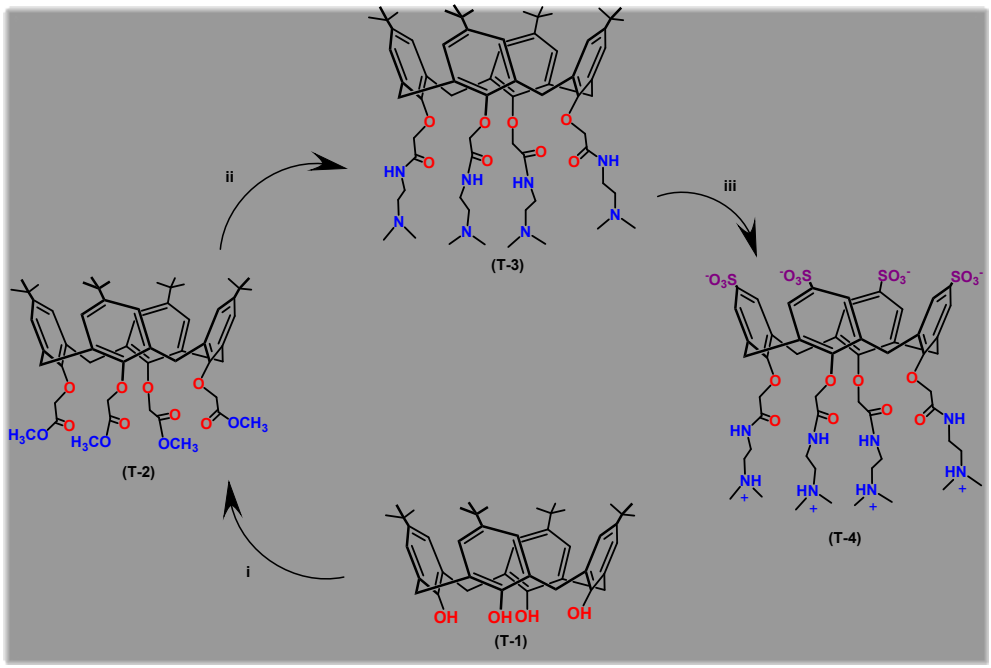
Supplementary Information

General Section

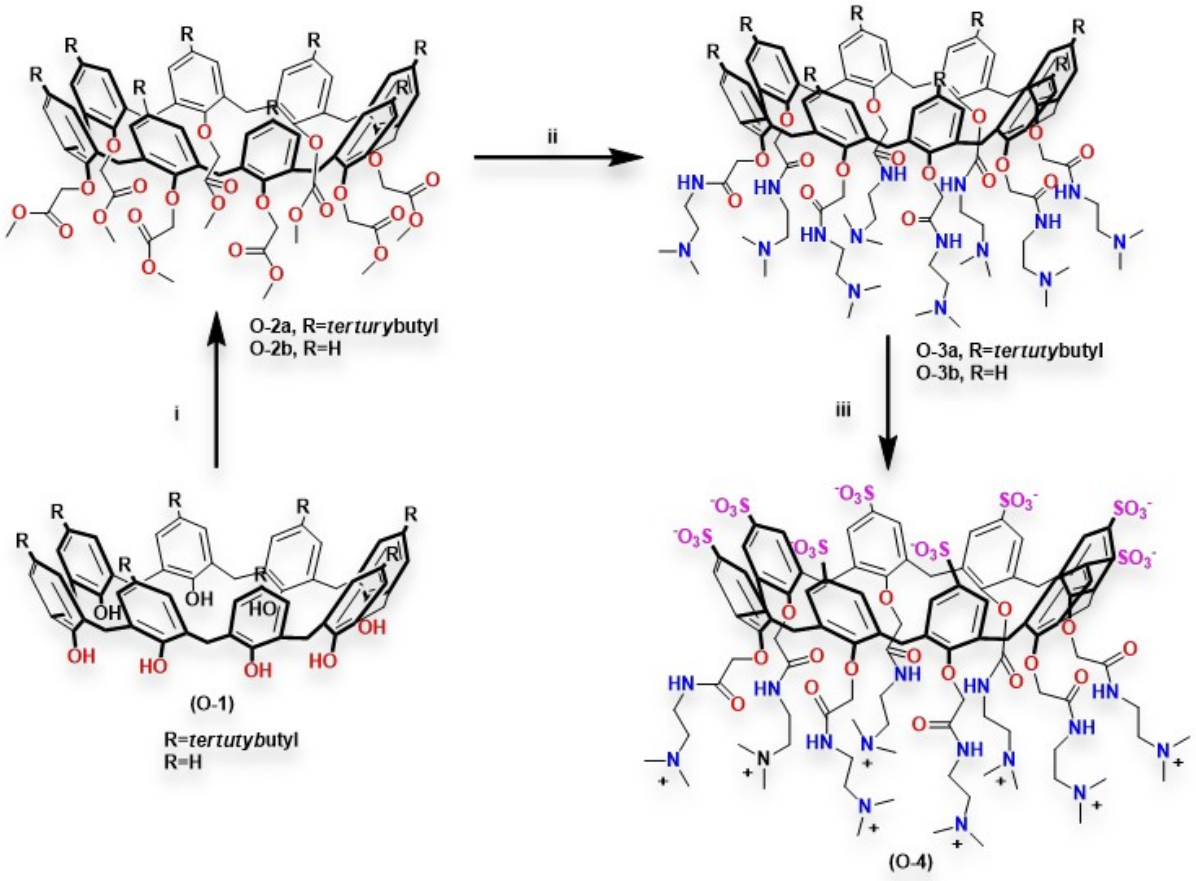
All reagents were commercial grade and supplied from various commercial sources such as Sigma-Aldrich, Acros Organics, Merck used without a further purification. Fourier Transform Infrared (FTIR-ATR) spectra recorded on Bruker spectrometer. NMR spectra were obtained with Varian (400 MHz) spectrometer tetramethylsilane used as internal standard solution. pH was measured through Orion 410A+ pH meter. CEM-MDS 2000 closed vessel microwave system was used in this study to prepare real and certified samples. Bio-imaging studies were performed by using ZOE Fluorescent Cell Imager (Bio-Rad, California, USA).

Synthesis

Synthesis of calix[4,8]arene derivatives depicted in scheme 1(**T-1, T-2, T-3)** and scheme 2 (**O-1, O-2a, O-2b, O-3a** and **O-3b)** were carried out according to previously reported methods with some modifcations [1-3]. Compound **T-4**, and **O-4** were prepared by following procedures:



Scheme 1. Schematic route for the synthesis of calix[4]arene amide derivative (**T-4**). (i) $BrCH_2COOCH_3/K_2CO_3$/Acetone (ii) N,N-dimethyl ethylenediamine/Toluene/Methanol (iii) H2SO4, Heat.



Scheme 2. Schematic route for the synthesis of calix[8]arene derivatives. (i) $BrCH_2COOCH_3/K_2CO_3$/Acetone (ii) N,N-dimethyl ethylenediamine/Toluene/Methanol (iii) H_2SO_4, Heat.

Synthesis of compound T-3. To the 1 mmol solution of **T-2** in 40 mL of Toluene, 42 mmol of N,N-dimethyl ethylenediamine in methanol was poured through dropping funnel with continuous stirring at room temperature under nitrogen gas. The reaction was monitored by TLC and IR. After 48 h, the solvent was removed under vacuum and the resulting solid was washed with diethylether several times to yeild a white solid. **T-3**: Yield % 86; FTIR (ATR):1651cm-1 -COONH. $_1$H NMR (CDCl3) : δ (ppm): 1.27 (s, 36H, But), 2.43 (s, 24H, $N(CH_3)_2$), 2.67 (t, J=6.4 Hz, 8H, NCH_2), 3.45 (d, J=13.72 Hz, 4H, $ArCH_2Ar$), 3.66 (t, J=6.0Hz, 8H, NCH_2), 4.3 (m, 12H, OCH_2, $ArCH_2Ar$), 6.85 (s, 8H, ArH), 7.73 (br, 4H, NH).

Synthesis of compound O-3 (a,b). 1 mmol of compound **O-2**(**a,b**) was taken in 90 mL mixed solvent (Toluene:MeOH, 3:1) and 52 mmol N,N-dimethyl ethylenediamine was added through dropping funnel at room temperature under a nitrogen atmosphere. Reaction mixture stirred for 55h. The reaction was

monitored by TLC and IR. Solvent was evaporated at reduced pressure, remaining solid was washed with diethyl ether several times to give a white solid. **O-3a**: Yeild 95 %; FTIR υ: 1659cm^{-1} (C=O). 1207 (C-O). ^{1}H-NMR ($CDCl_3$, 25 ^{o}C) δ_H: 1.36 (s, 72H, t-Bu), 2.48 (s, 48H, N-CH_3), 2.67 (m, 16H, N-CH_2), 3.61 (m, 16H, CONH-$\underline{CH_2}$), 4.19-4.50 (m, 32H, Ar-$\underline{CH_2}$-Ar and O-CH_2), 7.19 (brs, 16H, ArH), 7.98 (br s, 8H, CO$\underline{NH}$). **O-3b:** 90 % yeild; FTIR (υ cm^{-1}): 3053 (N-H) 1650 (C=O). ^{1}H-NMR ($CDCl_3$, 25 ^{o}C) δ_H: 2.22 (s, 48H, N-CH_3), 2.47 (m, N-$\underline{CH_2}$), 3.31-3.41 (m, 16H, CONH-$\underline{CH_2}$), 4.01 (brs, 16H ArCH_2Ar), 4.18 (s, 16H, O-CH_2-C=O), 6.89 (d, *J*=7.35 Hz, 16H, ArH), 6.97 (t, *J*= 7.23 Hz, 8H, ArH), 7.36 (t, *J*= 5.25 Hz, 8H, CO$\underline{NH}$).

