Electronic Supplementary Material (ESI) for CrystEngComm

Supplementary Information

Hydrogen Bond Synthon Competition in the Stabilization of Theophylline Cocrystals

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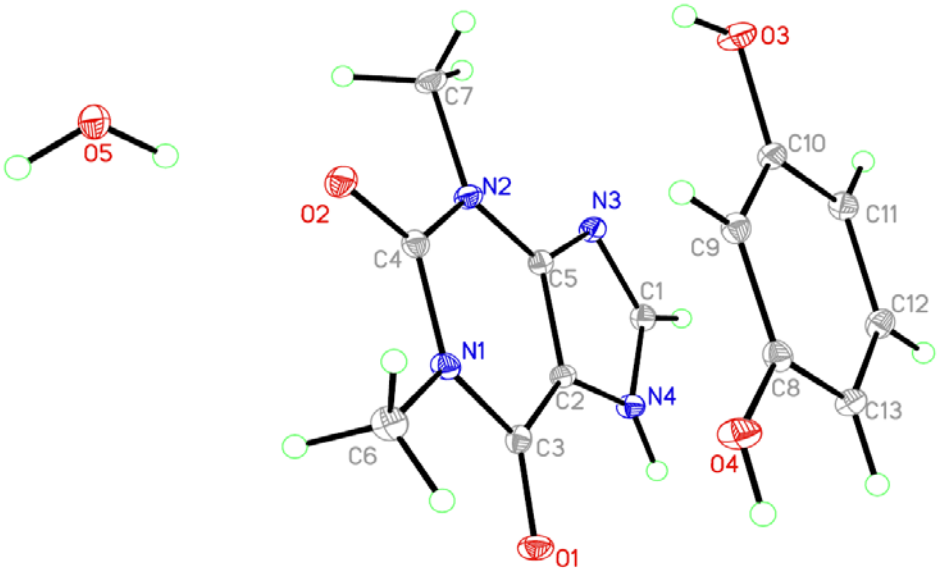
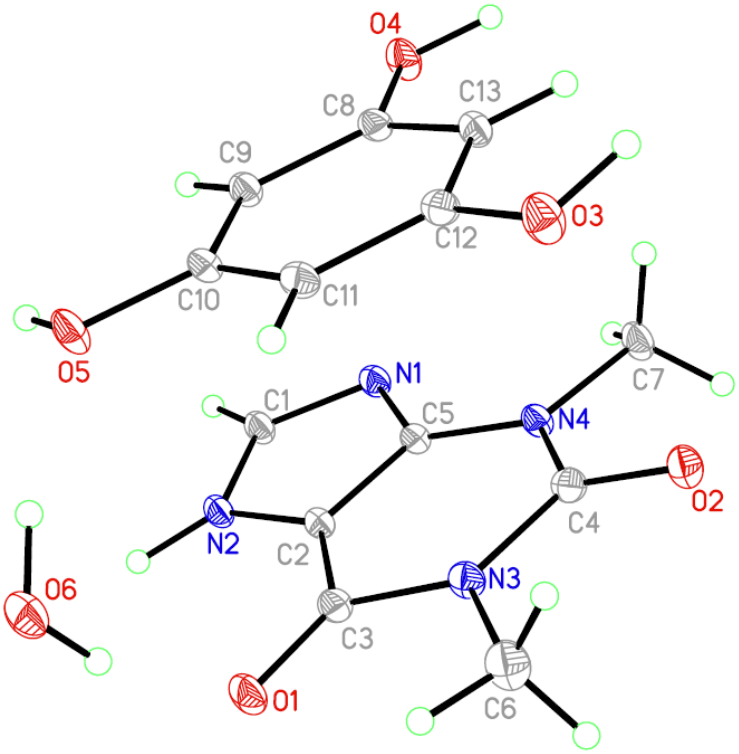
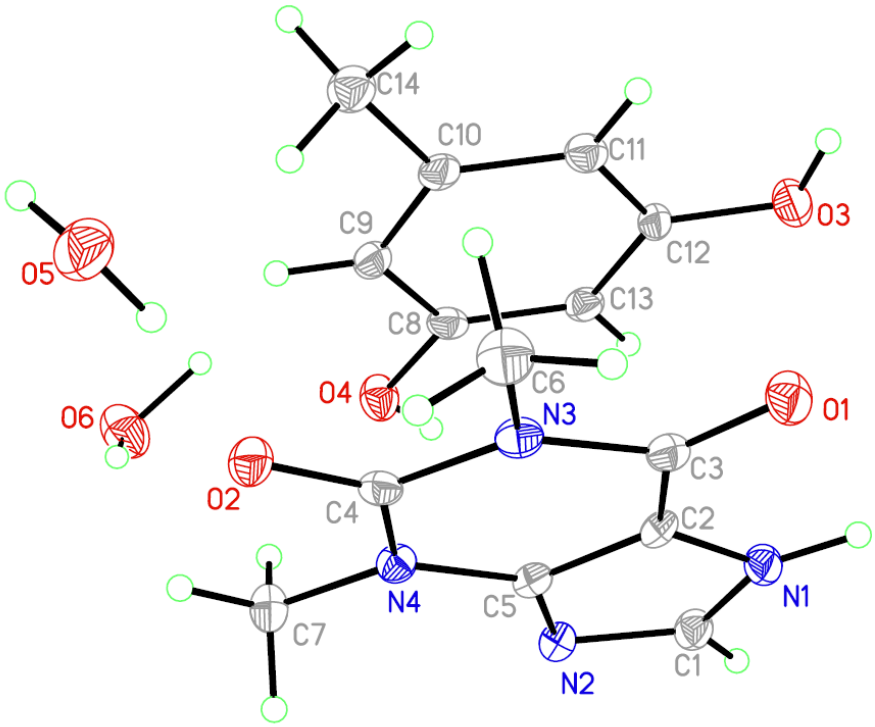
Figure S1 ORTEP of cocrystals **1-7**.



