Exploring the Cocrystal Landscape of Posaconazole by Combining High-throughput Screening Experimentation with Computational Chemistry

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Supporting Information

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1 Cocrystal screening

1.1 COSMOquick screening

Table S1. COSMOquick coformer screening performed on a list of 140 compounds. For each coformer the number of rotatable bonds, the F_{screen} function and the mixing enthalpy (ΔH_{mix}) are computed. Coformers are ranked according to the F_{screen} values. The 28 coformers employed in the experimental screening are highlighted in green. The 28 candidates were selected in order to span the whole range of screening function value, comprising in this way top-, middle- and low-ranked coformers. The selection was devised in order to test the prediction ability of COSMOquick, determining if the top-ranked compounds provide more experimental cocrystals compared to the low-ranked ones.

Coformer	number rotatable bonds	F_{screen}	coformer ranking	ΔH_{mix} (kcal/mol)
1,5-Naphthalenedisulfonic acid	4.0	0.24	1	-8.43
Oxalic acid	3.0	1.48	2	-6.68
Myricetin	7.0	1.83	3	-8.38
Gallic acid	5.0	2.61	4	-6.58
Benzenesulfonic acid	2.0	3.56	5	-4.09
3,4-Dihydroxybenzoic acid	4.0	3.58	6	-5.09
Naphthalene-2-sulfonic acid	2.0	3.61	7	-4.04
Toluenesulfonic acid	2.0	3.69	8	-3.96
Gentisic acid	4.0	3.84	9	-4.84
Fumaric acid	4.0	4.05	10	-4.63
DL-Tartaric acid	7.0	4.08	11	-6.12
L-Tartaric acid	7.0	4.08	12	-6.12
Cyclamic acid	3.0	4.22	13	-3.94
Maleic acid	4.0	4.47	14	-4.2
Trans-Aconitic acid	7.0	4.63	15	-5.57
1-Hydroxy-2-naphthoic acid	3.0	4.71	16	-3.46
Pamoic acid	8.0	4.81	17	-5.9
Methyl gallate	5.0	4.87	18	-4.31

2-Oxoglutaric acid	6.0	5.14	19	-4.55
3-Hydroxy-2-naphthoic acid	3.0	5.18	20	-2.98
Salicylic acid	3.0	5.2	21	-2.97
L-Malic acid	6.0	5.3	22	-4.39
Ethyl gallate	6.0	5.37	23	-4.32
Orotic acid	2.0	5.68	24	-1.98
5-Methylanthranilic acid	3.0	5.71	25	-2.45
Citric acid	9.0	5.72	26	-5.51
Benzoic acid	2.0	5.73	27	-1.92
Succinic acid	5.0	5.74	28	-3.44
4-Aminosalicylic acid	4.0	5.82	29	-2.85
Propyl gallate	7.0	5.9	30	-4.3
Saccharin	0.0	6.13	31	-1.02
Vanillic acid	4.0	6.14	32	-2.54
Piperazine	0.0	6.27	33	-0.87
DL-Mandelic acid	4.0	6.28	34	-2.39
Methyl paraben	3.0	6.33	35	-1.84
Malonic acid	4.0	6.35	36	-2.32
N-Hydroxy-succinimide	1.0	6.4	37	-0.74
Glycolic acid	3.0	6.43	38	-1.73
L-Lactic acid	3.0	6.46	39	-1.71
4-Aminobenzoic acid	3.0	6.48	40	-1.68
Acetylsalicylic acid	4.0	6.71	41	-1.96
Nicotinic acid	2.0	6.75	42	-0.9
Methyl phenyl sulfoxide	1.0	6.77	43	-0.37
Benzylamine	2.0	6.8	44	-0.85
Ascorbic acid	6.0	6.85	45	-2.84
Naphthalene-2-sulfonamide	2.0	6.92	46	-0.73
Ferulic acid	5.0	6.94	47	-2.25
Glutaric acid	6.0	6.96	48	-2.74
Phenylacrylic acid	3.0	6.96	49	-1.2

Beta-Alanine	4.0	6.97	50	-1.7
Sorbic acid	3.0	6.98	51	-1.18
Abietic acid	3.0	6.99	52	-1.17
Glucuronic acid	6.0	7.08	53	-2.62
Maltol	1.0	7.1	54	-0.04
L-Pyroglutamic acid	2.0	7.13	55	-0.53
p-Toluenesulfonamide	2.0	7.14	56	-0.51
2,4-Diamino-6-hydroxyPyrimidine	3.0	7.14	57	-1.02
Caffeine	0.0	7.16	58	0.02
Imidazole	0.0	7.17	59	0.02
3-Aminobenzyl alcohol	3.0	7.25	60	-0.91
Uric Acid	0.0	7.29	61	0.15
Thymine	0.0	7.31	62	0.17
Adenine	1.0	7.33	63	0.18
L-Aspartic acid	6.0	7.36	64	-2.34
L-Carnitine	4.0	7.36	65	-1.32
Uracil	0.0	7.41	66	0.27
Guanine	1.0	7.42	67	0.28
Acedoben	4.0	7.43	68	-1.24
Syringic acid	5.0	7.45	69	-1.74
Ethylmaltol	2.0	7.6	70	-0.05
Adipic acid	7.0	7.61	71	-2.59
Cytosine	1.0	7.62	72	0.48
Vanillin	3.0	7.63	73	-0.54
Propionic acid	2.0	7.66	74	0.01
L-Proline	2.0	7.71	75	0.06
Caproic acid	5.0	7.76	76	-1.43
2-Morpholinoethanol	3.0	7.79	77	-0.37
D-Ribose	4.0	7.8	78	-0.88
Eugenol	4.0	7.88	79	-0.8
Nicotinamide	2.0	7.88	80	0.23

L-Menthol	2.0	7.91	81	0.26
Urea	2.0	7.97	82	0.32
Pyridoxine	5.0	7.97	83	-1.21
L-4-Hydroxyproline	3.0	7.99	84	-0.17
Thymidine	4.0	8.0	85	-0.67
N-Acetylglycine	4.0	8.13	86	-0.54
L-Cysteine	3.0	8.19	87	0.03
Hippuric acid	5.0	8.25	88	-0.93
Quinic acid	6.0	8.3	89	-1.39
Tyramine	4.0	8.45	90	-0.22
L-Alanine	3.0	8.46	91	0.29
Glycine	3.0	8.6	92	0.44
D-Serine	5.0	8.76	93	-0.43
L-Serine	5.0	8.76	94	-0.43
L-Tyrosine	6.0	8.78	95	-0.91
L-Phenylglycine	4.0	8.83	96	0.16
Caprylic acid	7.0	8.84	97	-1.36
L-Valine	4.0	8.88	98	0.2
D-Galactose	6.0	8.92	99	-0.78
L-Tryptophan	5.0	8.98	100	-0.21
Creatine	5.0	9.16	101	-0.03
L-Phenylalanine	5.0	9.31	102	0.12
L-Leucine	5.0	9.35	103	0.17
L-Isoleucine	5.0	9.37	104	0.18
L-Histidine	5.0	9.37	105	0.18
myo-Inositol	6.0	9.42	106	-0.28
L-Glutamic acid	7.0	9.46	107	-0.75
L-Asparagine	6.0	9.53	108	-0.16
Galactaric acid	11.0	9.75	109	-2.49
Diethanolamine	6.0	9.77	110	0.08
L-Methionine	6.0	9.81	111	0.11

Sebacic acid	11.0	9.82	112	-2.43
D-Xylose	8.0	9.94	113	-0.78
D-Glucose	10.0	9.94	114	-1.8
D-Mannose	10.0	9.94	115	-1.8
Capric acid	9.0	9.94	116	-1.28
L-Lysine	6.0	9.95	117	0.26
Tromethamine	6.0	9.97	118	0.28
meso-Erythritol	7.0	10.0	119	-0.2
Undecylenic acid	10.0	10.34	120	-1.39
D-Gluconic acid	11.0	10.38	121	-1.87
L-Glutamine	7.0	10.43	122	0.22
Riboflavin	9.0	10.86	123	-0.36
L-Arabitol	9.0	11.05	124	-0.17
Xylitol	9.0	11.05	125	-0.17
Triethanolamine	9.0	11.15	126	-0.07
L-Arginine	9.0	11.38	127	0.16
D-Citrulline	9.0	11.72	128	0.5
L-Citrulline	9.0	11.72	129	0.5
D-Panthenol	10.0	11.73	130	0.0
D-Mannitol	11.0	11.8	131	-0.44
Sorbitol	11.0	11.8	132	-0.44
Gluceptate	13.0	12.07	133	-1.19
Lactose	12.0	12.18	134	-0.57
D-Maltose	12.0	12.18	135	-0.57
Aspartame	11.0	12.36	136	0.12
Meglumine	11.0	12.43	137	0.18
Sucrose	13.0	12.55	138	-0.72
Lactobionic acid	17.0	13.17	139	-2.13
Stearic acid	17.0	14.32	140	-0.98
Maltitol	17.0	15.28	141	-0.03

Table S2. List of the 28 coformers employed in PSZ cocrystal screening ranked according to COSMOquick F_{screen} function values. Acidic coformers are highlighted in orange, neutral coformers are highlighted in green.

Coformer	Abbreviation	MW (g/mol)	COSMOquick ranking	F_{screen}	ΔH_{mix} (Kcal/mol)
Oxalic acid	OXA	90.04	2	1.48	-6.68
3,4-Dihydroxybenzoic acid	DHB	154.12	6	3.58	-5.09
Gentisic acid	GEN	154.12	9	3.84	-4.84
Fumaric acid	FUM	116.07	10	4.05	-4.63
DL-Tartaric acid	TAR	150.09	11	4.08	-6.12
L-Tartaric acid	LTA	150.09	12	4.08	-6.12
Maleic acid	MLE	116.07	14	4.05	-4.20
trans-Aconitic acid	ACA	174.11	15	4.63	-5.57
1-Hydroxy-2-naphtoic acid	XIN	188.18	16	4.71	-3.46
Salicylic acid	SAL	138.12	21	5.20	-2.97
L-Malic acid	MLA	134.09	22	5.30	-4.39
Citric acid	CIT	192.12	26	5.72	-5.51
Benzoic acid	BNZ	122.12	27	5.73	-1.92
Succinic acid	SUC	118.09	28	5.74	-3.44
Vanillic acid	VAN	168.15	32	6.14	-2.54
L-Lactic acid	LLA	90.08	39	6.46	-1.71
4-aminobenzoic acid	ABA	137.14	40	6.48	-1.68
Nicotinic acid	NIC	123.11	42	6.75	-0.90
Ferulic acid	FER	194.18	47	6.94	-2.25
Maltol	MLL	126.11	54	7.10	-0.04

Adipic acid	ADI	146.14	71	7.61	-2.59
Vanillin	VLN	152.15	73	7.63	-0.54
L-Proline	PRO	115.13	75	7.71	0.06
Nicotinamide	NCT	122.13	80	7.88	0.23
Urea	URE	60.06	82	7.97	0.32
Pyridoxine	PYD	169.18	83	7.97	-1.21
Xylitol	XLT	152.15	125	11.05	-0.17
D-Mannitol	MNT	182.17	131	11.80	-0.44

	1	2	3	4	5	6	7	8	9	10	11	12
A	PSZ	PSZ MLA	PSZ MNT	PSZ	PSZ MLA	PSZ MNT	PSZ	PSZ MLA	PSZ MNT	PSZ	PSZ MLA	PSZ MNT
B	PSZ ADI	PSZ NIC	PSZ NCT	PSZ ADI	PSZ NIC	PSZ NCT	PSZ ADI	PSZ NIC	PSZ NCT	PSZ ADI	PSZ NIC	PSZ NCT
C	PSZ BNZ	PSZ OXA	PSZ PRO	PSZ BNZ	PSZ OXA	PSZ PRO	PSZ BNZ	PSZ OXA	PSZ PRO	PSZ BNZ	PSZ OXA	PSZ PRO
D	PSZ CIT	PSZ SUC	PSZ PYD	PSZ CIT	PSZ SUC	PSZ PYD	PSZ CIT	PSZ SUC	PSZ PYD	PSZ CIT	PSZ SUC	PSZ PYD
E	PSZ FUM	PSZ TAR	PSZ URE	PSZ FUM	PSZ TAR	PSZ URE	PSZ FUM	PSZ TAR	PSZ URE	PSZ FUM	PSZ TAR	PSZ URE
F	PSZ GEN	PSZ LTA	PSZ VLN	PSZ GEN	PSZ LTA	PSZ VLN	PSZ GEN	PSZ LTA	PSZ VLN	PSZ GEN	PSZ LTA	PSZ VLN
G	PSZ LLA	PSZ VAN	PSZ XLT	PSZ LLA	PSZ VAN	PSZ XLT	PSZ LLA	PSZ VAN	PSZ XLT	PSZ LLA	PSZ VAN	PSZ XLT
H	PSZ MLE	PSZ MLL	PSZ ACA	PSZ MLE	PSZ MLL	PSZ ACA	PSZ MLE	PSZ MLL	PSZ ACA	PSZ MLE	PSZ MLL	PSZ ACA
		Ethanol			Acetonitrile			Ethyl acetate			THF:H2O	

Figure S1. Layout of the 96-wells microtiter plate employed in the HTS of PSZ; the solvent employed in the slurry equilibration step is reported in red. Posaconazole was employed as control in wells A1, A4, A7 and A10.

2 Posaconazole

2.1 DSC

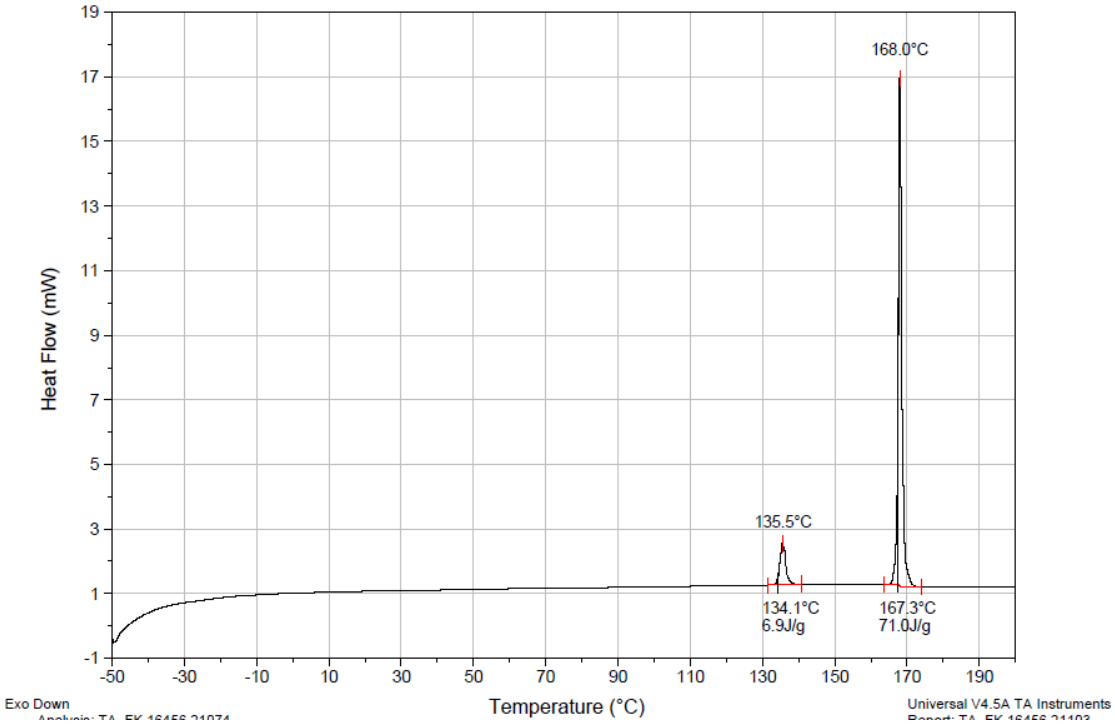

Figure S2. DSC thermogram of PSZ Form I, collected with a heating rate of 10 K/min. Posaconazole Form I was obtained by slurry equilibration of the purchased compound in ethanol for two days.

2.2 Raman Spectrum

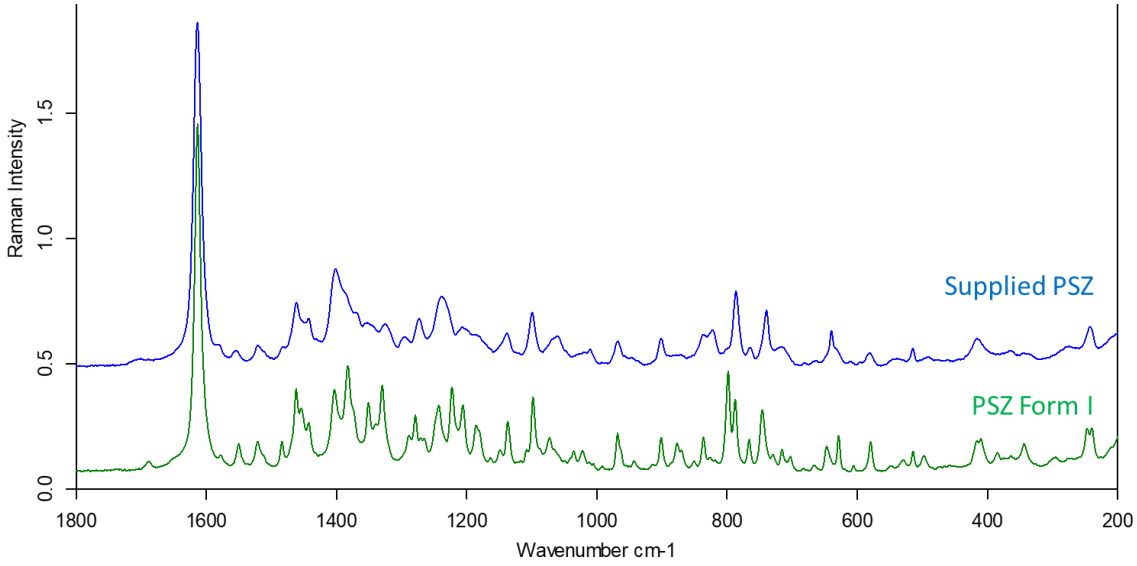

Figure S3. FT-Raman spectrum of PSZ form I and the purchased posaconazole, confirming the increased amorphicity of the latter.

2.3 Powder X-ray Diffraction Patterns

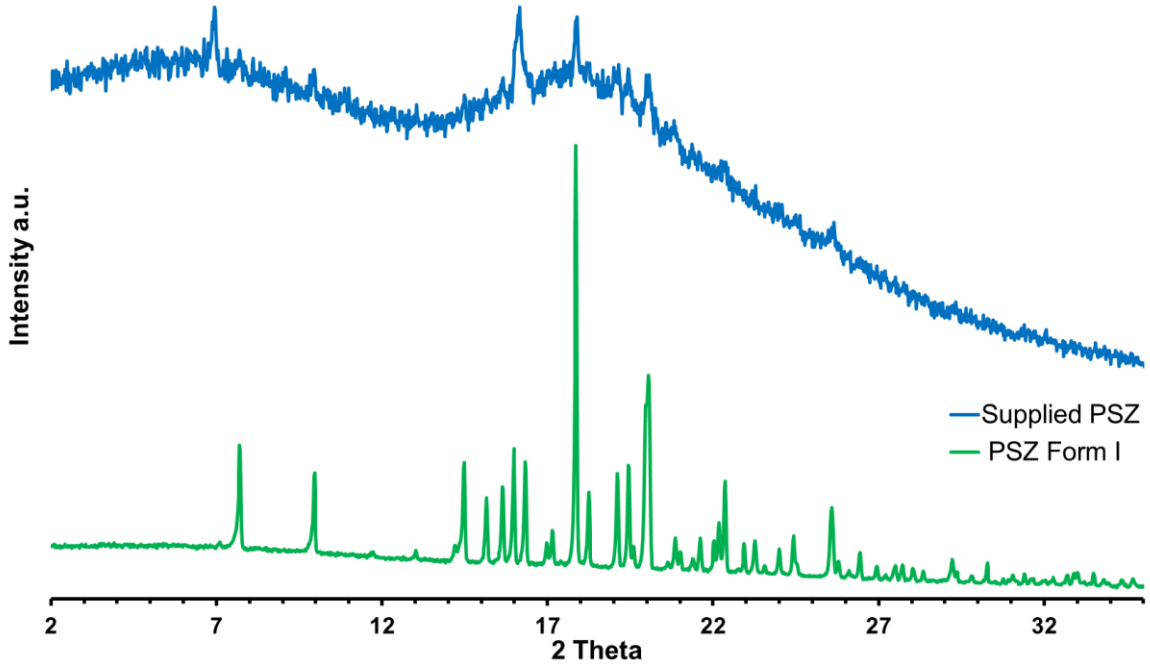

Figure S4. PXRD patterns of purchased posaconazole (blue, top) and PSZ Form I (green, bottom).

2.4 Proton Nuclear Magnetic resonance (^{1}H-NMR)

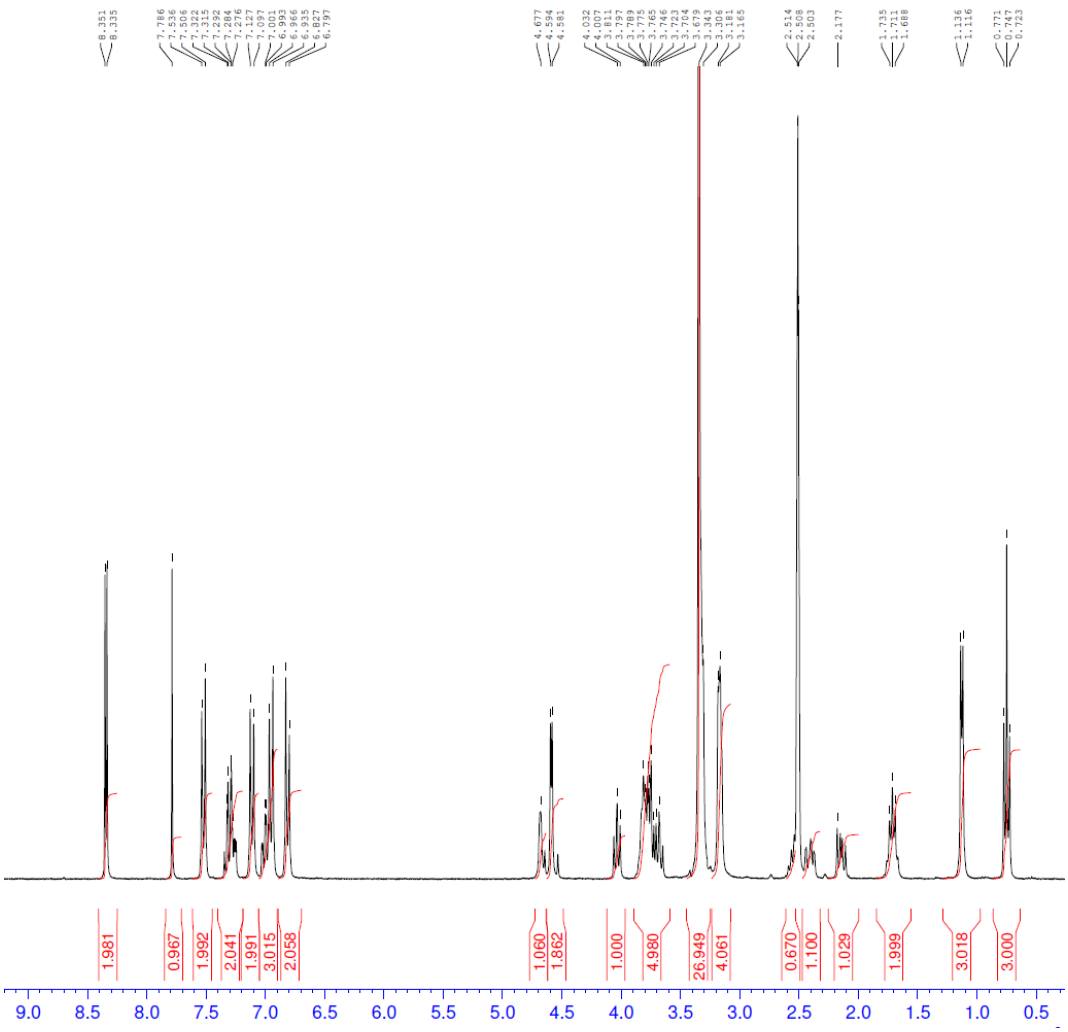

Figure S5. Proton NMR spectrum of purchased posaconazole collected in deuterated DMSO.

3 Posaconazole – Ferulic Acid Hydrate Cocrystal (PSZ-FER-H2O)

3.1 TG-FTIR

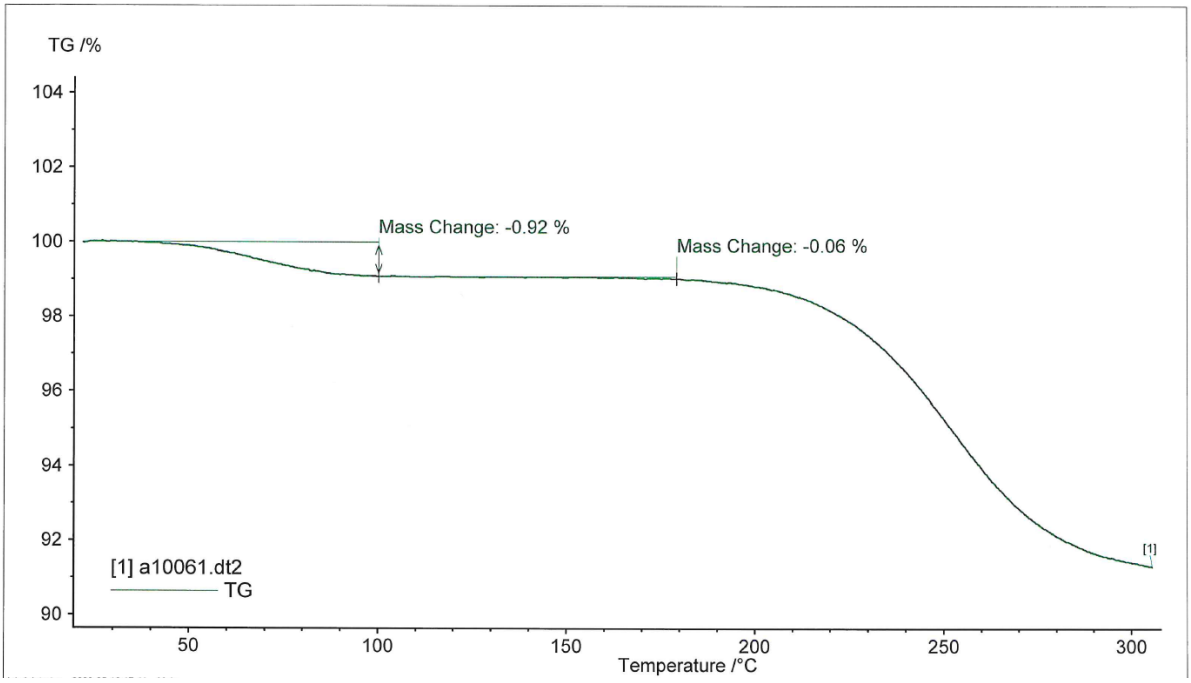

Figure S6. TG-FTIR thermogram of PSZ-FER-H2O, collected with a heating rate of 10 K/min.

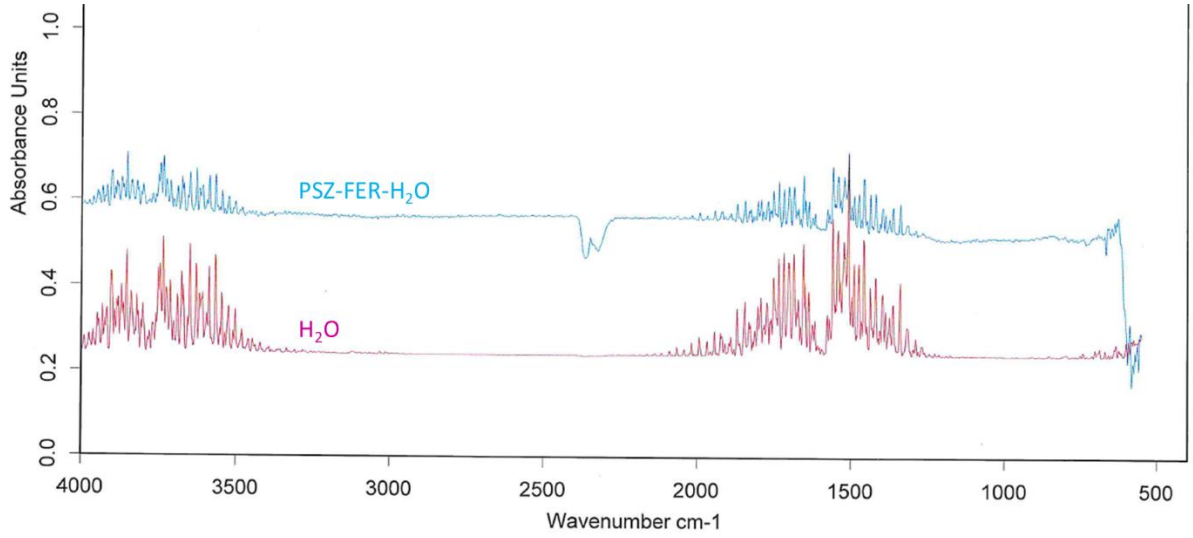

Figure S7. Comparison of the IR spectrum of the gas released at 70°C (blue) with the reference spectrum of H_2O (red).

