Salt formation of cabozantinib with hydrochloric and hydrobromic acids- influence on in-vitro dissolution behavior and food effect

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Supplementary material

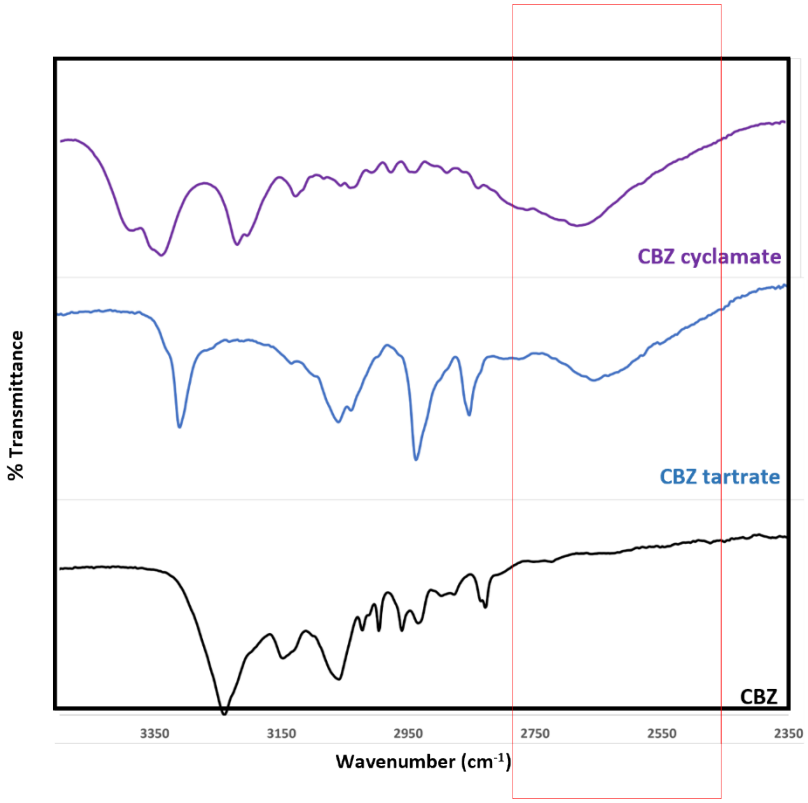


Fig. S1 IR spectra (wavenumber region 2300 cm^{-1} to 3500 cm^{-1}) of CBZ saccharinate and CBZ tartrate compared to that of CBZ.

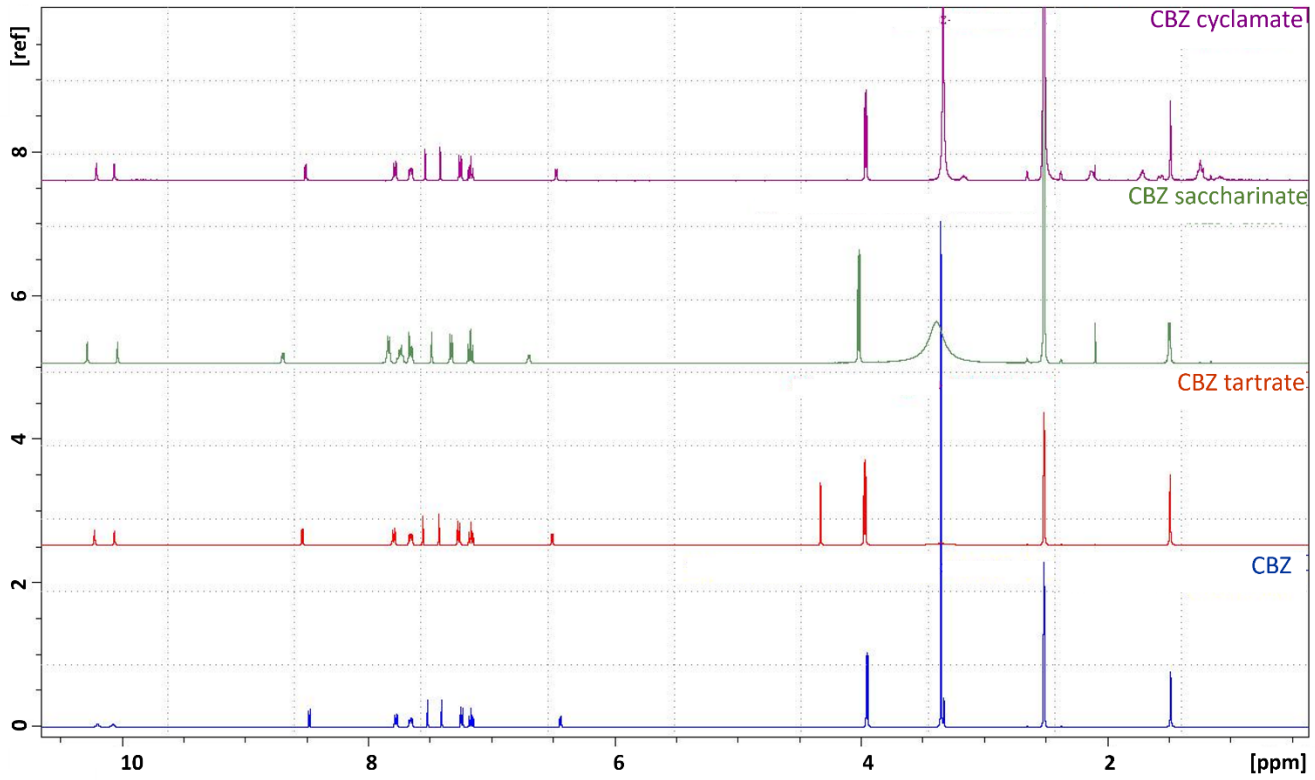


Fig S2 Solution ^{1}H NMR of CBZ, CBZ saccharinate, CBZ cyclamate and CBZ tartrate

