Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supplementary Information

Ketocalix[3]carbazole: facile synthesis, rigid conformation and baicalin-selective sensing

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1. **Generals**:

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Thin layer chromatography (TLC) analysis of reaction mixtures was performed on Dynamic adsorbents silica gel F-254 TLC plates. Column chromatography was performed on silica gel 200-300 mesh. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded with Bruker Avance-III 600 spectrometers at 298 K. Chemical shifts were reported in units (ppm) and all coupling constants (*J* values) were reported in Hertz (Hz). High-resolution mass spectra were measured using a matrix-assisted laser desorption/ionization (MALDI)-time of flight (TOF)/TOF mass spectrometer (Bruker Daltonik, Germany). The size and zeta potential of the NDs were measured by dynamic light scattering (DLS). The measurements were carried out in triplicate via a Zetasizer (Nano ZS, Malvern, UK). The morphology of NDs was observed through TEM (JEM2100, JEOL, Japan) operated at an accelerating voltage of 120 kV. For all the measurements, the solutions of compounds were freshly prepared before use.

Compound **5** and **6** were converted to be their ammonium salt before use. For UV-vis, Fluorescence and ^{1}HNMR titrations, the stock solutions of target compounds were prepared by dissolving them in DMSO (20 mM, 200 mM and 500 mM respectively). For UV-vis, Fluorescence, DLS and TEM titrations, the DMSO/H_2O solution were used. For fluorescent titration, both excitation and emission slit widths were 5 nm. Fluorescent titration was done using the excitation wavelength was 340 nm. Before the spectra were recorded, the sample solutions were mixed for 2 minutes after each addition of guests. The measurements are repeated at least three times.

Cytotoxicity assay

Cells were seeded into 96-well cell culture plates (Corning, NY, USA) at a density of 5×10^3 cells per well and cultured for 24 h. Next, cells were subsequently incubated in presence of increasing concentrations (0 to 100 μM) of ligands at 37 °C for 48 h. After treatment, the cells were rinsed twice with ice-cold PBS and incubated with 100 μL of 0.5 mg/mL MTT (3-(4,5-dimethylthiazolyl-2)-2,5-diphenyl-tetrazolium bromide, Sigma-Aldrich) solution at 37°C for 3 h. The supernatant were discarded and the residual cell layer was dissolved in 150 μL of DMSO, and optical density was measured using a microplate reader (Thermo Scientific, Shanghai, China). Cell viability was calculated using the following equation:

Cell growth inhibitory ratio (%) = $100 \times (A_{530,\ control} - A_{530,\ sample})/(A_{530,\ control} - A_{530,\ blank})$

Molecular models

Conformation analyses of **3** was optimized by means of the computer program SPARTAN'14 for windows (V1.1.4, Wavefunction Inc. 18401 Von Karman Avenue, Suite 370 Irvine, CA 92612) on a PC equip with Pentium IV (RAM: 4G). The optimized moiety of **3** was selected based on the ^{1}HNMR spectrum, for Molecular Mechanics Force Field (MMFF) calculation, the whole structure was used; for semi-expirical calculation, the side chains were omitted for the sake of both clarity and calculation expense. The energy-minimization of **3** was firstly examined using MMFF. Afterwards, based on the MMFF calculation, a few low-energy conformer were selected for further optimization by using semi-expirical calculation at PM_3 level.

2. Synthesis method:

Synthesis of Compound **2**:

DDQ (29.51 mg, 0.13 mmol) and the compound **1** (150.00 mg, 0.13 mmol) was added into the aqueous THF (1.50 mL of THF containing 0.02 mL of water). The mixture was stirred at room temperature for 10 h. Afterwards, the solvents was evaporated under vacuum, the residue was extracted by 3 × 100 mL CH_2Cl_2, washed with water. After drying with Na_2SO_4, CH_2Cl_2 was evaporated, the residue was further purified with 200-300 silicon column (DCM:MeOH=250:2 *V*/*V*) to give 58.70 mg of unreacted **1** (39.0%, *m*/*m*) and 25.50 mg of the target **2** (yield 27.6%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.53 (s, 2H, $\mathbf{H_5}$), 8.26 (d, *J*=8.4, Hz, 2H, $\mathbf{H_7}$), 8.25 (s, 2H, $\mathbf{H_4}$), 7.84 (s, 2H, $\mathbf{H_{4'}}$), 7.55 (d, *J*=8.4 Hz, 2H, $\mathbf{H_8}$), 7.38 (m, 4H, $\mathbf{H_{2, 2'}}$), 7.31 (d, *J*=8.4 Hz, 2H, $\mathbf{H_1}$), 7.17 (d, *J*=8.4 Hz, 2H, $\mathbf{H_{1'}}$), 5.13 (s, 4H, $\mathbf{H_a}$), 4.95 (s, 2H, $\mathbf{H_{a'}}$), 4.37 (t, J_1=J_2=4.8 Hz, 4H, $\mathbf{H_{b'}}$), 4.27 (t, J_1=J_2=4.8 Hz, 2H, $\mathbf{H_b}$), 4.20 (s, 2H, $\mathbf{H_i}$), 3.72 (t, J_1=J_2=4.8 Hz, 4H, $\mathbf{H_{c'}}$), 3.62-3.45 (m, 26H, $\mathbf{H_{c~g, d'~g'}}$), 3.36 (s, 9H, $\mathbf{H_{h, h'}}$). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 197.18, 168.55, 168.16, 143.00, 139.74, 139.43, 133.88, 132.54, 130.60, 128.07, 127.75, 126.17, 124.81, 123.73, 123.39, 122.08, 121.19, 119.29, 109.14, 109.08, 107.69, 71.88, 70.54, 70.53, 70.51, 70.48, 70.47, 68.78, 64.75, 64.61, 59.01, 44.71, 44.67, 41.65. HRMS (ESI/TOF-Q): m/z $[M+Na]^+$ calcd. for $C_{66}H_{73}N_3O_{16}Na$ 1186.4883, found 1186.4880.

Synthesis of Compound **3**:

DDQ (177.60 mg , 0.78 mmol) and the compound **1** (150.00 mg, 0.13 mmol) was added into the aqueous THF (1.50 mL of THF containing 0.05 mL of water), and then the mixture was stirred at room temperature for 10 h. Afterwards, the solvents was evaporated under vacuum, the residue was extracted by 3 × 100 mL CH_2Cl_2, washed with water. After drying with Na_2SO_4, CH_2Cl_2 was evaporated, the residue was further purified with 200-300 silicon column (DCM:MeOH = 250:2 *V/V*) to give 128.50 mg of the target **3** (yield, 83.6%).^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.64 (s, 2H, **H$_{4'}$**), 8.56 (s, 2H, **H$_4$**), 8.40 (d, *J*=8.4 Hz, 2H, **H$_{2'}$**), 8.16 (d, *J*=8.4 Hz, 2H, **H$_2$**), 8.14 (s, 2H, **H$_5$**), 7.63 (d, *J*=8.4 Hz, 2H, **H$_{1'}$**), 7.44-7.41 (m, 4H, **H$_{1,7}$**), 7.21 (d, *J*=8.4 Hz, 2H, **H$_8$**), 5.28 (s, 2H, **H$_{a'}$**), 5.00 (s, 4H, **H$_a$**), 4.44 (t, J_1=J_2=4.8 Hz, 2H, **H$_{b'}$**), 4.28 (t, J_1=J_2=4.8 Hz, 4H, **H$_b$**), 4.17 (br., 2H, **H$_i$**), 3.78 (t, J_1=J_2=4.8 Hz, 2H, **H$_{c,c'}$**), 3.68-3.52 (m, 12H, **H$_{d\sim g,d'\sim g'}$**), 3.38 (s, 3H, **H$_h$**), 3.35 (s, 6H, **H$_{h'}$**). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 195.35, 167.98, 167.85, 143.42, 143.06 , 139.63 , 136.46 , 131.78 , 129.34 , 128.81 , 128.28 , 126.39 , 125.55 , 124.24 , 122.23 , 122.05 , 119.54 , 109.79 , 109.39 , 109.01 , 71.94 , 71.90 , 70.63 , 70.61 , 70.55 , 70.53 , 70.52 , 68.82 , 68.73 , 65.02 , 64.74 , 59.05 , 59.02 , 44.68 , 44.62 , 43.13. HRMS (ESI/TOF-Q): m/z $[M+Na]^+$ calcd. for $C_{66}H_{71}N_3O_{17}Na$ 1200.4676, found 1200.4678.

Synthesis of Compound **4**：

DDQ (60.50mg , 0.27 mmol) and the compound **1** (50.00 mg, 0.043 mmol) was added into the mixture of aqueous THF (1.50 mL of THF containing 0.05 mL of water) and MeOH (0.5 mL), and then the mixture was stirred at room temperature for 10 h. Afterwards, the solvents was evaporated under vacuum, the residue was extracted by 3 × 100 mL CH_2Cl_2, washed with water. After drying with Na_2SO_4, the CH_2Cl_2 was evaporated, the residue was further purified with 200-300 silicon column (DCM: MeOH = 250:2 *V/V*) to give 32.50 mg of the target **4** (yield, 69.3%).

^{1}H-NMR (600 MHz, DMSO-d_6): δ 8.90 (s, 2H, **H$_{4'}$**), 8.80 (s, 2H, **H$_4$**), 8.54 (s, 2H, **H$_5$**), 8.20 (d, *J*=9.0 Hz, 2H, **H$_{2'}$**), 8.07 (d, *J*=9.0 Hz, 2H, **H$_2$**), 7.92 (d, *J*=9.0 Hz, 2H, **H$_{1'}$**), 7.74 (d, *J*=9.0 Hz, 2H, **H$_1$**), 7.61 (d, *J*=9.0 Hz, 2H, **H$_7$**), 7.46 (d, *J*=9.0 Hz, 2H, **H$_8$**), 5.65 (s, 2H, **H$_a$**), 5.40 (s, 4H, **H$_{a'}$**), 4.33 (t, J_1=J_2=4.8 Hz, 2H, **H$_b$**), 4.18 (t, J_1=J_2=4.8 Hz, 4H, **H$_{b'}$**), 3.69 (t, J_1=J_2=4.8 Hz, 2H, **H$_c$**), 3.58-3.41 (m, 28H, **H$_{d\sim g,c'\sim g'}$**), 3.40 (s, 1.5H, **H$_h$**), 3.30 (s, 1.5H, **H$_{h'}$**), 3.22 (s, 4.5H, **H$_{i,i'}$**). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 195.27, 167.89, 167.76, 143.35, 142.98, 139.56, 136.39, 131.72, 129.28, 128.75, 128.22, 126.31, 125.49, 124.18, 122.16, 121.99, 119.47, 109.90, 109.69, 109.31,

108.93, 71.86, 71.83, 70.57, 70.55, 70.48, 70.47, 70.45, 68.75, 68.66, 64.95, 64.69, 64.67, 58.98, 58.95, 44.62, 44.60. HRMS (ESI/TOF-Q): m/z $[M+Na]^+$ calcd. for $C_{68}H_{75}N_3O_{19}Na$ 1260.4887, found 1260.4871.

Table S1 The optimization of reactions conditions.

Solvents	Reaction time	Amount of DDQ	yield of **2**	yield of **3**
THF alone	10 h	10 eq	---	---
THF : H_2O = 100 : 1	10 h	1.0 eq	7%	---
THF : H_2O = 75 : 1	10 h	1.0 eq	28%	3%
THF : H_2O = 30 : 1	10 h	1.0 eq	22%	8%
THF : H_2O = 10 : 1	10 h	10 eq	11%	13%
THF : H_2O = 30 : 1	10 h	2.0 eq	6%	20%
THF : H_2O = 30 : 1	10 h	3.0 eq	2%	35%
THF : H_2O = 30 : 1	10 h	20.0 eq	---	84%

Synthesis of Compound **5**：

5 mL of 3N NaOH aqueous solution was added drop wise to the solution of **3** (150 mg, 0.125 mmol) in THF (5 mL). The mixture was stirred at room temperature for 8 h and concentrated in vacuum to remove THF. 1N hydrochloric acid was added to adjust pH = 2~3. The solid precipitated was filtered and dried to give 73.6 mg of the compound **5**. yield 80%. ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.05 (s, 3H), 8.92 (s, 2H), 8.75 (s, 2H), 8.51 (s, 2H), 8.22 (s, 2H), 8.00 (s, 2H), 7.90 (s, 2H), 7.73 (s, 2H), 7.48 (s, 2H), 7.42 (s, 2H), 5.50 (s, 2H), 5.23 (s, 4H), 4.13 (d ,2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 194.61, 170.31, 170.17, 143.68, 143.41, 139.85, 136.79, 130.91, 128.83, 128.16, 127.59, 126.72, 125.50, 123.67, 123.45, 122.00, 121.74, 120.32, 44.71, 44.52, 42.06. RMS (m/z): calcd for : $C_{45}H_{29}N_3O_8$ $[M]^+$: 739.1955, found: 739.1942.

Synthesis of Compound **6**：

5 mL of 3N NaOH aqueous solution was added drop wise to the solution of compound **1** (150 mg, 0.13 mmol) in THF (5 mL) . The mixture was stirred at room temperature for 8h and concentrated in vacuum to remove THF. 1N hydrochloric acid was added to adjust pH = 2~3. The solid precipitated was filtered, dried under vacuum to obtain 78 mg of compound **6** .yield 85%. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.88 (s, 3H), 8.21 (s, 6H), 7.39 (s, 6H), 7.36 (s, 6H), 5.08 (s, 6H), 4.21 (s, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 170.59, 139.76, 133.59, 126.84, 123.01, 119.86, 109.24, 44.41, 41.61. RMS (m/z): calcd for :$C_{45}H_{33}N_3O_6$ $[M]^+$: 711.2369, found: 711.2361.