3.2 Raman Spectrum

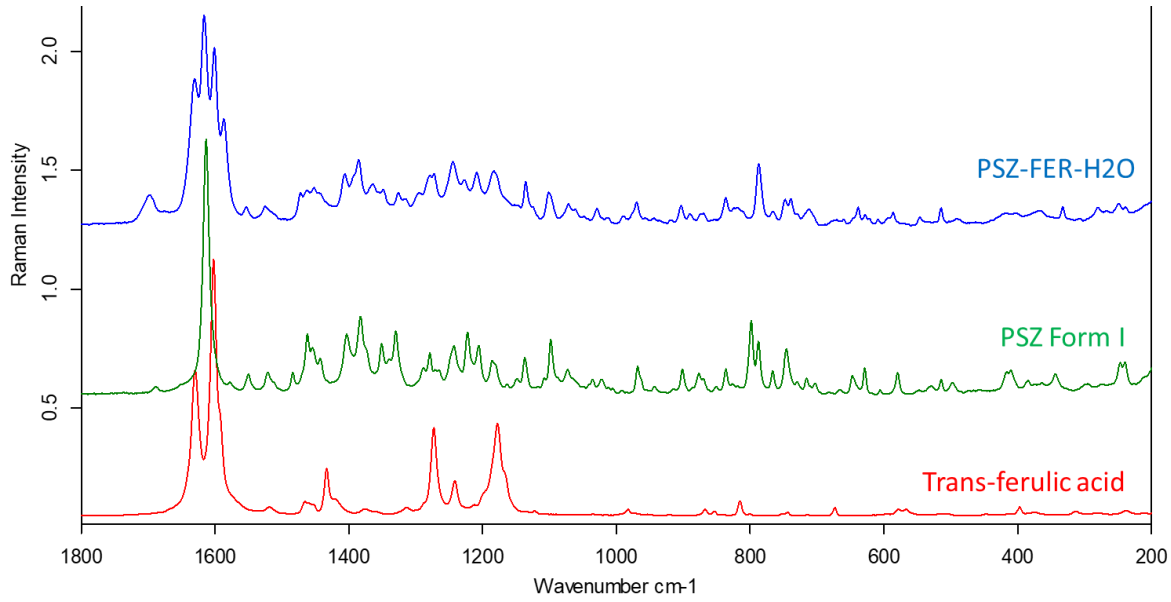

Figure S8. FT-Raman spectra of PSZ Form I, trans-ferulic acid and PSZ-FER-H2O.

3.3 Powder X-ray Diffraction Patterns

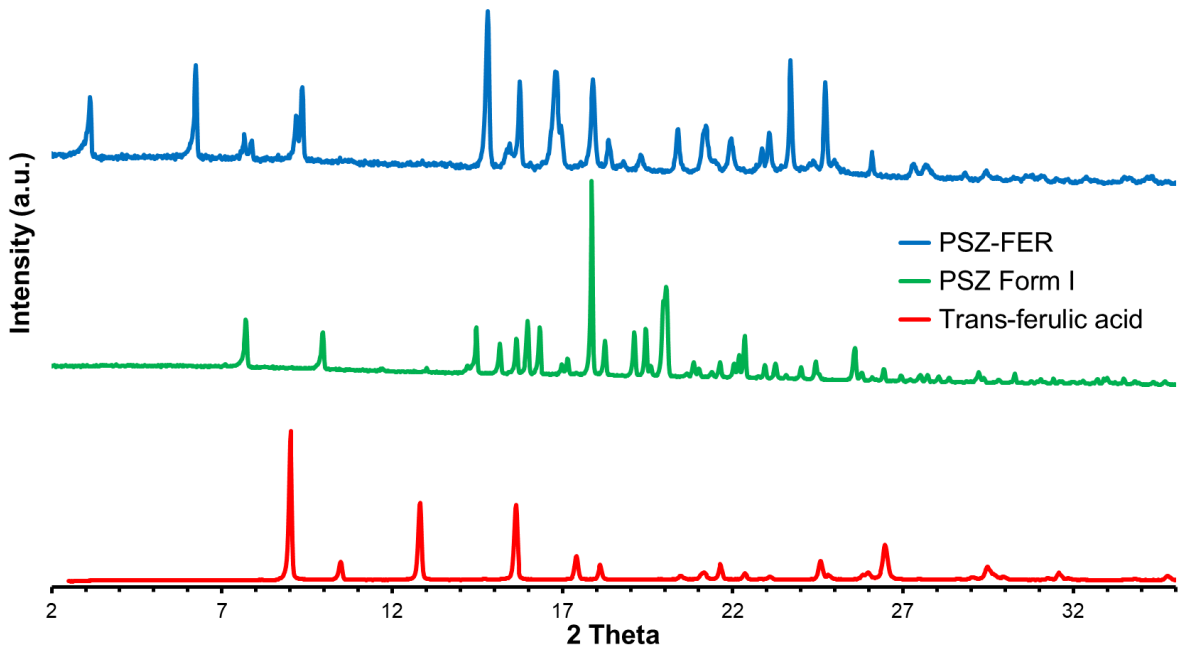

Figure S9. PXRD patterns of PSZ Form I, trans-ferulic acid and PSZ-FER-H2O.

3.4 Proton Nuclear Magnetic Resonance (^{1}H-NMR)

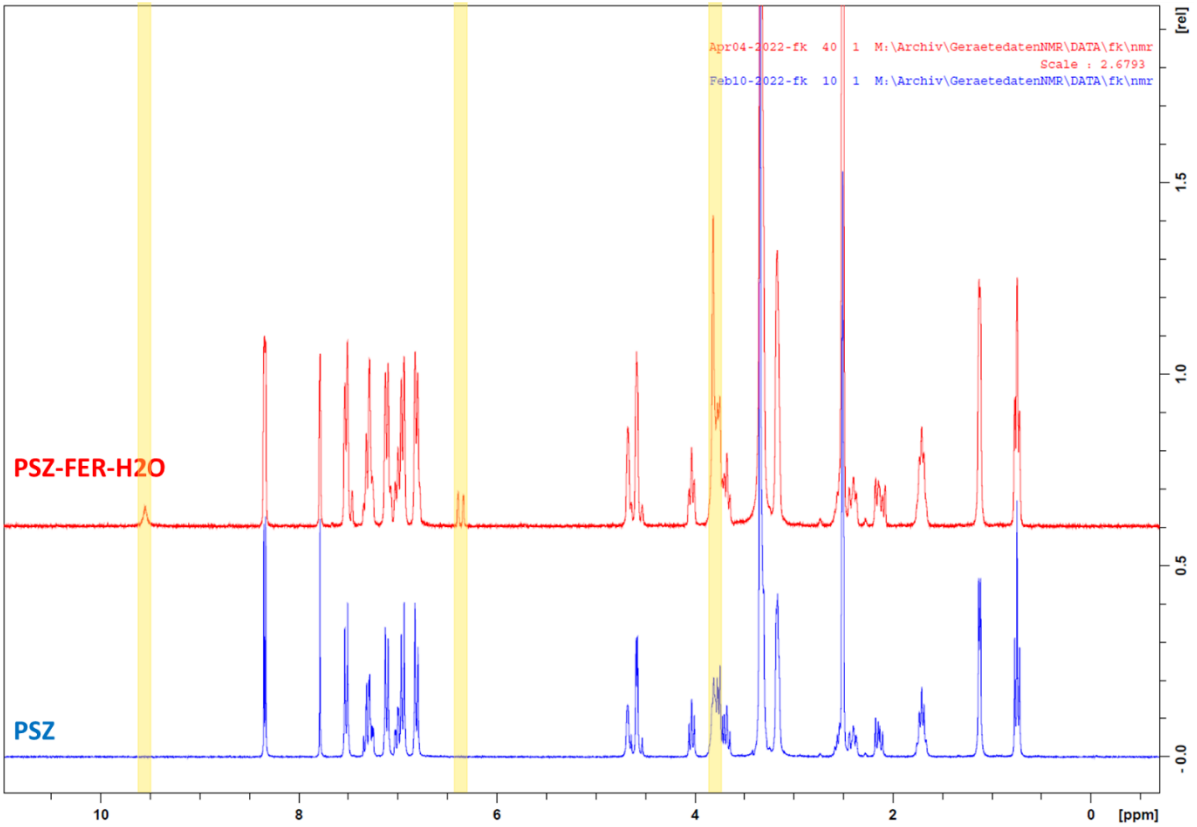

Figure S10. Proton NMR spectra of PSZ-FER-H2O and PSZ in deuterated DMSO; chemical shifts reported in ppm. The peaks of the coformer are highlighted in yellow.

4 Posaconazole – Maleic Acid Cocrystal (PSZ-MLE)

4.1 DSC

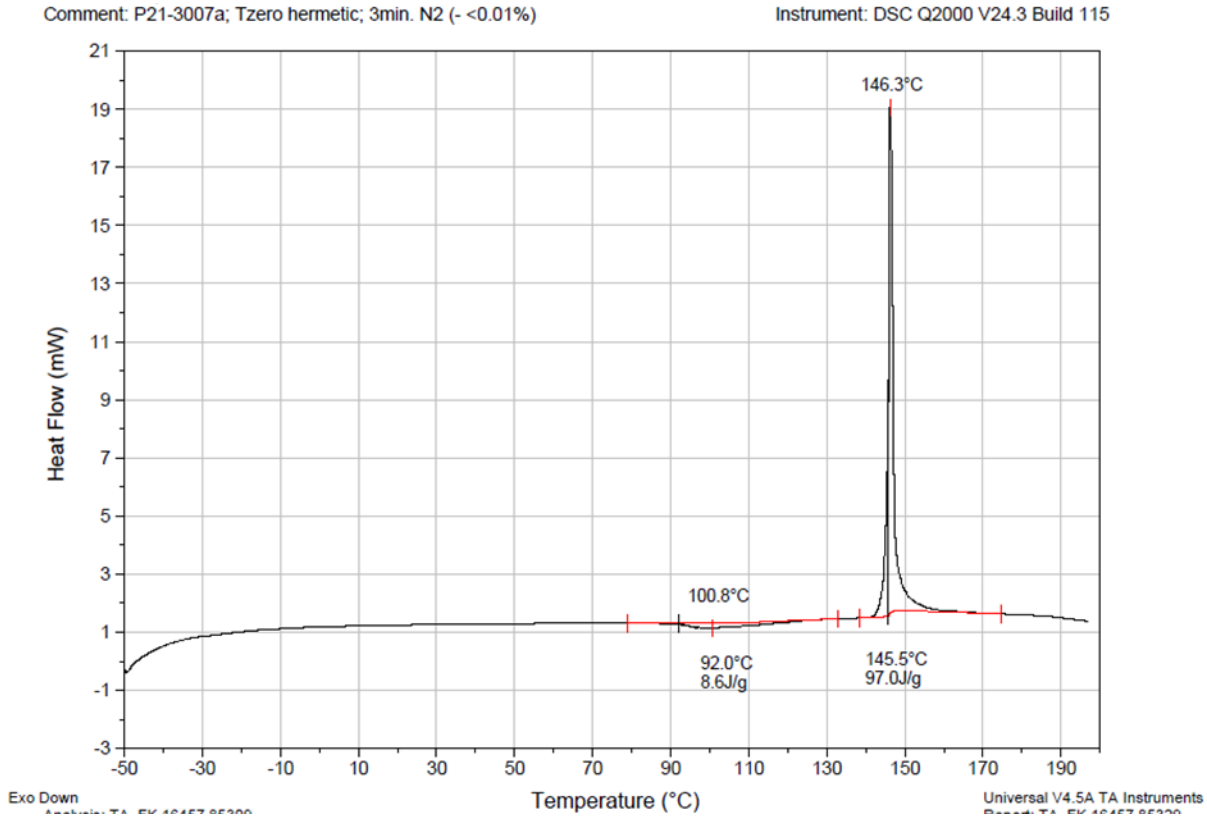

Figure S11. DSC thermogram of PSZ-MLE, collected with a heating rate of 10 K/min.

4.2 TG-FTIR

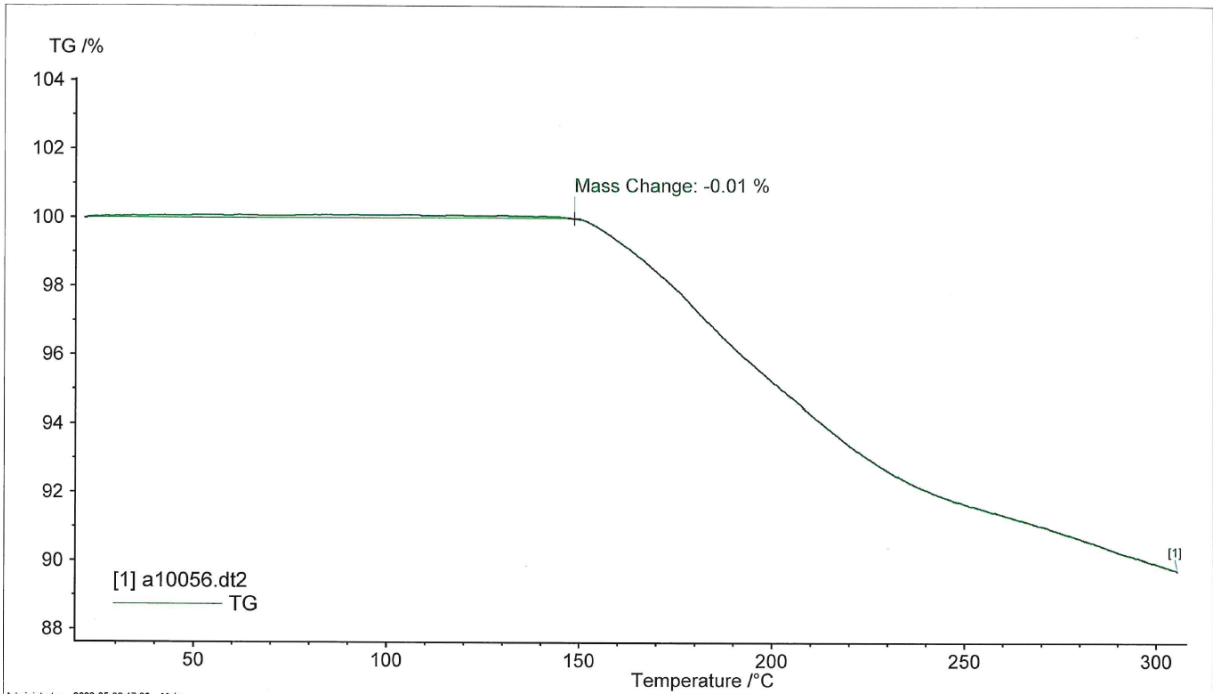

Figure S12. TG-FTIR thermogram of PSZ-MLE

4.3 Raman Spectrum

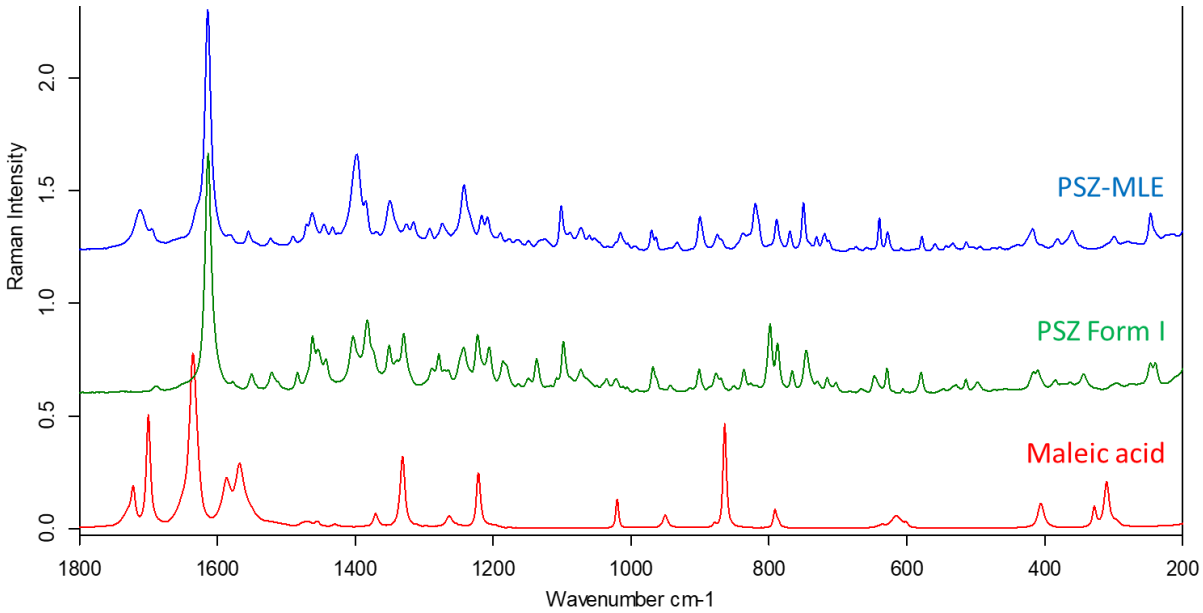

Figure S13. FT-Raman spectra of PSZ Form I, Maleic acid and PSZ-MLE.

4.4 Powder X-ray Diffraction Patterns

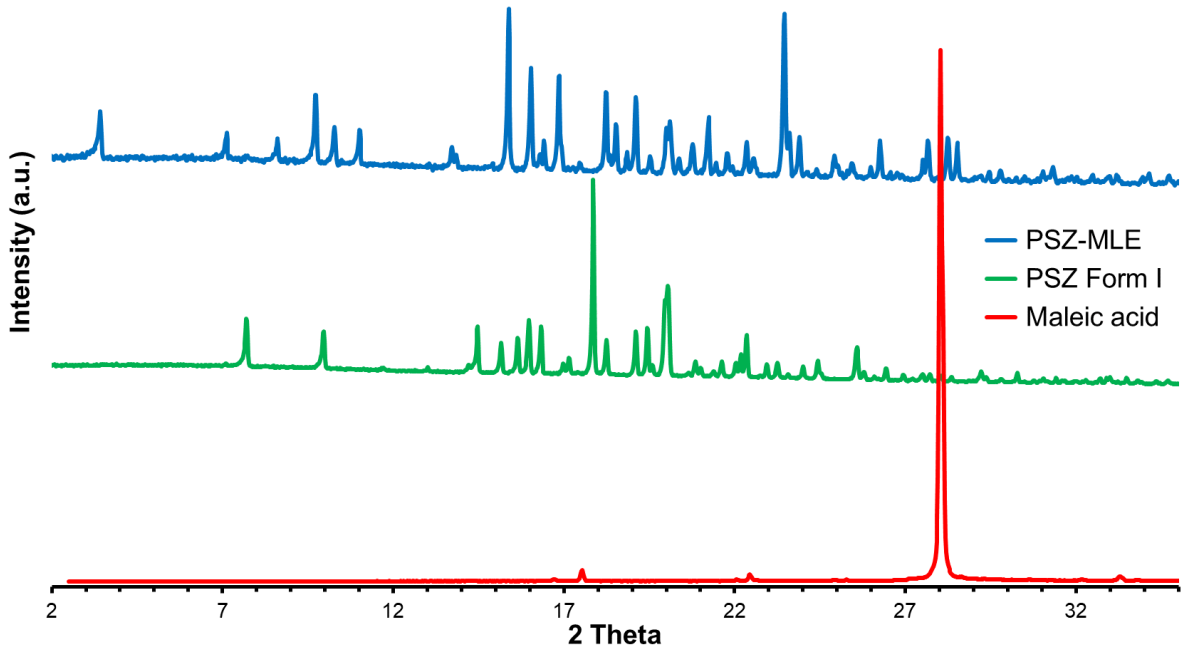

Figure S14. PXRD patterns of PSZ Form I, Maleic acid and PSZ-MLE.

4.5 Proton Nuclear Magnetic Resonance (^{1}H-NMR)

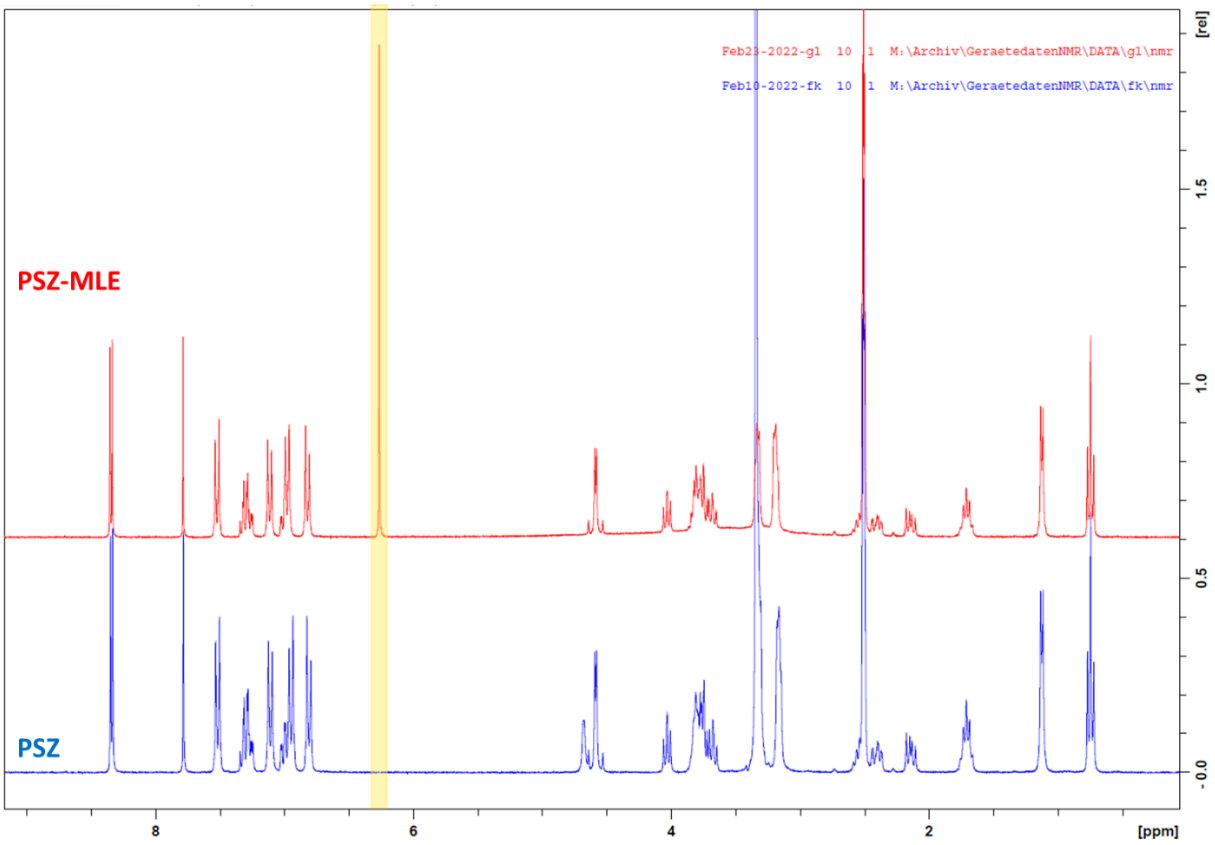

Figure S15. Proton NMR spectra of PSZ-MLE and PSZ in deuterated DMSO; chemical shifts reported in ppm. The peaks of the coformer are highlighted in yellow.

5 Posaconazole – L-Malic Acid Cocrystal (PSZ-MLA)

5.1 DSC

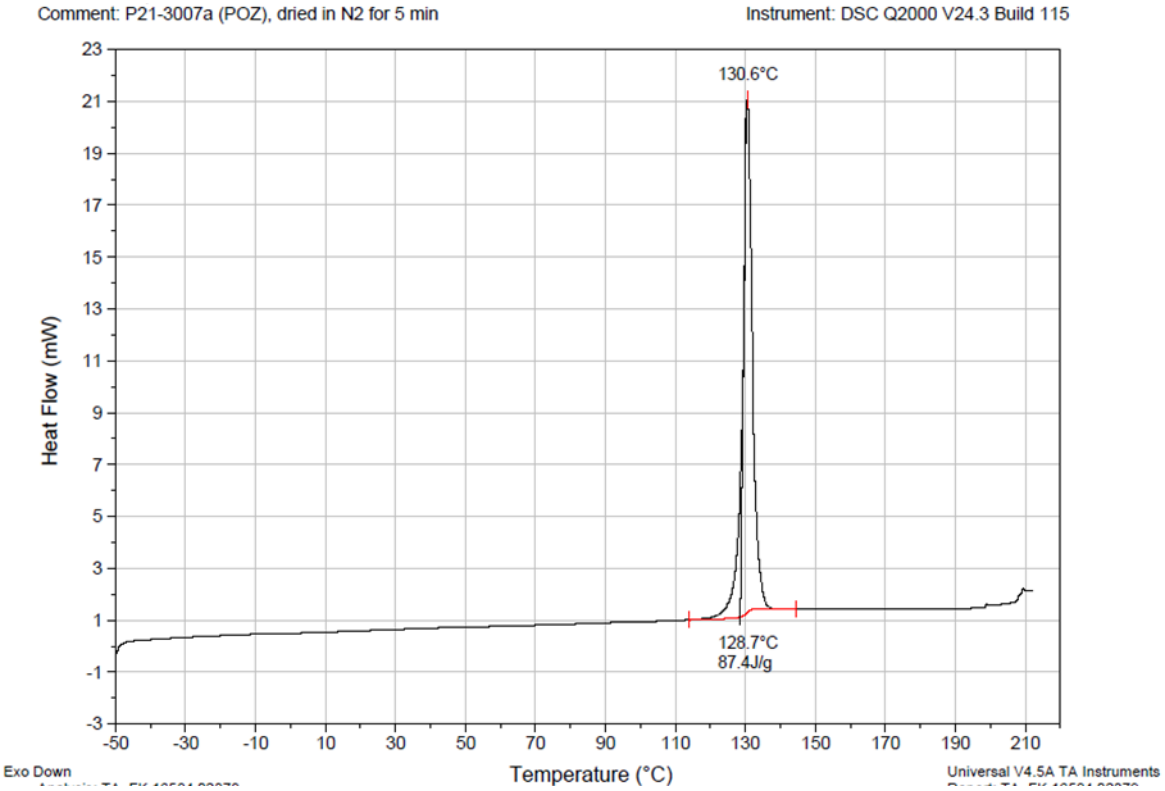

Figure S16. DSC thermogram of PSZ-MLA, collected with a heating rate of 10 K/min.

5.2 TG-FTIR

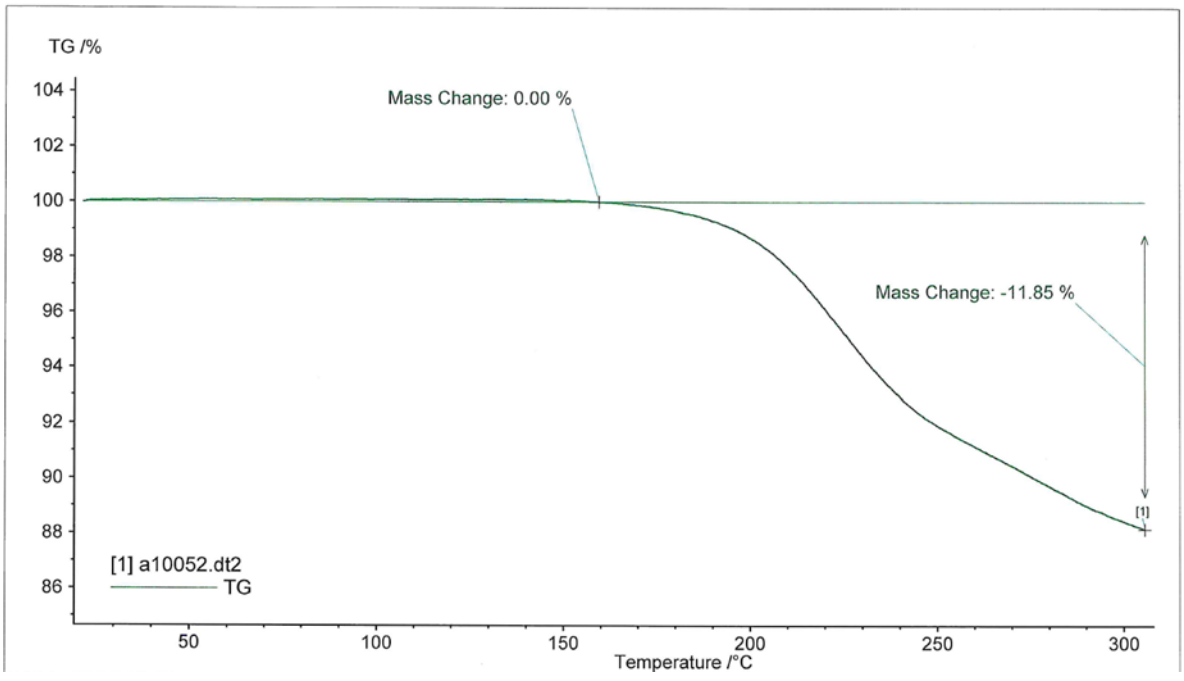

Figure S17. TG-FTIR thermogram of PSZ-MLA, collected with a heating rate of 10 K/min.

