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Synthesis, structural features and cytotoxicity of new calix[4]resorcinols with methanesulfonate fragments

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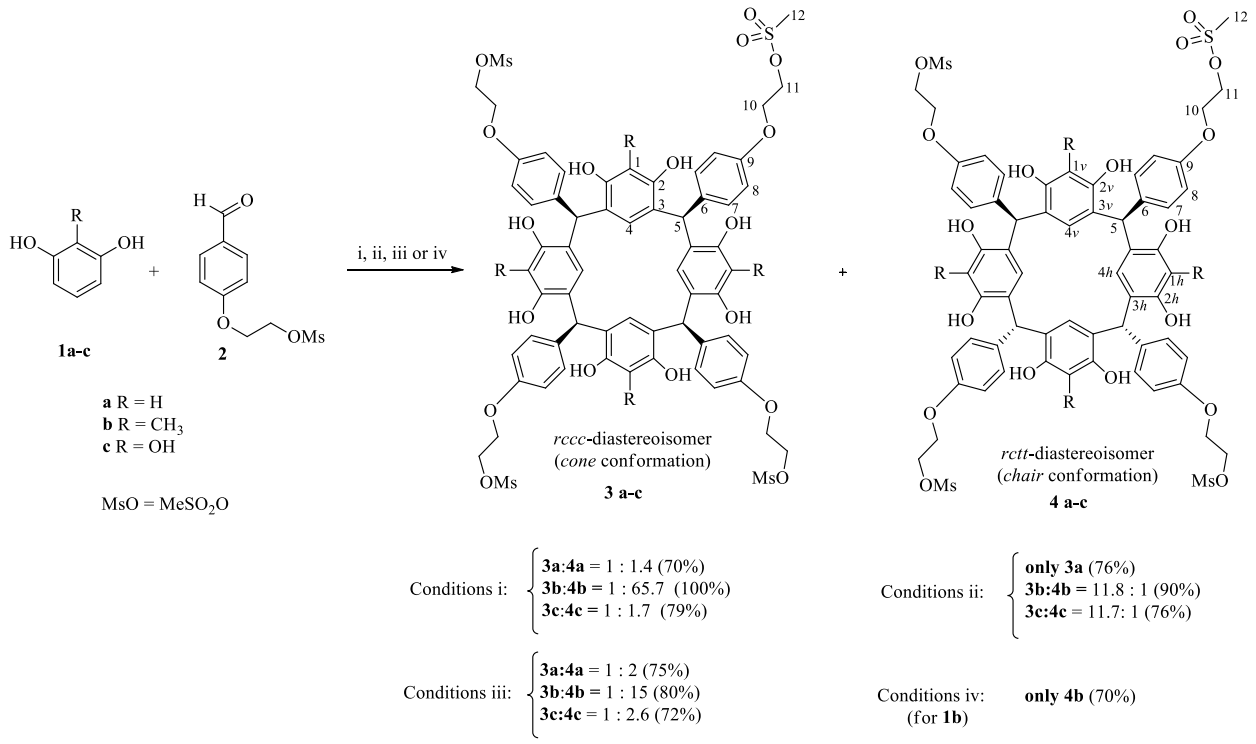
General

NMR experiments were performed on a Bruker AVANCE-600 spectrometer at 303 K equipped with 5 mm broadband probehead working at 500 MHz in ^{1}H and 125 MHz in ^{13}C NMR experiments. Chemical shifts were reported relative to residual signal of deuterated solvents. IR spectra of obtained compounds have been registered using Bruker Vector-27 FTIR spectrometer in the 400–4000 cm^{-1} range (optical resolution 4 cm^{-1}). The samples were prepared as KBr pellets. The ESI MS measurements were performed using an AmazonX ion trap mass spectrometer (Bruker Daltonic GmbH, Germany) in positive (and/or negative) mode in the mass range of 70–3000. The capillary voltage was −3500 V, nitrogen drying gas – 10 $L \cdot min^{-1}$, desolvation temperature – 250 °C. An methanol/water solution (70:30) was used as a mobile phase at a flow rate of 0.2 mL/min by binary pump (Agilent 1260 chromatograph, USA). The sample was dissolved in methanol to a concentration of 10-6 $g \cdot L^{-1}$. The instrument was calibrated with a tuning mixture (Agilent G2431A, USA). For instrument control and data acquiring the TrapControl 7.0 software (Bruker Daltonik GmbH, Germany) was used. Data processing was performed by DataAnalysis 4.0 SP4 software (Bruker Daltonik GmbH, Germany). The MALDI mass spectra were recorded on an Ultraflex III TOF/TOF mass spectrometer (Bruker Daltonic GmbH, Bremen, Germany) operated in the linear mode with the registration of positively charged ions or negatively charged ions. A Nd:YAG laser (λ = 355 nm, repetition rate 100 Hz) was used. The mass spectrum was obtained with an accelerating voltage of 25 kV and an ion extraction delay time of 30 ns. The resulting mass spectrum was formed due to multiple laser irradiation of the crystal (50 shots). The metal target MTP AnchorChipTM was used. Portions (0.5 μl) of a 1% matrix solution in acetonitrile and of a 0.1% sample solution in methanol were consecutively applied onto the target and evaporated. 2,5-Dihydroxybenzoic acid (DHB) was used as a matrix. The polyethylene glycol was used to calibrate the mass scale of the device. The data was obtained using the FlexControl program (Bruker Daltonik GmbH, Germany) and processed using the FlexAnalysis 3.0 program (Bruker Daltonik GmbH, Germany). The elemental analysis was carried out on a CHNS analyzer EuroEA3028-HT-OM (Eurovector SpA, Italy). The samples were weighed on Sartorius CP2P (Germany) microbalances in tin capsules. Callidus 4.1 software was used to perform quantitative measurements and evaluate the data received.



Scheme S1 *Reagents and conditions*: i, $CHCl_3/CF_3CO_2H$ (15 : 1 v/v), Δ; ii, $CHCl_3/CF_3CO_2H$ (1 : 1 v/v), Δ; iii, MeOH/HCl (15 : 1 v/v), Δ; iv, MeOH/HCl (4 : 1 v/v), room temperature.

*Experimental procedure for preparation and spectroscopic data of rccc-***3a** *and rctt-***4a** *calix[4]resorcinol diastereoisomers*

Procedure i*:* A mixture of resorcinol (**1a**) (0.11 g, 1 mmol) and 2-(4-formylphenoxy)ethyl methanesulfonate[S1] (**2**) (0.25 g, 1 mmol) in $CHCl_3$ (15 mL) and TFA (1 mL) was stirred under reflux for 21 h under an argon atmosphere. Then the solvent was evaporated to dryness, and the residue was recrystallized from ethanol to give the mixture of *rccc* and *rctt* isomers in a 1:1.4 ratio with overall yield 0.24 g (70%). The pure *rctt* isomer **4a** in the *chair* conformation was obtained as a white powder (yield 0.07 g, 20%) by repeated recrystallization from acetone and subsequent drying *in vacuo* at 40 ºC and 0.06 Torr. The corresponding *rccc* isomer **3a** was not obtained in pure form in this case; the impurities of the *rctt* isomer **4a** were presented.

Procedure ii*:* A mixture of **1a** (0.11 g, 1 mmol) and aldehyde **2** (0.25 g, 1 mmol) in $CHCl_3$ (15 mL) and TFA (15 mL) was stirred under reflux for 21 h under an argon atmosphere. The precipitate formed was filtered off, washed sequentially with $CHCl_3$ and Et_2O, the washing procedure was repeated until a colorless filtrate was observed. After drying *in vacuo* at 40 ºC and 0.06 Torr the pure *rccc* isomer **3a** in the *cone* conformation was obtained as a beige powder (0.26 g, 76%).

Procedure iii*:* A mixture of **1a** (0.11 g, 1 mmol) and aldehyde **2** (0.25 g, 1 mmol) in MeOH (15 mL) and concentrated HCl (1 mL) was stirred under reflux for 21 h under an argon atmosphere. The precipitate formed was filtered, washed sequentially with MeOH and Et_2O. After drying *in vacuo* (40 ºC, 0.06 Torr)

pure **4a** as *rctt* diastereoisomer in *chair* conformation was obtained as a white powder (0.14 g, 40%). The filtrate was evaporated and the residue was recrystallized from acetone into hexane to afford after drying *in vacuo* the mixture of *rccc*-**3a** and *rctt*-**4a** isomers in a 2:5 ratio with overall yield 0.12 g (35%). The additional quantity of pure *rctt* isomer **4a** was obtained by repeated recrystallization from acetone (yield 0.04 g, 10%). The total yield of *rctt* **4a** was 50%; the final *rccc*-**3a** and *rctt*-**4a** isomers ratio was 1:2. The corresponding isomer *rccc* **3a** was not obtained in pure form in this case either.

***Calix[4]resorcinol rccc diastereoisomer* 3a**: m.p. > 188 ºC (dec). ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.24 (s, 12H, H12), 4.20 (m, 8H, H10), 4.54 (m, 8H, H11), 5.60 (s, 4H, H5), 6.13 (s, 4H, H1), 6.23 (s, 4H, H4), 6.59 (d, $^{3}J_{HH}$ 8.9 Hz, 8H, H8), 6.63 (d, $^{3}J_{HH}$ 8.9 Hz, 8H, H7), 8.49 (s, 8H, OH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 36.8 (s, C12), 40.4 (s, C5), 65.7 (s, C10), 69.0 (s, C11), 102.0 (s, C1), 113.3 (s, C8), 120.6 (s, C3), 129.4 (s, C7), 130.3 (s, C4), 138.6 (s, C6), 152.4 (s, C2), 155.1 (s, C9) ppm. IR ν_{max} (KBr): 1172 (ν_s), 1346 (ν_{as}) (R-O-SO_2-R′), 3100–3650 (OH) cm^{-1}. Anal. Calcd. for $C_{64}H_{64}S_4O_{24}$ (%): C, 57.14; H, 4.76; S, 9.53. Found: C, 57.12; H, 4.70; S, 9.61. MALDI-MS, *m/z*: 1367 $[M+Na]^+$, 1383 $[M+K]^+$ (calcd. M = 1344). †

***Calix[4]resorcinol rctt diastereoisomer* 4a**: m.p. > 207 ºC (dec). ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.22 (s, 12H, H12), 4.12 (m, 8H, H10), 4.50 (m, 8H, H11), 5.49 (s, 4H, H5), 5.65 (s, 2H, H4^h), 6.13 (s, 2H, H1^v), 6.30 (s, 2H, H4^v), 6.31 (s, 2H, H1^h), 6.50 (d, $^{3}J_{HH}$ 8.9 Hz, 8H, H8), 6.53 (d, $^{3}J_{HH}$ 8.9 Hz, 8H, H7), 8.41 (s, 4H, OH^v), 8.48 (s, 4H, OH^h) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 36.8 (s, C12), 41.1 (s, C5), 65.7 (s, C10), 68.9 (s, C11), 101.6 (s, C1), 113.2 (s, C8), 120.7 (s, C3^h), 121.1 (s, C3^v), 128.9 (s, C4^v), 129.8 (s, C7), 131.7 (s, C4^h), 137.1 (s, C6), 152.4 (s, C2^v), 152.6 (s, C2^h), 155.1 (s, C9) ppm. IR ν_{max} (KBr): 1170 (ν_s), 1345 (ν_{as}) (R-O-SO_2-R′), 3100–3650 (OH) cm^{-1}. Anal. Calcd. for $C_{64}H_{64}S_4O_{24}$ (%): C, 57.14; H, 4.76; S, 9.53. Found: C, 57.10; H, 4.74; S, 9.59. MALDI-MS, *m/z*: 1367 $[M+Na]^+$, 1383 $[M+K]^+$ (calcd. M = 1344).

Experimental procedure for preparation and spectroscopic data of rccc-**3b** *and rctt*-**4b** *calix[4]resorcinol diastereoisomers*

Procedure i*:* A mixture of calix[4]resorcinol *rccc*-**3b** and *rctt*-**4b** diastereoisomers in a 1 : 65.7 ratio with total yield of 0.48 g (100%) was obtained by treatment of 2-methylresorcinol (**1b**) (0.17 g, 1.4 mmol) with aldehyde **2** (0.35 g, 1.4 mmol) in $CHCl_3$ (15 mL) and TFA (1 mL) at refluxing for 21 h under an argon atmosphere. The precipitate formed was filtered, washed sequentially with $CHCl_3$ and Et_2O. After drying in *vacuo* (40 ºC, 0.06 Torr) pure **4b** as its *rctt* diastereoisomer in *chair* conformation was obtained as a white powder (0.47 g, 98%). The filtrate was evaporated and the residue was recrystallized from acetone into hexane to afford after drying *in vacuo* the pure *rccc* diastereoisomer **3b** in *cone* conformation as an orange powder (0.01 g, 2%).

† In the NMR spectra of *rccc* diastereoisomer calix[4]resorcinols **3a-c** the one signal corresponds to each group of atoms, which indicates the existence of a highly symmetric *cone* conformation in solutions of these compounds. In the NMR spectra of *rctt* diastereoisomer calix[4]resorcinols **4a-c** in *chair* conformation the doubling of the signals of protons or carbon atoms of resorcinol residues is observed, i.e. opposite resorcinol aromatic rings are arranged vertically (*v*) or horizontally (*h*) with respect to the macrocycle cavity, as it was established in our earlier studies.[S2-S8]

Procedure ii*:* Calix[4]resorcinol *rccc* **3b** and *rctt* **4b** diastereoisomers in a 11.8 : 1 ratio with total yield of 0.43 g (90%) were obtained by treatment of **1b** (0.17 g, 1.4 mmol) with aldehyde **2** (0.35 g, 1.4 mmol) in $CHCl_3$ (15 mL) and TFA (15 mL) at refluxing for 21 h under an argon atmosphere. The precipitate formed was filtered, washed sequentially with $CHCl_3$ and Et_2O. After drying *in vacuo* (40 ºC, 0.06 Torr) pure **4b** as its *rctt* diastereoisomer in *chair* conformation was obtained (0.03 g, 7%) as a white powder. The filtrate was evaporated, and the crude residue was subjected to flash chromatography with CH_2Cl_2–MeOH (10:0.5) as eluent. After drying in *vacuo* the pure *rccc* diastereoisomer **3b** in the *cone* conformation was obtained as an orange powder (0.39 g, 83%, R_f =0.19).

Procedure iii*:* A mixture of **1b** (0.17 g, 1.4 mmol) with aldehyde **2** (0.35 g, 1.4 mmol) in MeOH (15 mL) and concentrated HCl (1 mL) was stirred under reflux for 21 h under an argon atmosphere. The precipitate formed was filtered, washed sequentially with MeOH and Et_2O. After drying in *vacuo* (40 ºC, 0.06 Torr) pure **4b** as its *rctt* diastereoisomer in *chair* conformation was obtained as a white powder (0.35 g, 73%). The filtrate was evaporated and the residue was recrystallized from acetone into hexane to afford after drying in *vacuo* the mixture of *rccc*-**3b** and *rctt*-**4b** isomers in a 5:2 ratio with overall yield 0.03 g (7%). The final *rccc*-**3b** and *rctt*-**4b** isomers ratio was 1:15. The corresponding *rccc* isomer **3b** was not obtained in pure form in this case; the impurities of the *rctt* isomer **4b** were presented.

Procedure iv*:* A mixture of **1b** (0.17 g, 1.4 mmol) and aldehyde **2** (0.35 g, 1 mmol) in MeOH (16 mL) and concentrated HCl (4 mL) was stirred at room temperature for 21 h under an argon atmosphere. The precipitate formed was filtered, washed sequentially with MeOH and Et_2O. After drying in vacuo (40 ºC, 0.06 Torr) pure **4b** as its *rctt* diastereoisomer in *chair* conformation was obtained (0.34 g, 70%) as a white powder.

***Calix[4]resorcinol rccc diastereoisomer* 3b**: m.p. > 140 ºC (dec). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1,90 (s, 12H, CH_3), 3.24 (s, 12H, H12), 4.20 (m, 8H, H10), 4.54 (m, 8H, H11), 5.72 (s, 4H, H5), 6.04 (s, 4H, H4), 6.62 (d, $^3J_{HH}$ 8.2 Hz, 8H, H8), 6.67 (d, $^3J_{HH}$ 8.2 Hz, 8H, H7), 7.39 (s, 8H, OH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 9.9 (s, CH_3), 36.8 (s, C12), 41.9 (s, C5), 65.7 (s, C10), 69.0 (s, C11), 111.3 (s, C1), 113.5 (s, C8), 122.4 (s, C3), 127.3 (s, C4), 129.7 (s, C7), 137.6 (s, C6), 150.5 (s, C2), 155.4 (s, C9) ppm. IR ν_{max} (KBr): 1173 (ν_s), 1349 (ν_{as}) (R-O-SO_2-R′), 3100–3650 (OH) cm^{-1}. Anal. Calcd. for $C_{68}H_{72}S_4O_{24}$ (%): C, 58.29; H, 5.14; S, 9.14. Found: C, 58.28; H, 5.18; S, 9.11. MALDI-MS, *m/z*: 1401 $[M+1]^+$, 1424 $[M+Na]^+$ (calcd. M = 1400).

***Calix[4]resorcinol rctt diastereoisomer* 4b**: m.p. > 145 ºC (dec). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.93 (s, 6H, CH_3^v), 2.11(s, 6H, CH_3^h), 3.23 (s, 12H, H12), 4.14 (m, 8H, H10), 4.52 (m, 8H, H11), 5.50 (s, 2H, $H4^h$), 5.59 (s, 4H, H5), 6.17 (s, 2H, $H4^v$), 6.54 (d, $^3J_{HH}$ 8.7 Hz, 8H, H8), 6.61 (d, $^3J_{HH}$ 8.7 Hz, 8H, H7), 7.22 (s, 4H, OH^h), 7.55 (s, 4H, OH^v) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 9.6 (s, $\underline{C}H_3^h$), 9.9 (s, $\underline{C}H_3^v$), 36.9 (s, C12),

42.8 (s, C5), 65.8 (s, C10), 69.0 (s, C11), 110.6 (s, $C1^h$), 111.0(s, $C1^v$), 113.5 (s, C8), 122.1 (s, $C3^h$), 123.0 (s, $C3^v$), 125.5 (s, $C4^v$), 128.0 (s, $C4^h$), 130.2 (s, C7), 136.2 (s, C6), 150.4 (s, $C2^h$), 150.5 (s, $C2^v$), 155.4 (s, C9) ppm. IR ν_{max} (KBr): 1175 (ν_s), 1350 (ν_{as}) (R-O-SO_2-R′), 3100–3650 (OH) cm^{-1}. Anal. Calcd. for $C_{68}H_{72}S_4O_{24}$ (%): C, 58.29; H, 5.14; S, 9.14. Found: C, 58.26; H, 5.18; S, 9.13. MALDI-MS, *m/z*: 1401 $[M+1]^+$, 1424 $[M+Na]^+$ (calcd. M = 1400).

Experimental procedure for preparation and spectroscopic data of rccc-*3c *and rctt-*4c *calix[4]resorcinol diastereoisomers

Procedure i*:* A mixture of pyrogallol (**1c**) (0.14 g, 1.1 mmol) and aldehyde **2** (0.27 g, 1.1 mmol) in $CHCl_3$ (15 mL) and TFA (1 mL) was stirred under reflux for 21 h under an argon atmosphere. Then the solvent was evaporated to dryness, and the residue was sequentially recrystallized from ethanol to give the mixture of *rccc* and *rctt* isomers in a 1:1.7 ratio with overall yield 0.31 g (79%). The pure *rctt* isomer **4c** in the *chair* conformation was obtained by repeated recrystallization from acetone and subsequent drying *in vacuo* as a grey powder (0.1 g, 25%). The corresponding *rccc* isomer **3c** was not obtained in pure form in this case; the impurities of the *rctt* isomer **4c** were presented.