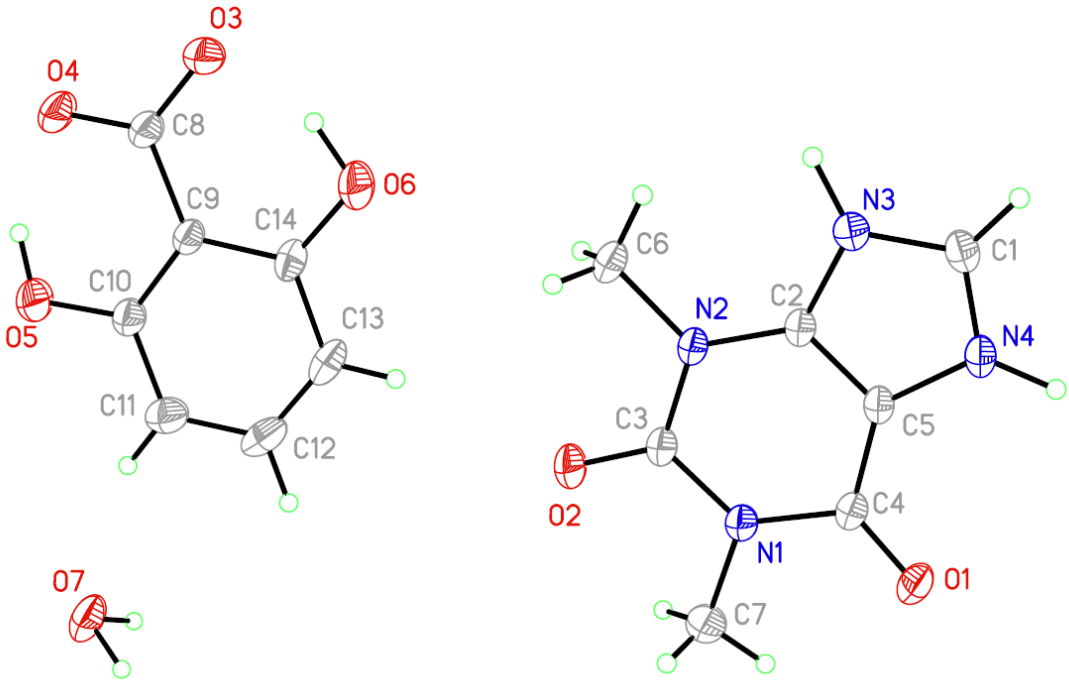
(a) Cocrystal **1 [Theo•Res•H_2O]**



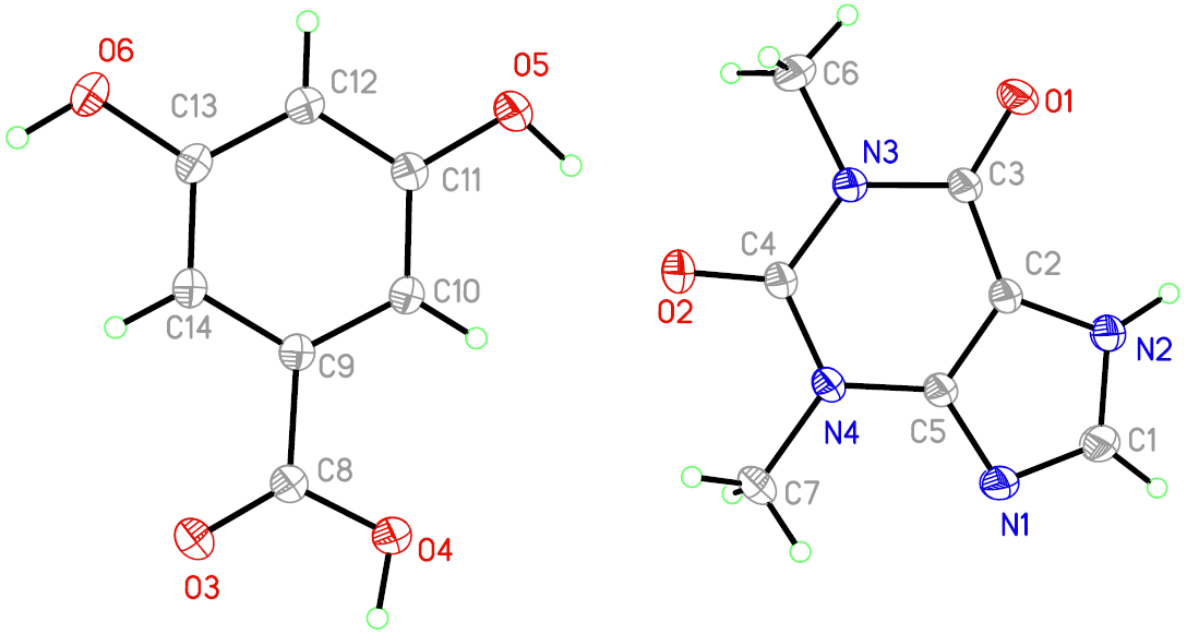
(b) Cocrystal **2 [Theo•Phu•H_2O]**



