Supporting Information

On-the-fly QM/MM Docking with Attracting Cavities

Prasad Chaskar, Vincent Zoete and Ute F. Röhrig**

SIB Swiss Institute of Bioinformatics, Molecular Modeling Group, CH-1015 Lausanne, Switzerland

Vincent.Zoete@sib.swiss, Ute.Roehrig@sib.swiss

Table S1: Heme-binding functionalities present in heme binding data set. Ligand–heme interaction energies were calculated with SCC-DFTB on model systems comprising the ligand, a porphyrin ring, iron(II), and a proximal imidazole ligand.

Heme-Binding Functionality (Iron-Bound Element)	**PDB**	**Interaction energy [kcal/mol]**
Aldoxime (N)	3a16, 3a17, 3a18	-24.2
Amine (N)	2v7j	-24.5
Carboxylate (O)	1tu9, 2v7k	-85.7
Hydrazide (N)	4ka6, 4kwq	-23.6
Hydroxamic Acid (O)	1v0h	-35.5
Hydroxyguanidine (O)	1dj5	-34.7
Imidazole (N)	1dp9, 1ike, 1lsx, 1np1, 2at3, 2d0t, 2fmy, 3czy, 3k4f, 3nn1, 3ph2, 3qma, 3tgm, 3vhb, 4hhr, 4kvl	-20.5
Nitrosobenzene (N)	2lh7, 2nss	-62.8
Pyridine (N)	1fsl, 2lh6, 3zjq	-23.0
Pyrimidine (N)	2gtf	-18.4

Table S2: Heme-Binding Dataset Enzyme Classification

Molecule	E.C.	NR.	PDB
Aldoxime-dehydratase	4.99.1.5	3	3a16, 3a17, 3a18
Alpha-dioxygenase		1	4hhr
Ascorbate-peroxidase	1.11.1.11	1	1v0h
Carbon-monoxide-oxidation-system-transcription-regulator		1	2fmy
Catalase-peroxidase	1.11.1.21	2	4ka6, 4kwq
Chlorite-dismutase	1.13.11.49	1	3nn1
Cytochrome c6		1	3ph2
Cytochrome-c-peroxidase	1.11.1.5	1	1dj5
Fatty-acid-alpha-oxidase		1	4kvl
FIXL		2	1dp9, 1lsx
Heme-oxygenase	1.14.99.3	3	3czy, 3k4f, 3tgm
Hemoglobin		1	3vhb
Hypothetical-protein-pa3967		1	1tu9
Indoleamine-2,3-dioxygenase	1.13.11.42	1	2d0t
Leghemoglobin		3	1fsl, 2lh6, 2lh7
Myoglobin		2	2nss, 3qma
Nitrophorin		4	1ike, 1np1, 2at3, 2gtf
PRNB		2	2v7j, 2v7k
Protoglobin		1	3zjq

Table S3: Heme Nonbinding Dataset Enzyme Classification

Molecule	E.C.	NR.	PDB
Catalase-peroxidase	1.11.1.21	2	3vll, 3wxo
Cytochrome-c-peroxidase	1.11.1.5	28	1kxm, 2anz, 2aqd, 2eun, 2euo, 2eup, 2eur, 2eut, 2euu, 2rbx, 2rby, 2rbz, 2rc1, 2y5a, 4jm8, 4jm9, 4jms, 4jmz, 4jqm, 4jqn, 4nvd, 4nvg, 4nvh, 4nvk, 4nvl, 4nvm, 4nvn, 4xv7
Horseradish-peroxidase	1.11.1.7	1	3atj
Myoglobin		2	3u3e, 4h07
Peroxidase	1.11.1.7	5	1ck6, 1gw2, 1gx2, 2atj, 7atj
Tryptophan-2,3-dioxygenase	1.13.11.11	1	3e08
Versatile-peroxidase-vpl2	1.11.1.6	1	4g05

Table S4: Prediction Rate of any Atom Binding to Iron (< 3 Å) In the Best Pose of the Heme Datasets.

Docking Scheme	**Mini**[b]	**Heme Binding Set [%]**		**Heme Nonbinding Set [%]**	
		Docking Ensemble	**Ensemble+ X-ray Pose**	**Docking Ensemble**	**Ensemble+ X-ray Pose**
Classical AC	-	34.4	34.4	0.0	0.0
Classical AC + MMBP	-	87.5	90.6	0.0	0.0
AutoDock[a]	-	65.6	-	7.5	-
AutoDock (Fe +2)[a]	-	84.4	-	25.0	-
AutoDock Vina[a]	-	25.0	-	0.0	-
GOLD[a]	-	90.6	-	2.5	-
QM/MM Scheme 1	200	84.4	93.8	2.5	2.5
QM/MM Scheme 1	1200	81.3	90.6	2.5	2.5
QM/MM Scheme 2	200	84.4	96.9	2.5	2.5
QM/MM Scheme 2	1200	81.3	90.6	2.5	2.5
QM/MM Scheme 2 1000 poses	200	87.5	96.9	2.5	2.5
QM/MM Scheme 2 +MMBP	200	84.4	90.6	2.5	2.5
QM/MM Scheme 2 +PT	200	87.5	96.9	2.5	2.5

a: Starting from bioactive conformation. *b:* Minimization scheme (200: 100 steps of SD and 100 steps of ABNR; 1200: 200 steps of SD and 1000 steps of ABNR).