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Electronic Supplementary Information (ESI)

for

Mono-Benzimidazole Functionalized β-Cyclodextrins as Supramolecular Nanovalves for pH-Triggered Release of *p*-Coumaric Acid

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1. Materials and Methods

Tetraethylorthosilicate (TEOS, ≥99.0%), (3-aminopropyl) trimethoxysilane (APTES, 97%), hexadecyltrimethylammonium bromide (CTAB, ≥98.0%), β-Cyclodextrin (β-CD, ≥97%), lithium hydride (powder, 95%), propargyl bromide (80% in toluene), lithium iodide (anhydrous, 99.9%), *o*-phenylenediamine (99.5%), triethyl phosphite (99.8%), *p*-coumaric acid (≥98%), sodium methoxide (≥97%), sodium azide (≥99%), and chloroacetic acid (≥97%) were purchased from Sigma-Aldrich. Copper iodide (≥99.5%) and triphenylphosphine (≥99.5) were obtained from Aladdin Industrial Inc. (Shanghai, China). All other reagents were of analytical grade and used as received. Phosphate buffered saline (PBS, pH 7.0) was used in the experiments. ^{1}H, ^{13}C and 2D ROESY NMR spectra were recorded using a Bruker Avance Ⅲ 500 spectrometer. Chemical shifts are given in ppm and referenced to internal tetramethylsilane (TMS, δ_H, δ_C 0.00) as a reference. High-resolution mass spectra were recorded on Thermo Trace DSQ GC-MS spectrometer. The solid state ^{13}C and ^{29}Si CP-MAS NMR spectra were collected on a Bruker DSX 400 NMR spectrometer, operating at Larmor frequency of 100.6 and 79.5 MHz and equipped with a 7 mm probe. Fourier transform infrared (FTIR) spectra of samples were collected by Bruker Tensor 27 FTIR spectrometer. Transmission electron microscopy (TEM) images were obtained on a JEM-2100 microscope with an accelerating voltage of 100 kV. A small angle powder X-ray diffraction (SA-XRD) pattern of the materials was obtained in Bruker D8 Advanced diffractometer using Cu Kα irradiation (λ=0.15406 Å). The N_2 adsorption-desorption isotherms were obtained at 77 K on a Quanta chrome Nova 1000 Micrometric apparatus by static adsorption procedures. Thermogravimetric analysis (TGA) of the materials was performed using a Mettler TGA-SDTA 851e instrument with a heating rate of 10 ℃ min^{-1} under nitrogen flow as protective gas. UV/Vis spectroscopy was carried out with a Shimadzu UV-1800 spectrometer. All fluorescence spectra were recorded on a Shimadzu RF-5201 spectrophotometer. The pH of solutions was measured with a Mettler FE20-FiveEasy Plus pH meter. Zeta

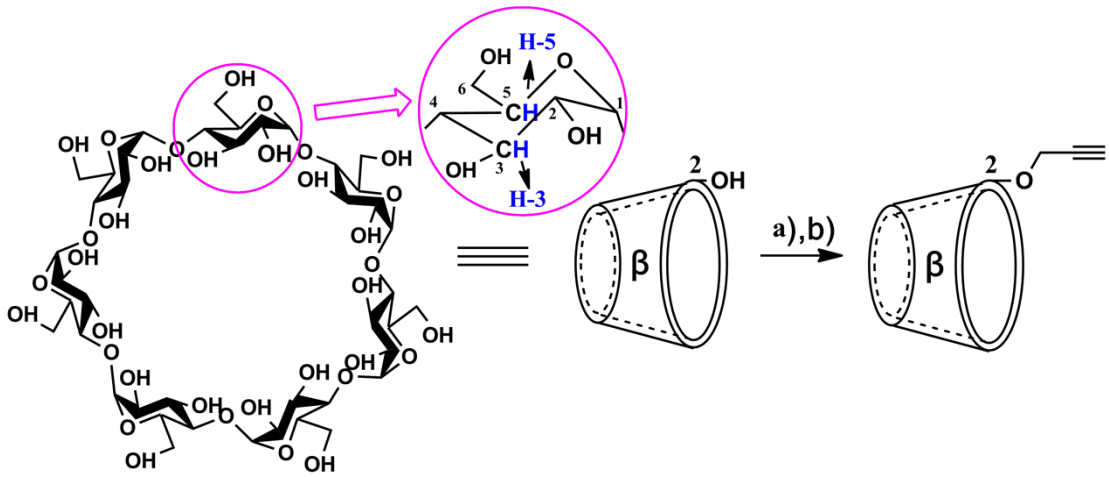
potential was performed using a NanoBrook ZetaPALS.

2. Preparation and Synthesis

2.1 Preparation of MSNs

A brief synthesis of MSNs was performed as follows: A mixture of 0.6 g CTAB, 1.75 mL NaOH (aq. 2.0 M) were added to 240 mL deionized H_2O. After stirring vigorously at 80 ℃ for 1 h, the mixture turned to a clear solution. The mixture was stirred for another 3 h after adding with 2.5 mL TEOS drop by drop. The as-synthesized materials were collected by filtration, washed with deionized H_2O and MeOH, and dried. To remove the soft template, the as-synthesized materials (0.55 g) were redispersed in the mixture of 100 mL 2-propanol and 10 mL HCl (37%), and heated at 80 ℃ for 8 h. Finally, the resulting MSNs were filtered, washed with abundant H_2O and MeOH, and dried under vacuum overnight for further use.

2.2 Synthesis of Compound 1 (mono-2-O-propargyl-β-CD)



Scheme S1. Synthesis route of Compound **1**. a) LiH (1.5 equiv), DMSO, RT, 24h, b) $BrCH_2C{\equiv}CH$ (1.0 equiv), LiI, 55℃, 5h.

To a solution of β-cyclodextrin (1 g, 0.881 mmol) and dry DMSO (15 mL), lithium hydride (11 mg, 1.322 mmol) was added slowly and the suspension was stirred under nitrogen atmosphere at room temperature until it became clear (24 h). A solution of propargyl bromide in toluene (98 μL, 0.881 mmol) and the small amount of lithium

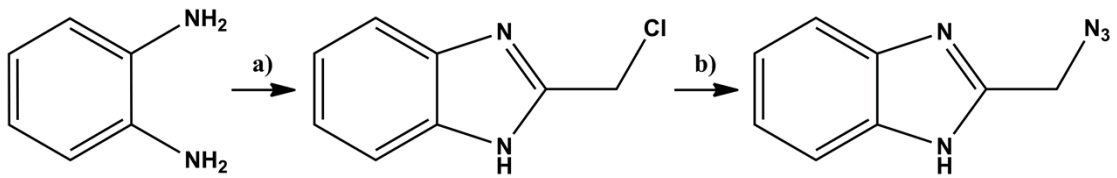
iodide were then added and the stirring was continued at 55 ℃ in the darkness for 5 h. The reaction solution was poured into acetone (300 mL) and the precipitate was filtered and washed with acetone. The crude product was purified by column chromatography on silica gel (elute: CH_3CN:H_2O:NH_4OH=10:5:2) to afford Compound **1** as a white solid (308 mg, yield 29%).

