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Stability Study and Structural Insights into Cannabidiol Cocrystals

Supplementary Information

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SI 1 Single crystals measurement

Table SI 1. Crystallographic data and details of refinement of CBD cocrystals

	CBD-BP	**CBD-CR**	**CBD-PR**
Sample	Single crystal	Powder	Single crystal
Empirical formula	$C_{31}H_{38}N_2O_2$	$C_{28}H_{45}NO_4$	$C_{26}H_{39}NO_4$
Formula weight	470.65	475.7	429.6
Crystal system	Monoclinic	Orthorhombic	Orthorhombic
Space group	$P2_1$	$P2_12_12_1$	$P22_12_1$
T (K)	95	293	95
Radiation	Cu *K*α	Cu *K*α1	Cu *K*α
a (Å)	9.9190 (2)	20.0237 (6)	8.9467 (1)
b (Å)	18.6995 (4)	17.0222 (5)	16.7061 (3)
c (Å)	14.2034 (3)	8.20215 (19)	32.6593 (5)
α (°)	90	90	90
β (°)	91.711 (2)	90	90

γ (°)	90	90	90
V (Å^3)	2633.28 (10)	2795.68 (13)	4881.40 (13)
Z	4	4	8
Reflns. collected	19066	-	36993
Indep. reflns	9315	-	9678
GOF	0.9309	4.6825	1.0315
R_1, wR_2 [I > 2δ(I)]	0.0585, 0.1533	0.0675, 0.0803	0.0446, 0.1115
R_1, wR_2 (all data)	0.0678, 0.1573	0.0699, 0.0805	0.0482, 0.1137
Δρmax, Δρmin (e Å -3)	0.39, -0.38	0.18, -0.23	0.24, -0.23
R_p, R_{wp}, R_{exp}	-	0.025, 0.036, 0.008	-
CCDC number	2333022	2333084	2333083

The crystal structure of CBD-CR was solved using the direct space approach implemented in the program FOX [1], where model of CBD was used from the CSD entry with ref. code CANDOM12 and carnitine was modelled using the online tool molview. The Rietveld refinement was made in Jana2020 [2] using bond and bond angle restraints. All hydrogen atoms were kept in the positions calculated from the geometry and all atoms shared one isotropic ADP. The final refinement led to the R_{wp} = 3.6%, see final profile fit in Figure SI 1.

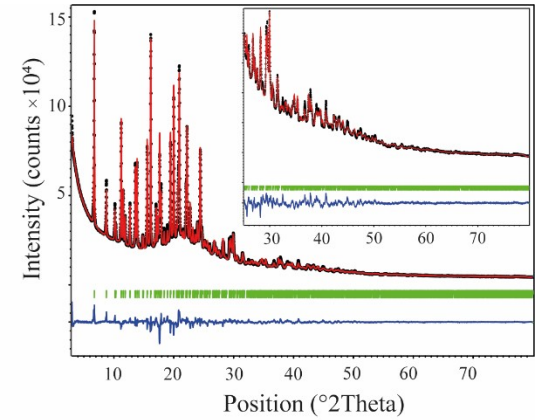

Figure SI 1. The final Rietveld profile fit of the XRPD of CBD-CR. Black dots represent measured data, red curve represents the calculated profile, blue line is a difference curve and green lines are Bragg's positions.

