Supplementary Information

A Quaternary Solid-form of Ritonavir: an Oxalate Salt Oxalic Acid Co-crystal Acetone Solvate

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This supplementary material supports the main manuscript by providing further details of the following; **Figure S1** presents DSC thermograms for ritonavir forms I and II. **Figure S1** shows the optical micrograph of a single crystal of the new oxalate salt form as mounted upon the single crystal XRD system with the identified orientation of the crystallographic axes. **Figure S3** defines the atom labelling system for the forms I, II, IIIb and the new salt form. **Figure S4** highlights key torsion angle differences between Forms I, II, IIIb and the new salt form with the "folding" ritonavir molecular conformation leading to two thiazole groups "stacking" in the new salt form. **Figure S5** shows a comprehensive comparison of 16 torsion angles which show large differences between forms I, II, IIIb and the new salt form. **Figure S6** shows the major hydrogen bonding motifs of ritonavir form IIIb and the new salt form. **Figure S7** shows molecular overlays of ritonavir forms I, II, IIIb and the new salt form to visualise the impact of different molecular conformations. **Table S1** shows the conformation angle data for the 16 torsions highlighted in **Figure S5**. **Table S2** provides a calculation of the ΔpKas for various functional groups in the ritonavir molecule from DFT calculations.

S1. Solid Form Characterisation: DSC experimental results of ritonavir forms I and II

The melting points (**Figure S1**) of forms I and II obtained in this study by DSC experiments were found to be consistent with literature [1].

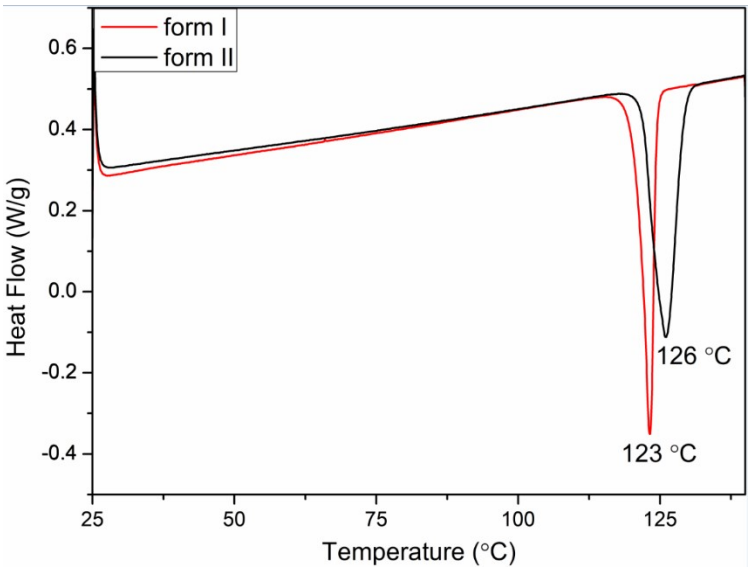


Figure S1. DSC thermograms of ritonavir forms I and II for their melting points.

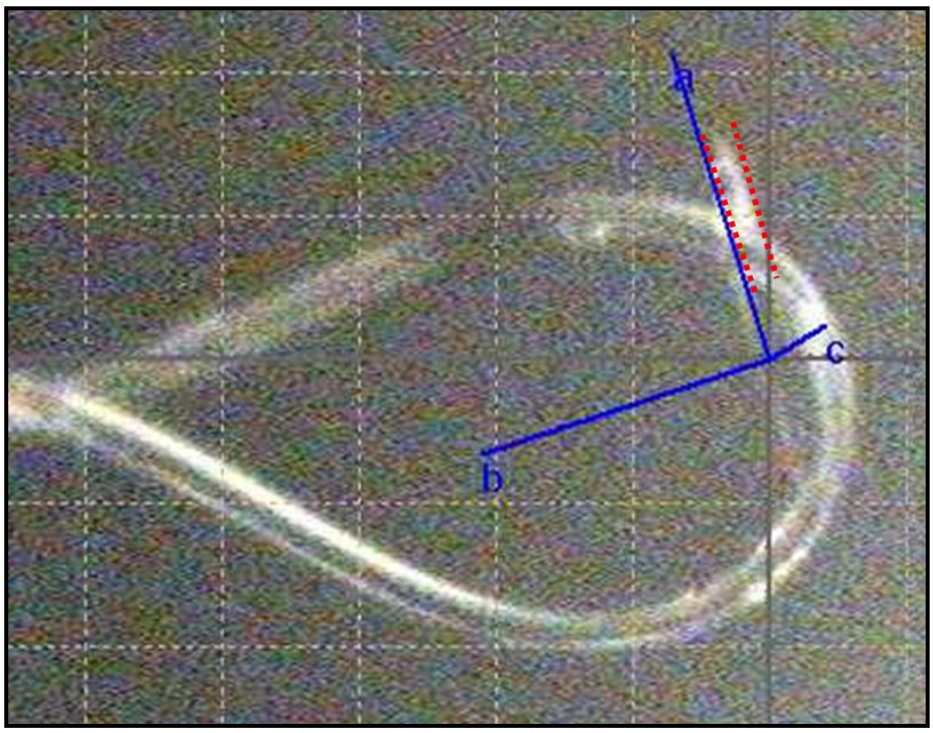
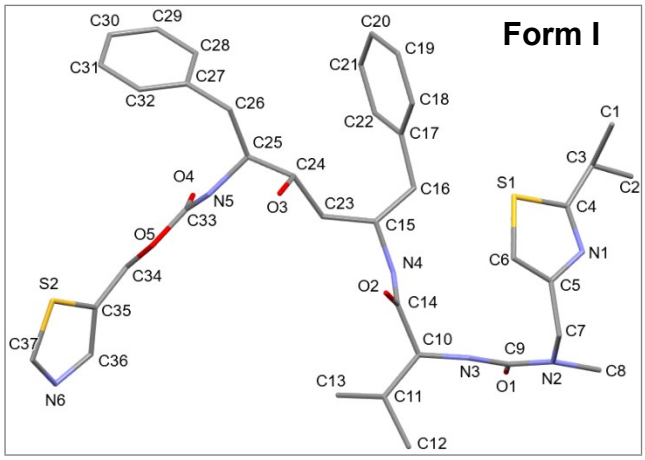
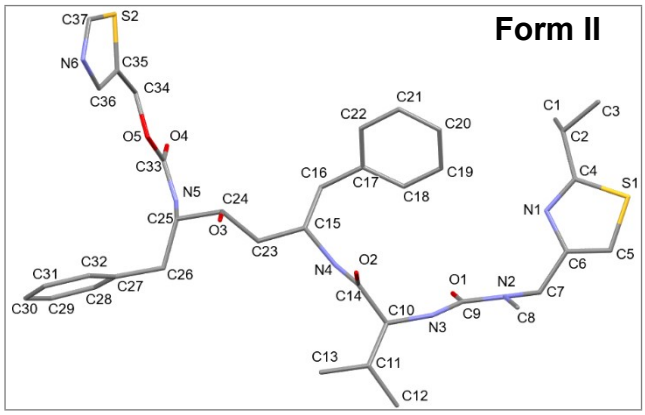
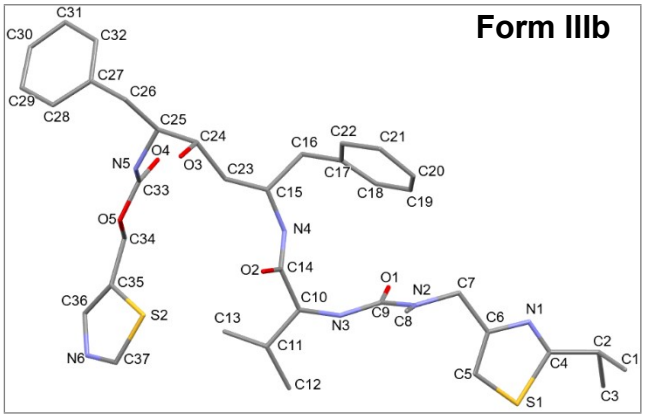


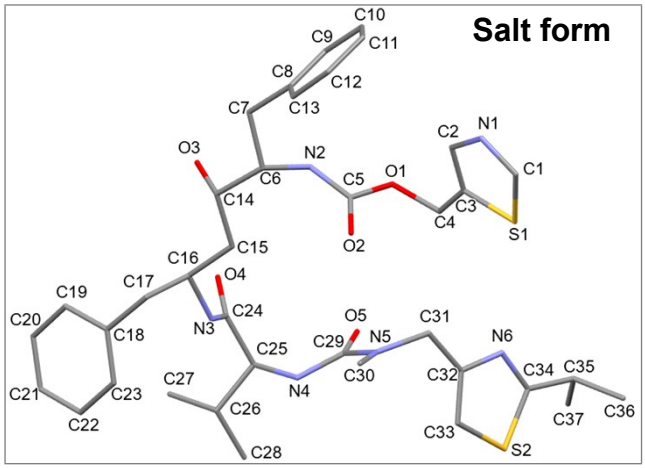
Figure S2. Optical micrograph of a single crystal of the new oxalate salt form as mounted upon the single crystal XRD system with the identified orientation of the crystallographic axes.

