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Supplementary Information

In *vitro* controlled release of theophylline based on metal-drug complexes

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1. Materials

Theophylline and fumaric acid were purchased from Aladdin reagent Co. (Shanghai, China). HPMC was obtained from Colorcon (Methocel K4M). MC was received from Guangfu fine chemical research Institute (Tianjin, China). The other chemicals used were of analytical grade and commercially available.

2. Experimental

2.1. Preparation of tablets

Theophylline (~100 mg), complex **1** (~100 mg) and complex **2** (~100 mg) were micronized and sieved using standard-mesh sieves (mesh size 75 μm), and placed in a 13-mm diameter of die and compressed directly by IR compressor under 20Mpa for 30s. Different compositions of TPL and excipient (50% HPMC, 40% HPMC + 10% MC, 25% HPMC + 25% MC w/w, total ~200 mg) were weighed and mixed well, then compressed directly by IR compressor under 20Mpa for 30s. Various compositions of complexes and excipient (50% HPMC, 40% HPMC + 10% MC, 25% HPMC + 25% MC w/w, total ~200 mg) were prepared in the same manner as above.

2.2. X-ray Data Collection and Structure Determinations.

X-ray single-crystal diffraction data for complexes **1** and **2** were collected on a Rigaku SCX-mini diffractometer at 293(2) K with Mo-Kα radiation (λ = 0.71073 Å) by ω scan mode. The program *CrystalClear*[1] was used for integration of the diffraction profiles. Both the structures were solved by direct methods using the SHELXS program of the SHELXTL package and refined by full-matrix least-squares methods with SHELXL (semi-empirical absorption corrections were applied using SADABS program)[2]. Metal atoms in each complex were located from the *E*-maps and other non-hydrogen atoms were located in successive difference Fourier syntheses and refined with anisotropic thermal parameters on F^2. The hydrogen atoms of the ligands were generated theoretically onto the specific atoms and refined isotropically with fixed thermal factors. However, the hydrogen atoms of the water molecules were added by difference Fourier maps.

2.3. General methods

IR spectra were measured on a Tensor 27 OPUS (Bruker) FT-IR spectrometer with KBr tablets. Elemental analyses (C, H and N) were performed on a Perkin-Elemer 240C analyzer. Thermogravimetric (TG) analyses were carried out on a Rigaku standard TG-DTA analyzer with a heating rate of 10 °C min^{-1} from ambient temperature to 700 °C, and an empty Al_2O_3 crucible was used as reference. The X-ray powder diffraction spectra (XRPD) were recorded on a Rigaku D/Max-2500 diffractometer at 40 kV, 100 mA for a Cu-target tube and a graphite monochromator. Simulation of the XRPD pattern was carried out by the single-crystal data and diffraction-crystal module of the Mercury (Hg) program version 1.4.2 available free of charge via the Internet at http://www.iucr.org.

2.4. In *vitro* release study

The release of theophylline from the tablets was conducted using paddle apparatus on a dissolution tester according the Chinese Pharmacopoeia. Deionized water was used as the dissolution medium and maintained at 37±0.5℃. The stirring speed was set at 50 rpm. Samples (5 ml) were withdrawn at specific time points, and the same volume of fresh dissolution medium was replaced. The concentration of the theophylline in each sample was determined by validated UV spectrophotometer at 272 nm. Several TPL solutions at different concentrations in deionized water were used as standards. The calibrated plot showed a good correlation coefficient > 0.99 (Figure S1). In all cases, six runs were carried out for each formulation. The accumulated amount of drug released at each sampling point was corrected with the dissolution medium. The release of drug from tablets was further fitted by Eq. (1) in order to propose the possible release mechanism.[3-4]

$$\left[\frac{M_t}{M_\infty}\right] = Kt^n \qquad (1)$$

Where M_t: the amount of drug released at time t; M_∞: total amount of drug in each tablet; K: the release rate constant; n: exponent constant. The constant n was usually related to the release mechanism of drug from dosage forms.

