

Supporting Information

Polymorphism in Phenobarbital: Discovery of a New Polymorph and Crystal Structure of Elusive form V

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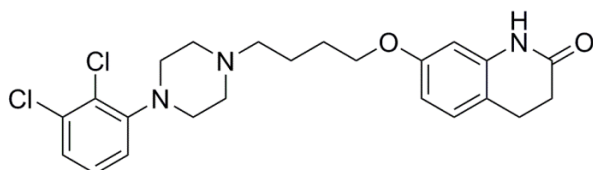
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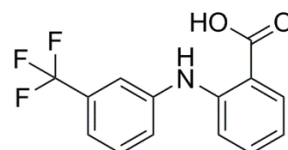
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SI 1. CSD Search and Chemical Structures of API's

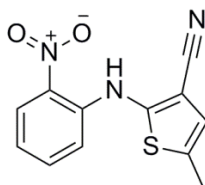
CSD search results described in the manuscript were performed on CSD version 5.37 (November 2015) + 1 update. Search was performed using polymorph, phase, form, modification and “3D structures determined” “no polymers” “no errors” “organics only” as filters. While counting the number of compounds with five or more structurally characterized polymorphs only the Active Pharmaceutical Ingredients (API's) are taken into consideration.



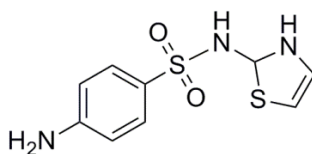
Aripiprazole, APZ



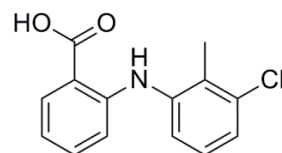
Flufenamic Acid, FFA



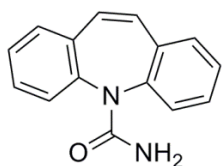
ROY



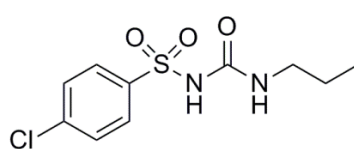
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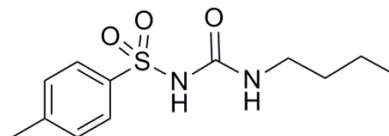
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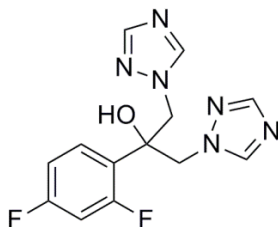
Carbamazepine



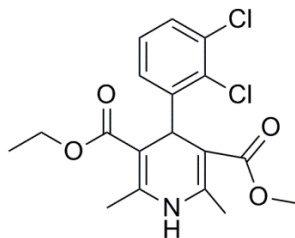
Chlorpropamide



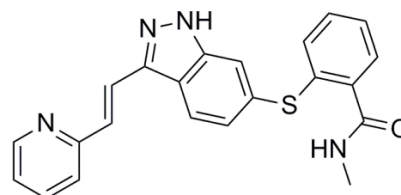
Tolbutamide



Fluconazole



Felodipine



Axitinib

Figure S1. Chemical structures of Nonamorphic Aripiprazole (APZ), Octamorphic Flufenamic Acid (FFA), heptomorphic ROY and other pentamorphic pharmaceuticals.

SI 2. Experimental Section

A saturated solution of PB was prepared by dissolving the material in absolute ethanol (30 mg/mL) and acetonitrile (24 mg/mL) at 80 °C. The solution was filtered using a 0.45 µm pore size PTFE filter and dispensed over 4-(benzyloxy) benzonitrile modified polystyrene for crystallization. This experiment resulted in form I-III. Melt crystallization was performed on a temperature controlled hot plate at 175-180 °C. PB (5-10 mg) mixed with 4-(benzyloxy) benzonitrile modified polystyrene and melted over glass plate followed by cooling to 0 °C to obtain form XV. Sublimation was carried out on a Linkam LTS350 hot stage connected to a Linksys32 control processor with 1-2 mg of sample covered with a glass cover slip. This experiment resulted in thin form V needles.

SI 3. Optical Microscopy

Optical images of PB polymorphs were collected using a Spot Advanced camera through Leica microscope coupled with a 2.5× 5× and 10× objectives. Images were processed using Spot Advanced software (version 4.6).

