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ORIGINAL ARTICLE

Functionalized calix[4]arene-based receptor for saccharide recognition

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Abstract A novel class of functionalized-calix[4]arene such as 1,4-dihydropyridine-calix[4]arene, acridine-calix[4]arene and pyrimidine-calix[4]arene were synthesized using multicomponent reaction. These compounds have been characterized by ^{1}H NMR, ^{13}C NMR and HRMS. Fluorescent and ^{1}H NMR titration investigations reveal that these derivatives have the high binding constant towards the monosaccharide and disaccharide in aqueous solution. The formation of complex was also supported by electrospray mass spectrometry.

Keywords Functionalized-calix[4]arene · Multicomponent reaction · Fluorescent titration · Saccharide recognition

Introduction

A carbohydrate is a large biological molecule or macromolecule and performs numerous roles in living organisms [1–3]. The development of biomolecule recognition is one of the interesting topics of the modern biology, medicine and chemistry. Several host system have been described for the recognition of biological important substrate. Schumacher and co-workers [4] have reported that Alizarin Red S (ARS) in equilibrium with a phenyl boronic acid can be used for fructose recognition at pH 7.4. Another report indicates that phenylboronic acid-functionalized tetrathiafulvalene (TTFAQ) system to show pronounced electrochemical responses selectively toward fructose and ribose [5]. In recent years the development of supramolecular macrocyclic architectures has received intensive interest [6–8]. Supramolecular chemistry examines the weaker and reversible noncovalent interactions between molecules. These forces include hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces, pi–pi interactions and electrostatic effects [9–11]. Several water soluble porphyrines investigated such as the suitable receptors for the recognition of saccharides in water [12]. Fluorescent and ^{1}H NMR investigations of Chen et al. reveal that metallocyclophanes can efficiently complex mono- and disaccharide derivatives in chloroform, with a binding selectivity for disaccharides, which is driven by intermolecular hydrogen bonding [13]. Calixarenes are used in several areas of supramolecular chemistry such as macrocyclic receptors for anions, amino acids, and small peptides [14–17]. In 2003 Segura et al. explored the potential of functionalized calix[4]arenes in carbohydrate recognition [18].

1,4-Dihydropyridines (DHPs) have attracted immense attention of synthetic chemists due to their pharmacological properties [19, 20] and display prominent biological activities [21–23]. They are known as neuroprotectants, antiplatelet treatment of aggregators and are important in Alzheimer's disease as antiischemic agents [24–26]. Pyrimidines display also a diverse range of biological activities such as antibacterial, antiviral, antitumor, anti-inflammatory and antihypertensive as well as calcium channel blockers, α-1a-antagonists, and neuropeptide Y (NPY) antagonists [27]. Many synthetic methods for the

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synthesis of 1,4-dihydropyridines [28–34] and pyrimidine [35–38] derivatives have been reported but into the best of our knowledge there is no report for the synthesis of functionalized-calix[4]arene derivatives with 1,4-dihydropyridine or pyrimidine compound.

Recently we have synthesized acridine-calix[4]arene derivatives **1**, **2**, **3** via multicomponent reaction (MCR) of aminocalix[4]arene with dimedone and 3-hydroxybenzaldehyde or 4-bromobenzaldehyde which selectively bind Calf Thymus DNA and ds DNA with submicromolar K_f values in buffered aqueous solution (Scheme 1) [39].

In continuation of our investigations on the synthesis of 1,4-dihydropyridines (DHPs) [40] and pyrimidines [41] via a MCR reaction, herein we describe a simple and efficient method for the preparation of the novel 1,4-dihydropyridine-calix[4]arene **4** and 2-amino-pyrimidine-calix[4]arene **5**. In this work, we introduce an efficient reaction of monoaldehyde calix[4]arene **6** in the cone conformation with methyl 3-aminocrotonate using chlorotrimethylsilane (TMSCl) or with ethyl cyanoacetate and guanidinium carbonate in the presence of amino-functionalized SBA-15 catalyst that provides an easy access to 1,4-dihydropyridine-calix[4]arene derivative **4** and 2-amino-pyrimidine-calix[4]arene derivative **5** blocked in the cone conformation respectively. Furthermore, we studied the interaction of the synthesized calix[4]arene derivatives **1**–**5** with several saccharides using fluorescence titration experiments in aqueous solution (Scheme 2).

