Electronic Supplementary Information, ESI

Salts, Solvates and Hydrates of Multi-kinase Inhibitor Drug Pazopanib with Hydroxybenzoic Acids

Sunil K. Rai,*[,†] Debjani Baidya,[†] and Ashwini K. Nangia*[†,‡]

[†] Division of Organic Chemistry, CSIR – National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India

[‡] School of Chemistry, University of Hyderabad, Prof. C. R. Rao Road, Gachibowli, Central University P.O., Hyderabad 500 046, India

Table S1. Hydrogen bonds in salts of Pazopanib.

D–H···A	H···A (Å)	D···A (Å)	D–H···A (deg)	Symmetry code
		PAZ		
N6–H3···N5	2.35	3.1413(2)	173	-x,1-y,-z
N7–H4A···O2	2.03	2.9061(2)	173	1-x,-y,-z
N7–H4B···O1	2.00	2.8716(2)	168	2-x,-y,-z
C13–H13···O2	2.53	3.3542(2)	145	-x,1-y,-z
C16–H16···N4	2.30	2.8845(2)	119	Intra
C20–H20···O2	2.38	2.8201(2)	108	Intra
C21–H21A···O1	2.30	3.0260(2)	130	Intra
C21–H21C···N2	2.58	3.4184(2)	144	1+x,-1+y,z
		PAZ•THF		
N6–H6···N12	2.18	3.0406(13)	175	1-x,-y,-z
N7–H7A···N2	2.11	2.9329(13)	154	1-x,-y,-z
N7–H7B···O5	1.91	2.7985(12)	174	1-x,-y,-z
N13–H13A···N5	2.18	3.0222(13)	167	1-x,-y,-z
N14–H14A···N8	2.09	2.9552(13)	177	-x,1-y,-z
N14–H14B···O1	2.08	2.9337(13)	163	1-x,-y,-1-z
C1–H1C···O4	2.49	3.3377(14)	147	x,y,1+z
C3–H3B···O2	2.52	3.4749(15)	176	x,1+y,1+z
C16–H16···N4	2.34	2.9292(13)	121	Intra
C20–H20···O2	2.38	2.8109(12)	108	Intra
C21–H21A···O1	2.59	2.9823(13)	105	Intra
C22–H22B···O3	2.41	3.2925(14)	152	x,1+y,1+z
C37–H37···N11	2.40	2.9384(13)	117	Intra
C41–H41···O3	2.34	2.7863(12)	109	Intra
		PAZ•2HBA•MeOH		
N5–H5···O3	1.81	2.6518(5)	171	1/2-x,3/2-y,1-z
O5–H5B···O4	1.70	2.5402(5)	149	Intra

