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SUPPLEMENTARY INFORMATION

Supramolecular synthesis and thermochemical investigations of pharmaceutical inorganic Isoniazid salts

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Table S1. Crystal data and refinement parameters of INH salts

Compound		INH hydrobromide	INH nitrate	INH sulfate	INH sulfate hemihydrate
Formula		$C_6H_8BrN_3O$	$C_6H_8N_4O_4$	$C_6H_9N_3O_5S$	$C_{12}H_{20}N_6O_{11}S_2$
Formula weight (g.mol^{-1})		218.06	200.16	235.22	488.46
Wavelength (λ)		0.71073	0.71073	0.71073	0.71073
Crystal system		Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group		$P2_1/c$	Cc	$P2_1/n$	$P2_1/c$
Temperature (K)		293(2)	293(2)	293(2)	120(2)
Unit cell	a (Å)	6.6307(4)	6.3630(13)	7.3259(2)	6.9562(3)
	b (Å)	16.3280(13)	15.970(6)	6.3982(2)	19.7321(8)
	c (Å)	7.4836(5)	8.043(2)	19.5779(7)	13.4459(6)
	α (º)	90	90	90	90
	β (º)	92.183(7)	92.151(16)	98.2460(10)	93.4175(13)
	γ (º)	90	90	90	90
Volume (Å^3)		809.63(10)	816.7(4)	908.18(5)	1842.31(14)
Z		4	4	4	4
Density (calculated) (mg/m^3)		1.789	1.628	1.720	1.761
Absorption coefficient (mm^{-1})		5.022	0.138	0.365	0.367
Absorption correction		Gaussian T_{min}= 0.458 T_{max}= 0.937	---------	--------	--------
θ range for data collection		2.996 to 26.385°	3.449 to 25.331°	3.138 to 26.399°	2.562 to 26.709°
Index range	h	-8 to 8	-7 to 7	-9 to 9	-8 to 7
	k	-20 to 20	-19 to -19	-8 to 7	-22 to 23
	l	-8 to 9	-9 to 9	-24 to 24	-16 to 12
Measured data		5442	1462	1859	10216
Unique data		1654	1454	1859	3830
Symmetry factor (R_{int})		0.0802	0.0494	0.101	0.055
Completeness to θ_{max}		99.8%	99.6%	99.8%	98.7%
F(000)		432	416	488	1018
Parameters refined		100	128	136	282
Goodness-of-fit on F^2		0.979	1.055	1.052	1.059
R [I >2σ(I)]		R1 = 0.0448 wR2 = 0.1056	R1 = 0.0495 wR2 = 0.1261	R1 = 0.0463 wR2 = 0.1207	R1 = 0.0366 wR2 = 0.0929
R (all data)		R1 = 0.086 wR2 = 0.125	R1 = 0.0636 wR2 = 0.1374	R1 = 0.0636 wR2 = 0.1291	R1 = 0.0460 wR2 = 0.0986
Largest diff. peak/hole (e Å^{-3})		0.504/-0.397	0.161/-0.148	0.475/-0.418	0.4715/-0.6114