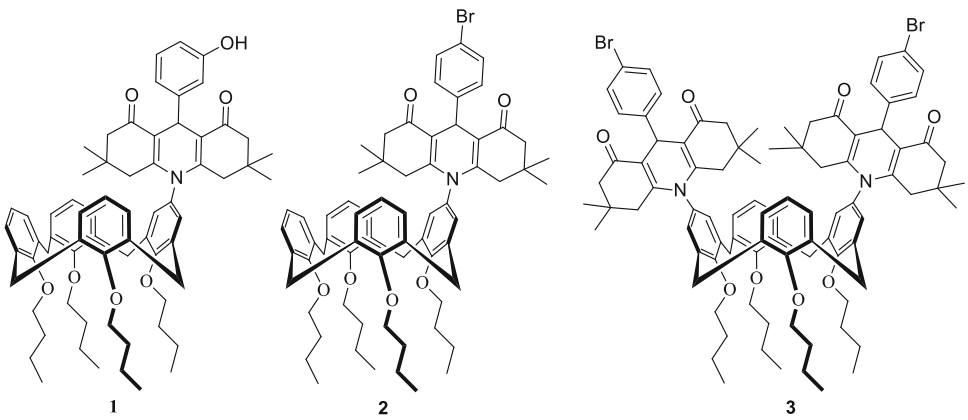
Results and discussion

1,4-Dihydropyridine-calix[4]arene derivative **4** is synthesized from MCR reaction of monoaldehyde calix[4]arenes **6** under the optimized reaction conditions in our previously report [40]. The results shown that the reaction of monoaldehyde calix[4]arene **6** (1 mmol) with methyl 3-aminocrotonate (4 mmol) using TMSCl at 80 °C afforded 1,4-dihydropyridine-calix[4]arene derivative **4** in the cone conformation in 82 % yield after 5 min (Scheme 2). We also investigated the synthesis of pyrimidine-calix[4]arene **5** by multicomponent reaction of monoaldehyde calix[4]arenes **6** under the optimized reaction conditions in our previously report [41]. The obtained results shown that the three component reaction of monoaldehyde calix[4]arene **6** (1 mmol), ethyl cyanoacetate (1 mmol) and guanidinium carbonate (1 mmol) in the presence of amino-functionalized SBA-15 catalyst (60 mol %) in ethanol afforded 2-amino-pyrimidine-calix[4]arene building block **5** in the cone conformation in 83 % yield after 2 h (Scheme 2). The 1,4-dihydropyridine-calix[4]arene derivative **4** and 2-amino-pyrimidine-calix[4]arene **5** were characterized on the basis of its spectroscopic data such as ^{1}H and ^{13}C NMR, mass spectroscopy, and infrared (IR) spectra. It should be noted that the spectroscopic data confirm the cone conformation for 1,4-dihydropyridine-calix[4]arene derivative **4** and 2-amino-pyrimidine-calix[4]arene derivative **5** [42].

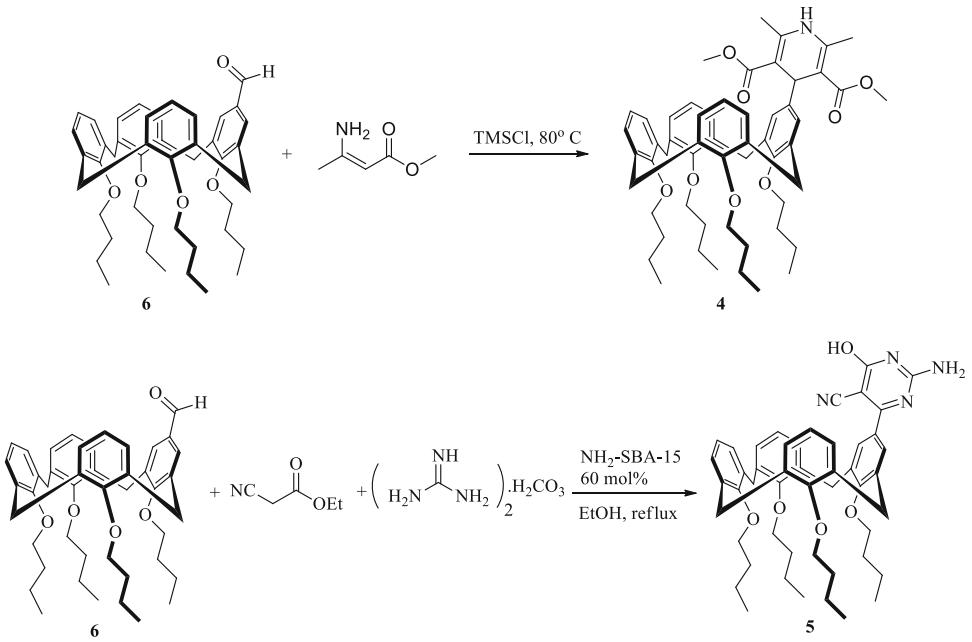
It should be noted that for comparison of binding constant of the 1,4-dihydropyridine-calix[4]arene derivative **4** with an ordinary 1,4-dihydropyridine derivative, we have synthesized the 1,4-dihydropyridine **7** from the reaction of benzaldehyde with methyl-3-aminocrotonate in the presence of TMSCl (Scheme 3) [40].

