Electronic Supplementary Material (ESI) for CrystEngComm

Tautomeric Bias in Polymorphs and Pseudopolymorphs of Succinylsulfathiazole: Fast Evaporation Screening and Thermal Studies

*Partha Pratim Bag, Raghuram Reddy Kothur and C. Malla Reddy**

Department of Chemical Sciences, Indian Institute of Science Education and Research, Kolkata, 741252, West Bengal, India. Fax: +91 33 25873020; Tel:+91 33 25873118 (Ext. No: 238)

* To whom correspondence should be addressed. E-mail: cmallareddy@gmail.com

Table S1. Geometrical parameters of hydrogen bonds in all the polymorphs, hydrate and solvates.

D—H…A	D…H (Å)	H…A(Å)	D…A (Å)	D—H…A (deg)
Polymorph I				
N1 -- H1 .. O7	0.8800	2.0400	2.9140	174.00
O2 -- H2C .. O4	0.8300	1.9700	2.7399	155.00
N3 -- H3 .. O8	0.8700	2.0100	2.8599	166.00
N4 -- H4 .. O1	0.8400	2.0900	2.9004	160.00
N6 -- H6A .. O3	0.9200	1.9100	2.8139	168.00
O6 -- H6B .. O9	0.8900	1.9000	2.7560	160.00
C2 -- H2A .. N5	0.9700	2.5900	3.3938	141.00
C9 -- H9 .. O5	0.9300	2.5800	2.9414	104.00
C10 -- H10 .. O3	0.9300	2.4100	2.9051	113.00
C22 -- H22 .. O10	0.9300	2.4800	3.3867	164.00
C23 -- H23 .. O8	0.9300	2.3600	2.9227	119.00

Polymorph II

N1	-- H1	.. O5	0.8100	2.1500	2.9542	170.00
O2	-- H2C	.. N2	0.8600	1.9400	2.7875	166.00
N3	-- H3	.. O1	0.7900	1.9600	2.7413	174.00
C9	-- H9	.. O5	0.9300	2.5500	2.9301	105.00
C10	-- H10	.. O3	0.9300	2.3000	2.8838	120.00
C13	-- H13	.. O4	0.9300	2.4300	3.1757	137.00

SST/H_2O

N1	-- H1	.. O2	0.7600	2.1900	2.9474	178.00
O1	-- H1A	.. O6	0.9500	1.7400	2.6375	158.00
N3	-- H3	.. N2	1.0800	1.8000	2.8655	166.00
O6	-- H6A	.. O3	0.9300	1.8400	2.7722	174.00
O6	-- H6B	.. O4	0.7800	2.1900	2.8172	138.00
C6	-- H6	.. O6	0.9300	2.5500	3.2751	135.00
C9	-- H9	.. O5	0.9300	2.5500	2.9228	104.00
C10	-- H10	.. O3	0.9300	2.2600	2.8482	121.00

SST/AcMe

O1	-- H1	.. O8	0.8600	1.9000	2.7162	159.00
N1	-- H1A	.. O2	0.8000	2.1000	2.8901	171.00
N3	-- H3	.. N2	0.8900	2.0000	2.8841	176.00
N4	-- H4	.. O7	0.8100	2.4500	3.1883	153.00
N6	-- H6	.. O10	1.0900	2.3900	3.2612	136.00

N6	-- H6	.. N5	1.0900	1.7700	2.7888	154.00
O6	-- H6B	.. O3	0.8200	2.0700	2.7209	136.00
C6	-- H6A	.. O8	0.9300	2.5800	3.3547	141.00
C7	-- H7	.. O5	0.9300	2.4600	2.8605	106.00
C10	-- H10	.. O3	0.9300	2.3500	2.9051	118.00
C19	-- H19	.. O8	0.9300	2.2900	2.8525	118.00
C20	-- H20	.. O9	0.9300	2.5600	2.9280	104.00
C22	-- H22	.. O11	0.9300	2.5700	3.2601	132.00

