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Novel Molecular Adducts of An Anti-cancer Drug Vandetanib with Enhanced Solubility

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Table of Figures:

List of Tables:

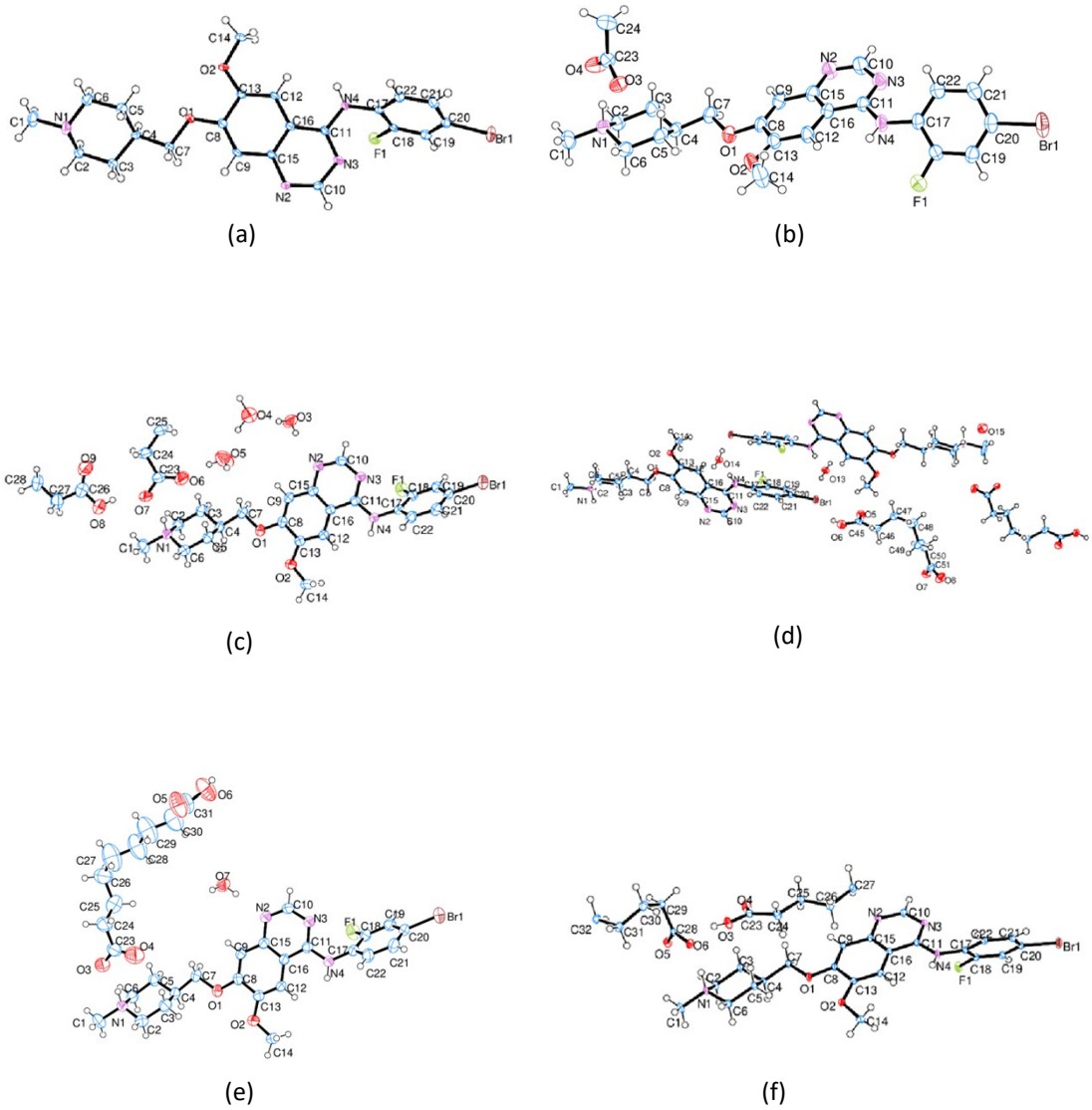

Figure S1. ORTEP diagrams of (a) VDTB, (b) VDTB: SUA, (c) VDTB: ADA: 3H2O, (d) VDTB: PIA: 1.25H2O, (e) VDTB: AZA: H2O, (f) VDTB: SBA. Herein, the ellipsoids are drawn with a 50% probability.

