Discovery of New Proxyphylline Based Chiral Cocrystals: Solid State Landscape and Dehydration Mechanism

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Content:

Table S 1. Purity and suppliers list of the used coformers.

Coformer	Purity	Supplier
4-methoxybenzoic acid	> 98%	Alfa Aesar
3-chlorobenzoic acid	> 99%	Acros Organics
4-dimethylaminobenzoic acid	> 98%	Acros organics
3-hydroxy-4-nitrobenzoic acid	> 98%	Acros organics
3,4-dichlorobenzoic acid	> 99%	Acros organics
2,6-dichlorobenzoic acid	> 98%	Acros organics
Benzamide	> 98%	Alfa Aesar
Urea	> 98%	VWR Chemicals
Adipic acid	> 99%	Alfa Aesar
Saccharin	> 98%	Acros organics
Stearic acid	> 97%	Acros organics
Methyl urea	> 97%	Acros organics
Citric acid	> 98%	Acros organics
Salicylic acid	> 99%	Acros organics
Acetylsalicylic acid	> 99%	Acros organics
Anthranilic acid	> 99%	Merck
Oxalic acid	> 98%	Alfa Aesar
3,4-dimethoxycinnamic acid	> 99%	Alfa Aesar
2,5-dichlorobenzoic acid	> 97%	Acros Organics
3-hydroxybenzoic acid	> 99%	Acros organics

Table S 2. Preparation methods to obtain new cocrystal forms of PXL with six different coformers.

Coformer	Neat Grinding	LAG	Evaporation
Oxalic acid *(OA)*	+	Acetone, IPA, DCM, $CHCl_3$	/
Acetylsalicylic acid *(AA)*	+	Acetone, heptane, DCM, MeOH, EtOH	MeOH
Anthranilic acid *(Ant)*	+	Acetone, EtOH, MeOH, DCM	/
3-hydroxybenzoic acid *(HBA)*	/	MeOH	/
3,4-dimethoxycinnamic acid *(DMCA)*	+	/	/
2,5-dichlorobenzoic acid *(DClBA)*	+	/	Heptane

+ : co-crystal formation

/ : no new solid phase was identified

Table S 3. SHG activity for the solid forms obtained with 1:1 molar ratio mixtures of (RS)-PXL and different coformers.

Coformer	SHG signal	SHG intensity
Oxalic acid (OA)	-	0
Acetylsalicylic acid (AA)	+	7
Anthranilic acid (Ant)	+	10
3-hydroxybenzoic acid (HBA)	+	5
3,4-dimethoxycinnamic acid (DMCA)	+	135
2,5-dichlorobenzoic acid (DClBA)	+	2258

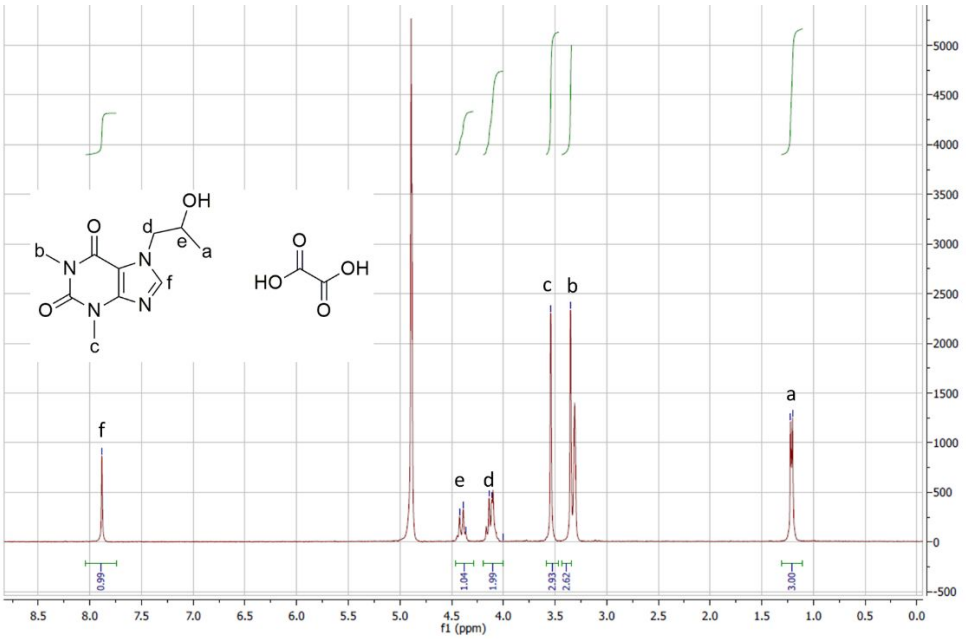

Figure S 1. ^{1}H NMR of the cocrystal obtained between PXL and OA in MeOD. Hydrogens of OA were not detected by NMR in MeOD.

