Serendipitous discovery of a novel polymorph of an immunosuppressant drug azathioprine: Phase transformation, solubility, dissolution and stability study

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Table S1 Hydrogen-bond geometries AZP forms.

AZP Form-III				
D—H···A	D—H (Å)	H···A (Å)	D···A (Å)	∠D—H···A (°)
C1—H1···N6^{i}	0.93	2.48	3.401 (2)	174
C5—H5···O2^{ii}	0.93	2.33	3.172 (2)	150
N2—H2N···N3^{iii}	0.88 (2)	2.05 (2)	2.915 (2)	167 (2)
Symmetry codes: (i) x−1, −y+3/2, z−1/2; (ii) −x+2, y−1/2, −z+1/2; (iii) −x+1, −y+1, −z.				
AZP-H2O				
N2A—H1N···N3A^{i}	0.89 (2)	2.06 (2)	2.919 (5)	164 (5)
N1B—H2N···N3B^{ii}	0.89 (2)	2.03 (2)	2.918 (5)	173 (3)
Symmetry codes: (i) −x+1, −y+2, −z+1; (ii) −x+1, −y+1, −z+1.				
AZP-MEE				
N2A—H1N···N3A^{i}	0.94 (2)	1.98 (3)	2.867 (4)	157 (4)
O1W—H2W···O1^{ii}	0.93 (2)	2.49 (4)	3.204 (5)	134 (4)
O1W—H2W···O2^{ii}	0.93 (2)	2.05 (3)	2.881 (5)	147 (5)
N2B—H2N···N3B^{iii}	0.88 (2)	2.04 (2)	2.916 (4)	177 (3)
O2—H2O···N1B	0.88 (2)	2.01 (2)	2.876 (4)	168 (6)
O1W—H1W···O1	0.91 (2)	1.91 (3)	2.777 (5)	160 (6)
C5A—H5A···O2B	0.95	2.49	3.337 (5)	149
Symmetry codes: (i) −*x*−2, −*y*+1, −*z*+2; (ii) *x*+1, *y*, *z*; (iii) −*x*, −*y*+1, −*z*+1.				
AZP-DOX				
C1—H1···N6^{i}	0.95	2.39	3.325 (3)	170
C4—H4···O2^{ii}	0.95	2.40	3.293 (3)	156
C7—H7*A*···O3^{iii}	0.98	2.66	3.636 (3)	177
C7—H7*B*···N4^{iii}	0.98	2.46	3.389 (4)	158
C7—H7*C*···O1^{iv}	0.98	2.60	3.542 (3)	162
C8—H8···O3	0.95	2.50	3.260 (4)	137
N2—H2···N3^{v}	0.86 (3)	2.05 (3)	2.892 (3)	164 (3)
Symmetry codes: (i) *x*−1, −*y*+3/2, *z*+1/2; (ii) −*x*+2, *y*−1/2, −*z*+1/2; (iii) *x*−1, *y*, *z*; (iv) −*x*+1, *y*−1/2, −*z*+1/2; (v) −*x*+1, −*y*+1, −*z*+1.				

Table S2 Experimental details of AZP F-III bulk scale preparation trials.

S.no	**Method**	**Temperature and stirring time**	**Solvents**	**Remarks based on PXRD analysis**
1.	Ball mill method	Liquid-assisted grinding using Ball-mill for 2 hrs with 1000 rpm.	2 drops of acetone	Form I
2.	Ball mill method	Liquid-assisted grinding using Ball-mill for 2 hrs with 1000 rpm.	2 drops of cyclohexanol.	Form I
3.	Slurry method	Stirred at 100°C, 400rpm for 48 hrs.	Cyclohexanol and Toluene in 1:1 ratio.	AZP form I.
4.	Slurry method	Reflux at 100°C for 24 hrs.	1:2 mixture of cyclohexanol and	AZP form I.

