Supporting Information: **STACKED** – **S**olvation **T**heory of **A**romatic **C**omplexes as **K**ey for **E**stimating **D**rug binding

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Table S1: Comparison of the stacking energies calculated in this study, stacking energies calculated using a grid-based approach, the hydration free energies of the monomers and the desolvation penalty of the optimized stacked complexes. The cells framed by the black gridlines correspond to stacking on toluene, red blacklines to stacking on 4-methyphenol and green to stacked complexes of 3-Methyl-1H-indole.

IPUAC Name	Vacuum Stacking Interaction Optimized / kcal/mol	Vacuum Stacking Interaction Grid Based / kcal/mol	Hydration Free Energy Monomer / kcal/mol	Desolvation Penalty / kcal/mol
furan	-4.25	-4.20	-2.44	2.99
thiophene	-4.13	-4.50	-1.76	2.01
isooxazole	-5.27	-5.10	-5.31	2.77
oxazole	-4.62	-5.10	-4.83	2.80
isothiazole	-4.75	-5.50	-3.56	1.72
thia-3,4-diazole	-4.56	-6.10	-6.15	2.16
benzene	-4.55	-4.50	-1.44	2.36
pyridine	-5.07	-5.60	-3.92	2.05
pyrazine	-5.86	-6.00	-3.94	3.12
pyrimidine	-6.21	-6.10	-6.23	2.36
pyridazine	-5.71	-6.50	-5.89	2.03
1,3,5-triazin	-5.77	-5.90	-7.46	2.18
1,2,5-triazin	-6.65	-7.00	-6.38	2.75
Triazine	-7.15	-7.30	-7.06	3.01
1,2,4,5-tetrazin	-6.42	-6.80	-6.44	2.92
1,2,3,5-tetrazin	-6.65	-7.10	-6.61	2.26
tetrazin	-6.44	-8.00	-6.80	3.20
pyrimidone	-8.34	-7.30	-14.18	3.50
Furan	-4.15	-4.30	-2.44	2.70
thiophene	-4.81	-5.20	-1.76	2.42
isooxazole	-5.25	-5.10	-5.31	2.64
oxazole	-4.79	-5.80	-4.83	2.31
isothiazole	-5.36		-3.56	2.04
thia-3,4-diazole	-5.86	-6.30	-6.15	2.44

benzene	-4.74	-4.90	-1.44	2.21
pyridine	-5.91	-5.80	-3.92	1.58
pyrazine	-5.64	-6.40	-3.94	2.74
pyrimidine	-5.04	-6.40	-6.23	2.00
pyridazine	-6.46	-6.70	-5.89	2.55
1,3,5-triazin	-6.06	-6.60	-7.46	2.06
1,2,5-triazin	-7.27	-7.60	-6.38	2.16
triazine	-7.58	-8.60	-7.06	2.99
1,2,4,5-tetrazin	-6.99	-7.20	-6.44	2.86
1,2,3,5-tetrazin	-7.50	-7.80	-6.61	4.88
tetrazin	-8.38	-8.70	-6.80	5.13
pyrimidone	-9.13	-7.30	-14.18	3.78
furan	-5.22	-5.30	-2.44	4.27
thiophene	-5.44	-5.80	-1.76	2.57
isooxazole	-6.41	-7.20	-5.31	3.58
oxazole	-5.87	-7.20	-4.83	3.37
thia-3,4-diazole	-8.04	-9.10	-6.15	4.69
benzene	-5.86	-6.00	-1.44	3.46
pyridine	-6.73	-7.70	-3.92	3.17
pyrazine	-7.69	-8.10	-3.94	3.64
pyrimidine	-8.20	-8.40	-6.23	3.32
pyridazine	-8.91	-9.50	-5.89	4.58
1,3,5-triazin	-8.18	-4.50	-7.46	3.42
1,2,5-triazin	-8.78	-5.30	-6.38	3.80
triazine	-9.66	-8.40	-7.06	5.22
1,2,4,5-tetrazin	-9.23	-9.90	-6.44	4.18
1,2,3,5-tetrazin	-8.74	-10.30	-6.61	3.51
tetrazin	-9.82	-9.80	-6.80	4.97
pyrimidone	-9.70	-9.90	-14.18	3.92