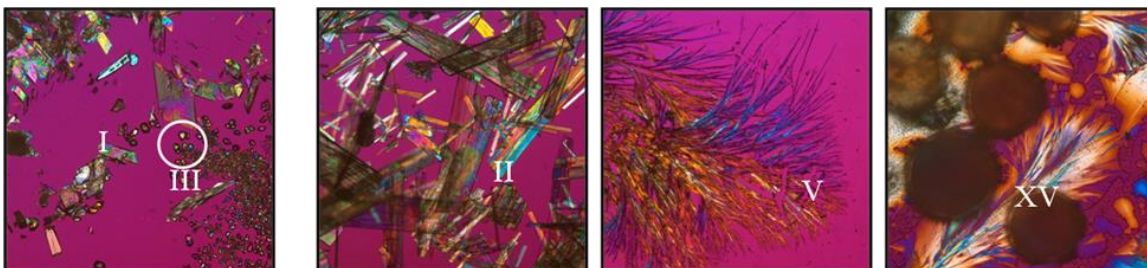


Figure S2. Optical microscopy of PB forms I, III, II, V and XV.

SI 4. Raman Spectroscopy

Raman spectra were collected using a Renishaw inVia Raman microscope equipped with a Leica microscope, RenCam CCD detector, 633 nm He-Ne laser, 1800 lines/nm grating, and 50 μm slit. Spectra were collected in extended scan mode in the range of 3600-100 cm^{-1} and then analyzed using Wire 3.1 software package. Calibration was performed using a silicon standard.

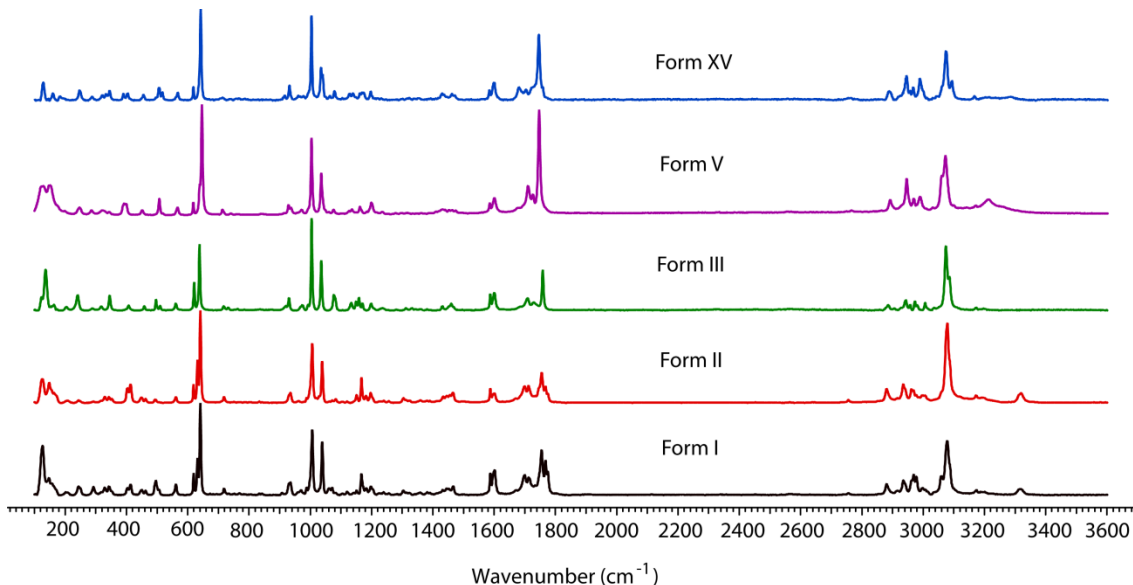


Figure S3. Raman spectra of phenobarbital polymorphs I, II, III, V and XV.

SI 5. Powder X-ray Diffraction

Powder X-ray diffraction (PXRD) patterns were collected at ambient temperature using a Rigaku R-Axis Spider diffractometer with an image plate detector and graphite monochromated $\text{Cu-K}\alpha$ radiation (1.5406 \AA). Samples were mounted on a cryoloop and images were collected for five minutes while rotating the sample about the ϕ -axis at $10^\circ/\text{sec}$, oscillating ω between 120° and 180° at $1^\circ/\text{sec}$ and χ fixed at 45° . Images were integrated from 5° to 40° with a 0.05° step size using AreaMax^[1] software. Powder patterns were processed in Jade Plus^[2] to calculate peak positions and intensities.