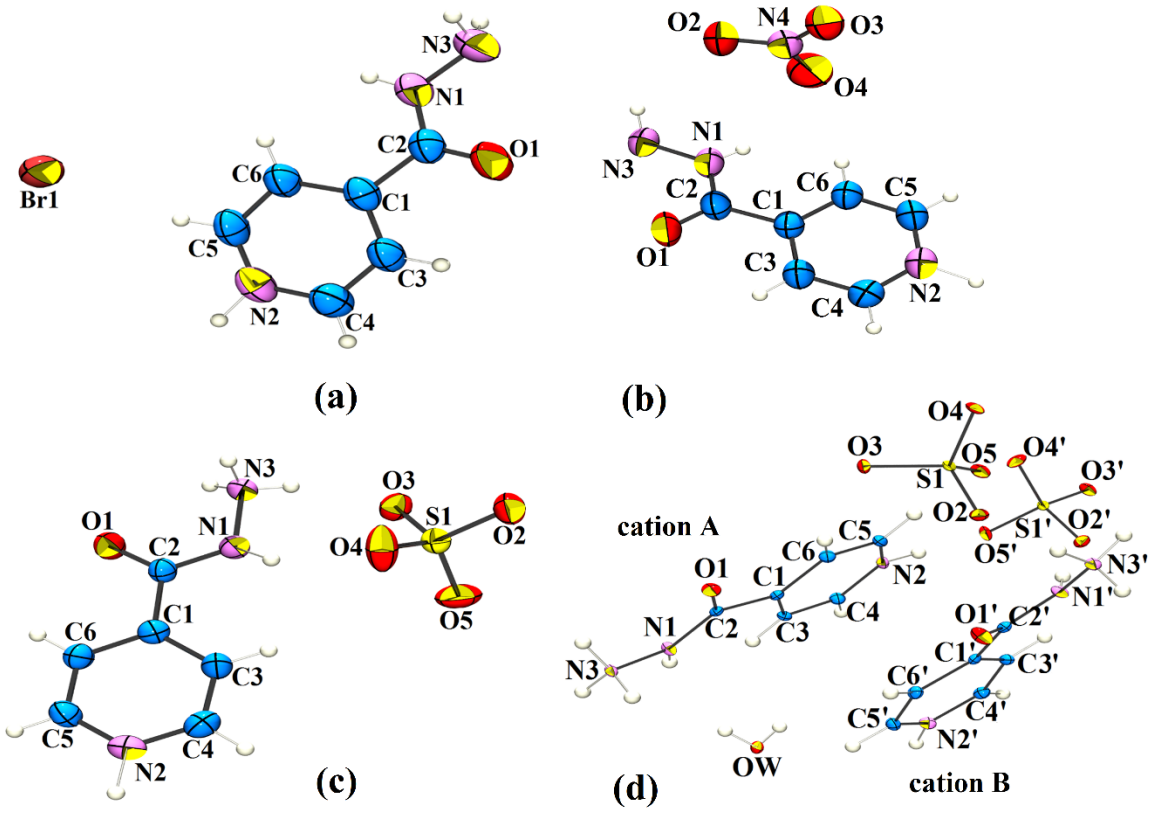

Figure S1. Ortep-3 view of the asymmetric unit of Isoniazid salts showing the atomic numbering scheme: (a) INH hydrobromide, (b) INH nitrate, (c) INH sulfate and (d) INH sulfate hemihydrate. Ellipsoids are drawn at the 50% probability level and hydrogen atoms are shown as spheres of arbitrary radii.

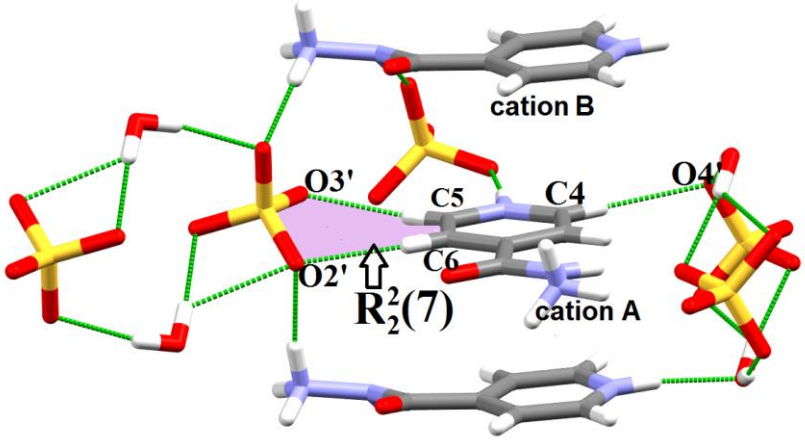

Figure S2. Partial view of the supramolecular assembly of INH sulfate hemihydrate highligting the $R_2^2(7)$ motif formed by cation A and the sulfate anion *via* C5-H5···O3' and C6-H6···O2' H-bonds.