3. NMR spectra and HRMS:

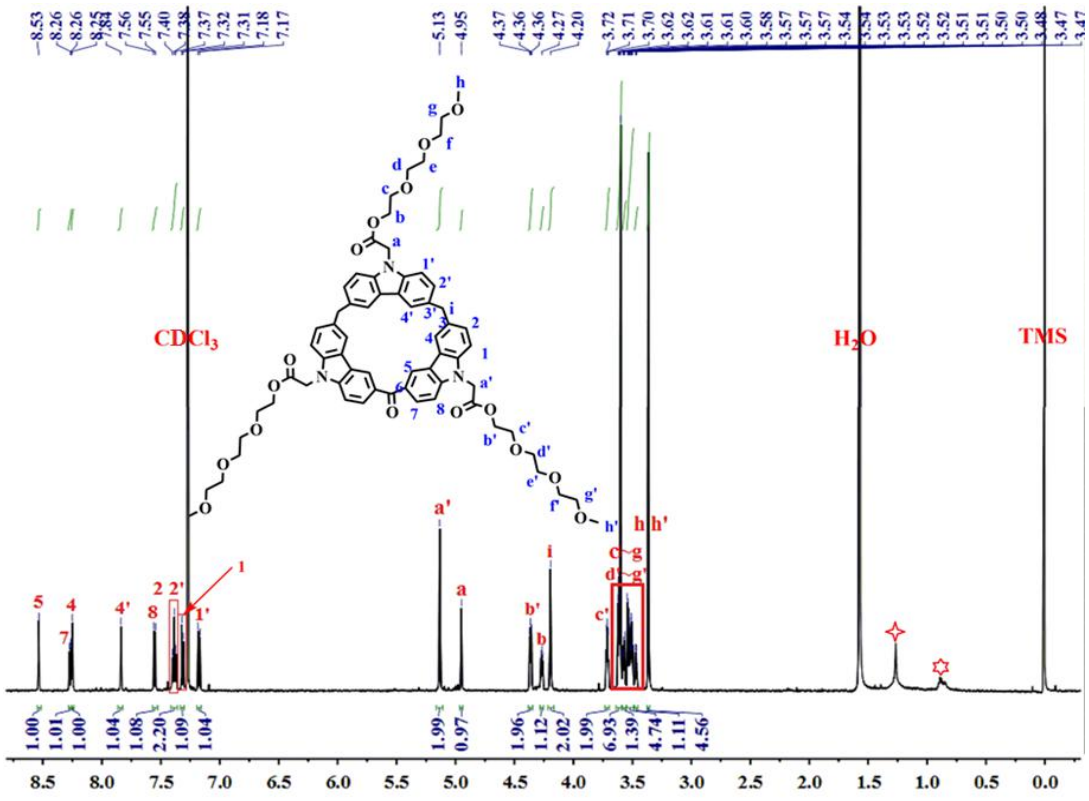

Fig. S1. ^{1}H-NMR spectrum of **2** in $CDCl_3$ (600 MHz, 25 °C) (☆: impurities)

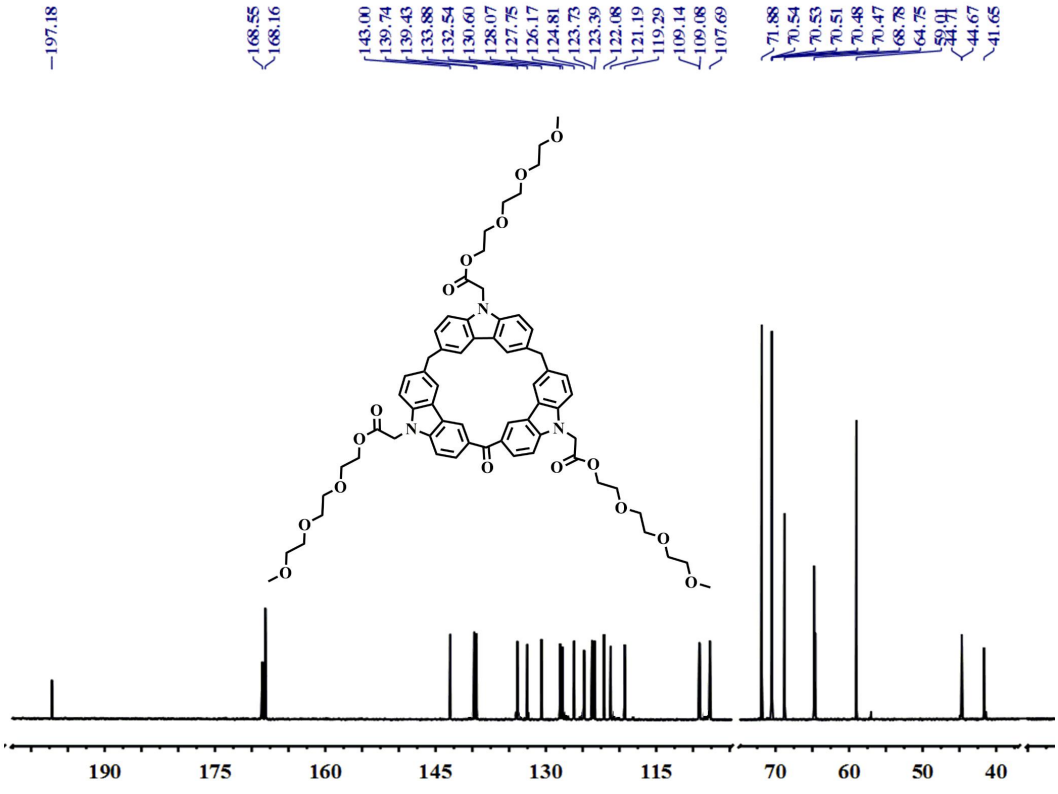

Fig. S2. ^{13}C-NMR spectrum of **2** in $CDCl_3$ (150 MHz, 25 °C)

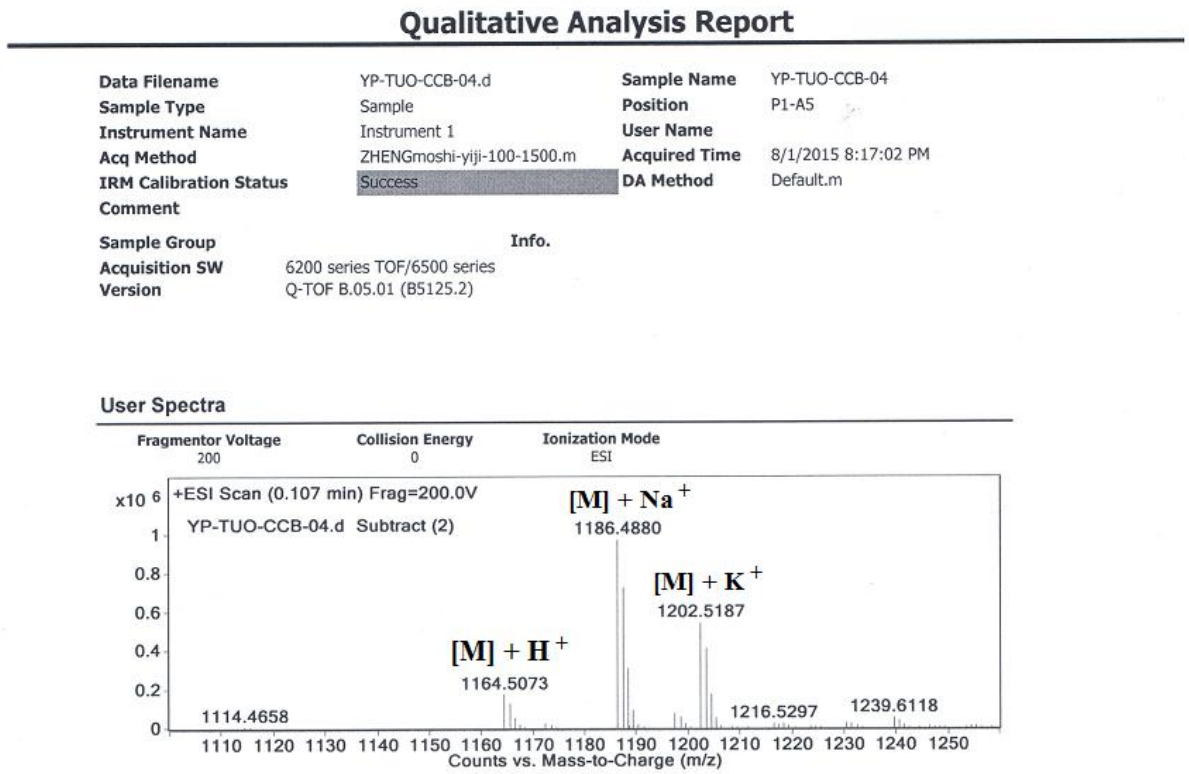

Fig. S3. High resolution mass spectrum of **2**

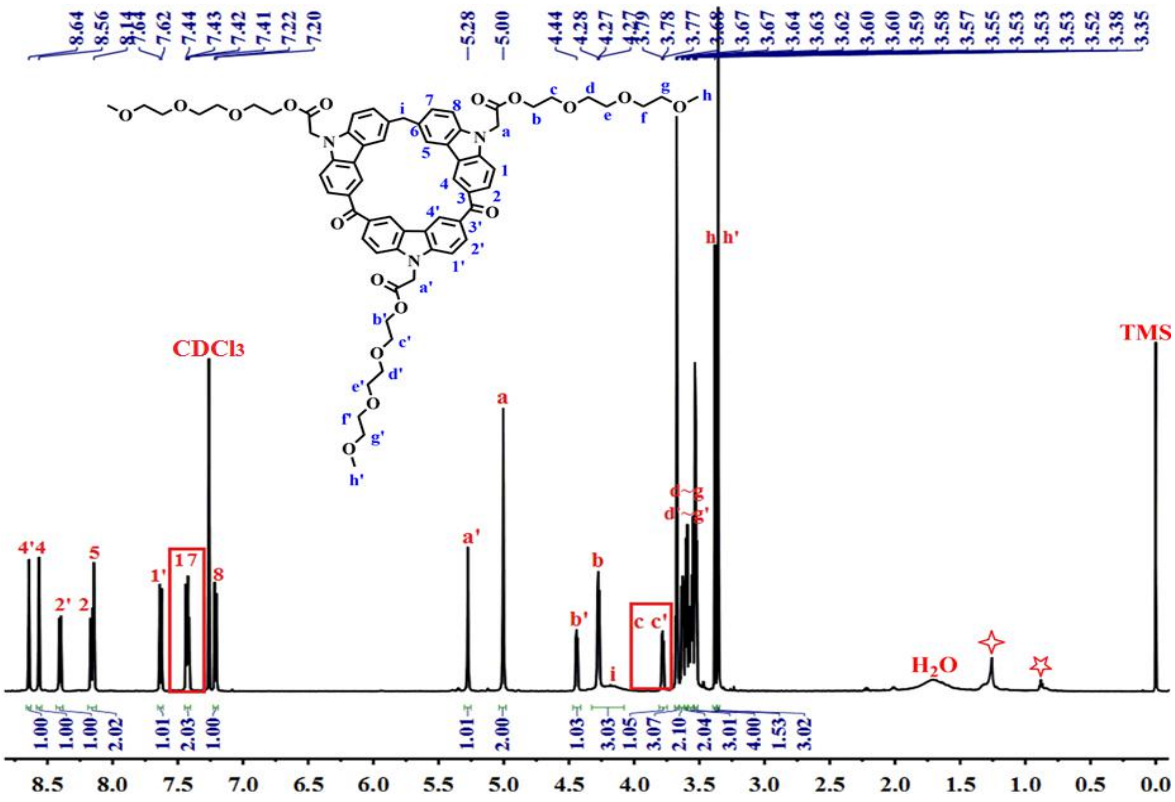

Fig. S4. ^{1}H-NMR spectrum of **3** in $CDCl_3$ (600 MHz, 25 °C) (☆: impurities)

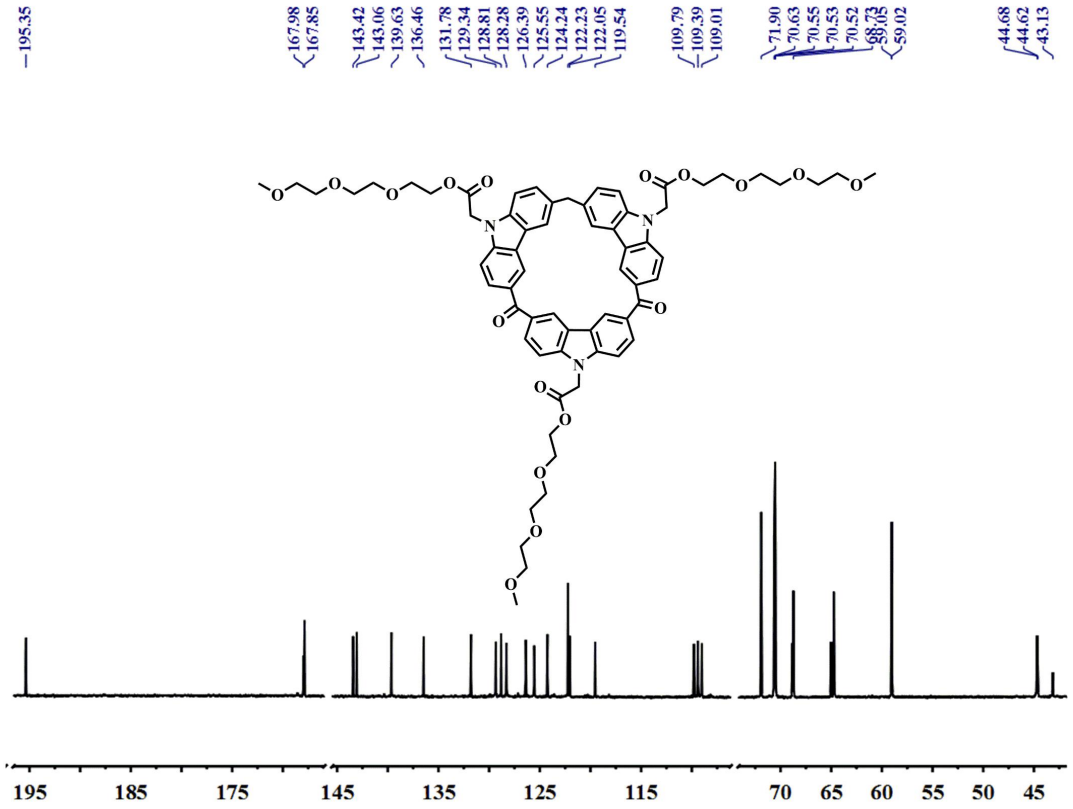

Fig. S5. ^{13}C-NMR spectrum of **3** in $CDCl_3$ (150 MHz, 25 °C)

Qualitative Analysis Report

Data Filename	YP-TUO-CCB-03.d	**Sample Name**	YP-TUO-CCB-03
Sample Type	Sample	**Position**	P1-A3
Instrument Name	Instrument 1	**User Name**	
Acq Method	ZHENGmoshi-yiji-100-1500.m	**Acquired Time**	8/1/2015 8:09:37 PM
IRM Calibration Status	Success	**DA Method**	Default.m
Comment			

Sample Group	**Info.**
Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.05.01 (B5125.2)

User Spectra

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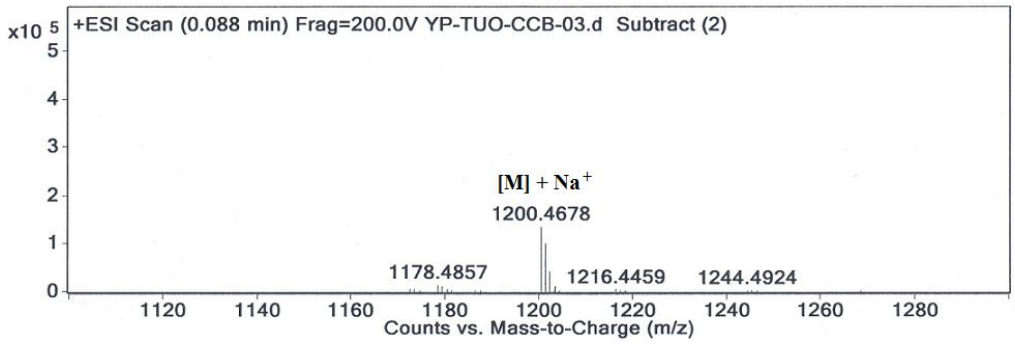


