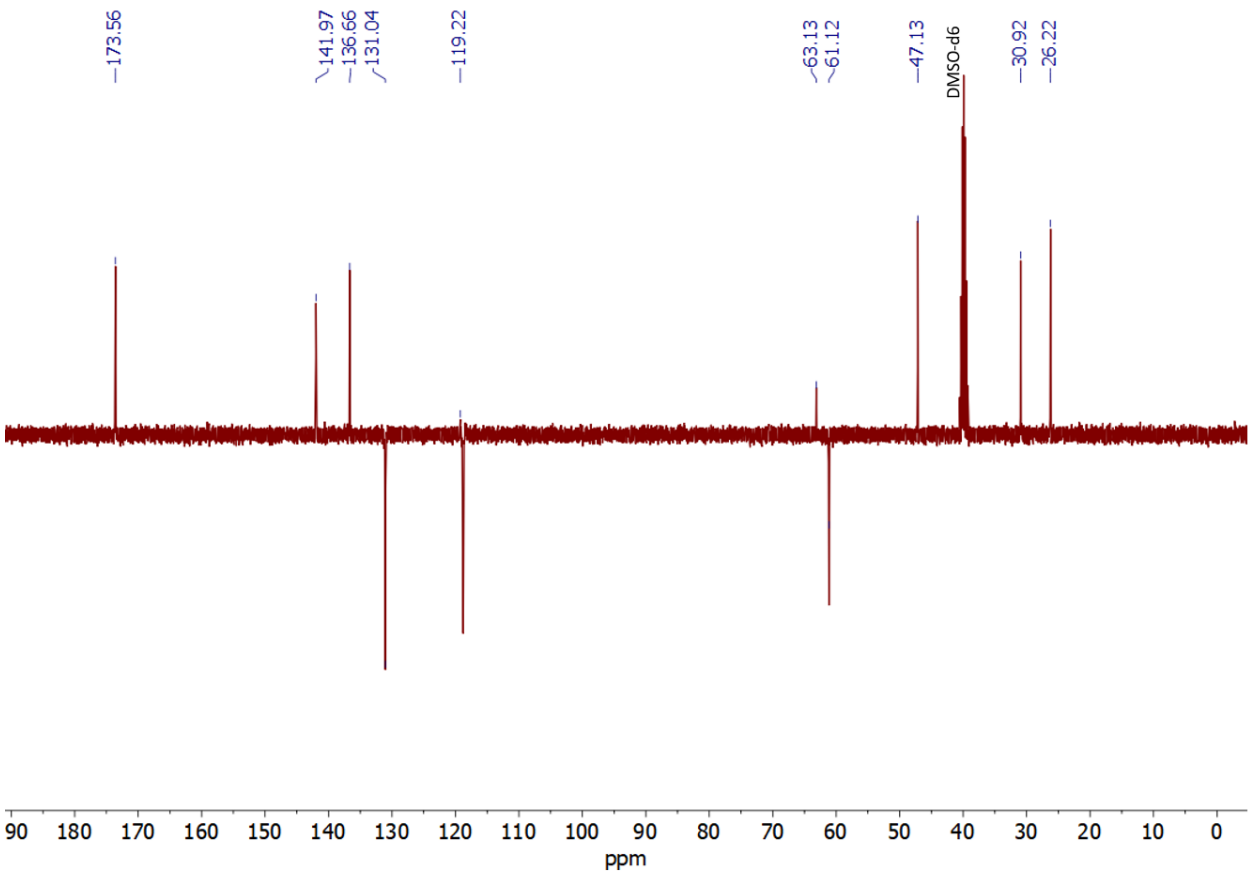

Figure S9. ^{13}C-NMR spectrum (J-mode) of **TPA**

Di-tert-butyl 2,2'-((1,2-phenylenebis(azanediyl))bis(carbonyl)) bis(pyrrolidine-1-carboxylate) (**Boc-DPA**). To a solution of 1.99 g (9.25 mmol) of Boc-proline in 20 mL of absolute CH_2Cl_2 was added a suspension of 1.99 g (9.65 mmol) of DCC in 20 mL of absolute CH_2Cl_2 under stirring. The mixture was cooled to 0°C, after which 0.5 g (4.62 mmol) o phenylenediamine was added under stirring. The mixture was left under stirring for 30 minutes at 0°C, after which it was warmed to room temperature and stirred for 12 hours. The precipitate was filtered off. The organic layer was washed three times successively with saturated aqueous $NaHCO_3$ solution (3x40 mL) and 0.1 M HCl (3x40 mL). The organic fraction was dried over Na_2SO_4. The precipitate was filtered (paper filter) and the filtrate was evaporated in vacuo. Yield 55%. Yellow solid. mp 155-158 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.02 – 9.62 (m, 2H), 7.14 – 7.97 (m, 4H), 4.31 – 4.44 (m, 2H), 3.42 – 3.7 (m, 4H), 1.82 – 2.3 (m, 8H), 1.45 – 1.52 (m, 18H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 171.2, 156.6, 128.8, 126.5, 124.3, 80.3, 62.1, 46.9, 31.5, 28.4, 23.9. FTIR (ν/cm^{-1}): 3239, 2975, 2929, 2873, 1696, 1664, 1597, 1541, 1477, 1450, 1396, 1363, 1293, 1257, 1160, 1120, 1084, 1037, 983, 919, 769, 738, 608, 543. Elemental analysis calculated for $C_{26}H_{38}N_4O_6$: C, 62.13; H, 7.62; N, 11.15. Found: C, 62.03; H, 7.68; N, 11.02. $[\alpha]_D^{20}$= -149° (c = 1, $CHCl_3$).

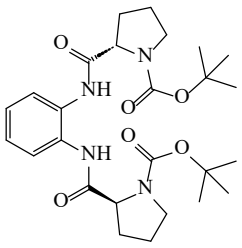

Figure S10. Structure of **Boc-DPA**

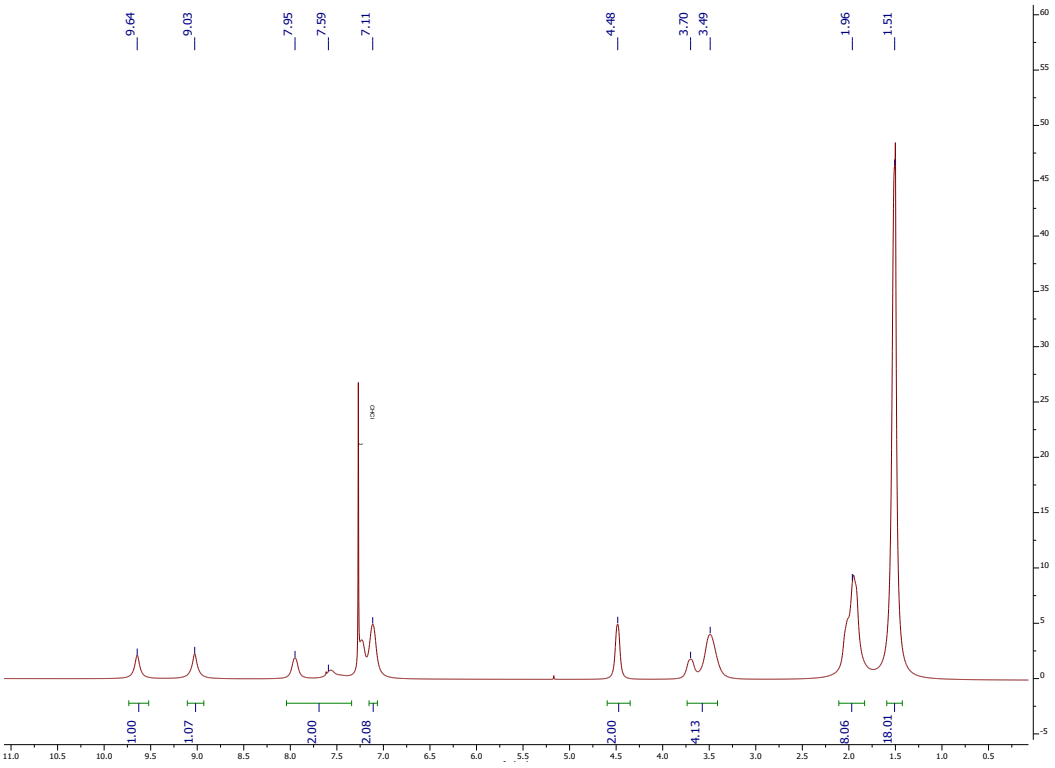

Figure S11. ^{1}H-NMR spectrum of **Boc-DPA**

2,2'-((1,2-Phenylenebis(azanediyl))bis(carbonyl))bis(pyrrolidin-1-ium) di-trifluoro-acetate (**DPA·2TFA**). To a solution of 0.518 g (1.7 mmol) of **Boc-DPA** in 10 mL CH2Cl2 was added 10 mL trifluoroacetic acid. The reaction mixture was left under stirring for 3 days at room temperature. The resulting solution was evaporated in vacuo. Oily brown solid. Yield 72%. ^{1}H-NMR (400 MHz, D_2O) δ: 7.36 – 7.14 (m, 4H), 4.44 – 4.32 (m, 2H), 3.38 – 3.14 (m, 4H), 2.46 – 2.31 (m, 2H), 2.09 – 1.86 (m, 6H). ^{13}C-NMR (101 MHz, D_2O) δ: 168.8, 129.9, 128.1, 126.8, 59.9, 46.4, 29.7, 23.7. Elemental analysis calculated for $C_{20}H_{24}F_6N_4O_6$: C, 45.29; H, 4.56; F, 21.49; N, 10.56. Found: C, 45.21; H, 4.51; F, 21.58; N, 10.10. $[\alpha]_D^{20}$= -5° (*c* = 0.5, H_2O).

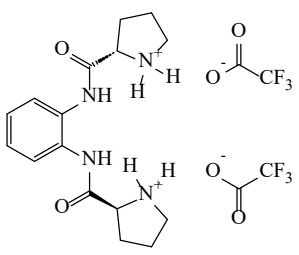

Figure S12. Structure of **DPA·2TFA**

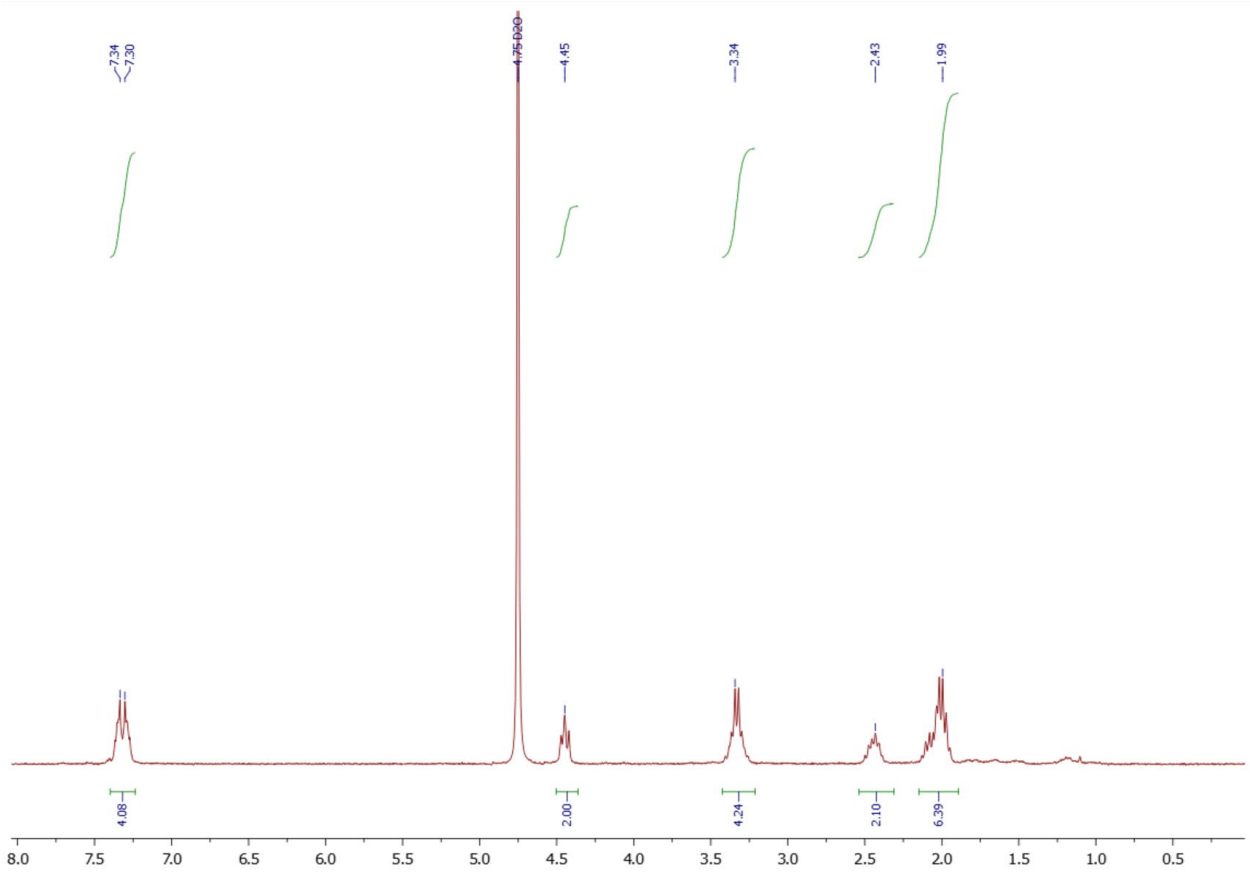

Figure S13. ^{1}H-NMR spectrum of **DPA·2TFA**

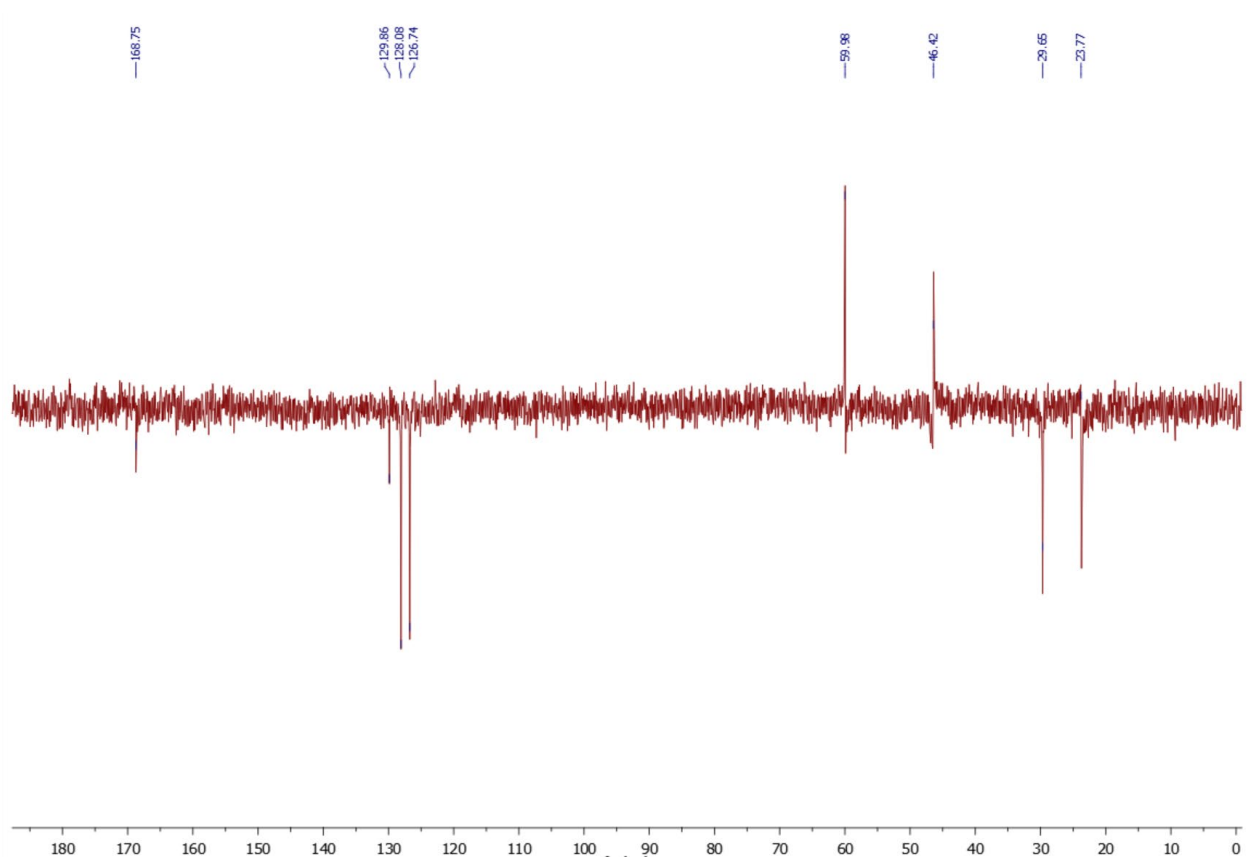

Figure S14. ^{13}C-NMR spectrum (J-mode) of **DPA·2TFA**

(2S,2'S)-N,N'-(1,2-Phenylene)bis(pyrrolidine-2-carboxamide) (**DPA**). To a solution of 0.637 g (0.742 mmol) of **DPA·2TFA** in 10 mL water was added 15 mL of 1M NaOH solution and precipitation was observed. The resulting mixture is extracted twice in 40 mL ethyl acetate, the organic layer is dried with anhydrous Na_2SO_4, filtered and evaporated at a rotary evaporator. Yield 86%. mp 140-142 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.71 (s, 2H), 7.67 – 7.70 (m, 2H), 7.14 – 7.17 (m, 2H), 3.87 – 3.89 (m, 2H), 2.97 – 3.07 (m, 4H), 2.12 – 2.24 (s, 2H), 2.01 – 2.24 (m, 4H), 1.72 – 1.80 (m, 4H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 174.2, 129.7, 125.6, 124.0, 61.1, 47.4, 30.9, 26.3. FTIR (ν/cm^{-1}): 3228, 2928, 1670, 1596, 1516, 1448, 1293, 1242, 1199, 1173, 1126, 1044, 829, 798, 753, 719, 650. Elemental analysis calculated for $C_{16}H_{22}N_4O_2$: C, 63.55; H, 7.33; N, 18.53. Found: C, 63.46; H, 7.34; N, 18.47. $[\alpha]_D^{20}$= -3° (c = 0.5, $CHCl_3$).