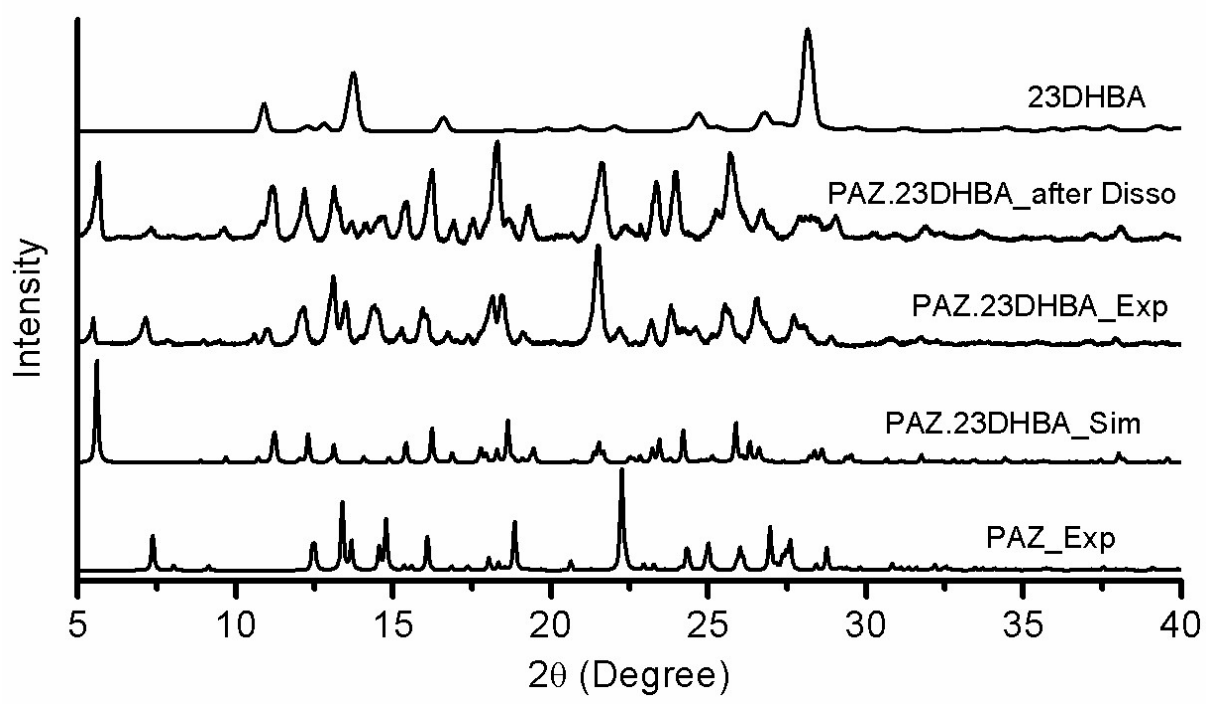
N6–H6···O4	1.97	2.8252(6)	170	1/2-x,3/2-y,1-z
O6–H6B···N2	1.88	2.8084(6)	161	x,y,z
N7–H7A···O3	2.05	2.8627(6)	167	x,y,z
N7–H7B···O6	2.04	2.9658(6)	174	1/2+x,1/2-y,1/2+z
C2–H2C···O2	2.49	3.2491(7)	135	-1/2+x,3/2-y,-1/2+z
C5–H5A···O2	2.46	3.2897(7)	148	1/2-x,1/2+y,1/2-z
C10–H10A···O4	2.59	3.4064(7)	143	x,y,z
C16–H16···O1	2.40	2.8275(6)	108	Intra
C16–H16···N4	2.32	2.9230(6)	122	Intra
C21–H21C···O2	2.37	2.9731(6)	120	Intra
		PAZ•4HBA•H_2O		
N5–H3···O4	1.85	2.6904(2)	169	1-x,-y,-z
N6–H4···O3	1.79	2.7204(2)	175	1-x,-y,-z
O5–H5···O4	1.95	2.6640(2)	167	1-x,1/2+y,1/2-z
N7–H7A···N2	2.09	2.9192(2)	170	1-x,-1/2+y,1/2-z
N7–7B···O5	2.17	3.0893(2)	170	1-x,-1/2+y,1/2-z
O6–H9A···O1	2.20	2.9321(2)	170	-1+x,y,z
O6–H9B···N2	2.30	3.0501(2)	178	x,y,z
C1–H1B···O2	2.57	3.4969(3)	155	-1+x,1+y,z
C2–H2A···O6	2.49	3.3345(2)	144	-x,1-y,-z
C2–H2B···O2	2.56	3.4565(3)	152	-1+x,1+y,z
C12–H12···O2	2.50	3.2318(2)	134	1-x,-y,-z
C15–H15···N4	2.34	2.9340(2)	120	Intra
C19–H19···O2	2.35	2.7940(2)	108	Intra
C20–H20A···O1	2.26	3.0294(2)	134	Intra
		PAZ•23HBA		
N5–H3···O5	2.05	2.9067(6)	166	-1+x,y,z
O7–H18···O4	1.68	2.5201(5)	152	Intra
N5–H26···O6	2.39	3.0942(6)	139	x,y,z
N5–H26···O7	2.26	3.0453(6)	151	x,y,z
N3–H27···O5	1.95	2.8186(5)	170	2-x,1-y,-z
N4–H28···O4	1.82	2.7197(5)	177	2-x,1-y,-z
O6–H29···N6	1.83	2.7075(5)	163	1-x,1-y,1-z
C15–H4···N2	2.37	2.9624(6)	121	Intra
C15–H4···N5	2.58	3.0110(6)	109	Intra
C13–H7···O2	2.54	3.1901(6)	125	-x,2-y,-z
C16–H9···O3	2.50	3.2648(6)	140	1+x,-1+y,z
C23–H22···O7	2.49	3.4197(7)	163	x,y,z
		PAZ•24HBA•EtOH		
N5–H3···O4	1.78	2.6835(2)	171	-x,1-y,-z
N6–H4···O3	1.98	2.8503(3)	171	-x,1-y,-z
O5–H5···O3	1.72	2.5779(2)	151	Intra