			acetone.	
5.	Slurry method	Reflux at 100°C for 24 hrs.	1:1 mixture of cyclohexanol and acetonitrile.	AZP form I.
6.	Slurry method	Stirred at 100°C, 400rpm for 48 hrs.	Cyclohexanol and Toluene in 1:2 ratio.	AZP form I.
7.	Slurry method	Stirred at RT for 21 hrs.	Acetone	AZP form I.
8.	Slurry method	Stirred at room temperature for 72 hours.	6 drops of lactic acid, and 1:1 ratio of 1-propanol and 2-butanol.	AZP form I.
9.	Slurry method	Stirred at 80°C for 24 hrs.	Malic acid (2 mol equivalent) and 1ml of cyclohexanol	AZP form I.
10.	Slurry method	Reflux at 100°C for 24 hrs.	5% Cyclohexanol in Isopropyl alcohol.	Form I with less percentage of Form III.
11.	Solvent evaporation	Reflux at 100-150°C until clear solution obtained.	Cyclohexanol and Acetone in 1:7 ratio.	Form I
12.	Slurry method	Stirred at room temperature for 96 hours.	5% Cyclohexanol in Isopropyl alcohol.	AZP form I.
13.	Slurry method	Stirred at room temperature for 96 hours.	5% Cyclohexanol in acetone.	AZP form I.
14.	Slurry method	Stirred at room temperature for 96 hours.	Toluene and Acetone in 1:1 ratio	AZP form I.
15.	Recrystallization method	Reflux at 100-110°C for 1 hour until clear solution obtained. The obtained clear solution was stirred at room temperature for 72 hours, that resulted in precipitate which was filtered and dried in oven at 40°C.	10% cyclohexanol in Acetone.	AZP form I.
16.	Solvent evaporation	Stirred at 104°C until clear solution obtained.	1-propanol (1.5ml), 2-butanol(1.5ml) and lactic acid (3 drops, 19.64mol equivalent)	**Phase pure Form III crystals.**
17.	Slurry method	Stirred at room temperature for 24 hrs.	1-propanol and 2-butanol in 1:1 ratio.	AZP form I.
18.	Recrystallization	Reflux at 110°C for 2-3 hrs until clear solution was obtained. The obtained solution was stirred at room temperature for 21 hours	1-propanol and 2-butanol in 1:1 ratio.	**Form III.**

		that resulted in precipitate, which was filtered and dried at 40°C.		
19.	Slurry method	Stirred at room temperature for 72 hrs.	13% lactic acid in 1:1 mixture of 1-propanol and 2-butanol.	Form I.
20.	Slurry method	Stirred at room temperature for 72 hrs.	13% lactic acid in 1-propanol.	Form I.
21.	Recrystallization	Reflux at 110°C for 1 hr, at 150°C for 1hr until clear solution was obtained. The obtained solution was stirred at room temperature for 21 hours that resulted in precipitate, which was filtered and dried at 40°C.	10% lactic acid in 1:1 mixture of 1-propanol and 2-butanol.	**Form III.**
22.	Recrystallization	Reflux at 150°C for 1 hour until clear solution was obtained, which was stirred in ice bath for 45 minutes, followed by room temperature stirring for 21 hours.	11% lactic acid in 1:1 mixture of 1-propanol and 2-butanol.	Concomitant form I and form III.
23.	Recrystallization	Reflux at 150°C for 1 hour and 110°C for 1 hour, until clear solution was obtained, which was stirred at room temperature for 3 hours. The obtained precipitate at room temperature was filtered and dried in oven at 40°C.	6.3% of lactic acid in 1:1 mixture of 1-propanol and 2-butanol.	**Form III.** Yield : 52%

Table S3 Percentage of F-I and F-III after 7, 14 and 30 days of exposure to 70-75% RH condition.

S. No	Solid forms	% of F-I and F-III by Rietveld refinement
1.	F-III After 7 days	100% F-III
2.	F-III After 14 days	98.57% F-III and 1.43% F-I
3.	F-III After 30 days	95.95% F-III and 4.05% F-I

4.	F-I After 7 days	100% F-I
5.	F-I After 14 days	100% F-I
6.	F-I After 30 days	100% F-I

Table S4 Percentage of F-I and F-III after 7, 14 and 30 days of exposure to 90-95% RH condition.