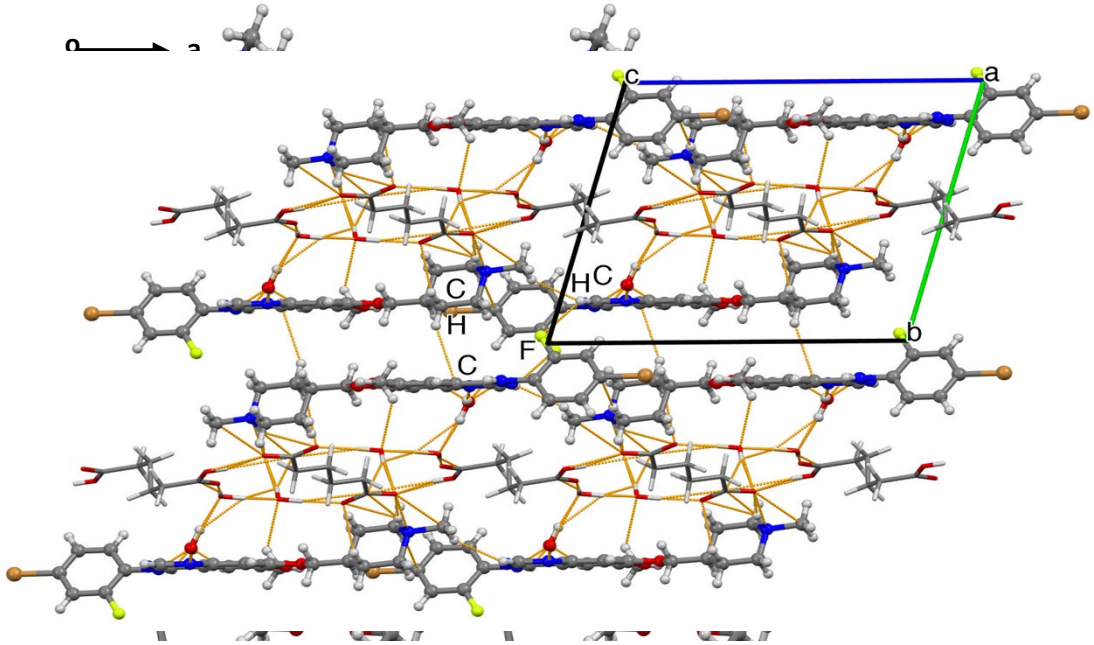

Figure S4. Packing diagram of VDTB: ADA: $3H_2O$, showing C–H···π and C–H···F short contact interactions.

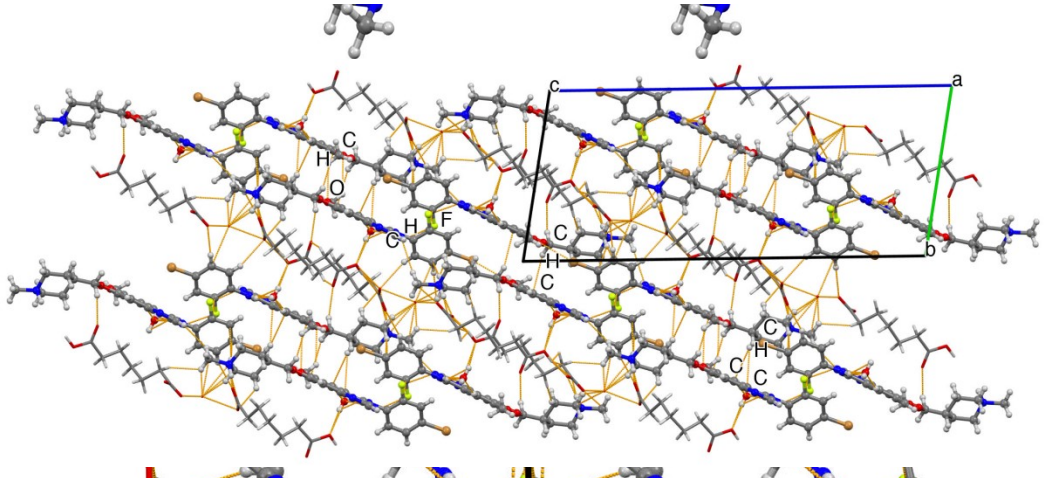

Figure S5. Packing diagram of VDTB: PIA: $1.25H_2O$, showing C–H···F, C–H···O and C–H···π short contact interactions.

