Supporting Information for Structural Motifs in Salts of Sulfathiazole: Implications for Design of Salt Forms in Pharmaceuticals APIs.

Table S1. Crystal data and structure refinement for **I, II, III, V, VI**.

Identification code	**I**	**II**	**III**
Empirical formula	C_{18} H_{21} N_9 O_{13} S_4	C_9 H_{10} B F_4 N_3 O_2 S_2	C_{18} H_{22} N_6 O_9 S_5
Formula weight	699.68	343.13	626.71
Temperature (K)	173(3)	173(2)	173(2)
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	P2(1)/n	P2(1)/c	C2/c
Unit cell dimensions (Å, °)	a = 14.9484(4) b = 8.2585(2) c = 22.9621(6) α = 90 β = 100.8180(10) γ = 90°	a = 8.0557(2) b = 9.9422(3) c = 17.2090(5) α= 90 β= 90.5700(10) γ = 90	a = 17.4737(9) b = 11.6240(5) c = 11.7557(5) α = 90 β = 90.072 (2) γ = 90
Volume ($Å^3$)	2784.32 (12) Å3	1378.22(7)	2387.8 (2)
Z	4	4	4
Density (calculated) (Mg/m^3)	1.669	1.654	1.743
Absorption coefficient (mm^{-1})	0.42	0.438	0.551
Theta range for data collection (°)	1.79 to 30.07	2.53 to 30.06	2.33 to 30.23
Index ranges	−21 ≤ h ≤ 21 −11 ≤ k ≤ 11 −30 ≤ l ≤ 31	–11 ≤ h ≤ 11 –13 ≤ k ≤ 13 –22 ≤ l ≤ 24	−24 ≤ h ≤ 24 −16 ≤ k ≤ 16 −16 ≤ l ≤ 15
Reflections collected	67503	36555	29335
Independent reflections	8100 [R(int) = 0.046]	4023 [R(int) = 0.0309]	3526 [R(int) = 0.053]
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	8100 / 0 / 565	4023 / 0 / 206	3526/ 0 /238
Goodness-of-fit on F^2	1.026	1.096	1.055
Final R indices [I>2sigma(I)]	R1 = 0.039, wR2 = 0.0897	R1 = 0.0369, wR2 = 0.0963	R1 = 0.0504, wR2 = 0.0961
R indices (all data)	R1 = 0.0638, wR2 = 0.1022	R1 = 0.0422, wR2 = 0.1008	R1 = 0.0922, wR2 = 0.1134
Largest diff. peak and hole ($e.Å^{-3}$)	0.415 and -0.392	0.556 and -0.448	0.487 and -0.548

Identification code	**V**	**VI**
Empirical formula	C_{15} H_{15} N_3 O_5 S_3	C_{22} H_{27} N_3 O_6 S_3
Formula weight	413.48	525.64
Temperature (K)	173(3)	173(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Orthorhombic	Triclinic
Space group	Pbcn	P -1
Unit cell dimensions (Å, °)	a = 28.4964(13) b = 8.1448 (3) c = 15.5302 (7)	a = 13.1054(4) b = 13.3838(3) c = 17.8464(4) α = 109.9580(10) β = 92.029(2) γ = 111.5910(10)
Volume ($Å^3$)	3604.5(3)	2688.99
Z	8	4
Density (calculated) (Mg/m^3)	1.524	1.298
Absorption coefficient (mm^{-1})	0.444	0.315
Theta range for data collection (°)	2.60 to 20.30	2.28 to 26.14
Index ranges	$-37 \le h \le 36$ $-9 \le k \le 10$ $-20 \le l \le 20$	$-17 \le h \le 17$ $-17 \le k \le 18$ $-24 \le l \le 24$
Reflections collected	85436	70608
Independent reflections	4115 [R(int) = 0.116]	13884 [R(int) = 0.060
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	4115 / 0 / 354	13884 / 0 / 715
Goodness-of-fit on F^2	1.102	1.208
Final R indices [I>2sigma(I)]	R1 = 0.0537, wR2 = 0.0998	R1 = 0.0496, wR2 = 0.1100
R indices (all data)	R1 = 0.1032, wR2 = 0.1220	R1 = 0.0978, wR2 = 0.1382
Largest diff. peak and hole ($e.Å^{-3}$)	0.391 and -0.561	0.456 and -0.463

Table S2. Published Crystal Structures of STZ Co-crystals

REFCODE	Co-Former
ADEDIX (polymorphic)	pyridine
BABYIN	acetonitrile
BABYOT	N-formylpiperidine
FIZFUR	4-nitrobenzoic acid
FURDIF	Dioxane
HADMUU	18-crown-6/acetonitrile
KUFWOZ	4-aminobenzamide
LOFLUP	Glutaric acid
SOGSEO	dimethylformamide
STHSAM	sulfanilamide
SULTHE	theophylline
WIYLAT	2,4,6-tris(pyridin-2-yl)-1,3,5-triazine

Crystal Structure Packing Analysis of CSD Salts

Systems where STZ acts as a base.

BUWDUT

STZ dimers are formed from $^{+}$NH…N= H-bonds. These are linked into a 2-D sheet in the b-c plane through a collection of NH…F H-bonds (Figure 1). Sheets then stack in a-direction through weaker ring…ring motifs (Figure 2).