Fig. S6. High resolution mass spectrum of **3**

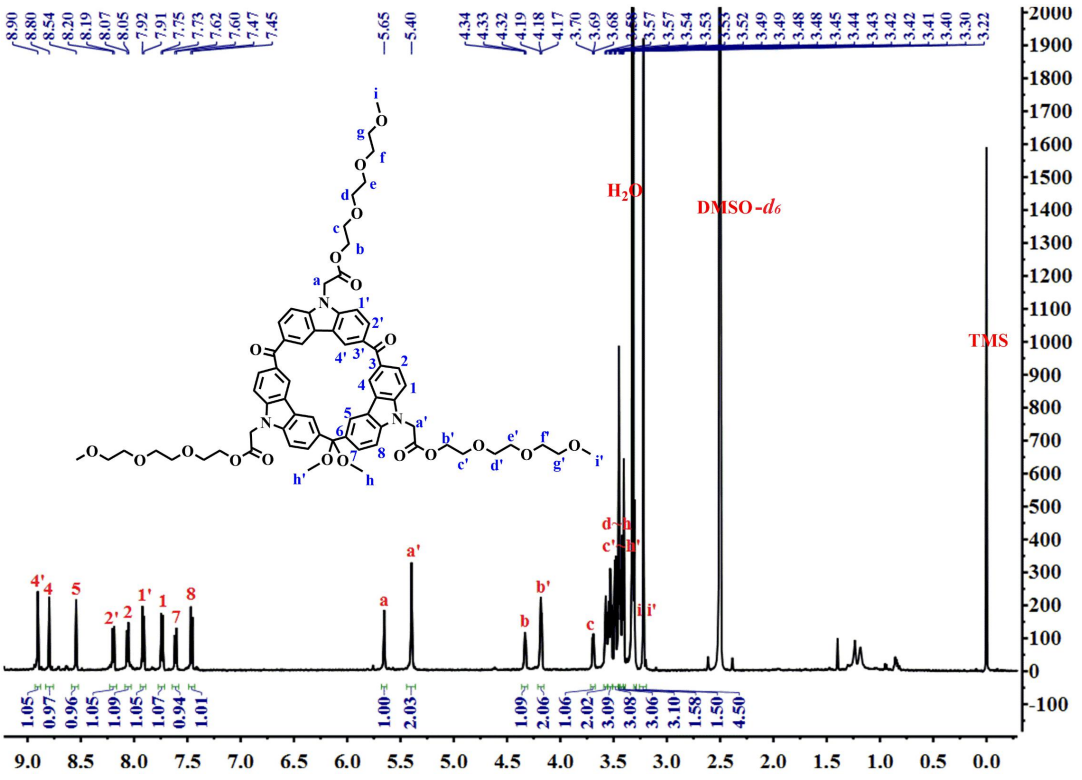


Fig. S7. [1]H-NMR spectrum of **4** in DMSO-d_6 (600 MHz, 25 °C)

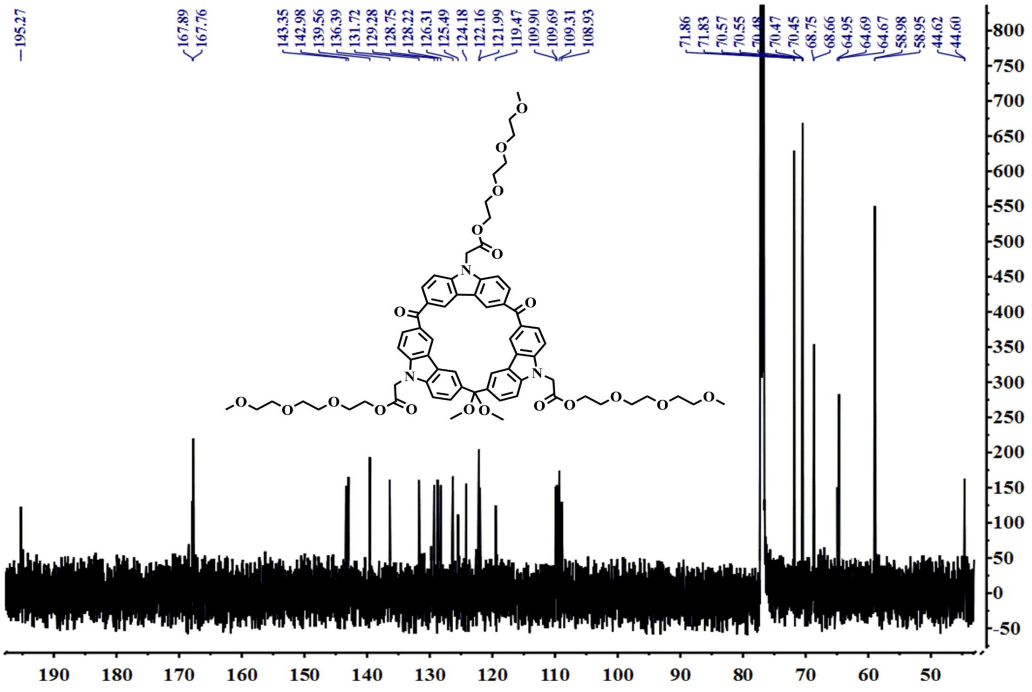


Fig. S8. [13]C-NMR spectrum of **4** in DMSO-d_6 (150 MHz, 25 °C)

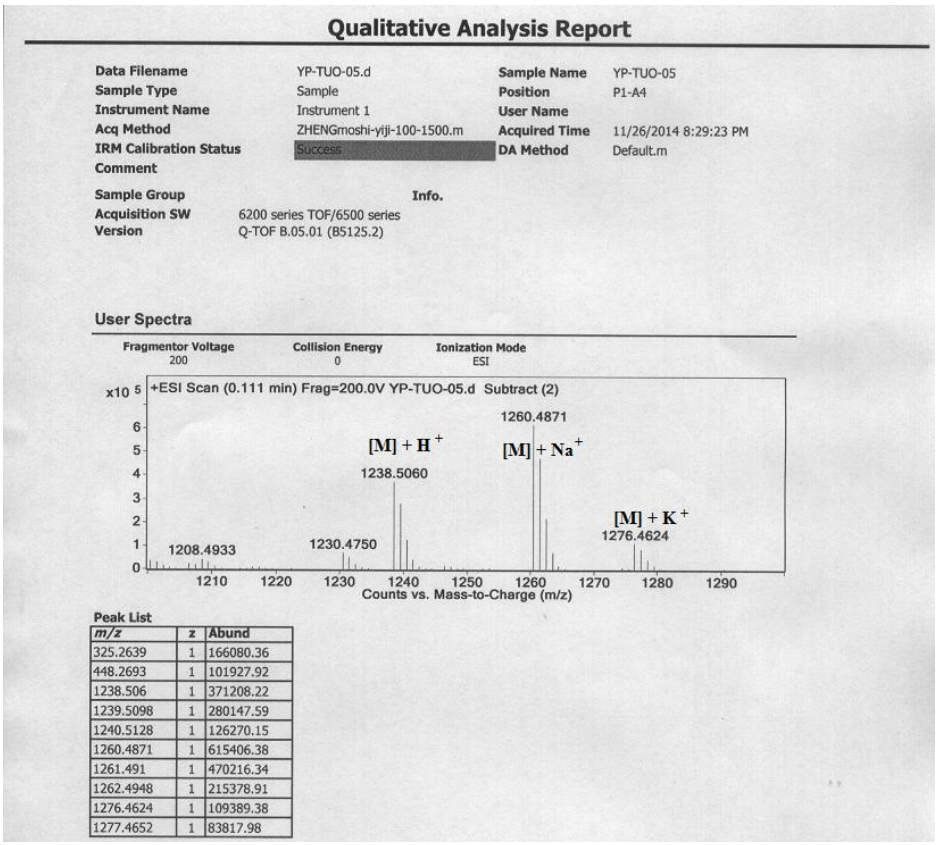


Fig. S9 High resolution mass spectrum of **4**

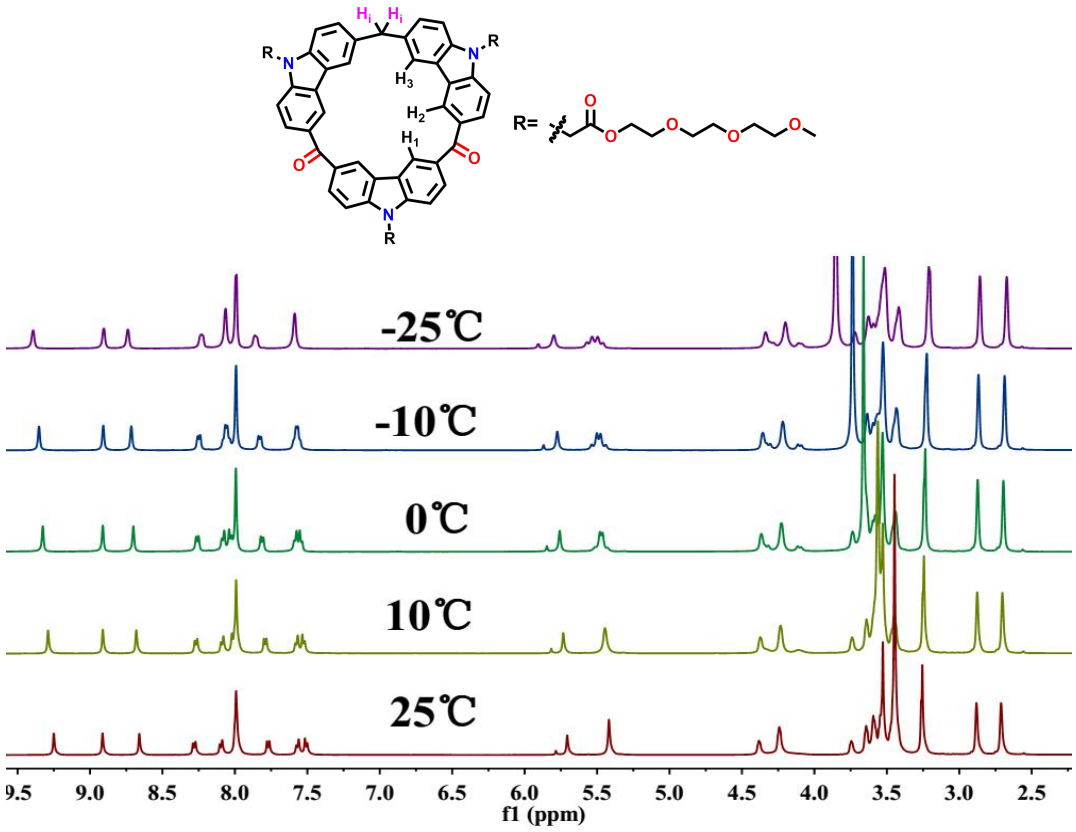


Fig. S10. Full spectra of VT-NMR of **3** in DMF-d7

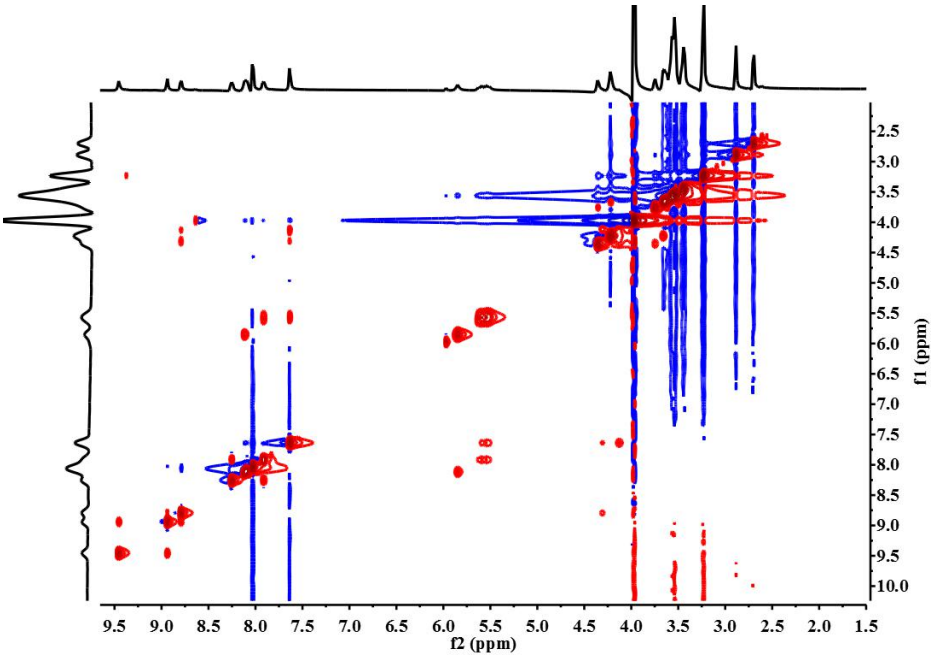


Fig. S11. 2D NOESY of **3** in DMF-d_7 at -25℃ (T_m = 100 ms)

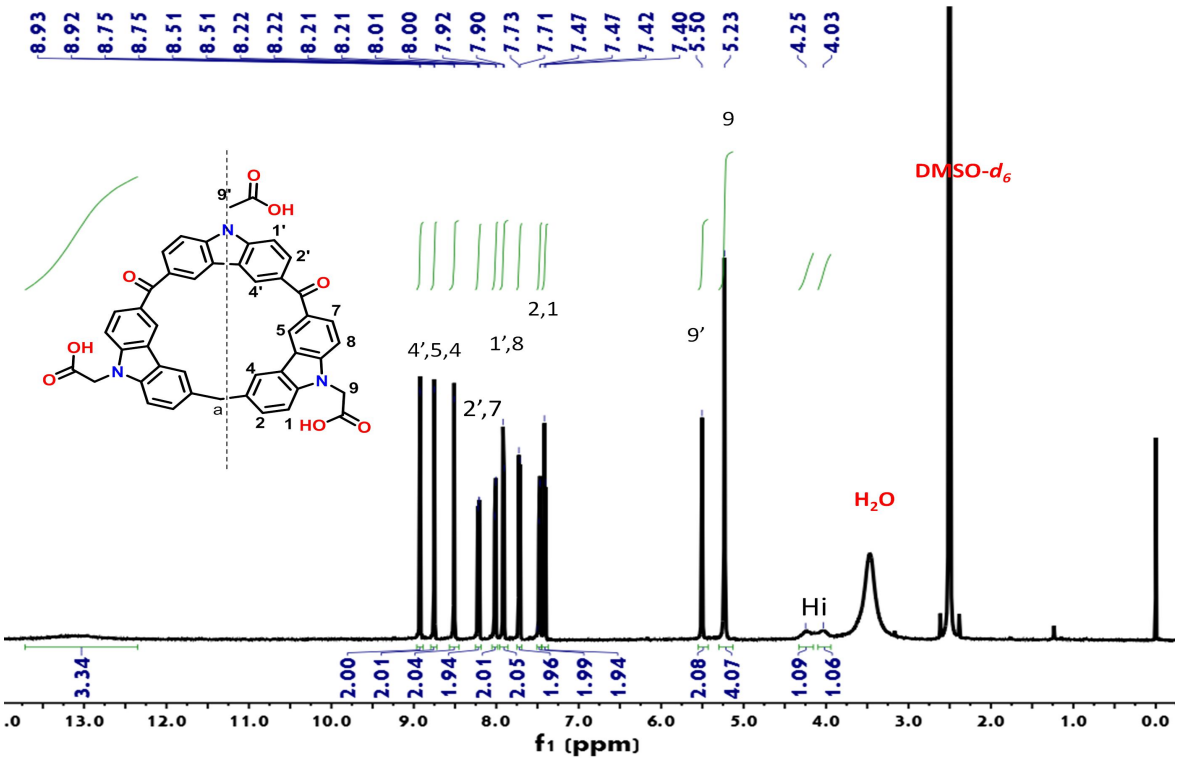


Fig. S12. [1]H-NMR spectrum of **5** in DMSO-d_6 (600 MHz, 25 °C)