Fluorescence titration is widely used, because of its sensitivity, and the availability of the spectroscopic technique [43]. To evaluate the binding ability of the synthesized calix[4]arene derivaitives **1**–**5**, fluorescence titration experiments were performed with monosaccharides such as fructose, glucose, sorbitol and mannitol, and disaccharides such as maltose and sucrose in aqueous solution. So, the binding constants ($K_{association}$ value) were determined by using the fluorescence titration experiments by addition of the functionalized-calix[4]arene **1**–**5** into the different guest molecules. The binding ability of the receptors **1**–**5** towards saccharides were investigated in aqueous solution

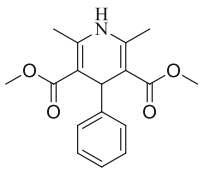
Scheme 1 Acridine-calix[4]arene derivatives **1**, **2**, and **3**



Scheme 2 Synthesis of 1,4-dihydropyridine-calix[4]arene derivative **4** and 2-amino-pyrimidine-calix[4]arene derivative **5**



Scheme 3 4-Phenyl-1,4-dihydropyridine **7**



(except receptor **3** that was investigated in water/methanol (4:1) solution). The fluorescence titrations of calix[4]arene **1-5** (1×10^{-6} M) were performed in aqueous solutions at room temperature. For each compound, 1700 μL of the receptors solution (1×10^{-6} M) was filled into cuvettes and fluorescence intensity was measured (F_0), then up to 50 μL of saccharide solution (1×10^{-5} M) was added stepwise. For each addition, after stirring for 30 s and standing for 2 min, the change of the emission intensity was measured (F_{obs}). The change of the emission intensity was observed. As an example, the plot of the emission intensity of **1**, **2**, **4** and **5** with sucrose in aqueous solution are provided in Fig. 1. According to the fluorescence titration chart in Fig. 1, after each addition (sucrose) the intensity of fluorescence emission is decreased.

The calculation of the binding constant (K) was carried out using Benesi–Hildebrand analysis [44]. The Eq. (1) was used for calculation of binding constants.

$$1/\Delta I = 1/(K[G]\Delta I_{max}) + 1/\Delta I_{max} \quad (1)$$

In this equation, $\Delta I = I_0 - I_{obs}$ and $\Delta I_{max} = I_0 - I_{max}$, where I_{min}, I_{obs}, and I_{max} are the emission intensities of receptor considered in the absence of guest, observed intensity of each point during titration and at a concentration of complete saturation, respectively. K is the binding constant and [G] is the guest concentration. Plotting $[1/(I_0 - I_{obs})]$ versus $[G]^{-1}$ yields a linear plot with a slope corresponding to $1/(K\Delta I_{max})$ and intercept to $1/\Delta I_{max}$.

The results of binding constants are summarized in Table 1, and calculations and full data are given in supplementary data. The investigations of fluorescence titrations of **1**–**5** derivatives indicated the high binding constant value for the monosaccharides, and disaccharides. We assume that the formation of the multiple hydrogen bonds between host molecule and sugar are possible and can be justifying the binding constant. Indeed the hydrogen bonding forces and WDW interactions could justify the binding constant. The obtained binding constant values were between 7.50×10^3 M^{-1} and 9.50×10^5 M^{-1} in aqueous solution (Table 1).

From the results in Table 1, the binding constants obtained for these molecules indicated that they are attractive receptors to the range of receptors already known for saccharides recognition [13]. For example, the association constants complex obtained by Chen and co-workers, between metallocyclophanes and monosaccharides or disaccharides in chloroform solution were between 9.40×10^2 and 4.30×10^4 M^{-1}. The obtained results show that acridine-calix[4]arene derivative **2** exhibits a greater binding ability for sorbitol (6.60×10^5 M^{-1}), mannitol (8.75×10^5 M^{-1}), maltose (7.20×10^5 M^{-1}) and sucrose (9.50×10^5 M^{-1}). In the case of the monosaccharides recognition, 2-amino-pyrimidine-calix[4]arene derivative **5** exhibits a greater binding ability for fructose (3.60×10^5 M^{-1}) and glucose (3.13×10^5 M^{-1}) in comparison with the other receptors.