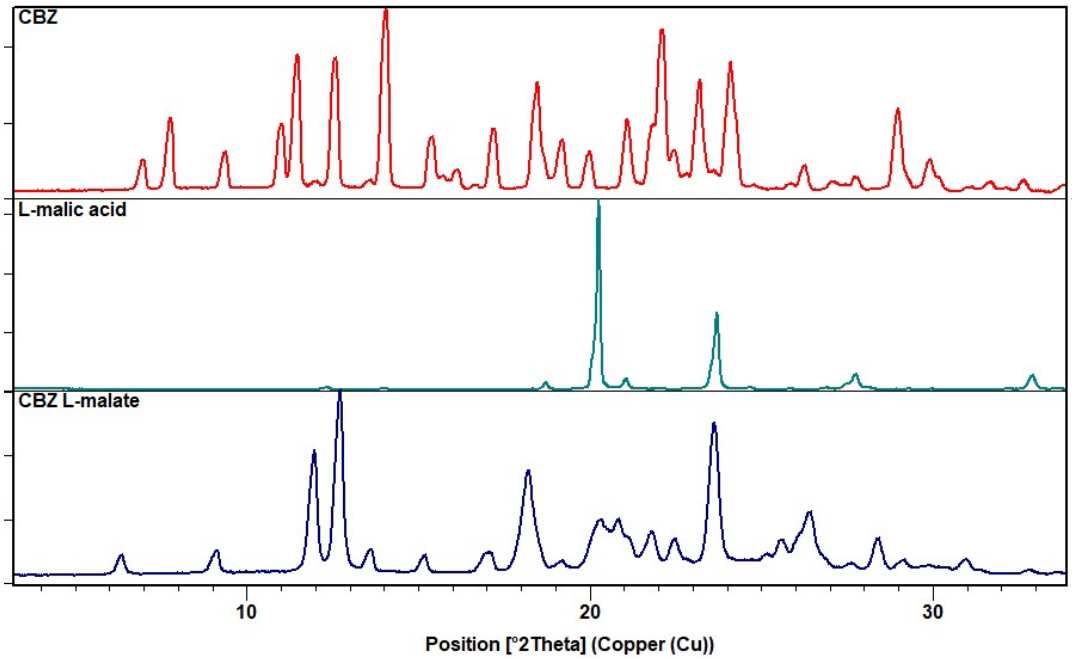
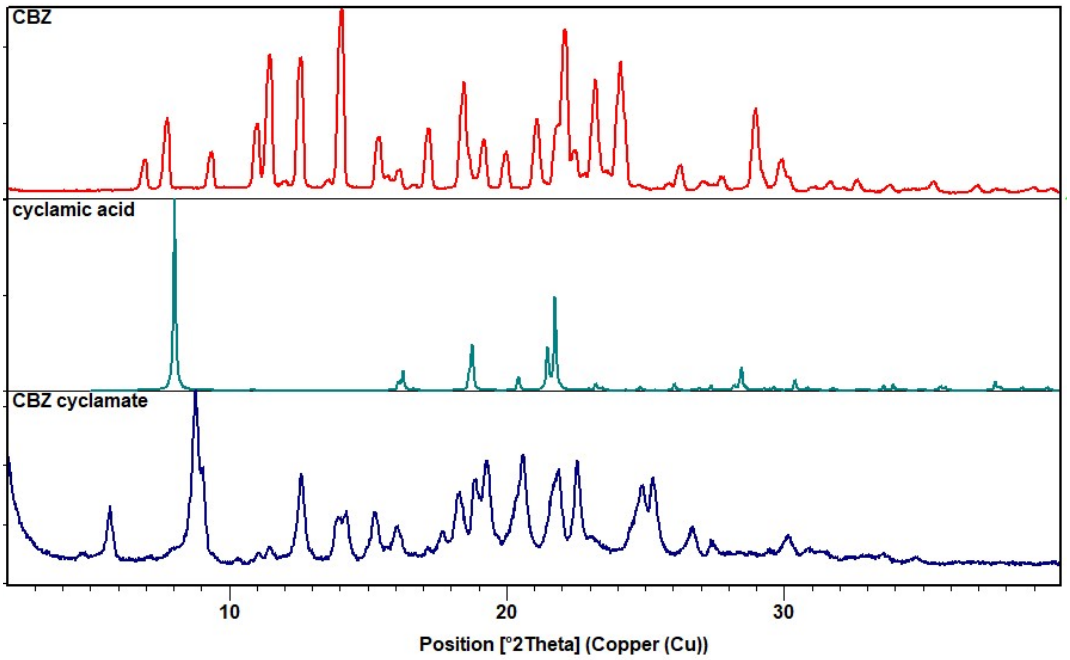
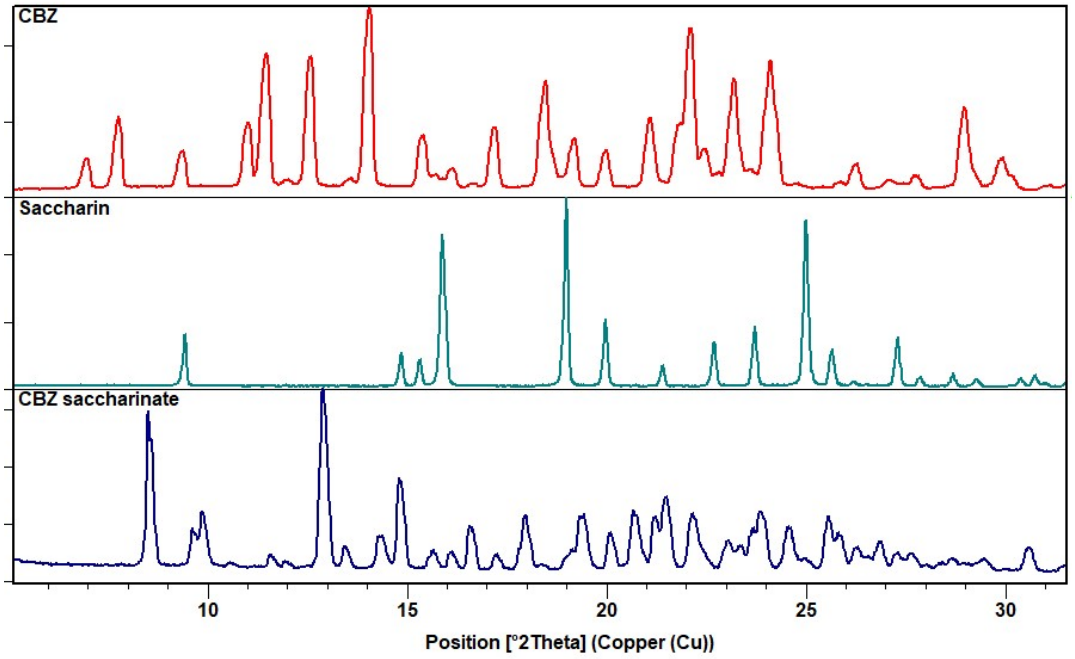