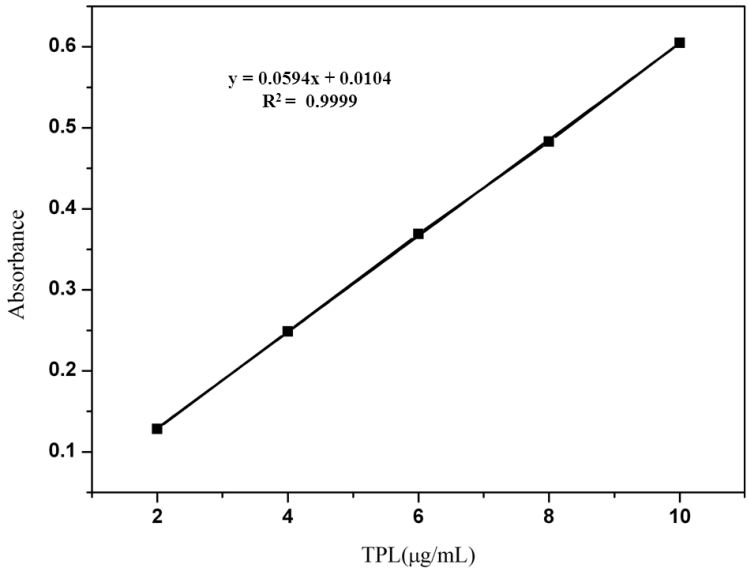


Figure S1. Calibration plot of standard TPL by UV method.

2.5 Evaluation of cytotoxicity

The cytotoxicity was determined using NIH-3T3 cells by the MTT method.[5] The metal-drug samples (**1** and **2**) diluted to suspension with sterile water, and TPL was dissolved with sterile water. NIH-3T3 cells at a density of 1×10^4/ml were seeded into 48-well plates. 50 μl samples of complexes or TPL were added to the plates with various concentrations (60, 120, 240 μg/ml) in a final volume of 300 μl well. After incubation, supernatants were removed, and 300 μl DMSO was added. Plates were placed on a shaking water bath at 37 °C for 20 min to solubilize the formazan products and the absorbance was recorded at 570 nm. Cells treated with blank medium without any sample were used as the negative control. They were treated by the same way as above. Every group had 4 replications. The percent of viability was expressed as the relative growth rate (RGR) as follows:

$$RGR\% = \frac{D_t}{D_{nc}} \times 100\% \qquad (2)$$

where D_t and D_{nc} are the absorbances of the tested sample and the negative control.

Reference

1. *CrystalClear*, Rigaku Corporation, Tokyo, Japan, 2008.

2. G. M. Sheldrick, SHELXTL NT Version 5.1. Program for solution and refinement of crystal structures, University of Göttingen: Germany, 1997.

3. P. L. Ritger and N. A. Peppas, *J. Control. Release*, 1987, **5**, 37.

4. P. L. Ritger and N. A. Peppas, *J. Control. Release*, 1987, **5**, 23.

5. W.-F. Zhang, H.-Y. Zhou, X.-G. Chen, S.-H. Tang and J.-J. Zhang, *J. Mater. Sci: Mater. Med.*, 2009, **20**, 1321.

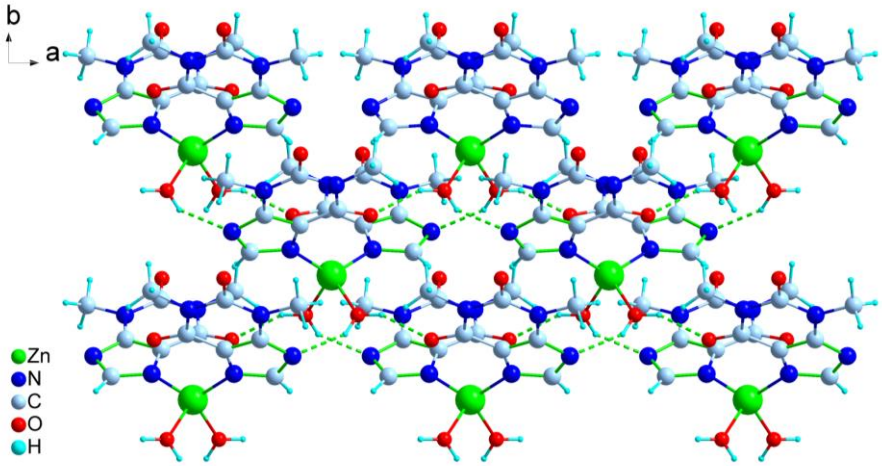


Figure S2. The 2D layer of **1** containing two types of hydrogen bonds including O-H···O and O-H···N (green dash lines stand for the hydrogen bonds).