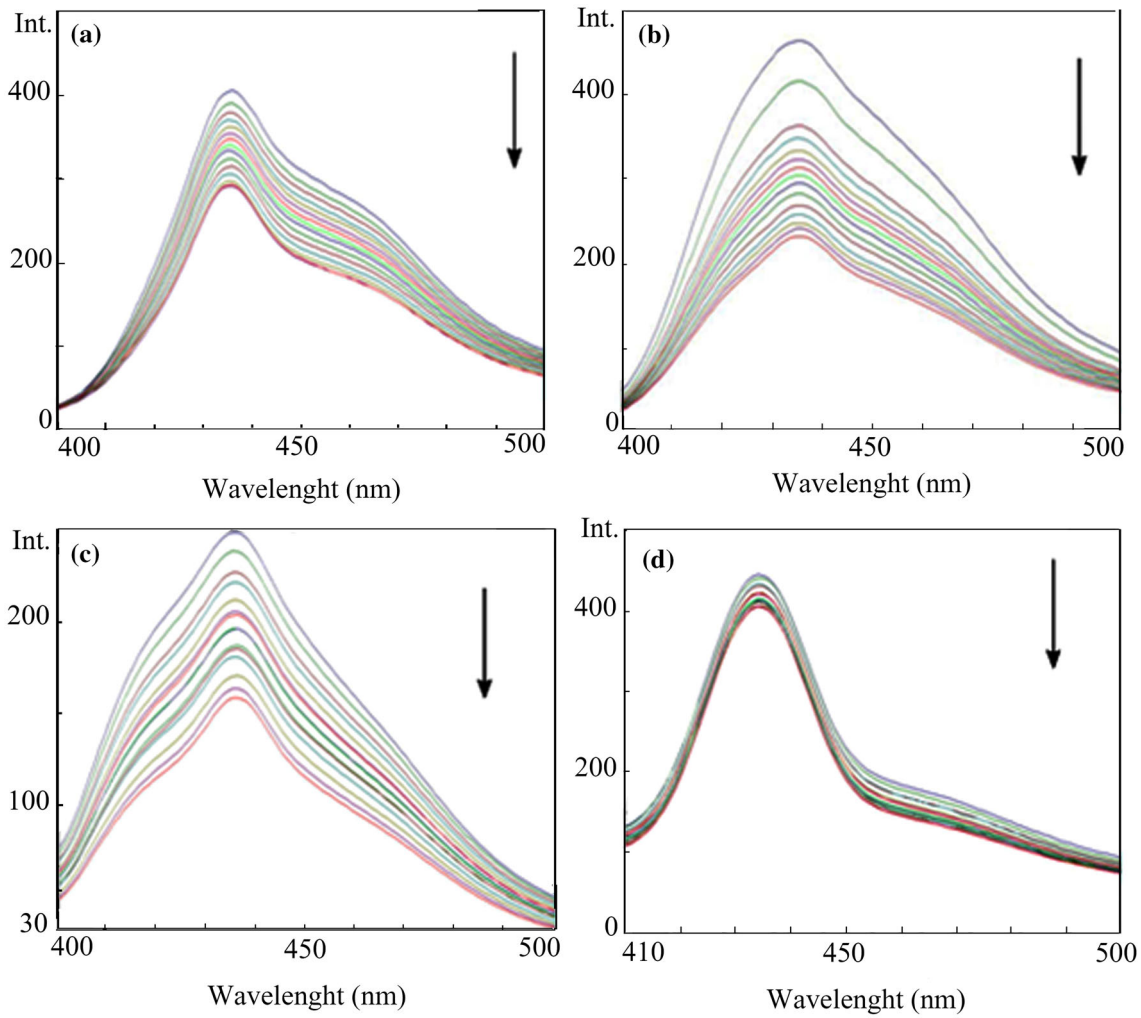


Fig. 1 Fluorescence titration of 3-hydroxy-calix[4]arene **1** with sucrose (**a**), 4-bromo-calix[4]arene **2** with sucrose (**b**), 1,4-dihydropyridine-calix[4]arene **4** with sucrose (**c**), and 2-amino-pyrimidine-calix[4]arene **5** with sucrose (**d**)

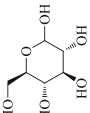
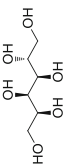
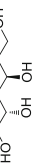
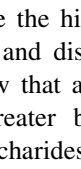
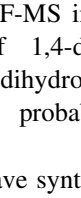
Table 1 also shows that the acridine-calix[4]arene derivative **3** is good receptor only for the recognition of glucose with a binding constant of 8.00×10^4 M^{-1}.