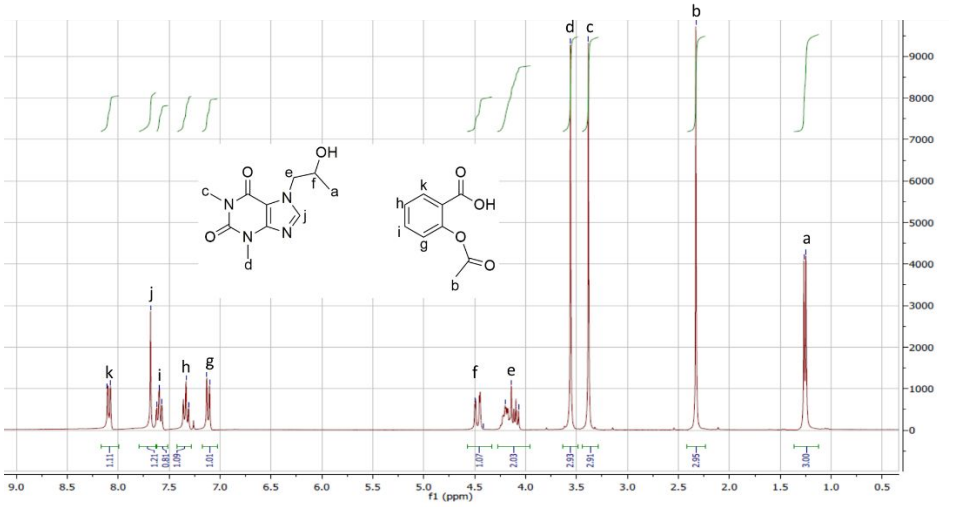

Figure S 2. ^{1}H NMR of the cocrystal between PXL and AA in $CDCl_3$.

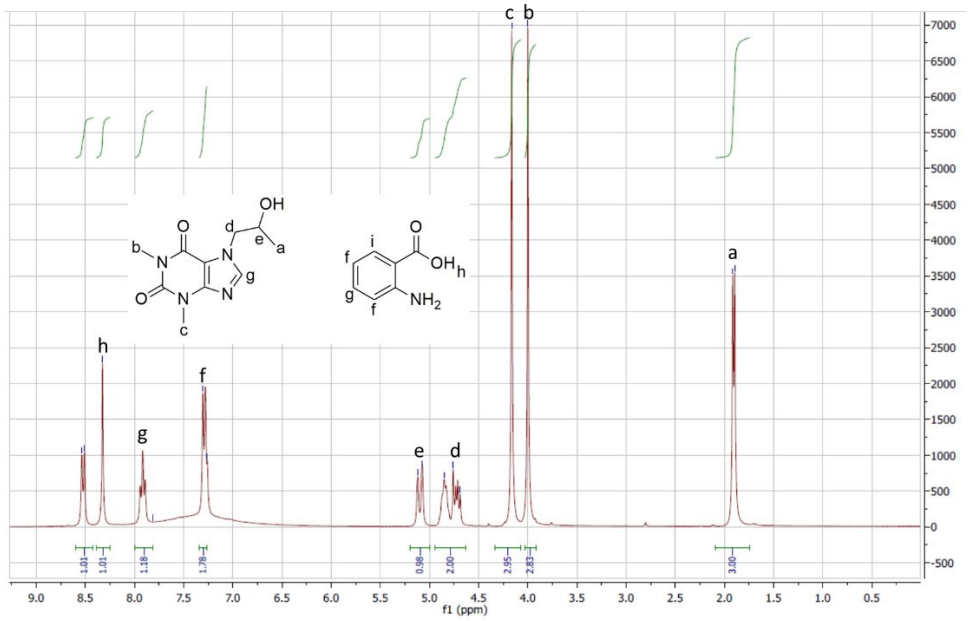

Figure S 3. ^{1}H NMR of the cocrystal between PXL and Ant in $CDCl_3$.

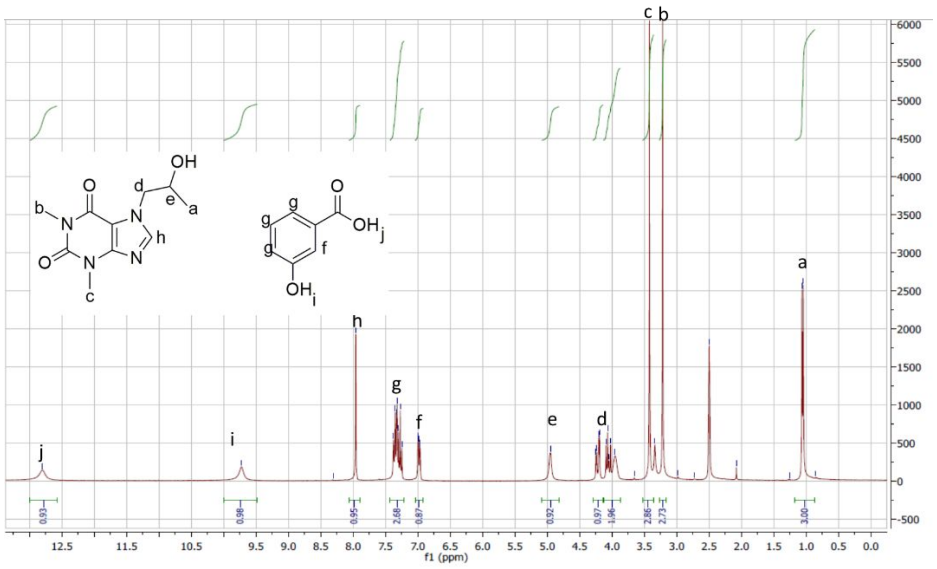

Figure S 4. ^{1}H NMR of the cocrystal between PXL and HBA in $(CD_3)_2SO$.