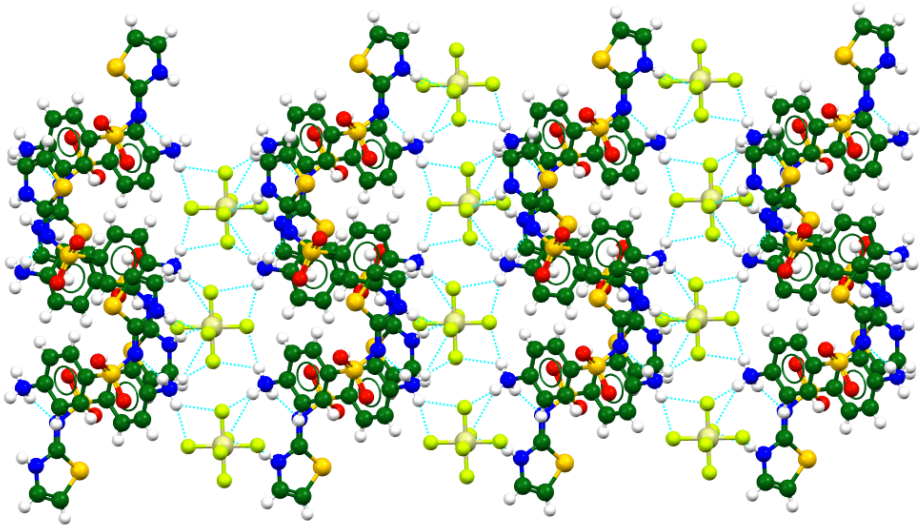

Figure S1. Formation of 2-D sheet in STZ.SiF_6

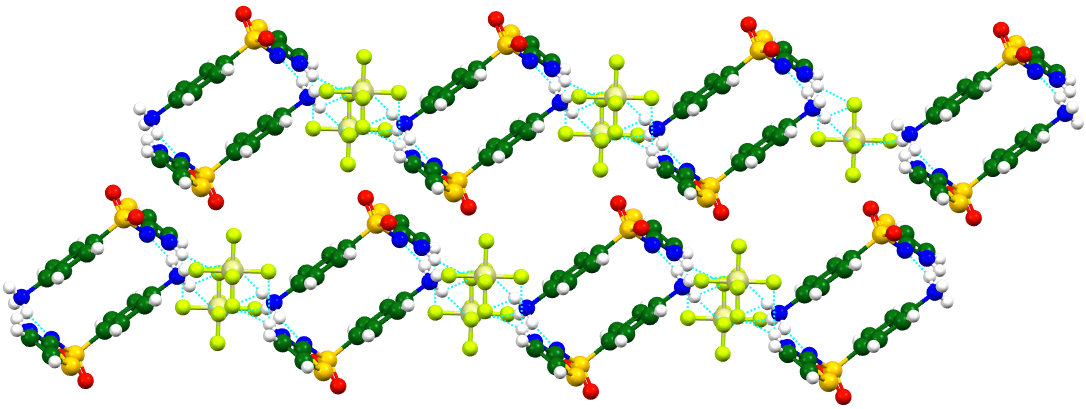

Figure S2. Packing of sheets along a-axis.

UDAKOA

STZ molecules form a 1-D chain through a NH…O=S H-bond. These are supported by two NH…O bonds to the water molecules (Figure 3) and an OH…O=S hydrogen bond then links these chains into a 2-D sheet (Figure 4). The sheets are linked into the final 3-D structure by the NO_3^- anions forming an OH…O and NH…O hydrogen bonds (Figure 5).

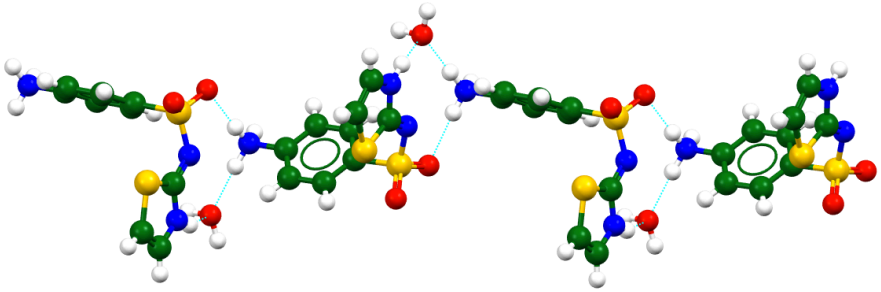

Figure S3. 1-D chain formed between STZ and H_2O in UDAKOA.

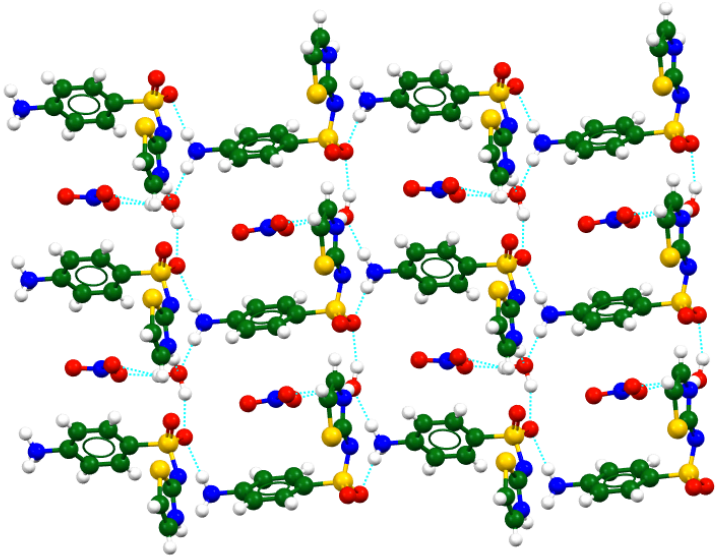

Figure S4. 2-D sheet formed through NO_3/H_2O interactions.

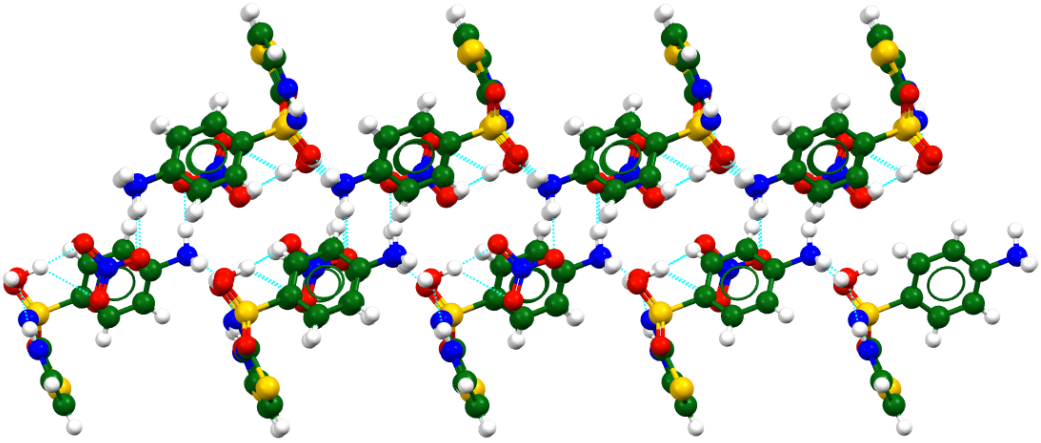

Figure S5. Completion of 3-D structure through packing of 2-D sheet.

KUFWIT

STZ molecules dimerise through a $R^2_2(16)$ motif (NH…O=S bond). These dimers then form a 1-D chain through further NH…N and NH…O=S bonds, the carboxylate anion links to the chain through two NH…O bonds (Figure 6). To this the neutral acid H-bonds through an OH…O interaction. These chains then interweave between each other through π…π and CH…O interactions to form final crystal structure (Figure 7).