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 5.78 (dddd, *J*=29.2, 20.4, 18.2, 6.5 Hz, 11H,OH), 4.99 (d, *J*=3.2 Hz, 1H, H-1^{I}), 4.82 (s, 6H, H-1^{II-VII}), 4.55–4.50 (m, 1H, CH_2), 4.50–4.42 (m, 9H, OH), 4.39 (dd, *J*=15.8, 2.2 Hz, 2H, CH_2), 3.79 (t, *J*=9.3 Hz, 1H, H-3^{I}), 3.75–3.52 (m, 27H, H-3^{II-VII}, 5^{I-VII}, 6^{I-VII}, 6'$^{I-VII}$), 3.51 (t, *J*=2.2 Hz, 1H, ≡CH), 3.44 – 3.39 (m, 2H, H-2^{I}, 4^{I}), 3.39–3.26 (m, H-2^{II-VII}, 4^{II-VII}, HDO)

^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 102.03–101.77 (C-1^{II-VII}), 100.18 (C-1^{I}), 82.26–81.53 (C-4^{I-VII}), 79.94 (C≡), 79.18 (C-2^{I}), 77.86 (≡CH), 73.12–71.80 (C-2^{II-VII}, 3^{I-VII}, 5^{I-VII}), 59.99 (C-6^{I-VII}), 58.80 (CH_2)

MS (ESI): m/z calcd. for $C_{45}H_{72}O_{35}$: 1172.35; found: 1195.55 $[M+Na]^+$

2.3 Synthesis of Compound 2 (2-(azidomethyl)-1*H*-benzimidazole)



Scheme S2. Synthesis route of Compound **2**. a) $ClCH_2COOH$ (1.1 equiv), HCl, 7.5 h, reflux, b) NaN_3 (2.0 equiv.), DMF-EtOH (1:5), 5 h, reflux.

A mixture of *o*-phenylenediamine (7.57 g, 70 mmol) and chloroacetic acid (7.5 g, 80 mmol) was added into a solution of 5 N HCl (60 mL). After being heated under reflux for 7.5 h, the reaction mixture was cooled to room temperature slowly and neutralized with ammonia. A yellow residue was obtained by filtration and washed with water. The crude product was recrystallized from CH_3CH_2OH-H_2O to give 2-(chloromethyl) -1*H*-benzimidazole as intermediate (6.767 g, yield 57%).

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 7.55 (dd, *J*=5.9, 3.2 Hz, 2H, Ar-H), 7.21 (dd, *J*=6.0, 3.2 Hz, 2H, Ar-H), 4.92 (s, 2H, CH_2)

^{13}C NMR (75MHz, DMSO-d_6) δ 150.01, 138.96, 122.68, 115.68, 31.02

MS (ESI): m/z calcd. for $C_8H_7N_2Cl$: 166.03; found: 166.99 $[M+H]^+$

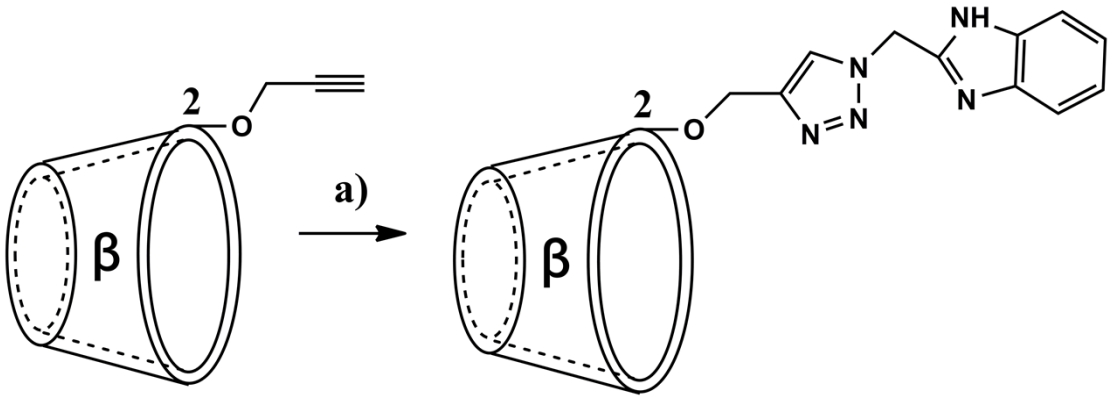
To an aqueous solution (5 mL) of NaN_3 (0.78 g, 12.0 mmol) and DMF (2 mL), a solution of 2-(chloromethyl) -1*H*-Benzimidazole (1.0 g, 6.0 mmol) in ethanol (10 mL) were added. After being heated under reflux for 5 h, the reaction solution was mixed with water and extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. After thoroughly washed with water, the crude product was recrystallized from n-hexane-chloroform to give Compound **2** as a yellow solid (0.683 g, yield 66%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 12.60 (s, 1H, NH), 7.56 (d, *J*=55.3 Hz, 2H, Ar-H), 7.19 (s, 2H, Ar-H), 4.68 (s, 2H, CH_2)

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.85, 138.29, 122.99, 115.24, 48.29

MS (ESI): m/z calcd. for $C_8H_7N_5$: 173.07; found: 174.01 $[M+H]^+$

2.4 Synthesis of Compound 3 (mono-2-O-{1-(1*H*-benzoimidazol-2-ylmethyl) -1H-[1,2,3]triazole-4-ylmethyl}-β-cyclodextrin)



Scheme S3. Synthesis route of Compound **3**. a) Compound **2** (1.5 equiv), iodo(triethyl phosphite) copper, DMF, 105℃, 5.5 h.

The mixture of Compound **1** (257 mg, 0.219 mmol) and iodo (triethyl phosphite) copper (15 mg, 0.042 mmol) was added to a solution of Compound **2** (57 mg, 0.329 mmol) in dry DMF (9 mL). The mixture was stirred at 105 ℃ for 5.5 h under nitrogen atmosphere. The solution was then poured into acetone (200 mL) and the precipitate

was filtered and washed with acetone to give the Compound **3** as a grey solid (285 mg, yield 97%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 12.68 (s, 1H, NH), 8.25 (s, 1H, CH), 7.57 (d, *J*= 45.1 Hz, 2H, Ar-H), 7.19 (s, 2H, Ar-H), 5.92–5.69 (m, 13H, OH), 4.90–4.83 (m, 7H, H-1^{I-VII}), 4.59 (s, 2H, CH_2), 4.47 (m, 9H, OH, CH_2), 3.83 (t, *J*= 9.2 Hz, 1H, H-3^{I}), 3.64–3.55(m, 27H, H3^{II-VII}, 5$^{I–VII}$, 6$^{I–VII}$, 6'$^{I–VII}$), 3.43 (d, *J*=9.3 Hz, 2H, H-2^{I}, H-4^{I}), 3.35–3.30 (m, H-2^{II-VII}, 4^{II-VII}, HDO)

^{13}C NMR (75 MHz, DMSO-d_6) δ 144.50, 125.29, 123.12, 122.06, 119.38, 112.22, 102.32 (C-1^{II-VII}), 100.50 (C-1^{I}), 82.45-81.87 (C-4^{I-VII}), 79.89 (C-2^{I}), 73.42–72.42(C-2^{II-VII}, C-3^{I-VII}, C-5^{I-VII}), 64.74, 60.30 (C-6^{I-VII}), 47.77