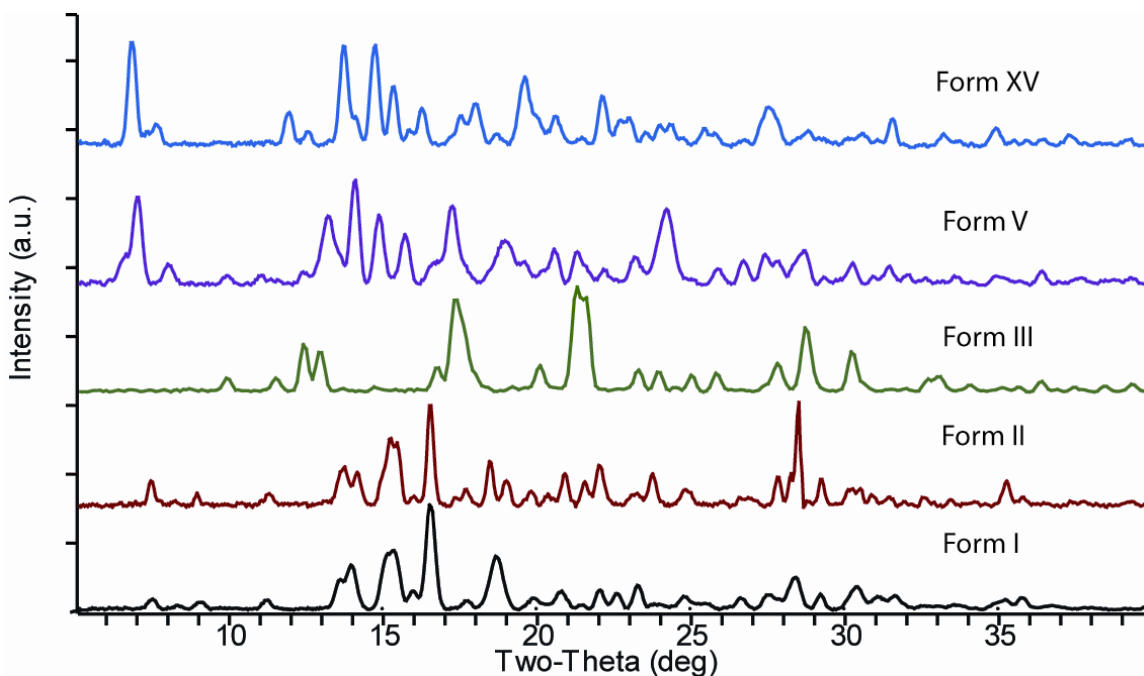


Figure S4. Powder diffraction profile for form I, II, III, V and XV.

Table S1. Experimental PXRD peak positions (°) and the relative intensity (%) of PB forms I, II, III, V and XV.

Form I		Form II		Form III		Form V		Form XV	
2θ	I/I ₀	2θ	I/I ₀	2θ	I/I ₀	2θ	I/I ₀	2θ	I/I ₀
3.8	9.7	3.8	20.5			7.0	100.0	6.8	100.0
7.5	8.9	7.4	21.6	9.9	12.6	8.0	19.9	7.3	16.0
8.3	2.5	13.7	43.0	11.5	10.4	13.2	57.4	7.6	17.0
9.1	5.4	14.2	29.6	12.4	42.8	14.1	89.6	11.9	30.0
11.2	8.4	15.3	88.0	17.4	89.1	14.9	70.0	12.6	11.3
14.0	41.7	16.5	100.0	20.1	21.5	15.7	46.3	13.7	91.4
15.3	55.7	17.7	13.5	21.3	100.0	16.7	17.3	14.7	86.6
16.5	100.0	18.5	29.7	23.3	17.7	17.2	89.3	15.3	45.4
18.7	47.9	19.0	12.2	28.7	53.8	18.9	44.7	16.3	25.4
20.8	12.4	19.8	11.6	30.2	38.0	20.6	30.8	17.5	25.8
22.0	15.1	20.4	12.3	33.1	12.4	21.3	30.5	18.0	37.8
22.6	10.9	22.0	43.2	39.3	5.5	23.2	21.6	19.6	58.9
23.3	19.0					24.2	79.0	22.1	38.9
28.4	23.6					26.7	22.2	27.5	35.5
29.2	12.5					27.4	25.7	31.5	24.0
30.4	15.6					28.7	32.3		
						30.2	22.7		
						31.4	18.5		