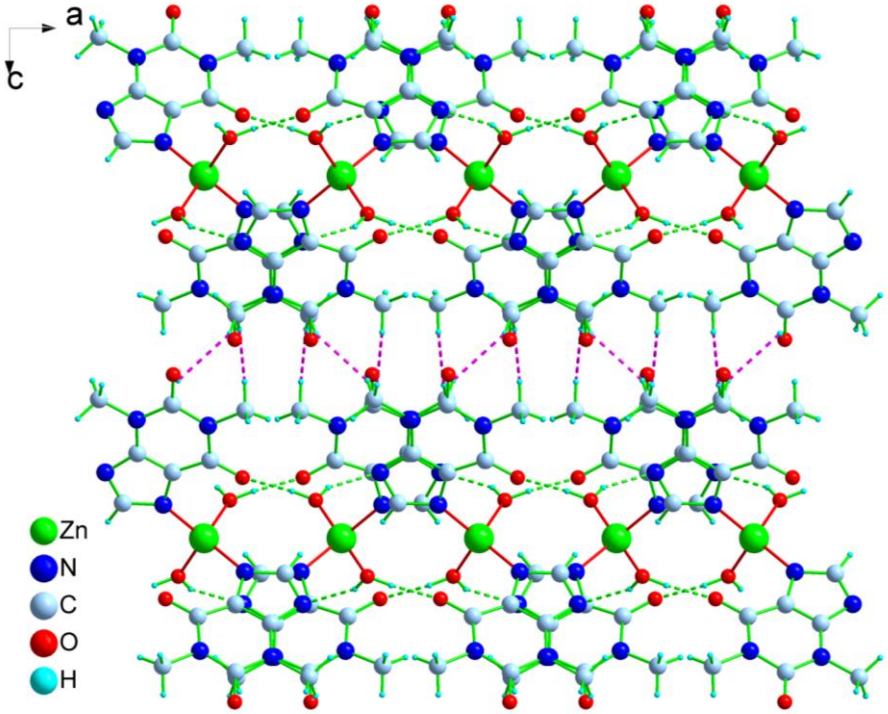


Figure S3. The 3D structure of **1** built via the hydrogen bonds and the weak interaction C-H···H-C (green dash lines stand for the hydrogen bonds, purple dash lines stand for the weak interactions.).

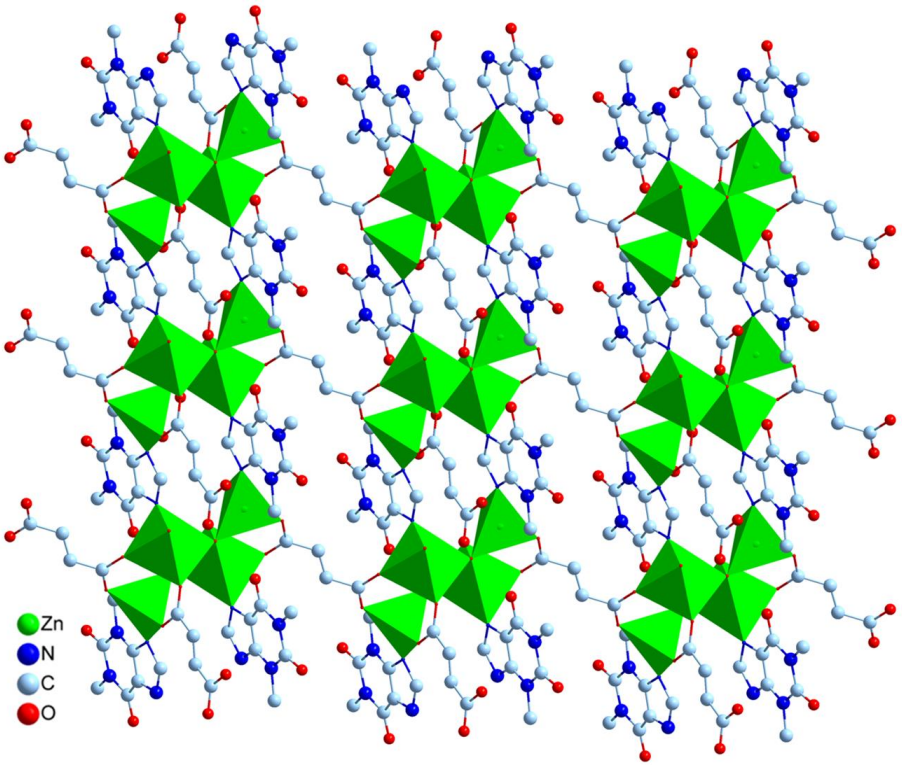


Figure S4. The 3D structure of **2** based on the $[Zn_4(\mu_3\text{-}OH)_2]^{6+}$ cluster (Hydrogen atoms have been omitted for clarity).

