

## Clues from cocrystals: A ternary solid, polymorphism, and rare supramolecular isomerism involving resveratrol and 5-fluorouracil

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### Supplemental Information

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Figure S2. Overlay of PXRD patterns of A) **5-fu**; B) **bpe**; C) **4(5-fu)·(bpe)<sup>4</sup>**; D) **4(5-fu)·(bpe)** (simulated from crystal structure); and E) **4(5-fu)·(bpe)** (experimental).

4. NMR spectrum and analysis

Figure S3. <sup>1</sup>H NMR of ternary cocrystal **(5-fu)·(resv)·(bpe)**.

### 1. Reagents and Experimental

5-fluorouracil and resveratrol were purchased from Oakwood Chemicals, 1,2-bis(4-pyridyl)ethylene was purchased from TCI Chemicals. Methanol was purchased from Sigma-Aldrich. All chemicals were used as received and without further purification.

Liquid-assisted grinding (LAG) experiments were carried out in an FTS-1000 shaker mill using stainless steel jars.

**Preparation of single crystals of (5-fu)·(resv)·(bpe).** An equimolar mixture of **resv** (0.17 mmol), **bpe** (0.17 mmol) and **5-fu** (0.17 mmol) was combined in MeOH (2.0 mL) to afford plate-like single crystals.

**Preparation of single crystals of 4(5-fu)·(bpe) form II.** An equimolar mixture of **5-fu** (0.13 mmol) and **bpe** (0.13 mmol) was combined in acetone (2.0 mL) to afford prism-like single crystals.

**Preparation of (5-fu)·(resv)·(bpe) via liquid-assisted grinding (LAG).** An equimolar mixture of **resv** (0.13 mmol) **5-fu** (0.13 mmol) and **bpe** (0.13 mmol) was milled with 20  $\mu$ L of MeOH in a 5mL stainless steel jar at 20 Hz for 30 min.

**Preparation of 4(5-fu)·(bpe) via LAG.** A mixture of **5-fu** (0.54 mmol) and **bpe** (0.13 mmol) was milled with 20  $\mu$ L of acetone in a 5mL stainless steel jar at 20 Hz for 30 min.

## 2. Single-crystal X-ray diffraction (SCXRD) measurements

SCXRD data were collected on a Bruker Nonius Kappa CCD single crystal X-ray diffractometer using MoK $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ). Reflections were harvested from  $\varphi$  and  $\omega$  scans with an intensity threshold of  $I > 2\sigma(I)$ . Data collection, reduction, and cell refinement were accomplished using the Bruker Apex2 software suite. Using Olex2,<sup>1</sup> structure solution and refinement were accomplished using SHELXT<sup>2</sup> and SHELXL,<sup>3</sup> respectively. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms associated with carbon atoms were refined in geometrically constrained positions.

Table S1. Summary of crystallographic data for (5-fu)·(resv)·(bpe) and (5-fu)·(bpe).