SI 6. Single Crystal X-ray Diffraction

Single crystal X-ray data for form V was collected on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with Micromax-007HF Cu-target micro-focus rotating anode. Data measurements on form XV were made on a Rigaku RAXIS SPIDER diffractometer with an image plate area detector. In both the cases graphite monochromated Cu-K α radiation (1.5406 Å) was used. Data collection was made at 85 K for form V and 95 K for form XV. Both the structures were solved by direct methods^[3] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement was made on F². An empirical absorption correction was applied to the structure. All calculations were performed using the CrystalStructure^[4] crystallographic software package except for refinement, which was performed using SHELXL-97.^[5]

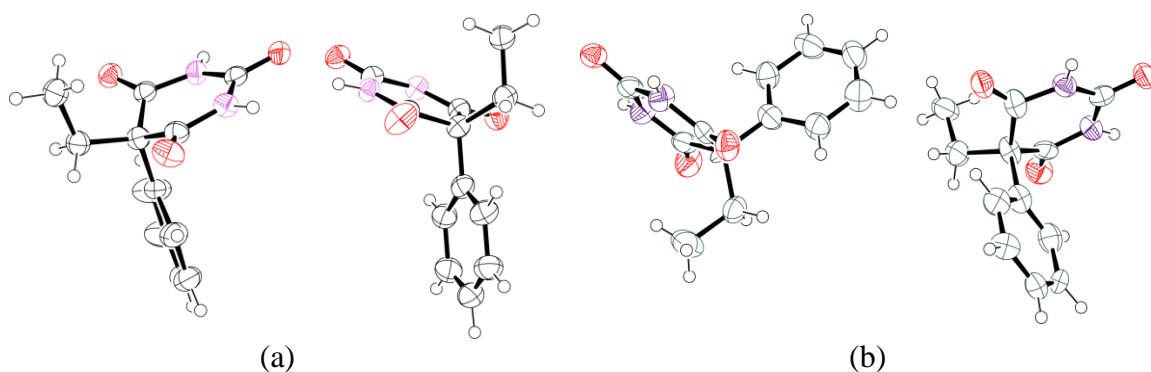


Figure S5. ORTEP of (a) form V and (b) form XV with 50% probability ellipsoids.

Table S2. Crystallographic parameters for form I^{6a}, form II^{6b}, form III^{6a}, form V and form XV.

	Form I	Form II	Form III	Form V	Form XV
<i>a</i>	10.700(1)	10.731	9.546(1)	13.0764(3)	14.5744(4)
<i>b</i>	47.259(5)	23.511	11.852(2)	6.72680(10)	6.88000(19)
<i>c</i>	6.803(1)	6.783	10.809(2)	26.5912(18)	22.9964(16)
α	90.00	90.97	90.00	90.00	90.00
β	94.20	94.48	111.60(1)	99.083(7)	93.987(7)
$-\gamma$	90.00	88.15	90.00	90.00	90.00
<i>V</i>	3430.8	1705.13	1136.98	2309.69(17)	2300.31(18)
<i>Z'</i>	3	3	1	2	2
<i>Z</i>	12	6	4	8	8
<i>R1</i>	0.0486	0.0751	0.0435	0.0876	0.0818
<i>Space Group</i>	P2 ₁ /n	P-1	P2 ₁ /c	P2 ₁ /n	P2 ₁ /n

SI 7. Hirshfeld Surface Analysis

The program CrystalExplorer (version 2.1)^[7] was used to render all surface and fingerprint plots. All bond lengths to hydrogen atoms are set to typical neutron values (C–H = 1.083 Å, O–H = 0.983 Å, N–H = 1.009 Å) for the generation of plots.