SI 2 Nuclear magnetic resonance

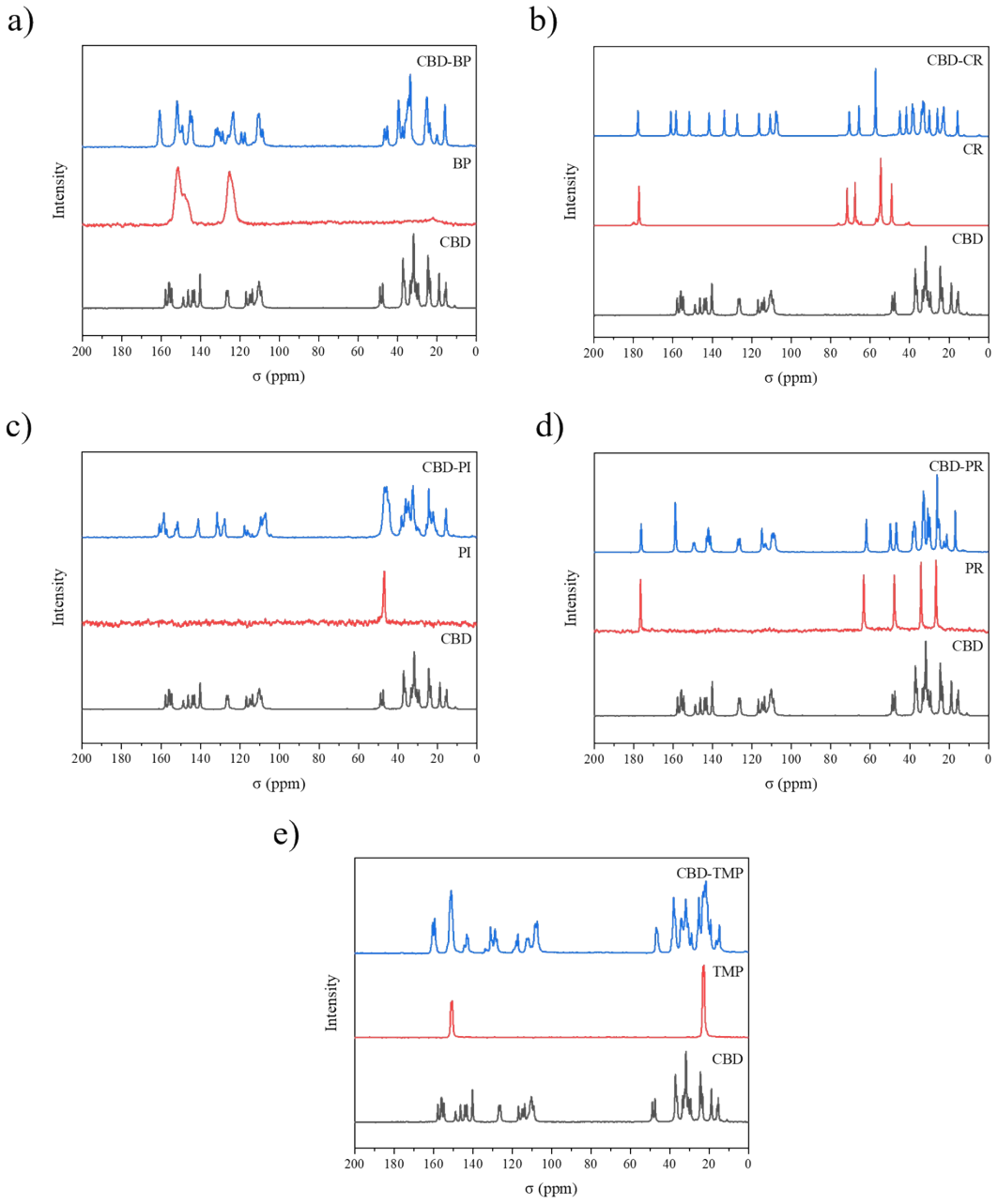

Figure SI 2. Solid-state NMR spectra of cocrystals a) CBD-BP, b) CBD-CR, c) CBD-PI, d) CBD-PR and e) CBD-TMP.

SI 3 Crystals structures of the solid forms

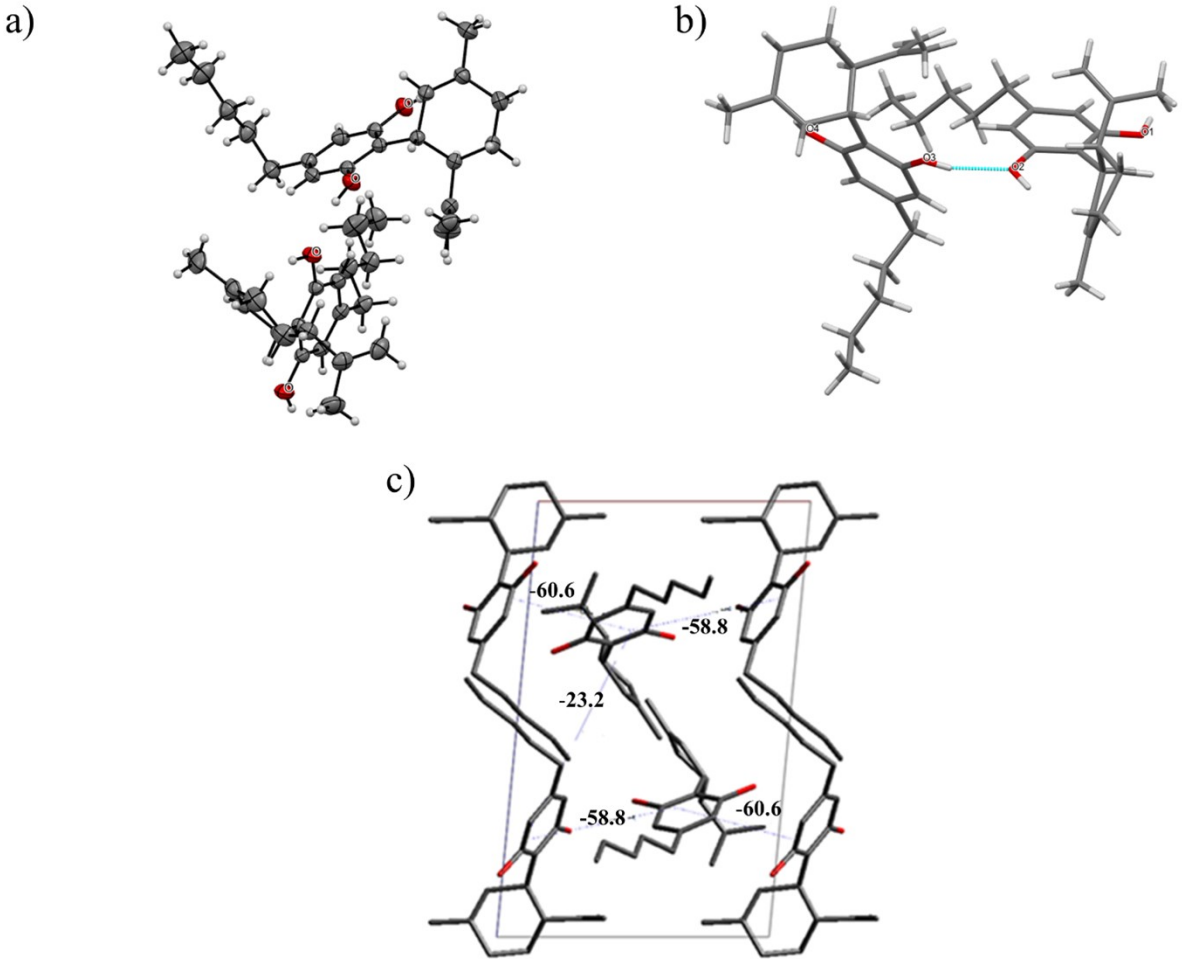

Figure SI 3. Crystal structure of CBD of a) asymmetric unit, b) hydrogen bonding and c) calculated interaction energy.