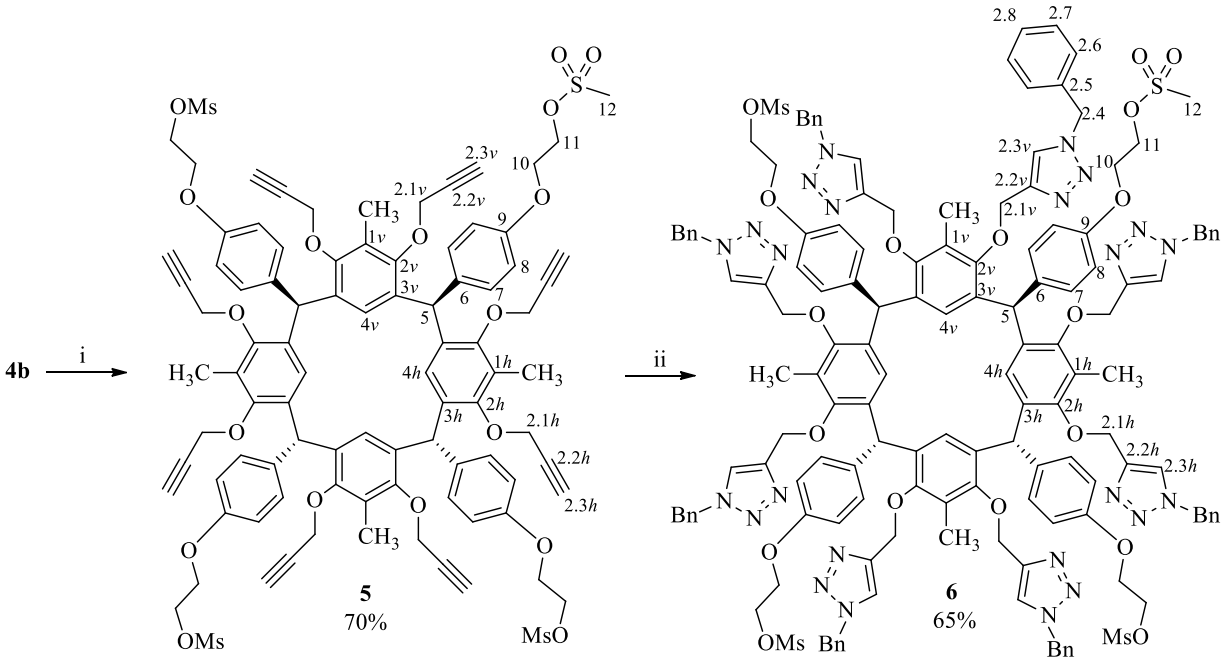
Procedure ii*:* Calix[4]resorcinol *rccc* **3c** and *rctt* **4c** diastereoisomers in a 11.7 : 1 ratio with total yield of 0.30 g (76%) were obtained by treatment of **1c** (0.14 g, 1.1 mmol) and aldehyde **2** (0.27 g, 1.1 mmol) in $CHCl_3$ (15 mL) and TFA (15 mL) at refluxing for 21 h under an argon atmosphere. The precipitate formed was filtered, washed sequentially with $CHCl_3$ and Et_2O. After drying *in vacuo* (40 ºC, 0.06 Torr) pure **4c** as *rctt* diastereoisomer in *chair* conformation was obtained as a grey powder (0.08 g, 6%). The filtrate was evaporated and the residue was recrystallized from acetone into hexane to afford after drying *in vacuo* the pure *rccc* diastereoisomer **3c** in the *cone* conformation as a beige powder (0.21 g, 70%).

Procedure iii*:* A mixture of **1c** (0.14 g, 1.1 mmol) and aldehyde **2** (0.27 g, 1.1 mmol) in MeOH (15 mL) and concentrated HCl (1 mL) was stirred under reflux for 21 h under an argon atmosphere. The precipitate formed was filtered, washed sequentially with MeOH and Et_2O. After drying *in vacuo* (40 ºC, 0.06 Torr) pure **4c** as its *rctt* diastereoisomer in *chair* conformation was obtained as a grey powder (0.15 g, 50 %). The filtrate was evaporated and the residue was recrystallized from acetone into hexane to afford after drying *in vacuo* the mixture of *rccc*-**3c** and *rctt*-**4c** isomers in a 10:1 ratio with overall yield 0.07 g (22%). The final *rccc*-**3c** and *rctt*-**4c** isomers ratio was 1:2.6. The corresponding *rccc* isomer **3c** was not obtained in pure form in this case either.

***Calix[4]resorcinol rccc diastereoisomer* 3c**: m.p. > 162 ºC (dec). ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.24 (s, 12H, H12), 4.20 (m, 8H, H10), 4.54 (m, 8H, H11), 5.74 (s, 4H, H5), 5.96 (s, 4H, H4), 6.59 (d, $^3J_{HH}$ 8.5 Hz, 8H, H8), 6.65 (d, $^3J_{HH}$ 8.5 Hz, 8H, H7), 7.63 (s, 12H, OH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 36.9 (s, C12), 40.9 (s, C5), 65.8 (s, C10), 69.0 (s, C11), 113.3 (s, C8), 121.5 (s, C4), 121.7 (s, C3), 129.5 (s, C7), 131.7 (s, C1), 138.4 (s, C6), 142.0 (s, C2), 155.2 (s, C9) ppm. IR ν_{max} (KBr): 1172 (ν_s), 1347 (ν_{as}) (R-O-

SO_2-R′), 3100–3650 (OH) cm^{-1}. Anal. Calcd. for $C_{64}H_{64}S_4O_{28}$ (%): C, 54.55; H, 4.55; S, 9.09. Found: C, 54.53; H, 4.59; S, 9.07. MALDI-MS, *m/z*: 1431 $[M+Na]^+$ (calcd. M = 1408).

***Calix[4]resorcinol rctt diastereoisomer* 4c:** m.p. > 173 ºC (dec). ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.22 (s, 12H, H12), 4.11 (m, 8H, H10), 4.50 (m, 8H, H11), 5.27 (s, 2H, H4^h), 5.61 (s, 4H, H5), 5.96 (s, 2H, H4^v), 6.52 (d, $^3J_{HH}$ 8.9 Hz, 8H, H8), 6.54 (d, $^3J_{HH}$ 8.9 Hz, 8H, H7), 7.38 (s, 2H, OH1^h), 7.39 (s, 4H, OH2^v), 7.54 (s, 4H, OH2^h), 7.85 (s, 2H, OH1^v) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 36.9 (s, C12), 42.8 (s, C5), 65.7 (s, C10), 69.0 (s, C11), 113.3 (s, C8), 119.6 (s, C4^v), 121.7 (s, C3), 122.6 (s, C4^h), 129.9 (s, C7), 131.5 (s, C1^v), 131.9 (s, C1^h), 136.8 (s, C6), 141.8 (s, C2^h), 142.1 (s, C2^v), 155.2 (s, C9) ppm. IR ν_{max} (KBr): 1170 (ν_s), 1345 (ν_{as}) (R-O-SO_2-R′), 3100–3650 (OH) cm^{-1}. Anal. Calcd. for $C_{64}H_{64}S_4O_{28}$ (%): C, 54.55; H, 4.55; S, 9.09. Found: C, 54.54; H, 4.59; S, 9.08. MALDI-MS, *m/z*: 1431 $[M+Na]^+$ (calcd. M = 1408).



Scheme S2 *Synthetic route to multifunctional calix[4]resorcinols **5**, **6***

Reagent and conditions: i, propargyl bromide, CH_3CN, K_2CO_3, reflux, 12 h;

ii, benzyl azide, sodium ascorbate, $CuSO_4 \cdot 5H_2O$, THF/H_2O, reflux, 14 h.

***Experimental procedure for preparation and spectroscopic data of compound* 5.** To a suspension of calix[4]resorcinol **4b** (0.4 g, 0.28 mmol) and anhydrous K_2CO_3 (0.2 g, 1.4 mmol) in dry MeCN (45 ml) propargyl bromide (0.55 g, 4.6 mmol) was added. The mixture was stirred and heated to 90 °C for 24 h under an argon atmosphere. The course of the reaction was controlled by MALDI mass spectrometry and the reaction was stopped when only peak of the fully substituted product was observed. The precipitate formed was filtered, washed with acetonitrile; the filtrate was evaporated to dryness. The residue was reprecipitated from chloroform with hexane. After drying *in vacuo* (40 ºC, 0.06 Torr) pure **5** as its *rctt* isomer in the *chair* conformation was obtained as an orange powder (0.34 g, 70%), mp 125-126 ºC (dec). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.29 (s, 6H, CH_3^v), 2.37 (s, 6H, CH_3^h), 2.46 (d, 4H, $^4J_{HH}$ 2.3 Hz, H2.3^h), 2.49 (d, $^4J_{HH}$ 2.3 Hz, 4H, H2.3^v), 3.09 (s, 12H, H12), 4.06 and 4.18 (dd, $^4J_{HH}$ 2.3 Hz, $^2J_{HH}$ 15.1 Hz, 8H, H2.1^h), 4.17 (m, 8H, H10), 4.29 and 4.39 (dd, $^4J_{HH}$ 2.3 Hz, $^2J_{HH}$ 15.1 Hz, 8H, H2.1^v), 4.56 (m, 8H, H11), 5.73 (s, 2H, H4^h), 5.96 (s, 4H, H5), 6.22 (s, 2H, H4^v), 6.49 (d, $^3J_{HH}$ 8.7 Hz, 8H, H8), 6.55 (d, $^3J_{HH}$ 8.7Hz, 8H, H7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.7 (s, CH_3^h), 11.7 (s, CH_3^v), 37.9 (s, C12), 43.8 (s, C5), 60.6 (s, C2.1^v), 60.9 (s, C2.1^h), 66.3 (s, C10), 68.7 (s, C11), 75.3 (s, C2.2^v), 75.8 (s, C2.2^h), 79.3 (s, C2.3^v), 79.5 (s, C2.3^h), 114.4 (s, C8), 125.1 (s, C1^h), 126.3 (s, C1^v), 127.4 (s, C4^v), 130.2 (s, C7), 130.5 (s, C4^h), 133.4 (s, C3^v), 133.6 (s, C3^h), 135.9 (s, C6), 154.3 (s, C2^h), 154.5 (s, C2^v), 156.4 (s, C9) ppm. IR ν_{max} (KBr): 1175 (ν_s), 1354 (ν_{as}) (R-O-SO_2-R′), 2124 (C≡C), 3286 (C≡CH) cm^{-1}. Anal. Calcd. for $C_{92}H_{88}S_4O_{24}$ (%): C, 64.79; H, 5.16; S, 7.51. Found (%): C, 64.77; H, 5.14; S, 7.55. MALDI-MS: *m/z*: 1743 $[M+K]^+$ (calcd. M = 1704).

***Experimental procedure for preparation of compound* 6.** To a suspension of calix[4[resorcinol **5** (0.2 g, 0.12 mmol), sodium ascorbate (0.43 g, 2.16 mmol) and $CuSO_4 \cdot 5H_2O$ (0.54 g, 2.16 mmol) in THF/H_2O mixture (1:1, 30 ml), benzyl azide (0.25 g, 1.88 mmol) was added. The mixture was stirred at 60-65 ºC for 24 h under argon atmosphere. Then the mixture was diluted with $CHCl_3$ (25 ml), washed with H_2O, and concentrated *in vacuo*. The residue was purified by precipitation from chloroform with hexane. After drying *in vacuo* (40 ºC, 0.06 Torr), pure **6** as its *rctt* isomer in the *chair* conformation was obtained as a beige powder (0.22 g, 65%), mp 106-107 ºC (dec). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.99 (s, 6H, CH_3^v), 2.38 (s, 6H, CH_3^h), 3.18 (s, 12H, H12), 4.06 (m, 8H, H10), 4.24 and 4.85 (dd, $^2J_{HH}$ 11.6 Hz, 8H, H2.1^h), 4.41 and 4.78 (dd, $^2J_{HH}$ 11.0 Hz, 8H, H2.1^v), 4.45 (m, 8H, H11), 5.60 (s, 16H, H2.4), 5.89 (s, 4H, H5), 5.91 (s, 2H, H4^h), 6.45 (m, 8H, H8), 6.53 (m, 8H, H7), 6.54 (s, 2H, H4^v), 7.15 (m, 8H, H2.8), 7.19 (m, 16H, H2.7), 7.33 (m, 16H, H2.6), 7.97 (s, 4H, H2.3^h), 8.15 (s, 4H, H2.3^v) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 10.1 (s, CH_3^v), 10.8 (s, CH_3^h), 36.7 (s, C12), 43.3 (s, C5), 52.8 (s, C2.4), 65.2 (s, C10), 65.6 (s, C2.1^v), 65.7 (s, C11), 67.6 (s, C2.1^h), 113.8 (s, C8), 124.2 (s, C2.3^v), 124.3 (s, C1^h), 124.8 (s, C1^v), 126.0 (s, C4^v), 127.7 (s, C2.7), 127.9 (s, C2.3^h), 128.1 (s, C2.8), 128.7 (s, C2.6), 129.8 (s, C7), 129.6 (s, C4^h), 131.8 (s, C3^v), 133.4 (s, C3^h), 134.5 (s, C6), 135.6 (s, C2.5), 143.2 (s, C2.2^v), 143.3 (s, C2.2^h), 153.8 (s, C2^h), 153.8 (s, C2^v), 155.8 (s, C9) ppm. IR ν_{max} (KBr): 1174 (ν_s), 1353 (ν_{as}) (R-O-SO_2-R′) cm^{-1}. Anal. Calcd. for $C_{148}H_{144}N_{24}S_4O_{24}$ (%): C, 64.16; H, 5.20; N, 12.14; S, 4.62. Found (%): C, 64.18; H, 5.19; N, 12.15; S, 4.60. MALDI-MS: *m/z*: 2770 $[M+1]^+$, 2791 $[M+Na]^+$, 2808 $[M+K]^+$ (calcd. M = 2769).

Cytotoxicity

The following cell lines were used for the study: M-HeLa clone 11 (cervical epithelioid carcinoma, a HeLa subline, clone M-HeLa); HuTu 80, a human duodenal cell line; and Wi-38, embryonic lung cells from the shared research facility "Vertebrate Cell Culture Collection" at the Institute of Cytology, Russian Academy of Sciences (St. Petersburg).

The cells were grown in standard Igla nutrient medium (PanEco, Moscow) supplemented with 10% fetal calf serum and 1% nonessential amino acids. In vitro cytotoxic activity was determined using the MTT assay.[S9] Results were detected using an InVitroLogic plate reader (Medico-Biological Union, Russia). Absorbance was recorded at 540 nm. IC_{50} values were determined using the online MLA calculator - Quest Graph™ IC50 Calculator (AAT Bioquest, Inc, March 17, 2025).[S10] Experiments for all compounds were repeated three times.

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S10. *Quest Graph™ IC50 Calculator*, AAT Bioquest, Inc., 2025; https://www.aatbio.com/tools/ic50-calculator.

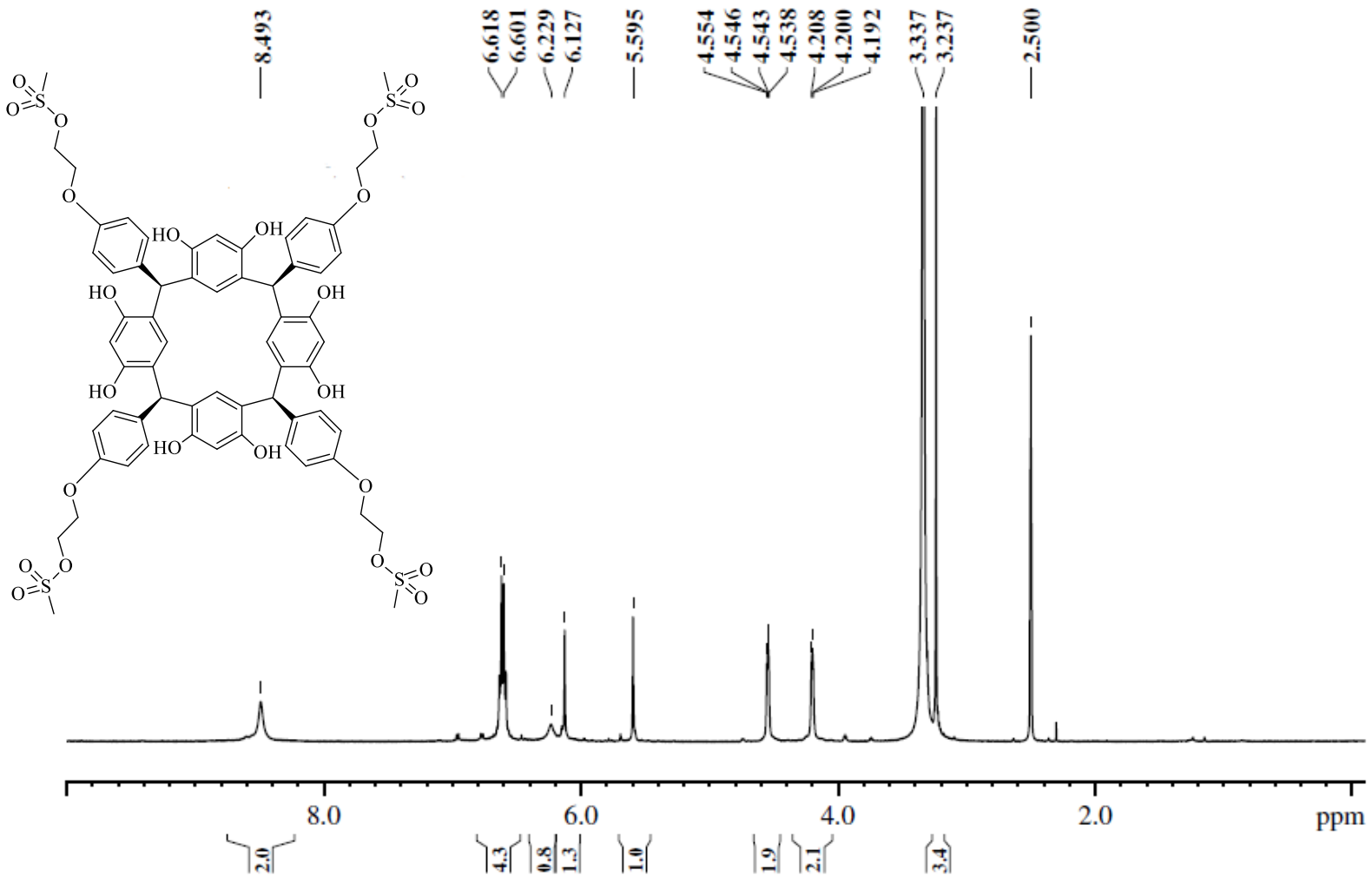

Figure S1. ^{1}H NMR spectrum of calix[4]resorcinol *rccc*-**3a** in DMSO-d_6 (T=303 K)

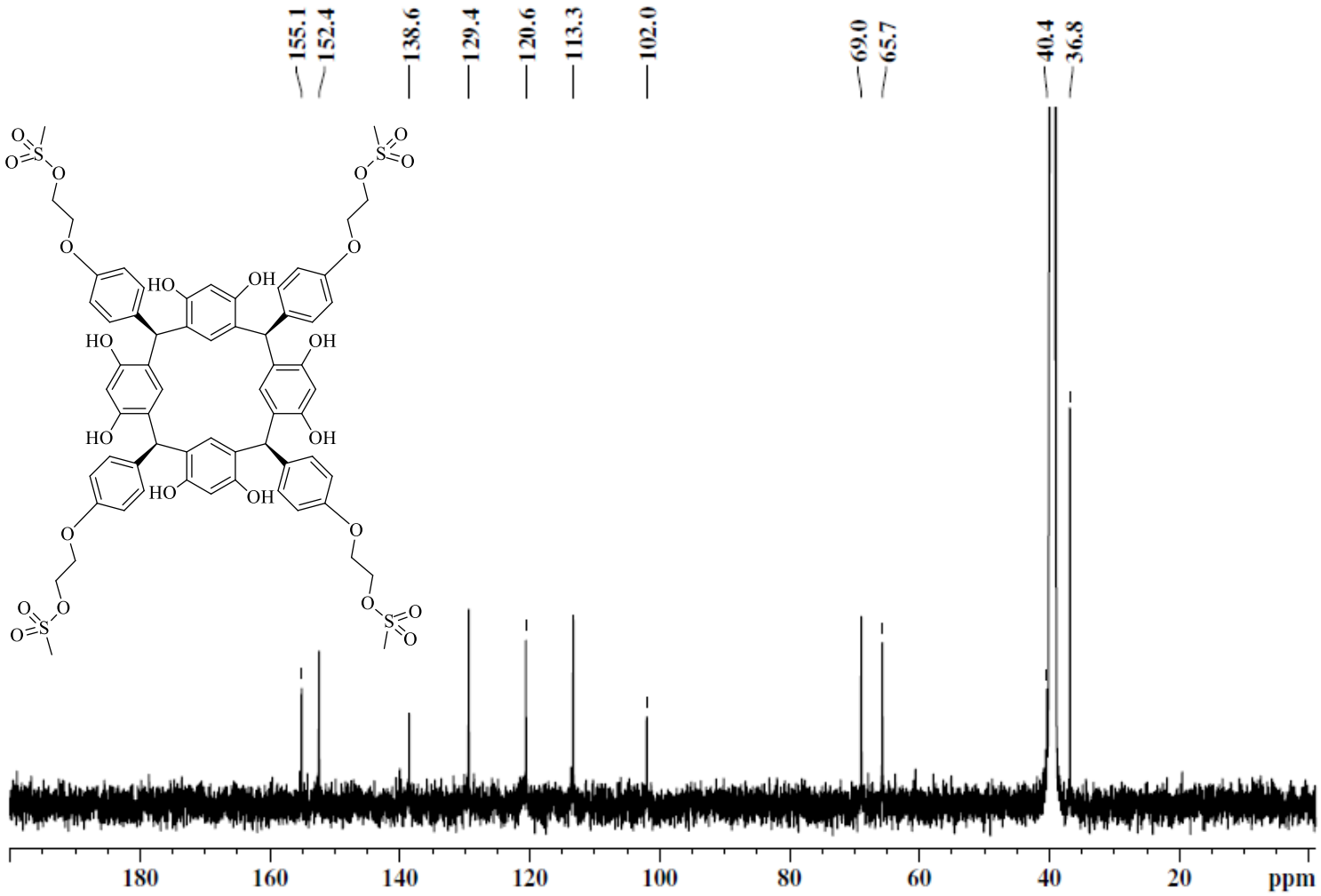

Figure S2. ^{13}C NMR spectrum of calix[4]resorcinol *rccc*-**3a** in DMSO-d_6 (T=303 K)

