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Supporting Information

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Unmasking a Third Polymorph of a Benchmark Crystal Structure Prediction Compound

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SI 1. Experimental:

6-amino-2-phenylsulfonyl-imino-1,2-dihydropyridine (**1**) was prepared and purified according to the literature procedure.[1]

Crystallization:

A saturated solution (3.5 mg/mL) of molecule **1** was prepared by dissolving the material in absolute ethanol at 80 ºC. The solution was filtered using a 0.45 μm pore size PTFE filter and dispensed over benzyloxy-4-bromobenzene modified polystyrene for crystallization.

SI 2. Optical Microscopy

Images of form I-III of molecule **1** were collected using a Spot Advanced camera through Leica microscope coupled with a 10× objective. Images were processed using Spot Advanced software (version 4.6).

Form I   **Form II**   **Form III**
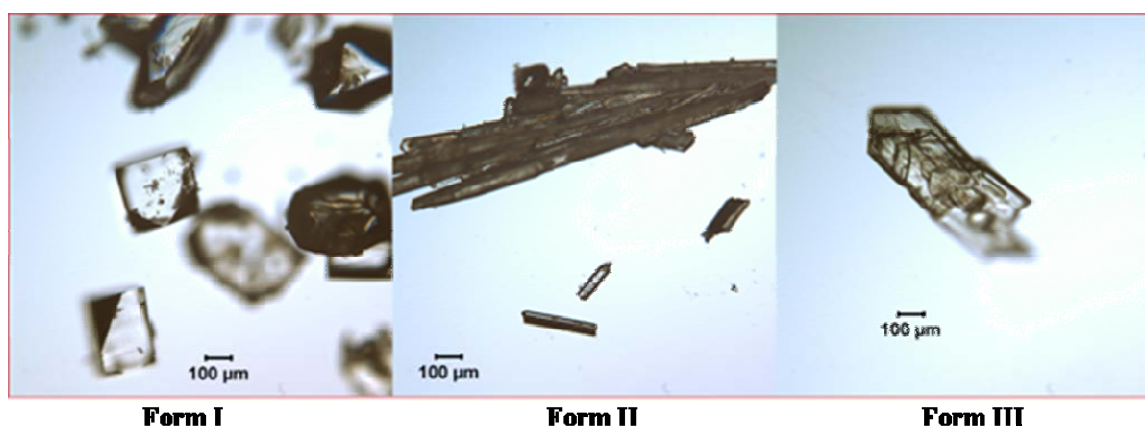
Figure S1. Optical microscopy of molecule **1** forms I, II and III.

SI 3. 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 3600-200 cm^{-1} and then analyzed using Wire 3.1 software package. Calibration was performed using a silicon standard.
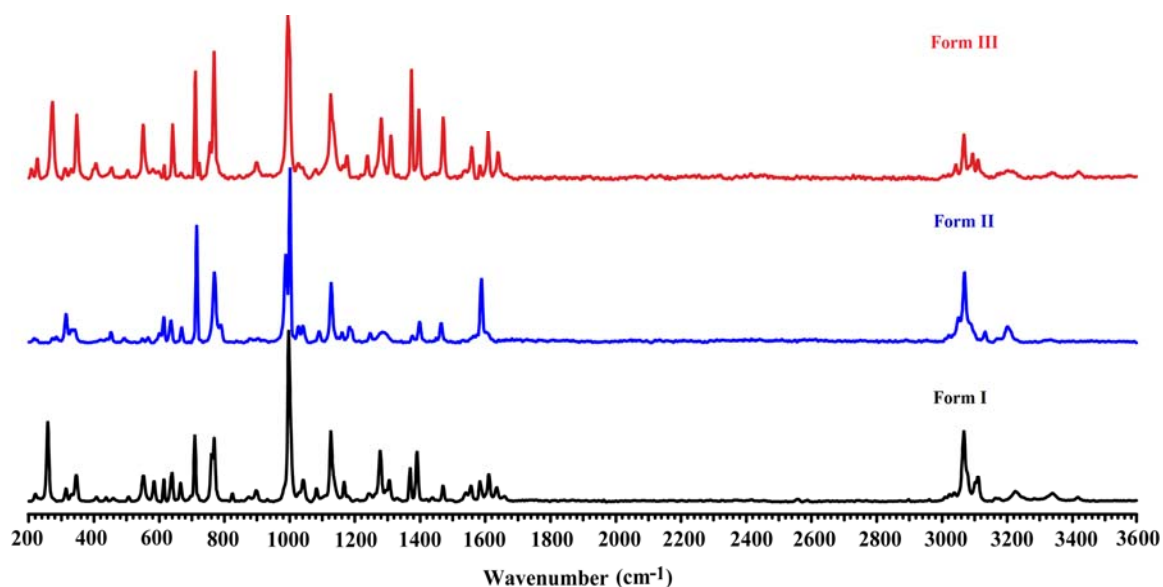
Figure S2. Raman spectra of molecule **1** polymorphs I-III.