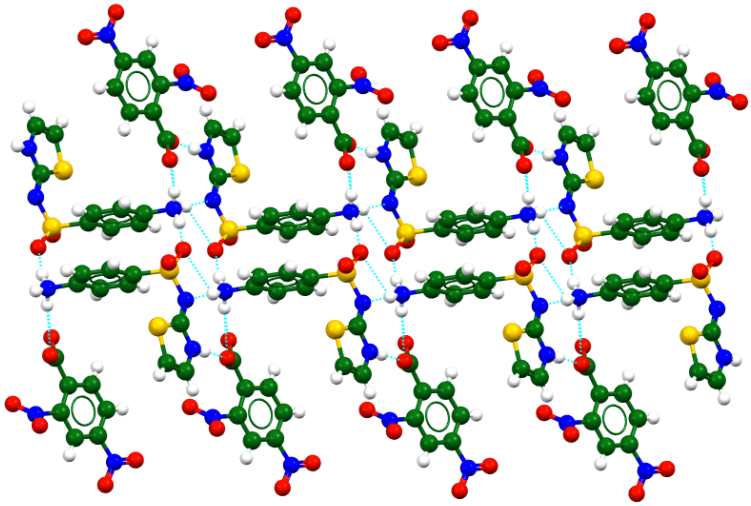

Figure S6. Formation of 1-D ribbon.

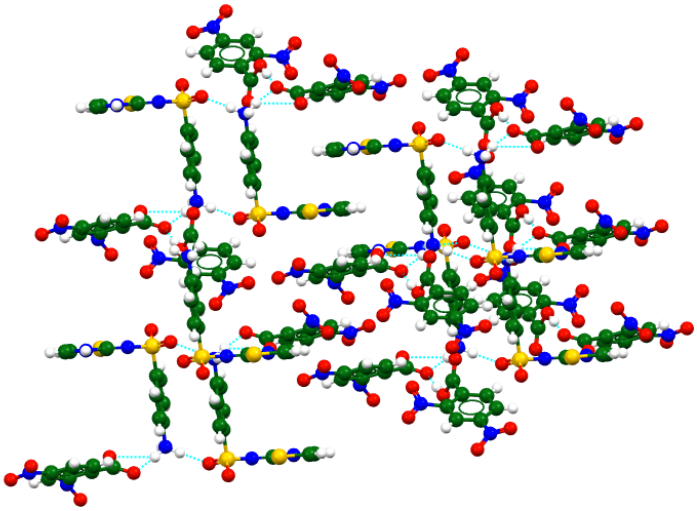

Figure S7. Interlocking of 1-D chains.

LOFMAW

Polymorphic system.

Form I

1-D ladder form between both components along the a-axis formed by NH…O, OH…O and NH…N H-bonds (Figure 8), which are linked through NH…O bonds to form a 2-D sheet motif (Figure 9), which forming the final 3-D structure through NH…O bonds.

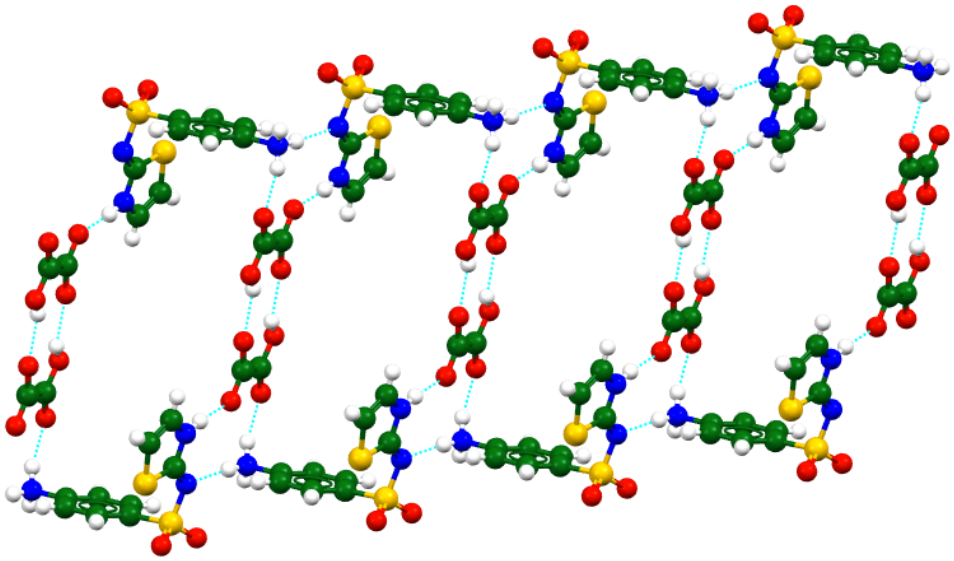

Figure S8. Ladder motif in LOFMAW.

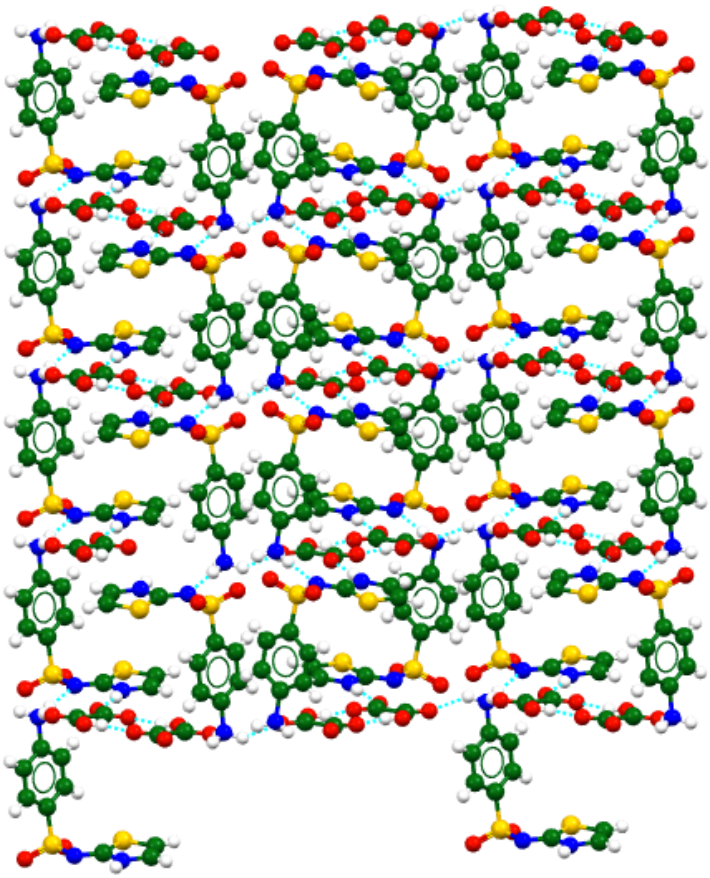

Figure S9. 2-D sheet formed by linking 1-D chains.

Form II (LOFMAW01)

1-D chain is formed between STZ and oxalate anions through NH…O=S and NH…O H-bonds (Figure 10), which are interlinked into a 2-D sheet through oxalate to oxalate hydrogen bonds (Figure 11). 3-D structure is constructed through interweaving of the 2-D motifs held together by weak CH…O bonds (Figure 12).

