Supporting Information

Cage-based covalent organic framework for drug delivery

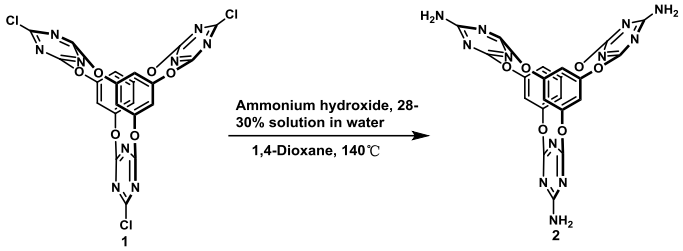
Ming Li,[a] Yu Peng,[a] Fei Yan,[a] Chunguang Li,[a] Yiqiang He,[a] Yue Lou,[a] Dingxuan Ma,[b] Yi Li,[a] Zhan Shi*[a] and Shouhua Feng[a]

[a.] State Key Laboratory of Inorganic Synthesis and Preparative Chemistry, College of Chemistry, Jilin University, Changchun 130012, China

[b.] College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao 266042, China

*E-mail: zshi@jlu.edu.cn.

Section I. Synthetic Procedures



Preparation of 1: 1 was prepared according to the literature with minor modifications.[S1] A mixture of phloroglucinol (0.252 g, 2 mmol) and cyanuric chloride (0.553 g, 3 mmol) in THF (200 mL) was made. After addition of DIPEA (2 mL, 11.4 mmol), the resulting mixture was stirred at room temperature for 4 days. The solvent was removed and residues were subjected to chromatography on a silica gel (100-200 mesh) column eluting with a mixture of petroleum ether and acetone. Pure cage molecule 1 was obtained as white solid (a yield rate of 35%). M.p. >300 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz): d = 6.69 ppm (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): d = 175.1, 172.7, 153.2, 115.0 ppm; IR (KBr) ν = 1614, 1550 cm^{-1}; MS (EI): m/z (%): 591 (4), 590 (28), 589 (28), 588 (19), 587 (96), 586 (22), 585 (100) $[M]^+$; HRMS: m/z calcd for $C_{21}H_6N_9O_6Cl_3$: 584.9507; found: 584.0513.

Preparation of 2: **2** was prepared according to the literature with minor modifications.[S2] To **1** (578mg, 1mmol) 2ml of 1, 4-dioxane was added in portions at 0 ℃ with vigorous stirring. To this mixture 450 uL of Ammonium hydroxide was slowly added and stirred for about 10 minutes. Finally the reaction mixture in the reactor was sealed, the temperature was raised to 140℃, and the reaction was carried out for 4h. The resulting yellow precipitate was washed with 1, 4-dioxane and water. The crude product was recrystallized with methanol to obtain yellow powder of **2** (405 mg, 76.7% yield). M.p. >300 ℃; ^{1}H NMR (300 MHz, *d*$_6$ DMSO): d = 6.71 ppm (s, 6H), d = 7.76 ppm (s, 6H); ^{13}C NMR (*d*$_6$ DMSO, 75 MHz): d = 171.98, 170.04, 152.74, 114.98 ppm; IR (KBr) ν = 3336, 1733, 1635 cm^{-1}; MS (EI): m/z (%): 439 (5), 531 (28), 528 (28), 530 (19), 527 (96), 529 (100) $[M]^+$; HRMS: m/z calcd for $C_{21}H_{12}N_{12}O_6$: 528.1007; found: 528.1013.

Section II. Drug loading and release

Drug loading was carried out through the immersion of Cage-COF-TT in an ibuprofen solution in hexane with a specific concentration. A typical procedure for loading ibuprofen into Cage-COF-TT follows: 200 mg of Cage-COF-TT was suspended in 10 mL of 0.1 M ibuprofen solution with stirring for 6 h while preventing hexane evaporation by covering with a cap. The drug-loaded sample was separated from the solution by vacuum filtration, washed with hexane, and dried at room temperature. The filtrate (1.0 mL) was sucked and properly diluted to determine the drug-loading amount using a UV-Vis spectrophotometer.

A typical procedure for releasing ibuprofen from Cage-COF-TT is as follows: after transfering the drug-loaded samples (50 mg) to a semipermeable bag, the release rate was determined by soaking the drug-loaded samples in 200 mL of simulated body fluid (SBF, 37 ℃, pH = 7.4, standard buffer solution from Fisher Chemical). At predetermined time intervals, samples (3 mL) were withdrawn and their ibuprofen contents immediately determined by analysis at 222 or 264 nm using a UV-Vis spectrophometer. The samples were then added back to the system to maintain constant volumes. The IBU concentration was subsequently determined based on a calibration curve. The release study was continued until the ibuprofen concentration did not change.

In addition, the procedures for loading and releasing 5-fluorouracil (λ_{max} = 265 nm) or captopril (λ_{max} = 204 nm) were similar to those used for ibuprofen.