SST/THF

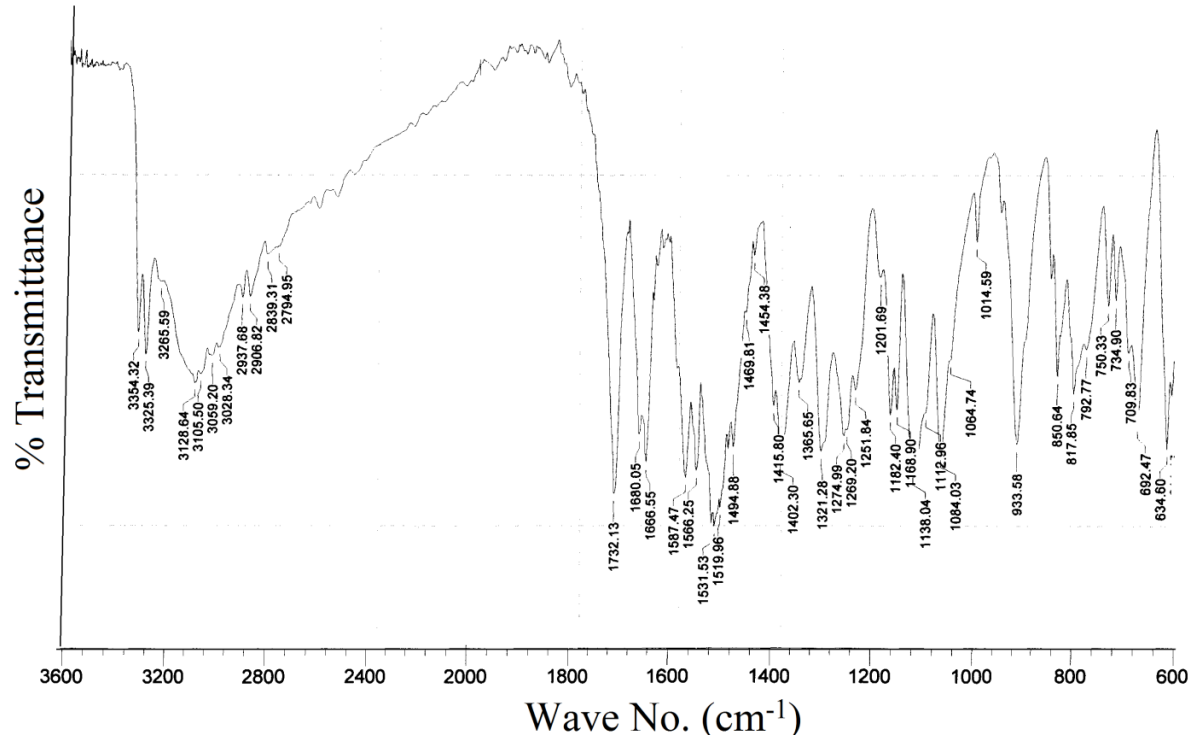
N1	-- H1	.. O6	0.8400	2.5800	3.0682	118.00
N1	-- H1	.. O2	0.8400	2.4800	3.2322	150.00
O1	-- H1A	.. O8	1.0200	1.8300	2.7432	147.00
N3	-- H3	.. N2	0.9400	1.8900	2.8104	169.00
N4	-- H4	.. O7	0.8000	2.1100	2.9053	175.00
O6	-- H6A	.. O3	0.7900	1.9300	2.7066	165.00
N6	-- H6B	.. N5	0.8400	2.0400	2.8724	173.00
C6	-- H6	.. O3	0.9300	2.2800	2.8561	120.00
C7	-- H7	.. O4	0.9300	2.5200	2.8998	105.00
C19	-- H19	.. O8	0.9300	2.3600	2.9081	118.00
C22	-- H22	.. O10	0.9300	2.4700	2.8600	106.00
C23	-- H23	.. O3	0.9300	2.6000	3.3570	139.00

Table S2. Conditions used at rotary evaporator for the preparation of succinylsulfathiazole (SST) polymorphs. The revolution speed (130 rpm) and water bath temperature (50 °C) were always constant. In all the batches 70 mg of SST (0.1969 mmol; Sigma-Aldrich) was dissolved in suitable solvents (30-40 mL) for preparing the solid forms.

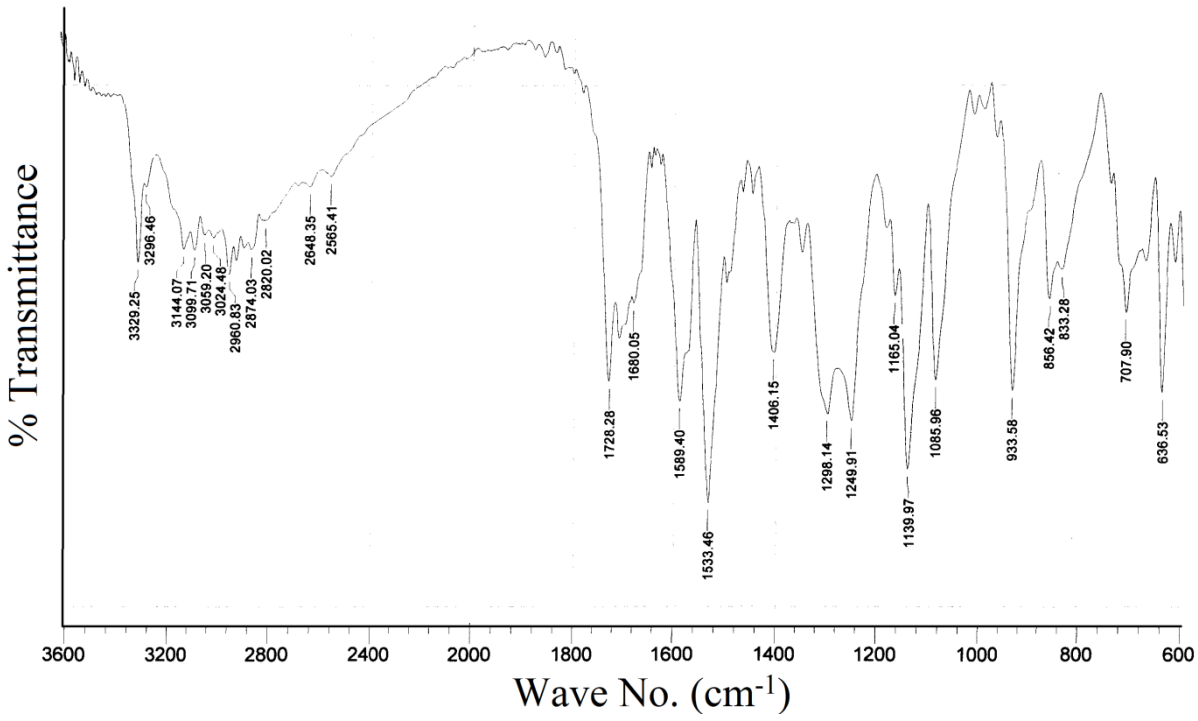
Solvent/No of attempts	**Pressure (mbar) (± 5)**	**Forms Obtained**
EA	250	Polymorph I
EtOH	250	Polymorph II
H_2O	30	SST/H_2O
AcMe	400	SST/AcMe
THF	250	SST/THF
MeOH	300	SST/H_2O
MeCN	180	SST/H_2O
MeCN/ MeOH	200	SST/H_2O

