Electronic Supplementary Information

Development of New Multicomponent Crystals of the Antifungal Drug Tioconazole and the Assessment of their Biopharmaceutical Attributes

Avinash Madhesiya,[a] Sibananda G. Dash,[a,c] Princi Gupta,[a] Abdul Akhir,[b] Deepanshi Saxena,[b] Rahul Maitra,[b] Sidharth Chopra[b] and Tejender S. Thakur[a,c,*]

[a]Biochemistry and Structural Biology Division, CSIR-Central Drug Research Institute, Lucknow 226 031 INDIA

[b]Molecular Microbiology and Immunology Division, CSIR-Central Drug Research Institute, Lucknow 226 031 INDIA

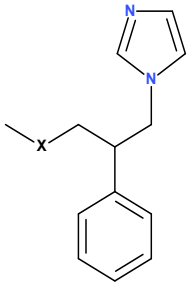
[c]Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201 002, INDIA

E-mail: tejender.thakur@cdri.res.in

Table of Contents

Cambridge structural database (CSD version 5.44, April 2023) analysis of known multicomponent crystalline forms of azole antifungals in CSD.

Search Criteria:



Scheme S1 'Azole scaffold' used in CSD search

- Structures with a given scaffold 'and' number of residues ≥1
- 3D coordinates determined
- Only organic

Table S1 Summary of Cambridge structural database search results.

Azole drug/derivative	Coformer	Refcode	Reference/DOI
Econazole	HBr	GAPSOF	10.3891/acta.chem.scand.41a-0496
Econazole	Fumaric acid	TEJRIN	10.1016/j.molstruc.2022.133183
Econazole	Maleic acid	TEJROT	10.1016/j.molstruc.2022.133183
Miconazole	HNO_3	ETEWUV	10.1107/S1600536804003058
Miconazole	H_2O	MICONZ, MICONZ01 MICONZ02 PAVQAI	10.1002/bscb.19790880501 10.1039/D1CP00956G 10.1107/S2053229622004909 10.1021/acs.cgd.2c00112
Miconazole	C_2H_5OH	PAVPOV PAVPOV01	10.1021/acs.cgd.2c00112 10.1107/S2053229622004909
Miconazole	CH_3OH	PAVPUB	10.1021/acs.cgd.2c00112
Miconazole	H_2O_2	UDUROD	10.1039/C8CC04530E
Miconazole	CH_3SO_4	WUFJEP	10.1021/acs.molpharmaceut.7b00694
Miconazole	Succinic acid	EVATAZ	10.1039/D1CP00956G
Miconazole	Fumaric acid	EVATED	10.1039/D1CP00956G
Miconazole	Fumaric acid	EVATIH	10.1039/D1CP00956G
Miconazole	Adipic acid	EVATON	10.1039/D1CP00956G
Miconazole derivative	HCl	TONTEY	10.1016/j.ejmech.2019.06.083
Ketoconazole metabolite	HCl	CUTDIH	10.1016/j.molstruc.2020.128737
Ketoconazole epimer	CH3OH	MEBJOT	10.1107/S1600536805041048
Ketoconazole	Oxalic acid	YINVUO	10.1021/cg400638g
Ketoconazole	Fumaric acid	YINWAV	10.1021/cg400638g
Ketoconazole	Succinic acid	YINWEZ	10.1021/cg400638g
Ketoconazole	Hexanedioic acid	YINWID	10.1021/cg400638g
Ketoconazole	2,4-dihydroxy benzoic acid	RADXED	10.1021/acs.cgd.0c01014
Ketoconazole	2,5-dihydroxy benzoic acid	RADXIH	10.1021/acs.cgd.0c01014
Ketoconazole	3,4-dihydroxy benzoic acid	RADXON	10.1021/acs.cgd.0c01014
Ketoconazole	3,4,5-trihydroxy benzoic acid	RAXXUT	10.1021/acs.cgd.0c01014
Ketoconazole	3-(4-hydroxyphenyl)prop-2-enoic acid	RADYAA	10.1021/acs.cgd.0c01014
Ketoconazole	4-aminobenzoic acid	IRIBET, IRIBET01	10.1021/acs.molpharmaceut.9b01178
Tioconazole	Malonic acid	SAPBAQ	10.1021/acs.cgd.1c01139
Tioconazole	Fumaric acid	SAPBEU	10.1021/acs.cgd.1c01139
Tioconazole	DL-tartaric acid	SAPBIY	10.1021/acs.cgd.1c01139
Sulconazole	HNO_3	LINQII	Bull. Korean Chem. Soc. 1997, 18, 14

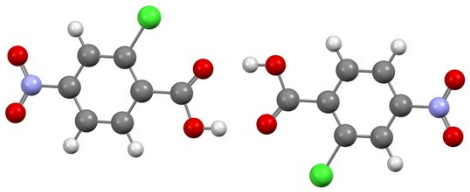
Table S2 Site pair interaction energy differences ($\Delta E^1_{SitePair}$ in kJ/mol) obtained for tioconazole complexes with various coformers.

Sr No.	Coformer	$\Delta E^1_{SitePair}$
1	**2-Chloro-4-nitrobenzoic acid**	**-14.30**
2	Salicylic acid	-13.30
3	2,5-Dihydroxybenzoic acid	-9.94
4	2,4-Dihydroxybenzoic acid	-9.89
5	Mandelic acid	-9.00
6	Isonicotinic acid	-8.90
7	Benzoic acid	-8.10
8	**Nicotinic acid**	**-7.29**
9	4-Hydroxybenzoic acid	-7.20
10	4-Aminosalicylic acid	-6.55
11	Hydroquinone	-5.64
12	Gallic acid	-5.20
13	**Fumaric acid**	**-5.10**
14	**Terephthalic acid**	**-4.90**
15	Succinic acid	-4.00
16	**Malonic acid**	**-3.84**
17	**Oxalic acid**	**-3.80**
18	Salicylamide	-2.30
19	Caffeine	-2.20
20	5-Fluorouracil	-2.20
21	2-aminopyridine	-1.90
22	Maleic acid	-1.70
23	Malic acid	-1.40
24	Acetamide	-1.35
25	Adipic acid	-1.00
26	Picolinamide	-1.00
27	2-Aminopyrimidine	-0.50
28	Ascorbic acid	-0.12
29	Urea	-0.10
30	Pyrazinamide	0.60
31	4-Aminobenzamide	1.20
32	Nicotinamide	1.30
33	3,4-Dihydroxybenzoic acid	1.41
34	Isonicotinamide	1.50
35	Glutaric acid	1.80
36	Citric acid	2.00
37	**Tartaric acid**	**4.20**
38	Benzamide	4.90
39	*trans*-Aconitic acid	6.25
40	Mucic acid	10.80

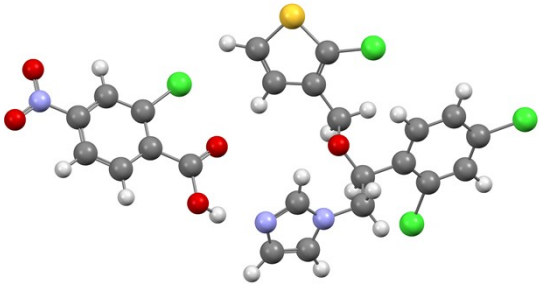
[#] Multicomponent crystals observed in the experimental screening are boldfaced.

Table S3 The secondary site pair interaction energy differences ($\Delta E^2_{SitePair}$ in kJ mol^{-1}) for potential coformers.

