Electronic Supplementary Material (ESI) for CrystEngComm.

Electronic Supporting Information

Role of Mechanochemical Synthesis in the Crystal Chemistry of Leflunomide

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#: Equal contribution of both the authors

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A) List of Pharmaceutical Additives and Crystallization Table

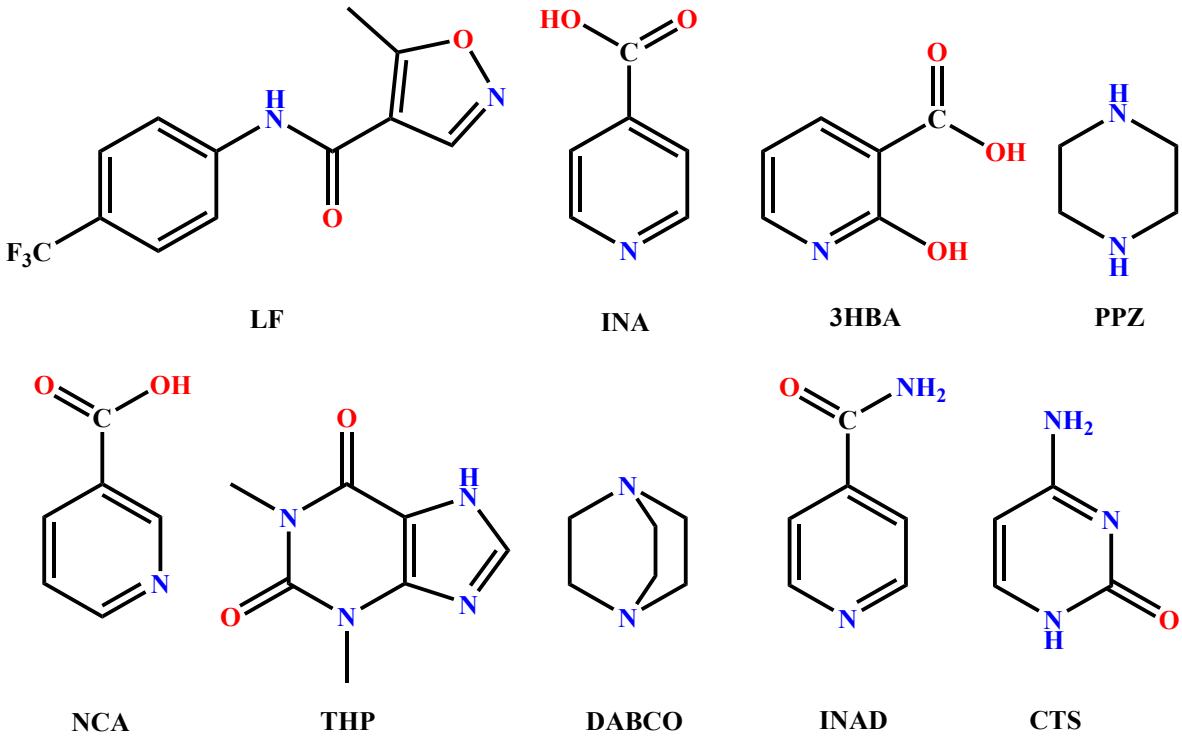


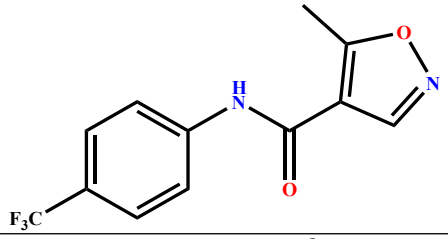
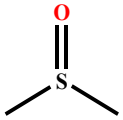
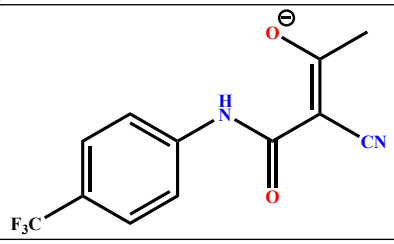
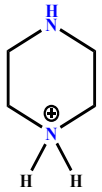
Figure S1: Chemical structures of LF drug and list of additives used for mechanochemical LAG experiments.