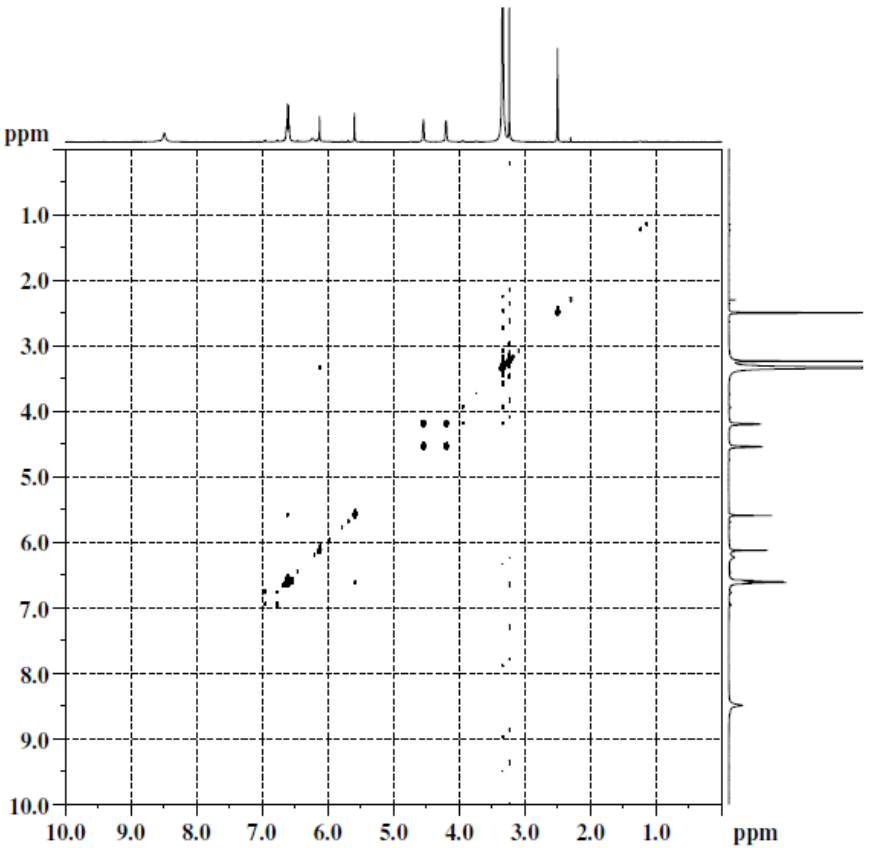

Figure S3. COSY NMR spectrum of calix[4]resorcinol *rccc*-**3a** in DMSO-d_6 (T=303 K)

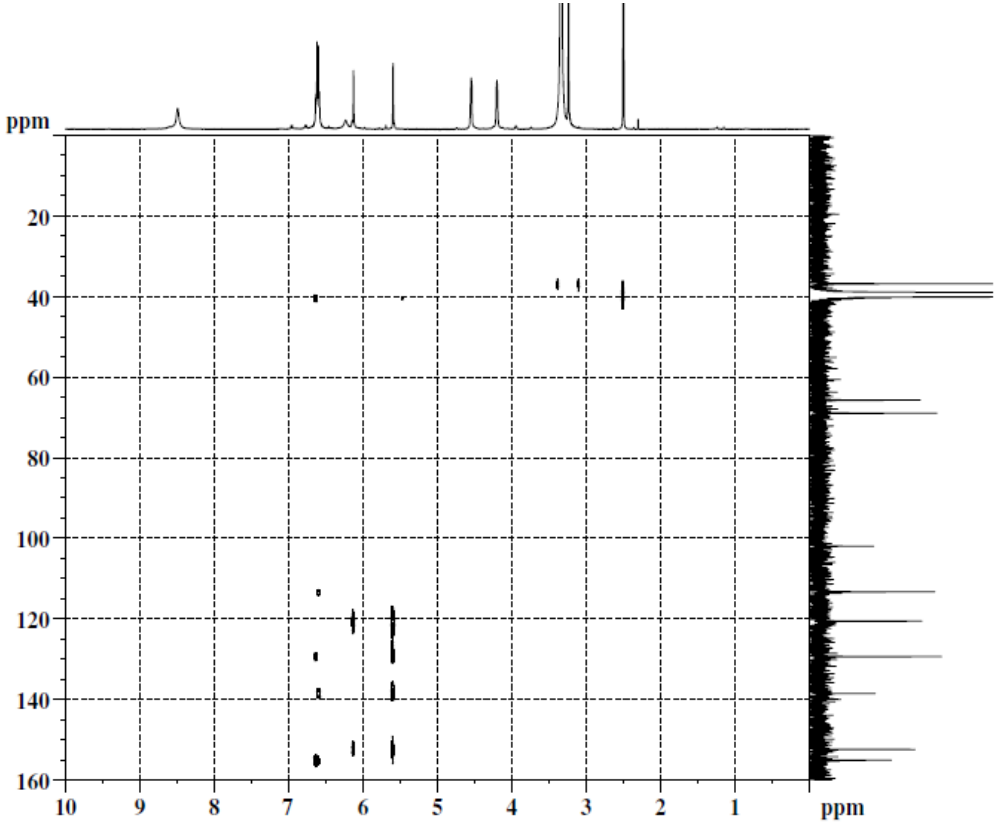

Figure S4. HMBC (^{13}C) NMR spectrum of calix[4]resorcinol *rccc*-**3a** in DMSO-d_6 (T=303 K)

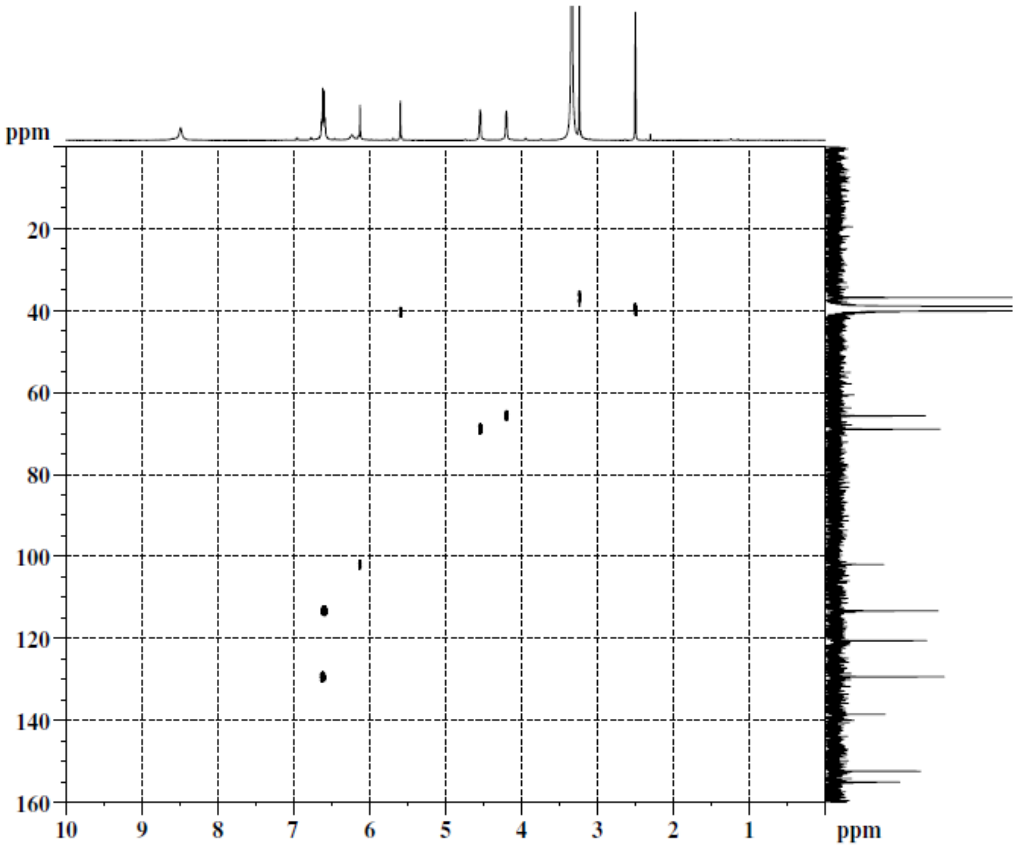

Figure S5. HSQC (^{13}C) NMR spectrum of calix[4]resorcinol *rccc*-**3a** in DMSO-d_6 (T=303 K)

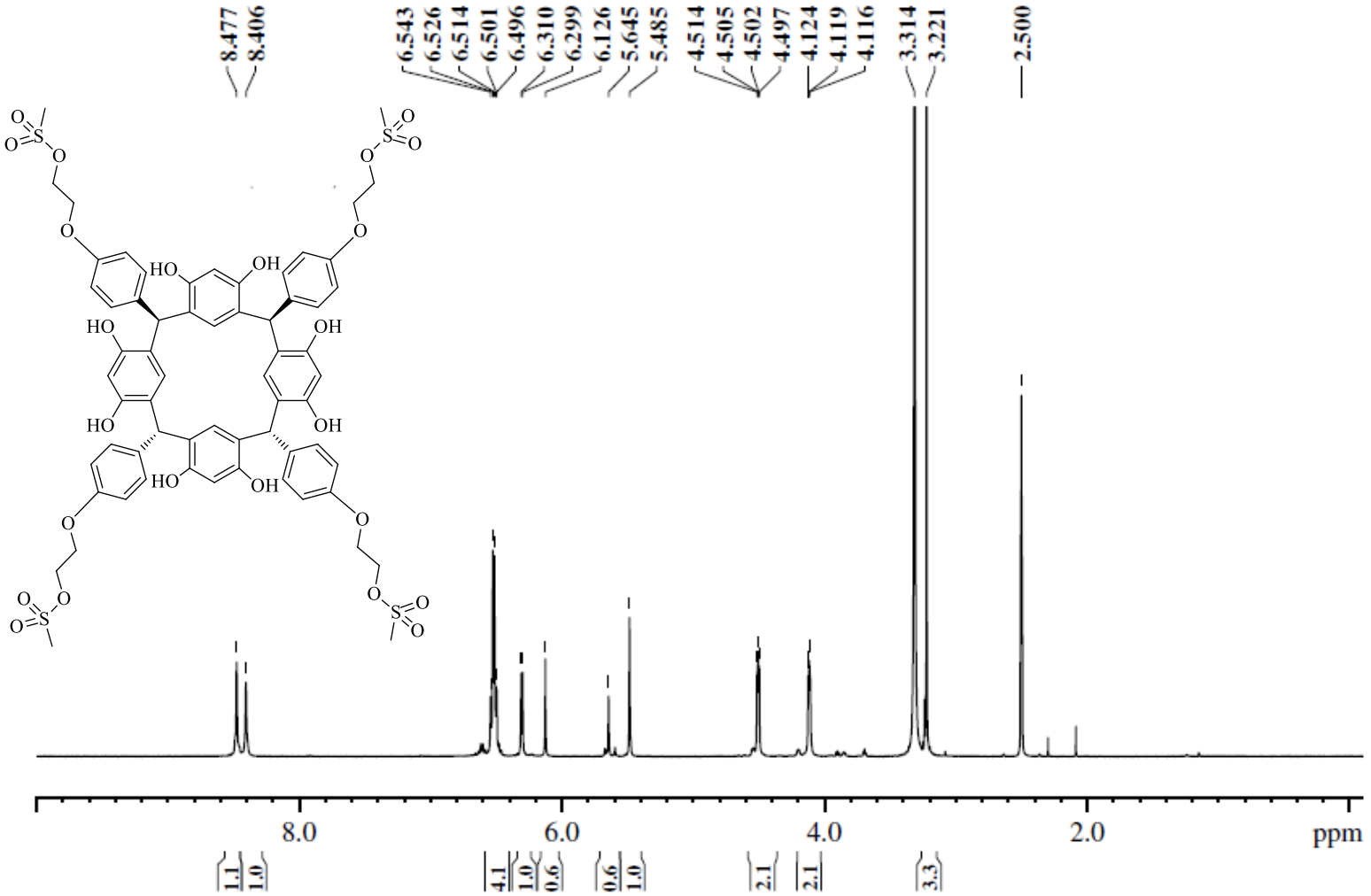

Figure S6. ^{1}H NMR spectrum of calix[4]resorcinol *rctt*-**4a** in DMSO-d_6 (T=303 K)

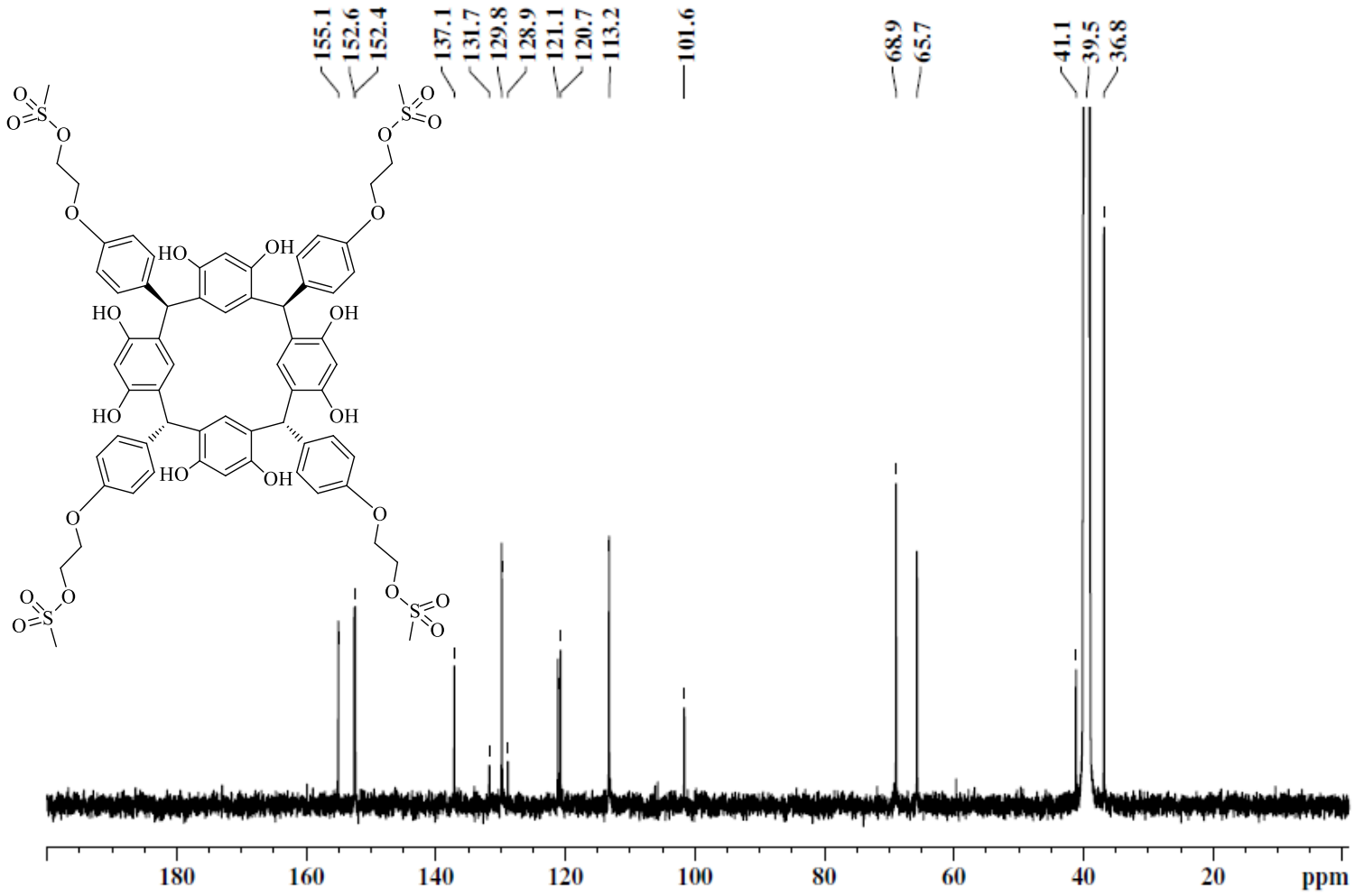

Figure S7. ^{13}C NMR spectrum of calix[4]resorcinol *rctt*-**4a** in DMSO-d_6 (T=303 K)

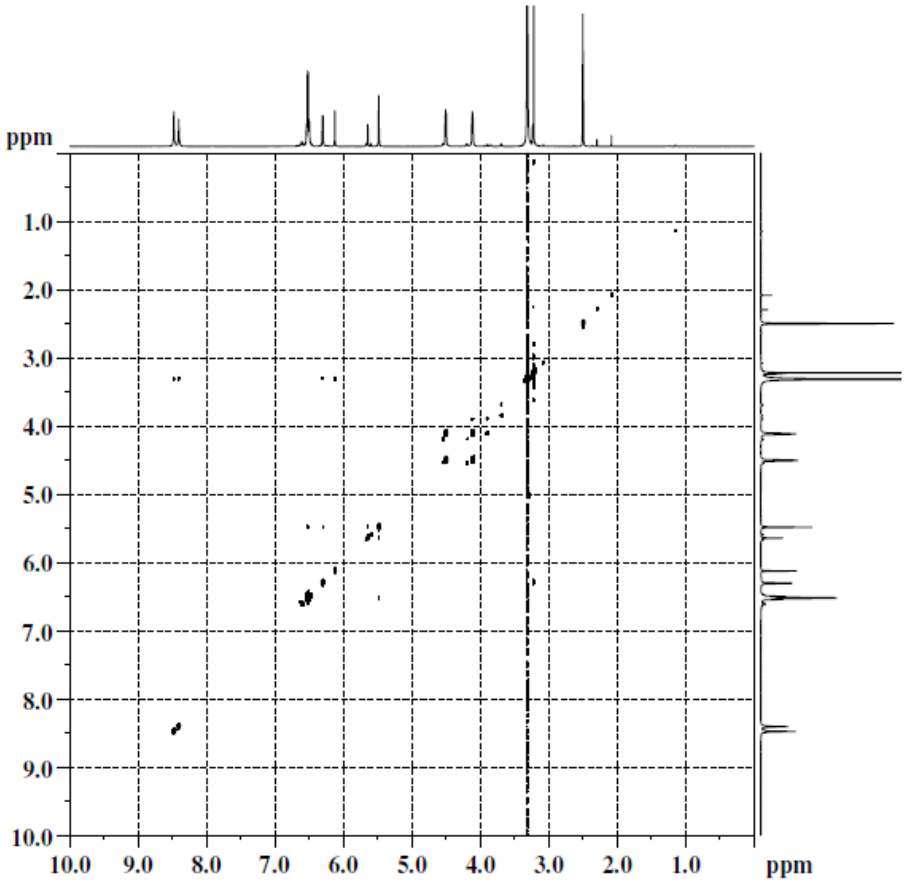

Figure S8. COSY NMR spectrum of calix[4]resorcinol *rctt*-**4a** in DMSO-d_6 (T=303 K)