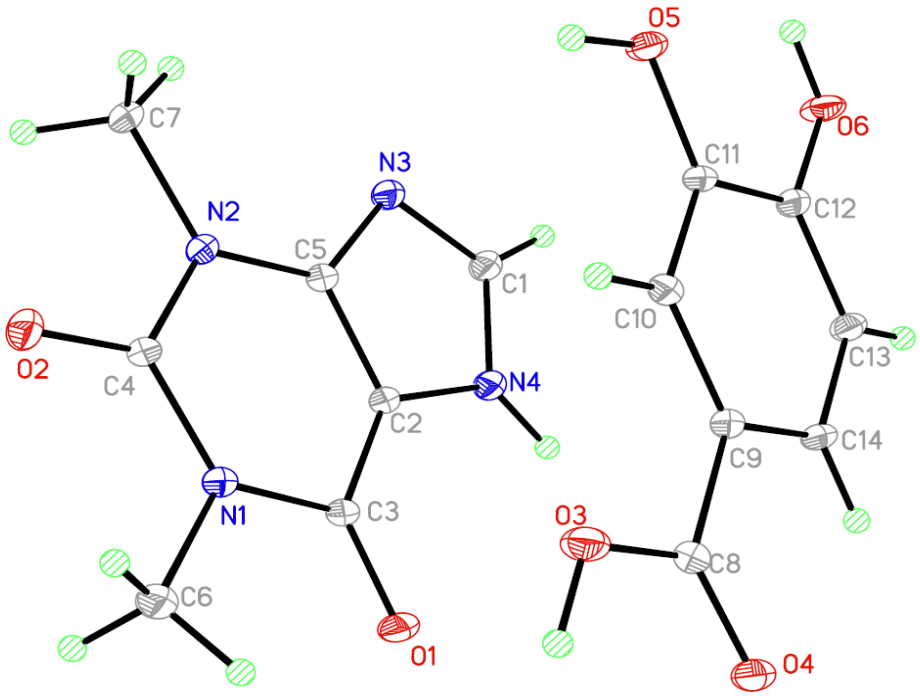
(c) Cocrystal **3 [Theo•Orc•2H$_2$O]**



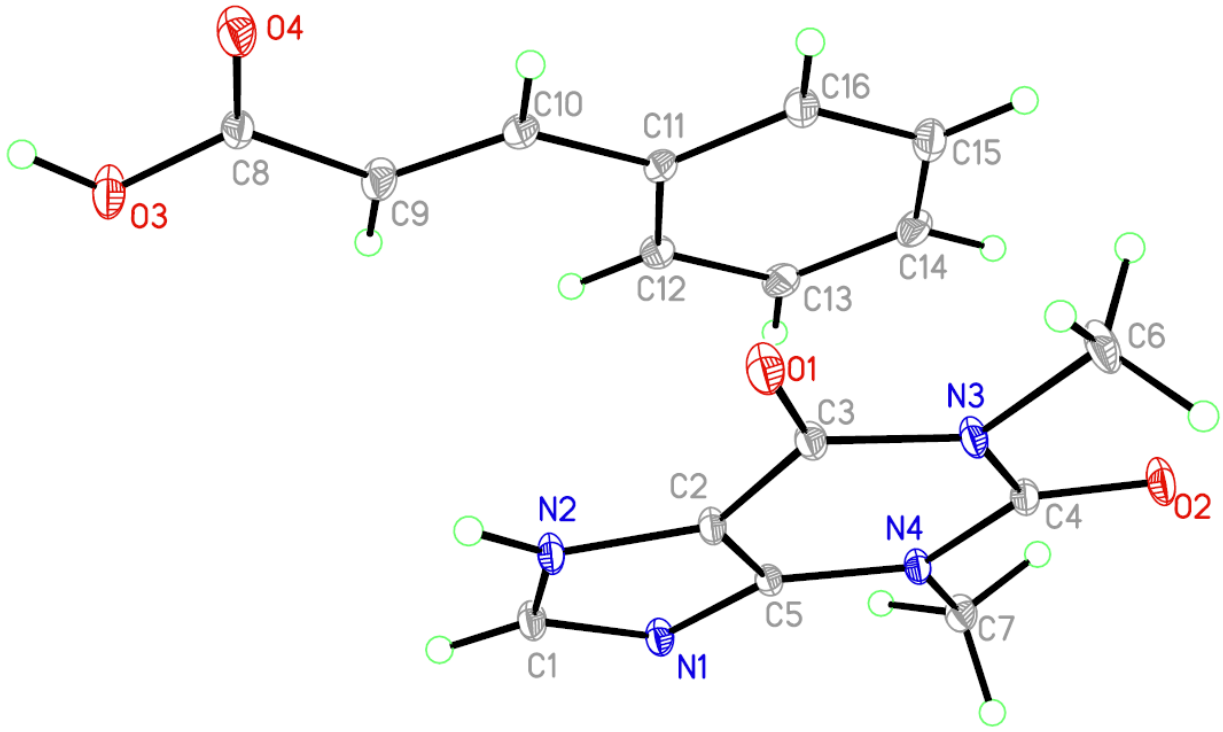
(d) Cocrystal/salt **4 [Theo•2,6-DHBA•H$_2$O]**