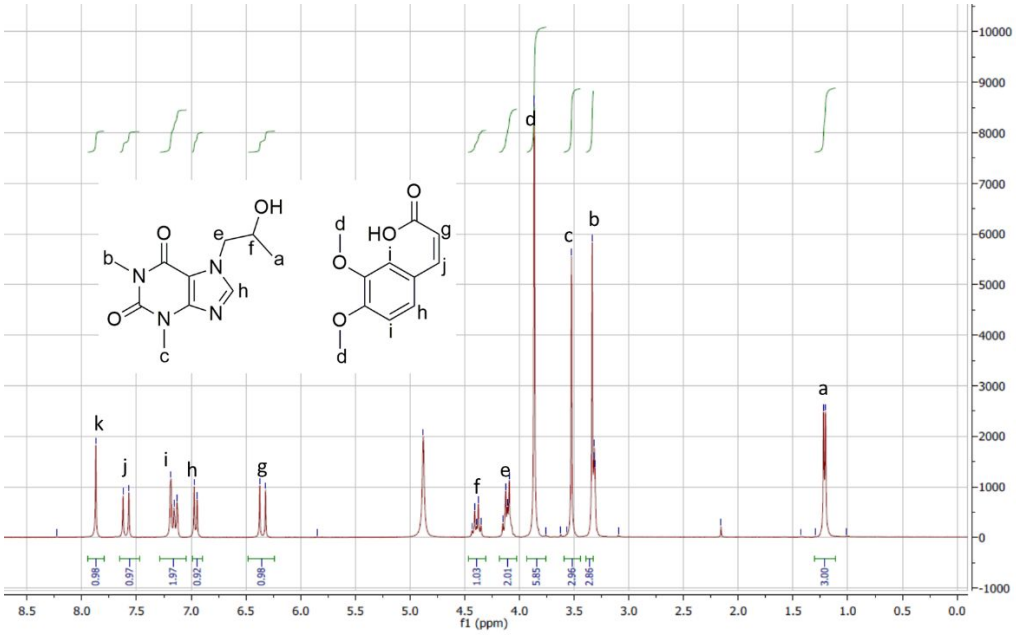

Figure S 5. ^{1}H NMR of the cocrystal between PXL and DMCA in MeOD.

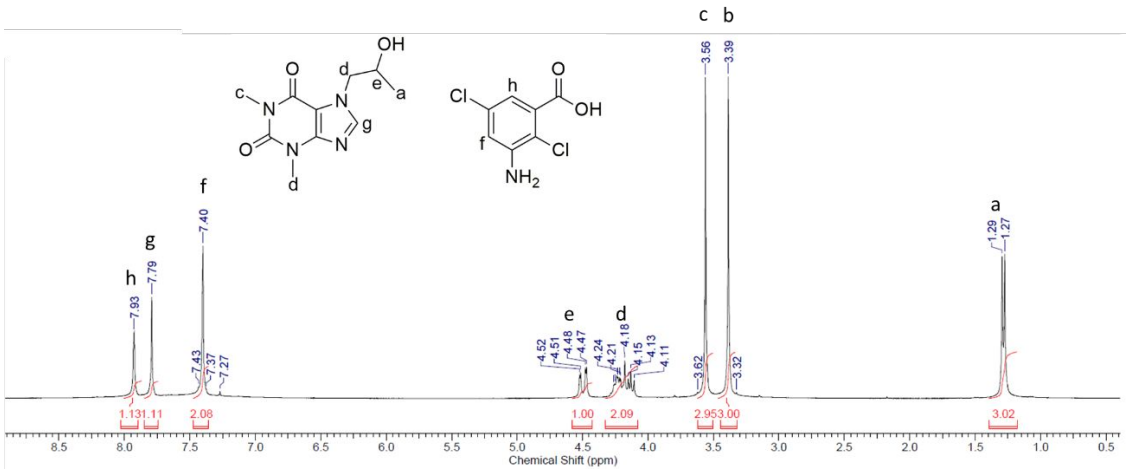

Figure S 6. [1]H NMR of the cocrystal obtained between PXL and DClBA.

