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Electronic Supplementary Information (ESI)

Crystal Engineering of Multiple-Component Organic Solids: Pharmaceutical Cocrystals of Tadalafil with Persistent Hydrogen Bonding Motifs

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1. SYNTHESIS OF TADALAFIL COCRYSTALS

1.1 Synthesis of Tadalafil:Methylparaben Cocrystal (1)

Solvent-drop grinding: 100 mg of tadalafil was ground with 39 mg of methylparaben and 20 μL of acetonitrile was added to the solid mixture. The resulting cocrystals of **1** gathered after grinding were stored in screw cap vials for subsequent analysis.

Slurry: 200 mg of tadalafil was slurried with 156 mg of methylparaben and 1 mL of acetonitrile. The resulting cocrystals of **1** gathered after the slurry were dried and stored in a screw cap vials for subsequent analysis.

1.2 Synthesis of Tadalafil:Propylparaben Cocrystal (2)

Solvent-drop grinding: 100 mg of tadalafil was ground with 46 mg of propylparaben and 20 μL of acetonitrile was added to the solid mixture. The resulting cocrystals of **2** gathered after grinding were stored in screw cap vials for subsequent analysis.

Slurry: 200 mg of tadalafil was slurried with 184 mg of propylparaben and 1 mL of acetonitrile. The resulting crystals of **2** gathered after the slurry were dried and stored in a screw cap vials for subsequent analysis.

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1.3 Synthesis of Tadalafil:Hydrocinnamic Acid Cocrystal (3)

Solvent-drop grinding: 110 mg of tadalafil was ground with 42 mg of 3-phenylpropanoic acid and 20 μL of acetonitrile was added to the solid mixture. The resulting crystals of **3** gathered after grinding were stored in screw cap vials for subsequent analysis.

Slurry: 50 mg of tadalafil was slurried with 288.75 mg of 3-phenylpropanoic acid and 1 mL of acetonitrile. The resulting crystals of **3** gathered after the slurry were dried and stored in a screw cap vials for subsequent analysis.

1.4 Synthesis of Tadalafil:4-Hydroxybenzoic Acid Cocrystal (4)

Solvent-drop grinding: 123.2 mg of tadalafil was ground with 88.3 mg of 4-hydroxybenzoic acid and 40 μL of acetonitrile was added to the solid mixture. The resulting cocrystals of **4** gathered after grinding were stored in screw cap vials for subsequent analysis.

Slurry: 1000 mg of tadalafil was slurried with 710 mg of 4-hydroxybenzoic acid and 5 mL of acetonitrile. The resulting crystals of **4** gathered after the slurry were dried and stored in a screw cap vials for subsequent analysis.

2. CRYSTAL FORM CHARACTERIZATION

2.1 Single-Crystal X-ray Diffraction

The X-ray diffraction data were collected using Bruker-AXS SMART-APEXII CCD diffractometer (Cu Kα, λ = 1.54178Å). Indexing was performed using *APEX2* [1] (Difference Vectors method). Data integration and reduction were performed using SaintPlus 6.01 [2]. Absorption correction was performed by multi-scan method implemented in SADABS [3]. Space groups were determined using XPREP implemented in APEX2 [1]. The structure was solved using SHELXS-97 (direct methods) and refined using SHELXL-97 (full-matrix least-squares on F^2) contained in APEX2 [1] and WinGX v1.70.01 [4-7] programs packages. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in geometrically calculated positions and included in the refinement process using riding model with isotropic thermal parameters: $U_{iso}(H) = 1.5*U_{eq}(-CH3)$, $U_{iso}(H) = 1.2*U_{eq}(-CH2,-CH,-NH)$.

[1] Bruker (2010). APEX2). Bruker AXS Inc., Madison, Wisconsin, USA.

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[2] Bruker (2009). SAINT. Data Reduction Software. Bruker AXS Inc., Madison, Wisconsin, USA.

[3] Sheldrick, G. M. (2008). SADABS. Program for Empirical Absorption Correction. University of Gottingen, Germany.

[4] Farrugia L.J. Appl. Cryst. (1999). 32, 837±838

[5] Sheldrick, G.M. (1997) SHELXL-97. Program for the Refinement of Crystal

[6] Sheldrick, G.M. (1990) Acta Cryst. A46, 467-473

[7] Sheldrick, G. M. (2008). Acta Cryst. A64, 112-122.

2.2 Powder X-Ray Diffraction (PXRD)

Crystals of **1-4** were characterized using a D-8 Bruker X-ray Powder Diffractometer using Cu Kα radiation (λ = 1.54178 Å), 40 kV, 40 mA. Data were collected over an angular range of 3° to 40° 2θ value in continuous scan mode using a step size of 0.05 ° 2θ value and a scan rate of 5º/min.