Table S1: Observed crystals with their morphologies. (DMSO: Dimethyl sulphoxide, IPA: Isopropyl alcohol, MeOH: Methanol, EtOH: Ethanol, DEE: Diethyl ether, THF: Tetrahydrofuran, TFT: Trifluorotoluene, MeOAc: Methyl acetate, EtOAc: Ethyl acetate, DCM: Dichloromethane, etc.)

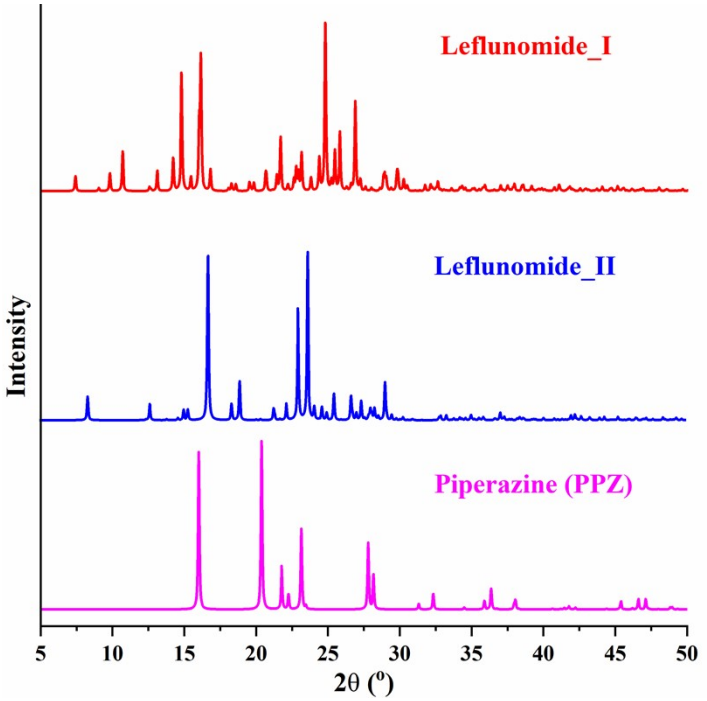
Leflunomide: Isonicotinic Acid (1:1)				
Solvent	**Solubility**	**Condition**	**Morphology**	**Result**
Methanol	Soluble	LT	Plate	LF_I & LF_II
Ethanol	Soluble	LT	Plate	LF_I
DCM	Soluble	LT	Aggregate	-
Chloroform	Sonicat^{n} → Filter	LT	Aggregate	-
IPA	Sonicat^{n} → Soluble	LT	Plate	LF_I & LF_II
DMSO	Soluble	LT	Plate	Solvate
Acetone + IPA	Sonicat^{n} → Soluble	LT	Plate	LF_I & LF_II
Leflunomide: 2-Hydroxypyridine-3-Carboxylic Acid (1:1)				
Methanol	Soluble	LT	Plate	LF_I
Ethanol	Soluble	LT	Plate	LF_I & LF_II
Acetonitrile	Soluble	LT	Aggregate	-
DMSO	Soluble	LT	Plate	Solvate
IPA	Soluble	LT	Plate	LF_I & LF_II
DEE + Acetone	Soluble	LT	Aggregate	-
Leflunomide: Nicotinic Acid (1:1)				
Methanol	Soluble	LT	Plate	LF_II
Ethanol	Soluble	LT	Plate	LF_I & LF_II
IPA	Soluble	LT	Plate + Needle	LF_I + Additive
DMSO	Soluble	LT	Plate	Solvate