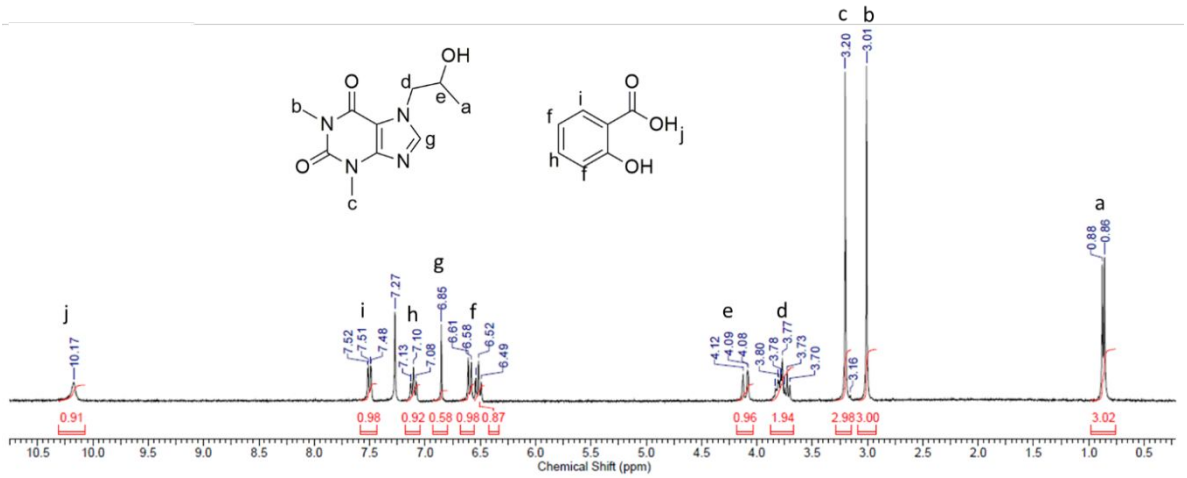

Figure S 7. [1]H NMR of the cocrystal obtained between PXL and SA.

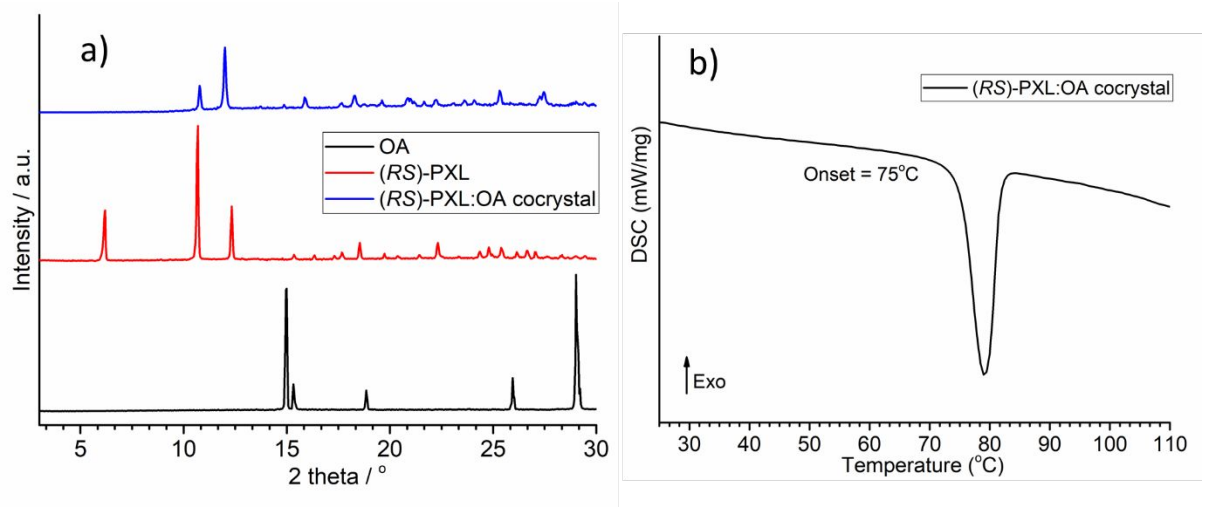

Figure S 8. a) XRPD pattern of the starting material (RS)-PXL, Oxalic acid (OA) and (RS)-PXL:OA cocrystal and b) DSC plot of the obtained cocrystal.