Section III. Characterization Details

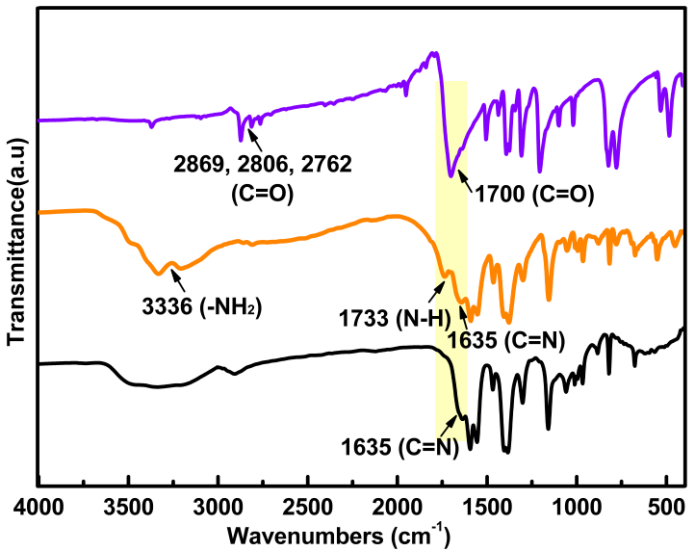


Fig. S1 FT-IR spectra of (a) p-benzaldehyde, (b) cage molecule, and (c) Cage-COF-TT.

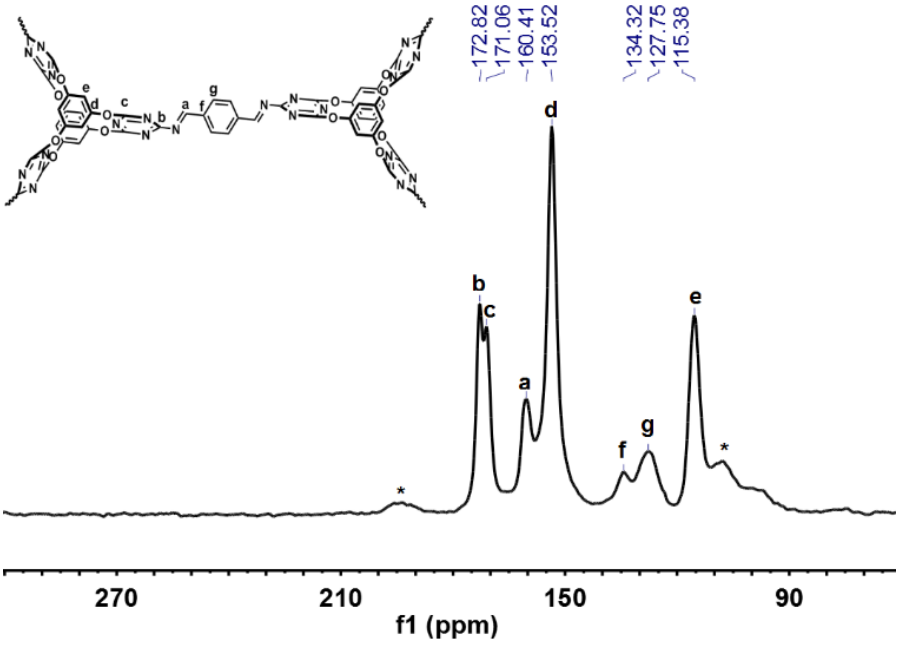


Fig. S2 Solid-state ^{13}C NMR spectrum of Cage-COF-TT.

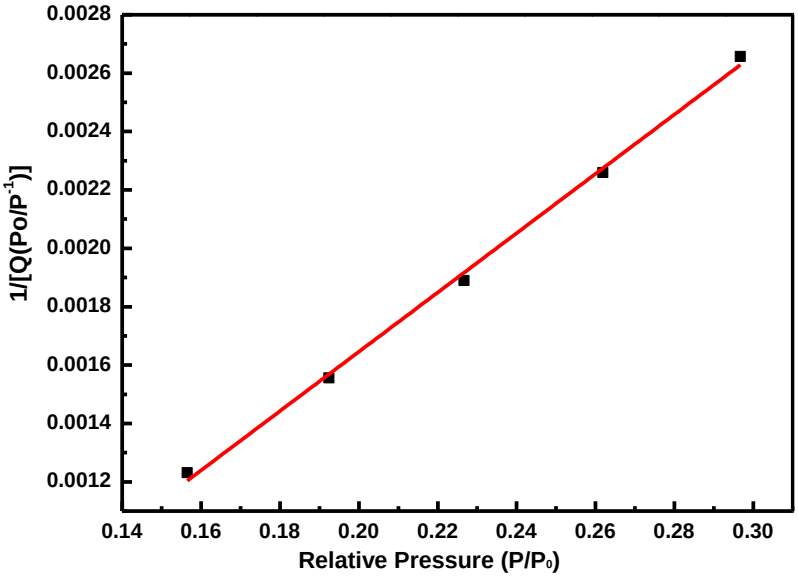


Fig. S3 BET plots for Cage-COF-TT.