2.3 Calculated PXRD

Calculated PXRD profiles were generated from the single crystal structures of **1-3** using Mercury 2.4 (Cambridge Crystallographic Data Centre, UK).

2.4 Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry analysis was performed for **1-4** on a Perkin Elmer Diamond DSC with a typical scan range of 25 ºC – 280 ºC, scan rate of 10 ºC/min, and nitrogen purge of ca. 30 psi.

2.5 Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR analysis was performed for **1-4** on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a solid-state ATR accessory.

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3. CSD ANALYSIS

An analysis of the Cambridge Structural Database (CSD) was conducted for the selection of tadalafil (TDF) cocrystal formers. A CSD survey of lactam and indole molecules indicated that TDF would be amenable to form cocrystals with coformers that contain alcohol or carboxylic acid moieties, due to the greater propensity for supramolecular heterosynthon versus supramolecular homosynthon formation. Specifically, the alcohol and carboxylic acid moieties were approximately five and two times more likely, respectively, to form a supramolecular heterosynthon with the lactam moiety, when compared to the occurrence of the corresponding supramolecular homosynthons which were found to occur less than 15% of the time. A similar trend was found upon examination of the indole moiety where the tendency for supramolecular heterosynthon formation was ca. 50% greater than supramolecular homosynthon formation in the presence of an alcohol or a carboxylic acid. The details of the survey are included in Table S1. The supramolecular homosynthons considered in this study included carboxylic acid-carboxylic acid and alcohol-alcohol interactions. Certain restrictions were placed upon the CSD survey to include crystal structures with 3D coordinates determined, *R*-factor $\leq$ 0.075, no ions and only organic molecules.

Table S1: CSD Statistics for tertiary lactam and indole interactions[a]

Tadalafil Moiety	Complementary Moiety	Total Entries with Both Moieties	Number of Entries with Homosynthon	%	Bond Distance (Å)	Number of Entries with Heterosynthon	%	Bond Distance (Å)
Tertiary Lactam	Indole	9	N/A	N/A	N/A	5	55%	2.5-3.0
Tertiary Lactam	Carboxylic acid	46	5	11%	2.5-3.0	13	28%	2.5-2.8
Tertiary Lactam	Alcohol	365	43	12%	2.6-3.2	204	56%	2.5-3.0
Indole	Carboxylic acid	153	26	17%	2.5-3.0	54	35%	2.6-3.1
Indole	Alcohol	344	76	22%	2.6-3.2	147	43%	2.6-3.1

[a] The CSD searches were conducted with the following criteria: 3D coordinates determined, R-factor $\leq$0.075, no ions, only organics

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4. CRYSTAL FORM CHARACTERIZATION RESULTS OF 1-4

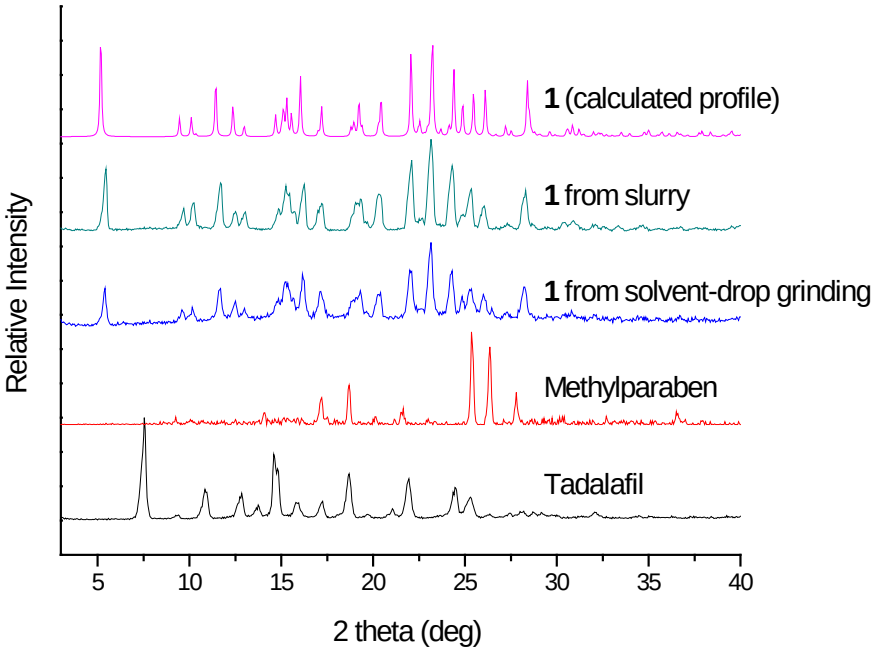

Figure S1: PXRD data for **1**.