MS (ESI): m/z calcd. for $C_{53}H_{79}N_5O_{35}$: 1345.46; found: 1368.53 $[M+Na]^+$

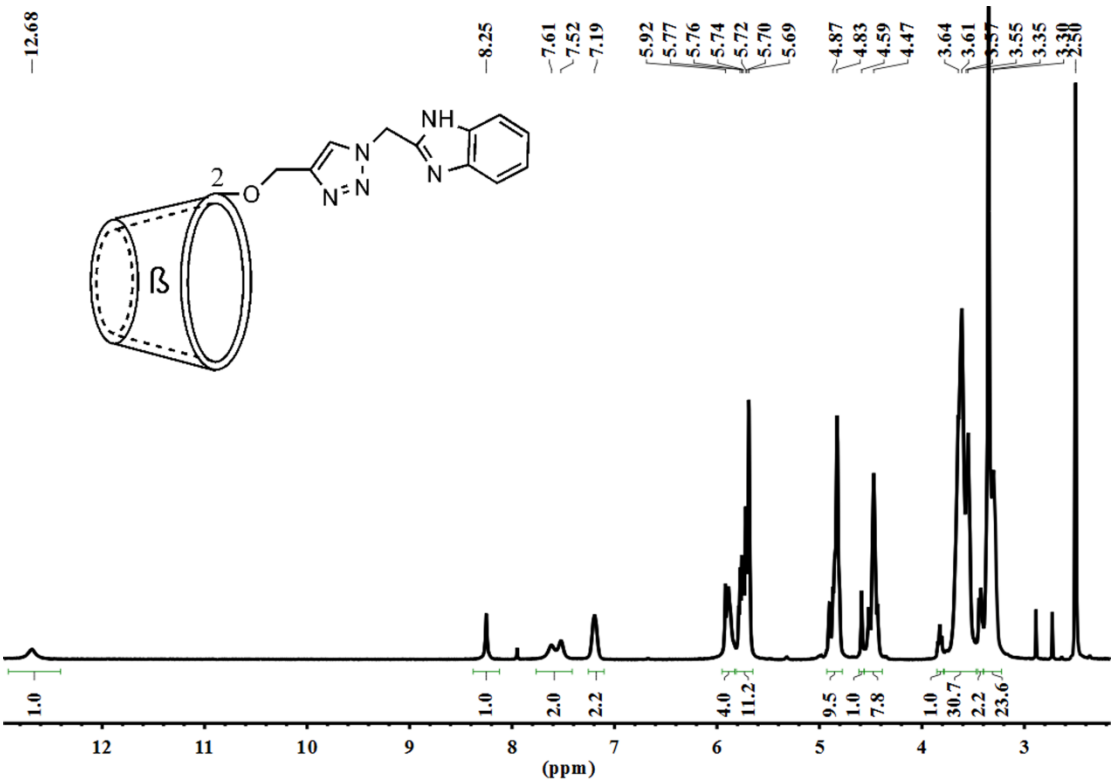


Fig. S1. ^{1}H NMR spectrum of Compound **3**.

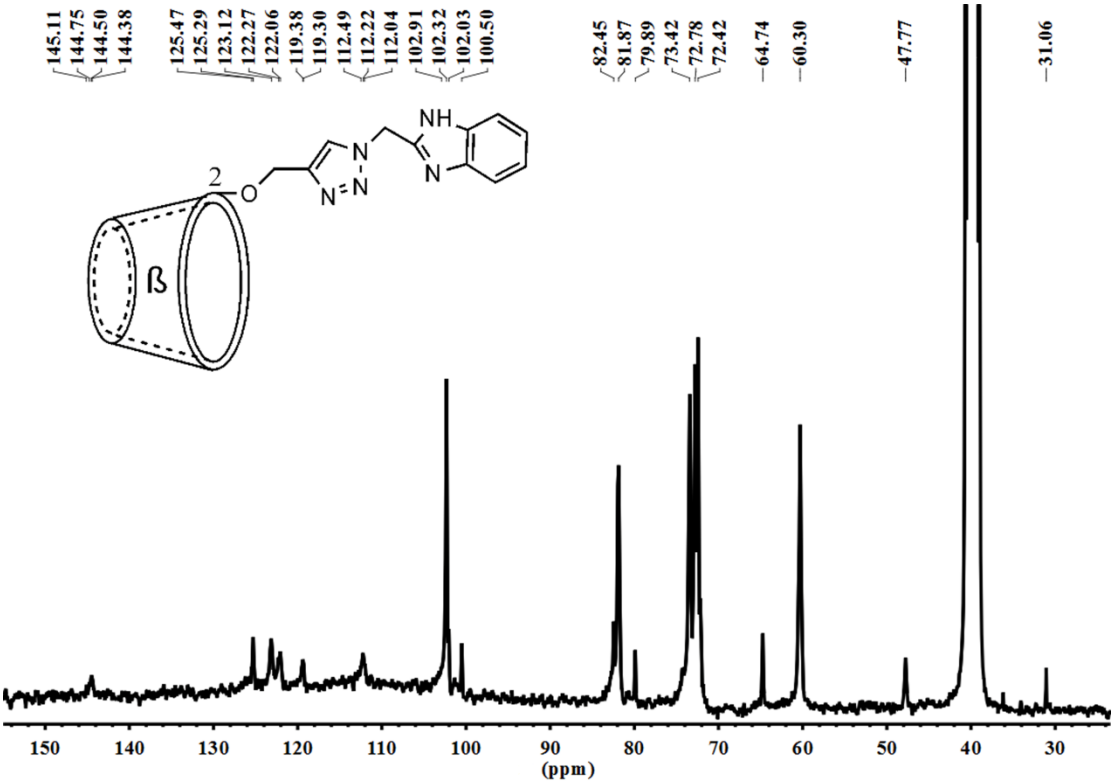


Fig. S2. ^{13}C NMR spectrum of Compound **3**.

