Electronic Supplementary Information (ESI)

for

Ca^{2+}, pH and thermo triple-responsive mechanized Zr-based MOFs for on-command drug release in bone diseases

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Contents

1. Materials and Methods

Starting materials and reagents were purchased from Aladdin, and used as received. All reagents were purchased from commercial sources and used without further purification, unless otherwise noted. Deionized water was used in all relevant experiments. CP5 was synthesized according to the reported procedures.[S1-S3] Powder X-ray diffraction (PXRD) measurements were carried out using a Rigaku SmartLab III powder diffractometer. Transmission Electron Microscope (TEM) images were collected on a JEM 2100F instrument at an accelerating voltage of 200 kV. The X-ray photoelectron spectra (XPS) of the powders were collected on a ESCALAB 250 X-ray photoelectron spectrometer, using a monochromatic Al Kα radiation as the exciting source. Ultraviolet-visible (UV-vis) spectra were recorded on a Shimadzu UV-2550 instrument. *In vitro* cytotoxicity was tested according to the reference for 48 hours.[S4] The source of normal human embryonic kidney (HEK) 293 cells is American type culture collection (ATCC).

2. Materials Characterization

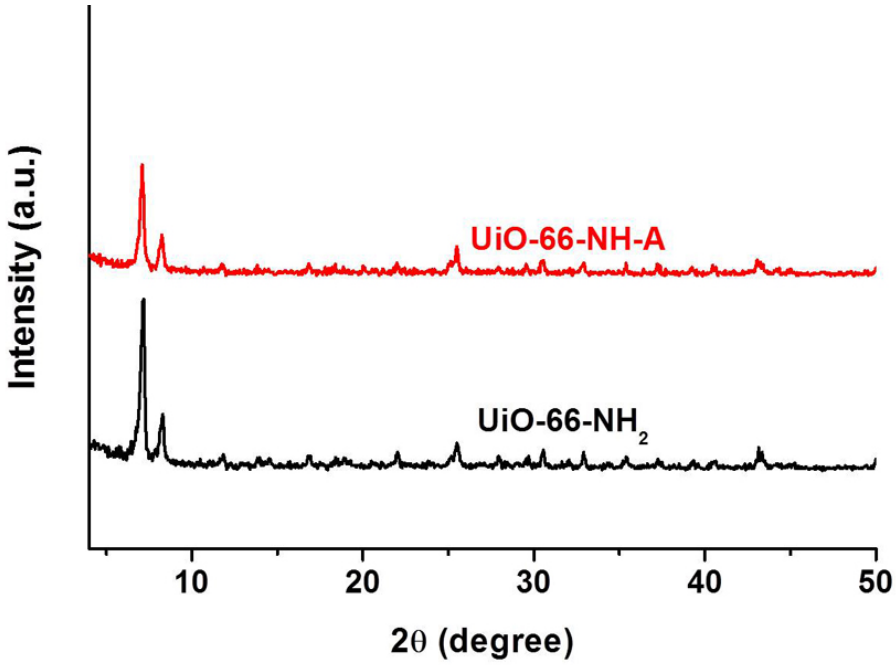

Fig. S1 Powder X-ray diffraction (PXRD) of UiO-66-NH-A and UiO-66-NH_2.