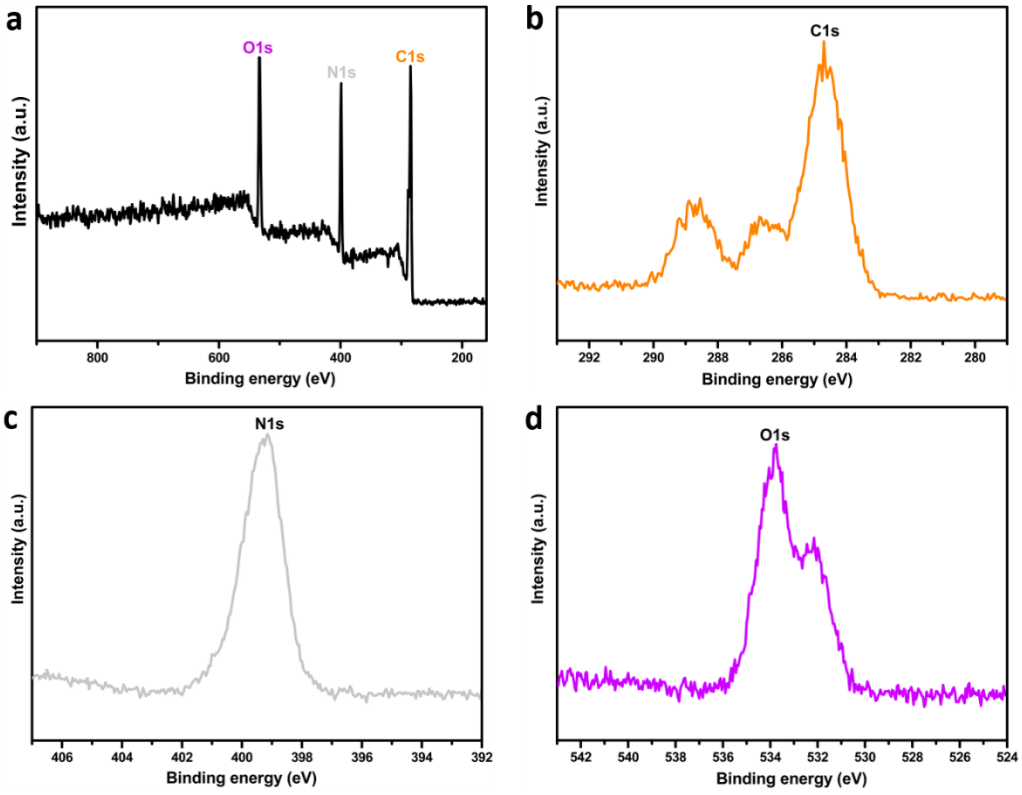


Fig. S4 (a) XPS whole spectral survey, (b) C 1s, (c) N 1s, and (d) O 1s XPS spectra of cage-COF-TT.

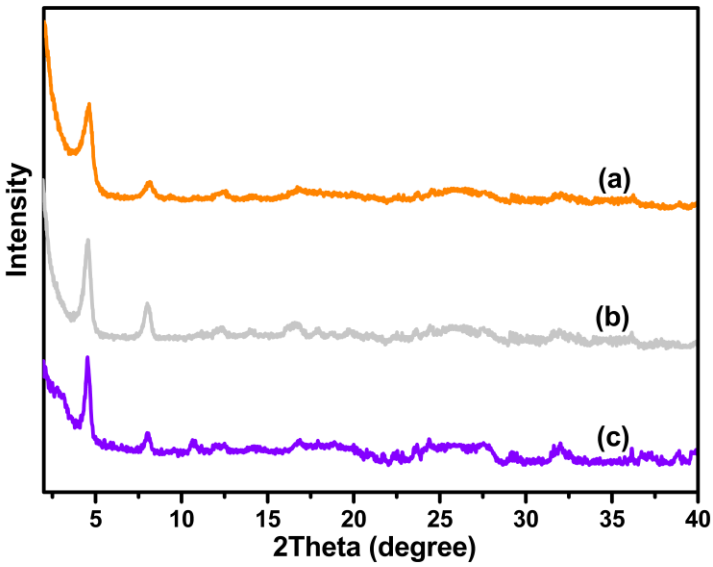


Fig. S5 PXRD of (a) Cage-COF-TT, (b) IBU-loaded Cage-COF-TT, (b) FLU-loaded Cage-COF-TT, and (c) CAP-loaded Cage-COF-TT.