5.3 Raman Spectrum

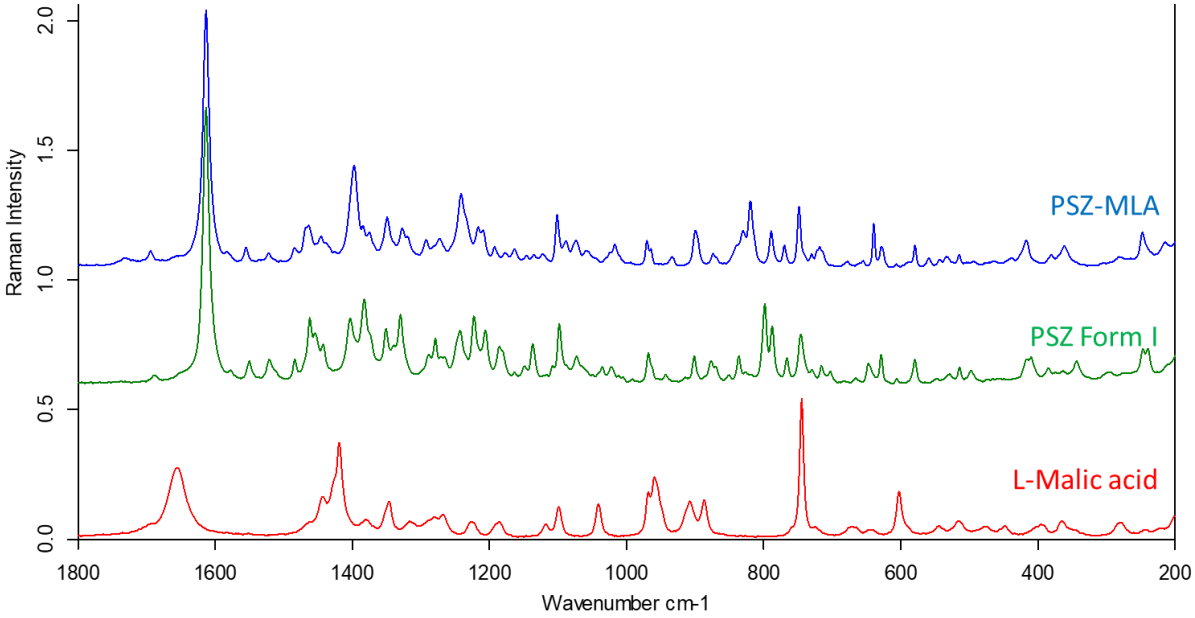

Figure S18. FT-Raman spectra of PSZ Form I, L-malic acid and PSZ-MLA.

5.4 Powder X-ray Diffraction Patterns

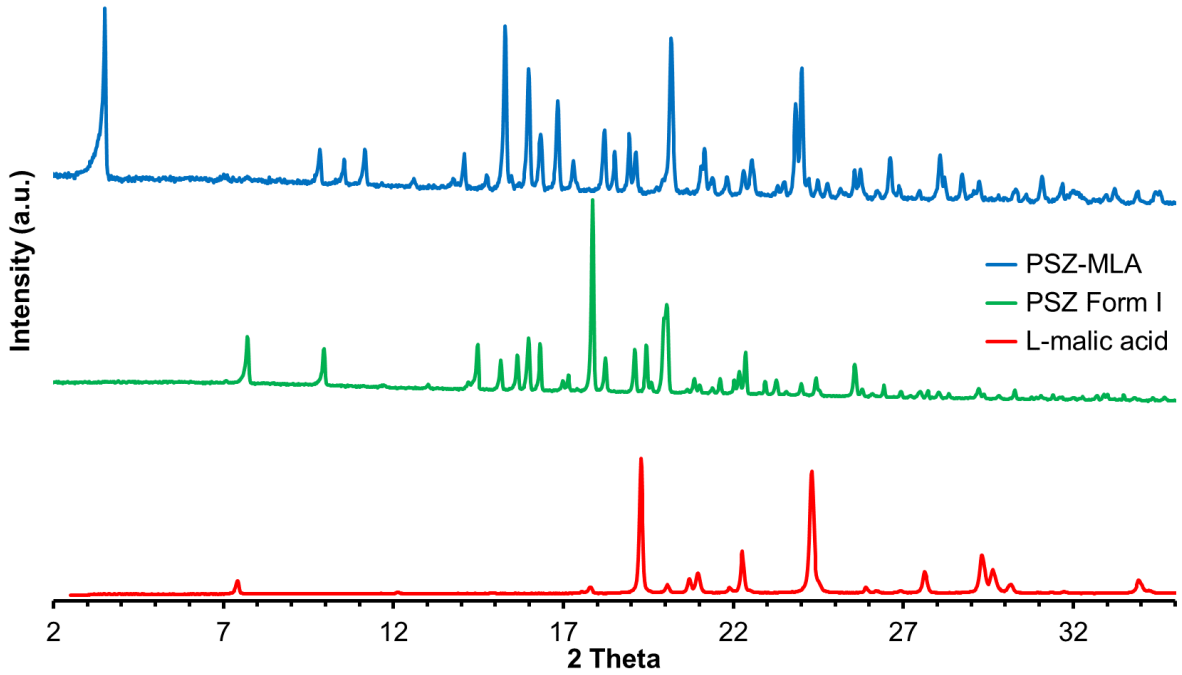

Figure S19. PXRD patterns of PSZ Form I, L-malic acid and PSZ-MLA.

5.5 Proton Nuclear Magnetic Resonance (^{1}H-NMR)

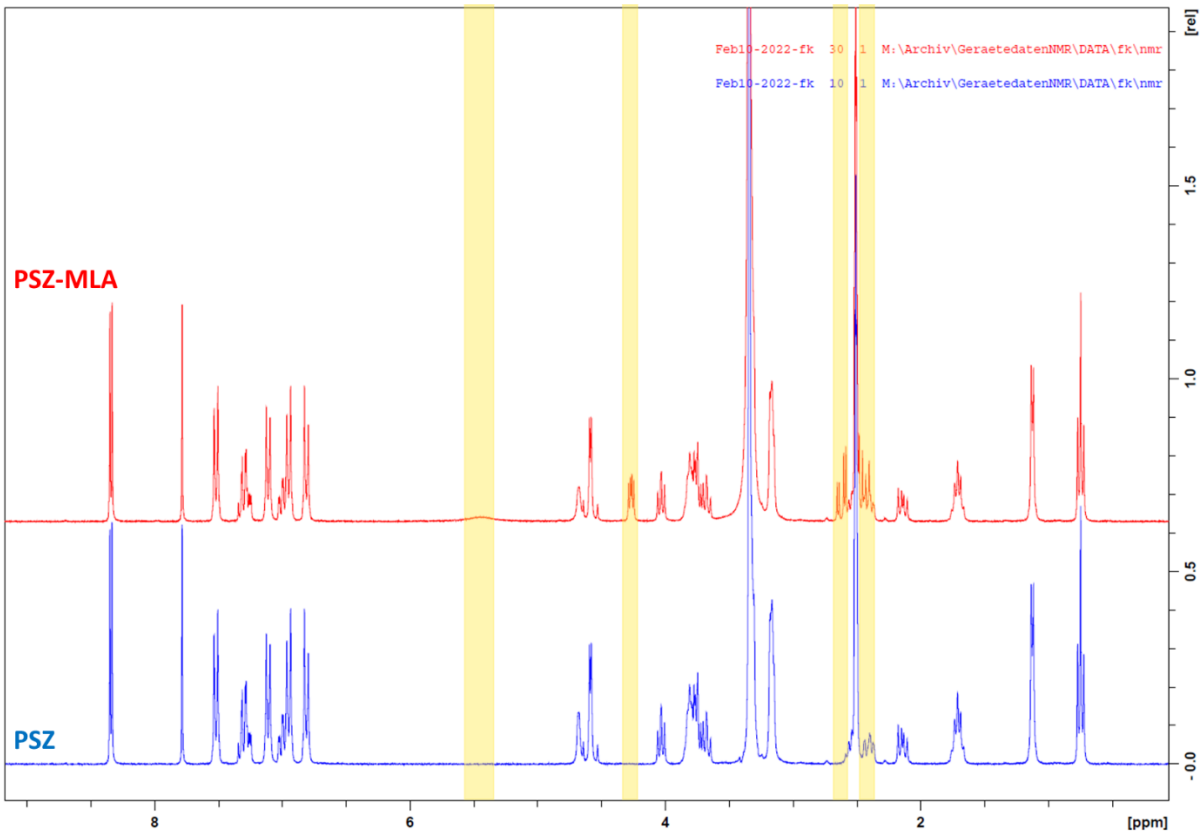

Figure S20. Proton NMR spectra of PSZ-MLA and PSZ in deuterated DMSO; chemical shifts reported in ppm. The peaks of the coformer are highlighted in yellow.

6 Posaconazole – Citric Acid Cocrystal (PSZ-CIT)

6.1 DSC

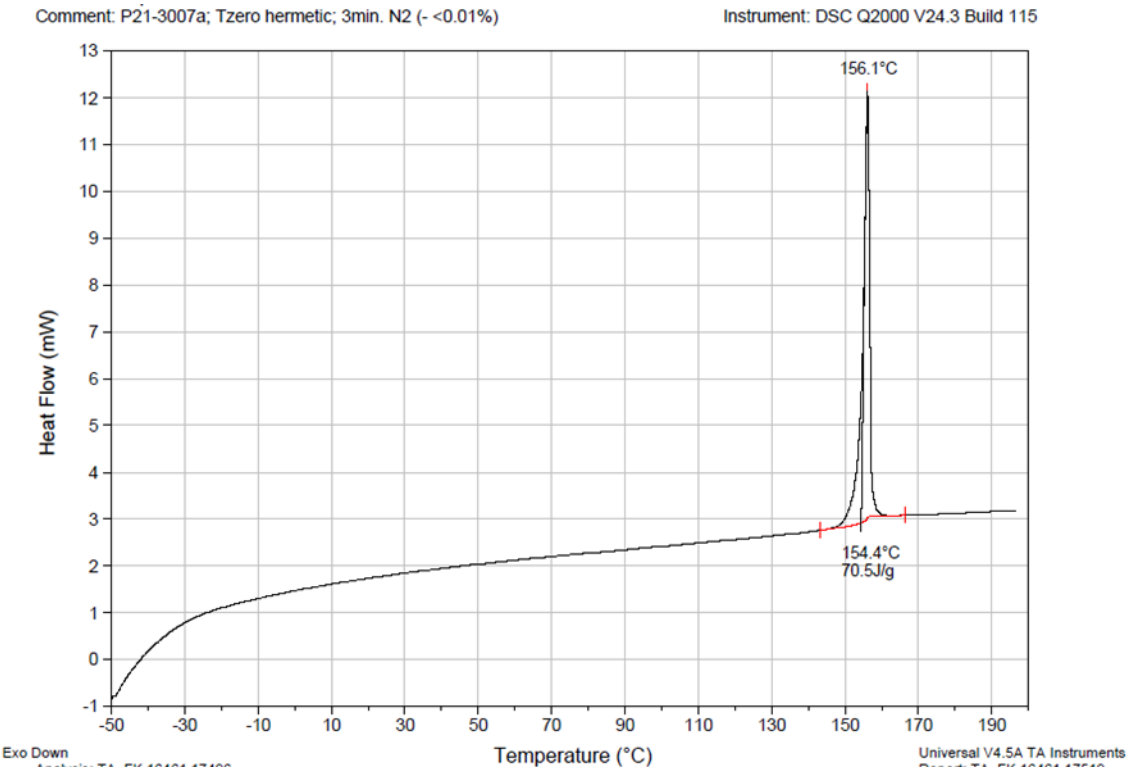

Figure S21. DSC thermogram of PSZ-CIT, collected with a heating rate of 10 K/min.

6.2 TG-FTIR

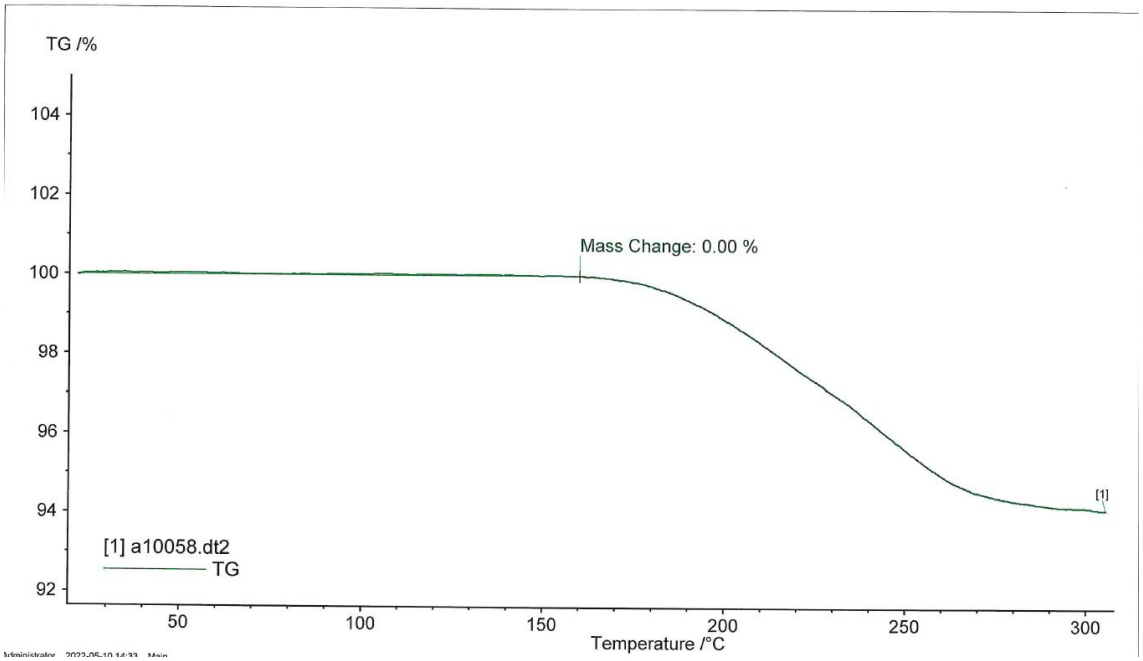

Figure S22. TG-FTIR thermogram of PSZ-CIT, collected with a heating rate of 10 K/min.

6.3 Raman Spectrum

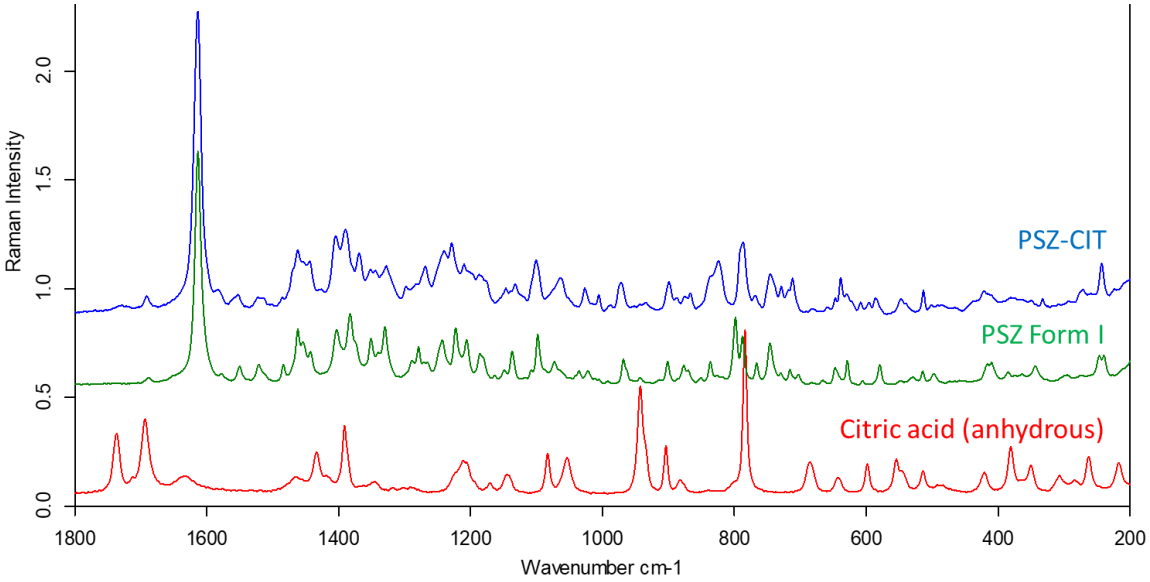

Figure S23. FT-Raman spectra of PSZ Form I, citric acid and PSZ-CIT.

6.4 Powder X-ray Diffraction Patterns

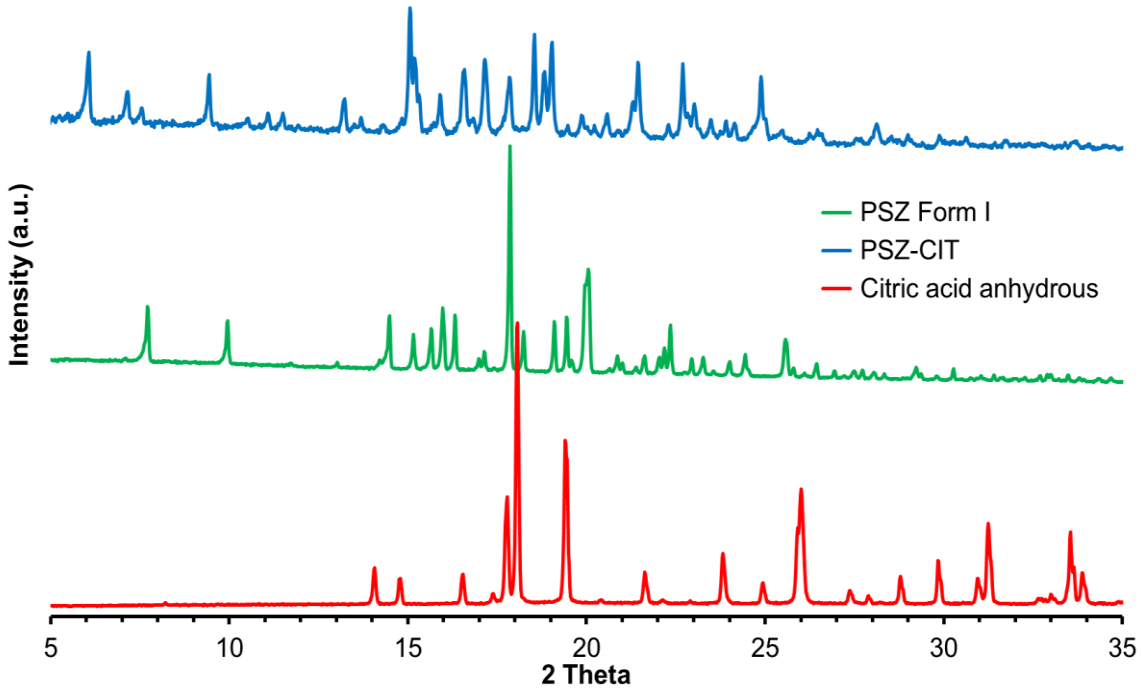

Figure S24. PXRD patterns of PSZ Form I, citric acid and PSZ-CIT.

6.5 Proton Nuclear Magnetic Resonance (^{1}H-NMR)

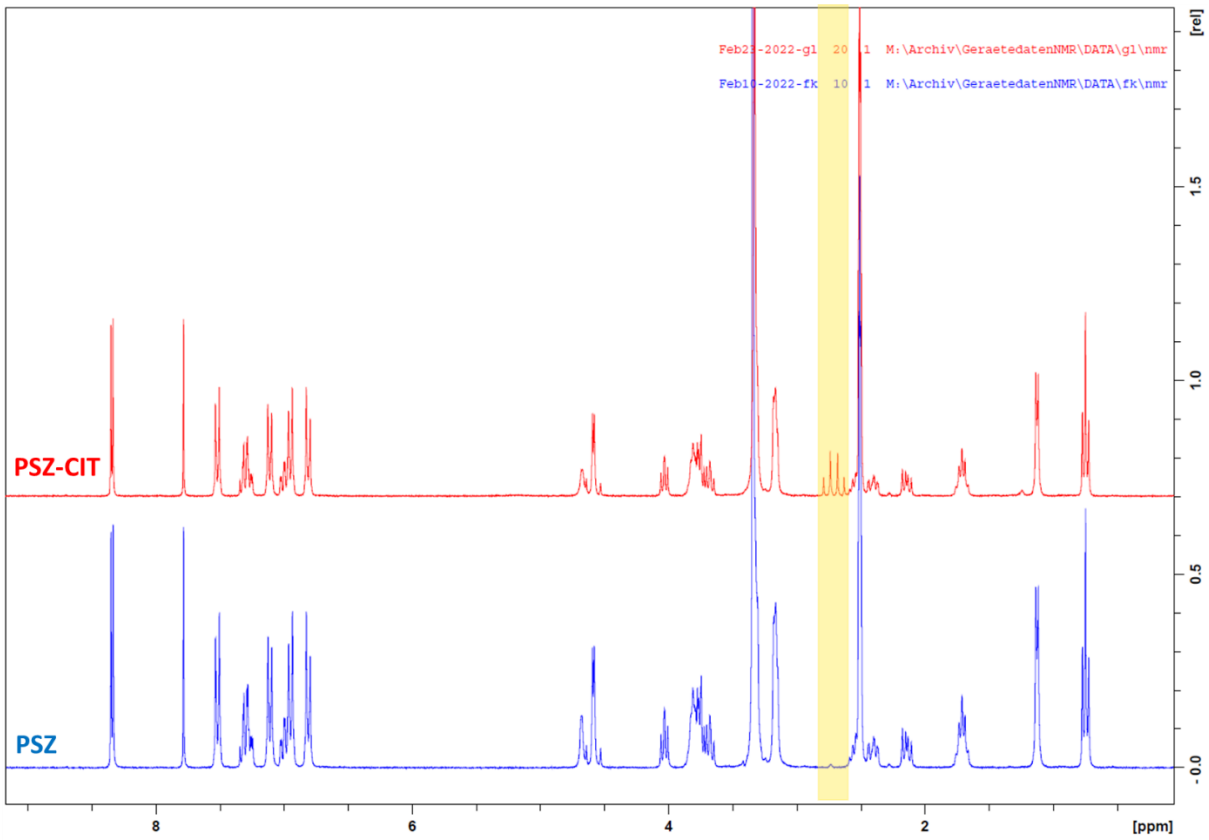

Figure S25. Proton NMR spectra of PSZ-CIT and PSZ collected in deuterated DMSO; chemical shifts reported in ppm. The peaks of the coformer are highlighted in yellow.

7 Posaconazole – 1-Hydroxy-2-Naphthoic Acid Cocrystal (PSZ-XIN)

7.1 DSC

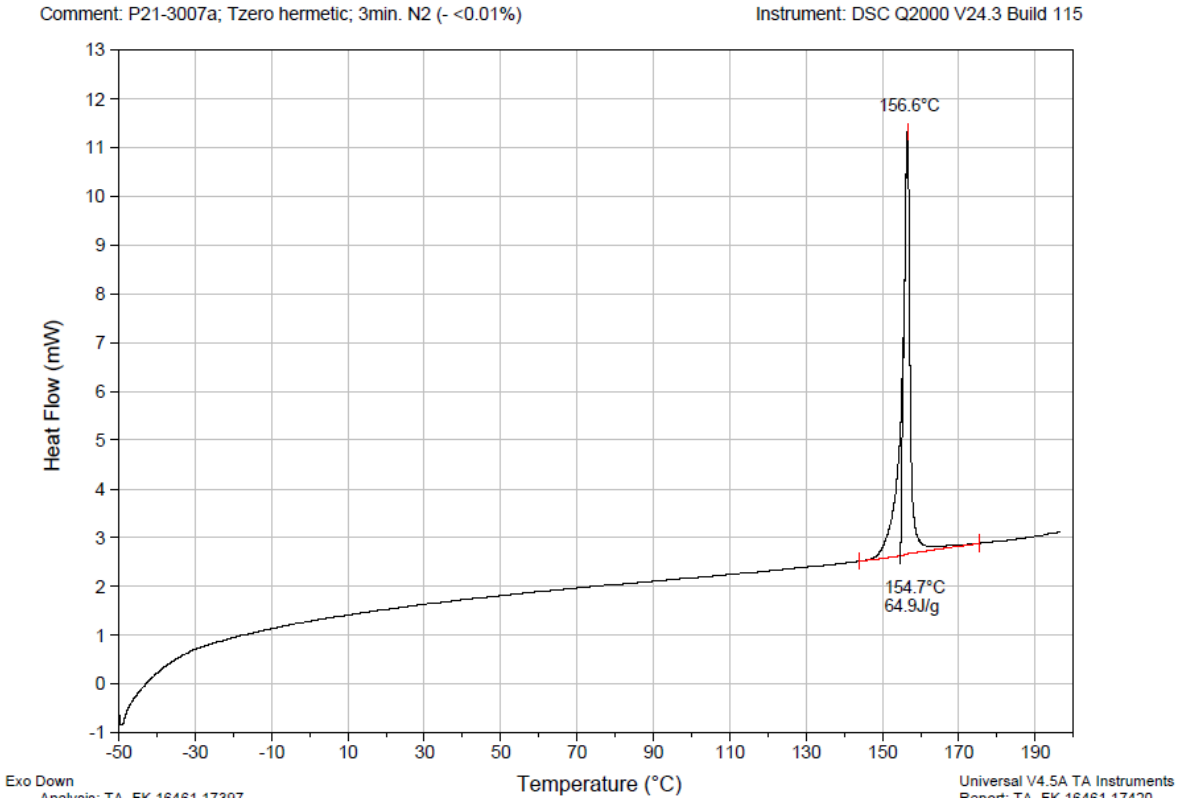

Figure S26. DSC thermogram of PSZ-XIN, collected with a heating rate of 10 K/min.

7.2 TG-FTIR

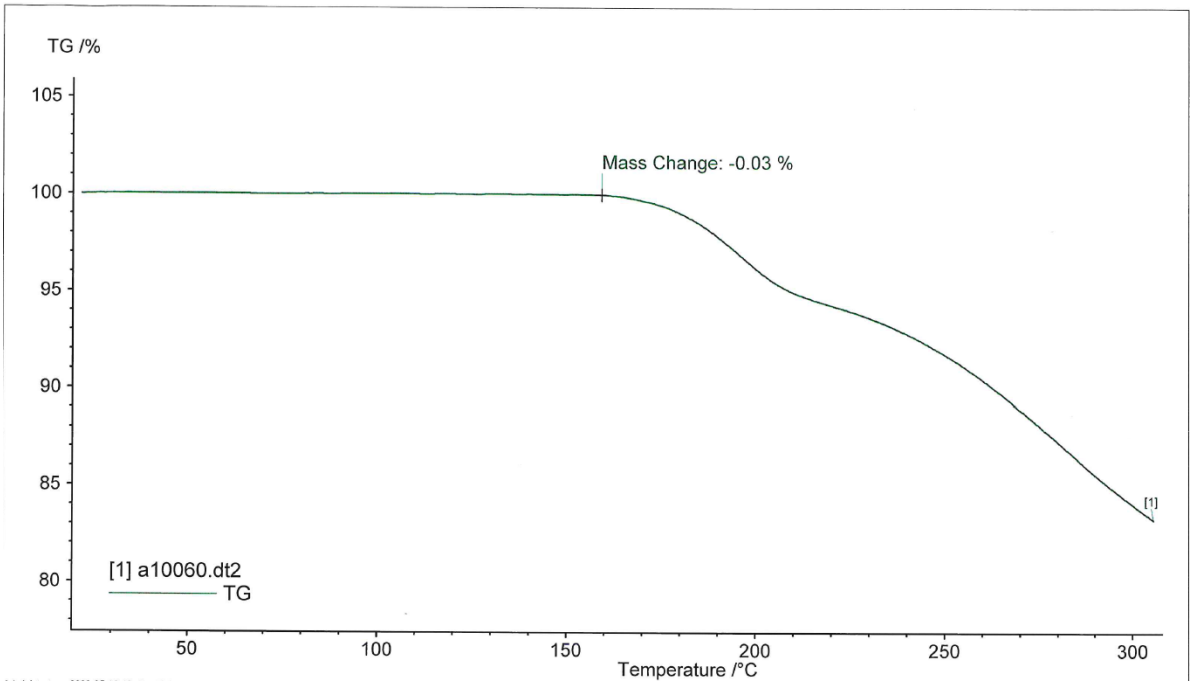

Figure S27. TG-FTIR thermogram of PSZ-XIN, collected with a heating rate of 10 K/min.

7.3 Raman Spectrum

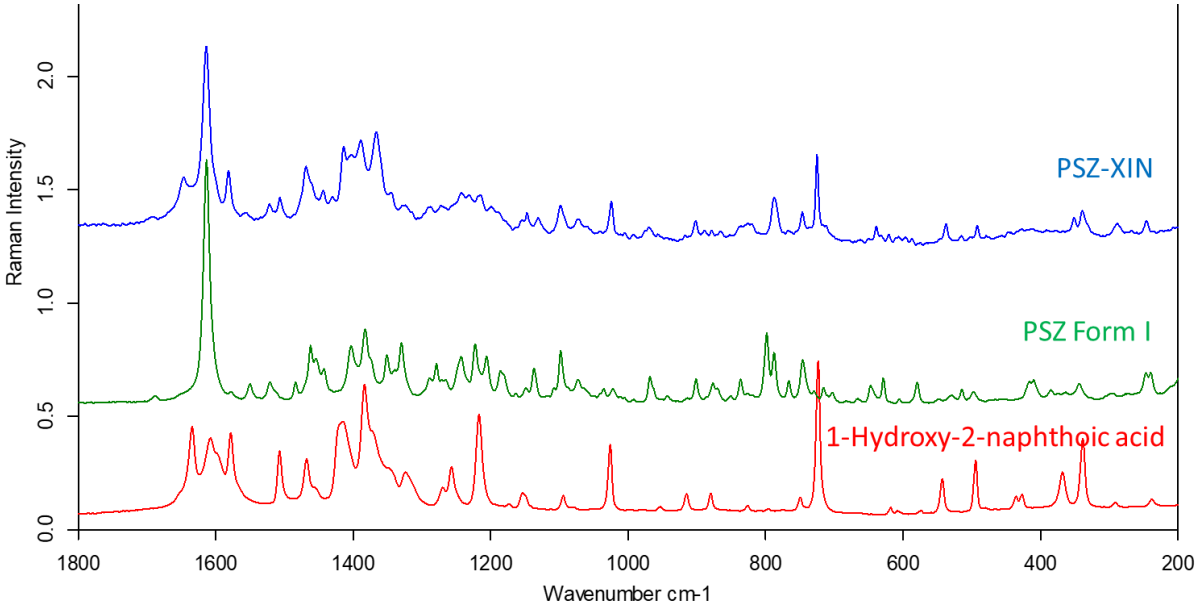

Figure S28. FT-Raman spectra of PSZ form I, 1-hydroxy-2-naphthoic acid and PSZ-XIN.