S2. Crystal Structure: Atom labelling systems for ritonavir forms I, II, IIIb and the new salt form







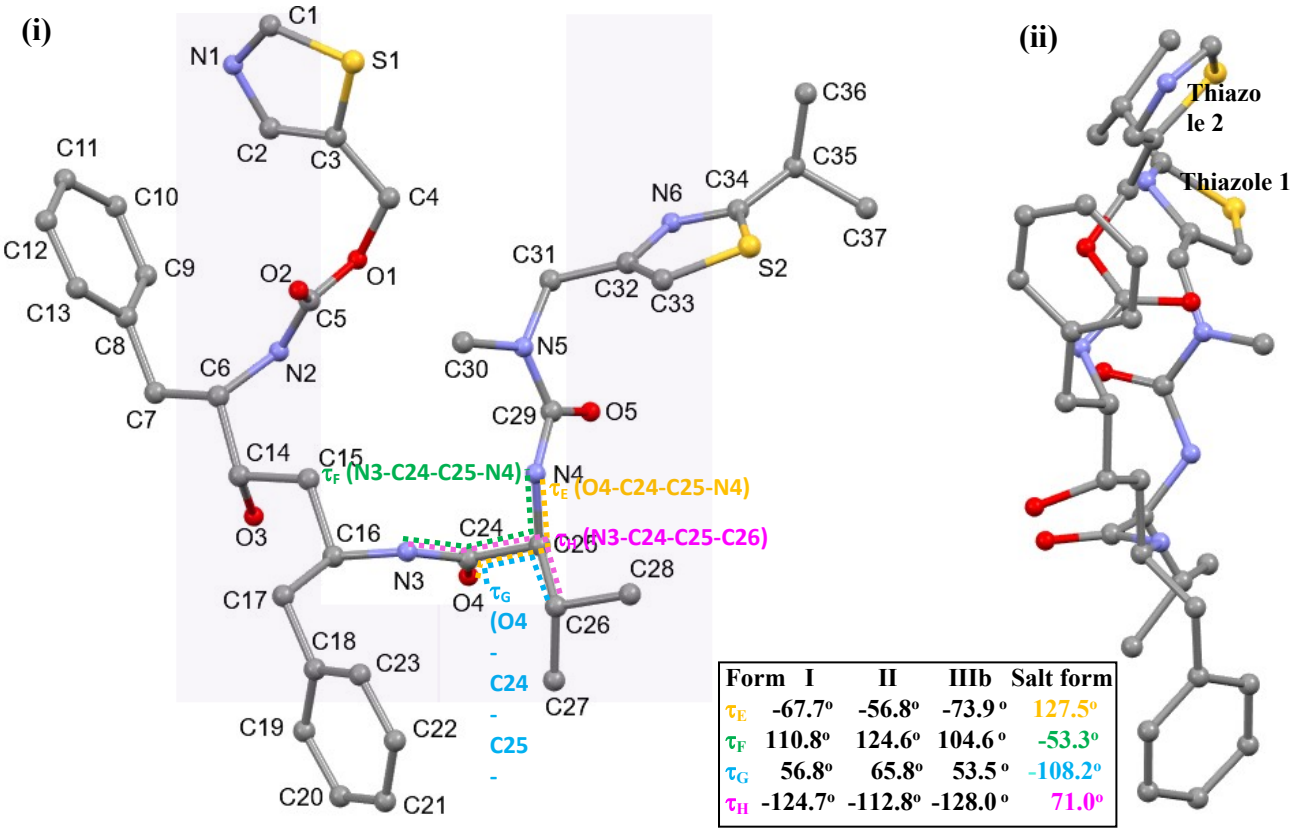


Atom labelling			
Form I[(Bauer et al., 2001)]	**Form II**[(Bauer et al., 2001)]	**Form IIIb** (Yao et al., 2022)	**Oxalate Salt Form**[(this study)]
C1	C3	C1	C37
C2	C1	C3	C36
C3	C2	C2	C35
C4	C4	C4	C34
C5	C6	C6	C32
C6	C5	C5	C33
C7	C7	C7	C31
C8	C8	C8	C30
C9	C9	C9	C29
C10	C10	C10	C25
C11	C11	C11	C26
C12	C12	C12	C28
C13	C13	C13	C27
C14	C14	C14	C24
C15	C15	C15	C16
C16	C16	C16	C17
C17	C17	C17	C18
C18	C18	C18	C19
C19	C19	C19	C20
C20	C20	C20	C21
C21	C21	C21	C22
C22	C22	C22	C23
C23	C23	C23	C15
C24	C24	C24	C14
C25	C25	C25	C6
C26	C26	C26	C7
C27	C27	C27	C8
C28	C28	C28	C9
C29	C29	C29	C10
C30	C30	C30	C11
C31	C31	C31	C12
C32	C32	C32	C13
C33	C33	C33	C5
C34	C34	C34	C4
C35	C35	C35	C3
C36	C36	C36	C2
C37	C37	C37	C1
N1	N1	N1	N6
N2	N2	N2	N5
N3	N3	N3	N4
N4	N4	N4	N3
N5	N5	N5	N2
N6	N6	N6	N1
O1	O1	O1	O5
O2	O2	O2	O4
O3	O3	O3	O3
O4	O4	O4	O2
O5	O5	O5	O1
S1	S1	S1	S2
S2	S2	S2	S1

Figure S3. Molecular structures of ritonavir forms I [1], II [1], IIIb [2] & the new oxalate salt form (CCDC deposition

number 2009282) for atoms labelling comparisons.

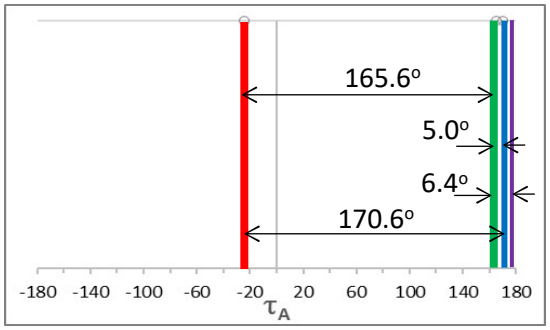
S3. Conformation Analysis

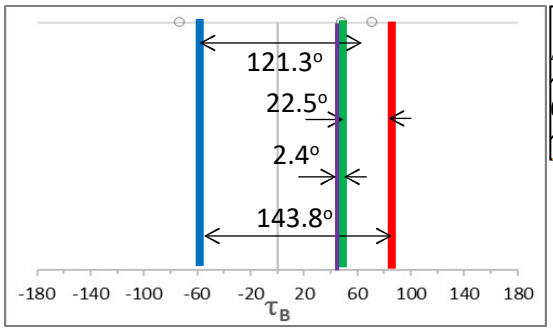


Form	I	II	IIIb	Salt form
τ_E	-67.7°	-56.8°	-73.9 °	127.5°
τ_F	110.8°	124.6°	104.6 °	-53.3°
τ_G	56.8°	65.8°	53.5 °	-108.2°
τ_H	-124.7°	-112.8°	-128.0 °	71.0°

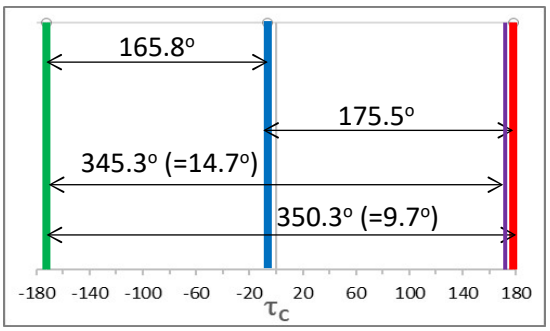
Figure S4. (i) The group of torsion angles in ritonavir oxalate salt form that causes about a 165° (comparing to form I) or 177° (comparing to form II) or 160° (comparing to form IIIb) rotation of the molecular fragments containing the phenyl–hydroxyl–phenyl–carbamate–thiazole_1 groups; (ii) The view from the left side of the ritonavir molecule in (a) with the two thiazole ring groups (1 and 2) tending to "stack" together.