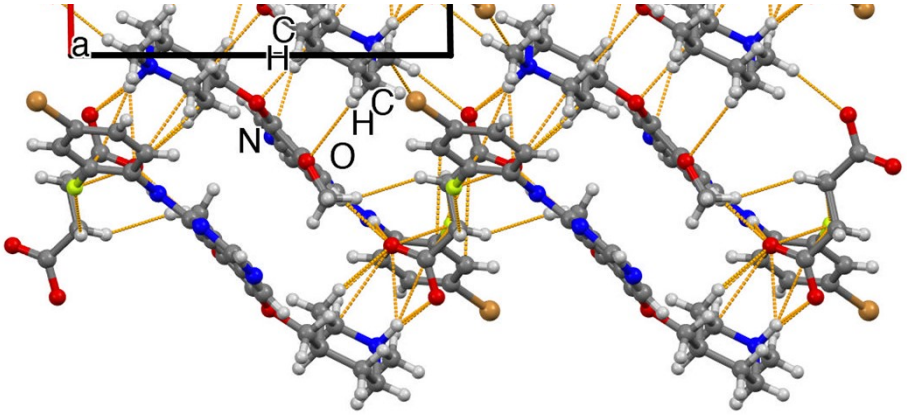

Figure S3. Packing diagram of VDTB: SUA, showing C−H···N and C−H···O short contact interactions.

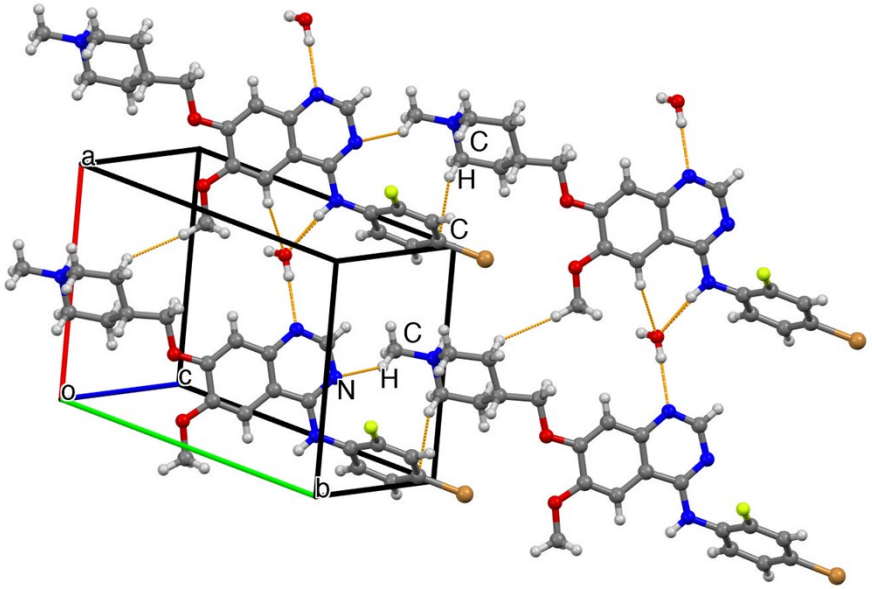

Figure S6. 2D sheet structure formed by the C–H···N and C–H···π interaction between VDTB: H_2O chains in VDTB: AZA: H_2O.

