Supplementary Information

Self-assembly of antifungal agent 5-fluorocytosine and nutrient *trans*-*p*-coumaric acid furnishes a cocrystallization clue with the potential to reduce toxicity and side effects for the drug: a case research of combining theory with experiment

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Section 1. The formulae related to planarity analysis

Firstly, a plane is fitted by least square method according to the coordinates of the atoms in the the investigated local region, and the plane is required to pass through the geometric centers of these atoms. The resulting plane is the best description of the plane in which the atom in question resides, and can be expressed by the plane equation Ax+By+Cz+D=0. The molecular planarity parameter (MPP), which is the square mean root deviation of each atom's distance fitting plane, can then be calculated, as shown in the below formula (1):[1]

$$MPP = \sqrt{\frac{1}{N_{atom}} \sum_i d_i^2} \qquad (1)$$

Where $\mathbf{N_{atom}}$ is the total number of atoms to be considered. $\mathbf{d_i}$ represents the distance of atom **i** from the fitting plane, which can be obtained by the following formula (2):

$$d_i = \frac{|Ax_i + By_i + Cz_i + D|}{\sqrt{A^2 + B^2 + C^2}} \qquad (2)$$

Distance **d** does not distinguish which side of the fitting plane the atom is on. In order to distinguish, Lu Tian defined the signed distance $\mathbf{d_s}$ of the distance fitting plane,[1] that is, the absolute value sign of the above formula (2) is removed, and $\mathbf{d_s}$ values are positive and negative corresponding to atoms on different sides of the fitting plane, as following formula (3):

$$d_i^s = \frac{Ax_i + By_i + Cz_i + D}{\sqrt{A^2 + B^2 + C^2}} \qquad (3)$$

The span of deviation from plane (SDP) parameters are defined as follows, where $\mathbf{d^s_{max}}$ and $\mathbf{d^s_{min}}$ are the most positive and negative values of $\mathbf{d_s}$ respectively for all atoms considered, as following formula (4):[1]

$$SDP = d^s_{\max} - d^s_{\min} \qquad (4)$$

References

(1) Lu, T. *J. Mol. Model* **2021,** *27*, 263.

Section 2. Supplementary figures

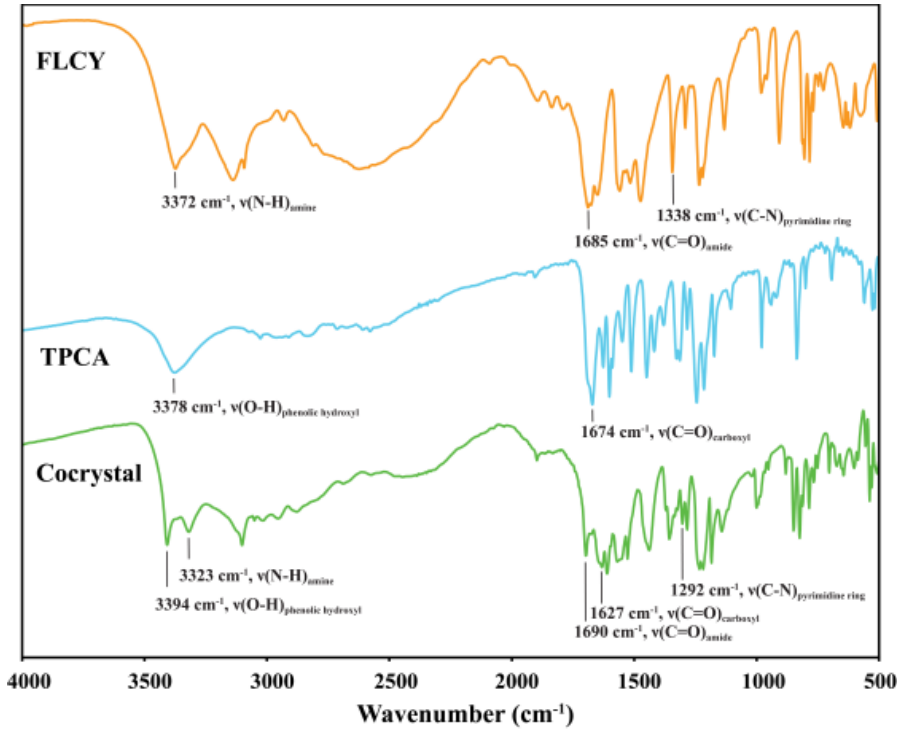

Fig. S1 FT-IR spectra of FLCY, TPCA and cocrystal FLCY-TPCA.