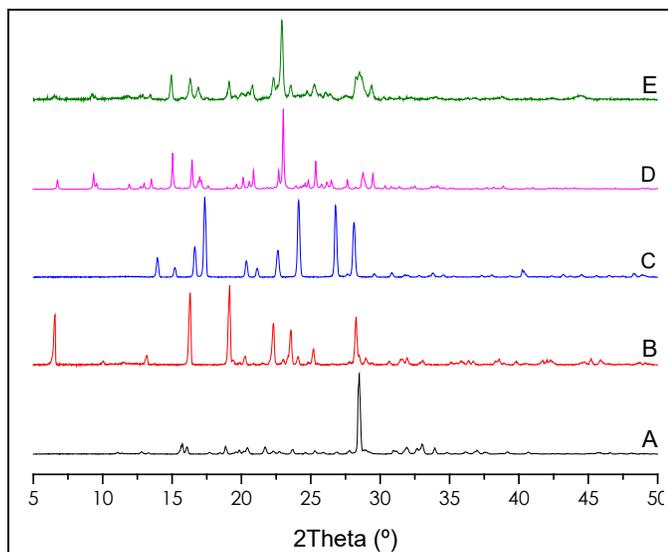
Crystal data <sup>a</sup>	(5-fu)·(resv)·(bpe)	4(5-fu)·(bpe)
Chemical formula	C <sub>4</sub> H <sub>3</sub> FN <sub>2</sub> O <sub>2</sub> ·C <sub>14</sub> H <sub>12</sub> O <sub>3</sub> ·C <sub>12</sub> H <sub>10</sub> N <sub>2</sub>	C <sub>28</sub> H <sub>22</sub> F <sub>4</sub> N <sub>10</sub> O <sub>8</sub>
MW (g mol <sup>-1</sup> )	540.54	702.55
Space group	<i>P</i> $\bar{1}$	<i>P</i> 2 <sub>1</sub> / <i>n</i>
<i>a</i> (Å)	9.4819(9)	9.1087(9)
<i>b</i> (Å)	10.652(1)	10.997(1)
<i>c</i> (Å)	13.506(1)	14.935(1)
$\alpha$ (°)	76.407(5)	90
$\beta$ (°)	85.696(5)	93.732(5)
$\gamma$ (°)	88.382(5)	90

$V$ (Å <sup>3</sup> )	1322.1(2)	1492.7(3)
$Z$	2	2
$\mu$ (mm <sup>-1</sup> )	0.099	0.134
$\rho_{\text{calcd}}$ (g/cm <sup>3</sup> )	1.358	1.563
$R_1^b$	0.0583	0.0388
$wR_2^c$	0.1656	0.1128
$\text{Goof on } F^2$	0.974	1.050
CCDC	2050224	2050223

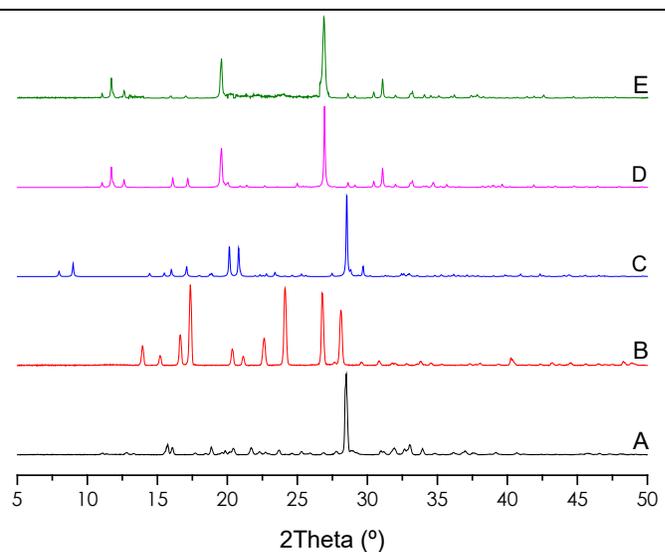
<sup>a</sup> $\lambda$  (Mo-K $\alpha$ ) = 0.71073 Å. <sup>b</sup> $I \geq 2\sigma(I)$ . <sup>c</sup> All data.

### 3. Powder X-ray diffraction measurements

Powder X-ray diffraction (PXRD) data were collected on a Bruker D8 Advance X-ray diffractometer using CuK $\alpha_1$  radiation ( $\lambda = 1.5418$  Å) in the range 5–45° (scan type: coupled TwoTheta/Theta; scan mode: continuous PSD fast; step size: 0.019°) (40 kV and 30 mA).



**Figure S1.** Overlay of PXRD patterns of A) 5-fu; B) resv; C) bpe; D) (resv)·(5-fu)·(bpe) (simulated from crystal structure); and E) (resv)·(5-fu)·(bpe) (experimental).