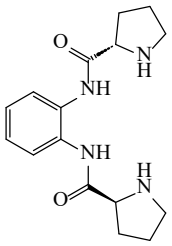

Figure S15. Structure of **DPA**

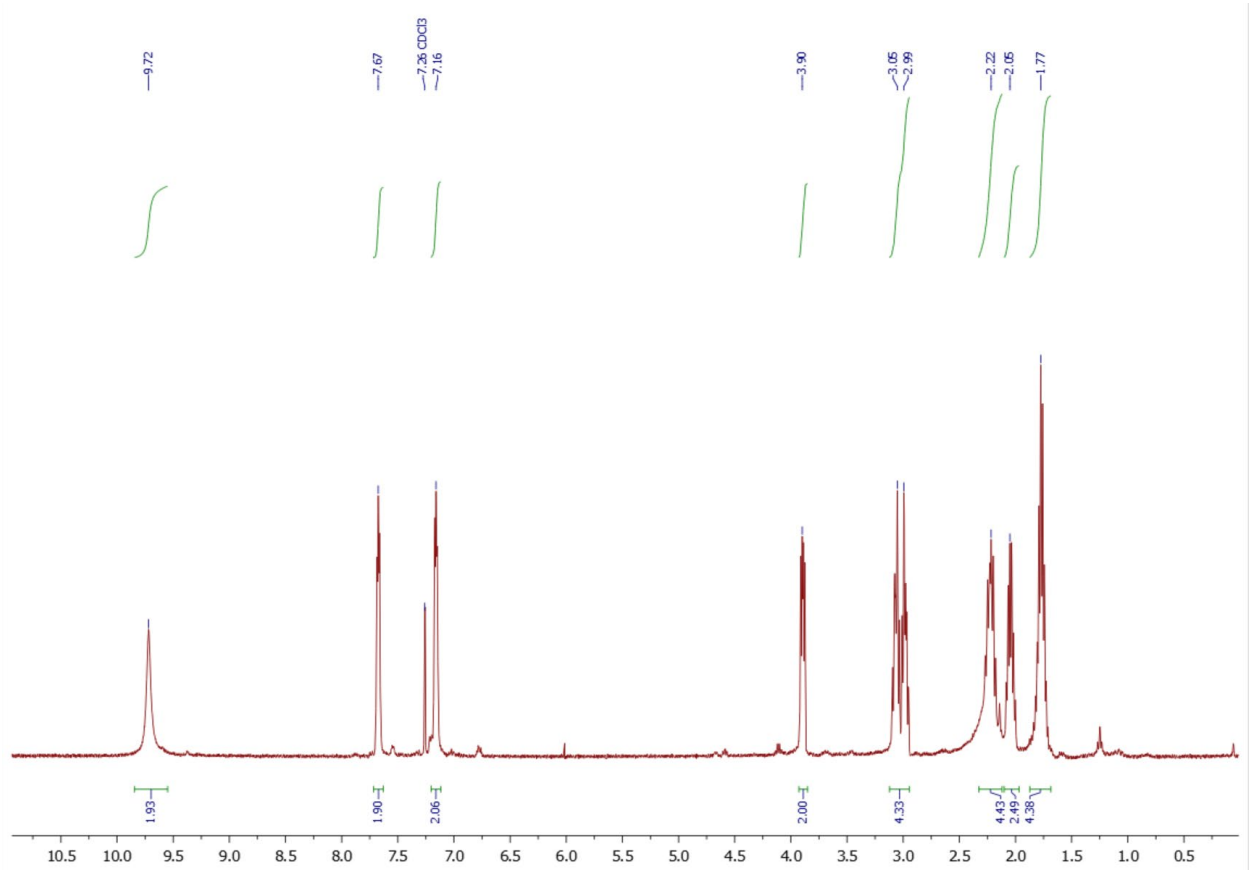

Figure S16. ^{1}H-NMR spectrum of **DPA**

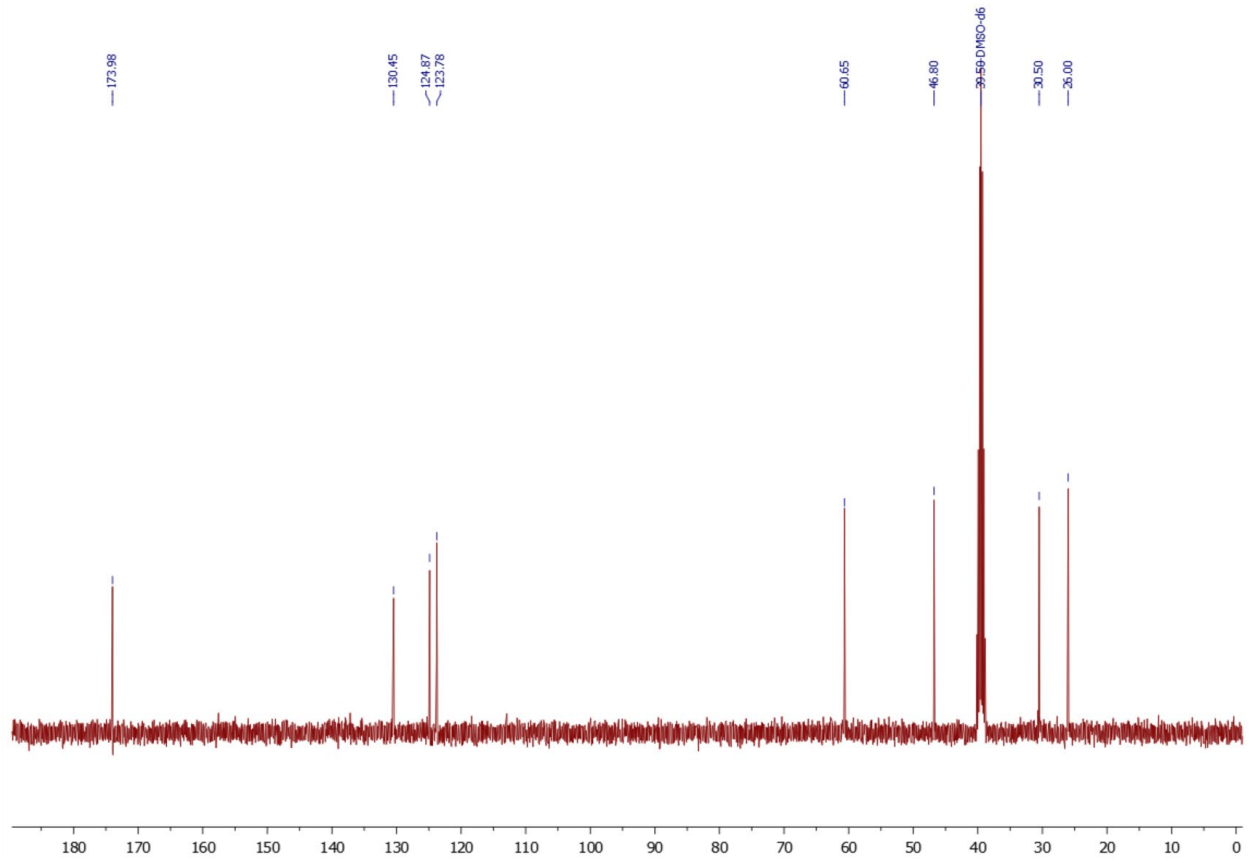

Figure S17. ^{13}C-NMR spectrum of **DPA**

(2'S,2''S,2'''S)-(Methanetetrayltetrakis(benzenesulfonyl))tetra-L-proline (L-**5**). To a suspension of 5.653 g (0.009 mol) of **2** in 15 mL of absolute toluene was added an aliquot of 9.8 mL (0.135 mol) of $SOCl_2$ under stirring. The reaction mixture was stirred for 24 hours at room temperature followed by removal of the solvent by evaporation in vacuo. A suspension of 3.177 g (0.079 mol) NaOH was dissolved in 50 mL H2O with the addition of 4.572 g (0.040 mol) (L)-proline and stirring for 15 minutes at room temperature. The resulting solution was added to a suspension of the solid obtained earlier in 80 mL of methylene chloride. The resulting system was stirred for 2 days at room temperature without mixing of layers. Then 50 mL of a solution (1 M) of trifluoroacetic acid in H_2O was added to the aqueous layer. The resulting precipitate was filtered, washed with 80 mL H_2O and dried in vacuo and recrystallized in isopropyl alcohol. Yellow-ish solid. Yield 8%. mp 160-165 °C with decomp. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 13.04 – 12.47 (br. s), 7.83 (d, J = 8.5 Hz, 8H), 7.40 (d, J = 8.5 Hz, 8H), 4.15 – 4.07 (m, 4H), 3.24 – 3.15 (m, 4H), 2.35 – 2.25 (m, 3H), 1.97 – 1.75 (m, 13H), 1.64 – 1.51 (m, 4H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 173.5, 149.6, 136.4, 131.7, 127.7, 62.0, 60.9, 48.9, 30.9, 24.7. FTIR (ν/cm^{-1}): 3499, 2957, 2875, 1723, 1591, 1403, 1334, 1196, 1151, 1091, 1008, 882, 737, 703, 605, 567. Elemental analysis calculated for $C_{45}H_{48}N_4O_{16}S_4$: C, 52.52; H, 4.70; N, 5.44; S, 12.46. Found: C, 52.13; H, 4.99; N, 5.21; S, 12.20. $[\alpha]_D^{20}$= -46° (*c* = 1, acetone).

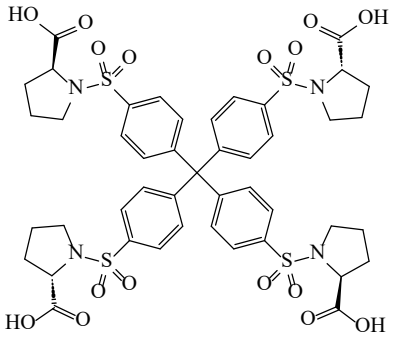

Figure S18. Structure of L-**5**

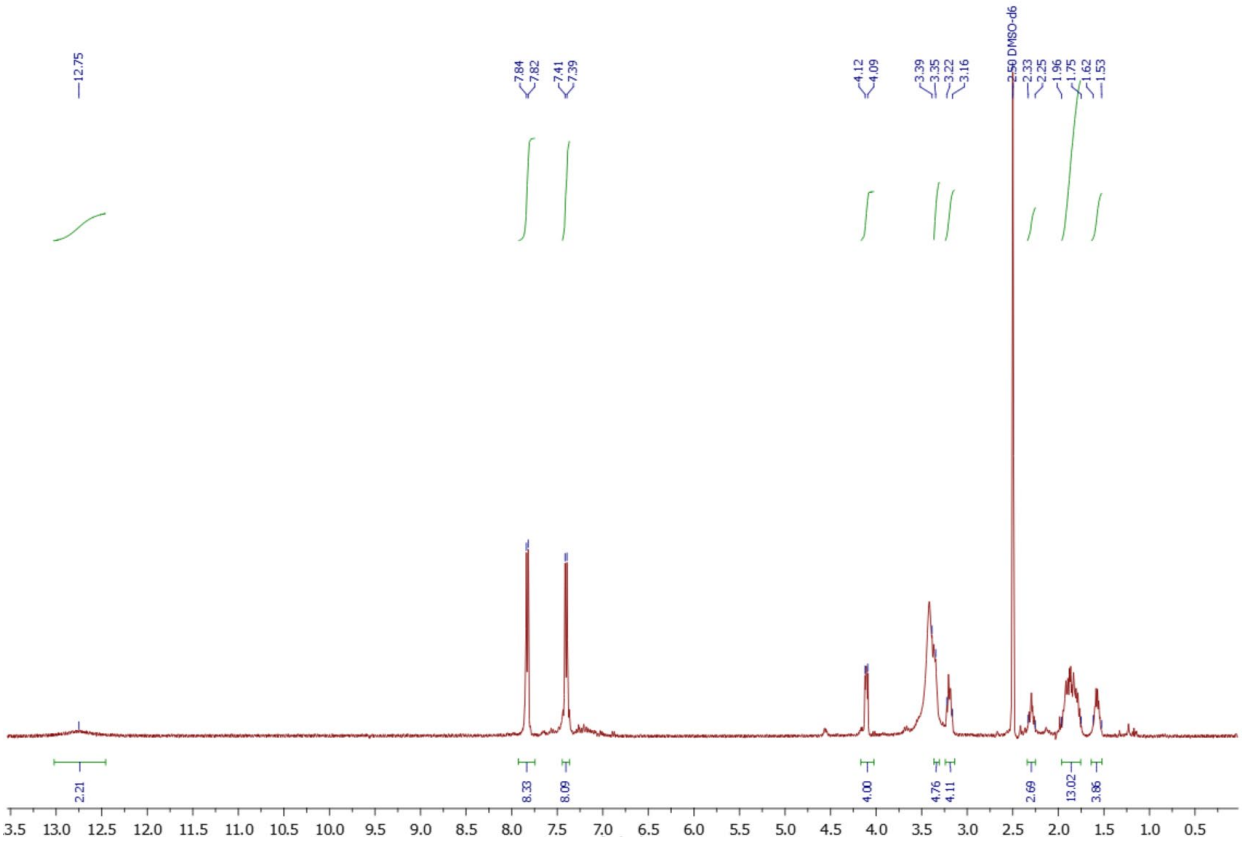

Figure S19. ^{1}H-NMR spectrum of L-**5**

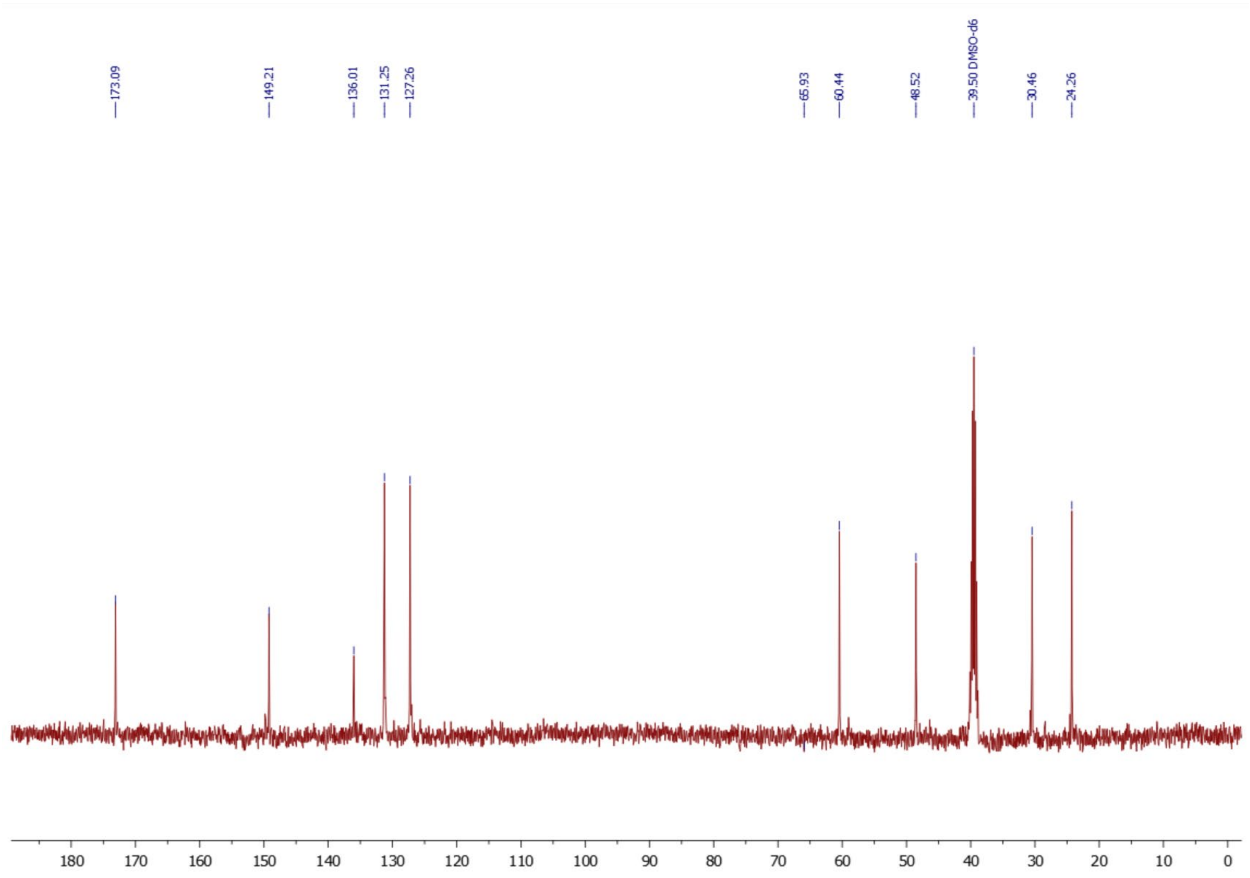

Figure S20. ^{13}C-NMR spectrum of L-**5**

Preparation of hydrogen-bonded organic frameworks ***TPA·(1-5)*** *(general procedure)*. Aqueous solution of 1 eq of trifluoroacetate of TPA was mixed with 2 eq sodium salt of bidentant or 1 eq sodium salt of tetradentant sulfonic or carboxylic acid with vigorous stirring. Mix stirred for 30 minutes and precipitate filtered, rinsed with water 3 times, and dried in vacuo.

