Supporting Information for

Fragment-based drug discovery using a multi-domain, parallel MD-MM/PBSA screening protocol

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1. Summary table of full screening results by NMR, SPR and computational methods.

Table S1. NMR, SPR and computational screening results against Zenobia library.

ID	Binding by NMR	Binding by SPR	Competition STD NMR	NHA	Delta_H (kcal/mol)	SD[4]	Delta_S (kcal/mol)	Delta_G (kcal/mol)	LE	Gold Score
ZT0004	N[1]	Y[2]	ND[3]	11.0	-24.4	2.7	-23.8	-0.6	0.1	25.0
ZT0006	N	N	ND	9.0	-13.6	1.9	-14.0	0.4	0.0	35.0
ZT0010	Y	Y	Y	11.0	-40.4	4.4	-12.0	-28.4	2.6	32.4
ZT0008	Y	N	ND	9.0	-20.1	2.8	-17.8	-2.3	0.3	24.4
ZT0009	N	N	ND	11.0	-15.4	2.7	-14.0	-1.4	0.1	19.4
ZT0054	Y	Y	Y	8.0	-34.8	3.6	-19.1	-15.7	2.0	34.8
ZT0012	N	N	ND	7.0	-15.6	2.0	-22.6	7.1	-1.0	22.5
ZT0013	N	N	ND	8.0	-11.9	1.5	-10.1	-1.8	0.2	29.4
ZT0017	N	Y	ND	11.0	-29.9	3.7	-22.4	-7.5	0.7	31.4
ZT0788	Y	Y	ND	12.0	-29.9	3.5	-10.8	-19.1	1.6	30.7
ZT0020	N	Y	ND	10.0	-16.2	2.2	-14.0	-2.2	0.2	26.4
ZT0763	Y	Y	Y	11.0	-21.0	2.8	-5.5	-15.5	1.4	30.2
ZT0023	N	N	ND	9.0	-4.9	1.0	-21.6	16.6	-1.8	24.3
ZT0024	N	N	ND	8.0	-16.1	2.3	-14.3	-1.8	0.2	28.2
ZT0025	N	Y	ND	8.0	-18.6	2.6	-23.0	4.4	-0.5	27.6
ZT0073	Y	Y	Y	13.0	-31.7	3.9	-13.9	-17.8	1.4	30.3
ZT0027	N	N	ND	8.0	-15.4	3.3	-23.0	7.6	-0.9	27.5
ZT0028	N	Y	ND	8.0	-14.1	2.4	-16.5	2.4	-0.3	28.5
ZT0029	N	N	ND	8.0	-18.0	2.6	-17.1	-0.9	0.1	26.2
ZT0030	N	N	ND	8.0	-17.9	2.4	-20.2	2.2	-0.3	28.2
ZT0031	N	N	ND	8.0	-20.3	3.0	-22.3	1.9	-0.2	27.8
ZT0032	N	N	ND	8.0	-14.9	2.1	-12.6	-2.2	0.3	26.5
ZT0037	N	N	ND	7.0	-9.3	1.6	-12.9	3.6	-0.5	28.5
ZT0038	N	N	ND	7.0	-22.3	3.0	-24.6	2.3	-0.3	23.0
ZT0039	N	N	ND	7.0	-14.1	2.1	-13.3	-0.9	0.1	22.9
ZT0040	N	N	ND	7.0	-9.9	1.7	-7.9	-2.0	0.3	26.9
ZT0041	N	N	ND	7.0	-15.4	2.6	-19.1	3.7	-0.5	22.1
ZT0042	N	N	ND	7.0	-16.4	2.5	-19.3	2.9	-0.4	24.5
ZT0044	Y	N	ND	8.0	-22.6	2.5	-15.7	-6.9	0.9	29.5
ZT0393	Y	Y	Y	9.0	-18.0	2.4	-6.2	-11.8	1.3	29.3
ZT0048	Y	N	ND	8.0	-17.5	2.6	-15.2	-2.3	0.3	30.2
ZT0049	N	N	ND	8.0	-16.5	2.3	-23.0	6.4	-0.8	27.5
ZT0050	N	N	ND	8.0	-33.3	3.0	-25.3	-8.1	1.0	24.7
ZT0007	Y	Y	Y	10.0	-26.7	3.6	-14.8	-11.9	1.2	26.1
ZT0056	N	N	ND	8.0	-18.8	2.6	-18.3	-0.5	0.1	24.9
ZT0057	N	N	ND	8.0	-22.3	2.5	-27.5	5.1	-0.6	25.3
ZT0068	N	Y	ND	12.0	-27.3	3.6	-17.8	-9.5	0.8	30.3
ZT0069	N	N	ND	12.0	-21.5	3.3	-26.2	4.7	-0.4	34.6
ZT0071	N	N	ND	13.0	-22.4	3.1	-22.9	0.5	0.0	38.1
ZT0072	Y	N	N	13.0	-28.1	3.2	-14.3	-13.8	1.1	30.9