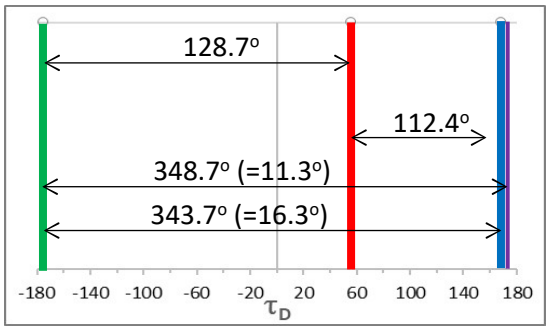
τ_A:	C7-N2-C9-N3 (I)	C7-N2-C9-N3 (II)	C7-N2-C9-N3 (IIIb)	C31-N5-C29-N4 (salt - S)
τ_B:	C23-C24-C25-N5 (I)	C23-C24-C25-N5 (II)	C23-C24-C25-N5 (IIIb)	C15-C14-C6-N2 (salt - S)
τ_C:	C25-N5-C33-O5 (I)	C25-N5-C33-O5 (II)	C25-N5-C33-O5 (IIIb)	C6-N2-C5-O1 (salt - S)
τ_D:	C23-C15-C16-C17 (I)	C23-C15-C16-C17 (II)	C23-C15-C16-C17 (IIIb)	C15-C16-C17-C18 (salt - S)
τ_E:	O2-C14-C10-N3 (I)	O2-C14-C10-N3 (II)	O2-C14-C10-N3 (IIIb)	O4-C24-C25-N4 (salt – S)
τ_F:	N3-C10-C14-N4 (I)	N3-C10-C14-N4 (II)	N3-C10-C14-N4 (IIIb)	N4-C25-C24-N3 (salt - S)
τ_G:	O2-C14-C10-C11 (I)	O2-C14-C10-C11 (II)	O2-C14-C10-C11 (IIIb)	O4-C24-C25-C26 (salt - S)
τ_H:	C11-C10-C14-N4 (I)	C11-C10-C14-N4 (II)	C11-C10-C14-N4 (IIIb)	C26-C25-C24-N3 (salt - S)
τ_I:	C5-C7-N2-C8 (I)	C6-C7-N2-C8 (II)	C5-C7-N2-C8 (IIIb)	C32-C31-N5-C30 (salt - S)
τ_J:	N1-C5-C7-N2 (I)	N1-C6-C7-N2 (II)	N1-C5-C7-N2 (IIIb)	N6-C32-C31-N5 (salt - S)
τ_k:	C6-C5-C7-N2 (I)	C5-C6-C7-N2 (II)	C6-C5-C7-N2 (IIIb)	C33-C32-C31-N5 (salt - S)
τ_L:	C2-C3-C4-S1 (I)	C1-C2-C4-S1 (II)	C2-C3-C4-S1 (IIIb)	C36-C35-C34-S2 (salt - S)
τ_M:	C2-C3-C4-N1 (I)	C1-C2-C4-N1 (II)	C2-C3-C4-N1 (IIIb)	C36-C35-C34-N6 (salt - S)
τ_N:	C18-C17-C16-C15 (I)	C18-C17-C16-C15 (II)	C18-C17-C16-C15 (IIIb)	C19-C18-C17-C16 (salt - S)
τ_O:	C22-C17-C16-C15 (I)	C22-C17-C16-C15 (II)	C22-C17-C16-C15 (IIIb)	C23-C18-C17-C16 (salt - S)
τ_P:	C33-O5-C34-C35 (I)	C11-O5-C34-C35 (II)	C33-O5-C34-C35 (IIIb)	C5-O1-C4-C3 (salt - S)

