Supporting Information

Cocrystal Hydrate of Bandrowski's Base and Clotrimazole: A Prospective Ingredient for Hair Dye Formulation

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Crystallographic details

Single crystal X-ray data for crystal CLT-BB-H_2O were collected on a Rigaku Mercury 375/M CCD (XtaLAB mini) diffractometer using graphite monochromator Mo-Kα radiation at 133 K and were processed with Rigaku crystal clear software.[1] Data reduction was carried out using the SAINTPLUS program. Structure solution and refinement were completed using SHELXT[2] and SHELXL,[3] respectively embedded in WinGX suite.[4] The hydrogen atoms were added for all the atoms either from difference Fourier maps or in their calculated positions using the riding model. Mercury 2020.2.0 was used for molecular representations.[5] Crystallographic data are given in the Supporting Information (Table S1). Structural data are available at CCDC **2070859.**

References

1. *Rigaku Mercury375R/M CCD. Crystal Clear-SM Expert 2.0 Rc14;* Rigaku Corp., Tokyo, Japan, 2009.

2. G. M. Sheldrick, *Acta Crystallogr. Sect. A: Found. Adv.,* 2015, **71**, 3-8.

3. G. M. Sheldrick, *Acta Crystallogr. Sect. C: Struct. Chem.,* 2015, **71**, 3-8.

4. L. J. Farrugia, *J. Appl. Crystallogr.,* 2012, **45**, 849-854.

5. C. F. Macrae, I. Sovago, S. J. Cottrell, P. T. A. Galek, P. McCabe, E. Pidcock, M. Platings, G. P. Shields, J. S. Stevens, M. Towler and P. A. Wood, *J. Appl. Crystallogr.,* 2020, **53**, 226-235.

Table S1. Crystal data and structure refinement for CLT-BB-H_2O

CCDC No.	2070859
Empirical formula	$C_{31}H_{28}ClN_5O$
Formula weight	522.03
Temperature	133(2) K
Wavelength	0.71075 Å
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a = 8.695(9) Å α= 71.182(11)°
	b = 11.849(13) Å β= 88.994(11)°
	c = 13.515(14) Å γ = 80.250(11)°
Volume	1298(2) $Å^3$
Z	2
Density (calculated)	1.336 Mg/m^3
Absorption coefficient	0.182 mm^{-1}
F(000)	548
Crystal size	0.200 x 0.200 x 0.200 mm^3
Theta range for data collection	3.122 to 24.498°.
Index ranges	-9<=h<=10, -13<=k<=13, -15<=l<=15
Reflections collected	7235
Independent reflections	4140 [R(int) = 0.1790]
Completeness to theta = 24.498°	96.20%
Max. and min. transmission	0.964 and 0.964
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4140 / 0 / 349
Goodness-of-fit on F^2	0.953
Final R indices [I>2sigma(I)]	R1 = 0.1016, wR2 = 0.2055
R indices (all data)	R1 = 0.2314, wR2 = 0.2649
Extinction coefficient	0.018(5)
Largest diff. peak and hole	0.434 and -0.405 e.Å-3

Table S2. Hydrogen bonding interactions in CLT-BB-H_2O

Donor–H···Acceptor	D–H	H···A	D···A	<D–H···A
O1–H1A···N2	0.85	1.96	2.801(9)	171
O1–H1B···N4	0.85	2.09	2.927(9)	168
N3–H3B···Cl01	0.87	2.78	3.602(9)	159
N5–H5A···O1	0.86	2.04	2.882(9)	168
N5–H5B···O1	0.86	2.52	3.310(9)	152
N5–H5B···N4	0.86	2.31	2.646(9)	103
C3–H3···N1	0.93	2.51	2.849(11)	102