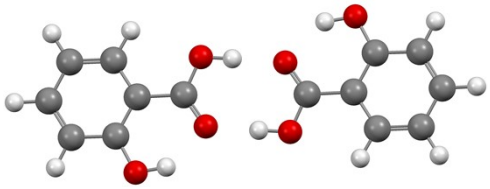
Sr No.	Coformer[#]	$E^2_{sitepair}$ (Homo pair)	$E^2_{sitepair}$ (Hetero pair)	$\Delta E^2_{sitepair}$ (Hetero-Homo)
1	**2-Chloro-4-nitrobenzoic acid**	**–13.00**	**–17.50**	**–4.50**
2	Salicylic acid	–12.47	–19.80	–7.33
3	2,5-Dihydroxybenzoic acid	–30.97	–30.90	0.07
4	2,4-Dihydroxybenzoic acid	–27.80	–28.40	–0.60
5	Mandelic acid	–44.28	–39.80	4.48
6	Isonicotinic acid	–40.50	–18.40	22.10
7	Benzoic acid	–7.53	–21.20	–13.67
8	**Nicotinic acid**	**–39.02**	**–18.50**	**20.52**
9	4-hydroxybenzoic acid	–28.20	–35.30	–7.10
10	4-aminosalicylic acid	–25.40	–26.90	–1.50
11	Hydroquinone	–42.90	–36.30	6.60
12	Gallic acid	–35.82	–49.60	–13.78
13	**Fumaric acid**	**–37.61**	**–33.80**	**3.81**
14	**Terephthalic acid**	**–35.85**	**–33.80**	**2.05**
15	Succinic acid	–34.98	–34.80	0.18
16	**Malonic acid**	**–39.15**	**–35.40**	**3.75**
17	**Oxalic acid**	**–43.92**	**–50.80**	**–6.88**
18	Salicylamide	–28.81	–26.90	1.91
19	Caffeine	–25.97	–25.40	0.57
20	5-Fluorouracil	–57.80	–43.70	14.10
21	2-aminopyridine	-18.30	-21.90	-3.60
22	Maleic acid	-77.04	-43.10	33.94
23	Malic acid	-35.62	-37.70	-2.08
24	Acetamide	-38.60	-31.00	7.60
25	Adipic acid	-38.20	-37.70	0.50
26	Picolinamide	-58.84	-14.50	44.34
27	2-Aminopyrimidine	-23.04	-20.80	2.24
28	L-Ascorbic acid	-57.10	-48.00	9.10
29	Urea	-70.60	-32.80	37.80
30	Pyrazinamide	-19.94	-23.10	-3.16
31	4-Aminobenzamide	-38.33	-34.20	4.13
32	Nicotinamide	-33.53	-31.20	2.33
33	3,4-Dihydroxybenzoic acid	-38.60	-33.80	4.80
34	Isonicotinamide	-37.99	-33.10	4.89
35	Glutaric acid	-42.04	-42.10	-0.06
36	Citric acid	-43.94	-58.10	-14.16
37	**Tartaric acid**	**–60.96**	**–75.40**	**–14.44**
38	Benzamide	-31.95	-27.00	4.95
39	*trans*-Acotinic acid	-36.46	-47.60	-11.14
40	Mucic acid	-60.97	-50.10	10.87
41	Tioconazole	–13.21	–13.21	0.00



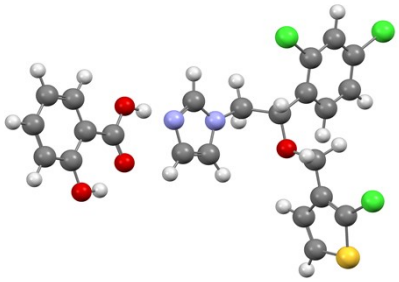
2-Chloro-4-nitrobenzoic acid (CNBA)



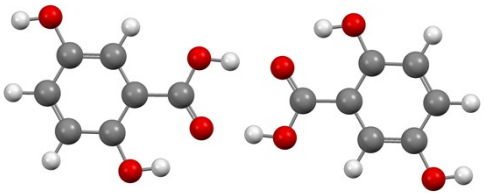
TCZ-CNBA



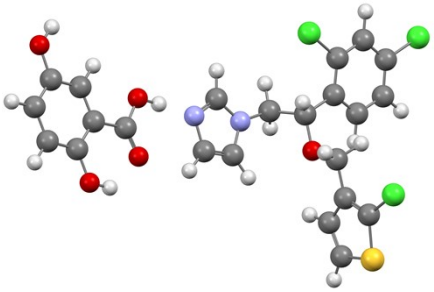
Salicylic acid



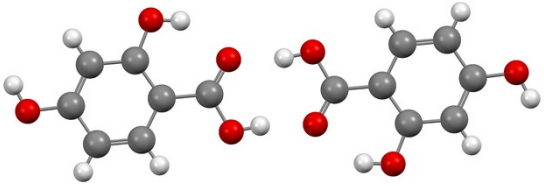
TCZ-Salicylic acid



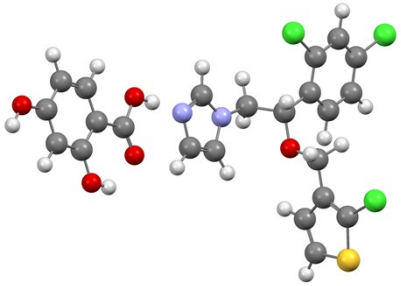
2,5-Dihydroxybenzoic acid (25DHBA)



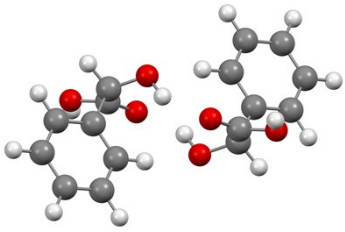
TCZ-25DHBA



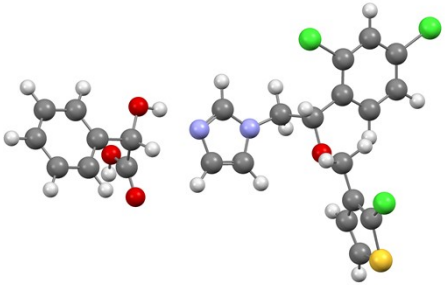
2,4-Dihydroxybenzoic acid (24DHBA)