Table S1. Frequency of Raman vibrational modes (cm^{-1}) of molecule **1** forms I-III.

Form I		Form II		Form III	
3416.8	1082.6	3200.3	636.6	3419.5	1126.0
3339.2	1041.7	3133.4	613.8	3217.9	994.3
3229.7	996.8	3069.7	452.0	3110.9	768.0
3110.5	898.0	1588.9	341.0	3095.3	711.2
3068.0	768.1	1464.0	314.0	3068.2	641.2
1633.9	709.3	1397.8		3042.6	550.7
1610.2	665.2	1375.8		1637.8	346.6
1583.2	639.1	1283.5		1609.0	272.6
1556.3	614.6	1247.5		1558.0	227.3
1469.7	584.4	1182.2		1470.8	
1390.5	551.7	1127.5		1396.7	
1369.3	345.9	1000.9		1373.7	
1304.7	314.8	987.8		1311.1	
1277.8	258.5	768.9		1280.7	
1166.7		715.0		1238.7	
1126.7		668.5		1176.2	

Different peak positions in three main spectral regions (3450-3000, 1640-1550 and 1000-990 cm^{-1}) were identified for the three forms (Table S1) of molecule **1**. Characteristic strong bands were observed for aromatic C–H stretching (3068.0, 3069.7 and 3068.2 cm^{-1} for form I, form II and form III respectively) and for ring breathing (996.8, 1000.9 and 994.3 cm^{-1} for form I, form II and form III respectively). The sulfonamide SO$_2$ stretching frequency of form I (1369.3 cm^{-1}) shifts towards higher energy in form II (1375.8 cm^{-1}) and form III (1373.7 cm^{-1}) suggesting weaker hydrogen bonding. Overall the Raman band position and spectral pattern for form II is quite different from form I and form III.

SI 4. 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 Cu-Kα radiation (1.5406 Å). Samples were mounted on a cryoloop and images were collected for five minutes while rotating the

sample about the φ-axis at 10º/sec, oscillating ω between 120º and 180º at 1º/sec and Φ fixed at 45º. Images were integrated from 5º to 50º with a 0.05º step size using AreaMax[2] software. Powder patterns were processed in Jade Plus[3] to calculate peak positions and intensities.

Table S2. Experimental PXRD peak positions (º) and the relative intensity (%) of molecule **1** forms I-III.

Form I		Form II		Form III	
2θ	I/I_0	2θ	I/I_0	2θ	I/I_0
10.3	64.2	7.4	24.7	7.3	43.2
11.6	6.2	10.5	6.9	11.0	29.6
14.2	27.1	14.7	46.7	14.6	76.3
15.4	100.0	16.1	100.0	16.6	53.5
18.6	21.9	19.7	24.1	18.1	9.1
19.6	7.8	21.7	20.5	19.3	49.2
20.4	92.5	22.4	69.1	20.5	13.9
22.9	52.7	24.1	5.0	22.2	100.0
23.6	31.2	24.8	7.5	23.8	17.8
24.1	51.5	25.8	28.0	24.2	22.4
25.4	21.7	26.5	7.6	25.6	20.3
26.1	50.1	30.0	13.0	26.0	8.6
28.7	9.9	31.9	6.9	27.8	25.9
29.4	27.3	32.7	8.9	29.0	13.6
31.4	23.4			30.0	8.9
31.9	20.1			30.9	10.5
32.7	7.0			32.4	5.9
33.4	6.9			33.5	5.3
34.7	7.6			35.2	5.2
35.4	14.6			39.3	6.4
43.0	7.4				
43.5	13.2				
44.3	7.5				
45.3	8.6				