ZT0082	Y	Y	Y	10.0	-28.6	3.1	-17.2	-11.4	1.1	25.2
ZT0074	Y	N	ND	9.0	-26.4	3.1	-13.2	-13.2	1.5	25.5
ZT0075	N	Y	ND	10.0	-21.1	2.6	-15.1	-6.0	0.6	34.9
ZT0820	Y	Y	ND	15.0	-29.7	3.6	-15.8	-14.0	0.9	34.6
ZT0078	N	N	ND	10.0	-17.2	3.0	-16.8	-0.4	0.0	26.5
ZT0784	Y	Y	ND	15.0	-29.1	3.5	-15.1	-14.0	0.9	32.2
ZT0470	Y	Y	N	13.0	-29.0	3.2	-17.3	-11.7	0.9	28.1
ZT0818	Y	Y	N	14.0	-25.8	3.1	-13.3	-12.5	0.9	33.6
ZT0083	N	Y	ND	12.0	-21.7	2.6	-18.1	-3.6	0.3	30.4
ZT0084	N	Y	ND	14.0	-11.8	1.7	-8.6	-3.2	0.2	24.3
ZT0087	N	N	ND	11.0	-23.2	3.0	-20.6	-2.7	0.2	26.0
ZT0089	N	N	ND	10.0	-13.6	2.0	-17.5	3.9	-0.4	24.6
ZT0090	N	N	ND	11.0	-21.7	2.8	-26.2	4.5	-0.4	24.1
ZT0022	Y	Y	Y	11.0	-23.5	2.6	-13.8	-9.6	0.9	28.8
ZT0563	Y	Y	N	9.0	-25.0	3.1	-17.7	-7.4	0.8	28.1
ZT0794	Y	Y	N	11.0	-20.5	2.6	-11.5	-9.0	0.8	29.8
ZT0091	Y	Y	N	12.0	-25.6	3.0	-16.0	-9.6	0.8	32.7
ZT0748	Y	Y	ND	10.0	-24.7	2.5	-17.1	-7.6	0.8	30.4
ZT0199	Y	Y	ND	12.0	-26.3	3.2	-17.2	-9.1	0.8	27.8
ZT0789	Y	Y	ND	13.0	-26.6	2.8	-16.8	-9.8	0.8	23.4
ZT0102	N	Y	ND	11.0	-10.2	1.7	-15.8	5.6	-0.5	27.5
ZT0103	Y	N	N	11.0	-14.4	2.0	-14.6	0.3	0.0	29.0
ZT0817	Y	Y	ND	14.0	-25.8	3.1	-15.8	-10.0	0.7	30.6
ZT0447	Y	Y	N	12.0	-23.9	3.0	-15.5	-8.4	0.7	38.2
ZT0110	Y	N	ND	11.0	-19.6	2.5	-18.0	-1.6	0.1	29.1
ZT0119	N	N	ND	13.0	-19.8	2.5	-20.3	0.5	0.0	33.2
ZT0125	N	N	ND	10.0	-16.2	2.3	-15.9	-0.3	0.0	26.8
ZT0126	Y	N	ND	10.0	-20.2	2.8	-12.8	-7.4	0.7	25.3
ZT0131	N	N	ND	7.0	-26.5	3.3	-25.1	-1.4	0.2	22.6
ZT0280	Y	Y	ND	11.0	-20.2	2.8	-12.7	-7.5	0.7	30.9
ZT0173	N	N	ND	8.0	-17.8	2.3	-18.6	0.8	-0.1	24.4
ZT0184	N	N	ND	6.0	-14.1	1.8	-12.9	-1.2	0.2	24.3
ZT0191	N	N	ND	9.0	-13.9	1.9	-14.7	0.8	-0.1	26.0
ZT0196	N	N	ND	13.0	-17.6	2.4	-18.0	0.4	0.0	23.7
ZT0426	Y	Y	ND	10.0	-20.4	3.0	-13.8	-6.7	0.7	25.3
ZT0431	Y	Y	N	9.0	-20.2	2.8	-14.4	-5.8	0.6	26.3
ZT0834	Y	Y	ND	15.0	-29.1	3.3	-20.0	-9.2	0.6	29.9
ZT0759	Y	Y	N	10.0	-23.2	2.8	-17.1	-6.0	0.6	27.6
ZT0206	N	N	ND	12.0	-13.1	1.6	-21.4	8.3	-0.7	29.2
ZT0209	N	N	ND	10.0	-7.8	1.3	-9.5	1.7	-0.2	25.7
ZT0212	N	N	ND	7.0	-29.3	3.4	-22.4	-6.9	1.0	20.4
ZT0772	Y	Y	ND	10.0	-20.7	2.6	-14.9	-5.9	0.6	29.1
ZT0215	N	N	ND	11.0	-20.4	2.6	-24.1	3.7	-0.3	28.9
ZT0200	Y	Y	ND	12.0	-21.0	3.1	-14.4	-6.6	0.6	27.8
ZT0218	N	N	ND	12.0	-18.4	2.3	-21.8	3.4	-0.3	33.5
ZT0219	N	Y	ND	10.0	-23.8	2.9	-15.7	-8.1	0.8	30.6
ZT0220	N	N	ND	9.0	-18.9	2.0	-18.8	-0.1	0.0	30.9
ZT0244	N	N	ND	11.0	-17.3	2.4	-20.3	3.0	-0.3	27.0

ZT0246	Y	N	ND	12.0	-21.3	3.1	-14.7	-6.6	0.6	28.8
ZT0247	N	N	ND	12.0	-16.2	2.3	-13.9	-2.3	0.2	28.1
ZT0109	Y	Y	N	11.0	-20.2	2.8	-14.1	-6.1	0.6	29.1
ZT0250	N	Y	ND	12.0	-18.4	2.3	-19.3	0.9	-0.1	29.1
ZT0252	Y	N	ND	11.0	-21.2	2.5	-16.2	-5.0	0.5	26.8
ZT0256	N	N	ND	14.0	-16.2	1.8	-17.5	1.3	-0.1	31.2
ZT0623	Y	Y	ND	10.0	-16.3	2.0	-10.9	-5.4	0.5	28.1
ZT0260	Y	N	ND	12.0	-19.8	2.5	-21.2	1.4	-0.1	27.4
ZT0261	Y	N	ND	12.0	-13.6	2.0	-11.0	-2.6	0.2	25.9
ZT0262	N	N	ND	12.0	-34.3	4.1	-16.5	-17.8	1.5	29.7
ZT0428	Y	Y	N	11.0	-21.7	2.8	-16.2	-5.5	0.5	26.2
ZT0303	Y	Y	ND	12.0	-20.7	2.5	-15.3	-5.4	0.4	31.4
ZT0101	Y	Y	Y	12.0	-20.4	2.6	-15.2	-5.3	0.4	31.9
ZT0268	Y	N	ND	13.0	-23.5	3.0	-2.2	-21.4	1.6	31.1
ZT0265	Y	Y	Y	13.0	-22.0	2.8	-16.4	-5.6	0.4	31.6
ZT0270	N	N	ND	14.0	-29.7	3.6	-21.5	-8.2	0.6	30.4
ZT0271	N	Y	ND	16.0	-30.9	3.7	-29.5	-1.4	0.1	39.0
ZT0272	Y	N	ND	16.0	-17.4	2.3	-21.0	3.7	-0.2	28.1
ZT0448	Y	Y	N	12.0	-21.9	2.8	-17.0	-4.9	0.4	28.3
ZT0274	N	N	ND	10.0	-25.5	3.1	-22.4	-3.1	0.3	32.8
ZT0275	N	N	ND	11.0	-24.7	3.0	-20.7	-4.0	0.4	37.1
ZT0278	N	N	ND	11.0	-13.6	2.0	-12.1	-1.5	0.1	31.5
ZT0279	Y	N	ND	11.0	-13.0	2.1	-6.1	-6.9	0.6	33.5
ZT0761	Y	Y	N	11.0	-17.1	2.4	-12.5	-4.5	0.4	28.5
ZT0281	Y	N	ND	13.0	-13.9	2.0	-16.0	2.1	-0.2	32.3
ZT0266	Y	Y	N	13.0	-18.0	2.5	-12.6	-5.4	0.4	29.5
ZT0287	Y	N	ND	10.0	-15.6	2.2	-18.2	2.6	-0.3	27.1
ZT0289	N	N	ND	10.0	-15.1	2.3	-14.5	-0.5	0.1	27.8
ZT0290	N	Y	ND	10.0	-16.5	2.1	-21.0	4.4	-0.4	28.8
ZT0292	N	Y	ND	10.0	-16.7	2.0	-18.4	1.6	-0.2	28.5
ZT0296	N	N	ND	10.0	-19.2	2.2	-21.1	2.0	-0.2	28.0
ZT0269	Y	Y	N	12.0	-16.5	2.0	-11.6	-4.9	0.4	26.3
ZT0305	N	N	ND	8.0	-20.3	2.8	-18.6	-1.7	0.2	27.0
ZT0143	Y	Y	N	11.0	-20.7	3.2	-16.4	-4.3	0.4	26.4
ZT0312	N	N	ND	8.0	-12.9	2.0	-14.7	1.8	-0.2	21.8
ZT0313	Y	N	ND	9.0	-15.6	1.9	-14.9	-0.7	0.1	27.7
ZT0316	N	N	ND	9.0	-18.1	2.2	-22.5	4.4	-0.5	27.7
ZT0320	Y	N	ND	10.0	-17.5	1.8	-21.3	3.7	-0.4	28.2
ZT0326	N	Y	ND	10.0	-18.6	1.9	-21.0	2.4	-0.2	29.4
ZT0327	N	Y	ND	10.0	-23.1	2.6	-26.4	3.3	-0.3	29.5
ZT0328	N	N	ND	10.0	-17.6	2.4	-20.7	3.2	-0.3	32.3
ZT0329	Y	N	ND	10.0	-14.6	2.0	-18.4	3.8	-0.4	26.3
ZT0100	Y	Y	N	12.0	-24.2	3.0	-19.6	-4.6	0.4	33.0
ZT0336	N	N	ND	9.0	-19.3	2.3	-17.5	-1.8	0.2	23.8
ZT0356	N	N	ND	8.0	-8.9	1.5	-9.4	0.5	-0.1	25.7
ZT0357	N	N	ND	8.0	-16.3	2.3	-18.9	2.7	-0.3	24.8
ZT0358	N	N	ND	8.0	-13.7	2.0	-13.8	0.1	0.0	24.1
ZT0370	Y	N	ND	8.0	-16.4	2.1	-18.4	2.0	-0.2	24.5