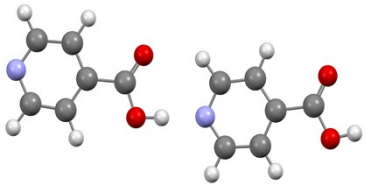
TCZ-24DHBA



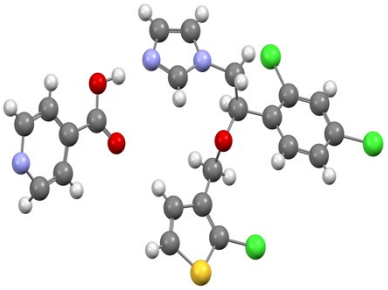
Mandelic Acid



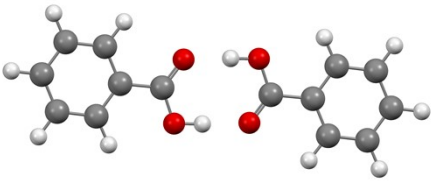
TCZ-Mandelic Acid



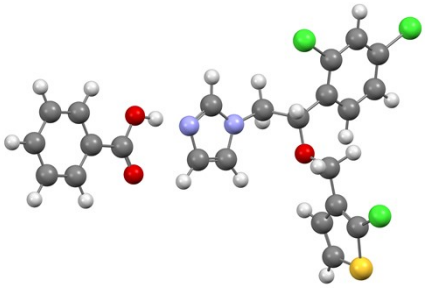
Isonicotinic acid



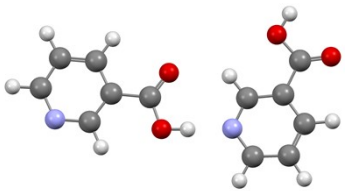
TCZ-Isonicotinic acid



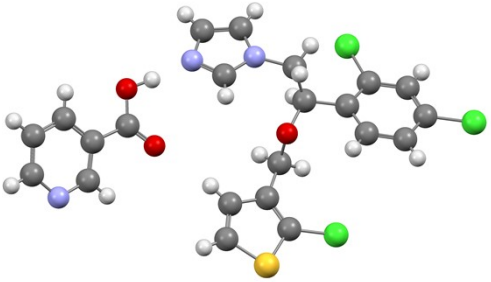
Benzoic acid



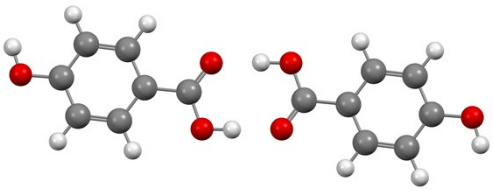
TCZ-Benzoic acid



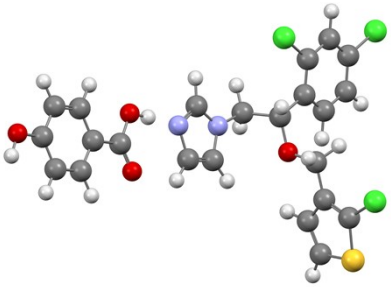
Nicotinic acid



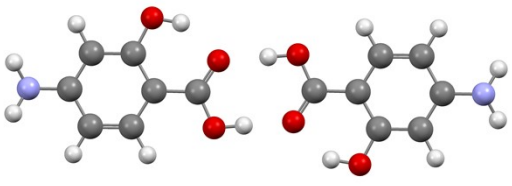
TCZ-Nicotinic acid



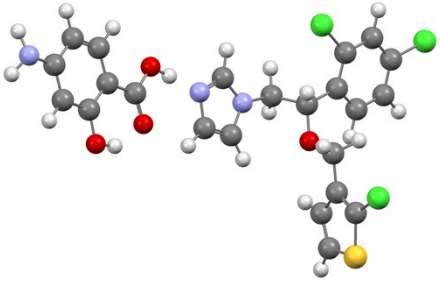
4-Hydroxybenzoic acid



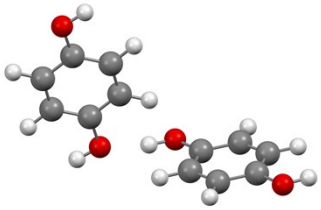
TCZ-4-Hydroxybenzoic acid



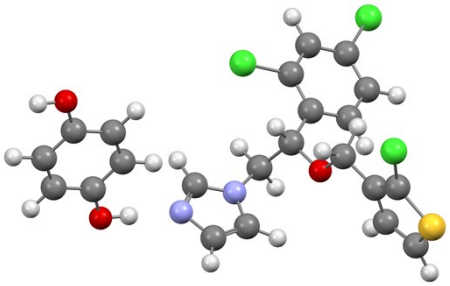
4-Aminosalicylic acid



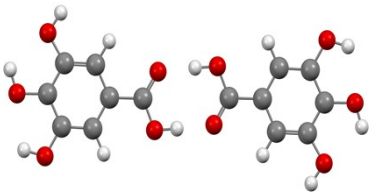
TCZ-4-Aminosalicylic acid



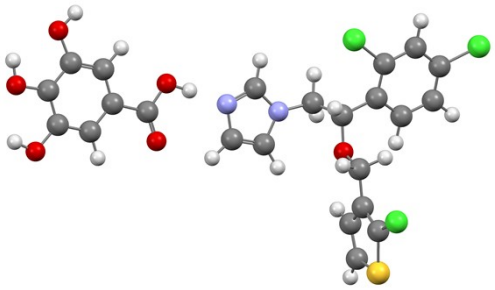
Hydroquinone



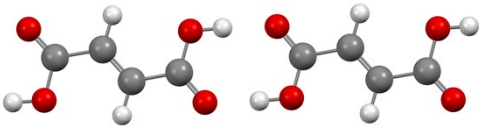
TCZ-Hydroquinone



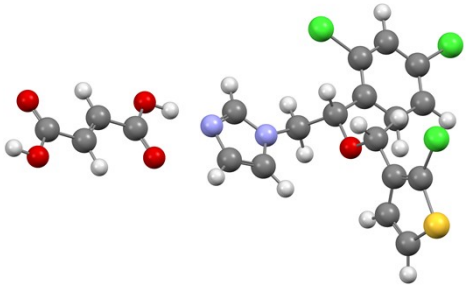
Gallic acid



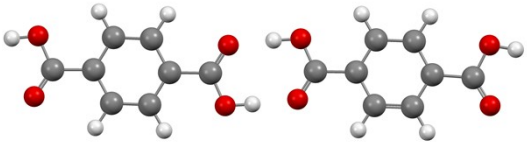
TCZ-Gallic acid



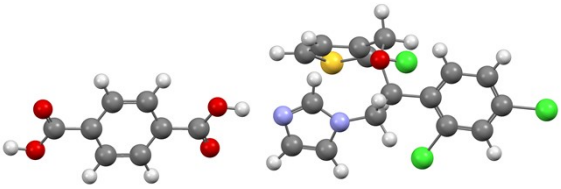
Fumaric acid



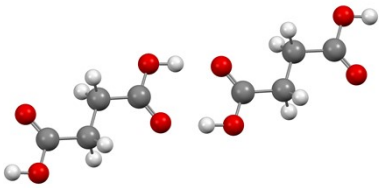
TCZ-Fumaric acid



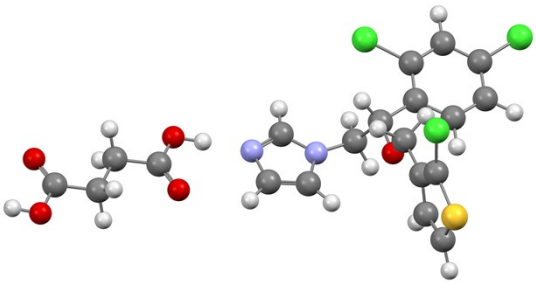
Terephthalic acid



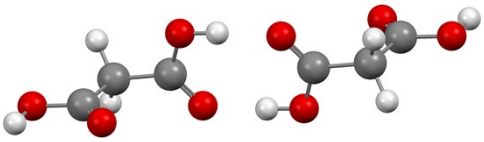
TCZ-Terephthalic acid



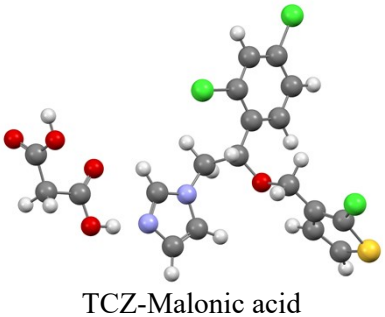