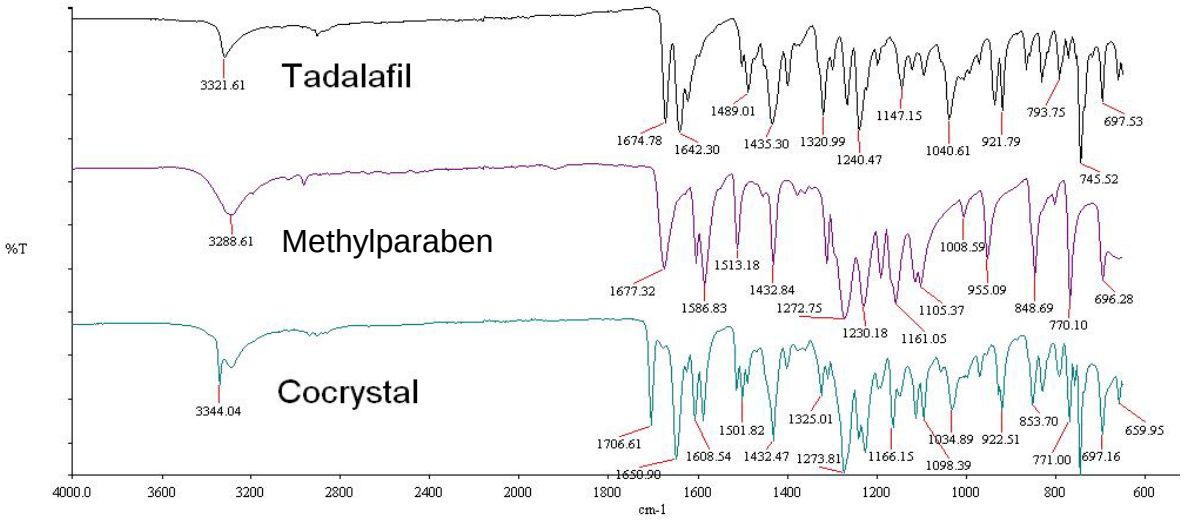

Figure S2: FT-IR data for **1**.

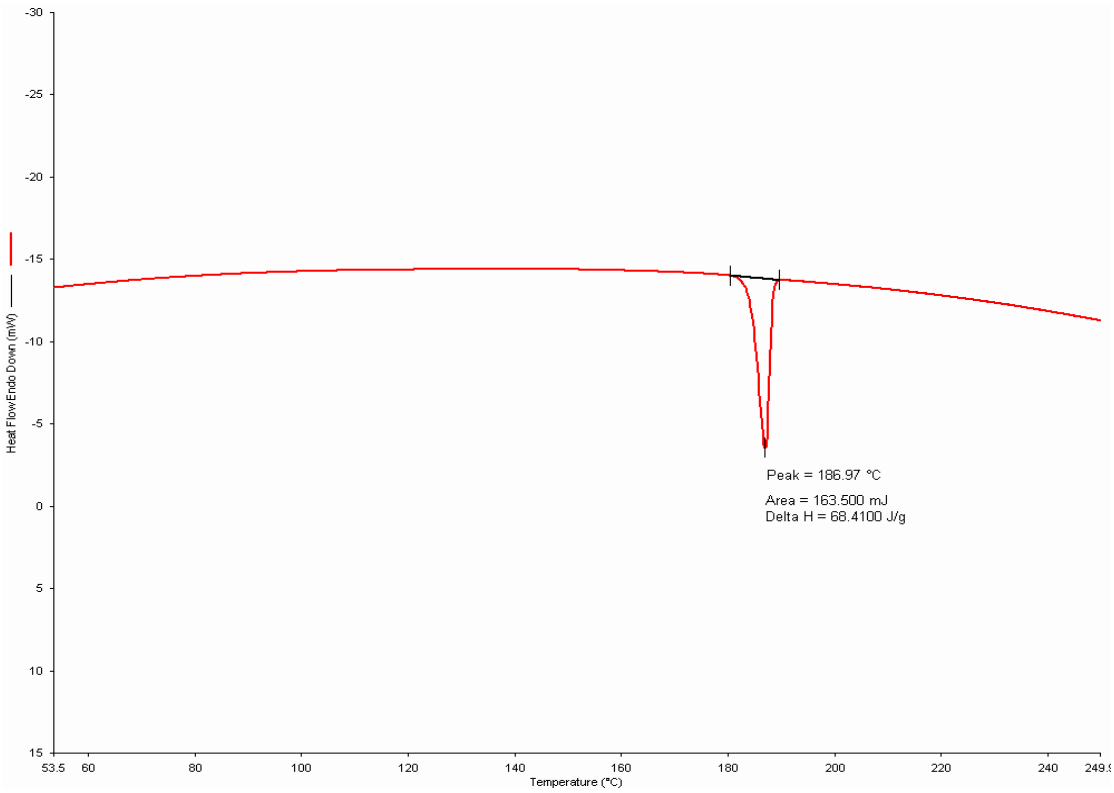

Figure S3: DSC data for **1**.