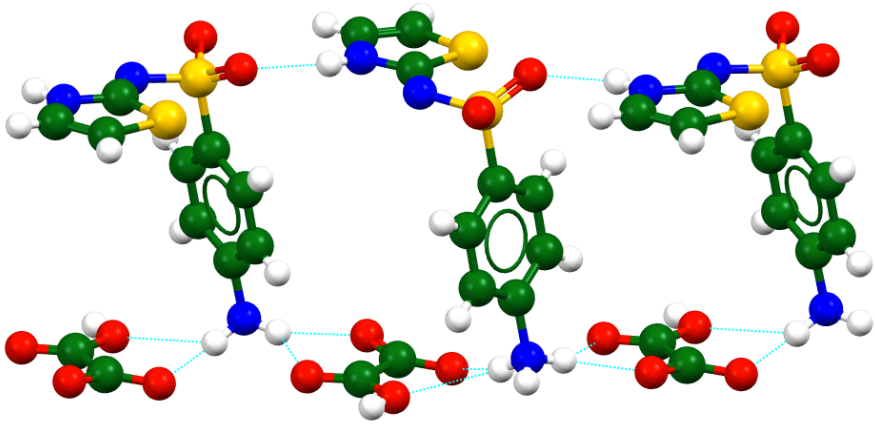

Figure S10. 1-D Chain of STZ…oxalate anions.

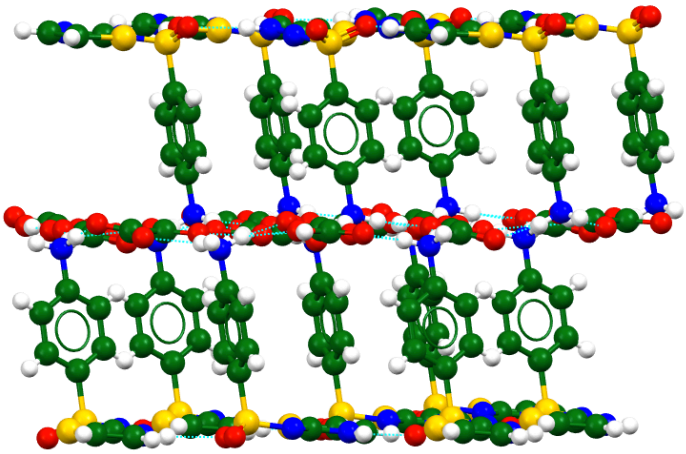

Figure S11. 2-D sheet formed between the 1-D chains.

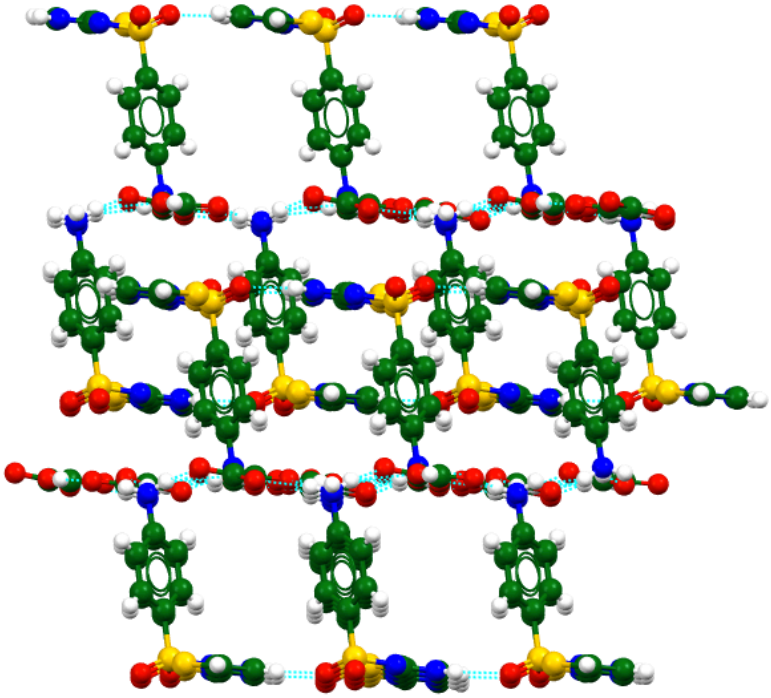

Figure S12. Final 3-D packing through interweaving of 2-D layers.

Systems where STZ acts as an acid.

BUHMOI

Components are bound in a pair through NH…N $R^2_2(8)$ H-bond. STZ molecules form a 1-D chain through NH…O=S bond and chains combine into a 2-D sheet by NH…O=S interaction (Figure 13). 3-D structure is formed by stacking the sheets along the a-axis through weaker NH…S bonds.

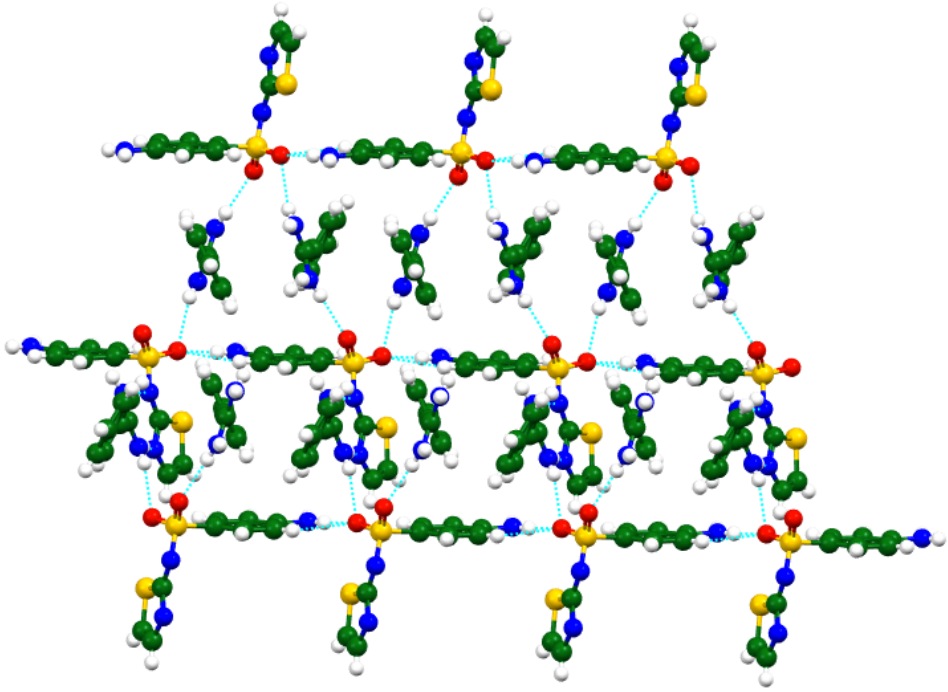

Figure S13. 2-D sheet structure in BUHMOI

DOWPUC

STZ molecules form a 2-D sheet in *ab* plane through NH…O=S H-bonds (Figure 14). The counterion bonds to the STZ through a NH…N_{ring} H-bond, weker CH…N bonds between these molecules links the sheet together to form the final structure (Figure 15).