Synthesis of compound T-4 and O-4. 1.20 mmol of calixarene derivative was mixed with concentrated H_2SO_4 (10ml) and stirred for 2 h at 60 ^{o}C (Scheme 1 and 2). The reaction was stopped when no water-insoluble material was observed. After cooling, the product was poured in diethylether, the precipitates were washed several time with diethyl ether. Freeze drying yield greyish solid. **T-4** yeild 55 %; ^{1}H-NMR (D_2O, 25 ^{o}C) δ_H: 2.42 (br, 24H, N(CH_3)$_2$), 3.38 (br, 8H, NCH_2), 3.81(br, 12H, ArCH_2Ar, NCH_2), 4.27 (m, 4H, ArCH_2Ar), 5.18 (br, 8H, -OCH_2 ve $D_2O_{(solvent)}$) 7.42 (s, 8H, ArH). **O-4**: 45 % yeild; ^{1}H-NMR (D_2O, 25 ^{o}C) δ_H: 2.37 (brs, 48H, N(CH_3)$_2$), 3.16 (br, 16H, NCH_2), 3.51(br, 24H, ArCH_2Ar, NCH_2), 4.19 (s, 8H, ArCH_2Ar), 4.88 (br, 16H, -OCH_2, 7.37 (s, 16H, ArH).