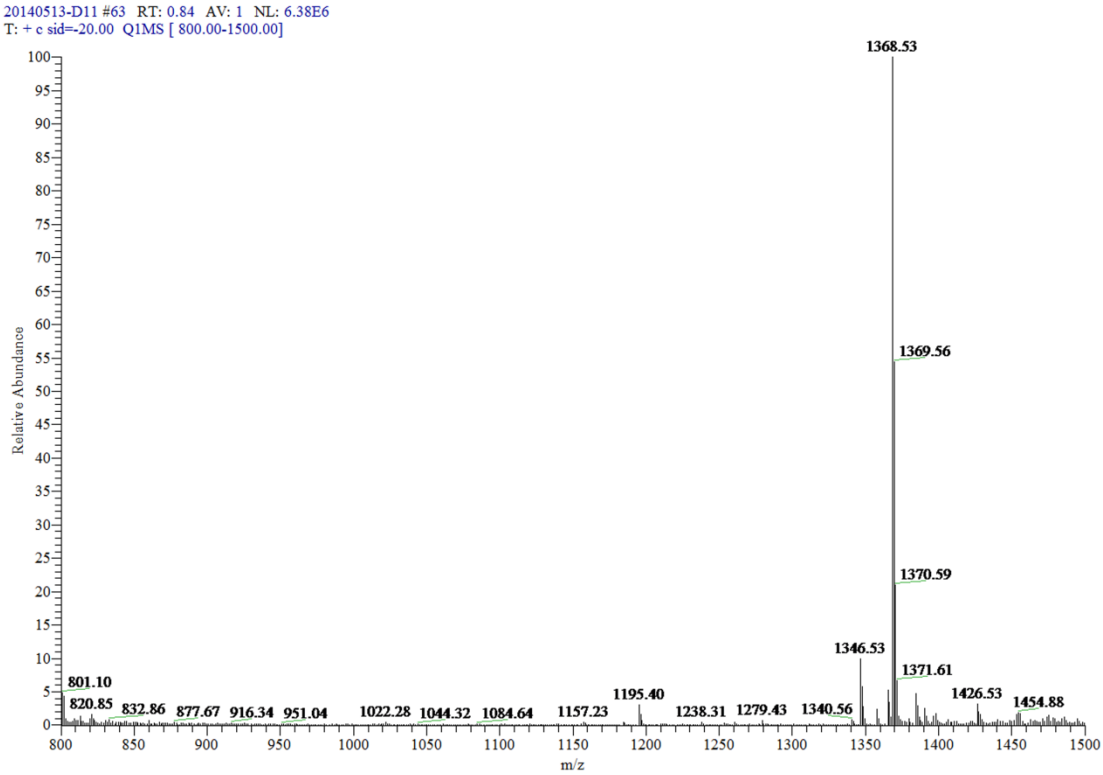
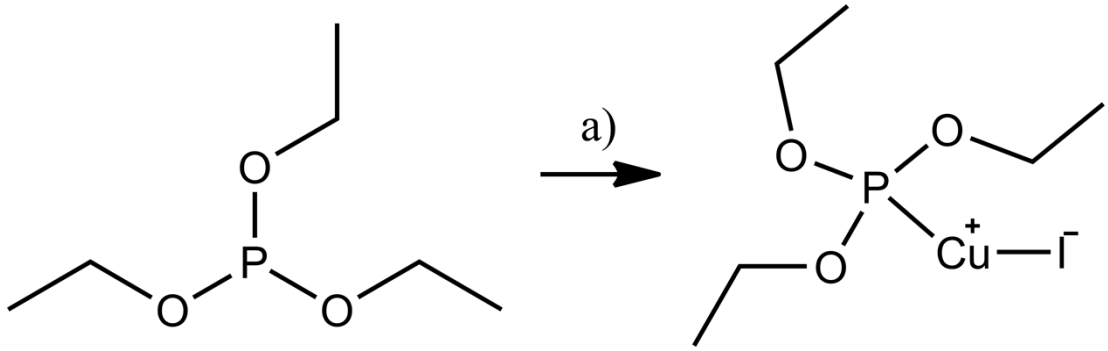


Fig. S3. MS spectrum of Compound **3**.

2.4.1 Synthesis of iodo(triethyl phosphite)



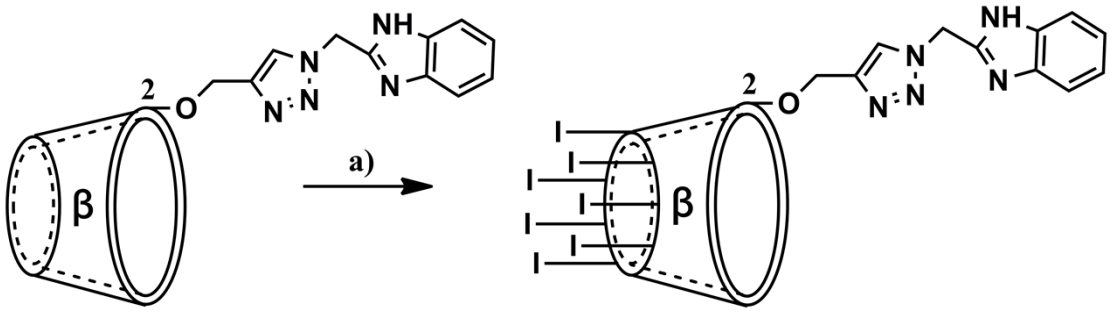
Scheme S4. Synthesis route of iodo(triethyl phosphite). a) CuI (1.0 equiv), benzene, RT, 1h.

Triethyl phosphite (2.76 mL, 15.8 mmol) was dissolved in benzene (16 mL), and copper iodide (3 g, 15.8 mmol) was added slowly within 10 min. The reaction mixture was stirred at room temperature in the darkness. The solvent was evaporated under reduced pressure, and the residue was crystallized from cyclohexane to give desired product as a white solid (2 g, yield 36%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 4.06–3.96 (m, 6H, CH_2), 1.21 (t, J=7.0 Hz, 9H, CH_3)

^{13}C NMR (75 MHz, DMSO-d_6) δ 59.73, 16.39

2.5 Synthesis of Compound 4 (mono-2-O-{1-(1*H*-benzoimidazol-2-ylmethyl) -1*H*-[1,2,3]triazol-4-ylmethyl}-heptakis(6-deoxy-6-iodo)-β-cyclodextrin)



Scheme S5. Synthesis route of Compound **4**. a) I_2 (20 equiv.), triphenylphosphine (20 equiv.), DMF, 70 ℃, 18 h.

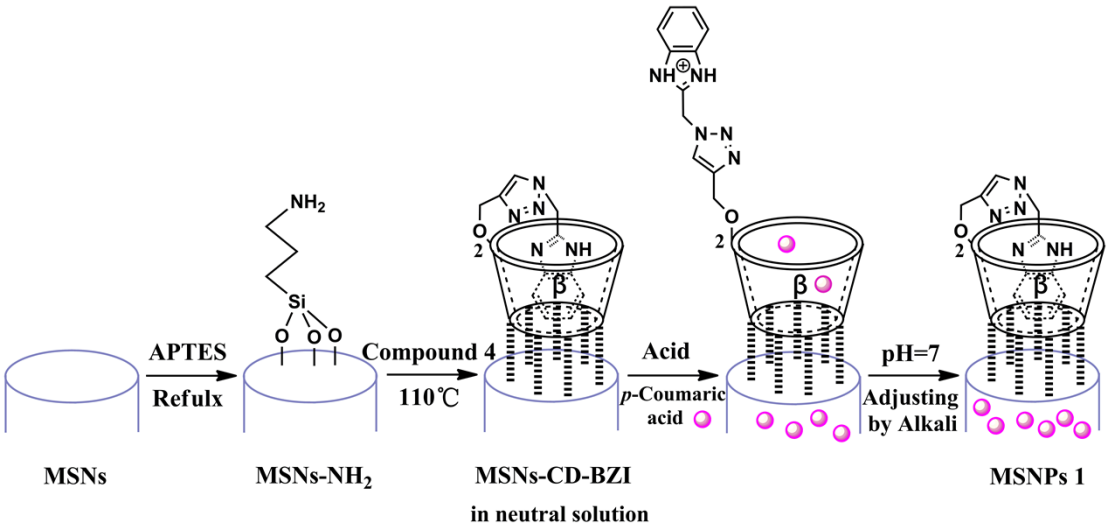
Compound **3** (0.592 g, 0.44 mmol) were added to the solution of triphenylphosphine (2.308g, 8.8 mmol) and iodine (2.234 g, 8.8 mmol). After the mixture stirred at 70 ℃

for 18 h under nitrogen atmosphere, sodium methoxide (0.56 g) in methanol (8 mL) was added dropwise to the mixture in the ice bath under the protection of nitrogen. After several minutes, the reaction mixture was poured into methanol (60 mL), and the precipitates were filtered, washed with methanol, dried *in vacuo* at 60 ℃ to afford Compound **4** as a yellow solid (82 mg, yield 8.6%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.14 (s, 1H, CH), 7.61 (d, *J*=45.1 Hz, 2H, Ar-H), 7.16 (s, 2H, Ar-H), 6.09–5.90 (m, 13H, OH), 5.10–4.73 (m, 7H, H-1^{I-VII}), 3.79–3.31 (m, CH_2, OH, H-2^{I-VII}, H-3^{I-VII}, 4^{I-VII}, 5^{I-VII}, 6^{I-VII}, 6'$^{I-VII}$, HDO)