(2S,2'S,2''S,2'''S)-2,2',2'',2'''-(((Methanetetrayltetrakis(benzene-4,1-diyl))tetrakis(azanediyl))tetrakis(carbonyl))tetrakis(pyrrolidin-1-ium) 4,4',4'',4'''-methanetetrayltetrabenzenesulfonate (**TPA·1**). Yield 89%. Brown-ish solid. mp >300 °C with decomp. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 4H), 9.25 (br.s, 4H), 8.76 (br.s, 4H), 7.64-7.44 (m, 16H), 7.14-6.94 (m, 16H), 4.45-4.30 (m, 4H), 3.30-3.11 (m, 8H), 2.46-2.30 (m, 4H), 2.00-1.80 (m, 12H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 167.2, 146.9, 145.7, 142.5, 136.4, 131.3, 130.4, 125.6, 119.2, 64.4, 63.3, 60.3, 46.3, 30.1, 23.8 ppm. FTIR (ν/cm^{-1}): 3412, 3063, 1684, 1606, 1541, 1506, 1402, 1177, 1129, 1035, 1007 cm^{-1}. Calculated for $C_{70}H_{72}N_8O_{16}S_4 \times 5H_2O$: C, 56.06; H, 5.51; N, 7.47; S, 8.55; Found: C, 56.45; H, 5.38; N, 7.41; S, 8.79. $[\alpha]_D^{20}$= -26° (*c* = 0.1, DMSO).

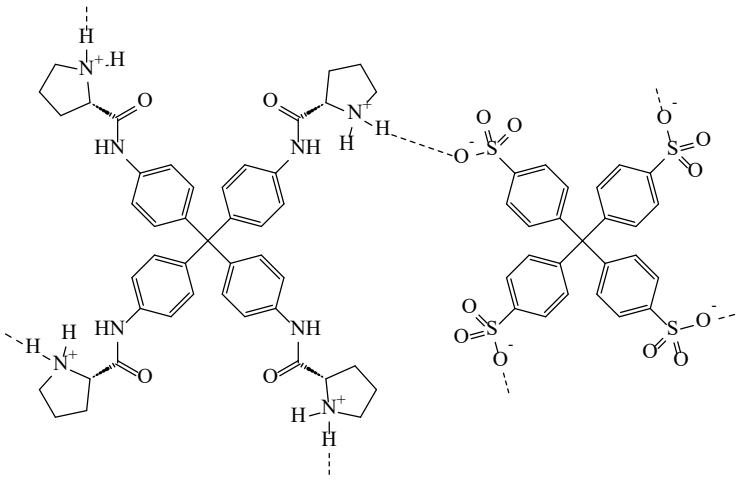

Figure S21. Structure of **TPA·1**

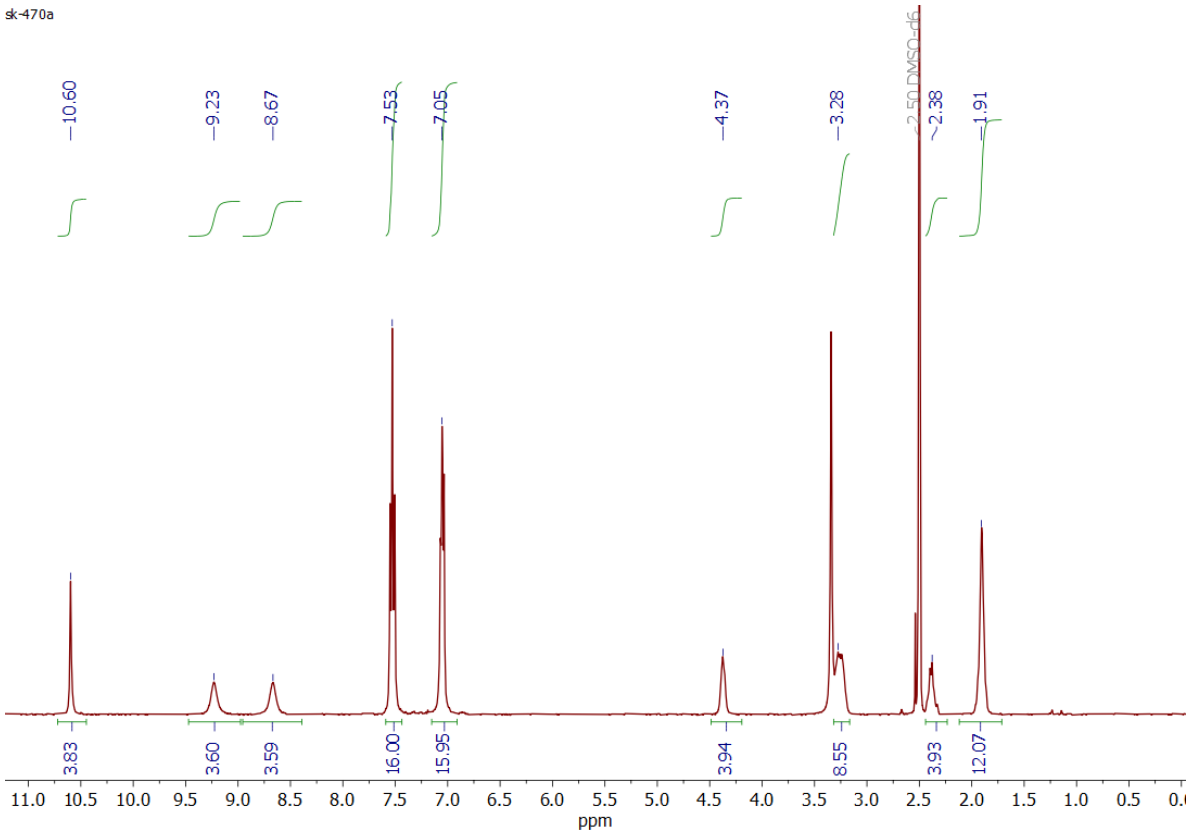

Figure S22. ^{1}H-NMR spectrum of **TPA·1**

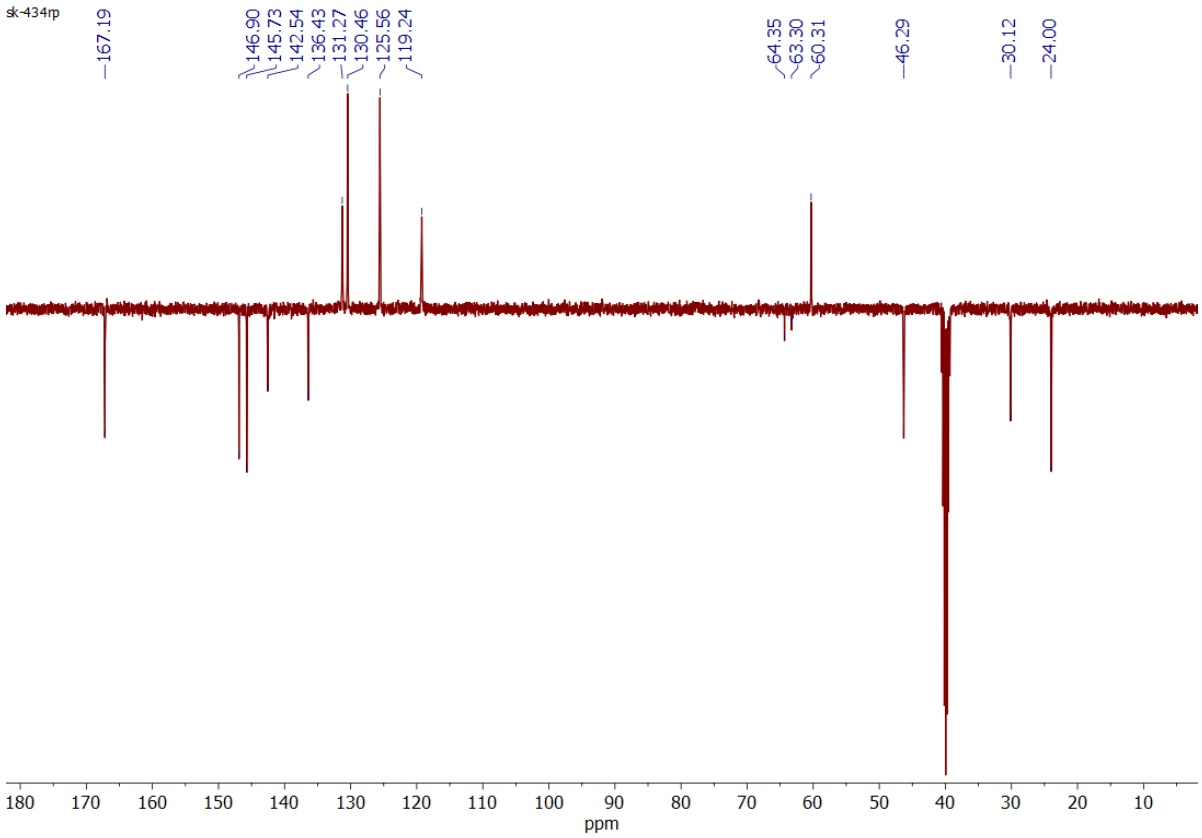

Figure S23. ^{13}C-NMR spectrum (J-mode) of **TPA·1**

(2S,2'S,2''S,2'''S)-2,2',2'',2'''-(((Methanetetrayltetrakis(benzene-4,1-diyl))tetrakis-(azanediyl))tetrakis(carbonyl))tetrakis(pyrrolidin-1-ium) di-naphthalene-2,6-disulfonate (**TPA·2**). Yield 87%. Brown-ish solid. mp >300 °C with decomp. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.63 (s, 4H), 9.27 (s, 4H), 8.71 (s, 4H), 8.18 (s, 4H), 7.92 (d, J = 8.3 Hz, 4H), 7.74 (d, J = 8.3 Hz, 4H), 7.55 (d, J = 8.1 Hz, 8H), 7.08 (d, J = 8.2 Hz, 8H), 4.39 (s, 4H), 3.30 (s, 8H), 2.41 (s, 4H), 1.93 (s, 12H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 167.0, 145.8, 142.3, 136.2, 132.2, 131.1, 128.5, 124.5, 124.2, 119.0, 64.6, 60.1, 46.0, 29.9, 23.8. FTIR (ν/cm^{-1}): 3225, 3186, 3048, 2772, 1684, 1603, 1541, 1506, 1162, 1084, 1023, 812, 658, 620. Elemental analysis calculated for $C_{65}H_{68}N_8O_{16}S_4 \times 4H_2O$: C, 55.07; H, 5.40; N, 7.90; S, 9.05. Found: C, 55.29; H, 5.58; N, 7.77; S, 8.91. $[\alpha]_D^{20}$= -30° (c = 0.1, DMSO).

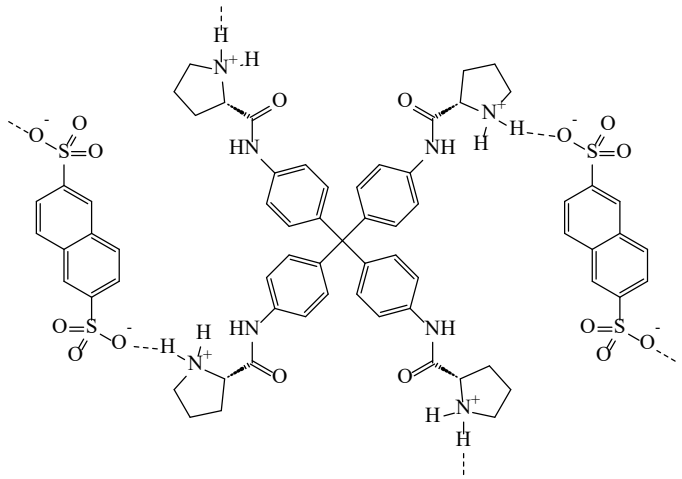

Figure S24. Structure of **TPA·2**

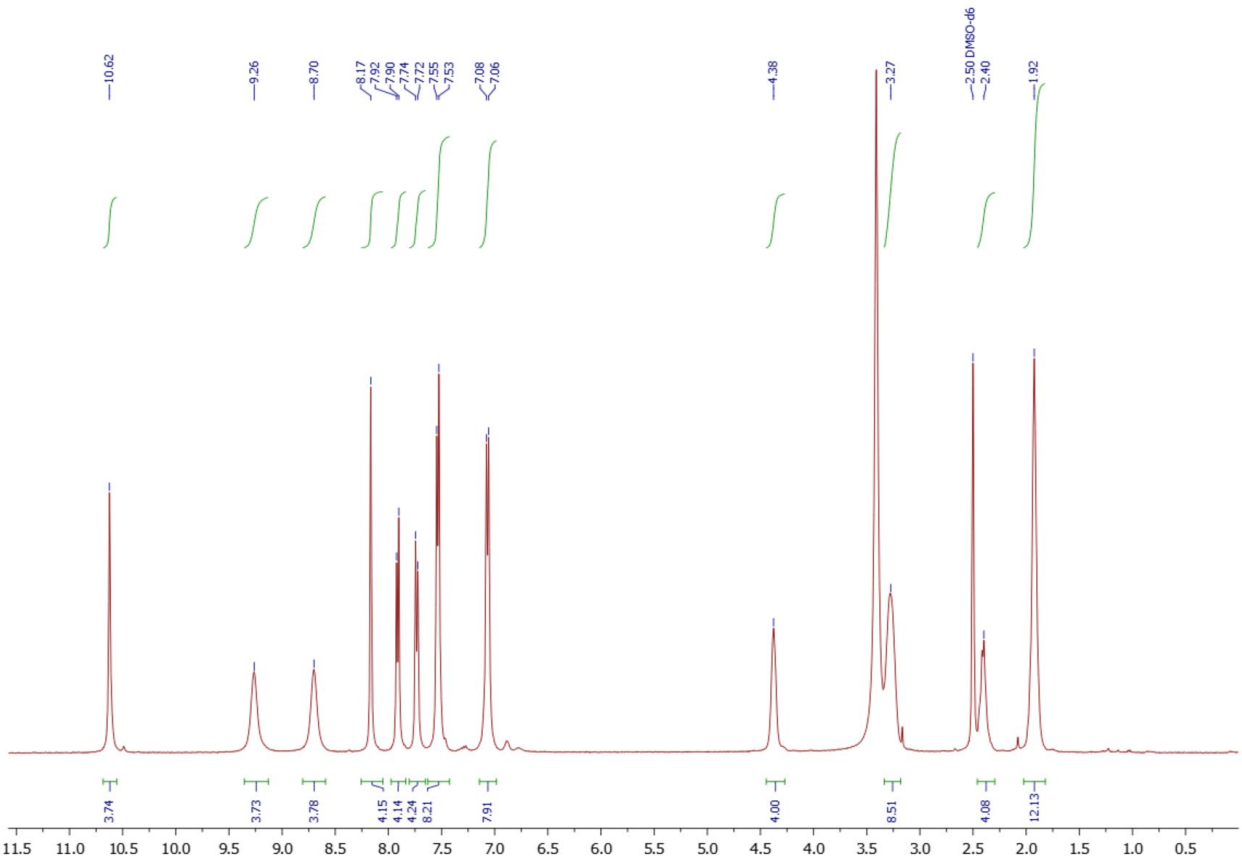

Figure S25. ^{1}H-NMR spectrum of **TPA·2**

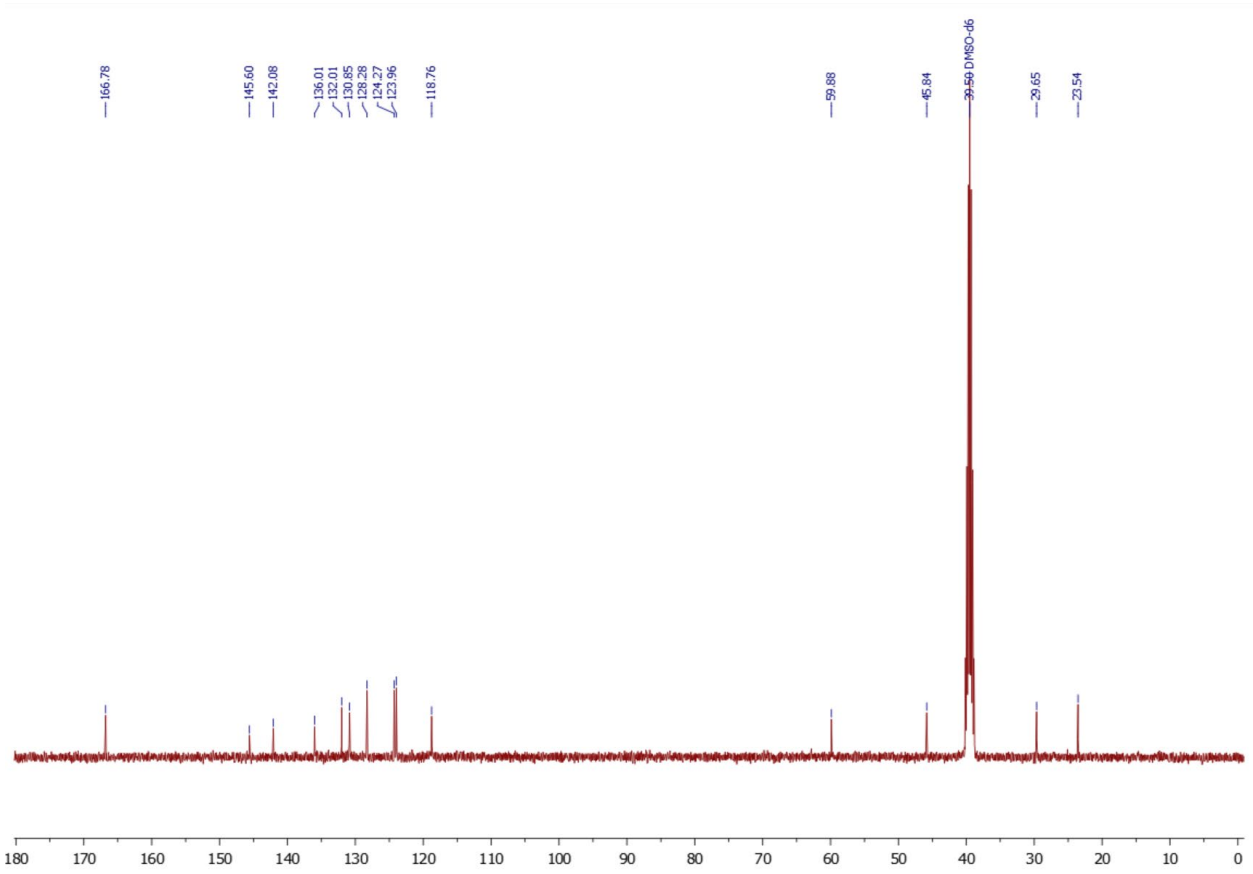

Figure S26. ^{13}C-NMR spectrum of **TPA·2**

(2S,2'S,2''S,2'''S)-2,2',2'',2'''-(((Methanetetrayltetrakis(benzene-4,1-diyl))tetrakis-(azanediyl))tetrakis(carbonyl))tetrakis(pyrrolidin-1-ium) di-[1,1'-biphenyl]-4,4'-dicarboxylate (**TPA·3**).Yield 74%. White solid. mp >300 °C with decomp. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.09 (s, 4H), 8.03 (d, J = 8.0 Hz, 8H), 7.82 (d, J = 8.0 Hz, 8H), 7.54 (d, J = 8.5 Hz, 8H), 7.02 (d, J = 8.6 Hz, 8H), 3.80 (t, J = 7.3 Hz, 8H), 2.94 (t, J = 6.7 Hz, 8H), 2.15 – 2.00 (m, 5H), 1.86 – 1.73 (m, 5H), 1.73 – 1.62 (m, 10H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 168.1, 142.1, 136.4, 130.9, 130.2, 127.1, 126.0, 122.5, 122.2, 118.8, 63.0, 60.0, 46.1, 30.2, 24.4. FTIR (ν/cm^{-1}): 2973, 1682, 1605, 1508, 1373, 1297, 1186, 817, 757. Elemental analysis calculated for $C_{73}H_{72}N_8O_{12} \times 4H_2O$: C, 66.15; H, 6.08; N, 8.45. Found: C, 66.55; H, 6.01; N, 8.21. $[\alpha]_D^{20}$= -41° (*c* = 0.1, DMSO).