9

4' 5 4

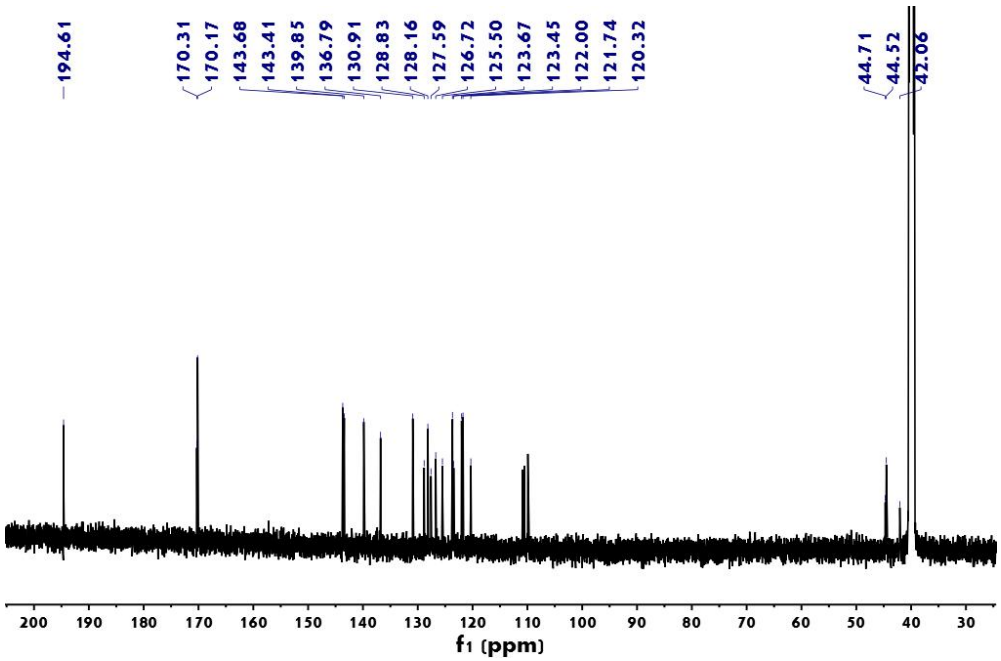
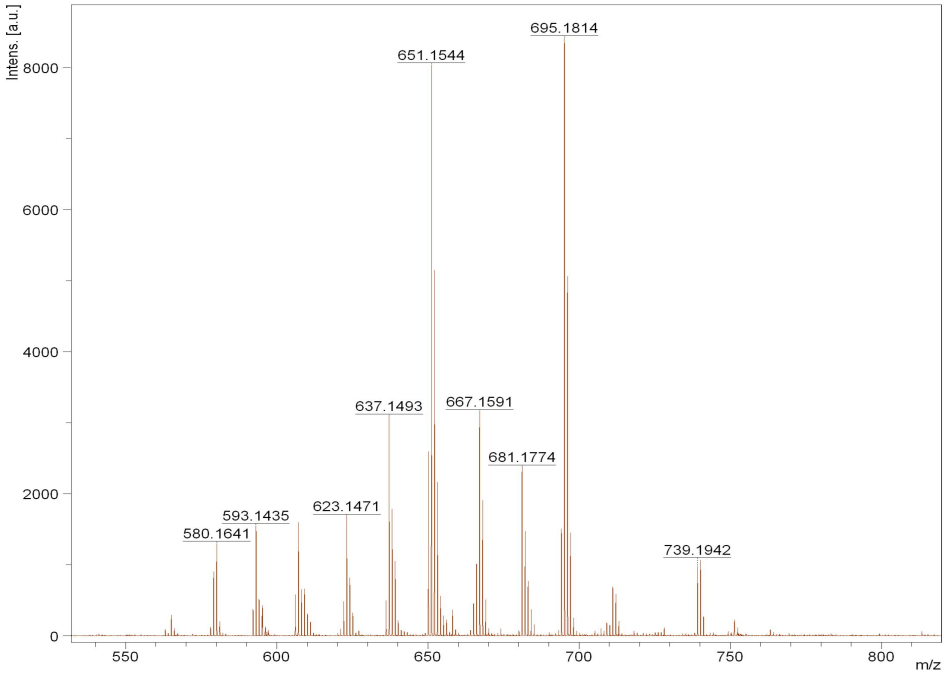


Fig. S13. ^{13}C-NMR spectrum of **5** in DMSO-d_6 (150 MHz, 25 °C)



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Calibration reference list used	sample

Instrument Info

User	BDAL@CN
Instrument	FLEX-PC
Instrument type	ultraflexTOF/TOF

Bruker Daltonics flexAnalysis printed: 2020-1-12 15:54:38

Fig. S14 High resolution mass spectrum of **5**

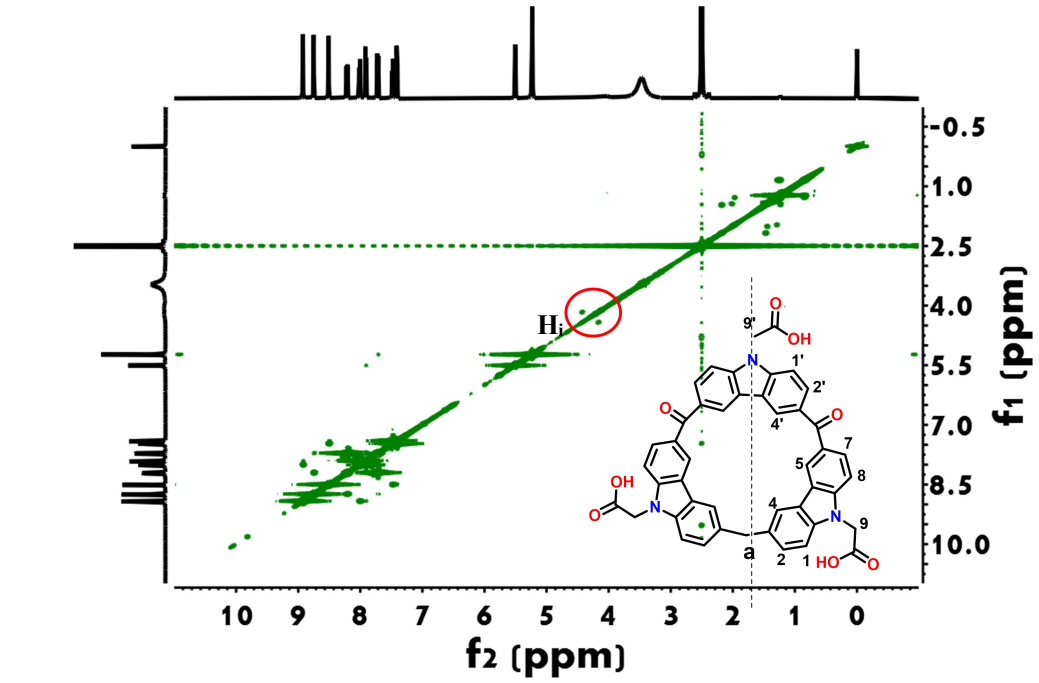


Fig.S15 H-H COSY spectrum of **5** in DMSO-d_6

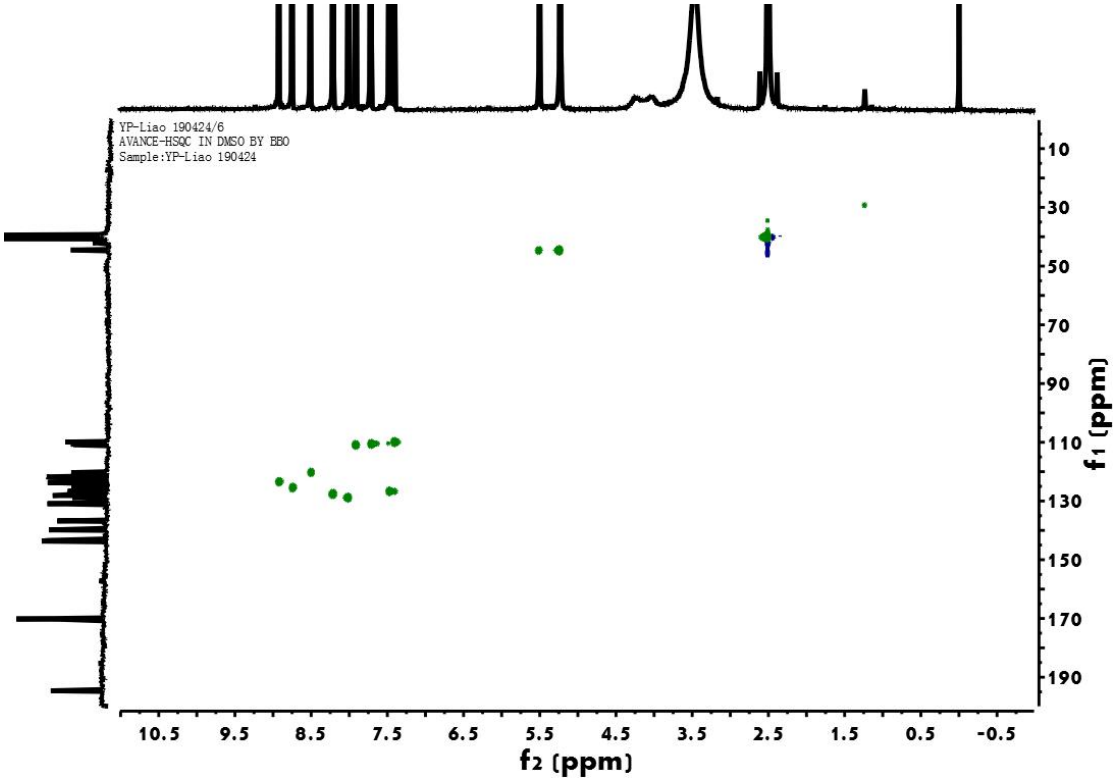


Fig. S16 Full QC spectrum of **5** in DMSO-d_6

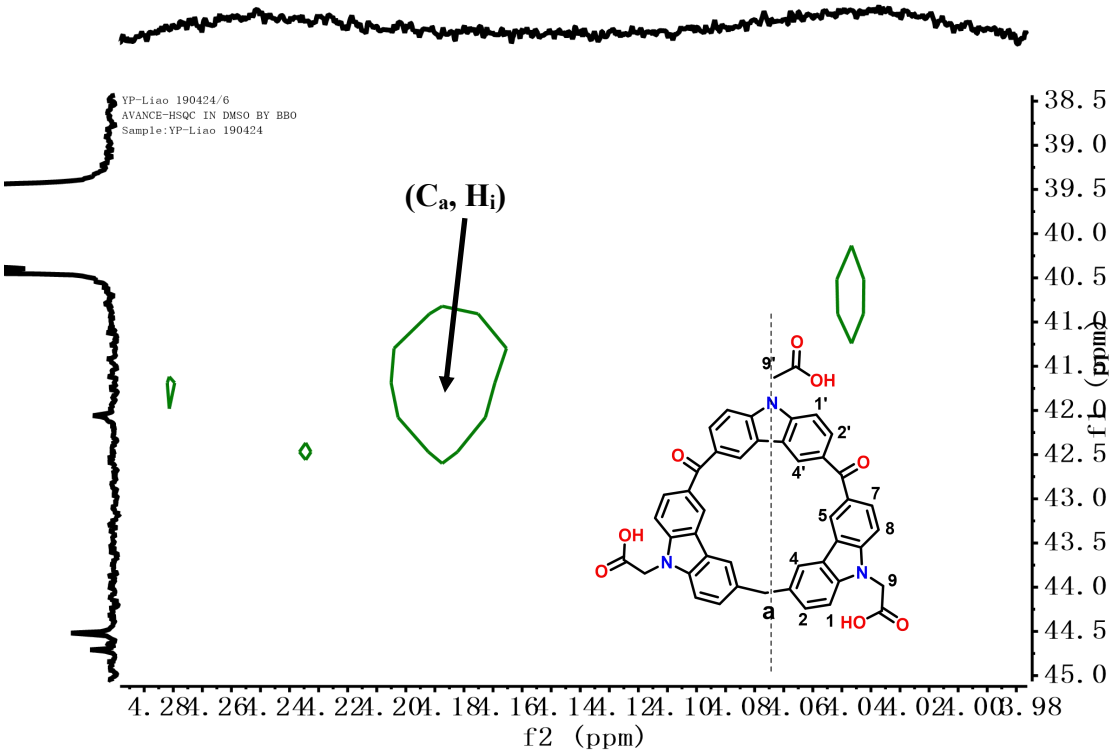


Fig. S17. Partial QC spectrum of **5** in DMSO-d_6

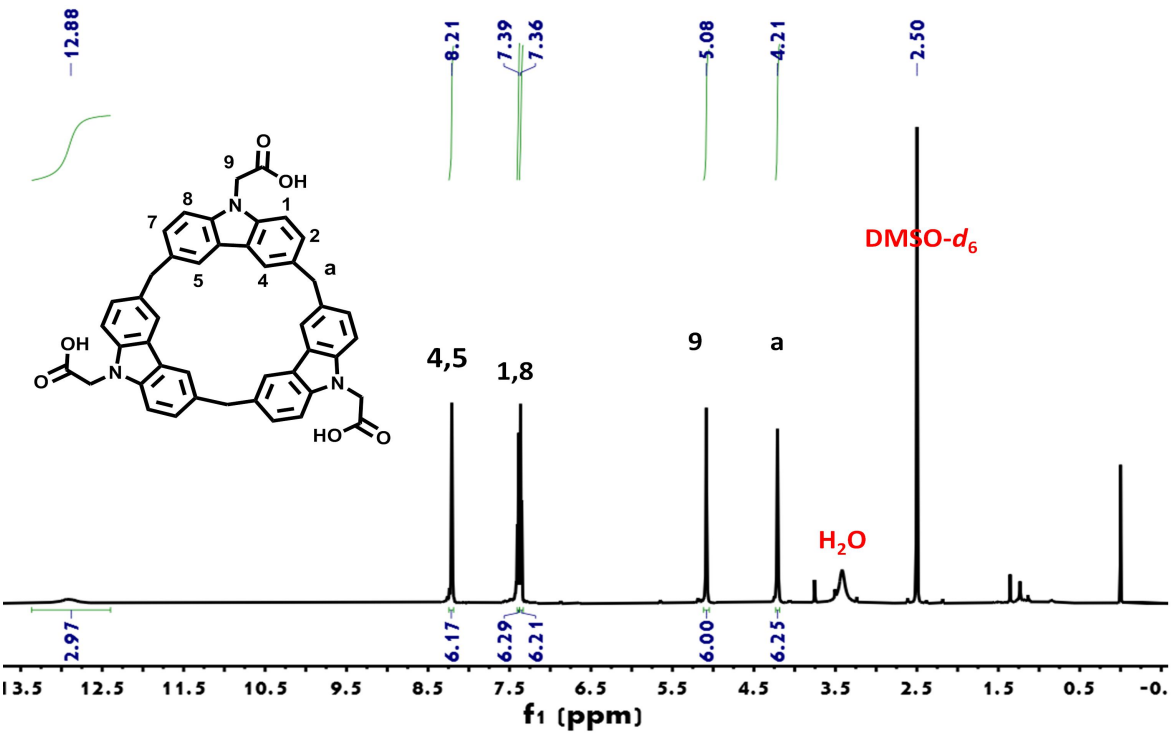


Fig. S18. ^{1}H-NMR spectrum of **6** in DMSO-d_6 (600 MHz, 25 °C)