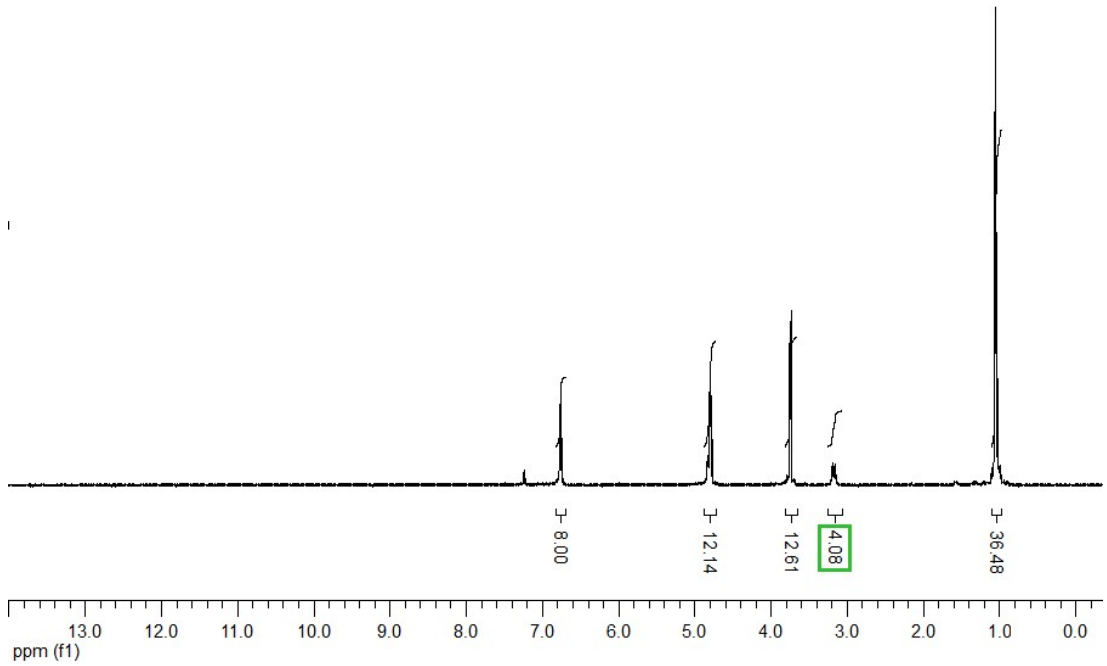


Figure S1. ^{1}H-NMR spectrum of **T-2**

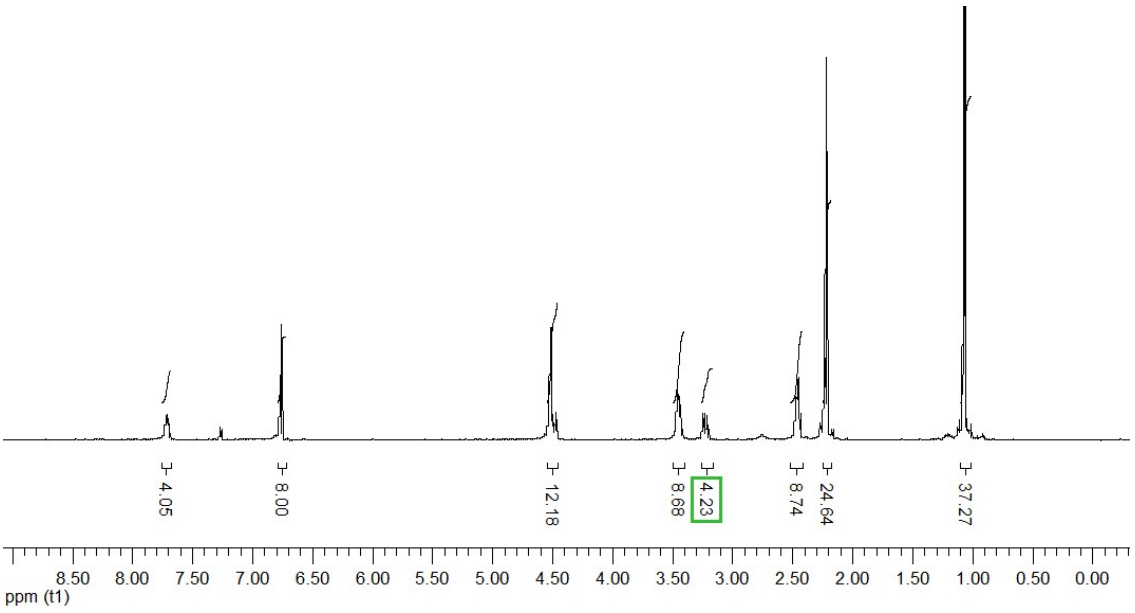


Figure S2. ^{1}H-NMR spectrum of **T-3**

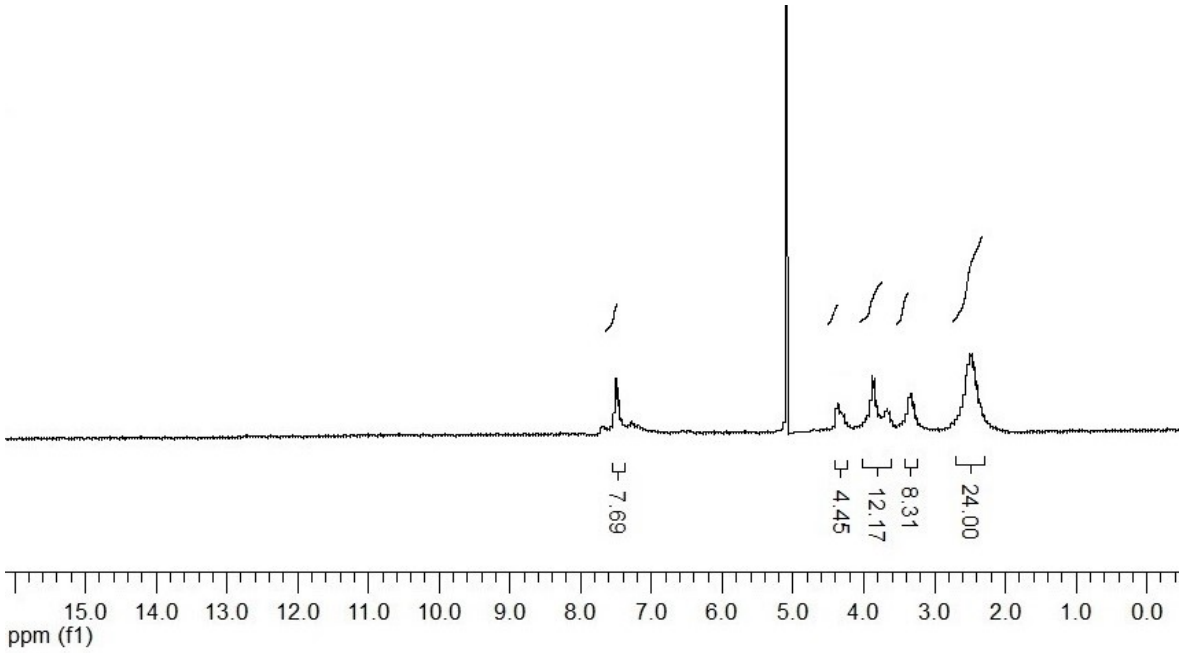


Figure S3. ^{1}H-NMR spectrum of **T-4**

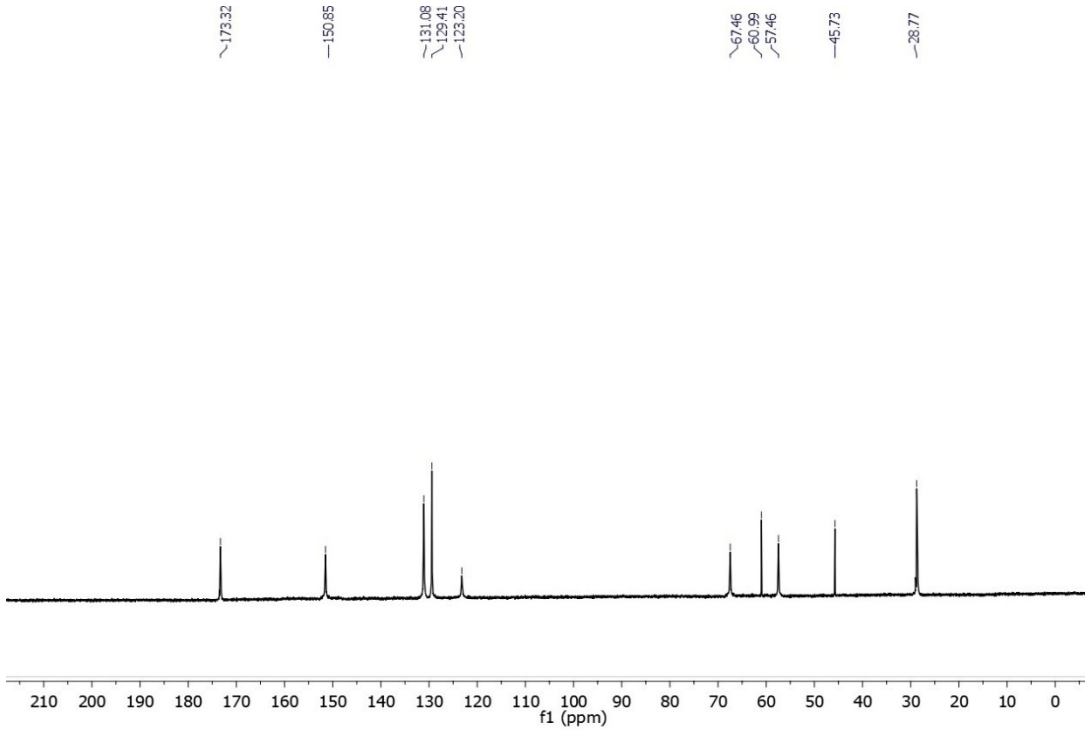


Figure S4. ^{13}C-NMR spectrum of **T-4**

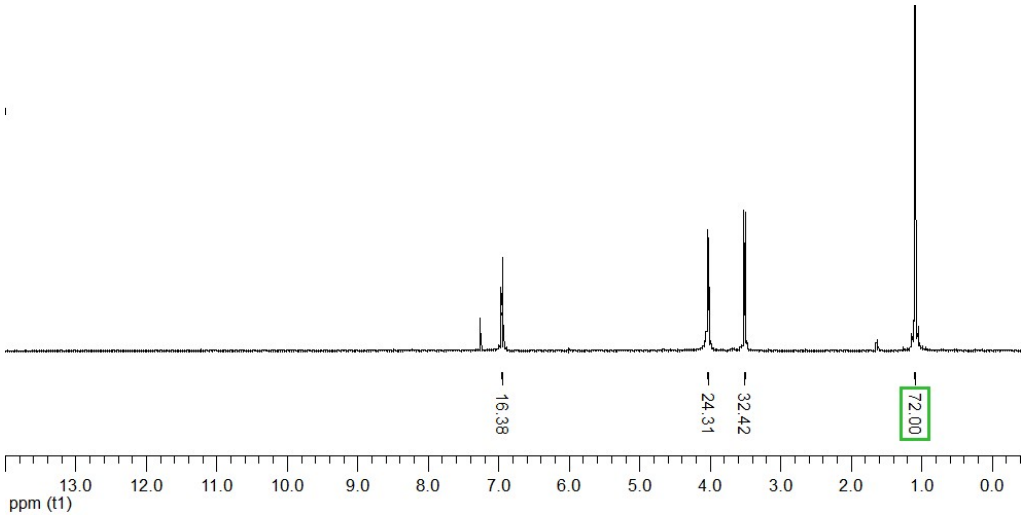


Figure S5. ^{1}H-NMR spectrum of **O-2a**

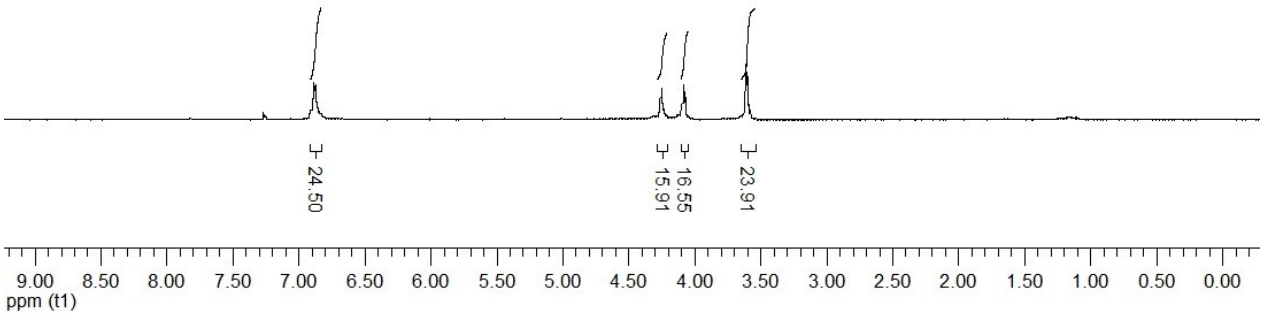


Figure S6. ^{1}H-NMR spectrum of **O-2b**

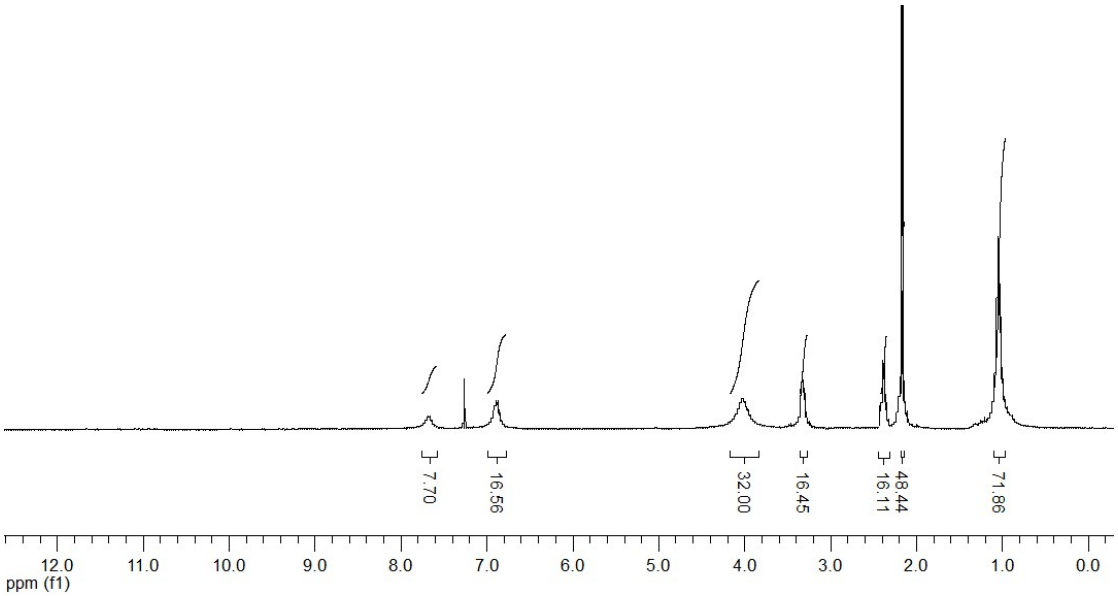


Figure S7. ^{1}H-NMR spectrum of **O-3a**

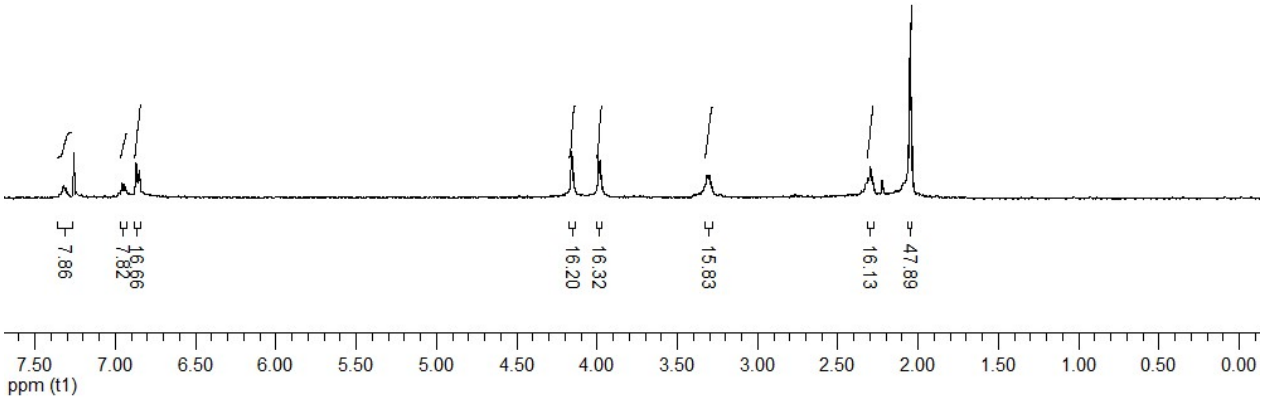


Figure S8. ^{1}H-NMR spectrum of O-3b.

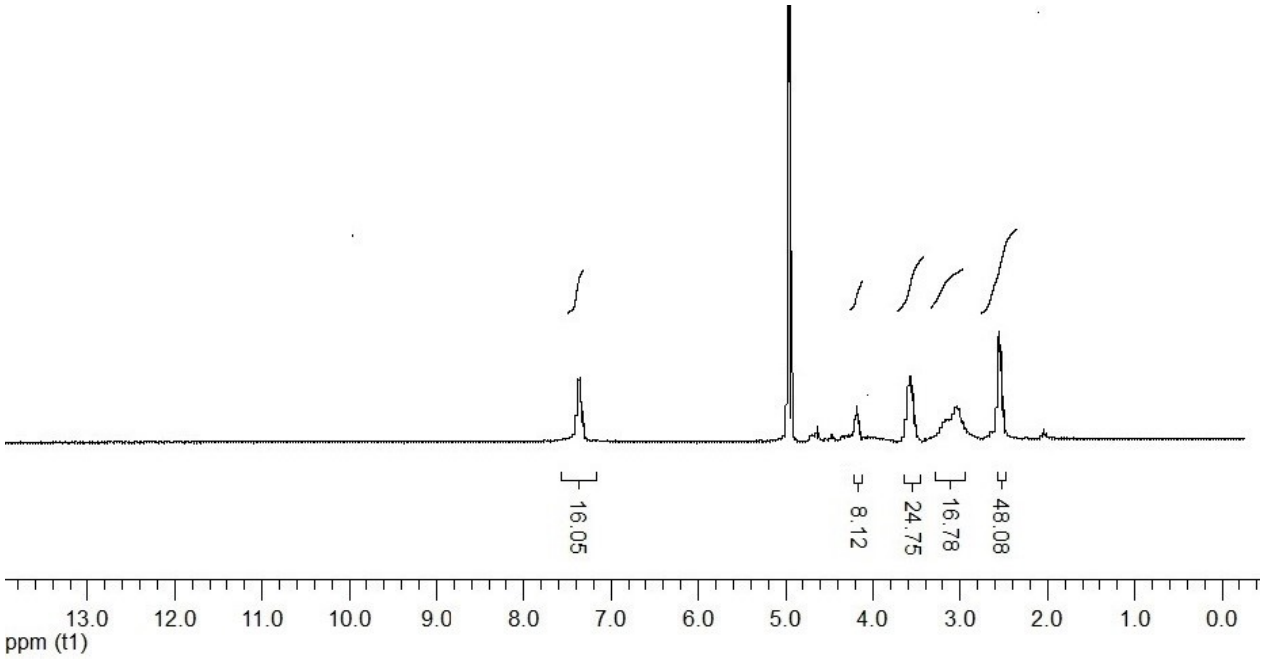


Figure S9. ^{1}H-NMR spectrum of O-4.