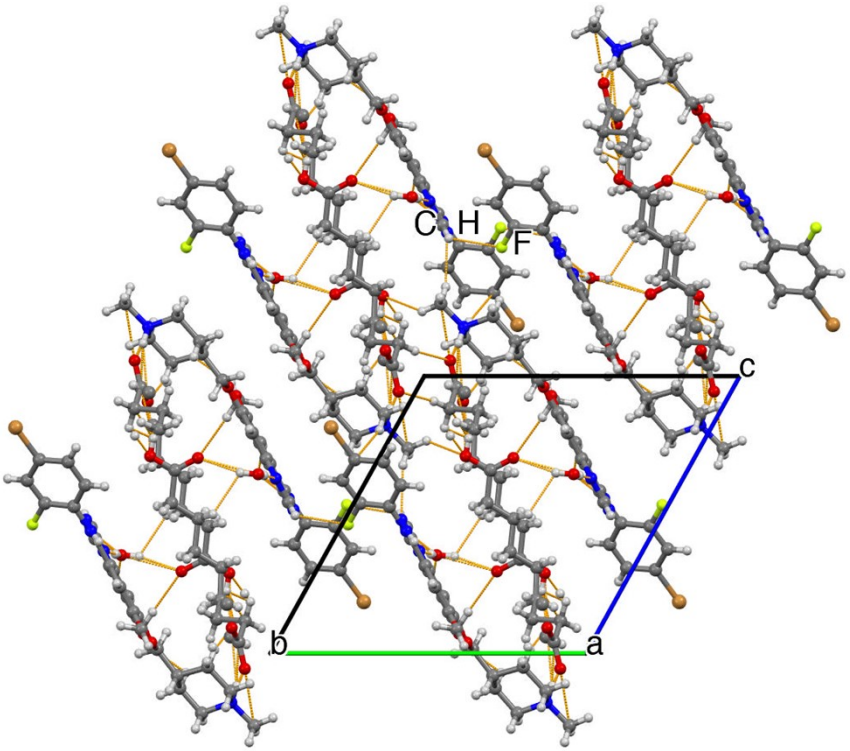

Figure S7. Packing diagram of VDTB: AZA: H_2O, showing C–H···F short contact interactions.

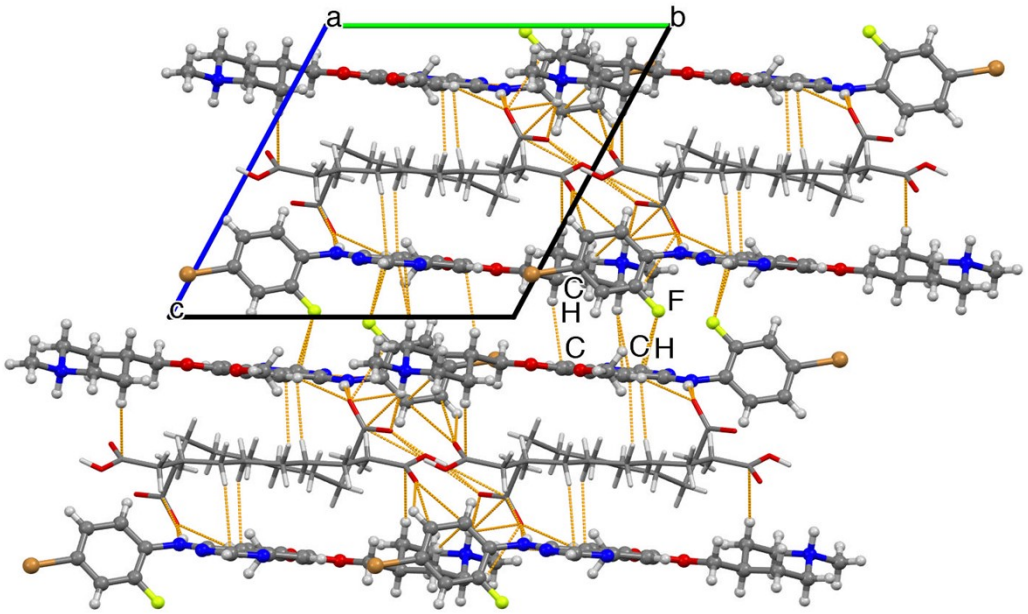

Figure S8. Packing diagram of VDTB: SBA showing C−H···C and C−H···F short contact interactions.

Table S1. Hydrogen bond distances (Å) and angles (°) of the molecular salts of VDTB.

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
VDTB				
N4-H4···N2#1	0.86	2.08	2.902(5)	158.6
#1	x-1/4, -y+3/4, z+1/4			
VDTB: ADA: 3H$_2$O				
N1-H1···O7	0.98	1.74	2.677(3)	157.6
O3-H1I···N2	0.70(5)	2.18(5)	2.875(3)	167.0(5)
N4-H4A···O3#1	0.86	2.09	2.844(3)	146.5
O5-H1F···O7#3	0.76(5)	2.22(5)	2.971(4)	171.0(5)
O8-H8···O7	0.82	1.82	2.602(3)	158.9
O5-H1G···O6	0.95(4)	1.78(5)	2.712(4)	170.0(4)
O4-H1E···O5	0.99(3)	1.75(3)	2.723(4)	165.0(4)
O4-H1D···O9#2	1.01(3)	1.84(3)	2.849(4)	177.0(4)
O3-H1H···O4	0.90(4)	1.91(5)	2.783(4)	163.0(4)
#1	x+1, y, z			
#2	-x, -y+1, -z+1			
#3	-x+1, -y+1, -z+1			
VDTB: AZA: H$_2$O				
N1-H1···O3	0.98	1.69	2.618(4)	157
O7-H1E···N2	0.81(5)	2.03(5)	2.840(4)	176.0(5)
N4-H4···O7#1	0.86	2.04	2.878(4)	162.9
O7-H1D···O5#2	0.81(5)	2.08(5)	2.858(4)	162.0(5)
O6-H6···O4#2	0.82	1.7	2.496(5)	161.8
#1	x+1, y, z			

