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Supporting information for article:

First-line antituberculosis drug, pyrazinamide, its pharmaceutically relevant cocrystals and a salt

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S1. Experimental

Pyrazinamide (Pyz) was purchased from TCI chemicals (India) Pvt. Ltd. and used as received. All other coformers were purchased from commercial sources and used without further purification.

S1.1. Preparation of Pyz cocrystals and salt

S1.1.1. Liquid Assisted Grinding (LAG).

All the cocrystals and salt of Pyz were synthesized using liquid assisted grinding (LAG). Stoichiometric amount of Pyz and all coformers are taken in a mortar-pestle, 4-5 drops of acetonitrile was used as liquid for grinding. After 20 min of manual grinding, powdered samples were heated again in a hot air oven at 80 °C for another half an hour. The resultant powdered materials were analysed using various solid-state characterization techniques such as PXRD, DSC and FT-IR spectroscopy.

S1.1.2. Solution Crystallization.

Solution crystallization of all Pyz solid forms were carried out using powdered samples obtained from LAG using various laboratory solvents by placing around 30-40 mg of the powdered material in ~ 20 mL of the corresponding solvent, heated at 80 °C until the solids disappeared. The clear solution was kept at room temperature for crystallization.

S1.2. Single Crystal X-ray Diffraction.

X-ray reflections were collected on a Bruker SMART APEX II CCD equipped with a graphite monochromator and a Mo K α fine-focus sealed tube ($\lambda = 0.71073$ Å). Data integration was done using SAINT. Intensities for absorption were corrected using SADABS. Structure solution and refinement were carried out using Bruker SHELXTL. The hydrogen atoms were refined isotropically, and the heavy atoms anisotropically. N–H and O–H hydrogens were located from difference electron density maps, and C–H hydrogens were fixed using the HFIX command in SHELXTL. Crystallographic .cif files are deposited with the CCDC (Nos. 1504475-1504479) and may be accessed at www.ccdc.cam.ac.uk/data.

S1.3. Powder X-ray Diffraction (PXRD).

Powder X-ray diffraction was carried out on a Bruker D8 Advance diffractometer (Bruker-AXS, Karlsruhe, Germany) using Cu-K α X-radiation ($\lambda = 1.5406$ Å). Samples were ground using a mortar and pestle to reduce the crystal size and orientation effects. Material was then tightly packed in a glass

holder using glass slides to match the surface level of the sample holder and analyzed using 40 kV voltage and 30 mA current, in a range $5\text{--}50^\circ 2\theta$ at a scan rate of $1^\circ/\text{min}$.

S1.4. Thermal Analysis (DSC).

DSC was performed on a Mettler Toledo DSC 822e module. Samples were placed in crimped but vented aluminum sample pans. The typical sample size is 4–6 mg, temperature range was $30\text{--}300^\circ\text{C}$ @ $10^\circ\text{C min}^{-1}$. Samples were purged by a stream of nitrogen flowing at 80 mL/min .

TGA was performed on a Mettler Toledo TGA instrument. Samples were placed in a silica crucible. The temperature range was $30\text{--}500^\circ\text{C}$ @ $10^\circ\text{C min}^{-1}$. Samples were purged by a stream of nitrogen flowing at 80 mL min^{-1} .

S1.5. Vibrational Spectroscopy (FT-IR).

FT-IR spectra were recorded in Nicolet 6700 FT-IR spectrometer with an NXR FT-Raman module. FT-IR spectra were recorded on samples dispersed in KBr pellets for a scanning range of $4000\text{ to }500\text{ cm}^{-1}$ taking a scan number of 100 with a resolution of 4 cm^{-1} .

S2. Solubility Measurements

The absorption coefficient of each solid phase was measured by the slope of the absorbance (A) versus concentration (c) curve of at least six known concentrated solutions in distilled water medium and measured at different λ_{max} in a Shimadzu UV-Vis spectrometer. For Pyz•24DHBA, Pyz•26DHBA, Pyz•35DHBA, Pyz•FRA, Pyz⁺•pTSA[−] and Pyz; λ_{max} was determined at 269, 269, 269, 277, 268 and 269 nm respectively. The solubility of each solid was measured after 24 h using the shake-flask method at room temperature ($27\pm 2^\circ\text{C}$) (for Pyz•FRA solubility was measured within half an hour). The experiments were repeated twice in order to have consistent value.