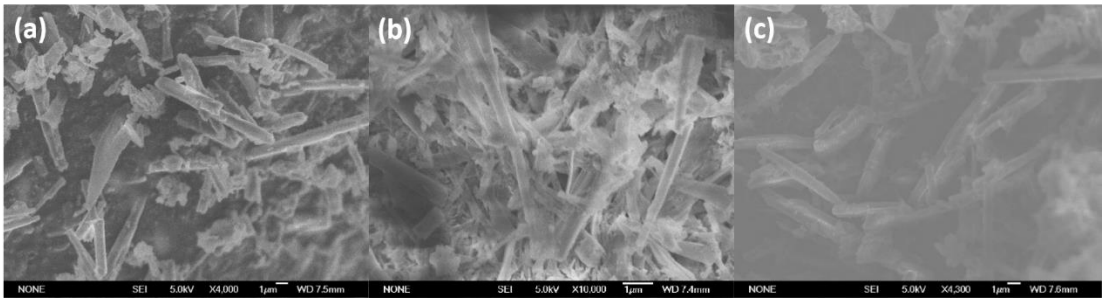


Fig. S6 SEM image of (a) IBU-loaded Cage-COF-TT, (b) FLU-loaded Cage-COF-TT, and (c) CAP-loaded Cage-COF-TT.

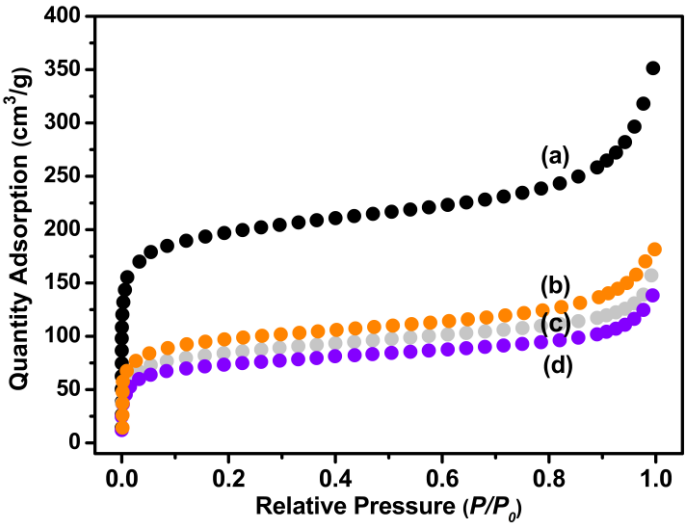


Fig. S7 N_2 sorption isotherms of (a) Cage-COF-TT, (b) IBU-loaded Cage-COF-TT, (c) FLU-loaded Cage-COF-TT, and (d) CAP-loaded Cage-COF-TT.

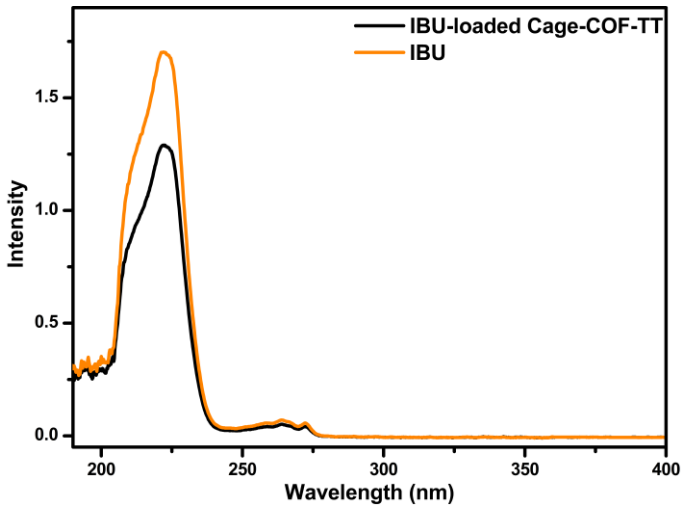


Fig. S8 UV-vis absorption spectra of IBU and IBU-loaded Cage-COF-TT.

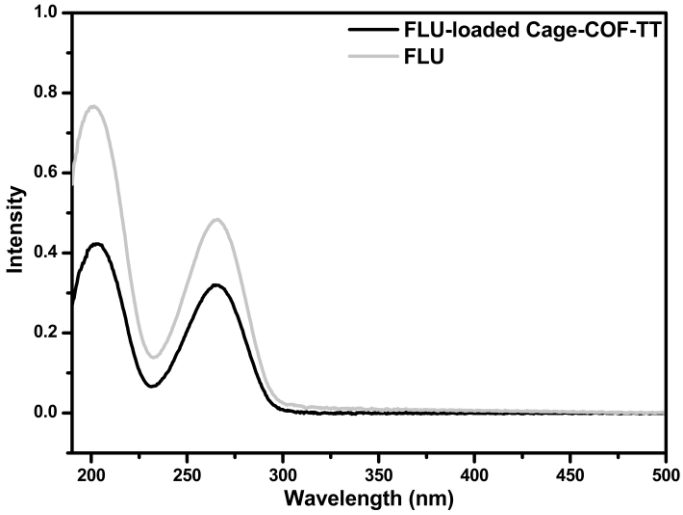


Fig. S9 UV-vis absorption spectra of FLU and FLU-loaded Cage-COF-TT.