S. No	Solid forms	% of F-I and F-III by Rietveld refinement
1.	F-III After 7 days	94.78% F-III and 5.22% F-I
2.	F-III After 14 days	42.92% F-III and 57.08% F-I
3.	F-III After 30 days	100% F-I
4.	F-I After 7 days	100% F-I
5.	F-I After 14 days	100% F-I
6.	F-I After 30 days	100% F-I

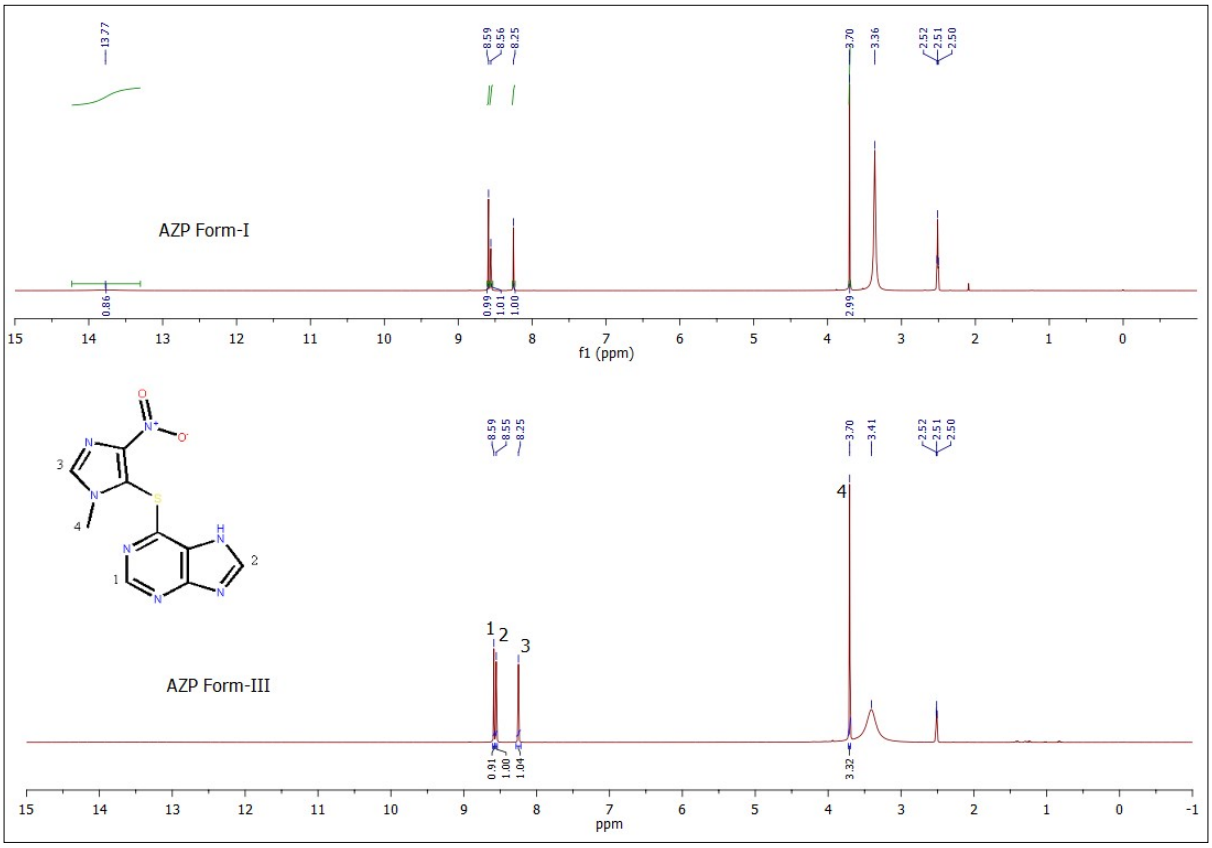

Figure S1 [1]H NMR spectrum of Form-I and Firm-III.