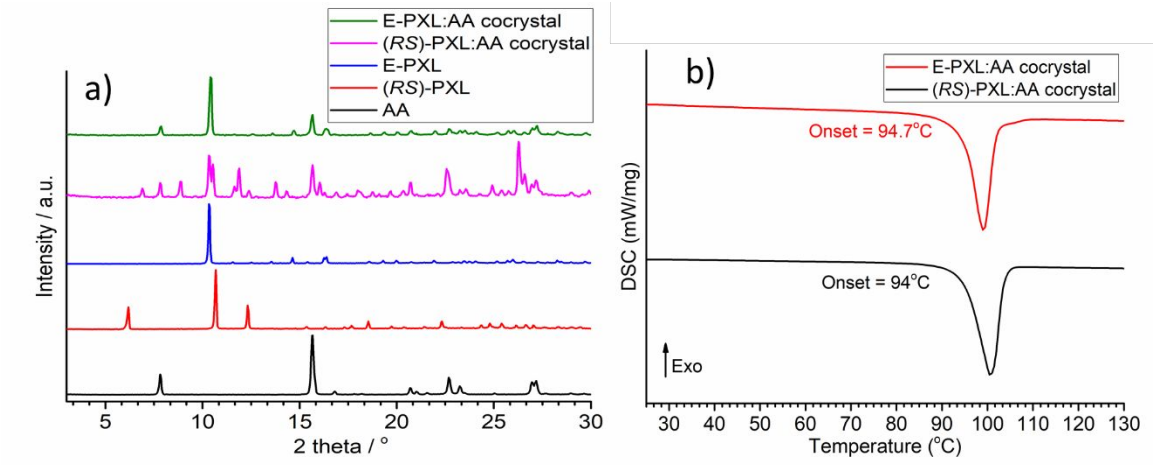

Figure S 9. a) XRPD pattern of (RS)-PXL, AA, E-PXL, (RS)-PXL:AA cocrystal and E-PXL:AA cocrystal in 1:1 molar ratio and b) DSC plot of the obtained cocrystals.

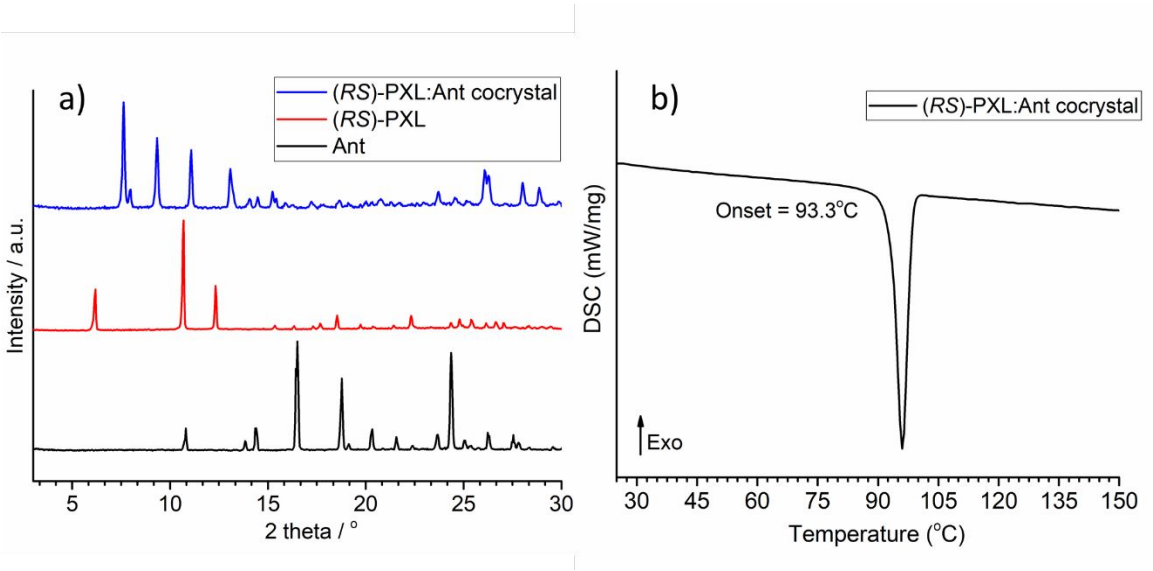

Figure S 10. a) XRPD pattern of (RS)-PXL, Ant and their mixture in 1:1 molar ratio. b) DSC plot for the obtained cocrystal.