^{13}C NMR (75 MHz, DMSO-d_6) δ 132.50, 131.91, 131.79, 129.24, 129.09, 123.37, 102.47 (C-1^{II-VII}), 100.67 (C-1^{I}), 86.25 (C-4^{I-VII}), 79.61 (C-2^{I}), 75.84–68.71 (C-2^{II-VII}, C-3^{I-VII}, C-5^{I-VII}), 64.80, 34.83, 9.75(C-6^{I-VII})

2.6 Synthetic procedure for preparing MSNPs 1



Scheme S6. Synthetic procedure for preparing MSNPs **1**.

2.7 Preparation of MSNs-NH_2

MSNs (200 mg) were suspended in anhydrous toluene (10 mL) by ultrasound. APTES (50 μL, 0.215mmol) was added dropwise to the solution and the suspension was stirred under refluxing in nitrogen atmosphere overnight. After this, the MSNs-NH_2 were separated by centrifugation, washed with anhydrous toluene and methanol, and

then dried under vacuum at 70 ℃ overnight.

2.8 Preparation of MSNs-CD-BZI

MSNs-NH_2 (200 mg) and Compound **4** (106 mg, 0.05 mmol) were suspended in anhydrous DMF (50 mL) and the reaction suspension was stirred at 110 ℃ under nitrogen atmosphere for 12 h. The MSNs-CD-BZI were isolated by centrifugation, washed with DMF and methanol, and dried under vacuum at 60 ℃ overnight.

2.9 Preparation of MSNPs 1

MSNs-CD-BZI (50 mg) were added to 5 mL HCl solution (pH=1.0) containing *p*-coumaric acid (0.82 mg) and sonicated to dispersion. The suspended solution was stirred for 48 h at 60 ℃. When the equilibrium was reached, the solution was rapidly cooled to room temperature and the pH of the solution was adjusted to neutrality by addition of NaOH. The MSNPs **1** were obtained by centrifugation, washed with PBS solution (pH 7.0) and dried under vacuum overnight for further use.

3. Release Experiments

In order to study the pH-triggered release property of MSNPs **1** in aqueous solution, fluorescence spectroscopy was used to determine the concentration of *p*-coumaric acid in solution released from MSNPs **1**. The maximum adsorption amount of *p*-coumaric acid was calculated to be 0.61 mmol g^{-1} MSNs, which was determined by measuring the cargo molecules concentration of supernatant after thorough releasing.

3.1 Acid-triggered release experiment

MSNPs **1** (2 mg) were placed in the dialysis bag at the top of the quartz cuvette to avoid particle interference. The PBS buffer solution (3.8 mL, pH 7.0) was carefully added into the cuvette at room temperature in order to ensure that MSNPs **1** were immersed into the solution. A 351 nm excitation laser beam was used to excite the emission of *p*-coumaric acid, the fluorescence spectra of the released cargo molecules

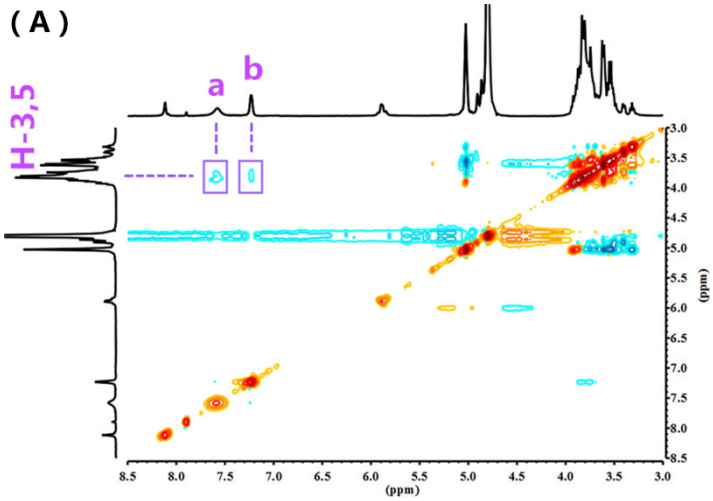
were recorded at 2 s intervals by a spectrophotometer. After collecting fluorescence intensity at the emission maximum of cargo molecules (λ=439 nm) under neutral solution, the solution pH was adjusted to the desired values with HCl solution to activate MSNPs **1**. The release profiles were plotted as a function of time.

3.2 Staged release experiment

MSNPs **1** (2 mg) placed in the dialysis bag were firstly immersed in the PBS solution (3.8 mL, pH 7.0) at room temperature. Fifty minutes later, the solution pH was tuned to acidity by addition a few drops of HCl solution. After 50 min of releasing, the solution pH was returned to neutrality by addition of NaOH solution (0.1 M). The phenomenon of the closure of nanovalves was observed for 100 min. Finally, MSNPs **1** were activated again by changing the solution pH to acidity to release the remaining *p*-coumaric acid molecules.

4. Analytical Data

4.1 2D ROESY NMR spectra of Compound 3



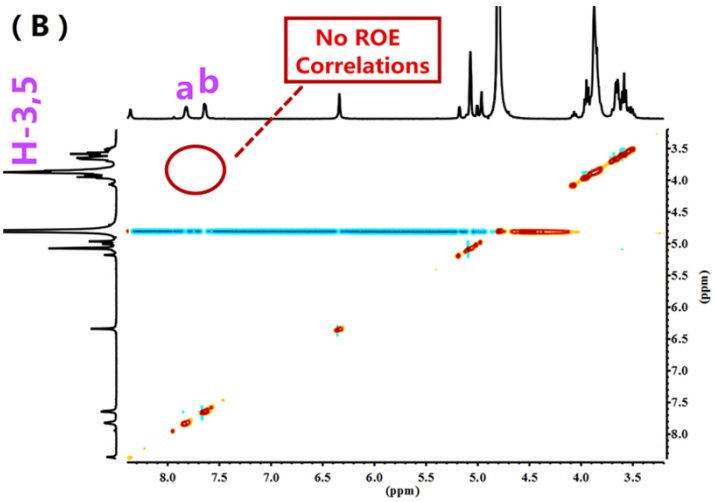


Fig. S4. Partial 2D ROESY NMR spectra of Compound **3** in D_2O at room temperature (A) at neutral pH, (B) at acidic pH, adjusting with deuterium chloride.