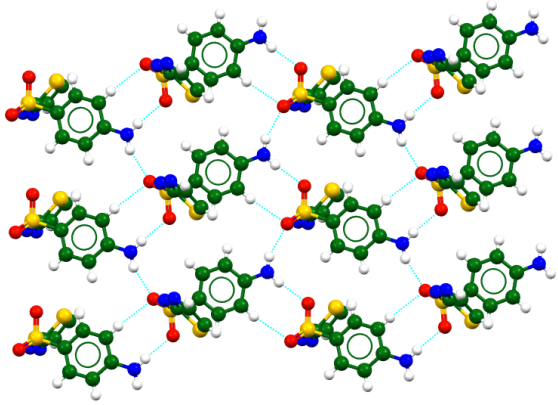

Figure S14. Formation of 2-D sheet in DOWPUC.

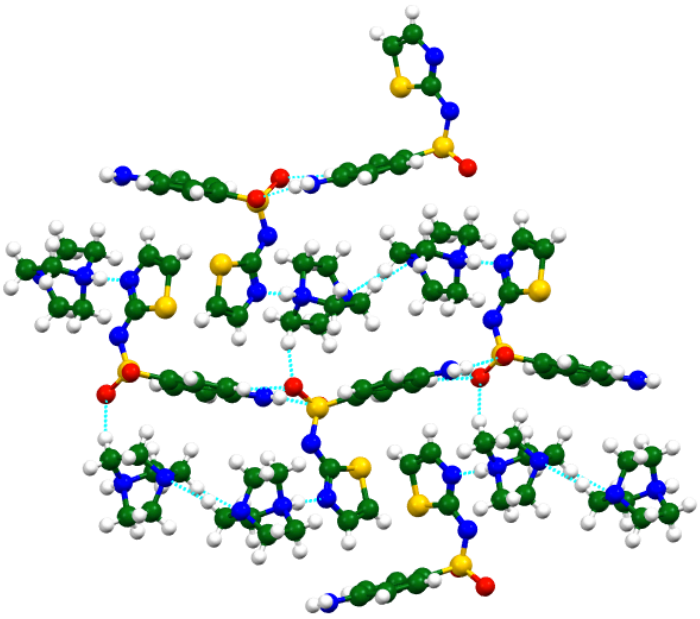

Figure S15. Packing of second molecule into 2-D to form 3-D structure.

DOWQAJ

Channel clathrate with a 1-D chain of piperazine molecules (along a-axis) within a STZ channel formed by NH…O=S bonds (Figure 16), which a linked through further NH…O=S bonds to form 3-D structure.

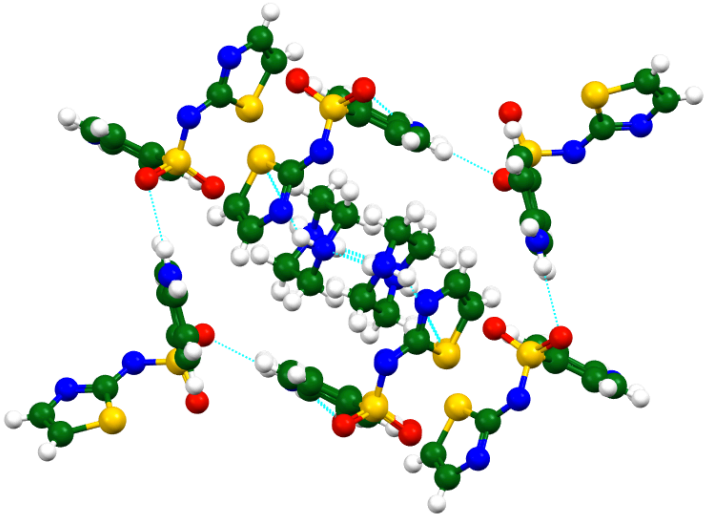

Figure S16. 1-D channel formed from STZ molecules with piperazine inclusion.

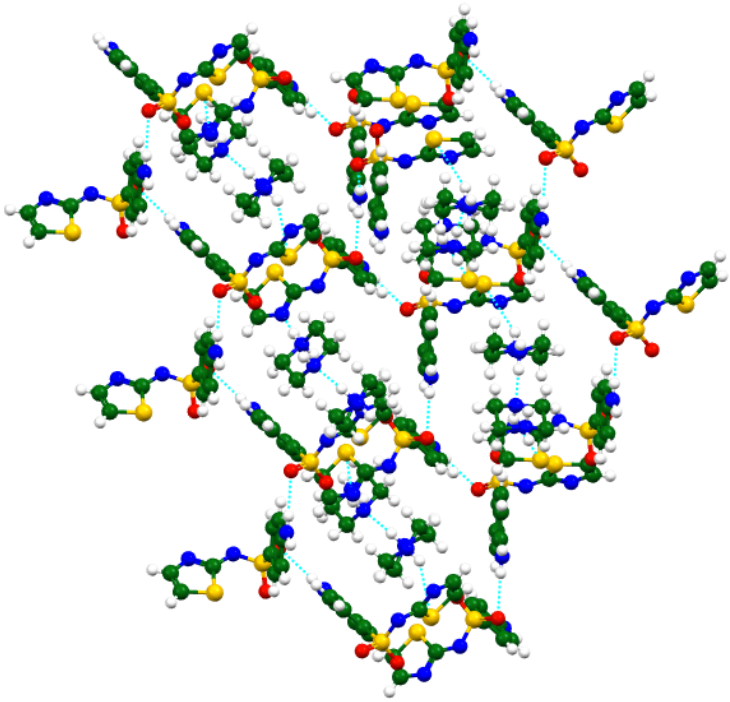

Figure S17. Interlocking channels to form final structure.

HSLSTZ

2-D sheet formed through direct interaction of the two sulfonamides (Figure 18) through a collection of NH…O=S and NH…N H-bonds. These are linked through a NH…O=S H-bond forming the final structure (Figure 19).