Toluene	Soluble	LT	Plate	LF_II
Acetonitrile	Soluble	LT	Aggregate	-
Leflunomide: Theophylline (1:1)				
Methanol	Soluble	LT	Plate	LF_I
Ethanol	Soluble	LT	Plate	LF_I & LF_II
DMSO	Soluble	LT	Plate	Solvate
TFT	Soluble	LT	Plate	LF_II
Acetonitrile	Soluble	LT	Aggregate	-
Hexane	Soluble	LT	Plate	LF_II
Leflunomide: Piperazine (1:1) → TF^-_PPZ^+ Salt				
Methanol	Soluble	LT	Plate	Salt
Isopropanol	Soluble	LT	Aggregate	-
Acetonitrile	Soluble	LT	Block	Salt
DMSO	Soluble	LT	Aggregate	-
Nitromethane	Soluble	LT	Block	Salt
THF	Soluble	LT	Aggregate	-
Leflunomide: DABCO (1:1)				
IPA	Soluble	LT	Plate	LF_I & LF_II
Acetone	Soluble	LT	Plate	LF_II
Ethanol	Soluble	LT	Aggregate	-
Methanol	Soluble	LT	Aggregate	-
DMSO	Soluble	LT	Plate	Solvate
Acetonitrile	Soluble	LT	Aggregate	-
Leflunomide: Isonicotinamide (1:1)				
MeOH	Soluble	LT	Block	LF_I
Acetonitrile	Soluble	LT	Needle	
EtOAc	Soluble	LT	Needle	
MeOAc	Soluble	LT	Needle	
Nitromethane	Soluble	LT	Needle + Plate	
Isopropanol	Soluble	LT	Block	
DCM	Soluble	LT	Needle + Block	LF_II + Additive
Butan-2-one	Soluble	LT	Aggregate	-
1,4-Dioxane	Soluble	LT	Block	LF_II
Leflunomide: Cytosine (1:1)				
MeOH	Soluble	LT	Aggregate	-
DCM + Methanol	Δ → Soluble	LT	Aggregate	
ACN + MeOH	Δ → Soluble	LT	Aggregate	
Nitromethane + MeOH	Δ → Soluble	LT	Aggregate	
EtOAc + MeOH	Δ → Soluble	LT	Aggregate	
MeOAc + MeOH	Δ → Soluble	LT	Aggregate	
Isopropanol + MeOH	Δ → Soluble	LT	Aggregate	
1,4-Dioxane + MeOH	Δ → Soluble	LT	Aggregate	
Acetone + MeOH	Δ → Soluble	LT	Aggregate	

Table S2: Chemical structures of the solid-state forms LF-DMSO and $TF^-\_PPZ^+$.

Sample Code	API	
LF-DMSO (Solvate)		**Solvent** 
$TF^-\_PPZ^+$ (Salt)		**Additive** 

B) PXRD Patterns of Reactants with their Polymorphs



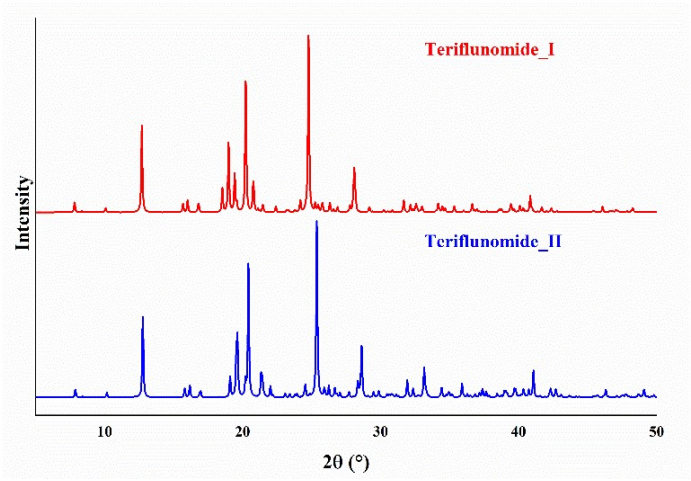


Figure S2: PXRD peak patterns of LF_I, LF_II, PPZ, TF_I and TF_II.