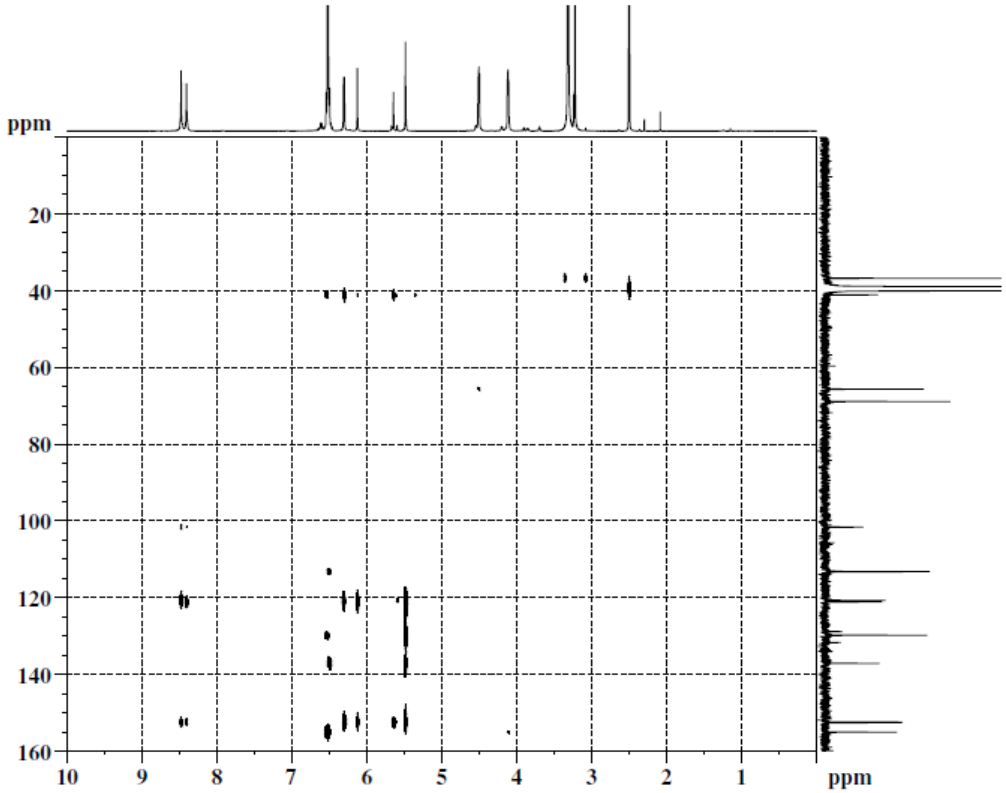

Figure S9. HMBC (^{13}C) NMR spectrum of calix[4]resorcinol *rctt*-**4a** in DMSO-d_6 (T=303 K)

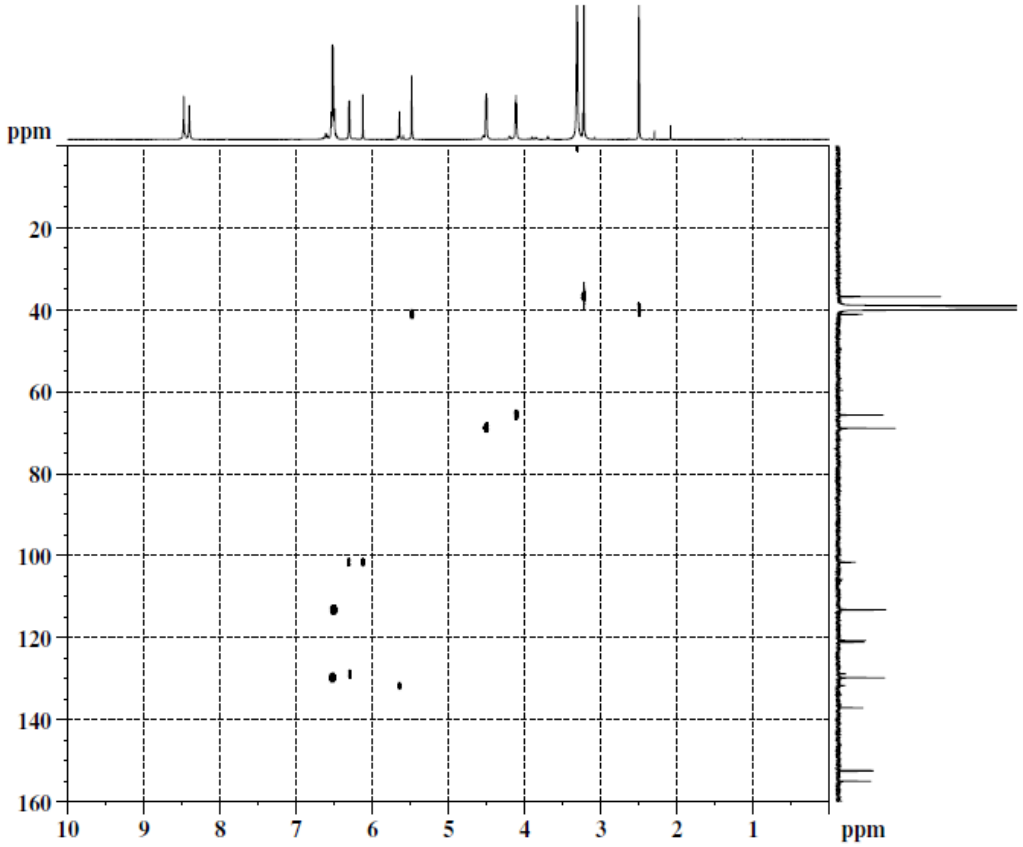

Figure S10. HSQC (^{13}C) NMR spectrum of calix[4]resorcinol *rctt*-**4a** in DMSO-d_6 (T=303 K)

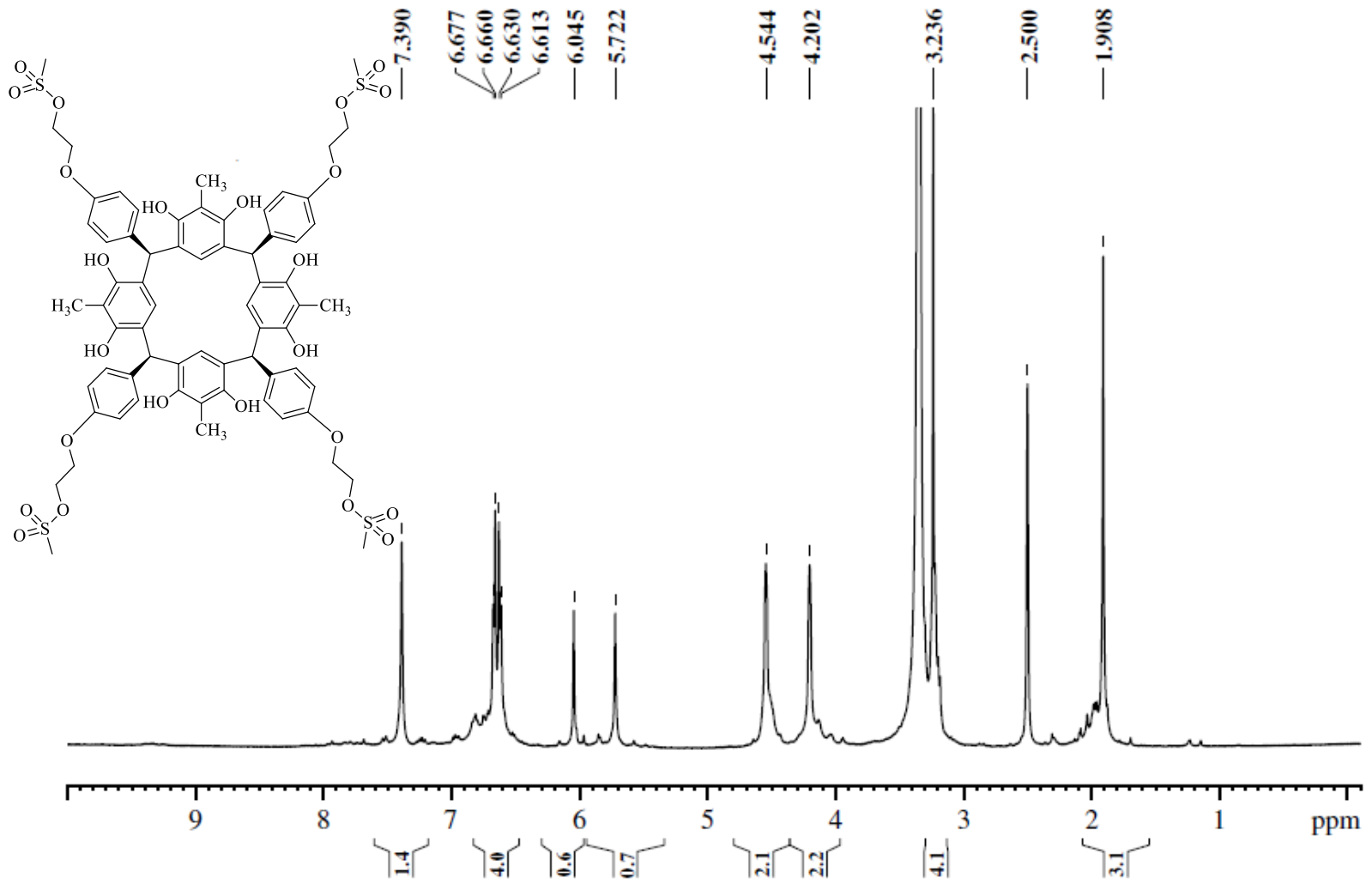

Figure S11. ^{1}H NMR spectrum of calix[4]resorcinol *rccc*-**3b** in DMSO-d_6 (T=303 K)

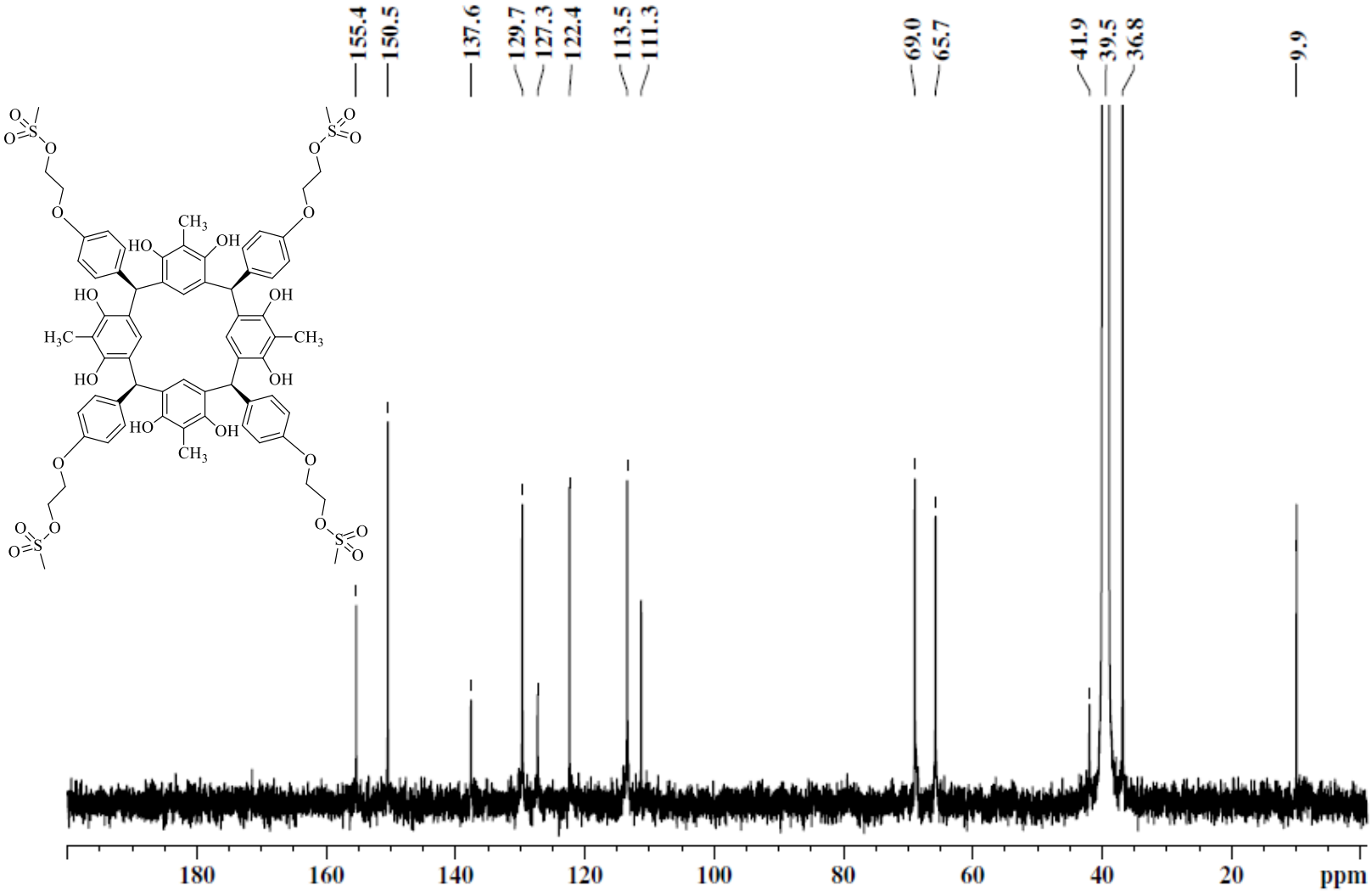

Figure S12. ^{13}C NMR spectrum of calix[4]resorcinol *rccc*-**3b** in DMSO-d_6 (T=303 K)

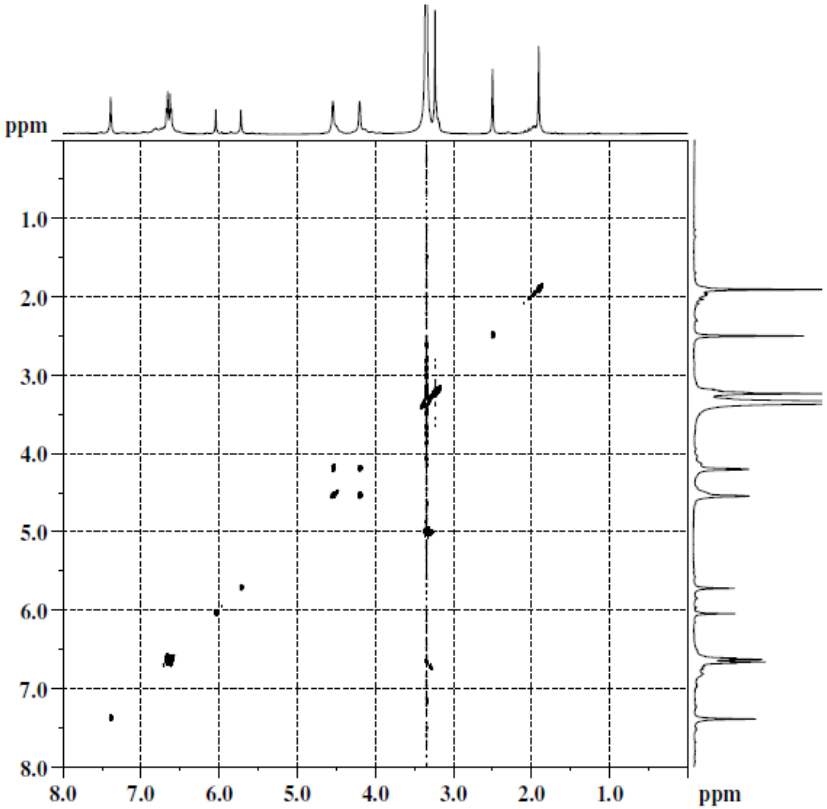

Figure S13. COSY NMR spectrum of calix[4]resorcinol *rccc*-**3b** in DMSO-d_6 (T=303 K)

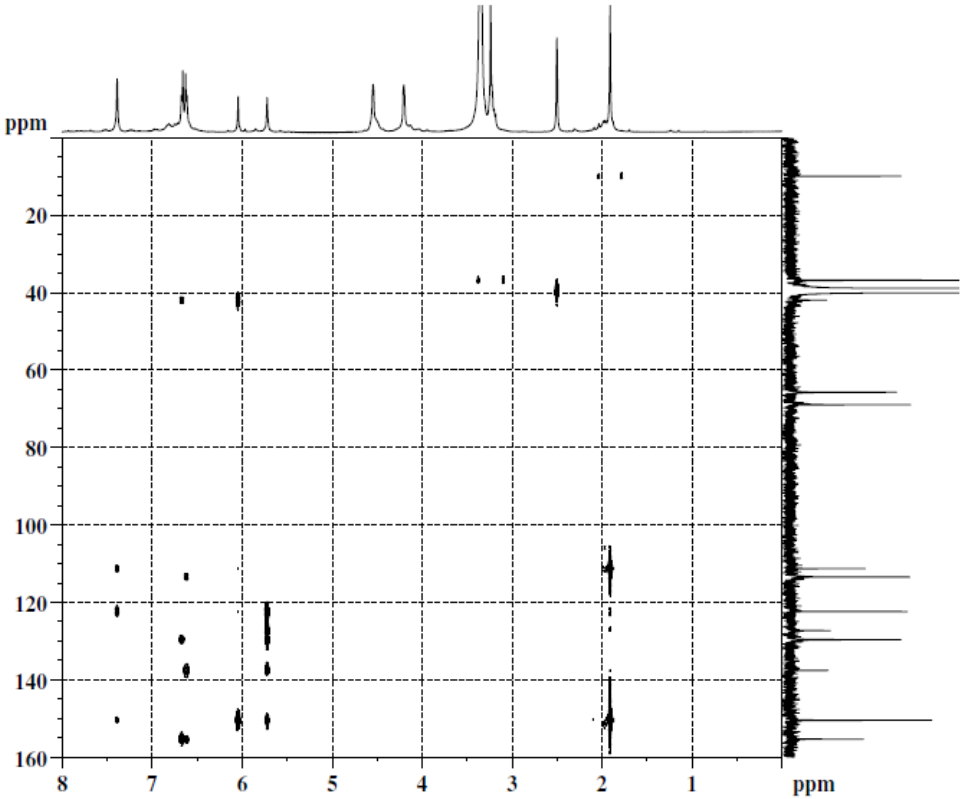

Figure S14. HMBC (^{13}C) NMR spectrum of calix[4]resorcinol *rccc*-**3b** in DMSO-d_6 (T=303 K)

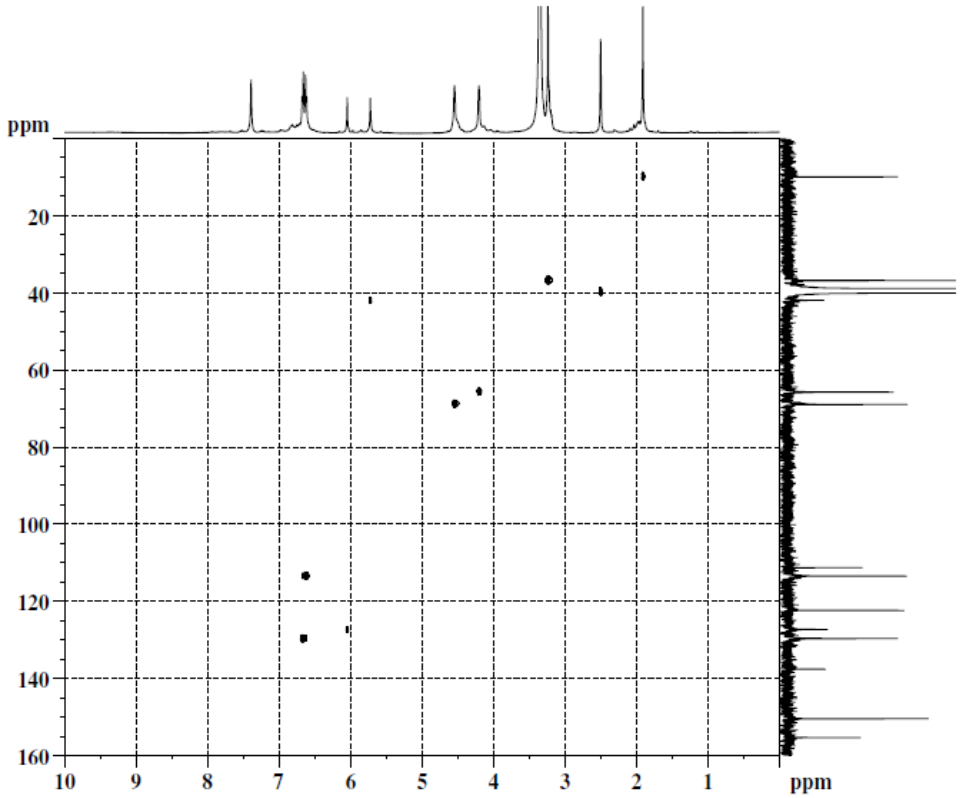

Figure S15. HSQC (^{13}C) NMR spectrum of calix[4]resorcinol *rccc*-**3b** in DMSO-d_6 (T=303 K)