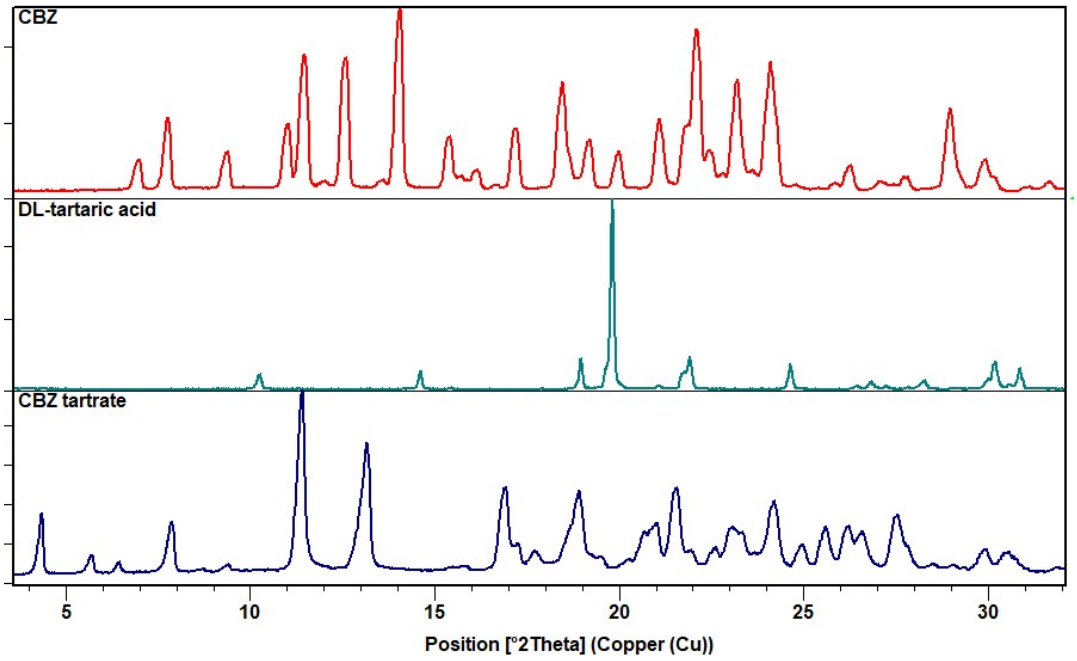
Fig S3 XRPD pattern of CBZ L-malate salt compared to the starting materials