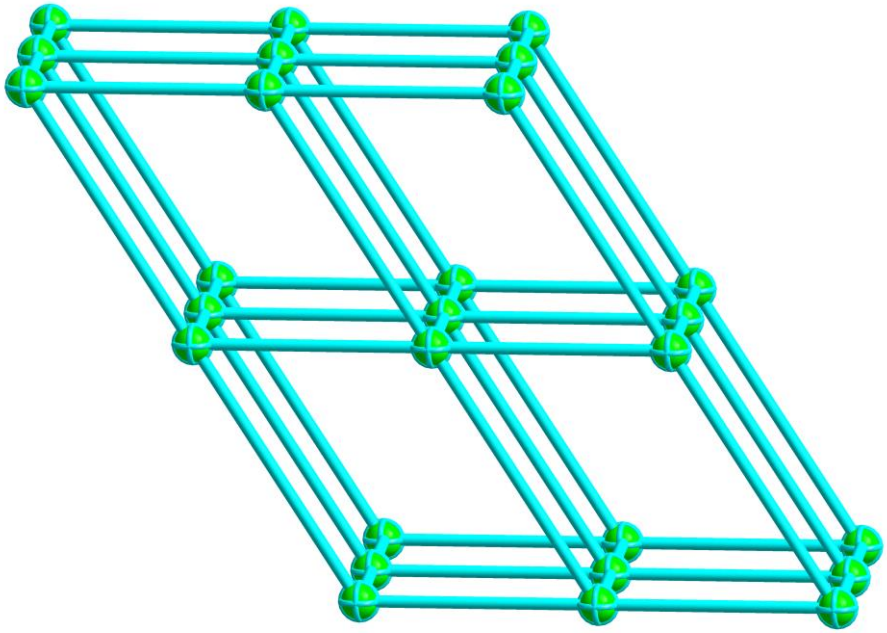


Figure S5. The 3D *pcu* topology of **2**.

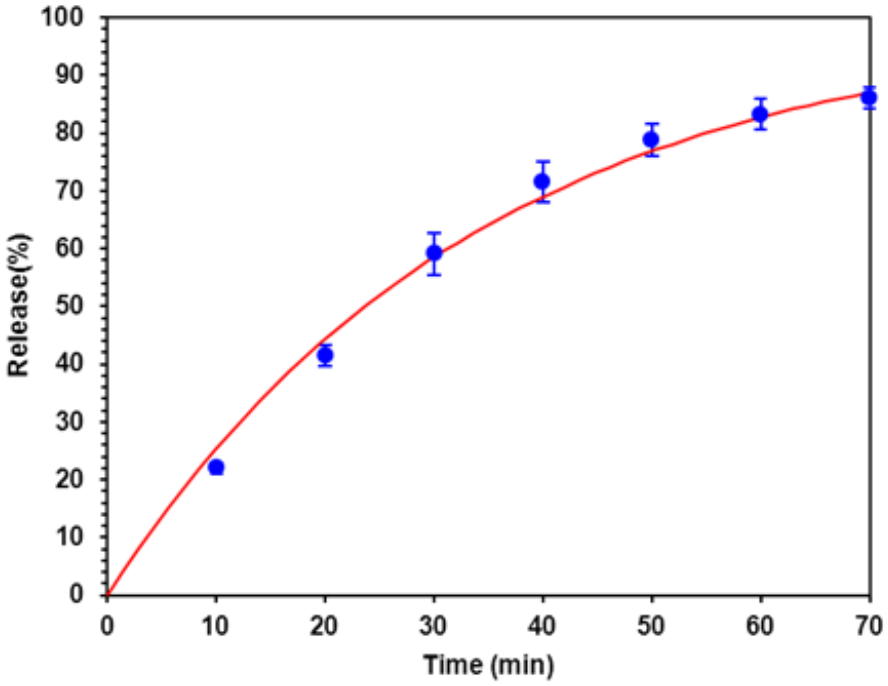


Figure S6. The release of TPL from the pure TPLs tablets.