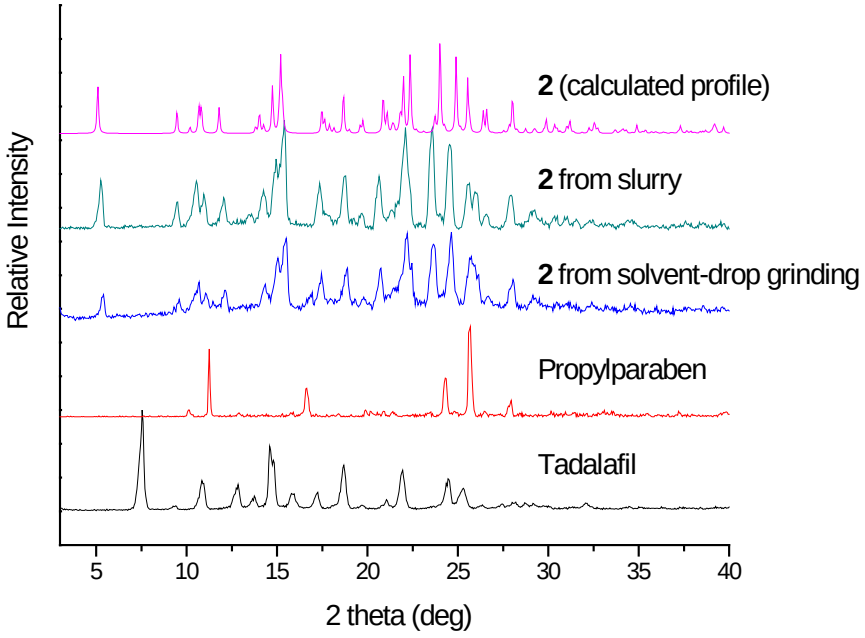

Figure S4: PXRD data for **2**.

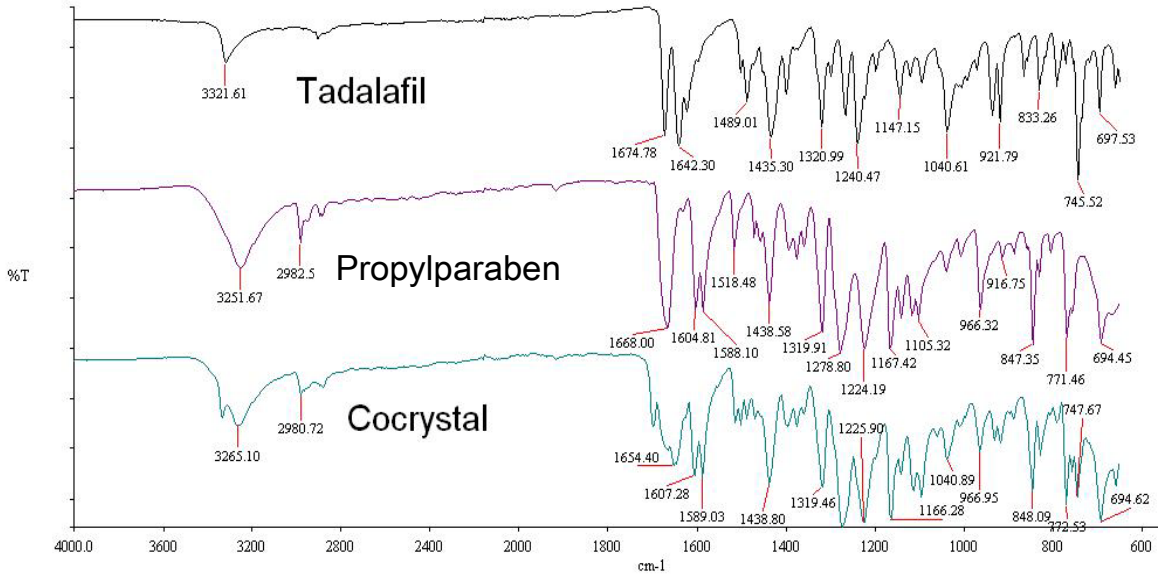

Figure S5: FT-IR data for **2**.