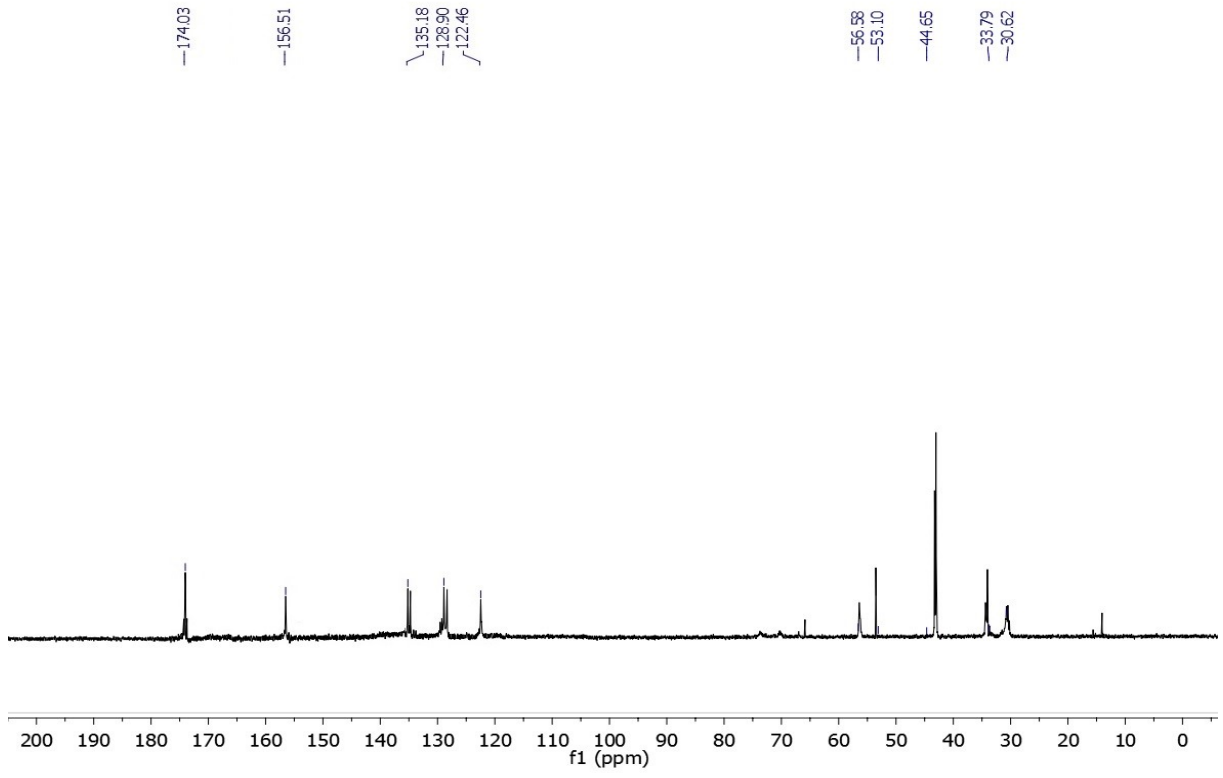


Figure S10. ^{13}C-NMR spectrum of O-4

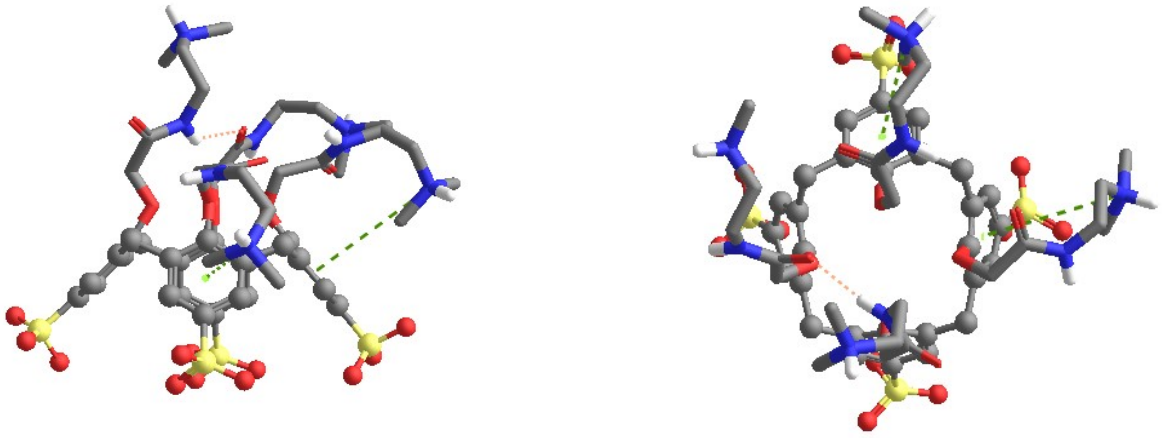


Figure S11. The optimized structure of compound **T-4** with gray, red, blue, yellow and white colored spheres represent C, O, N, S and polar H atoms respectively. Light pink dashed lines show h-bonds, green dashed lines π-cation interactions. For clarity the calix[4]arene part of the compound shown with ball and stick representation while upper rim group represented as tubes.

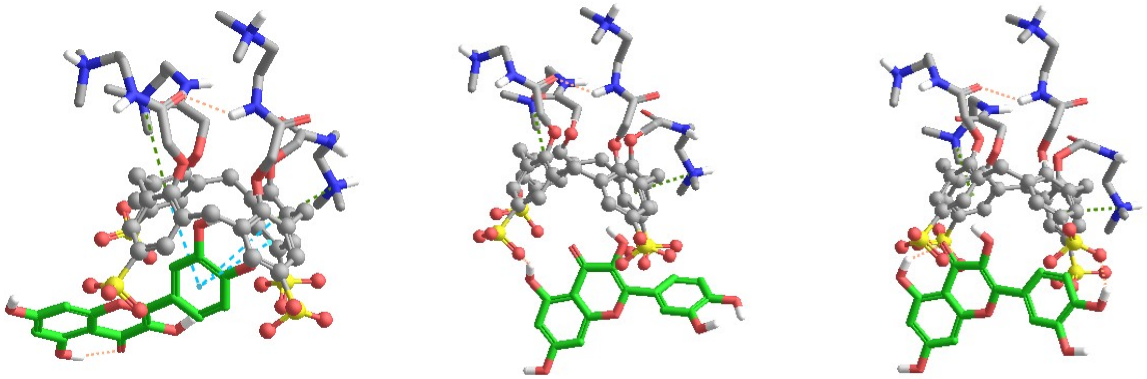


Figure S12. The three docking poses for compound **T-4** and quercetin complex. While red, blue, yellow and white colored spheres represent O, N, S and polar H atoms for both host and guest compound, C atoms of compound T-4 are displayed with gray colors while C atoms of quercetin are displayed with green. Light pink, green and blue dashed lines represent h-bond, π-cation and π-π interactions respectively. Both intramolecular and intermolecular interactions are displayed. For clarity the calix[4]arene part of the compound shown with ball and stick representation while upper rim group represented as tubes.

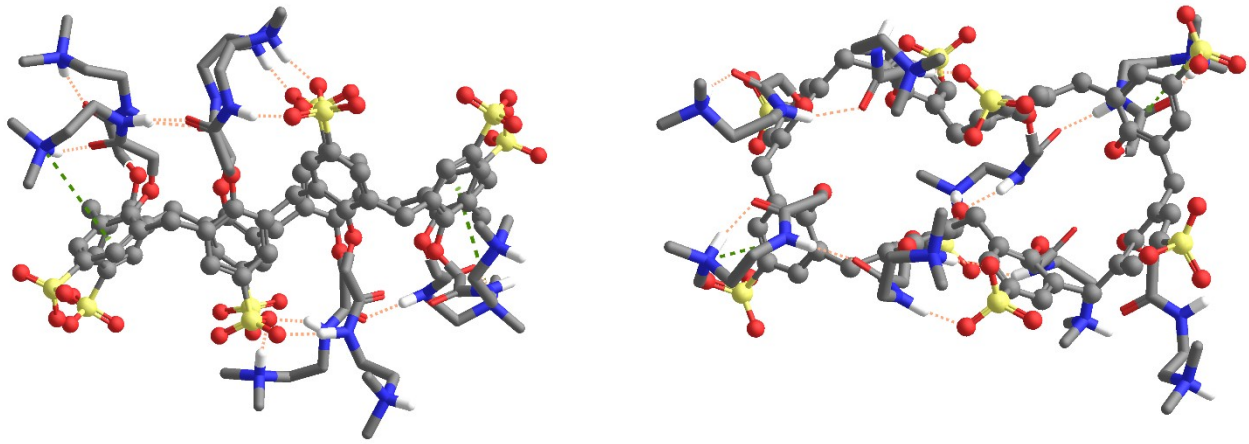


Figure S13. The optimized structure of compound **O-4_A** with gray, red, blue, yellow and white colored spheres represent C, O, N, S and polar H atoms respectively. Light pink dashed lines show h-bonds, green dashed lines π-cation interactions while purple dashed lines represents salt-bridge interactions. For clarity the calix[8]arene part of the compound shown with ball and stick representation while upper rim group represented as tubes.