(e) Cocrystal **5 [Theo•3,5-DHBA]**

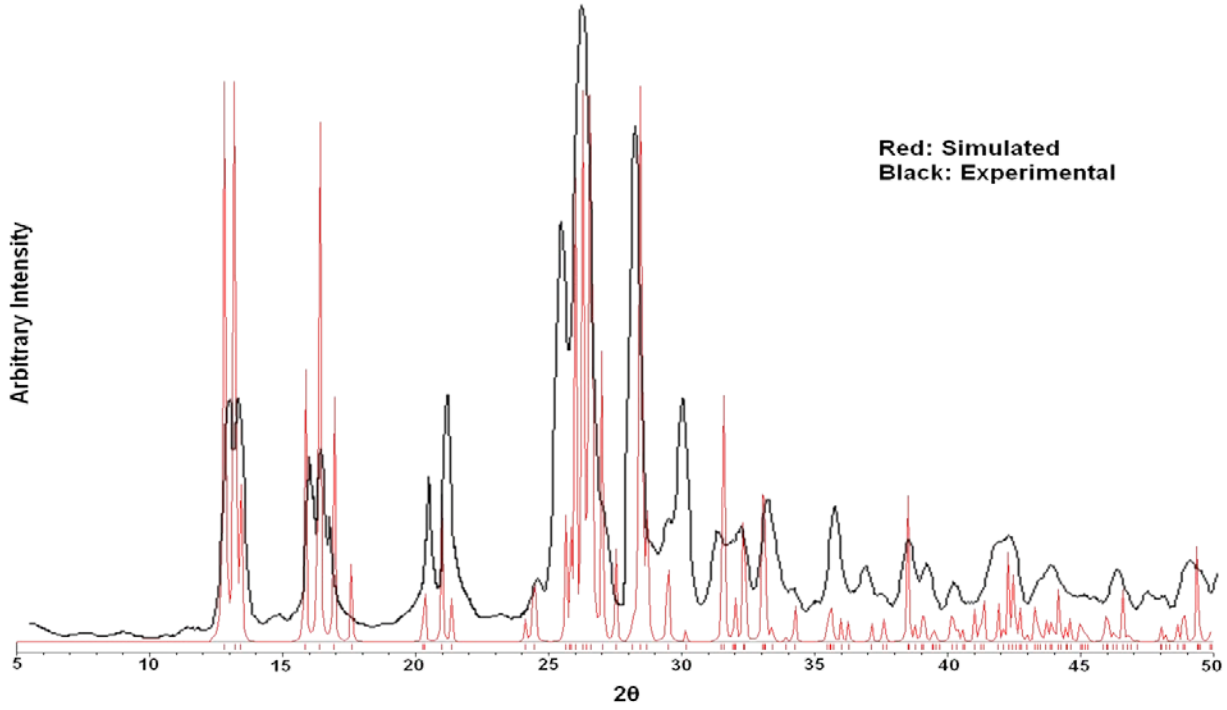


(f) Cocrystal **6 [Theo•3,4-DHBA]**

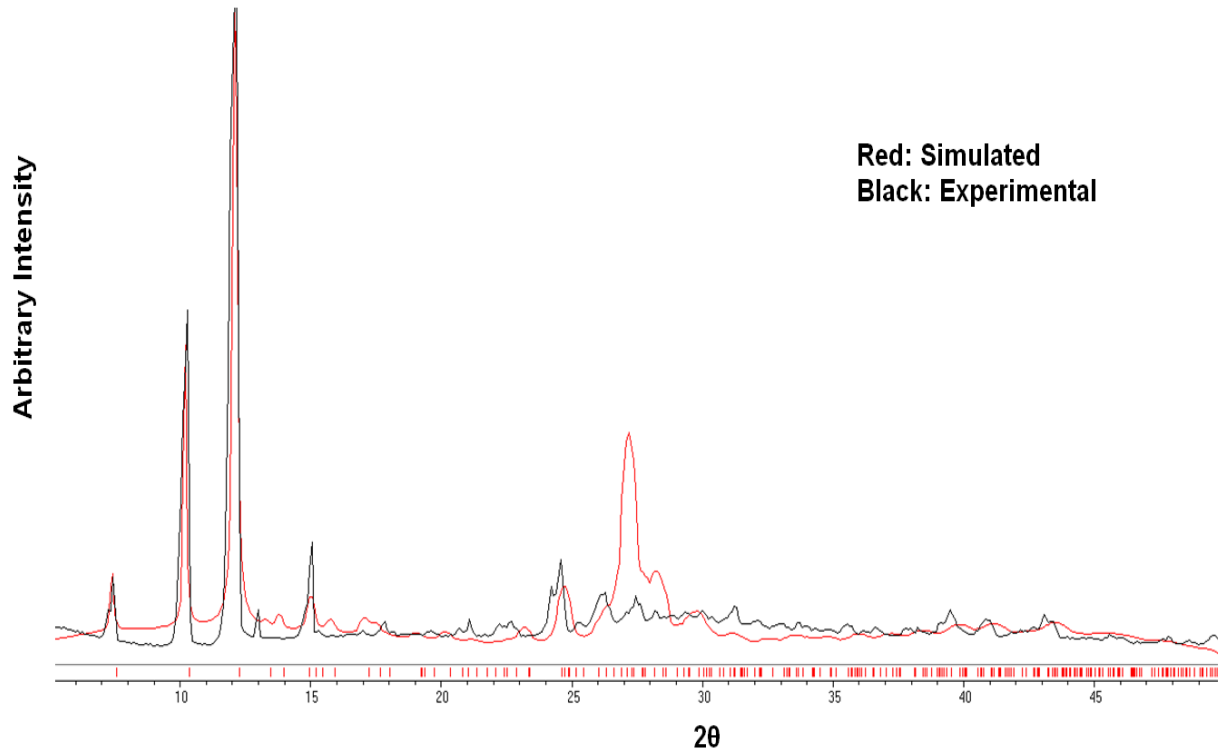


(g) Cocrystal **7 [Theo•CA]**

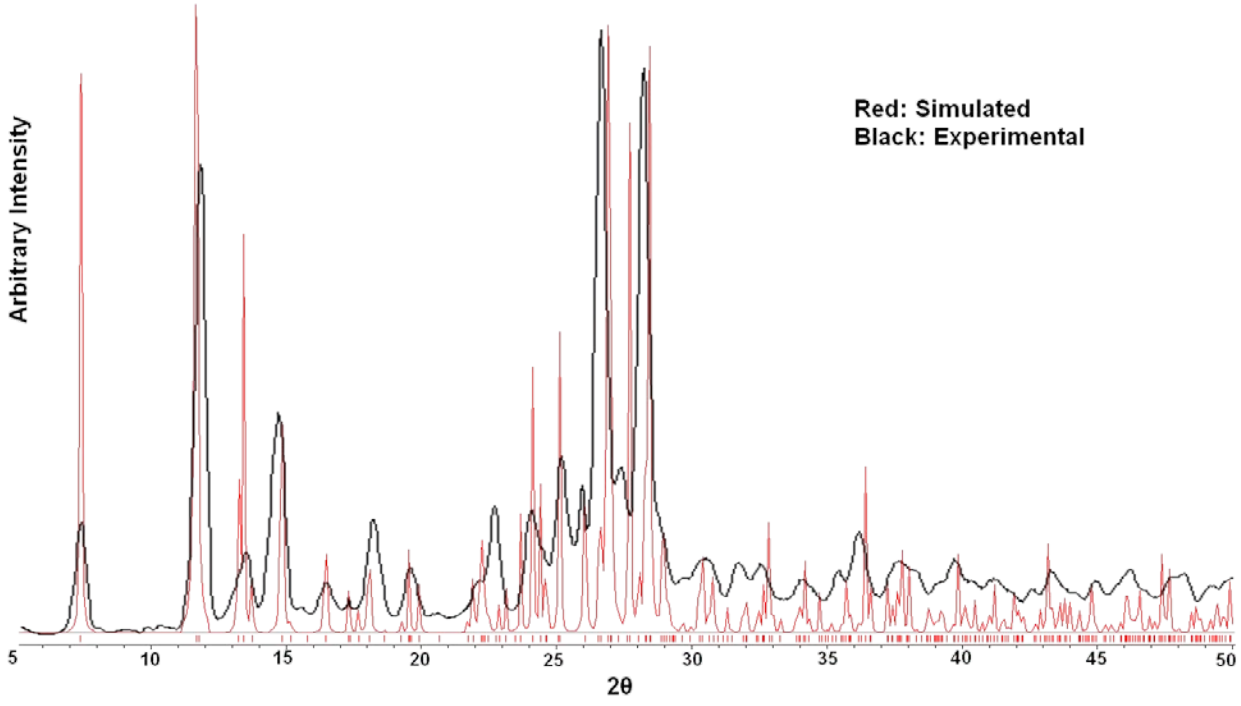
Figure S2 Powder X-ray diffraction of cocrystals **1-7** compared with simulated from corresponding crystal structure. Slight shifting of few peaks from the original crystal structure is due to the data collection temperature difference (Crystal structure at 100K, experimental PXRD at 298K for cocrystals **1** to **4**) which is not corrected during Reitvelt refinement.