1. Pyz•24DHBA cocrystal (1:1):

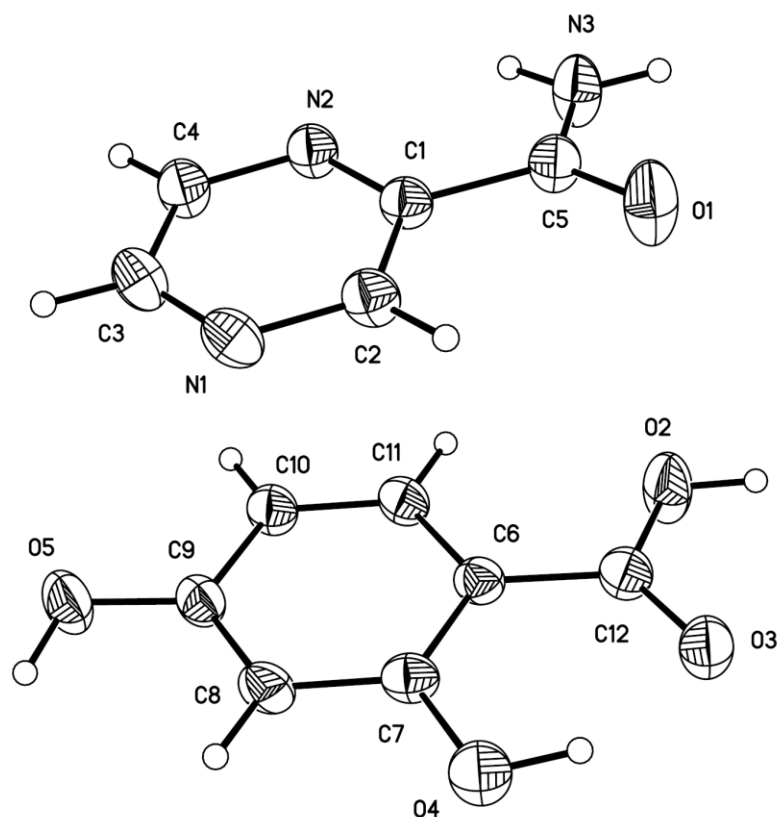


Figure S1 ORTEP diagram of Pyz•24DHBA cocrystal with 35 % polarizability ellipsoid.

2. Pyz•26DHBA cocrystal (1:1):

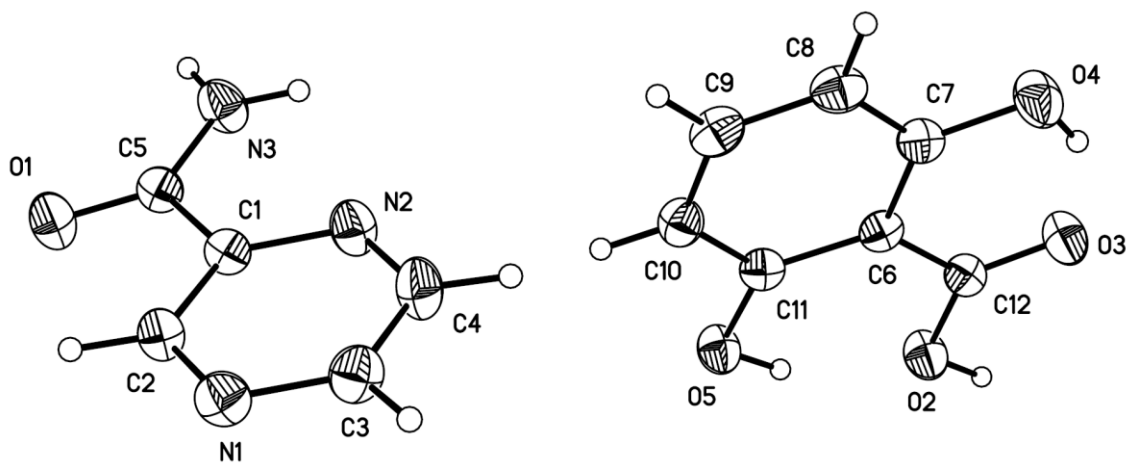
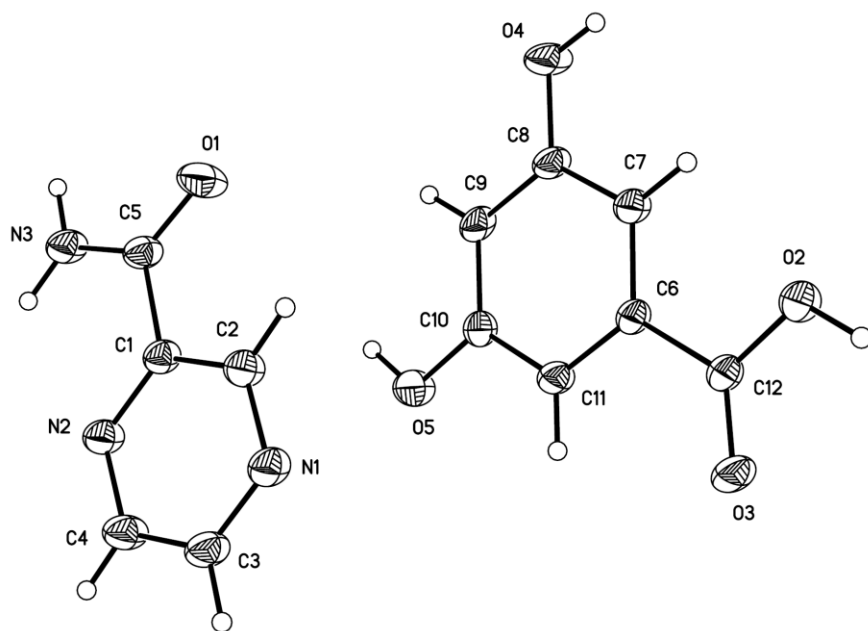
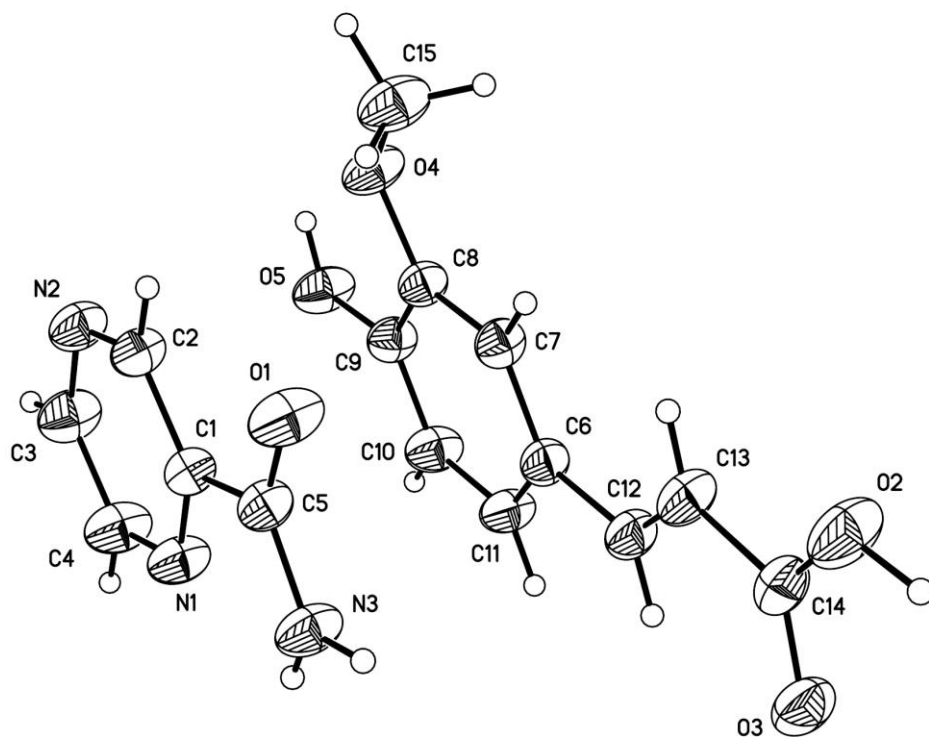