Table S3. New SST Solid Forms and Corresponding Melting Points

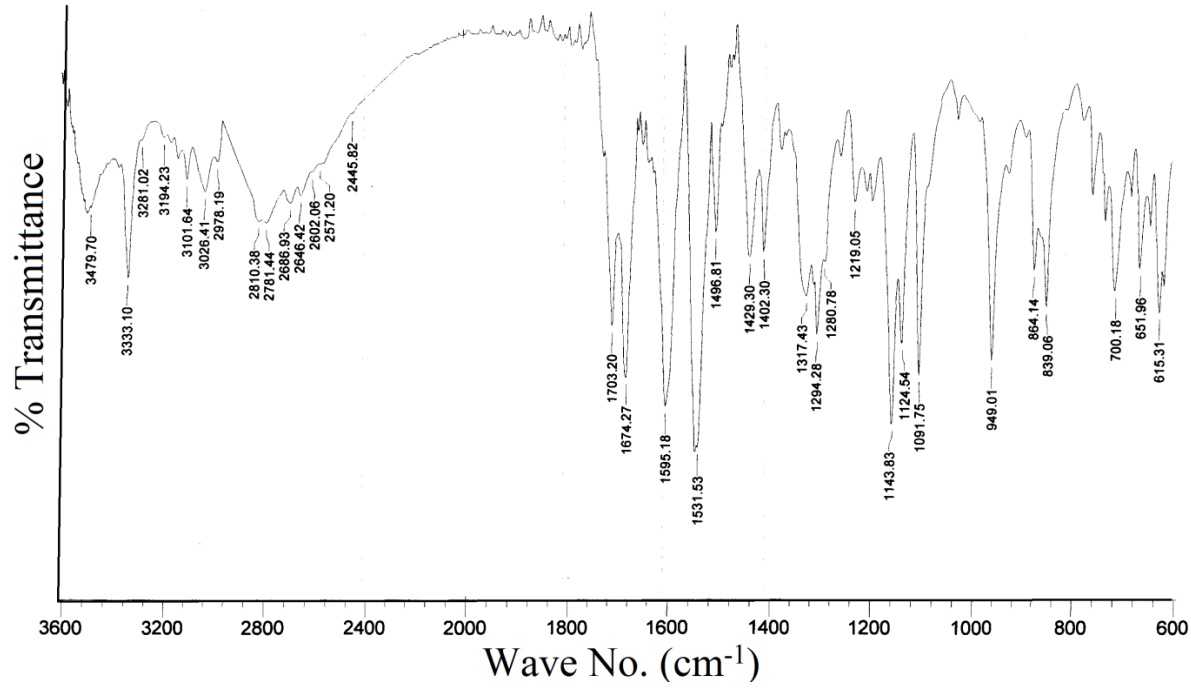
Name of solid forms	**mp (°C), T_{max} from DSC**
Polymorph I	207.65
Polymorph II	192.54
SST/H_2O	193.02
SST/AcMe	191.70
SST/THF	189.55