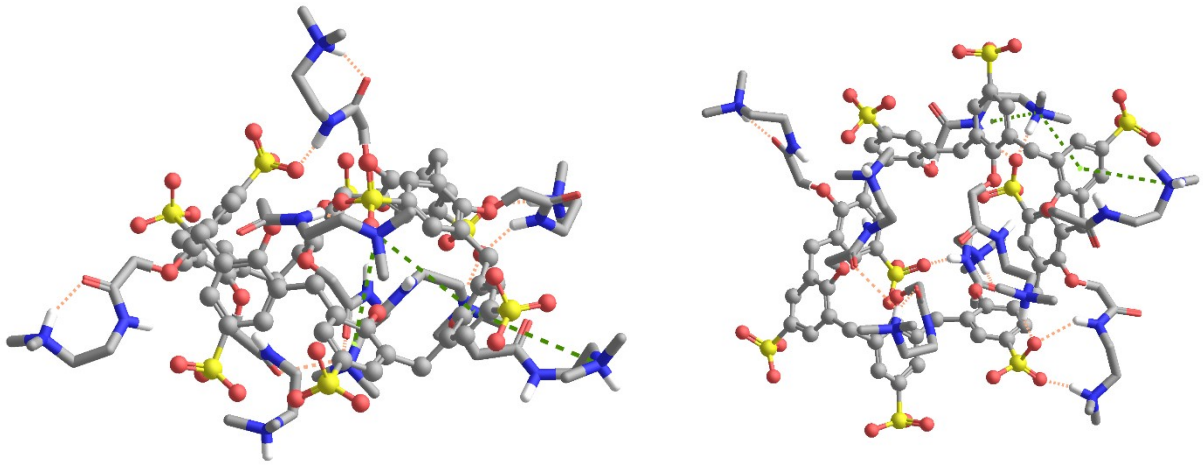


Figure S14. The optimized structure of compound **O-4_C** with gray, red, blue, yellow and white colored spheres represent C, O, N, S and polar H atoms respectively. Light pink dashed lines show h-bonds, green dashed lines π-cation interactions while purple dashed lines represents salt-bridge interactions. For clarity the calix[8]arene part of the compound shown with ball and stick representation while upper rim group represented as tubes.

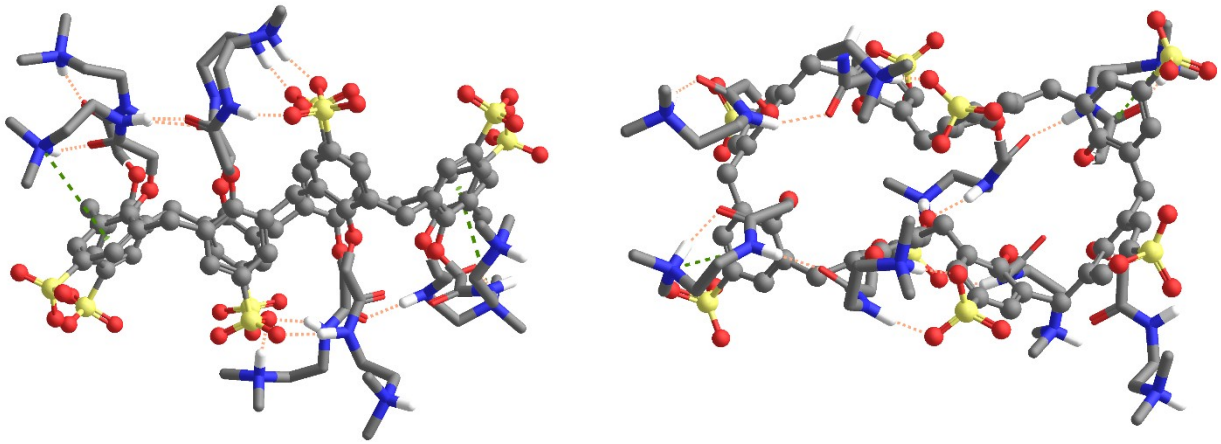


Figure S15. The optimized structure of compound **O-4_D** with gray, red, blue, yellow and white colored spheres represent C, O, N, S and polar H atoms respectively. Light pink dashed lines show h-bonds, green dashed lines π-cation interactions while purple dashed lines represents salt-bridge interactions. For clarity the calix[8]arene part of the compound shown with ball and stick representation while upper rim group represented as tubes.

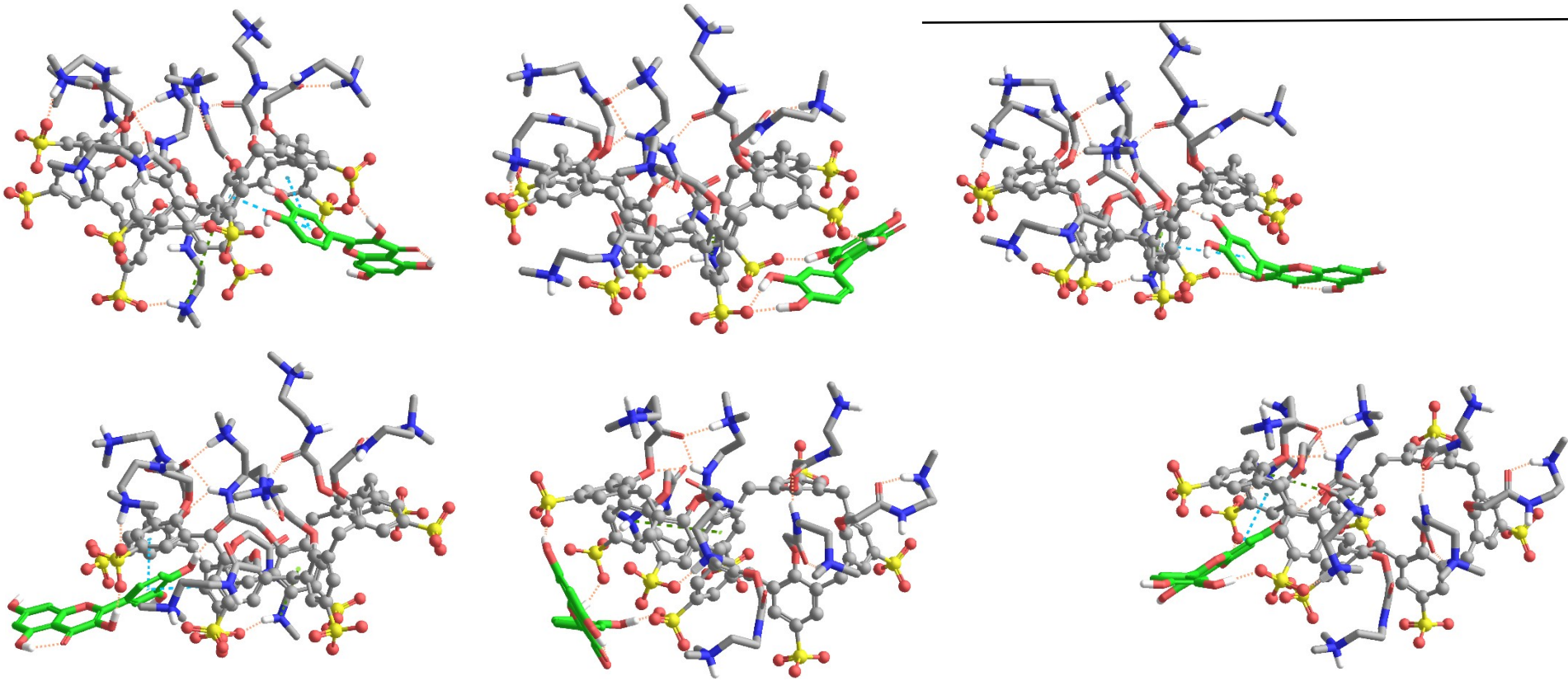


Figure S16. The three docking poses for compound **O-4_D** and quercetin complex. The structures on the upper and lower part of the figure show the docking poses obtained at different binding pockets defined for the host compound. While red, blue, yellow and white colored spheres represent O, N, S and polar H atoms for both host and guest compound, C atoms of compound **O-4_D** are displayed with gray colors while C atoms of quercetin are displayed with green. Light pink, green and blue dashed lines represent h-bond, π-cation and π-π interactions respectively. Both intramolecular and intermolecular interactions are displayed. For clarity the calix[8]arene part of the compound shown with ball and stick representation while upper rim group represented as tubes.