Succinic acid



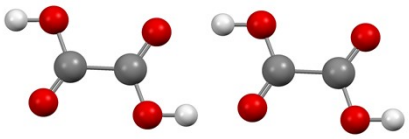
TCZ-Succinic acid



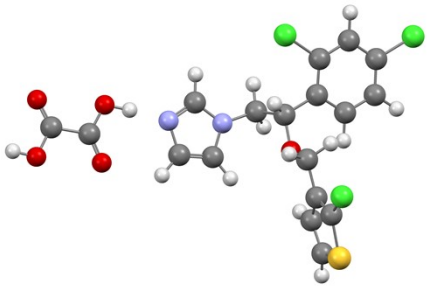
Malonic acid



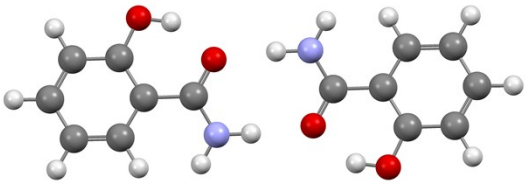
TCZ-Malonic acid



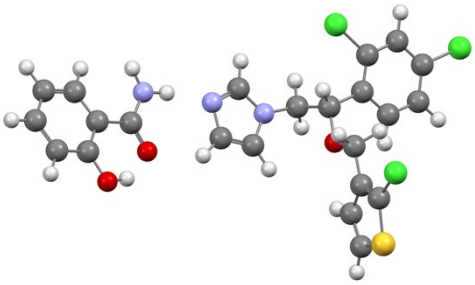
Oxalic acid



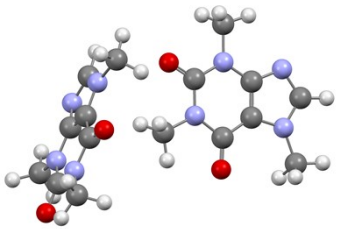
TCZ-Oxalic acid



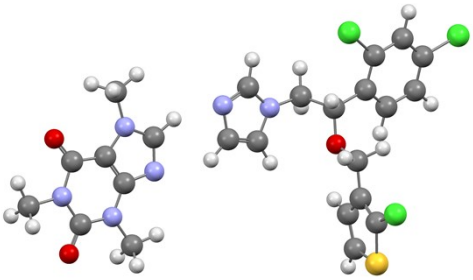
Salicylamide



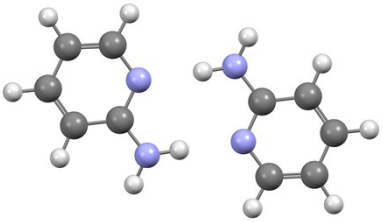
TCZ-Salicylamide



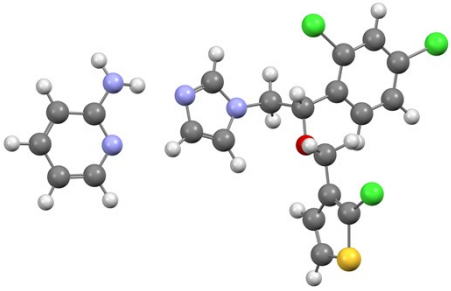
Caffeine



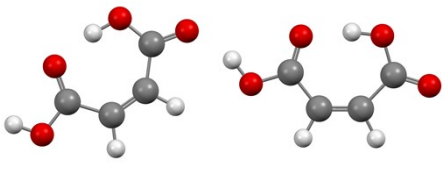
TCZ-Caffeine



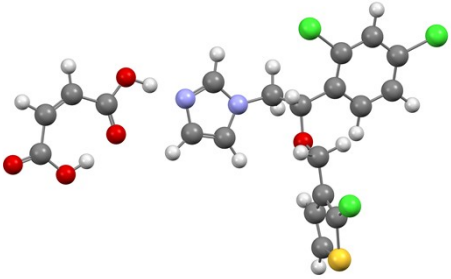
2-Aminopyridine



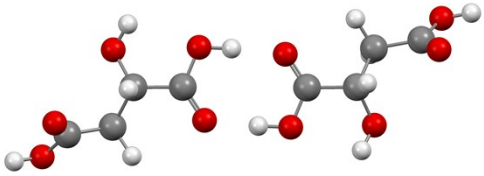
TCZ-2-Aminopyridine



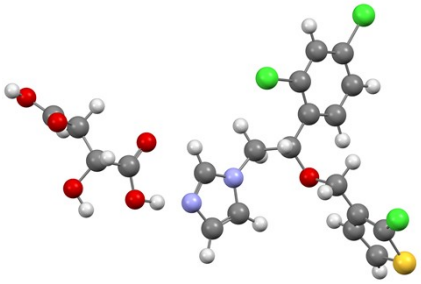
Maleic acid



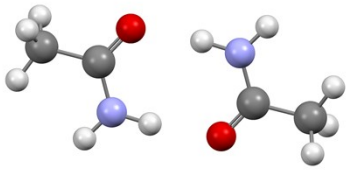
TCZ-Maleic acid



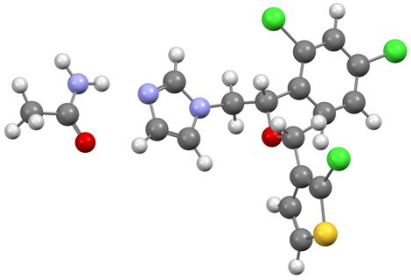
Malic acid



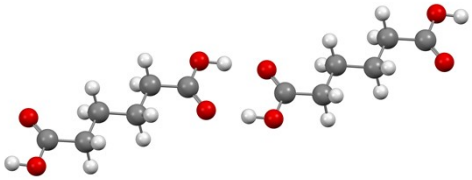
TCZ-malic acid



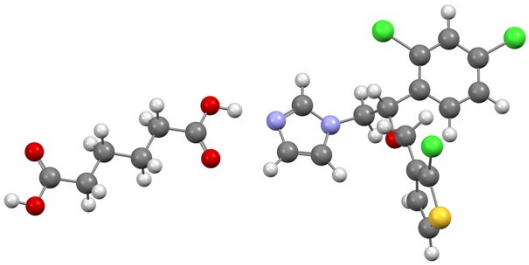
Acetamide



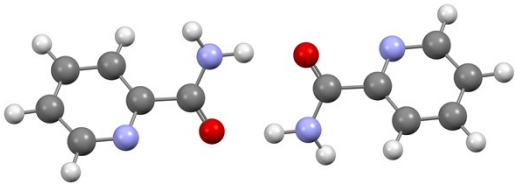
TCZ-Acetamide



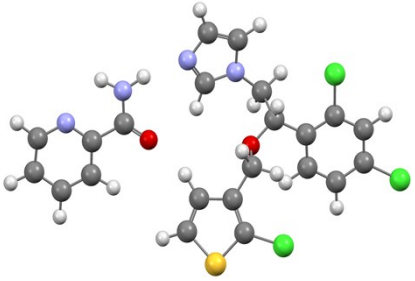
Adipic acid



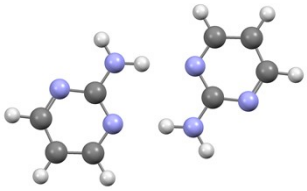
TCZ-Adipic acid



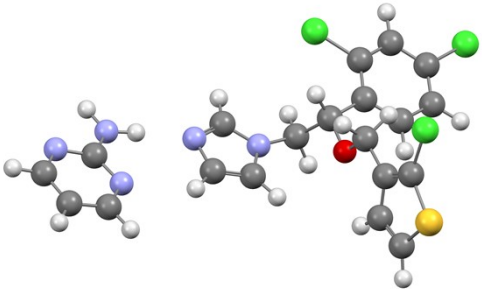
Picolinamide



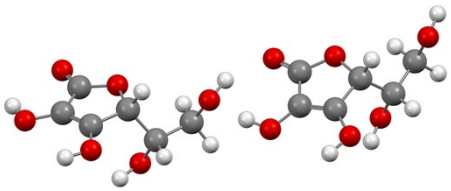
TCZ-Piconilamide



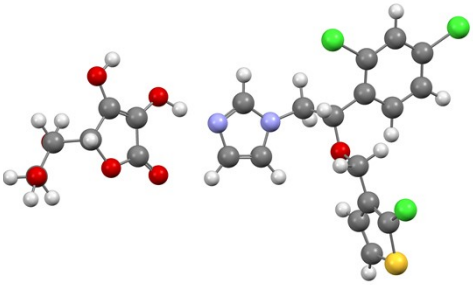
2-Aminopyrimidine