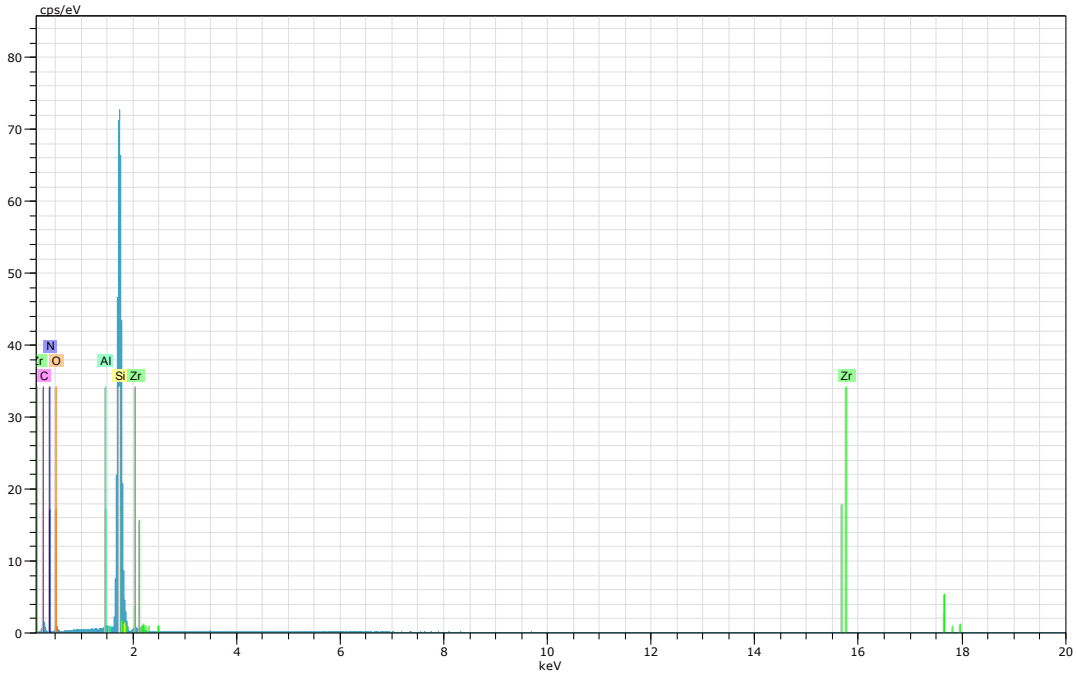

Fig. S2 SEM-EDS of UiO-66-NH_2.

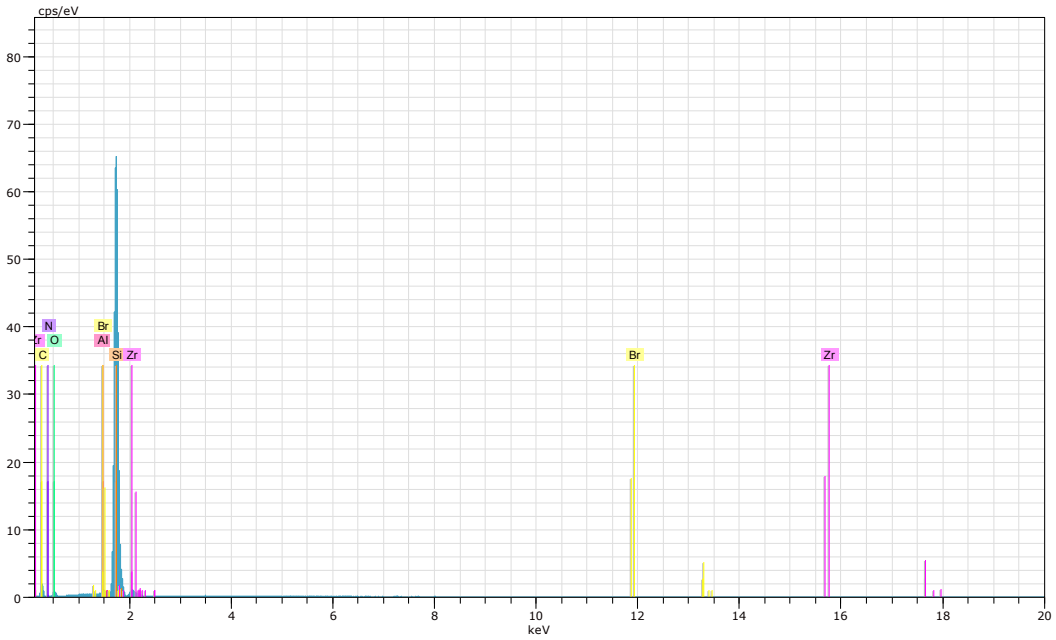

Fig. S3 SEM-EDS of UiO-66-NH-A.