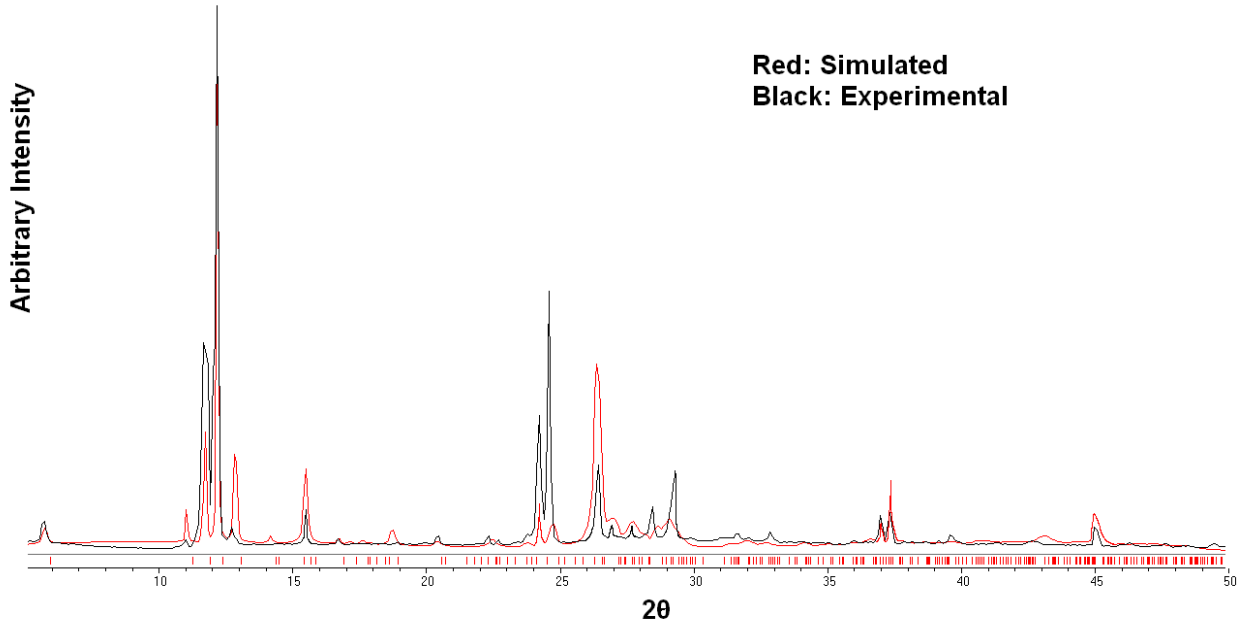
(a) Cocrystal **1 [Theo•Res•H_2O]** (overlay only)