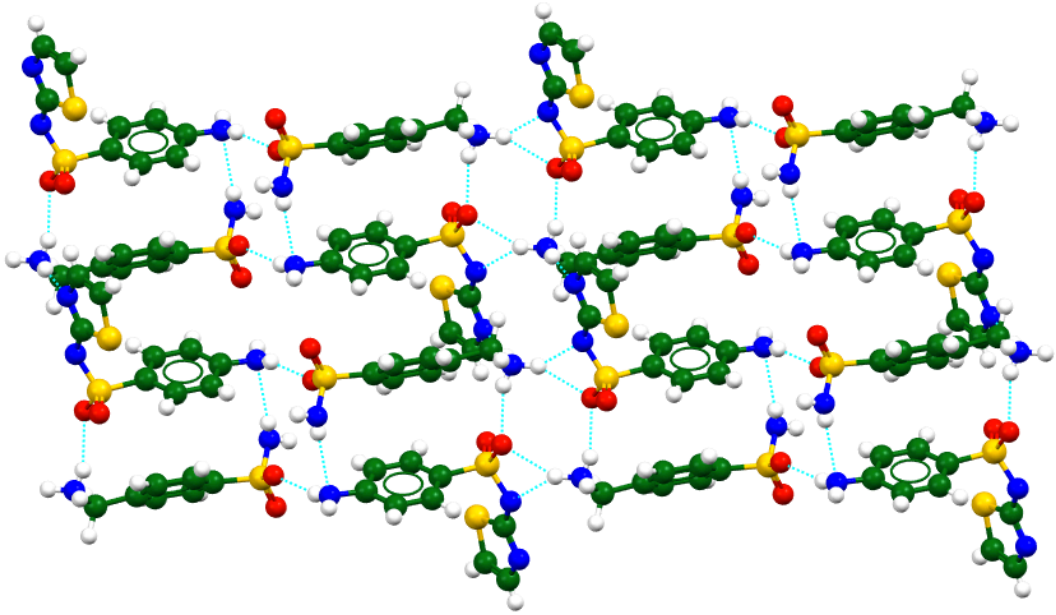

Figure S18. 2-D sheet formed for HSLSTZ

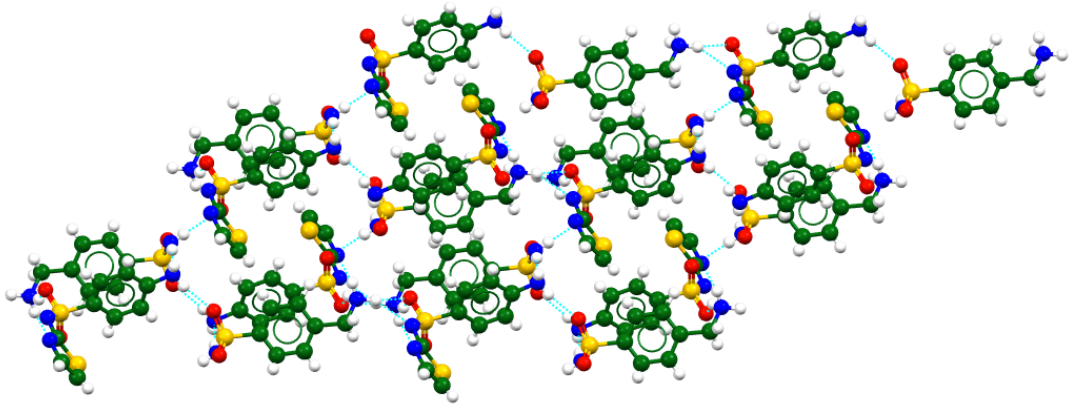

Figure S19. Stacking of 2-D sheets to form 3-D structure.

OHUWAR

The two components of the salt form a tetramer through a $R^4_4(18)$ set of NH…N and OH…N hydrogen bonds. These are linked into a 1-D ribbon through NH…N hydrogen bonds (Figure 20), which further forms a 2-D sheet with C-H…O=S links (Figure 21). Final structure formed by stacking along a-axis with further CH…O=S bonds.

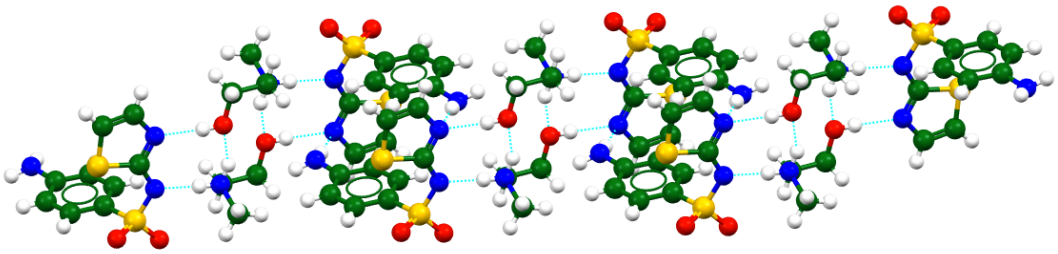

Figure S20. Linking of tetramers into 1-D chain.

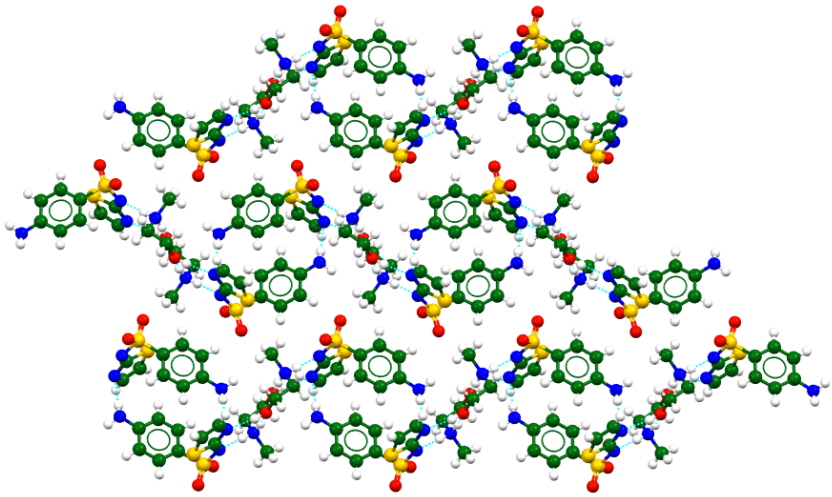

Figure S21. 2-D sheet in *bc* plane.

OHUWEV

STZ molecules form a 2-D sheet through NH…O=S bonds (Figure 22), these are linked through pairs of anions with OH…N/NH…N hydrogen bonds to form the final structure.

