Supporting Information for:

A tris(2-aminoethyl)amine-based zinc complex as a highly water-soluble drug carrier for the anti-COVID-19 drug favipiravir: A joint Experimental and Theoretical study

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Contains:

Table S1. Crystal data and structure refinement for **1**, **2** and **3** complexes.

Empirical formula	$C_{11}H_{23}ClFN_7O_3Zn$	$C_{12}H_{25}ClFN_7O_3Zn$	$C_{12}H_{36}Cl_6N_8Zn_3$
Formula weight	421.18	435.21	701.30
Temperature/K	100.0(2)	100.0(10)	100.0(2)
Crystal system	triclinic	monoclinic	monoclinic
Space group	P-1	Cc	P21/c
a/Å	7.5403(15)	13.1029(4)	8.0201(16)
b/Å	10.171(2)	18.5099(6)	16.781(3)
c/Å	11.342(2)	7.7230(2)	19.809(4)
α/°	79.19(3)	90	90
β/°	88.86(3)	90.067(3)	95.86(3)
γ/°	74.13(3)	90	90
Volume/Å^3	821.4(3)	1873.08(10)	2652.0(9)
Z	2	4	4
ρ_{calc}g/cm^3	1.703	1.543	1.756
μ/mm^{-1}	1.696	1.490	3.313
F(000)	436.0	904.0	1424.0
Crystal size/mm^3	0.04 × 0.01 × 0.01	0.59 × 0.18 × 0.11	0.04 × 0.005 × 0.005
Radiation	Synchrotron (λ = 0.71076Å)	Mo Kα (λ = 0.71073 Å)	Synchrotron (λ = 0.71092 Å)
2Θ range for data collection/°	3.658 to 58.414	6.218 to 60.744	3.188 to 64.358
Index ranges	-10 ≤ h ≤ 10, -13 ≤ k ≤ 13, -15 ≤ l ≤ 14	-18 ≤ h ≤ 18, -25 ≤ k ≤ 25, -10 ≤ l ≤ 10	-11 ≤ h ≤ 11, -25 ≤ k ≤ 25, -29 ≤ l ≤ 29
Reflections collected	21370	15847	91824
Independent reflections	3766 [Rint = 0.0424, Rsigma = 0.0297]	5008 [Rint = 0.0216, Rsigma = 0.0226]	8417 [Rint = 0.0331, Rsigma = 0.0156]
Data/restraints/parameters	3766/0/220	5008/2/228	8417/10/279
Goodness-of-fit on F^2	1.097	1.040	1.056
Final R indexes [I>=2σ (I)]	R1 = 0.0363, wR2 = 0.1044	R1 = 0.0183, wR2 = 0.0455	R1 = 0.0268, wR2 = 0.0740
Final R indexes [all data]	R1 = 0.0379, wR2 = 0.1058	R1 = 0.0193, wR2 = 0.0461	R1 = 0.0274, wR2 = 0.0744
Largest diff. peak/hole / e Å^{-3}	1.07/-0.92	0.32/-0.19	0.82/-1.22
Flack parameter		-0.005(3)	

Table S2. Selected Bond Lengths (Å) and Angles (°) for *N/O*-coordinated complexes and FAV anion in a previously reported organic salt [Ref. 45].