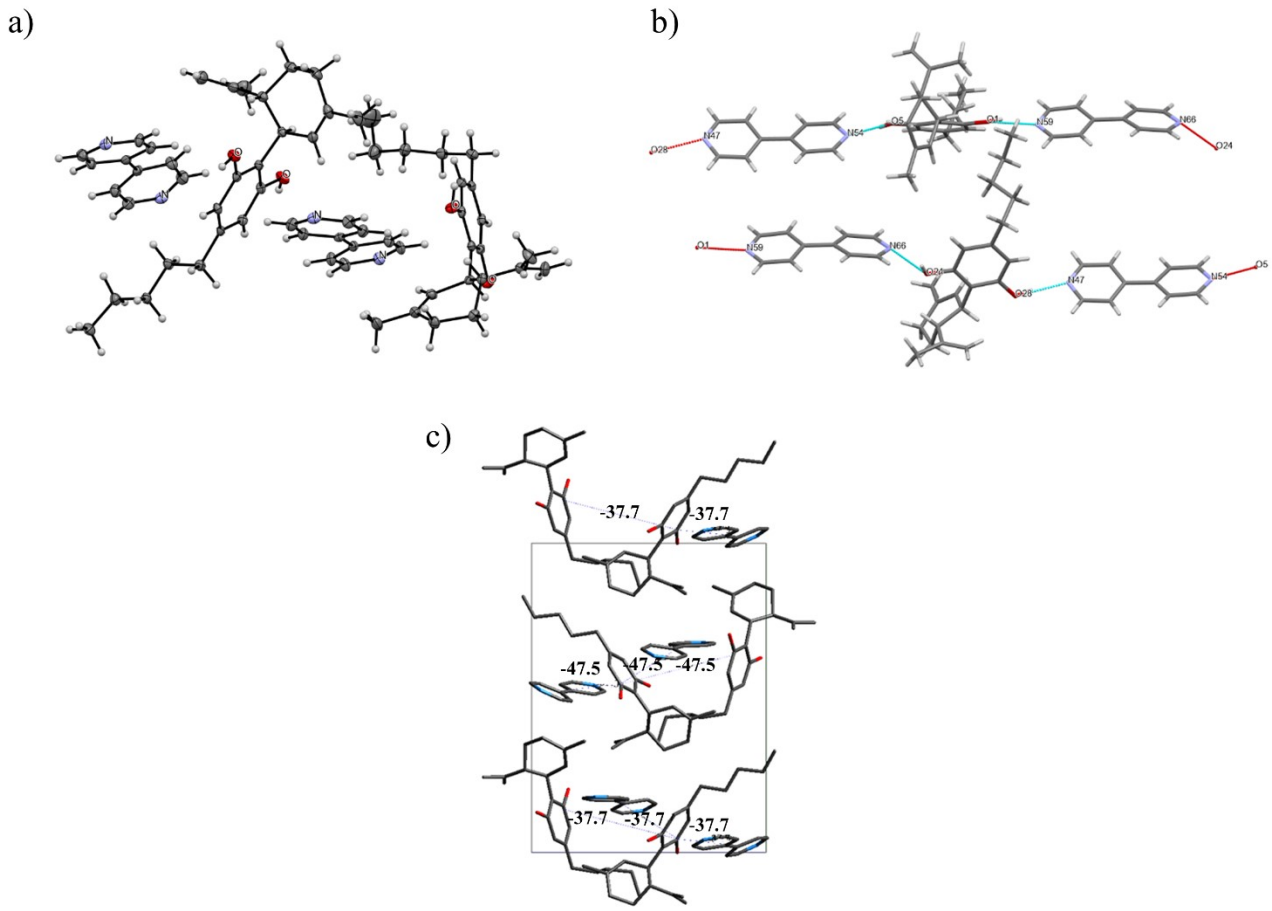

Figure SI 4. Crystal structure of CBD-BP of a) asymmetric unit, b) hydrogen bonding and c) calculated interaction energy.