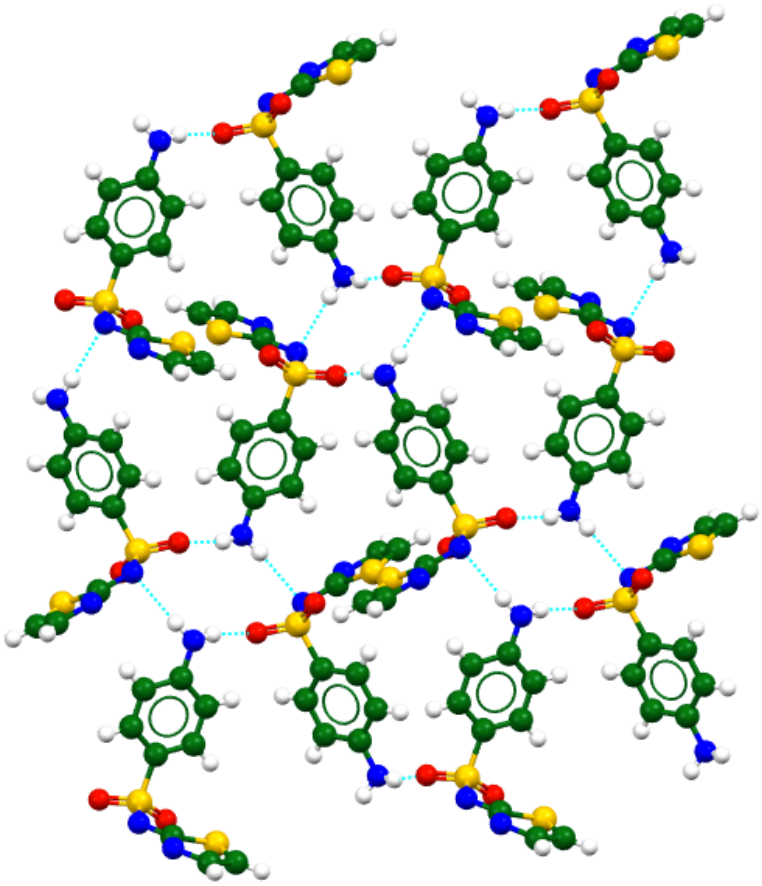

Figure S22. 2-D sheet formed solely from STZ molecules.

OHUWIZ

STZ molecules form a dimer and are linked together with anion dimers to form a 1-D chain through a range of hydrogen bonds (Figure 23). These chains are linked through NH…O=S bonds to form a 2-D structure which are stacked in the c-axis with weak CH…O=S bonds to give the final structure.

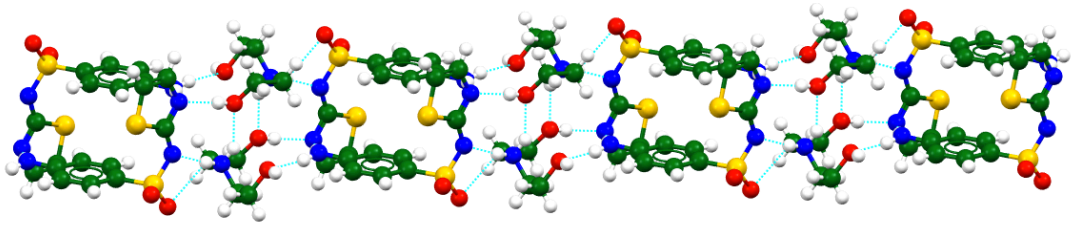

Figure S23. 1-D linked chain of molecules in OHUWIZ

QEDWAZ

STZ molecules link through NH…O=S bonds to form a 1-D ribbon, which are linked though dimers of counterion with OH…N bonds to form 2-D sheet (Figure 24). Final structure is formed by stacking held together with NH…O=S H-bonds.

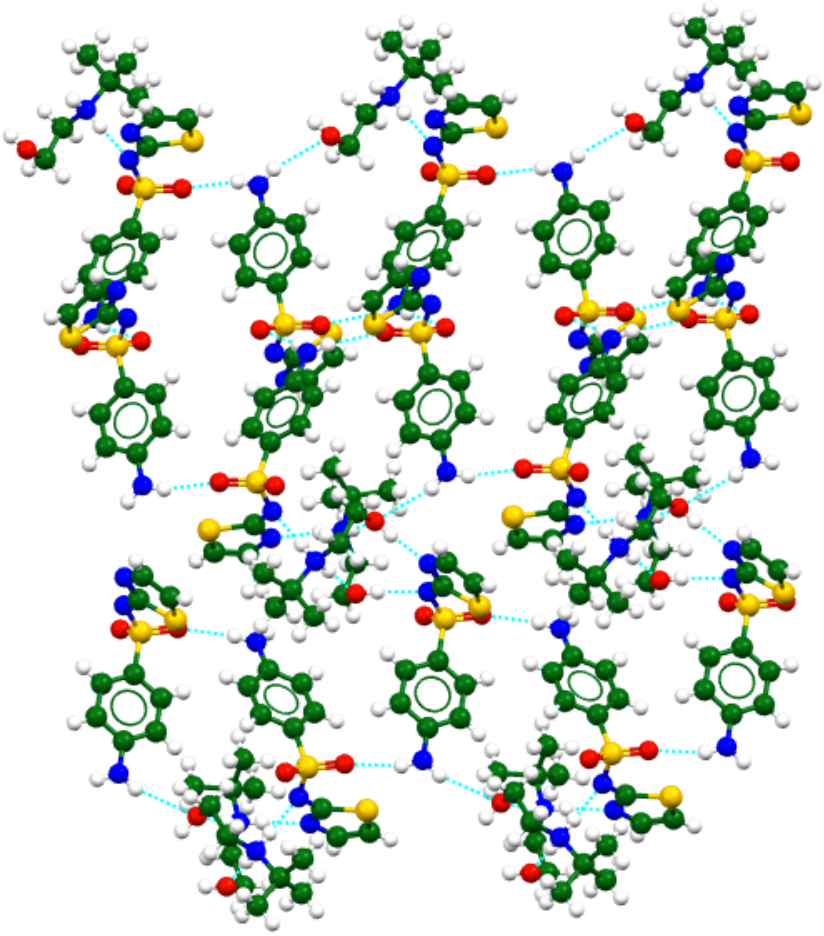

Figure S24. 2-D sheet in QEDWAZ structure.

XIFPEI01

1-D ribbon is formed through the two components (Figure 25) by a combination of NH…O=S interactions between both species, a second NH…O=S H-bond then links these chains into a 2-D structure (Figure 26). Final structure is formed from stacking of these sheets with interweaving of thiazole rings (Figure 27).