ZT0371	N	N	ND	9.0	-32.6	3.7	-31.9	-0.8	0.1	29.2
ZT0372	N	N	ND	9.0	-16.7	2.2	-14.4	-2.3	0.3	26.7
ZT0373	N	N	ND	8.0	-8.2	1.3	-14.9	6.7	-0.8	23.6
ZT0380	N	N	ND	9.0	-7.8	1.3	-11.1	3.3	-0.4	29.7
ZT0764	Y	Y	N	11.0	-16.5	2.3	-12.3	-4.2	0.4	26.1
ZT0389	N	N	ND	9.0	-20.8	3.1	-21.4	0.6	-0.1	26.4
ZT0391	N	N	ND	9.0	-17.8	2.5	-18.4	0.5	-0.1	26.9
ZT0782	Y	Y	N	13.0	-22.6	2.8	-17.7	-4.9	0.4	27.9
ZT0394	N	Y	ND	9.0	-17.3	2.2	-21.9	4.6	-0.5	29.4
ZT0395	N	N	ND	9.0	-15.2	2.1	-18.0	2.8	-0.3	27.8
ZT0396	N	N	ND	9.0	-20.2	2.7	-19.1	-1.1	0.1	28.1
ZT0080	Y	Y	ND	11.0	-21.1	2.8	-17.0	-4.1	0.4	29.3
ZT0399	N	Y	ND	9.0	-25.3	3.1	-18.8	-6.5	0.7	27.8
ZT0400	N	Y	ND	9.0	-17.8	2.3	-16.3	-1.5	0.2	29.7
ZT0401	N	Y	ND	9.0	-18.3	2.5	-17.5	-0.8	0.1	29.0
ZT0402	Y	N	Y	9.0	-23.8	3.0	-10.9	-12.9	1.4	27.4
ZT0791	Y	Y	ND	14.0	-18.7	2.4	-13.5	-5.2	0.4	28.8
ZT0404	Y	N	ND	9.0	-17.5	3.5	-12.3	-5.2	0.6	30.6
ZT0405	Y	N	ND	9.0	-22.7	3.0	-21.8	-0.9	0.1	30.0
ZT0097	Y	Y	Y	12.0	-23.8	2.5	-19.4	-4.3	0.4	32.7
ZT0407	N	N	ND	9.0	-13.0	1.8	-11.6	-1.4	0.2	29.6
ZT0408	N	Y	ND	9.0	-15.9	2.1	-15.6	-0.3	0.0	30.6
ZT0409	Y	N	ND	9.0	-18.1	2.4	-17.9	-0.2	0.0	31.5
ZT0410	N	Y	ND	9.0	-16.1	2.1	-17.7	1.5	-0.2	31.2
ZT0411	N	N	ND	10.0	-29.2	3.5	-26.7	-2.5	0.2	29.5
ZT0412	N	N	ND	10.0	-26.7	3.1	-18.3	-8.4	0.8	29.9
ZT0413	N	N	ND	10.0	-9.9	1.5	-16.0	6.1	-0.6	27.6
ZT0414	N	N	ND	10.0	-22.9	2.8	-23.0	0.1	0.0	23.9
ZT0415	N	N	ND	11.0	-12.6	1.8	-16.6	4.0	-0.4	27.1
ZT0417	Y	N	ND	11.0	-23.5	3.0	-17.3	-6.2	0.6	27.0
ZT0418	N	N	ND	11.0	-15.4	2.1	-18.8	3.4	-0.3	25.6
ZT0419	N	N	ND	11.0	-11.1	1.7	-10.9	-0.2	0.0	33.6
ZT0421	N	N	ND	10.0	-13.5	2.1	-16.5	3.1	-0.3	31.7
ZT0422	N	N	ND	10.0	-22.1	2.8	-20.9	-1.2	0.1	26.8
ZT0424	N	N	ND	8.0	-23.2	2.5	-23.4	0.2	0.0	22.5
ZT0308	Y	Y	Y	11.0	-22.6	2.5	-18.7	-3.9	0.4	30.0
ZT0452	Y	Y	ND	13.0	-16.8	2.0	-12.4	-4.5	0.3	32.2
ZT0427	Y	N	ND	10.0	-13.4	1.9	-12.8	-0.6	0.1	25.9
ZT0106	Y	Y	N	11.0	-22.5	2.8	-18.9	-3.6	0.3	30.3
ZT0429	Y	N	N	11.0	-18.0	2.4	-19.3	1.3	-0.1	27.7
ZT0430	Y	N	ND	9.0	-19.9	2.4	-18.1	-1.8	0.2	25.8
ZT0096	Y	Y	ND	12.0	-24.0	2.8	-20.2	-3.8	0.3	33.2
ZT0045	Y	Y	ND	8.0	-18.9	2.5	-16.4	-2.5	0.3	34.7
ZT0434	N	N	ND	9.0	-18.8	2.4	-15.8	-3.0	0.3	25.8
ZT0435	N	N	ND	9.0	-13.9	1.8	-17.9	4.0	-0.4	25.3
ZT0437	N	N	ND	9.0	-21.8	2.5	-20.2	-1.6	0.2	24.6
ZT0438	N	N	ND	9.0	-12.4	1.7	-17.3	4.8	-0.5	24.1
ZT0439	N	N	ND	9.0	-24.8	2.7	-23.4	-1.5	0.2	22.7