Figure S2 ORTEP diagram of Pyz•26DHBA cocrystal with 35 % polarizability ellipsoid.

3. Pyz•35DHBA cocrystal (1:1):

**Figure S3** ORTEP diagram of Pyz•35DHBA cocrystal with 35 % polarizability ellipsoid.

4. Pyz•FRA cocrystal (1:1):

**Figure S4** ORTEP diagram of Pyz•FRA cocrystal with 35 % polarizability ellipsoid.5. Pyz⁺•pTSA⁻ molecular salt (2:2):

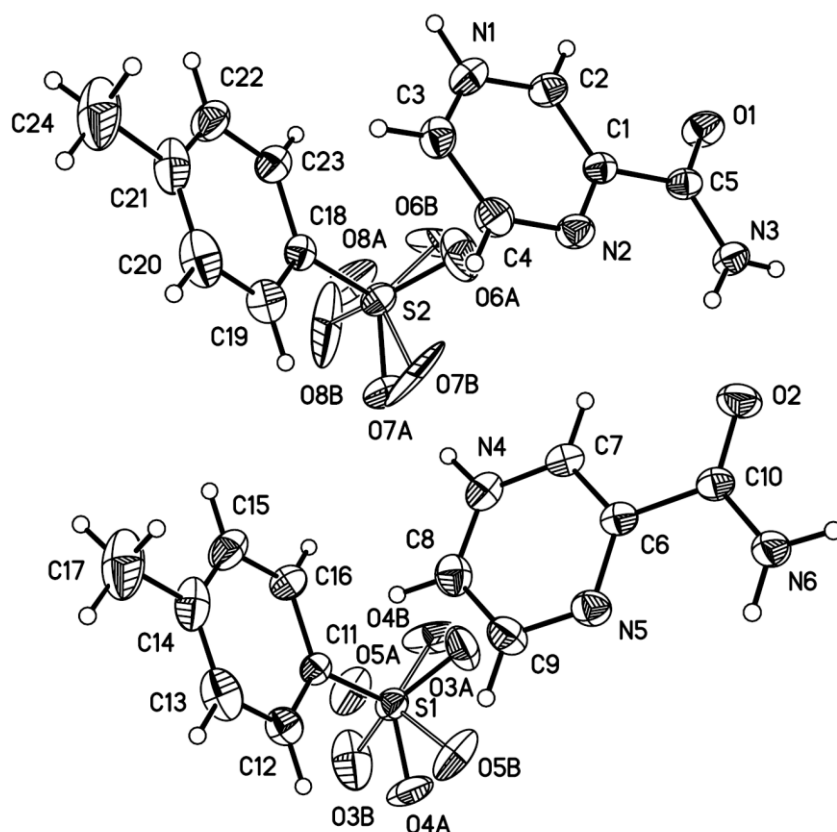


Figure S5 ORTEP diagram of $\text{Pyz}^+\cdot p\text{TSA}^-$ molecular salt with 35 % polarizability ellipsoid.