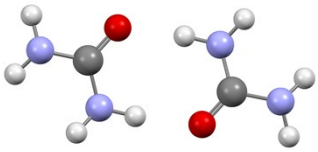
TCZ-2-Aminopyrimidine



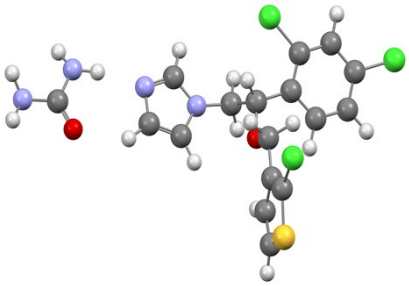
Ascorbic acid



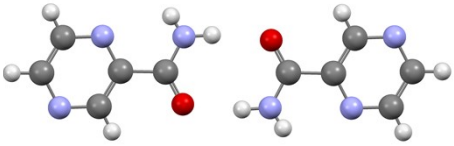
TCZ-Ascorbic acid



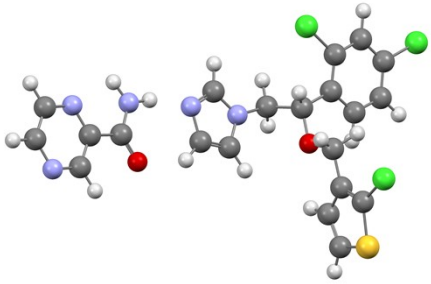
Urea



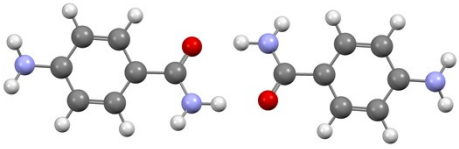
TCZ-Urea



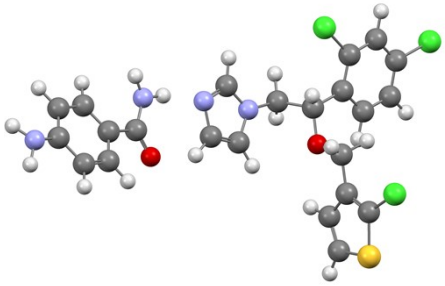
Pyrazinamide



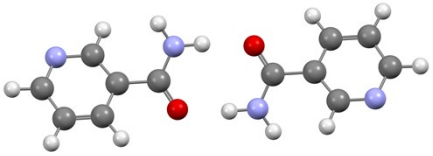
TCZ-Pyrazinamide



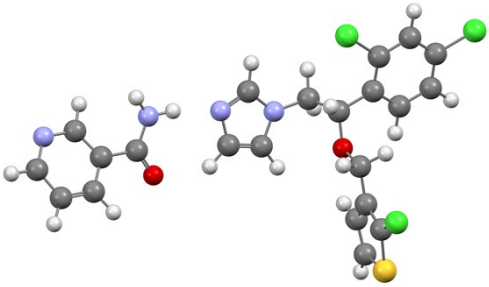
4-Aminobenzamide



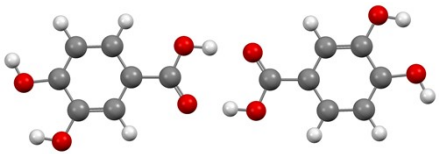
TCZ-4-Aminobenzamide



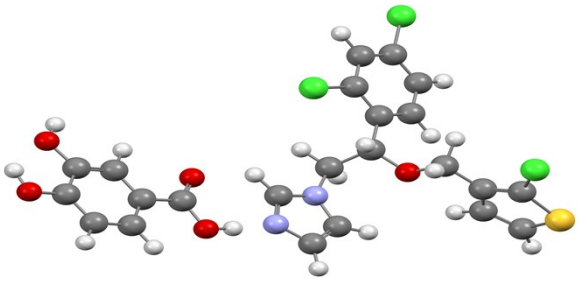
Nicotinamide



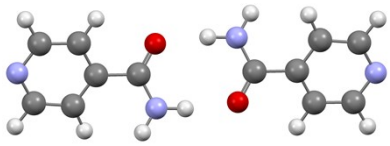
TCZ-Nicotinamide



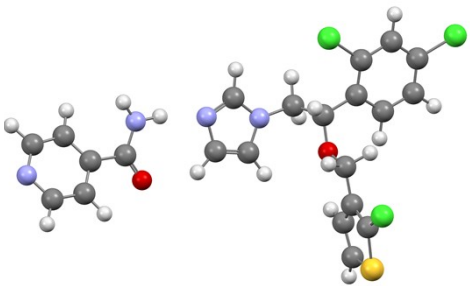
3,4-Dihydroxybenzoic acid (34DHBA))



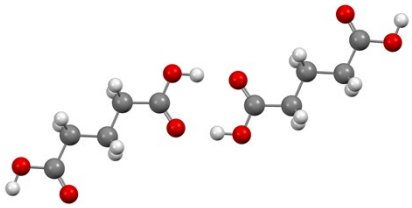
TCZ-34DHBA



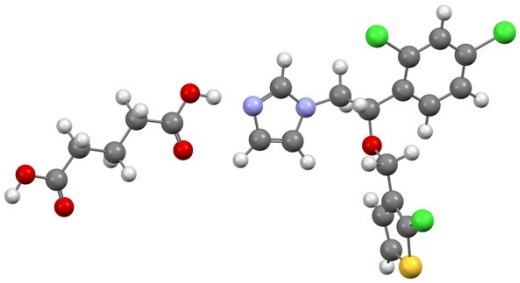
Isonicotinamide



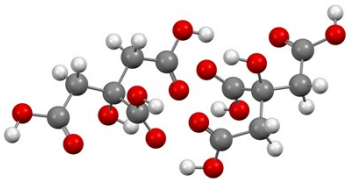
TCZ-Isonicotinamide



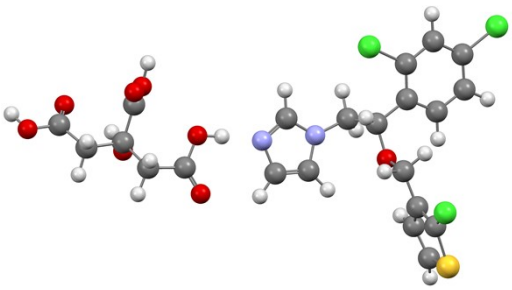
Glutaric acid



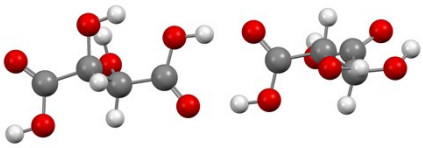
TCZ-Glutaric acid



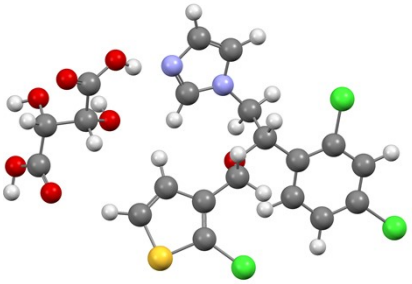
Citric acid



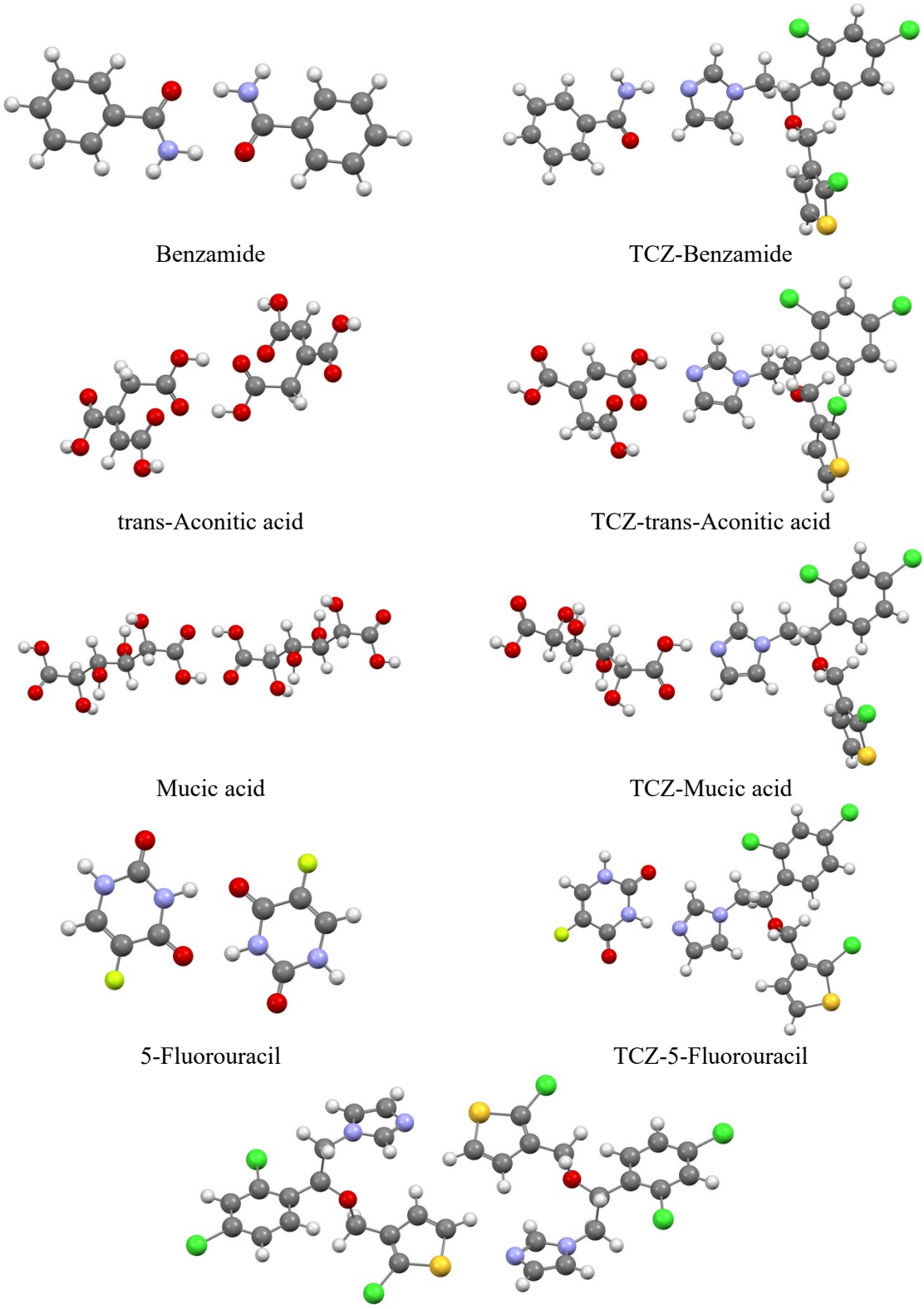
TCZ-Citric acid



Tartaric acid



TCZ-Tartaric acid



Scheme S2 Optimized geometries of homomeric and heteromeric molecular pairs used in the secondary site-pair interaction energy computation.