7.4 Powder X-ray Diffraction Patterns

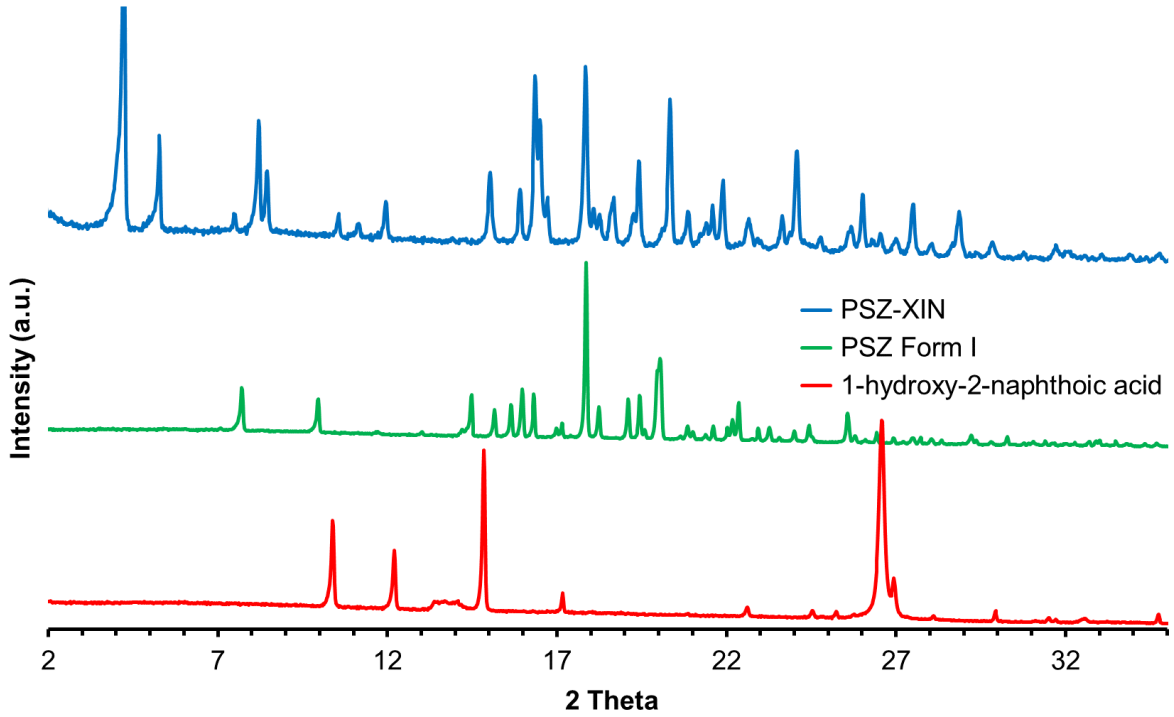

Figure S29. PXRD patterns of PSZ Form I, 1-hydroxy-2-naphthoic acid and PSZ-XIN.

7.5 Proton Nuclear Magnetic Resonance (^{1}H-NMR)

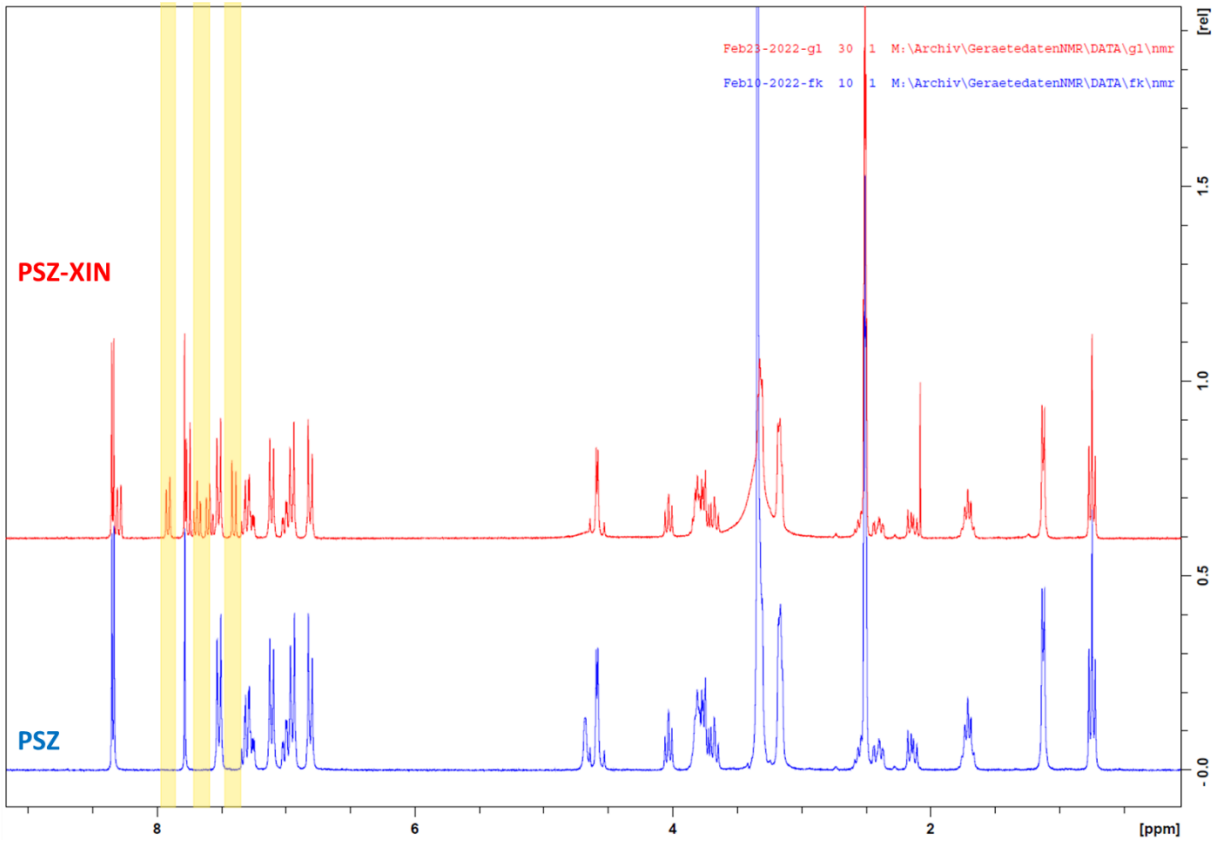

Figure S30. Proton NMR spectra of PSZ-XIN and PSZ collected in deuterated DMSO; chemical shifts reported in ppm. The peaks of the coformer are highlighted in yellow.

8 Posaconazole – Gentisic Acid Cocrystal (PSZ-GEN)

8.1 DSC

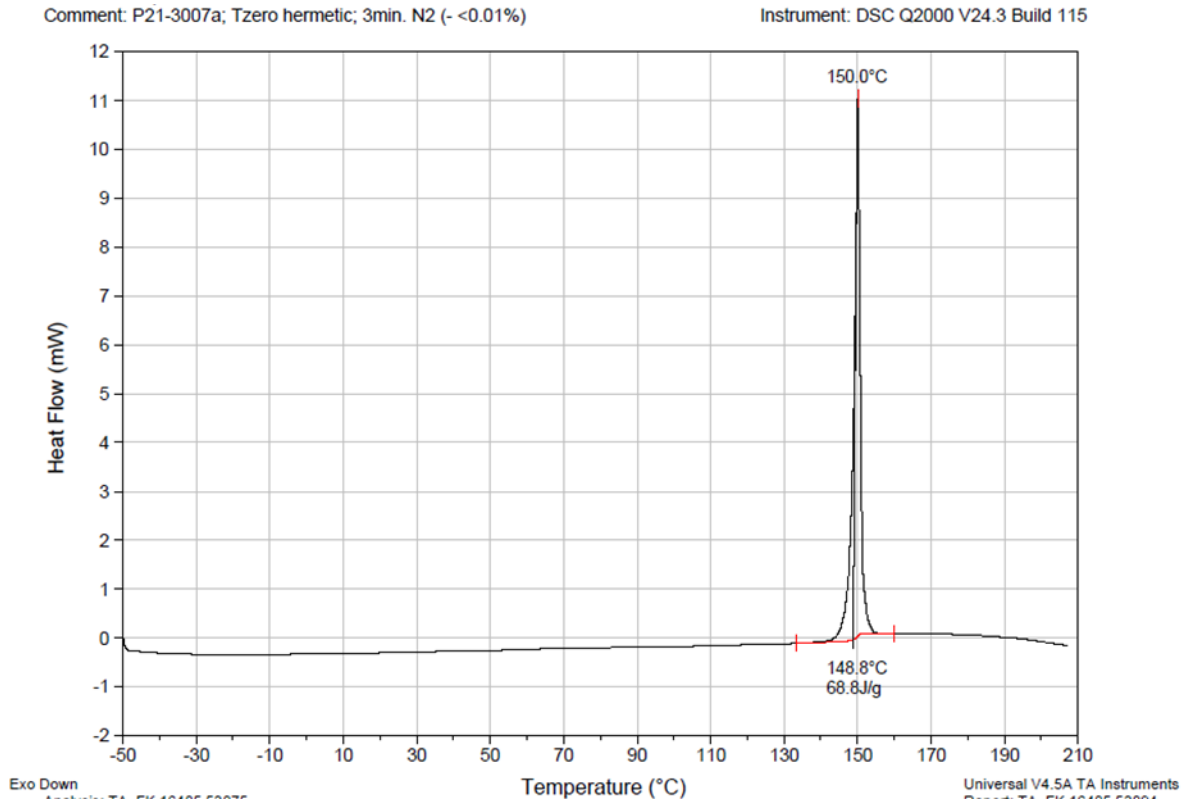

Figure S31. DSC thermogram of PSZ-GEN, collected with a heating rate of 10 K/min.

8.2 TG-FTIR

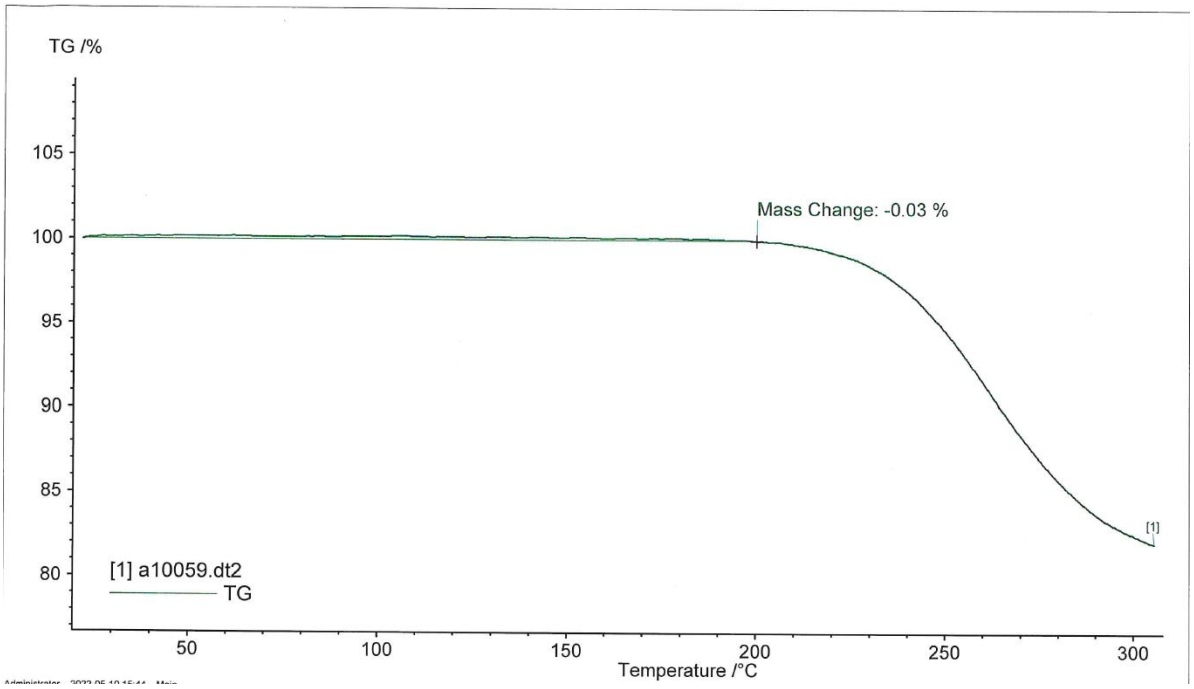

Figure S32. TG-FTIR thermogram of PSZ-GEN, collected with a heating rate of 10 K/min.

8.3 Raman Spectrum

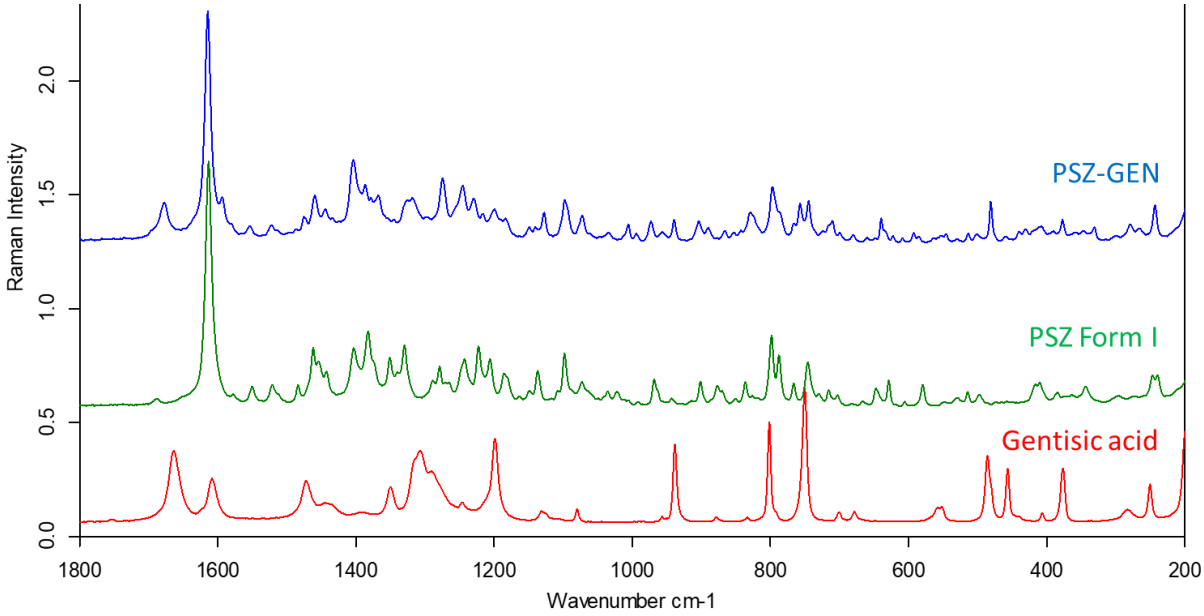

Figure S33. FT-Raman spectra of PSZ Form I, gentisic acid and PSZ-GEN.

8.4 Powder X-ray Diffraction Patterns

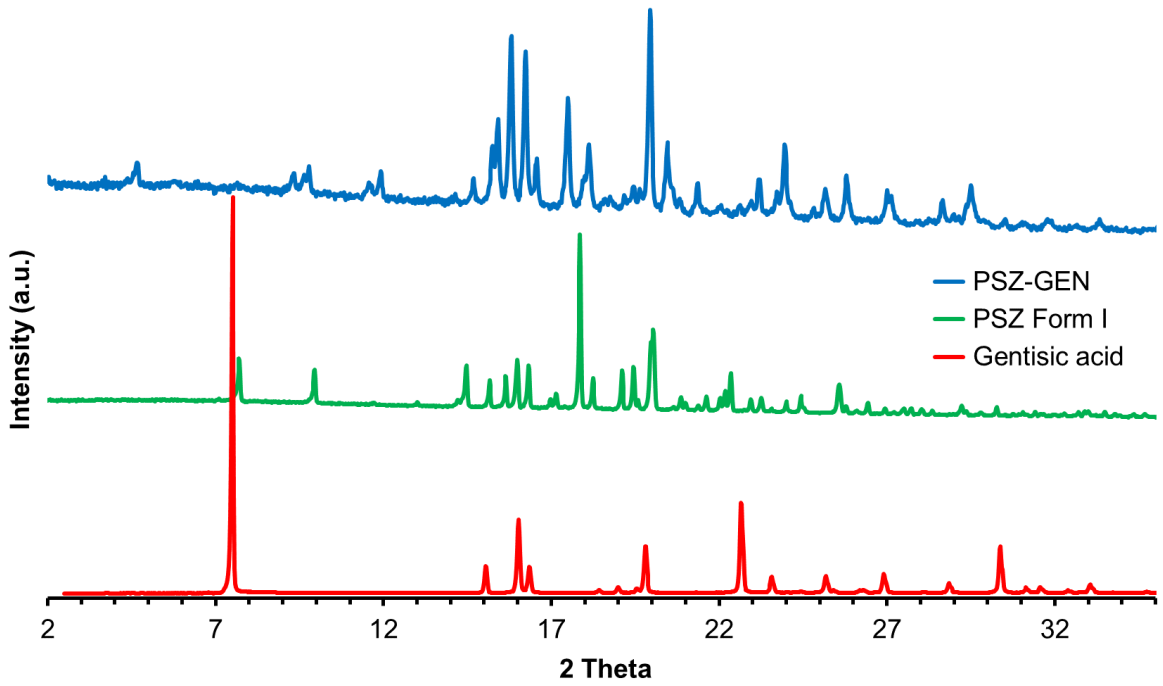

Figure S34. PXRD patterns of PSZ Form I, gentisic acid and PSZ-GEN.

8.5 Proton Nuclear Magnetic Resonance (^{1}H-NMR)

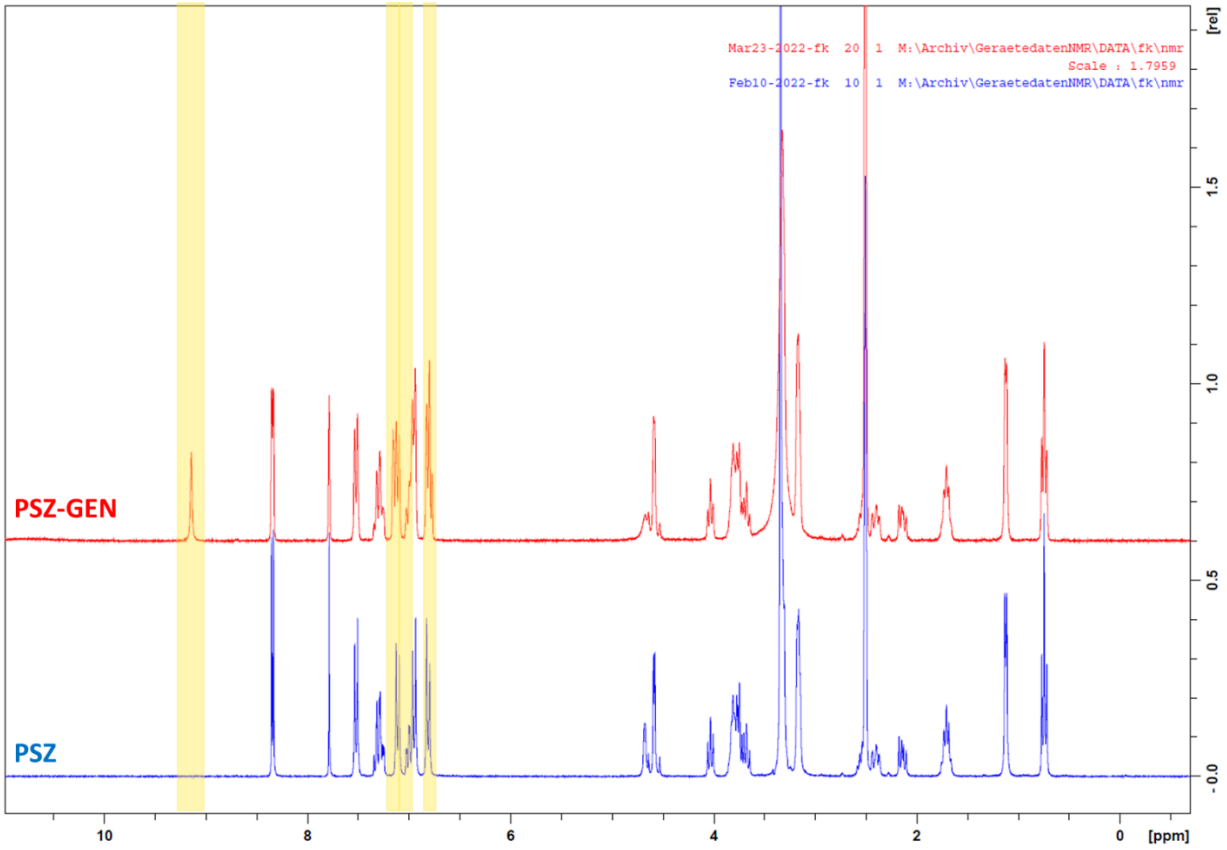

Figure S35. Proton NMR spectra of PSZ-GEN and PSZ collected in deuterated DMSO; chemical shifts reported in ppm. The peaks of the coformer are highlighted in yellow.

9 Posaconazole – Salicylic Acid Cocrystal (PSZ-SAL)

9.1 DSC

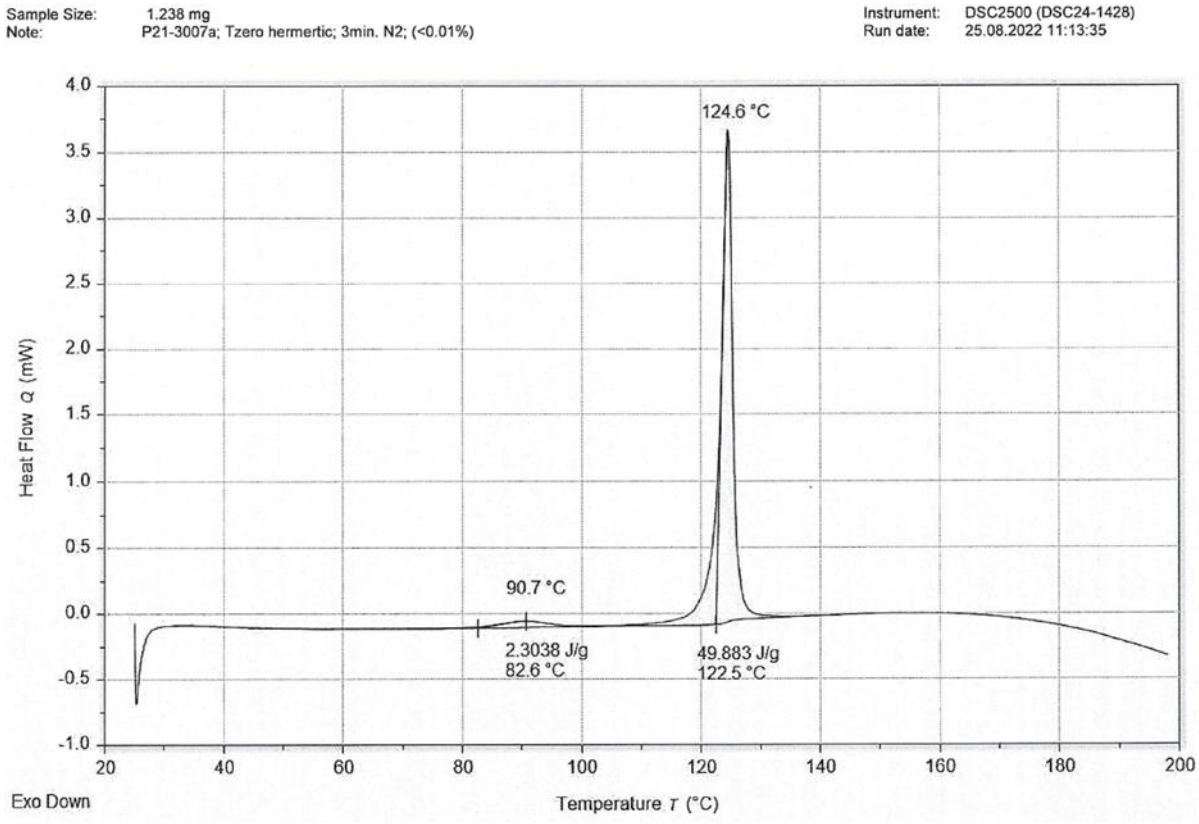

Figure S36. DSC thermogram of PSZ-SAL, collected with a heating rate of 10 K/min.

9.2 TG-FTIR

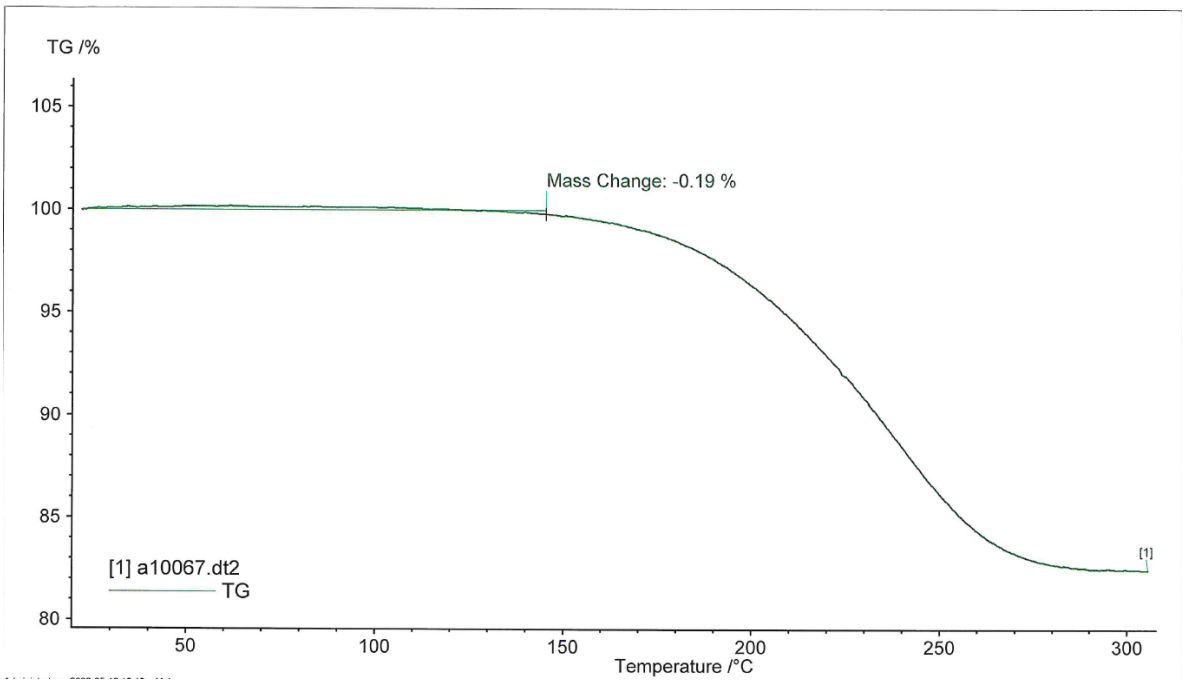

Figure S37. TG-FTIR thermogram of PSZ-SAL, collected with a heating rate of 10 K/min.

9.3 Raman Spectrum

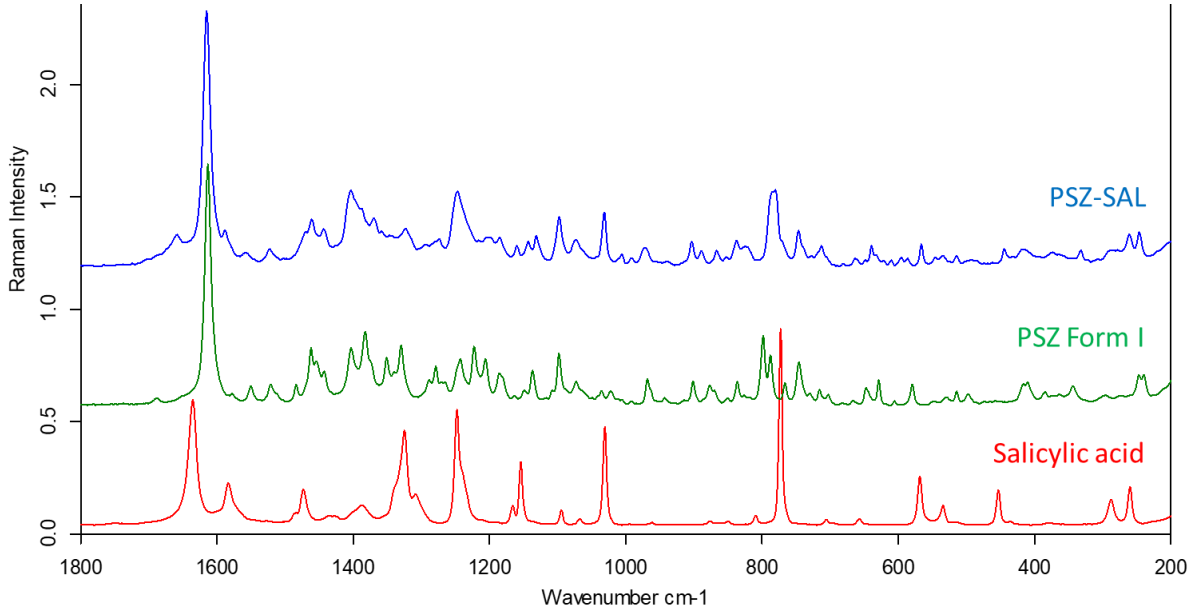

Figure S38. FT-Raman spectra of PSZ Form I, salicylic acid and PSZ-SAL.