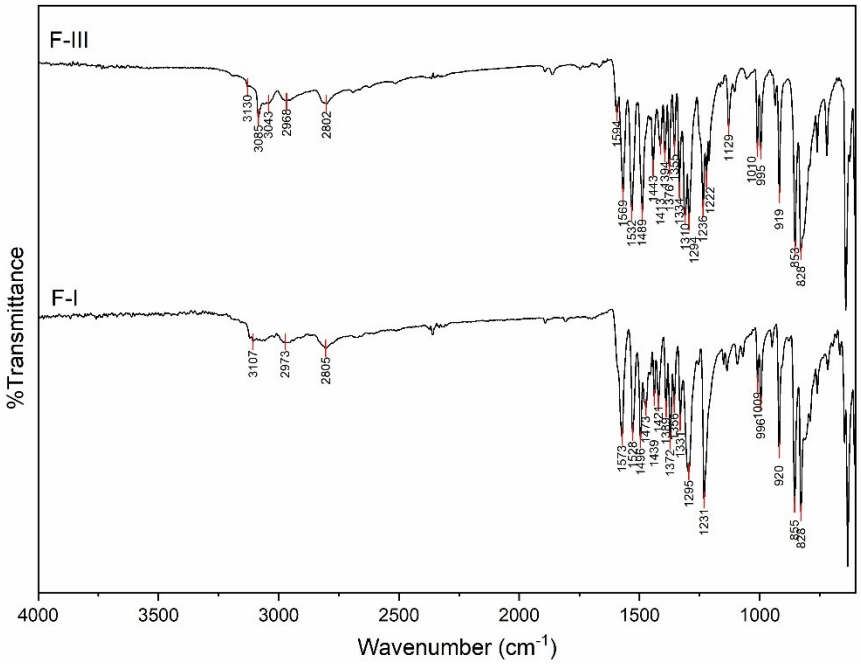

Figure S2 FT-IR spectrum overlay of F-I and F-III.

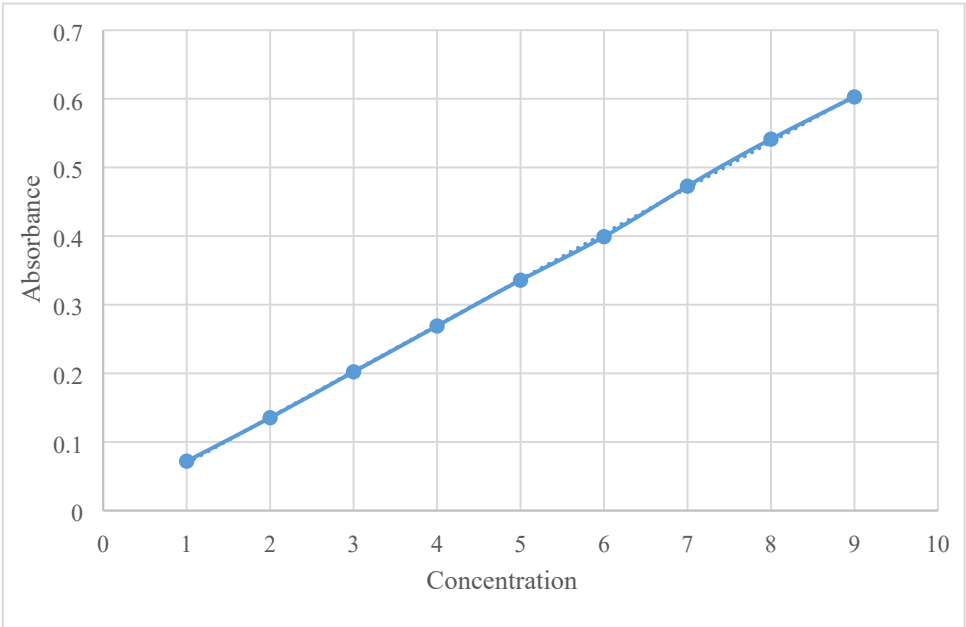

Figure S3 Standard linearity plot of AZP.

