Supplementary Information

Accurate Receptor-Ligand Binding Free Energies from Fast QM Conformational Chemical Space Sampling

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Table S1:

Table S1. Typical CREST settings

T /K		298.15	
Constrain force constant		0.5	
Wall potential:		ellipsoidal, polynomial	
list of V_{bias} parameters applied		V_{bias} prefactor k	V_{bias} exponent alpha
	Metadyn 1	0.00100	1.000
	Metadyn 2	0.00050	1.000
	Metadyn 3	0.00100	0.500
	Metadyn 4	0.00050	0.500
	Metadyn 5	0.00100	0.250
	Metadyn 6	0.00050	0.250

Table S2. Number of unique structures in the conformer-rotamer ensemble at each stage of the workflow (ligand-receptor complex/free ligand)

	Number of Unique Structure in CRE of Complex/Ligand		
CB[8] Ligands	CREST	Tight reoptimization	Hessian
G0^{2+}	16/12	10/12	8/12
G0^{+}	33/11	17/11	12/9
G1	63/11	22/11	21/11
G2	155/175	149/175	137/158
G3	4/5	4/5	4/5
G4	8/4	8/4	8/4
G5	10/9	10/9	10/9
G6	20/14	20/14	19/14
G7	43/17	43/17	39/16
G8	143/18	85/17	90/17
G9	206/23	193/23	175/22