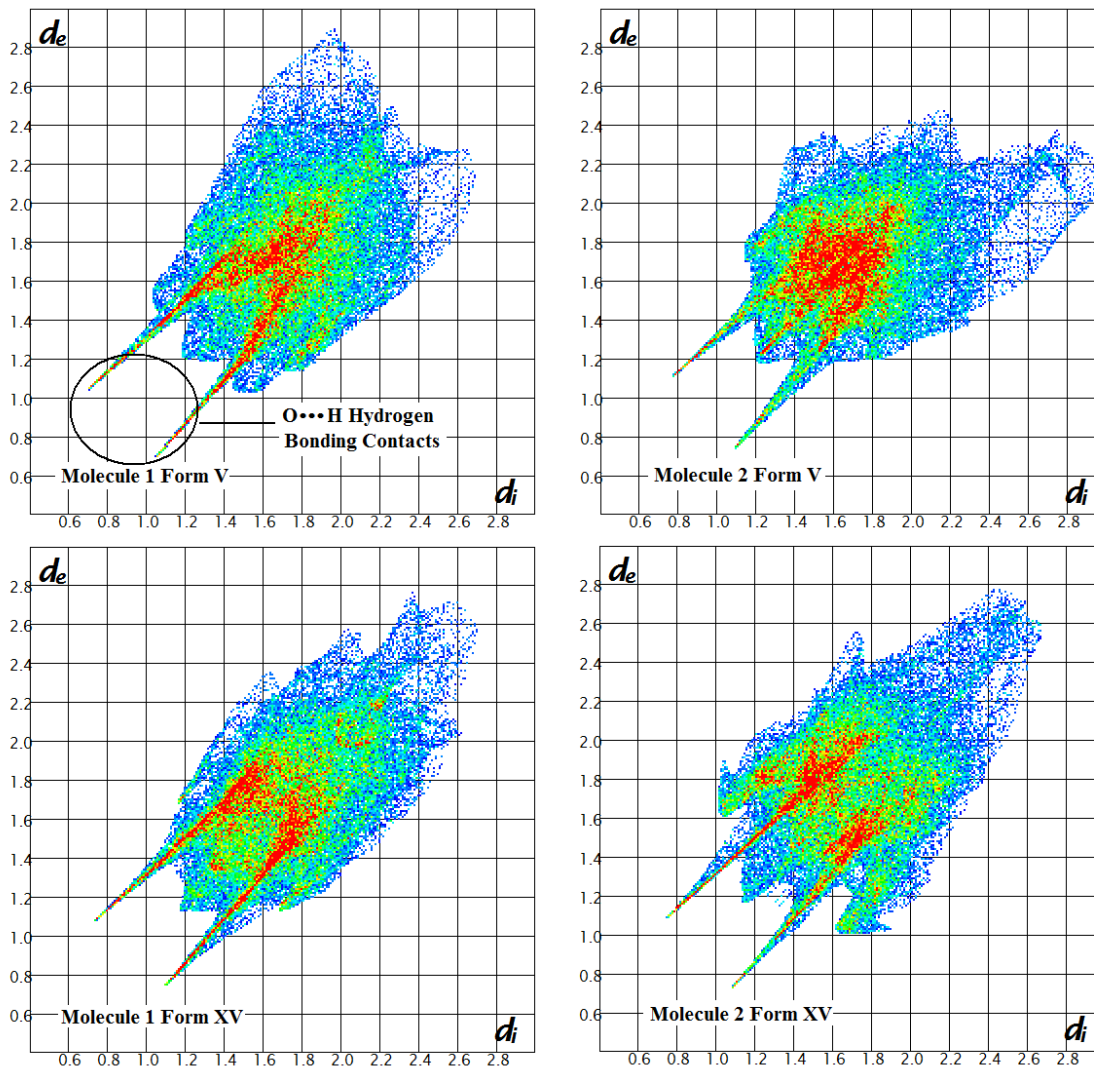


Figure S6. 2D fingerprint plot (Hirshfeld surface) of form V (molecule 1 and 2), form XV (molecule 1 and 2).

SI 8. Differential Scanning Calorimetry

Thermograms of the samples were recorded on a TA Instruments Q10 DSC. The thermal behavior of the samples, placed in sealed aluminum pans, was studied under nitrogen purge with a heating/cooling rate of 5 °C min⁻¹ covering the temperature range 35 °C to 200 °C. The instrument was calibrated with an indium standard. Endotherms were integrated with start and stop from onset to complete melting of the sample.