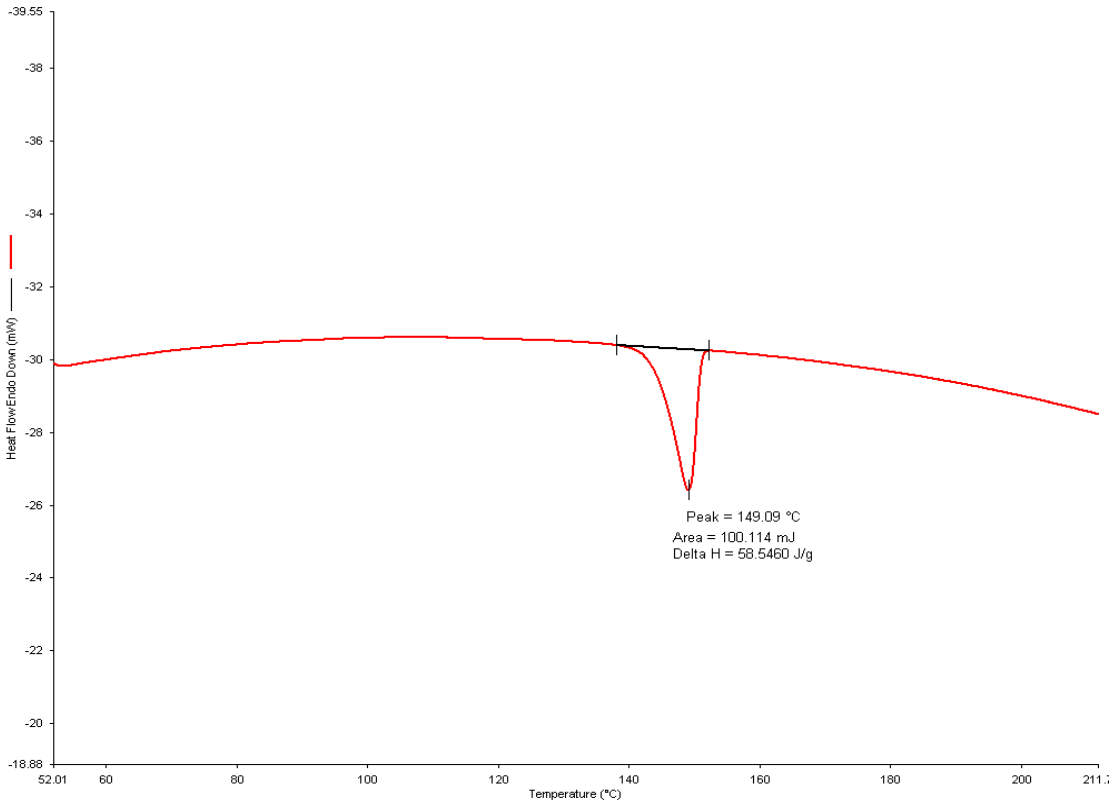

Figure S6: DSC data for **2**.

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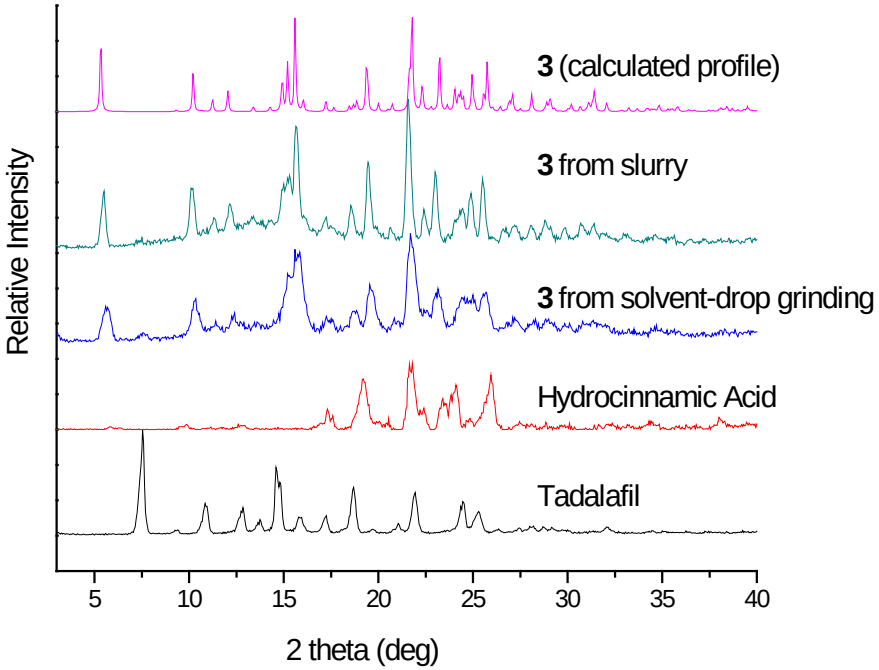

Figure S7: PXRD data for **3**.