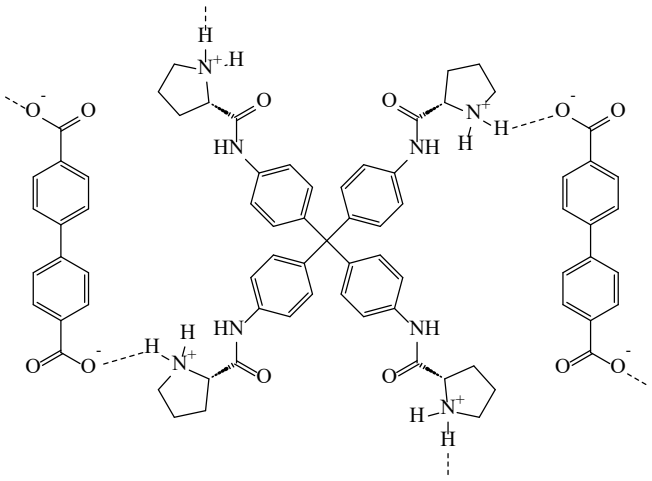

Figure S27. Structure of **TPA·3**

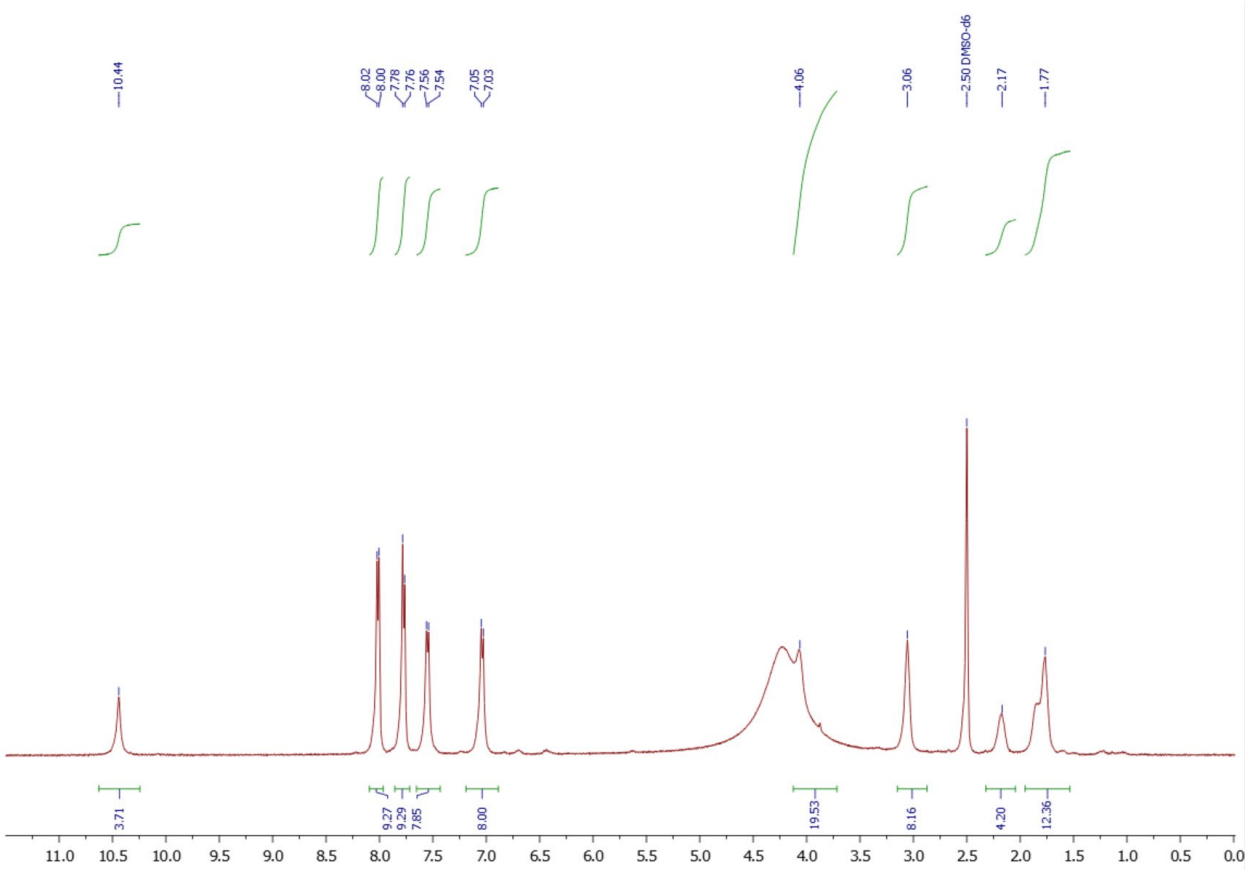

Figure S28. ^{1}H-NMR spectrum of **TPA·3**

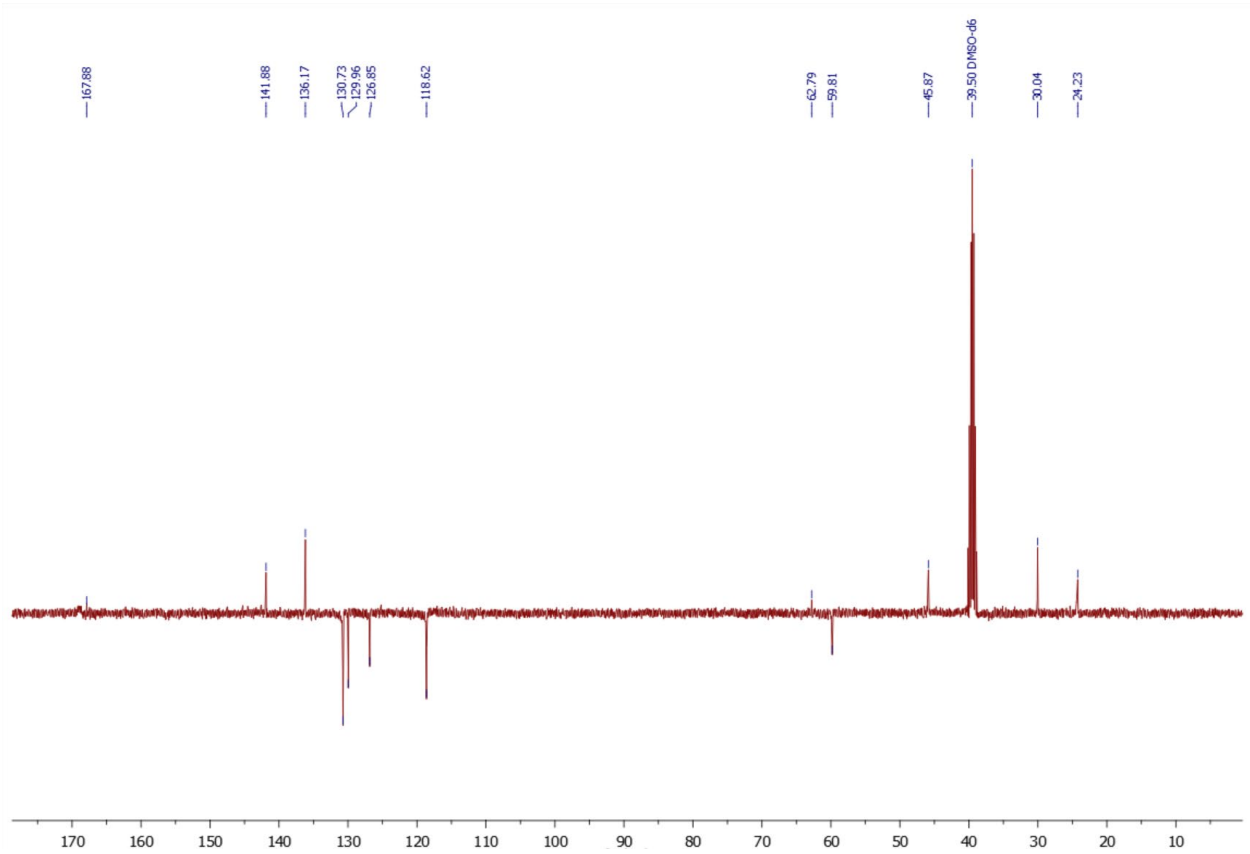

Figure S29. ^{13}C-NMR spectrum (J-mode) of **TPA·3**

(2S,2'S,2''S,2'''S)-2,2',2'',2'''-(((Methanetetrayltetrakis(benzene-4,1-diyl))tetrakis-(azanediyl))tetrakis(carbonyl))tetrakis(pyrrolidin-1-ium) 4,4',4'',4'''-silanetetrayltetrabenzoate (**TPA-4**). Yield 91%. White solid. mp >300 °C with decomp. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.40 (s, 4H), 7.96 (d, J = 7.6 Hz, 12H), 7.59 – 7.43 (m, 20H), 6.99 (d, J = 6.4 Hz, 8H), 4.12 – 3.82 (m, 4H), 3.08 – 2.94 (m, 8H), 2.21 – 2.04 (m, 4H), 1.88 – 1.64 (m, 12H). FTIR (ν/cm^{-1}): 2975, 1684, 1601, 1508, 1373, 1318, 1255, 1187, 1094, 1018, 815, 774, 720, 550. Elemental analysis calculated for $C_{45}H_{52}N_8O_4 \times 1.5C_{28}H_{20}O_8Si \times 4H_2O$: C, 65.28; H, 5.60; N, 7.00; Si, 2.63. Found: C, 65.01; H, 5.78; N, 6.89; Si, 2.59. $[\alpha]_D^{20}$= -26° (c = 0.1, DMSO).

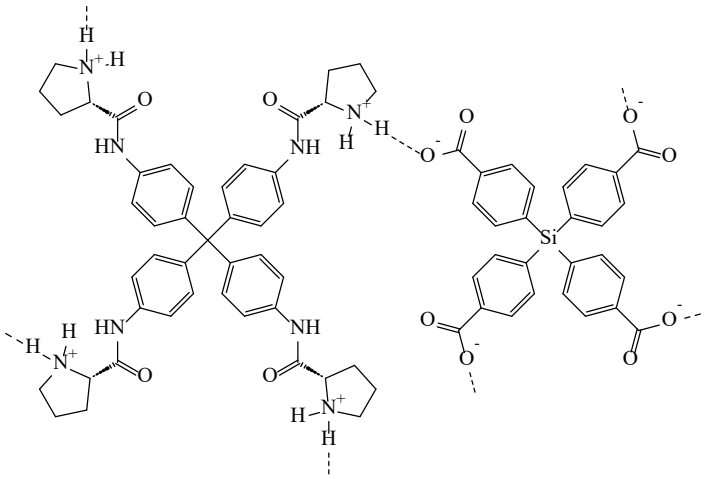

Figure S30. Structure of **TPA·4**

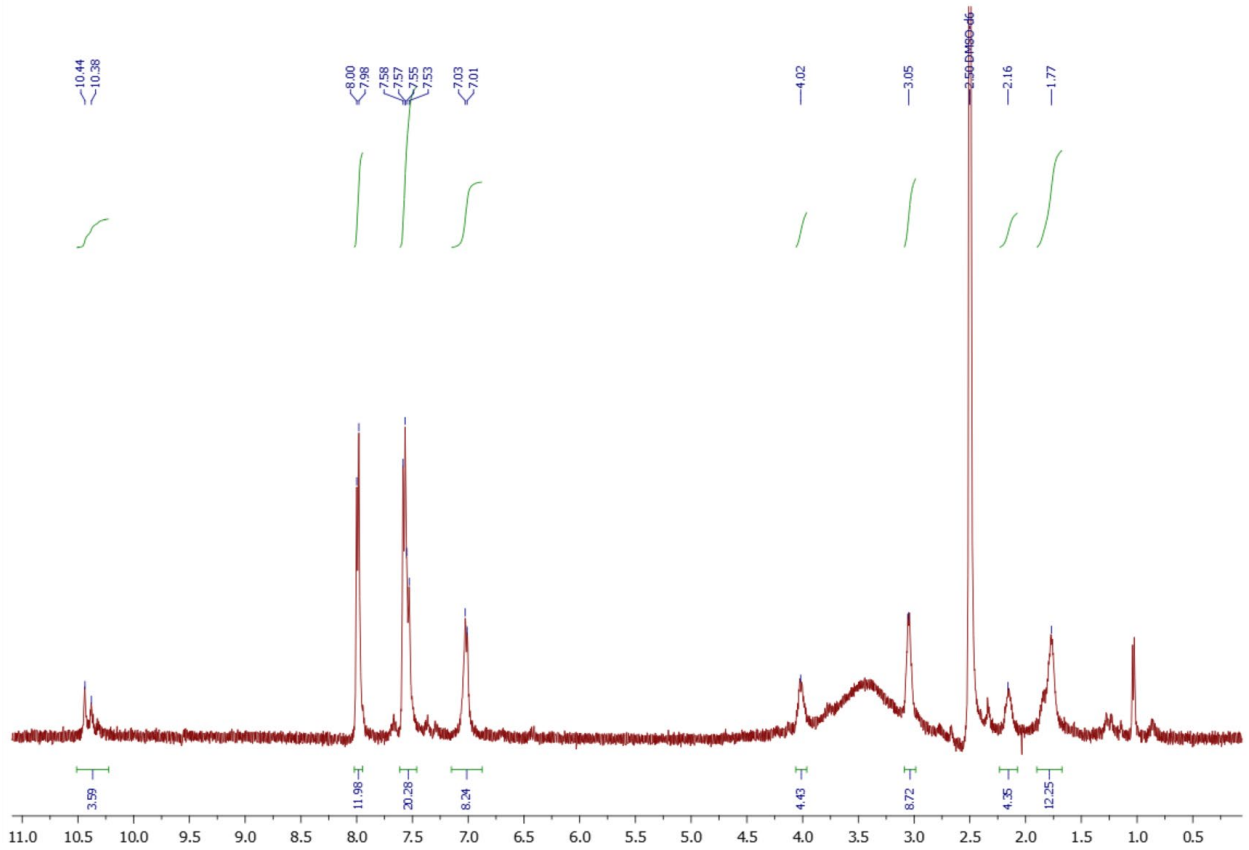

Figure S31. ^{1}H-NMR spectrum of **TPA·4**

(2S,2'S,2''S,2'''S)-2,2',2'',2'''-(((Methanetetrayltetrakis(benzene-4,1-diyl))tetrakis-(azanediyl))tetrakis(carbonyl))tetrakis(pyrrolidin-1-ium) (2'S,2''S,2'''S)-(methanetetrayltetrakis-(benzenesulfonyl))tetra-L-prolinate (**TPA·[L-5]**). Yield 70%. White solid. mp >300 °C with decomp. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.58 (s, 4H), 7.72 (d, J = 6.4 Hz, 8H), 7.49 (d, J = 5.5 Hz, 8H), 7.29 (d, J = 6.4 Hz, 8H), 6.98 (d, J = 5.5 Hz, 8H), 4.11 – 3.93 (m, 8H), 3.29 – 3.19 (m, 4H), 3.18 – 3.07 (m, 4H), 3.09 – 2.91 (m, 8H), 2.23 – 2.06 (m, 4H), 1.88 – 1.63 (m, 24H), 1.50 – 1.33 (m, 4H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 174.5, 149.3, 142.1, 137.0, 136.7, 131.4, 131.1, 127.5, 118.9, 62.1, 60.5, 48.7, 46.4, 31.0, 30.3, 25.9, 25.2, 24.5. FTIR (ν/cm^{-1}): 2970, 1686, 1593, 1542, 1508, 1400, 1320, 1196, 1153, 1096, 1011, 821, 706, 608, 571. Elemental analysis calculated for $C_{90}H_{100}N_{12}O_{20}S_4 \times 4H_2O$: C, 57.80; H, 5.82; N, 8.99; S, 6.86. Found: C, 57.69; H, 5.91; N, 8.66; S, 6.55. $[\alpha]_D^{20}$= -69° (c = 0.1, DMSO).