ZT0440	N	N	ND	9.0	-15.4	2.1	-13.2	-2.2	0.2	28.5
ZT0441	N	N	ND	9.0	-14.9	2.0	-12.9	-2.0	0.2	25.2
ZT0442	N	N	ND	9.0	-14.8	1.9	-12.5	-2.3	0.3	29.3
ZT0443	Y	N	ND	9.0	-23.7	2.7	-22.4	-1.3	0.1	22.9
ZT0773	Y	Y	ND	11.0	-27.7	3.2	-24.3	-3.3	0.3	28.8
ZT0717	Y	Y	ND	11.0	-16.2	2.1	-13.0	-3.3	0.3	28.1
ZT0249	Y	Y	N	11.0	-19.1	1.8	-15.9	-3.2	0.3	27.6
ZT0432	Y	Y	ND	9.0	-19.1	2.1	-16.5	-2.5	0.3	25.7
ZT0762	Y	Y	N	11.0	-15.4	2.1	-12.4	-3.0	0.3	29.9
ZT0026	Y	Y	ND	8.0	-16.2	2.2	-14.2	-2.0	0.2	28.0
ZT0740	Y	Y	ND	13.0	-26.7	3.3	-23.5	-3.1	0.2	31.5
ZT0449	Y	Y	ND	12.0	-22.0	2.8	-19.3	-2.7	0.2	30.2
ZT0462	N	N	ND	12.0	-12.7	1.8	-14.6	1.9	-0.2	27.7
ZT0463	Y	N	Y	12.0	-21.4	3.0	-20.6	-0.8	0.1	27.9
ZT0019	Y	Y	N	10.0	-19.2	2.4	-17.0	-2.2	0.2	28.5
ZT0465	N	N	ND	13.0	-14.8	2.0	-16.6	1.8	-0.1	30.9
ZT0468	N	N	ND	13.0	-29.2	3.6	-29.3	0.1	0.0	32.3
ZT0282	Y	Y	ND	14.0	-20.4	2.6	-17.4	-3.0	0.2	34.1
ZT0478	N	N	ND	9.0	-18.3	2.4	-16.2	-2.1	0.2	26.0
ZT0529	N	N	ND	10.0	-19.7	2.8	-13.5	-6.2	0.6	32.9
ZT0530	Y	N	ND	10.0	-13.8	2.0	-15.4	1.6	-0.2	32.1
ZT0425	Y	Y	ND	9.0	-18.0	2.1	-16.1	-1.9	0.2	31.2
ZT0537	N	N	ND	11.0	-22.6	2.5	-26.9	4.3	-0.4	31.3
ZT0543	Y	N	ND	10.0	-42.1	4.8	-19.8	-22.4	2.2	31.4
ZT0545	N	N	ND	11.0	-19.8	2.5	-21.1	1.3	-0.1	36.8
ZT0546	N	N	ND	11.0	-20.7	3.0	-20.6	-0.2	0.0	28.9
ZT0547	N	N	ND	11.0	-19.1	2.1	-0.5	-18.6	1.7	37.3
ZT0550	N	N	ND	12.0	-15.1	2.1	-20.3	5.2	-0.4	34.3
ZT0557	N	N	ND	10.0	-22.9	2.8	-20.1	-2.8	0.3	30.9
ZT0807	Y	Y	ND	14.0	-23.2	3.0	-20.2	-2.9	0.2	28.8
ZT0580	Y	N	Y	11.0	-28.1	3.2	-14.4	-13.7	1.2	34.5
ZT0581	N	Y	ND	12.0	-31.7	3.5	-20.3	-11.4	1.0	36.4
ZT0582	N	N	ND	13.0	-14.8	2.0	-16.5	1.8	-0.1	34.7
ZT0583	N	N	ND	13.0	-16.5	2.1	-14.5	-1.9	0.1	36.4
ZT0446	Y	Y	Y	13.0	-20.7	2.6	-18.1	-2.6	0.2	30.0
ZT0403	Y	Y	ND	9.0	-16.5	1.8	-14.7	-1.8	0.2	29.2
ZT0587	Y	N	Y	11.0	-33.1	3.5	-14.5	-18.5	1.7	33.2
ZT0588	N	N	ND	12.0	-20.3	2.5	-32.6	12.3	-1.0	32.0
ZT0267	Y	Y	N	13.0	-13.3	1.8	-10.7	-2.6	0.2	30.4
ZT0591	N	N	ND	12.0	-19.5	2.4	-18.8	-0.7	0.1	33.8
ZT0592	Y	N	N	12.0	-11.7	1.8	-17.8	6.2	-0.5	27.4
ZT0596	N	N	ND	9.0	-17.8	2.3	-18.4	0.6	-0.1	24.9
ZT0600	N	N	ND	11.0	-14.4	2.0	-14.6	0.2	0.0	26.0
ZT0601	N	N	ND	11.0	-15.7	2.1	-13.5	-2.3	0.2	25.1
ZT0602	N	N	ND	11.0	-17.0	1.8	-16.6	-0.5	0.0	25.6
ZT0604	N	N	ND	11.0	-15.3	1.8	-17.0	1.7	-0.2	31.1
ZT0605	N	N	ND	12.0	-17.2	2.2	-17.3	0.1	0.0	29.8
ZT0609	N	N	ND	11.0	-12.5	1.5	-14.7	2.2	-0.2	27.3