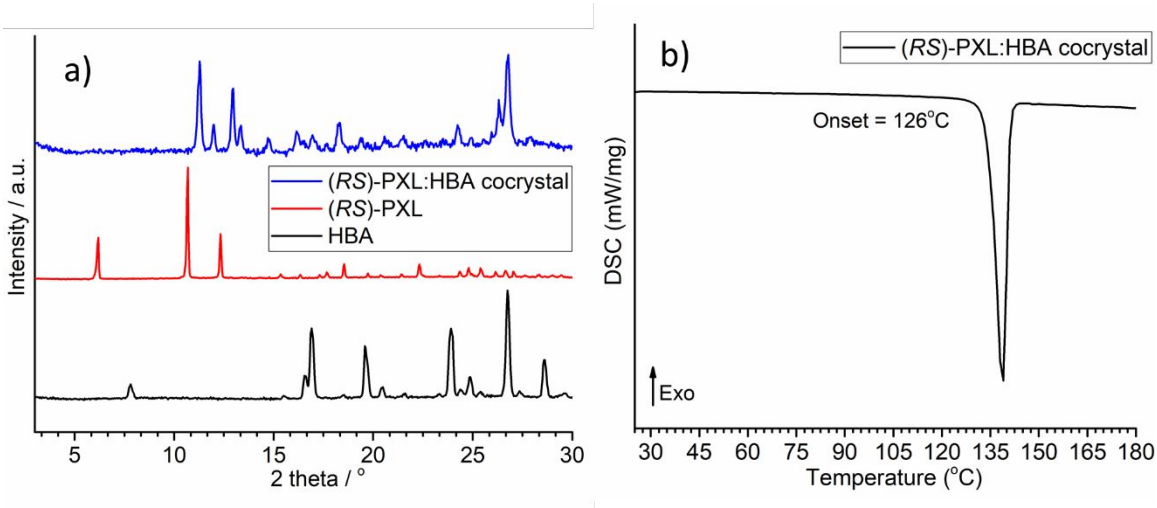

Figure S 11. a) Powder X-ray diffraction for (RS)-PXL, HBA and (RS)-PXL:HBA cocrystal and b) DSC melting curves of the cocrystal.

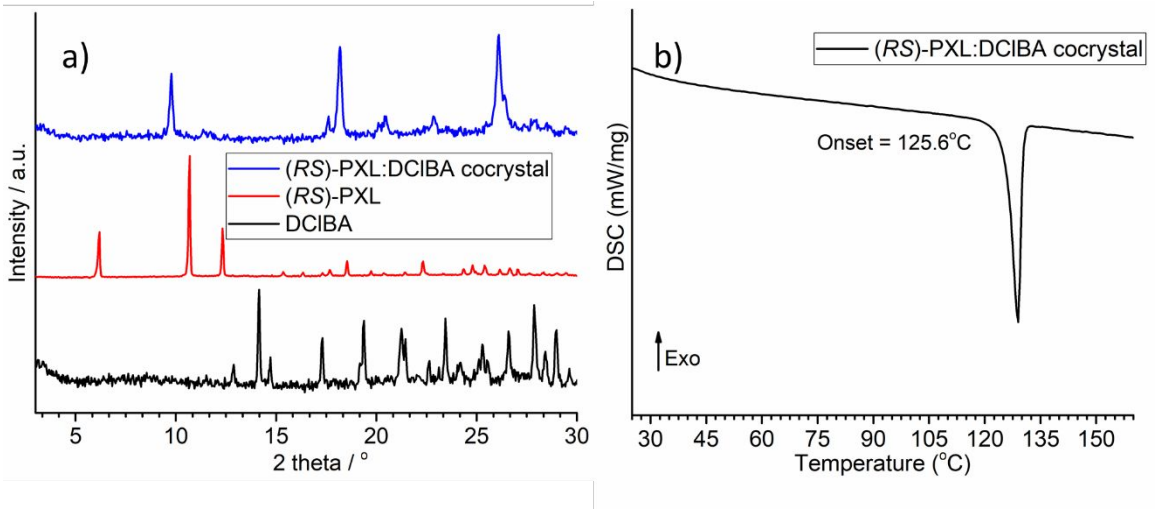

Figure S 12. a) XRPD for (RS)-PXL, DClBA and PXL-DClBA cocrystal and b) DSC melting curve of the new cocrystal form.

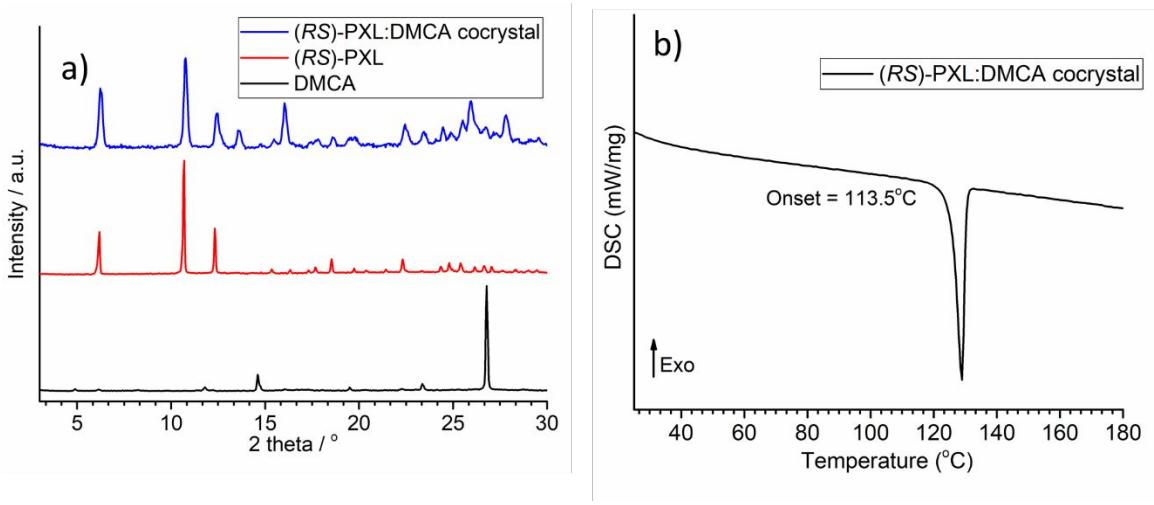

Figure S 13. a) XRPD for (RS)-PXL, DMCA and (RS)-PXL-DMCA cocrystal and b) DSC melting curve of the obtained cocrystal.