Section S1

Comparison of XRPD patterns of salts to starting materials

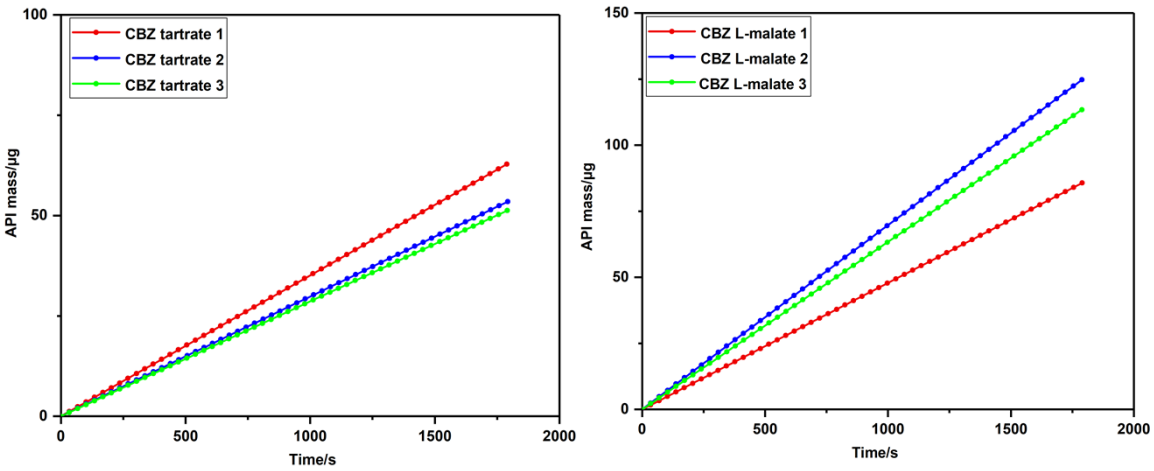


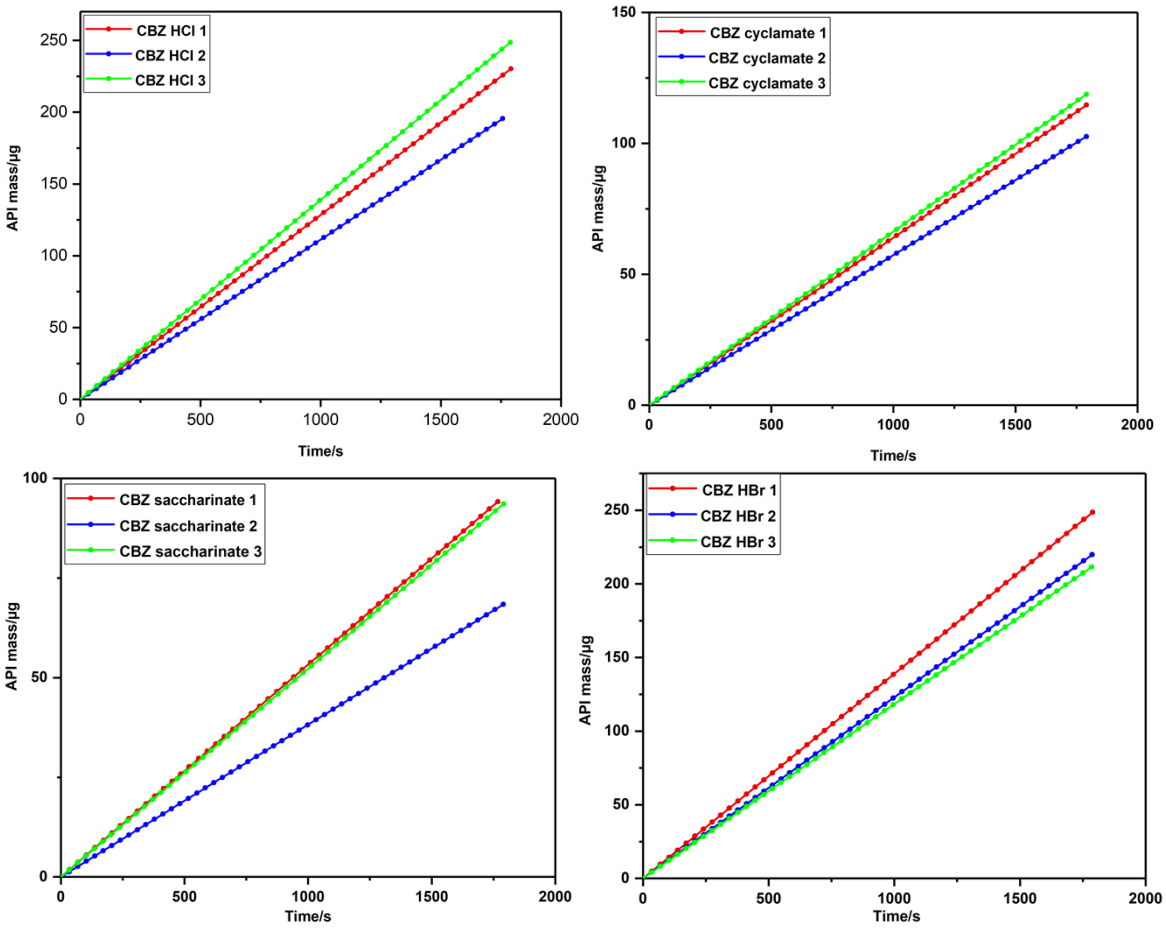




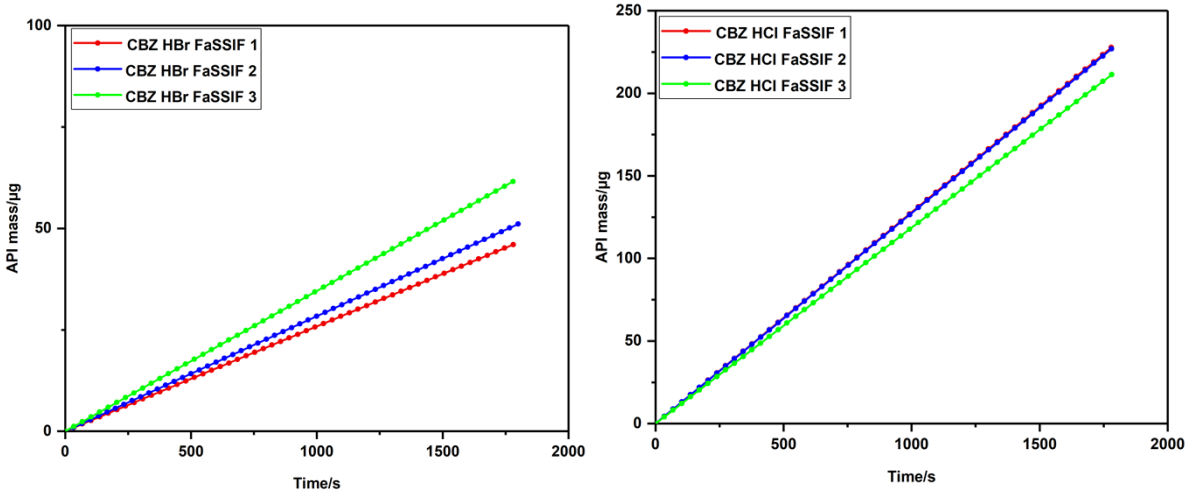
Section S2

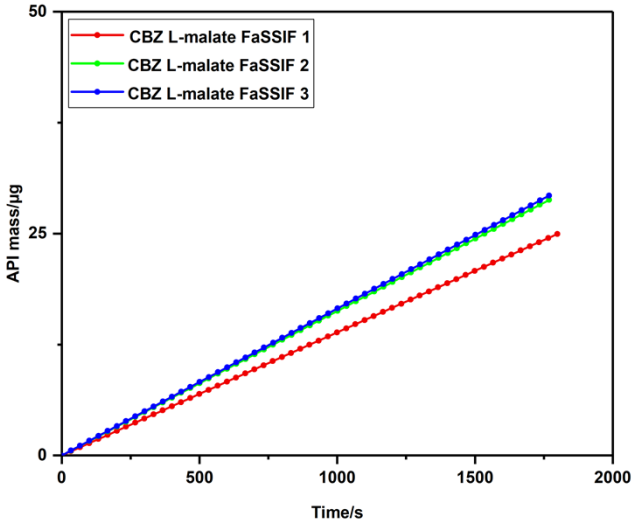
IDR curves recorded at pH 6.8 in phosphate buffer solution with 0.1% SDS



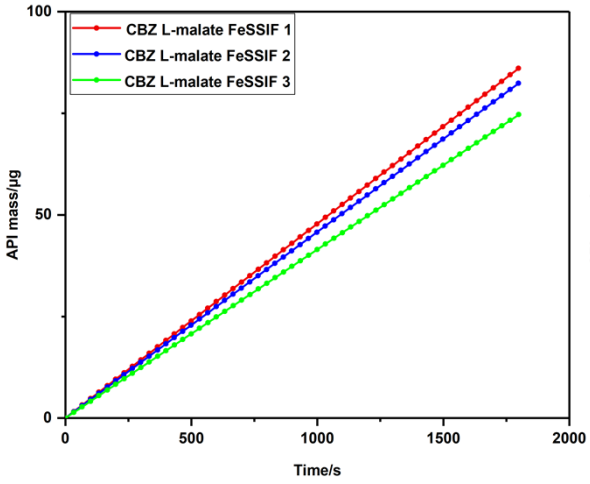


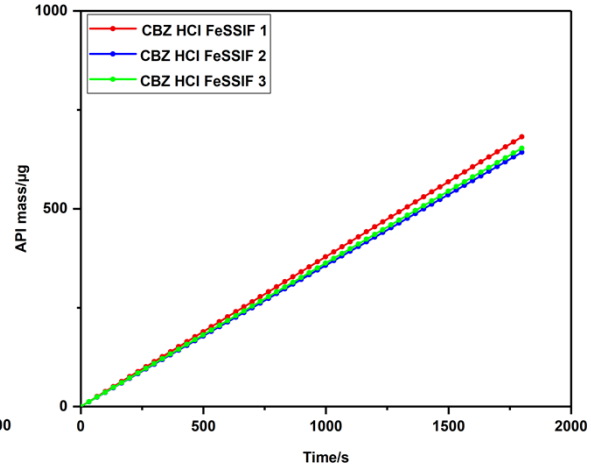
IDR curves of CBZ. HBr, CBZ. HCl and CBZ L_malate recorded in FaSSIF