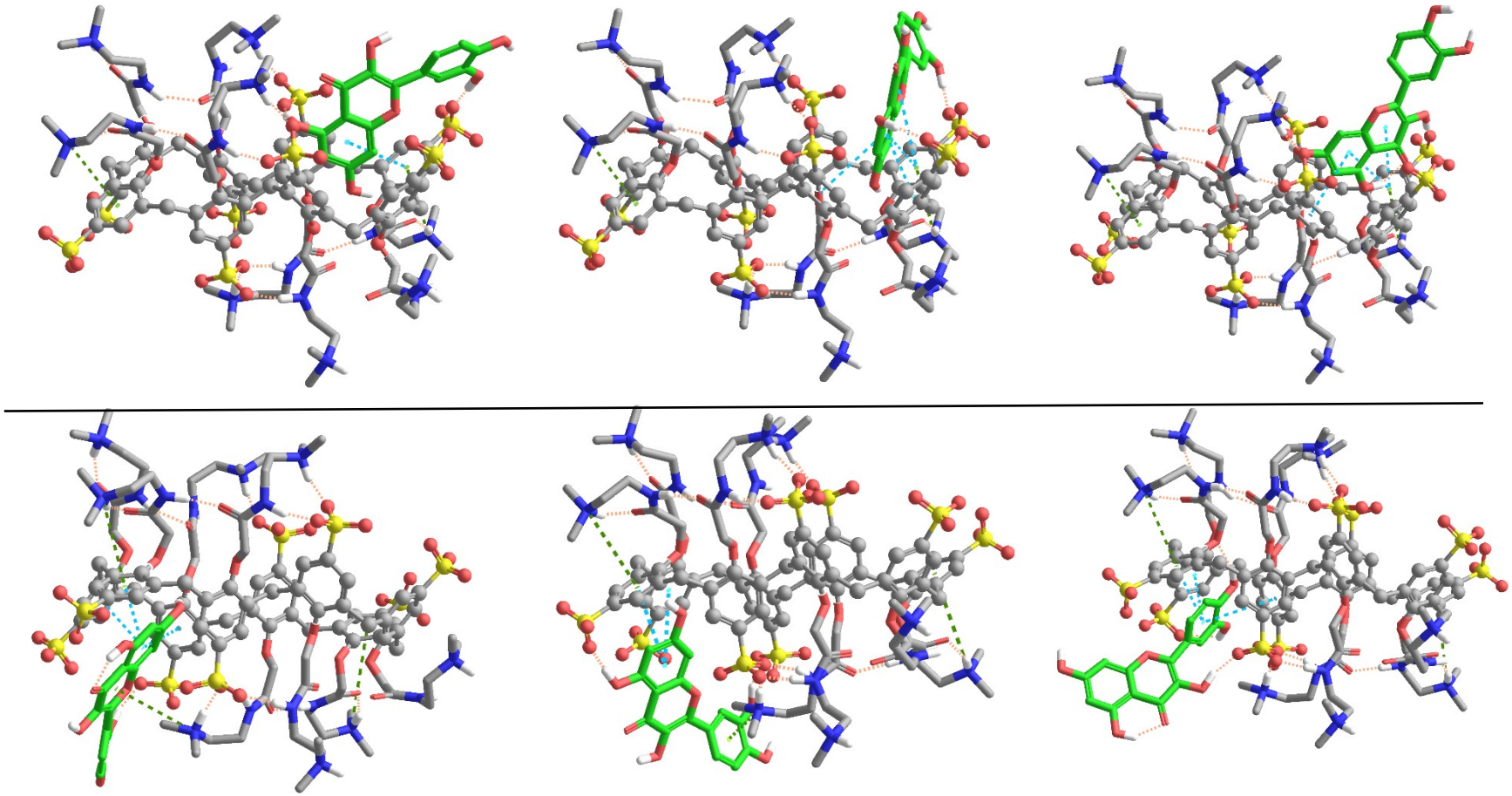


Figure S17. The three docking poses for compound **O-4_A** and quercetin complex. The structures on the upper and lower part of the figure show the docking poses obtained at different binding pockets defined for the host compound. While red, blue, yellow and white colored spheres represent O, N, S and polar H atoms for both host and guest compound, C atoms of compound **O-4_A** are displayed with gray colors while C atoms of quercetin are displayed with green. Light pink, green and blue dashed lines represent h-bond, π-cation and π-π interactions respectively. Both intramolecular and intermolecular interactions are displayed. For clarity the calix[8]arene part of the compound shown with ball and stick representation while upper rim group represented as tubes.

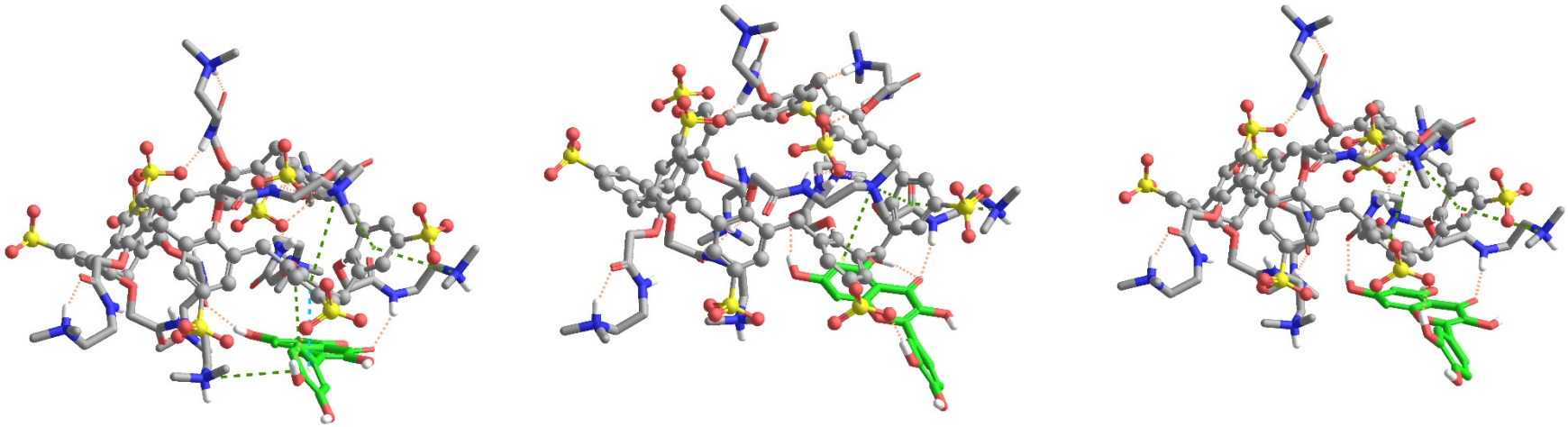


Figure S18. The three docking poses for compound **O-4_C** and quercetin complex. While red, blue, yellow and white colored spheres represent O, N, S and polar H atoms for both host and guest compound, C atoms of compound **O-4_A** are displayed with gray colors while C atoms of quercetin are displayed with green. Light pink, green and blue dashed lines represent h-bond, π-cation and π-π interactions respectively. Both intramolecular and intermolecular interactions are displayed. For clarity the calix[8]arene part of the compound shown with ball and stick representation while upper rim group represented as tubes.

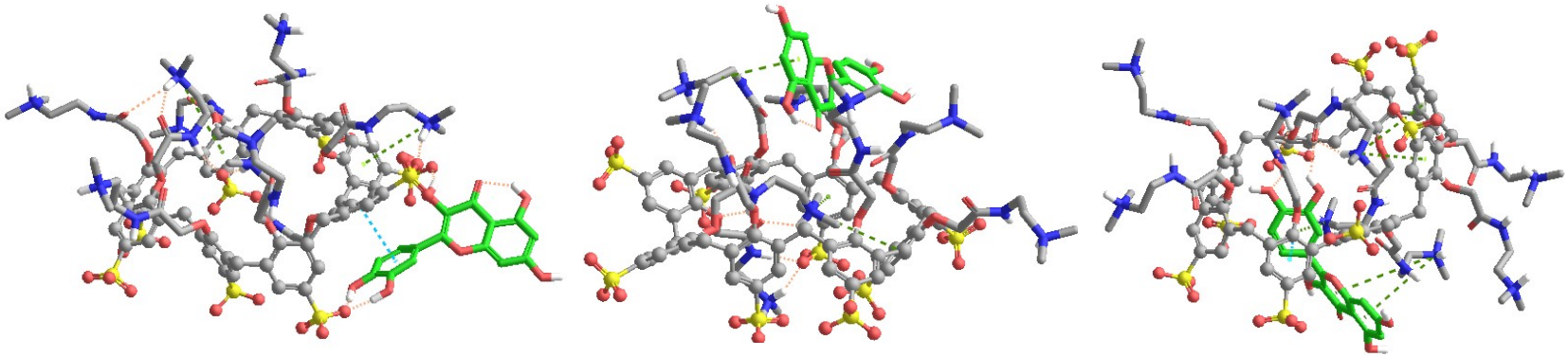


Figure S19. The selected representative structures obtained after MD simulations for compound **O-4_D** and quercetin complex. While red, blue, yellow and white colored spheres represent O, N, S and polar H atoms for both host and guest compound, C atoms of compound **O-4** are displayed with gray colors while C atoms of quercetin are displayed with green. Light pink, green and blue dashed lines represent h-bond, π-cation and π-π interactions respectively. Both intramolecular and intermolecular interactions are displayed. For clarity the calix[8]arene part of the compound shown with ball and stick representation while upper rim group represented as tubes.

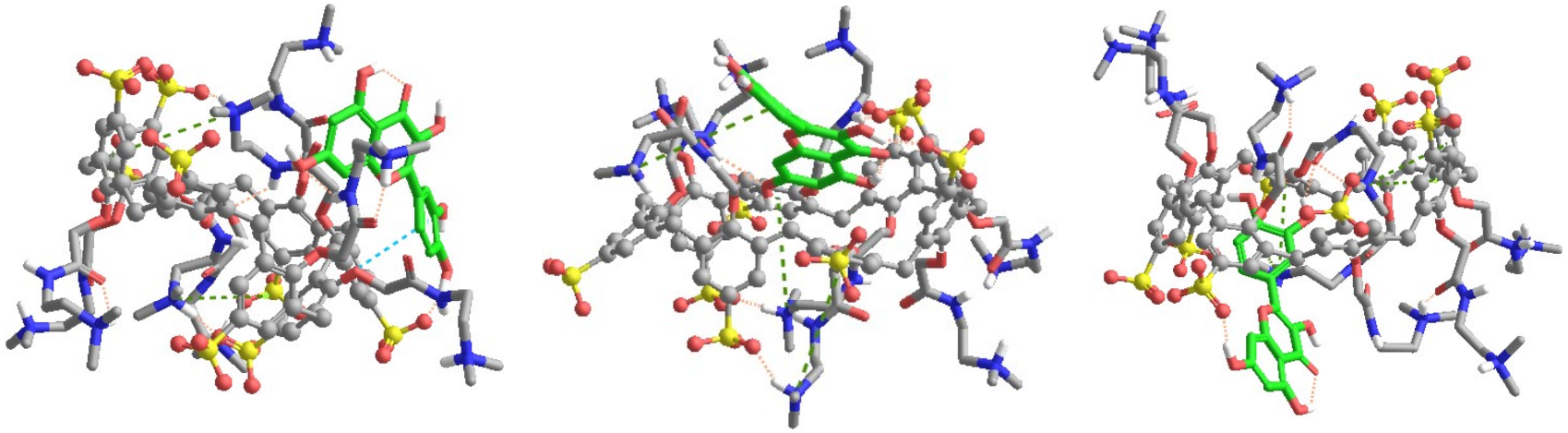


Figure S20. The selected representative structures obtained after MD simulations for compound **O-4_A** and quercetin complex. While red, blue, yellow and white colored spheres represent O, N, S and polar H atoms for both host and guest compound, C atoms of compound **O-4** are displayed with gray colors while C atoms of quercetin are displayed with green. Light pink, green and blue dashed lines represent h-bond, π-cation and π-π interactions respectively. Both intramolecular and intermolecular interactions are displayed. For clarity the calix[8]arene part of the compound shown with ball and stick representation while upper rim group represented as tubes.