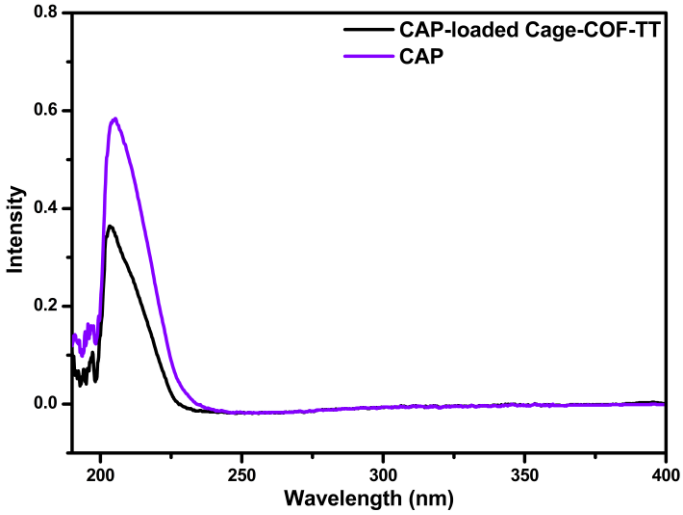


Fig. S10 UV-vis absorption spectra of CAP and CAP-loaded Cage-COF-TT.

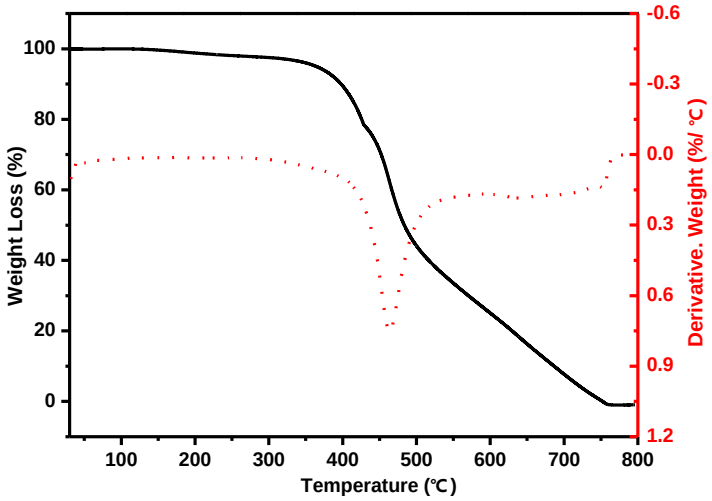


Fig. S11 TGA trace for an activated sample of Cage-COF-TT under air atmosphere.

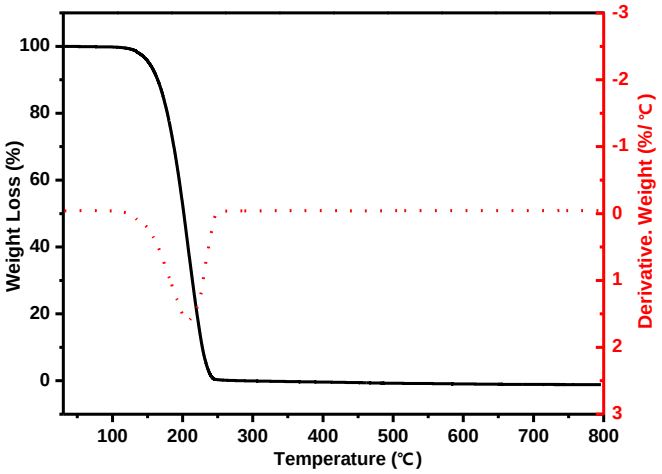


Fig. S12 TGA trace for an activated sample of IBU under air atmosphere.

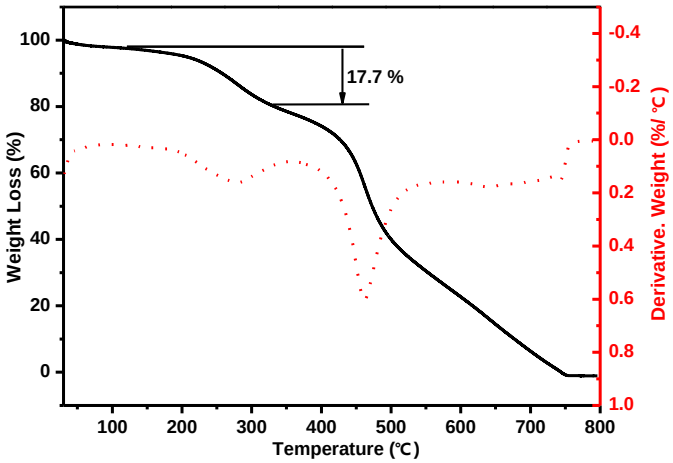


Fig. S13 TGA trace for an activated sample of IBU-loaded Cage-COF-TT under air atmosphere.