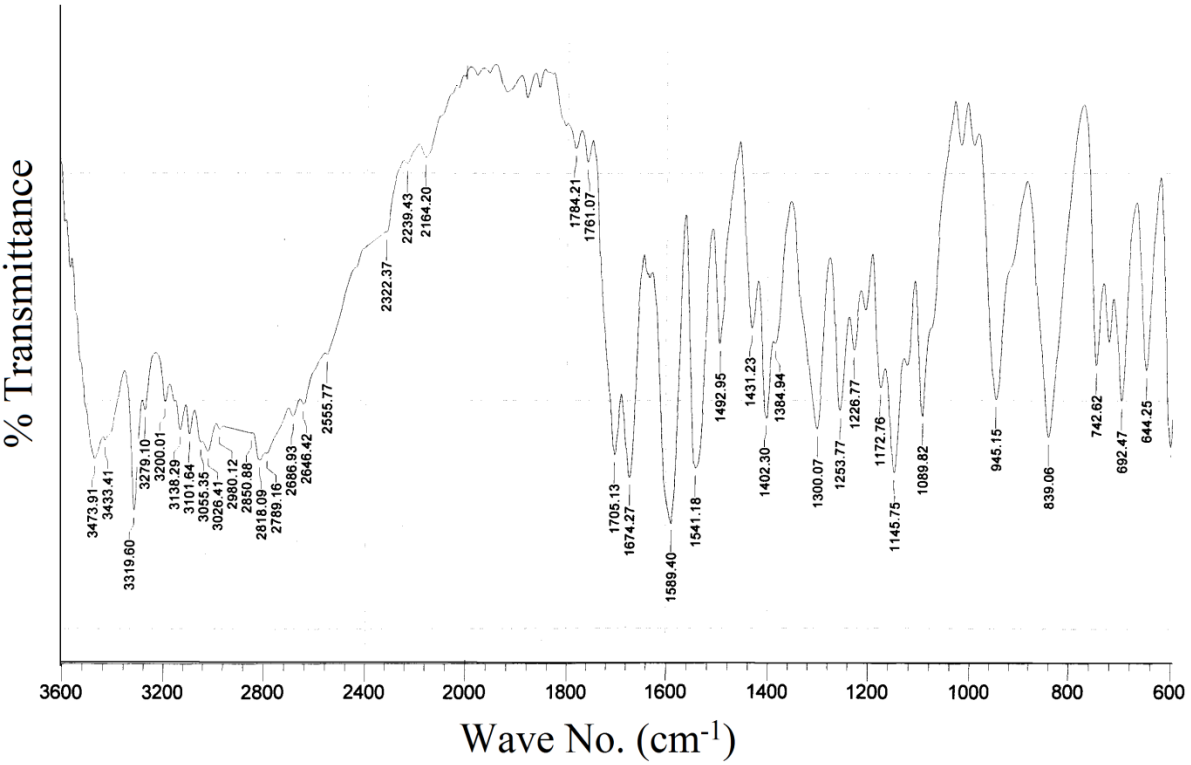
(a)



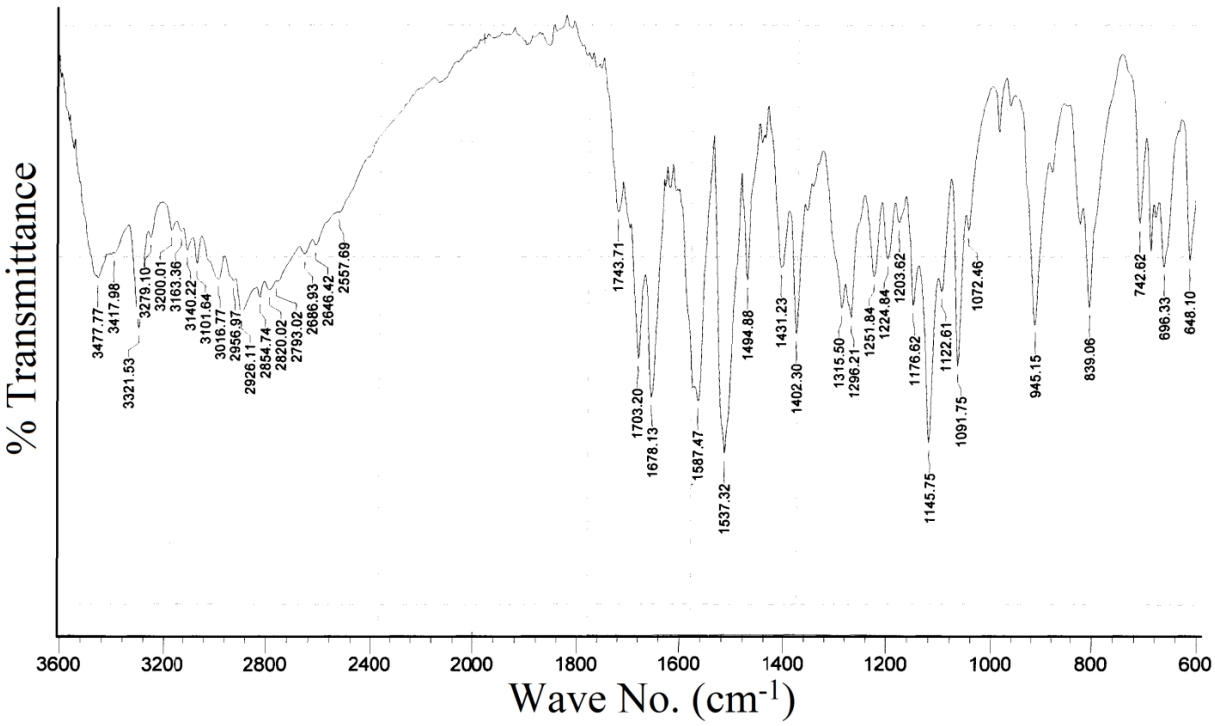
(b)



(c)

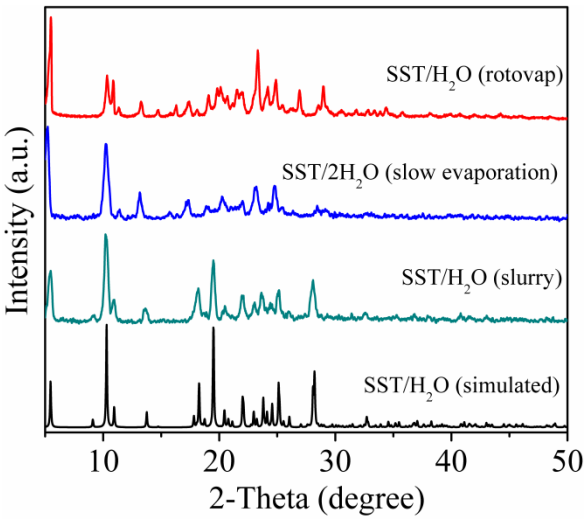


(d)