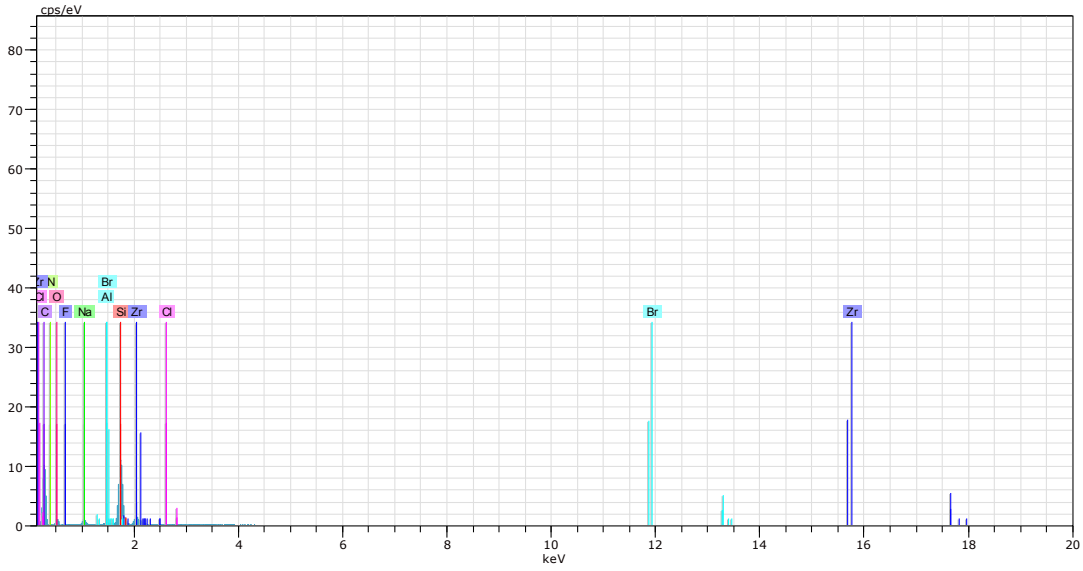

Fig. S4 SEM-EDS of 5-Fu-loaded, CP5-capped UiO-66-NH-A.

3. Association Constant (Ka) of CP5 and Ca^{2+}

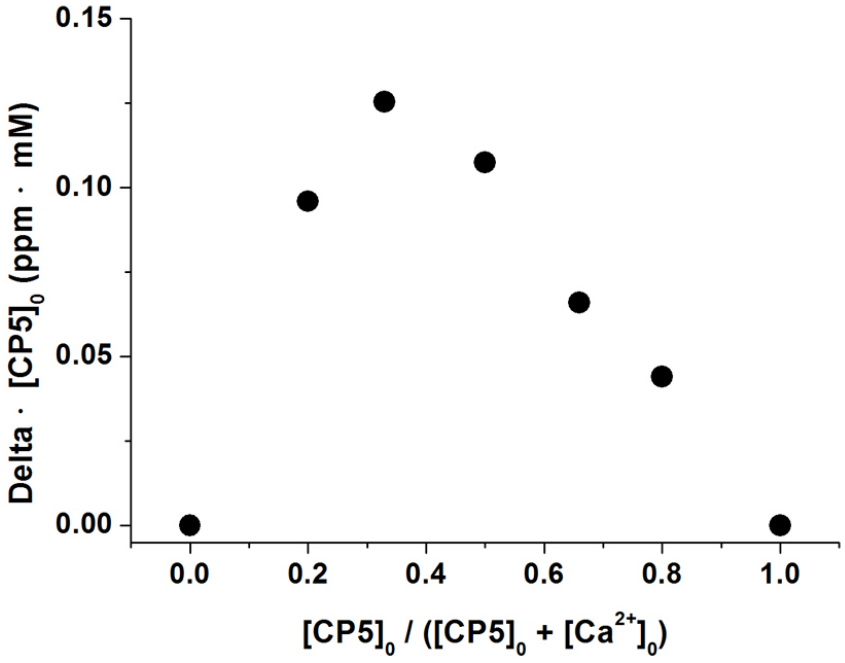

Fig. S5 Job plot showing the 1:2 stoichiometry of the complexation between CP5 and Ca^{2+} in D_2O using the proton NMR data for H_a. Delta is the chemical shift change of H_b. $[CP5]_0 + [Ca^{2+}]_0 = 5$ mM. $[CP5]_0$ and $[Ca^{2+}]_0$ are initial concentrations of CP5 and Ca^{2+}.