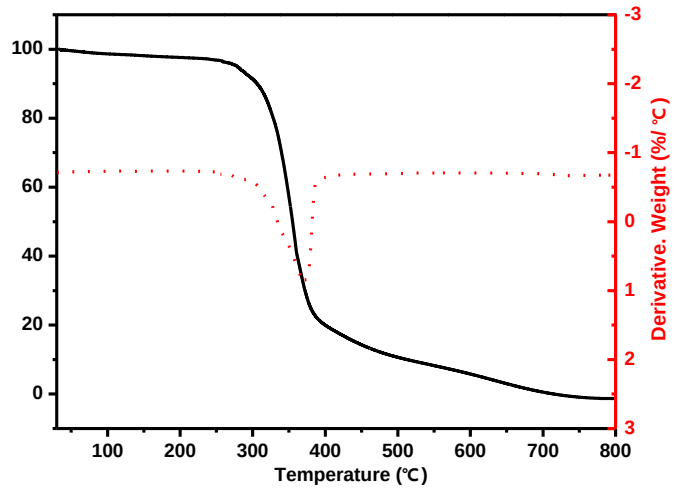


Fig. S14 TGA trace for an activated sample of FLU under air atmosphere.

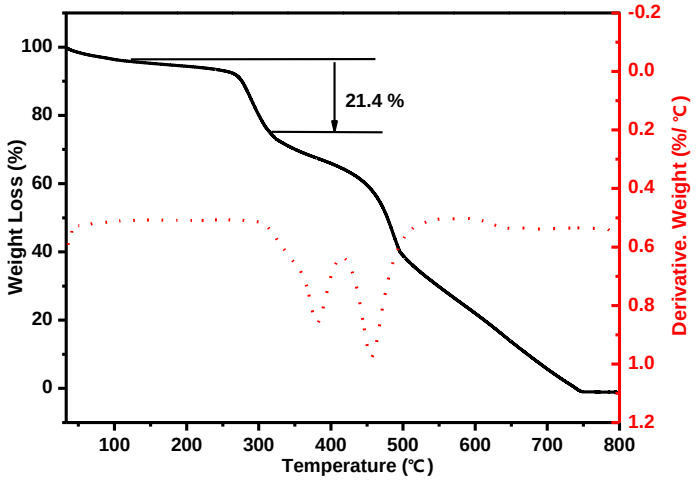


Fig. S15 TGA trace for an activated sample of FLU-loaded Cage-COF-TT under air atmosphere.

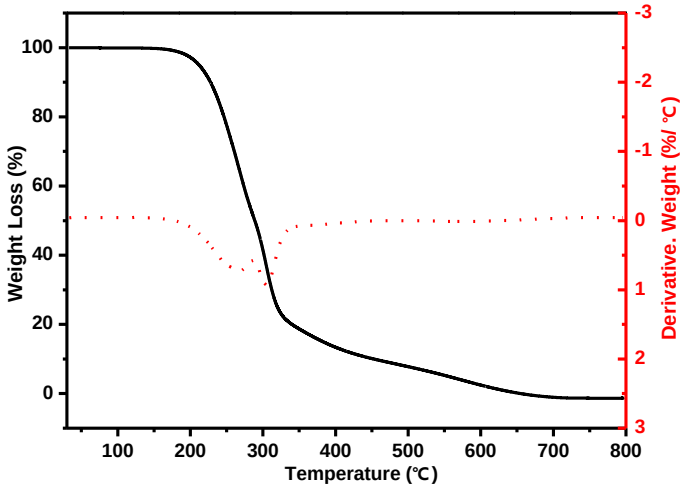


Fig. S16 TGA trace for an activated sample of CAP under air atmosphere.

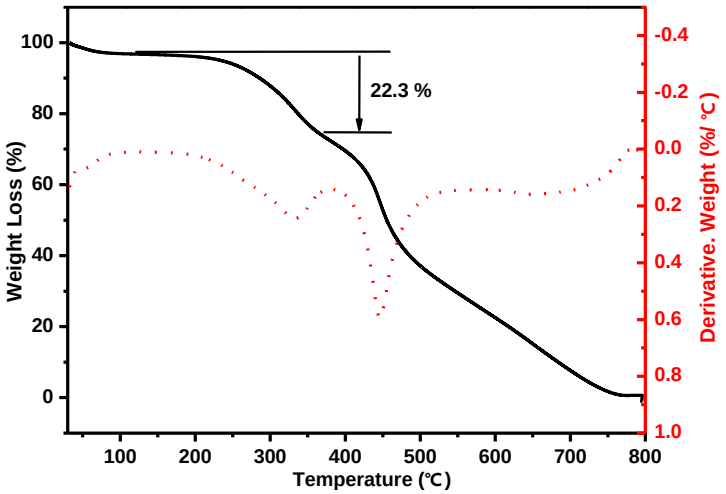


Fig. S17 TGA trace for an activated sample of CAP-loaded Cage-COF-TT under air atmosphere.