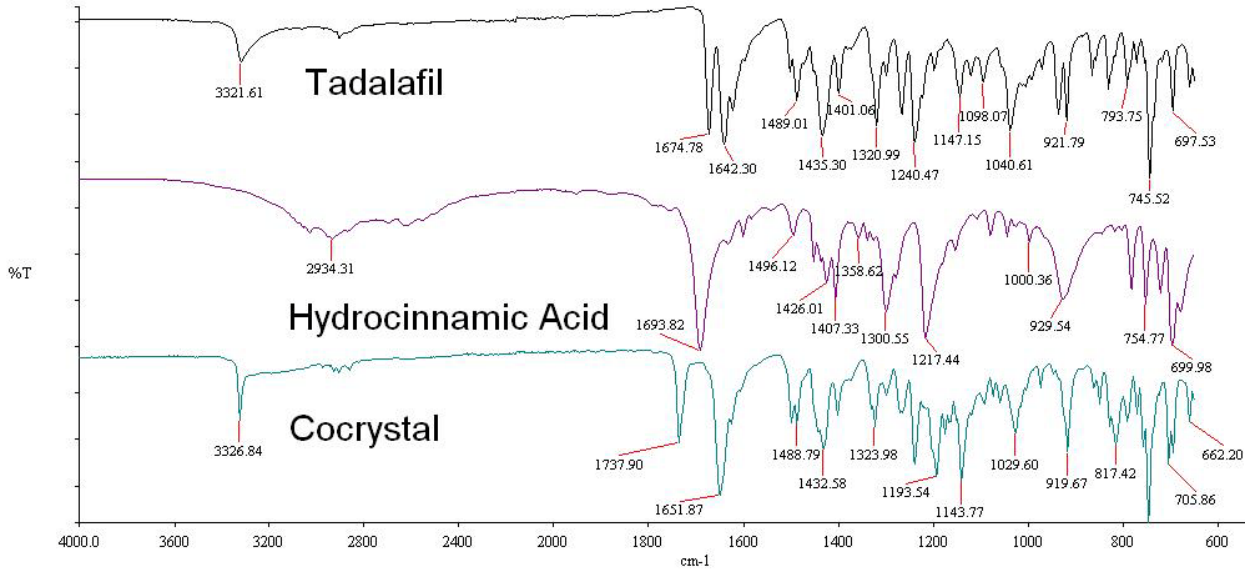

Figure S8: FT-IR data for **3**.

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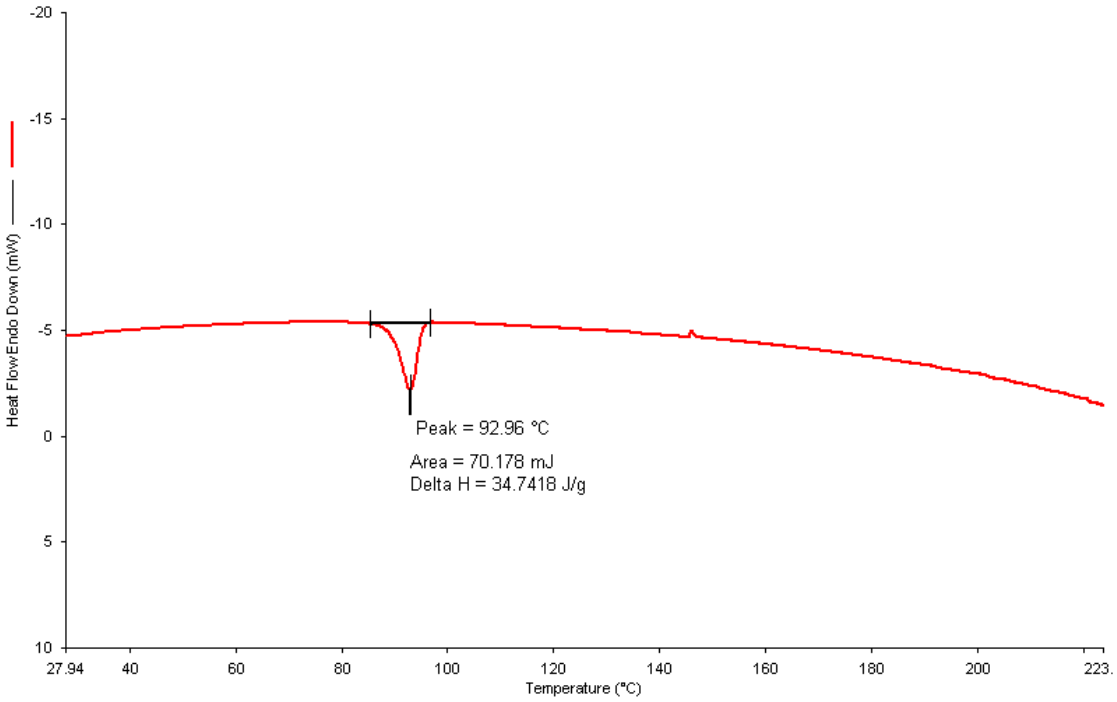

Figure S9: DSC data for **3**.