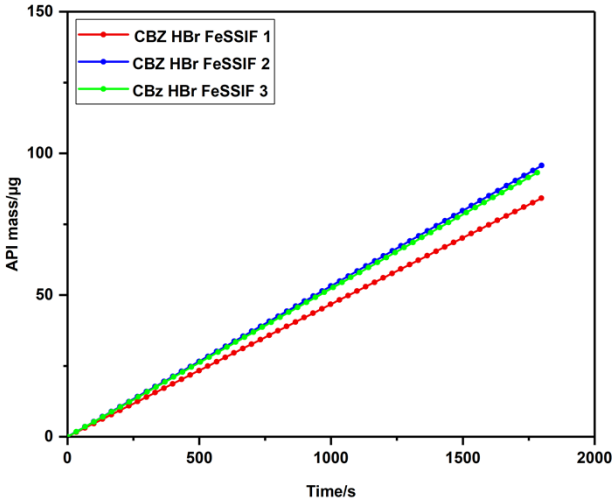




IDR curves of CBZ. HBr, CBZ. HCl and CBZ L_malate recorded in FeSSIF







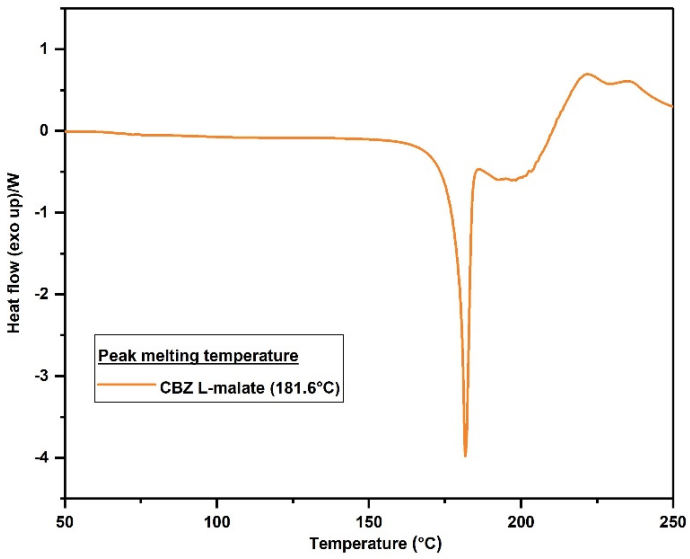
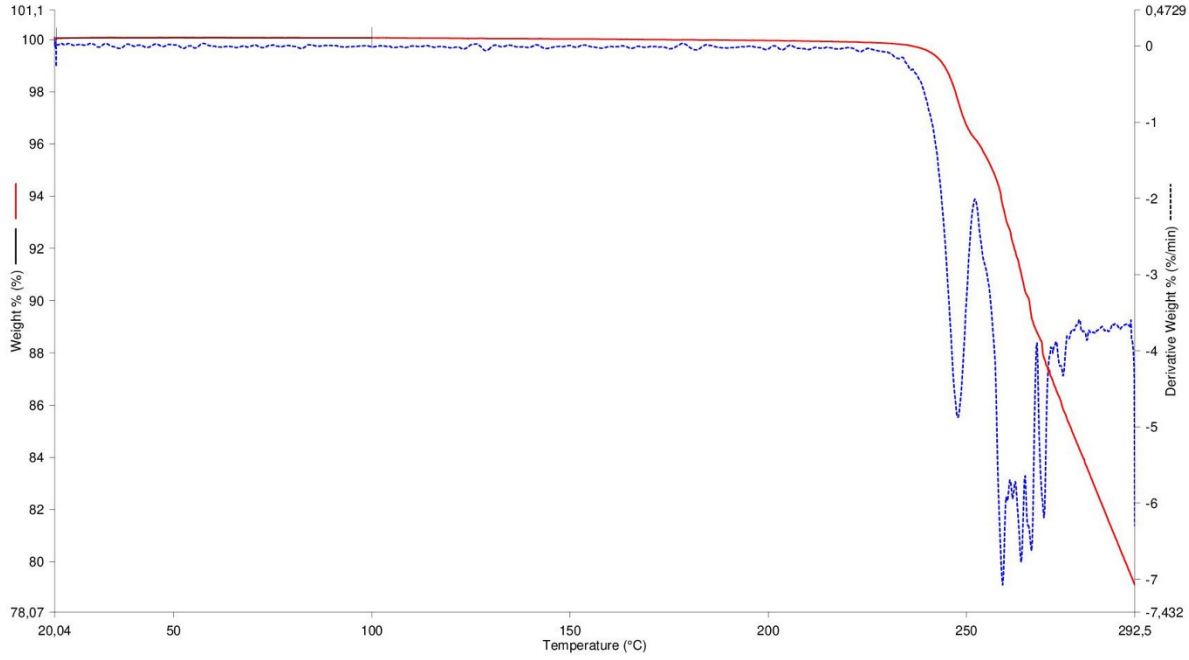


Fig S4 DSC curve of CBZ L-malate salt

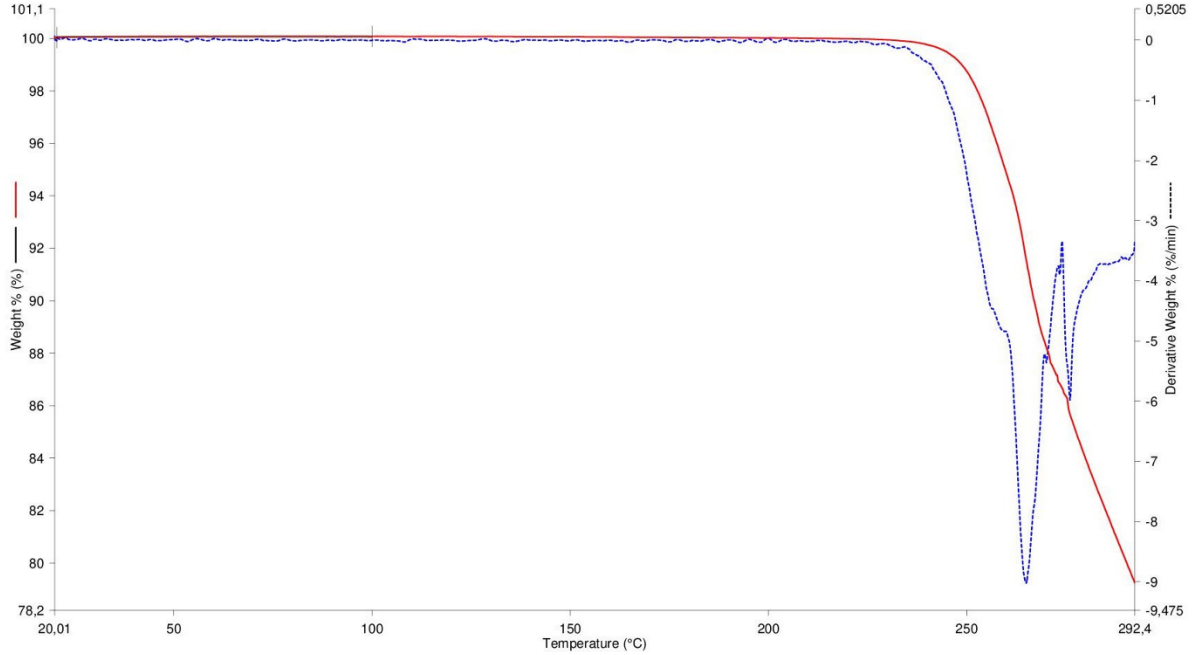
Section S3

TGA curves

a)



b)



c)