In order to avoid intermolecular self-assembly, the concentration of Compound **3** is fixed as 0.1 mM. The self-complexation/decomplexation of compound **3** is obtained from Fig. S4. The strong dipolar interactions between H-3/H-5 localized inside the β-CD core and the H_a /H_b in benzimidazole groups are observed under neutral pH, indicating the self-complexation of Compound **3**. The non-covalent interactions between β-CD and benzimidazole groups disappear under acidic pH. Importantly, the process is reversible and the ROE correlations are reappear when the solution pH turns from acidity to neutrality. It is no doubt that the self-switched actions of Compound **3** are controlled by pH values.

4.2 UV-Vis analysis

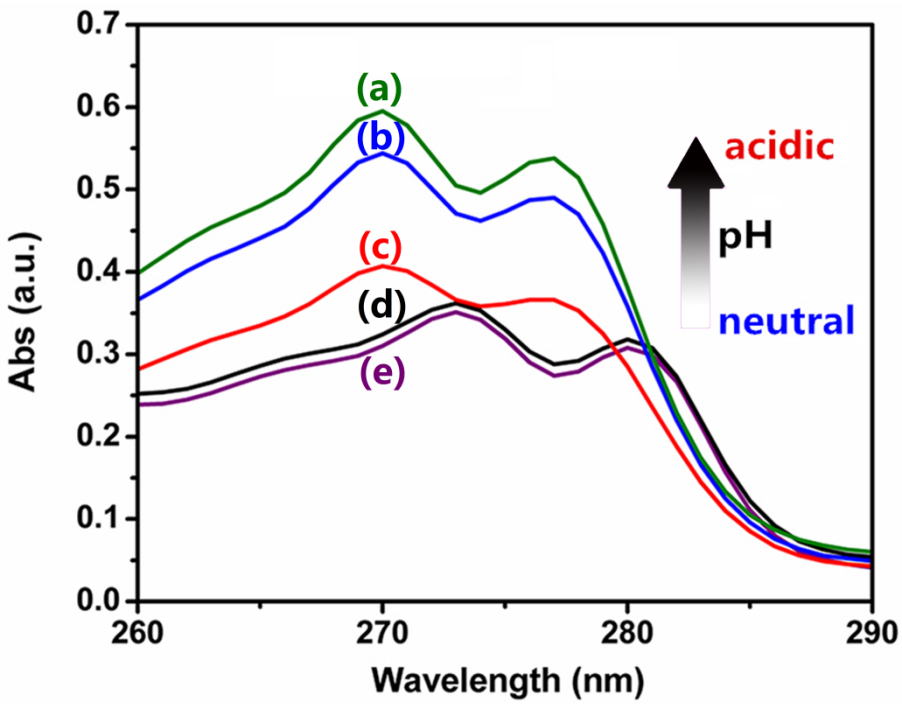


Fig. S5. UV-Vis of Compound **3** (0.1 mM) under pH (a) 2.4, olive line, (b) 2.8, blue line, (c) 3.2, red line, (d) 5.2, black line, (e) 6.0, purple line in water at room temperature.

With the decrease in pH value, the absorption band intensity arising from benzimidazole groups is significantly increased. This result proves that in the transition process of solution pH from neutrality to acidity, more and more benzimidazole groups are excluded from β-CD cavities. It is worthwhile to note that when the pH value was turned from 5.2 to 3.2, the phenomenon of blue shift (λ=277→270 nm; 280→273nm) was observed, which can be ascribed to the protonation of benzimidazole groups influencing the conjugated range of the molecular structure.

4.3 Characterization of MSNs

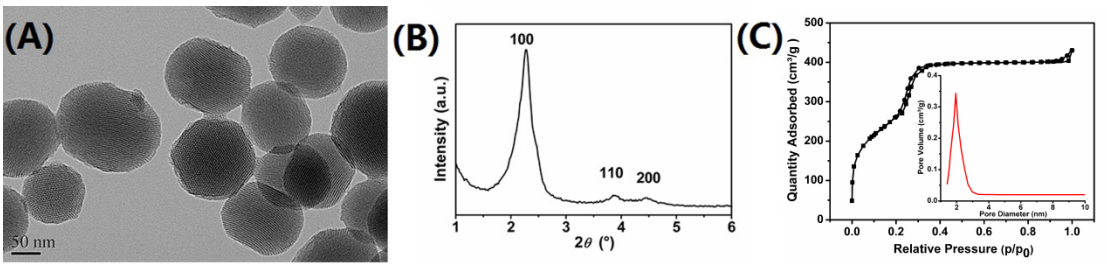


Fig. S6. A) TEM image, B) SA-XRD pattern, and C) N_2 adsorption-desorption isotherm and pore size distribution of MSNs.

SA-XRD pattern of MSNs displays three well-resolved reflections indexed as (100), (110), and (200), which is characteristic of a hexagonal mesoporous structure. N_2 adsorption-desorption isotherms of MSNs shows typical curves of type Ⅳ. The specific surface area was calculated by the Brunauer-Emmett-Teller (BET) method. Pore size distribution and pore volume were estimated from the adsorption branch of the isotherm by the Barrett-Joyner-Halenda (BJH) method. The detailed parameters of MSNs are shown in Table S1.

Table S1. Physicochemical properties of the MSNs.

Materials	Specific surface area (m^2 g^{-1})	Pore size (nm)	Pore volume (cm^3 g^{-1})
MSNs	1000.82	2.29	0.76

4.4 FTIR spectra of MSNs, MSNs-NH_2 and MSNs-CD-BZI

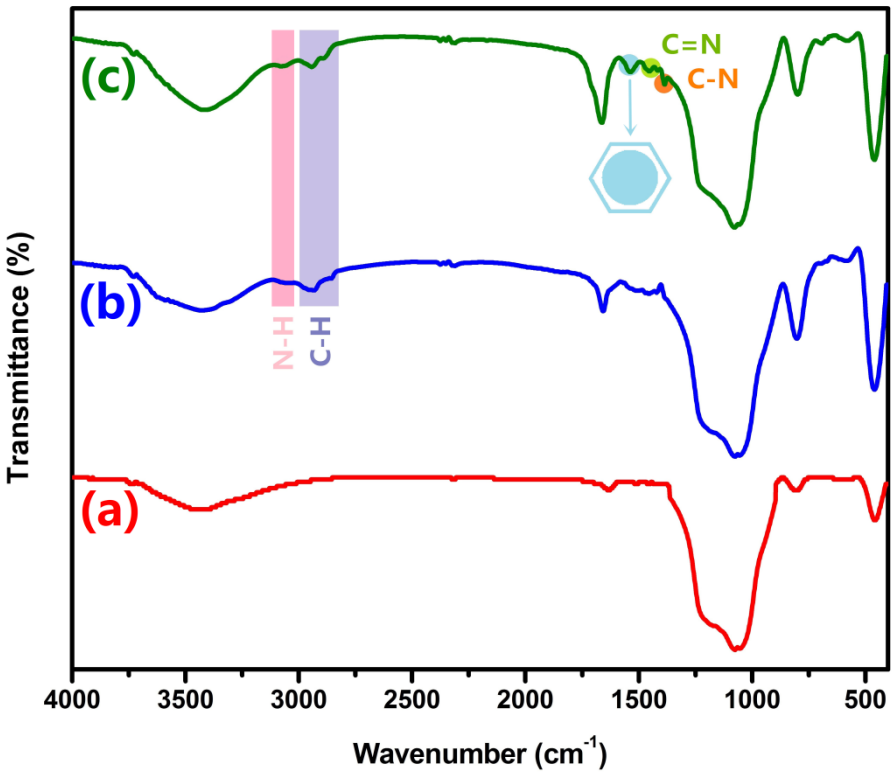


Fig. S7. FTIR spectra of (a) MSNs, (b) MSNs-NH_2, and (c) MSNs-CD-BZI.