The 1,4-dihydropyridine-calix[4]arene derivative **4** has a binding selectivity for sorbitol with a binding constant of 2.35×10^5 M^{-1}. It can be found that 1,4-dihydropyridine-calix[4]arene derivative **4** has 31 times greater binding ability for sorbitol (2.35×10^5 M^{-1}) than for mannitol (7.50×10^3 M^{-1}) as sugar alcohol. It should be noted that the formation of complex between sorbitol and 1,4-dihydropyridine-calix[4]arene derivative **4** was also supported by electrospray ionization time of flight mass spectrometry (ESI-TOF-MS). The spectrum of an equimolar solution of sorbitol and **4** in CH_3OH shows the charged signal of the complex as the base peak at m/z 1053.5244 (calcd for $[sorbitol@\mathbf{4}]^+$: 1053.5814) (Fig. 2).

Moreover, the ^1H NMR titration spectra of 1,4-dihydropyridine-calix[4]arene **4** and sorbitol were analyzed in more details. Remarkably, the CH protons of methyl group (indicated with number 1 in Fig. 3), CH protons of methyl ester ($OCOCH_3$, indicated with number 2 in Fig. 3), CH proton of dihydropyridine (indicated with number 3) and CH protons of calixarene ring (in the *ortho* position, indicated with number 4) shown a significant upfield shift ~0.14, 0.14, 0.15 and 0.12 ppm respectively upon sorbitol addition. This can be explained by possible complexation through an intermolecular hydrogen bonding between host 1,4-dihydropyridine-calix[4]arene **4** and sorbitol.

The binding constants obtained for 1,4-dihydropyridine **7** with the monosaccharides indicated that this compound is not selective towards the sorbitol (1.58×10^5 M^{-1}) or mannitol (2.23×10^5 M^{-1}). We assume that in the solution, the aggregation process take place between sorbitol and 1,4-dihydropyridine **7**. The aggregation between sorbitol and 1,4-dihydropyridine **7** in ratio 2:1 was also

Table 1 Association constants (M^{-1}) between host calix[4]arene derivatives **1–5** and saccharide guest in aqueous solution

Receptor	Monosaccharide				Disaccharide	
	Fructose 	Glucose 	Sorbitol 	Mannitol 	Maltose 	Sucrose 
1	2.00×10^4 (0.994)	1.80×10^5 (0.992)	6.00×10^4 (0.988)	1.55×10^5 (0.995)	1.65×10^5 (0.998)	1.80×10^5 (0.996)
2	3.10×10^5 (0.977)	1.80×10^5 (0.998)	6.60×10^5 (0.980)	8.75×10^5 (0.980)	7.20×10^5 (0.952)	9.50×10^5 (0.957)
3[a]	–	8.00×10^4 (0.879)	–	–	–	–
4	1.48×10^5 (0.948)	6.00×10^4 (0.967)	2.35×10^5 (0.946)	7.50×10^3 (0.979)	6.86×10^5 (0.911)	3.15×10^5 (0.987)
5	3.60×10^5 (0.994)	3.13×10^5 (0.992)	5.40×10^5 (0.962)	3.90×10^5 (0.972)	5.03×10^5 (0.975)	5.80×10^5 (0.967)
7	–	–	1.58×10^5 (0.985)	2.23×10^5 (0.987)	–	–

[a] In water/methanol (4:1) solution. The number between parentheses shows the correlation coefficient (R^2) for each mixture

supported by ESI-TOF-MS in Fig. 4. The comparison of binding constant of 1,4-dihydropyridine-calix[4]arene derivative **4** with 1,4-dihydropyridine **7** indicated that the binding takes place probably in the cavity of the calix[4]arene.

In summary, we have synthesized a new family of 1,4-dihydropyridine-calix[4]arene and 2-amino-pyrimidine-calix[4]arene receptor for saccharide recognition in water solution. Fluorescent titration investigations reveal that these derivatives have the high binding constant towards the monosaccharides and disaccharides in aqueous solution. The results show that acridine-calix[4]arene derivative **2** exhibits a greater binding ability for sorbitol, mannitol and disaccharides and 2-amino-pyrimidine-calix[4]arene derivative **5** for fructose and glucose respectively in comparison with the other receptors. 1,4-Dihydropyridine-calix[4]arene derivative **4** has 31 times greater binding ability for sorbitol than for mannitol as sugar alcohol.

