Electronic Supplementary Material for CrystEngComm

Supporting Information for

Discovery of three polymorphs of 7-fluoroisatin reveals challenges in using computational crystal structure prediction as a complement to experimental screening

Contents

Figure S1 Pictures of crystals of (a) form I, (b) form II and (c) form III of **1** mounted for single crystal X-ray diffraction.

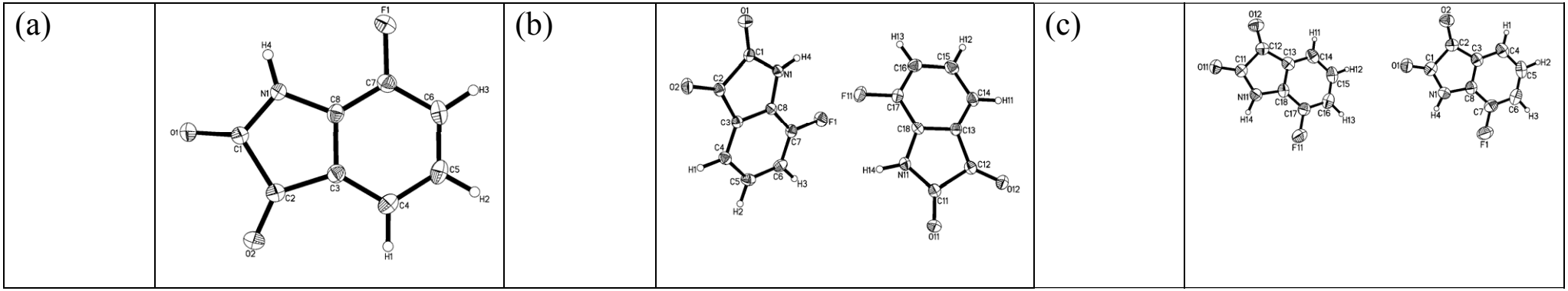


Figure S2 Ortep plots of (a) form I, (b) form II and (c) form III of **1**

Electronic Supplementary Material for CrystEngComm

Table S1: Hypothetical low energy crystal structures of 7-fluoroisatin, **1**, as obtained from the computational crystal structure prediction.

Structure [a]	Space group	Lattice energy kJmol^{-1}	Free energy [c] kJmol^{-1}	Density g cm^{-3}	Cell parameters [d] Set						Graph Set
					a(Å)	b(Å)	c(Å)	α(°)	β(°)	γ(°)	
am100	$P2_1/c$	-104.45	-121.70	1.505	4.45	11.74	13.98	90	92.96	90	$R_2^2(8)$
Form I [b]	$P2_1/c$	-104.44	-121.69	1.504	4.45	11.74	13.98	90	87.04	90	$R_2^2(8)$
am33	$P2_1/c$	-104.37	-120.02	1.572	6.55	14.84	7.19	90	93.26	90	$R_2^2(8)$
fc13	$P2_1/c$	-102.87	-122.11	1.587	3.82	7.66	23.65	90	87.76	90	$R_2^2(8)$
fc22	$P2_1/n$	-102.35	-121.60	1.590	7.61	3.80	23.84	90	91.54	90	$R_2^2(8)$
Form III [b]	$P2_1/a$	-102.35	-119.34	1.496	8.83	13.27	12.81	90	102.31	90	$R_2^2(8)$
av3	$Pna2_1$	-101.94	-118.61	1.584	7.27	14.32	6.65	90	90	90	$C_1^1(4)$
ai19	$P2_1/c$	-101.79	-120.21	1.580	12.27	3.84	15.31	90	74.31	90	$R_2^2(8)$
Form II [b]	P-1	-101.7	-119.07	1.529	7.93	8.43	13.08	68.07	83.49	62.38	$R_4^4(18)$
cb102	$Pbca$	-101.33	-118.09	1.555	7.12	13.25	14.95	90	90	90	$R_2^2(8)$
am84	$P2_1/n$	-101.31	-116.97	1.551	5.85	10.45	12.36	90	69.49	90	$R_2^2(8)$
cd48	$Pbcn$	-101.3	-118.00	1.539	15.07	7.02	13.48	90	90	90	$R_2^2(8)$
am26	$P2_1/n$	-101.28	-119.10	1.517	4.36	14.94	11.63	90	72.85	90	$R_2^2(8)$
af45	$P2_1$	-101.12	-118.16	1.565	4.09	7.37	14.33	90	54.25	90	$C_1^1(4)$
cd77	$P1$	-101.03	-101.03	1.502	13.21	17.02	6.82	107.12	84.96	89.65	$R_2^2(8)$
fa39	$P2_1$	-100.5	-119.88	1.574	7.56	24.30	3.80	90	88.51	90	$R_2^2(8)$
ca99	P-1	-99.89	-117.31	1.568	8.61	3.83	12.57	90	75.22	118.27	$R_2^2(8)$
aq85	$P2_12_12_1$	-99.86	-120.89	1.576	7.60	24.32	3.77	90	90	90	$C_1^1(4)$
am6	$P2_1/c$	-99.85	-118.89	1.523	3.93	12.19	15.02	90	89.63	90	$R_2^2(8)$
af46	$P2_1$	-99.8	-118.83	1.572	7.55	3.80	12.62	90	74.46	90	$R_2^2(8)$
fc70	$P2_1/n$	-99.58	-118.80	1.547	4.14	7.40	23.94	90	75.19	90	$R_2^2(8)$
am11	$P2_1/c$	-99.57	-116.59	1.498	7.35	13.15	7.60	90	85.91	90	$R_2^2(8)$
ai10	$P2_1/c$	-99.56	-118.16	1.589	12.75	3.81	15.13	90	109.90	90	$R_2^2(8)$
ab34	P-1	-99.54	-118.05	1.552	7.51	3.78	14.62	112.23	68.03	91.82	$R_2^2(8)$
am5	$P2_1/n$	-99.53	-117.71	1.511	4.19	13.12	13.68	90	74.79	90	$R_2^2(8)$