ZT0614	N	N	ND	11.0	-18.7	2.1	-14.0	-4.8	0.4	29.8
ZT0615	N	N	ND	11.0	-17.3	2.4	-14.7	-2.6	0.2	28.3
ZT0621	N	N	ND	14.0	-13.3	2.1	-10.5	-2.8	0.2	36.2
ZT0622	Y	N	ND	9.0	-14.9	2.5	-14.9	0.0	0.0	28.5
ZT0273	Y	Y	N	16.0	-19.7	2.6	-16.6	-3.1	0.2	30.5
ZT0625	N	N	ND	10.0	-13.5	2.0	-20.8	7.3	-0.7	29.2
ZT0626	N	N	ND	10.0	-17.9	2.3	-15.9	-1.9	0.2	29.9
ZT0627	N	N	ND	10.0	-7.0	1.1	-13.9	7.0	-0.7	29.6
ZT0628	Y	N	ND	11.0	-17.1	2.3	-23.5	6.4	-0.6	27.9
ZT0629	N	N	ND	12.0	-24.3	3.1	-21.0	-3.3	0.3	31.1
ZT0630	N	N	ND	11.0	-6.1	1.2	-18.6	12.5	-1.1	33.3
ZT0633	N	N	ND	12.0	-26.2	3.1	-25.9	-0.3	0.0	36.0
ZT0634	Y	N	N	13.0	-21.7	2.8	-18.4	-3.3	0.3	32.0
ZT0635	N	N	ND	13.0	-25.7	3.1	-24.8	-0.9	0.1	35.8
ZT0642	N	Y	ND	10.0	-29.5	3.8	-19.5	-10.0	1.0	31.5
ZT0647	N	N	ND	11.0	-17.3	2.3	-17.5	0.2	0.0	35.5
ZT0652	N	Y	ND	12.0	-18.0	2.4	-21.6	3.6	-0.3	35.1
ZT0669	N	N	ND	10.0	-11.4	1.8	-19.8	8.5	-0.8	24.8
ZT0675	N	N	ND	12.0	-10.4	1.6	-9.7	-0.7	0.1	34.6
ZT0676	N	N	ND	13.0	-15.6	2.3	-10.9	-4.7	0.4	34.4
ZT0680	N	N	ND	14.0	-29.9	3.5	-29.4	-0.5	0.0	26.9
ZT0686	Y	N	ND	11.0	-19.6	2.5	-13.8	-5.8	0.5	25.3
ZT0687	Y	N	ND	11.0	-27.1	3.3	-15.2	-11.9	1.1	30.7
ZT0688	N	N	ND	11.0	-16.6	2.2	-15.7	-0.9	0.1	32.4
ZT0689	N	Y	ND	11.0	-19.3	2.3	-15.8	-3.5	0.3	29.1
ZT0690	N	N	ND	11.0	-12.3	1.7	-22.4	10.1	-0.9	32.0
ZT0445	Y	Y	ND	12.0	-21.3	3.5	-19.0	-2.3	0.2	28.5
ZT0692	N	N	ND	11.0	-9.9	1.3	-11.4	1.5	-0.1	29.0
ZT0693	N	N	ND	12.0	-32.8	3.5	-26.9	-5.9	0.5	26.1
ZT0694	N	N	ND	12.0	-25.4	3.0	-21.8	-3.7	0.3	32.8
ZT0695	N	N	ND	12.0	-16.4	2.1	-28.6	12.2	-1.0	31.7
ZT0696	N	N	ND	11.0	-17.9	2.3	-18.3	0.4	0.0	28.6
ZT0698	Y	N	ND	13.0	-34.2	3.6	-18.0	-16.3	1.3	28.8
ZT0699	Y	N	N	13.0	-25.6	3.0	-22.7	-2.9	0.2	27.0
ZT0701	Y	N	Y	10.0	-26.8	3.1	-12.0	-14.8	1.5	26.4
ZT0795	Y	Y	ND	11.0	-19.1	2.5	-17.1	-2.1	0.2	31.2
ZT0703	Y	N	N	11.0	-20.7	2.6	-18.9	-1.9	0.2	27.0
ZT0705	N	N	ND	12.0	-18.8	2.4	-10.2	-8.5	0.7	32.3
ZT0707	N	N	ND	13.0	-12.2	1.8	-15.1	3.0	-0.2	19.9
ZT0708	N	N	ND	14.0	-9.4	1.5	-16.0	6.5	-0.5	19.2
ZT0709	Y	N	ND	14.0	-14.9	2.0	-17.5	2.5	-0.2	21.9
ZT0716	Y	N	ND	12.0	-29.3	3.6	-29.3	0.0	0.0	30.8
ZT0214	Y	Y	ND	11.0	-18.6	2.4	-16.7	-1.9	0.2	29.4
ZT0718	N	N	ND	12.0	-11.4	1.7	-25.3	13.9	-1.2	32.9
ZT0723	N	N	ND	10.0	-23.9	3.5	-15.6	-8.3	0.8	30.1
ZT0724	N	N	ND	11.0	-20.4	2.6	-14.9	-5.5	0.5	33.5
ZT0725	N	Y	ND	12.0	-13.1	2.1	-15.7	2.5	-0.2	27.1
ZT0726	N	Y	ND	13.0	-20.0	3.0	-23.3	3.3	-0.3	30.2