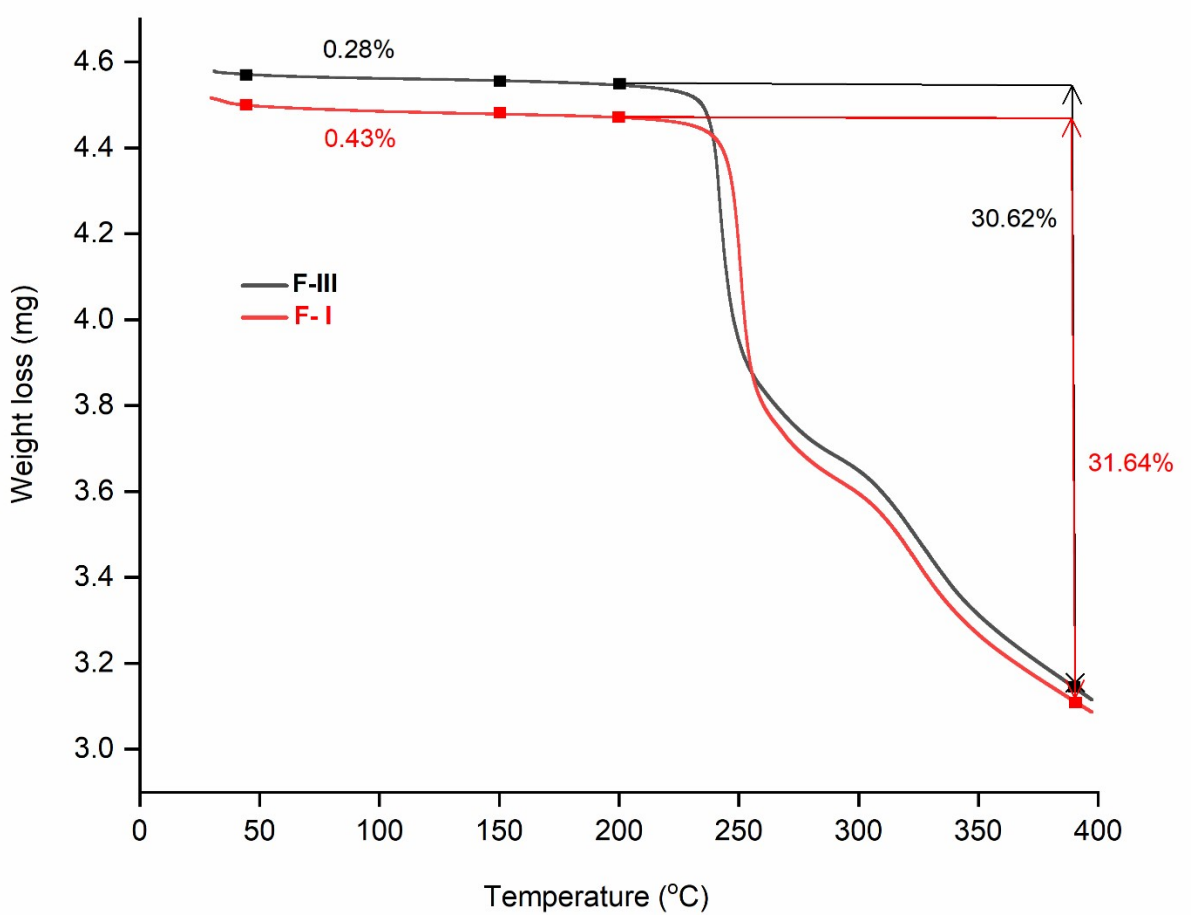

Figure S4 The TGA plot of AZP F-I and F-III.

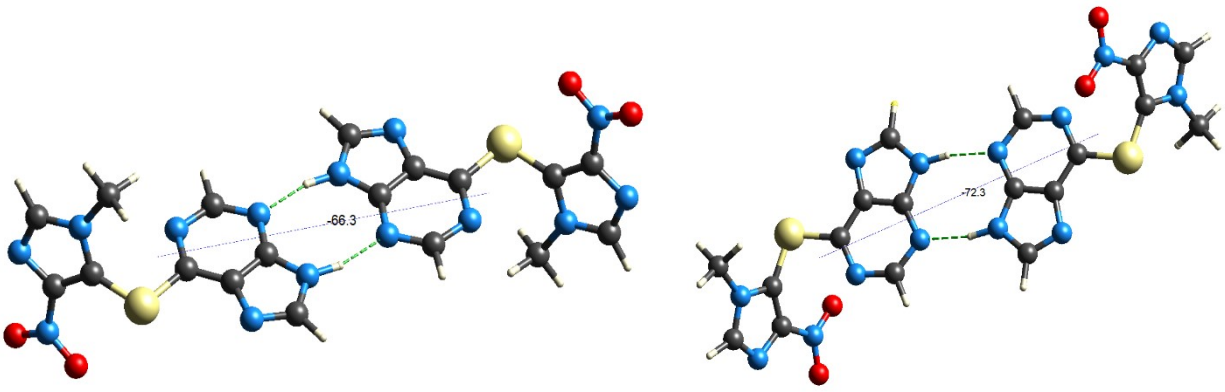

Figure S5 Synthon interaction energy in F-I and F-III.