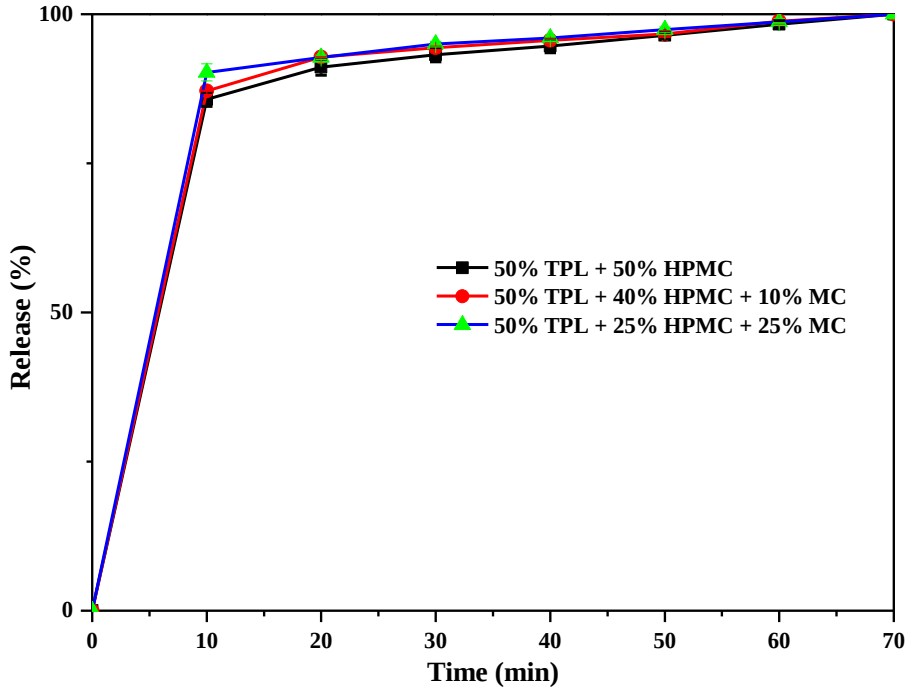
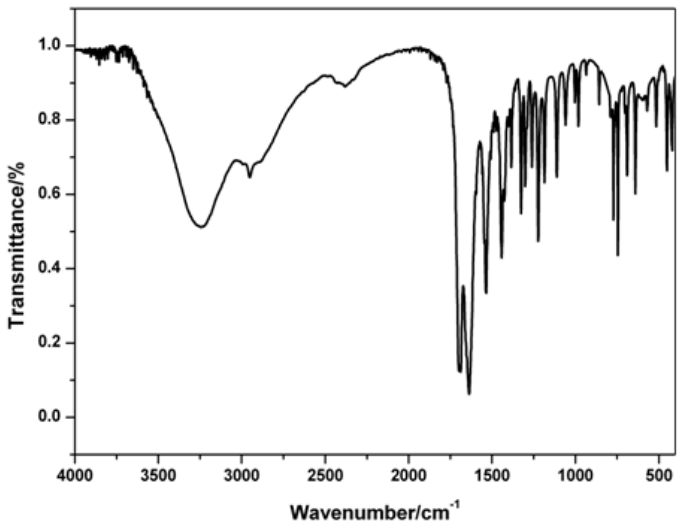
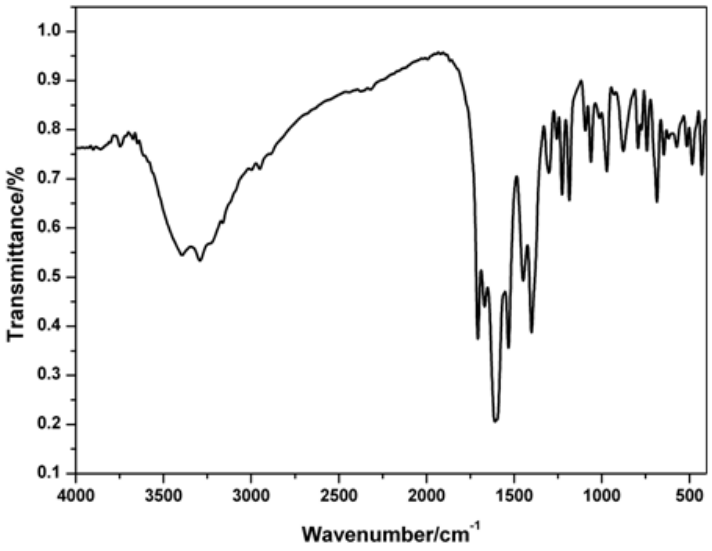


Figure S7. The release of TPL from the pure TPLs tablets with different composition.



(a)



(b)

Figure S8. The FTIR spectra of **1** (a) and **2** (b).