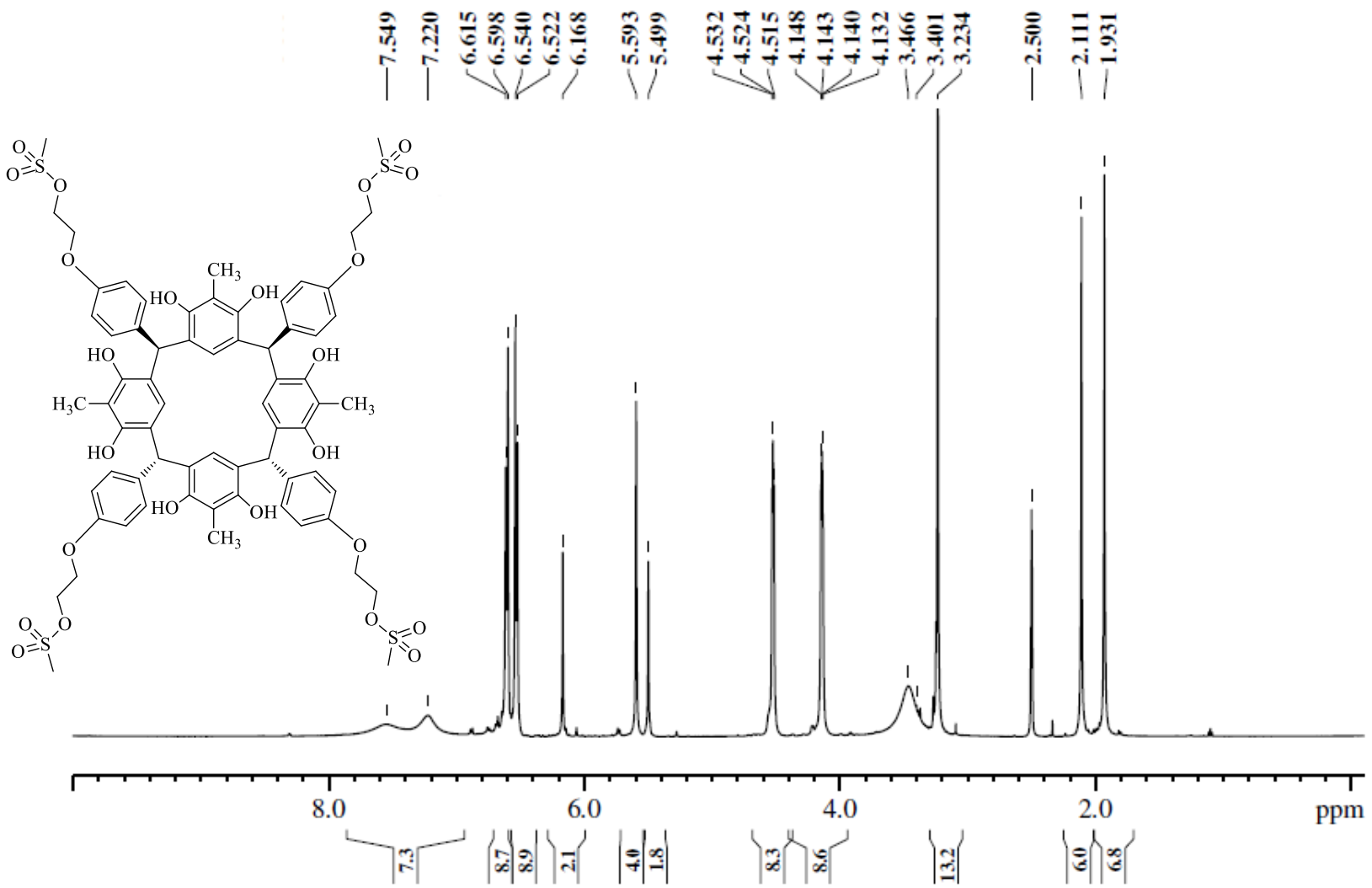

Figure S16. ^{1}H NMR spectrum of calix[4]resorcinol *rctt*-**4b** in DMSO-d_6 (T=303 K)

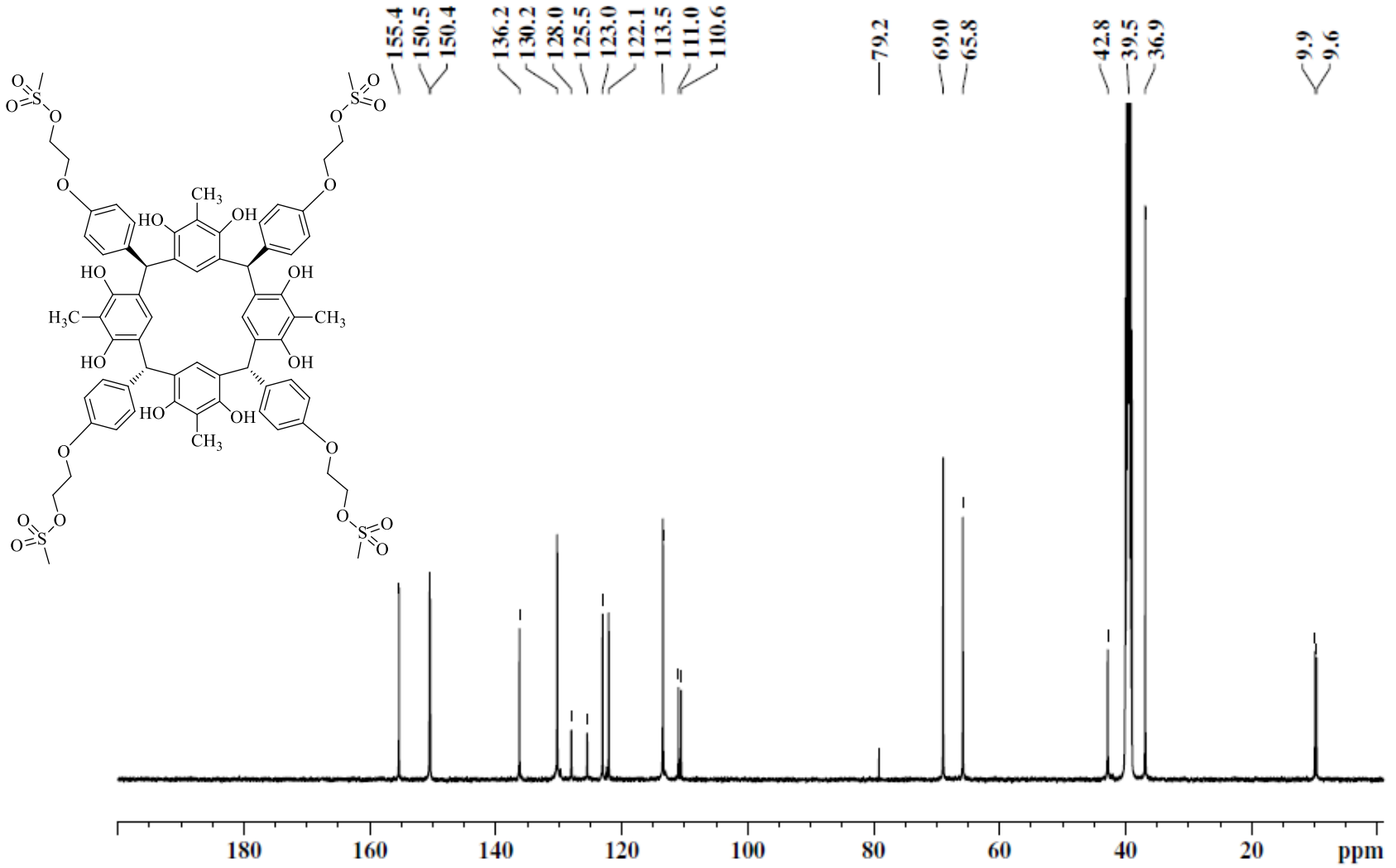

Figure S17. ^{13}C NMR spectrum of calix[4]resorcinol *rctt*-**4b** in DMSO-d_6 (T=303 K)

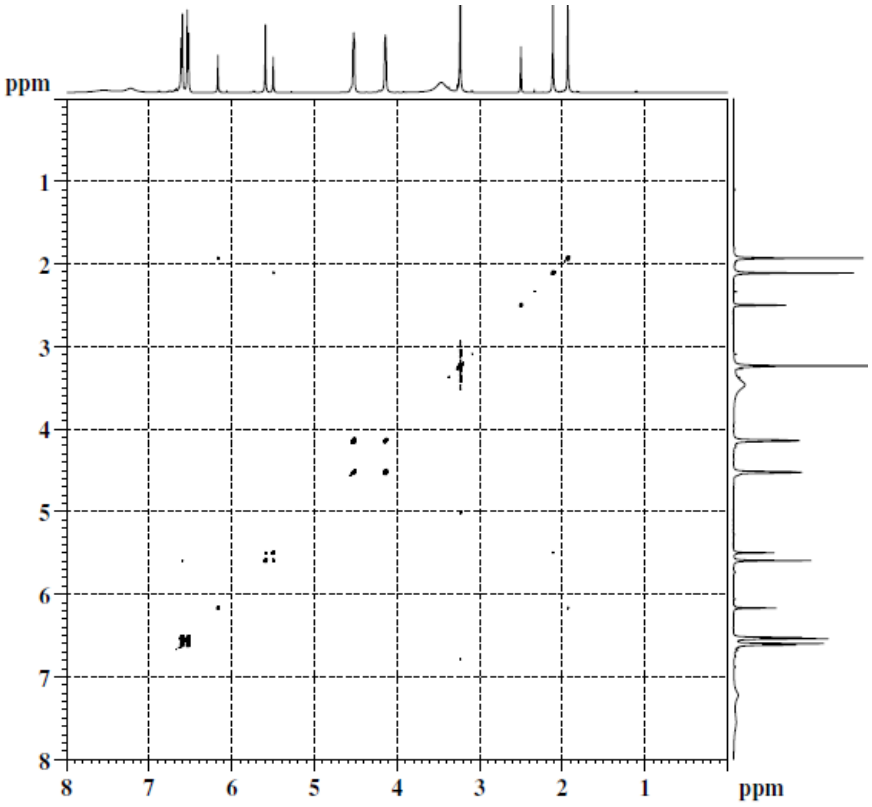

Figure S18. COSY NMR spectrum of calix[4]resorcinol *rctt*-**4b** in DMSO-d_6 (T=303 K)

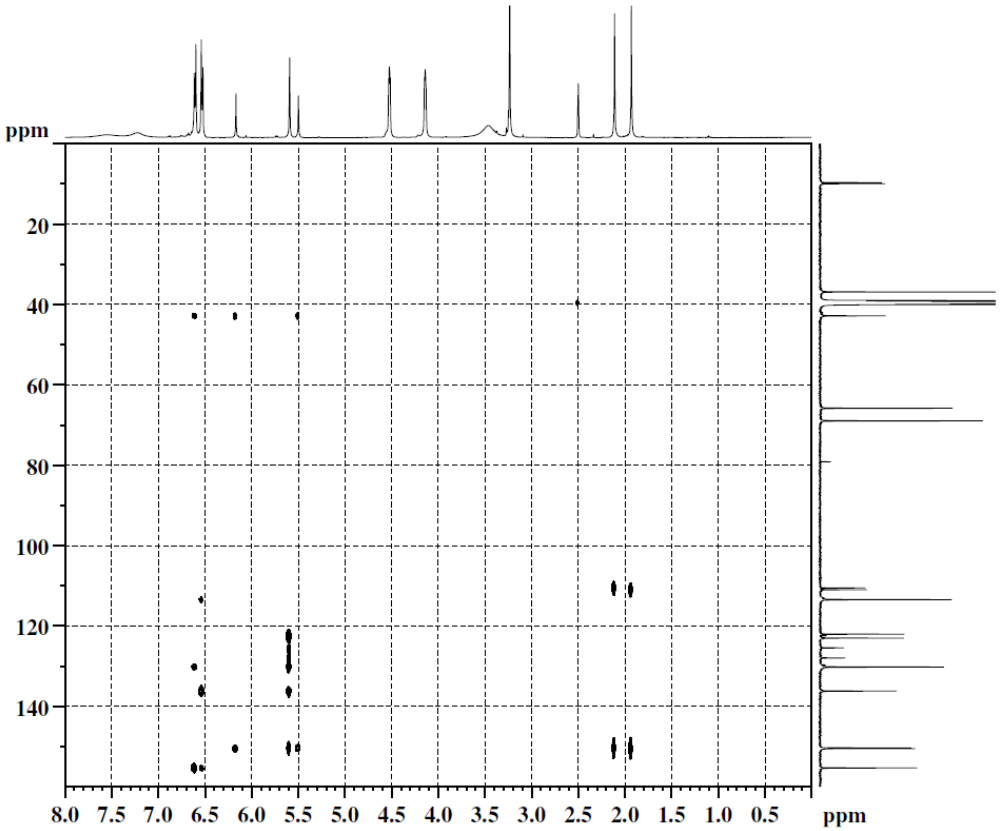

Figure S19. HMBC (^{13}C) NMR spectrum of calix[4]resorcinol *rctt*-**4b** in DMSO-d_6 (T=303 K)

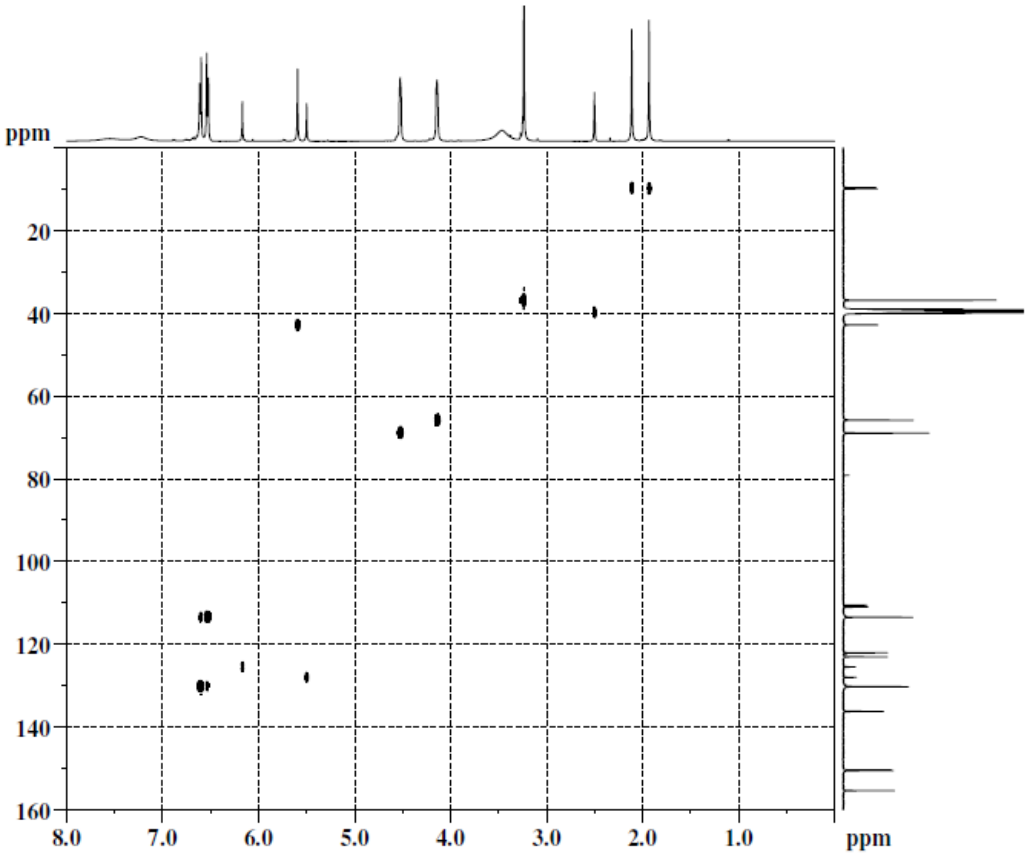

Figure S20. HSQC (^{13}C) NMR spectrum of calix[4]resorcinol *rctt*-**4b** in DMSO-d_6 (T=303 K)

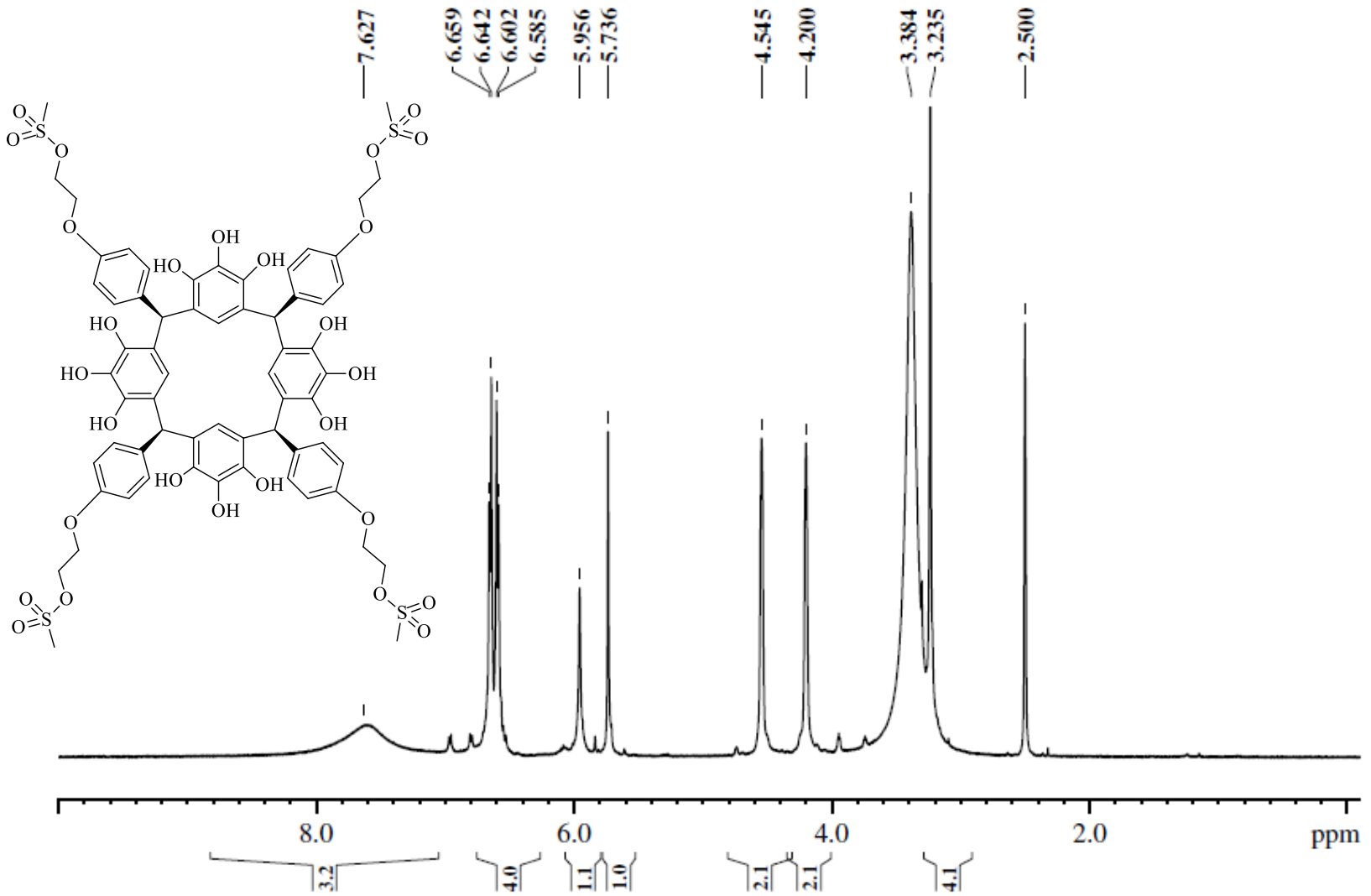

Figure S21. ^{1}H NMR spectrum of calix[4]resorcinol *rccc*-**3c** in DMSO-d_6 (T=303 K)

