Supporting Information

The importance of protonation and tautomerization in relative binding affinity prediction: a comparison of AMBER TI and Schrödinger FEP

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Table S1. Relative binding affinities of the neutral ligands transformation predicted by using AMBER TI workflow using ff99SB (*) and ff12SB force fields (unit: kcal/mol). Experimental result, and predictions with uncertainties using extrapolation (etp) and no extrapolation (noetp) coupled with convergence method 1 (c1) and convergence method 2 (c2) are shown in the table.

Neutral Ligands	Experiment	$\Delta\Delta G_{TI\ c1\text{-}etp}$	$\Delta\Delta G_{TI\ c1\text{-}noetp}$	$\Delta\Delta G_{TI\ c2\text{-}etp}$	$\Delta\Delta G_{TI\ c2\text{-}noetp}$	$\Delta\Delta G_{TI\ c1\text{-}etp}^{*}$	$\Delta\Delta G_{TI\ c1\text{-}noetp}^{*}$	$\Delta\Delta G_{TI\ c2\text{-}etp}^{*}$	$\Delta\Delta G_{TI\ c2\text{-}noetp}^{*}$
L51a→L51b	-1.45	2.23±0.09	1.40±0.09	1.62±0.07	0.99±0.07	3.73±0.11	2.44±0.11	3.43±0.07	2.35±0.07
L51a→L51bt	-1.45	0.16±0.09	-0.69±0.08	-0.21±0.07	-0.96±0.07	NA	NA	NA	NA
L51c→L51d	3.36	2.67±0.05	2.13±0.05	2.62±0.06	2.12±0.06	3.17±0.05	2.40±0.05	3.22±0.05	2.49±0.05
L51c→L51f	-0.59	-2.81±0.04	-2.51±0.04	-2.90±0.06	-2.55±0.06	-2.95±0.04	-2.60±0.04	-2.94±0.06	-2.64±0.05
L51c→L51g	-0.36	-0.11±0.04	-0.41±0.04	-0.14±0.06	-0.38±0.06	-1.45±0.04	-1.18±0.04	-1.49±0.06	-1.24±0.06
L51e→L51f	-2.32	-3.21±0.05	-2.42±0.05	-2.75±0.06	-2.09±0.06	-3.04±0.05	-2.55±0.05	-3.29±0.06	-2.74±0.06
L51g→L51a	0.77	-0.36±0.10	-0.51±0.10	-1.40±0.09	-0.89±0.08	-0.10±0.13	0.51±0.12	-0.33±0.11	0.14±0.11
L51h→L51c	0.41	2.55±0.09	2.48±0.09	2.62±0.07	2.43±0.07	1.31±0.10	1.20±0.10	0.16±0.07	0.46±0.07
L51i→L51k	-2.95	-2.17±0.04	-1.98±0.04	-2.22±0.06	-2.04±0.05	-1.69±0.04	-1.38±0.04	-1.52±0.06	-1.30±0.06
L51k→L51h	-0.11	0.13±0.07	0.10±0.07	0.08±0.06	0.05±0.06	0.09±0.07	0.14±0.07	0.14±0.06	0.14±0.06

Table S2. Relative binding affinities of the ligand transformations at pH=7.4 predicted by using AMBER TI workflow (unit: kcal/mol). Protonated state structures were used for all the ligands involved in the transformations

Charged Ligands	Experiment	$\Delta\Delta G_{TI\ etp,c1}$	$\Delta\Delta G_{TI\ etp,c2}$	$\Delta\Delta G_{TI\ noetp,c1}$	$\Delta\Delta G_{TI\ noetp,c2}$
L51a→L51b	-1.45	1.52	1.68	1.18	1.37
L51a→L51bt	-1.45	-1.17	-1.31	-1.09	-1.18
L51c→L51d	3.36	3.60	3.78	2.90	3.00
L51c→L51f	-0.59	-0.98	-0.85	-1.16	-1.05
L51c→L51g	-0.36	0.34	0.36	-0.06	-0.17
L51e→L51f	-2.32	-2.14	-2.23	-1.89	-1.96
L51g→L51a	0.77	-0.40	-0.74	0.19	-0.01
L51h→L51c	0.41	0.40	1.61	-0.05	0.79
L51i→L51k	-2.95	-1.76	-1.75	-1.67	-1.63
L51k→L51h	-0.11	-3.05	-2.68	-2.39	-2.22

Table S3. Predicted relative binding affinities of neutral and charged ligands transformation using Schrödinger FEP (unit: kcal/mol).