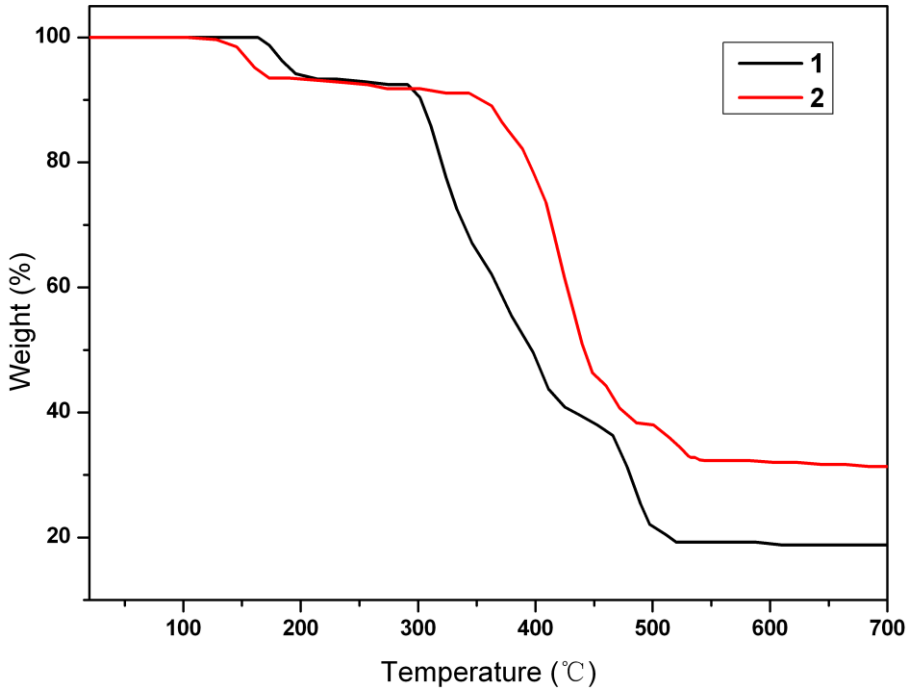


Figure S9. The thermal stabilities of **1** and **2**.

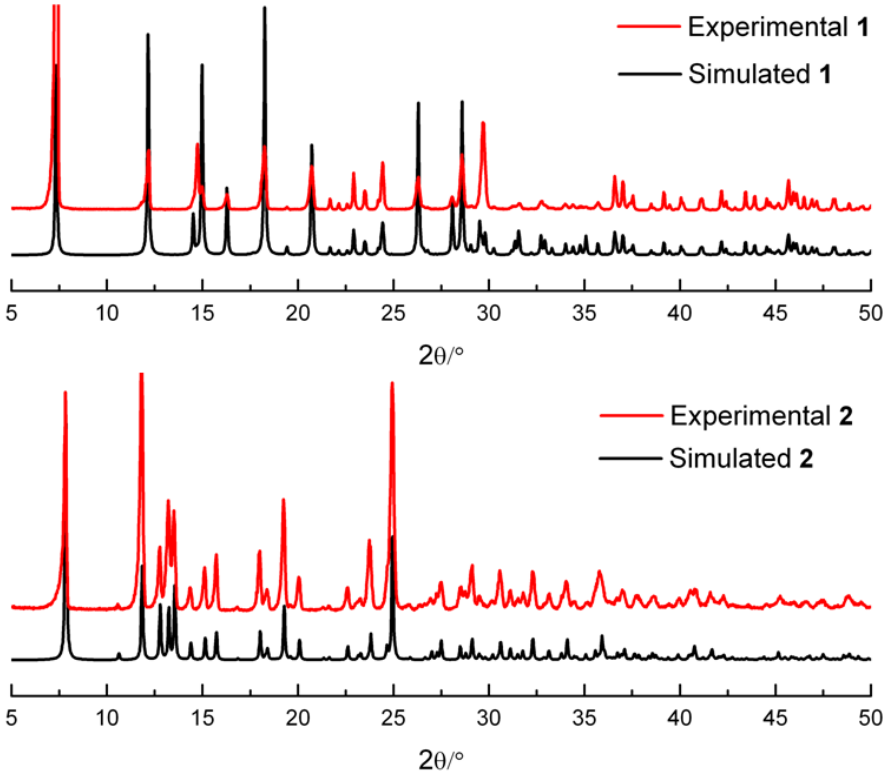


Figure S10. The XRPD spectra of **1** (top) and **2** (down).