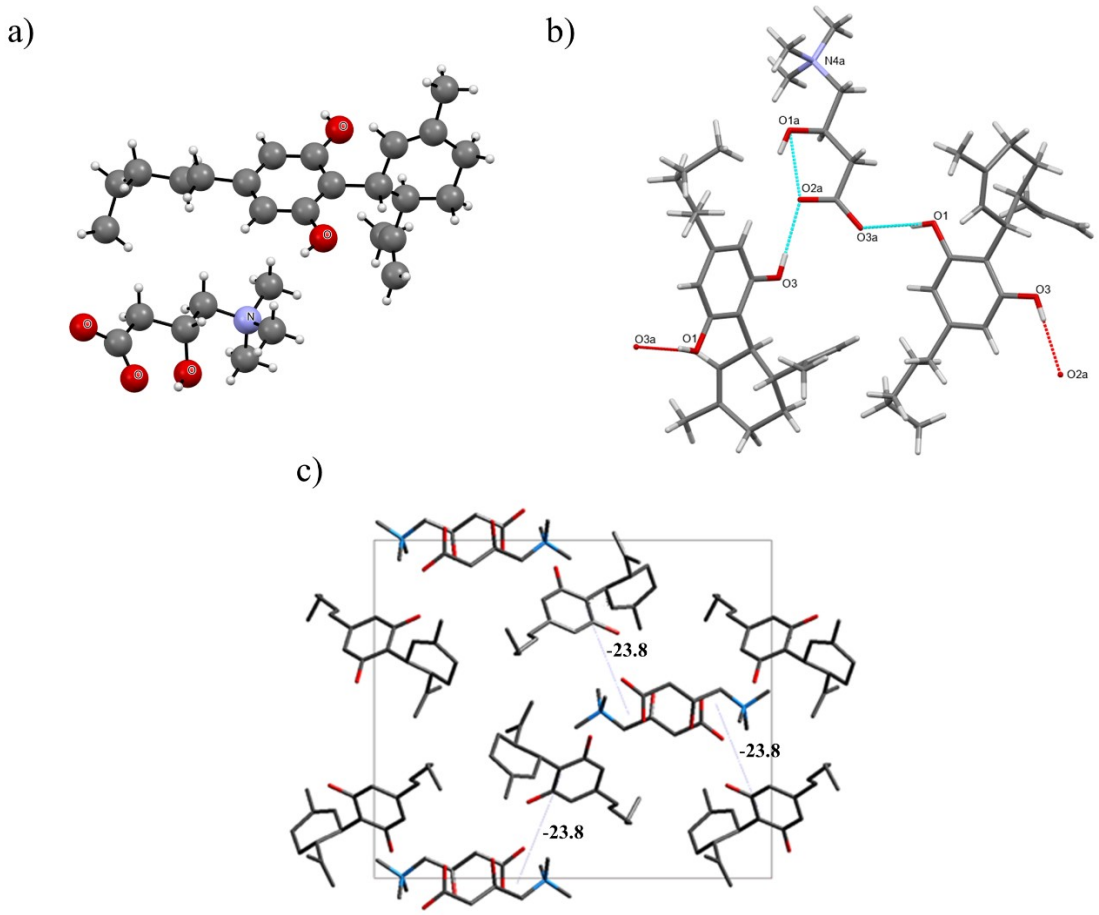

Figure SI 5. Crystal structure of CBD-CR of a) asymmetric unit, b) hydrogen bonding and c) calculated interaction energy.

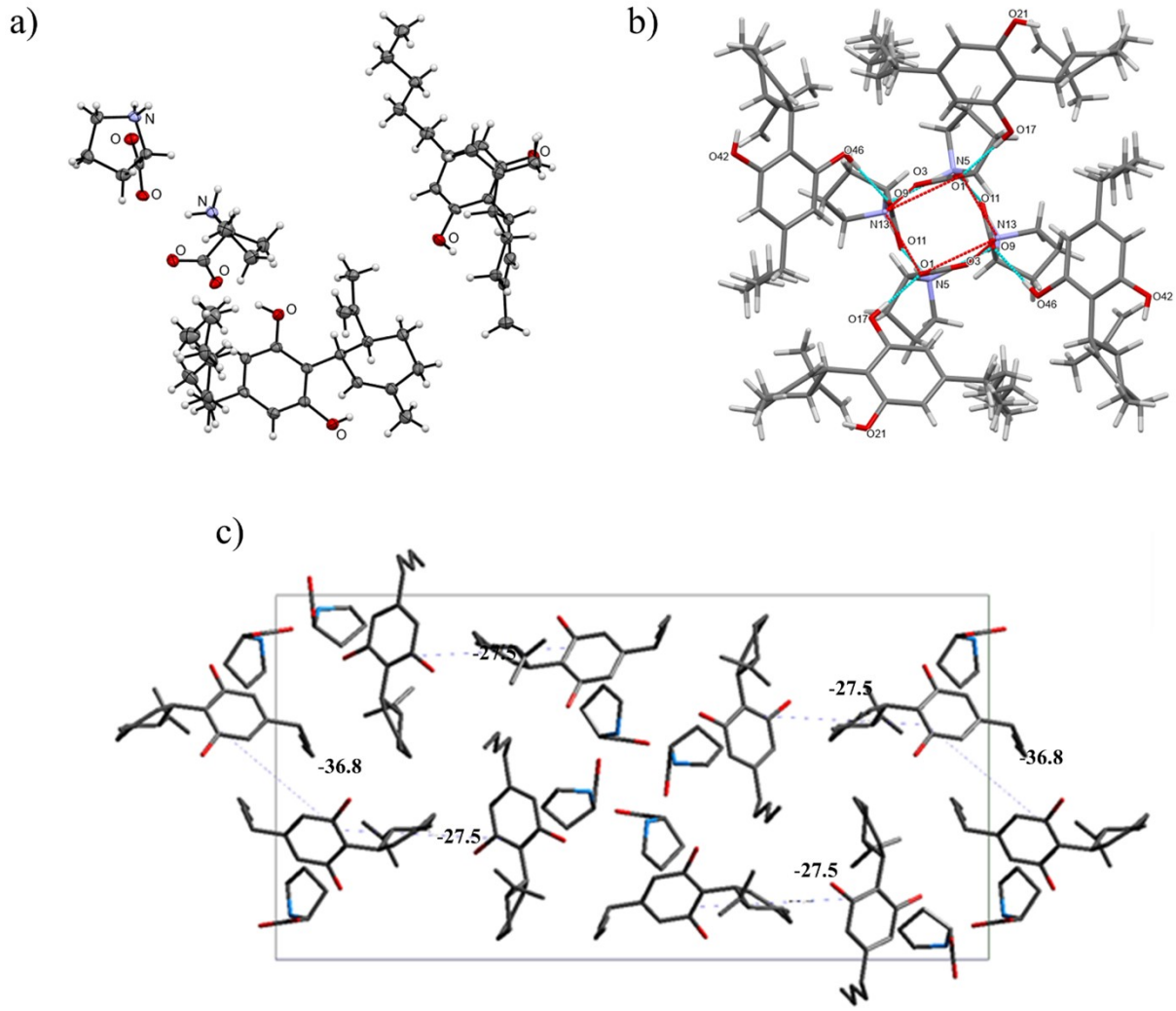

Figure SI 6. Crystal structure of CBD-PR of a) asymmetric unit, b) hydrogen bonding and c) calculated interaction energy.