Trans	Experiment	Neutral $\Delta\Delta G_{FEP}$	Neutral $\Delta\Delta G_{FEP}$*	Charged $\Delta\Delta G_{FEP}$	Charged $\Delta\Delta G_{FEP}$*
L51b→L51a	1.45	-1.4	-1.63	-1.07	-1.31
L51c→L51d	3.36	2.95	2.96	2.64	2.38
L51f→L51c	0.59	0.36	0.83	1.06	0.76
L51c→L51g	-0.36	-0.64	-0.61	-0.06	-0.1
L51e→L51f	-2.32	-1.11	-0.52	-1.17	-1.26
L51g→L51a	0.77	0.04	0.21	-0.29	-0.5
L51h→L51c	0.41	1.13	1.56	NA	NA
L51k→L51i	2.95	0.24	0.58	0.74	0.74
L51h→L51k	0.11	0	-0.34	NA	NA

* Cycle closure corrected FEP predictions.

Repeating the AMBER TI calculations using FEW

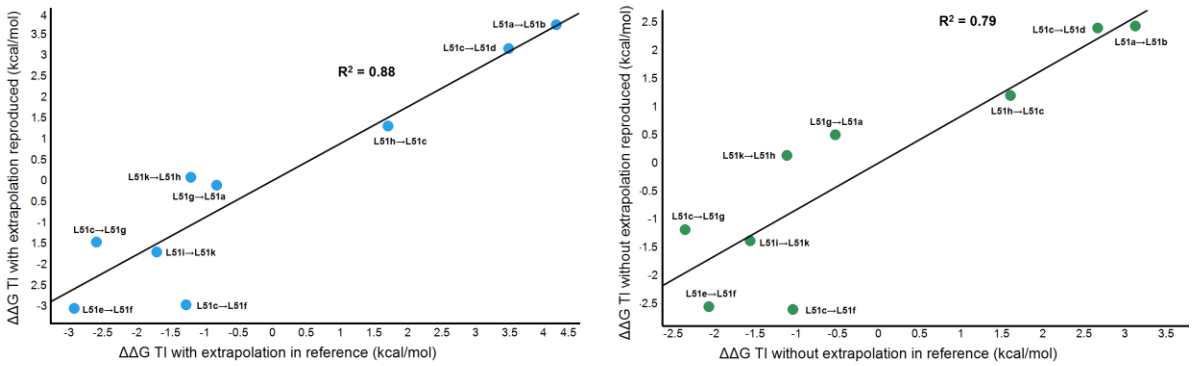

Figure S1. Correlation of the repeated AMBER FEW TI prediction with the relative binding affinities of ligand transformations at neutral state to the TI ΔΔG in the reference [1]. Left plot shows the AMBER TI result using extrapolation and convergence method 1, and right plot shows the result of using convergence method 1 but without extrapolation.

Correlation of AMBER TI to Schrödinger FEP predictions

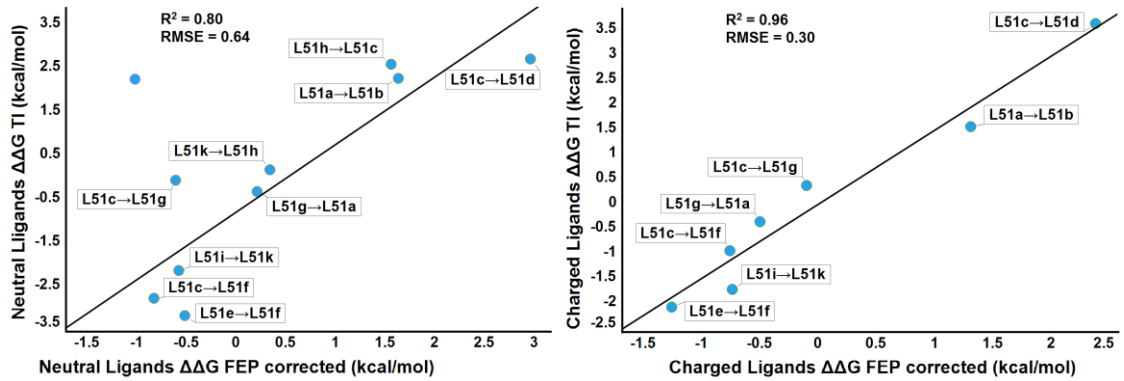

Figure S2. Correlation of AMBER FEW TI prediction with Schrödinger FEP for the relative binding affinities of ligand transformations at neutral state (left panel) and charged state (right panel). Both plots showed the AMBER TI result using extrapolation and convergence method 1. Similar correlations were found by using no extrapolation or convergence method 2 (shown in Figure S3).