Bond lengths	***O*-coordinated**	***N*-coordinated**	**FAV Anion Ref. 45**	
Zn1-O1/N5	2.0192(15)	2.0992(18)		
Zn1-N1	2.3107(16)	2.3108(18)		
Zn1-N2	2.0505(17)	2.0542(19)		
Zn1-N3	2.0693(17)	2.0650(18)		
Zn1-N4	2.0690(17)	2.0992(18)		
F1-C9	1.356(2)	1.357(2)	1.352(3)	1.359(3)
O1-C7	1.286(2)	1.263(3)	1.280(3)	1.281(3)
O2-C11	1.237(3)	1.242(3)	1.244(3)	1.243(3)
N5-C7	1.356(3)	1.380(3)	1.368(3)	1.367(3)
N5-C8	1.320(3)	1.336(3)	1.317(4)	1.318(4)
N6-C9	1.301(3)	1.309(3)	1.297(3)	1.299(3)
N6-C10	1.341(3)	1.333(3)	1.333(3)	1.342(3)
N7-C11	1.333(3)	1.332(3)	1.321(3)	1.331(3)
C7-C10	1.430(3)	1.451(3)	1.443(3)	1.430(3)
C8-C9	1.376(3)	1.376(3)	1.379(4)	1.384(4)
C10-C11	1.503(3)	1.503(3)	1.495(3)	1.495(3)
Angles				
O1/N5-Zn1-N1	172.75(6)	178.23(6)		
O1/N5-Zn1-N2	105.95(7)	101.41(7)		
O1/N5-Zn1-N3	100.78(7)	99.17(7)		
O1/N5-Zn1-N4	92.56(6)	99.31(7)		
N2-Zn1-N1	79.73(6)	80.29(7)		
N2-Zn1-N3	118.97(7)	120.37(7)		
N2-Zn1-N4	117.67(7)	110.24(8)		
N3-Zn1-N1	79.87(6)	80.33(7)		
N4-Zn1-N1	80.70(6)	79.56(7)		
N4-Zn1-N3	114.66(7)	120.60(8)		
Torsion Angles				
N2-Zn1-O1/N5-C7	-40.82(17)	161.89(13)		
N3-Zn1-O1/N5-C7	83.73(16)	-74.40(14)		
N4-Zn1-O1/N5-C7	-160.57(16)	48.89(14)		
N1-C1-C2-N2	53.2(2)	-53.2(2)		
N1-C3-C4-N3	56.8(2)	-54.5(2)		
N1-C5-C6-N4	57.2(2)	-50.8(2)		

Table S3. Calculated[a] **gas phase** electronic energies, enthalpies and Gibbs free energies (Hartree) of optimized structures of all studied conformers of keto and enol tautomers of FAV at M06-D3/def2-TZVPP level of theory.

	E (Eel + ZPE)	H	G
Enol-1	-607.324520	-607.314926	-607.358484
Enol-1'	-607.311484	-607.301387	-607.346699
Enol-2	-607.307899	-607.297823	-607.343288
Keto-1	-607.306247	-607.296389	-607.340967
Keto-2	-607.301249	-607.291122	-607.336658
Enol-2'	-607.300596	-607.290785	-607.335041

Table S4. Solvation energies (G_{solv}, Hartree) and Gibbs free energies (G_{solut}, Hartree)[a] of the studied keto and enol isomers/conformers of FAV in H_2O, CH_3OH and DMSO solutions at M06-D3/def2-TZVPP level of theory.

	H_2O		**CH_3OH**		**DMSO**	
Conformer/ isomer	**G_{solv}**	**G_{solut}**	**G_{solv}**	**G_{solut}[a]**	**G_{solv}**	**G_{solut}[a]**
Enol-1						
PCM	-0.01045402	-607.368938	-0.01015124	-607.368635	-0.010310601	-607.368794
CPCM	-0.01053370	-607.369018	-0.01031060	-607.368794	-0.010422153	-607.368906
SMD	-0.01627067	-607.374754	-0.01344999	-607.371934	-0.013226891	-607.371711
Enol-1'						
PCM	-0.01351374	-607.360213	-0.01309940	-607.359798	-0.013306571	-607.360005
CPCM	-0.01360935	-607.360308	-0.01332250	-607.360021	-0.013465931	-607.360165
SMD	-0.02197576	-607.368675	-0.01996782	-607.366667	-0.014677068	-607.361376
Enol-2						
PCM	-0.01623880	-607.359527	-0.01572884	-607.359017	-0.015983821	-607.359272
CPCM	-0.01635035	-607.359638	-0.01598382	-607.359272	-0.016175054	-607.359463
SMD	-0.02482831	-607.368116	-0.02215106	-607.365439	-0.017210895	-607.360498
Keto-1						
PCM	-0.02113115	-607.362098	-0.02047778	-607.361445	-0.020812434	-607.361779
CPCM	-0.02127458	-607.362242	-0.02079650	-607.361763	-0.021051474	-607.362018
SMD	-0.02868482	-607.369652	-0.02739401	-607.368361	-0.025115157	-607.366082
Keto-2						
PCM	-0.02197576	-607.358633	-0.02129051	-607.357948	-0.021641106	-607.358299
CPCM	-0.02211919	-607.358777	-0.02160923	-607.358267	-0.021880147	-607.358538
SMD	-0.03019874	-607.366857	-0.02930633	-607.365964	-0.025513558	-607.362171
Enol-2'						
PCM	-0.01719496	-607.352236	-0.01663719	-607.351678	-0.016924046	-607.351965
CPCM	-0.01732244	-607.352363	-0.01695592	-607.351997	-0.017147150	-607.352188
SMD	-0.02656533	-607.361606	-0.02315503	-607.358196	-0.020573393	-607.355613