#2	-x, -y+1, -z+1			
VDTB: SBA				
N1-H1···O6	1	1.66	2.6579(15)	173.7
O3-H3···O6	0.85	1.83	2.6457(14)	162.2
N4-H4···O5#1	0.88	1.93	2.7879(14)	163.9
#1	x, y-1, z			
VDTB: SUA				
N1-H1···O4	0.98	1.66	2.633(3)	170.6
N4-H4···O3#1	0.86	1.99	2.823(3)	164.4
#1	-x+1, -y+1, -z+1			
VDTB: PIA:1.25H_2O				
N1-H1···O9#5	0.98	1.73	2.704(5)	174.9
O14-H1E···N2#1	0.77(4)	2.03(4)	2.788(4)	171.0(5)
N4-H1D···O14	0.85(4)	2.02(5)	2.851(4)	167.0(5)
N5-H5···O8#2	0.98	1.78	2.704(5)	156.2
O13-H1H···N6#6	0.87(4)	1.93(4)	2.790(4)	174.0(4)
N8-H1EE···O13	0.92(4)	1.96(5)	2.851(4)	165.0(4)
O12-H1J···O9#8	0.95(5)	1.58(5)	2.516(4)	170.0(5)
O14-H1G···O12#3	0.80(5)	2.12(5)	2.856(5)	154.0(5)
O6-H1F···O7#7	0.86(5)	1.70(5)	2.521(5)	160.0(5)
O13-H1I···O6#4	0.70(5)	2.18(5)	2.858(5)	164.0(6)
#1	x-1, y, z			
#2	x-1, y+1, z			
#3	x, y, z-1			
#4	x, y+1, z			
#5	x+1, y, z-1			
#6	x+1, y, z			
#7	-x+1, -y, -z+1			
#8	-x+1, -y+1, -z+2			

Table S2. Details of the temperature range and the accompanying TGA weight loss of VDTB and its respective salt forms.

Solid form	Molecular weight of empirical formula	% wight of H_2O	Experimental weight loss % observed TGA	Inference
VDTB	475.35	-	0.4	Negligible (due to adsorbed moisture)
VDTB: ADA: $3H_2O$	675.54	7.99	7.23	Complies
VDTB: AZA: H_2O	681.59	2.64	2.72	Complies
VDTB: PIA: $1.25H_2O$	657.53	3.42	3.46	Complies
VDTB: SBA	677.60	-	-	-
VDTB: SUA	566.40	-	-	-

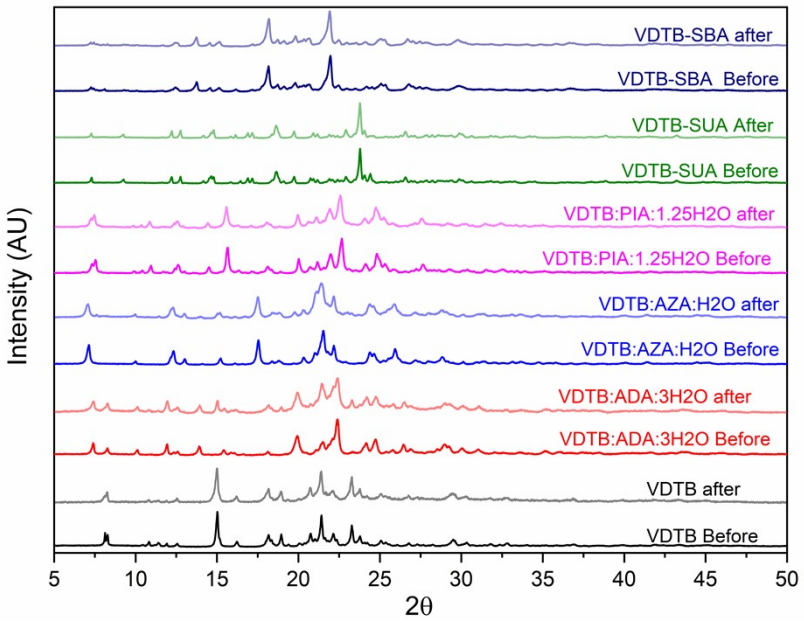

Figure S9. PXRD patterns of VDTB and its molecular salts before and after DVS.