4.4 TG analyses

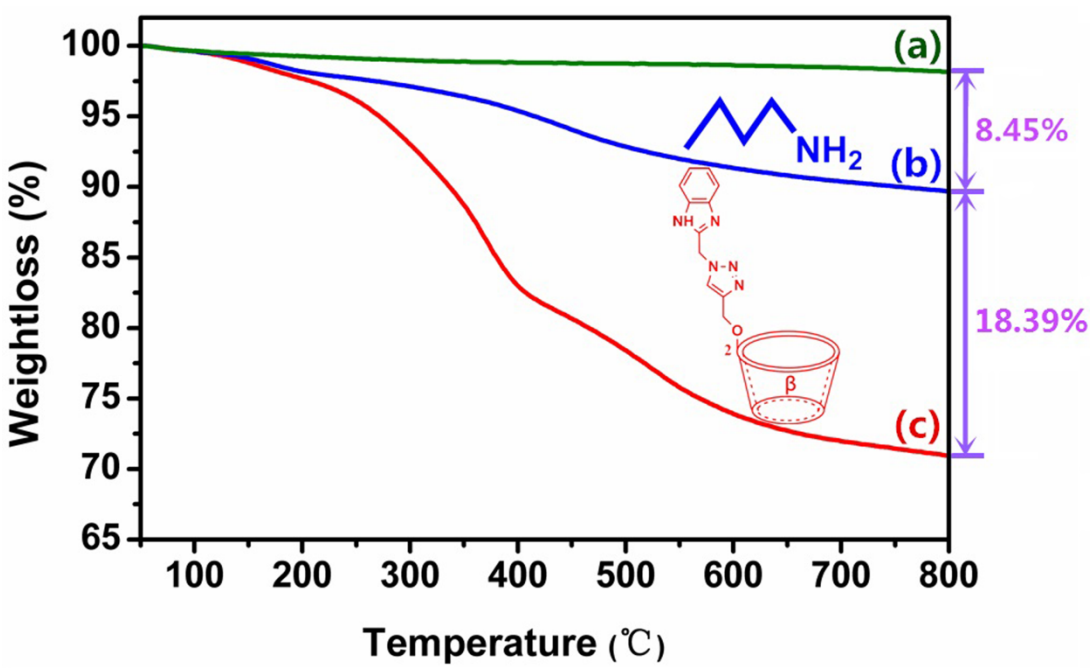


Fig. S8. TGA analyses of (a) MSNs, (b) MSNs-NH_2, and (c) MSNs-CD-BZI.

4.5 N_2 adsorption-desorption isotherms, SA-XRD and TEM analysis of

functionalization process

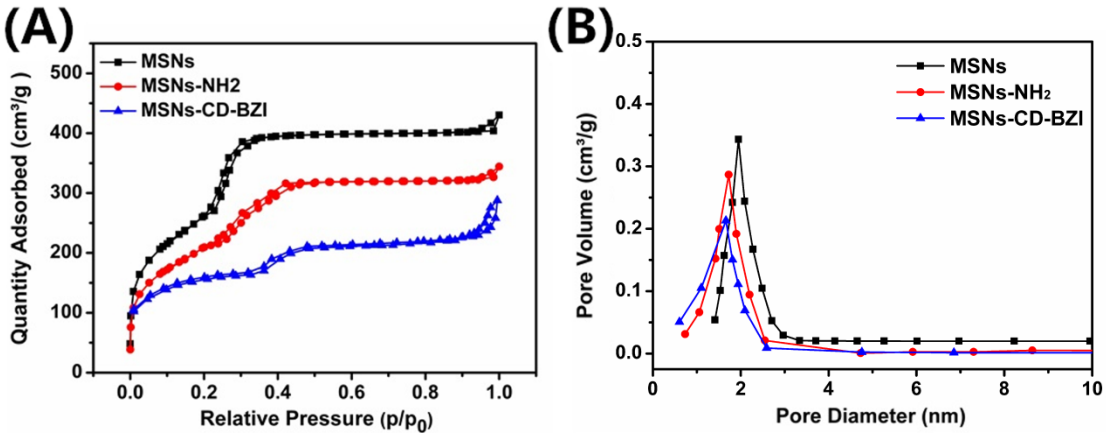


Fig. S9. (A) N_2 adsorption-desorption isotherms and (B) pore size distributions of MSNs, MSNs-NH_2, and MSNs-CD-BZI.

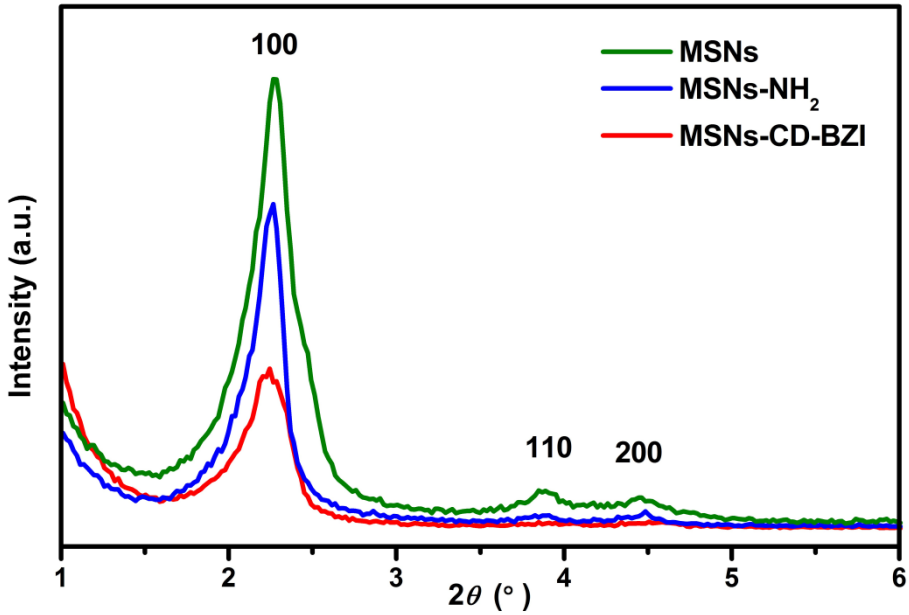


Fig. S10. SA-XRD pattern of MSNs (olive line), MSNs-NH_2 (blue line), and MSNs-CD-BZI (red line).

Table S2. Physicochemical properties of the MSNs, MSNs-NH_2 and MSNs-CD-BZI.