[a] $G_{solut} = G_{gas} + G_{solv}$

Table S5. Calculated Gibbs free energies (G, Hartree) of the optimized structures of studied keto and enol isomers/conformers of FAV in H_2O, CH_3OH and DMSO solutions at M06-D3/def2-TZVPP level of theory.

Isomer/conformer	Solvent	Model		
		PCM	CPCM	SMD
	H_2O			
Enol-1		-607.369620	-607.369695	-607.376366
Keto-1		-607.362384	-607.362537	-607.371100
Enol-1'		-607.360765	-607.360850	-607.368290
Enol-2		-607.359870	-607.359975	-607.368966
Keto-2		-607.359552	-607.359680	-607.368387
Enol-2'		-607.353062	-607.353222	-607.363991
	CH_3OH			
Enol-1		-607.369282	-607.369456	-607.373305
Keto-1		-607.361684	-607.362037	-607.369494
Enol-1'		-607.360343	-607.360547	-607.368252
Enol-2		-607.359387	-607.359590	-607.366170
Keto-2		-607.358853	-607.359157	-607.367883
Enol-2'		-607.352447	-607.352814	-607.360190
	DMSO			
Enol-1		-607.369456	-607.369580	-607.372455
Keto-1		-607.362045	-607.362296	-607.366935
Enol-1'		-607.360562	-607.360704	-607.361846
Enol-2		-607.359636	-607.359790	-607.362173
Keto-2		-607.359214	-607.359424	-607.363234
Enol-2'		-607.352764	-607.353026	-607.356860

Table S6. The comparison of calculated[a] and experimental selected distances (Å) for $[Zn(tren)(N\text{-}FAV)]^+$ and $[Zn(tren)(O\text{-}FAV)]^+$ complexes.

Bond	**$[Zn(tren)(N\text{-}FAV)]^+$**		**$[Zn(tren)(O\text{-}FAV)]^+$**	
	Exp.	Theo.	Exp.	Theo.
Length				
Zn1-O1/N5	2.0992(18)	2.0354	2.0192(15)	1.9494
Zn1-N1	2.3108(18)	2.3198	2.3107(16)	2.3502
Zn1-N2	2.0542(19)	2.1478	2.0505(17)	2.1179
Zn1-N3	2.0650(18)	2.1331	2.0693(17)	2.1128
Zn1-N4	2.0992(18)	2.1374	2.0690(17)	2.1233
Angle				
O1/N5-Zn1-N1	178.23(6)	173.87	172.75(6)	178.09
O1/N5-Zn1-N2	101.41(7)	105.99	105.95(7)	100.54
O1/N5-Zn1-N3	99.17(7)	100.24	100.78(7)	102.83
O1/N5-Zn1-N4	99.31(7)	97.33	92.56(6)	99.66
N2-Zn1-N1	80.29(7)	79.77	79.73(6)	78.37
N2-Zn1-N3	120.37(7)	110.71	118.97(7)	124.20
N2-Zn1-N4	110.24(8)	110.11	117.67(7)	112.76
N3-Zn1-N1	80.33(7)	79.28	79.87(6)	79.06
N4-Zn1-N1	79.56(7)	78.47	80.70(6)	79.41
N4-Zn1-N3	120.60(8)	128.51	114.66(7)	112.13

