Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Table S1. The detailed information of Dataset I

PDBID	Resolution	Ligand	Activity	Activity_Type	pK_i/pK_d
1ARJ	NMR	['ARG']	1mM	Kd	3.00
1FYP	NMR	['PAR']	2.5uM	Kd	5.60
1Q8N	NMR	['MGR']	800nM	Kd	6.10
1UTS	NMR	['P13']	0.039uM	Ki	7.41
1UUD	NMR	['P14']	1.54uM	Ki	5.81
2AU4	NMR	['GTP']	75nM	Kd	7.12
2F4S	2.8	['XXX']	19uM	Kd	4.72
2F4T	3	['AB9']	2.2uM	Kd	5.66
2F4U	2.6	['AB6']	5.9uM	Kd	5.23
2KGP	NMR	['MIX']	1uM	Kd	6.00
2KTZ	NMR	['ISH']	9uM	Kd	5.05
2KU0	NMR	['ISI']	2.6uM	Kd	5.59
2KX8	NMR	['ARG']	6.31uM	Kd	5.20
2L94	NMR	['L94']	360uM	Kd	3.44
2LWK	NMR	['0EC']	50.5uM	Kd	4.30
2MXS	NMR	['PAR']	5.1uM	Kd	5.29
2N0J	NMR	['RIO']	0.33uM	Kd	6.48
4LVZ	1.77	['6AP']	0.5uM	Kd	6.30
4LW0	1.89	['ADE']	8uM	Kd	5.10
6HAG	NMR	['SAH']	3.7uM	Kd	5.43
1QD3	NMR	['BDG', 'CYY', 'IDG', 'RIB']	5.9uM	Kd	5.23

1BYJ	NMR	['GE1', 'GE2', 'GE3']	2uM	Kd	5.70
3S4P	2.56	['JS6']	1.0uM	Ki	6.00
4LVW	1.77	['7DG']	66uM	Kd	4.18
4LVY	2	['LYA']	110uM	Kd	3.96
2O3W	2.8	['PAR']	2.6uM	Kd	5.59
2O3X	2.9	['N30']	50uM	Kd	4.30
3NPN	2.79	['SAH']	32nM	Kd	7.49
2BE0	2.63	['JS5']	0.13uM	Kd	6.89

Table S2. The PDBIDs of Dataset II.

PDBIDs of Dataset II
6VA2,4LVZ,2O3V,3NPN,2M4Q,6XB7,6GZR,1Q8N,2LWK,2AU4,2F4T,2MIY,2L94,4LW0,6VA3,2F4S,2KTZ,2KXM,7A3Y,1PBR,2ET8,1NEM,2MXS,1TOB,5VCF,5Z1I,7RWR,1EHT,2N0J,1KOC,1FMN,2O3X,1AKX,1AM0,1AJU,6JBF,2KX8,3Q50,5SWE,6U8F,1UUD,2OE8,2F4U,2KU0,2KGP,2L1V,1BYJ,6HAG,2TOB,7FJ0,5VCI,1KOD,1ARJ,1O15,1LVJ,6GZK

Table S3. The correlation (R_p) comparison of three water models including TIP3P, OPC and SPC based on the minimized structure in OL3 force field. The binding free energy was calculated using GB^{GBn2} method.

Interior Dielectric	Force Field	GB^{GBn2} (TIP3P)	GB^{GBn2} (OPC)	GB^{GBn2} (SPC)
1	OL3	-0.383	-0.185	-0.136
2		-0.418	-0.275	-0.233
4		-0.438	-0.338	-0.307
8		-0.440	-0.373	-0.350
12		-0.437	-0.384	-0.365
16		-0.434	-0.389	-0.372
20		-0.432	-0.392	-0.377

Table S4. The RMSE (kcal/mol) between the experimentally determined binding free energy and the binding free energy predicted by MM/GBSA or MM/PBSA for the structures extracted from the 6 ns MD trajectories in explicit solvent model.