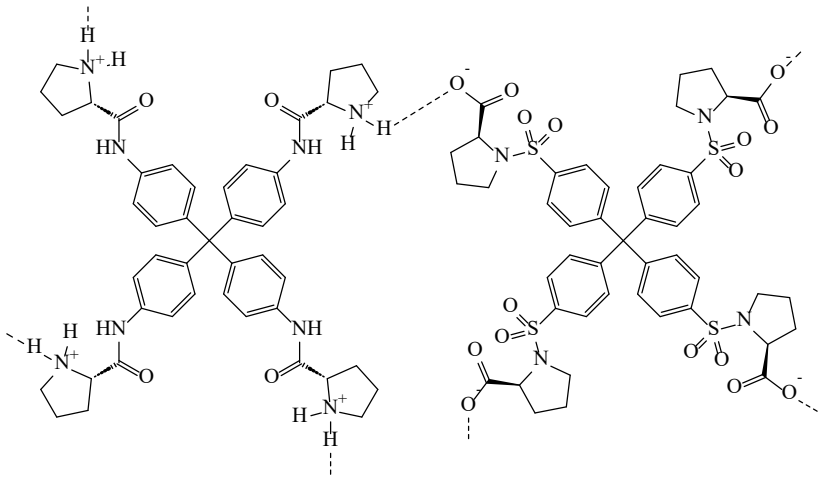

Figure S32. Structure of **TPA·[L-5]**

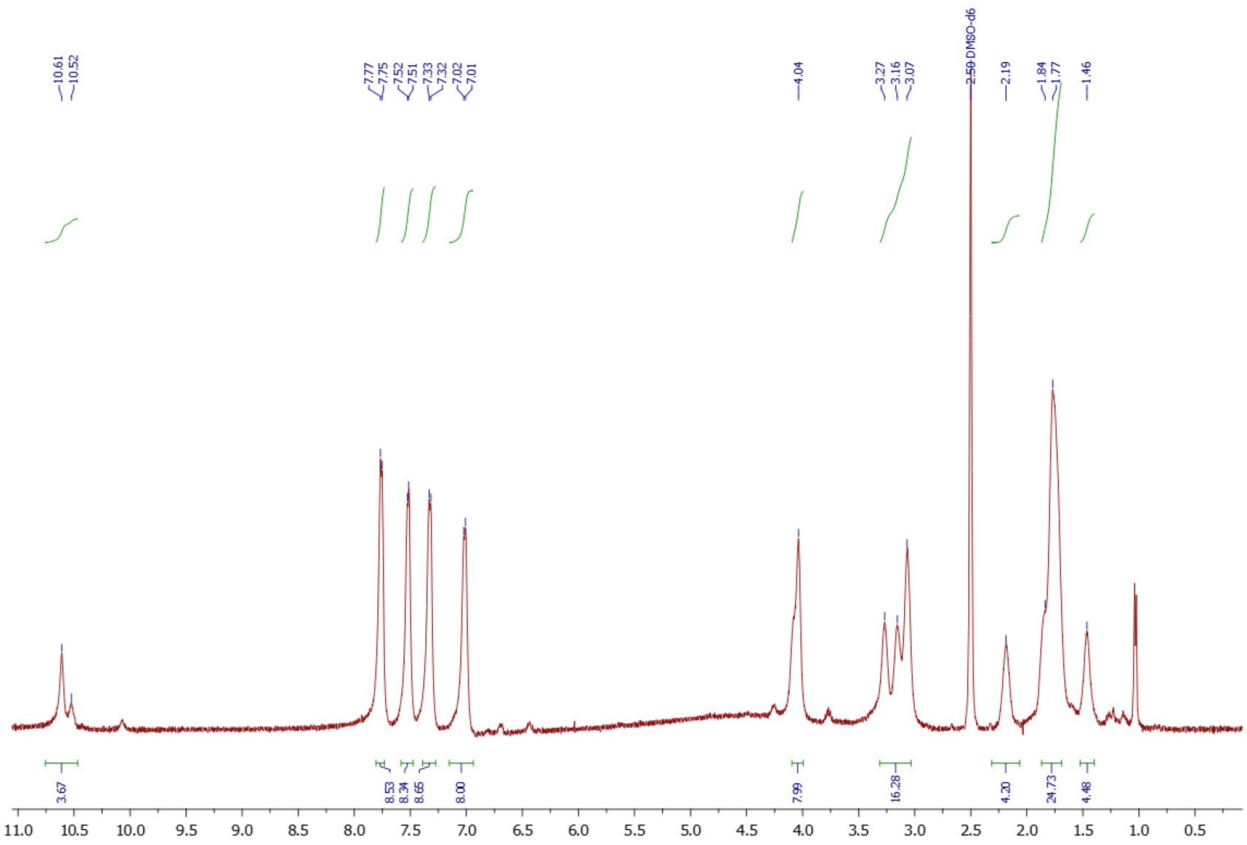

Figure S33. ^{1}H-NMR spectrum of **TPA·[L-5]**

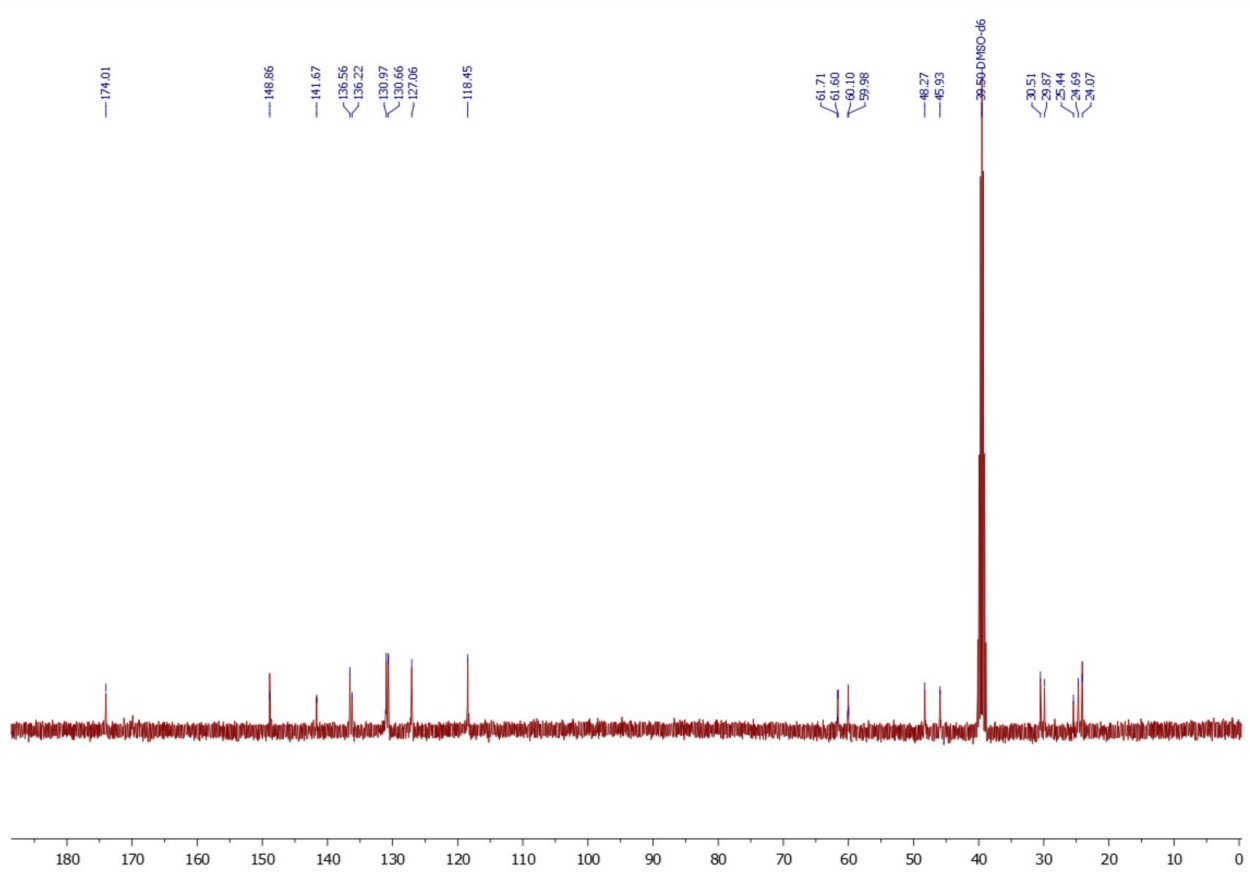

Figure S34. ^{13}C-NMR spectrum of **TPA·[L-5]**

(2S,2'S,2''S,2'''S)-2,2',2'',2'''-(((Methanetetrayltetrakis(benzene-4,1-diyl))tetrakis-(azanediyl))tetrakis(carbonyl))tetrakis(pyrrolidin-1-ium) (2'R,2''R,2'''R)-(methanetetrayl-tetrakis(benzenesulfonyl))tetra-D-prolinate (**TPA·[D-5]**). Yield 71%. White solid. mp >300 °C with decomp. ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ: 10.58 (s, 4H), 7.72 (d, J = 6.5 Hz, 8H), 7.49 (d, J = 5.5 Hz, 8H), 7.29 (d, J = 6.5 Hz, 8H), 6.98 (d, J = 5.5 Hz, 8H), 4.11 – 3.93 (m, 8H), 3.29 – 3.19 (m, 4H), 3.18 – 3.07 (m, 4H), 3.09 – 2.91 (m, 8H), 2.23 – 2.06 (m, 4H), 1.88 – 1.63 (m, 24H), 1.50 – 1.33 (m, 4H). ^{13}C-NMR (101 MHz, DMSO-d$_6$) δ: 174.5, 149.3, 142.1, 137.0, 136.7, 131.4, 131.1, 127.5, 118.9, 62.1, 60.5, 48.7, 46.4, 31.0, 30.3, 25.9, 25.2, 24.5. FTIR (ν/cm^{-1}): 2970, 1686, 1593, 1542, 1508, 1400, 1320, 1196, 1153, 1096, 1011, 821, 706, 608, 571. Elemental analysis calculated for $C_{90}H_{100}N_{12}O_{20}S_4 \times 4H_2O$: C, 57.80; H, 5.82; N, 8.99; S, 6.86. Found: C, 57.69; H, 5.91; N, 8.66; S, 6.55. $[\alpha]_D^{20}$= +29° (*c* = 0.1, DMSO).

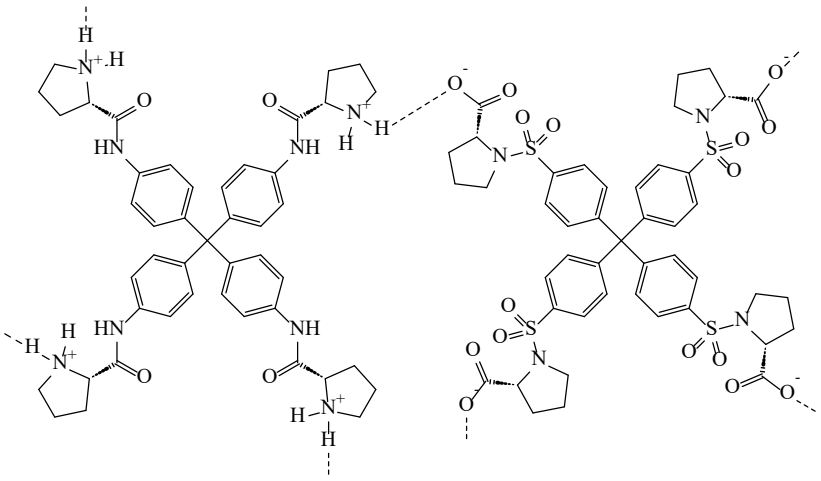

Figure S35. Structure of **TPA·[D-5]**

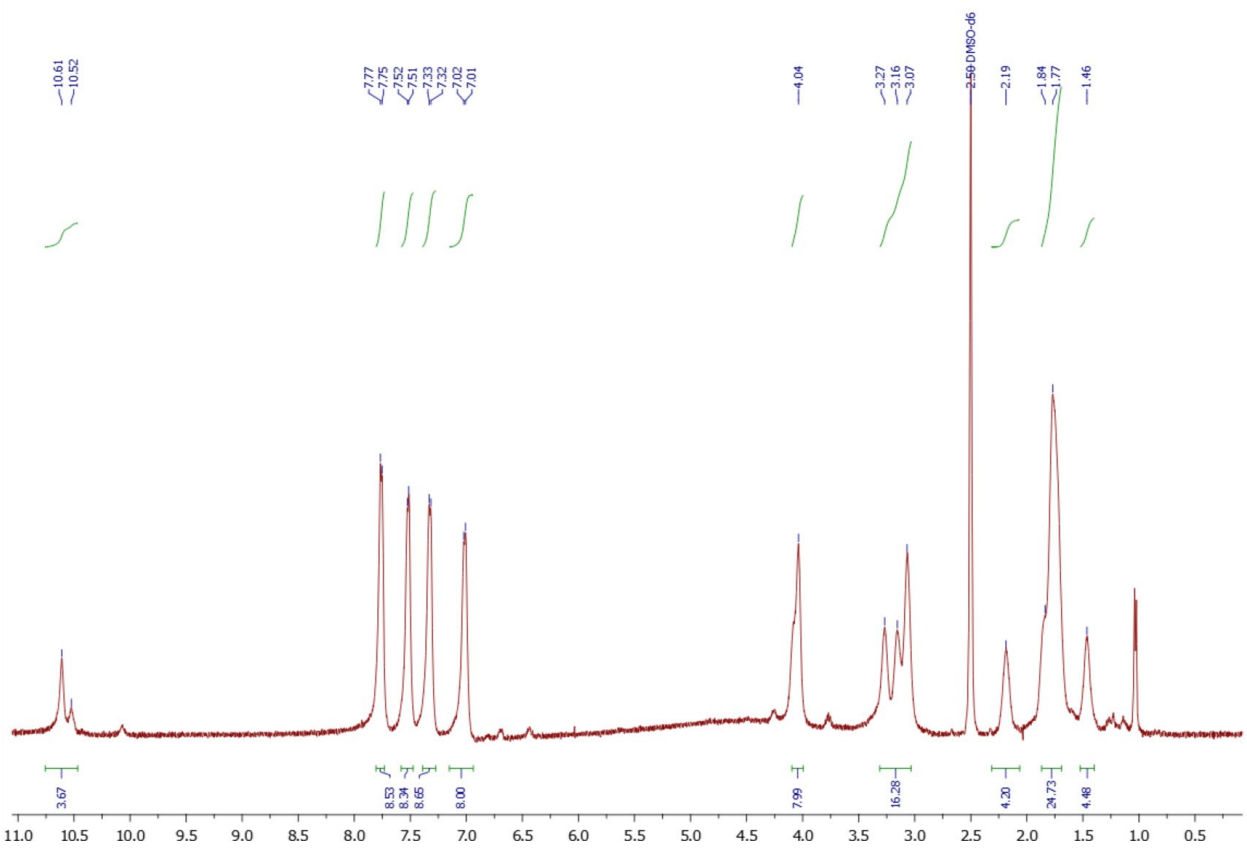

Figure S36. ^{1}H-NMR spectrum of **TPA·[D-5]**

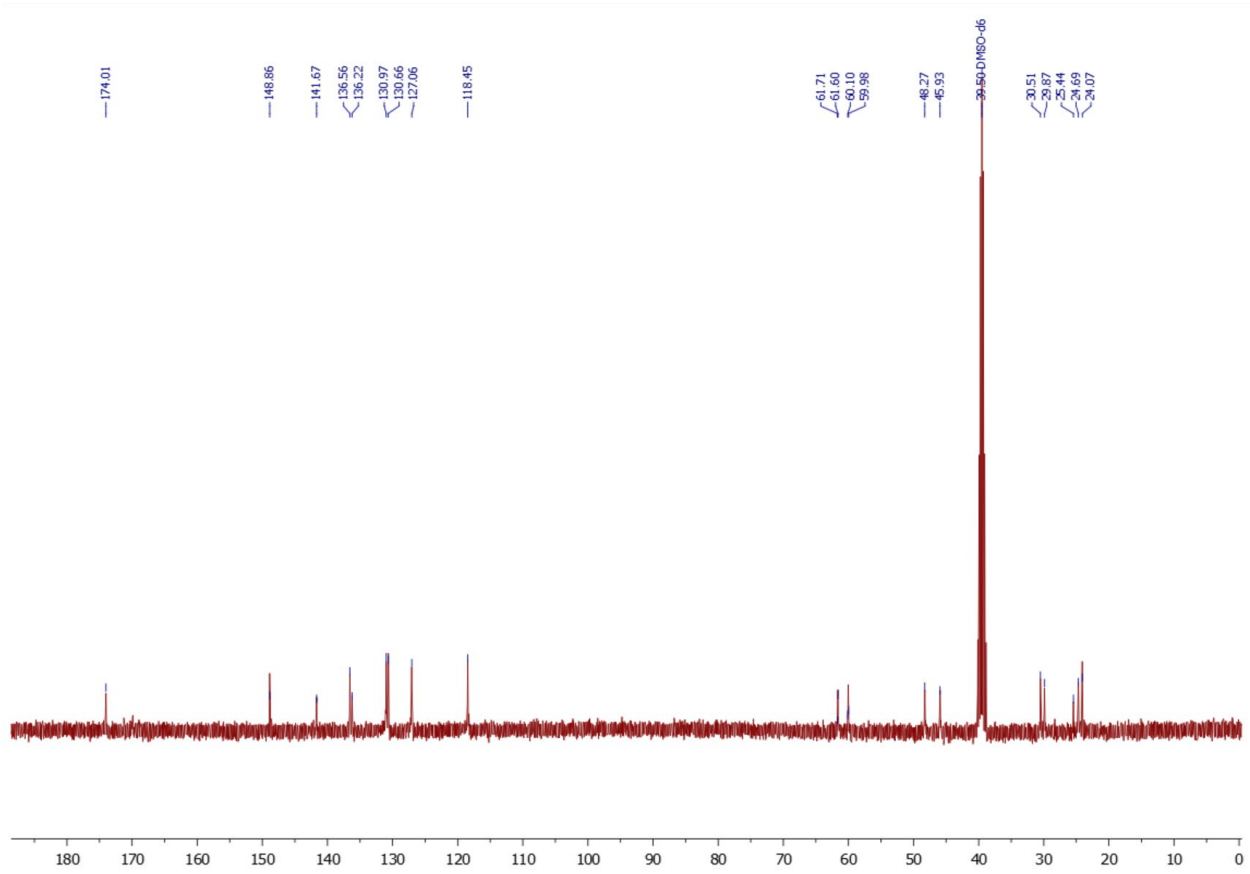

Figure S37. ^{13}C-NMR spectrum of **TPA·[D-5]**

2,2'-((1,2-Phenylenebis(azanediyl))bis(carbonyl))bis(pyrrolidin-1-ium) 4,4',4'',4'''-methanetetrayltetrabenzenesulfonate (**DPA·1**). Yield 77%. Yellowish solid. mp > 300 °C. ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ: 9.98 (s, 4H), 7.57 (d, J = 7.7 Hz, 8H), 7.29 – 7.17 (m, 4H), 7.11 (d, J = 7.8 Hz, 8H), 4.48 – 4.34 (m, 4H), 3.31 – 3.15 (m, 8H), 2.44 – 2.25 (m, 4H), 2.09 – 1.95 (m, 4H), 1.93 – 1.77 (m, 8H). ^{13}C-NMR (101 MHz, DMSO-d$_6$) δ: 168.2, 147.0, 130.4, 126.4, 125.7, 125.6, 60.2, 46.4, 30.0, 24.2. FTIR (ν/cm^{-1}): 2956, 1680, 1605, 1453, 1402, 1291, 1177, 1035, 1007. Elemental analysis calculated for $C_{61}H_{76}N_8O_{16}S_4$: C, 56.12; H, 5.87; N, 8.58; S, 9.82. Found: C, 55.94; H, 5.93; N, 8.47; S, 9.79. $[\alpha]_D^{20}$= -24° (c = 0.1, DMSO).