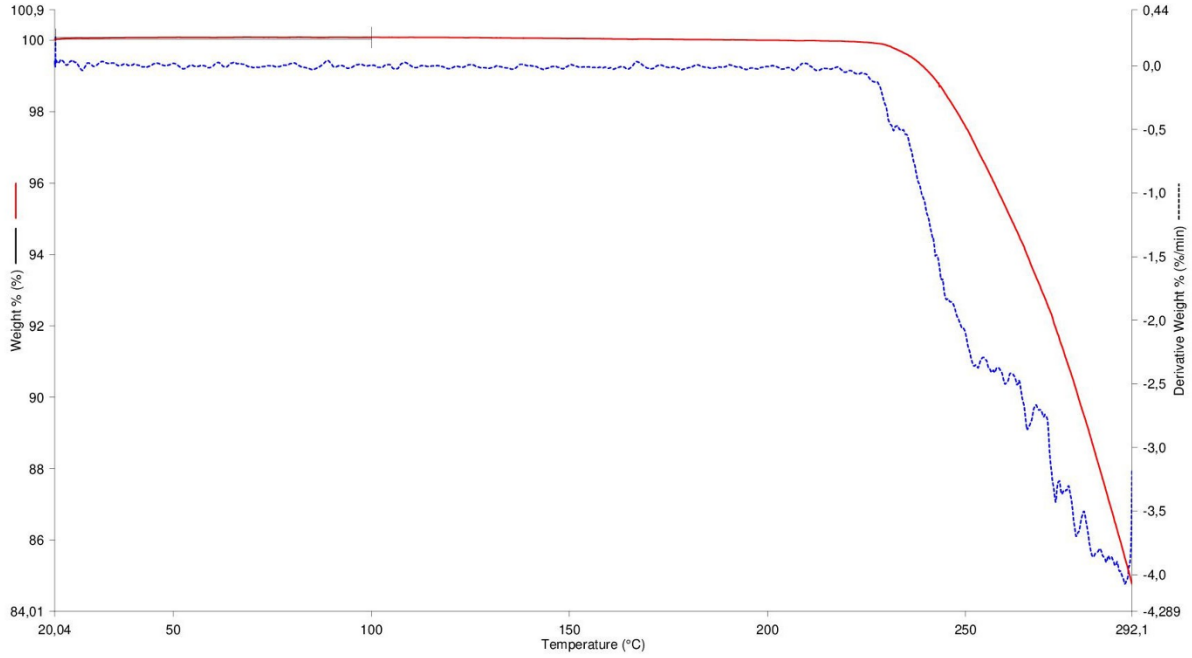
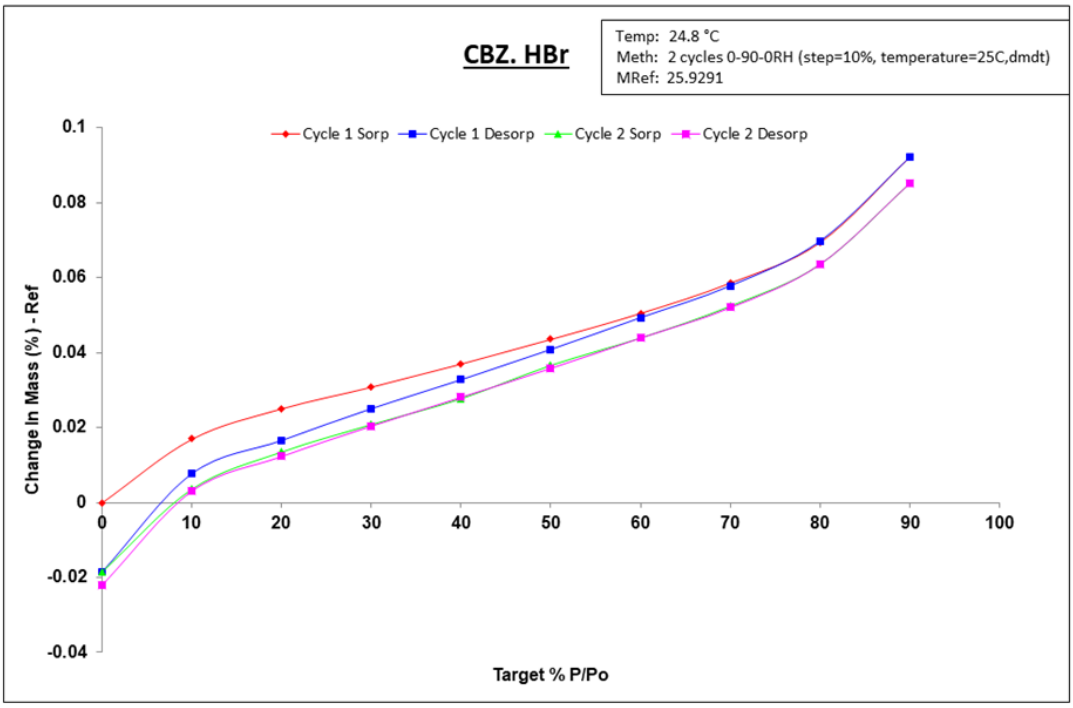
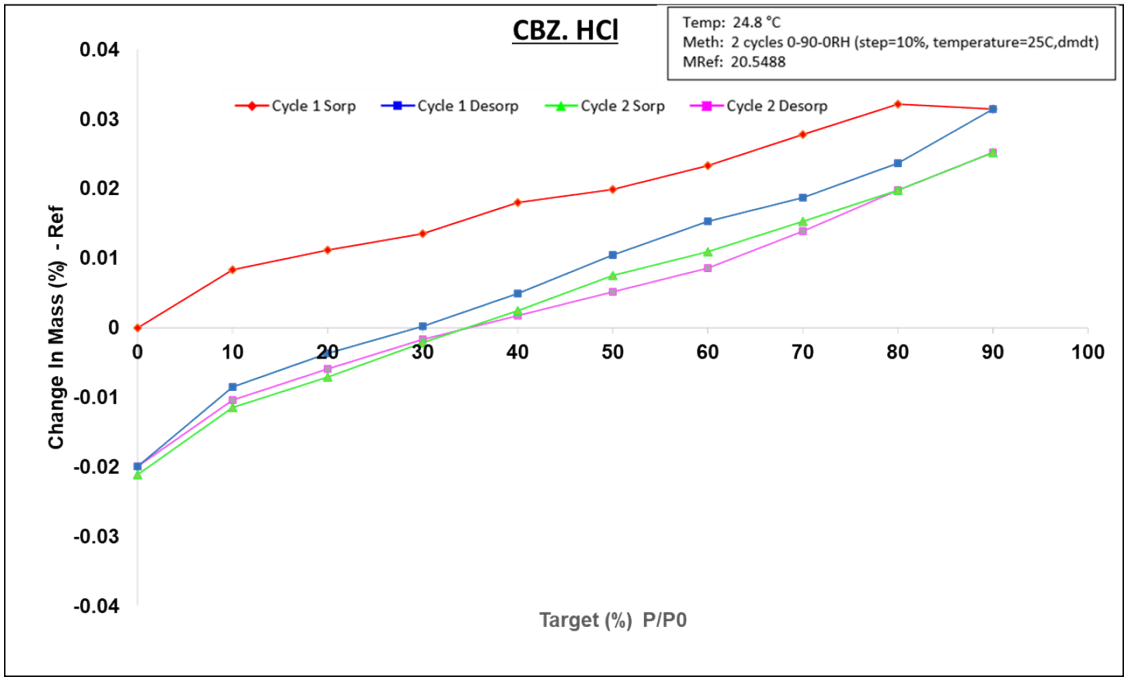