SI 4 Thermal analyses

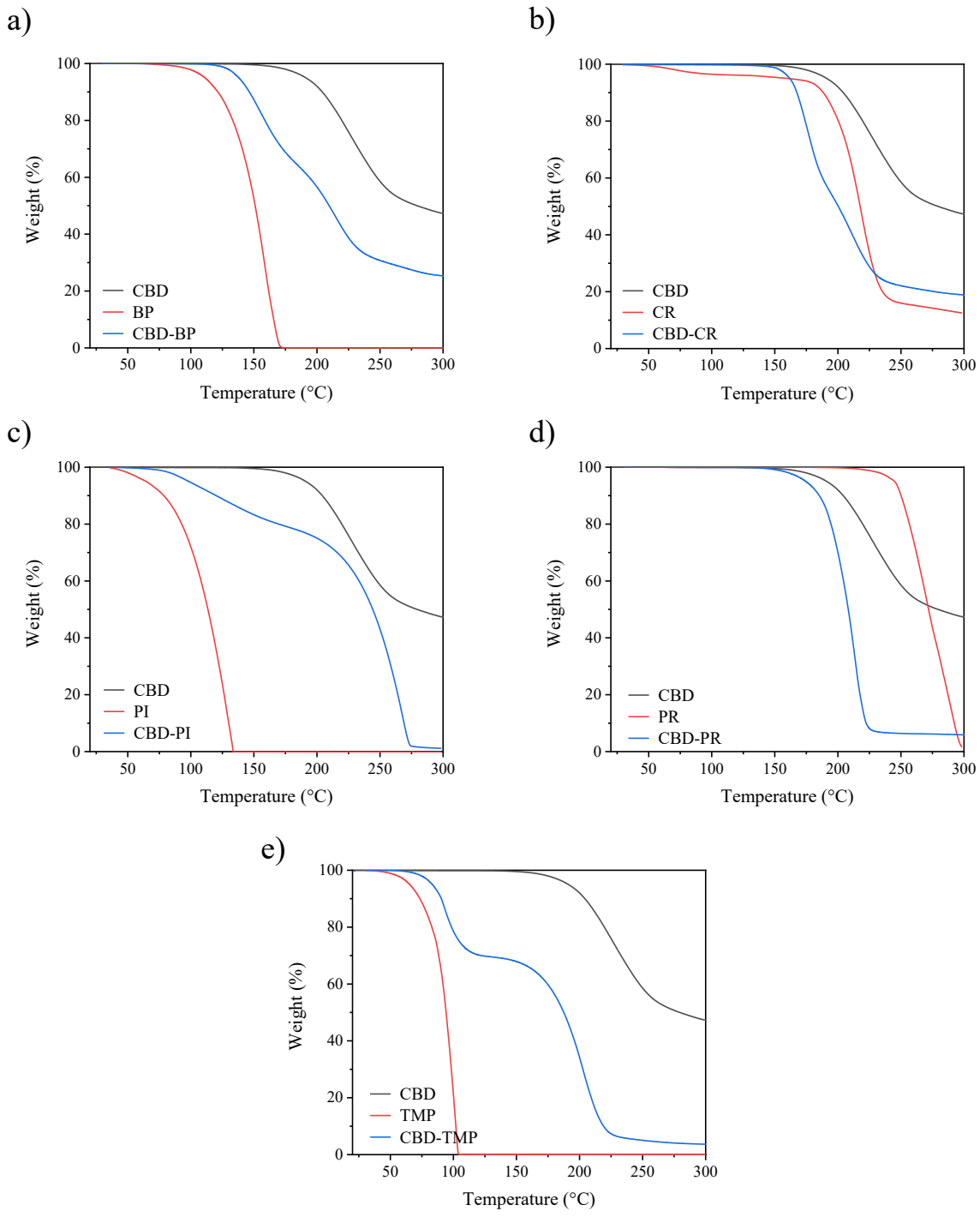

Figure SI 7. TGA curves for all cocrystals and their starting materials.