[a] At the M06-D3/def2-TZVPP level of theory

Table S7. The calculated[a] and experimental data for intramolecular hydrogen bond in $[Zn(tren)(N\text{-}FAV)]^+$ and $[Zn(tren)(O\text{-}FAV)]^+$ complexes.

Complex	**X-Ray**		
	d(D-H)/Å	d(H-A)/Å	D-H-A/°
N-Coord	0.86	1.94	139.3
O-Coord	0.88	1.94	137.3
	Theo.		
N-Coord	1.00	1.95	133.7
O-Coord	1.00	1.94	132.9

[a] At the M06-D3/def2-TZVPP level of theory

Table S8. Calculated interaction energy (IE, kcal/mol) between the FAV anion and $[Zn(tren)]^{2+}$ cation in $[Zn(tren)(N\text{-FAV})]^{+}$ and $[Zn(tren)(O\text{-FAV})]^{+}$ complexes, and also their total interaction energy ($IE_{total,}$ kcal/mol) at the M06-D3/def2-TZVPP and B3LYP/def2-TZVPP levels of theory

	M06-D3		B3LYP	
	O-Coord	**N-Coord**	**O-Coord**	**N-Coord**
IE	-208.80	-210.57	-199.03	-199.28
IE_{total}[a]	-561.43	-561.00	-554.25	-551.72

[a] $IE_{total} = E_{Complex} - (E_{FAV} + E_{Zn} + E_{tren})$

Table S9. Gas phase calculated[a] electronic energy (E, kcal/mol) and Gibbs free energy (G, kcal/mol) of *N/O*-coordinated complexes of FAV and the transition state (TS) of interconversion between them

	E (E_{el} + ZPE)	$\mathbf{G_{gas}}$
$[Zn(tren)(O\text{-FAV})]^{+}$	-2844.047176 (0.29)[b]	-2844.099479 (0.00)
$[Zn(tren)(N\text{-FAV})]^{+}$	-2844.047644 (0.00)	-2844.099300 (0.11)
TS	-2844.042242 (3.39)	-2844.093907 (3.49)

[a] At M06-D3/def2-TZVPP level of theory

[b] Figures in parentheses show their relative energies

Table S10. Comparison of calculated solvation energies for *N/O*-coordinated complexes of FAV and the transition state (TS) of interconversion between them

	G_{solv}					
	SMD			CPCM		
	CH_3OH	H_2O	DMSO	CH_3OH	H_2O	DMSO
$[Zn(tren)(O\text{-FAV})]^{+}$	-80.68	-76.73	-76.52	-64.08	-65.41	-64.77
$[Zn(tren)(N\text{-FAV})]^{+}$	-79.28	-75.78	-75.13	-63.36	-64.68	-64.04
TS	-80.36	-76.73	-75.96	-63.37	-64.69	-64.06

Table S11. Calculated[a] **gas phase** electronic energies, enthalpies and Gibbs free energies (Hartree) of all species involved in equations **1-3**[b]

	E (E_{el} +ZPE)	**H**	**G**
$[Zn(tren)(N\text{-}FAV)]^+$	-2844.047644	-2844.024320	-2844.099300
$[Zn(tren)(O\text{-}FAV)]^+$	-2844.047176	-2844.023776	-2844.099479
$[Zn(tren)Cl]^+$	-2697.545260	-2697.530060	-2697.586074
FAV	-607.324520	-607.314926	-607.358484
H_2O	-76.404885	-76.401105	-76.423165
H_3O^+	-76.669535	-76.665657	-76.688667
Cl^-	-460.249229	-460.246869	-460.264252
CH_3OH_2	-115.936896	-115.932084	-115.961361
CH_3OH	-115.651860	-115.647497	-115.674698
$[ZnTrenH_2O]^{2+}$	-2313.376398	-2313.360160	-2313.417333