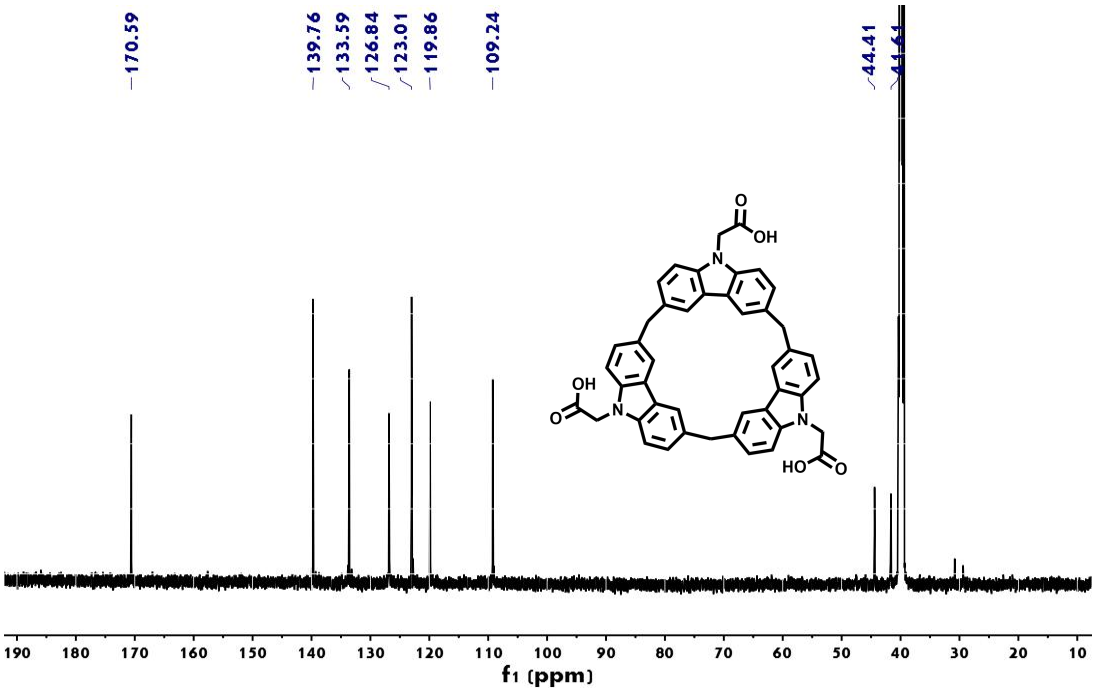
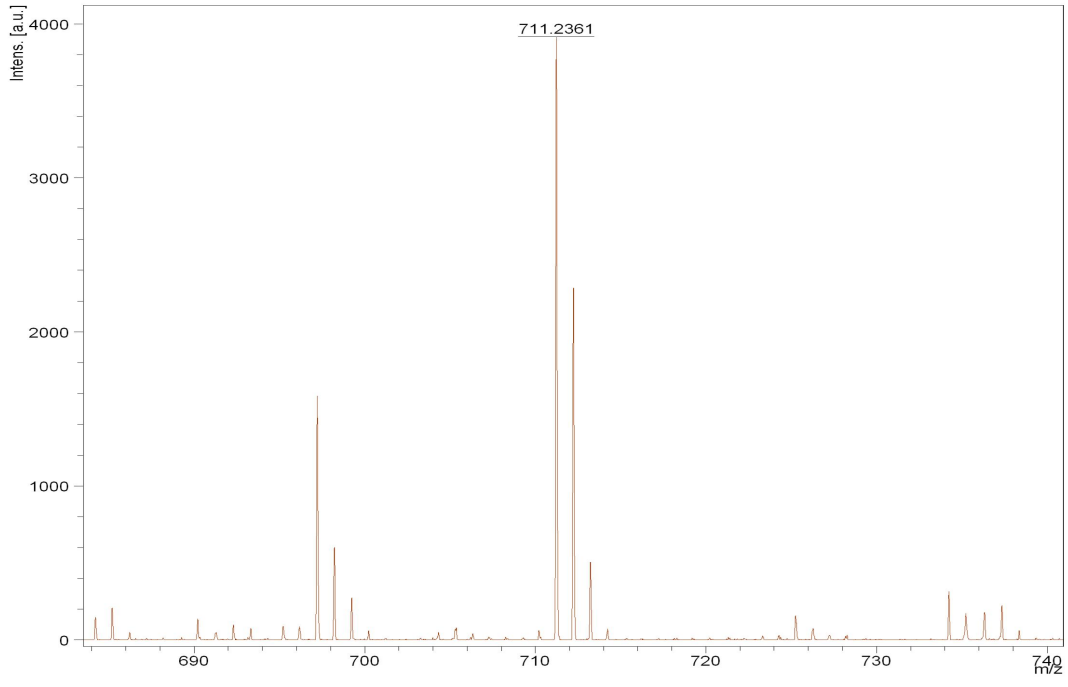


Fig. S19. ^{13}C-NMR spectrum of **6** in DMSO-d_6 (150 MHz, 25 °C)



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Calibration reference list used	sample

Instrument Info

User	BDAL@CN
Instrument	FLEX-PC
Instrument type	ultraflexTOF/TOF

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Fig. S20 High resolution mass spectrum of **6**

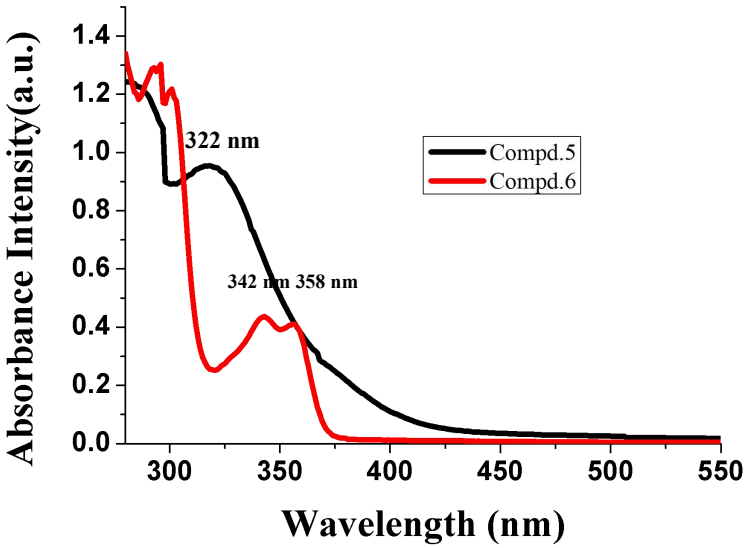


Fig. S21. UV-Vis spectra of ammonium salts of both **5** (30 μM) and **6** (30 μM) in water with 1% DMSO.

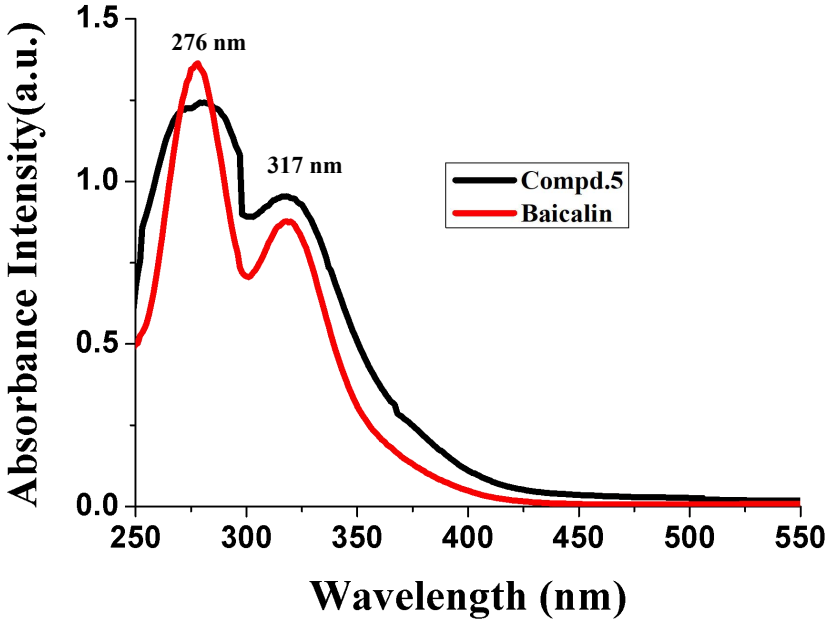


Fig. S22. UV-Vis spectra of ammonium salts of **5** (30 μM) and baicalin (30 μM) in water with 1% DMSO.

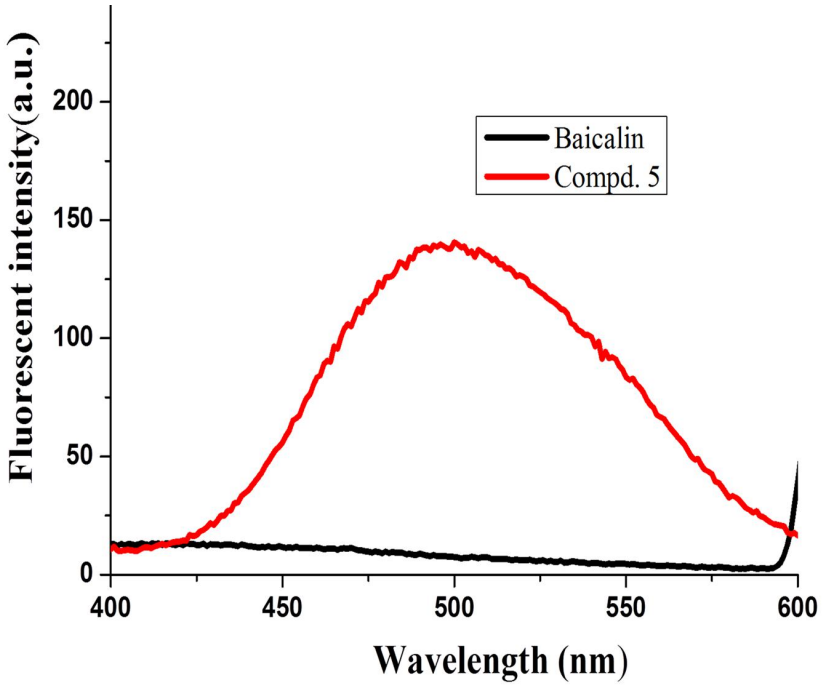


Fig.S23. Fluorescence of **5** (10 μM) and baicalin (30 μM**)** in water containing 1% DMSO (λ_{ex}=340 nm).

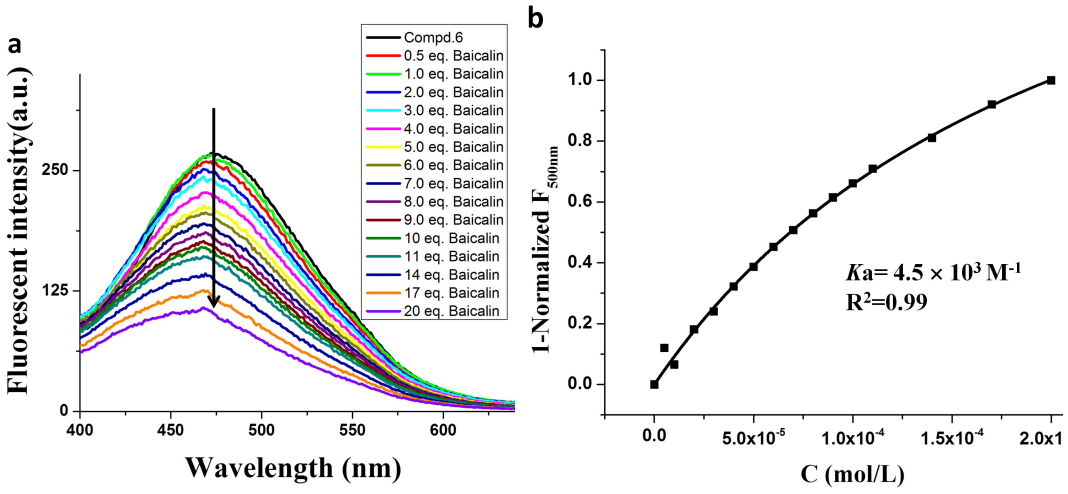


Fig. S24. (a) Fluorescence spectra of **6** (10 μM) upon addition of baicalin in water (DMSO=1%); (b)The fitted curves of F_{500nm} of **6**, as a function of baicalin concentration