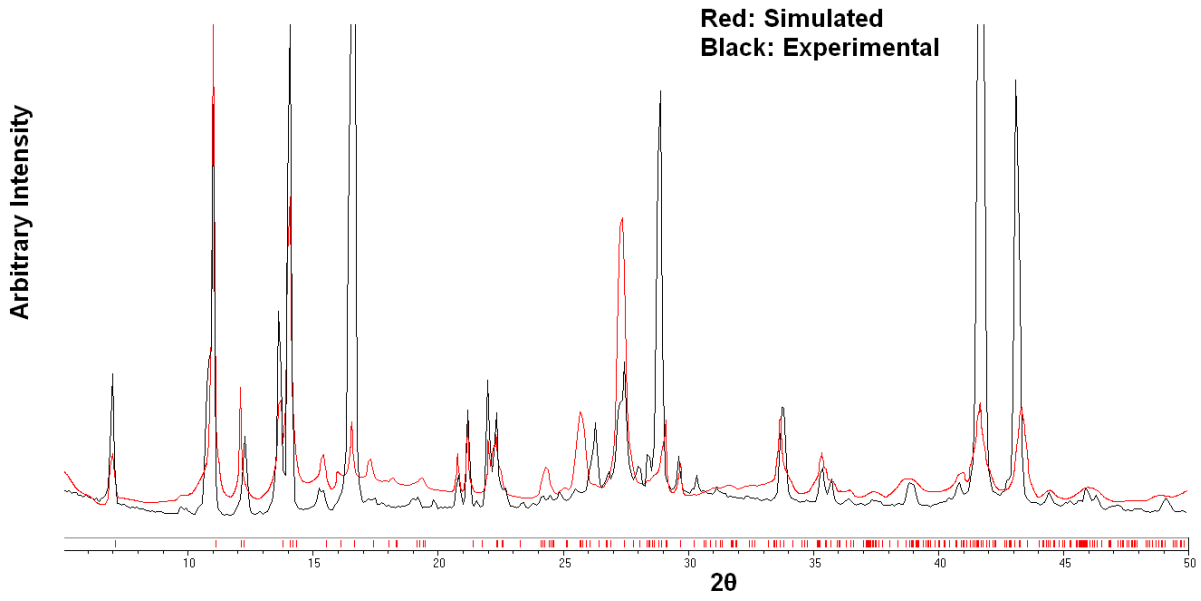
(b) Cocrystal **2 [Theo•Phu•H_2O]**



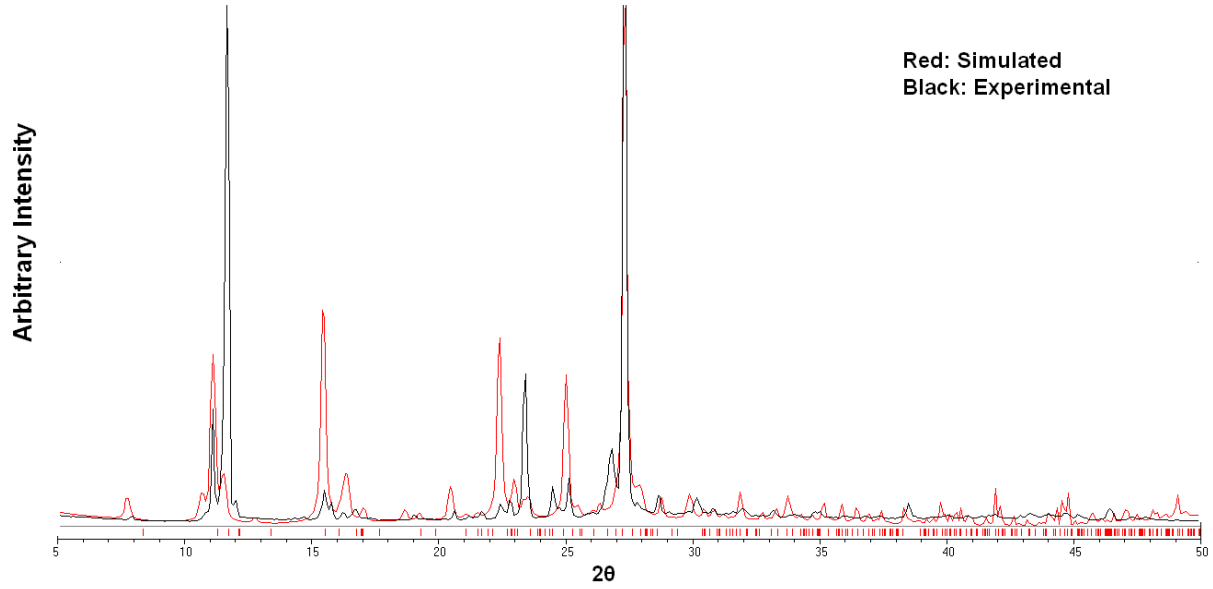
(c) Cocrystal **3 [Theo•Orc•2H_2O]** (overlay only)



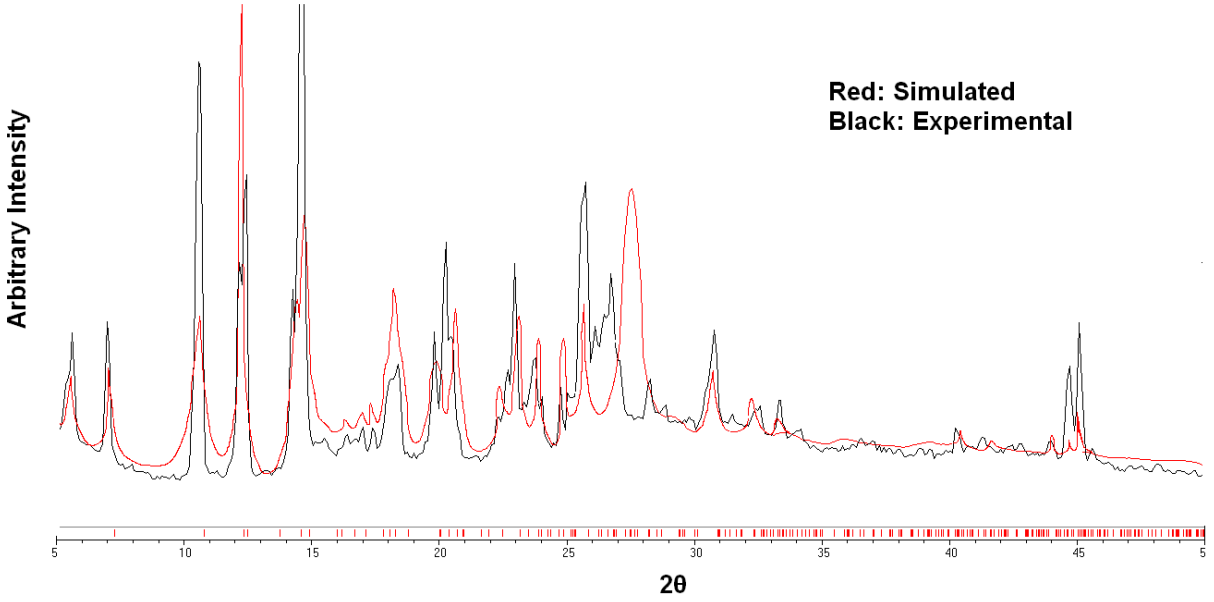
(d) Cocrystal **4 [Theo•2,6-DHBA•H_2O]**



(e) Cocrystal **5 [Theo•3,5-DHBA]**



(f) Cocrystal **6 [Theo•3,4-DHBA]**



(g) Cocrystal **7 [Theo•CA]**

Solubility determination of cocrystals 1-7 using UV-Vis spectroscopy:

Method: UV spectrometry was used to determine the water solubility of the cocrystals. For this, a series of standard solution of the cocrystals were prepared. The absorbance of the standard solution of each cocrystal was measured and the calibration curve with absorbance vs. conc. was plotted. The concentration of the unknown solution, C_u of the cocrystal measured from the slope and intercept of the calibration curve. Cocrystal concentration vs. absorbance curve is linear as it follows Beer's law.