[a]At M06-D3/def2-TZVPP level of theory
[b] see manuscript

Table S12. Calculated[a] electronic energies (ΔE, kcal/mol), enthalpies (ΔH, kcal/mol), and Gibbs free energies (ΔG, kcal/mol) of the **gas phase** protonation process of *N/O*-coordinated complexes by considering equations **1-3**[b]

Eq.	**Isomer**	**ΔE**	**ΔH**	**ΔG**
(1)	O-Coord	-193.73	-194.39	-197.87
	N-Coord	-193.43	-194.05	-197.98
(2)	O-Coord	-180.93	-181.82	-184.59
	N-Coord	-180.64	-181.48	-184.70
(3)	O-Coord	9.91	9.00	7.73
	N-Coord	10.20	9.34	7.62

[a] At M06-D3/def2-TZVPP level of theory
[b] see manuscript

Table S13. Solvation energies of all species involved in equations **1-3**[b] in H_2O and CH_3OH solutions

H_2O	**PCM**	**CPCM**	**SMD**
$[Zn(tren)(N\text{-}FAV)]^+$	-64.52	-64.68	-75.78
$[Zn(tren)(O\text{-}FAV)]^+$	-65.27	-65.41	-76.73
$[Zn(tren)Cl]^+$	-56.46	-56.53	-63.54
FAV	-6.56	-6.61	-10.21
H_2O	-4.22	-4.24	-7.36
H_3O^+	-77.36	-77.37	-95.57
Cl^-	-72.92	-72.92	-67.29
$[Zn(tren)H_2O]^{2+}$	-165.80	-165.82	-184.96
CH_3OH			
$[Zn(tren)(N\text{-}FAV)]^+$	-63.01	-63.36	-79.28
$[Zn(tren)(O\text{-}FAV)]^+$	-63.76	-64.08	-80.68
$[Zn(tren)Cl]^+$	-55.30	-55.45	-69.68
FAV	-6.37	-6.47	-8.44
H_2O	-4.10	-4.16	-7.45
H_3O^+	-75.95	-75.96	-95.52
Cl^-	-71.59	-71.59	-67.86
$CH_3OH_2^+$	-65.34	-65.35	-79.69
CH_3OH	-2.89	-2.94	-4.65

[b] see manuscript

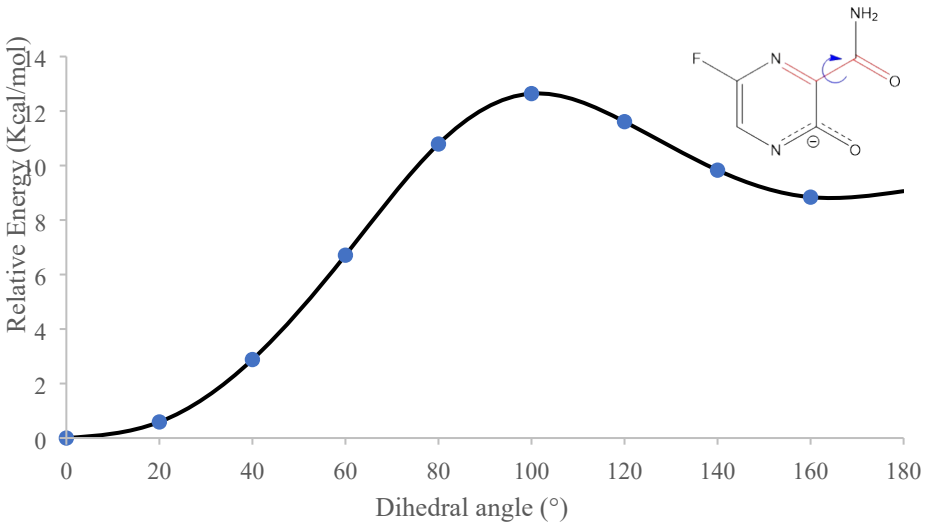

Figure S1. Potential energy scan for the rotation of the carboxamide group on the favipiravir anion.