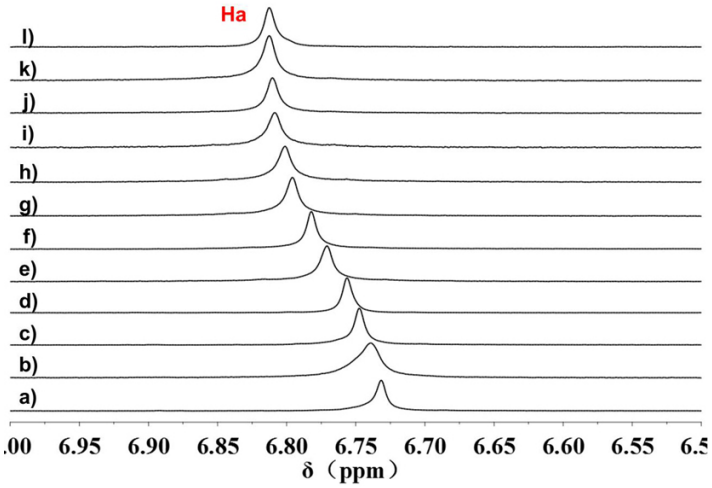

Fig. S6 Partial 1H NMR spectra (300 MHz, D_2O, 298 K) of CP5 at the concentration of 5 mM upon addition of Ca^{2+}: (a) 0 mM; (b) 0.904 mM; (c) 1.81 mM; (d) 2.71 mM; (e) 4.5 mM; (f) 6.78 mM; (g) 9.04 mM; (h) 11.3 mM; (i) 20 mM; (j) 30 mM; (k) 60 mM; (l) 100 mM. This set of data was used for the non-linear curve-fitting.

The association constant of CP5 with Ca^{2+} was calculated according to the reference.[S5]

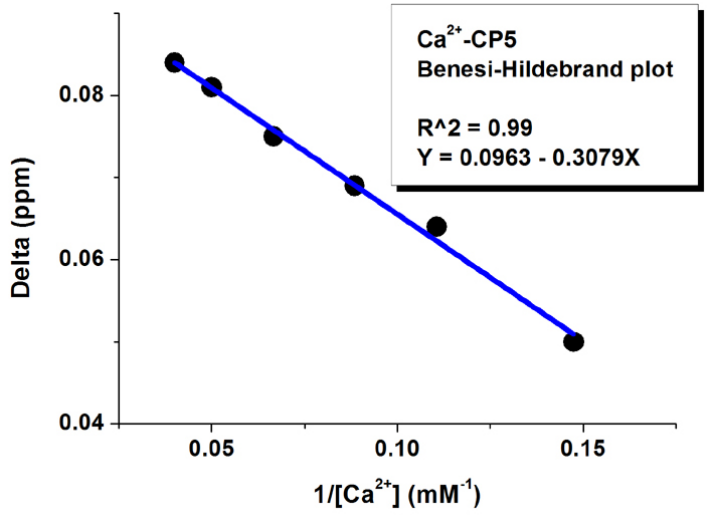

Fig. S7 Benesi-Hildebrand plot for the complexation of Ca^{2+} with CP5. Δ_0, the difference in δ values for H_a of CP5 in the uncomplexed and fully complexed species, was determined as the y-intercept of a plot of $\Delta = \delta - \delta_u$ versus $1/[Ca^{2+}]_0$ in the high initial concentration range of CP5. $\Delta_0 = 0.0963$ ppm.