[a] The structures found in the search are labelled according to their initial MOLPAK co-ordination geometry. [b] The experimental structures after minimisation with the same computational model used in the search (The experimental structures are in Table 1). [c] Estimated Helmholtz Free energy at 298 K. [d] Niggli reduced cell parameters.

Electronic Supplementary Material for CrystEngComm

Table S2: Hypothetical low energy crystal structures of 5-fluoroisatin, **2**, as obtained from the computational crystal structure prediction.

Structure [a]	Space group	Lattice energy kJmol^{-1}	Free energy [d] kJmol^{-1}	Density gcm^{-3}	Cell parameters [e]						Graph Set
					a(Å)	b(Å)	c(Å)	α(°)	β(°)	γ(°)	
Experimental 298 K [b]	$P2_1/c$			1.581	3.79	12.20	14.99	90	94.41	90	$R_2^2(8)$
ExpMinOpt [c]	$P2_1/c$	-112.15	-129.07	1.566	3.92	12.25	14.58	90	90.79	90	$R_2^2(8)$
am66	$P2_1/c$	-112.16	-129.07	1.566	3.92	12.25	14.58	90	90.79	90	$R_2^2(8)$
fc91	$P2_1/n$	-111.64	-127.54	1.560	5.64	5.33	27.12	90	120.38	90	$C_1^1(4)$
bb8	$P12_11$	-111.60	-127.70	1.561	23.55	5.51	5.41	90	90	90	$D_1^1(2)$
fc114	$P2_1/n$	-109.45	-126.88	1.561	6.13	5.04	24.25	90	110.33	90	$C_1^1(4)$
aq87	$P2_12_12_1$	-108.80	-127.09	1.549	6.16	23.18	4.95	90	90	90	$C_1^1(4)$
ca34	P-1	-107.75	-123.42	1.586	8.29	7.35	7.78	84.84	76.12	48.97	$R_2^2(8)$
ak27	$P2_1/c$	-107.75	-122.50	1.583	7.95	6.90	13.33	90	108.69	90	$R_2^2(8)$
am76	$P2_1/n$	-107.64	-125.73	1.576	3.78	15.26	12.32	90	101.92	90	$R_2^2(8)$
av8	$Pna2_1$	-107.60	-127.76	1.544	14.86	12.68	3.77	90	90	90	$C_1^1(4)$
aq7	$P2_12_12_1$	-106.86	-125.63	1.558	12.63	14.38	3.88	90	90	90	$C_1^1(4)$
bj119	Pn	-106.83	-125.08	1.519	24.54	5.60	5.38	90	77.59	90	$D_1^1(2)$
bh57	Pa	-106.79	-125.06	1.521	23.85	5.55	5.44	90	90	90	$D_1^1(2)$
cd96	$P2_111$	-106.54	-106.54	1.524	13.23	16.81	8.62	131.28	90	90	$R_2^2(8)$
cd109	$P1$	-106.50	-106.50	1.535	13.18	16.71	6.75	75.12	95.47	89.25	$R_2^2(8)$
af102	$P2_1$	-106.37	-121.99	1.553	5.99	5.23	17.48	90	139.83	90	$C_1^1(4)$
am9	$P2_1/c$	-106.16	-125.44	1.511	4.01	12.00	15.09	90	91.13	90	$R_2^2(8)$
af93	$P12_11$	-106.10	-124.05	1.528	5.61	5.29	12.67	90	107.31	90	$R_2^2(8)$
fa106	$P2_1/c$	-106.10	-122.50	1.529	4.69	25.77	8.26	90	45.89	90	$C_1^1(4)$
ar26	$P1$	-105.80	-105.80	1.594	9.55	15.38	6.10	90	129.91	90	$R_2^2(8)$
au47	$Pna2_1$	-105.75	-122.53	1.532	23.32	5.40	5.69	90	90	90	$C_1^1(4)$
cb75	$Pca2_1$	-105.70	-123.64	1.494	12.81	16.66	6.88	90	90	90	$R_2^2(8)$
fa110	$P2_1/c$	-104.94	-122.78	1.553	4.26	20.81	8.11	90	79.54	90	$R_2^2(8)$
am118	$P2_1/c$	-104.49	-120.83	1.500	5.32	13.38	10.56	90	103.46	90	$R_2^2(8)$