N7–H7A···O7	1.92	2.8235(3)	167	-1/2+x,1/2-y,-z
N7–H7B···O6	1.96	2.8691(3)	172	-1/2+x,1/2-y,-z
O6–H10···O4	1.71	2.6089(2)	169	1/2+x,1/2-y,-z
O7–H14···N2	1.85	2.7922(3)	164	x,y,z
C12–H12···O1	2.48	3.1317(3)	126	-x,1-y,-z
C15–H15···N4	2.35	2.9405(3)	120	Intra
C19–H19···O1	2.39	2.8216(3)	108	Intra
C19–H19···O3	2.56	3.3253(3)	137	-x,1-y,-z
C20–H20A···O2	2.44	3.1550(3)	129	Intra
C20–H20A···N7	2.52	3.1670(3)	123	Intra
		PAZ•25HBA•4H_2O		
N5–H5···O4	1.66	2.6067(7)	173	-x,1-y,1-z
O5–H5A···O3	1.62	2.5893(7)	149	Intra
N6–H6···O3	1.93	2.8241(8)	176	-x,1-y,1-z
O6–H6B···O2	1.94	2.9285(8)	166	x,y,z
N7–H7A···O4	2.02	2.8599(8)	163	1+x,y,z
N7–H7B···O9	2.21	2.9901(8)	159	1+x,y,z
O7–H7C···N1	1.97	2.8855(8)	177	x,y,-1+z
O7–H7D···O2	1.98	2.8409(8)	176	x,y,z
O8–H8A···O10	1.84	2.7744(8)	168	x,y,z
O8–H8B···O7	2.01	2.8260(8)	169	1-x,1-y,-z
O9–H9A···N1	2.06	2.9698(8)	172	x,y,-1+z
O9–H9B···O8	1.69	2.7847(8)	170	-x,1-y,-z
O10–H10D···O9	2.00	2.7720(8)	177	x,y,z
O10–H10E···O7	2.31	3.0618(9)	141	x,y,z
C10–H10A···O6	2.46	3.3219(9)	150	1-x,-y,1-z
C16–H16···O3	2.60	3.3462(9)	138	-x,1-y,1-z
C20–H20···O1	2.40	2.8236(8)	108	Intra
C20–H20···N4	2.31	2.9107(8)	122	Intra
C21–H21A···O9	2.51	3.3260(9)	142	1+x,y,z
C21–H21A···N7	2.48	3.2110(9)	133	Intra
C26–H26···O1	2.50	3.3100(9)	145	1-x,-y,1-z
C28–H28···O4	2.46	2.7709(8)	100	Intra
		PAZ•26HBA		
N5–H3···O3	1.80	2.7344(1)	172	-1+x,y,1+z
N6–H4···O4	1.87	2.7992(1)	174	-1+x,y,1+z
O5–H5···O3	1.67	2.5259(1)	159	Intra
N7–H7A···O5	2.04	2.9165(1)	167	2-x,-y,1-z
N7–H7B···N2	2.30	3.0919(1)	147	2-x,-1/2+y,3/2-z
O6–H10···O4	1.65	2.5289(1)	157	Intra
C1–H1C···O6	2.49	3.1344(1)	123	2-x,1/2+y,1/2-z
C2–H2C···N7	2.41	3.3376(1)	158	2-x,-y,1-z