Table S1 pK_a values of pyrazinamide and coformers used in this study (negative ΔpK_a values confirm formation of cocrystal).

Molecule	pK_a value	Product complex	ΔpK_a value
Pyrazinamide	0.7		
24DHBA	3.1	$\text{Pyz}\cdot 24\text{DHBA}$	−2.4
26DHBA	1.5	$\text{Pyz}\cdot 26\text{DHBA}$	−0.8
35DHBA	3.6	$\text{Pyz}\cdot 35\text{DHBA}$	−2.9
Ferulic acid	3.8	$\text{Pyz}\cdot \text{Ferulic acid}$	−3.1
p-TSA	−2.1	$\text{Pyz}\cdot p\text{TSA salt}$	2.8

Table S2 Hydrogen bond parameters of various cocrystals and salt prepared in this study.

Compound	Interaction	Donor...Acceptor	H...Acceptor	Donor-H.....Acceptor	Symmetry code
Pyz•24DHBA	N3–H3A...N2	2.748(2)	2.372	100	x, y, z (intra)
	O4–H4A...O3	2.634(2)	1.804	146	x, y, z (intra)
	O5–H5A...N1	2.764(2)	1.831	173	–x+1, +y–1/2, –z+1/2
	N3–H3A...N2	3.093(2)	2.289	134	–x, –y+1, –z
	O2–H2A...O1	2.586(2)	1.662	168	–x+1, –y+2, –z
	N3–H3B...O3	2.972(2)	1.963	166	–x+1, –y+2, –z
Pyz•26DHBA	O4–H4A...O3	2.556(2)	1.711	148	x, y, z (intra)
	O5–H5A...O2	2.601(2)	1.763	147	x, y, z (intra)
	N3–H3A...N2	2.682(2)	2.235	104	x, y, z (intra)
	O2–H2A...O1	2.536(2)	1.603	173	x, –y+1/2+1, z+1/2
	O5–H5A...N1	3.024(2)	2.455	119	–x+1, y+1/2+1, –z+1/2
	N3–H3B...O3	2.928(2)	1.944	159	x, –y+1/2+1, z–1/2
Pyz•35DHBA	N3–H3A...N2	2.752(2)	2.367	101	x, y, z (intra)
	O4–H4A...O1	2.619(2)	1.683	175	x, –y+1/2, z–1/2
	O5–H5A...N1	2.808(2)	1.902	162	x–1, y, z
	N3–H3B...O3	2.929(2)	1.913	168	x–1, y, z+1
	O2–H2A...O4	2.610(2)	1.675	174	x+1, –y+1/2, z–1/2
Pyz•Ferulic acid	O5–H5A...O4	2.723(1)	2.270	109	x, y, z (intra)
	N3–H3B...N1	2.692(2)	2.226	106	x, y, z (intra)
	O5–H5A...N2	2.795(1)	1.935	151	–x, –y, –z+1
	O2–H2A...O3	2.620(1)	1.685	174	–x+1, –y+2, –z
	N3–H3A...O1	2.887(2)	1.859	176	–x+1, –y+1, –z
Pyz•pTSA salt	N3–H3A...N2	2.729(3)	2.315	102	x, y, z (intra)
	N3–H3A...O2	2.854(3)	1.912	151	x, y, z
	N4 ⁺ –H4A...O7A [–]	2.699(6)	1.672	174	x, y, z
	N4 ⁺ –H4A...O7B [–]	2.425(7)	1.438	158	x, y, z
	N6–H6A...N5	2.728(3)	2.333	101	x, y, z (intra)
	N1 ⁺ –H1A...O4A [–]	2.619(4)	1.657	153	x+1, y–1, z
	N1 ⁺ –H1A...O5B [–]	2.669(8)	1.703	154	x+1, y–1, z
	N3–H3B...O6A [–]	2.936(6)	1.923	167	–x+1, –y+1, –z+2
	N3–H3B...O6B [–]	3.023(2)	2.053	156	–x+1, –y+1, –z+2
	N6–H6A...O1	2.906(3)	1.940	155	x, y+1, z
	N6–H6B...O3A [–]	2.871(6)	1.884	159	–x+1, –y+2, –z+2

Table S3 List of Pyz cocrystals reported in the Cambridge Structural Database along with hydrogen bond synthon present.