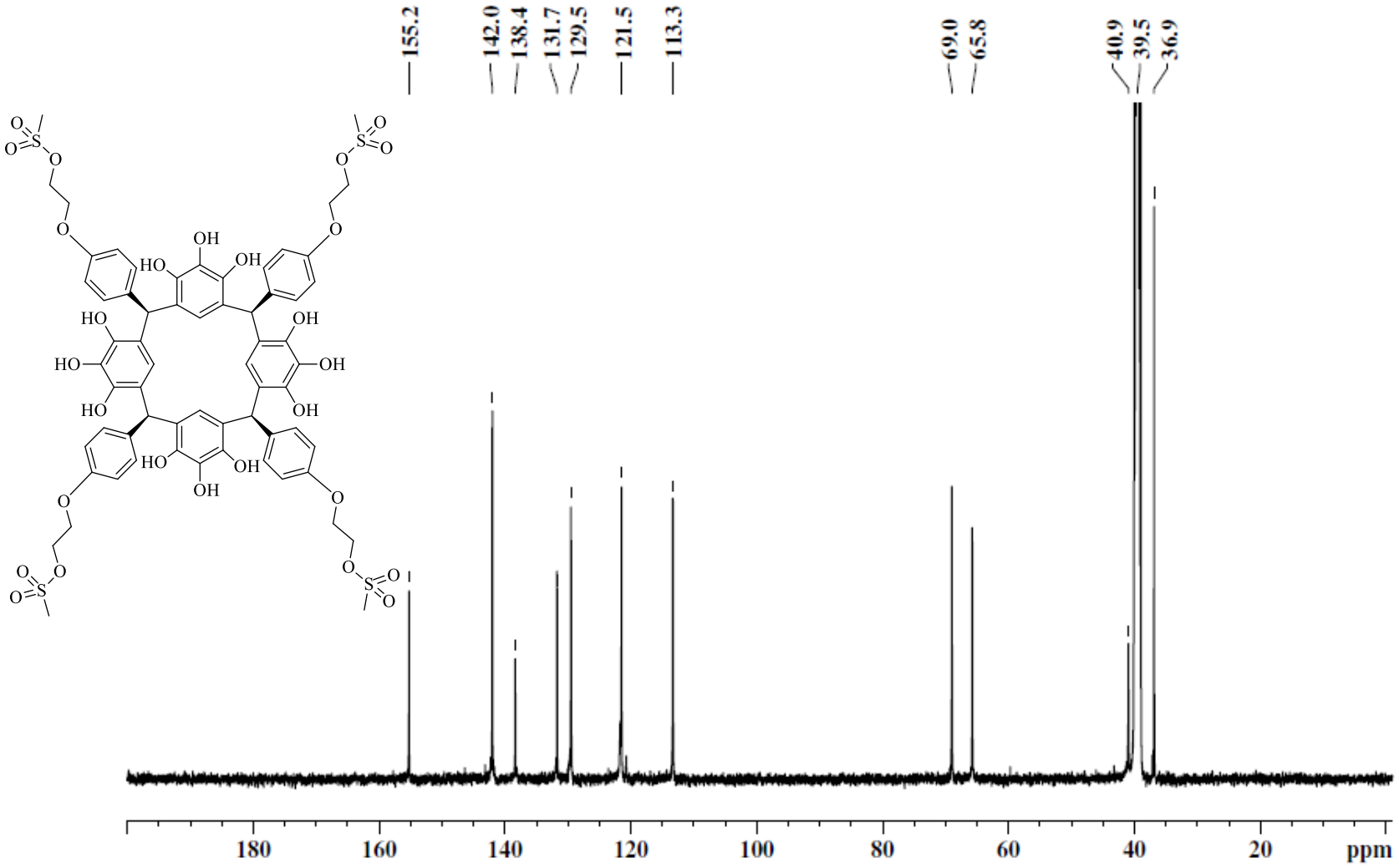

Figure S22. ^{13}C NMR spectrum of calix[4]resorcinol *rccc*-**3c** in DMSO-d_6 (T=303 K)

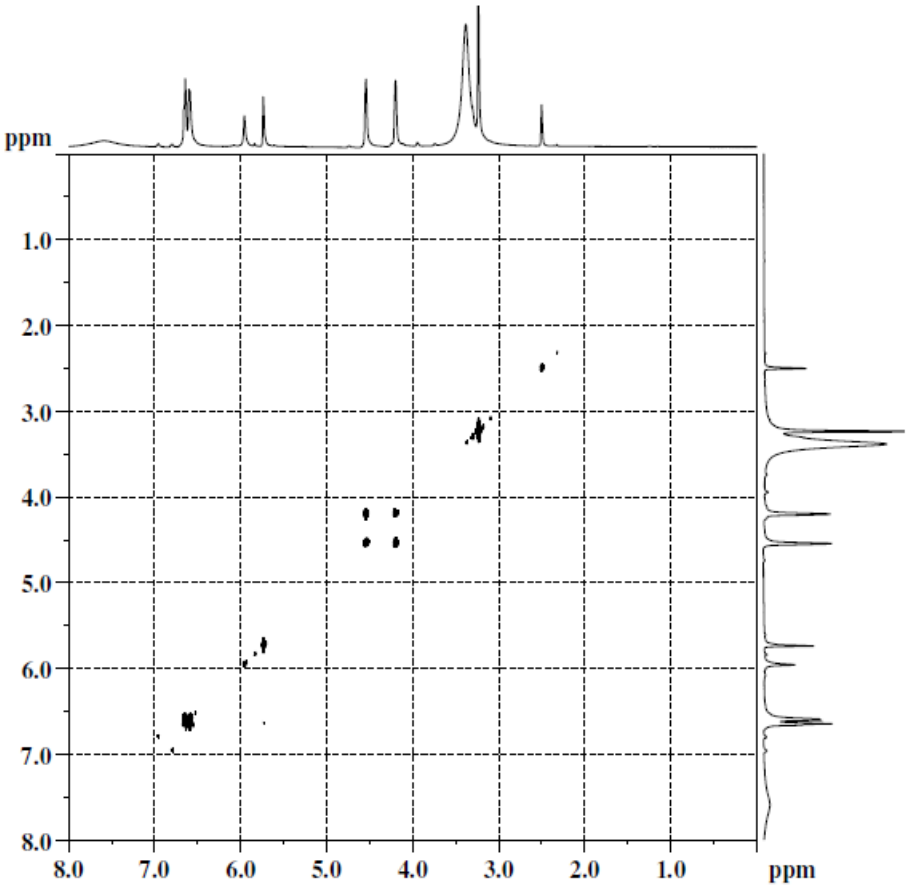

Figure S23. COSY NMR spectrum of calix[4]resorcinol *rccc*-**3c** in DMSO-d_6 (T=303 K)

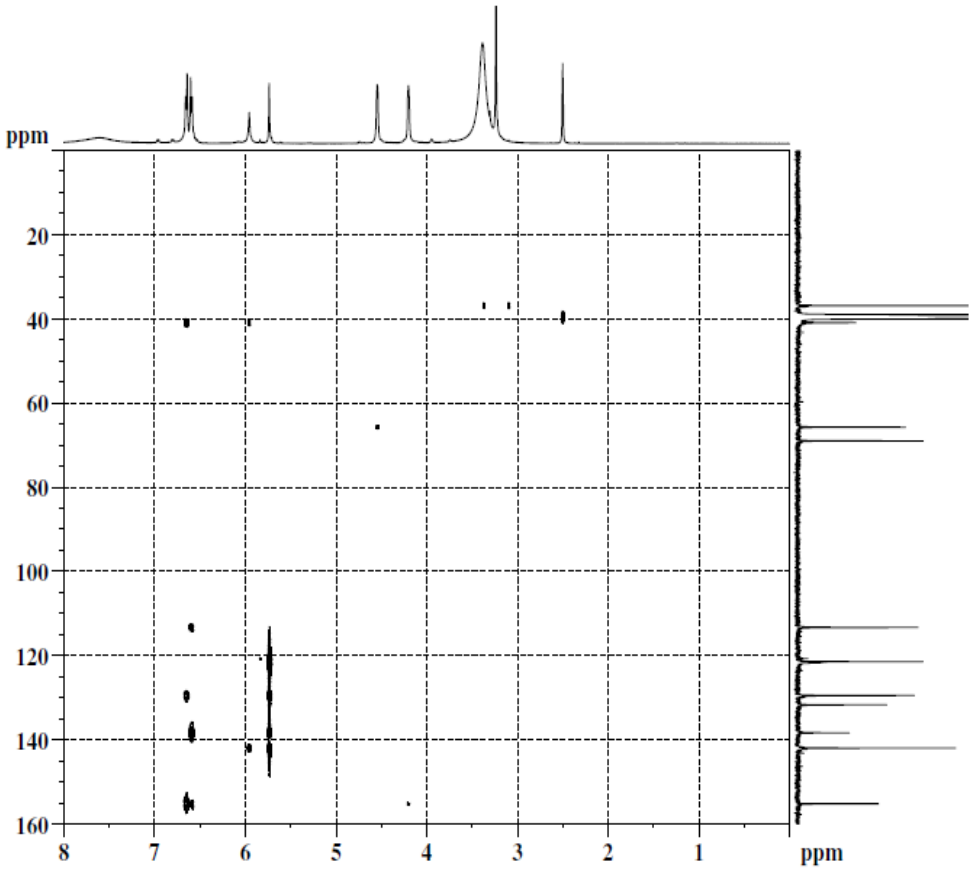

Figure S24. HMBC (^{13}C) NMR spectrum of calix[4]resorcinol *rccc*-**3c** in DMSO-d_6 (T=303 K)

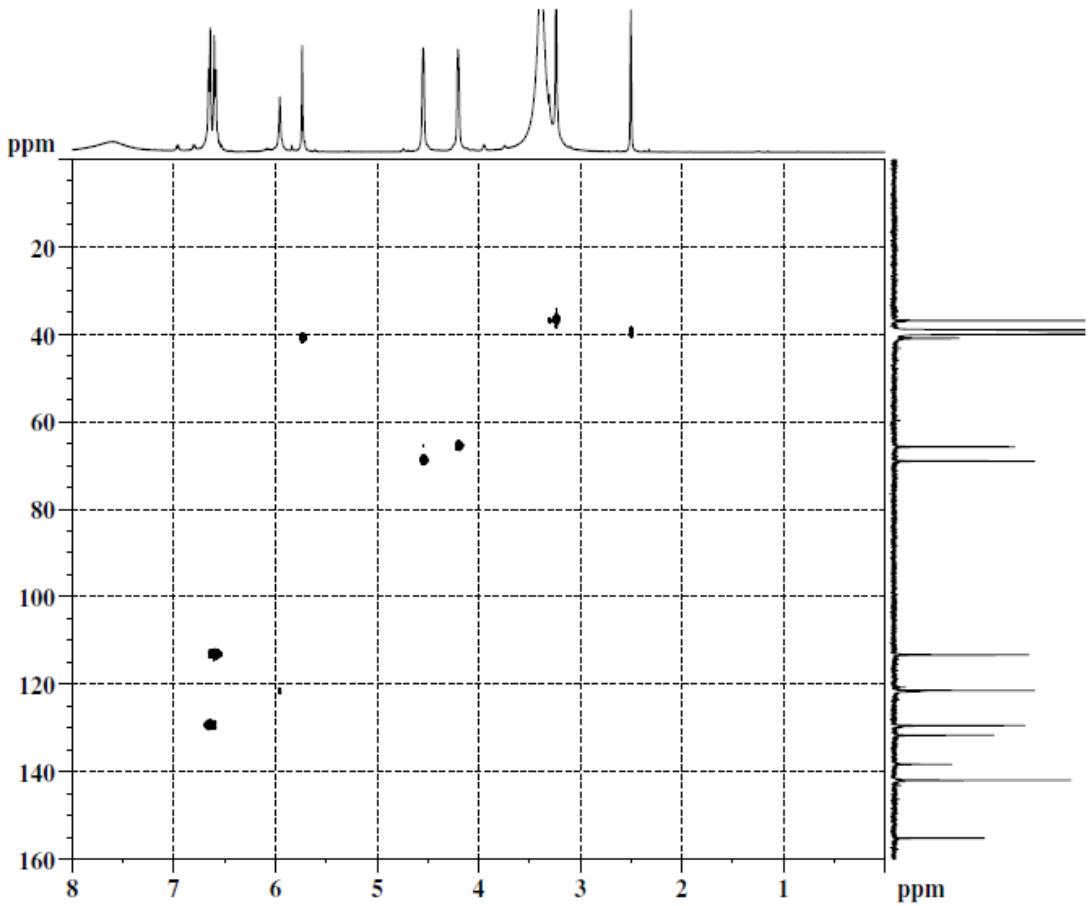

Figure S25. HSQC (^{13}C) NMR spectrum of calix[4]resorcinol *rccc*-**3c** in DMSO-d_6 (T=303 K)

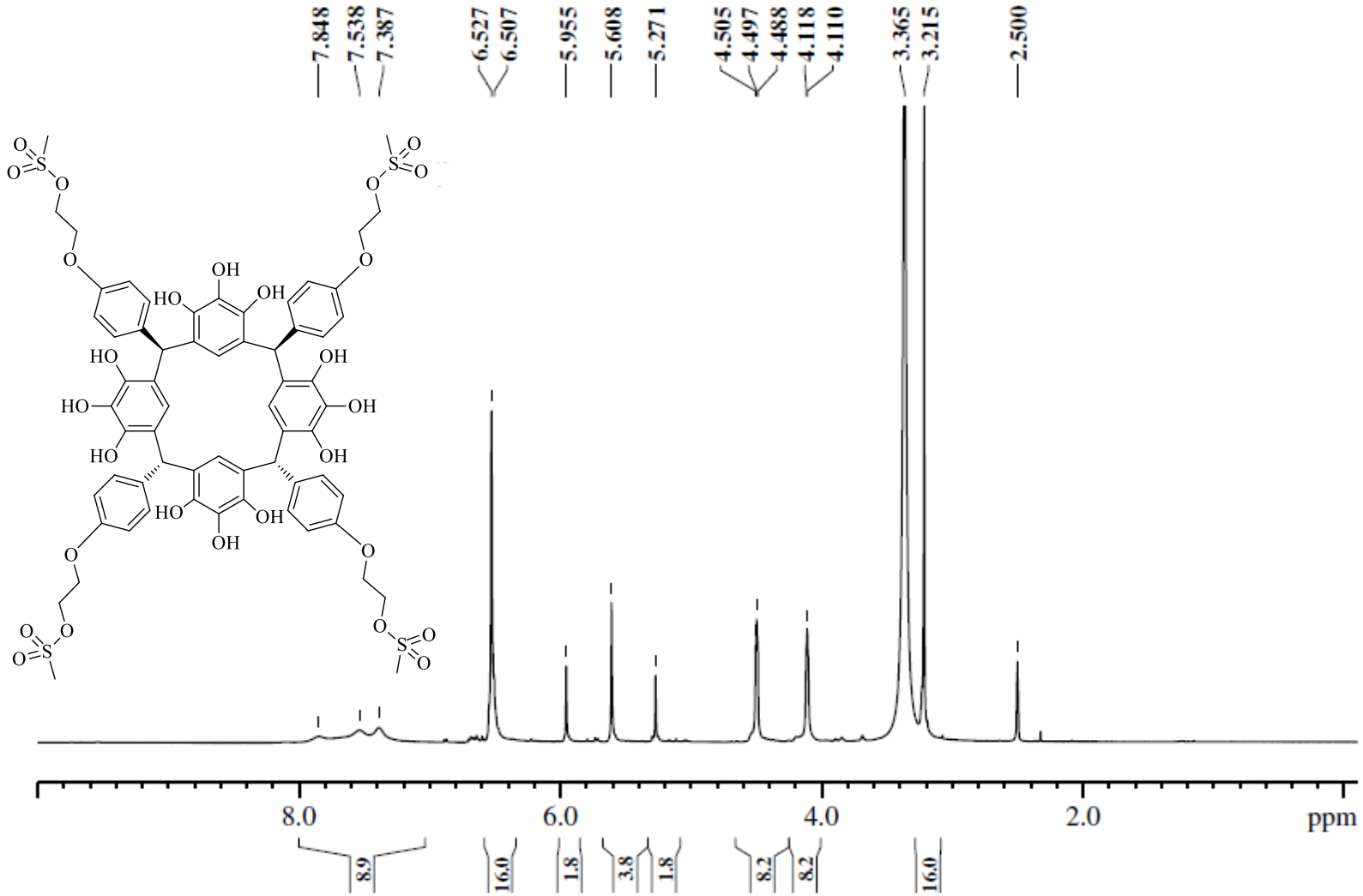

Figure S26. ^{1}H NMR spectrum of calix[4]resorcinol *rctt*-**4c** in DMSO-d_6 (T=303 K)

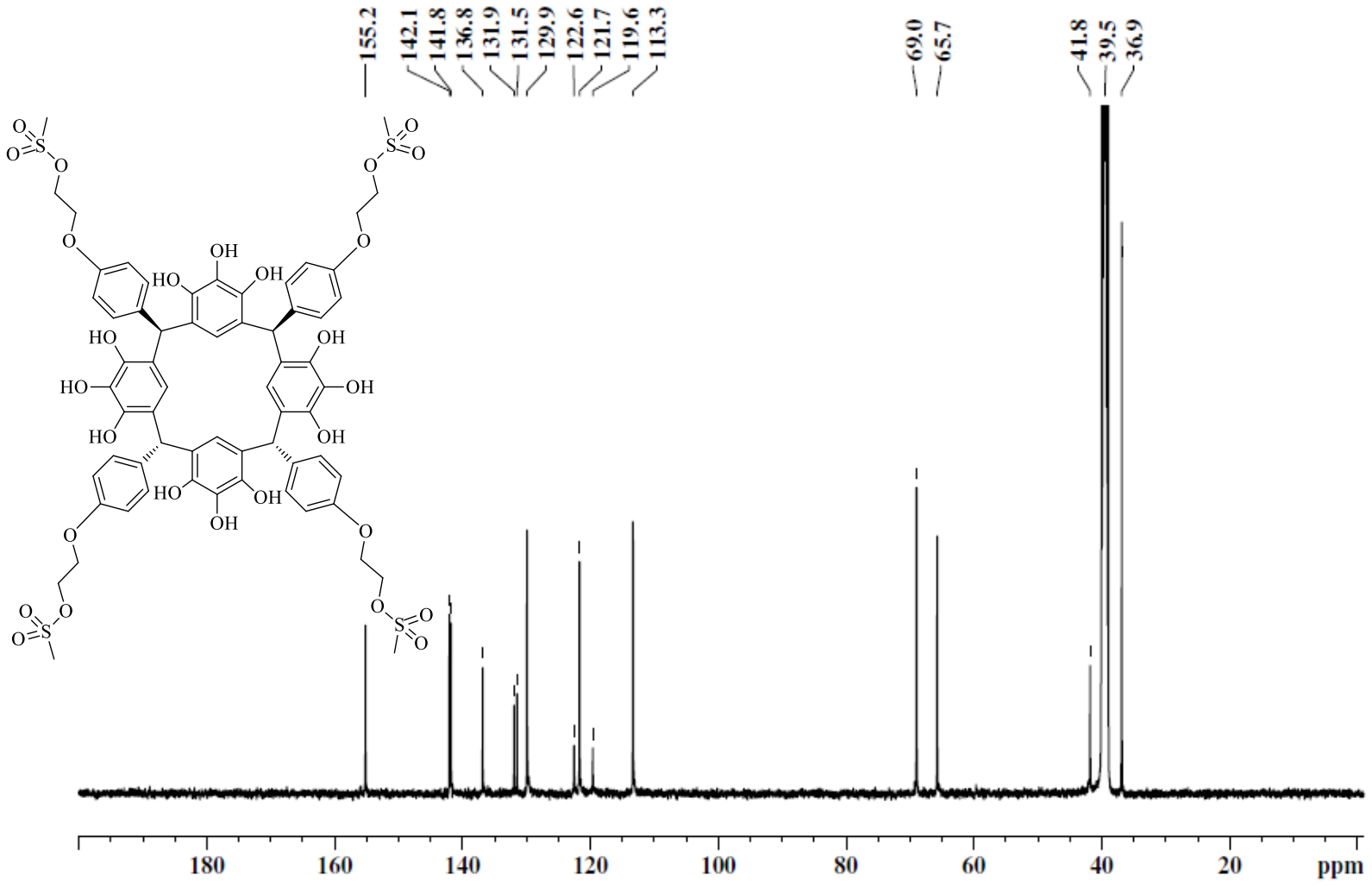

Figure S27. ^{13}C NMR spectrum of calix[4]resorcinol *rctt*-**4c** in DMSO-d_6 (T=303 K)

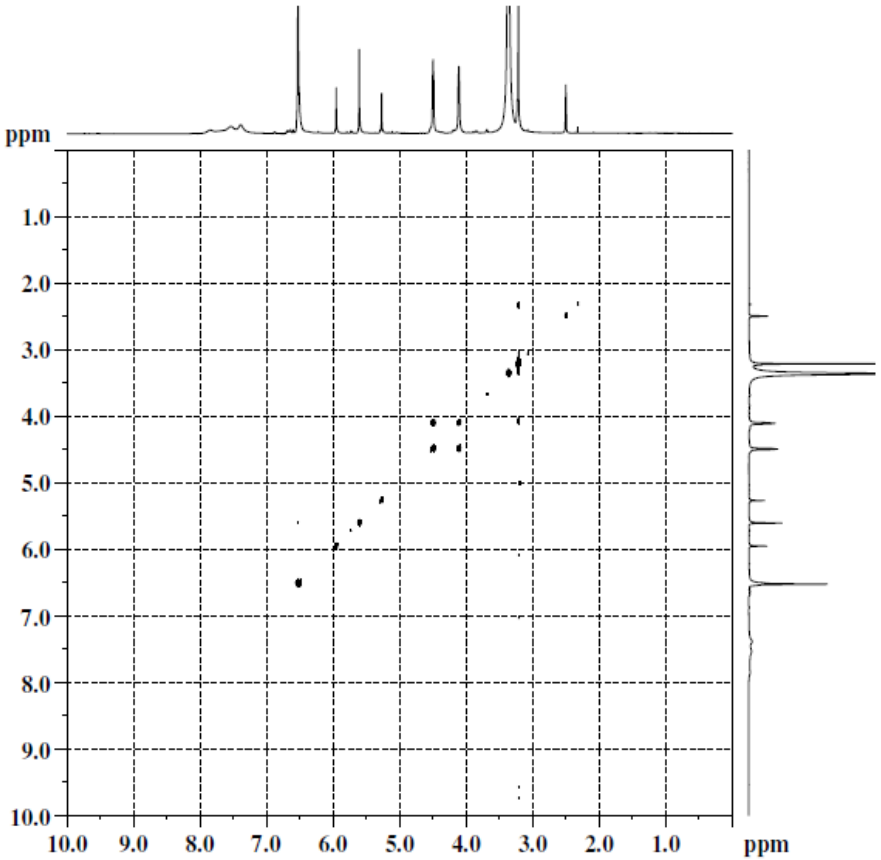

Figure S28. COSY NMR spectrum of calix[4]resorcinol *rctt*-**4c** in DMSO-d_6 (T=303 K)