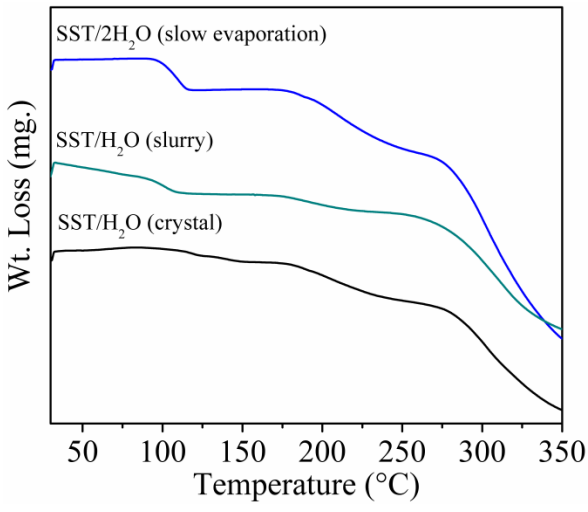


(e)

Figure S1. IR spectra of different forms of succinylsulfathiazole, obtained from using one single crystal of sufficient size, in each case. (a) Polymorph I, (b) polymorph II (c) SST/H_2O, (d) SST/AcMe and (e) SST/THF.

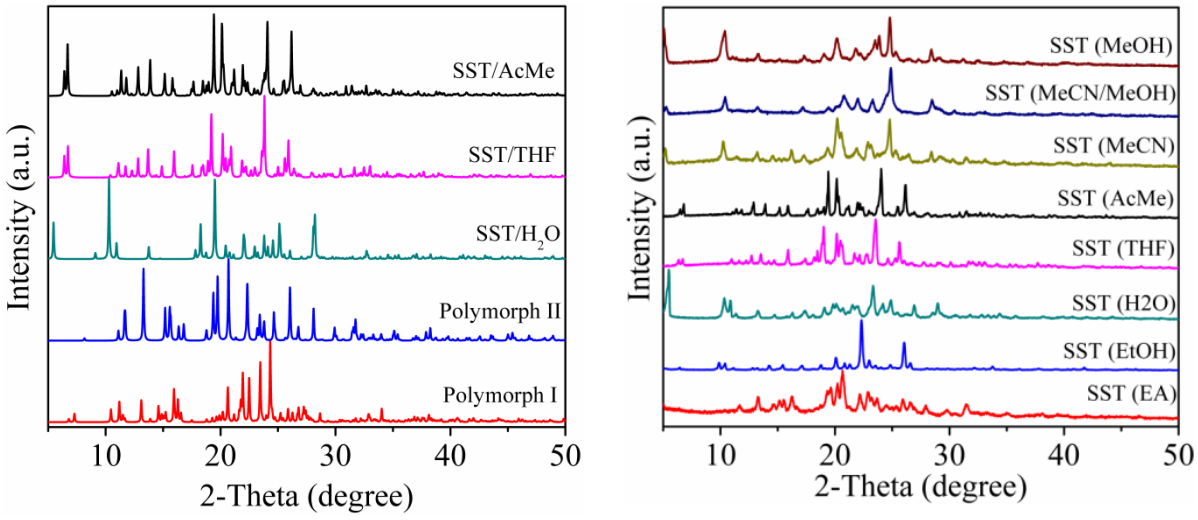


(a)



(b)

Figure S2. (a) PXRD and (b) TGA of hydrates of SST obtained by different method. Notice the PXRD of SST/2H_2O by slow evaporation method is different from other hydrated samples. See the fast evaporation (FE) product is the mixture of two hydrate forms.



(a) (b)

Figure S3. PXRD of (a) simulated and (b) experimental patterns of FE product, of succinylsulfathiazole polymorphs, hydrate and solvates (THF and AcMe).

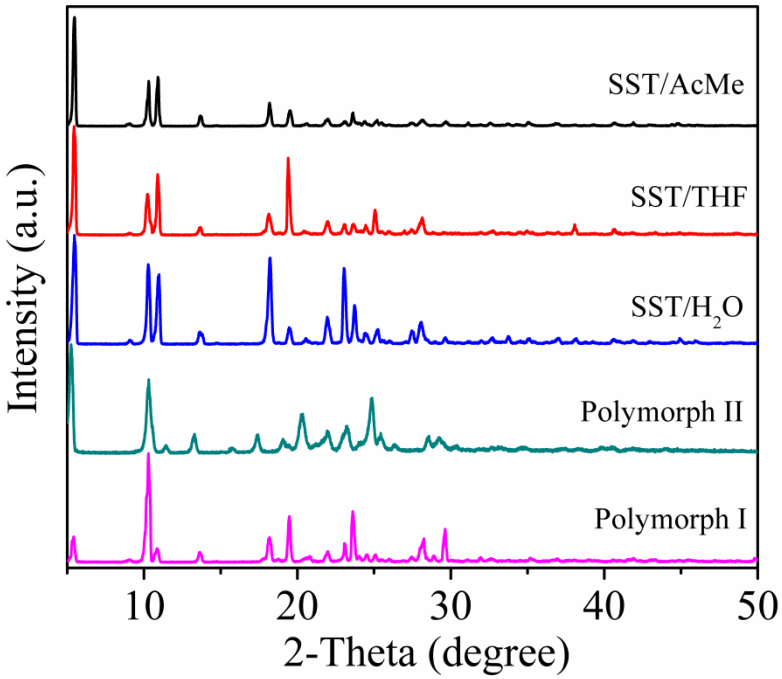


Figure S4. PXRD patterns of different forms of SST after a long exposure (1 yr) to atmosphere confirm their conversion to SST·H_2O, except polymorph II which is converted to SST·$2H_2O$ (Fig. S2a).