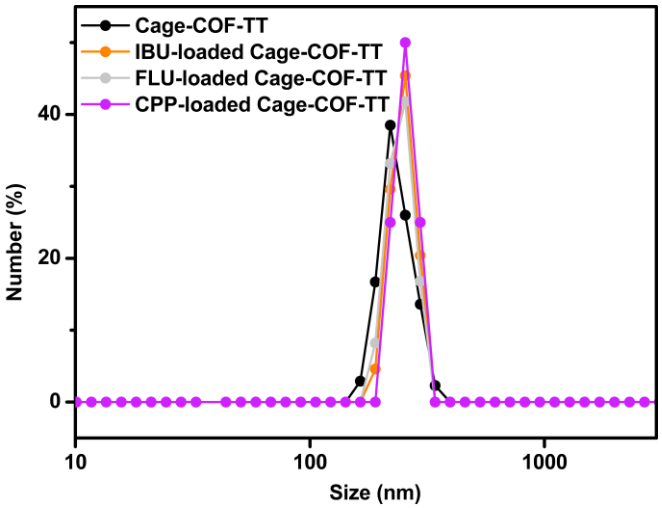


Fig. S18 DLS distribution of Cage-COF-TT and IBU-loaded, FLU-loaded, and CAP-loaded Cage-COF-TTs.

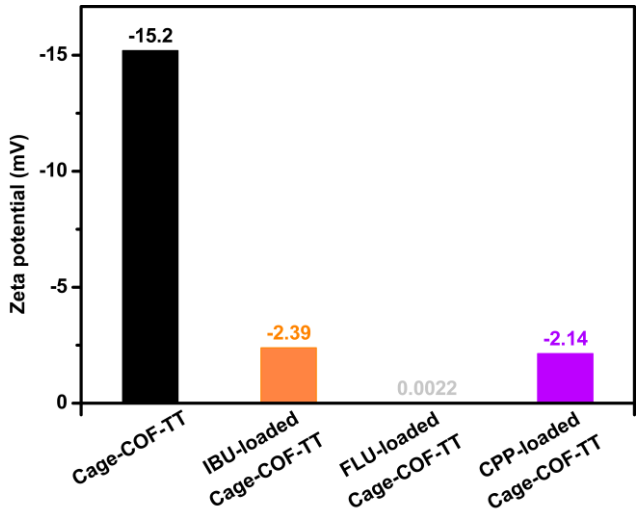


Fig. S19 Zeta potential of Cage-COF-TT and IBU-loaded, FLU-loaded, and CAP-loaded Cage-COF-TTs.

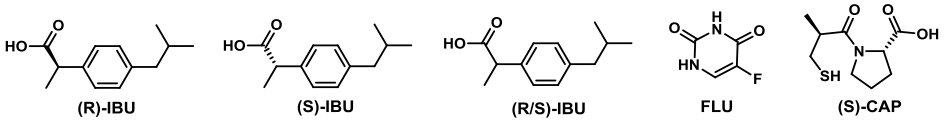


Fig. S20 The structural formulas of (R)-IBU, (S)-IBU, (R/S)-IBU, FLU, and (S)-CAP.

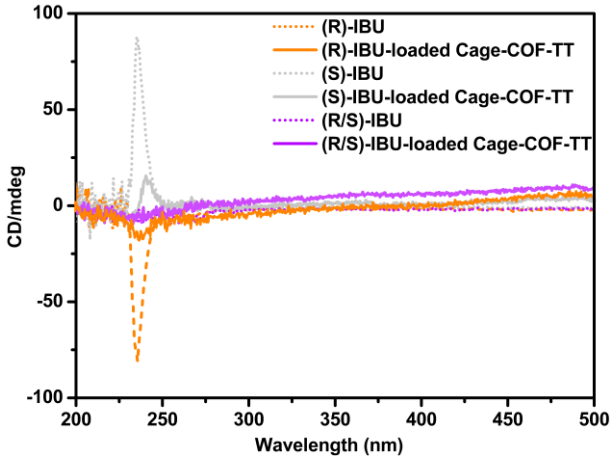


Fig. S21 Circular dichroism (CD) spectra of (R)-IBU, (S)-IBU, (R/S)-IBU, (R)-IBU-loaded, (S)-IBU-loaded, and (R/S)-IBU-loaded Cage-COF-TTs.

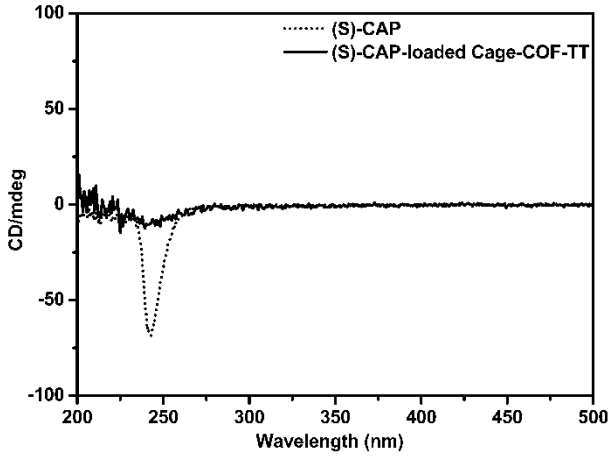


Fig. S22 Circular dichroism (CD) spectra of (S)-CAP and (S)-CAP-loaded Cage-COF-TT.