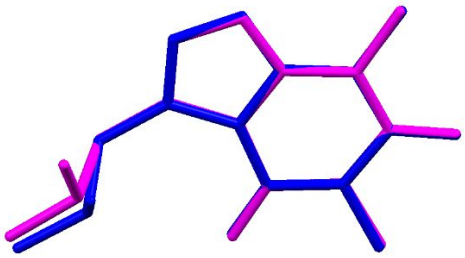

Figure S 14. Conformational similarity between the PXL molecules from the asymmetric unit of Form-H (Blue) and Form-A2 (Pink).

Figure S 15. Conformational similarity between the SA molecules from the asymmetric unit of Form-H (Blue) and Form-A2 (Pink).

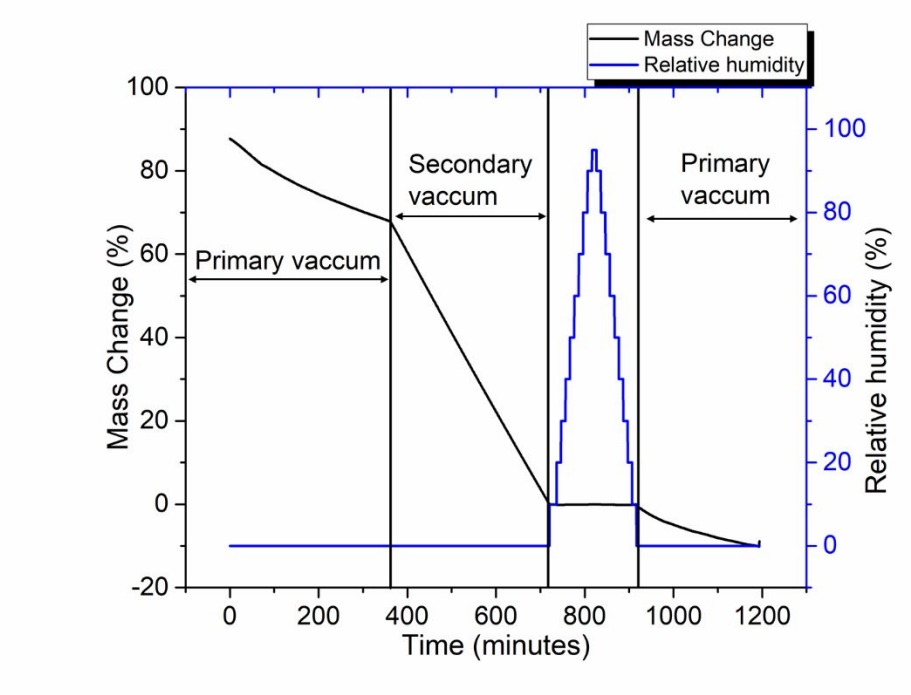

Figure S 16. Sorption-desorption cycle performed at 25 °C for SA with DVS vacuum. Mass change (%) is referred to the mass at the end of the first drying step.

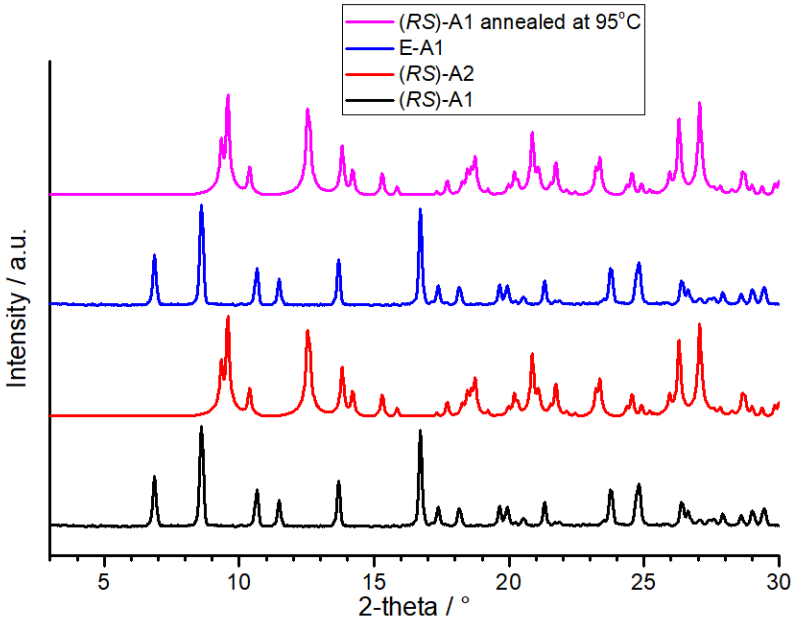

Figure S 17. XRPD patterns of (RS)-A1, (RS)-A2, E-A1 and the obtained solid after annealing (RS)-A1 at 95oC.

