Accurate Modeling of Scaffold Hopping Transformations in Drug Discovery
Supporting Information

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The R-group modification FEP predicted relative binding free energies for the CHK1 ligands are shown in Fig. S1. The Core Hopping FEP predicted relative binding free energies agree very well with the benchmark R-group modification FEP results, with a slight improvement in the average cycle closure convergence error.

Representative configurations sampled in the intermediate lambda windows of the Bace1 and TPSB2 ligand perturbations using the regular R group modification FEP are shown in Fig. S2. The ligands unbind in a significantly fraction of the simulation, resulting in very large sampling error and much worse free energy predictions as compared to Core Hopping FEP results.

A systematic comparison between the Core Hopping FEP predicted free energy results and the regular R group modification FEP results is shown in Table S1. The R group modification FEP performed much worse as compared to Core Hopping FEP, particularly when the resulting core is very small like the Bace1 ligands, or when the ring topology change is in the middle of the ligands like the TPSB2 ligands.

The input files used for the Core Hopping FEP calculations and along with the output files including the predicted ΔΔG values of all the perturbations are available for download.
https://drive.google.com/file/d/0BylmDElgu6QLOFp4MHowbUFzXzg/view?usp=sharing

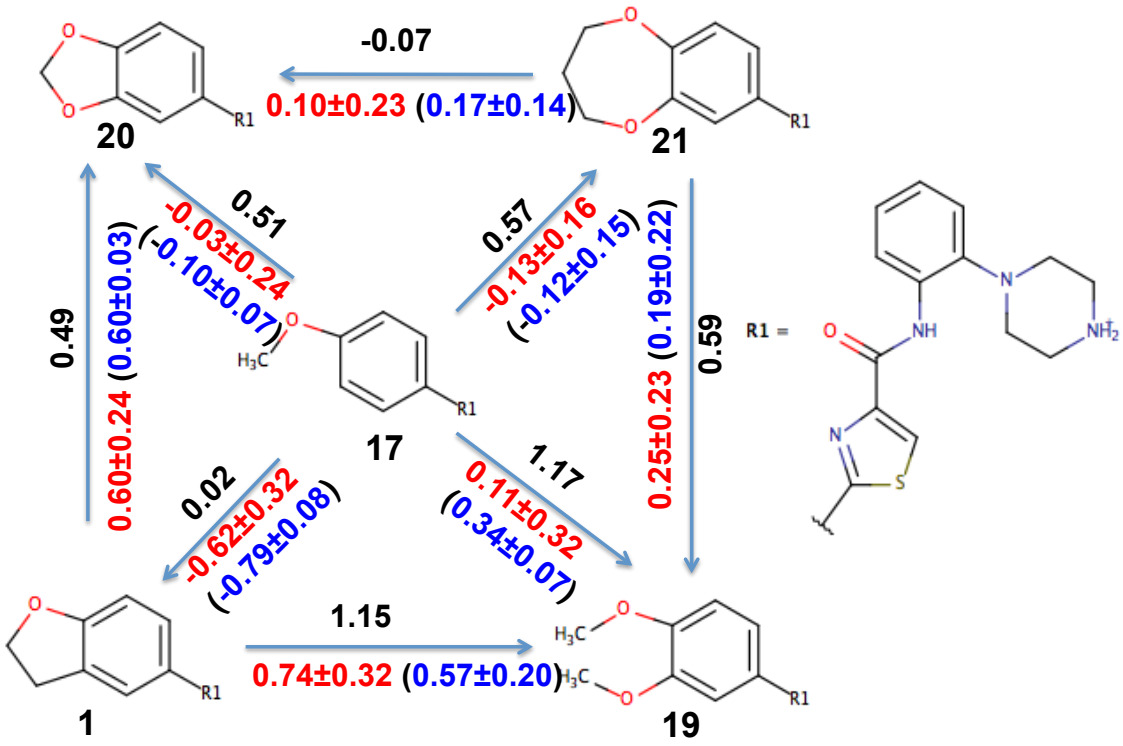
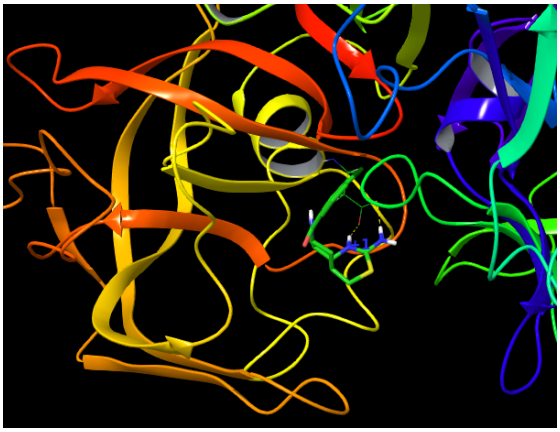
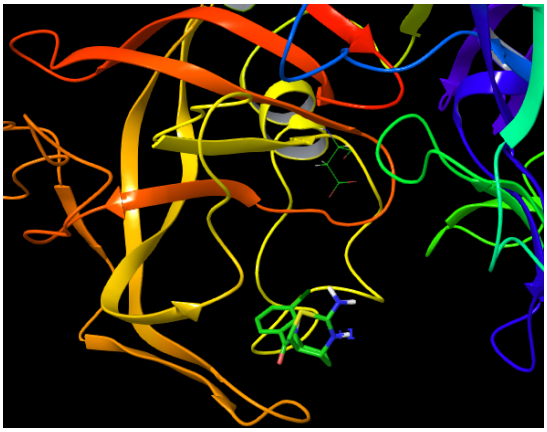