Sl. No.	Coformer	CSD ref code	Synthon
1.	3,4-dihydroxybenzoic acid	NUSMIZ	Synthon IV, VI
2.	4-hydroxybenzoic acid	NUVFIV	Synthon II, III, amino-phenol
3.	4-nitrobenzamide	ASAYIC	Synthon III
4.	2-Aminobenzoic acid	EBONUG	Synthon II, III
5.	Hydrochlorothiazide	EGENIP	amino-pyridine
6.	Pyrogallol	HEDRAL	Synthon VI, amino-phenol
7.	Temozolomide	KIJSER	amino-pyridine
8.	Hexanedioic acid	KOVSAR	Synthon I, III
9.	Decanedioic acid	KOVSEV	Synthon I, III
10.	Trans-aconitic acid	KOVSIK	Synthon II, IV
11.	Citric acid	KOVSOE	Synthon I, II, IV
12.	fumaric acid	LATTIL	Synthon I, III
13.	succinic acid	LATTOR	Synthon I, III
14.	4-nitrobenzoic acid	MUDVUE	Synthon I, III
15.	β -Cyclodextrin	NUFVEQ	
16.	Squaric acid	PAQNOM	Synthon I, IV
17.	Vanillic acid	REBXED	Synthon II, III, VI
18.	Gallic acid	REBXIH	Synthon II, III, VI
19.	1-Hydroxy-2-naphthoic acid	REBXON	Synthon I, III
20.	1H-Indole-2-carboxylic acid	REBXUT	Synthon IV
21.	glutaric acid	SIHQOR	Synthon I, IV
22.	malonic acid	SIHRAE	Synthon I, IV
23.	4-aminosalicylic acid	URUGIY	Synthon I, III
24.	2,5-dihydroxybenzoic acid	XAQQOW	Synthon IV, VI, amino-phenol
25.	theophylline (form II)	RACFIN	Synthon III

26.	theophylline (form I)	RACFIN01	amide-amide (theo)
27.	4-aminobenzoic acid	VUTNAB	Synthon IV

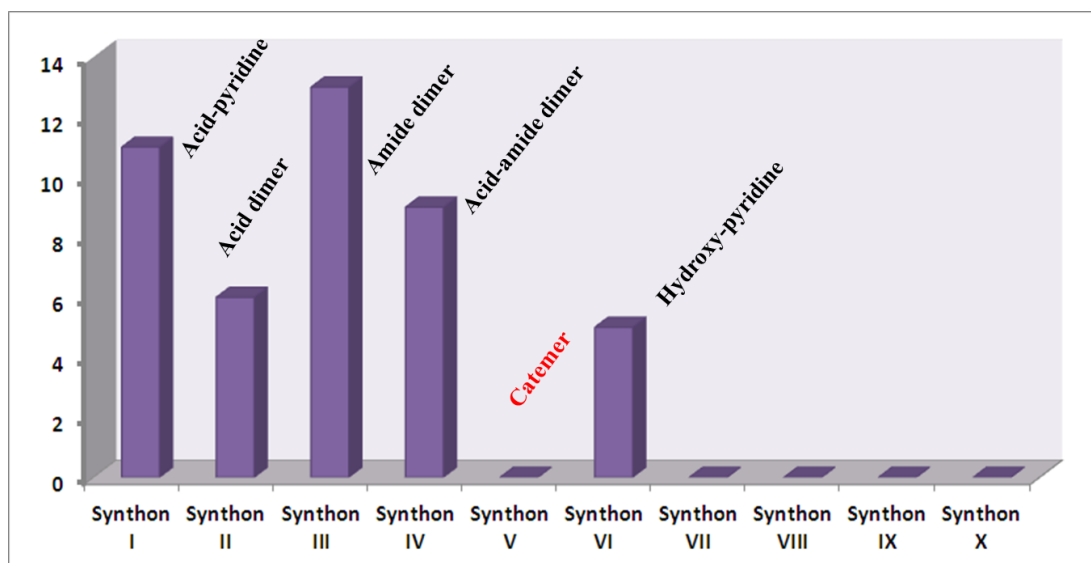


Figure S6 Bar diagram showing various synthon probabilities vs. number of Pyz crystal structures reported in CSD.