C) Thermal Characterization via DSC Curves

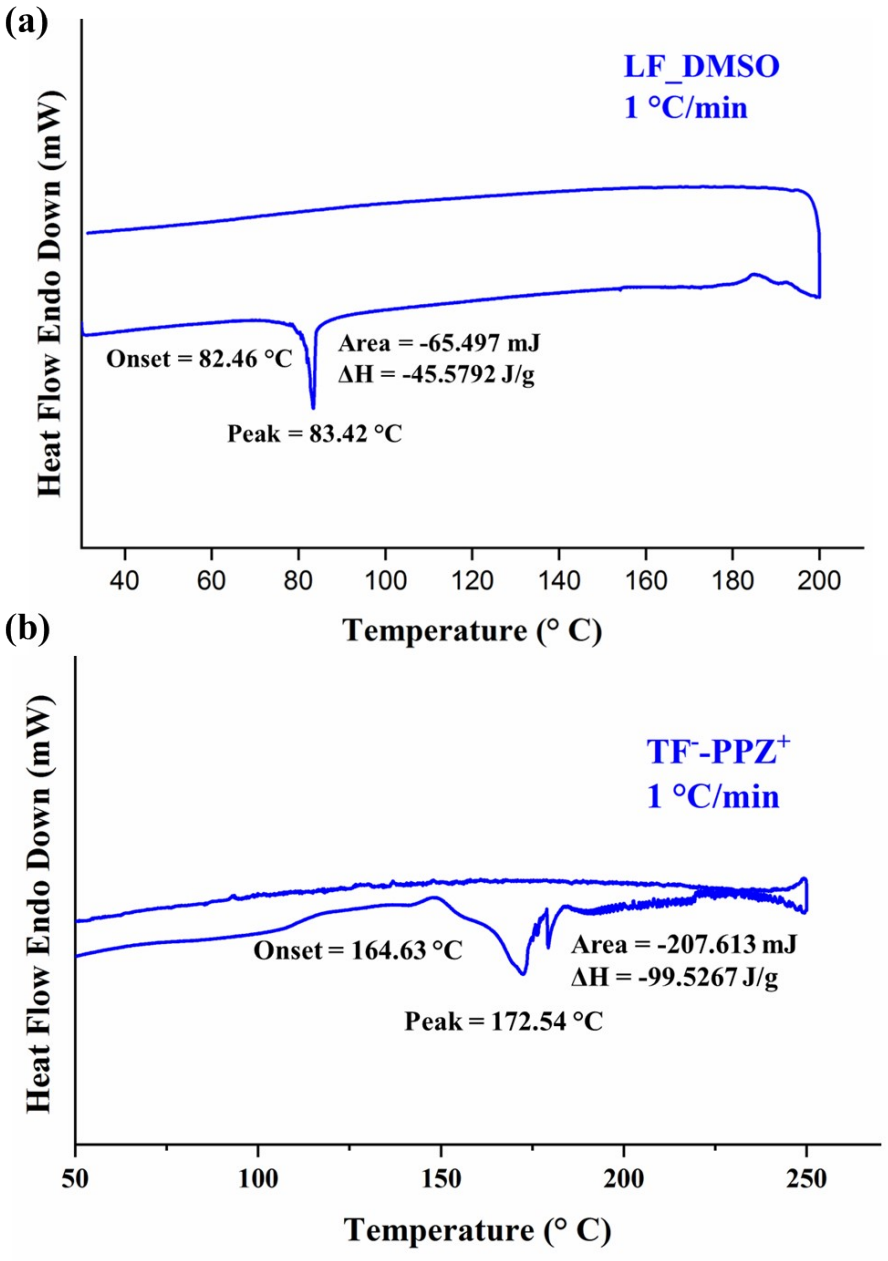


Figure S3: DSC trace for (a) LF_DMSO solvate and (b) TF - _PPZ + salt crystals.