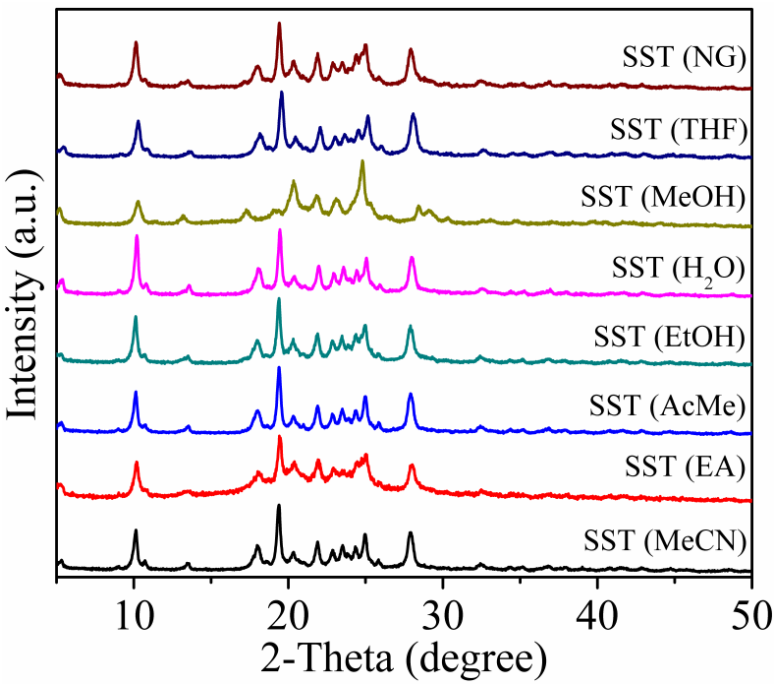


Figure S5. PXRD pattern of SST obtained by LAG method from different solvents. Notice the similarity of patterns of all the LAG products, which correspond to SST·H_2O.

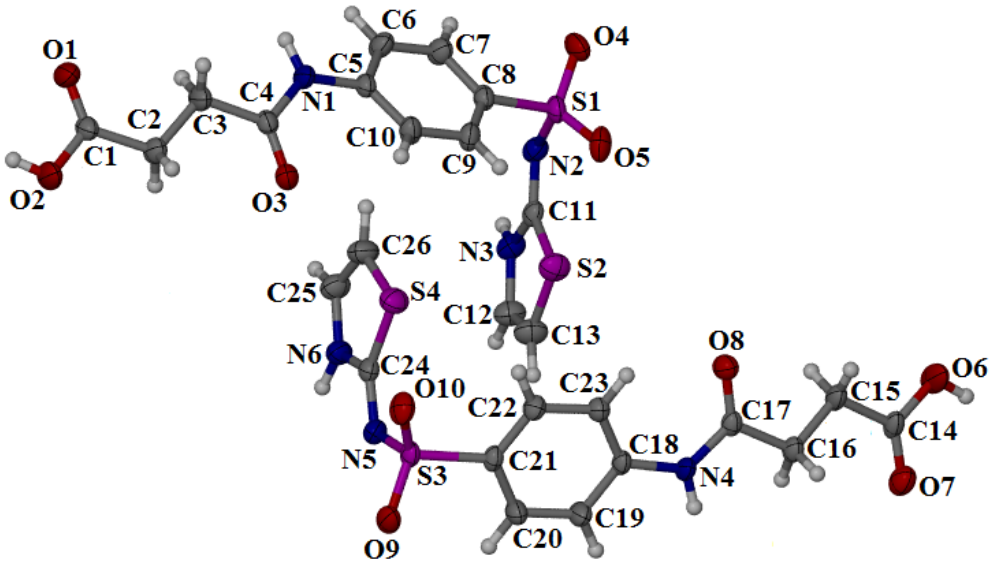


Figure S6. ORTEP diagram of the structure, succinylsulfathiazole polymorph I. Displacement ellipsoids are drawn at the 50% probability level.

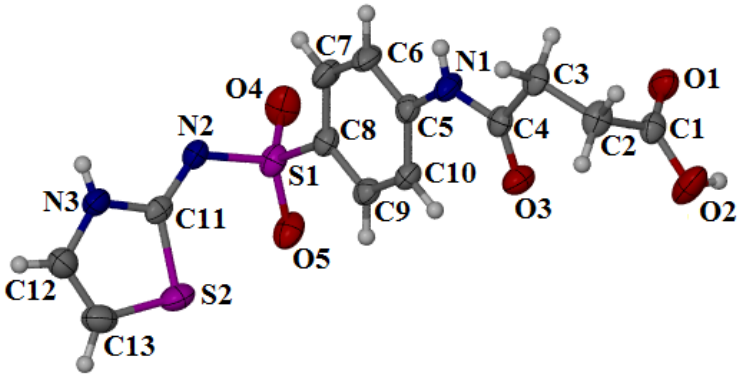


Figure S7. ORTEP diagram of the structure, succinylsulfathiazole polymorph II. Displacement ellipsoids are drawn at the 50% probability level.