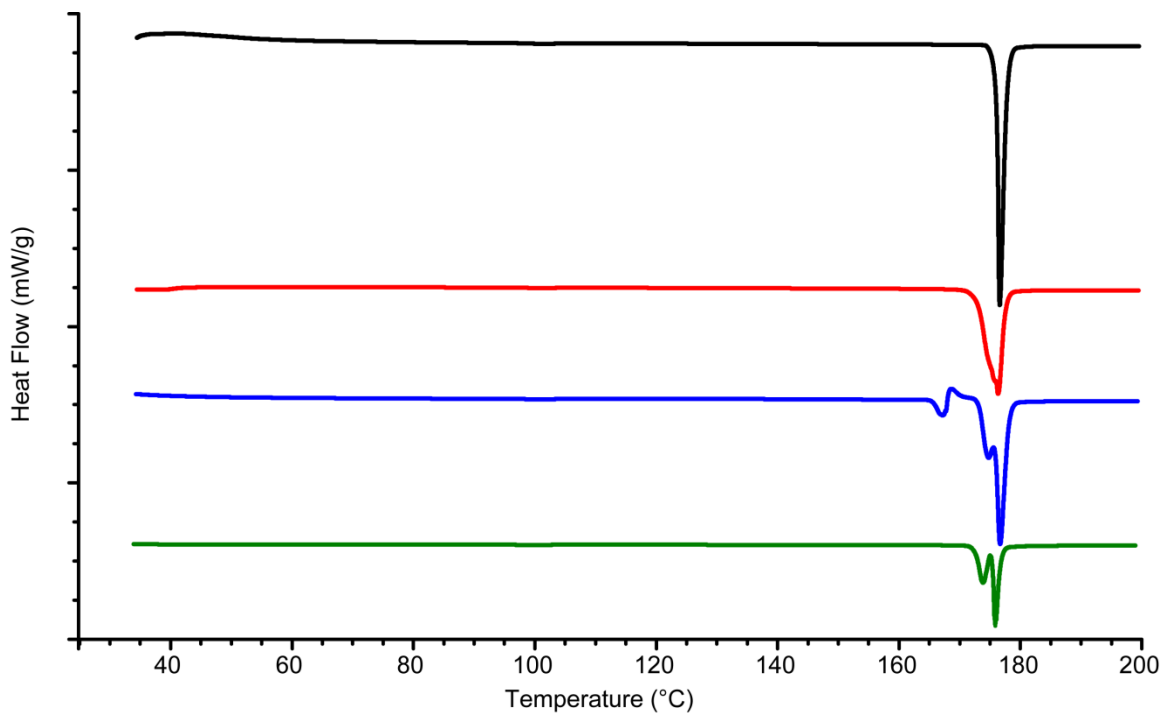
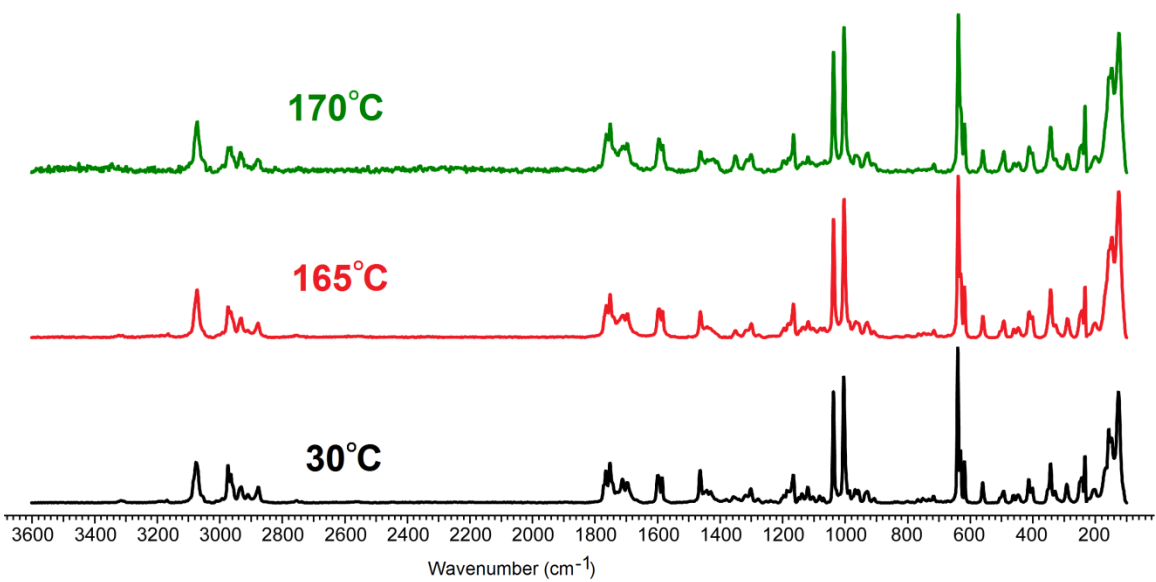