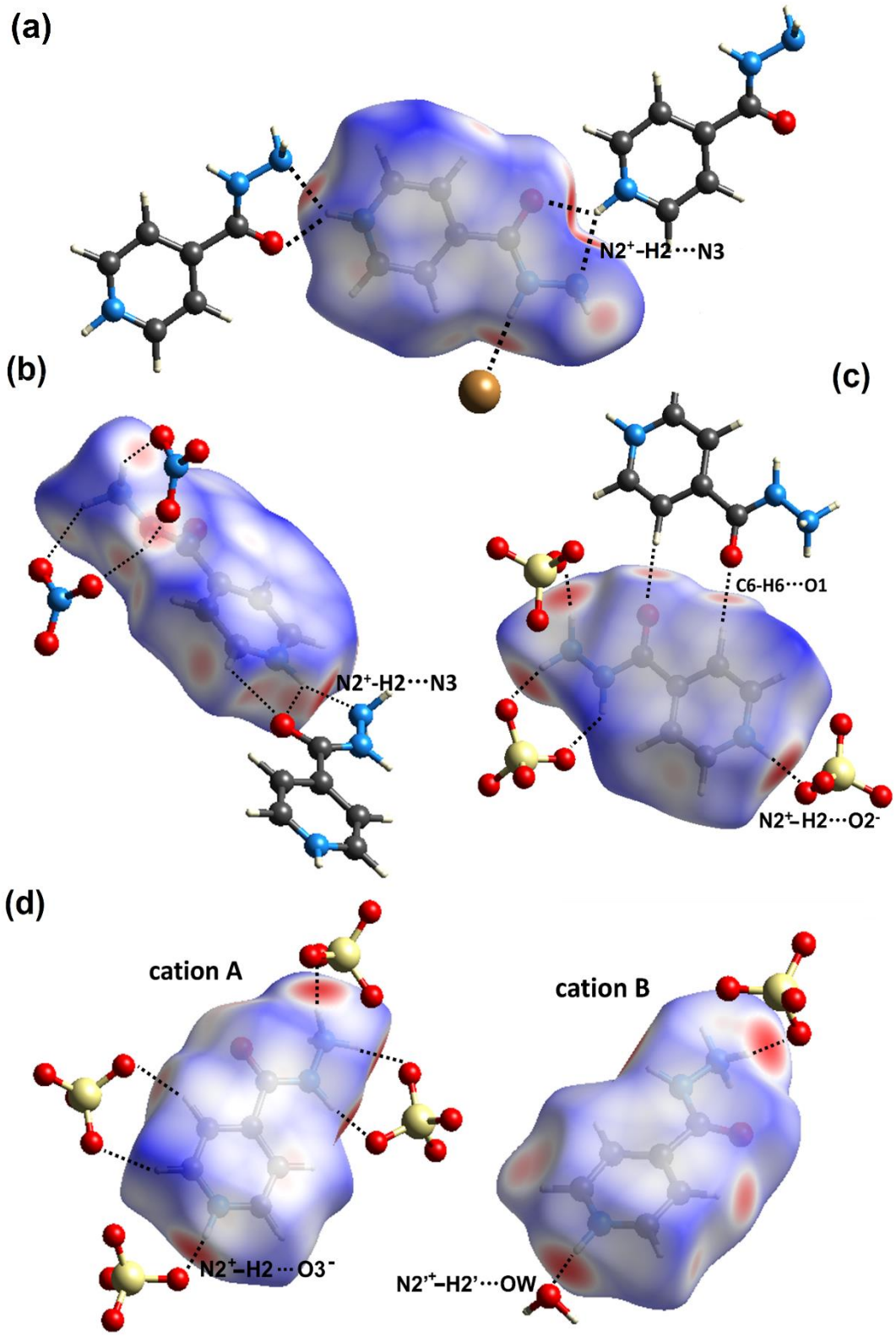

Figure S3. Hirshfeld surfaces for the Isoniazid salts: (a) INH hydrobromide, (b) INH nitrate, (c) INH sulfate and (d) INH sulfate hemihydrate.