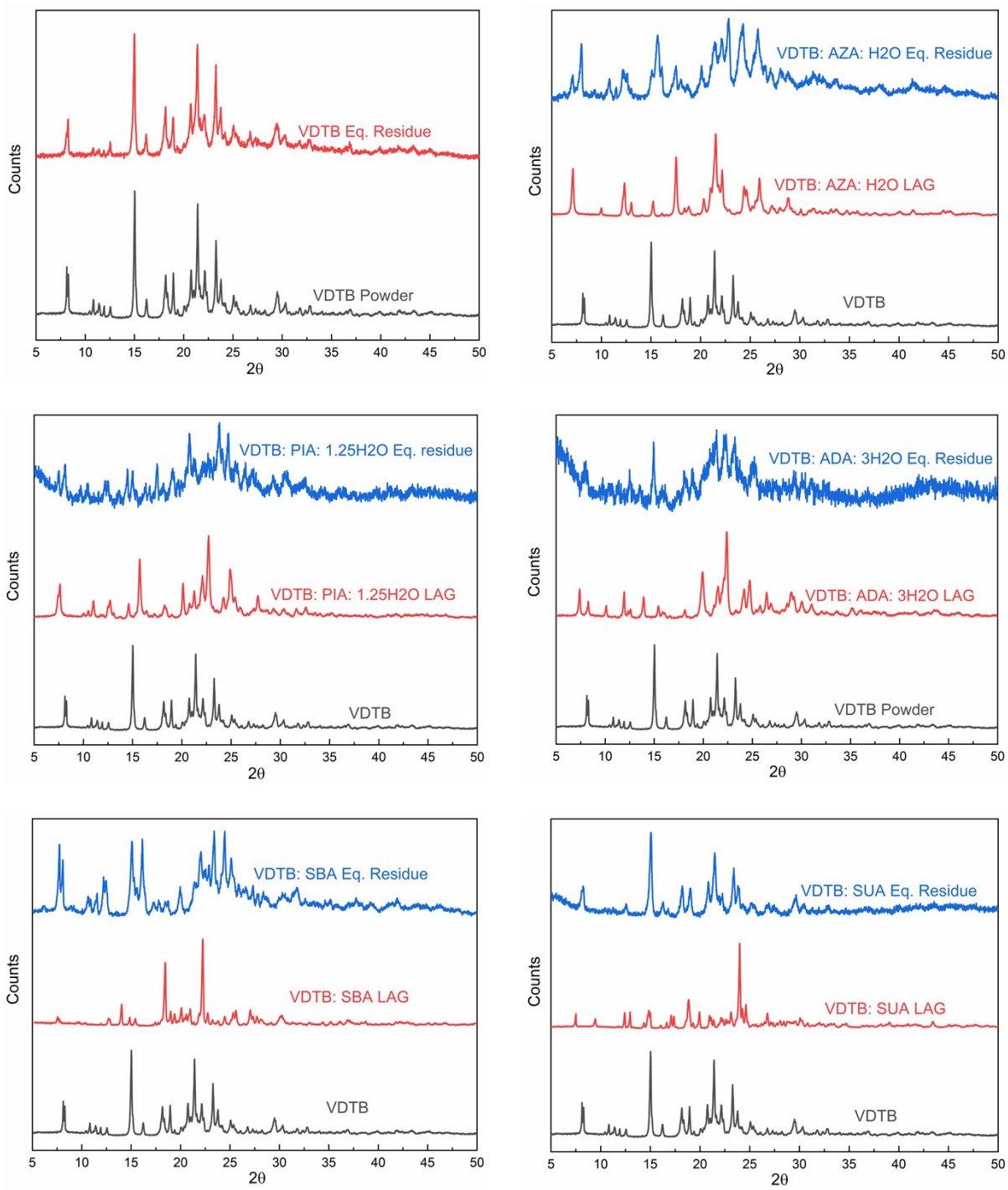

Figure S10. PXRD phase comparison of equilibrium solubility residues of VDTB and its molecular salts.