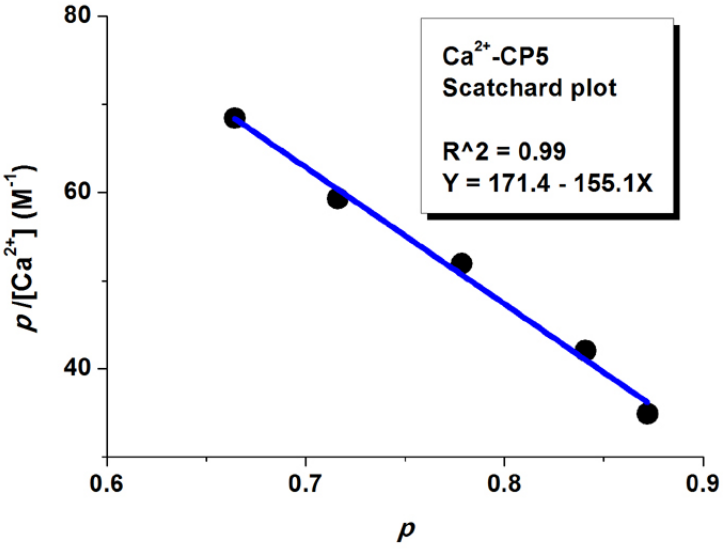

Fig. S8 Scatchard plot for the compexation of Ca^{2+} with CP5 in D_2O at RT. p = fraction of alkyl chains unit on CP5. Error bars in p: ± 0.03 absolute; error bars in p/[H]: ± 0.06 relative. The value of the K_{av} is 163.3 ± 11.5 M^{-1}.

4. UV Absorption Spectra of 5-Fu in Different Solutions Used for UV Analysis of Drug Release and Calibration Curve

The UV maximum absorption wavelength of 5-Fu same for all solutions used. They are assayed by the same calibration curve. The maximum absorption wavelength of 5-Fu is 265 nm, A = 17±1 C, b=1 cm.