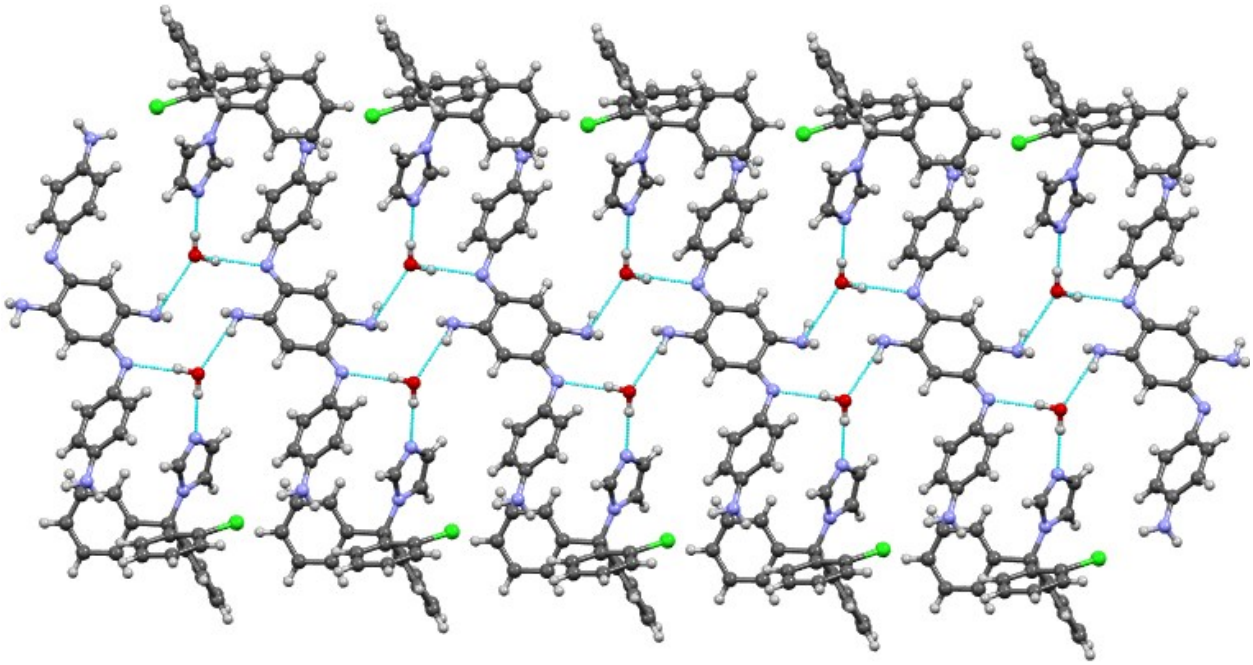

Fig.S1 3D assembly of CLT-BB-H_2O

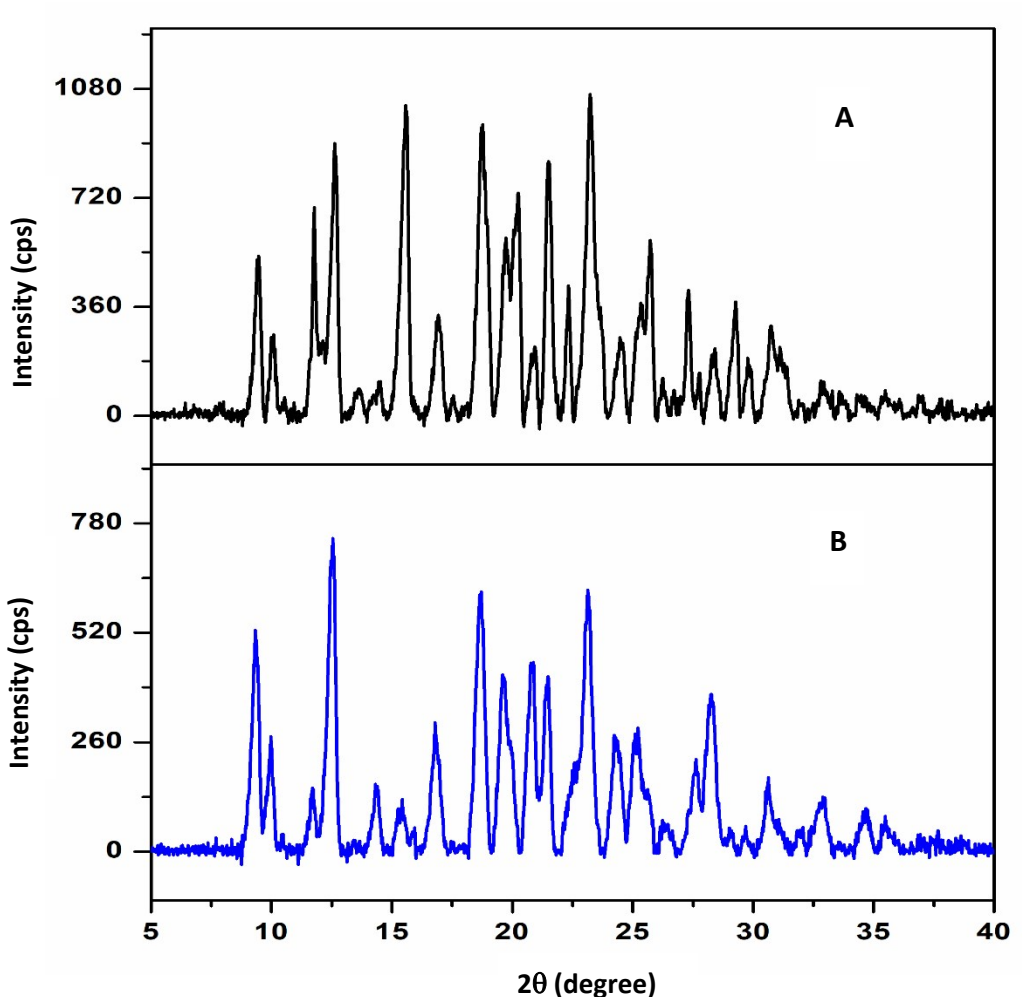

Fig. S2 (A) Powder XRD of PPD:CLT (3:1); (B) Powder XRD of PPD:CLT (1:1).

Table S3. Cocrystals tried with other conformers with variable pKa values

Sr. No.	Coformer	Stoichiometry	pK_a	Solvent	Inference (*the crystals were characterized by cell check measurements*)
1	Diglycolic Acid	1:1	2.79	EtOH, MeOH	PPD crystal was obtained
2	Diglycolic Acid	1:2	2.79	EtOH, MeOH	PPD crystal was obtained
4	Ascorbic Acid	1:1	4.2 and 11.6	EtOH, MeOH	PPD crystal was obtained
5	Boric Acid	1:1	9.2	EtOH, MeOH	PPD crystal was obtained
6	Alanine	1:1	9.78	EtOH, MeOH	PPD crystal was obtained

We also tried the cocrystallization of PPD with other ingredients of hair dye formulations with a wide range of pKa values. The rationale was to confirm the role of pKa of CLT in oxidizing PPD to BB and if some cocrystal were obtained, then its potential role in the hair dye formulation might be investigated. However, in all the cases (table 3), no BB and subsequently no cocrystal formation was observed.

The work reported in this manuscript might only be the tip of the iceberg and in future our work in this area is sought to cover a broad range. This is because this is the first observation which suggests a hair colouring formulation that is independent of PPD. We are already in the process of synthesizing cocrystals of *p*-aminophenol and other colour developers used in the hair dye formulations like *p*-phenyl-PPD with other antifungal agents specifically ketoconazole. In addition, the scope need not be limited to the synthesis of cocrystals but rather to use the ideas of crystal engineering for developing user-friendly commercial formulations in the form of gels. The antifungal properties of the formulations will also be studied on the strains of hair fungus for concluding the most effective formulation. We strongly believe the crystal engineering has the potential to transform the hair dye industry. Our long-term objective is to utilize crystal engineering for complete replacement of these synthetic colour developers *viz*. PPD, *p*-aminophenol and *p*-phenyl-PPD with natural products like lawsone, curcumin and caffeine.