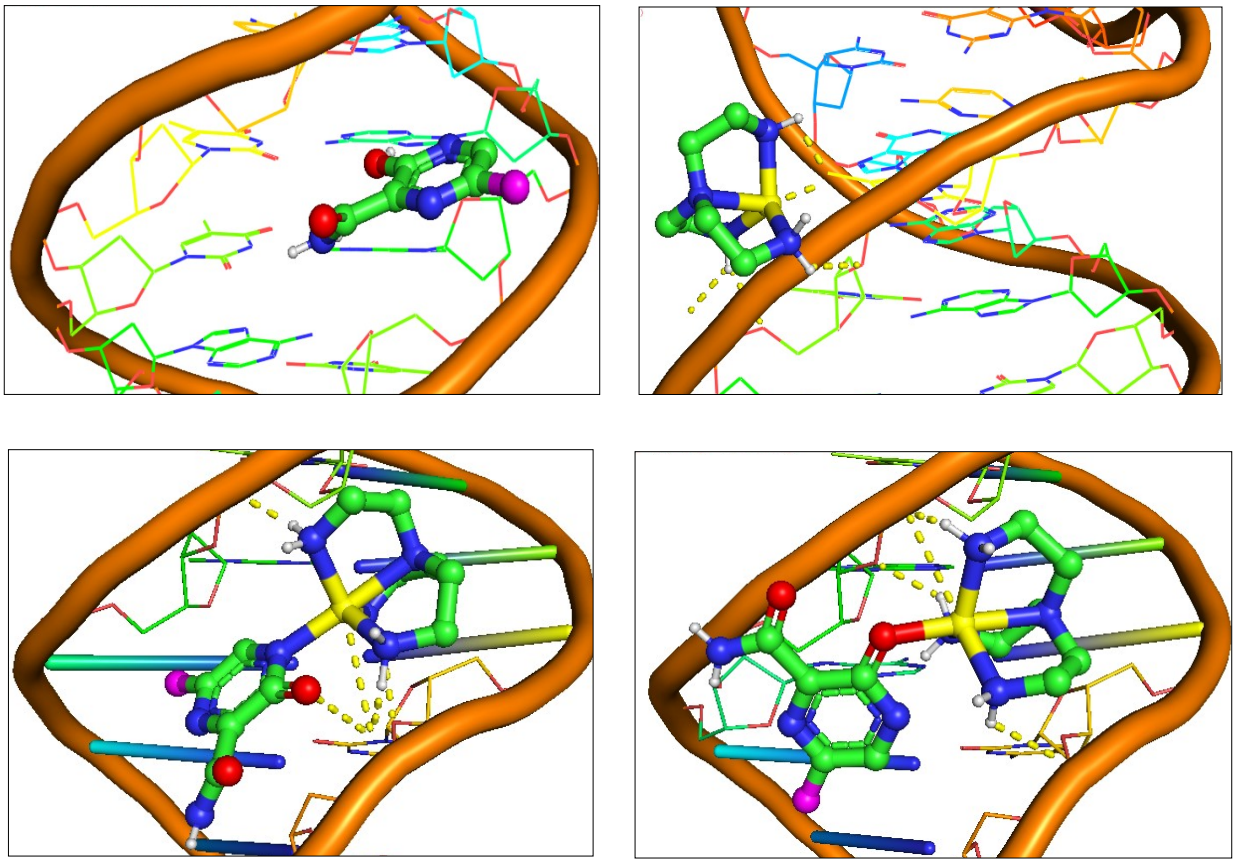

Figure S2. AutoDock4 poses of FAV (a), Drug carrier (b), *O*-Coord complex (c) and *N*-Coord complex (d) in the interaction with DNA (PDB ID: 1BND)