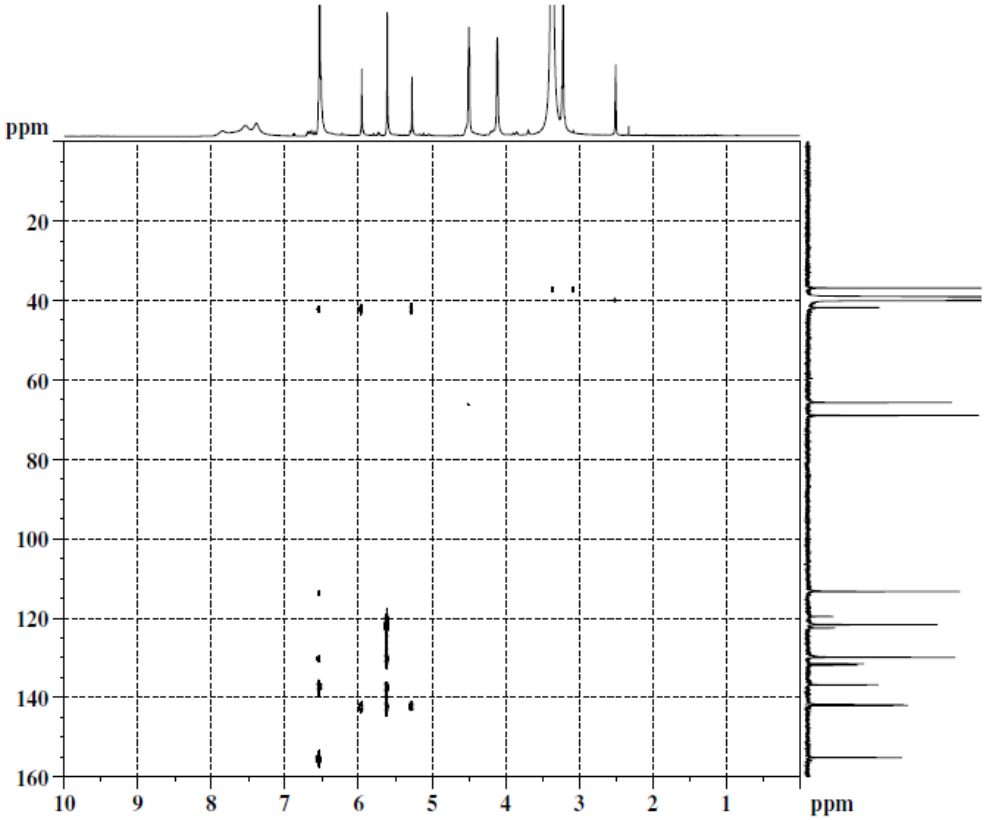

Figure S29. HMBC (^{13}C) NMR spectrum of calix[4]resorcinol *rctt*-**4c** in DMSO-d_6 (T=303 K)

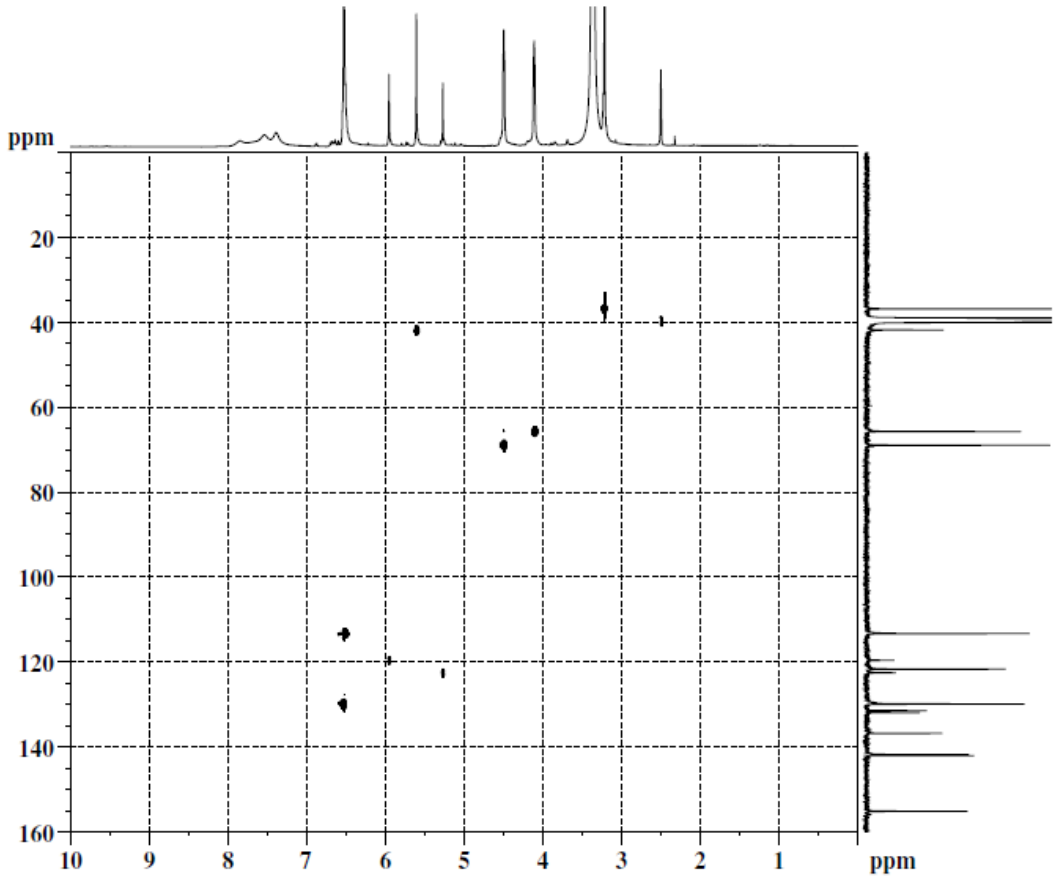

Figure S30. HSQC (^{13}C) NMR spectrum of calix[4]resorcinol *rctt*-**4c** in DMSO-d_6 (T=303 K)

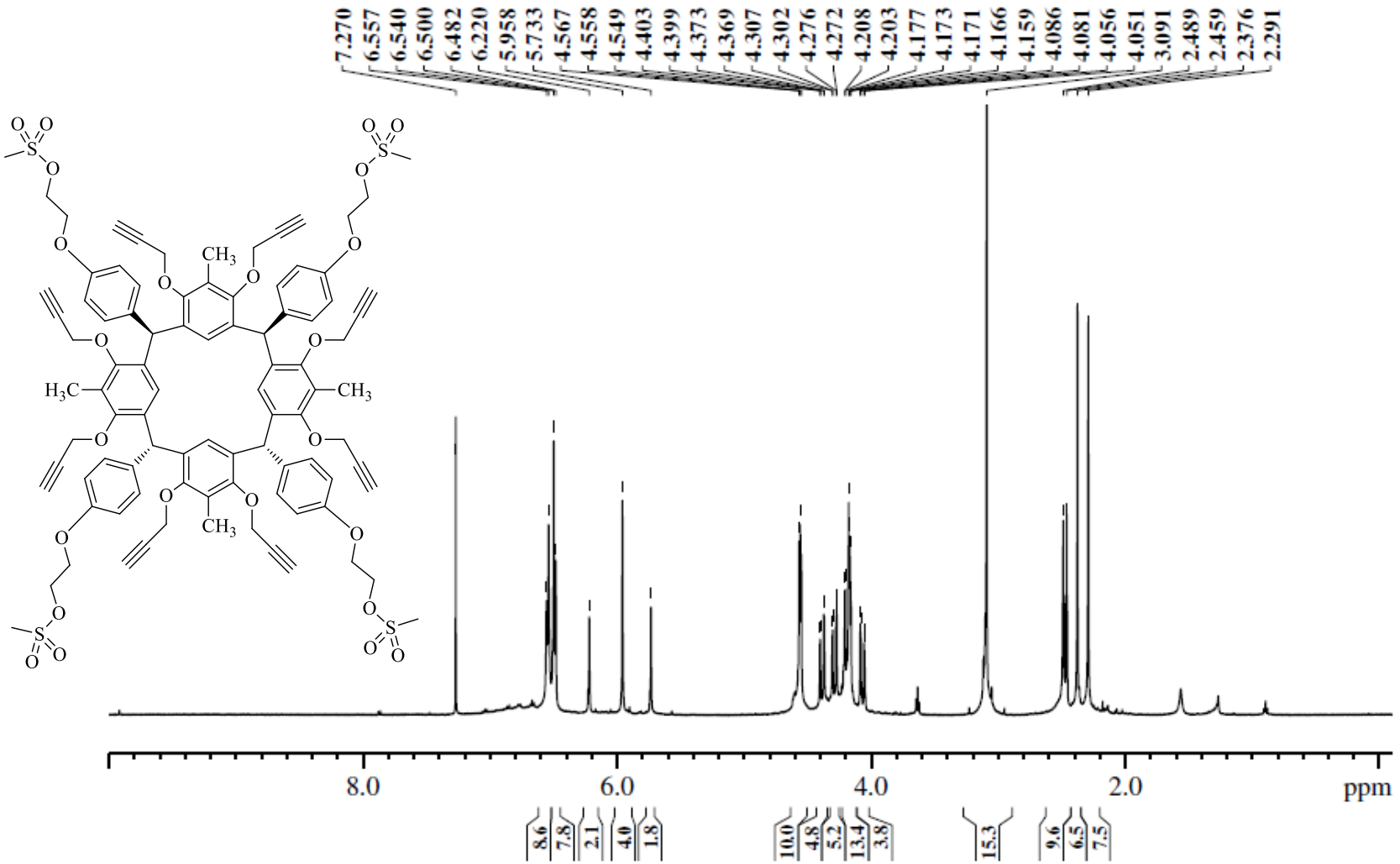

Figure S31. ^{1}H NMR spectrum of calix[4]resorcinol *rctt*-**5** in $CDCl_3$ (T=303 K)

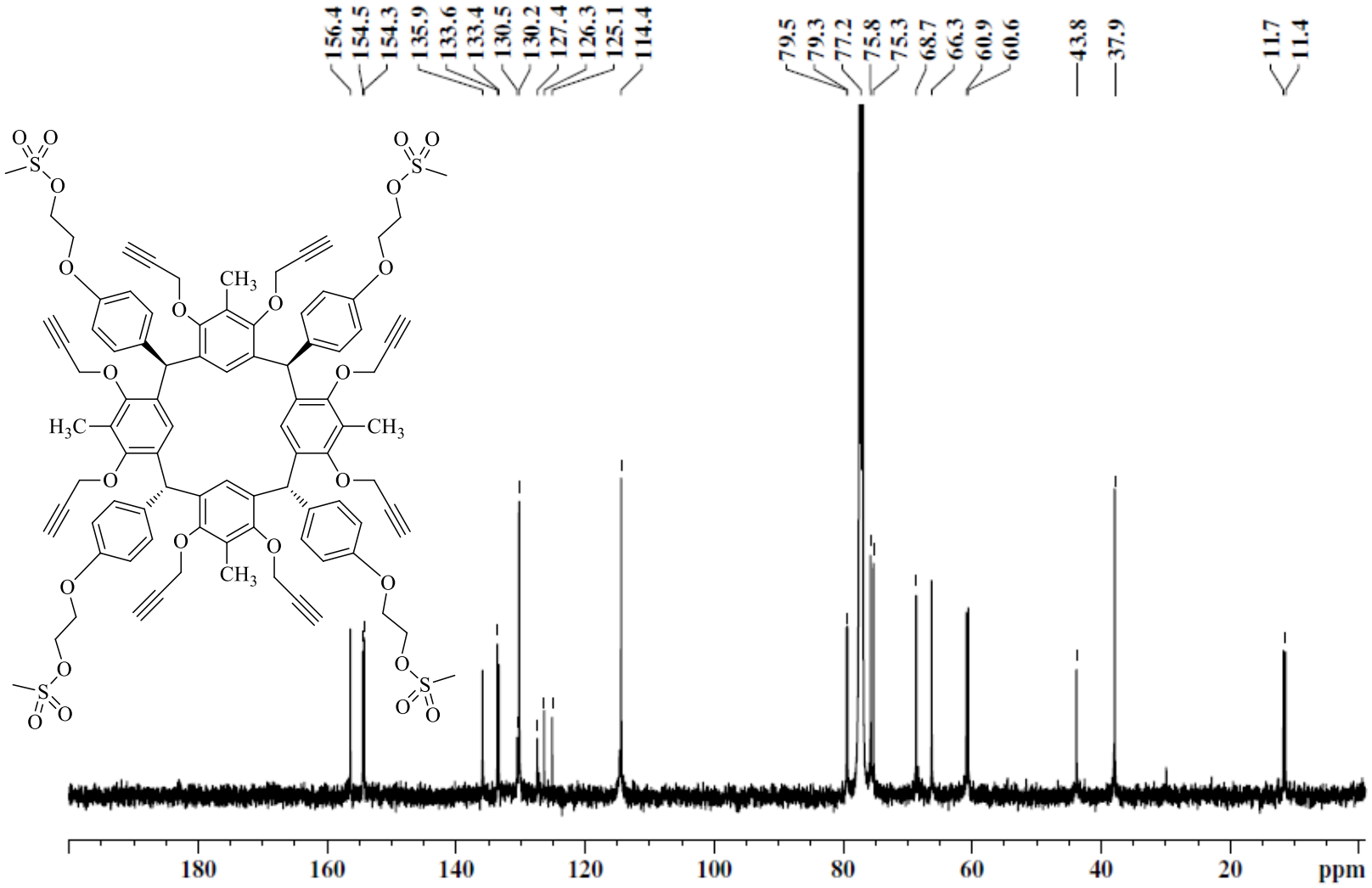

Figure S32. ^{13}C NMR spectrum of calix[4]resorcinol *rctt*-**5** in $CDCl_3$ (T=303 K)

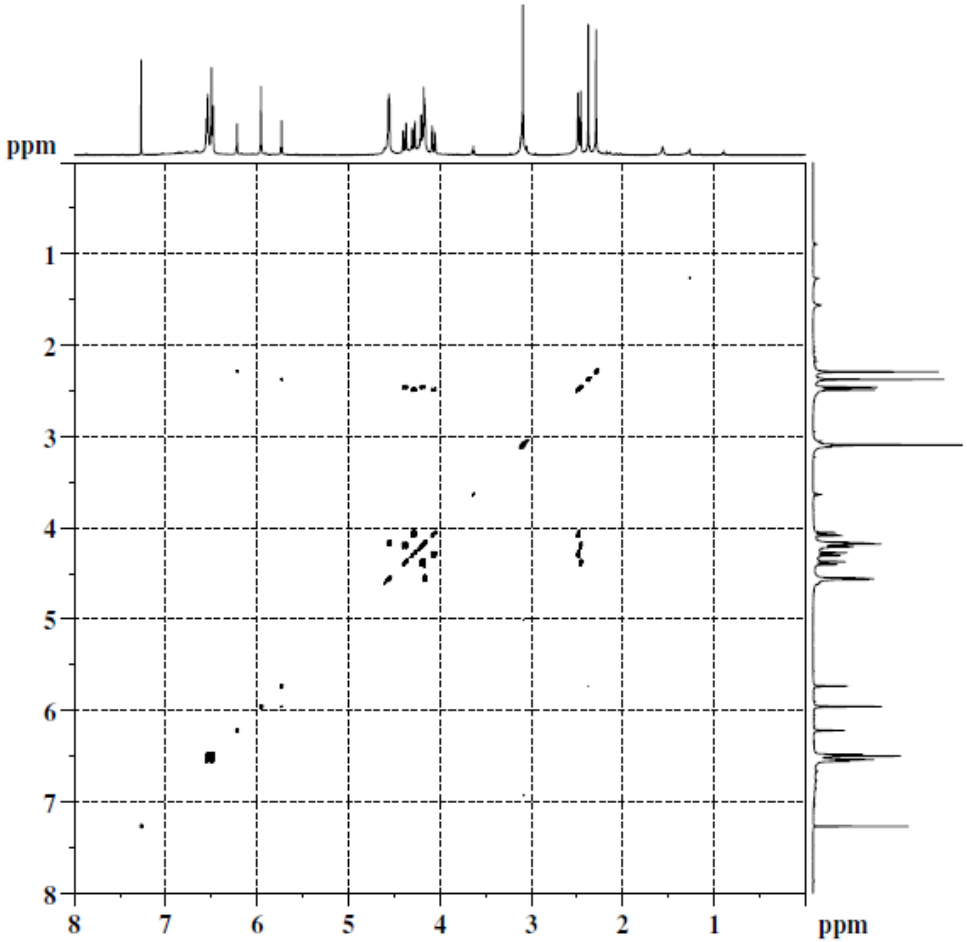

Figure S33. COSY NMR spectrum of calix[4]resorcinol *rctt*-**5** in $CDCl_3$ (T=303 K)

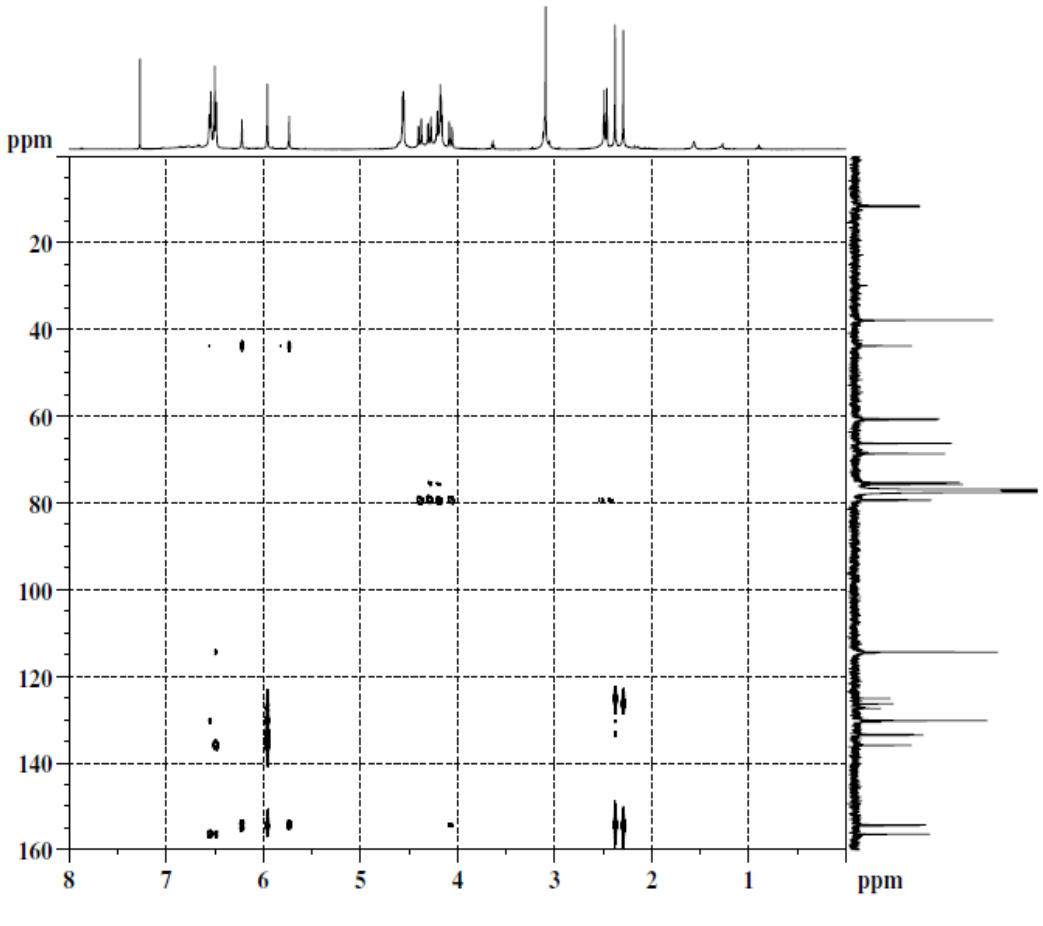

Figure S34. HMBC (^{13}C) NMR spectrum of calix[4]resorcinol *rctt*-**5** in $CDCl_3$ (T=303 K)