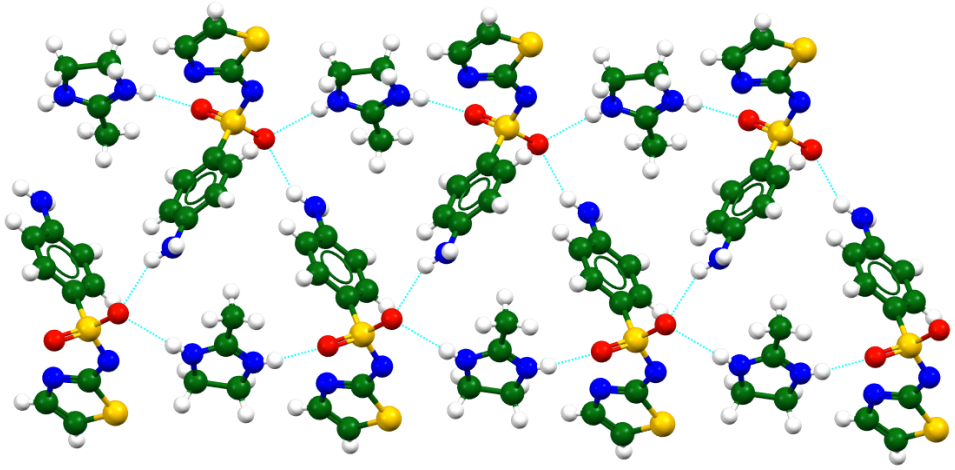

Figure S25. 1-D ribbon in XIFPEI

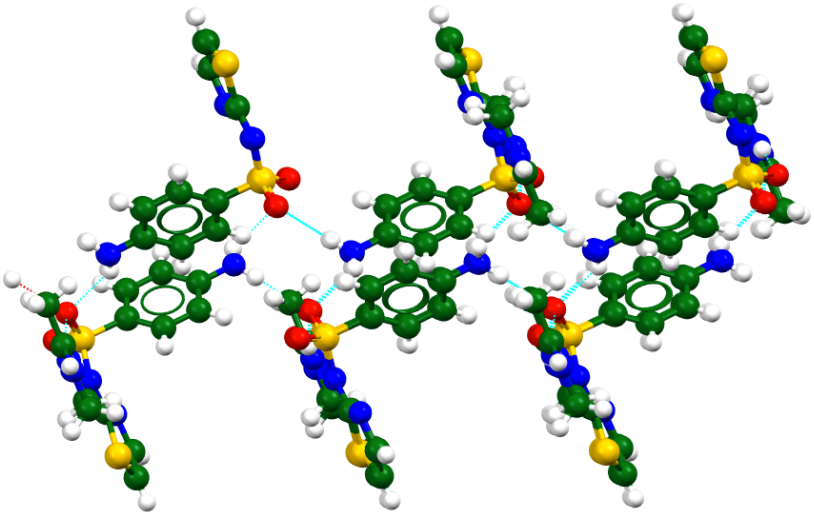

Figure S26. Rotation of Figure 25 chain, then linked through NH…O=S bonds.

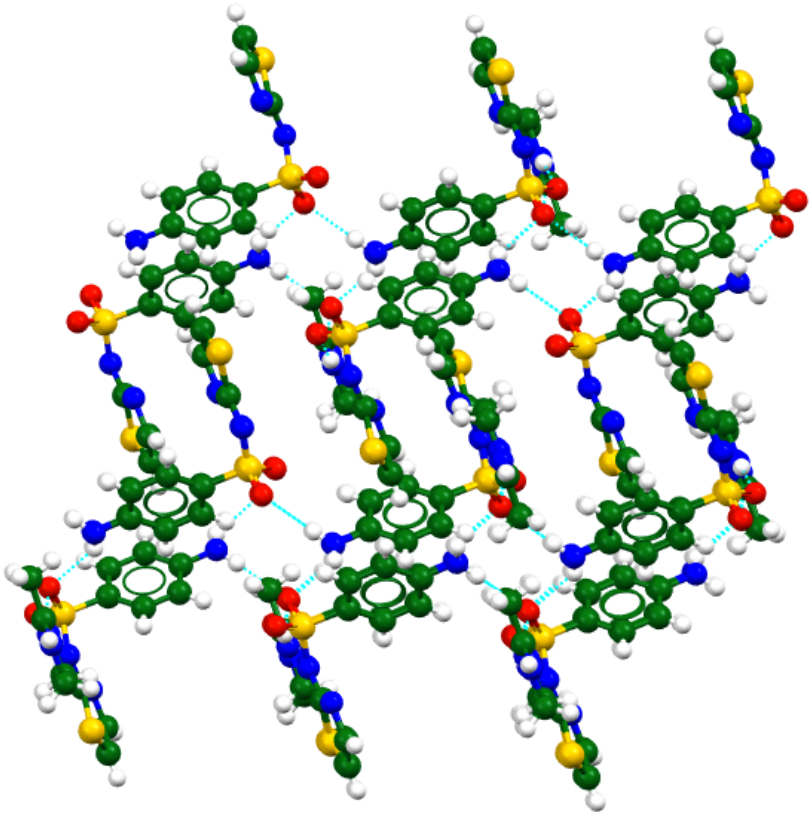

Figure S27. Stacking of 2-D sheets into final structure.

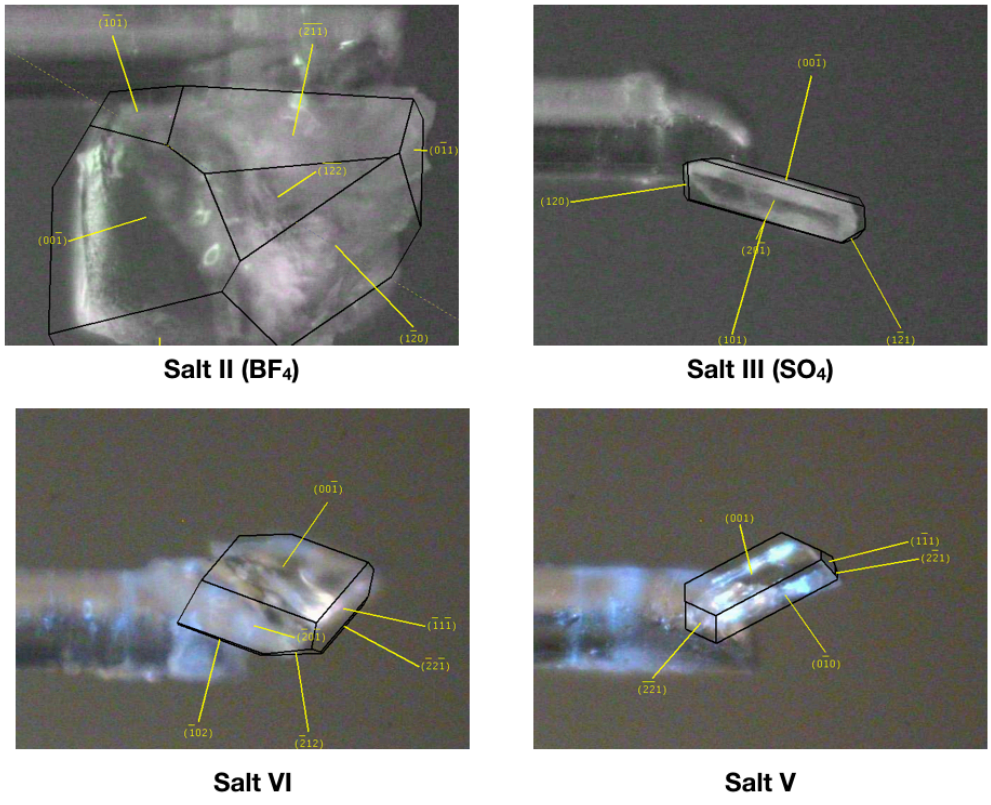

Figure S28. Morphologies of STZ salts studied.