Fig S5 TGA curves of a)CBZ. HBr b)CBZ. HCl c)CBZ

Section S4

DVS curves of CBZ. HBr and CBZ. HCl



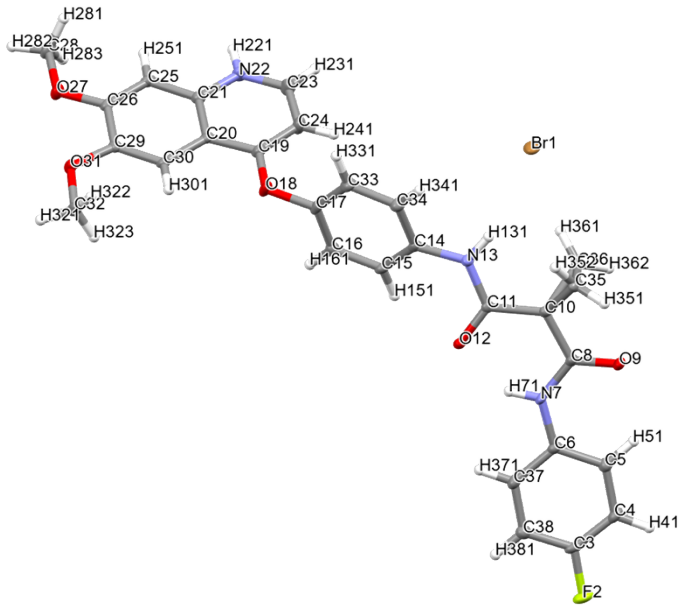


Section S5

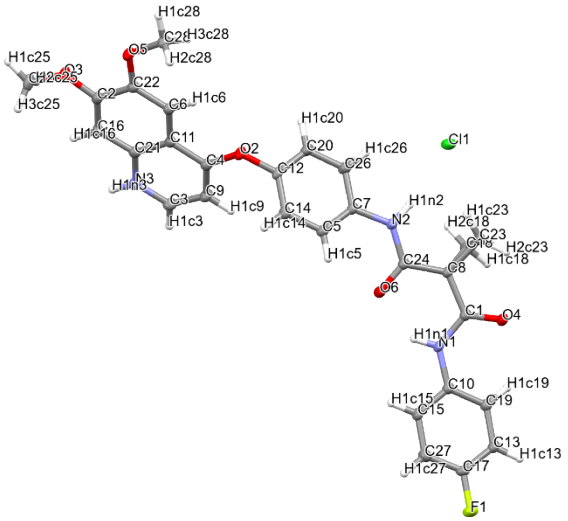
Extra structural data

Drawings of the asymmetric parts of the molecules with labeled atoms are shown below. Tab. S1 and Tab. S2 use the labeling as shown:

1. CBZ. HBr



2. CBZ. HCl



3. CBZ saccharinate

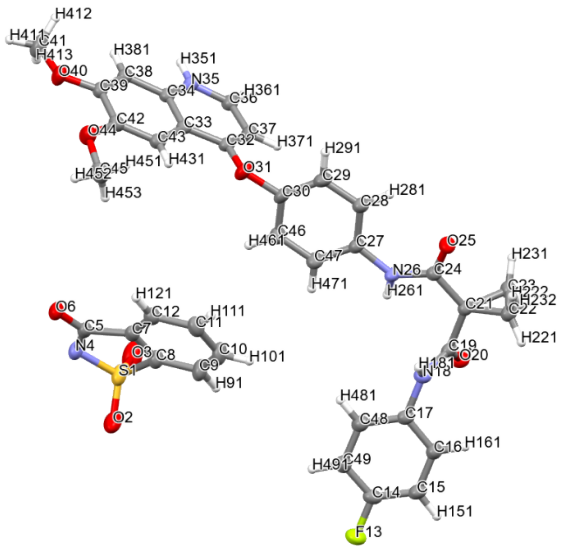


Table S1: Distances and angles of all the classical hydrogen bonds present in the salts of CBZ.

Salt	Interaction	Distance(D---A)(Å)	Distance(D---H)(Å)	Angle(°)
CBZ saccharinate	N18-H181---O25	2.791	0.883	172.57
	N35--H351---O6	2.662	0.906	168.98
CBZ. HBr	N22-H221---Br1	3.167	0.869	174.48
	N7-H71---O12	2.623	0.849	144.89
CBZ. HCl	N3-H1n3---C1	2.059	0.918	177.83
	N1-H1n1---O6	1.921	0.854	143.75

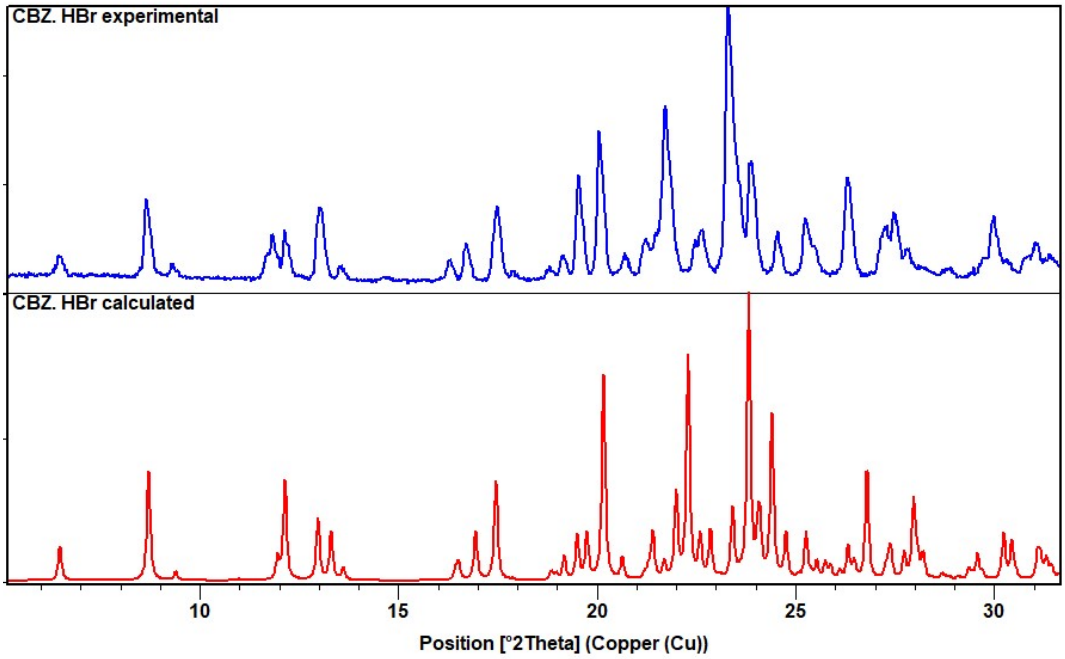
Table S2: Further crystallographic data of salts of CBZ