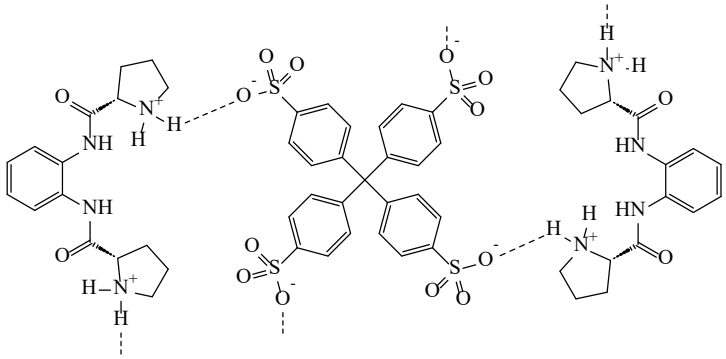

Figure S38. Structure of **DPA·1**

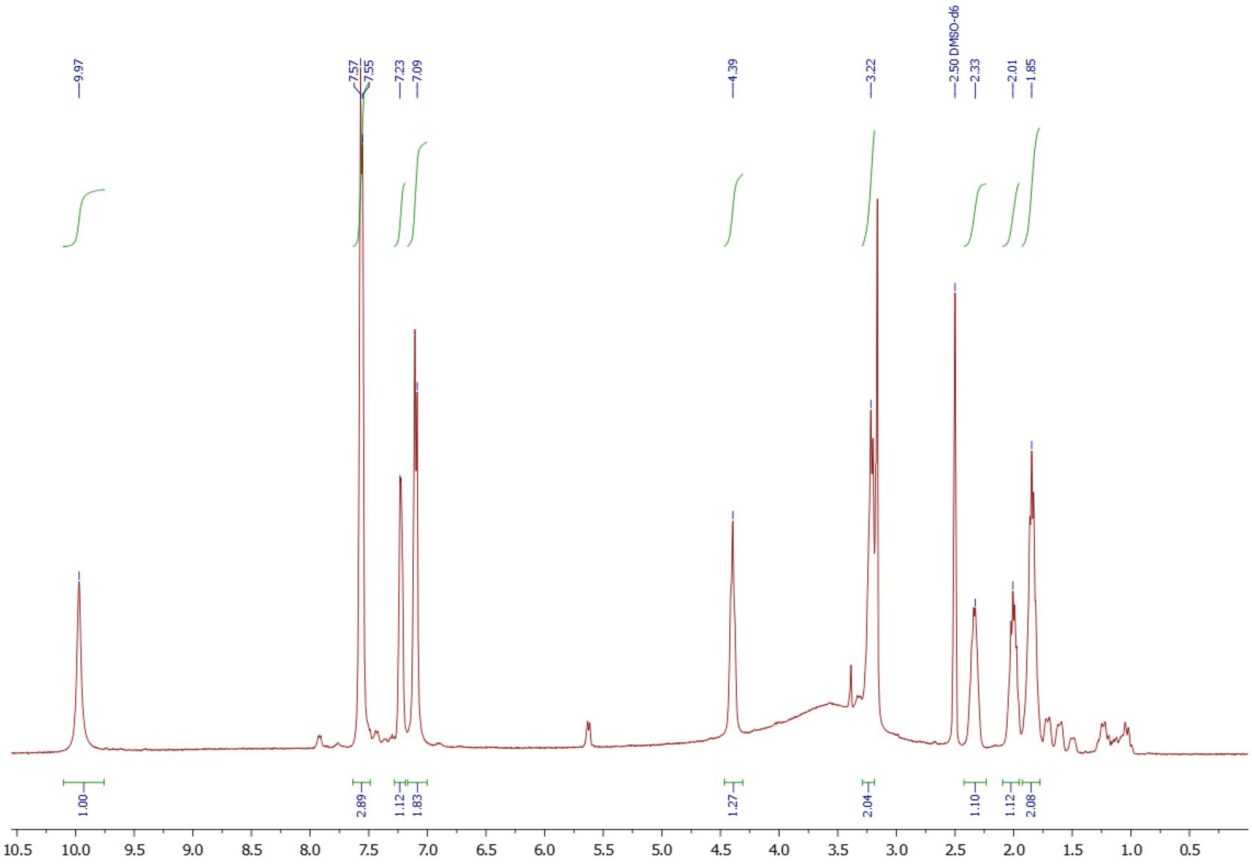

Figure S39. ^{1}H-NMR spectrum of **DPA·1**

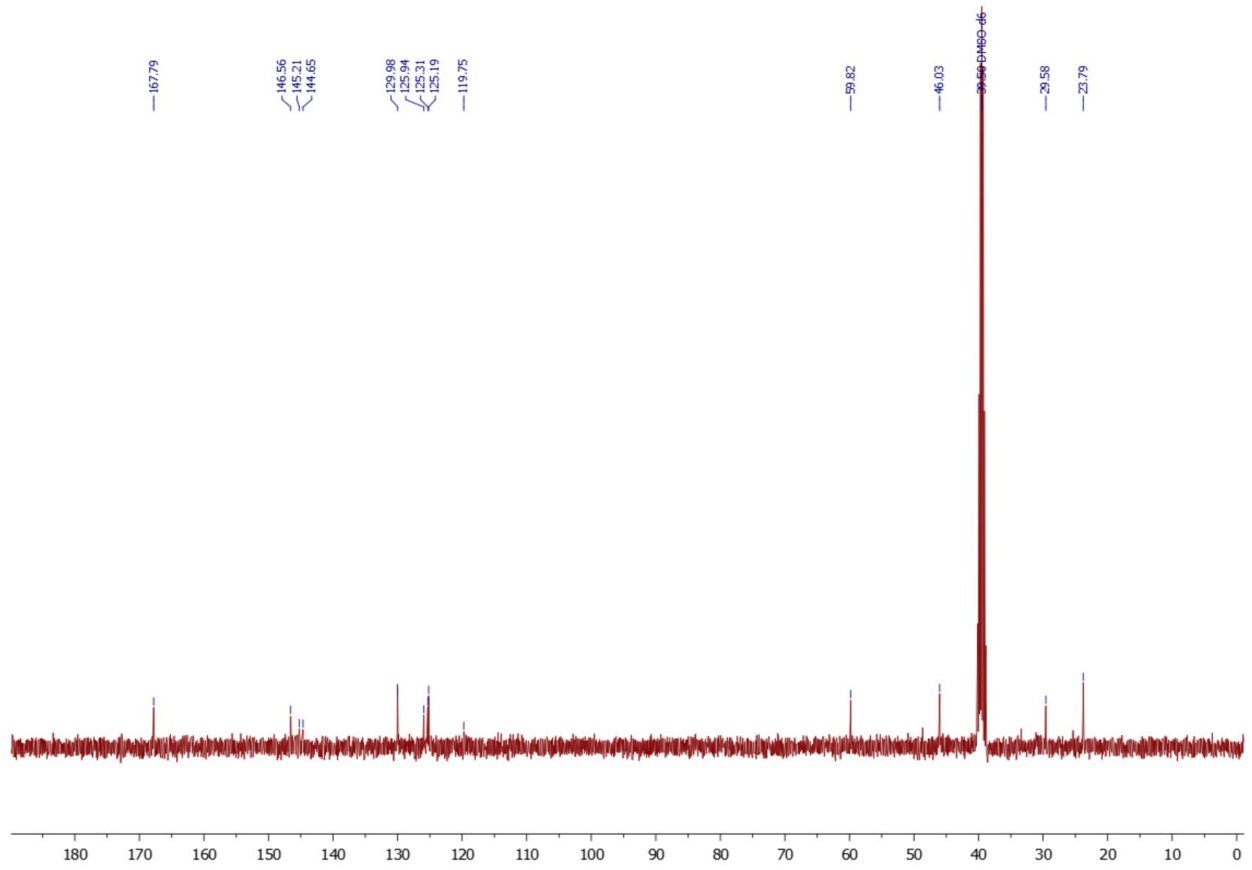

Figure S40. ^{13}C-NMR spectrum of **DPA-1**

2,2'-((1,2-Phenylenebis(azanediyl))bis(carbonyl))bis(pyrrolidin-1-ium) di-naphthalene-2,6-disulfonate (**DPA·2**). Yield 70%. Yellowish. mp > 300 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 9.94 (s, 1H), 9.31 (s, 4H), 8.68 (s, 4H), 8.18 (s, 4H), 7.95 (d, J = 8.4 Hz, 4H), 7.76 (d, J = 8.4 Hz, 4H), 7.59 – 7.52 (m, 4H), 7.31 – 7.21 (m, 4H), 4.52 – 4.41 (m, 4H), 3.36 – 3.19 (m, 8H), 2.46 – 2.34 (m, 4H), 2.12 – 2.00 (m, 4H), 1.96 – 1.85 (m, 8H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 167.8, 146.0, 132.5, 130.5, 128.8, 126.5, 126.0, 124.7, 124.4, 60.2, 46.5, 30.0, 24.1. FTIR (ν/cm^{-1}): 2956, 1680, 1605, 1453, 1291, 1162, 1084, 1023, 1009, 846, 755, 711, 550. Elemental analysis calculated for $C_{28}H_{36}N_4O_8S_2$: C, 54.18; H, 5.85; N, 9.03; S, 10.33. Found: C, 54.03; H, 5.90; N, 8.98; S, 10.01. $[\alpha]_D^{20}$= -37° (c = 0.1, DMSO).

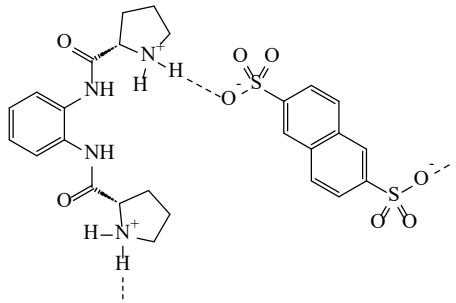

Figure S41. Structure of **DPA·2**

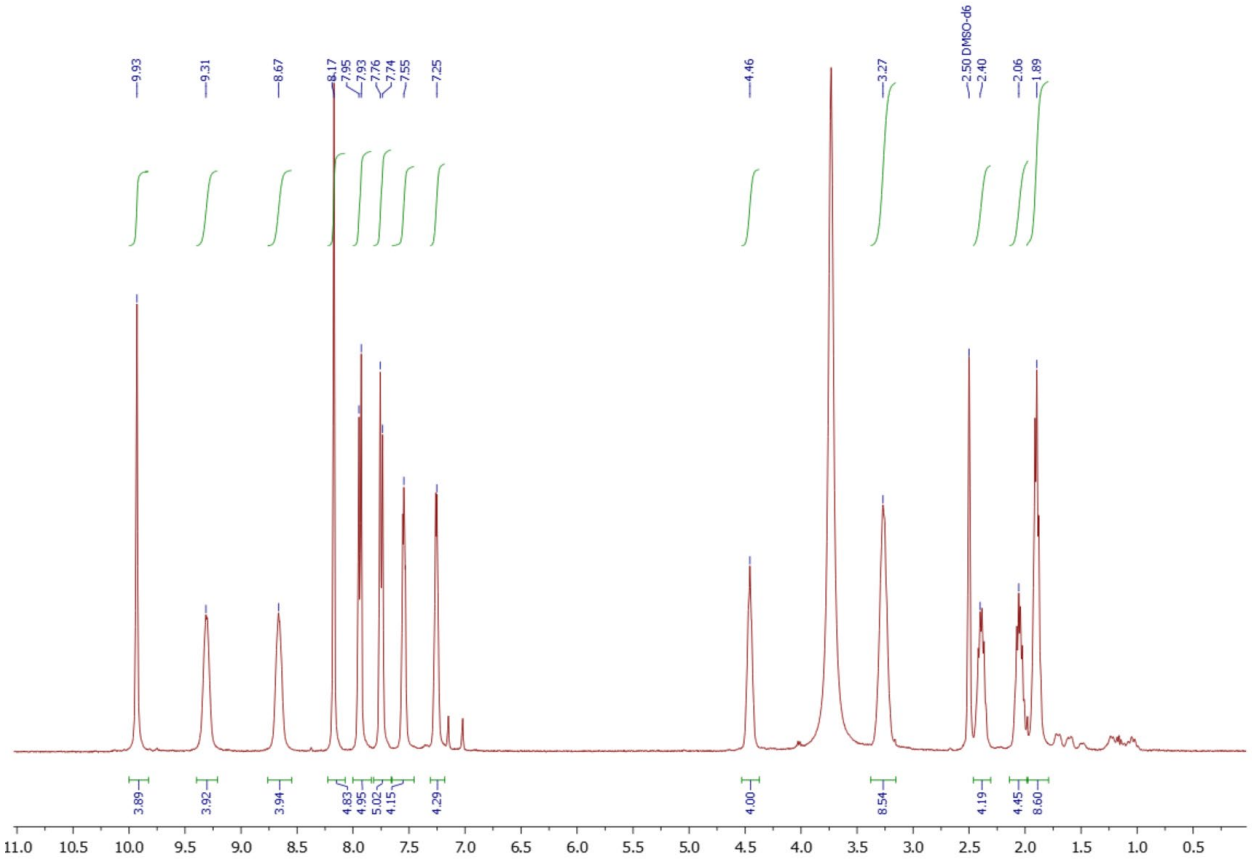

Figure S42. ^{1}H-NMR spectrum of **DPA·2**

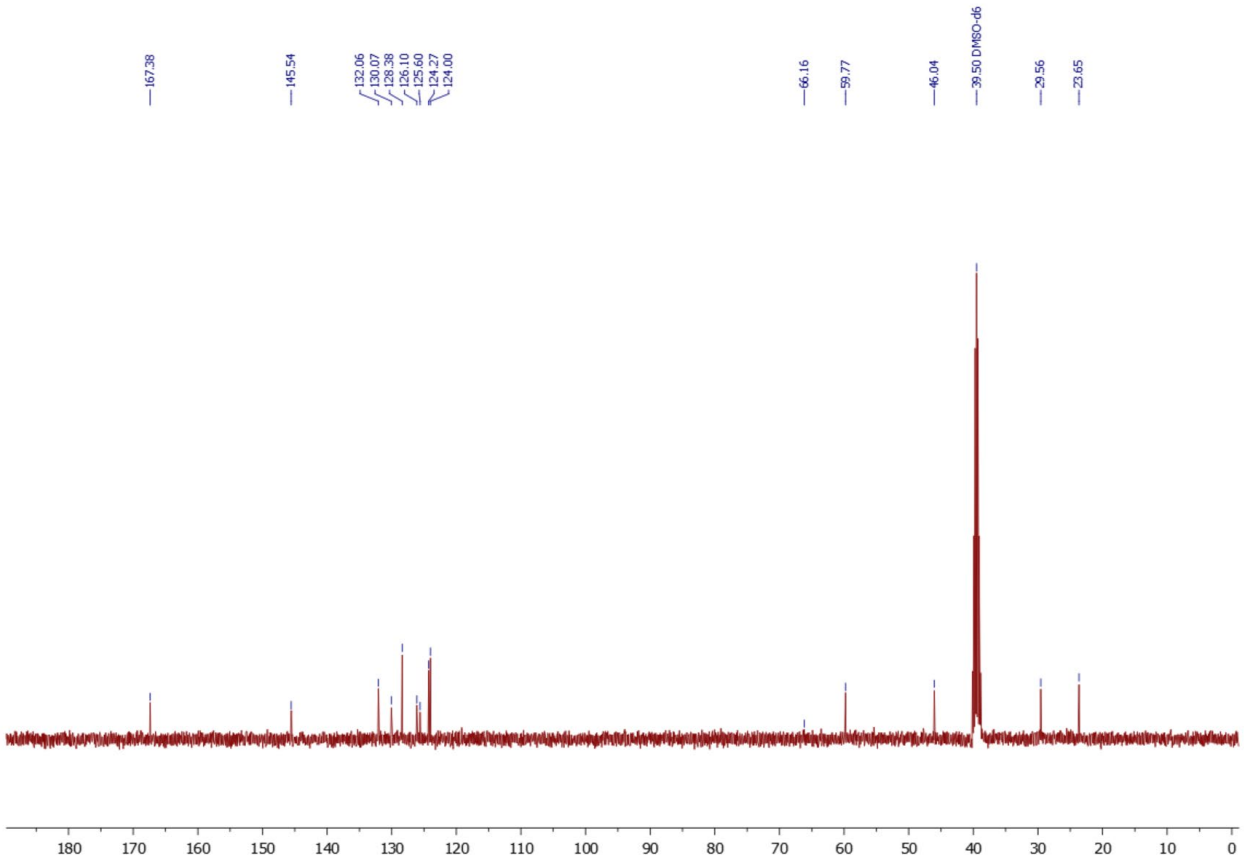

Figure S43. ^{13}C-NMR spectrum of **DPA·2**

2,2'-((1,2-Phenylenebis(azanediyl))bis(carbonyl))bis(pyrrolidin-1-ium) [1,1'-biphenyl]-4,4'-dicarboxylate (**DPA·3**). Yield 29%. White solid. mp > 300 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.11 (s, 2H), 8.00 (d, J = 8.0 Hz, 4H), 7.77 (d, J = 8.0 Hz, 4H), 7.67 – 7.55 (m, 2H), 7.21 – 7.05 (m, 2H), 4.01 – 3.86 (m, 2H), 3.05 – 2.83 (m, 4H), 2.21 – 2.05 (m, 2H), 1.95 – 1.80 (m, 2H), 1.78 – 1.59 (m, 4H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 171.7, 168.8, 142.7, 133.5, 130.4, 127.1, 125.7, 124.7, 60.4, 46.6, 30.7, 25.6. FTIR (ν/cm^{-1}): 2830, 2665, 2547, 1671, 1605, 1578, 1558, 1426, 1324, 1281, 1181, 1128, 1007, 924, 880, 845, 756, 554. Elemental analysis calculated for $C_{32}H_{38}N_4O_6$: C, 66.88; H, 6.67; N, 9.75. Found: C, 66.50; H, 6.68; N, 9.70. $[\alpha]_D^{20}$= -3° (*c* = 0.1, DMSO).