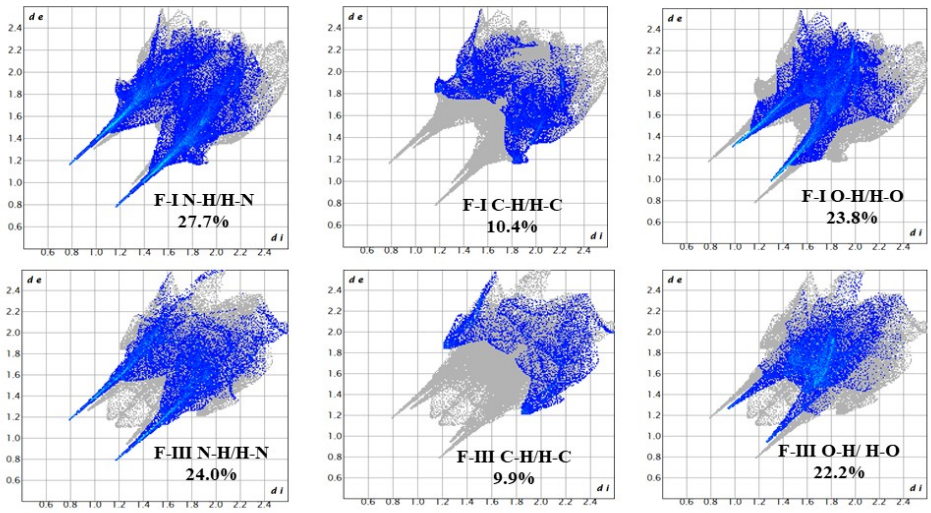

Figure S6 The 2D fingerprint plots showing N-H/H-N, C-H/H-C and O-H/H-O interactions in F-I and F-III forms.

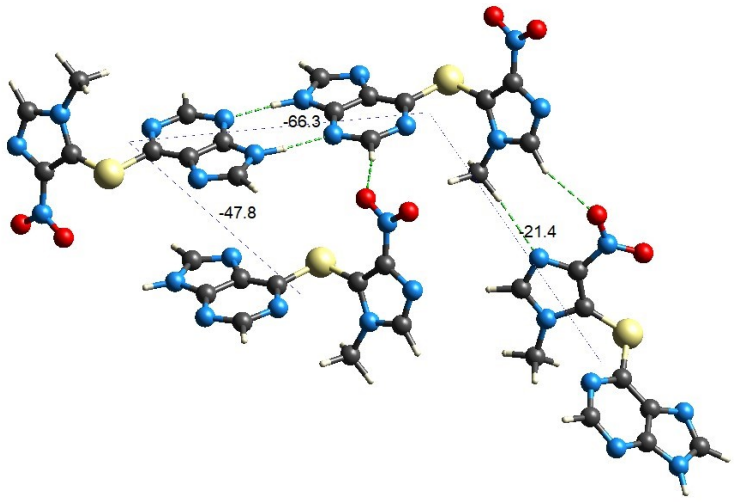

Figure S7 All interactions of AZP F-I.

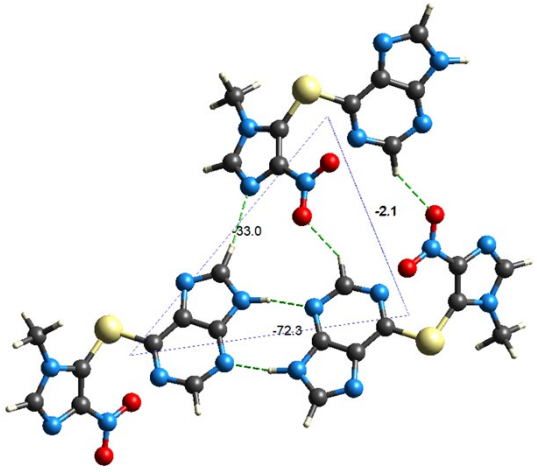

Figure S8 All interactions of AZP F-III.