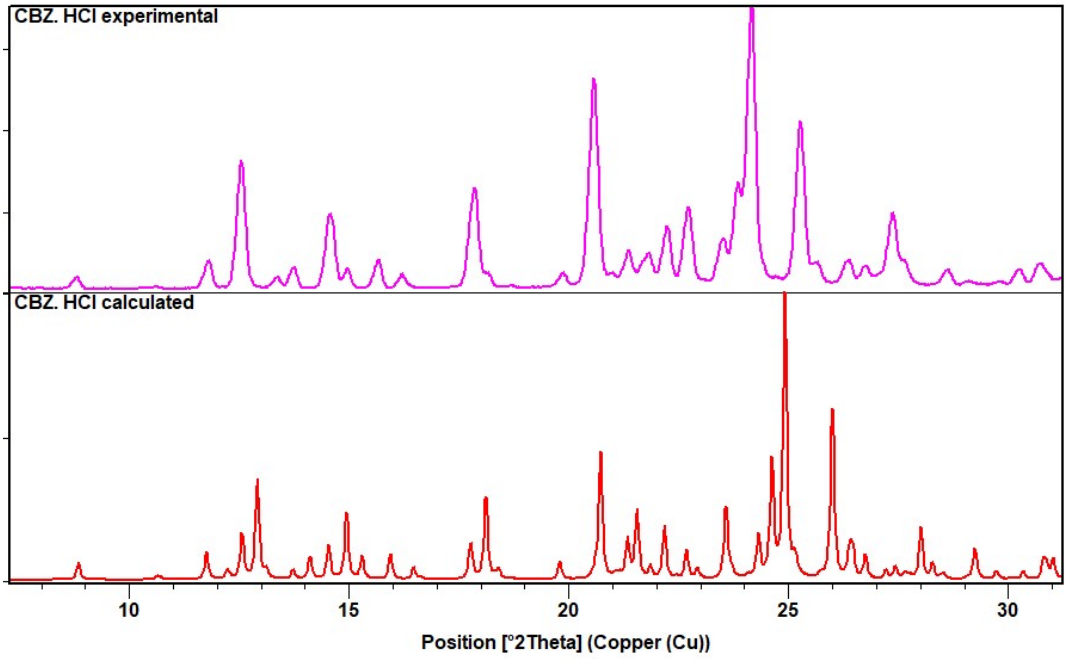
	CBZ. HCl	CBZ. HBr	CBZ saccharinate
Morphology	polygon	polygon	plate

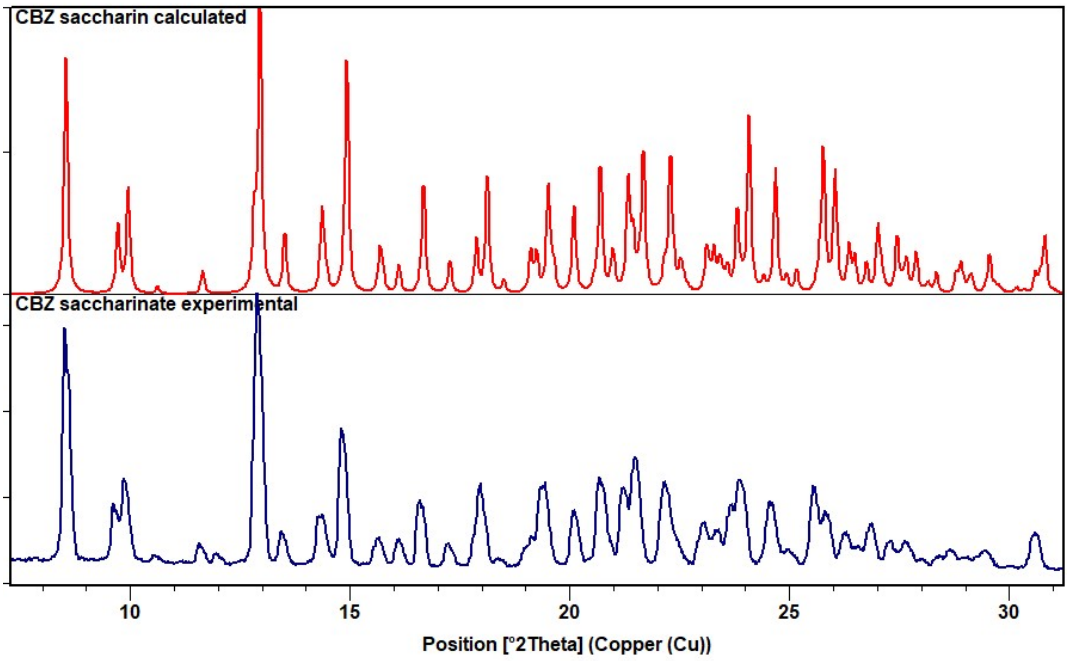
T(K)	95	95	140
Radiation	Cu Kα	Cu Kα	Cu Kα
ρcalc (g/cm3)	1.443	1.532	1.429
reflns. collected	14615	83998	33154
indept. reflns.	4881	4784	5706
R(int)	0.0199	0.061	0.039
GOF	1.641	1.0322	1.0167
R1, wR2 [I > 2σ(I)]	0.0330, 0.0951	0.0342, 0.0899	0.0376, 0.0945

Section S6

Comparison of experimental XRD patterns and XRD patterns calculated from crystal structures




CBZ. HCl experimental
CBZ. HCl calculated
10
15
20
25
30
Position [°2Theta] (Copper (Cu))


CBZ saccharin calculated
CBZ saccharinate experimental
10
15
20
25
30
Position [°2Theta] (Copper (Cu))

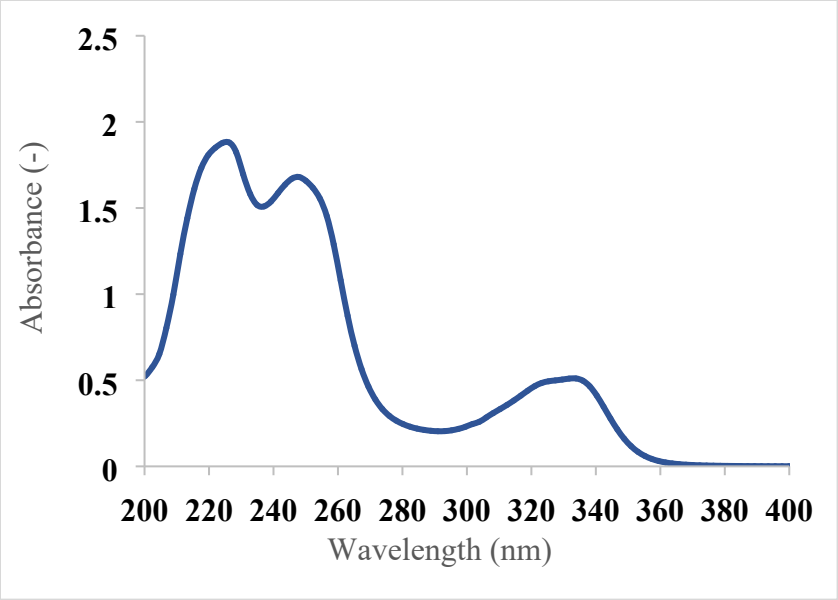


Fig. S6 UV-VIS absorbance of cabozantinib measured in phosphate buffer with 0.1% SDS