SI 5. Single Crystal X-ray Diffraction

All measurements were made on a Rigaku RAXIS SPIDER diffractometer with an imaging plate area detector using graphite monochromated Cu-Kα radiation (1.5406 Å). The data collection was made at 95 K. The structure was solved by direct methods[4] 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 F^2. An empirical absorption correction was applied to the structure. All calculations were performed using the CrystalStructure[5] crystallographic software package except for refinement, which was performed using SHELXL-97.[6]
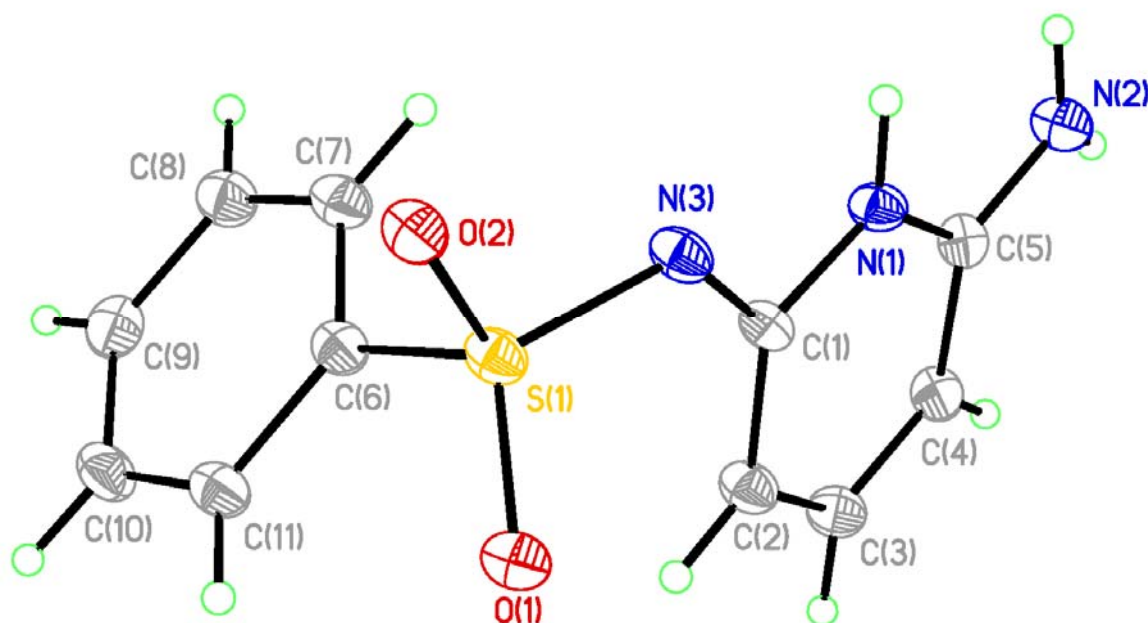
Figure S3. ORTEP diagram of form III with 30% probability ellipsoids.

Table S3. Crystallographic parameter for form I, form II[7] and form III.

	Form I (CCDC refcode: UJIRIO)	Form II (CCDC refcode:UJIRIO02)	Form III (New Polymorph)
Crystal system	Monoclinic	Monoclinic	Orthorhombic
Space group	$P2_1/c$	$P2_1/c$	$Pbca$
T [K]	183	203	95
a [Å]	8.479(5)	12.1099(15)	10.6177(2)
b [Å]	8.958(5)	10.7924(12)	9.31782(19)
c [Å]	14.894(8)	17.464(2)	23.0558(5)
α [deg]	90.00	90.00	90.00
β [deg]	91.856(10)	97.318(2)	90.00
γ [deg]	90.00	90.00	90.00
Z	4	8	8
Volume [Å^3]	1130.68	2263.864	2280.99(8)
D_{calc} [g/cm^3]	1.464	1.463	1.452