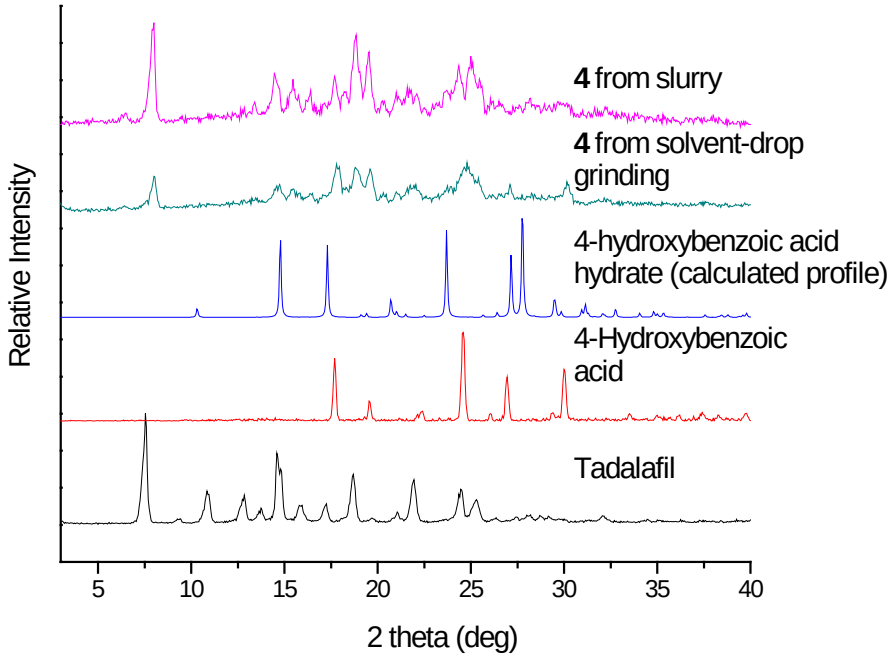

Figure S10: PXRD data for **4**.

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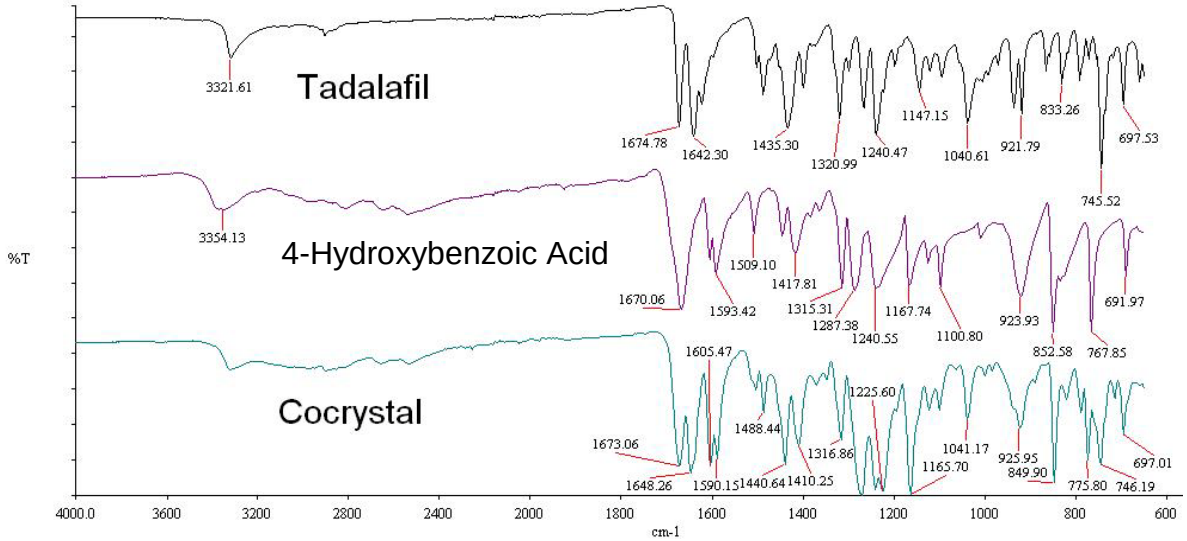

Figure S11: FT-IR data for **4**.