9.4 Powder X-ray Diffraction Patterns

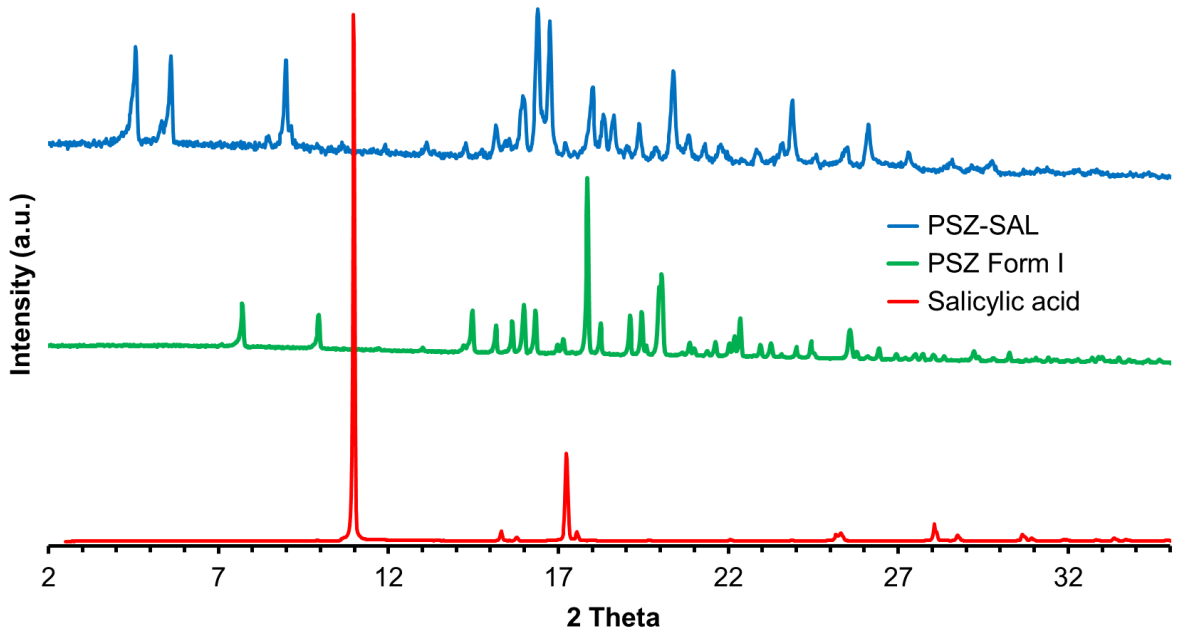

Figure S39. PXRD patterns of PSZ Form I, salicylic acid and PSZ-SAL.

9.5 Proton Nuclear Magnetic Resonance (^{1}H-NMR)

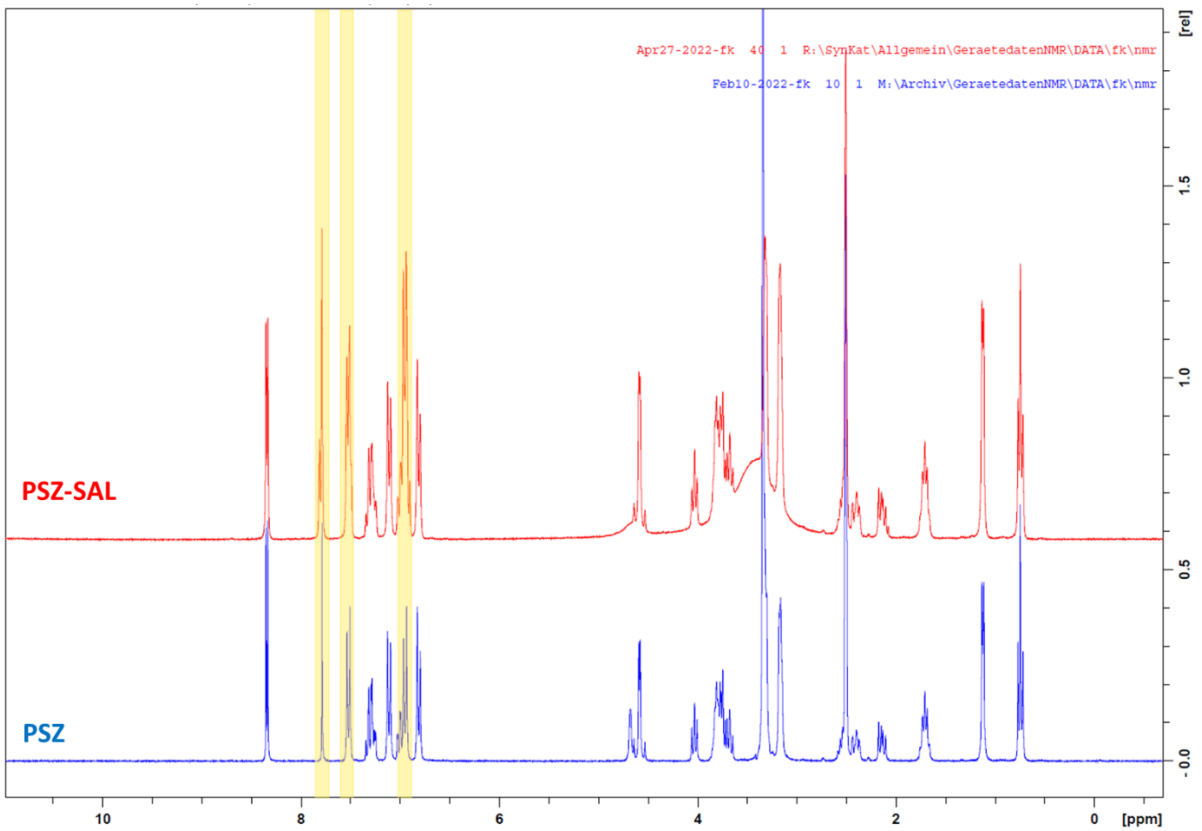

Figure S40. Proton NMR spectra of PSZ-SAL and PSZ collected in deuterated DMSO, chemical shifts reported in ppm. The peaks of the coformer are highlighted in yellow.

10 Posaconazole – 4-Aminobenzoic Acid Cocrystal (PSZ-ABA)

10.1 DSC

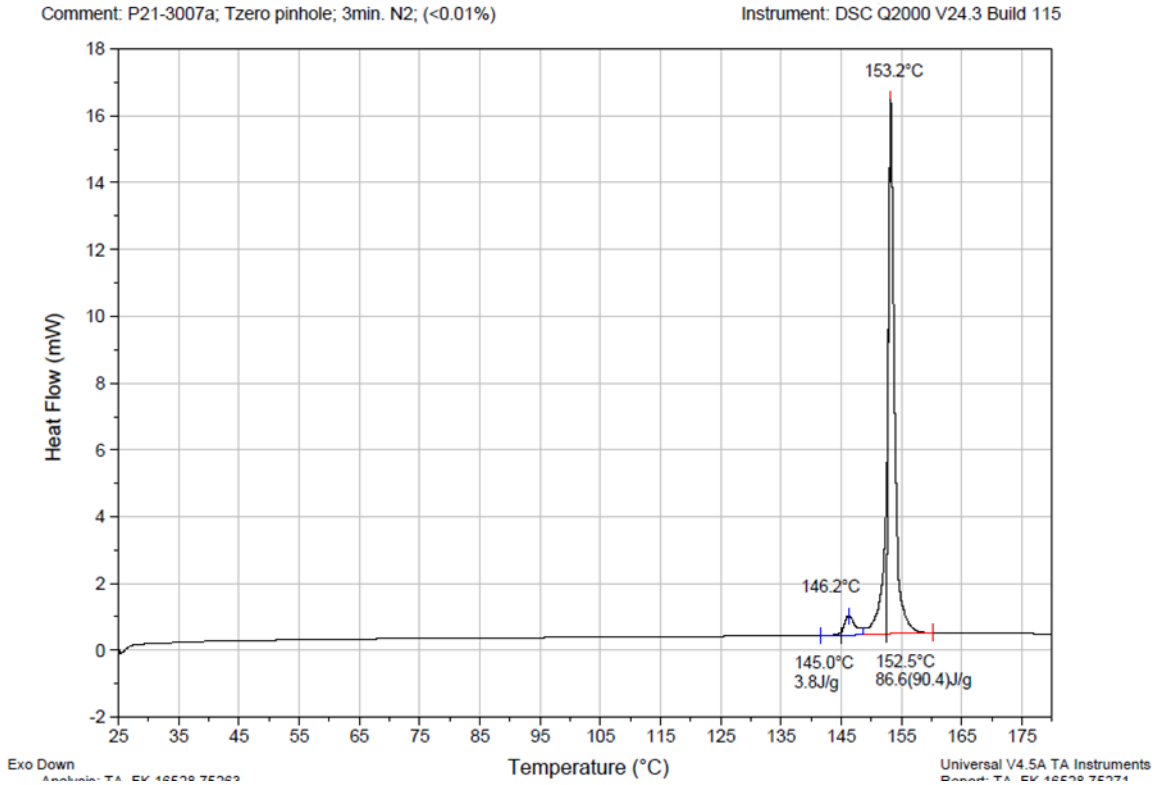

Figure S41. DSC thermogram of PSZ-ABA, collected with a heating rate of 10 K/min.

10.2 TG-FTIR

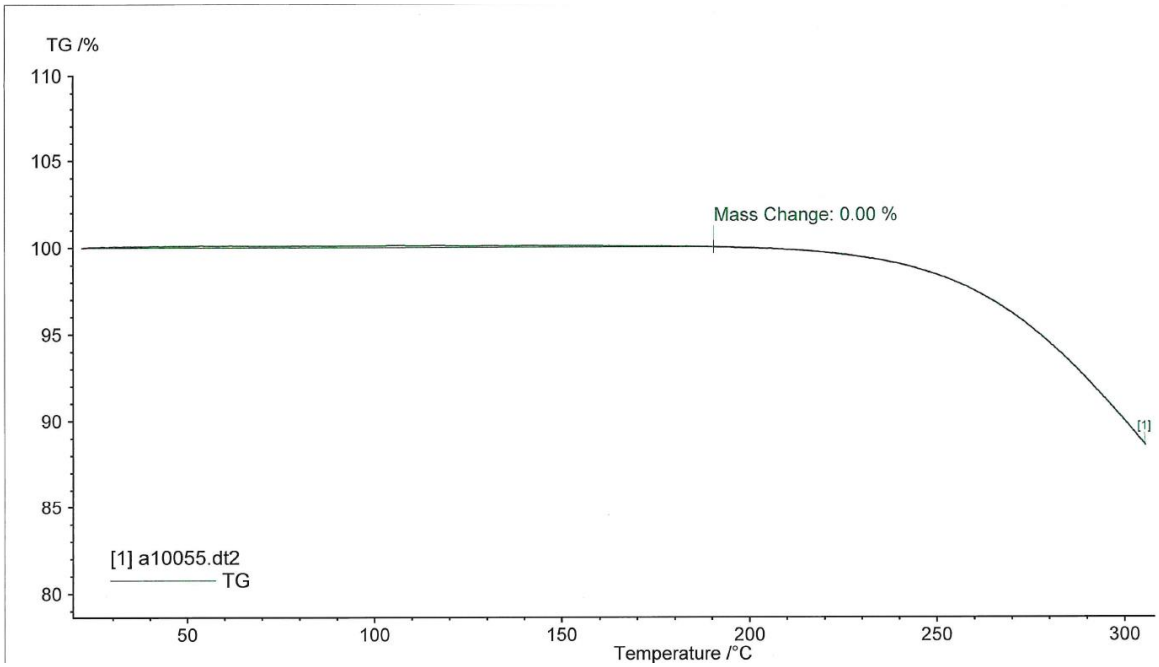

Figure S42. TG-FTIR thermogram of PSZ-ABA, collected with a heating rate of 10 K/min.

10.3 Raman Spectrum

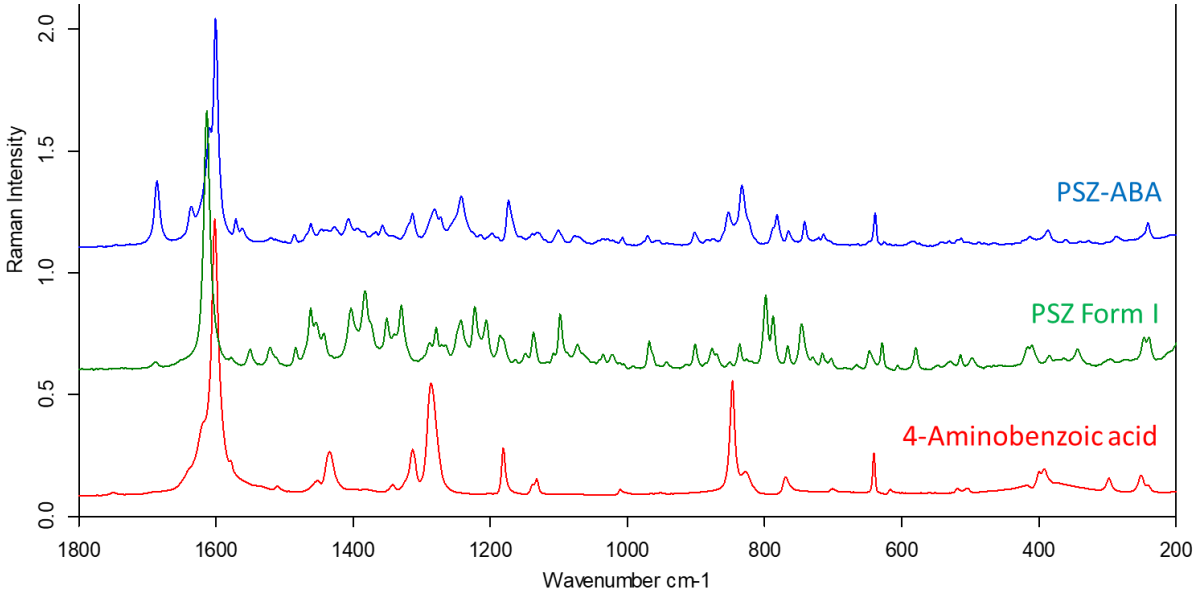

Figure S43. FT-Raman spectra of PSZ Form I, 4-aminobenzoic acid and PSZ-ABA.

10.4 Powder X-ray Diffraction Patterns

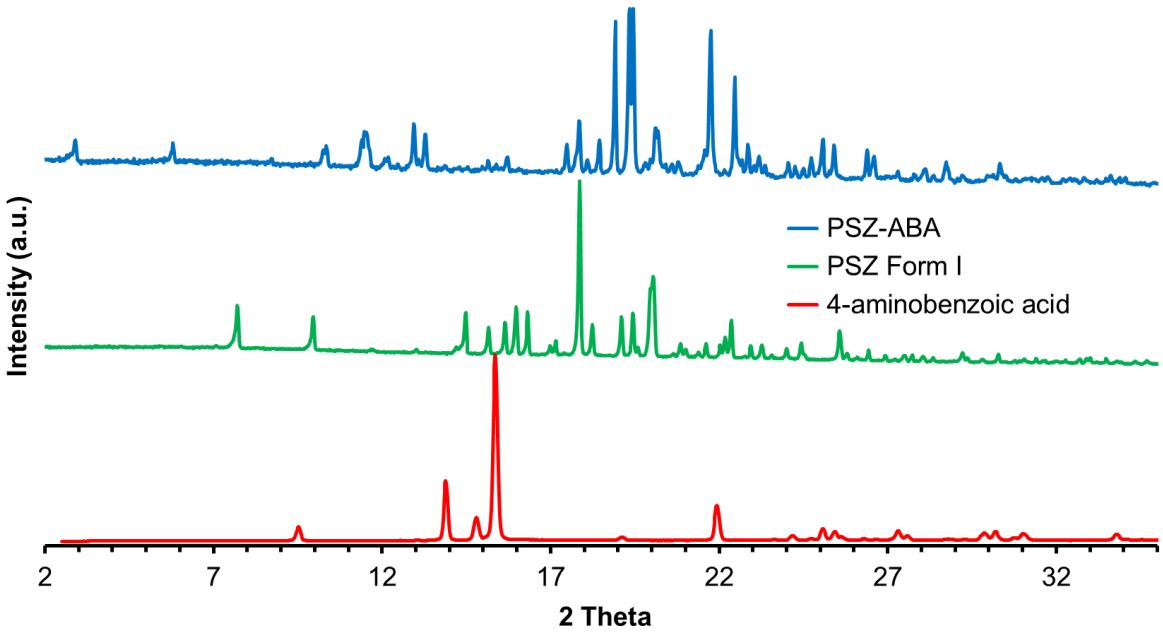

Figure S44. PXRD patterns of PSZ Form I, 4-aminobenzoic acid and PSZ-ABA.

10.5 Proton Nuclear Magnetic Resonance (^{1}H-NMR)

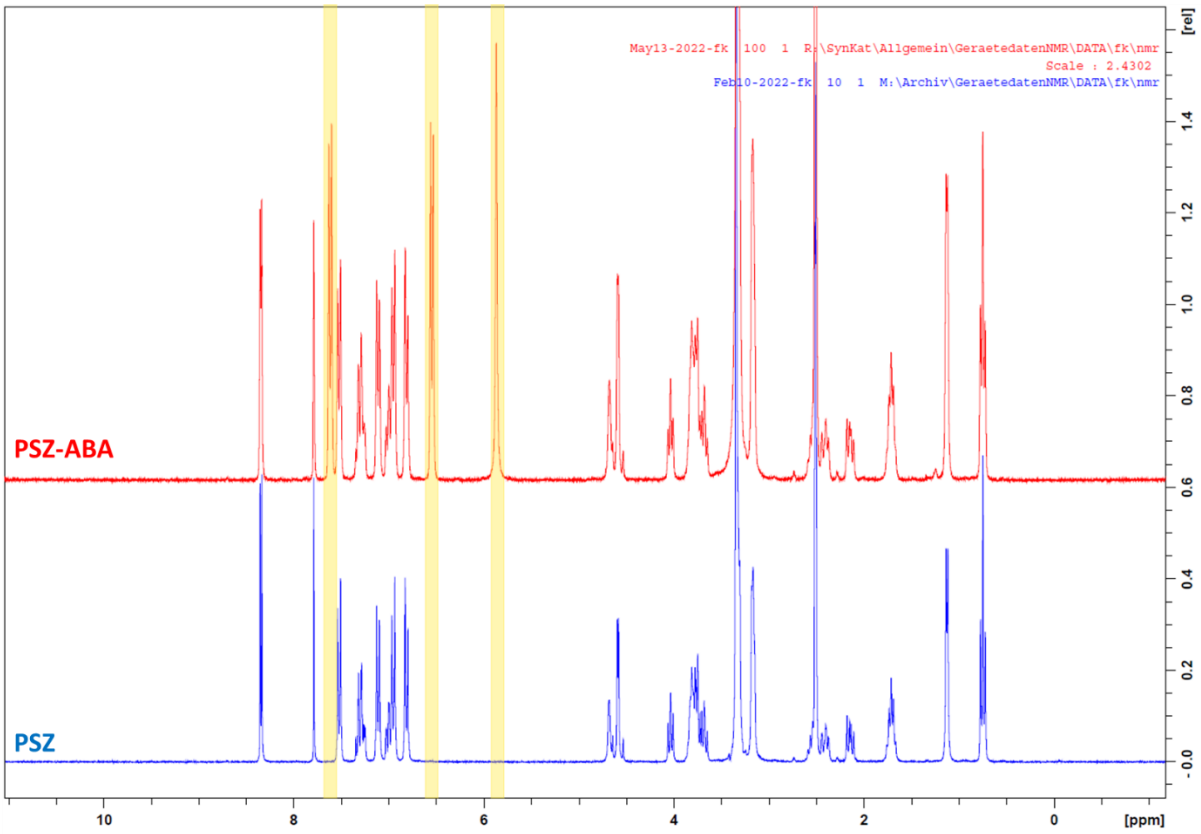

Figure S45. Proton NMR spectra of PSZ-ABA and PSZ collected in deuterated DMSO; chemical shifts reported in ppm. The peaks of the coformer are highlighted in yellow.

11 Posaconazole – L-Lactic Acid Cocrystal (PSZ-LLA)

11.1 DSC

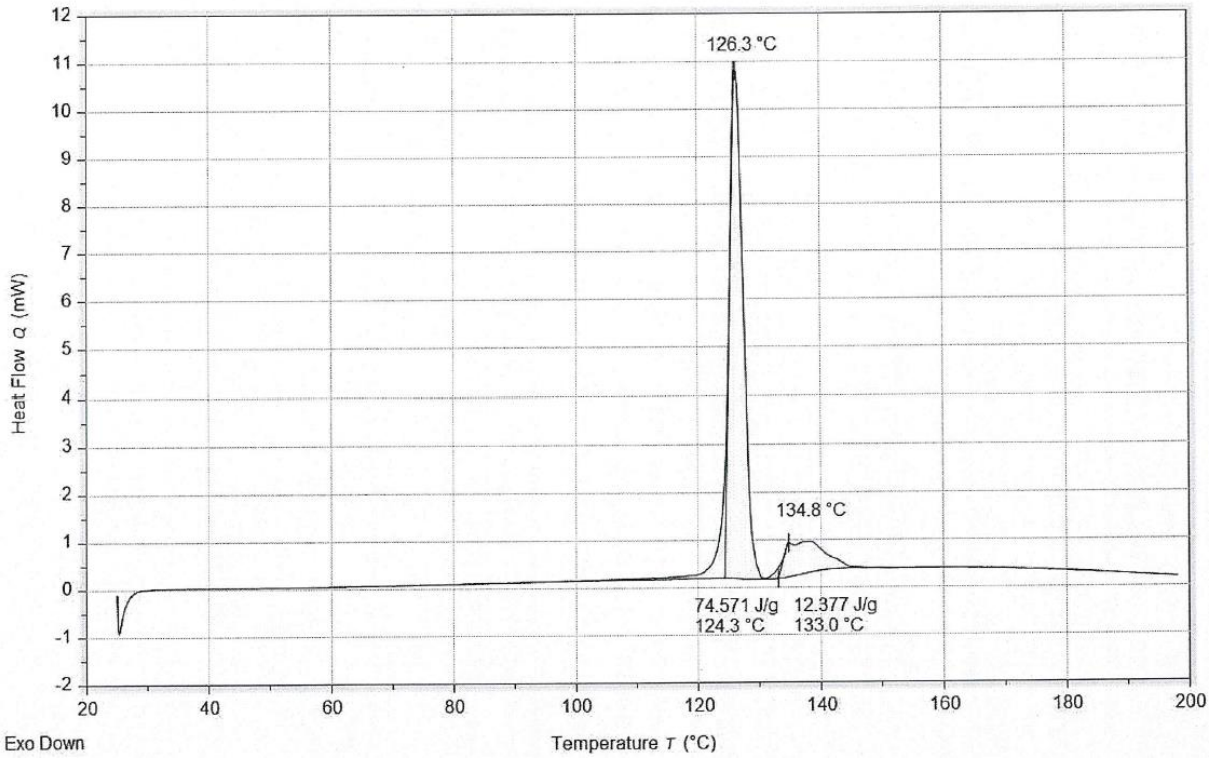

Figure S46. DSC thermogram of PSZ-LLA, collected with a heating rate of 10 K/min.

11.2 TG-FTIR

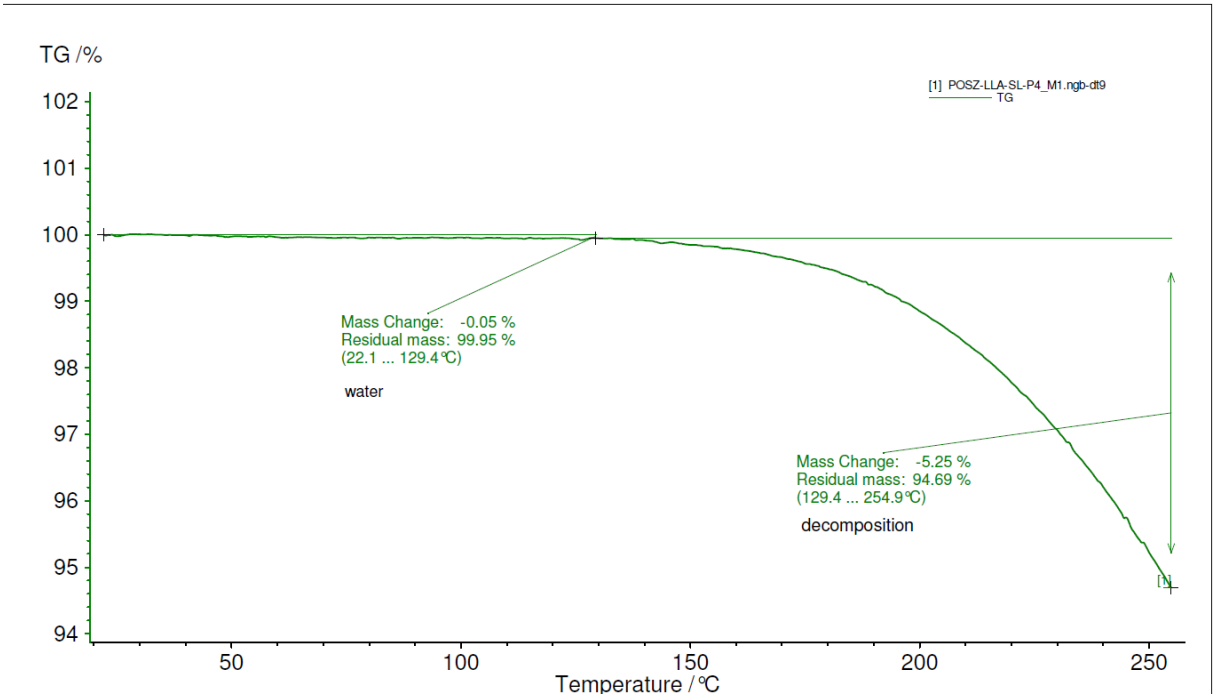

Figure S47. TG-FTIR thermogram of PSZ-LLA, collected with a heating rate of 10 K/min.

11.3 Raman Spectrum

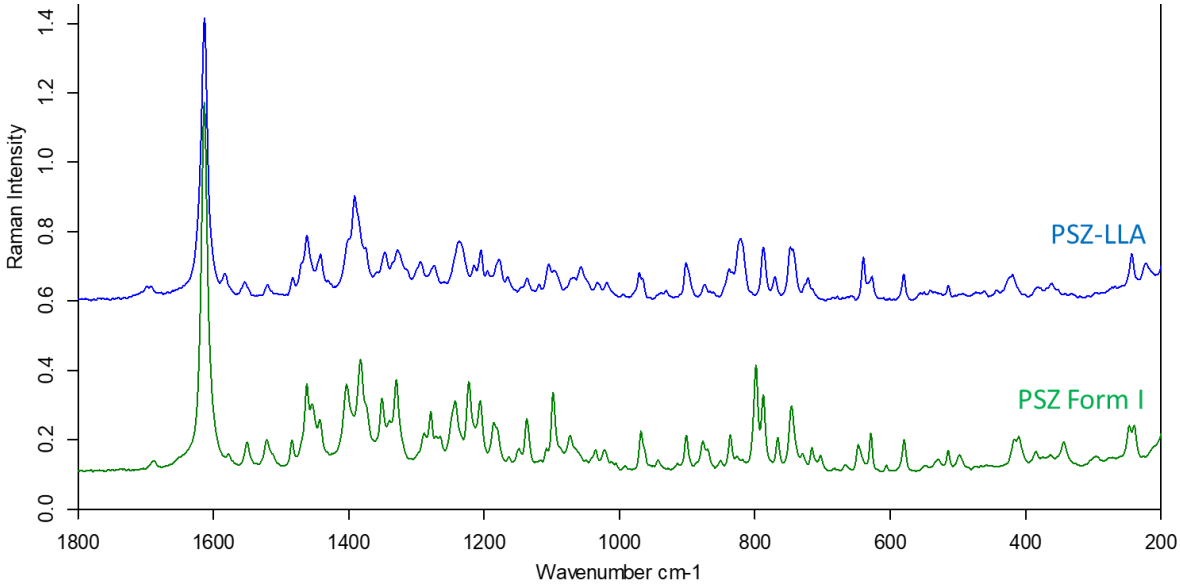

Figure S48. FT-Raman spectra of PSZ Form I and PSZ-LLA.