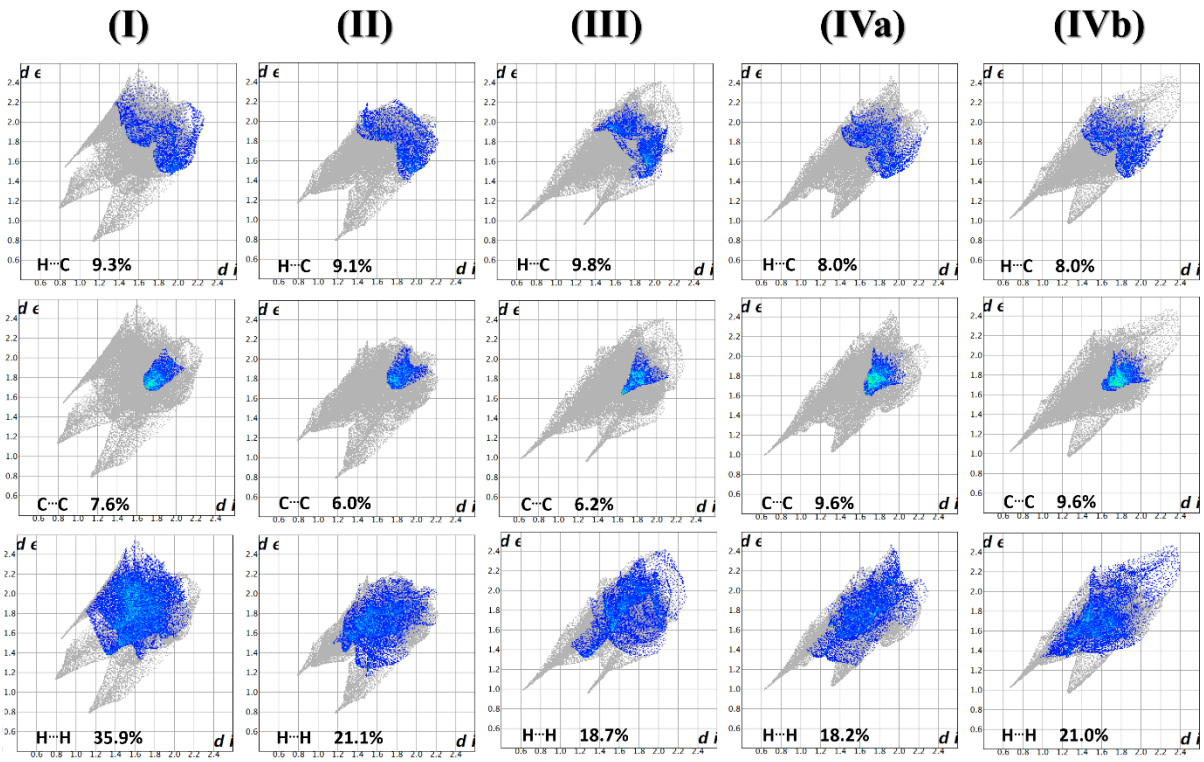

Figure S4. 2-D fingerprint plots for the different intermolecular contacts (H···C/C···H, C···C and H···H) in Isoniazid salts: (I) INH hydrobromide, (II) INH nitrate, (III) INH sulfate and (IV) INH sulfate hemihydrate. IVa and IVb denote the two cations in the asymmetric unit of IV.

DISCUSSION

Isoniazid drug-drug interactions

The chemotherapy of tuberculosis (TB) is in general based on the administration of Isoniazid (INH), Rifampicin (RMP), Pyrazinamide (PZA) and Ethambutol dihydrochloride (ETB). The administration of these drugs as fixed-dose combination (FDC) can simplify the TB treatment and limit the risk of drug-resistance. Ideally, it would be important that these drugs do not interact with each other. Although INH is stable at ambient temperature and other conditions (40ºC/75%RH), it undergoes degradation in FDC tablets due to drug-drug interactions. Because INH is susceptible to hydrolysis and oxidation, the presence of other compounds can lead to INH degradation. The main reactions were listed below [see reference 11-13]:

1. At low pH values (pH < 2) RMP can be converted to 3-formylrifamycin, which further reacts with isoniazid to form isonicotinyl hydrazine (HYD).
2. Even under non-acidic conditions, RMP can react directly with INH, yielding HYD as product *via* a transhydrazone formation.
3. The presence of PZA and ETB can also increase the rate of decomposition of RMP and INH, due to a base-catalyzed transhydrazone formation, in which the PZA/ETB acts a proton scavenger.

Dehydration of INH sulfate hemihydrate

Powder X-ray diffraction (PXRD) experiments were performed for supporting the thermal analysis results. In order to prove that INH sulfate hemihydrate converts into its anhydrous form, the following protocol was undertaken:

(a) PXRD data were initially collected at 25ºC for the crystalline sample of INH sulfate hemihydrate;

(b) Further, this sample was subjected to oven at 110 ºC for 2h to get complete dehydration;

(c) DSC measurements were performed to confirm the dehydration process;

(d) Finally, PXRD measurements were carried out at 25 ºC for the dehydrated sample.

The experimental PXRD patterns of INH sulfate ($INHSO_4$) hemihydrate and the dehydrate form ($INHSO_4$ anhydrous) were depicted in Fig. S5. They were exhibited together with their corresponding simulated PXRD patterns, calculated by the Mercury program using as input the single crystal X-ray structures of the anhydrous and the hemihydrate salts previously reported in this manuscript.