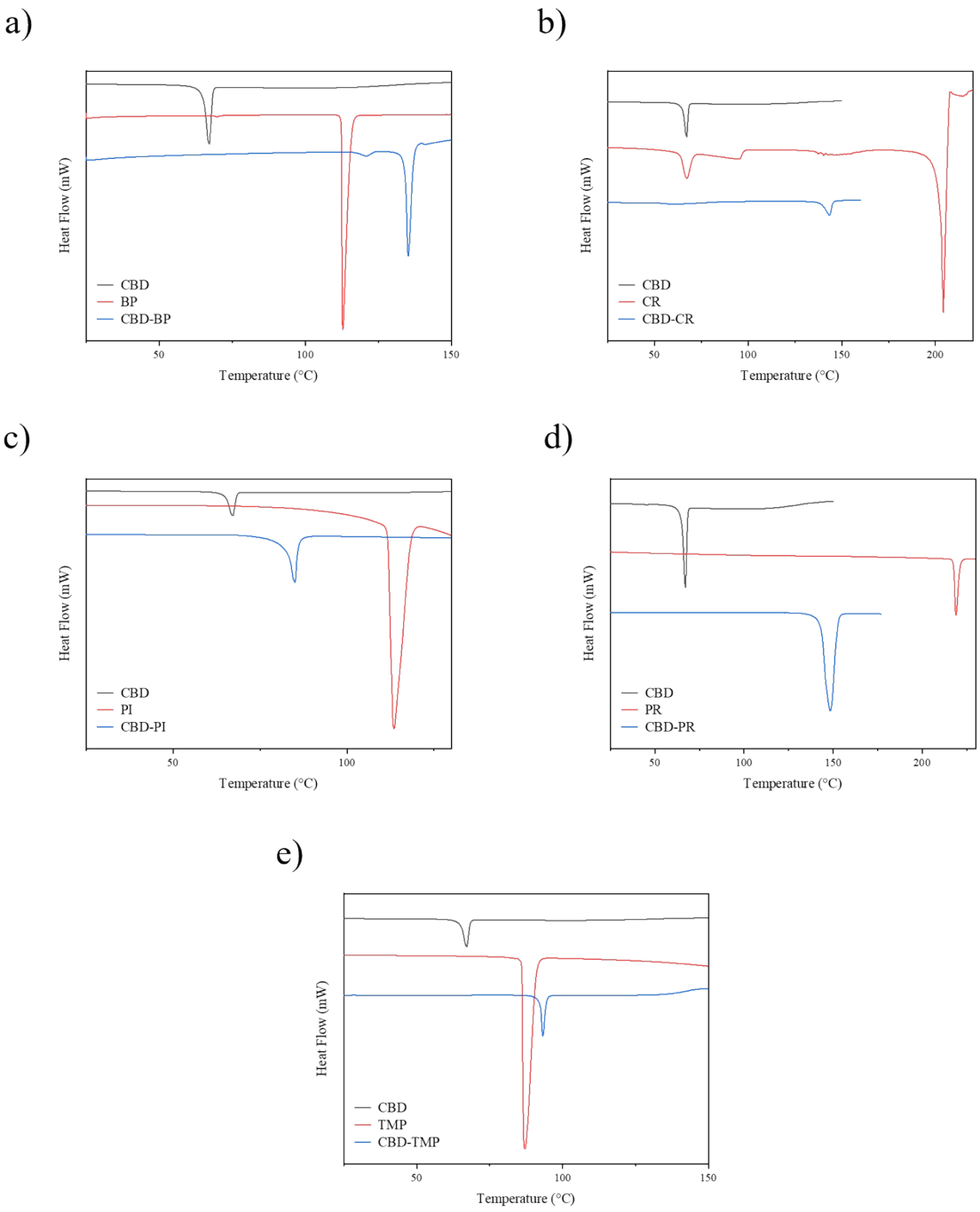

Figure SI 8. DSC curves for all cocrystals and their starting materials.

SI 5 Intrinsic dissolution rate

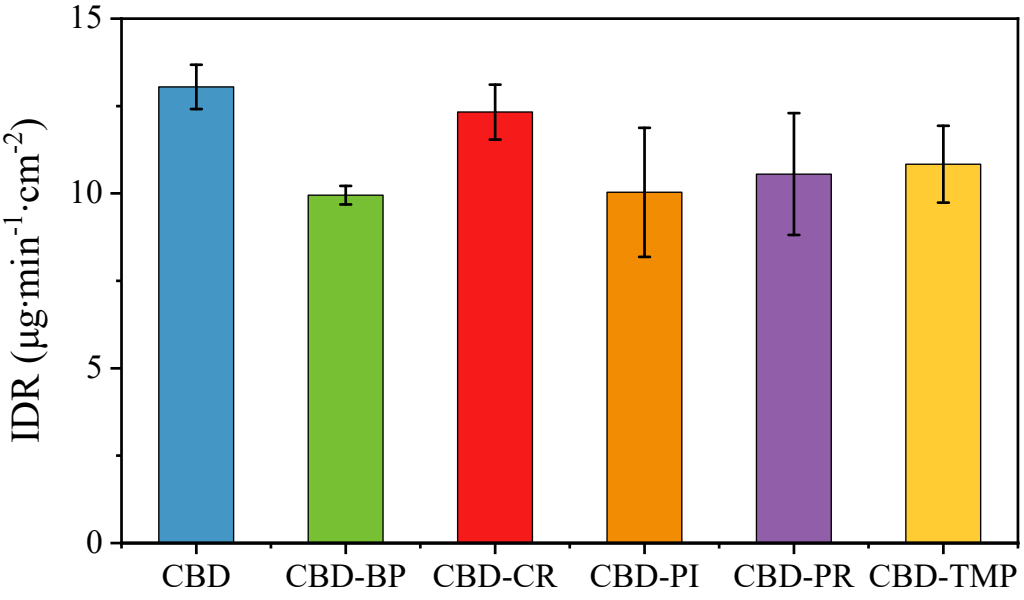

Figure SI 9. Comparison of intrinsic dissolution rates for pure CBD and its cocrystals.

Table SI 2. Intrinsic dissolution rate of the CBD and its cocrystals.

Solid form	Average dissolution rate (μg·min^{-1}·cm^{-2})
CBD	13.05 ± 0.32
CBD-BP	9.95 ± 0.13
CBD-CR	12.33 ± 0.39
CBD-PI	10.03 ± 0.92
CBD-PR	10.55 ± 0.87
CBD-TMP	10.84 ± 0.55