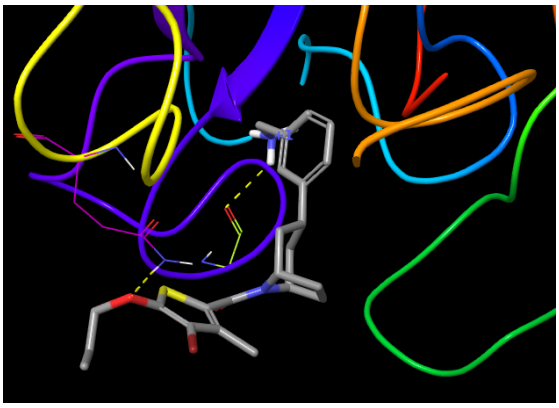
Fig. S1: The R-group modification FEP predicted relative binding free energies for the CHK1 ligands. The Core Hopping FEP predicted relative binding free energies agree very well with the benchmark R-group modification FEP results, with a slight improvement in the average cycle closure convergence error.



A: Bace1 crystal structure



B: Bace1 structure showing unbinding



C: TPSB2 crystal structure

D: TPSB2 structure showing unbinding

Fig. S2: The crystal structures and the representative structures sampled in the intermediate lambda windows of the Bace1 and TPSB2 ligand perturbations using the regular R group modification FEP. The ligands unbind in a significantly fraction of the simulation, resulting in very large sampling error and much worse free energy predictions as compared to Core Hopping FEP results. A: Crystal structure of ligand 6 binding to Bace1 receptor. B: Representative structure sampled in the eighth lambda window (A total number of 16 lambda windows) for perturbation between ligand 6 and 7 using the regular R group modification FEP. The ligand unbinds from the binding pocket, resulting in large sampling error. C: Crystal structure of ligand 2 binding to TPSB2 receptor. C: Representative structure sampled in the eighth lambda window (A total number of 16 lambda windows) for perturbation between

ligand 1 and 1 using the regular R group modification FEP. The ligand unbinds from the binding pocket, resulting in large sampling error.

Systems	Exp.ΔΔG	Pred. ΔΔG (CH)	CC sampling error (CH)	Error (CH)	Pred. ΔΔG (R FEP)	CC sampling error (R FEP)	Error (R FEP)
Bace	**-0.12**	**-0.67**	**0.14**	**0.55**	**-1.78**	**1.17**	**1.66**
Bace	**0.64**	**1.24**	**0.14**	**0.6**	**1.77**	**1.17**	**1.13**
CHK1	0.51	0.03	0.18	0.48	-0.03	0.24	0.54
CHK1	0.02	-0.7	0.24	0.72	-0.62	0.32	0.64
CHK1	0.57	0.22	0.21	0.35	-0.13	0.16	0.7
CHK1	-0.07	-0.19	0.24	0.12	0.1	0.23	0.17
CHK1	1.15	0.95	0.15	0.2	0.74	0.32	0.41
CHK1	0.59	0.03	0.24	0.56	0.25	0.32	0.34
EZH	1.32	0.99	0.5	0.33	1.29	0.13	0.03
EZH	0	0.56	0.5	0.56	0.78	0.17	0.78
EZH	**-0.58**	**-0.67**	**0.5**	**0.09**	**-1.19**	**0.29**	**0.61**
EZH	**1.9**	**2.23**	**0.5**	**0.33**	**3.25**	**0.54**	**1.35**
EZH	**-0.58**	**-1.24**	**0.36**	**0.66**	**-1.97**	**0.39**	**1.39**
Era	2.44	2.81	0.24	0.37	2.77	0.23	0.33
Era	1.78	1.45	0.11	0.33	1.44	0.15	0.34
Fxa	0.8	1.48	0.15	0.68	1.42	0.47	0.62
Fxa	0.87	1.69	0.16	0.82	1.8	0.47	0.93
TPSB2	0.62	**0.16**	**0.07**	**0.46**	**-0.15**	**0.38**	**0.77**
RMSE				**0.50**			**0.83**

CH: Core Hopping FEP

R FEP: Regular R group modification FEP

CC sampling error: Cycle Closure sampling error

Table. S1: Comparison between the Core Hopping FEP predicted free energy results and the regular R group modification FEP results. The R group modification FEP performed much worse as compared to Core Hopping FEP, particularly for the Bace1 perturbations, three of the EZH perturbations and the TPSB2 perturbation, with an overall RMSE of 0.83 and 0.50 kcal/mol for R group modification FEP and Core Hopping FEP respectively.