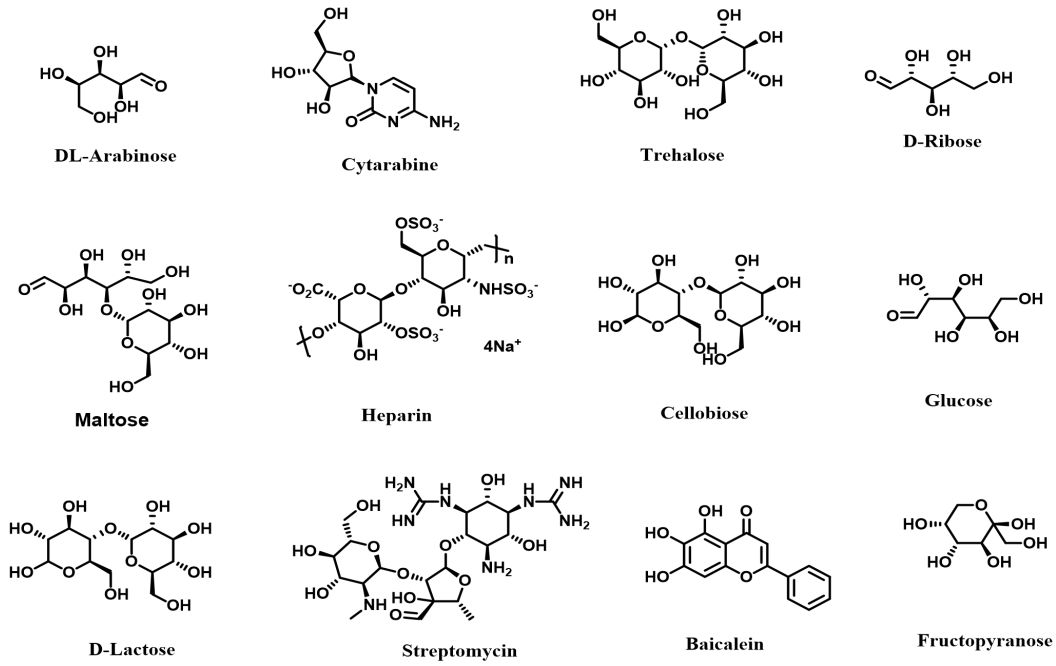


Fig. S25. Various tested guests

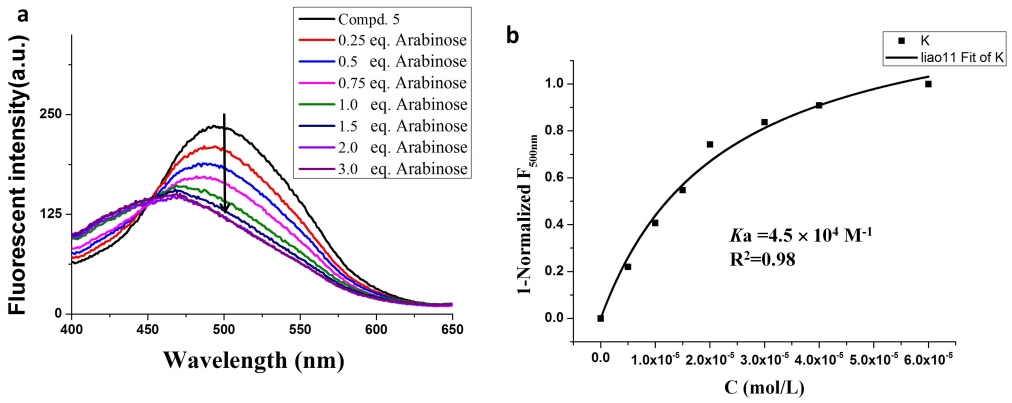


Fig. S26. (a) Fluorescence spectra of **5** (10 μM) upon addition of arabinose in water (DMSO=1%)
(b)The fitted curves of F_{500nm} of **5**, as a function of arabinose concentration

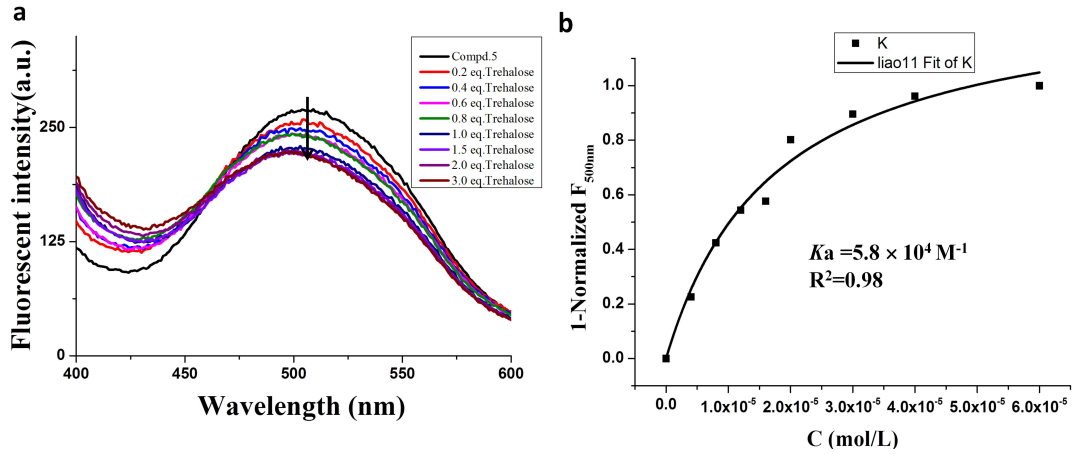


Fig. S27. (a) Fluorescence spectraof **5** (10 μM) upon addition of trehalose in water (DMSO=1%)
(b)The fitted curves of F_{500nm} of **5**, as a function of trehalose concentration

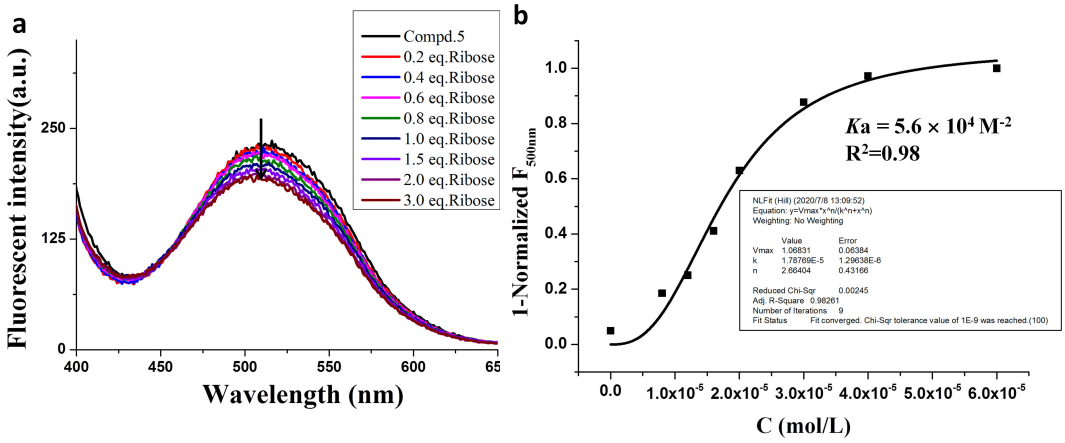


Fig. S28. (a) Fluorescence spectra of **5** (10 μM) upon addition of D-ribose in water (DMSO=1%) (b)The fitted curves of F_{500nm} of **5**, as a function of ribose concentration

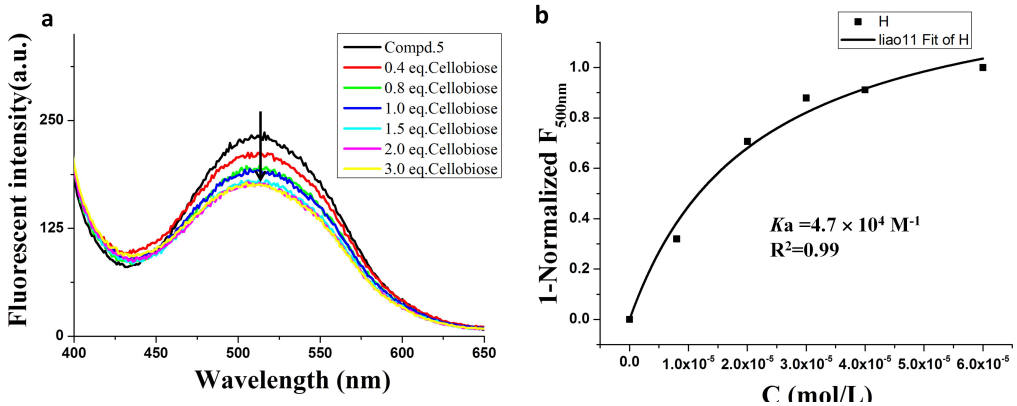


Fig. S29. (a) Fluorescence spectra of **5** (10 μM) upon addition of cellobiose water (DMSO=1%) (b) The fitted curves of F_{500nm} of **5**, as a function of cellobiose concentration

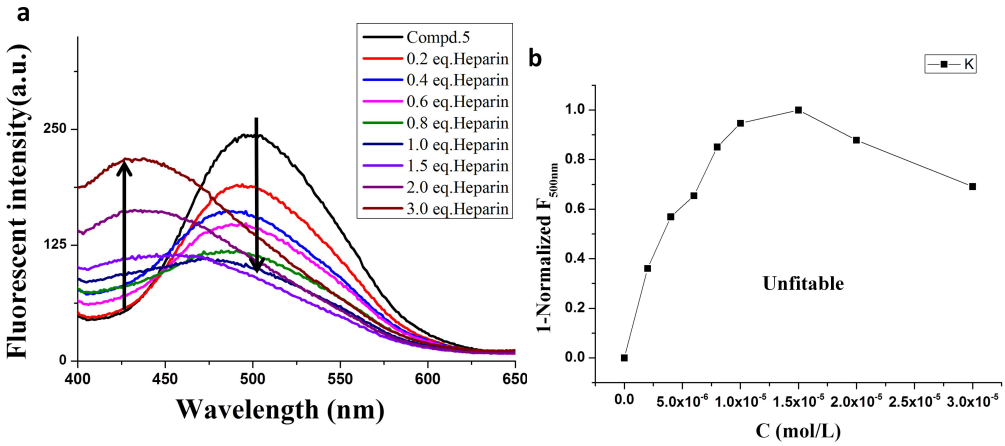


Fig. S30. (a) Fluorescence spectra of **5** (10 μM) upon addition of heparin in water (DMSO=1%) (b)The fitted curves of F_{500nm} of **5**, as a function of heparin concentration

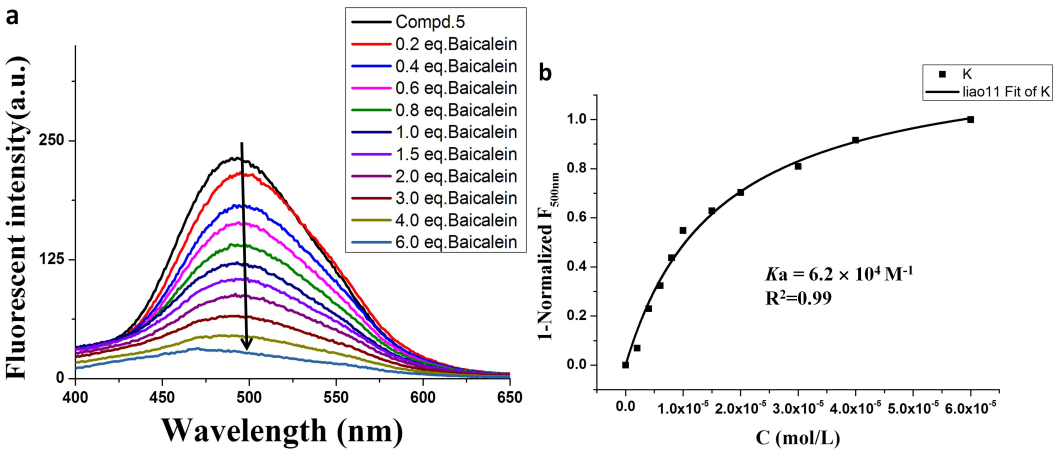


Fig. S31. (a) Fluorescence spectra of **5** (10 μM) upon addition of baicalein in water (DMSO=1%) (b)The fitted curves of F_{500nm} of **5**, as a function of baicalein concentration

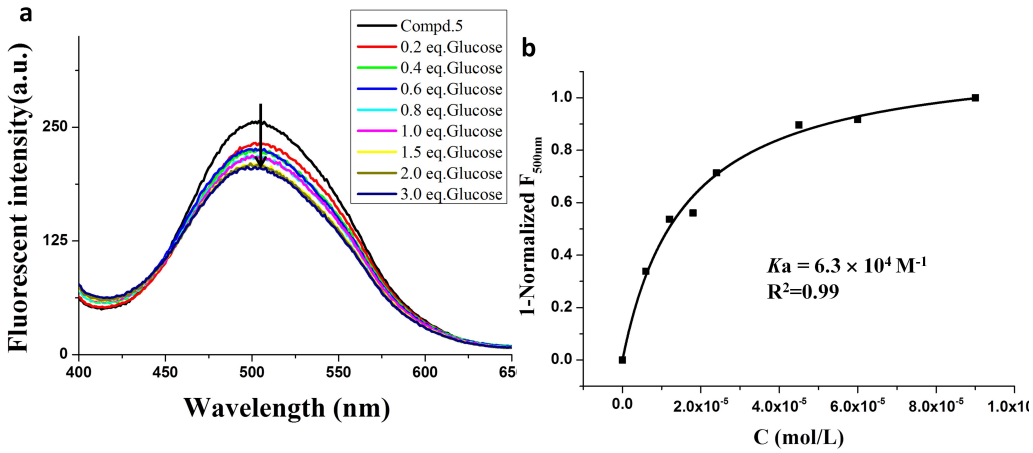


Fig. S32. (a) Fluorescence spectra of **5** (10 μM) upon addition of glucose in water (DMSO=1%) (b)The fitted curves of F_{500nm} of **5**, as a function of glucose concentration

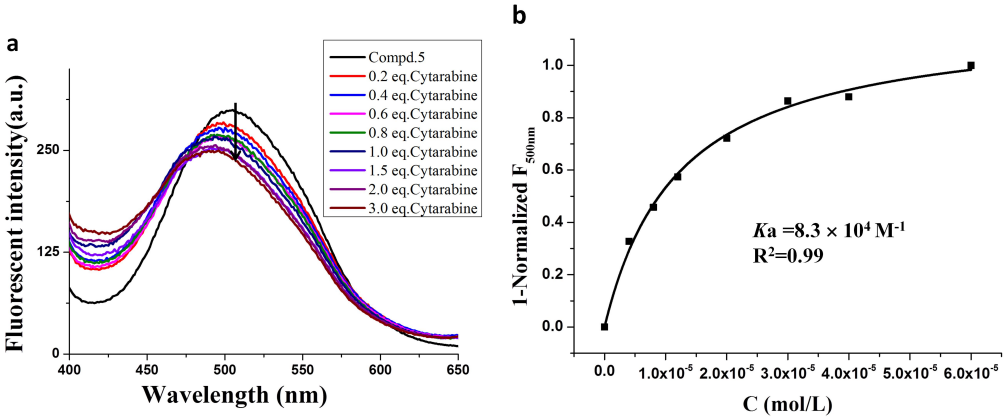


Fig. S33. (a) Fluorescence spectra of **5** (10 μM) upon addition of cytarabine in water (DMSO=1%) (b)The fitted curves of F_{500nm} of **5**, as a function of cytarabine concentration