SI 6. Hirshfeld Surface Analysis

The program CrystalExplorer (version 2.1)[8] 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 used for the generation of plots.
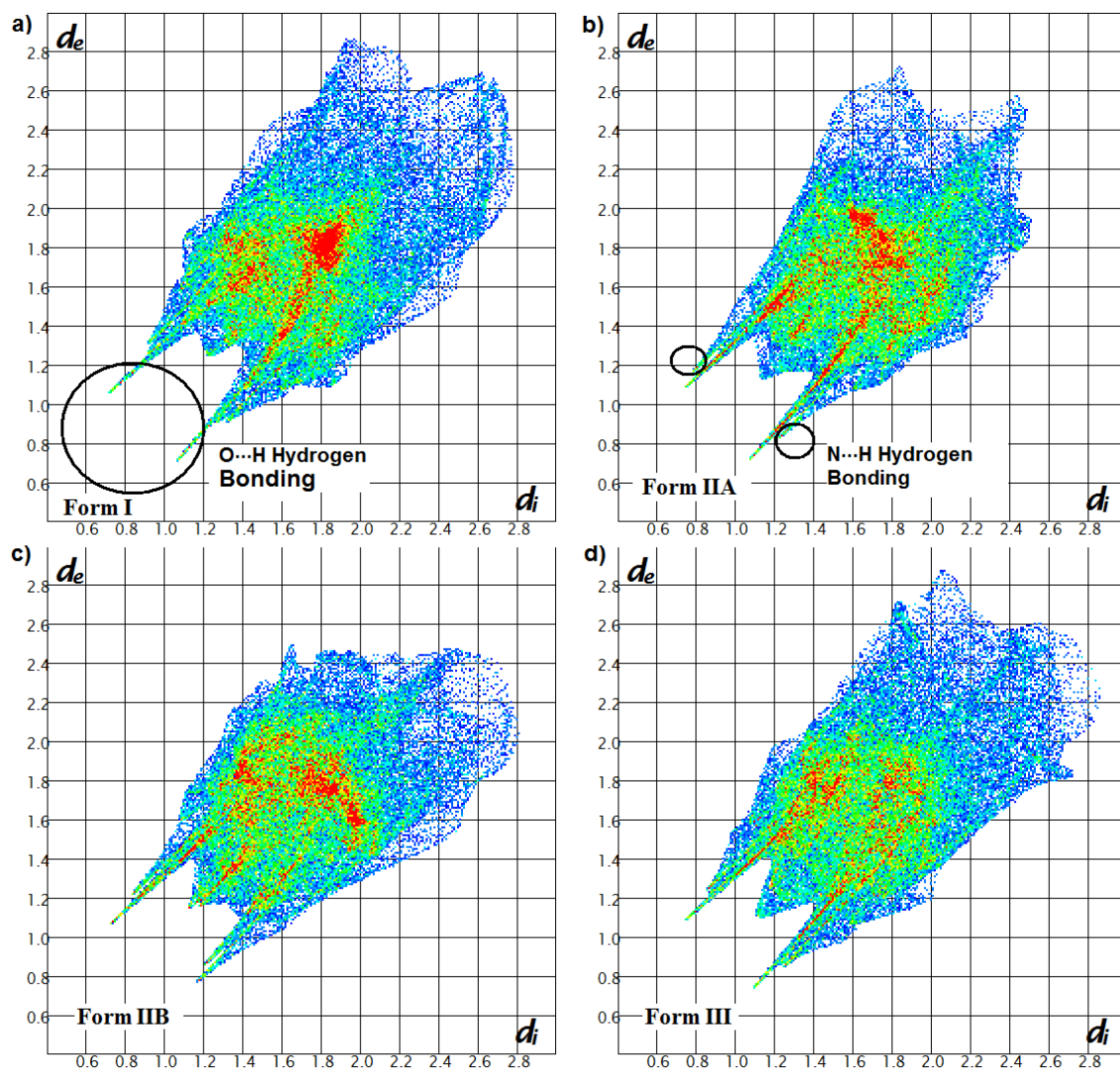
Figure S4. 2D fingerprint plot (Hirshfeld surface) of form I, form II (A and B) and form III.