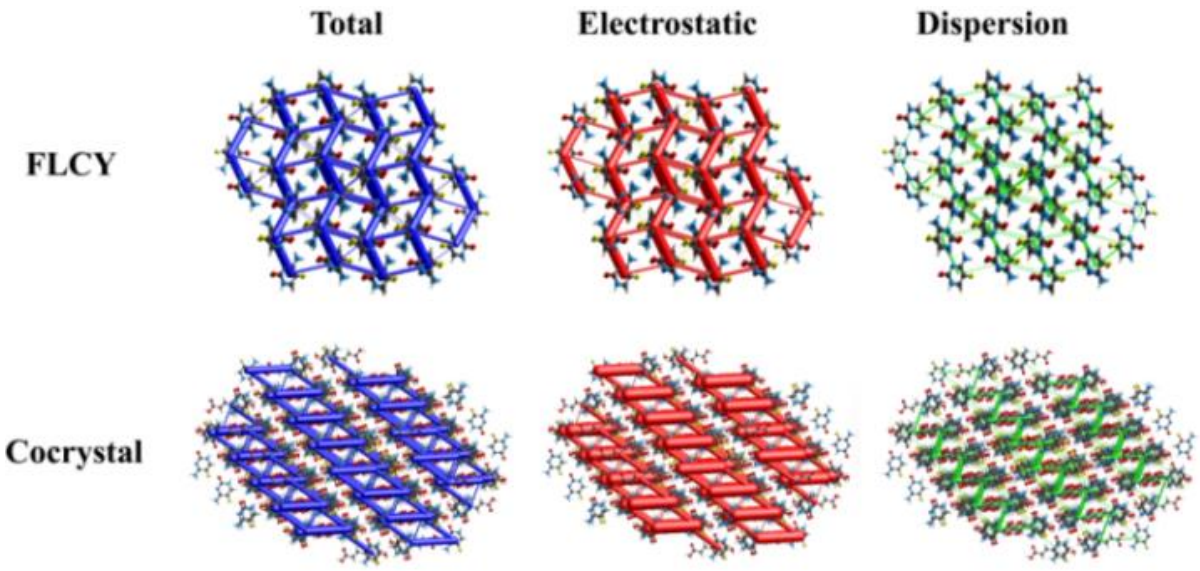

Fig. S2 FLCY and cocrystal: energy-frameworks for total interaction energies (blue) with the component of electrostatic (red) and dispersion (green). All drawings adopt the same cylinder scale and H atoms have been omitted for clarity.

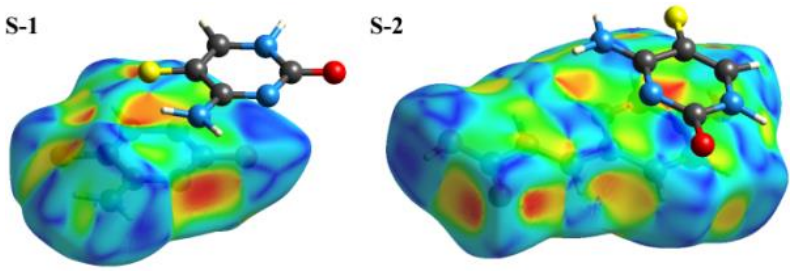

Fig. S3 The graph of Hirshfeld surface for the S-1 and S-2.

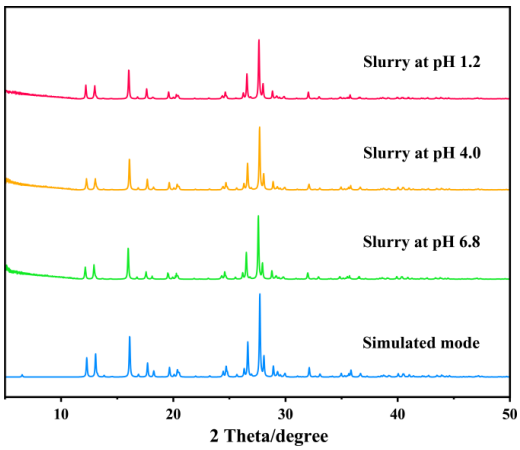

Fig. S4 PXRD comparison of the cocrystal's simulated pattern and the residual solids after the powder dissolution measurements.

Table S1. pH values measured in different media after solubility tests.

Solution	pH (dissolution media)		
	1.20	4.00	6.80
pH (FLCY-I solution)	1.89	4.17	6.89
pH (FLCY-II solution)	1.93	4.21	6.92
pH (cocrystal solution)	1.31	4.13	6.84

FLCY-I and FLCY-II represent Forms I and II of FLCY, respectively.

Table S2. pH values measured in different media after IDR tests.

Solution	pH (dissolution media)		
	1.20	4.00	6.80
pH (FLCY-I solution)	1.25	4.03	6.81
pH (FLCY-II solution)	1.27	4.06	6.86
pH (PM solution)	1.23	4.01	6.79
pH (cocrystal solution)	1.21	4.02	6.82

FLCY-I and FLCY-II represent Forms I and II of FLCY, respectively.