11.4 Powder X-ray Diffraction Patterns

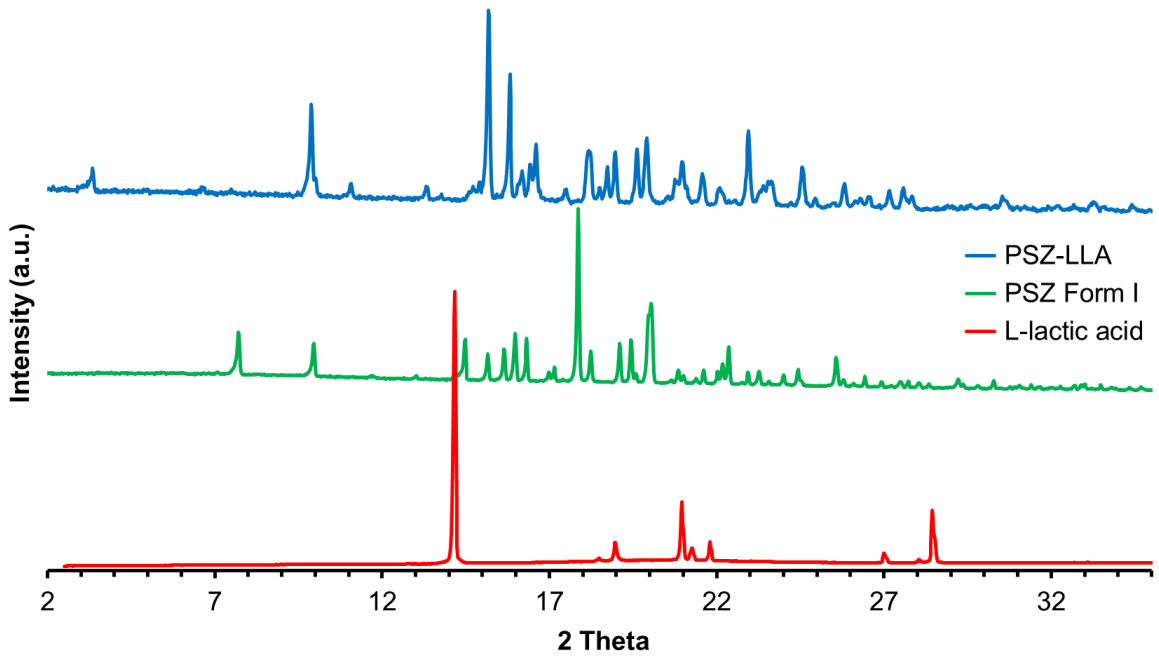

Figure S49. PXRD patterns of PSZ Form I, L-lactic acid and PSZ-LLA.

11.5 Proton Nuclear Magnetic Resonance (^{1}H-NMR)

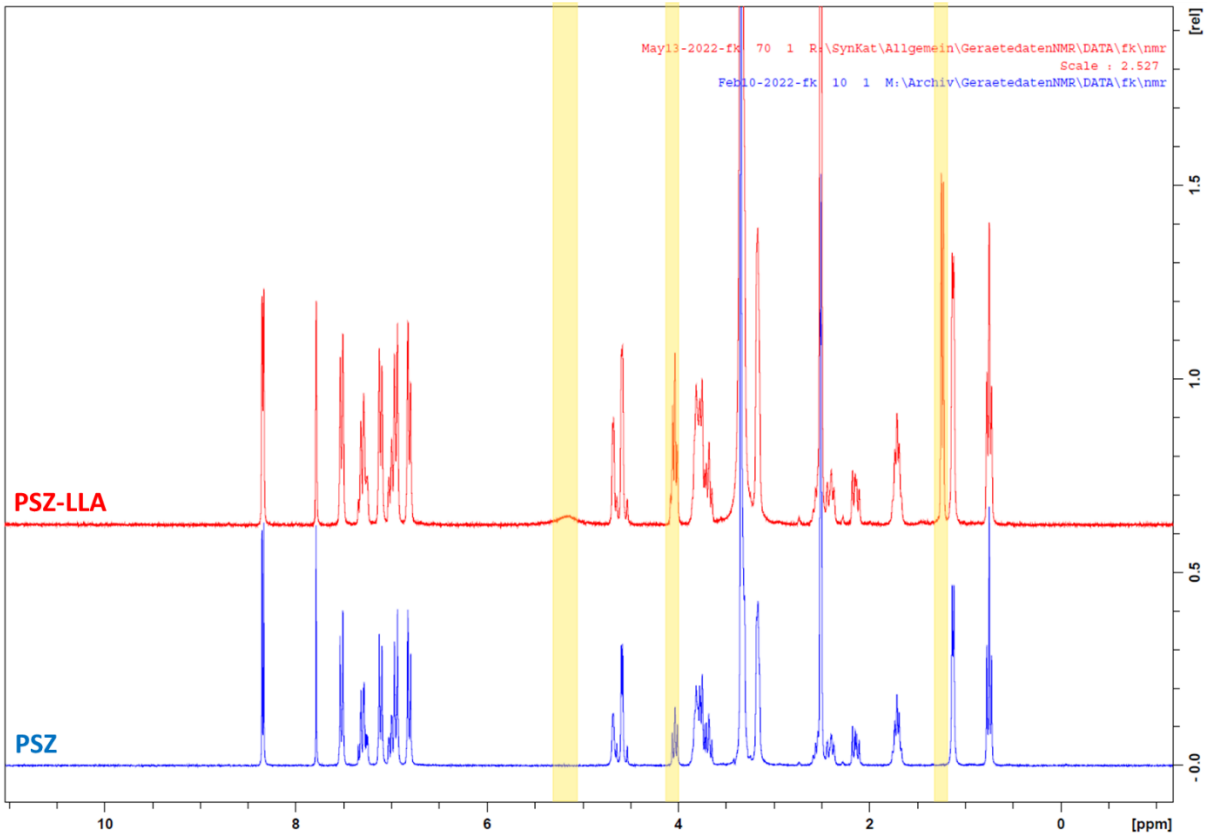

Figure S50. Proton NMR spectra of PSZ-LLA and PSZ collected in deuterated DMSO; chemical shifts reported in ppm. The peaks of the coformer are highlighted in yellow.

12 Posaconazole – Adipic Acid Hydrate Cocrystal (PSZ-ADI-H2O)

12.1 TG-FTIR

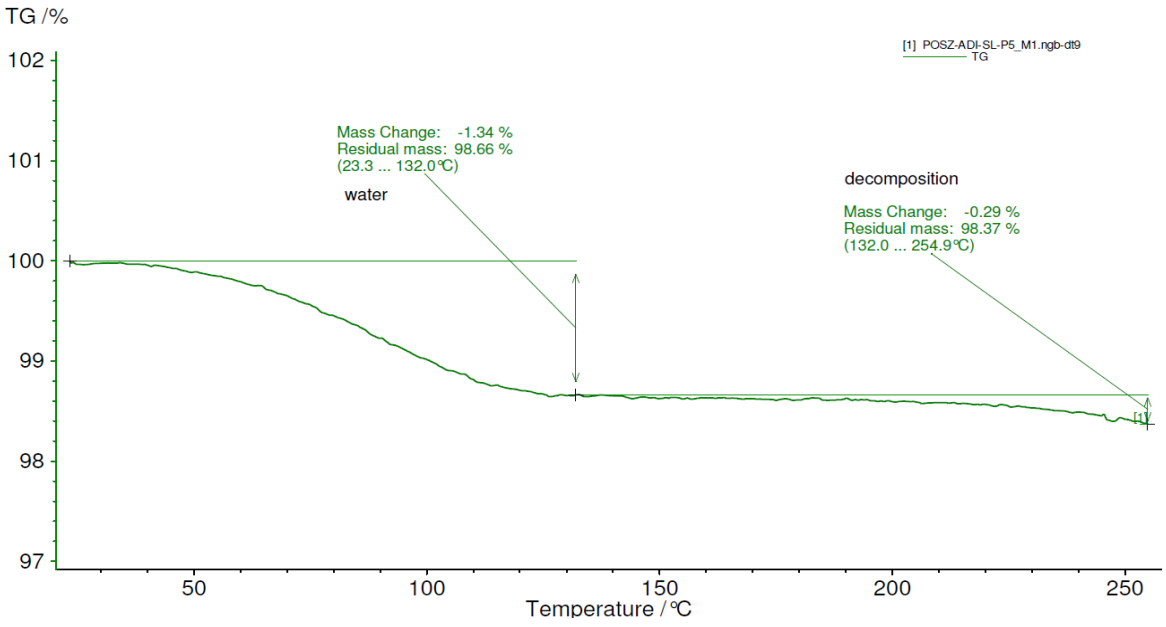

Figure S51. TG-FTIR thermogram of PSZ-ADI-H2O, collected with a heating rate of 10 K/min.

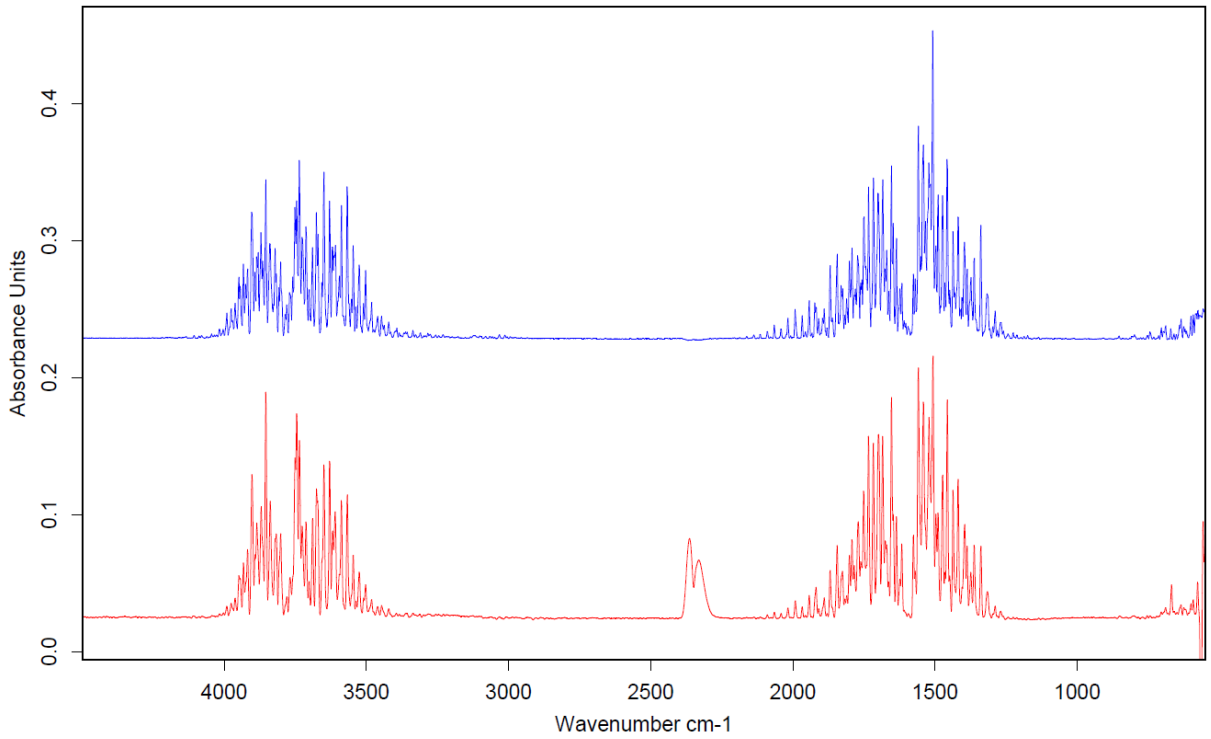

Figure S52. Comparison of the IR spectrum of the gas released at 25°C (red) with the spectrum of H_2O (blue).

12.2 Raman Spectrum

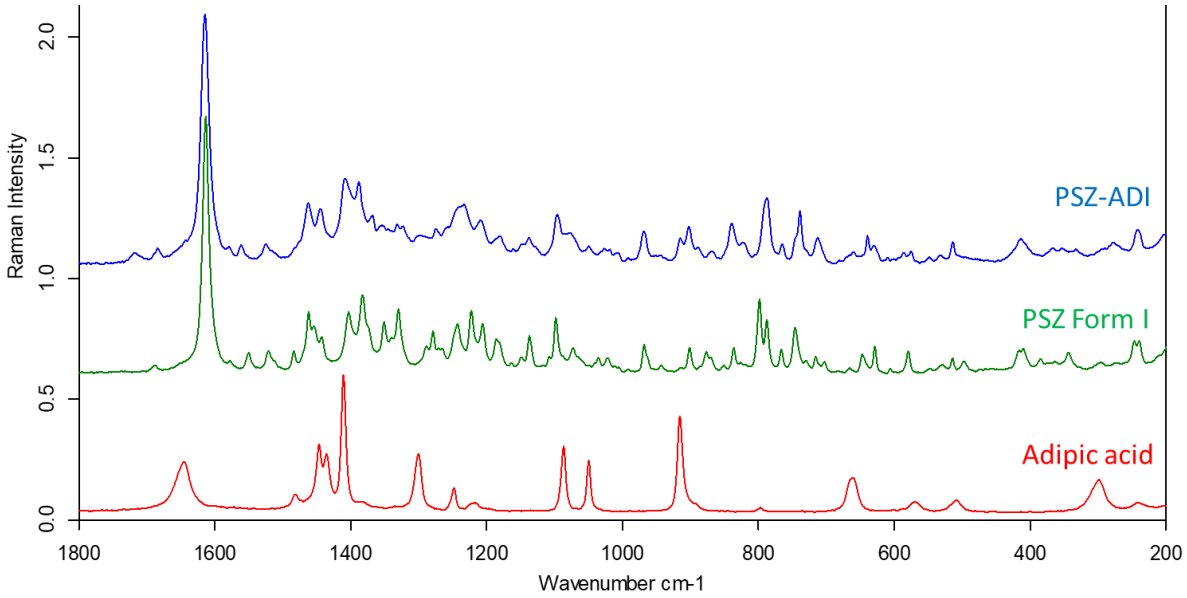

Figure S53. FT-Raman spectra of PSZ Form I, adipic acid and PSZ-ADI-H2O.

12.3 Powder X-ray Diffraction Patterns

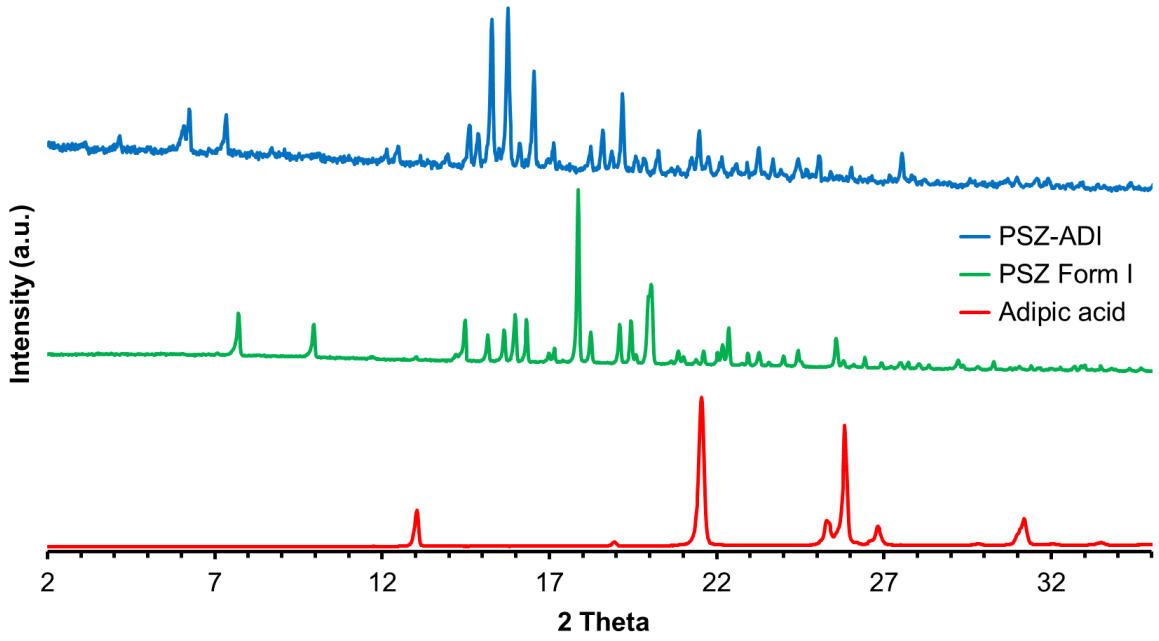

Figure S54. PXRD patterns of PSZ Form I, adipic acid and PSZ-ADI-H2O.

12.4 Proton Nuclear Magnetic Resonance (^{1}H-NMR)

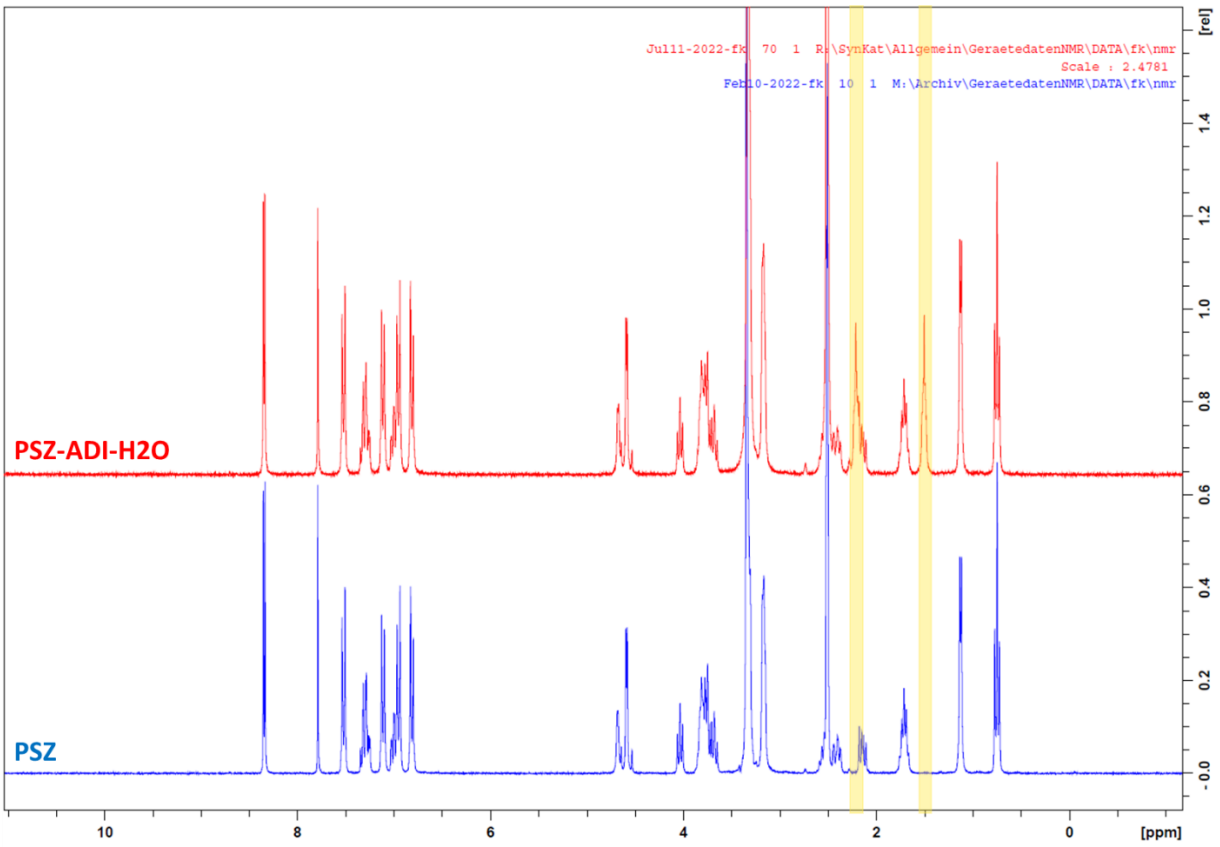

Figure S55. Proton NMR spectra of PSZ-ADI-H2O and PSZ collected in deuterated DMSO; chemical shifts reported in ppm. The peaks of the coformer are highlighted in yellow.

13 Posaconazole – Succinic Acid Hydrate Cocrystal (PSZ-SUC-H2O)

13.1 TG-FTIR

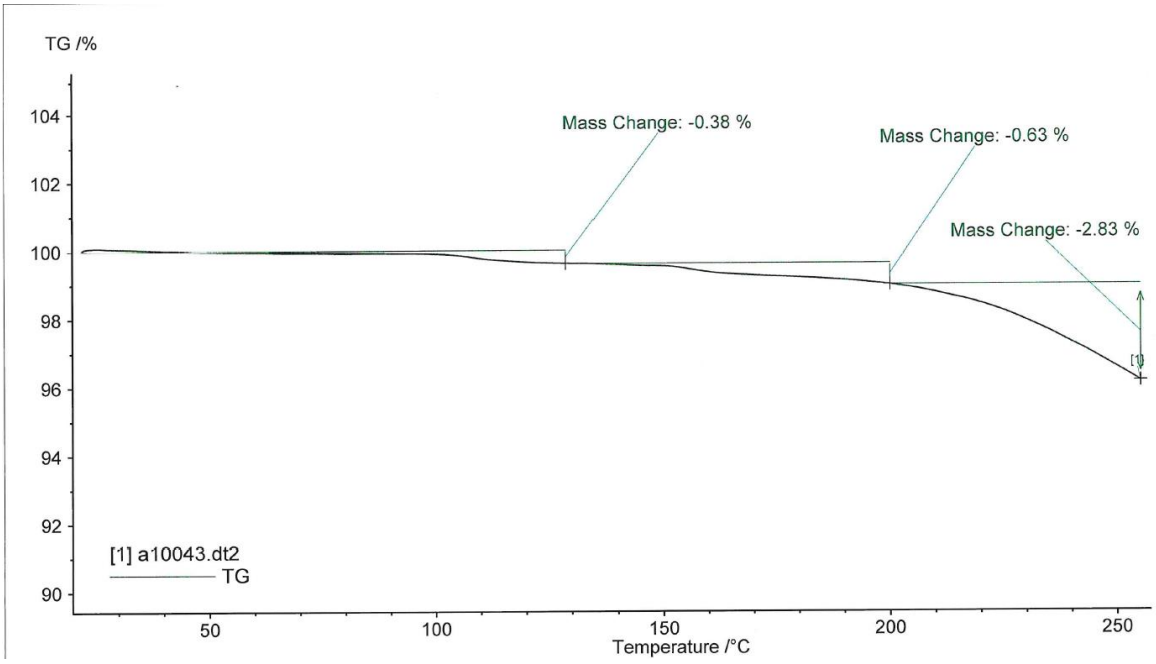

Figure S56. TG-FTIR thermogram of PSZ-SUC-H2O, collected with a heating rate of 10 K/min.

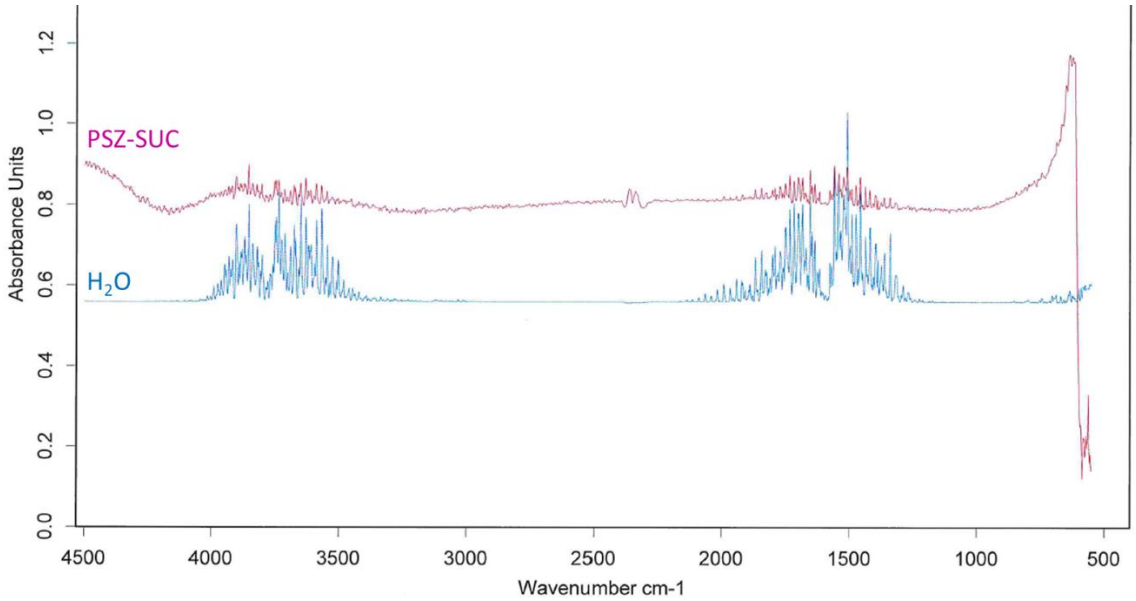

Figure S57. Comparison of the IR spectrum of the gas released at 100°C (red) with the spectrum of H_2O (blue).

13.2 Raman Spectrum

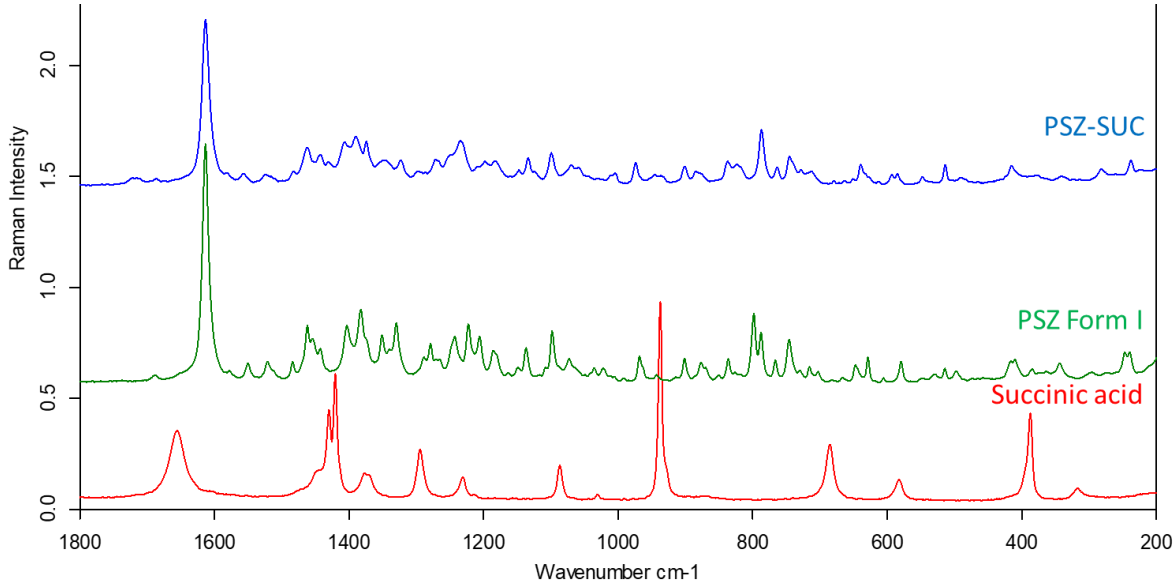

Figure S58. FT-Raman spectra of PSZ Form I, succinic acid and PSZ-SUC-H2O.

13.3 Powder X-ray Diffraction Patterns

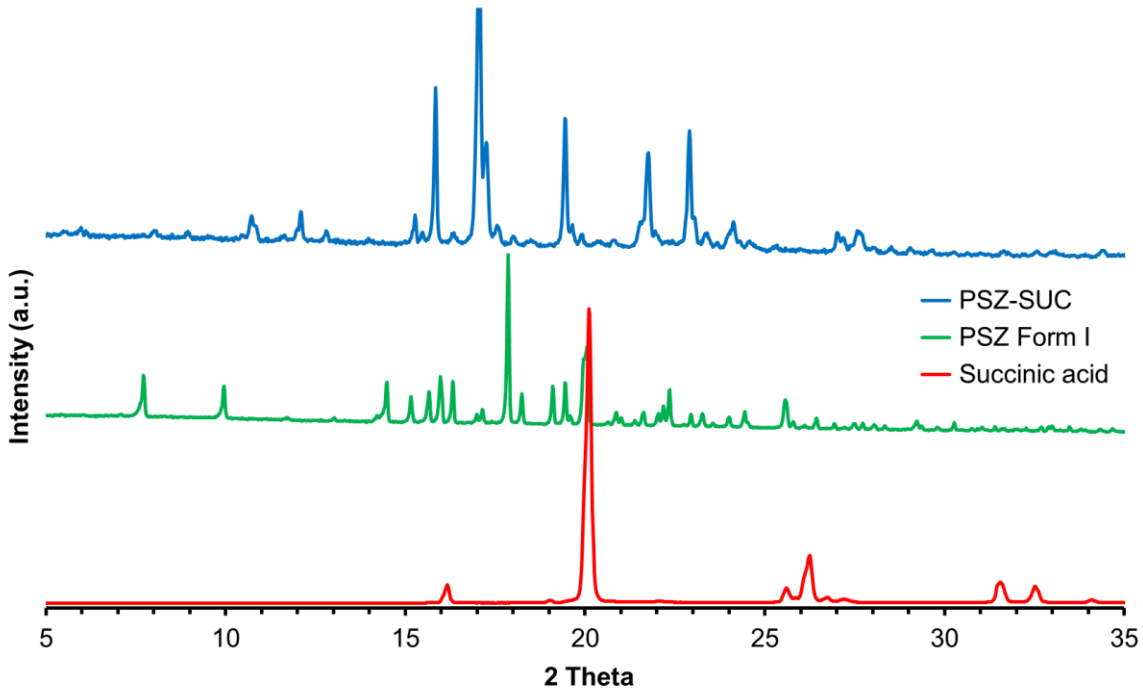

Figure S59. PXRD patterns of PSZ Form I, succinic acid and PSZ-SUC-H2O.