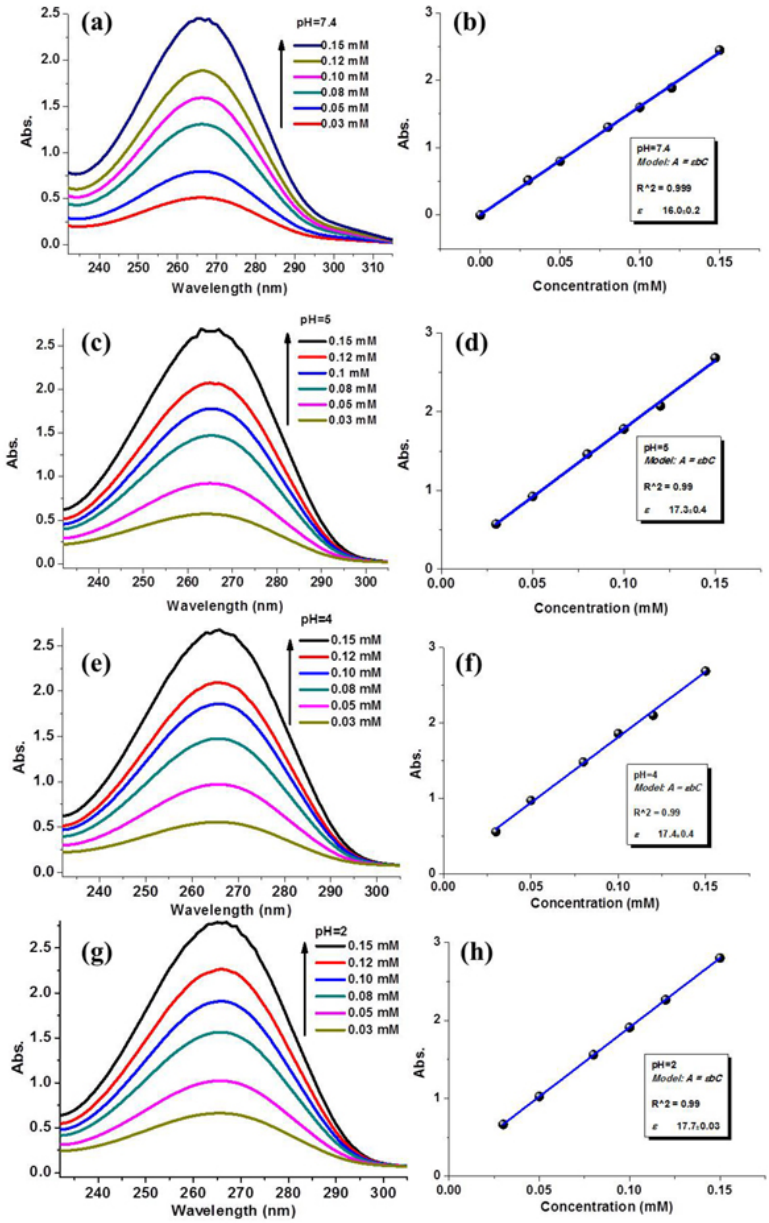

Fig. S9 UV absorption spectra of 5-Fu in buffer with different pH (7.4, 5, 4, 2) and its calibration curves. These results indicated that pH only has negligible influence to the maximum absorption wavelength of 5-Fu and its calibration curve.