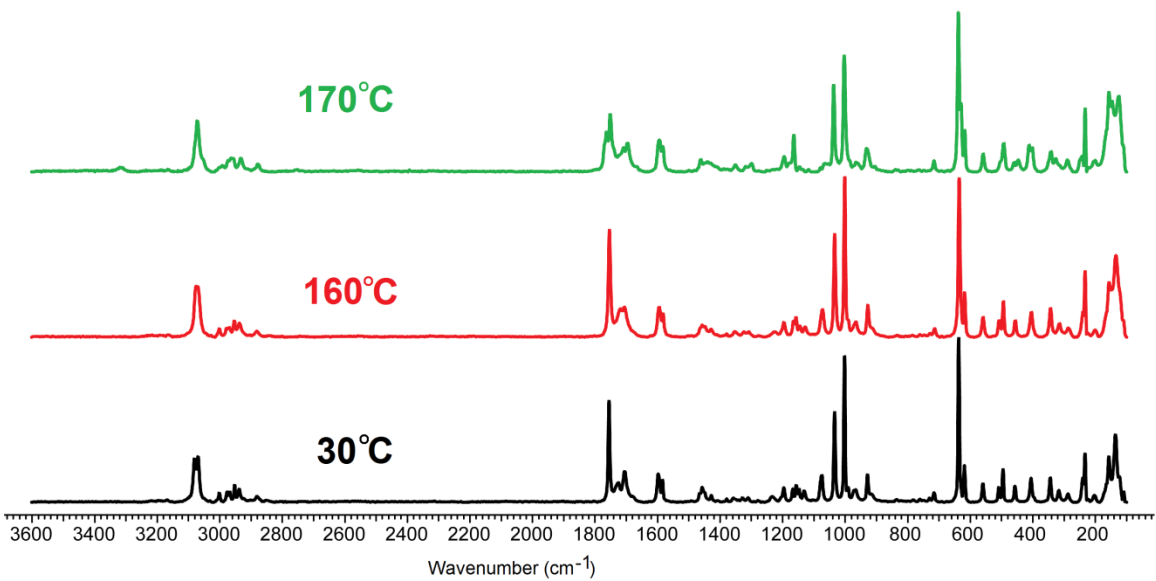
Figure S7. DSC traces of form I (black- onset 175.3 °C, $\Delta H= 6.93 \text{ kcal mol}^{-1}$), form II (red- onset 172.9 °C, $\Delta H= 6.73 \text{ kcal mol}^{-1}$), form III (blue- onset 175.6 °C, $\Delta H= 6.85 \text{ kcal mol}^{-1}$), form XV (green- onset 175.4 °C, $\Delta H= 5.93 \text{ kcal mol}^{-1}$).

SI 9. Variable Temperature Raman Spectroscopy

Variable temperature Raman spectra were collected using a Renishaw inVia Raman microscope equipped with a Leica microscope, RenCam CCD detector, 647 nm He-Ne laser, 1800 lines/nm grating, 65 μm slit coupled with LTS350 hot stage connected to a Wire 3.1 software control processor. Raman spectra collected on extended scan mode in the range of 3600-200 cm^{-1} for form I, II, III, XV and static mode at 1700 cm^{-1} for form V. Heating rates were 5.0 °C/min.



(a)



(b)