13.4 Proton Nuclear Magnetic Resonance (^{1}H-NMR)

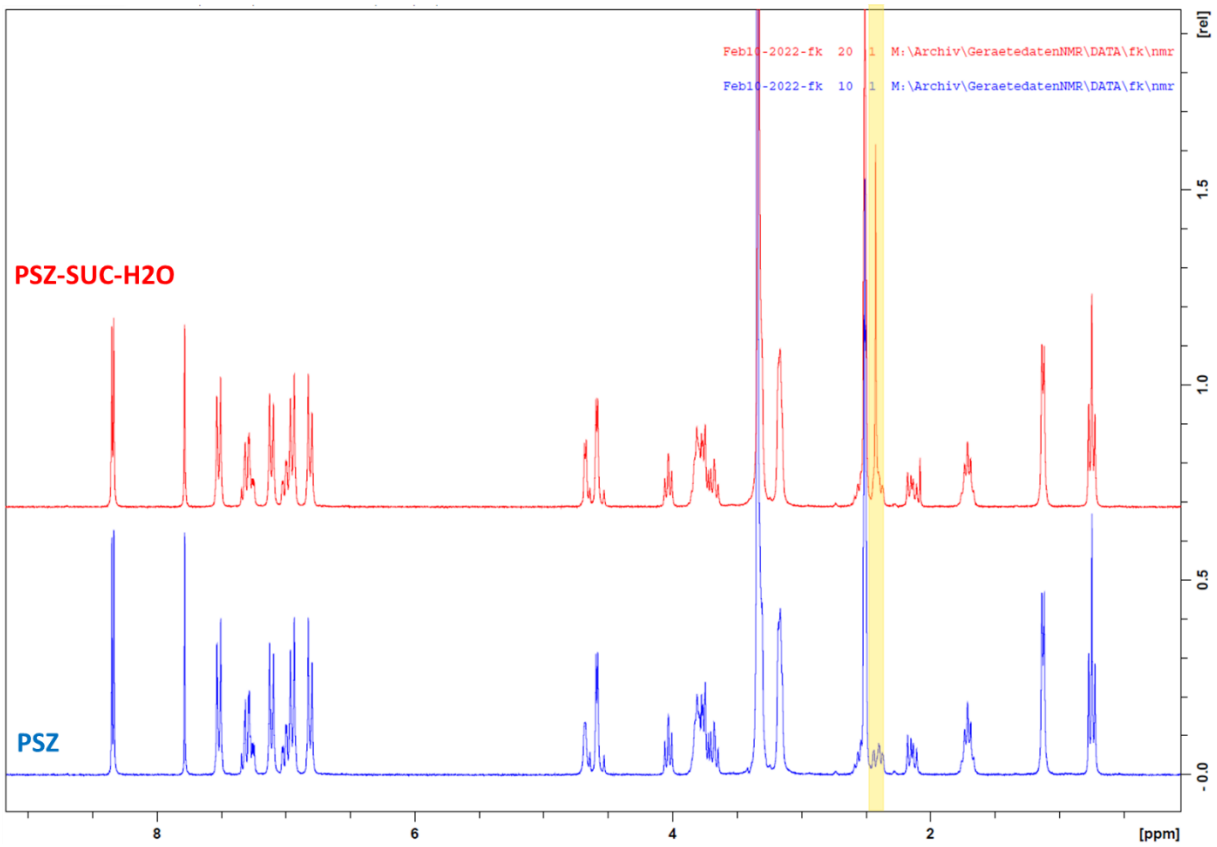

Figure S60. Proton NMR spectra of PSZ-SUC-H2O and PSZ collected in deuterated DMSO; chemical shifts reported in ppm. The peaks of the coformer are highlighted in yellow.

14 Posaconazole – Fumaric Acid THF Solvate Cocrystal (PSZ-FUM-THF)

14.1 TG-FTIR

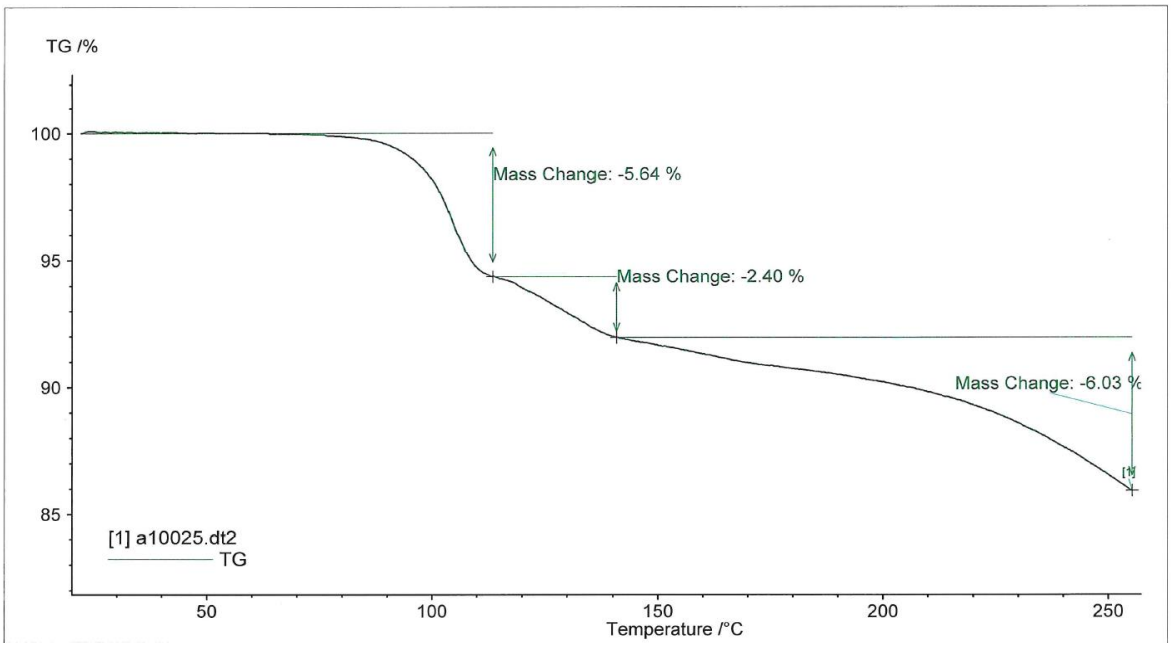

Figure S61. TG-FTIR thermogram of PSZ-FUM-THF, collected with a heating rate of 10 K/min.

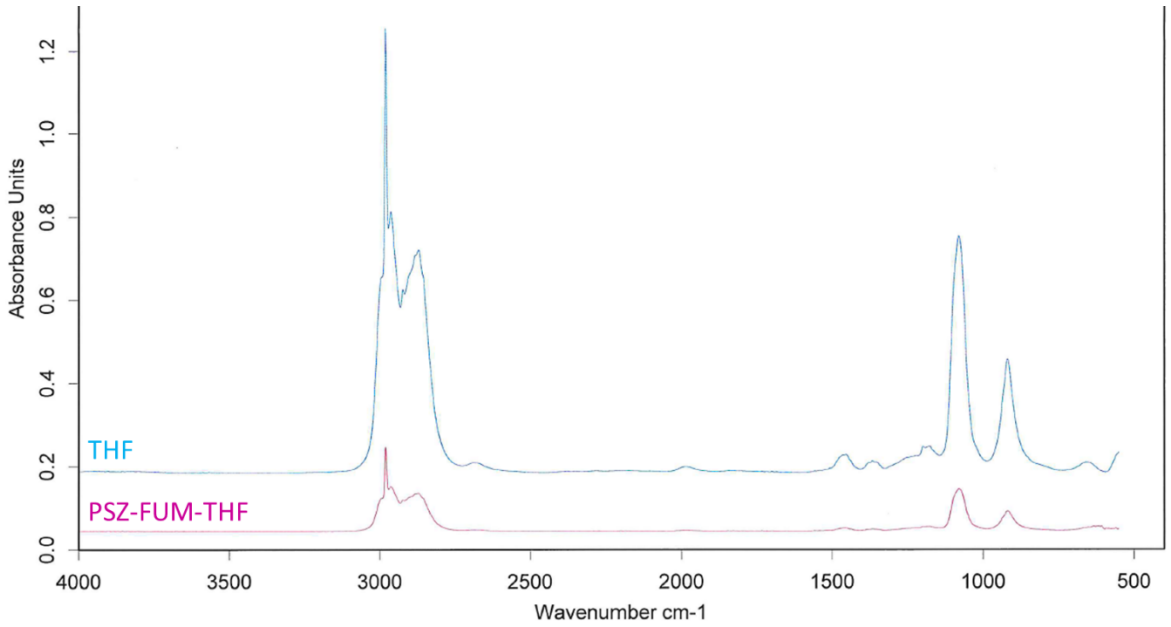

Figure S62. Comparison of the IR spectrum of the gas released at 100°C (red) with the spectrum of THF (blue).

14.2 Raman Spectrum

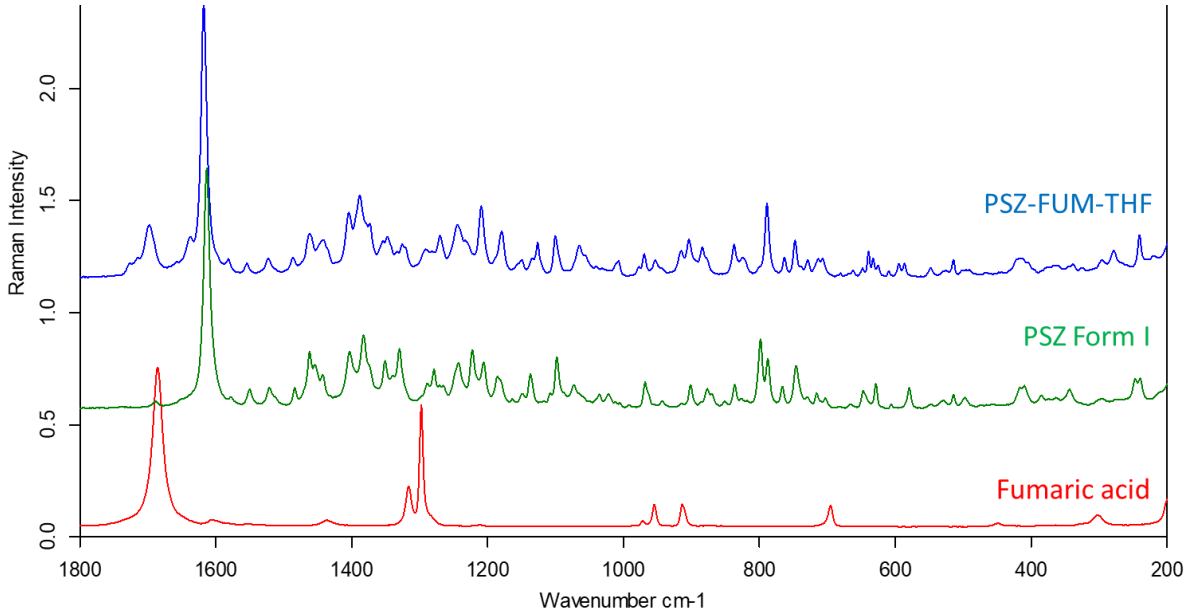

Figure S63. FT-Raman spectra of PSZ Form I, fumaric acid and PSZ-FUM-THF.

14.3 Powder X-ray Diffraction Patterns

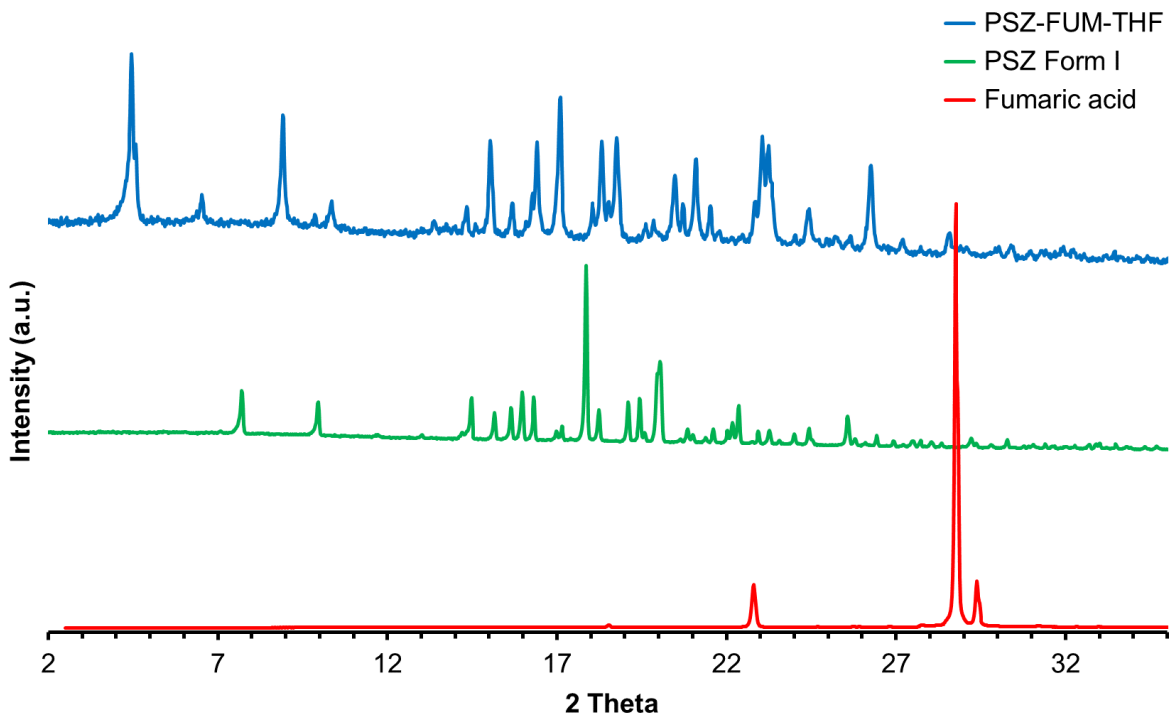

Figure S64. PXRD patterns of PSZ Form I, fumaric acid and PSZ-FUM-THF.

14.4 Proton Nuclear Magnetic Resonance (^{1}H-NMR)

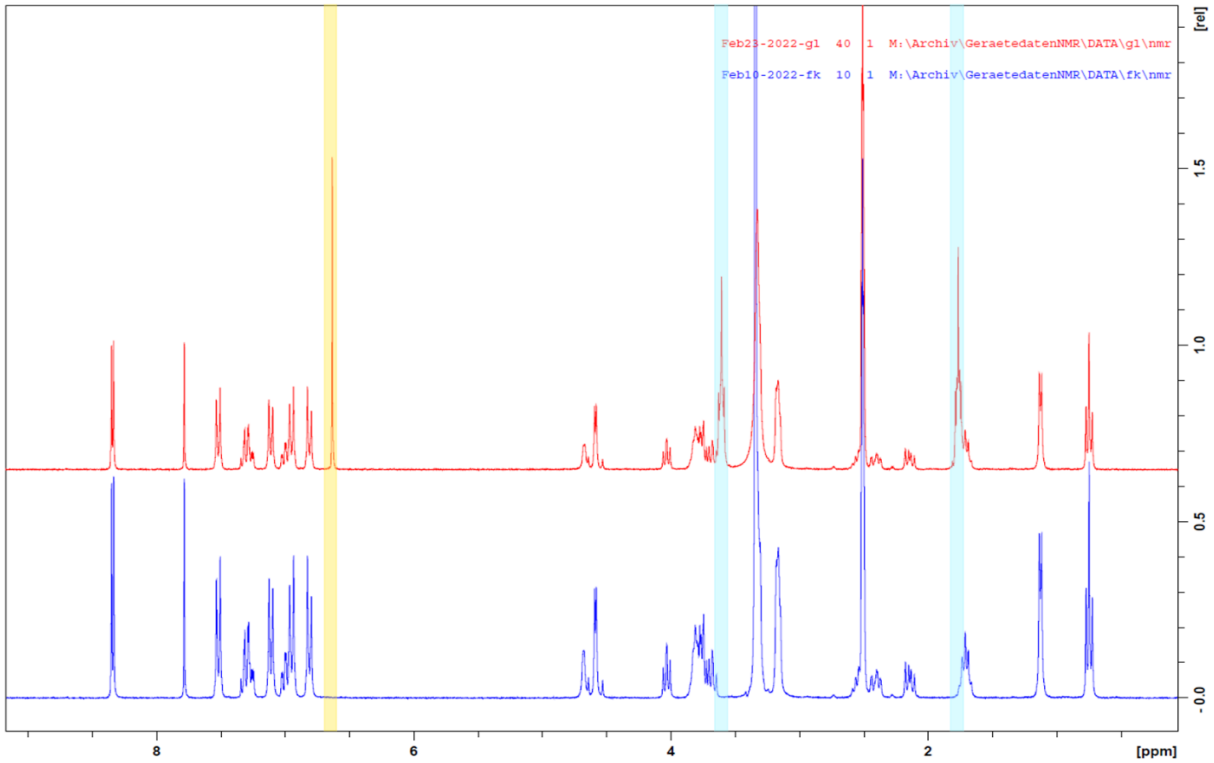

Figure S65. Proton NMR spectra of PSZ-FUM-THF and PSZ collected in deuterated DMSO; chemical shifts reported in ppm. The peaks of the coformer are highlighted in yellow, while the peaks of THF are highlighted in blue.

15 Posaconazole – Fumaric Acid Hydrate Cocrystal (PSZ-FUM-H2O)

15.1 TG-FTIR

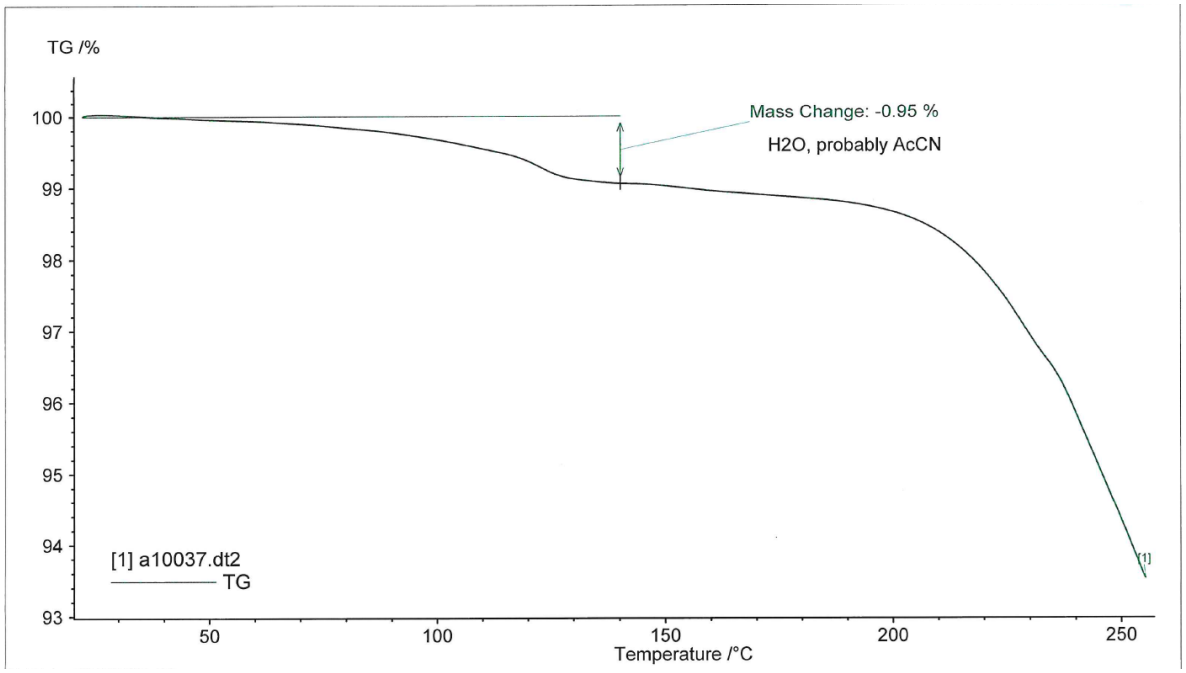

Figure S66. TG-FTIR thermogram of PSZ-FUM-H2O, collected with a heating rate of 10 K/min.

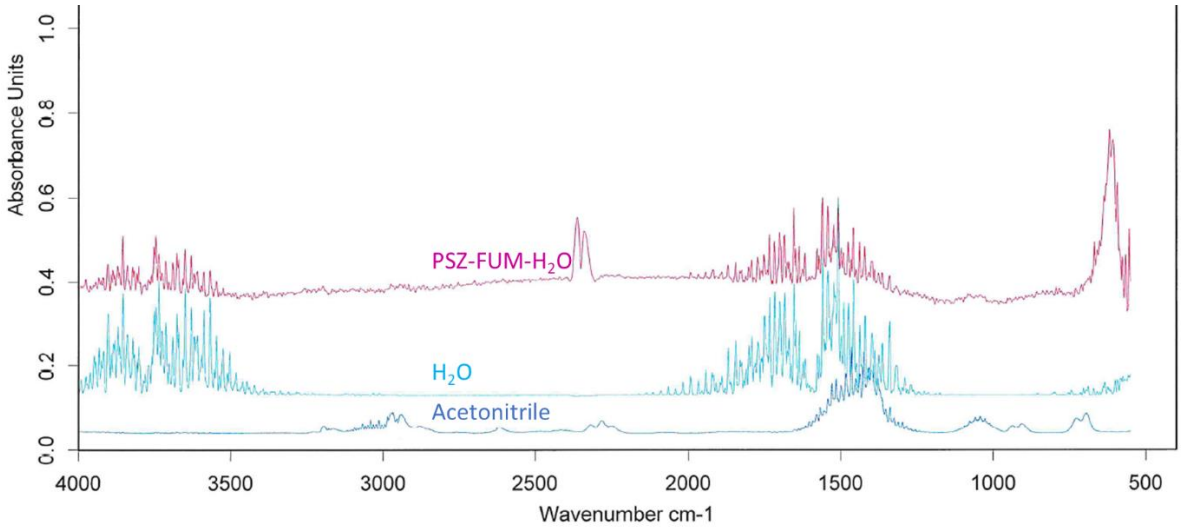

Figure S67. Comparison of the IR spectrum of the gas released at 100°C (red) with the spectrum of H_2O and acetonitrile.

15.2 Raman Spectrum

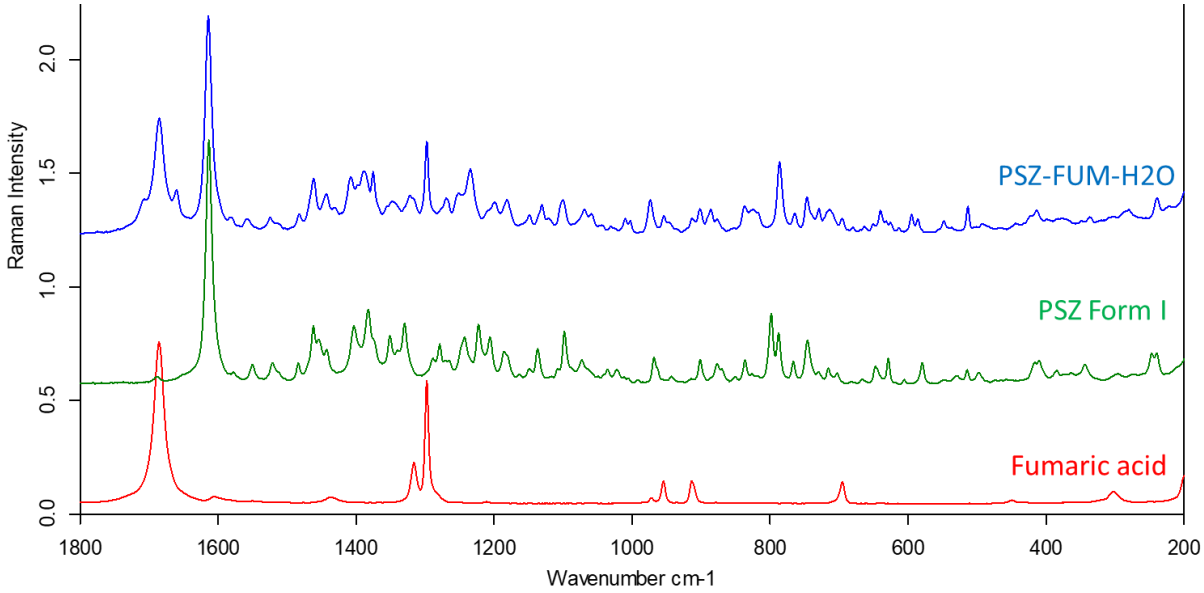

Figure S68. FT-Raman spectra of PSZ Form I, fumaric acid and PSZ-FUM-H2O.

15.3 Powder X-ray Diffraction Patterns

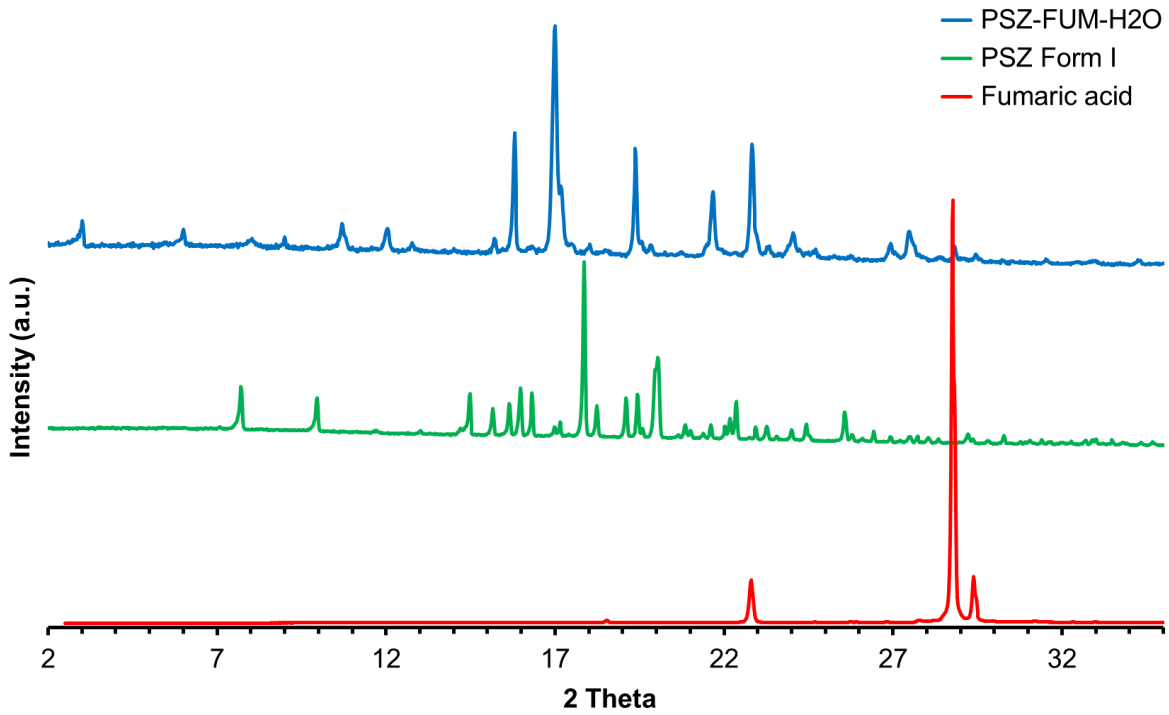

Figure S69. PXRD patterns of PSZ Form I, fumaric acid and PSZ-FUM-H2O.