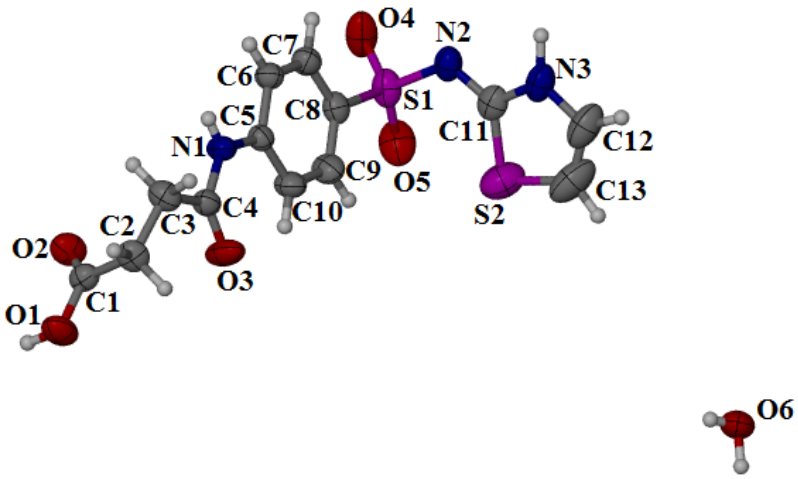


Figure S8. ORTEP diagram of the structure, SST/H_2O. Displacement ellipsoids are drawn at the 50% probability level.

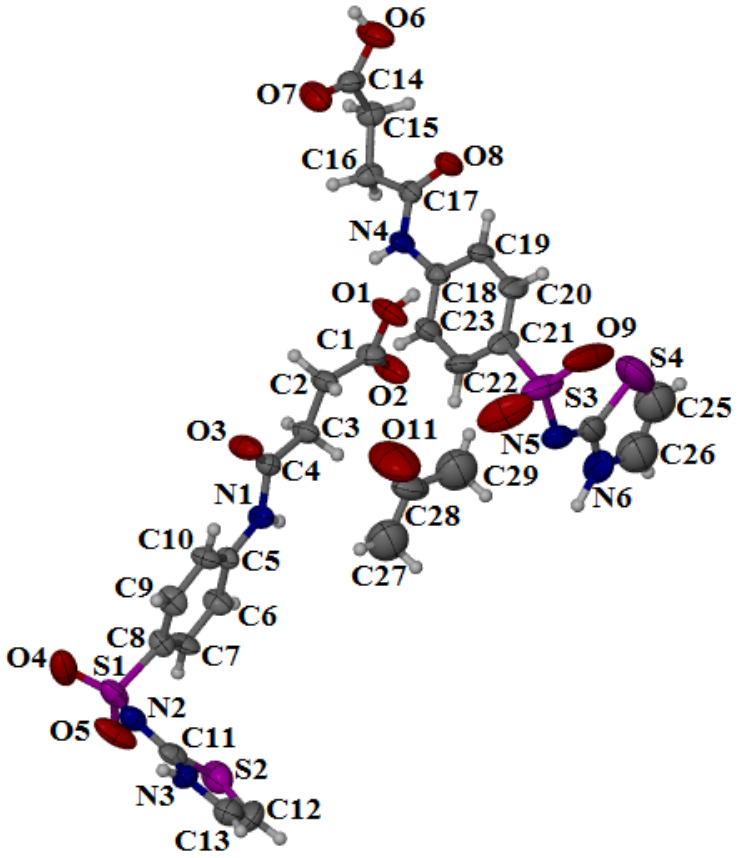


Figure S9. ORTEP diagram of the structure, SST/AcMe solvate. Displacement ellipsoids are drawn at the 50% probability level.

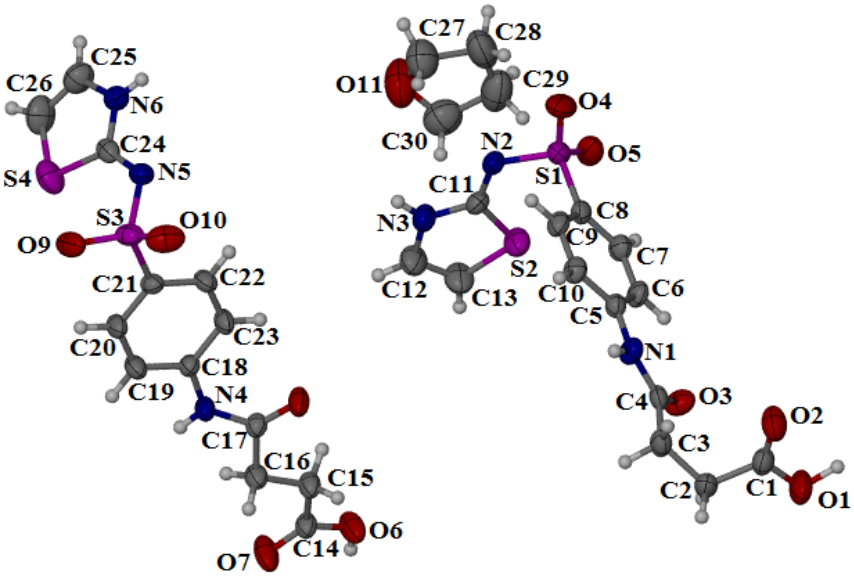
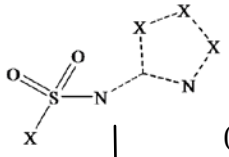