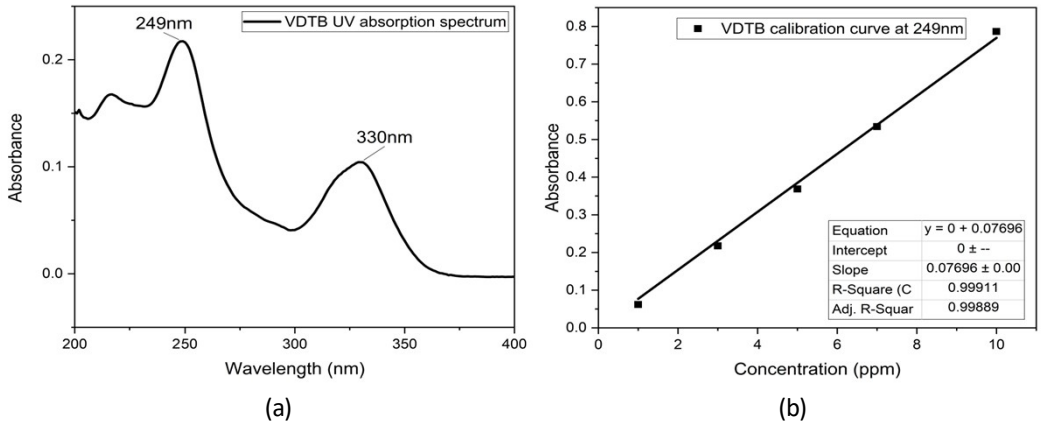

Figure S11. a) UV absorption spectrum of VDTB. (b) calibration curve at 249 nm.

Table S3. Equilibrium solubility of VDTB in its molecular salts.

S. No	Sample name	Solubility of VDTB at pH 7.4 (µg/mL)
1	VDTB	61.3 ± 3.3
2	VDTB: SUA	261.0 ± 3.1
3	VDTB: ADA: $3H_2O$	313.6 ± 8.1
4	VDTB: PIA: $1.25H_2O$	608.1 ± 11.5
5	VDTB: AZA: H_2O	220.8 ± 5.7
6	VDTB: SBA	19.3 ± 0.7

Table S4. Intrinsic dissolution data of VDTB and its salt forms in phosphate buffer (pH 7.4).

VDTB								
Time(h)	**Absorbance**	**Conc.(µg/mL)**	**Amount in 1 mL (µg)**	**Amount in 400 mL (mg)**	**Loss (mg)**	**CLA(mg)**	**CDR**	**%CDR**
0.5	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
1.5	0.023	0.298	7.467	2.987	0.007	0	2.987	1.493
2	0.027	0.350	8.766	3.506	0.008	0.007	3.513	1.756
4	0.031	0.402	10.064	4.025	0.010	0.016	4.042	2.021
6	0.042	0.545	13.636	5.454	0.013	0.026	5.480	2.740
12	0.091	1.181	29.545	11.818	0.029	0.039	11.858	5.929
14	0.178	2.311	57.792	23.116	0.057	0.069	23.186	11.593
18	0.269	3.493	87.337	34.935	0.087	0.127	35.062	17.531
22	0.344	4.467	111.688	44.675	0.111	0.214	44.889	22.444

VDTB: SUA

Time(h)	Absorbance	Conc.(µg/mL)	Amount in 1 mL (µg)	Amount in 400 mL (mg)	Loss (mg)	CLA(mg)	CDR	%CDR
0.5	0.01	0.129	3.246	1.298	0.003	0	1.298	0.649
1	0.024	0.311	7.792	3.116	0.007	0.003	3.120	1.560
1.5	0.056	0.727	18.181	7.272	0.018	0.011	7.283	3.641
2	0.077	1	25	10	0.025	0.029	10.029	5.014
4	0.087	1.129	28.246	11.298	0.028	0.054	11.352	5.676
6	0.119	1.545	38.636	15.454	0.038	0.082	15.537	7.768
12	0.331	4.298	107.467	42.987	0.107	0.121	43.108	21.554
14	0.428	5.5584	138.961	55.584	0.138	0.228	55.812	27.906
18	0.513	6.662	166.558	66.623	0.166	0.367	66.990	33.495
22	0.673	8.740	218.506	87.402	0.218	0.534	87.936	43.968