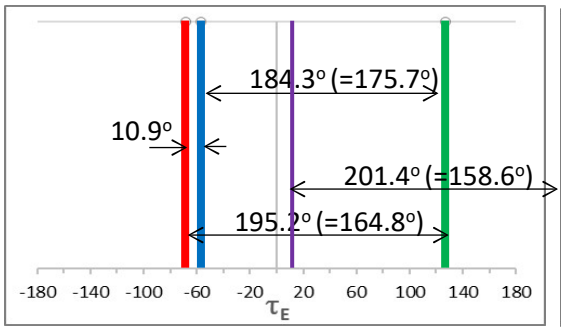


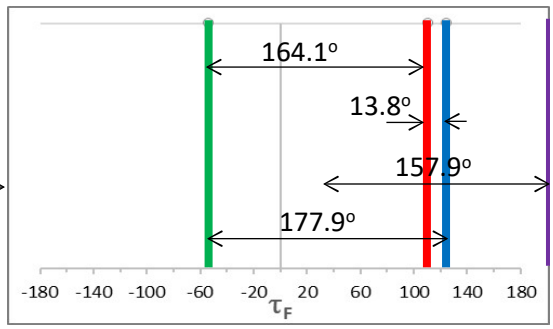


	Δ(I-II)	Δ(I-S)	Δ(II-S)	Δ(IIIb-S)
τ_A	170.6°	165.6°	5.0°	6.4°
τ_B	143.8°	22.5°	121.3°	









	Δ(I-II)	Δ(I-S)	Δ(II-S)	Δ(IIIb-S)
τ_E	10.9°	164.8°	175.7°	

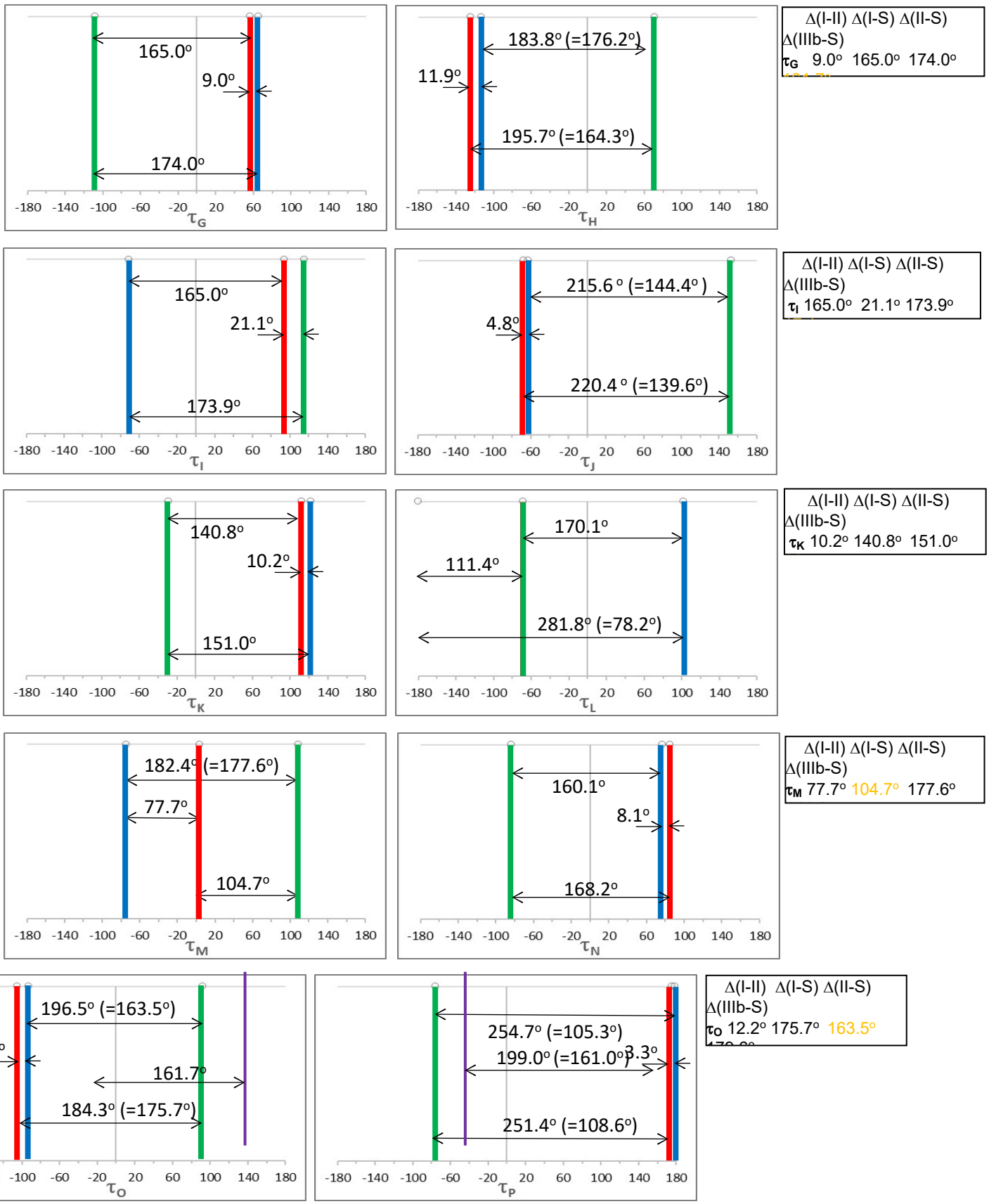


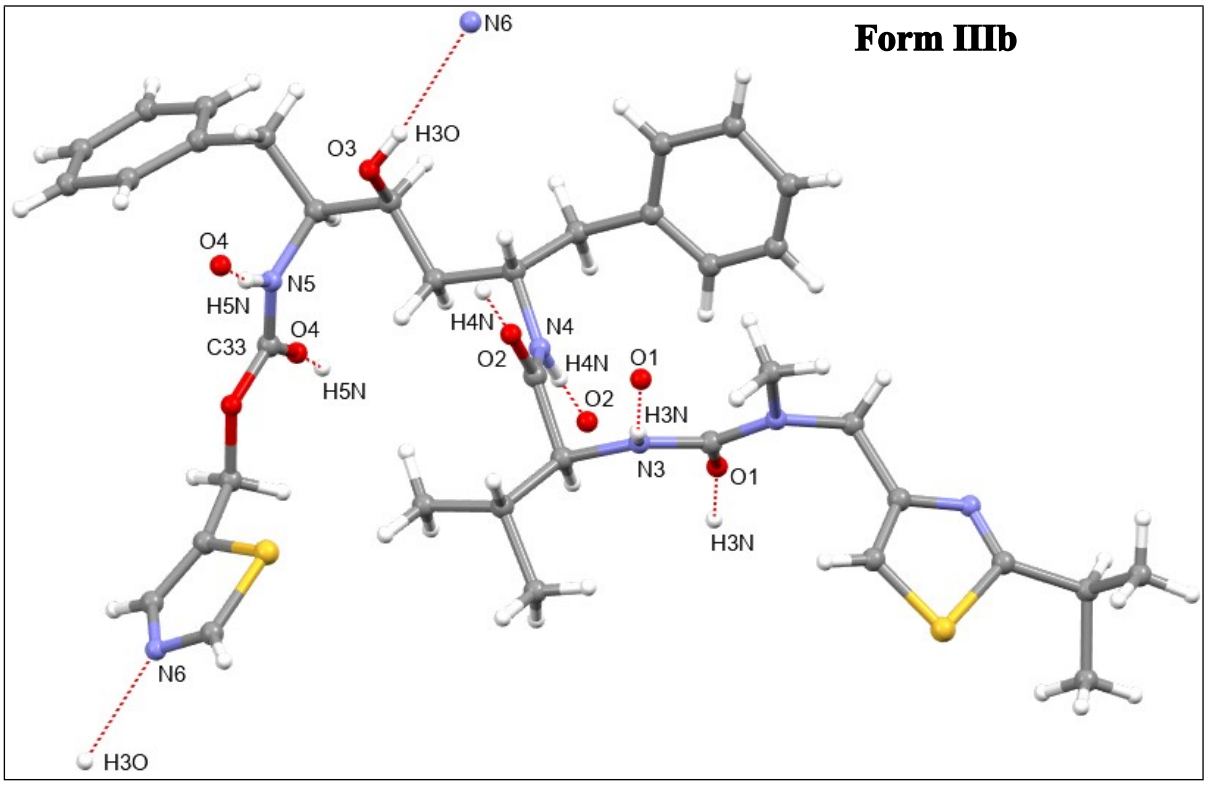
Figure S5. Torsion angles of 16 torsions (τ_A, τ_B, τ_C, τ_D, τ_E, τ_F, τ_G, τ_H, τ_I, τ_J, τ_K, τ_L, τ_M, τ_N, τ_O, τ_P) which have big differences between the new oxalate salt form (S) and forms I, II & IIIb. The red, blue, purple and green colours refer to form I, form II, form IIIb and new oxalate salt form (S), respectively.

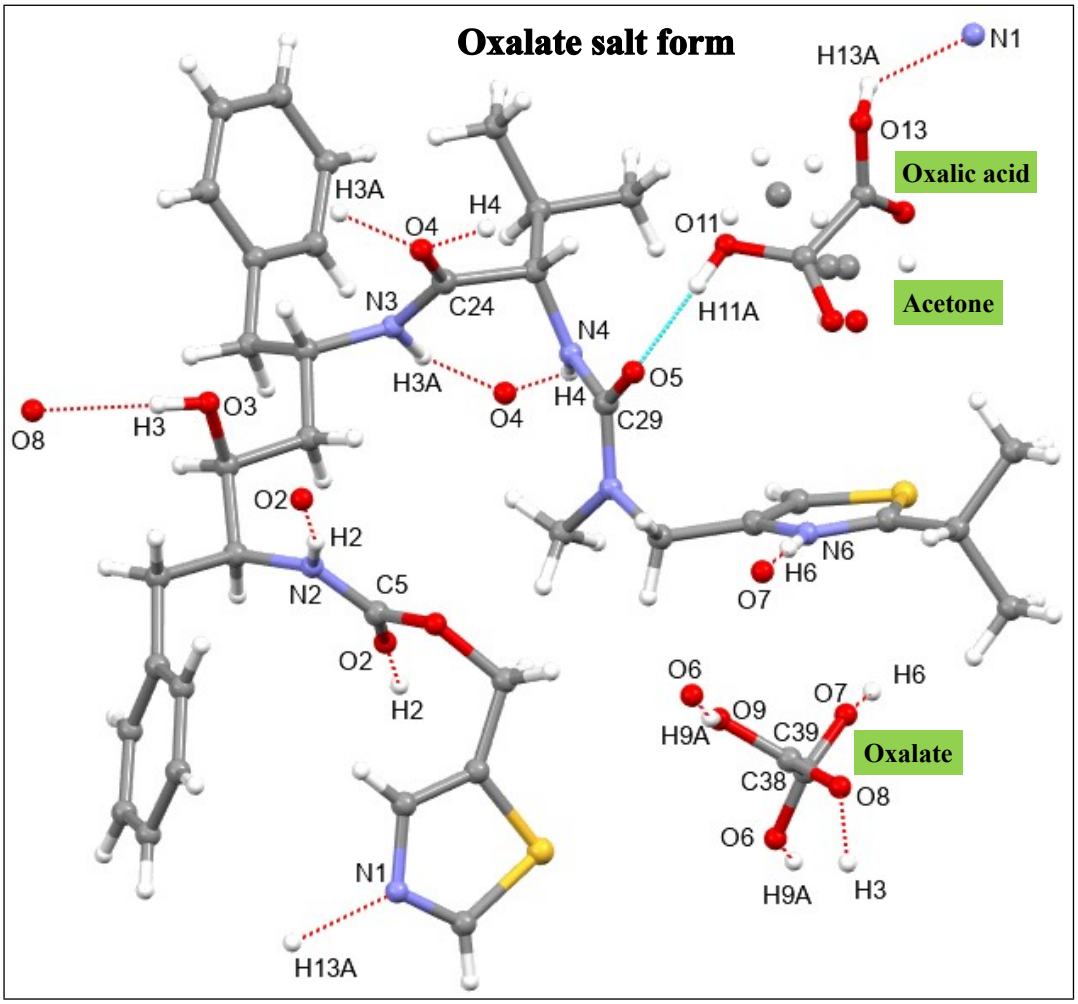
Table S1. The torsion angles (in degrees) of 16 torsions (τ_A, τ_B, τ_C, τ_D, τ_E, τ_F, τ_G, τ_H, τ_I, τ_J, τ_K, τ_L, τ_M, τ_N, τ_O, τ_P) and their differences between the new oxalate salt form and forms I, II and IIIb.