Experimental

Materials

All reagents were purchased at highest commercial grade from Merck Company and used as supplied. Reactions were monitored by thin layer chromatography (TLC) with Merck silica gel 60 F254 plates. Silica gel 60 for flash chromatography (particle size 230–400 mesh) was supplied by Merck Company. D-(−)-fructose was purchased from Sigma-Aldrich Company. D-(+)-glucose monohydrate, D-(−)-sorbitol, D-(−)-mannitol, maltose monohydrate and sucrose were purchased from Merck Company. All commercially available materials were used as received. The acridine-calix[4]arene derivatives **1**, **2** and **3** were synthesized according to our previously reported methods [39].

Instrumentation

Melting points were determined in evacuated capillaries with a Buchi B-545 apparatus. Mass spectra were obtained on a FISONS GC 8000/TRIO 1000 under 70 eV. ^1H or ^{13}C NMR spectra were recorded on a Bruker 80, 250 and 500 or 125 MHz, respectively in $CDCl_3$ using tetramethylsilane as internal standard. High resolution mass spectrometry (HRMS) was recorded with a Qstar ESI-q-TOF mass spectrometer (Applied Biosystems, Germany). The fluorescence spectra were recorded using a Jasco FP-6500 device.

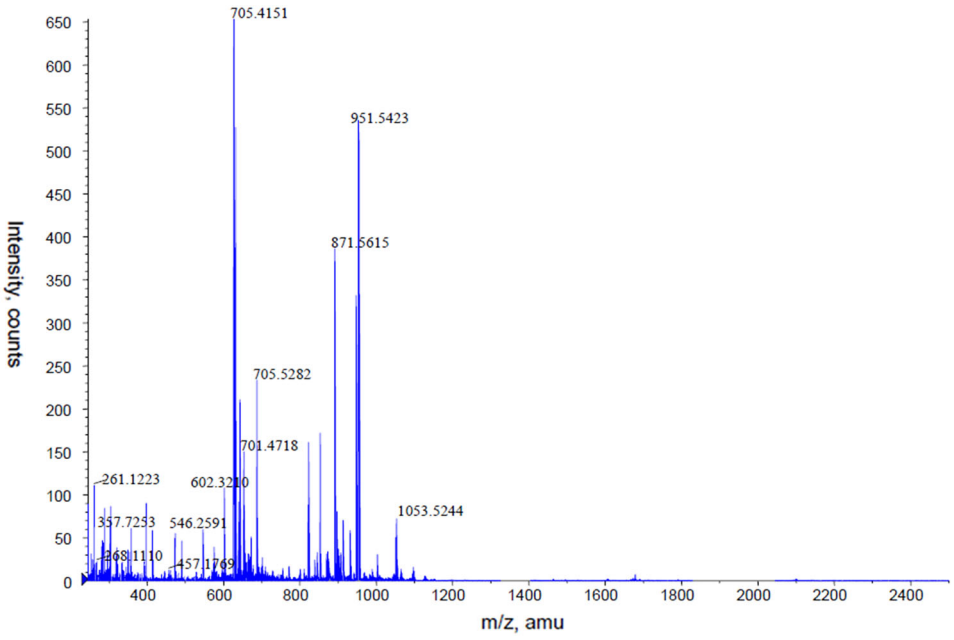


Fig. 2 ESI-TOF-MS spectrum for complex of sorbitol and 1,4-dihydropyridine-calix[4]arene derivative **4**

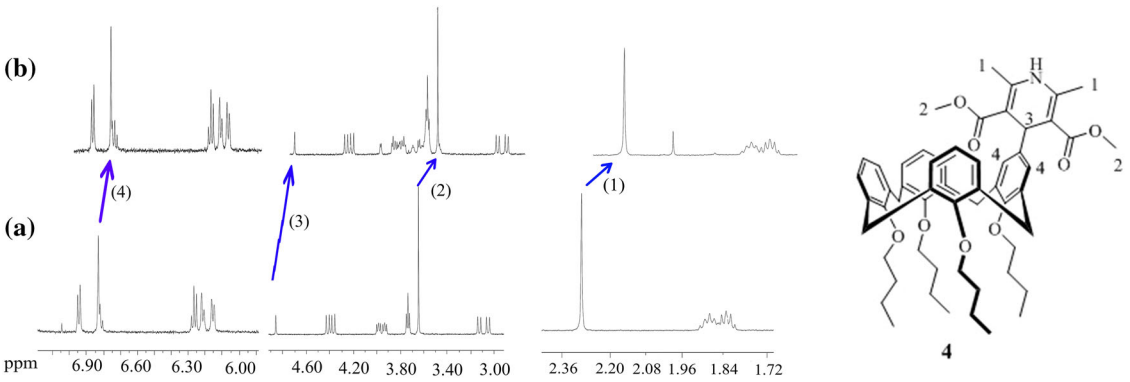


Fig. 3 **a** ^{1}H NMR spectra of pure 1,4-dihydropyridine calix[4]arene **4** in $CDCl_3$ solution, **b** ^{1}H NMR spectra of mixture 1,4-dihydropyridine calix[4]arene **4** and sorbitol solution in 3.63 equivalents point