VDTB: ADA: $3H_2O$								
Time(h)	Absorbance	Conc.(µg/mL)	Amount in 1 mL (µg)	Amount in 400 mL (mg)	Loss (mg)	CLA(mg)	CDR	%CDR
0.5	0.011	0.142	3.571	1.428	0.003	0	1.428	0.714
1	0.046	0.597	14.935	5.974	0.014	0.003	5.977	2.988
1.5	0.071	0.922	23.051	9.220	0.023	0.018	9.239	4.619
2	0.112	1.454	36.363	14.545	0.036	0.041	14.587	7.293
4	0.259	3.363	84.090	33.636	0.084	0.077	33.714	16.857
6	0.368	4.779	119.480	47.792	0.119	0.162	47.954	23.977
12	0.432	5.610	140.259	56.103	0.140	0.281	56.385	28.192
14	0.567	7.363	184.090	73.636	0.184	0.421	74.058	37.029
18	0.661	8.584	214.610	85.844	0.214	0.605	86.45	43.225
22	0.752	9.766	244.155	97.662	0.244	0.820	98.482	49.241

VDTB: PIA: $1.25H_2O$								
Time(h)	Absorbance	Conc.(µg/mL)	Amount in 1 mL (µg)	Amount in 400 mL (mg)	Loss (mg)	CLA(mg)	CDR	%CDR
0.5	0.093	1.207	30.194	12.077	0.030	0	12.077	6.038
1	0.116	1.506	37.662	15.064	0.037	0.030	15.095	7.547
1.5	0.265	3.441	86.038	34.415	0.086	0.067	34.483	17.241
2	0.467	6.064	151.623	60.649	0.151	0.153	60.803	30.401
4	0.763	9.909	247.727	99.090	0.247	0.305	99.396	49.698
6	0.985	12.792	319.805	127.922	0.319	0.553	128.475	64.237
12	1.184	15.376	384.415	153.766	0.384	0.873	154.639	77.319
14	1.213	15.753	393.831	157.532	0.393	1.257	158.789	79.394
18	1.228	15.948	398.701	159.480	0.398	1.651	161.131	80.565
22	1.224	15.896	397.402	158.961	0.397	2.05	161.011	80.505

VDTB: AZA: H_2O								
Time(h)	Absorbance	Conc.(µg/mL)	Amount in 1 mL (µg)	Amount in 400 mL (mg)	Loss (mg)	CLA(mg)	CDR	%CDR

0.5	0	0	0	0	0	0	0	0
1	0.02	0.259	6.493	2.597	0.006	0	2.597	1.298
1.5	0.048	0.623	15.584	6.233	0.015	0.006	6.240	3.120
2	0.059	0.766	19.155	7.662	0.019	0.022	7.684	3.842
4	0.073	0.948	23.701	9.480	0.023	0.041	9.521	4.760
6	0.093	1.207	30.194	12.077	0.030	0.064	12.142	6.071
12	0.126	1.636	40.909	16.363	0.040	0.095	16.458	8.229
14	0.297	3.857	96.428	38.571	0.096	0.136	38.707	19.353
18	0.428	5.558	138.961	55.584	0.138	0.232	55.816	27.908
22	0.611	7.935	198.376	79.350	0.198	0.371	79.722	39.861

VDTB: SBA								
Time(h)	**Absorbance**	**Conc.(µg/mL)**	**Amount in 1 mL (µg)**	**Amount in 400 mL (mg)**	**Loss (mg)**	**CLA(mg)**	**CDR**	**%CDR**
0.5	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
1.5	0	0	0	0	0	0	0	0
2	0.024	0.311	7.792	3.116	0.007	0	3.116	1.558
4	0.027	0.350	8.766	3.506	0.008	0.007	3.514	1.757
6	0.03	0.389	9.740	3.896	0.009	0.016	3.912	1.956
12	0.062	0.805	20.129	8.051	0.020	0.026	8.078	4.039
14	0.088	1.142	28.571	11.428	0.028	0.046	11.475	5.737
18	0.113	1.467	36.688	14.675	0.036	0.075	14.750	7.375
22	0.153	1.987	49.675	19.870	0.049	0.111	19.981	9.990

Table S5. pH of the supernatant solution after equilibration period.

Compound	pH observed
VDTB	7.40 ± 0.02
VDTB: SUA	6.93
VDTB: ADA: $3H_2O$	6.92
VDTB: PIA: $1.25H_2O$	6.98
VDTB: AZA: H_2O	6.98
VDTB: SBA	7.00