Torsion	(a) Form I	(b) Form II	(c) Form IIIb	(d) Oxalate Salt Form(this study)	Δ(a-b)	Δ(a-d)	Δ(b-d)	Δ(c-d)
τ_A	-23.8	165.6	177.0	170.6	170.6	165.6	5.0	6.4
τ_B	71.0	-72.8	46.1	48.5	143.8	22.5	121.3	2.4
τ_C	178.7	-5.8	173.7	-171.6	175.5	9.7	165.8	14.7
τ_D	55.9	168.3	173.3	-175.4	112.4	128.7	16.3	11.3
τ_E	-67.7	-56.8	-73.9	127.5	10.9	164.8	175.7	158.6
τ_F	110.8	124.6	104.6	-53.3	13.8	164.1	177.9	157.9
τ_G	56.8	65.8	53.5	-108.2	9.0	165.0	174.0	161.7
τ_H	-124.7	-112.8	-128.0	71.0	11.9	164.3	176.2	161.0
τ_I	93.7	-71.3	97.7	114.8	165.0	21.1	173.9	17.1
τ_J	-67.1	-62.3	-179.7	153.3	4.8	139.6	144.4	27.0
τ_K	112.0	122.2	3.7	-28.8	10.2	140.8	151.0	32.5
τ_L	-179.8	102.0	33.7	-68.4	78.2	111.4	170.4	102.1
τ_M	3.5	-74.2	-140.0	108.2	77.7	104.7	177.6	111.8
τ_N	84.7	76.6	89.5	-83.5	8.1	168.2	160.1	173.0
τ_O	-92.6	-104.8	-88.7	91.7	12.2	175.7	163.5	179.0
τ_P	175.4	178.7	166.2	-76.0	3.3	108.6	105.3	117.8

Note that the definitions of 16 torsion angles for form I, form II, form IIIb and the new oxalate salt form can be found in **Figures S3** and **S5**.

S4. Hydrogen Bonding Network Analysis: Major hydrogen binding motifs of form IIIb and new salt form