Bulk phase purity assessment of solid forms

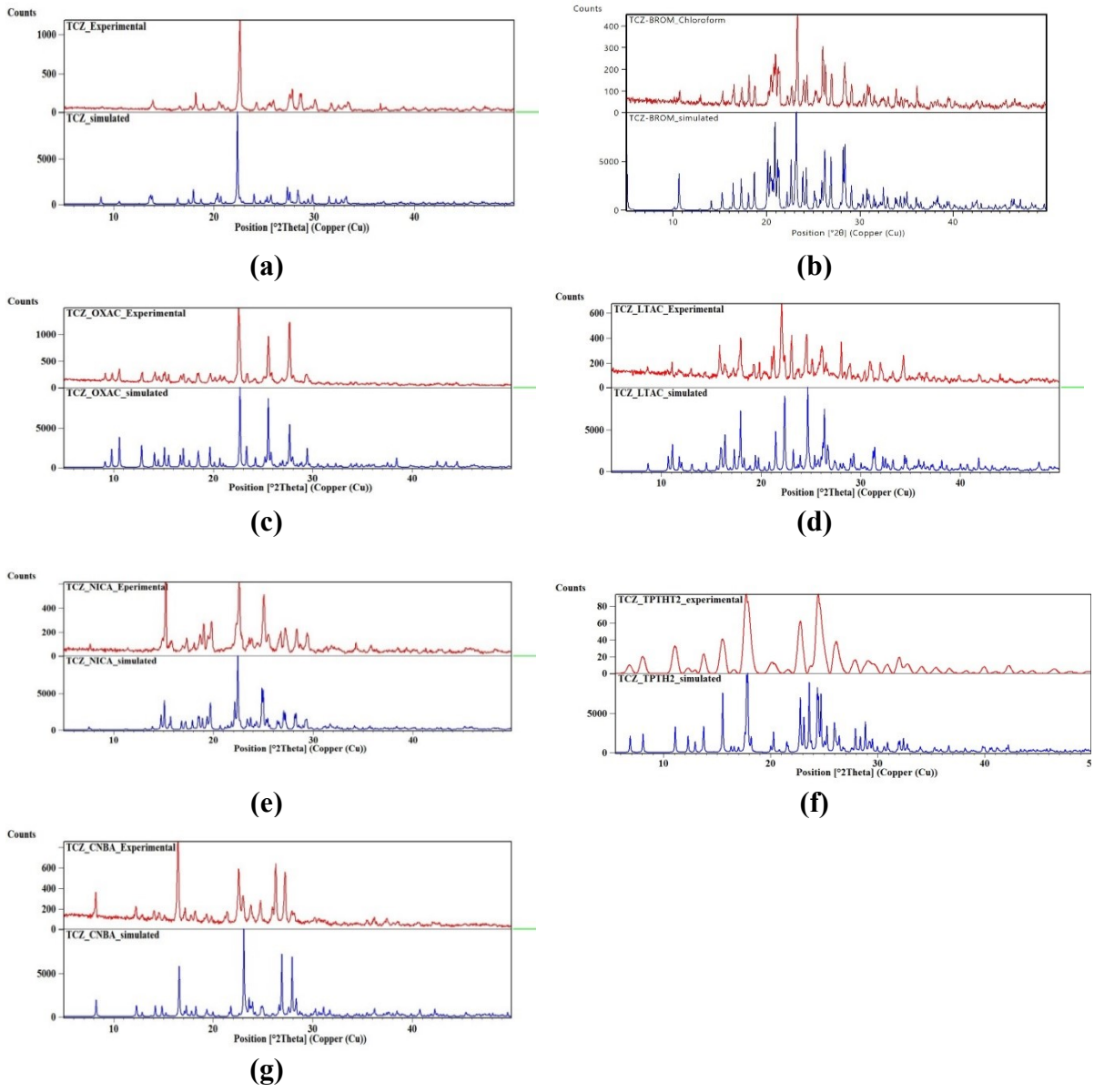
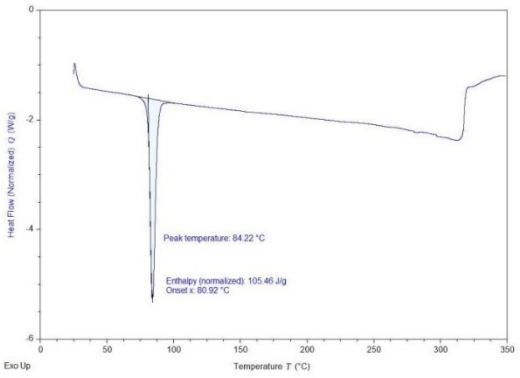
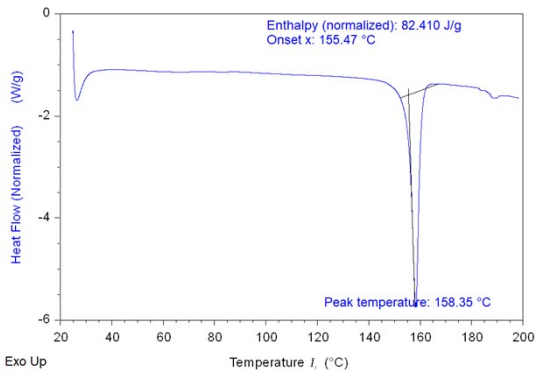


Figure S1 Comparison of experimental and simulated PXRD patterns for solid-forms (a) TCZ, (b) TCZ-BROM, (c) TCZ-OXAC, (d) TCZ-LTAC, (e) TCZ-NICA, (f) TCZ-TPTH2 and, (g) TCZ-CNBA.

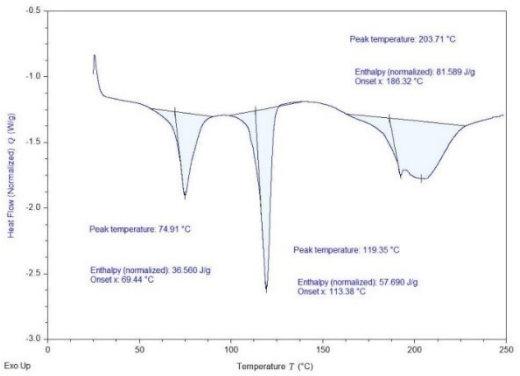
Thermal Analysis of Solid Forms



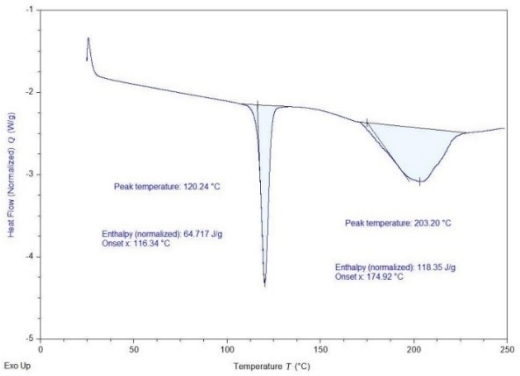
(a)



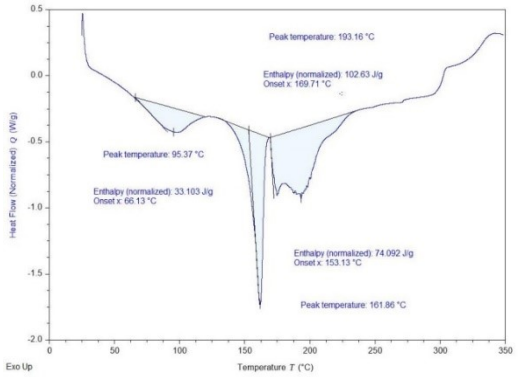
(b)



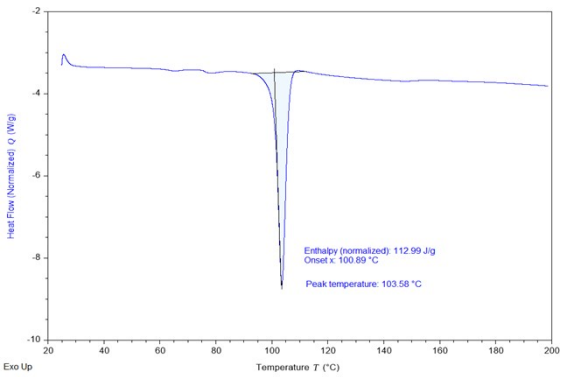
(c)



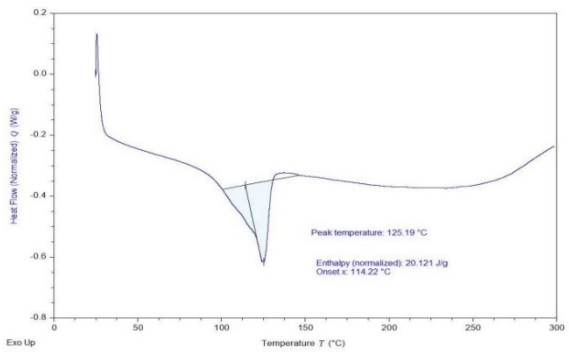
(d)