[a] The structures found in the search are labelled according to their initial MOLPAK co-ordination geometry. [b] The experimental crystal structure of **2** [c] The experimental structures after minimisation with the same computational model used in the search. [d] Estimated Helmholtz Free energy at 298 K. [e] Niggli reduced cell parameters.

Electronic Supplementary Material for CrystEngComm

Table S3: The solubility of 7-fluoroisatin, **1**, and 5-fluoroisatin, **2**, in the 29 solvents tested as well as the cell check results from all successful crystallisation experiments

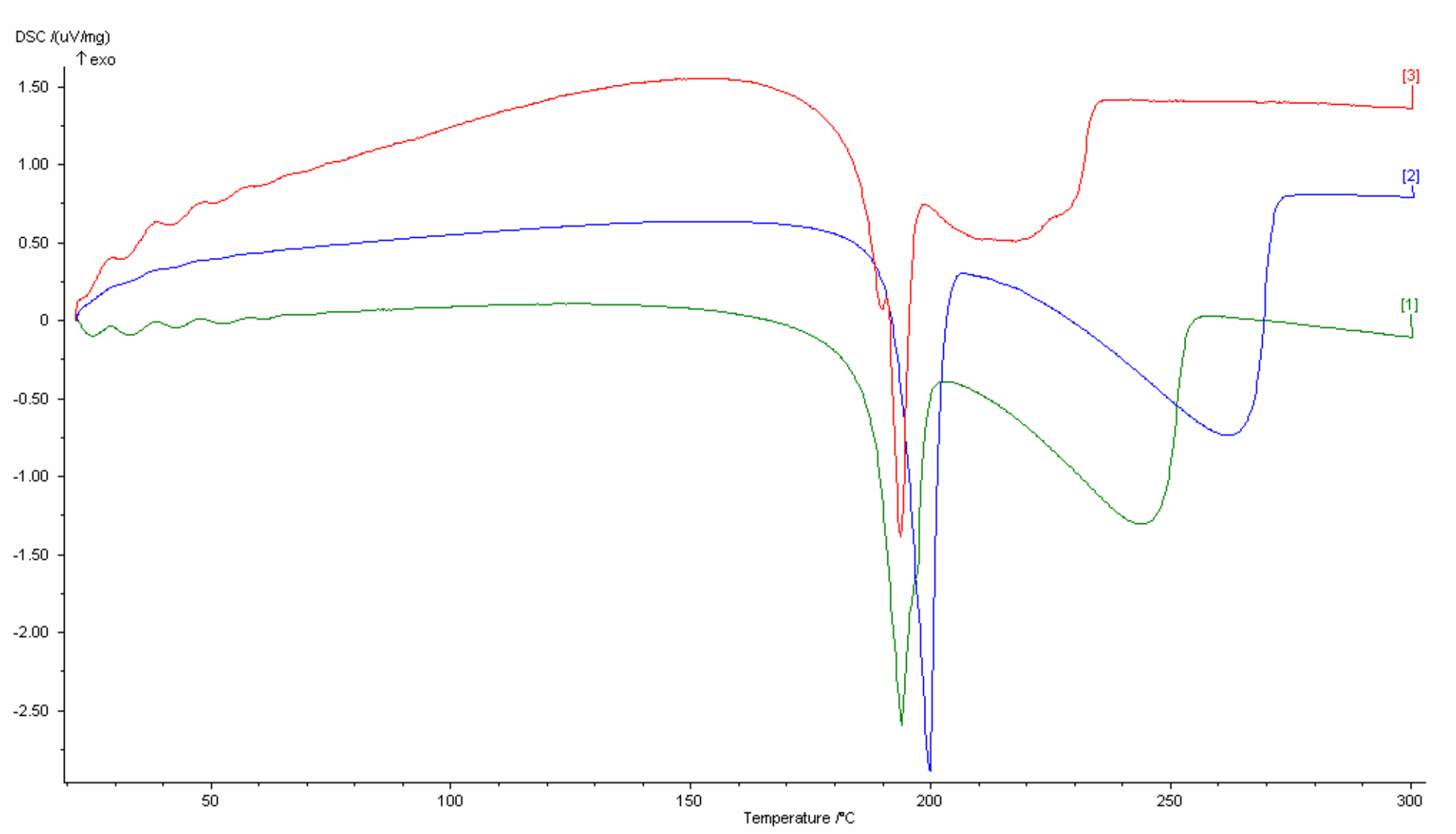
Solvent	Solubility (mg/ml)		Crystal habit		Cell check		T_{det} (K)	
	1	**2**	**1**	**2**	**1**	**2**	**1**	**2**
Acetone	71.8	25	Needles	Needles	Form I	Form I	200	150
Acetonitrile	51.67	18.47	Powder	Needles	NOT TESTED	Form I	-	150
1,4-Dioxane	41.88	11.83	Plates	Powder	Solvate	NOT TESTED	123	-
Ethanol	18.33	11.43	Needles and Plates	Needles	Form I and III	Form I	200	150
Methanol	65	25.07	Needles	Needles	Form I	Form I	200	150
2-Propanol	11.67	IS	Blocks	-	Form II	-	150	-
Butyl ether	IS	IS	-	-	-	-	-	-
t-Butylmethyl ether	IS	IS	-	-	-	-	-	-
Ethyl acetate	31.67	11.8	Needles	Needles	NOT TESTED	Form I	-	150
Isopropyl ether	IS	IS	-	-	-	-	-	-
Petroleum spirit (60-	IS	IS	-	-	-	-	-	-
Tetrahydrofuran	78.33	31.7	Needles and Blocks	Powder	Forms I and II	NOT TESTED	123	-
Toluene	IS	IS	-	-	-	-	-	-
Ethylmethyl ketone	45	18.6	Needles	Needles	Form I	Form I	123	150
Nitromethane	11.87	11.7	Needles	Blocks	Form I	REACTION	298	150
2,2,2-Trifluoroethanol	18.53	IS	Needles	-	Form I	-	150	-