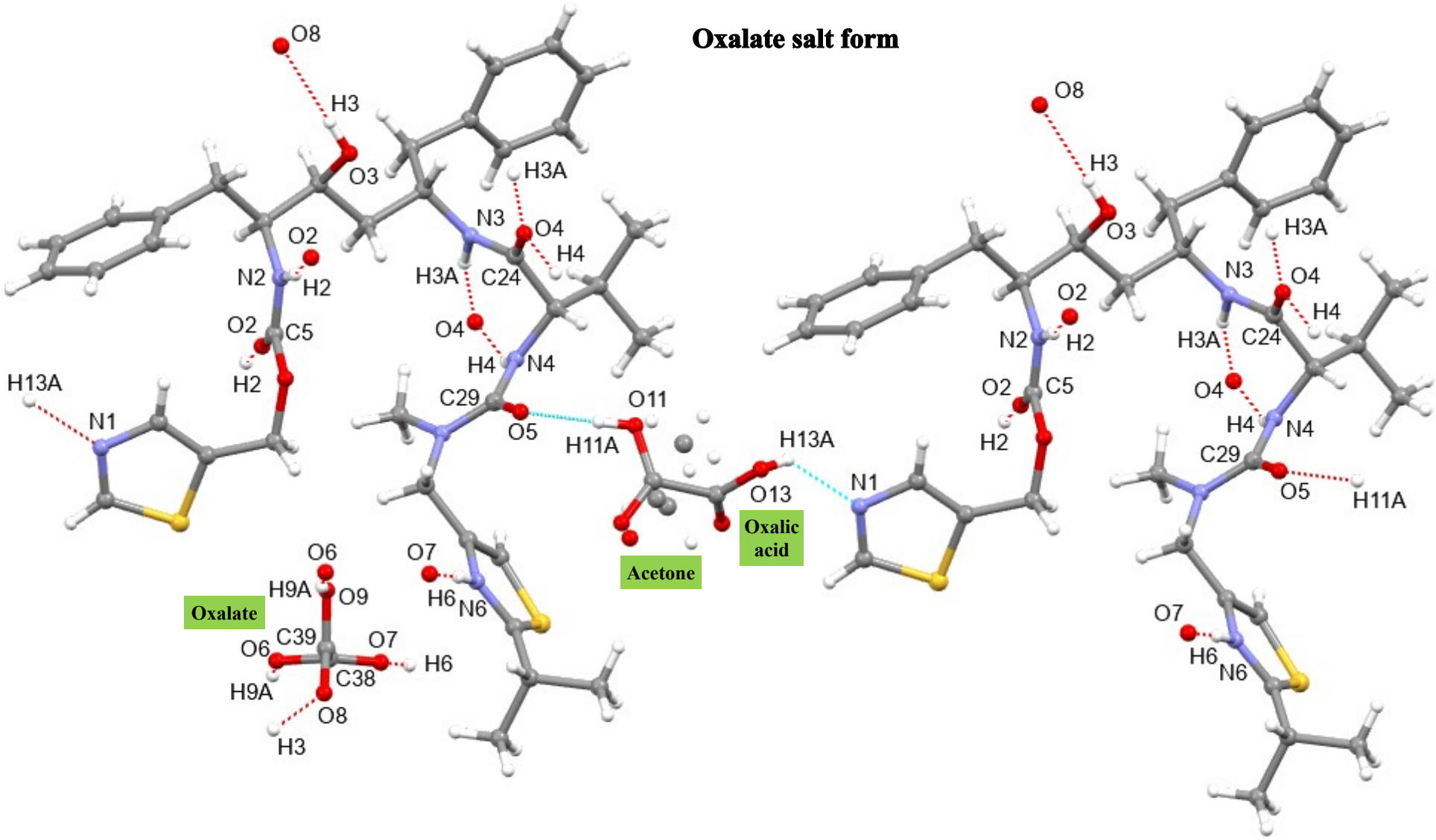
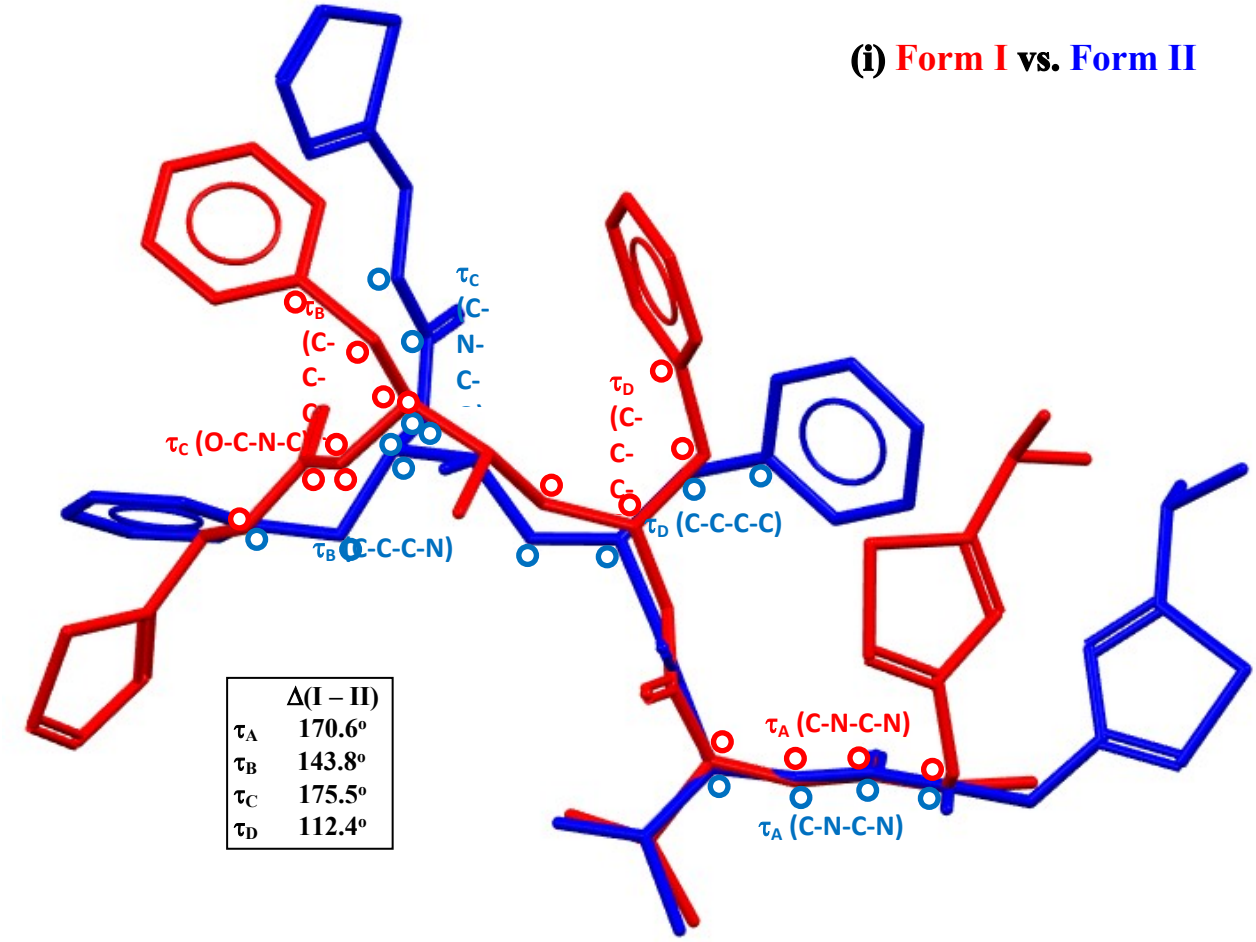
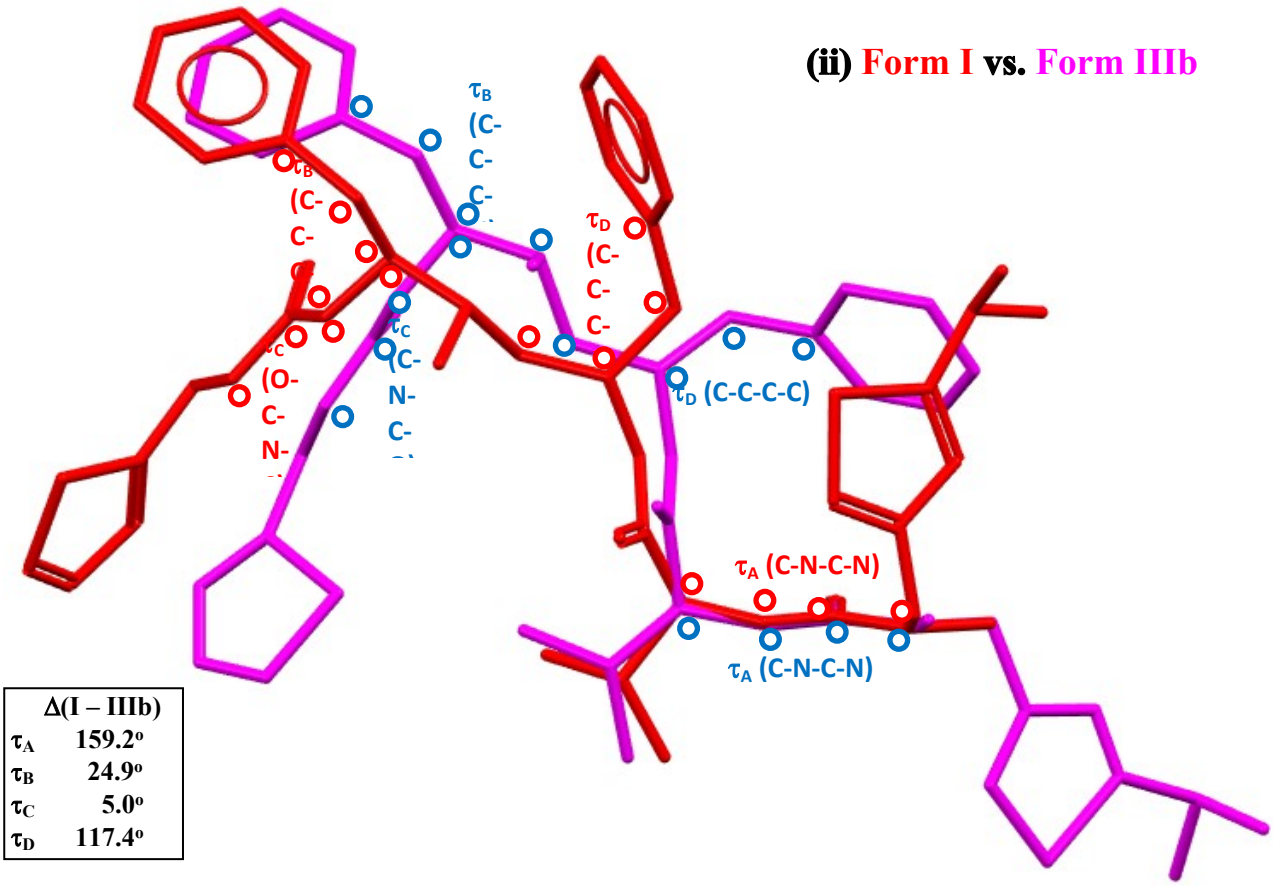