Monoaldehyde calix[4]arenes ***6***

Tin(IV) chloride (20 equiv.) was added rapidly to the 25,26,27,28-tetraboutoxycalix[4]arene [45] (1 equiv.) in 2 mL of dry chloroform at −30 °C in the presence of dichloro(methoxy)methane (1 equiv.). The reaction mixture was then stirred for 1 min and quenched with crushed ice. The organic layer was separated, washed three times with water, and dried over Na_2SO_4, and the solvent was removed under reduced pressure. Fine purification was achieved by column chromatography using hexane/ethylacetate (20:1) as eluent. The yield is 76 %. ^{1}H NMR ($CDCl_3$, 80 MHz): δ = 0.93 (t, J = 13.6 Hz, 12H, $4CH_3$), 1.42 (m, 8H, $4CH_2$), 1.88 (m, 8H, $4CH_2$), 3.03 (d, J = 13.3 Hz, 2H, $2CH_2$), 3.20 (d, J = 13.5 Hz, 2H, $2CH_2$), 3.81 (m, 8H, $4OCH_2$), 4.31 (d, J = 13.3 Hz, 2H, $2CH_2$), 4.48 (d, J = 13.5 Hz, 2H, $2CH_2$), 6.35 (s, 3H, 3CH Arom), 6.63 (m, 6H, 6CH Arom), 6.93 (s, 2H, 2CH Arom), 9.49 (s, 1H, CHO); MS (E. I) (70 eV): m/z (%) 676 (1) (M^+), 148 (1), 147 (1), 131 (10), 118 (5), 105 (20), 102 (18), 91 (5), 77 (40), 55 (8), 43 (65), 41 (75), 29 (100); IR (KBr): ν = 3013, 2957, 2930, 2870, 2728, 1693, 1586,1477, 1378 cm^{-1}.

1,4-Dihydropyridine-calix[4]arene ***4***

A mixture of monoaldehyde calix[4]arene **6** (1 mmol), methyl 3-aminocrotonate (4 mmol) and chlorotrimethylsilane (1 mmol) were stirred at 80 °C for 5 min. After completion of the reaction as indicated by TLC, the mixture was poured into ice cold water and extracted with ethyl acetate. The organic layer was dried and concentrated in

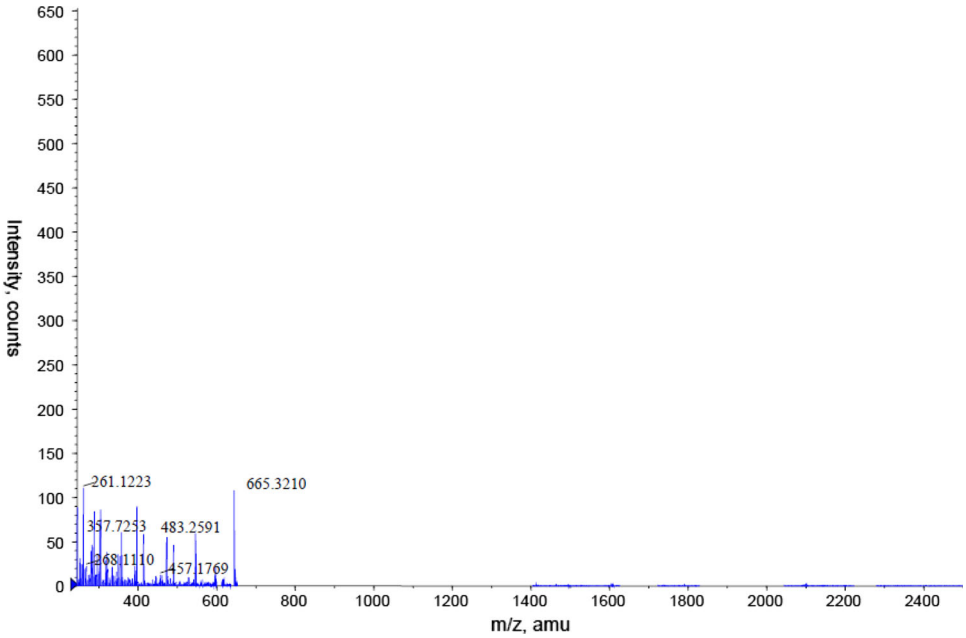


Fig. 4 Aggregation process between sorbitol and 1,4-dihydropyridine **7** supported by ESI-TOF-MS spectrum