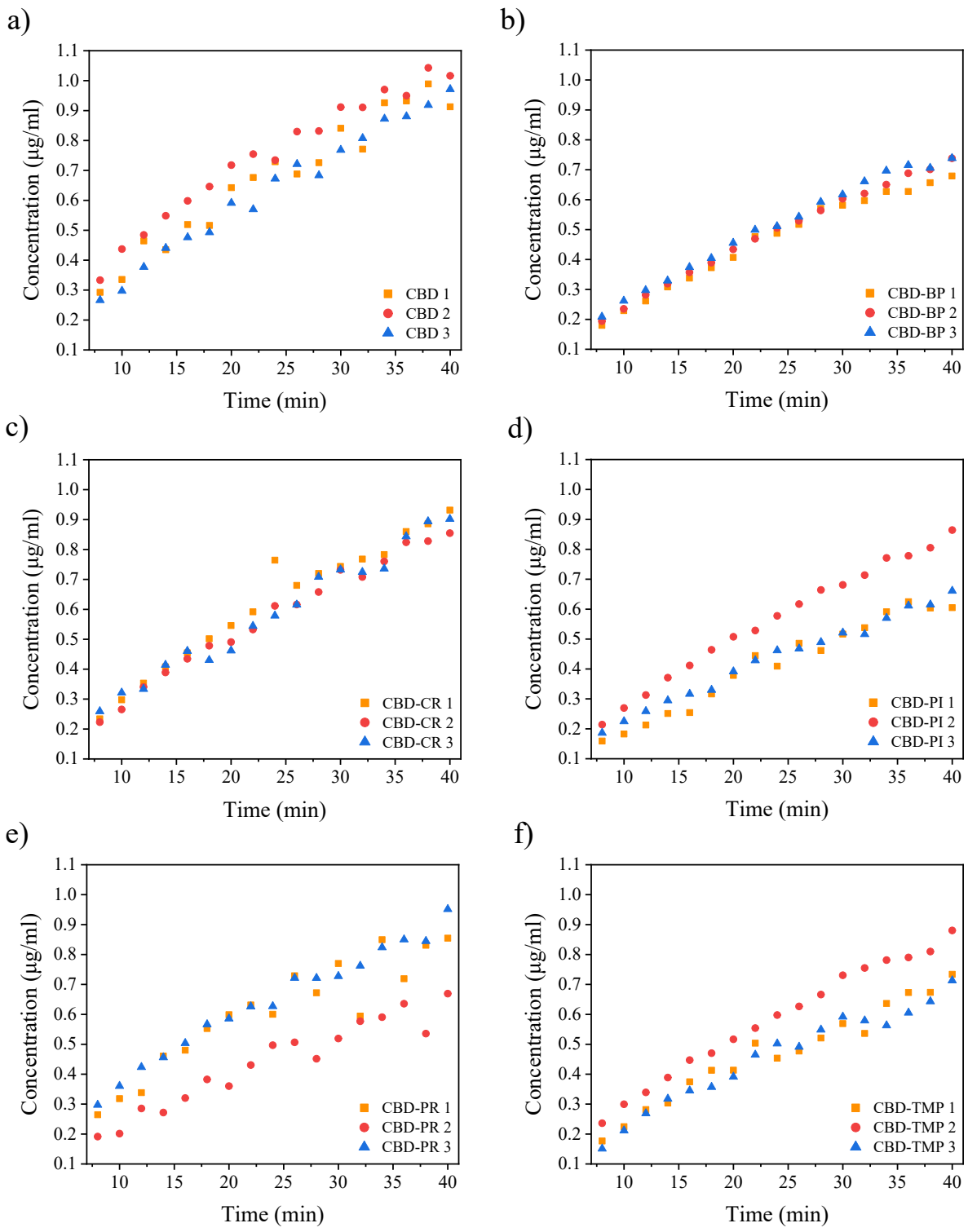

Figure SI 10. An example of dissolution rate profile of pure CBD and its cocrystals.