O-Xylene	IS	IS	-	-	-	-	-	-
1-Butanol	IS	IS	-	-	-	-	-	-
2-Butanol	IS	IS	-	-	-	-	-	-
Cyclohexane	IS	IS	-	-	-	-	-	-
1,2-Dichloroethane	IS	IS	-	-	-	-	-	-
Diethyl ether	IS	IS	-	-	-	-	-	-
n-Hexane	IS	IS	-	-	-	-	-	-
1-Propanol	IS	IS	-	-	-	-	-	-
Dichloromethane	IS	IS	-	-	-	-	-	-
Dimethylsulfoxide	38.43	25.23	Blocks	Tablet	Solvate	Solvate	298	298
Chloroform	IS	IS	-	-	-	-	-	-
Water	IS	IS	-	-	-	-	-	-

Dimethylformamide	171.83	91.93	Needles	Flakes	Form I	Form I	123	-

Form I of **2** denotes the known monoclinic crystal structure of 5-fluoroisatin while Forms I, II and III of **1** are those found in the manual crystallisation screen on 7-fluoroisatin. IS=insoluble and T_{det} = temperature of cell check determination.

Electronic Supplementary Material for CrystEngComm

Figure S3: Overlay of the DSC traces for forms I (green), II (blue) and a mixture of I/IIII (red). All crystallisation experiments from ethanol led to a concomitant polymorphic mixture of forms I and III with very little of the latter. The DSC traces confirm an experimental energy ordering for the polymorphs of **1** as $G_{II}<G_{I}<G_{III}$, though the experiments were unable to confirm whether form III is metastable with respect to form I.



Electronic Supplementary Material for CrystEngComm

Electronic Supplementary Material for CrystEngComm

Figure S4: Overlay of the powder diffraction patterns for commercial 7-fluoroisatin (blue) with that of Form II (black). Both powder patterns shown are experimental, and the overlay shows a match between Form II and commercially available 7-fluoroisatin.