The standard solution in water of the cocrystals were prepared with 0.1, 0.2, 0.3, 0.4 mmol concentration in a 25 mL volumetric flask. A saturated solution of the cocrystals in water, considered as unknown solution was prepared at constant temperature using jacketed vessel. For all experiments Millipore water was taken and considered as blank for UV absorption. Experiments were repeated for 3 times to optimize the result.

Solubility parameter table of the coformer and cocrystals

Coformer	*Coformer solubility mg/mL (mmol/mL)	$^{\$}$Theophylline solubility mg/mL (mmol/mL)	Cocrystal	$^{\$}$Cocrystal Solubility mg/mL (mmol/mL)
Resorcinol	11.00 (0.10)	8.24 (0.0457) at 20 °C	**1** [Theo.Res.H_2O]	23.60 (0.076)
Phluroglucinol	10.00 (0.08)		**2** [Theo.Phu.H_2O]	27.20 (0.0839)
Orcinol	16.50 (0.13)		**3** [Theo.Orc.$2H_2O$]	34.50 (0.1014)
2,6-Dihydroxy benzoic acid [2,6-DHBA]	2.50 (0.016)		**4** [Theo.2,6-DHBA.H_2O]	17.60 (0.0526)
3,5-Dihydroxy benzoic acid [3,5-DHBA]	8.40 (0.05)		**5** [Theo.3,5-DHBA]	0.14 (0.0004)
3,4-Dihydroxy benzoic acid [3,4-DHBA]	12.40 (0.08)		**6** [Theo.3,4-DHBA]	9.4 (0.0371)
Cinnamic acid [CA]	0.50 (0.003)		**7** [Theo.CA]	0.62 (0.0018)

* Collected from literature

$ Determined experimentally

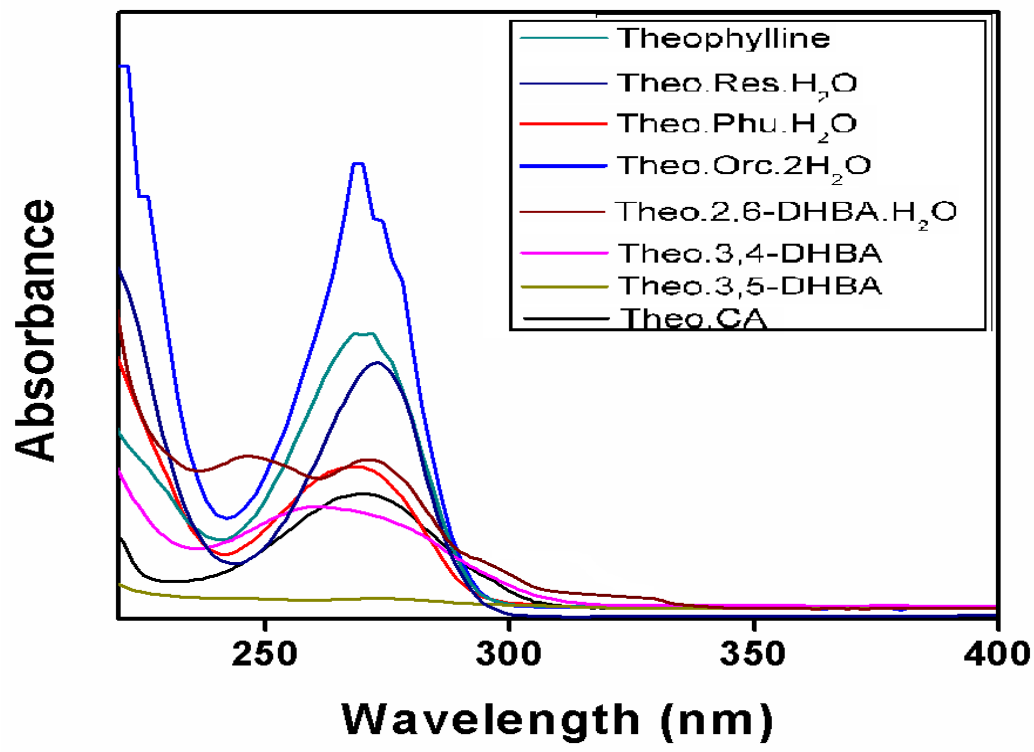


Figure S3a UV spectra for the cocrystals of API Theophylline at 270 nm wavelength. Hydrogen bonding plays a vital role in UV absorption. Predictable shifts in the wavelength occur with changes in substituents or the structure adjacent to a group. These shifts can be explained in terms of an inductive effect, hydrogen bonding, a mesomeric or resonance effect and steric factors such as ring strain. Functional groups such as −O H, N−H are involved in intermolecular hydrogen bonding in the presence of proton acceptors i.e. oxygen and nitrogen from theophylline. Intermolecular hydrogen bonding is increased as solute concentration increases but intramolecular hydrogen bonding is unaffected by changes in solute concentration. Hydrogen bonding shifts the UV absorption to shorter wavelength. The hypsochromic shift for the cocrystal Theo-3, 4 DHBA attributed from the extensive hydrogen bonding and the formation of −COOH acid homo dimer. Small hypsochromic shift for the cocrystal Theo.Orc.2H_2O is due to involvement of both the C=O groups in O−H···O hydrogen bonding with bridging water molecules.