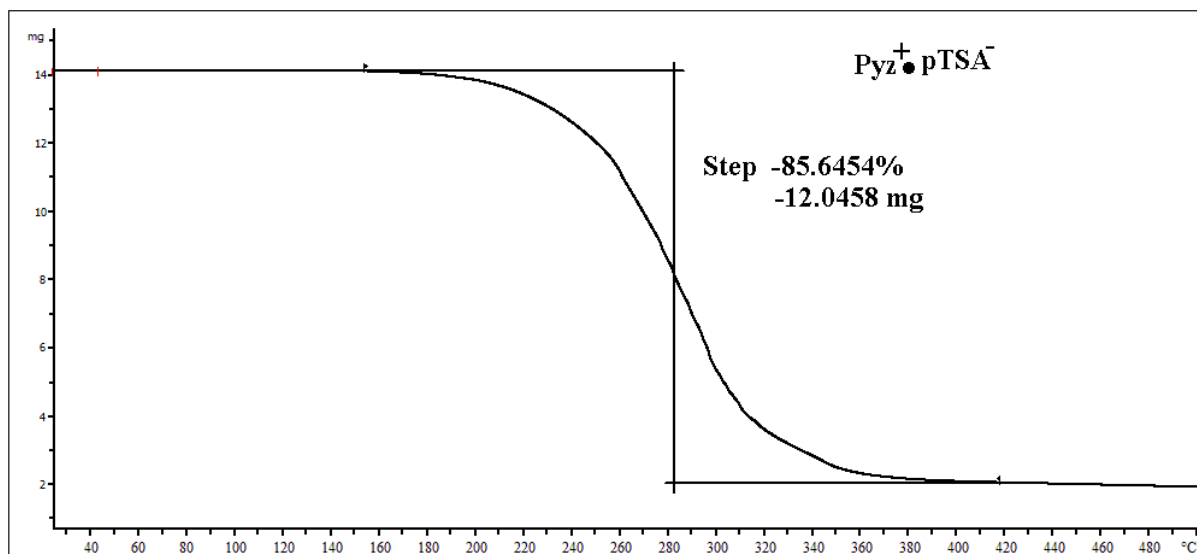


Figure S7 TGA of $\text{Pyz}^+\bullet\text{pTSA}^-$ salt showing degradation starting at ~150 °C and completed around 380 °C.

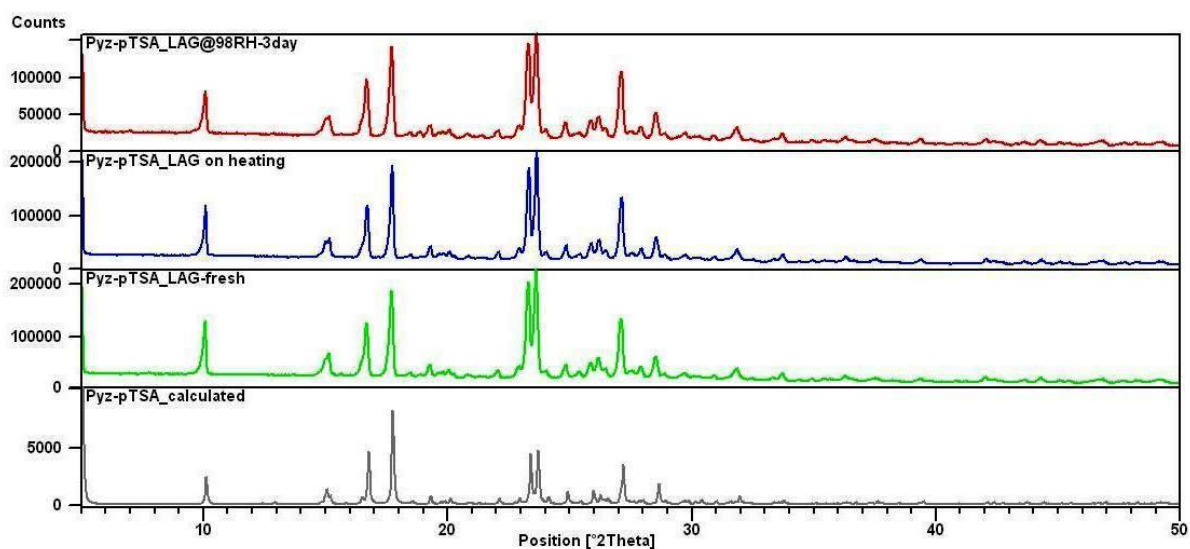
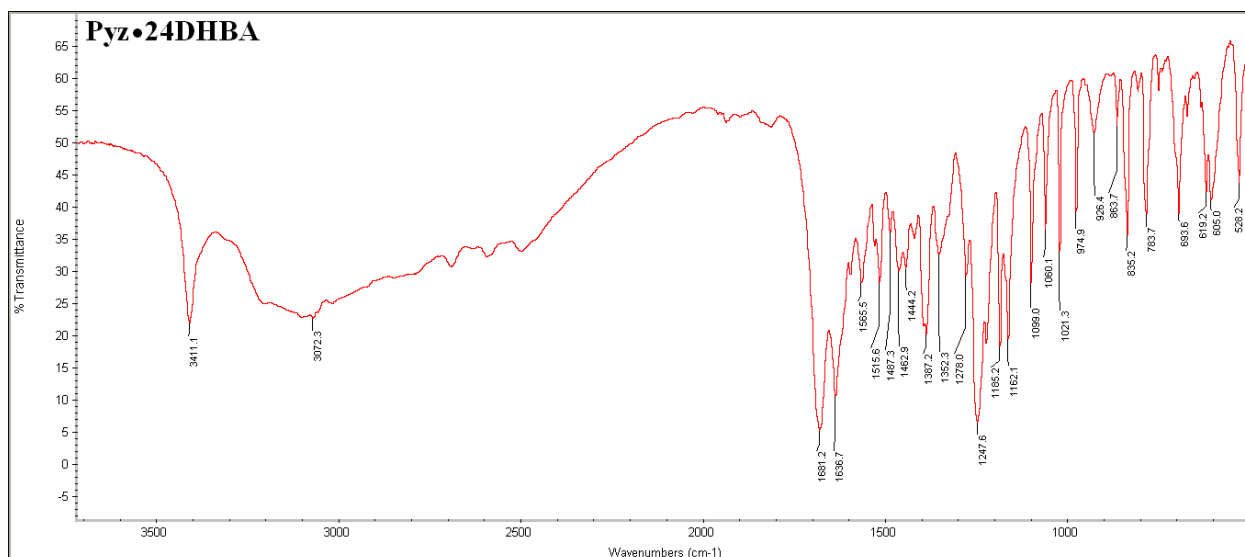
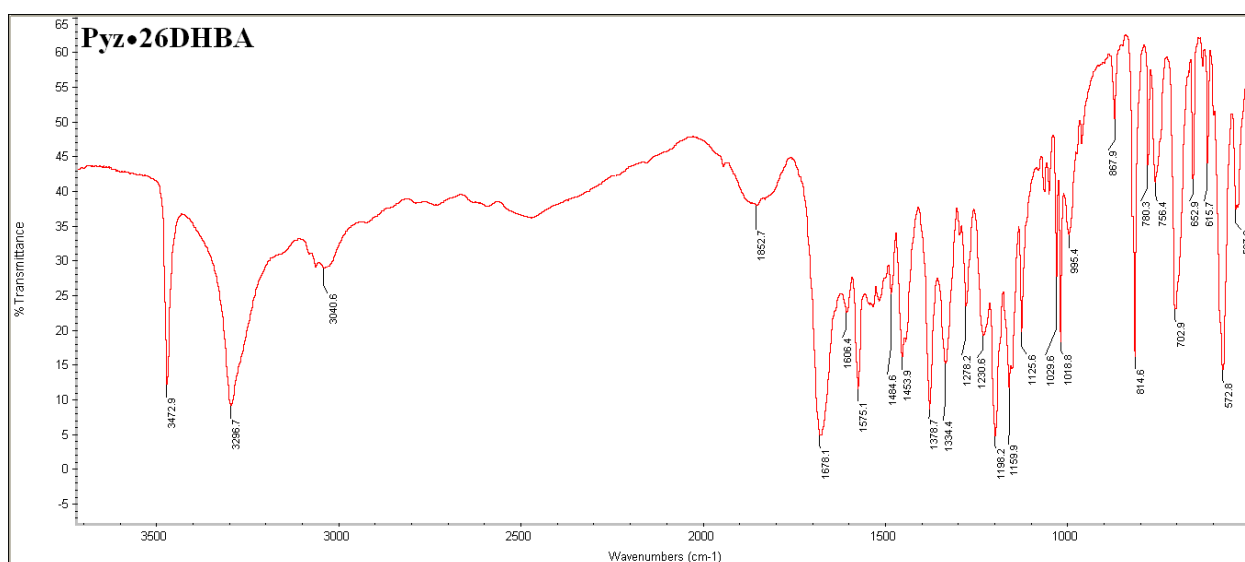