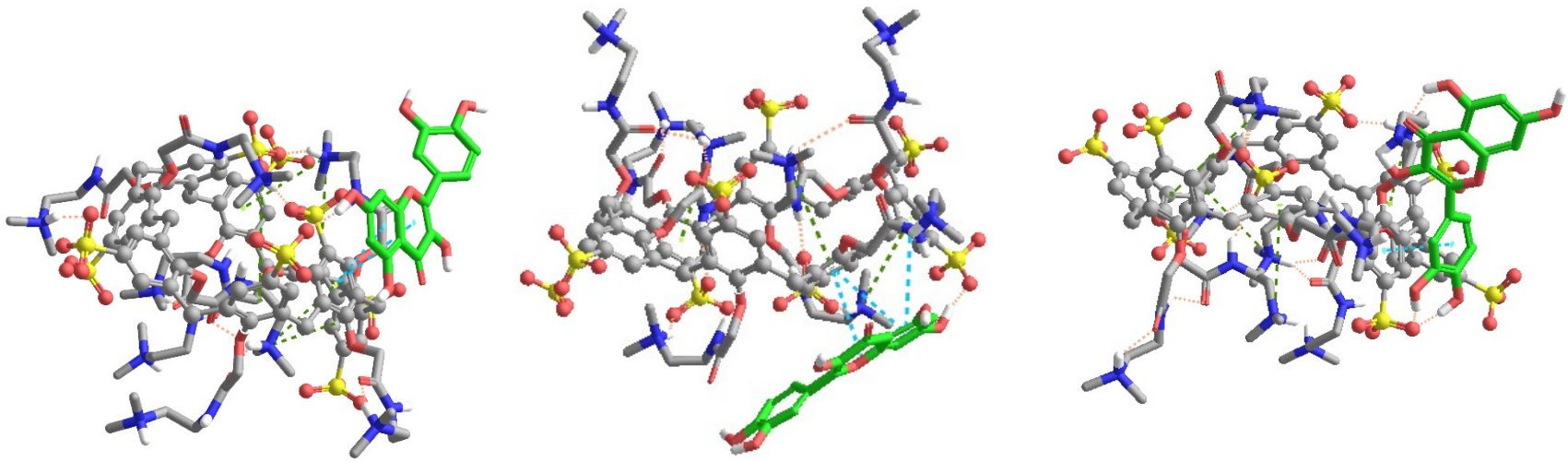


Figure S21. The selected representative structures obtained after MD simulations for compound **O-4_C** and quercetin complex. While red, blue, yellow and white colored spheres represent O, N, S and polar H atoms for both host and guest compound, C atoms of compound **O-4** are displayed with gray colors while C atoms of quercetin are displayed with green. Light pink, green and blue dashed lines represent h-bond, π-cation and π-π interactions respectively. Both intramolecular and intermolecular interactions are displayed. For clarity the calix[8]arene part of the compound shown with ball and stick representation while upper rim group represented as tubes.

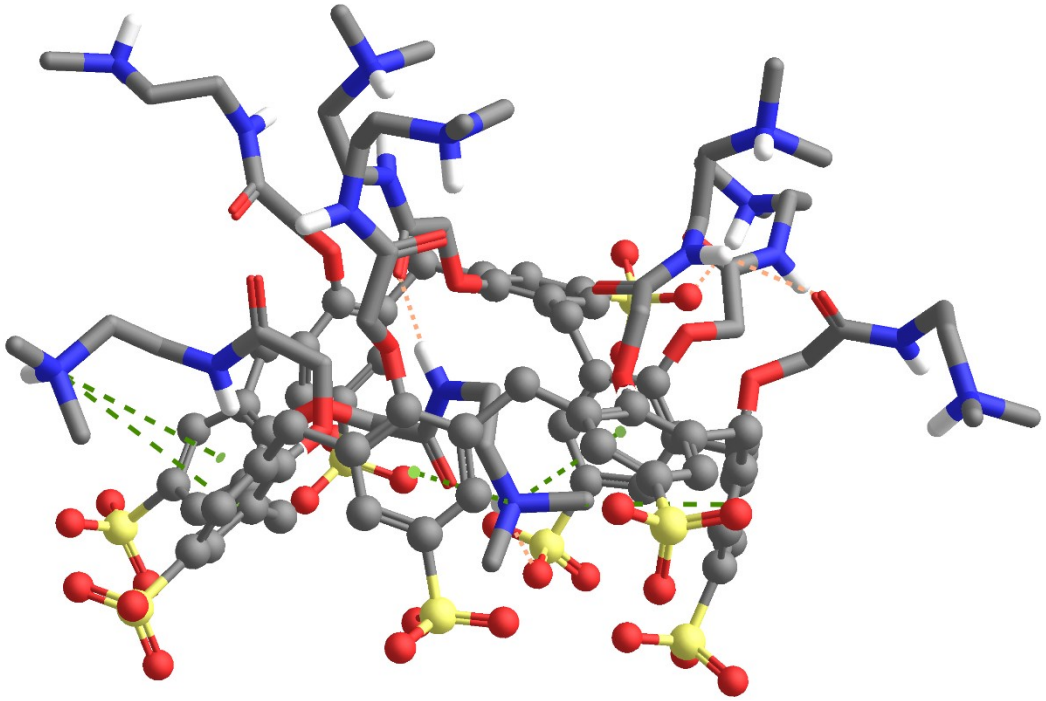


Figure S22. The representative structure obtained after MD simulations for compound **O-4** without guest compound. While red, blue, yellow and white colored spheres represent O, N, S and polar H atoms for both host and guest compound, C atoms of compound **O-4** are displayed with gray colors. Light pink, green and blue dashed lines represent h-bond, π-cation and π-π interactions respectively. Both intramolecular and intermolecular interactions are displayed. For clarity the calix[8]arene part of the compound shown with ball and stick representation while upper rim group represented as tubes.

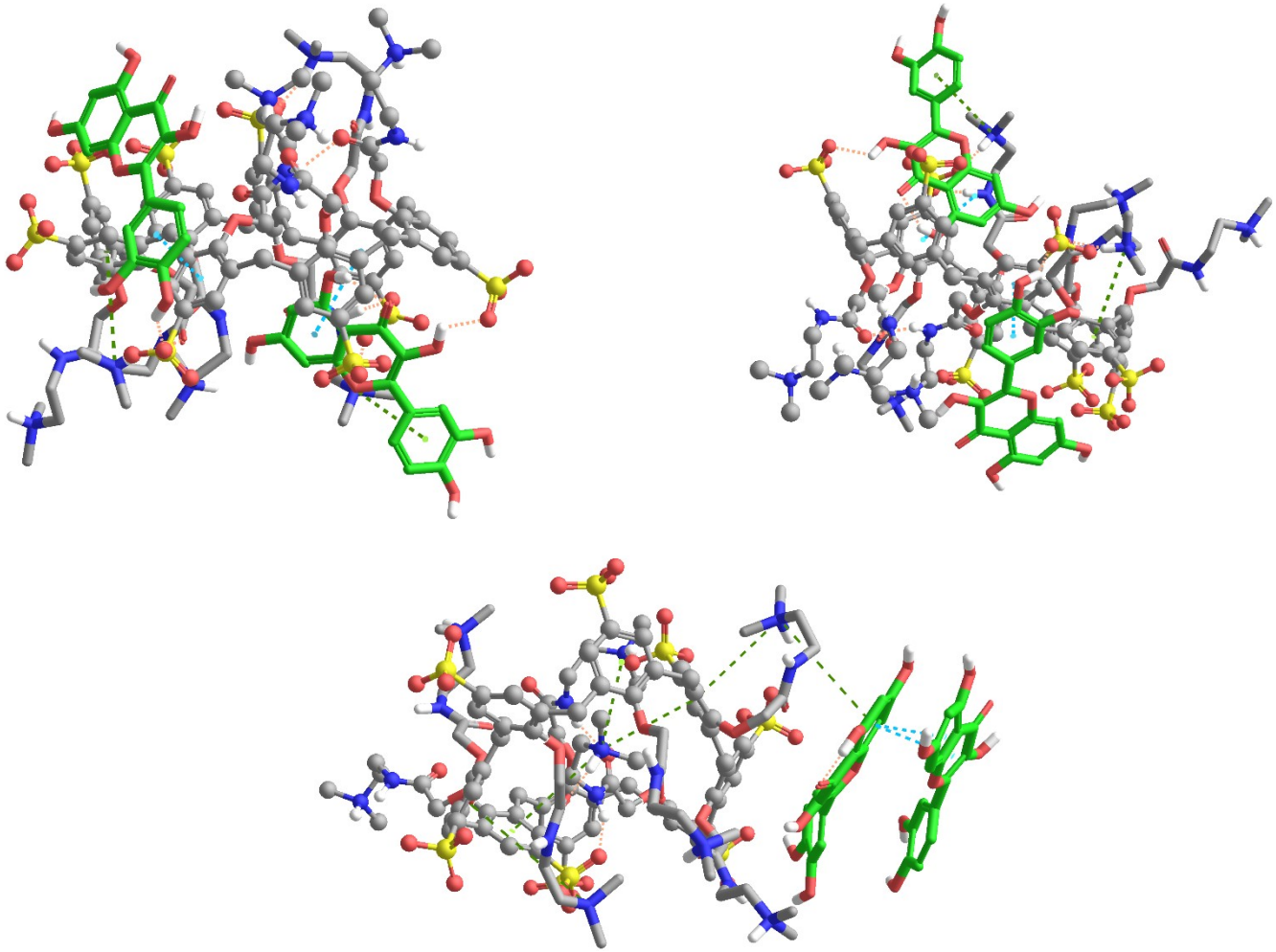


Figure S23. The representative structure obtained after MD simulations for compound **O-4** with two quercetin compounds. While red, blue, yellow and white colored spheres represent O, N, S and polar H atoms for both host and guest compound, C atoms of compound **O-4** are displayed with gray colors while C atoms of quercetin are displayed with green. Light pink, green and blue dashed lines represent h-bond, π-

cation and π-π interactions respectively. Both intramolecular and intermolecular interactions are displayed. For clarity the calix[8]arene part of the compound shown with ball and stick representation while upper rim group represented as tubes.