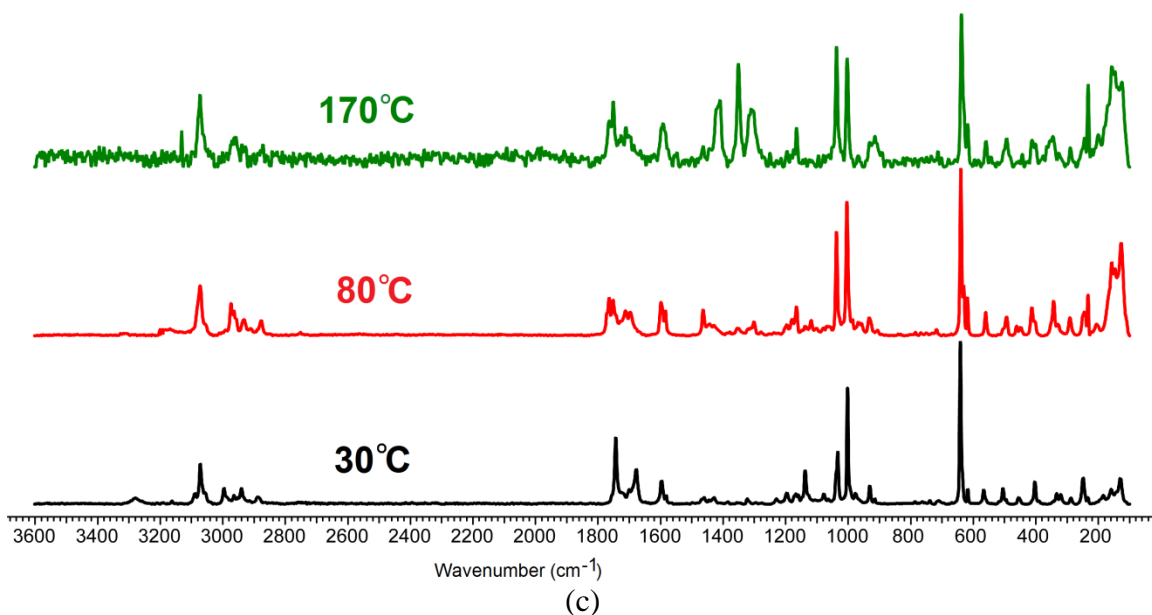


Figure S8. Variable temperature Raman spectra for (a) form II, (b) form III, (c) form XV.

SI 10. Equilibrium Solubility Experiments Polymorphs I, II, III and XV.

UV-vis spectra of saturated solutions of polymorphs I-III and XV were recorded on an Agilent 8453 UV-visible spectrophotometer. Saturated solutions of polymorphs were prepared by shaking in heptane for 24 hours at 299 ± 1 K. Absorbance was measured at 210 nm. Optical and Raman microscopy confirmed the polymorphic stability of the residual solid in each vial, indicating that no transformation to another crystal form occurred during the experiment. Equilibrium solubility suggests that form I and II are almost equi-energetic, while XV is least stable.

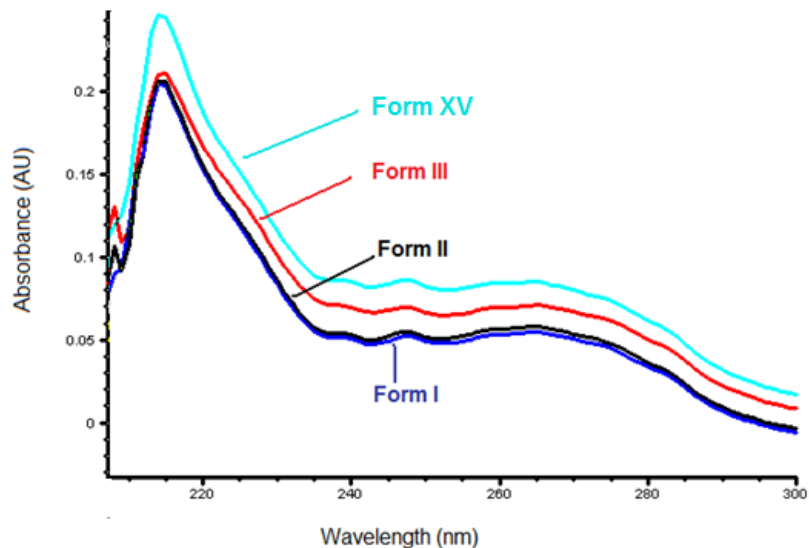


Figure S9. Absorbance of PB polymorph form I, II, III and XV at equilibrium with heptane.

SI 11. References

- [1] AreaMax 2.0.0.4 ed.; Rigaku, 2005.
- [2] Jade Plus 8.2 ed.; Materials Data, Inc, 1995-2007.
- [3] M. C. Burla, R. Caliendo, M. Camalli, B. Carrozzini, G. L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori, R. Spagna, *J. Appl. Crystallogr.*, 2005, **38**, 381.
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- [5] G. M. Sheldrick, SHELXS97 and SHELXL97. University of Göttingen, Germany, 1997.
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- [7] S. K. Wolf, D. J. Grimwood, J. J. McKinnon, D. Jayatilaka, M. A. Speckman, *CrystalExplorer 2.1*, University of Western Australia, Perth, 2007.