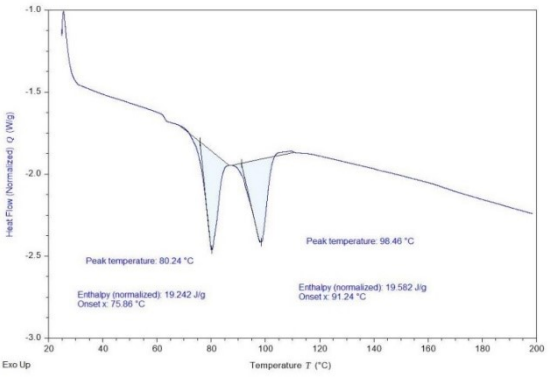
(e)



(f)



(g)



(h)

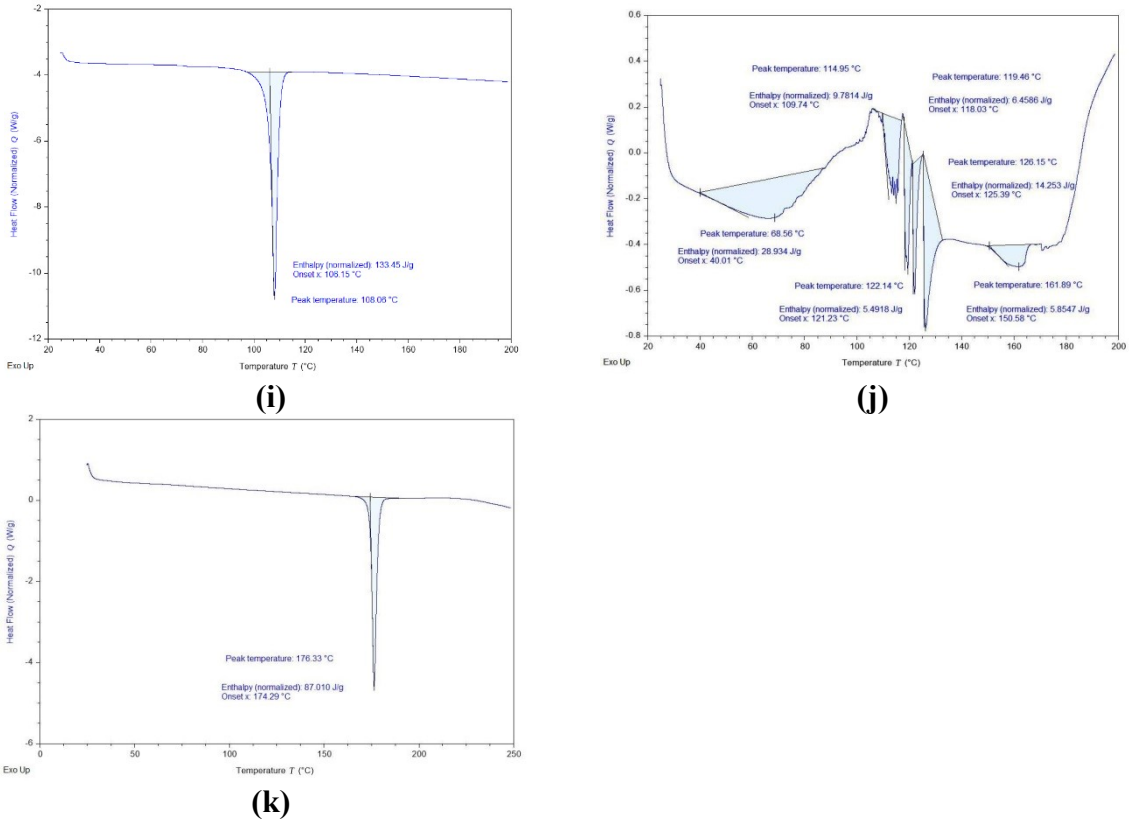
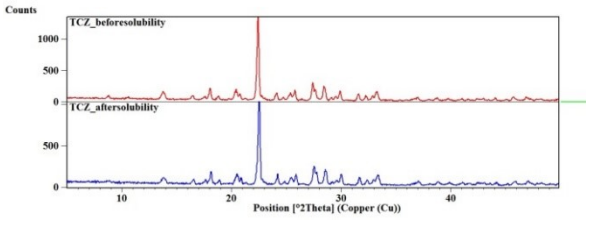


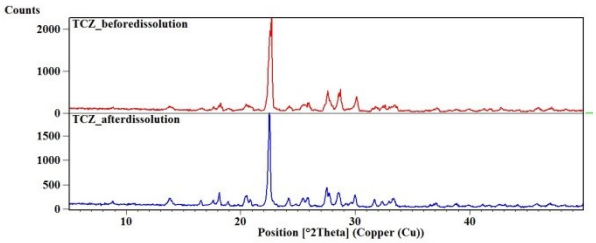
Figure S2 DSC thermograms of (a) TCZ, (b) TCZ-OXAC, (c) TCZ-FUMH1, (d) TCZ-FUMH2, (e) TCZ-LTAC, (f) TCZ-NICA, (g) TCZ-PTSA, (h) TCZ-TPTH2 (i) TCZ-CNBA, (j) TCZ-SULF and (k) TCZ-BROM

Aqueous Solubility Determinations of Solid Forms

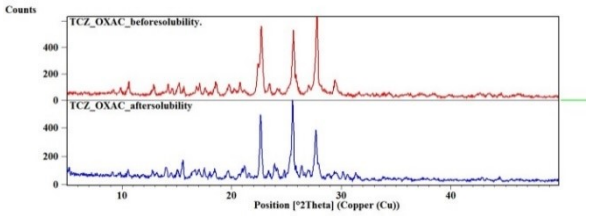
Phase Stability Assessments of Solid Forms in Aqueous Solutions



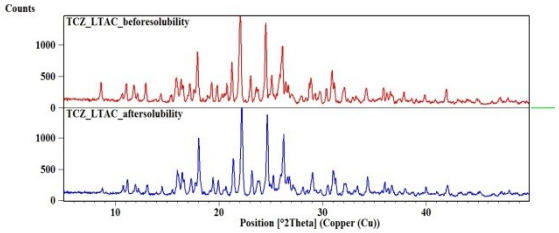
(a)



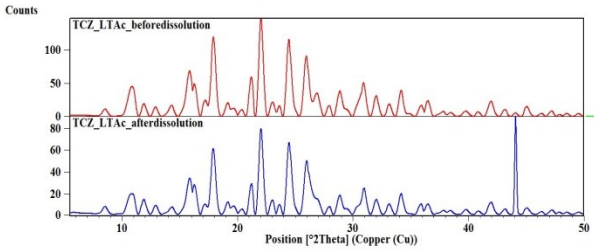
(b)



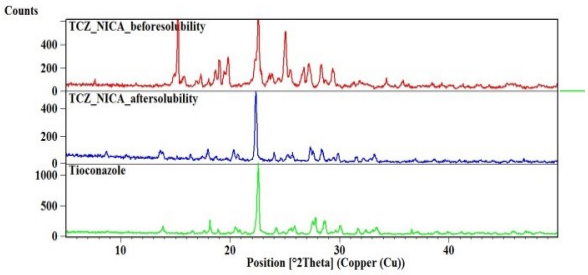
(c)



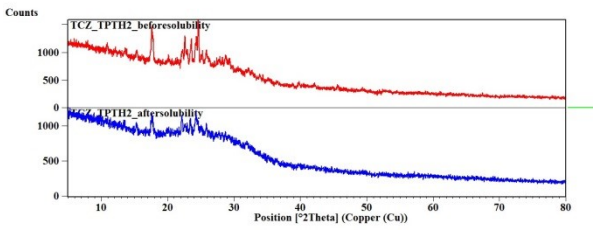
(d)



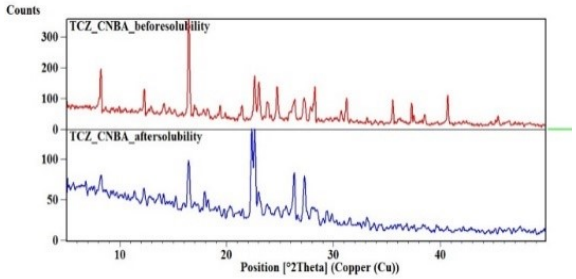
(e)



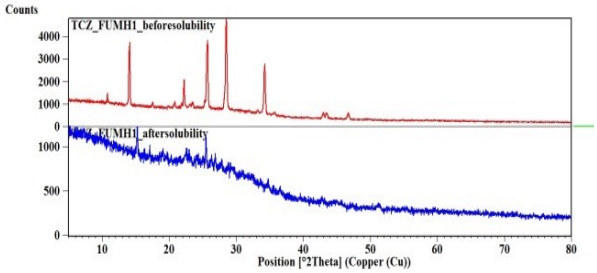
(f)