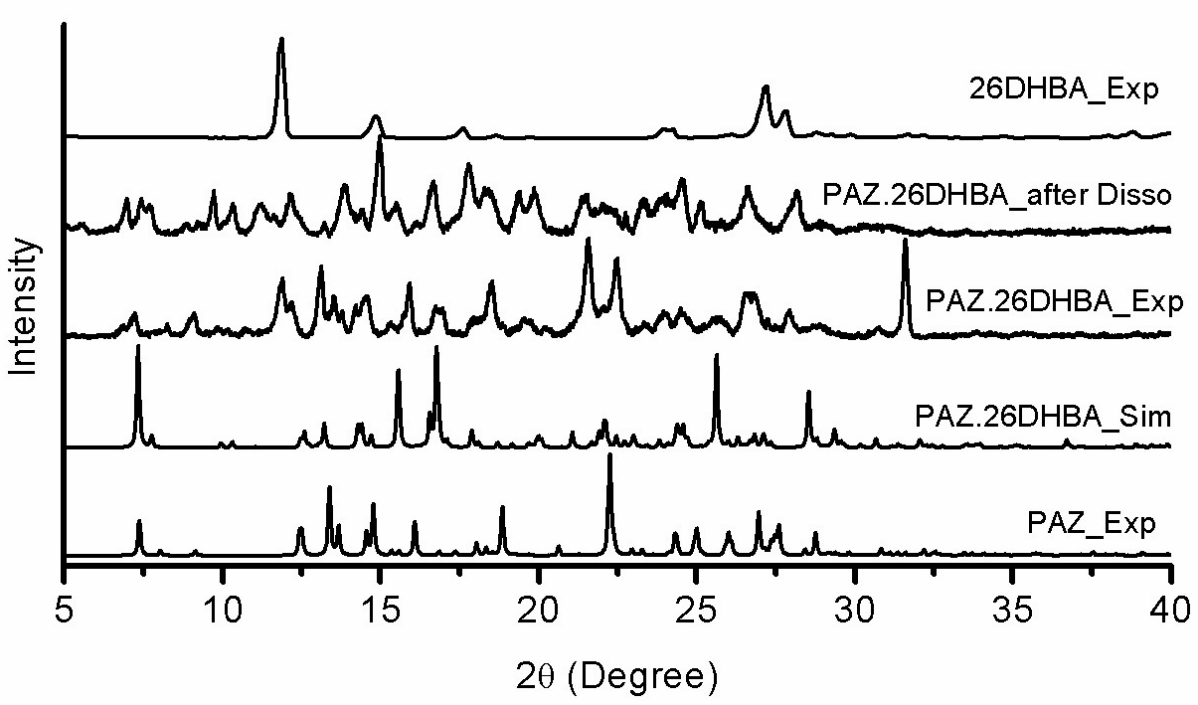
C6–H6···O6	2.32	3.2381(1)	163	2-x,-y,1-z
C12–H12···O2	2.40	3.1669(1)	137	1-x,1/2+y,3/2-z
C15–H15···O1	2.40	2.8243(1)	107	Intra
C15–H15···N4	2.34	2.9315(1)	120	Intra
C19–H19···O4	2.59	3.3459(1)	135	-1+x,y,1+z
C20–H20A···O2	2.29	3.0217(1)	130	Intra
		PAZ•35HBA•MeOH•H_2O		
N5–H5···O4	1.70	2.6239(2)	169	1-x,1-y,1-z
O5–H5A···O7	1.75	2.6667(2)	163	-x,-1/2+y,1/2-z
N6–H6···O3	2.00	2.8737(2)	176	1-x,1-y,1-z
O6–H6B···O8	1.78	2.6497(2)	175	x,-1+y,z
O7–H7···O3	1.78	2.7303(2)	169	x,y,z
N7–H7A···O2	2.12	2.8883(2)	148	1-x,1/2+y,1/2-z
N7–H7B···O4	1.95	2.7940(2)	168	x,y,z
O8–H8A···N2	1.82	2.7722(2)	179	-x,1/2+y,1/2-z
C2–H2A···O5	2.56	3.3503(2)	137	-x,-y,1-z
C2–H2C···O7	2.48	3.4074(2)	158	-x,1-y,1-z
C12–H12···O2	2.47	3.3663(2)	157	x,1/2-y,1/2+z
C15–H15···O1	2.40	2.8329(2)	107	Intra
C15–H15···N4	2.27	2.8623(2)	119	Intra
C20–H20A···O2	2.21	2.9475(2)	131	Intra
C26–H26···O8	2.52	3.1955(2)	128	x,-1+y,z
		PAZ•CFA•CH_3CN		
N6–H1···O3	2.09	2.9052(3)	176	1-x,1-y,1-z
N5–H2···O4	1.64	2.5923(3)	174	1-x,1-y,1-z
O5–H3···O6	2.37	2.7583(3)	106	Intra
O5–H3···N2	1.93	2.7838(3)	157	-x,-1/2+y,1/2-z
N7–H7A···O4	2.00	2.8074(3)	174	x,y,z
N7–H7B···O2	2.24	3.0116(3)	148	1-x,1/2+y,1/2-z
O6–H14···O3	1.87	2.7305(3)	171	-x,-1/2+y,1/2-z
C1–H1A···O5	2.49	3.3162(4)	142	-x,1/2+y,1/2-z
C2–H2C···N8	2.58	3.5581(4)	176	x,1/2-y,1/2+z
C8–H8···O6	2.35	3.1528(3)	142	-x,1/2+y,1/2-z
C12–H12···O2	2.39	3.3357(4)	174	x,1/2-y,1/2+z
C19–H19···O1	2.41	2.8386(3)	107	Intra
C19–H19···N4	2.30	2.9073(3)	121	Intra
C21–H21C···O2	2.54	2.9616(3)	106	Intra
C31–H31B···O1	2.51	3.3756(4)	147	x,1+y,z