D) Reciprocal Lattice Images for the LF_DMSO Crystal

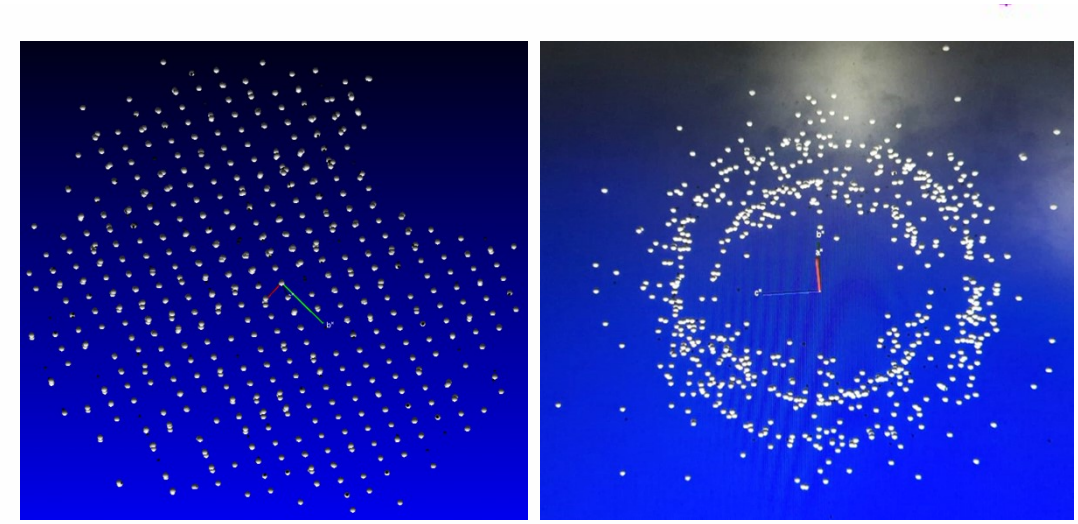


Figure S4: Gradual deviation of LF_DMSO solvate crystals from crystalline to amorphous nature shown by the SCXRD reciprocal lattice images, obtained by increasing the temperature.

E) d_{norm} Plotted over Hirshfeld Surface

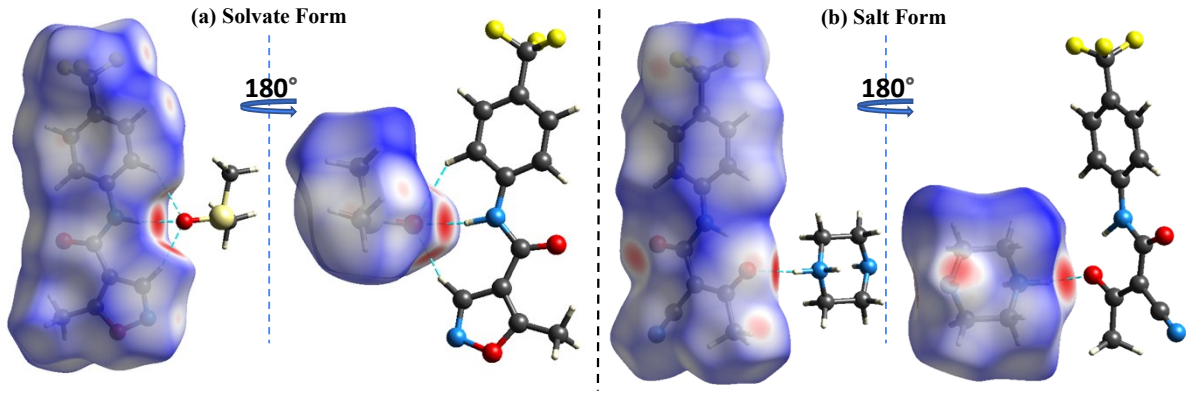


Figure S5: Hirshfeld surfaces of (a) solvate mapped with d_{norm} (left: Drug LF, right: DMSO); (b) salt mapped with d_{norm} (left: Drug TF^-, right: PPZ^+).