Interior Dielectric	Force Field	GB^{HCT}	GB^{OBC1}	GB^{OBC2}	GB^{GBn1}	GB^{GBn2}	PBSA	Interior Dielectric	Force Field	GB^{HCT}	GB^{OBC1}	GB^{OBC2}	GB^{GBn1}	GB^{GBn2}	PBSA
1	ff99bsc0	35.968	29.329	31.545	33.064	149.909	27.805	1	ROC	35.428	28.582	30.756	30.848	32.245	23.053
2		26.872	23.599	24.593	24.997	71.166	21.022	2		28.128	24.865	25.843	25.599	26.578	19.953
4		22.963	21.418	21.851	21.916	33.968	18.127	4		24.964	23.443	23.881	23.673	24.231	18.607
8		21.275	20.566	20.755	20.748	19.918	16.553	8		23.563	22.866	23.062	22.941	23.225	17.643

12		20.763	20.323	20.438	20.425	17.942	15.859	12		23.129	22.695	22.816	22.735	22.918	17.134
16		20.518	20.209	20.289	20.277	17.826	15.419	16		22.918	22.614	22.698	22.640	22.770	16.793
20		20.374	20.144	20.203	20.193	18.054	15.106	20		22.794	22.567	22.630	22.585	22.683	16.543
1		32.405	26.409	28.554	28.904	31.753	22.835	1		33.253	26.570	28.777	29.885	35.609	22.088
2		26.119	23.231	24.182	23.866	25.379	19.388	2		26.499	23.208	24.208	24.368	27.170	18.907
4		23.511	22.160	22.579	22.278	23.021	18.188	4		23.582	22.015	22.464	22.416	23.726	17.876
8	LJbb	22.398	21.778	21.964	21.785	22.133	17.411	8	Shaw	22.294	21.566	21.768	21.712	22.309	17.130
12		22.061	21.675	21.789	21.669	21.887	16.975	12		21.894	21.441	21.565	21.522	21.892	16.671
16		21.899	21.628	21.708	21.620	21.773	16.663	16		21.701	21.382	21.469	21.436	21.695	16.334
20		21.804	21.602	21.661	21.594	21.709	16.422	20		21.587	21.349	21.413	21.388	21.581	16.070
1		37.861	30.932	33.202	33.146	51.677	25.894	1		34.279	28.463	30.894	32.599	37.722	24.146
2		29.268	25.856	26.910	26.279	34.359	21.393	2		25.992	23.140	24.244	24.675	27.157	19.425
4		25.562	23.944	24.422	23.924	27.229	19.572	4		22.373	21.025	21.515	21.570	22.715	17.454
8	OL3	23.941	23.193	23.408	23.124	24.460	18.419	8	YIL	20.777	20.157	20.374	20.355	20.869	16.283
12		23.443	22.977	23.110	22.920	23.704	17.827	12		20.286	19.900	20.033	20.011	20.327	15.718
16		23.202	22.876	22.968	22.831	23.363	17.425	16		20.048	19.778	19.870	19.851	20.071	15.347
20		23.061	22.817	22.886	22.781	23.170	17.120	20		19.909	19.707	19.775	19.760	19.923	15.070

Table S5. The net charge (e^-) for each RNA-ligand system.

PDBID	Charge (e^-)
1ARJ	-25
1FYP	-21
1Q8N	-36
1UTS	-25
1UUD	-25
2AU4	-36
2F4S	-36

2F4T	-37
2F4U	-35
2KGP	-22
2KTZ	-34
2KU0	-34
2KX8	-39
2L94	-40
2LWK	-30
2MXS	-21
2N0J	-22
4LVZ	-88
4LW0	-88
6HAG	-40
1QD3	-22
3S4P	-28
4LVW	-88
4LVY	-88
2O3W	-39
2O3X	-40
3NPN	-51
2BE0	-30
1BYJ	-21