ZT0729	N	N	ND	10.0	-19.4	3.0	-13.9	-5.5	0.6	30.3
ZT0730	Y	N	ND	11.0	-31.1	3.8	-15.7	-15.4	1.4	31.6
ZT0731	N	N	ND	11.0	-10.7	1.7	-17.9	7.2	-0.7	30.5
ZT0732	Y	N	ND	11.0	-16.0	2.2	-19.4	3.4	-0.3	31.3
ZT0733	Y	N	ND	11.0	-46.3	5.1	-18.3	-28.0	2.5	31.3
ZT0738	N	N	ND	11.0	-16.5	2.1	-19.7	3.2	-0.3	28.9
ZT0739	N	N	ND	11.0	-17.6	2.6	-16.5	-1.1	0.1	28.7
ZT0819	Y	Y	N	14.0	-19.3	3.0	-16.9	-2.4	0.2	32.8
ZT0742	N	N	ND	11.0	-20.7	3.0	-15.1	-5.6	0.5	30.6
ZT0744	N	N	ND	9.0	-20.2	2.5	-18.8	-1.3	0.1	29.0
ZT0745	N	N	ND	10.0	-15.3	2.1	-15.3	0.0	0.0	27.5
ZT0746	N	N	ND	10.0	-14.9	2.0	-17.4	2.4	-0.2	30.9
ZT0747	N	N	ND	11.0	-26.8	3.2	-25.9	-0.9	0.1	29.3
ZT0099	Y	Y	ND	12.0	-23.7	2.8	-21.8	-1.9	0.2	32.9
ZT0749	N	N	ND	9.0	-19.5	2.8	-23.3	3.7	-0.4	31.6
ZT0750	Y	N	ND	10.0	-26.3	3.2	-24.2	-2.1	0.2	31.9
ZT0754	N	N	ND	11.0	-27.3	3.3	-21.8	-5.5	0.5	29.8
ZT0585	Y	Y	Y	12.0	-17.4	2.3	-15.5	-1.9	0.2	29.9
ZT0204	Y	Y	N	11.0	-19.0	2.5	-17.4	-1.6	0.1	28.1
ZT0803	Y	Y	N	12.0	-23.3	2.8	-22.0	-1.3	0.1	27.7
ZT0335	Y	Y	ND	10.0	-21.1	2.7	-20.1	-1.0	0.1	26.2
ZT0387	Y	Y	ND	9.0	-20.9	2.9	-20.2	-0.7	0.1	26.6
ZT0813	Y	Y	ND	12.0	-19.4	3.0	-18.5	-0.9	0.1	30.1
ZT0814	Y	Y	ND	12.0	-13.7	2.0	-13.4	-0.3	0.0	29.8
ZT0758	Y	Y	N	10.0	-10.9	1.6	-10.9	0.0	0.0	26.9
ZT0765	Y	N	N	12.0	-21.8	2.8	-28.2	6.4	-0.5	30.0
ZT0079	Y	Y	N	10.0	-17.9	2.4	-18.0	0.1	0.0	26.3
ZT0769	Y	N	ND	11.0	-24.8	3.1	-22.3	-2.4	0.2	35.1
ZT0771	N	N	ND	9.0	-8.7	1.5	-7.4	-1.3	0.1	20.4
ZT0398	Y	Y	ND	9.0	-14.8	2.1	-15.3	0.5	-0.1	28.3
ZT0093	Y	Y	N	12.0	-20.4	3.0	-21.1	0.7	-0.1	29.0
ZT0801	Y	Y	ND	12.0	-13.4	2.1	-14.2	0.8	-0.1	28.5
ZT0535	Y	Y	ND	12.0	-21.0	2.6	-22.0	1.0	-0.1	34.7
ZT0584	Y	Y	N	11.0	-13.4	2.0	-14.5	1.1	-0.1	29.5
ZT0786	N	Y	ND	12.0	-11.1	1.7	-14.5	3.4	-0.3	32.1
ZT0787	N	Y	ND	12.0	-14.7	2.0	-19.1	4.4	-0.4	29.3
ZT0702	Y	Y	ND	11.0	-17.6	2.4	-18.9	1.2	-0.1	25.7
ZT0450	Y	Y	N	13.0	-16.8	2.1	-18.5	1.6	-0.1	29.4
ZT0790	N	Y	ND	13.0	-29.4	3.5	-14.6	-14.8	1.1	29.7
ZT0406	Y	Y	ND	9.0	-13.1	2.1	-14.6	1.5	-0.2	29.4
ZT0792	N	Y	ND	11.0	-22.7	2.8	-20.2	-2.5	0.2	28.9
ZT0793	Y	N	ND	11.0	-16.8	2.2	-14.7	-2.0	0.2	28.1
ZT0760	Y	Y	N	11.0	-12.3	1.8	-14.2	1.9	-0.2	27.6
ZT0201	Y	Y	ND	12.0	-18.8	2.4	-20.9	2.2	-0.2	28.3
ZT0796	N	Y	ND	11.0	-20.2	2.8	-10.0	-10.1	0.9	30.8
ZT0259	Y	Y	N	13.0	-14.9	2.1	-17.3	2.4	-0.2	29.0
ZT0802	Y	N	ND	12.0	-16.7	2.1	-21.0	4.3	-0.4	29.9
ZT0464	Y	Y	ND	13.0	-17.9	2.2	-20.7	2.7	-0.2	28.7

ZT0804	N	N	ND	13.0	-32.8	3.7	-30.8	-2.0	0.2	31.5
ZT0805	N	N	ND	13.0	-32.7	3.8	-26.0	-6.7	0.5	34.0
ZT0077	Y	Y	ND	9.0	-16.1	2.1	-18.2	2.1	-0.2	28.1
ZT0808	N	N	ND	13.0	-9.9	1.8	-23.0	13.1	-1.0	29.9
ZT0809	N	Y	ND	11.0	-11.9	1.8	-13.3	1.4	-0.1	29.1
ZT0812	N	N	ND	13.0	-18.9	2.4	-18.6	-0.3	0.0	32.0
ZT0821	Y	Y	ND	15.0	-18.5	2.8	-22.5	4.0	-0.3	33.4
ZT0451	Y	Y	ND	13.0	-15.8	2.1	-20.1	4.3	-0.3	30.4
ZT0785	Y	Y	N	12.0	-16.9	2.3	-21.8	4.9	-0.4	25.1
ZT0757	Y	Y	ND	10.0	-14.4	2.0	-19.2	4.8	-0.5	27.4
ZT0766	Y	Y	N	11.0	-9.9	1.5	-15.6	5.7	-0.5	25.1
ZT0217	Y	Y	ND	12.0	-11.9	1.8	-19.6	7.7	-0.6	28.1
ZT0589	Y	Y	N	12.0	-16.5	2.3	-25.3	8.8	-0.7	29.9
ZT0823	N	Y	ND	14.0	-22.7	3.1	-11.4	-11.3	0.8	27.8
ZT0825	N	Y	ND	13.0	-21.1	2.8	-10.3	-10.8	0.8	23.9
ZT0826	N	Y	ND	13.0	-12.8	1.8	-10.9	-1.9	0.1	30.8
ZT0827	N	Y	ND	13.0	-20.6	2.8	-17.3	-3.3	0.3	31.9
ZT0832	N	N	ND	14.0	-15.7	2.1	-20.2	4.6	-0.3	35.0
ZT0691	Y	Y	Y	11.0	-14.1	2.0	-25.6	11.5	-1.0	32.6
ZT0835	N	N	ND	16.0	-19.7	2.3	-23.5	3.8	-0.2	26.7
ZT0848	N	N	ND	8.0	-18.5	1.8	-22.1	3.7	-0.5	27.0
ZT0850	N	N	ND	8.0	-13.2	1.8	-20.0	6.8	-0.9	35.0
ZT0851	N	N	ND	8.0	-24.9	3.1	-29.8	4.8	-0.6	28.0
ZT0852	N	N	ND	8.0	-26.4	3.3	-29.7	3.3	-0.4	30.2