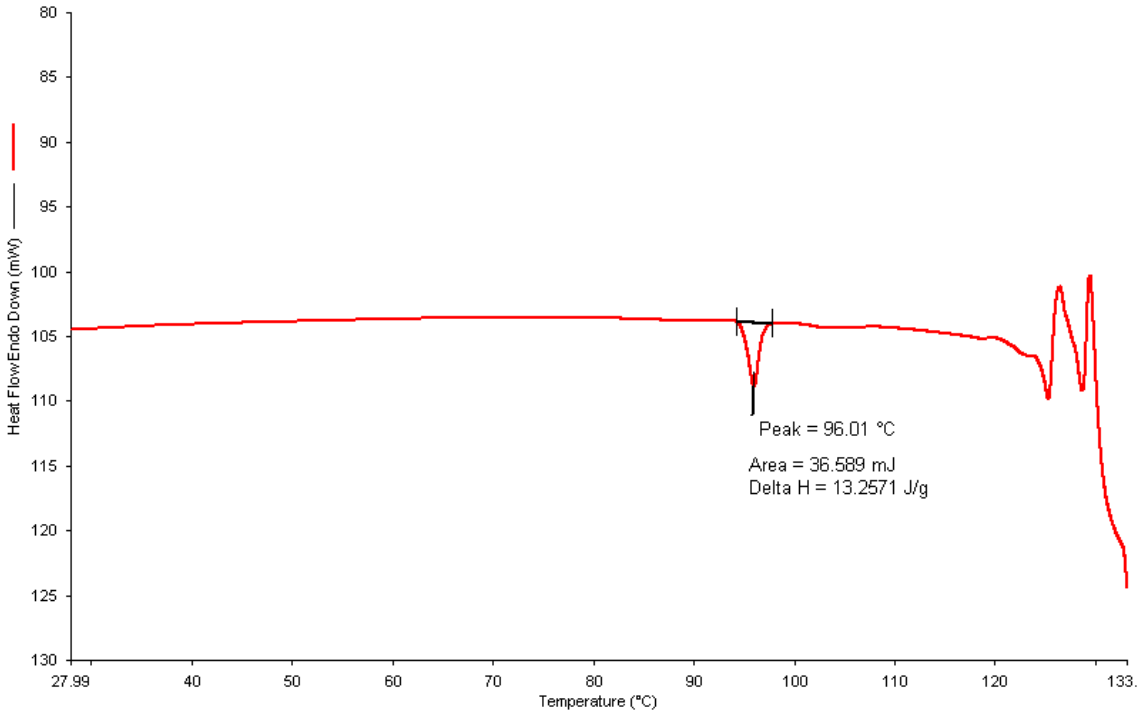

Figure S12: DSC data for **4**.

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5. MELTING POINTS OF TADALAFIL AND ITS COCRYSTALS

The melting points of tadalafil, coformers and cocrystals are presented in Table S2. The melting point correlation of **1**-**4** and corresponding coformers has been correlated. It is noted that good linear correlation was observed for the melting point data of **1**, **2** and **3**, as shown in Figure S13. However, **4** exhibited a melting point value which is inconsistent to the correlation trend.

Table S2: Melting points of API, coformers and cocrystals

	Melting Points of API or Coformer (°C)	Melting Points of Cocrystal (°C)
Tadalafil	301	Not applicable
1	127	186.97
2	95	149.09
3	47	92.96
4	215	95.77

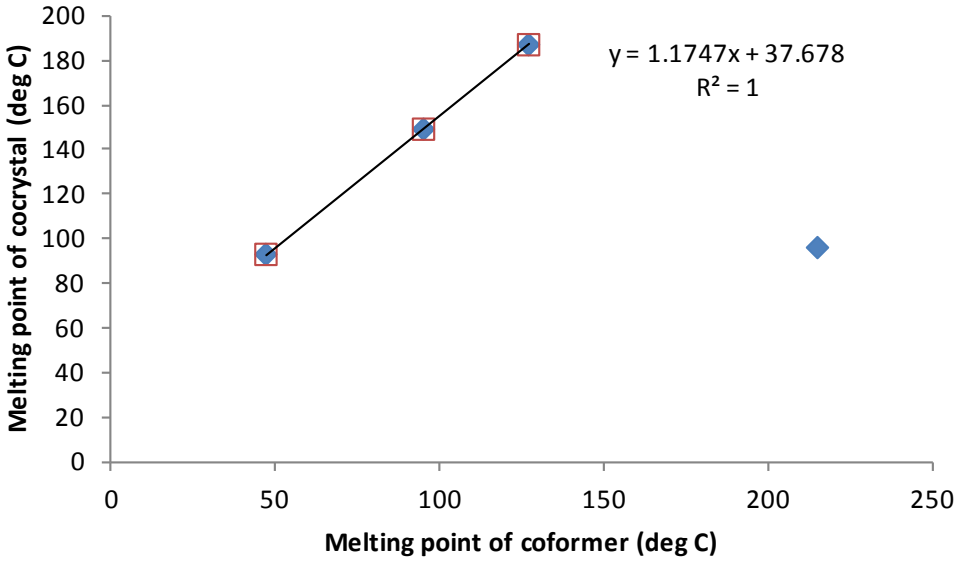

Figure S13: Melting point correlation of **1**-**4** and corresponding coformers. Good linear correlation was observed for the melting point data of **1**, **2** and **3** ($R^2 = 1$).