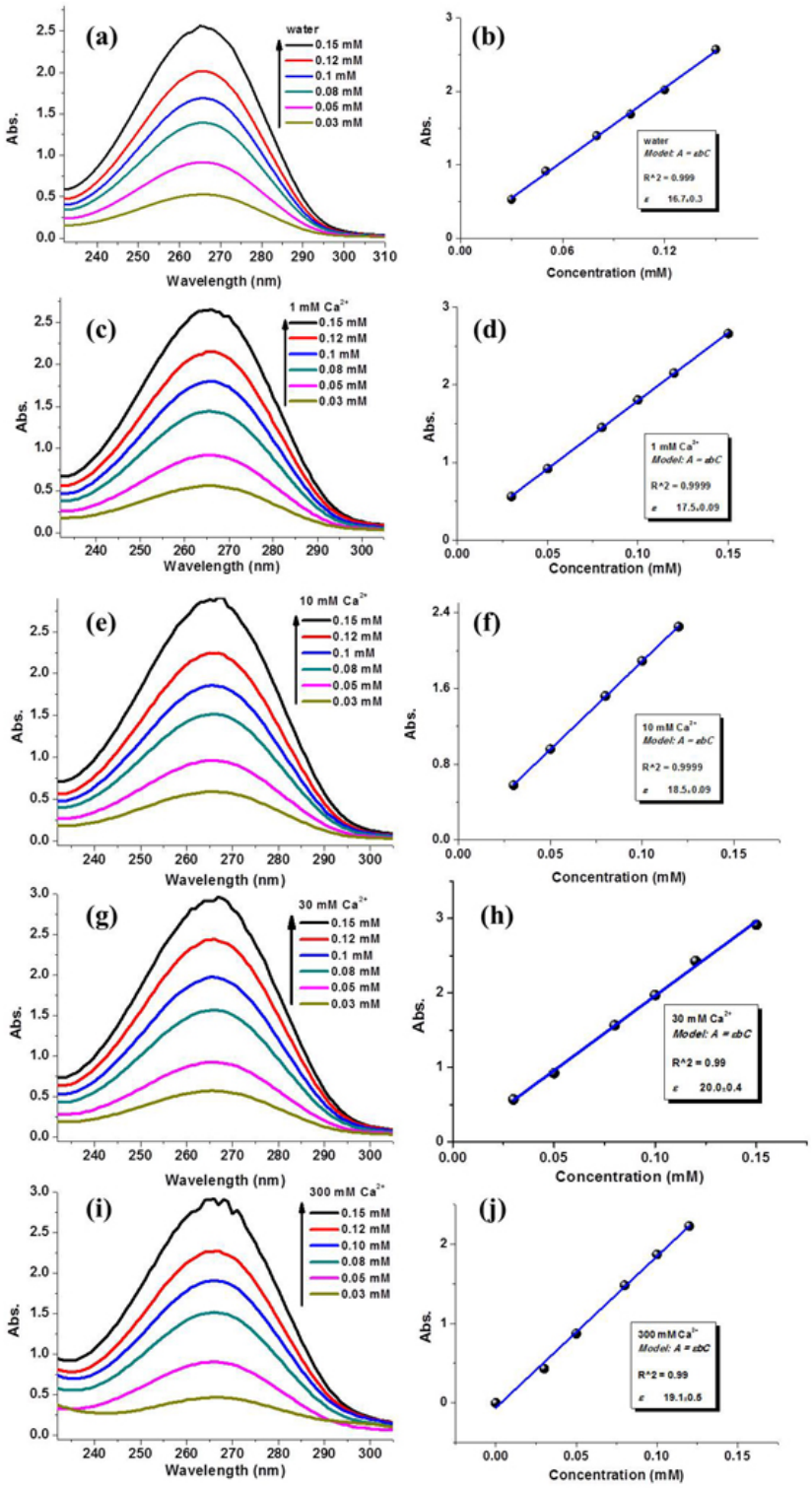

Fig. S10 UV absorption spectra of 5-Fu in Ca^{2+} solution (0, 1, 10, 30, 300 mM) and its calibration curves. These results indicated that Ca^{2+} concentration only has negligible influence to the maximum absorption wavelength of 5-Fu and its calibration curve.

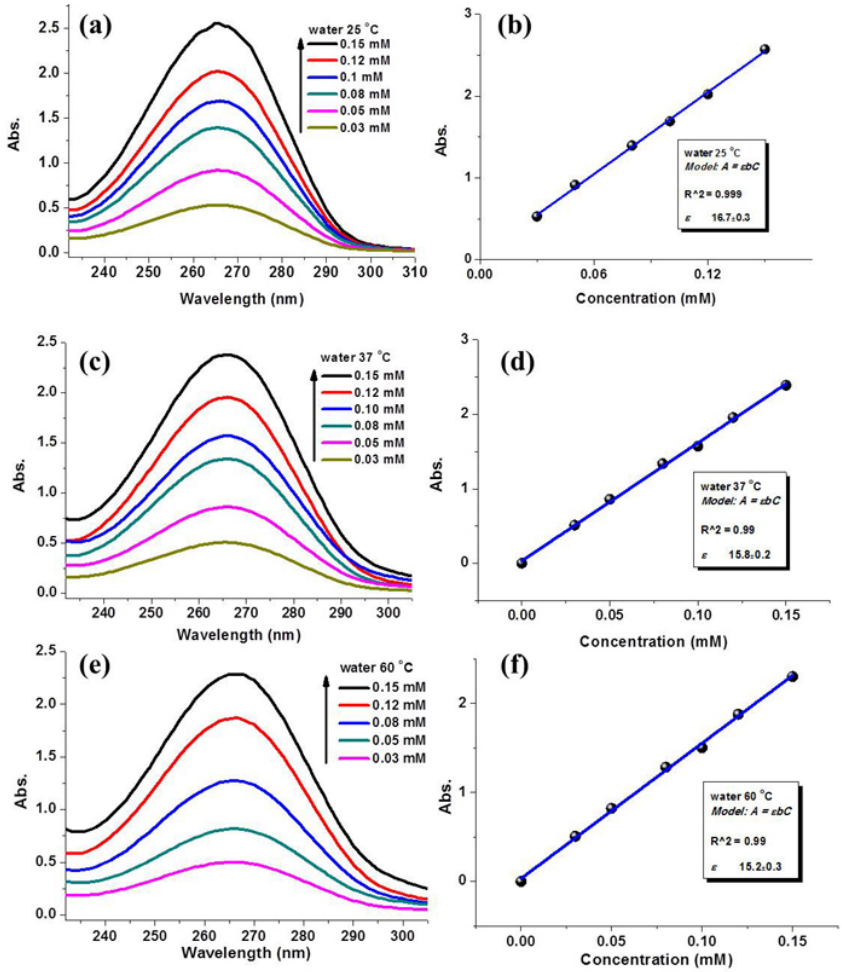

Fig. S11 UV absorption spectra of 5-Fu in water under different temperature (25 °C, 37 °C, 60 °C) and its calibration curves. These results indicated that temperature only has negligible influence to the maximum absorption wavelength of 5-Fu and its calibration curve.