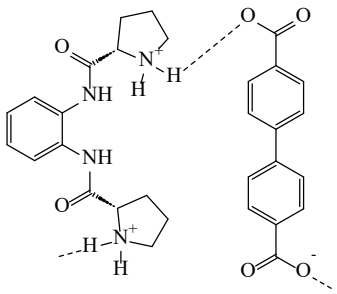

Figure S44. Structure of **DPA·3**

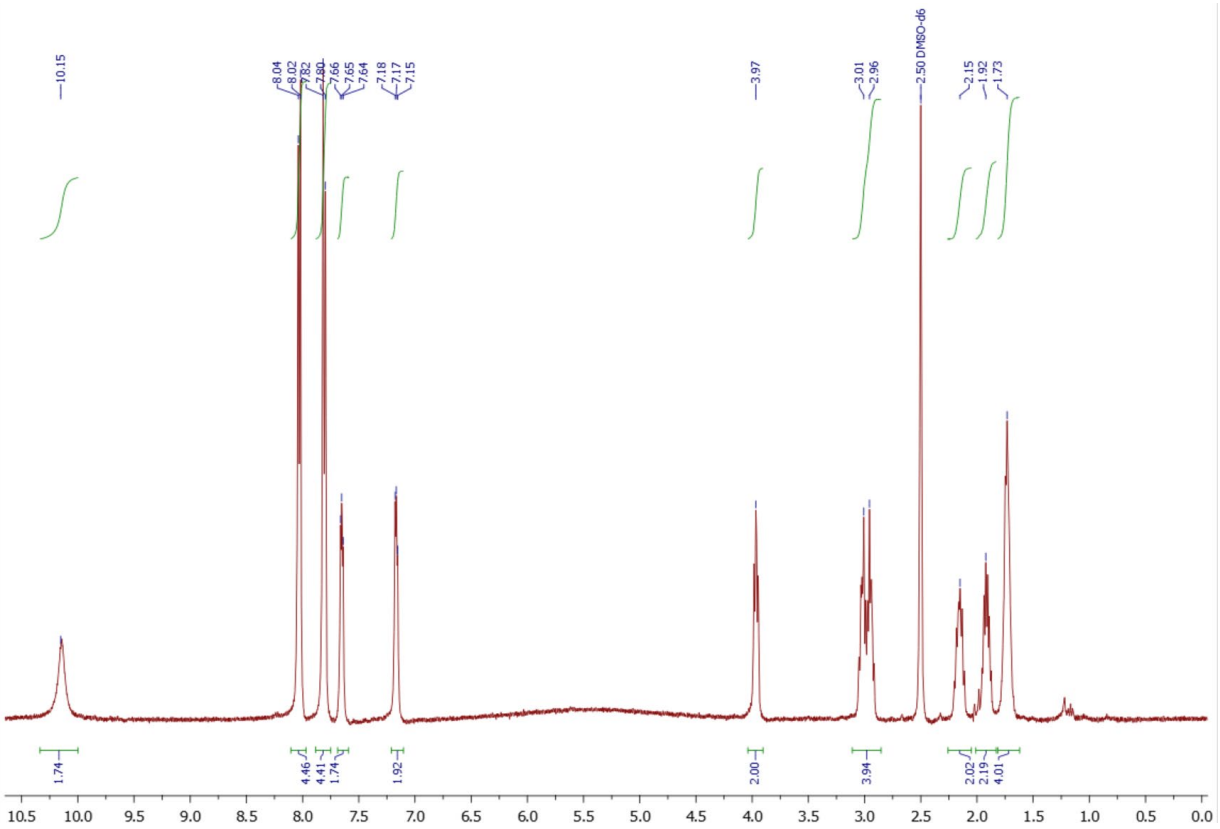

Figure S45. ^{1}H-NMR spectrum of **DPA·3**

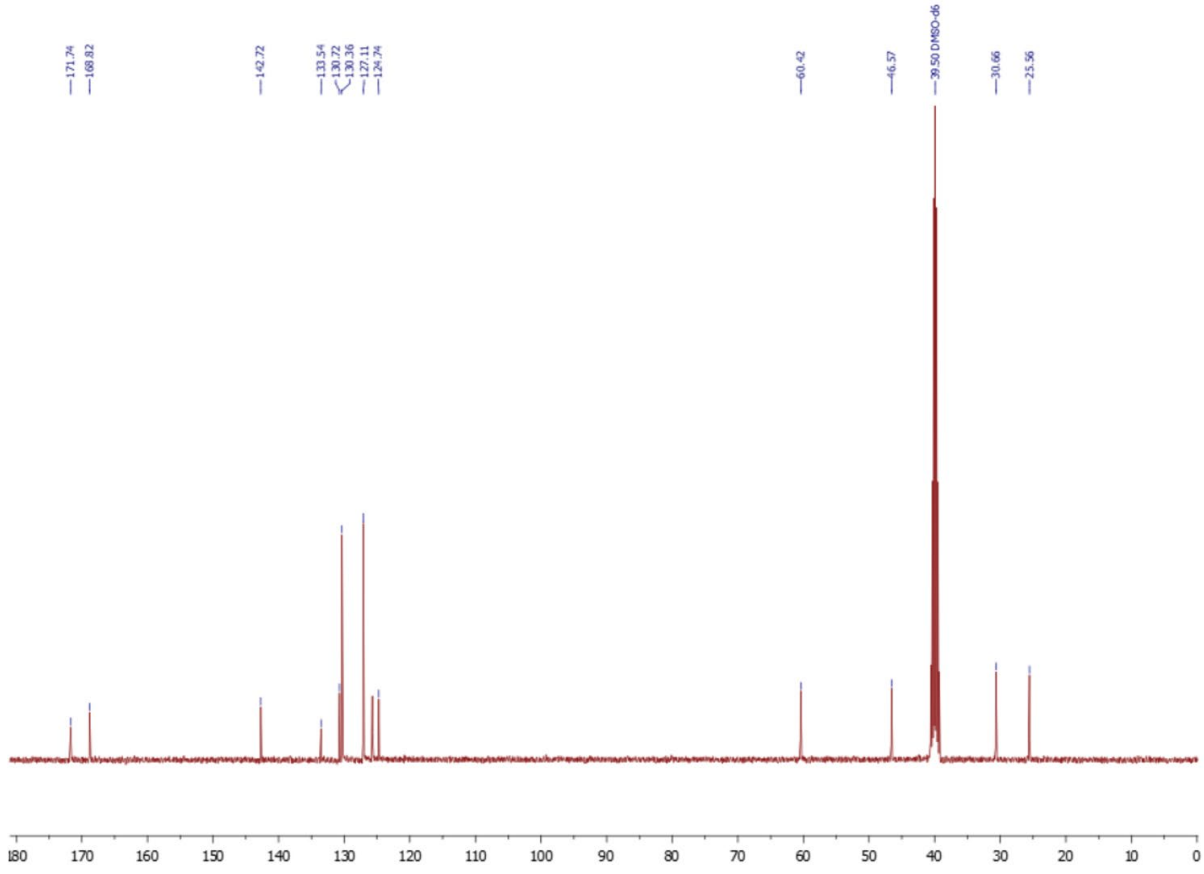

Figure S46. ^{13}C-NMR spectrum of **DPA-3**

Di-2,2'-((1,2-Phenylenebis(azanediyl))bis(carbonyl))bis(pyrrolidin-1-ium) 4,4',4'',4'''-silanetetrayltetrabenzoate (**DPA·4**). Yield 34%. White solid. mp > 300 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.12 (s, 4H), 7.94 (d, J = 7.6 Hz, 8H), 7.67 – 7.58 (m, 4H), 7.52 (d, J = 7.5 Hz, 8H), 7.18 – 7.06 (m, 4H), 4.05 – 3.85 (m, 4H), 3.06 – 2.81 (m, 8H), 2.22 – 2.03 (m, 4H), 1.92 – 1.80 (m, 4H), 1.77 – 1.57 (m, 8H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 172.1, 169.3, 136.8, 136.5, 136.1, 130.7, 129.2, 125.7, 124.7, 60.5, 46.6, 30.7, 25.7. FTIR (ν/cm^{-1}): 2956, 1682, 1582, 1520, 1453, 1368, 1291, 1093, 1017, 755, 719, 550. Elemental analysis calculated for $C_{64}H_{76}N_8O_{12}Si$: C, 65.29; H, 6.51; N, 9.52; Si, 2.39. Found: C, 64.99; H, 6.67; N, 9.49; Si, 2.26. $[\alpha]_D^{20}$= -17° (c = 0.1, DMSO).

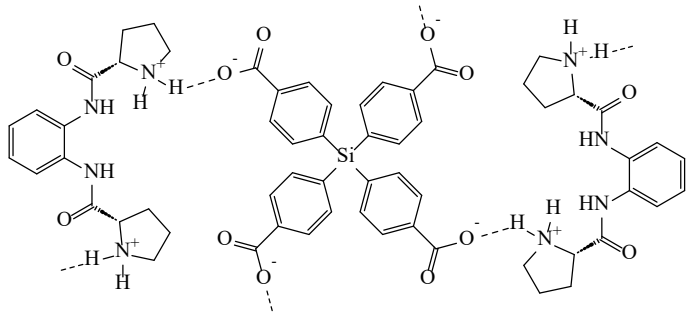

Figure S47. Structure of **DPA·4**

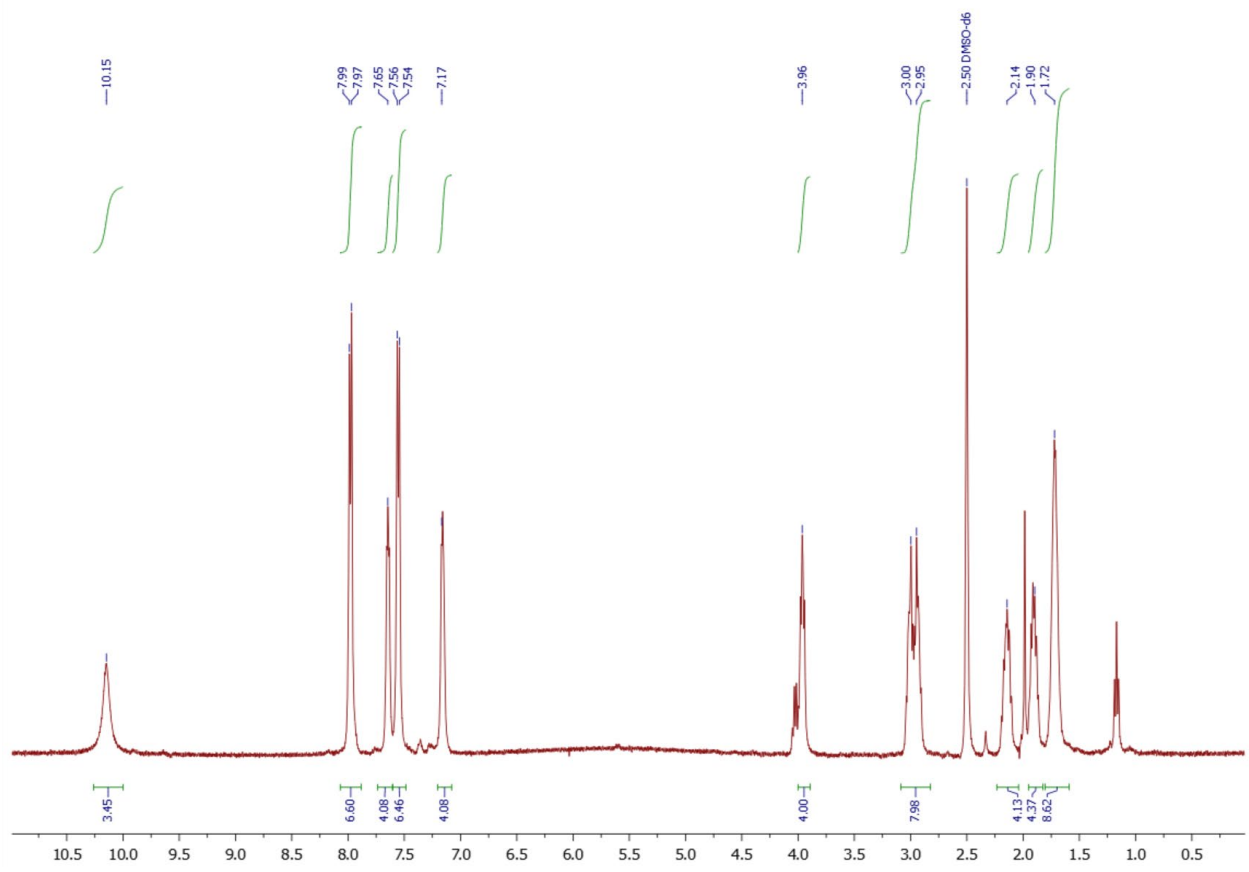

Figure S48. ^{1}H-NMR spectrum of **DPA·4**

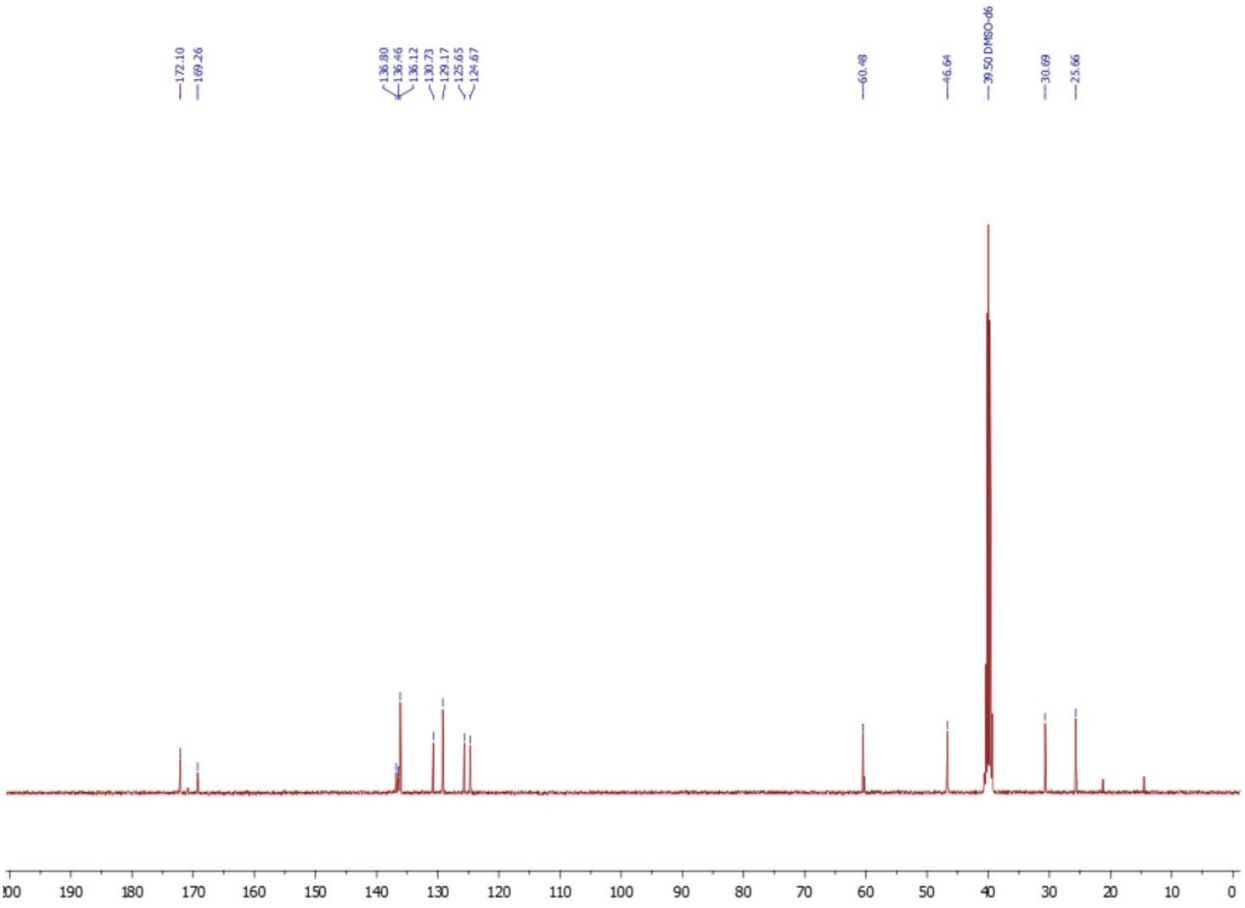

Figure S49. ^{13}C-NMR spectrum of **DPA·4**

Warfarin synthesis (general procedure). To a mixture of 16.2 mg (0.1 mmol) 4-hydroxycoumarin, 21.9 mg (0.15 mmol) of benzylideneacetone and **TPA·(1-5)** (0.005 mmol) or **DPA·3,4** (0.01 mmol) was added *n*-butanol (1 ml). The resulting slurry was stirred at room temperature for 5 days. White precipitate was separated from the solution. After removal of the solvent under the reduced pressure the residue was purified by flash chromatography (hexane/ethyl acetate, 3:1) to a afford a white solid.