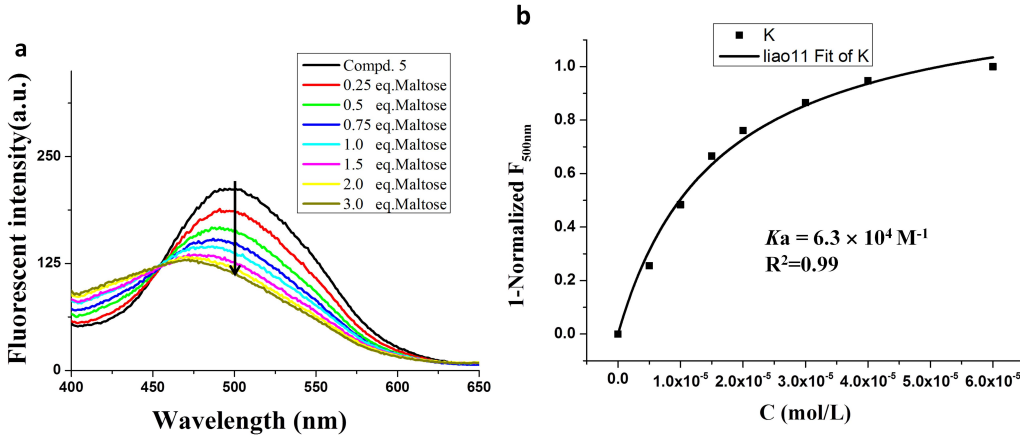


Fig. S34. (a) Fluorescence spectra of **5** (10 μM) upon addition of maltose in water (DMSO=1%) (b)The fitted curves of F_{500nm} of **5**, as a function of maltose concentration

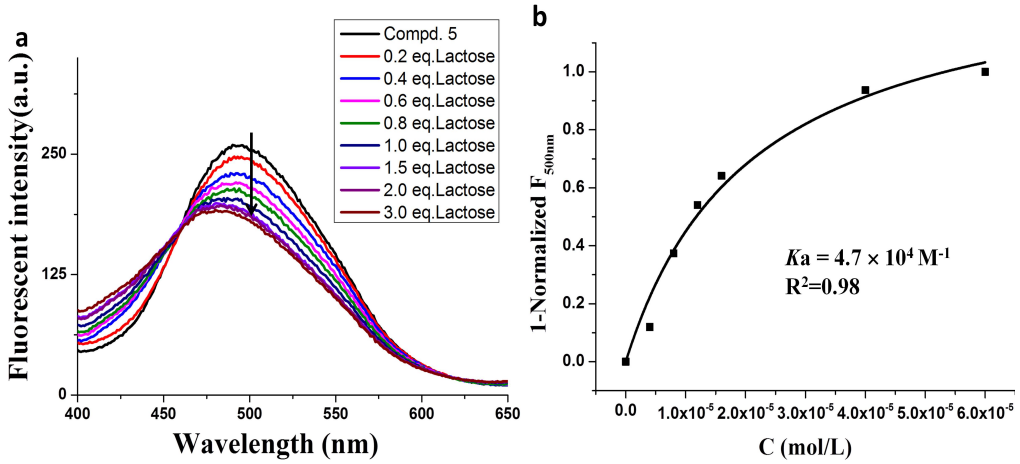


Fig. S35. (a) Fluorescence spectra of **5** (10 μM) upon addition of lactose in water (DMSO=1%) (b)The fitted curves of F_{500nm} of **5**, as a function of lactose concentration

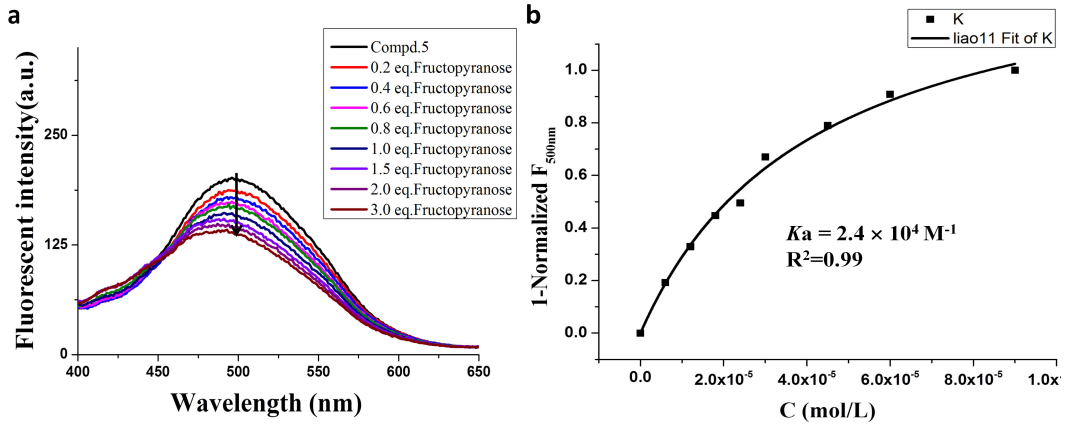


Fig.S36. (a) Fluorescence spectra of **5** (10 μM) upon addition of fructopyranose in water (DMSO=1%) (b)The fitted curves of F_{500nm} of **5**, as a function of fructopyranose concentration

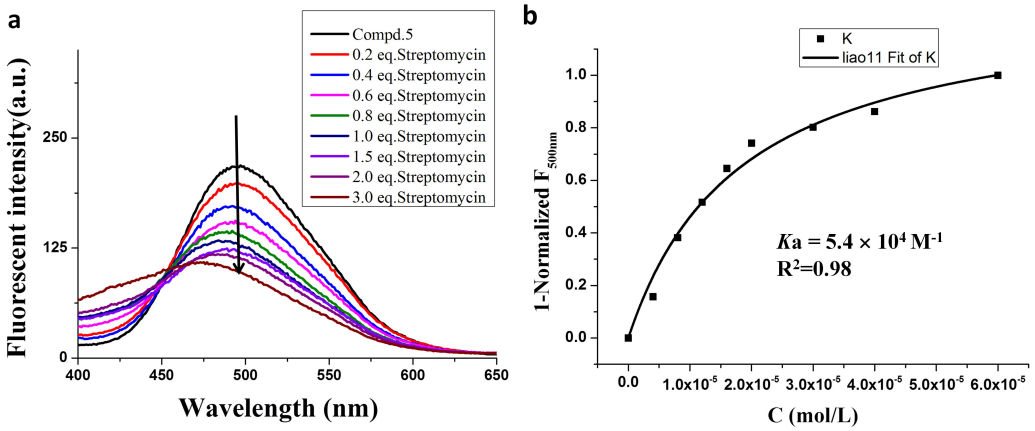
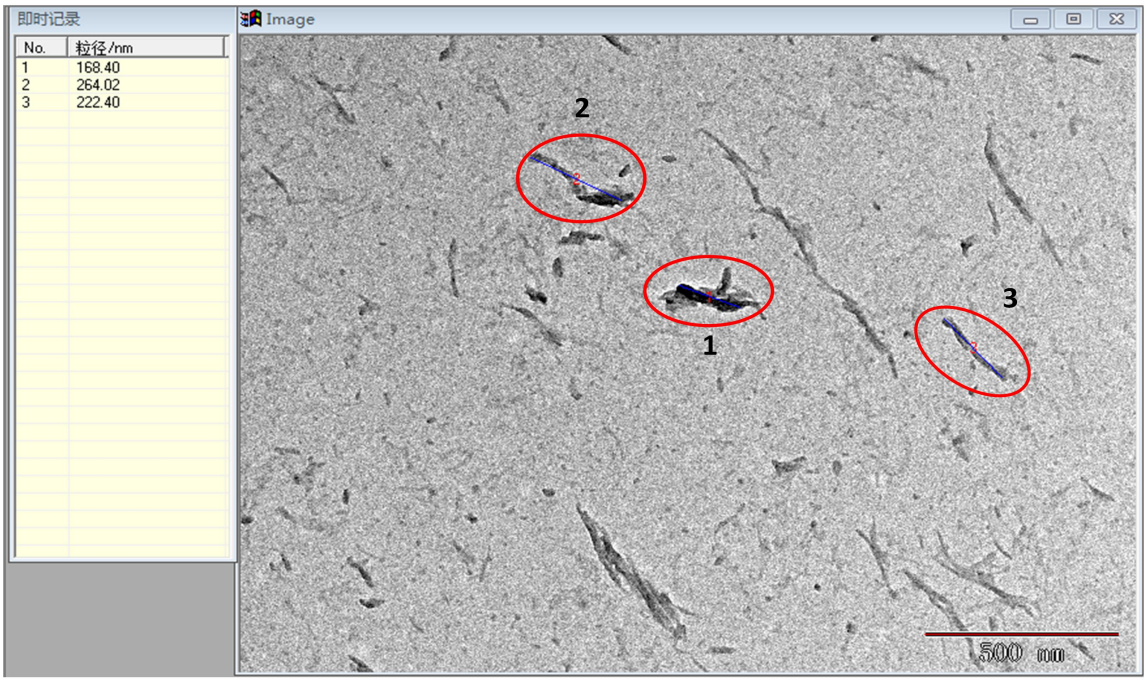


Fig. S37. (a) Fluorescence spectra of **5** (10 μM) upon addition of streptomycin in water (DMSO=1%) (b)The fitted curves of F_{500nm} of **5**, as a function of streptomycin concentration

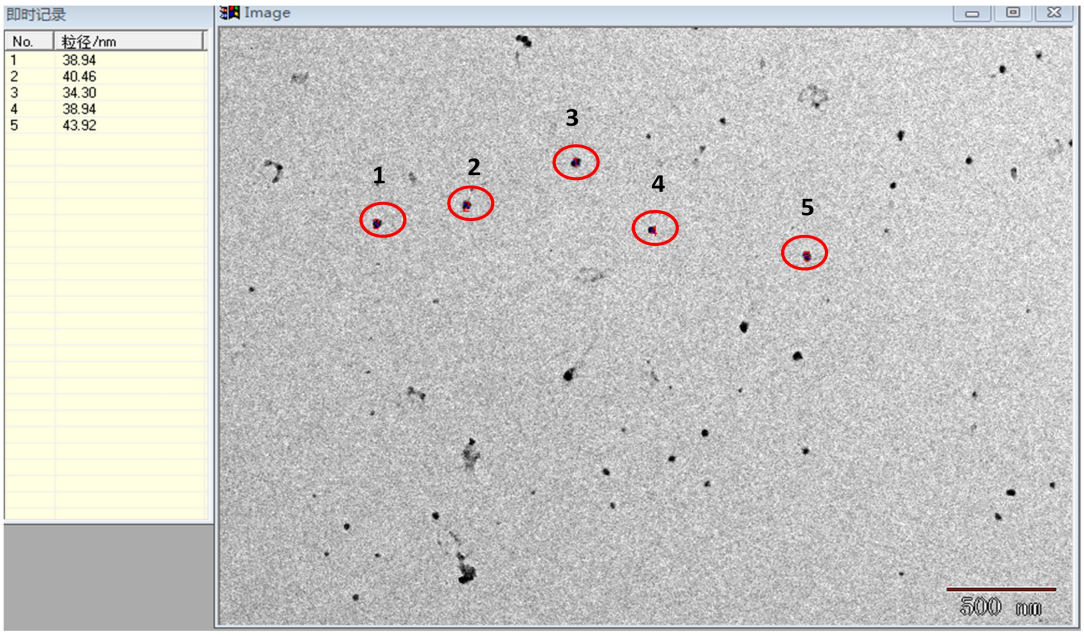
Table S2 The association constants of **5** binding to various guests calculated based on fluorescence titration.

Guests	*Ka*(M^{-1})	R^2
Baicalin	**1.6×10^5**	**0.98**
Arabinose	4.5×10^4	0.98
Trehalose	5.8×10^4	0.98
Ribose	5.6×10^4	0.98
Cellobiose	4.7×10^4	0.99
Heparin	---	---
Baicalein	6.2×10^4	0.99
Glucose	6.3×10^4	0.99
Cytarabine	8.3×10^4	0.99
Maltose	6.3×10^4	0.99
Lactose	4.7×10^4	0.98
Fructopyranose	2.4×10^4	0.99
Streptomycin	5.4×10^4	0.98

--- the titration curve cannot be fitted.

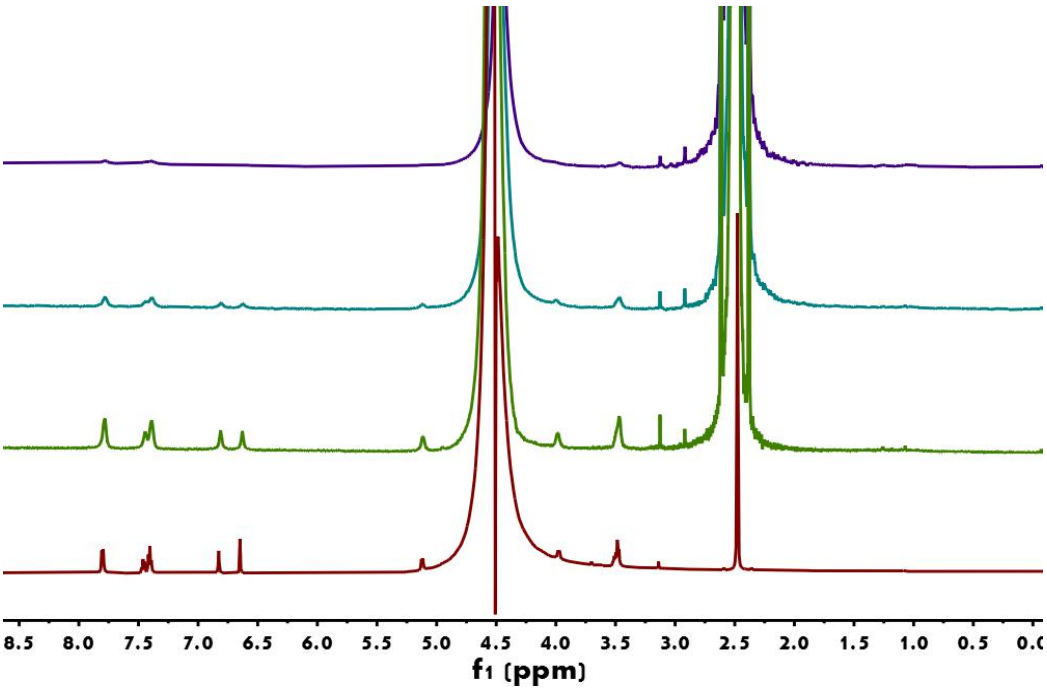


(a)