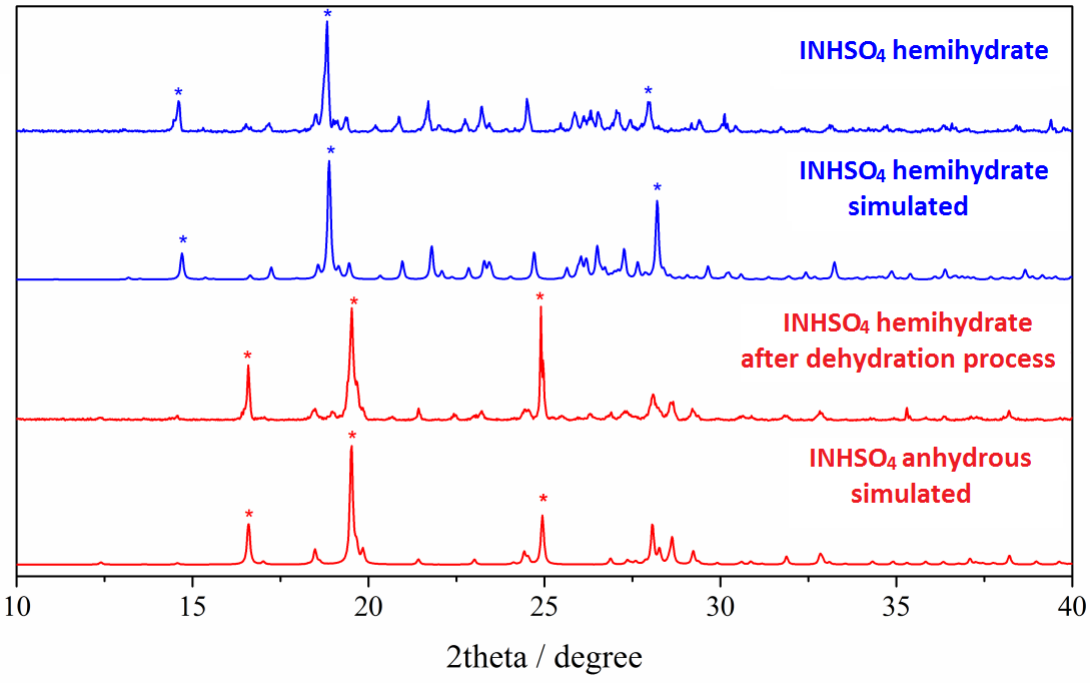

Figure S5. Experimental PXRD pattern of INH sulfate ($INHSO_4$) hemihydrate and its simulated pattern (blue). Experimental PXRD pattern of the dehydration sample together with the simulated pattern of the anhydrous INH sulfate salt (red).

INH sulfate hemihydrate is characterized by a unique and distinguishable PXRD pattern, in a good agreement with its simulated pattern. The more intensity Bragg peaks (marked with asterisks) were used for evaluating the match between the experimental and simulated patterns. After heating, the experimental PXRD pattern of the hemihydrate salt changed significantly, yielding a good match with the simulated PXRD pattern of the anhydrous salt.

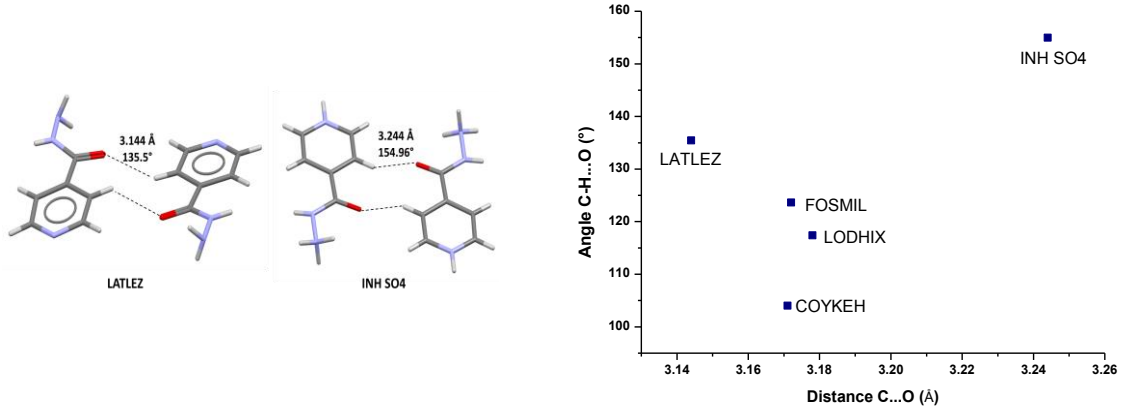

Figure S6. A survey for INH structures on CSD database has returned 86 entries among cocrystals, salts and metal complexes. For all them, a search for C-H…O interactions was performed, resulting in four entries with bond distances and angles reasonable for this type of interaction. Therefore, only one compound (ref. code LATLEZ) showed the spatial arranged and the form of the mentioned homodimer. It is important to mention that this homodimer and the one reported for us have C-H…O interactions in accordance with the default criterion (C-O distance threshold of 3.25-3.3 Å, and CHO ≥ 120º).