F) Analysis of Fingerprint Plots

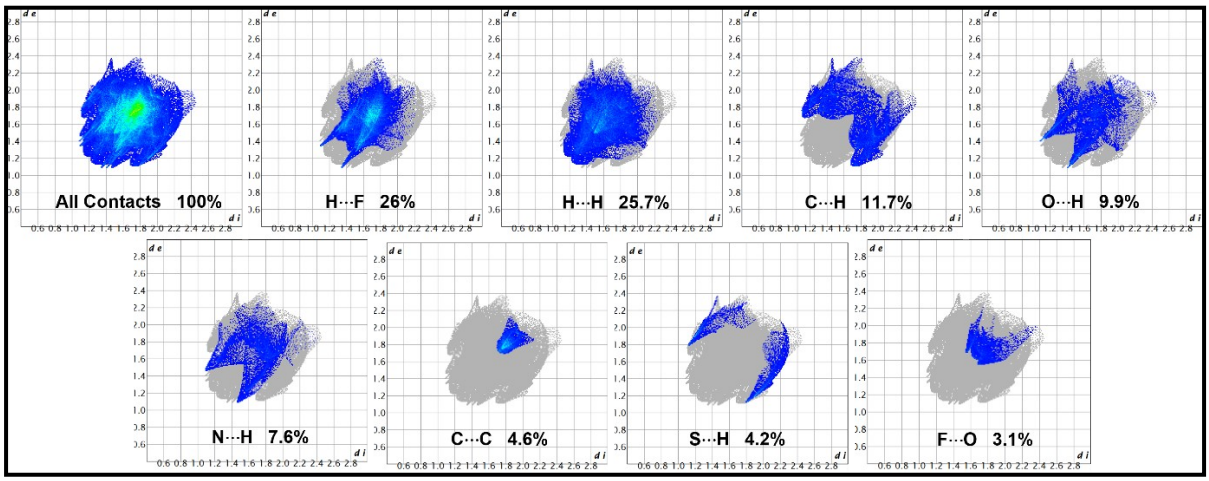


Figure S6: Fingerprint plots of **LF_DMSO** solvate showing the interaction type and percentage contribution to the crystal lattice.

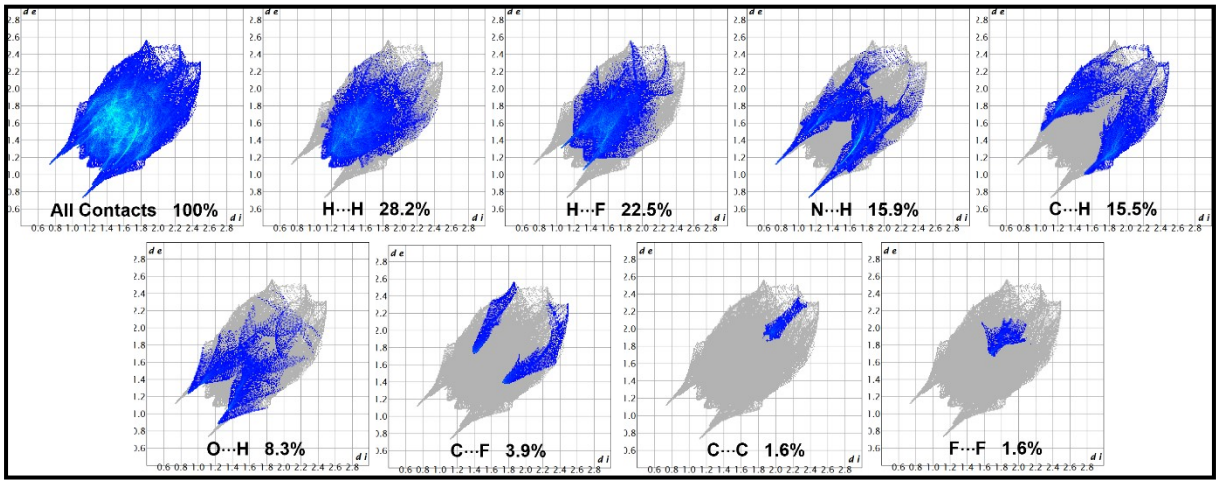


Figure S7: Fingerprint plots of **TF^-_PPZ^+** salt showing the interaction type and percentage contribution to the crystal lattice.

G) Cluster Energy Framework and Interaction Energy Calculations

Table S3: Results from Energy Frameworks for **LF_DMSO**.

Interaction Energies (kJ/mol)
R is the distance between molecular centroids (mean atomic position) in Å.

Total energies, only reported for two benchmarked energy models, are the sum of the four energy components, scaled appropriately (see the scale factor table below)