Effect of added water to catalytic activity

Table S1 Catalytic activity of **TPA·3** in warfarin synthesis in presense of water [a]

Entry	Volume of added water, µl	Yield, %[b]	*ee*, % (*R*)[c]
1	0	75	42
2	25	91	40
3	50	52	34
4	75	37	34
5	100	20	23

[a] Reaction was carried out with 4-hydroxycoumarin (0.1 mmol) and benzylideneacetone (0.15 mmol) in the presence of the **TPA-3** (5 mol. %) and 0-125µl of water in *n*-butanol (1.0 mL) at room temperature for 5 days. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis on a Chiralpak OD-H column.

The heterogeneity test for **TPA·3**. To a mixture of 16.2 mg (0.1 mmol) 4-hydroxycoumarin, 21.9 mg (0.15 mmol) of benzylideneacetone and 6.3 mg (0.005 mmol) **TPA·3** was added *n*-butanol (1 ml). The resulting slurry was stirred at room temperature for 1 days. White precipitate was separated from the solution. The solid-off solution was stirred at room temperature 4 days yet. After removal of the solvent under the reduced pressure the residue was purified by flash chromatography (hexane/ethyl acetate, 3:1) to a afford a white solid.

Table S2 Results of heterogeneity test for **TPA·3** [a]

Entry	Time of reaction, days	Yield, %[b]	*ee*, % (*R*)[c]
1	1	48	38
2	5	75	41
3[d]	5	44	46

[a] Reaction was carried out with 4-hydroxycoumarin (0.1 mmol) and benzylideneacetone (0.15 mmol) in the presence of the catalyst (5 mol. %) in n-butanol (1.0 mL) at room temperature for 5 days. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis on a Chiralpak OD-H column. [d] Catalyst was filtered after 1 day of reaction and solution stirred without it 4 days yet.

The heterogeneity test for **DPA·3**. To a mixture of 16.2 mg (0.1 mmol) 4-hydroxycoumarin, 21.9 mg (0.15 mmol) of benzylideneacetone and **DPA·3** (0.01 mmol) was added n-Butanol (1 ml). The resulting slurry was stirred at room temperature for 1 days. White precipitate was separated from the solution. The solid-off solution was stirred at room temperature 4 days yet. After removal of the solvent under the reduced pressure the residue was purified by flash chromatography (hexane/ethyl acetate, 3:1) to a afford a white solid.

Table S3 Results of heterogeneity test for **DPA·3**[a].

Entry	Time of reaction, days	Yield, %[b]	*ee*, % (*R*)[c]
1	1	69	69
2	5	84	72
3[d]	5	81	76

[a] Reaction was carried out with 4-hydroxycoumarin (0.1 mmol) and benzylideneacetone (0.15 mmol) in the presence of the catalyst (5 mol. %) in n-butanol (1.0 mL) at room temperature for 5 days. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis on a Chiralpak OD-H column. [d] Catalyst was filtered after 1 day of reaction and solution stirred without it 4 days yet.

Catalytic activity of frameworks prepared in situ. To a mixture of 16.2 mg (0.1 mmol) 4-hydroxycoumarin, 21.9 mg (0.15 mmol) of benzylideneacetone, **TPA** (0.005 mmol) or **DPA** (0.01 mmol) and **3** (0.01 mmol) or **4-5** (0.005 mmol) was added n-Butanol (1 ml). The resulting slurry was stirred at room temperature for 5 days. White precipitate was separated from the solution. After removal of the solvent under the reduced pressure the residue was purified by flash chromatography (hexane/ethyl acetate, 3:1) to a afford a white solid.

Table S4 Catalytic activity of frameworks prepared *in situ* in warfarin synthesis [a].

Entry	Catalyst[b]	Yield, %[c]	*ee*, % (*R*)[d]
1	**TPA·3**	79	46
2	**TPA·4**	66	29
3	**TPA·[**L-**5]**	53	47
4	**TPA·[**D-**5]**	44	50
5	**DPA·3**	84	71
6	**DPA·4**	60	63
7	**DPA·[**L-**5]**	81	72
8	**DPA·[**D-**5]**	79	84

[a] Reaction was carried out with 4-hydroxycoumarin (0.1 mmol) and benzylideneacetone (0.15 mmol) in the presence of the catalyst (5 mol. %) in n-butanol (1.0 mL) at room temperature for 5 days. [b] Catalyst prepared with with mixing **TPA** or **DPA** and acid **3-5**. [c] Isolated yield. [d] Enantiomeric excess was determined by HPLC analysis on a Chiralpak OD-H column.

Regeneration of **TPA·3**. The precipitate centrifuged from the reaction mixture is washed with butanol 2 times, after which a suspension is made in 1 mL butanol and run again in the reaction. General procedure of catalytic experiment is used.

Table S5 **TPA·3** activity after regeneration [a].

Entry	Number of iterations[b]	Yield, %[c]	*ee*, % (*R*)[d]
1	1	75	42
2	2	81	41
3	3	72	40

[a] Reaction was carried out with 4-hydroxycoumarin (0.1 mmol) and benzylideneacetone (0.15 mmol) in the presence of the **TPA·3** (5 mol. %) in n-butanol (1.0 mL) at room temperature for 5 days. [b] Catalyst saved after reaction and reused. [c] Isolated yield. [d] Enantiomeric excess was determined by HPLC analysis on a Chiralpak OD-H column.

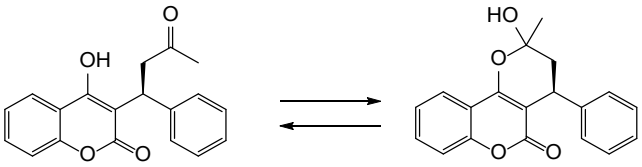

Figure S50. Structure of warfarin

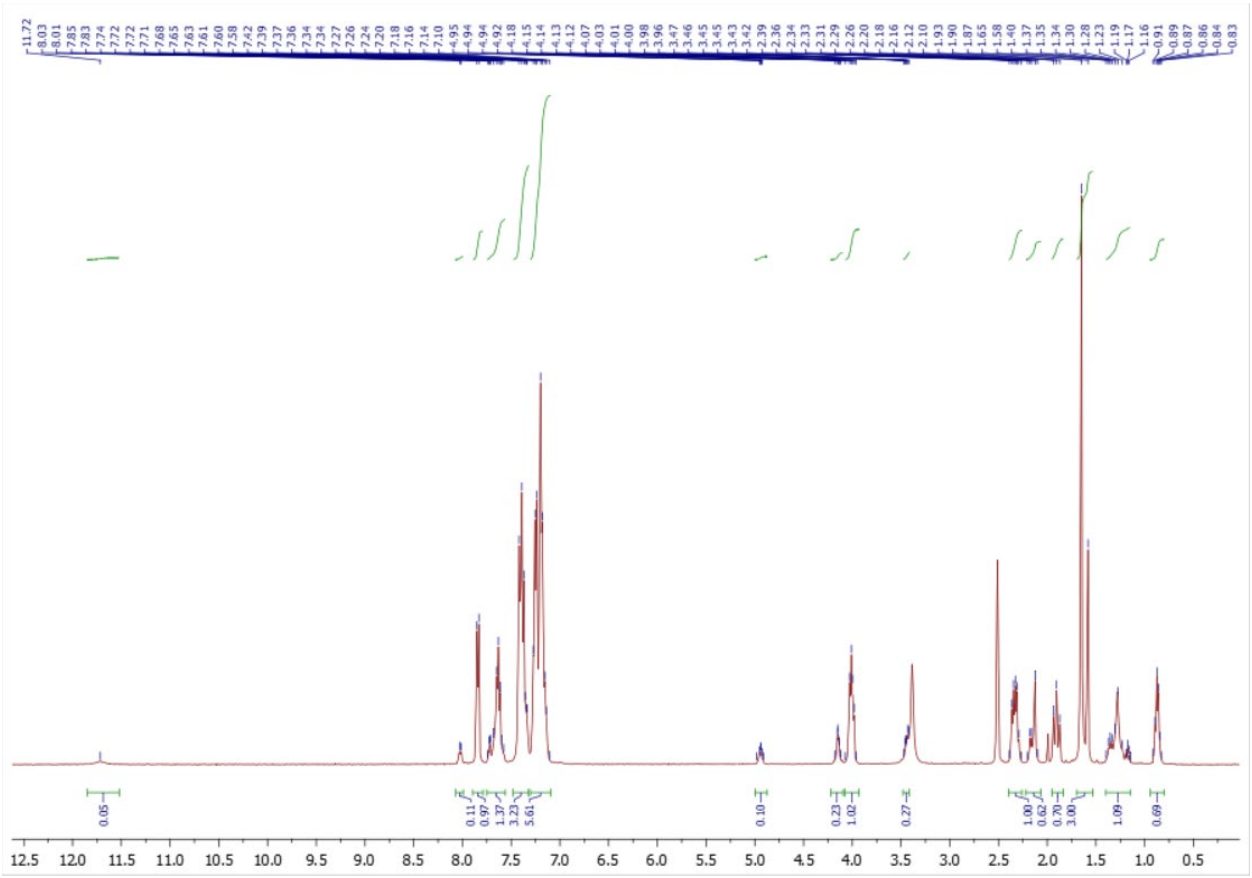

Figure S51. ^{1}H-NMR spectrum of warfarin

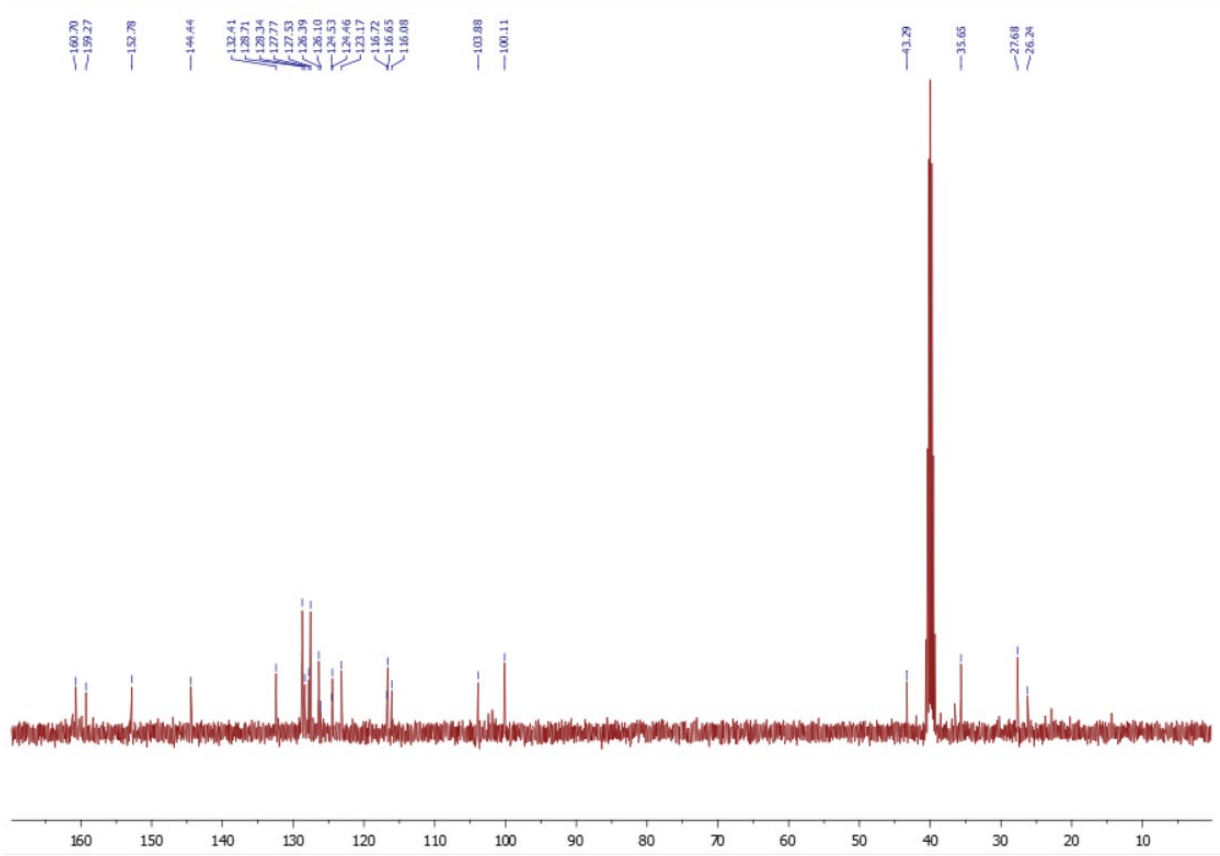

Figure S52. ^{13}C-NMR spectrum of warfarin

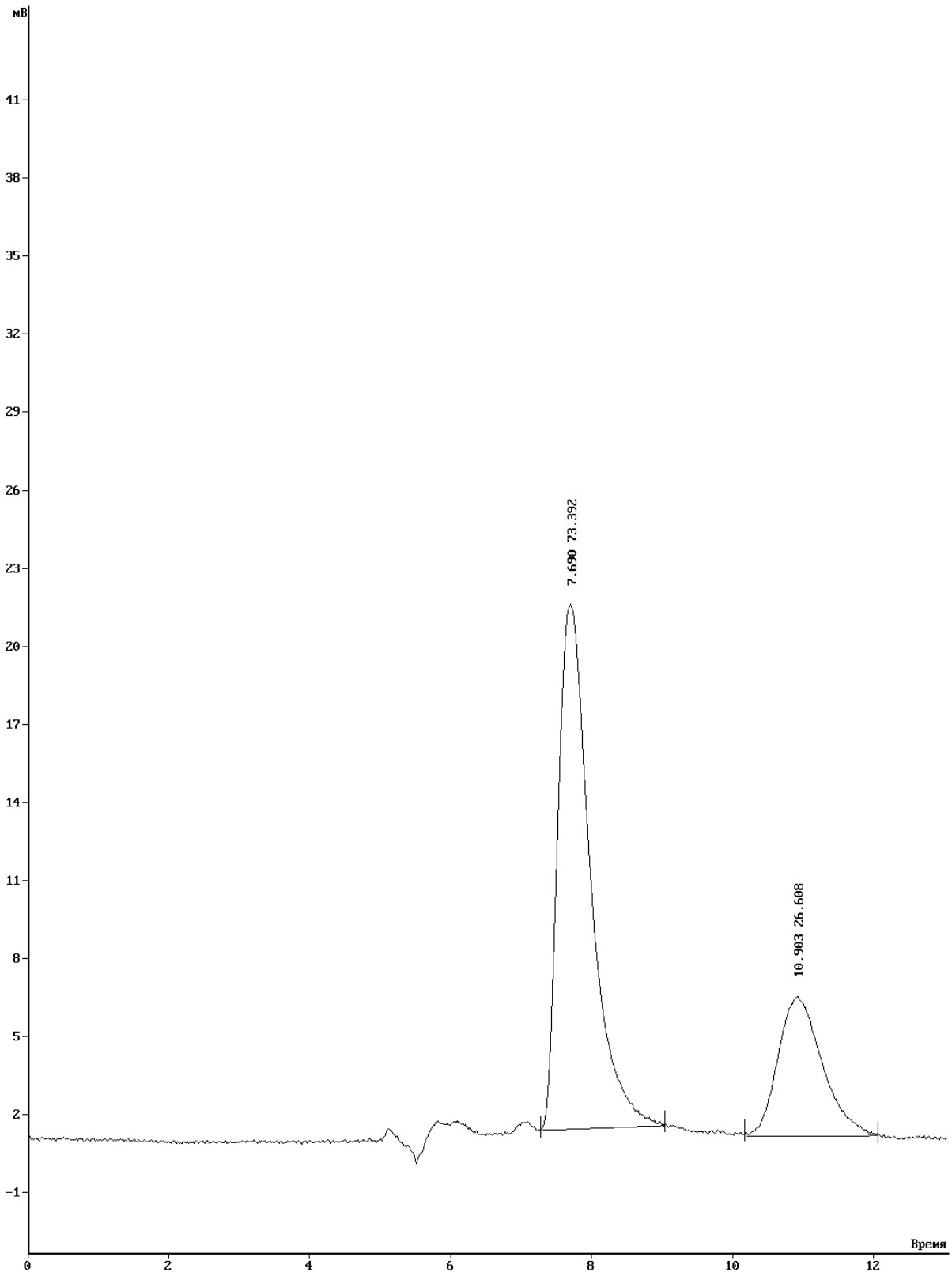

Figure S53. HPLC chromatogram of warfarin after optimization

Additional information. ^{13}C-NMR for **TPA·4** was not made because it has low solubility. The deviation of the results of yields and enantioselectivities is an acceptable deviation within the statistical error boundary.

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