1 No; [2] Yes; [3] Not determined; [4] Stand deviation of enthalpy (kcal/mol).

2. Effect of different entropy calculation methods and solute dielectric constants on enrichment of the subset.

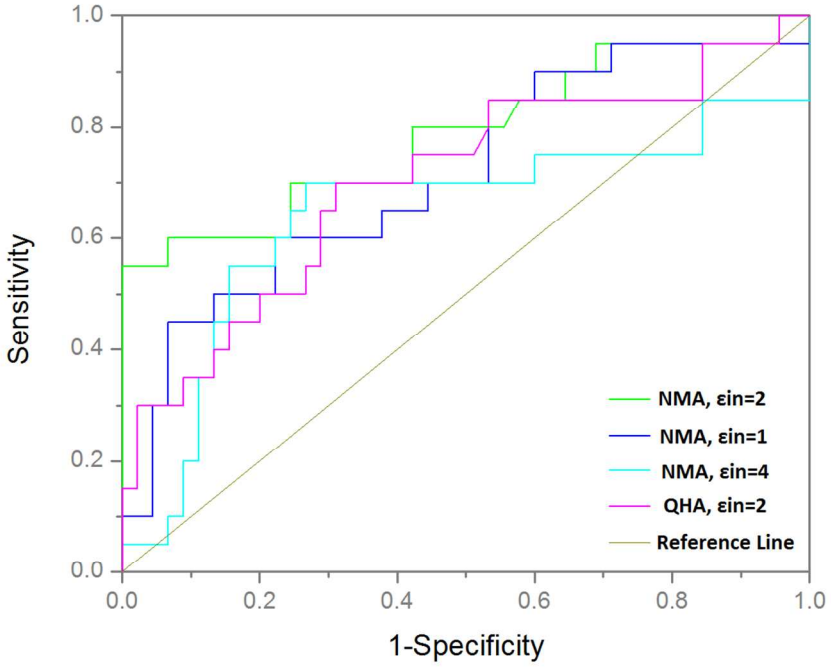

Figure S1. **Effect of different entropy calculation methods and solute dielectric constants on enrichment of the subset** (65 compound subset that has undergone CAIR competition studies). The AU-ROC value for NMA, Normal-mode analysis (AU-ROC: 0.78) was statistically significantly different from QHA, Quasi-harmonic analysis (AU-ROC: 0.70, *p*-value: <0.01). The AU-ROC value for εin = 2 (AU-ROC: 0.78) was statistically significantly different from εin = 1 (AU-ROC: 0.72, *p*-value: 0.01) or εin = 4 (AU-ROC: 0.64, *p*-value: <0.01).

3. Effect of MM/PBSA components on enrichment of the subset

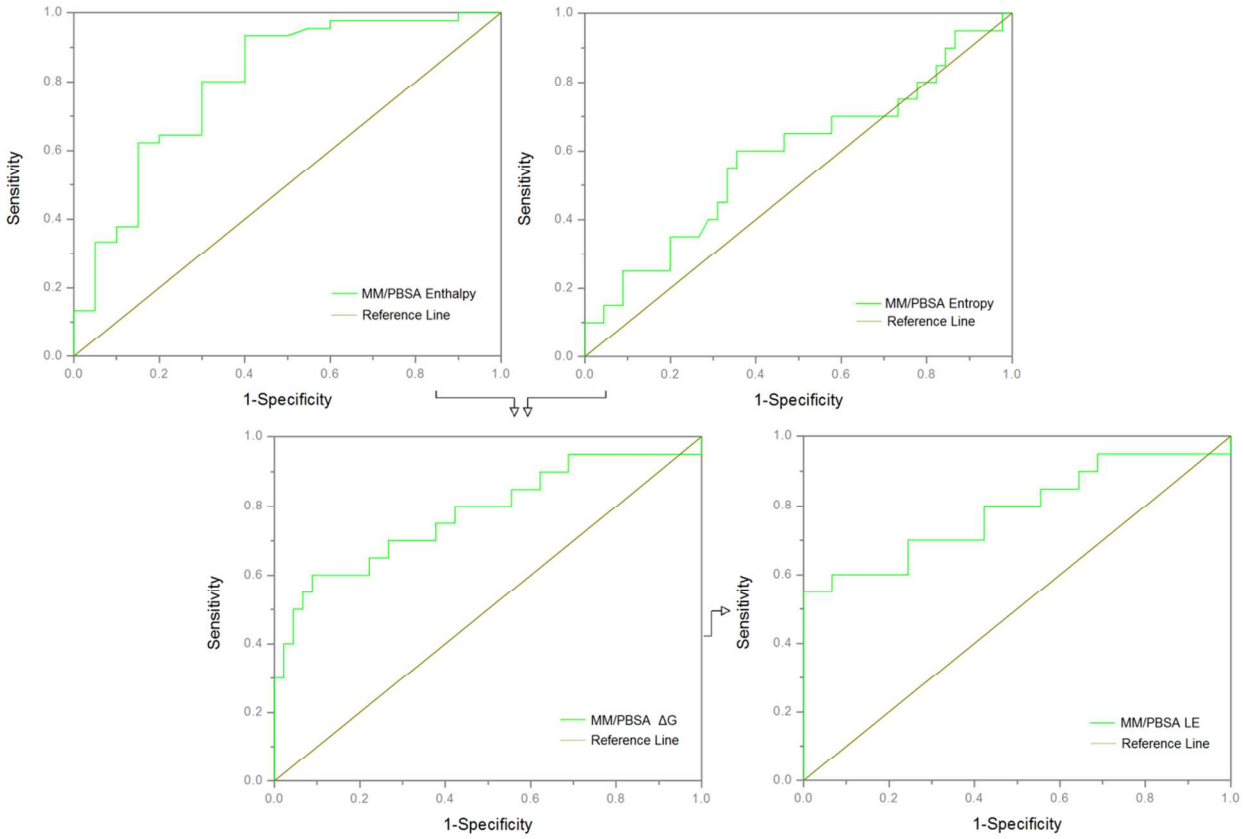

Figure S2. Effect of MM/PBSA components on enrichment (a 65 compound subset that has undergone CAIR competition studies). The contribution of enthalpy and entropy to overall binding energy and fragment screening enrichment are shown here using ROC plots: enthalpy AU-ROC 0.76, entropy AU-ROC 0.59, overall 0.79. A noticeable improvement in early enrichment is seen.