	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	1	-	4.56	B3LYP/6-31G(d,p)	-11.1	-1.5	-17.7	9.3	-22.4
	1	-x, -y, -z	6.30	B3LYP/6-31G(d,p)	4.9	-1.5	-25.6	13.8	-9.7
	1	-	7.69	B3LYP/6-31G(d,p)	-11.1	-2.9	-12.0	14.5	-15.4
	2	x, y, z	12.42	B3LYP/6-31G(d,p)	2.1	-0.4	-7.0	0.0	-4.1
	1	-x, -y, -z	13.98	B3LYP/6-31G(d,p)	1.5	-1.5	-12.2	0.0	-10.2
	1	-x, -y, -z	13.11	B3LYP/6-31G(d,p)	1.0	-0.1	-1.8	0.0	-0.6
	1	-	9.73	B3LYP/6-31G(d,p)	-3.1	-0.3	-7.5	3.6	-7.9
	1	-x, -y, -z	5.74	B3LYP/6-31G(d,p)	-11.6	-1.0	-26.6	13.9	-27.6
	1	-	5.35	B3LYP/6-31G(d,p)	-4.4	-1.5	-12.0	9.8	-10.2
	1	-	5.32	B3LYP/6-31G(d,p)	-5.7	-1.0	-20.4	17.4	-13.7
	1	-	10.35	B3LYP/6-31G(d,p)	1.9	-0.4	-3.3	1.5	-0.2
	1	-x, -y, -z	10.15	B3LYP/6-31G(d,p)	-7.8	-0.9	-11.0	8.5	-13.2
	2	x, y, z	12.31	B3LYP/6-31G(d,p)	0.2	-0.3	-3.8	0.0	-3.3
	1	-	4.83	B3LYP/6-31G(d,p)	-60.5	-17.5	-18.4	58.8	-56.5
	1	-x, -y, -z	4.07	B3LYP/6-31G(d,p)	-9.9	-2.5	-80.4	44.5	-54.8
	1	-x, -y, -z	13.94	B3LYP/6-31G(d,p)	0.6	-0.1	-1.3	0.0	-0.6
	1	-	6.36	B3LYP/6-31G(d,p)	-3.7	-0.5	-9.1	6.9	-8.0

Scale factors for benchmarked energy models
See Mackenzie et al. IUCrJ (2017)

Energy Model	k_ele	k_pol	k_disp	k_rep
CE-HF ... HF/3-21G electron densities	1.019	0.651	0.901	0.811
CE-B3LYP ... B3LYP/6-31G(d,p) electron densities	1.057	0.740	0.871	0.618

Table S4: Results from Energy Framework for **TF^-_PPZ^+**

Interaction Energies (kJ/mol)
R is the distance between molecular centroids (mean atomic position) in Å.

Total energies, only reported for two benchmarked energy models, are the sum of the four energy components, scaled appropriately (see the scale factor table below)

	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	2	-x, y+1/2, -z+1/2	7.95	B3LYP/6-31G(d,p)	130.6	0.0	-18.8	13.1	129.7
	1	-	6.17	B3LYP/6-31G(d,p)	-285.8	-3.5	-19.2	43.7	-294.5
	1	-x, -y, -z	13.53	B3LYP/6-31G(d,p)	0.0	-29.9	0.0	0.0	-22.1
	2	x+1/2, -y+1/2, -z	14.20	B3LYP/6-31G(d,p)	150.7	-9.6	-2.8	0.0	149.8
	2	x+1/2, y, -z+1/2	8.34	B3LYP/6-31G(d,p)	120.7	0.0	-15.5	7.5	118.7
	1	-	6.32	B3LYP/6-31G(d,p)	-104.4	-0.9	-0.0	0.0	-111.1
	1	-	5.19	B3LYP/6-31G(d,p)	-142.5	-7.7	-0.7	0.0	-157.0
	1	-	10.03	B3LYP/6-31G(d,p)	-124.3	-1.7	-0.1	0.0	-132.7
	1	-	9.39	B3LYP/6-31G(d,p)	-100.1	-1.2	-0.1	0.0	-106.9
	2	-x+1/2, y+1/2, z	4.62	B3LYP/6-31G(d,p)	198.8	-25.5	-47.1	34.1	171.3
	1	-	6.20	B3LYP/6-31G(d,p)	-275.2	-45.5	-30.2	28.7	-333.1
	1	-	10.76	B3LYP/6-31G(d,p)	-102.8	-1.1	-0.1	0.0	-109.6
	1	-	10.21	B3LYP/6-31G(d,p)	-78.6	-0.5	-0.0	0.0	-83.4
	0	-x+1/2, y+1/2, z	4.70	B3LYP/6-31G(d,p)	76.1	-0.2	-0.0	0.0	80.3

Scale factors for benchmarked energy models
See Mackenzie et al. IUCrJ (2017)

Energy Model	k_ele	k_pol	k_disp	k_rep
CE-HF ... HF/3-21G electron densities	1.019	0.651	0.901	0.811
CE-B3LYP ... B3LYP/6-31G(d,p) electron densities	1.057	0.740	0.871	0.618