SI 7. Thermomicroscopy

Samples were heated using a Linkam LTS350 hot stage connected to a Linkys32 control processor and viewed under a Nikon Eclipse E600 microscope, which was equipped with crossed polarizers. Images were processed using Qimaging camera and heating rates were 5.0 °C/min.

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 10 °C min^{-1} covering the temperature range 40 °C to 260 °C. The instrument was calibrated with an indium standard. Integration of endotherms calculated with start and stop from onset to complete melting of the sample.
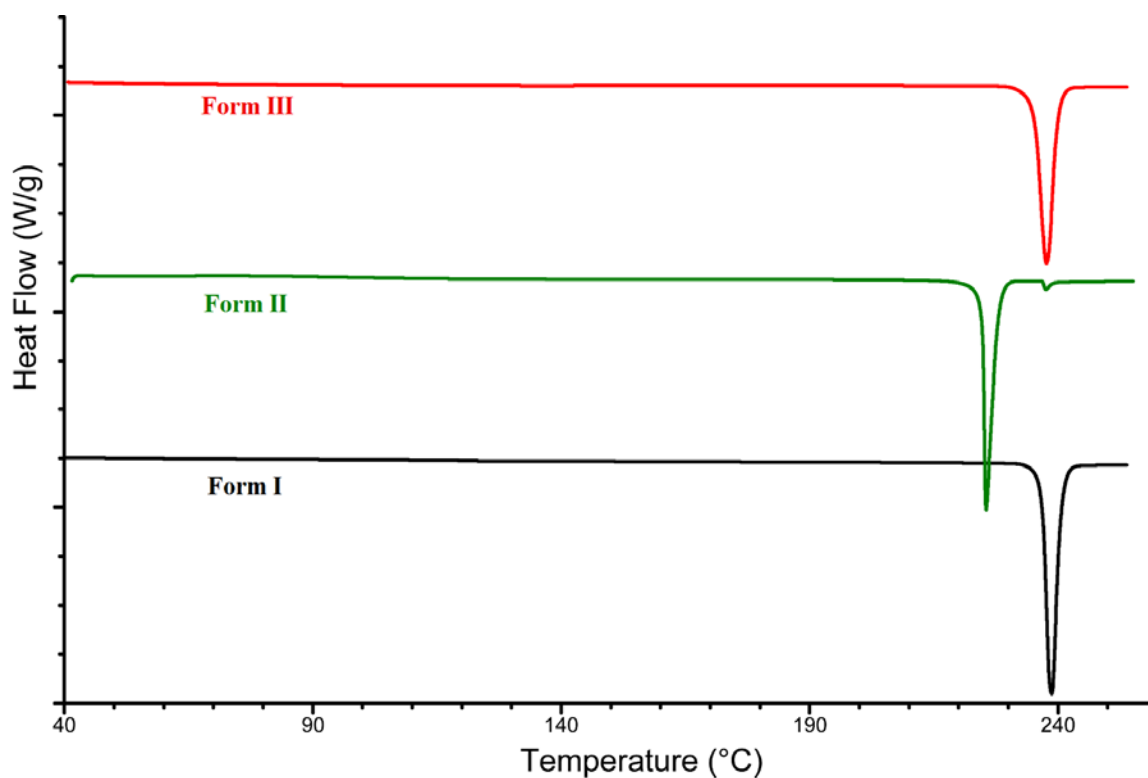
Figure S5. DSC traces of form I (onset 236.8 ˚C, ΔH= 11.81 kcal mol^{-1}), form II (onset 224.8 ˚C, ΔH= 9.56 kcal mol^{-1}) and form III (onset 235.2 ˚C, ΔH= 10.92 kcal mol^{-1}).

## SI 9. Equilibrium Solubility Experiments Polymorphs I-III.

UV-vis spectra of saturated solutions of polymorphs I-III were recorded on a Cary Bio 300 UV-visible spectrophotometer. Absorbance measured at 245nm for saturated solutions of polymorphs were prepared by shaking in water for three days at 299 ±1K. Optical and Raman microscopy confirmed the polymorphic identity of the residual solid in each vial, indicating that no transformation to another crystal form occurred during the experiment. Equilibrium solubility of form II is 2.1 times and form III is 1.5 times more than form I at 299K The difference in free energy was calculated from UV-visible absorbance by the equation $\Delta G = -RT \ln K$, with K = (abs form I)/ (abs form II).