4. The time evolutions of the RMSD plots for the complexes of CAIR and AIR with PurE.

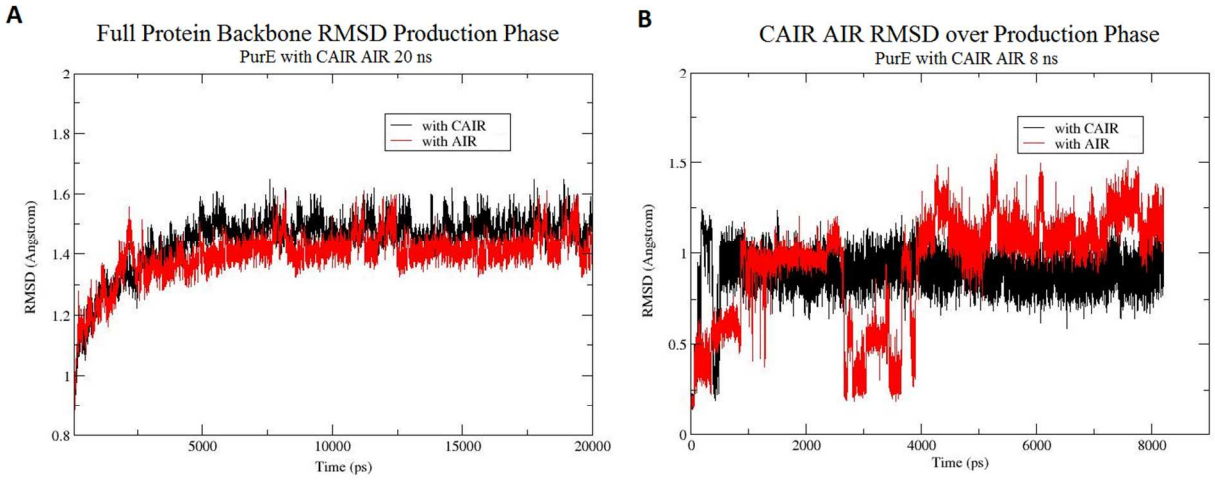

Figure S3. The time evolutions of the RMSD plots for the complexes of CAIR and AIR with PurE. A) Full protein backbone RMSD over 20 ns production phase; longer simulation time is shown here to ensure that the protein conformations have been converged. B) Ligands (AIR and CAIR) RMSD over 8 ns production phase.

5. The time evolutions of enthalpy fluctuations for the complexes of CAIR and AIR with PurE.

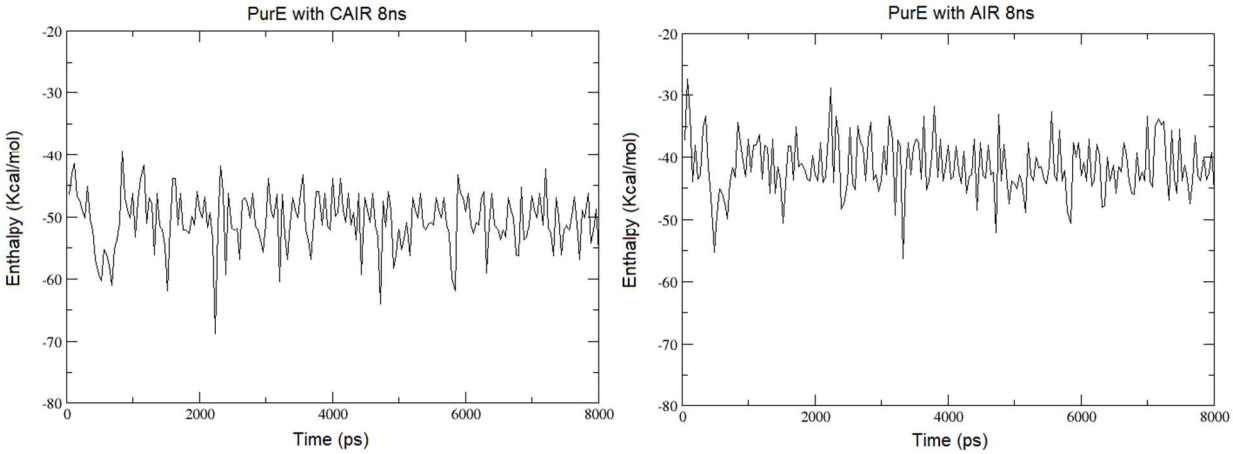

Figure S4. The fluctuations of enthalpies for the complexes of CAIR and AIR with PurE.

6. Effect of multiple conformations on enrichment.

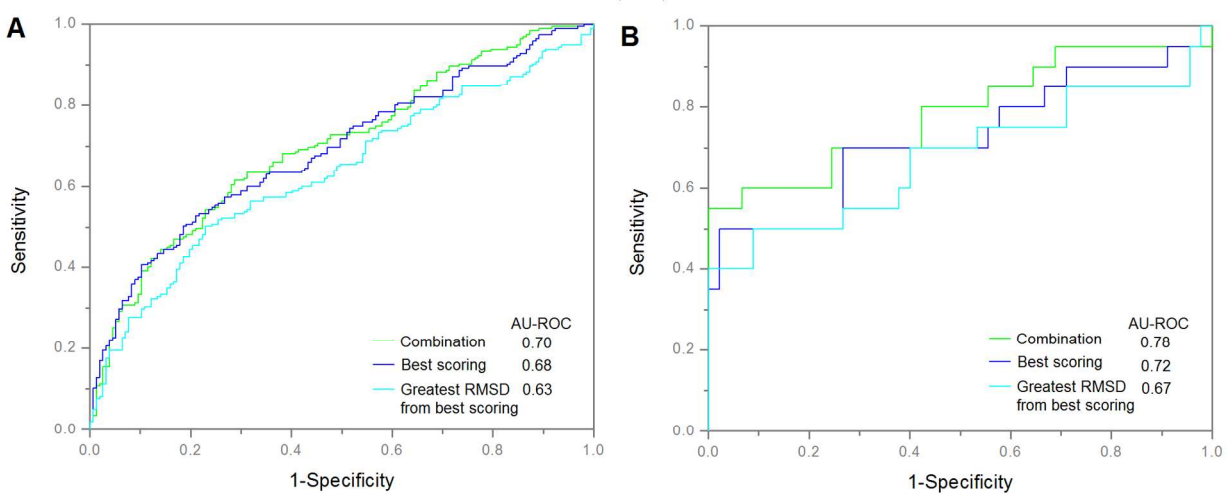

Figure S5. ROC Comparison of multiple conformations vs. single conformation for MD-MM/PBSA screening. A. The complete data set is shown; actives are defined as compounds determined to bind PurE by experimental methods. The AU-ROC value for the combination was not statistically significantly different from the best scoring conformation (AU-ROC: 0.68, *p*-value: 0.20), however, it is significant different from the greatest RMSD from the best scoring ones (AU-ROC: 0.63, *p*-value: 0.03). **B**. A 65 compound subset that has undergone CAIR competition studies is shown; actives are defined as compounds competitive for the CAIR ligand in the PurE active site. The AU-ROC value for the combination was statistically significantly different from the best scoring conformation (AU-ROC: 0.72, *p*-value: 0.01) or the greatest RMSD from the best scoring ones (AU-ROC: 0.67, *p*-value: <0.01).