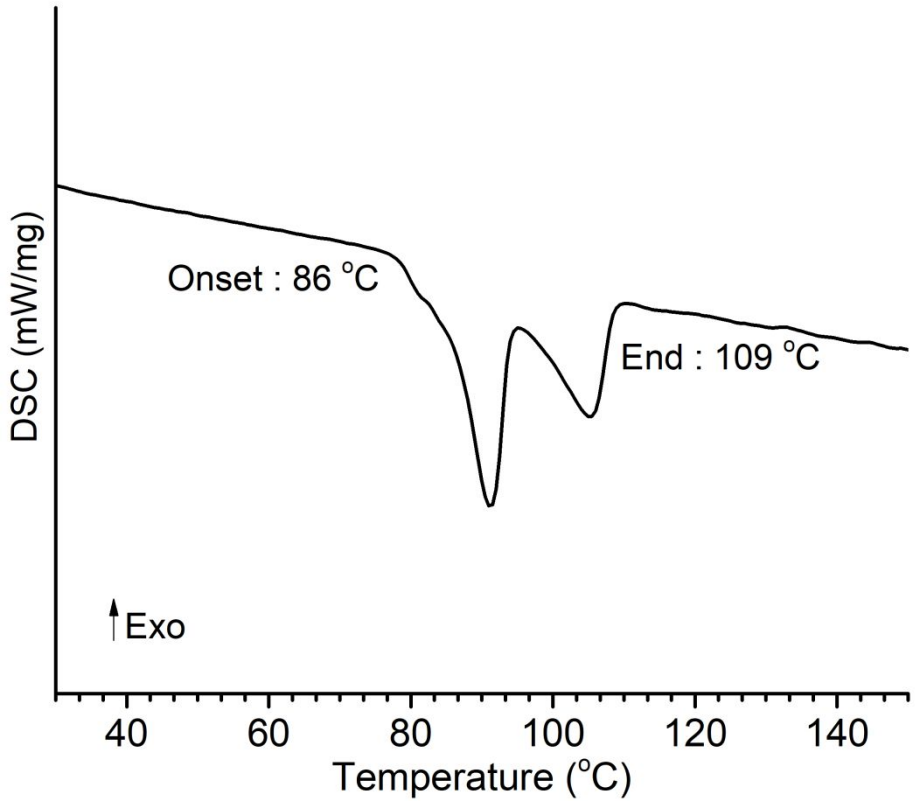

Figure S 18. DSC of the anhydrous form A3.

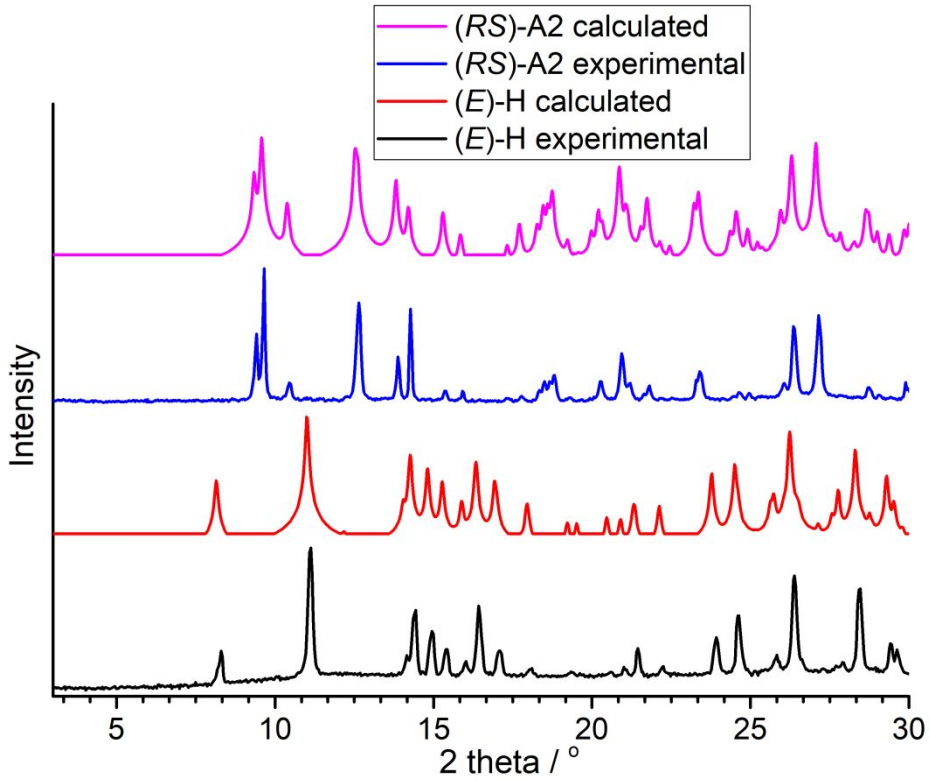

Figure S 19. Experimental and calculated patterns of (E)-H and (RS)-A2 respectively.