Figure S10. ORTEP diagram of the structure, SST/THF solvate. Displacement ellipsoids are drawn at the 50% probability level.

Scheme S1. Flow chart of the crystal structure database (ConQuest, V 5.34) search conducted to identify sulphonamide drugs in imidine tautomeric form. The entries in exlusively imidine form with more than 3 hits are highlighted in ***bold***.

(a) Five member ring fragment used for CSD Search



(x = any atom/fragment)
(---- = any bond)
(constraints: Only organics)

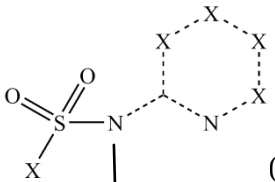
257 Hits

Exclusively Imidine

Amidine/Metal Complex/Ion/
N-substituted Compound/No 3D coordinates
(206 Hits)

Sulfathiazole (29 Hits)
(Ref. Code. **SUTHAZ**, **SUTHAZ01—SUTHAZ28**)
2-Phenylsulfonylimino-1,2-dihydrothiazole (2 Hits)
4-Phthalimido-N-(1,3-thiazol-2-yl)benzenesulfonamide (2 Hits)
2-(4-Amino-benzosulfonimido)-5-methyl-3H-1,3,4-thiadiazole (1 Hit)
N-(1,3-Thiazol-2(3H)-ylidene)naphthalene-2-sulfonamide (1 Hit)
4-Methyl-N-(1,3-thiazol-2(3H)-ylidene)benzene-2-sulfonamide (1 Hit)
SST solvates (Pnt, But, Diox, H_2O) (4 Hits)
2,4-Dichloro-N-(2,3-dihydro-4-(2,5-dimethoxyphenyl)thiazol-2-ylidene)benzenesulfonamide (1 Hit)
N-(2,3-Dihydro-1,3-thiazol-2-ylidene)-4-((2-hydroxybenzylidene)amino)benzenesulfonamide (1 Hit)
2-(Salicylidene-4-iminobenzosulfamido)-5-ethyl-1,3,4-thiadiazole (1 Hit)
Ethyl 2-((2Z)-2-[(1-naphthylsulfonyl)imino]-2,3-dihydro-1,3-thiazol-4-yl)acetate monohydrate (1 Hit)
N-(2,3-Dihydro-4-(2,5-dimethoxyphenyl)thiazol-2-ylidene)-4-fluorobenzensulfonamide (1 Hit)
N-(5-Methyl-3H-(1,3,4)thiadiazol-2-ylidene)benzenesulfonamide (1 Hit)
4-methyl-N-(5-methyl-1,3,4-thiadiazol-2(3H)-ylidene)benzenesulfonamide (1 Hit)

(b) Six member ring fragment used for CSD Search



(x = any atom/fragment)
(---- = any bond)
(constraints: Only organics)

433 Hits

Exclusively Imidine

Amidine/Metal Complex/Ion/
Substituted Compound/No 3D coordinates
406 Hits

Sulfapyridine (11 Hits)
(Ref. Code. **BEWKUJ**, **BEWKUJ01—BEWKUJ05,**
BEWKUJ11— BEWKUJ15)
6-Amino-2-(phenylsulfonylimino)-1,2-dihydropyridine (3 Hits)

Ethyl 3-(4,5-dimethoxy-2-(3-methyl-2-pyridylsulfamoyl)phenyl)propionate (1 Hit)
((4-Methylphenyl)sulfonyl)-imino-1H-pyridine (2 Hits)
4-Methyl-N-(4-methyl-3-phenylquinolin-2(1H)-ylidene)benzenesulfonamide (1 Hit)
2-Benzylthio-5-carbamoyl-4-chloro-N-(5,6-bis(4-methoxyphenyl)-1,2,4-triazin-3-ylidene)benzenesulfonamide dimethylsulfoxide solvate (1 Hit)
2,4,6-Trimethyl-N-(6-methylpyridin-2-yl)benzenesulfonamide (1 Hit)
N'-Trifluoromethansulfonyl-2-aminopyridine (1 Hit)
4-Amino-N-(4-methyl-1H-pyridin-2-ylidene)benzenesulfonamide (2 Hits)
N-(5-Methyl-pyridin-2(1H)-ylidene)benzenesulfonamide (1 Hit)
N-(3-Methyl-1H-pyridin-2-ylidene)benzenesulfonamide (1 Hit)
N-(4-((3-Methyl-1H-pyridin-2-ylidene)sulfamoyl)phenyl)acetamide (1 Hit)
N-(4-Methyl-1H-pyridin-2-ylidene)benzenesulfonamide (1 Hit)