**Figure S2.** Overlay of PXRD patterns of A) 5-fu; B) bpe; C) 4(5-fu)·(bpe)<sup>4</sup>; D) 4(5-fu)·(bpe) (simulated from crystal structure); and E) 4(5-fu)·(bpe) (experimental).

#### 4. NMR spectrum and analysis

$^1\text{H}$  NMR spectra for **(5-fu)·(resv)·(bpe)** was collected using a Bruker Avance-300 NMR spectrometer operating at 300 MHz.  $^1\text{H}$  chemical shifts were referenced from the  $^1\text{H}$  chemical shifts of DMSO- $d_6$  (2.50 ppm). The  $^1\text{H}$  spectrum with resonance assignments for **(resv)·(5-fu)·(bpe)** is provided below (Figure S3). Resonances for **resv** ( $\text{H}_a\text{-H}_f$ ), **5-fu** ( $\text{H}_c$ )<sup>6</sup> and **bpe** ( $\text{H}_i\text{-H}_k$ ) were assigned according to published spectra.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  9.55 (s, 1H), 9.20 (s, 2H), 8.60 (dd,  $J = 4.6, 1.5$  Hz, 4H), 7.77 (d,  $J = 6.1$  Hz, 1H), 7.69 – 7.47 (m, 6H), 7.39 (d,  $J = 8.6$  Hz, 2H), 6.99 – 6.70 (m, 4H), 6.37 (d,  $J = 2.0$  Hz, 2H), 6.11 (t,  $J = 2.0$  Hz, 1H).

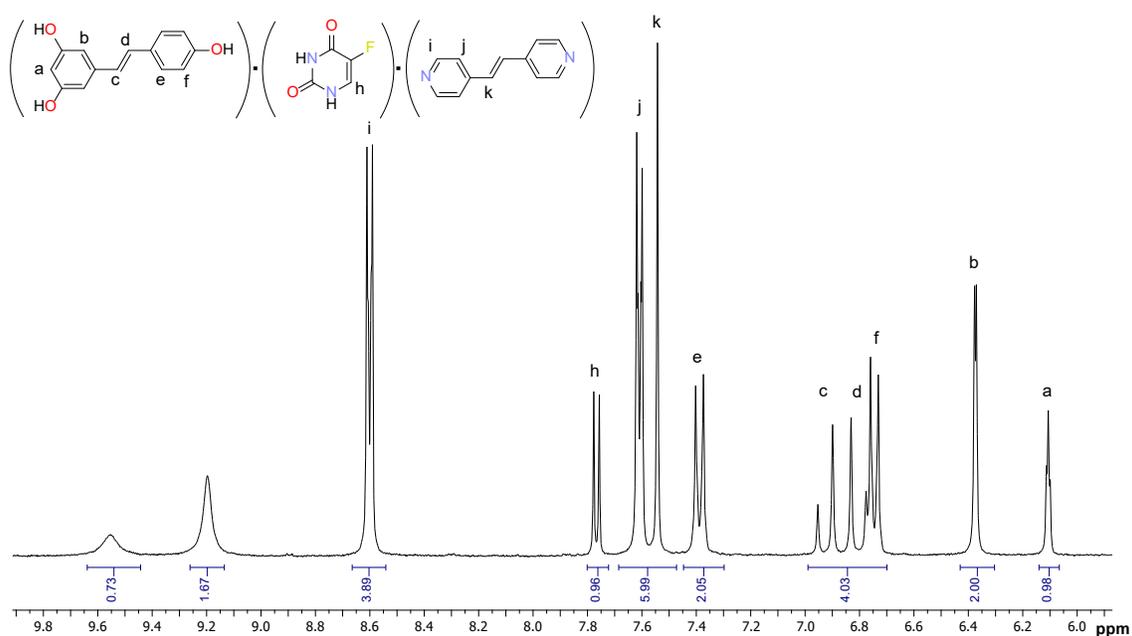


Figure S3.  $^1\text{H}$  NMR of ternary cocrystal **(5-fu)·(resv)·(bpe)**.

#### References

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