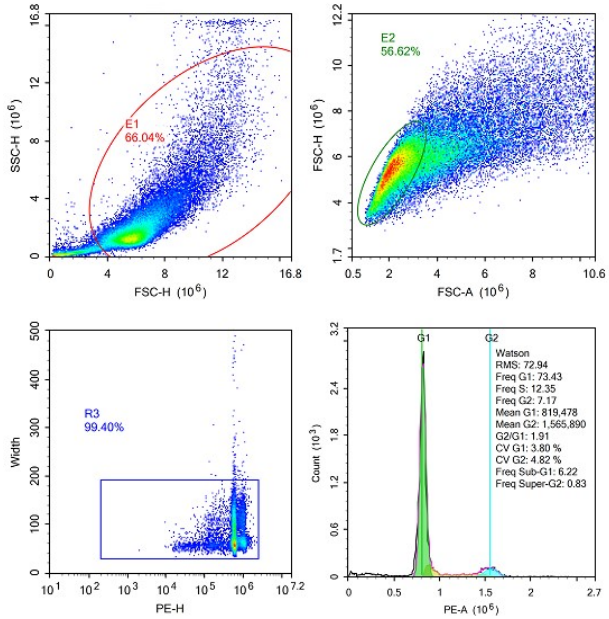


Figure S24 Analyses of cell cycle distribution of HeLa cells after treatment with **C-1**. After treated with 10 μM of **C-1** for 24 h, the HeLa cells were analyzed for cell cycle distribution with the ACEA Novocyte flow cytometer. The plot shows the cells in the G0/G1 phase (green), S phase (Yellow), and G2/M phase (blue).

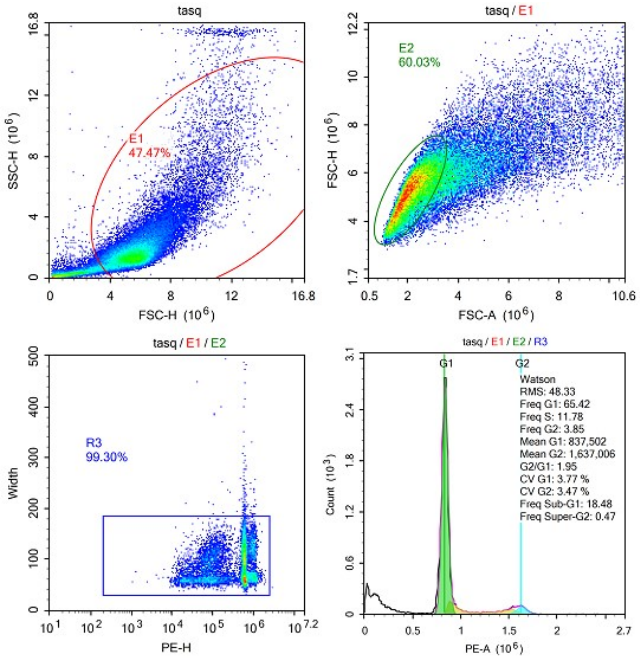


Figure S25 Analyses of cell cycle distribution of HeLa cells after treatment with **C-2**. After treated with 11 μM of **C-2** for 24 h, HeLa cells were analyzed for cell cycle distribution with the ACEA Novocyte flow cytometer. The plot shows the cells in the G0/G1 phase (green), S phase (Yellow), and G2/M phase (blue).

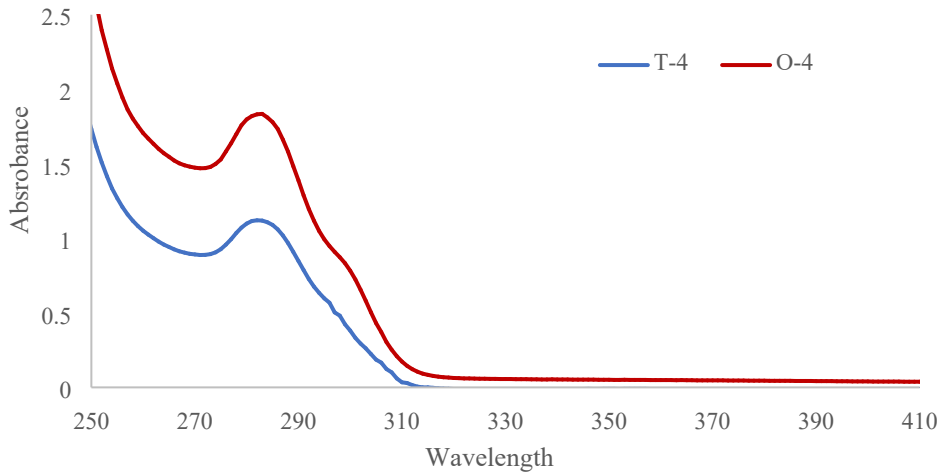


Figure S26UV-Visible spectrum of **T-4** and **O-4**

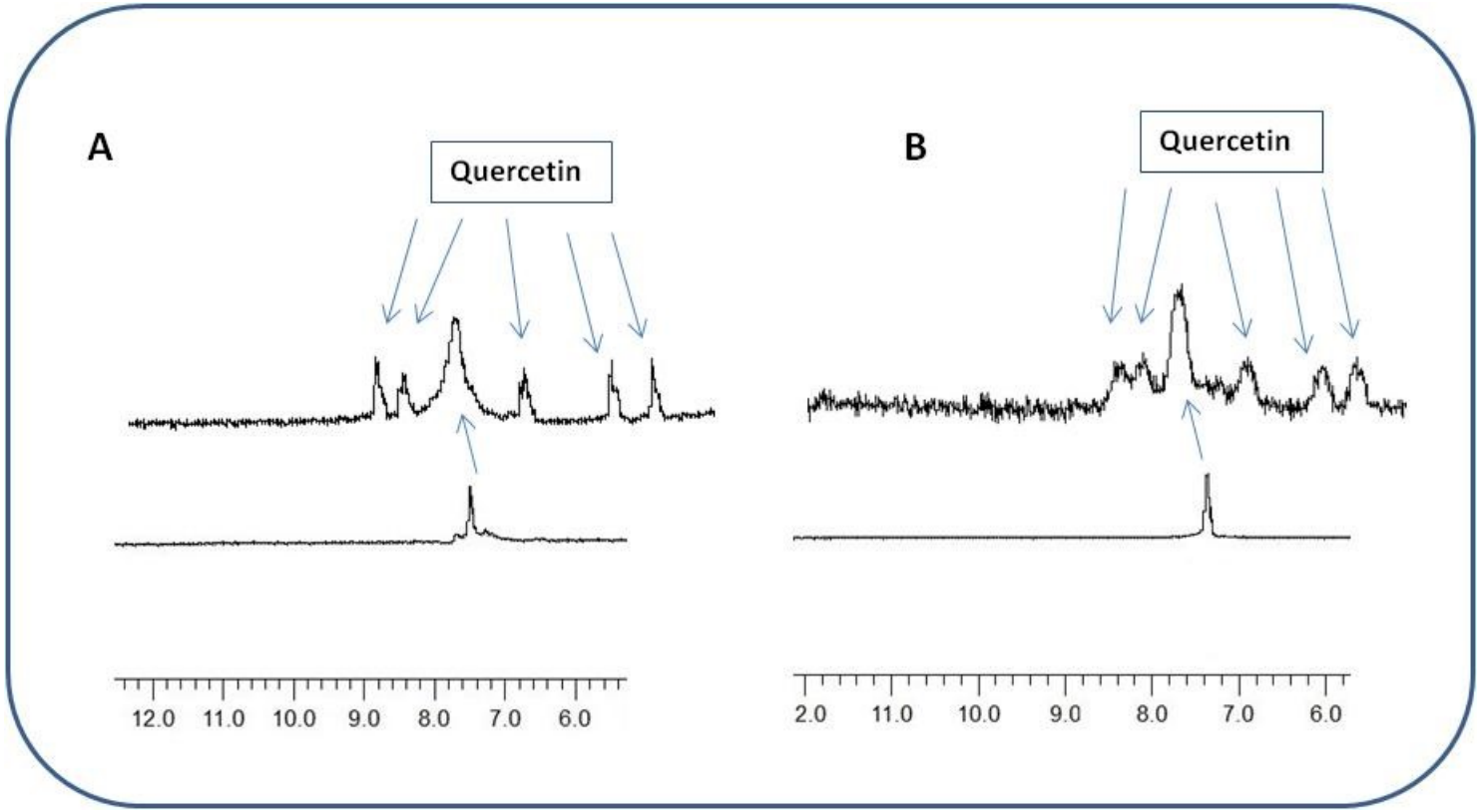


Figure S27 H NMR spectrum of *p*-sulfonated Calix[4,8]arenes: **A)** T-4 and C-1, **B)** O-4 and C-2 in D_2O.

Table S1 IC_{50} value of calixarene based compounds on human cancer (A549, HeLa, HEPG2, PC-3, and DLD-1) and healthy epithelium (PNT1A) cells

	IC_{50} Values (μM)					
	A549	**HeLa**	**HEPG2**	**PC-3**	**DLD-1)**	**PNT1A**
C-1	22±4	10±2	370±7	75±5	230±11	370±22
C-2	18±3	11±3	43±6	70±9	83±13	280±17

Table S2. Zeta potentials of T-4, T-4-Q, O-4, and O-4-Q.

	T-4	**T-4-Q**	**O-4**	**O-4-Q**
Zeta potential (mV)	-23.9	-18.7	-32.9	-24.1

References

1. C. D. Gutsche, M. Iqbal and D. Stewart, *The Journal of Organic Chemistry*, 1986, **51**, 742-745.
2. E. M. Collins, M. A. McKervey, E. Madigan, M. B. Moran, M. Owens, G. Ferguson and S. J. Harris, *Journal of the Chemical Society, Perkin Transactions 1*, 1991, **0**, 3137-3142.

3. X. Chen, R. P. Dings, I. Nesmelova, S. Debbert, J. R. Haseman, J. Maxwell, T. R. Hoye and K. H. Mayo, *Journal of medicinal chemistry*, 2006, **49**, 7754-7765.