Table S4. Difference in free energy derived from Equilibrium solubility.

Polymorph	ΔG (kcal mol^{-1})
Form I	0.00
Form II	0.44
Form III	0.23

SI 10. Schematic Energy *vs* Temperature Diagram
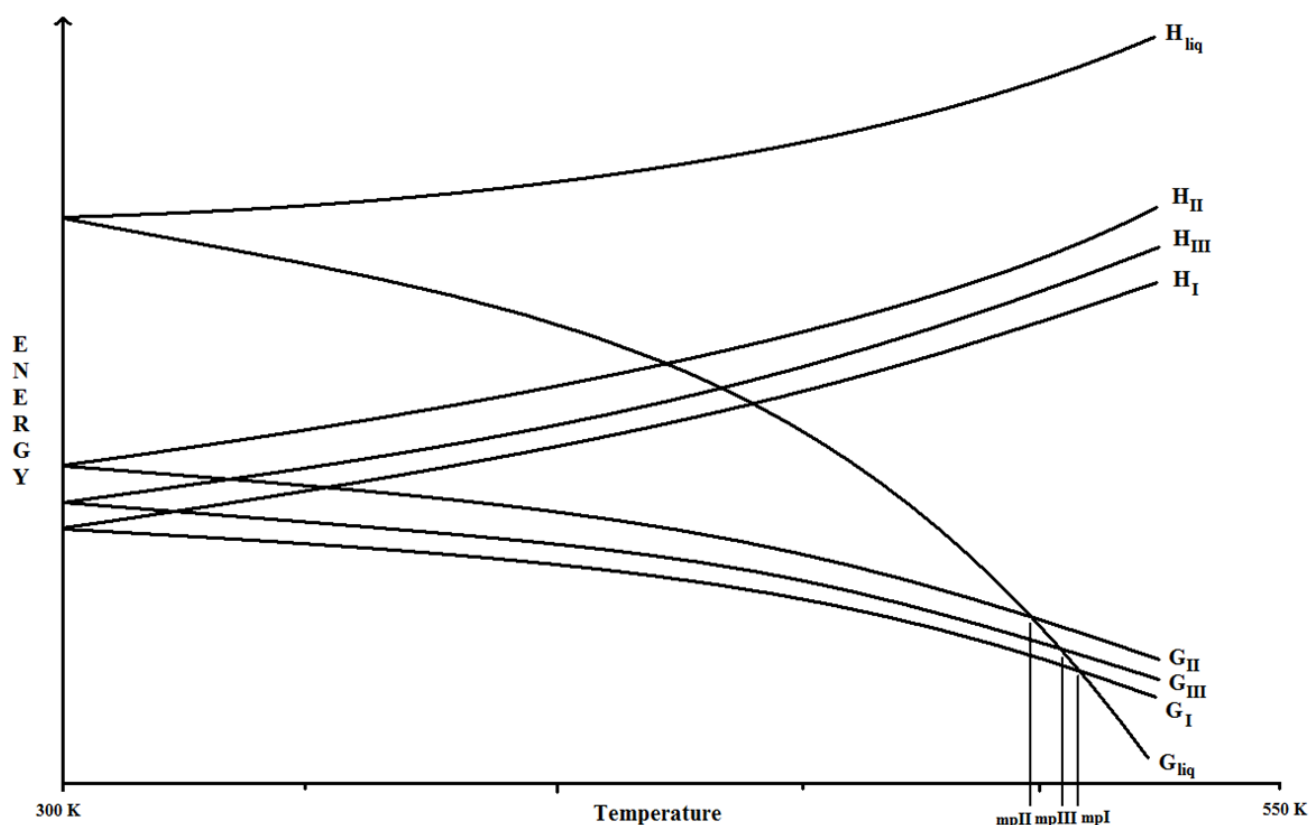
Figure S6. Qualitative Energy *vs* Temperature diagram for the three polymorphs of molecule **1**. Diagram drawn from the results of difference in free energy between polymorphs and DSC measurements.

SI 11. References

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