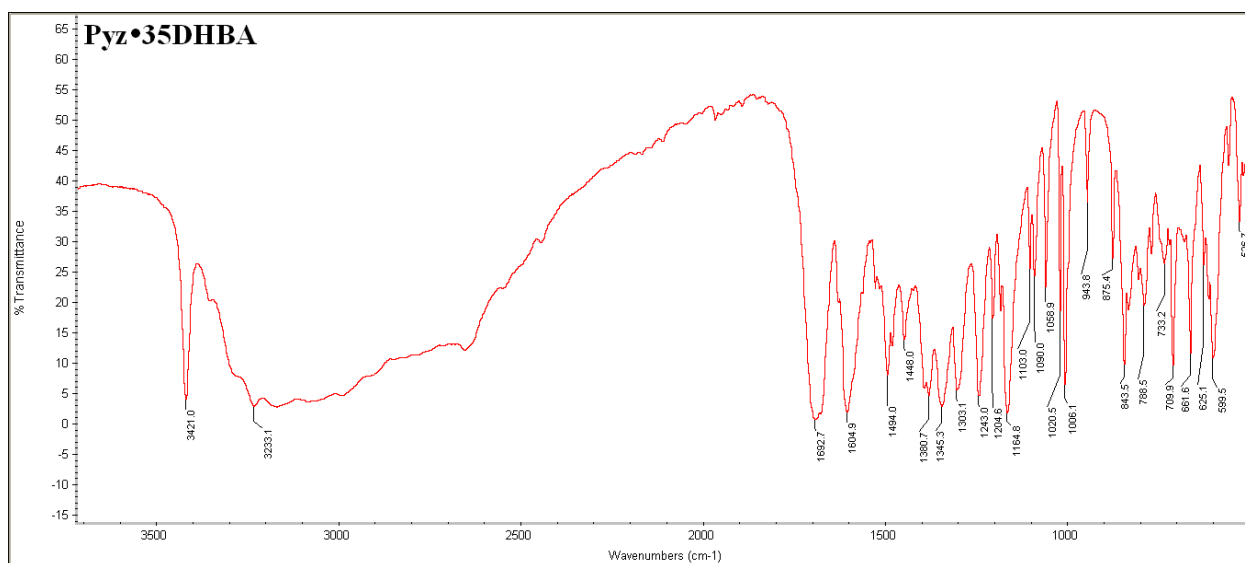
Figure S8 PXRD of freshly prepared, heated and sample stored under 98 % RH for 3 days compared with calculated powder pattern of $\text{Pyz}^+\bullet\text{pTSA}^-$ salt.