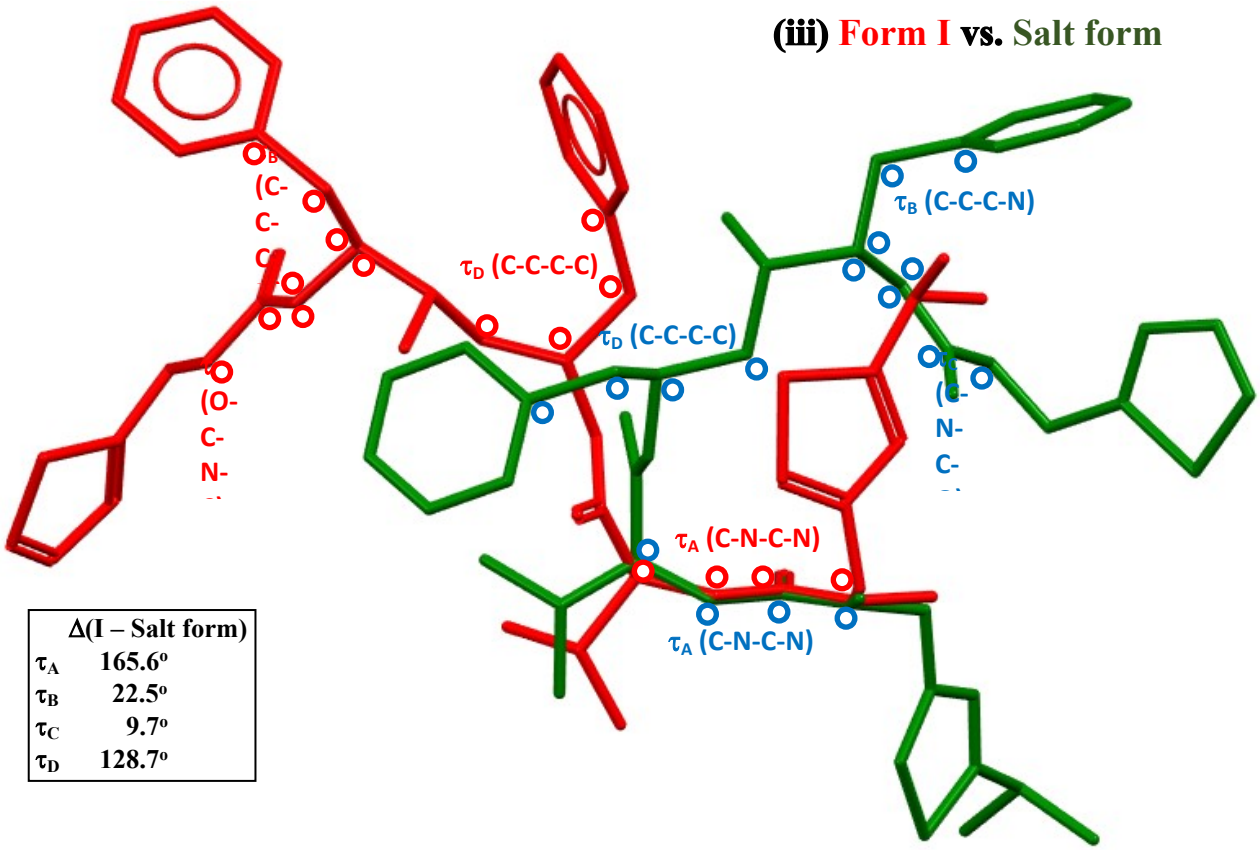
Figure S6. Four hydrogen bonds of form IIIb and Eight hydrogen bonds of ritonavir oxalate salt form as also listed in **Table 3**.

S5. Crystal Chemistry and Local Coordination



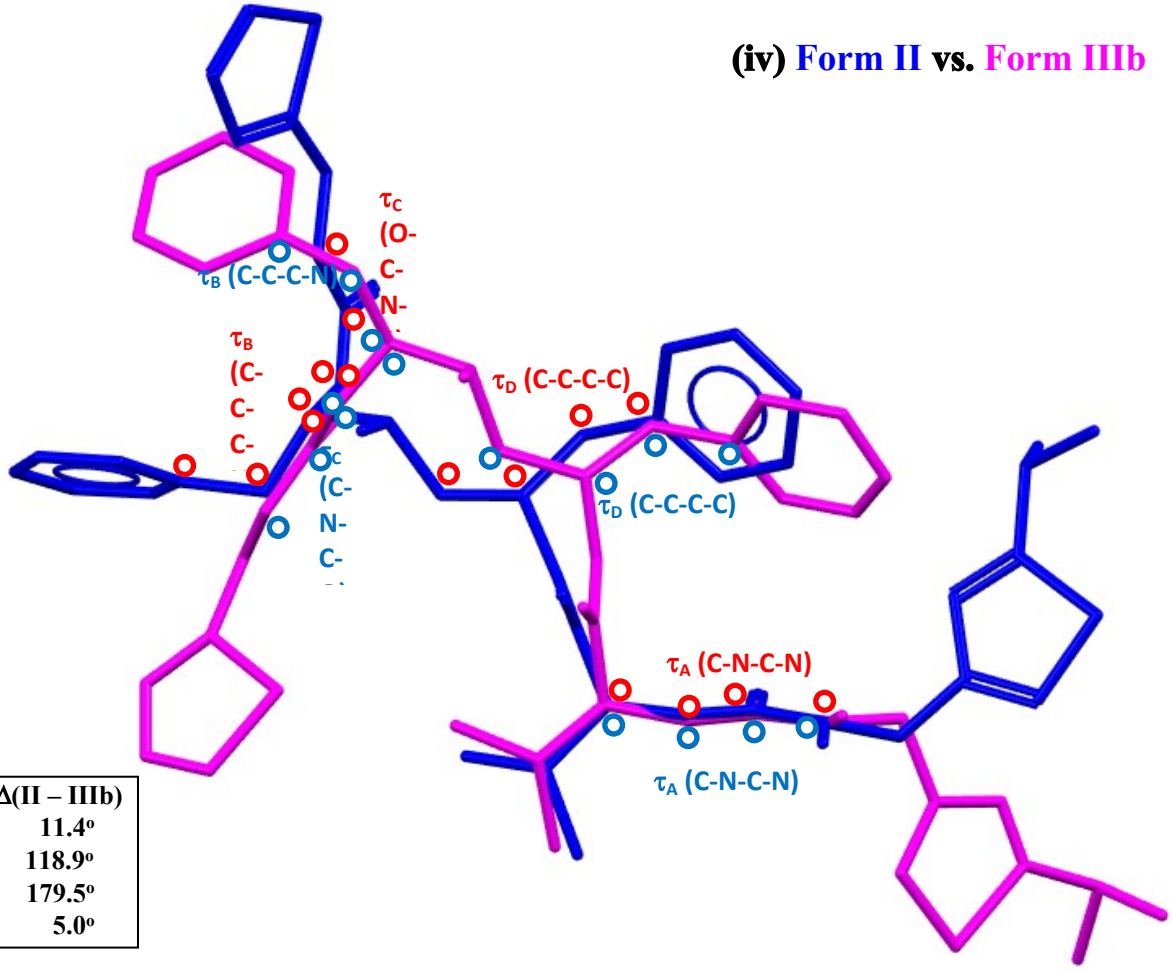


(iii) Form I vs. Salt form



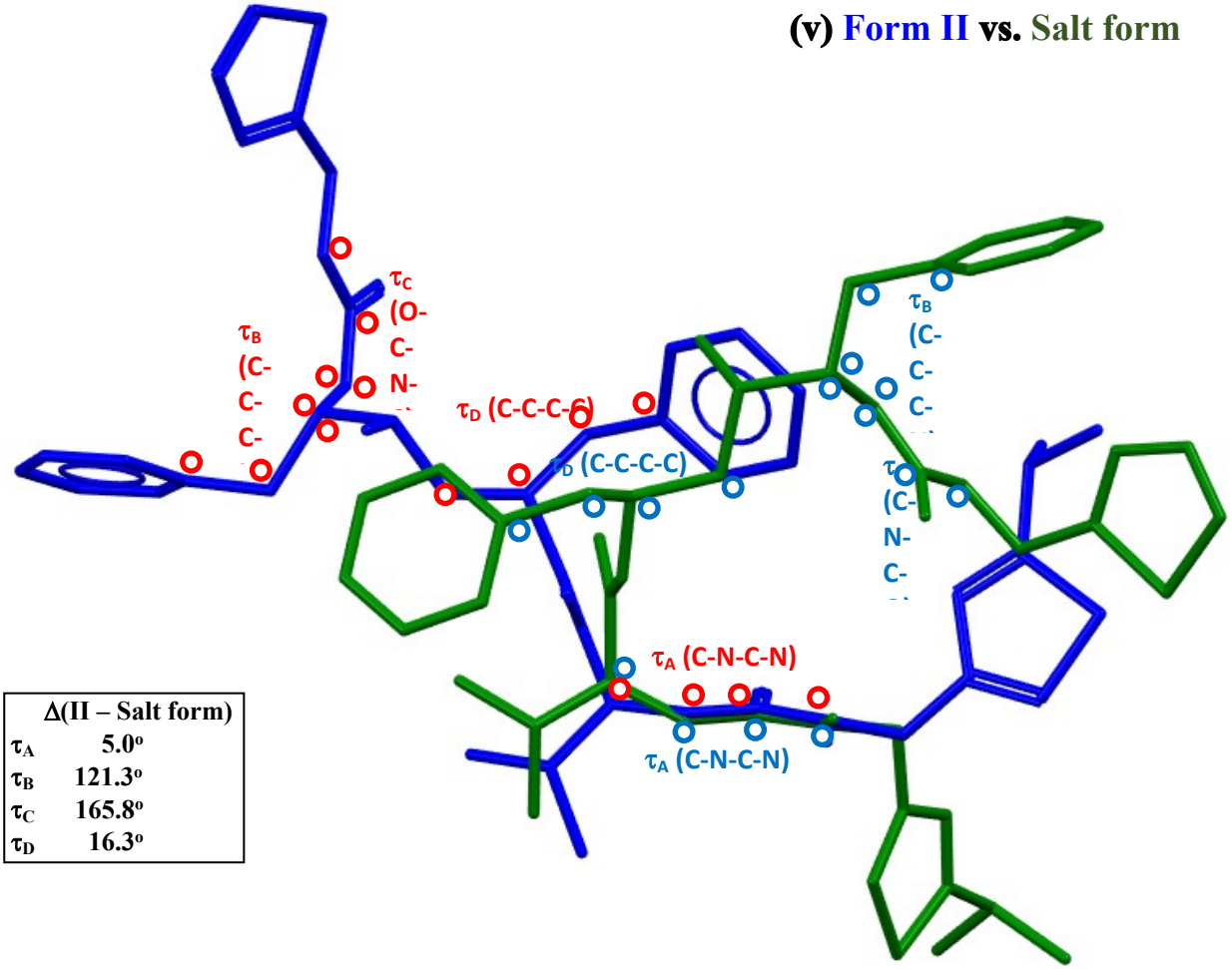
	Δ(I – Salt form)
τ_A	165.6°
τ_B	22.5°
τ_C	9.7°
τ_D	128.7°