15.4 Proton Nuclear Magnetic Resonance (^{1}H-NMR)

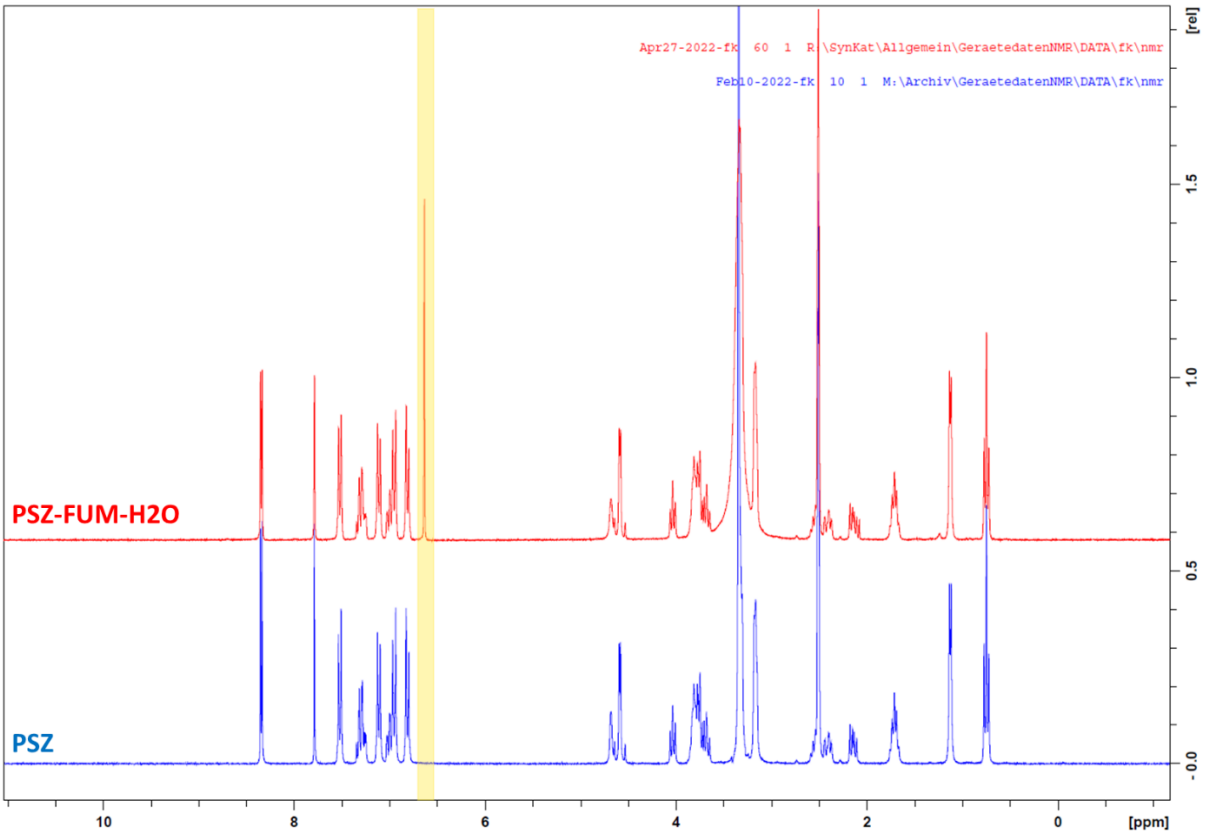

Figure S70. Proton NMR spectra of PSZ-FUM-H2O and PSZ collected in deuterated DMSO; chemical shifts reported in ppm. The peaks of the coformer are highlighted in yellow.

16 Posaconazole – 3,4-Dihydroxybenzoic Acid Hydrate Cocrystal (PSZ-DHB-H2O)

16.1 TG-FTIR

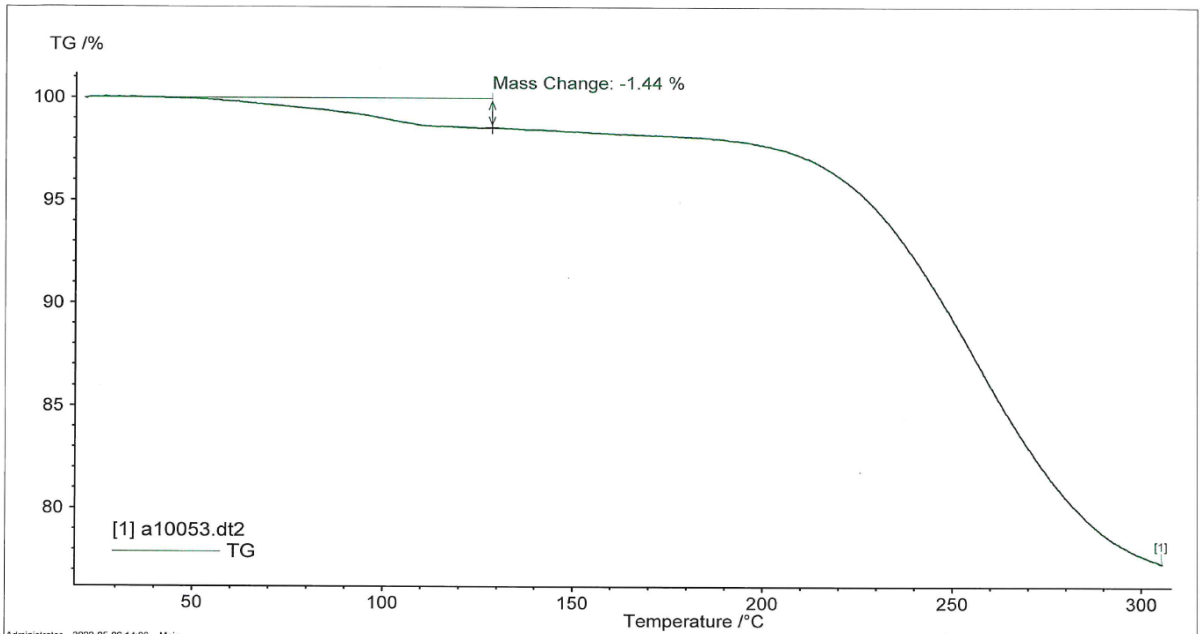

Figure S71. TG-FTIR thermogram of PSZ-DHB-H2O, collected with a heating rate of 10 K/min.

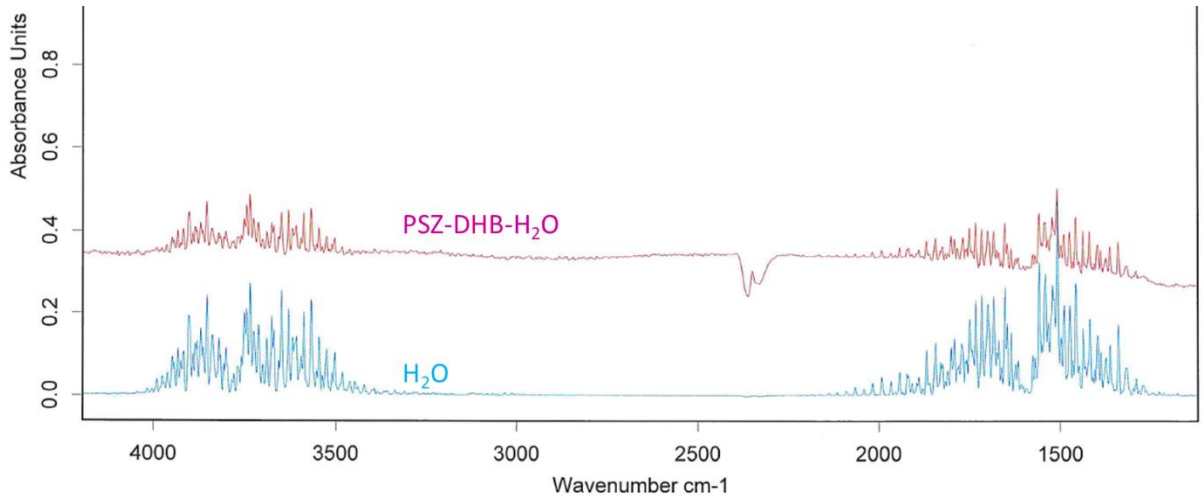

Figure S72. Comparison of the IR spectrum of the gas released at 90°C (red) with the spectrum of H_2O (blue).

16.2 Raman Spectrum

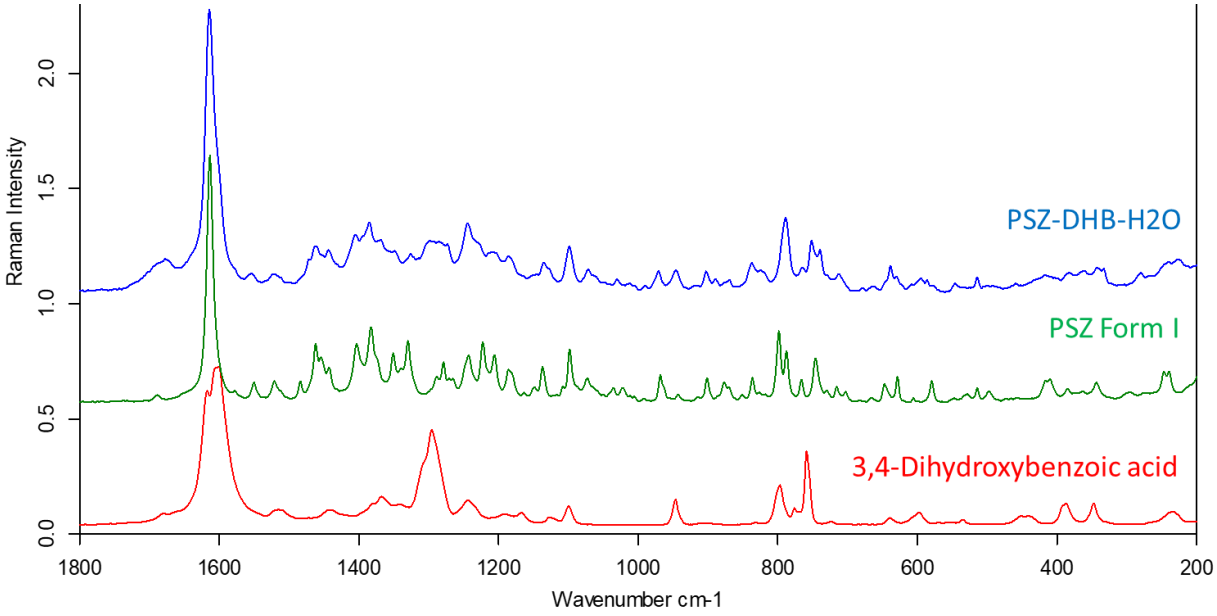

Figure S73. FT-Raman spectra of PSZ Form I, 3,4-dihydroxybenzoic acid and PSZ-DHB-H2O.

16.3 Powder X-ray Diffraction Patterns

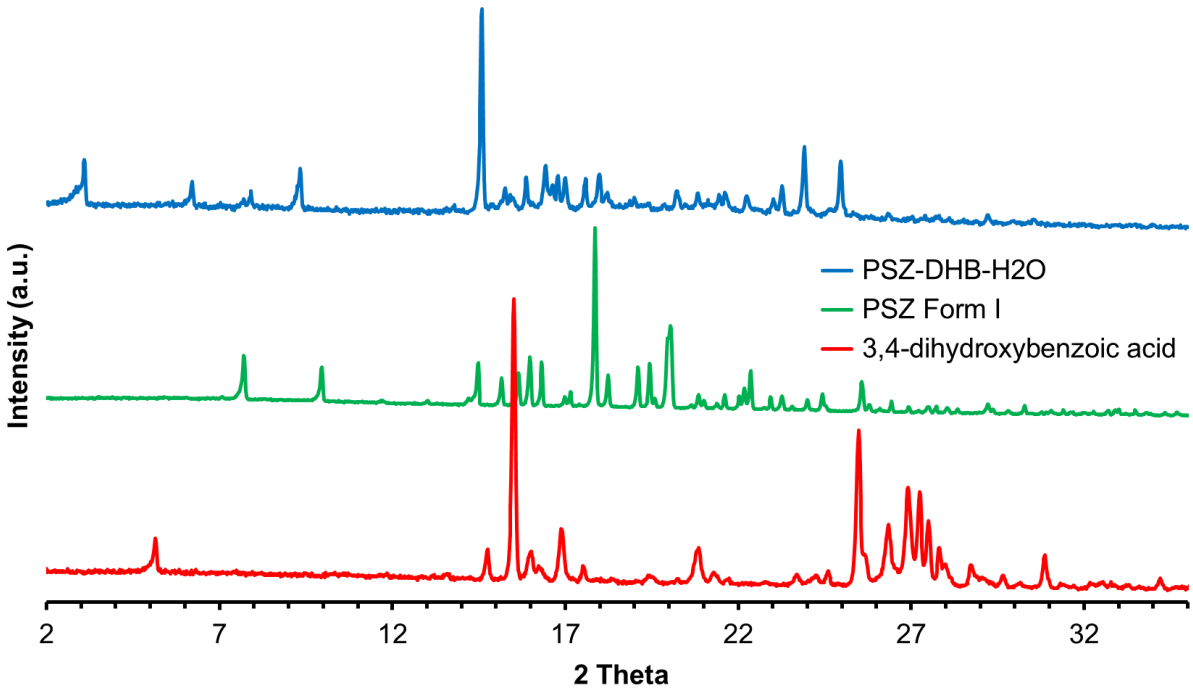

Figure S74. PXRD patterns of PSZ Form I, 3,4-dihydroxybenzoic acid and PSZ-DHB-H2O.

16.4 Proton Nuclear Magnetic Resonance (^{1}H-NMR)

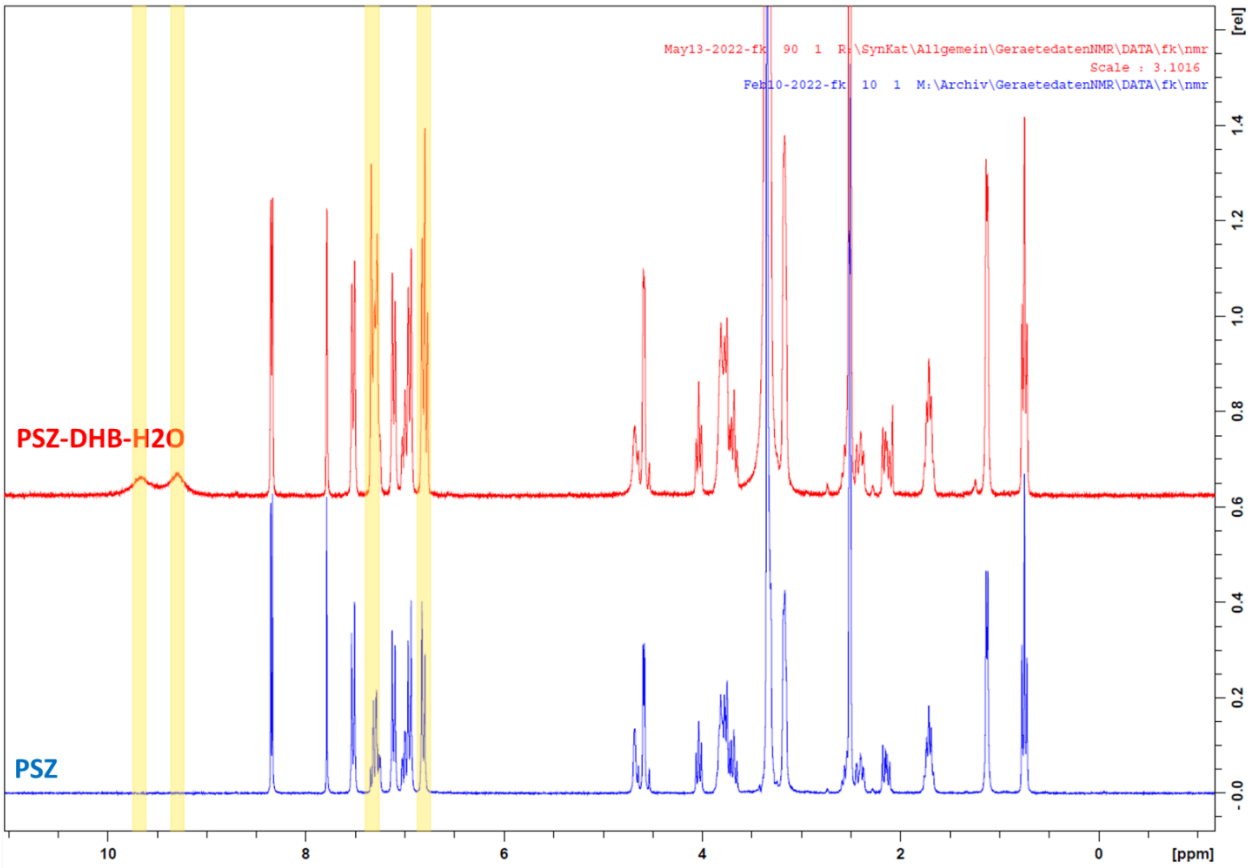

Figure S75. Proton NMR spectra of PSZ-DHB-H2O and PSZ collected in deuterated DMSO; chemical shifts reported in ppm. The peaks of the coformer are highlighted in yellow.

17 Posaconazole-Oxalic acid Complex

17.1.1 Powder X-ray Diffraction pattern

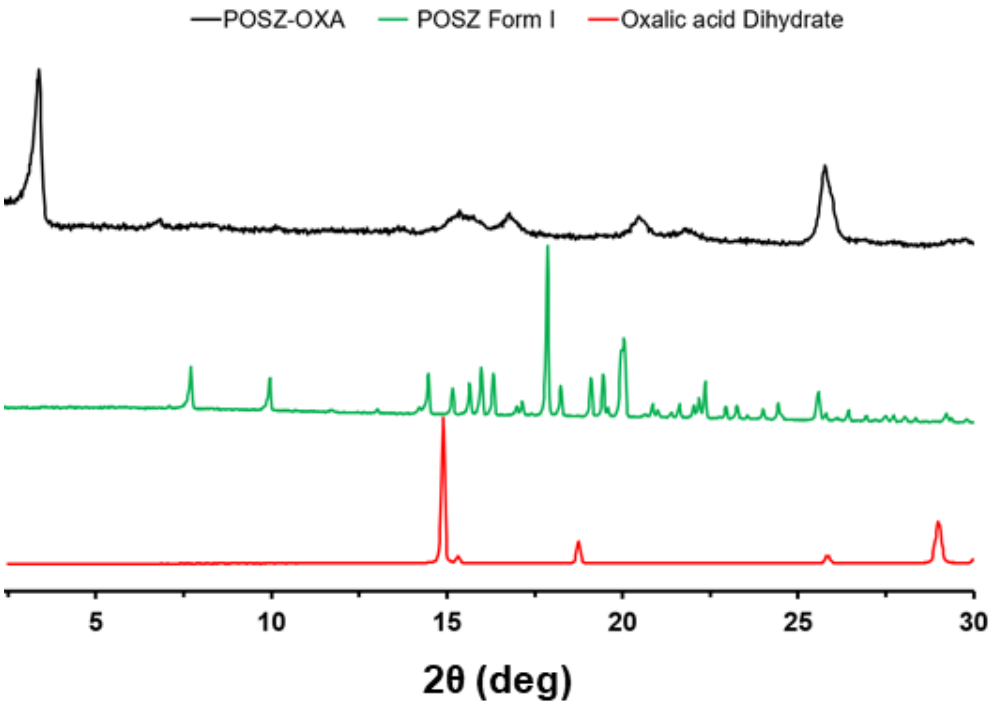

Figure S76. Experimental PXRD patterns of Posaconazole (PSZ Form I), oxalic acid dihydrate and the new solid form (POSZ-OXA) obtained with LAG and RC experiments.

18 Computational Tools Comparison

18.1 Hydrogen Bond Propensity

Table S3. HBP coformer ranking according to multicomponent score, area under ROC reported for the fitted model and comparison with the experimental results. Positive cocrystallization results are reported in green (v) while negative results are reported in blue (x).

Coformer	HBP prediction			Experimental cocrystal
	HBP ranking	multi-component score	Area under the ROC curve	
Maltol	1	0.127	0.815	x
3,4-Dihydroxybenzoic acid	2	0.119	0.833	v
4-Aminobenzoic acid	3	0.116	0.870	v
Salicylic acid	4	0.108	0.833	v

Vanillic acid	5	0.082	0.837	x
Pyridoxine	6	0.079	0.789	x
Ferulic acid	7	0.076	0.837	v
1-Hydroxy-2-naphtoic acid	8	0.075	0.833	v
Vanillin	9	0.071	0.834	x
Nicotinamide	10	0.060	0.837	x
Xylitol	11	0.053	0.834	x
D-Mannitol	12	0.050	0.835	x
trans-Aconitic acid	13	0.050	0.864	x
Maleic acid	14	0.043	0.865	v
Fumaric acid	15	0.042	0.864	v
Adipic acid	16	0.040	0.865	v
L-Proline	17	0.039	0.859	x
Succinic acid	18	0.036	0.865	v
Nicotinic acid	19	0.032	0.866	x
L-Lactic acid	20	0.027	0.864	v
L-Malic acid	21	0.016	0.864	v
Gentisic acid	22	0.012	0.871	v
Urea	23	0.012	0.894	x
DL-Tartaric acid	24	0.009	0.863	x
L-Tartaric acid	25	0.009	0.863	x
Citric acid	26	0.007	0.833	v
Benzoic acid	27	-0.022	0.875	x
Oxalic acid	28	-0.156	0.865	x

18.2 Molceular Complmentarity

Table S4. MC coformer ranking based on calculated complementarity score, hit rate percentage and comparison with experimental results. Positive cocrystallization results are reported in green (v) while negative results are reported in blue (x).

Coformer	MC ranking	Complementarity score	Hit rate (%)	Experimental cocrystal
Ferulic acid	1	2.98	30	v
Adipic acid	2	3.11	10	v
1-Hydroxy-2-naphthoic acid	3	3.32	0	v
4-Aminobenzoic acid	4	3.42	0	v
Benzoic acid	5	3.49	0	x
3,4-dihydroxybenzoic acid	6	3.56	0	v
Nicotinamide	7	3.60	0	x
Nicotinic acid	8	3.69	0	x
Fumaric acid	9	3.80	0	v
Vanillin	10	3.84	0	x
Salicylic acid	11	3.88	0	v
Succinic acid	12	3.91	10	v
Maleic acid	13	4.04	0	v
Malic acid	14	4.16	0	v
Gentisic acid	15	4.18	0	v
Citric acid	16	4.20	0	v
Pyridoxine	17	4.28	0	x
Vanillic acid	18	4.41	0	x
Xylitol	19	4.55	0	x
L-proline	20	4.55	0	x

Maltol	21	4.67	0	x
Mannitol	22	4.89	0	x
trans-Aconitic acid	23	4.98	0	x
L-lactic acid	24	5.56	0	v
Oxalic acid	25	5.58	0	x
DL-tartaric acid	26	5.71	0	x
L-tartaric acid	27	5.71	0	x
Urea	28	6.16	0	x

Table S5. Result of molecular complementarity analysis. For each posaconazole conformation the molecular descriptors that fail the complementarity criterion with the coformer are reported: M/L (red), S (blue), S/L (black), FNO (green), D (violet).

Coformer	Posaconazole Conformations									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Salicylic acid	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S
4-aminobenzoic acid	S	S	S	S	M/L, S	M/L, S	M/L, S	M/L, S	S	S, D
trans-aconitic acid	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S, D
Xinafoic acid	S	M/L, S	S	S	M/L, S	M/L, S	M/L, S	M/L, S	S	M/L, S, D
3,4-dihydroxybenzoic acid	S	M/L, S	S	S	M/L, S	M/L, S	M/L, S	M/L, S	S	M/L, S
gentisic acid	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S
Maleic acid	S	S	S	S	M/L, S	M/L, S	M/L, S	M/L, S	S	S
Malic acid	FNO	S, FNO	S/L, FNO	S, FNO	M/L, FNO	M/L, S, FNO	M/L, S, FNO	M/L, S, FNO	FNO	S, FNO
Oxalic acid	M/L, S, FNO	M/L, S, FNO	M/L, S, FNO	M/L, S, FNO	M/L, S, FNO	M/L, S, FNO	M/L, S, FNO	M/L, S, FNO	M/L, S, FNO	M/L, S, FNO
Pyridoxine	M/L	M/L, S	M/L, S/L	M/L, S	M/L	M/L, S	M/L, S/L	M/L, S	M/L	M/L, S, D
Vanillin	M/L, S	M/L, S	M/L	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S
Ferulic acid		S		S	M/L, S	M/L, S	M/L	M/L, S		S

Coformer	Posaconazole Conformations									
	1	2	3	4	5	6	7	8	9	10
Xylitol	S/L	S/L	S/L	S/L	M/L, S/L	M/L, S/L	M/L, S/L	M/L, S, S/L	S/L	S/L
Maltol	M/L, S	M/L, S	M/L	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S, D
Vanillic acid	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S
Nicotinic acid	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S, D
L-lactic acid	M/L, S/L	M/L, S/L	M/L, S/L	M/L, S/L	M/L, S/L	M/L, S, S/L	M/L, S, S/L	M/L, S, S/L	M/L, S/L	M/L, S, S/L
L-proline	M/L, S/L	M/L, S/L	M/L, S/L	M/L, S/L	M/L, S/L	M/L, S/L	M/L, S/L	M/L, S, S/L	M/L, S/L	M/L, S/L, D
	M/L, S/L,	M/L, S/L,	M/L, S/L,	M/L, S/L,	M/L, S/L,	M/L, S/L,	M/L, S/L,	M/L, S/L,	M/L, S/L,	M/L, S/L,
L-tartaric acid	FNO	FNO	FNO	FNO	FNO	FNO	FNO	FNO	FNO	FNO
Adipic acid	S	S		S	S	S	S	S	S	S, S/L
Benzoic acid	S	M/L, S	S	S	M/L, S	M/L, S	M/L, S	M/L, S	S	M/L, S, S/L
Citric acid	S/L, FNO	S/L, FNO	S/L, FNO	S/L, FNO	M/L, S/L, FNO	M/L, FNO	M/L, S/L, FNO	M/L, S/L, FNO	S/L, FNO	M/L, D, FNO
Fumaric acid	S	S	S	S	S	S	S	S	S	S
Mannitol	M/L, S/L	M/L, S/L	M/L, S/L	M/L, S/L	M/L, S/L	M/L, S/L	M/L, S/L	M/L, S/L	M/L, S/L	M/L, S/L
Nicotinamide	S	M/L, S	S	S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S	M/L, S
Succinic acid	S	S		S	S	S	S	S	S	S, S/L

Coformer	Posaconazole Conformations									
	1	2	3	4	5	6	7	8	9	10
Urea	M/L, S, S/L, FNO	M/L, S, FNO	M/L, S, S/L, FNO	M/L, S/L, FNO	M/L, S, S/L, FNO	M/L, S, FNO	M/L, S, S/L, FNO	M/L, S/L, FNO	M/L, S, FNO	M/L, S, D, FNO

Table S6. MC coformer ranking based on average complementarity score. The complementarity score is calculated for each posaconazole conformation and is averaged on the ten conformations in the last column.

Coformer	Posaconazole Conformations										Average
	1	2	3	4	5	6	7	8	9	10	C_{score}
Ferulic acid	2.79	2.79	2.56	2.92	3.18	3.25	3.07	3.18	2.65	3.36	2.98
Adipic acid	2.47	3.12	2.89	2.62	2.96	3.58	3.40	3.40	2.97	3.69	3.11
Xinafoic acid	2.69	3.33	3.10	2.83	3.17	3.79	3.61	3.61	3.19	3.90	3.32
4-Aminobenzoic acid	2.79	3.43	3.20	2.93	3.28	3.89	3.71	3.71	3.29	4.00	3.42
Benzoic acid	2.85	3.50	3.26	2.99	3.34	3.95	3.77	3.77	3.35	4.07	3.49
3,4-dihydroxybenzoic acid	3.25	3.44	3.21	3.38	3.64	3.90	3.72	3.72	3.30	4.01	3.56
Nicotinamide	3.14	3.55	3.32	3.28	3.53	4.01	3.84	3.83	3.41	4.12	3.60
Nicotinic acid	3.06	3.70	3.47	3.20	3.54	4.16	3.98	3.98	3.56	4.28	3.69

Coformer	Posaconazole Conformations										Average
	1	2	3	4	5	6	7	8	9	10	C_{score}
Ferulic acid	2.79	2.79	2.56	2.92	3.18	3.25	3.07	3.18	2.65	3.36	2.98
Fumaric acid	3.39	3.73	3.50	3.52	3.78	4.19	4.01	4.01	3.59	4.30	3.80
Vanillin	3.51	3.73	3.50	3.63	3.90	4.20	4.02	4.01	3.59	4.31	3.84
Salicylic acid	3.45	3.82	3.58	3.58	3.83	4.27	4.09	4.09	3.66	4.39	3.88
Succinic acid	3.27	3.92	3.69	3.42	3.76	4.38	4.20	4.20	3.77	4.49	3.91
Maleic acid	3.98	3.79	3.55	4.10	4.36	4.24	4.06	4.36	3.64	4.36	4.04
Malic acid	3.91	4.03	3.79	4.03	4.29	4.48	4.31	4.30	3.88	4.60	4.16
Gentisic acid	3.82	4.08	3.85	3.94	4.20	4.54	4.36	4.36	3.94	4.66	4.18
Citric acid	3.58	4.21	3.98	3.71	4.05	4.67	4.49	4.49	4.07	4.78	4.20
Pyridoxine	3.65	4.29	4.06	3.79	4.13	4.75	4.57	4.57	4.14	4.86	4.28
Vanillic acid	4.00	4.34	4.11	4.13	4.39	4.80	4.62	4.62	4.20	4.91	4.41
Xylitol	4.66	4.34	4.10	4.79	5.05	4.86	4.45	5.05	4.28	3.89	4.55
L-proline	3.92	4.56	4.33	4.06	4.40	5.02	4.84	4.84	4.41	5.13	4.55
Maltol	4.06	4.68	4.45	4.18	4.52	5.14	4.96	4.95	4.53	5.25	4.67
Mannitol	4.89	4.56	4.33	5.01	5.28	5.09	4.83	5.28	4.51	5.11	4.89

Coformer	Posaconazole Conformations										Average
	1	2	3	4	5	6	7	8	9	10	C_{score}
Ferulic acid	2.79	2.79	2.56	2.92	3.18	3.25	3.07	3.18	2.65	3.36	2.98
trans-Aconitic acid	4.35	4.99	4.76	4.49	4.83	5.45	5.27	5.27	4.84	5.56	4.98
L-Lactic acid	5.13	5.49	5.26	5.27	5.52	5.95	5.77	5.77	5.34	6.06	5.56
Oxalic acid	5.17	5.51	5.28	5.30	5.55	5.97	5.79	5.79	5.36	6.08	5.58
L-Tartaric acid	5.46	5.58	5.34	5.58	5.84	6.03	5.85	5.85	5.43	6.15	5.71
Urea	5.53	6.17	5.94	5.67	6.01	6.63	6.45	6.45	6.02	6.74	6.16