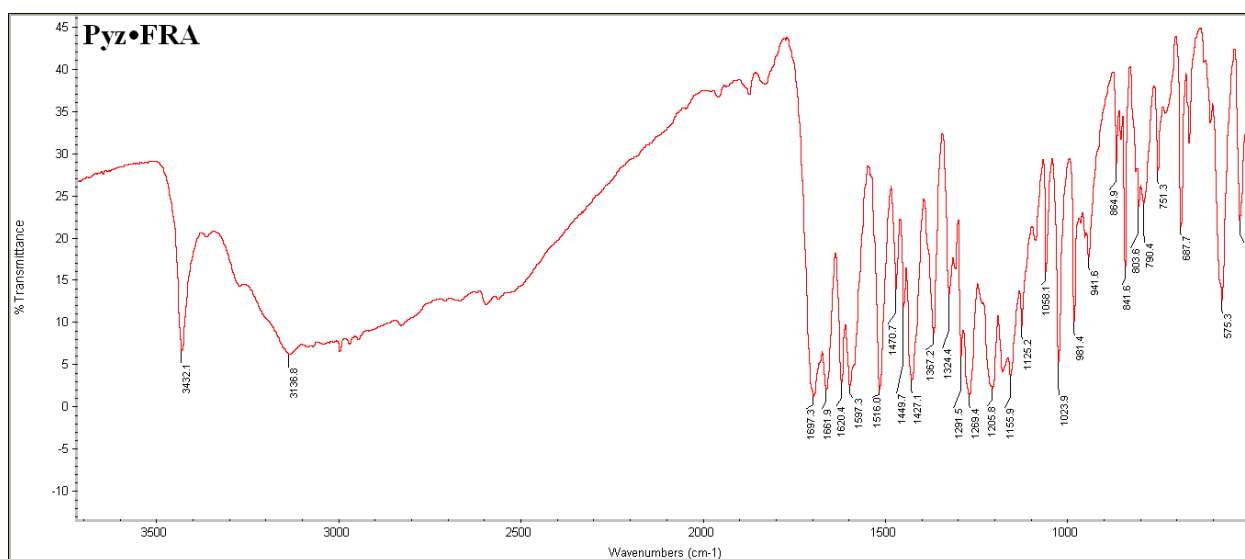
(a)



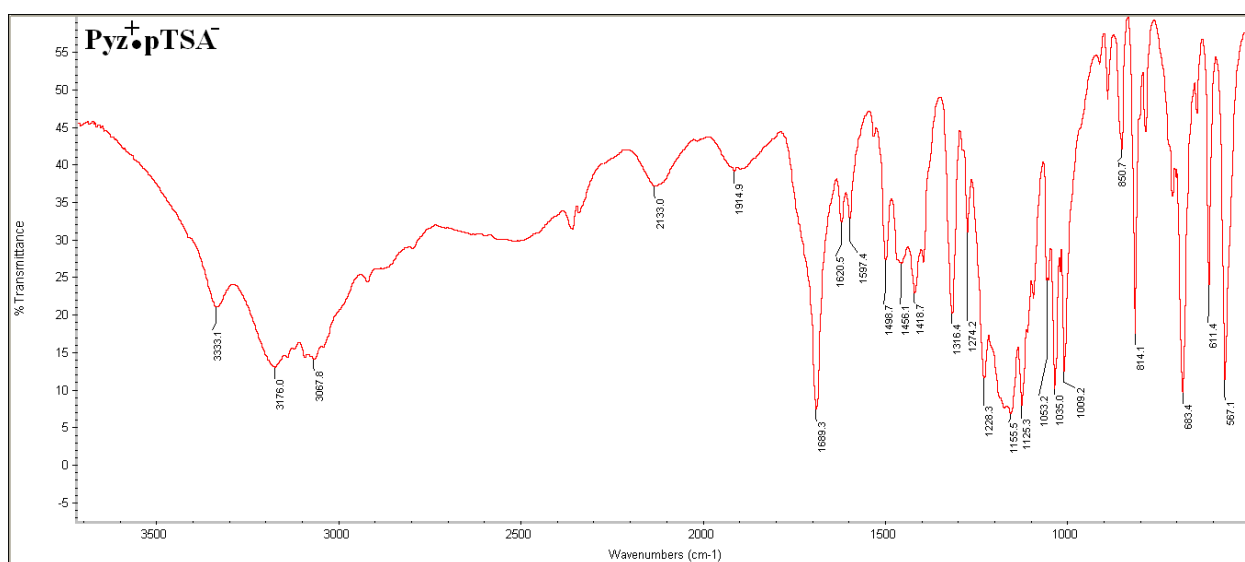
(b)



(c)



(d)



(e)

Figure S9 FT-IR spectra of Pyz cocrystals (a-d) and salt (e) prepared using liquid assisted grinding taking acetonitrile as liquid.