Table S2. Calculated and observed weight loss in TGA of selected PAZ salts (see Figure 13).

Salt	Calc. mol. weight	Calc. weight loss of fragments	Obs. weight loss	Comments
PAZ•24DHBA•EtOH	PAZ 437.52 24DHBA 154.12 EtOH 46.07 Total 637.71	24DHBA 24.17% EtOH 7.22% Total = 31.39%	28% at 220 ° C in Fig. 13e	Mainly loss of conformer 24DHBA
PAZ•35DHBA•MeOH•H_2O:	PAZ 437.52 35DHBA 154.12 MeOH 32.04 H_2O = 18.02 Total 641.70	35DHBA 24.02% MeOH 5.00% H_2O 2.81% Total 31.83%	32% up to 300 °C In Fig. 13h	Coformer 35DHBA and volatile solvent/ water loss
PAZ•CFA•CH3CN:	PAZ 437.52 CFA 180.16 CH_3CN 41.05 Total 658.73	CFA 27.35 CH_3CN 6.23 Total 33.58	12% at 210 °C In Fig. 13h	Loss of volatile solvent



(a)



(b)

Figure S1. Powder X-ray diffraction line profile of PAZ, DHBA coformer, and product salt to match with the single crystal X-ray structure and absence of starting components. (a) **PAZ.23DHBA**, (b) **PAZ.26DHBA**.