Materials	Specific surface area (m^2 g^{-1})	Pore size (nm)	Pore volume (cm^3 g^{-1})
MSNs	1000.82	2.29	0.76
MSNs-NH_2	712.66	1.73	0.58
MSNs-CD-BZI	316.48	1.66	0.33

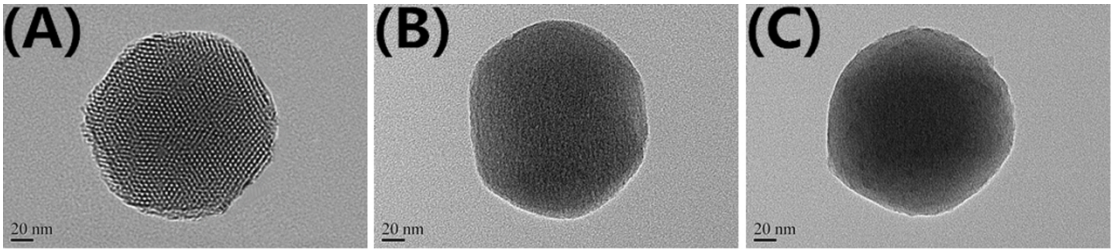
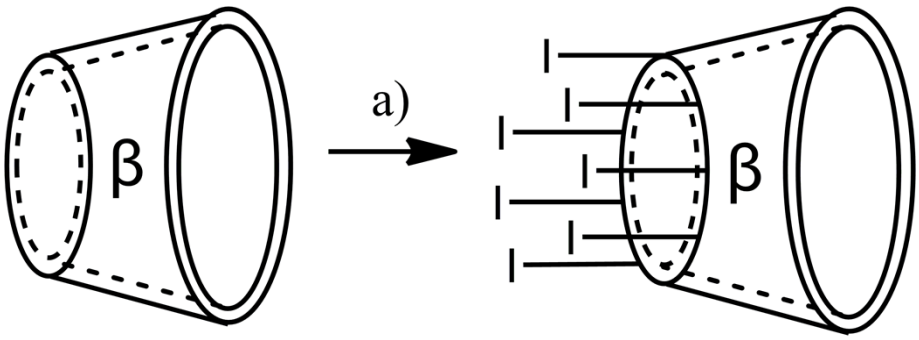


Fig. S11. TEM images of (A) MSNs, (B) MSNs-NH_2, and (C) MSNs-CD-BZI.

After functionalization, MSN-NH_2 and MSNs-CD-BZI basically maintain the XRD patterns similar to MSNs although the intensity of diffraction peaks drop sharply, indicating the incomplete order of the mesopores. The N_2 adsorption-desorption studies demonstrate that with the depth of the functionalization, the specific surface area, pore volume and average pore size of are all reduced a certain extent compared to the MSNs. However, combined with the TEM images, the two-step functionalization procedure is successful and does not alter the overall morphology and remains the mesoporous structure.

4.6 Control experiments

In order to further confirm the key function of mono-BZI functionalized β-CD in the operating process, heptakis (6-deoxy-6-iodo)-β-cyclodextrin was synthesized for comparison. The brief synthetic procedure is as follows.



Scheme S7. Synthesis route of heptakis (6-deoxy-6-iodo)-β-CD. a) I_2 (20 equiv.), PPh_3 (20 equiv.), DMF, 70 ℃, 18 h.

To a solution of the corresponding triphenylphosphine (4.616 g, 17.6 mmol) in anhydrous DMF (18 mL) was added iodine (4.468, 17.6 mmol) and β-cyclodextrin (1 g, 0.88 mmol). The reaction mixture was stirred at 70 ℃ for 18 h under nitrogen

atmosphere. After cooled to the room temperature, sodium methoxide (1.12 g) in methanol (16 mL) was added dropwise to the mixture at 0 ℃ under the protection of nitrogen. Several minutes later, the reaction mixture was poured into methanol (120 mL), and the precipitates were filtered, washed with methanol thoroughly, dried *in vacuo* at 60 ℃ to afford heptakis (6-deoxy-6-iodo)-β-cyclodextrin as a ivory solid (1.17 g, yield 70%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 6.03 (d, *J*=6.8 Hz, 7H, OH), 5.92 (d, *J*=1.4 Hz, 7H, OH), 4.99 (d, *J*= 3.1 Hz, 7H, H-1^{I-VII}), 3.81–3.27 (m, 42H, H-2^{I-VII} to H-6^{I-VII})

^{13}C NMR (75 MHz, DMSO-d_6) δ 102.50 (C-1^{I-VII}), 86.30 (C-4^{I-VII}), 72.53, 72.27, 71.33 (C-2^{I-VII}, C-3^{I-VII}, C-5^{I-VII}), 9.88 (C-6^{I-VII})

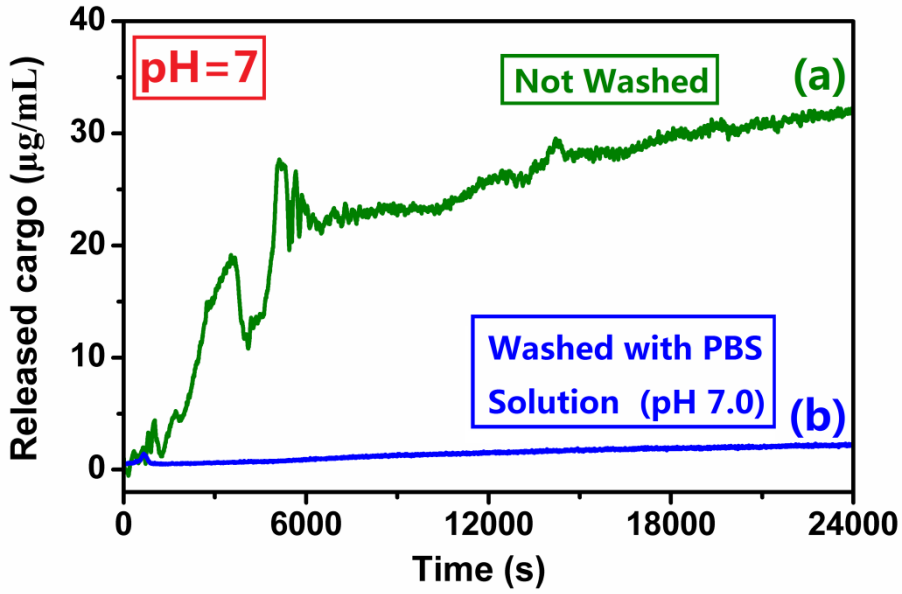


Fig. S12. Release profiles of *p*-coumaric acid loaded MSNs-CD under pH 7.0 (a) not washed and (b) washed with PBS solution (pH 7.0)

Heptakis (6-deoxy-6-iodo)-β-cyclodextrin was reacted with MSNs-NH_2 to obtain MSNs-CD (no benzimidazole groups linked through O2 position). After loading with *p*-coumaric acid, *p*-coumaric acid loaded MSNs-CD were taken to perform release experiments and the results are shown in Fig. S12. It can be easily seen that without key component of benzimidazole groups, *p*-coumaric acid loaded MSNs-CD show no pH-controlled release property. Under pH 7.0, the fluorescence intensity increased significantly, illustrating those p-coumaric acid molecules can freely flow out of the

mesopores. If *p*-coumaric acid loaded MSNs-CD were washed with PBS solution (pH 7.0), *p*-coumaric acid molecules remained in the mesopores are negligible due to the lack of the gatekeepers to regulate *p*-coumaric acid molecules.