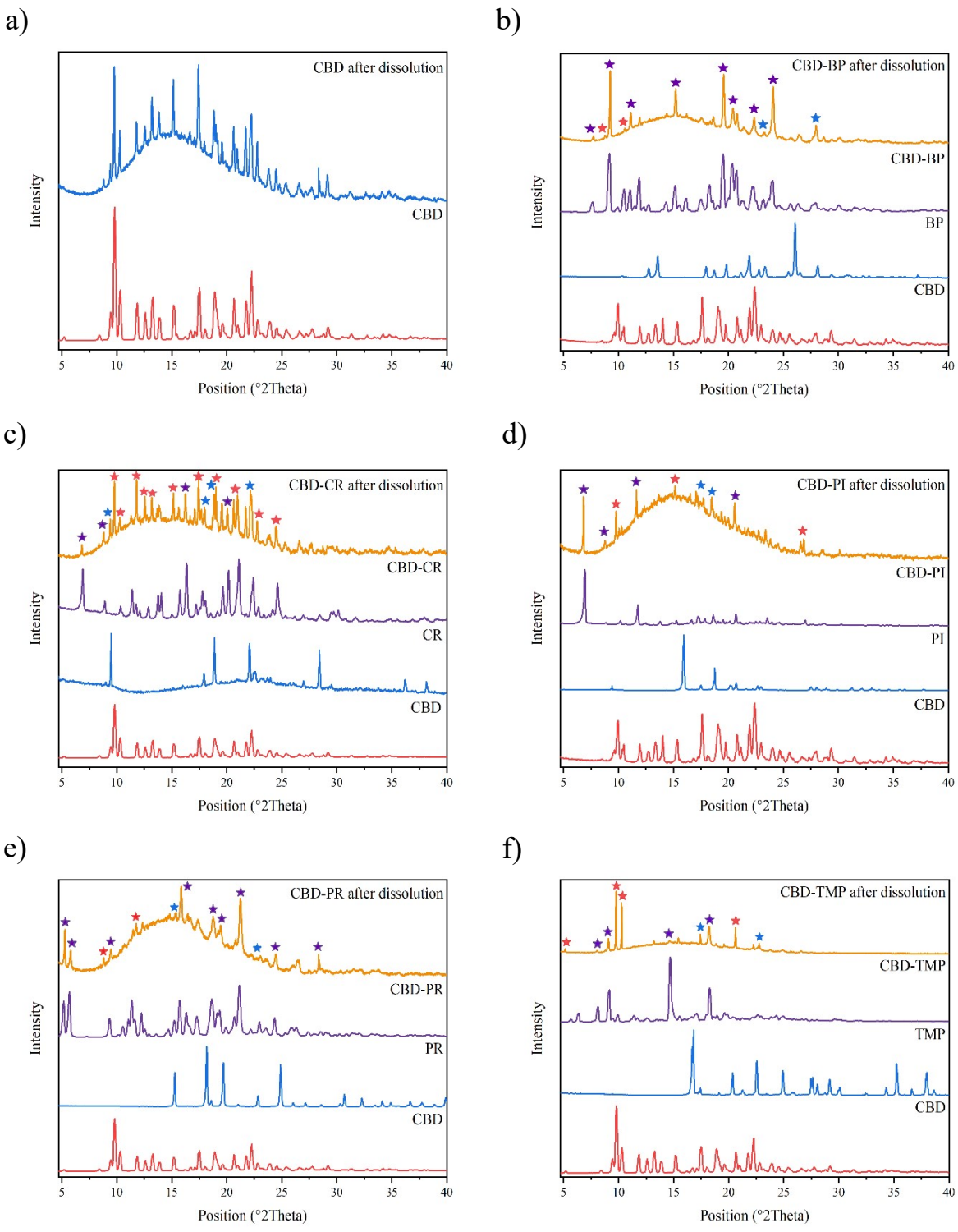

Figure SI 11. XRPD patterns after IDR measurement of a) CBD, b) CBD-BP, c) CBD-CR, d) CBD-PI, e) CBD-PR and f) CBD-TMP. Colour of the star represents the origin of the peak.

SI 6 Stability study

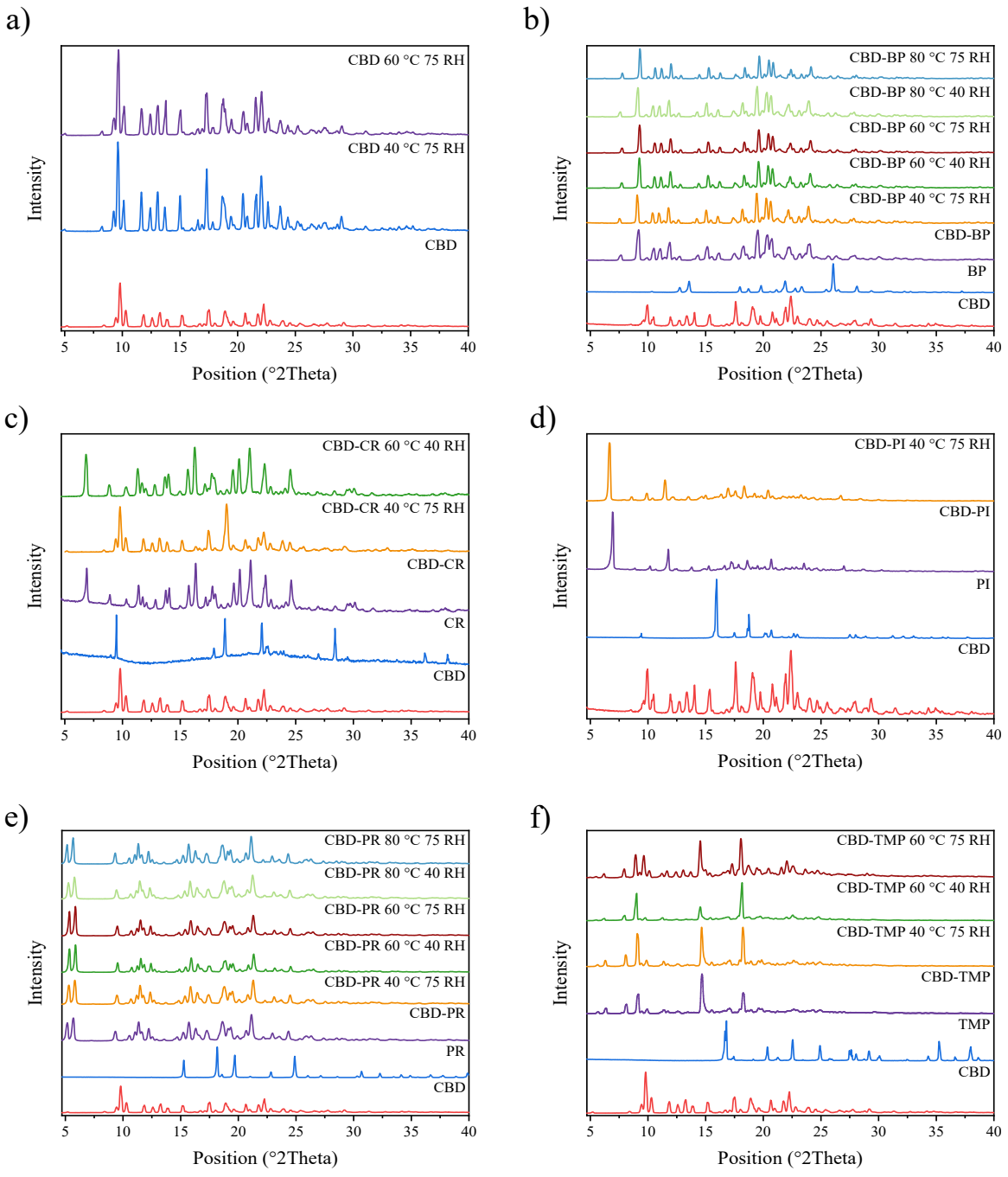

Figure SI 12. XRPD patterns of a) CBD, b) CBD-BP, c) CBD-CR, d) CBD-PI, e) CBD-PR and f) CBD-TMP.

Literature

1. Favre-Nicolin, V. and R. Cerny, *FOX, `free objects for crystallography': a modular approach to ab initio structure determination from powder diffraction.* Journal of Applied Crystallography, 2002. **35**(6): p. 734-743.
2. Petříček, V., et al., *Jana2020 – a new version of the crystallographic computing system Jana.* Zeitschrift für Kristallographie - Crystalline Materials, 2023. **238**(7-8): p. 271-282.