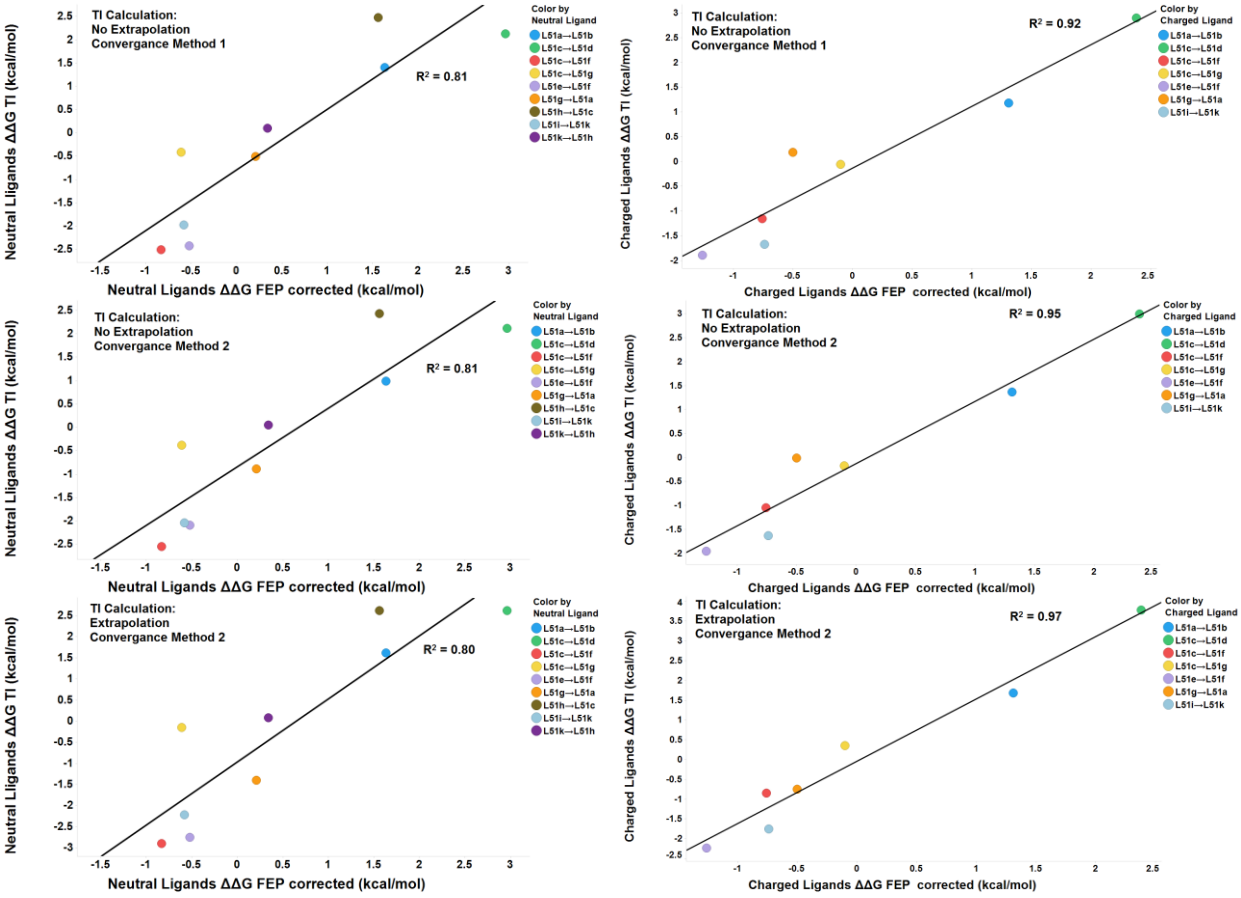

Figure S3. Correlation of AMBER FEW TI prediction with Schrödinger FEP for the relative binding affinities of ligand transformations at neutral state and charged state.

References

1. Homeyer N, Gohlke H (2013) FEW: A workflow tool for free energy calculations of ligand binding. J Comput Chem 34:965-973