vacuum. The crude products were purified by recrystallization in hexane/ethyl acetate (4:1). The yield is 82 %.^{1}H NMR: ($CDCl_3$, 250 MHz): δ = 0.95–1.02 (m, 12H, $4CH_3$), 1.26–1.37 (m, 4H, $2CH_2$), 1.48–1.62 (m, 4H, $2CH_2$), 1.80–1.97 (m, 8H, $4CH_2$), 2.34 (s, 6H, $2CH_3$), 3.02–3.15 (dd, J = 13.25, J = 18.75 Hz, 4H, $2CH_2$), 3.65 (s, 6H, $2OCH_3$), 3.71–3.76 (t, J = 6.7 Hz, 4H, $2OCH_2$), 3.90–4.02 (m, 4H, $2OCH_2$), 4.35–4.45 (t, J = 25.2 Hz, 4H, $2CH_2$), 4.87 (s, 1H, CH), 5.51 (s, 1H, NH), 6.14–6.30 (m, 6H, 6CH Arom), 6.79–6.85 (t, J = 7.5 Hz, 3H, 3CH Arom); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.02, 14.16, 14.20, 19.12, 19.55, 30.93, 32.05, 32.24, 32.44, 38.74, 50.86, 74.76, 104.44, 121.70, 121.84, 127.30, 127.41, 128.23, 128.58, 133.70, 133.89, 135.32, 136.51, 140.96, 143.38, 155.49, 155.90, 157.46, 168.29; HRMS (ESI): m/z $[M]^+$ Calcd. for $C_{55}H_{69}NO_8$: 872.14; Found: 871.4983; IR (KBr): ν = 3337, 2957, 2869, 1699, 1650, 14.58, 1433, 1382, 1304, 1215, 1119, 1091, 1021, 760 cm^{-1}.

2-Amino-pyrimidine-calix[4]arene ***5***

A solution of monoaldehyde calix[4]arene (1 mmol), ethyl cyanoacetate (1 mmol) and NH_2-SBA-15 (0.3 g, 60 mol %) in 2 mL ethanol was stirred mechanically for at least 10 min, then guanidinium carbonate (1 mmol) was added to the above reaction mixture and refluxed for 2 h. After the completion of reaction, the reaction mixture was poured into ice-cooled water and neutralized by 0.1 N HCl aqueous solutions. The mixture was filtered and washed with water. Fine purification was achieved by column chromatography using hexane/ethyl acetate (10:1) as eluent. The yield is 83 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.04 (m, 12H, Hz, $4CH_3$), 1.44 (m, 4H, $2CH_2$), 1.52 (m, 4H, $2CH_2$), 1.91 (m, 8H, $4CH_2$), 3.19 (d, J = 13.3 Hz, 2H, $2CH_2$), 3.28 (d, J = 13.3 Hz, 2H, $2CH_2$), 3.86 (m, 4H, $2OCH_2$), 3.99 (m, 4H, $2OCH_2$), 4.48 (d, J = 13.5 Hz, 2H, $2CH_2$), 4.52 (d, J = 13.3 Hz, 2H, $2CH_2$), 6.51 (m, 6H, 6CH Arom), 6.64 (s, 2H, NH_2), 6.80 (m, 3H, 3CH Arom), 7.58 (s, 2H, 2CH Arom), 12.01 (br. s, 1H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.01, 19.19, 19.25, 19.44, 29.67, 30.98, 31.08, 32.20, 32.26, 32.36, 74.77, 74.90, 77.18, 121.83, 122.26, 127.97, 128.20, 128.50, 128.85, 129.23, 133.57, 134.52, 135.71, 136.26, 155.29, 155.99, 156.98, 161.01, 165.12, 171.80; MS (E. I) (70 eV): m/z (%) 783 (10) (M^+), 703 (8), 635 (5), 608 (10), 566 (10), 488 (10), 387 (10), 281 (15), 265 (15), 239 (15), 221 (25), 149 (30), 129 (30), 105 (100), 77 (100), 57 (100); IR (KBr): ν = 3432, 2959, 2930, 2870, 2244, 2215, 1655, 1622, 1457, 1382 cm^{-1}.

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