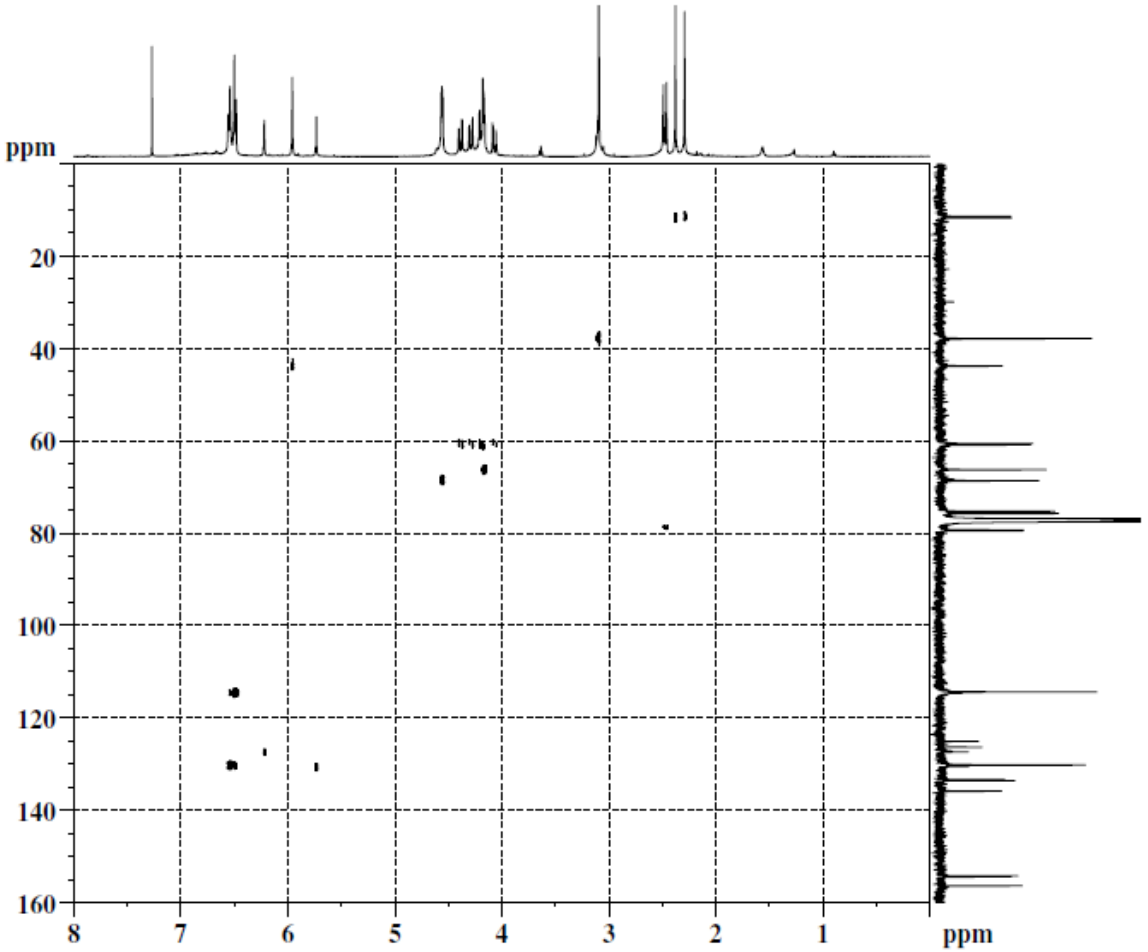

Figure S35. HSQC (^{13}C) NMR spectrum of calix[4]resorcinol *rctt*-**5** in $CDCl_3$ (T=303 K)

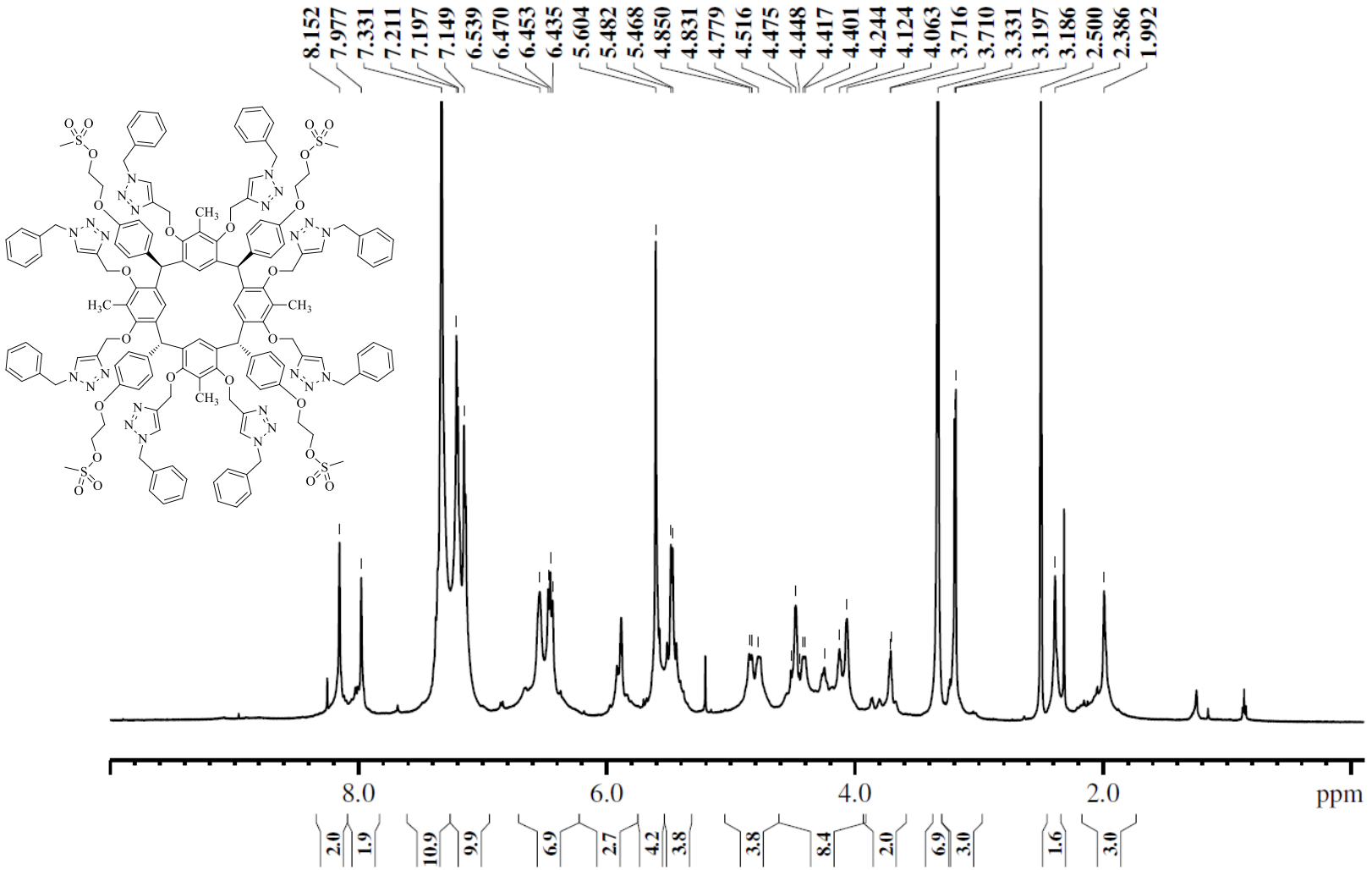

Figure S36. ^{1}H NMR spectrum of calix[4]resorcinol *rctt*-**6** in DMSO-d_6 (T=303 K)

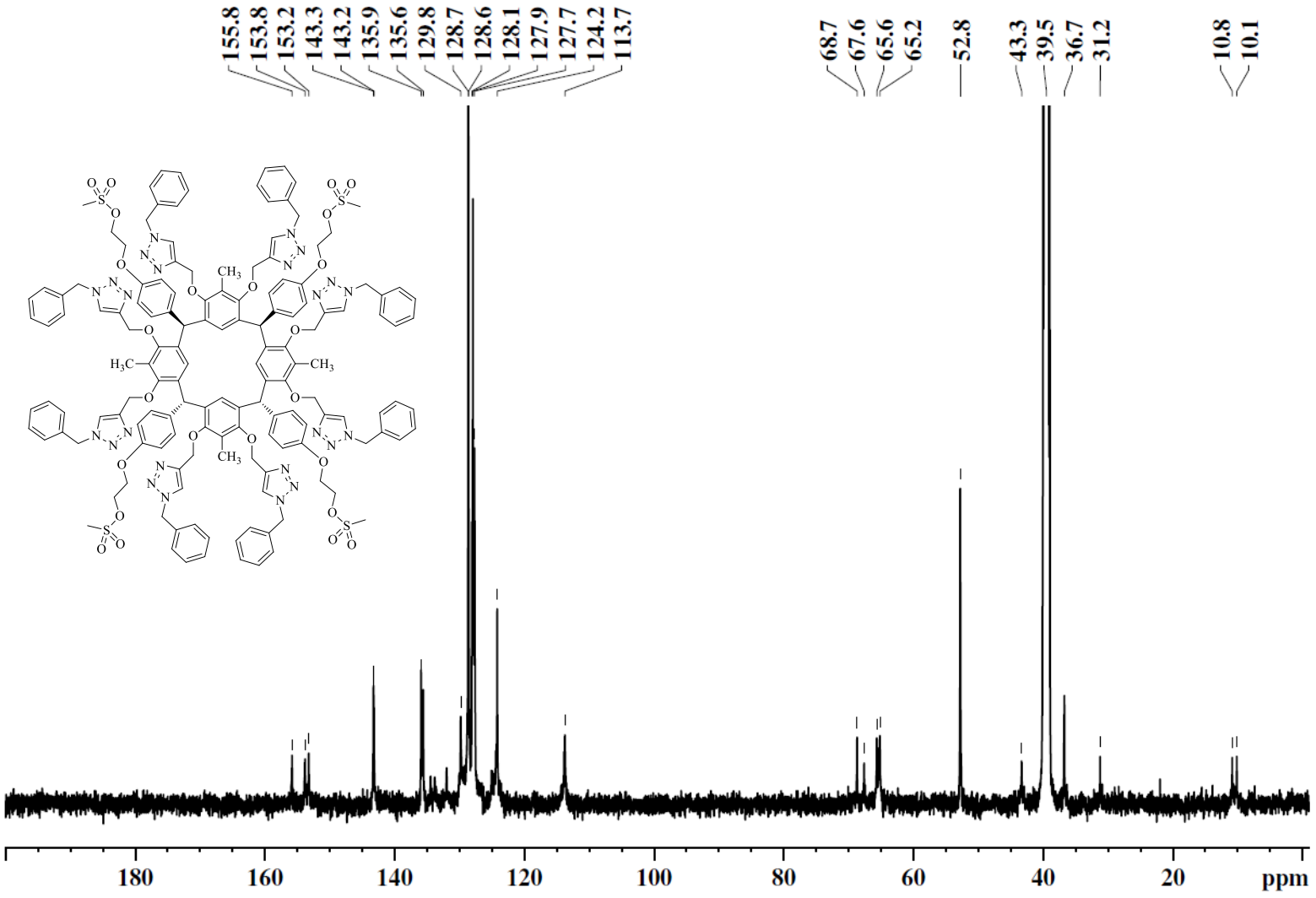

Figure S37. ^{13}C NMR spectrum of calix[4]resorcinol *rctt*-**6** in DMSO-d_6 (T=303 K)

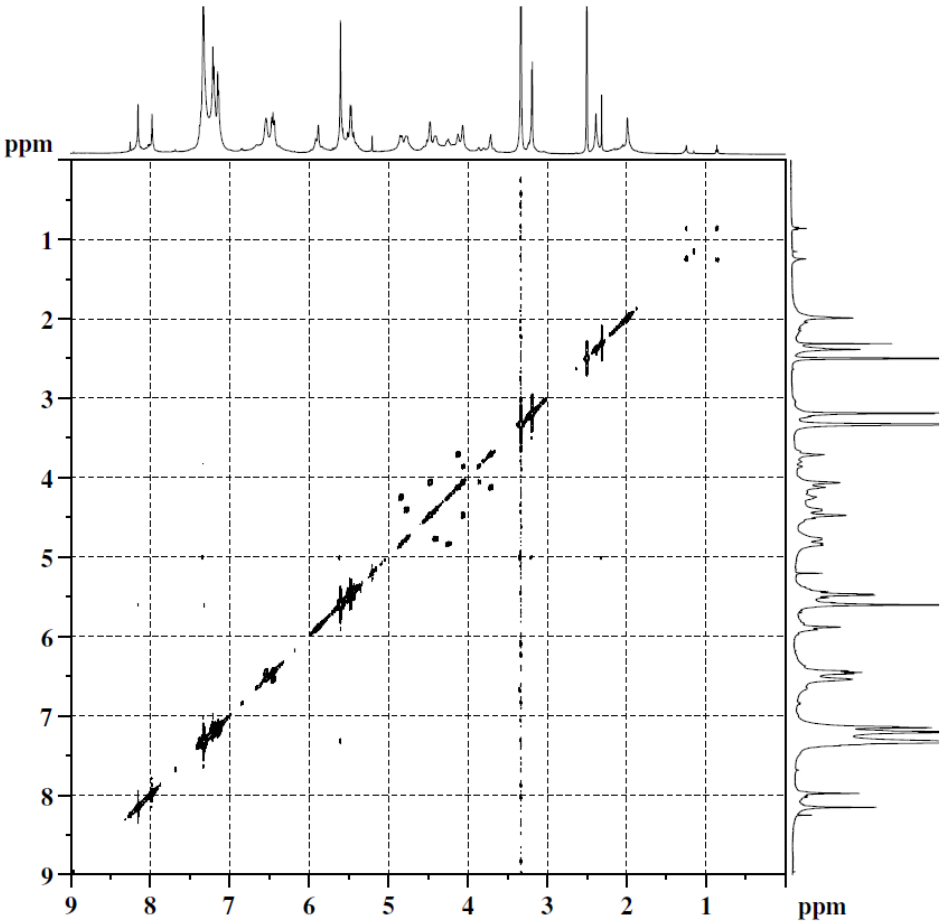

Figure S38. COSY NMR spectrum of calix[4]resorcinol *rctt*-**6** in DMSO-d_6 (T=303 K)

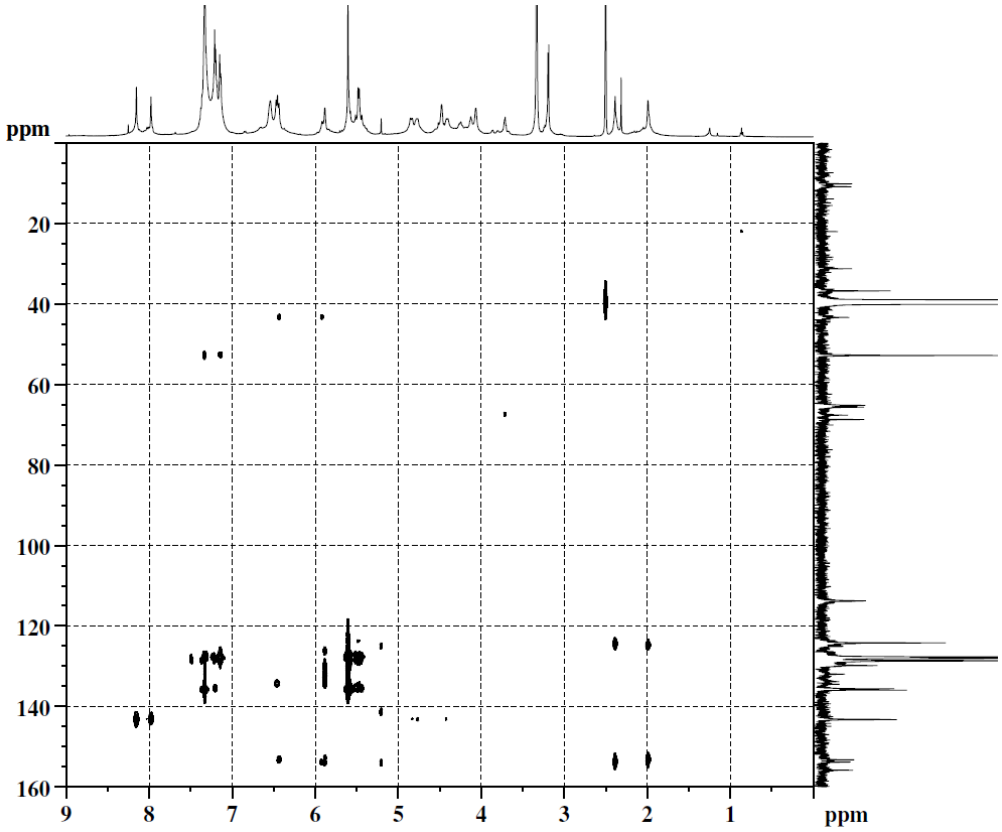

Figure S39. HMBC (^{13}C) NMR spectrum of calix[4]resorcinol *rctt*-**6** in DMSO-d_6 (T=303 K)

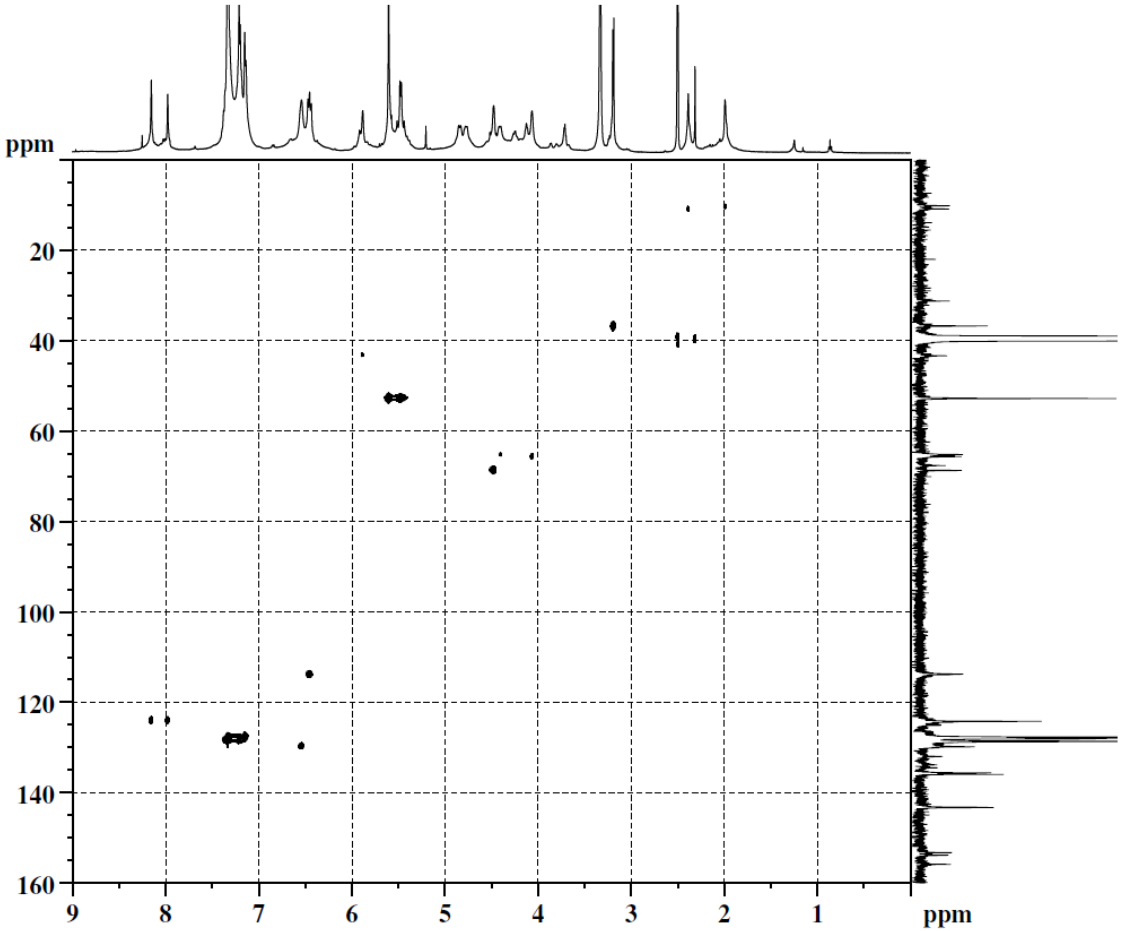

Figure S40. HSQC (^{13}C) NMR spectrum of calix[4]resorcinol *rctt*-**6** in DMSO-d_6 (T=303 K)