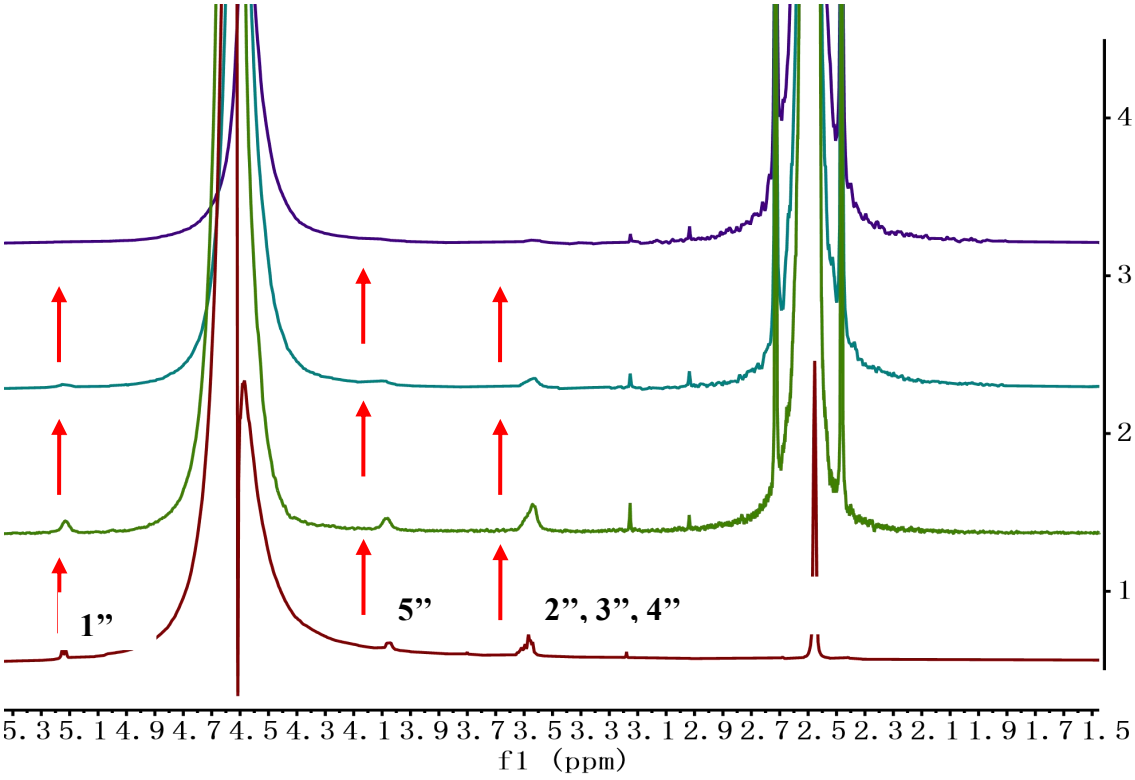


(b)

Fig. S38. The diameter of **5** alone (a) and that of **5**/baicalin complexes (1:1) (b) measured on TEM

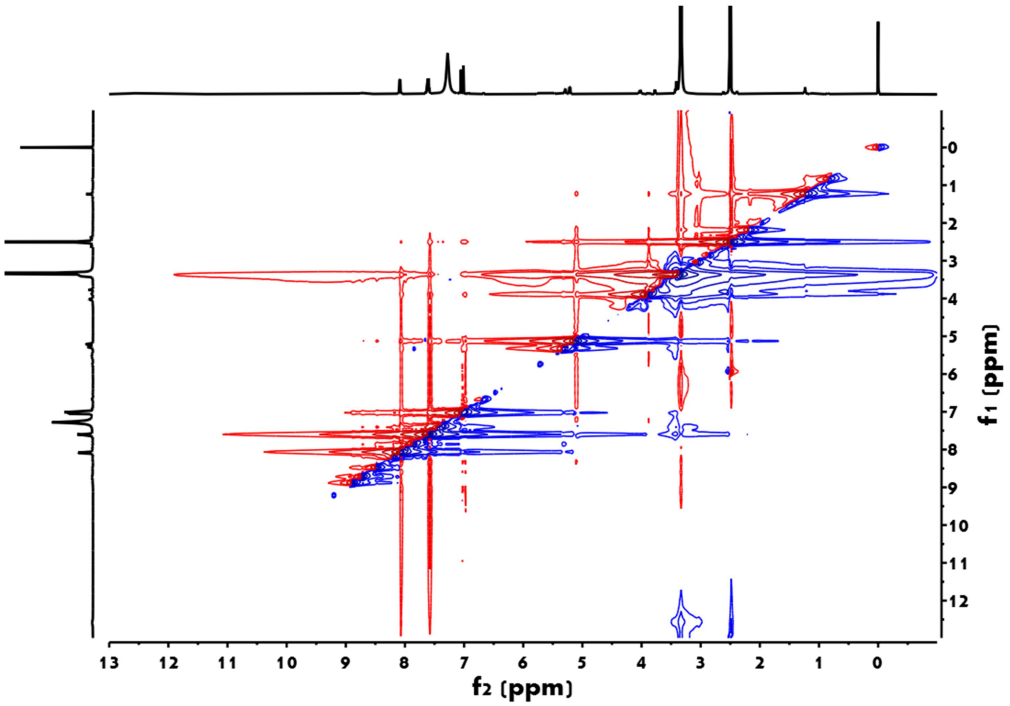


(a)

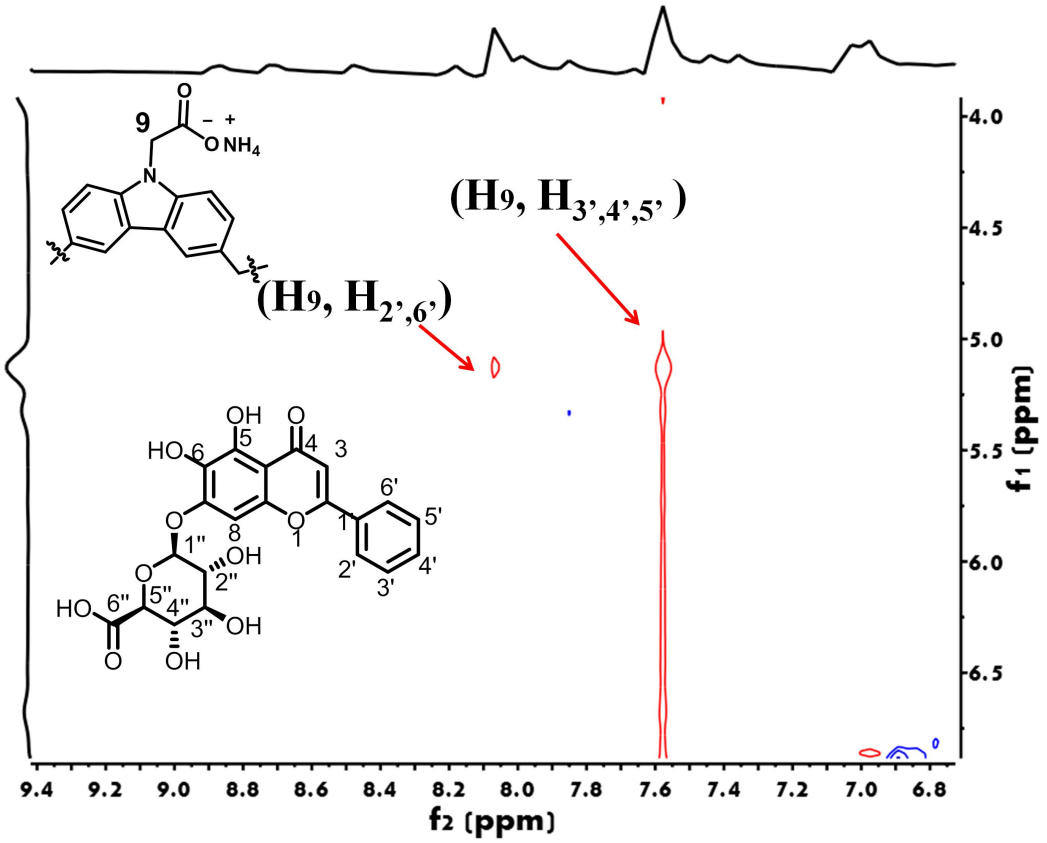


(b)

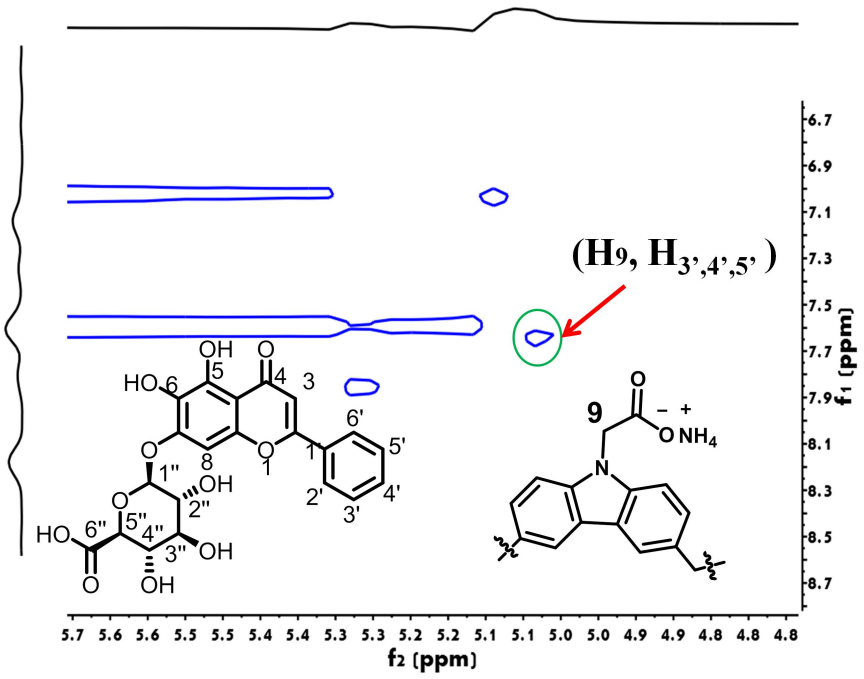
Figure S39. Full (a) and Partial (b) ^{1}H-NMR spectra of baicalin (2 mM) upon addition of **5** (40% DMSO-d_6 + 60 % D_2O)


f2 (ppm)
f1 (ppm)

(a)


9
O
NH4
(H9, H2',6')
(H9, H3',4',5')
OH
HO
6
5
4
3
6'
5'
8
1
1'
2'
4'
3'
1"
OH
2"
5"
4"
6"
HO
3"
OH
O
OH
f2 (ppm)
f1 (ppm)

(b)



(c)

Figure S40. Full (a) and Partial (b, c) 2D-NOESY spectra of baicalin (4 mM) + **5** (4 mM) in DMSO-d_6

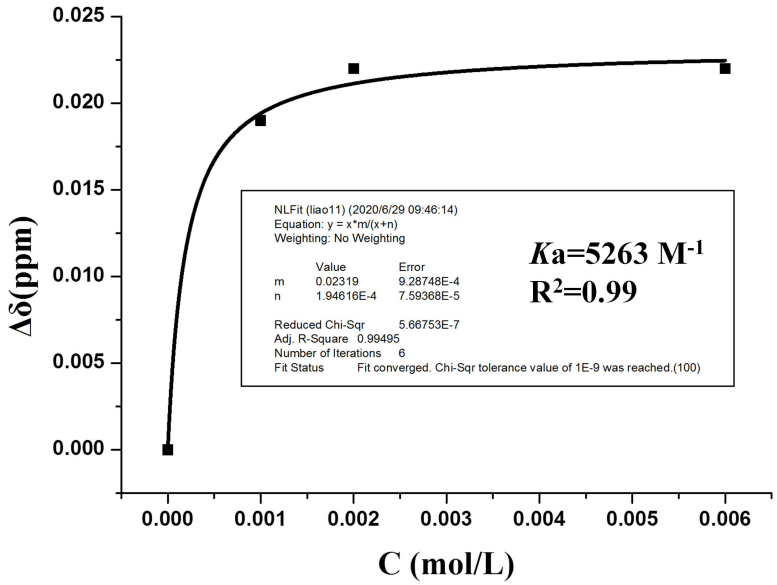


Figure S41. The fitted curves of $\delta_{7.80}$ of **5**, as a function of baicalin concentration

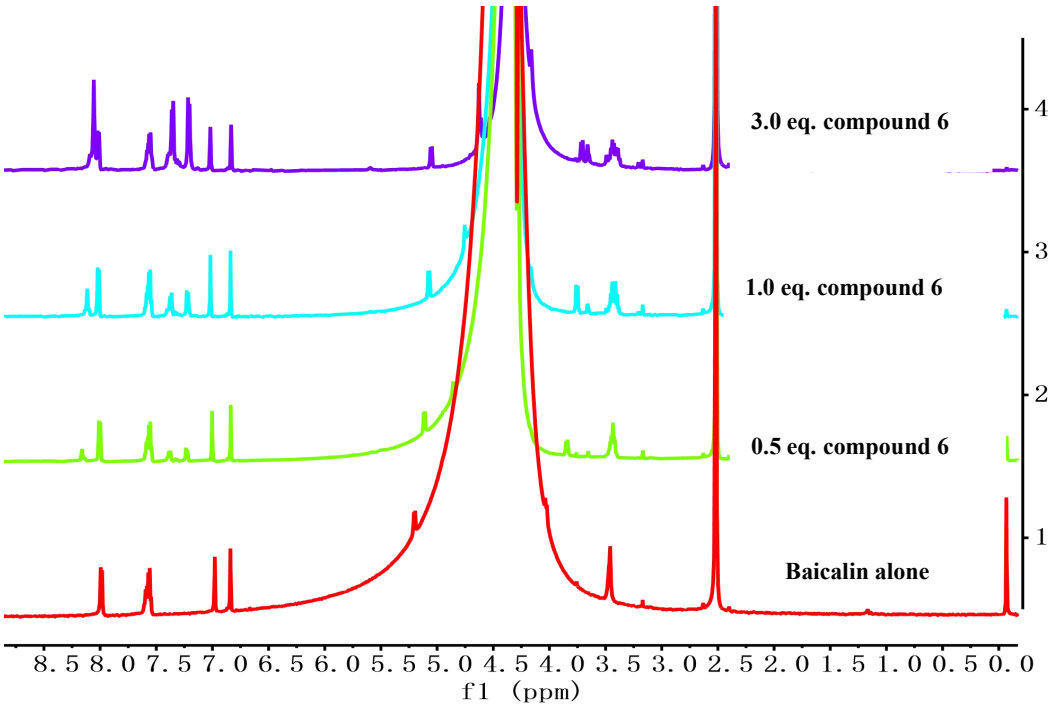


Figure S42. Full ^{1}H-NMR spectra of baicalin (4 mM) upon addition of **6**

(40% DMSO-d_6 + 60 % D_2O)