(iv) Form II vs. Form IIIb



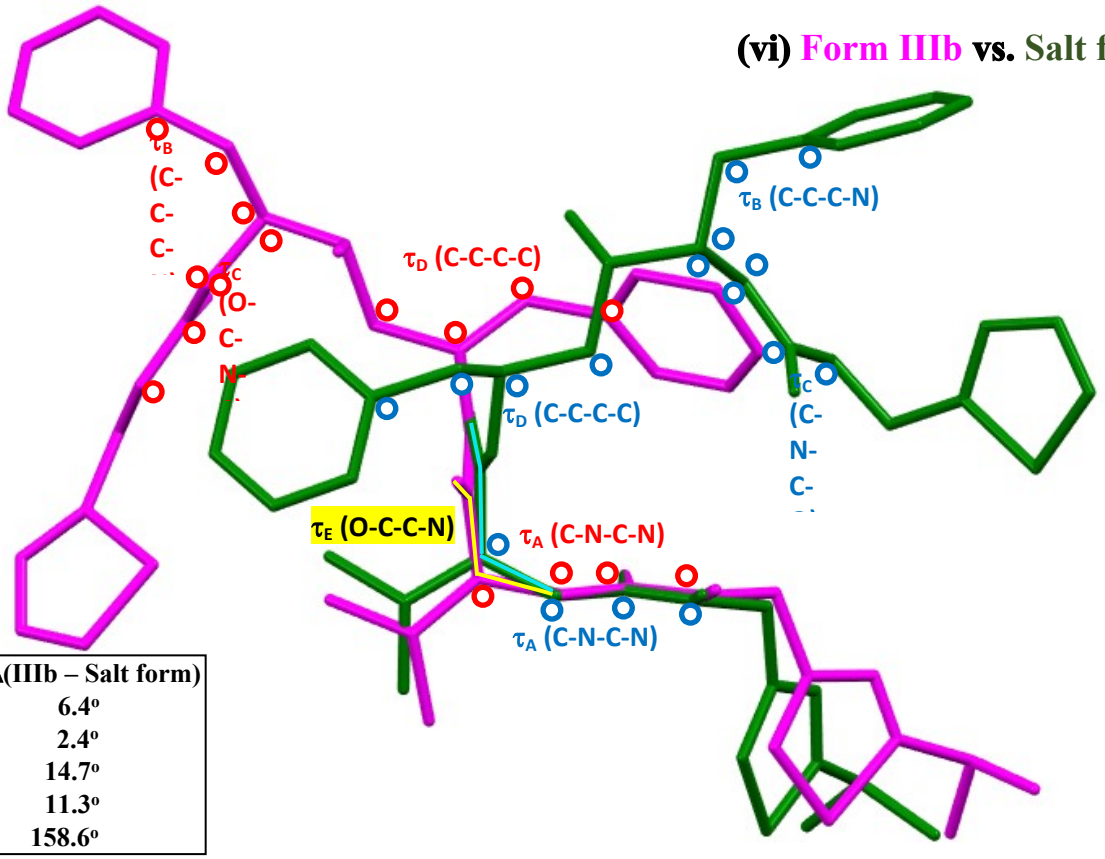
	Δ(II – IIIb)
τ_A	11.4°
τ_B	118.9°
τ_C	179.5°
τ_D	5.0°

(v) Form II vs. Salt form



Δ(II – Salt form)	
τ_A	5.0°
τ_B	121.3°
τ_C	165.8°
τ_D	16.3°

(vi) Form IIIb vs. Salt form



Δ(IIIb – Salt form)	
τ_A	6.4°
τ_B	2.4°
τ_C	14.7°
τ_D	11.3°
τ_E	158.6°

Figure S7. Comparisons of form I (red), form II (purple), form IIIb (magenta) and new oxalate salt form (green) with four torsions in red (form I, or II or IIIb), blue (oxalate salt form). Torsion τ_E (C-N-C-N) in (vi) is highlighted as yellow.

There are other torsion angles (τ_I, τ_J, τ_K, τ_L, τ_M, τ_N, τ_O, τ_P) which were found to exhibit large differences between these four forms and these are plotted in **Figure S5** and listed in **Table S1**. The torsions (τ_I, τ_J, τ_K) containing atoms from both thiazole 1 and τ_A have torsional differences of 21° / 174° between the oxalate salt form and form I / II with Δ(I - II) = 165°, and 140° / 144° between oxalate salt form and form I / II with Δ(I - II) = 5°, and 141° / 151° between oxalate salt form and form I / II with Δ(I - II) = 10° for torsions τ_I, τ_J, and τ_K, respectively. This indicates that only τ_I in the salt form is close to form I with large torsional angular differences being observed for the other cases. The similar comparisons of torsions (τ_I, τ_J, τ_K) revealed the similar trend (**Table S1**) for form IIIb with both form IIIb and oxalate salt form having < 33° differences of these torsions. For the torsions (τ_L, τ_M) related to Thiazole 1 and the isopropyl group, the isopropyl group in the oxalate salt form rotates about (105° ~ 111°), (170° ~ 178°) and (102° ~ 112°) compared to these in form I, form II and form IIIb, respectively. As shown in **Table S1** and **Figure S5**, the torsions (τ_N, τ_O) formed with the atoms from phenyl 1 and τ_D in the oxalate salt form molecular conformation have about a 160° – 180° angle of rotation compared to those in forms I, II and IIIb. The torsion (τ_P) of oxalate salt form determines the orientation of thiazole 2 which is ~110° away from the orientation found in form I or II or IIIb (**Table S1** and **Figure S5**). Interestingly, as shown in **Figure S7(vi)**, the ureido and thiazole 1 functional groups are roughly overlaid between form IIIb and new oxalate salt form. However, the rest of the molecular structures (including amide, hydroxyl, carbamate, thiazole 2 and two aromatic rings) of form IIIb and oxalate salt form rotate about 160° to each other as evidencing by the torsion angle τ_x in **Figure S7(vi)**.

Table S2. The calculated ΔpKa values for the functional groups in Ritonavir when using oxalic acid as a conformer / salt former, and % probability of co-crystal formation (AB) versus salt formation (A+ B-)

Oxalic Acid pKa	Ritonavir Functional Group	pKa	Δ pKa	% AB probability (H-bond)*	% A+B- probability (Salt Formation)*
1.27	**Thiazole 1**	4.05	2.78	24.74	75.26
	Thiazole 2	1.1	-0.17	74.89	25.11

*Probability % calculated from linear equations presented in [3]

References

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