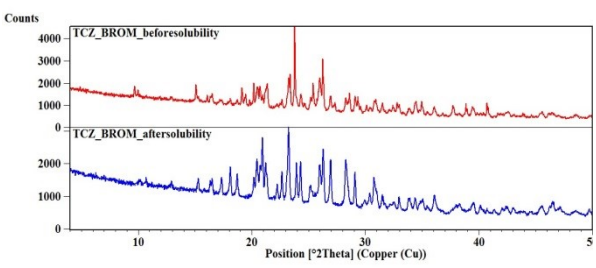
(g)



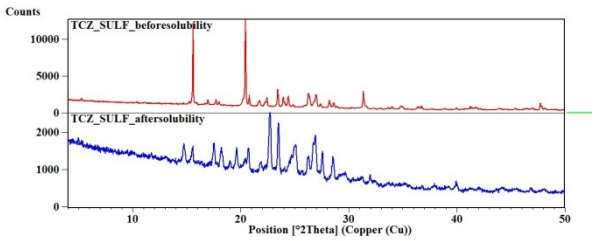
(h)



(i)



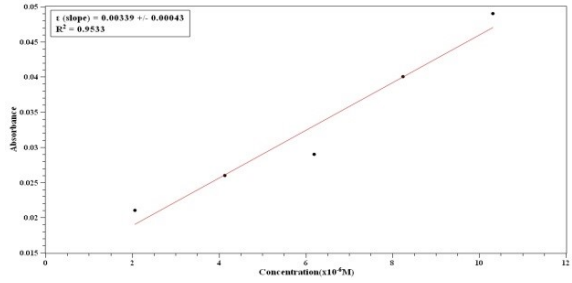
(j)



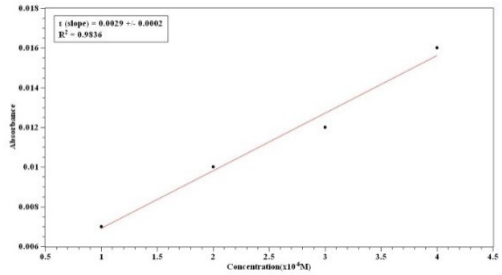
(k)

Figure S3 Comparison of PXRD patterns TCZ solid forms with that of solid residue obtained after solubility measurement study (a) TCZ, (b) TCZ at pH 6.8 (c) TCZ-OXAC, (d) TCZ-LTAC, (e) TCZ-LTAC at pH6.8, (f) TCZ-TPTH2, (g) TCZ-NICA, (h) TCZ-CNBA, (i) TCZ-FUMH1, (j) TCZ-BROM and (k) TCZ-SULF

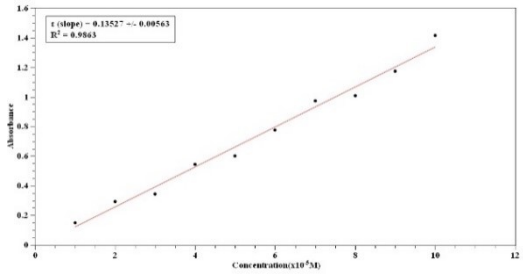
UV calibration plots are drawn from the known concentration solutions



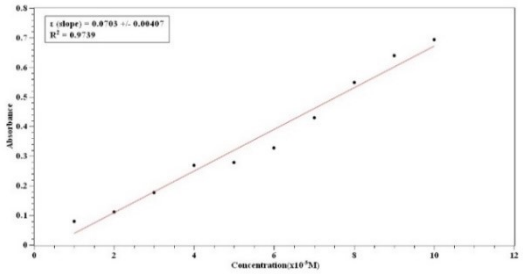
(a)



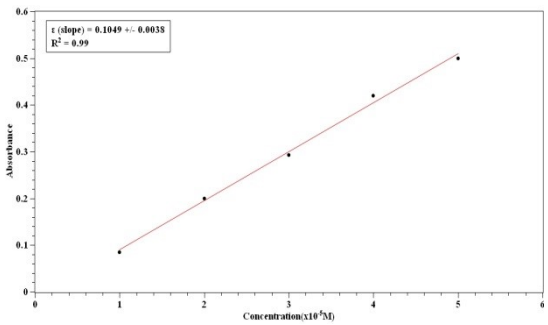
(b)

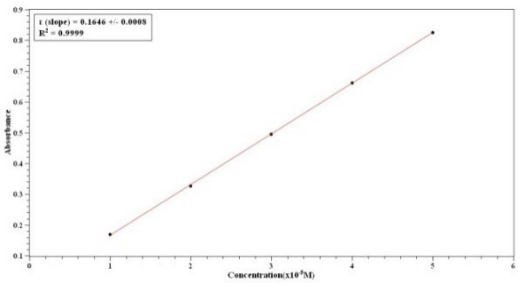


(c)



(d)





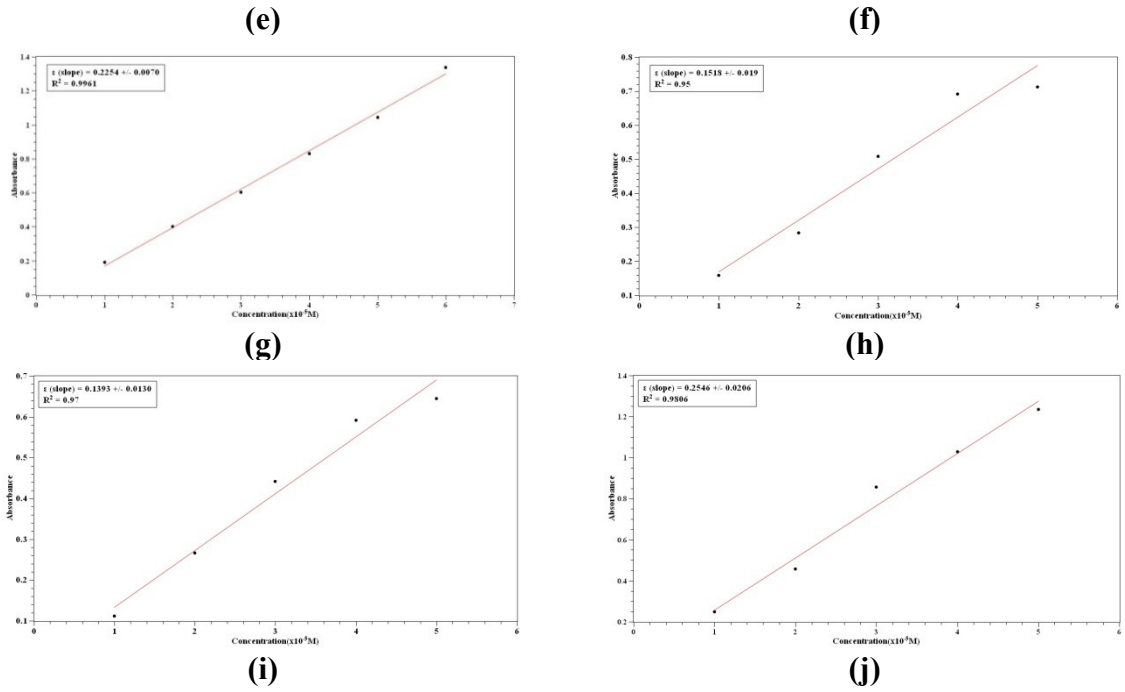


Figure S4 UV calibration plots for solid-form (a) TCZ, (b) TCZ at pH 6.8 (c) TCZ-OXAC, (d) TCZ-LTAC, (e) TCZ-LTAC at pH 6.8, (f) TCZ-TPTH2, (g) TCZ-CNBA, (h) TCZ-BROM , (i) TCZ-SULF and (j) TCZ-FUMH1

Table S4 Molecular extinction coefficients determined for the tioconazole solid forms in aqueous solutions by UV method.

Solid-Form	Molar extinction coefficient (ε)	Goodness-of-fit (R^2)
TCZ	0.003±0.001	0.95
TCZ[#]	0.003±0.001	0.98
TCZ-OXAC	0.135±0.006	0.99
TCZ-LTAC	0.070±0.004	0.97
TCZ-LTAC[#]	0.105±0.004	0.99
TCZ-TPTH2	0.165±0.001	0.99
TCZ-CNBA	0.225±0.007	0.99
TCZ-BROM	0.152±0.029	0.95
TCZ-SULF	0.139±0.013	0.97
TCZ-FUMH1	0.255±0.021	0.98

[#]Determined in phosphate buffer at pH 6.8