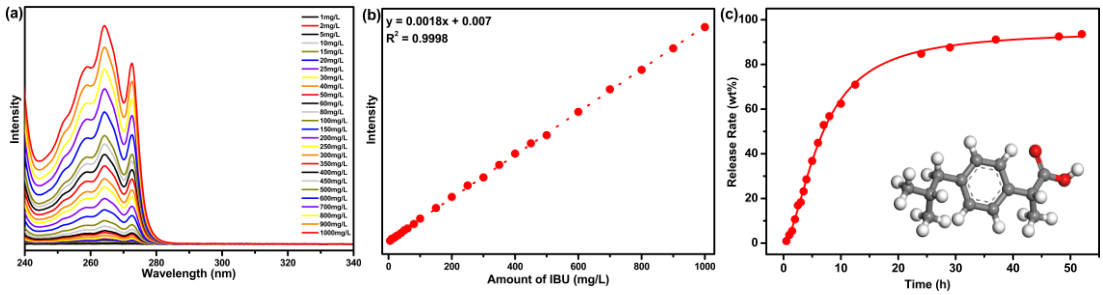


Fig. S23 (a) UV-vis spectra of ibuprofen (IBU) in simulated body fluid (SBF) (pH 7.4, buffer solution) at different concentrations, (b) IBU calibration curve, and (c) Release profile of IBU-loaded Cage-COF-TT. Inset: the structure of IBU. C, black; H, gray; O, red.

Section IV. Copies of ^{1}H and ^{13}C NMR for new compounds

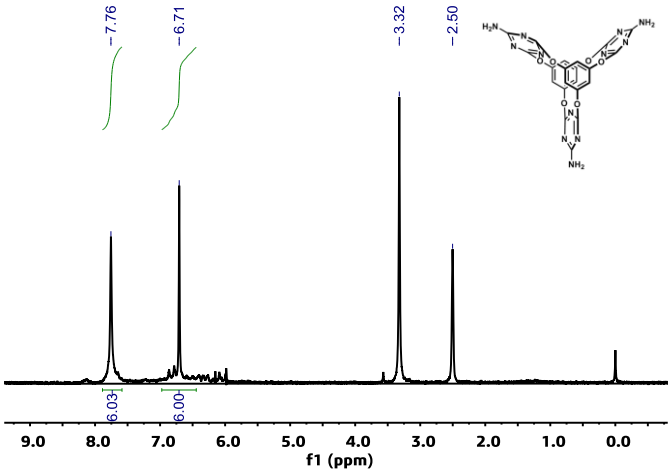


Fig. S24 ^{1}H NMR of **2** in *d*$_6$-DMSO.

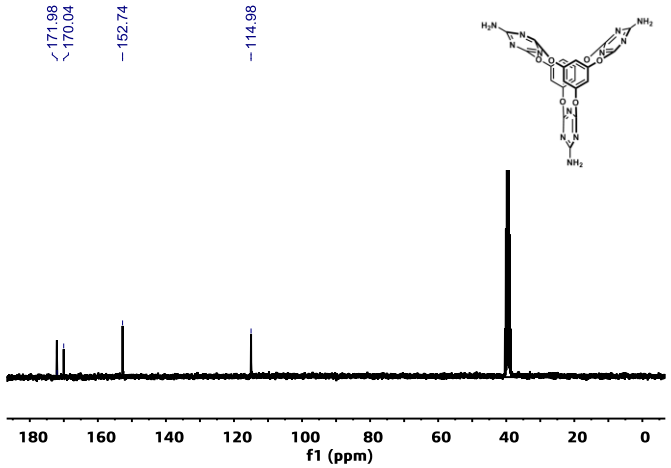


Fig. S25 ^{13}C NMR of **2** in *d*$_6$-DMSO.

References

S1. Wang, Q. Q.; Luo, N.; Wang, X. D.; Ao, Y. F.; Chen, Y. F.; Liu, J. M.; Su, C. Y.; Wang, D. X.; Wang, M. X., *J. Am. Chem. Soc.* 2017, ***139***, 635-638.

S2. (a) Luo, Y.; Zhang, L.; Yang, W.; Liu, W.; Lu, W.; Li, M., Synthesis of [$^{15}N_3$]melamine and [$^{13}C_3$] cyanuric acid. *J. Label Compd. Radiopharm.* 2011, ***54***, 171-172；(b) Han, B.; Wang, H.; Wang, C.; Wu, H.; Zhou, W.; Chen, B.; Jiang, J. Postsynthetic metalation of a robust hydrogen-bonded organic framework for heterogeneous catalysis. *J. Am. Chem. Soc.* 2019, **141**, 8737-8740.