5. Control Experiments

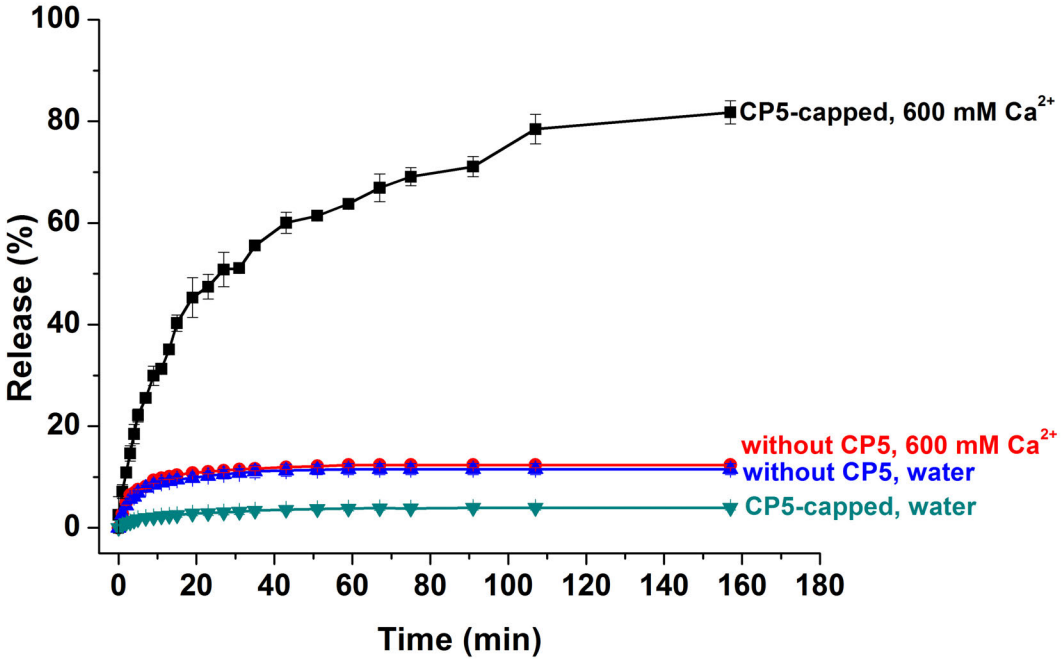

Fig. S12 Controlled release profiles of 5-Fu-loaded, CP5-capped UiO-66-NH-A and 5-Fu-loaded UiO-66-NH-A without CP5 capping, triggered by adding 600 mM Ca^{2+}.

6. References

S1. H. Li, D.-X. Chen, Y.-L. Sun, Y. B. Zheng, P. S. Weiss and Y.-W. Yang, *J. Am. Chem. Soc.,* 2013, **135**, 1570-1576.

S2. Y.-L. Sun, Y.-W. Yang, D.-X. Chen, G. Wang, Y. Zhou, C.-Y. Wang and J. F. Stoddart, *Small,* 2013, **9**, 3224-3229.

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S4. L.-L. Tan, H. Li, Y. Zhou, Y. Zhang, X. Feng, B. Wang and Y.-W. Yang, *Small*, 2015, **11**, 3807-3813.

S5. (a) F. Huang, L. N. Zakharov, A. L. Rheingold, M. Ashraf-Khorassani and H. W. Gibson, *J. Org. Chem.,* 2005, **70**, 809-813; (b) K. Zhu, J. He, S. Li, M. Liu, F. Wang, M. Zhang, Z. Abliz, H. Yang and F. Huang, *J. Org. Chem.,* 2009, **74**, 3905-3912; (c) L. Gao, C. Han, B. Zheng, S. Dong and F. Huang, *Chem. Commun*., 2013, **49**, 472-474.