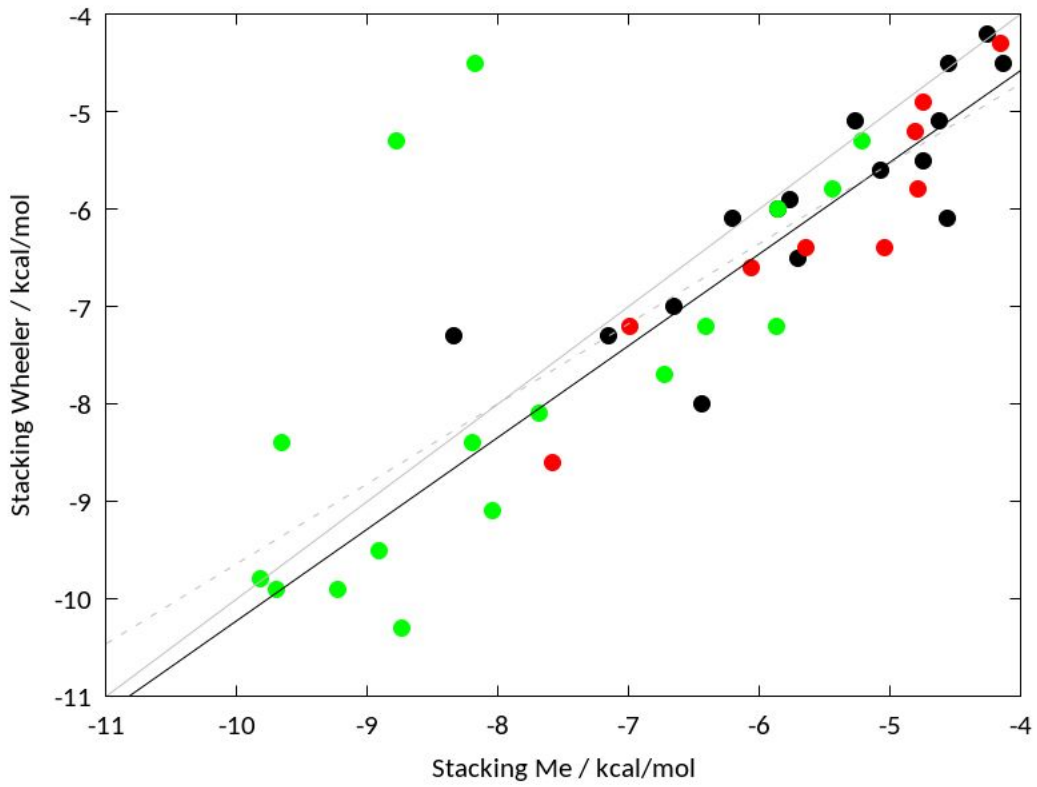

Figure S1: Comparing the stacking interactions obtained using the free optimisation with the recently published grid-based results. We find a Pearson correlation of 0.82 for all complexes. Splitting into the different amino acid mimics, we find 0.86 for stacking on toluene (black circles), 0.88 for stacking on 4-methylphenol (red circles) and 0.64 for complexes containing 3-methylindole (green circles). For the latter complexes, if the two outliers are neglected the correlation increases to 0.92.

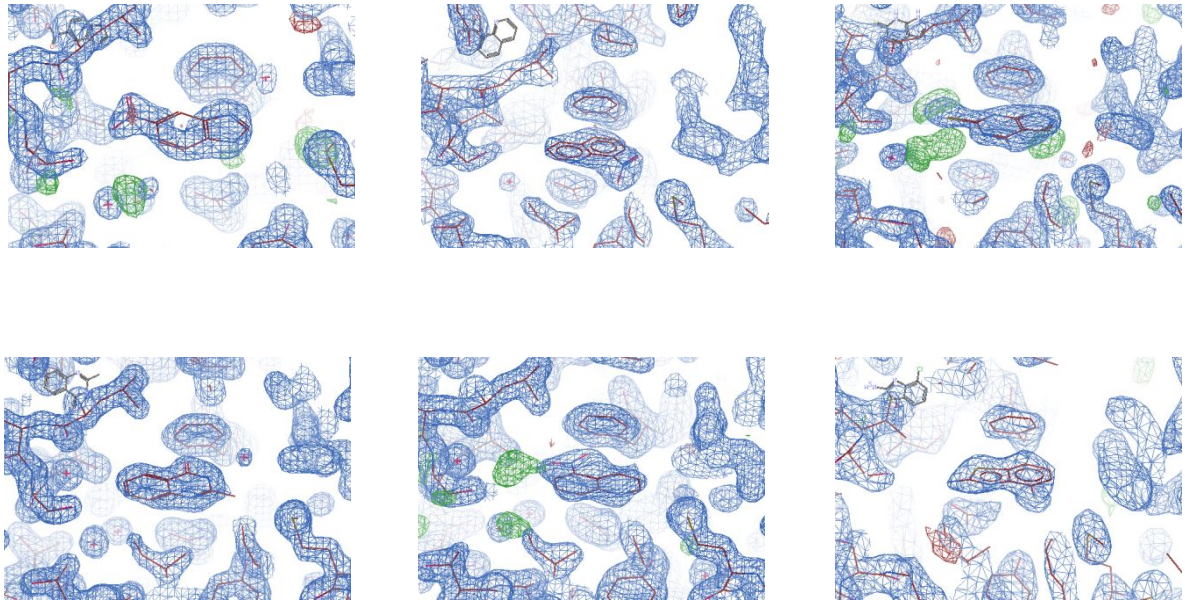

Figure S2: Electron densities for ligands from the FBLD study.

Table S2: Pearson correlations of the experimentally determined binding free energy for the FBLD study on PDE10, the vacuum stacking interactions, the solvation free energy of the fragments and the desolvation penalty based on the crystallized structures.

	DG Bind Experiment / kcal/mol	Vacuum Stacking / kcal/mol	Solvation Monomer / kcal/mol	Desolvation Penalty / kcal/mol
DG Bind Experiment / kcal/mol	1.00	-0.18	-0.26	-0.79
Vacuum Stacking Interaction / kcal/mol	-0.18	1.00	0.07	-0.26
Solvation Monomer / kcal/mol	-0.26	0.07	1.00	-0.49
Desolvation Penalty / kcal/mol	-0.79	-0.26	-0.49	1.00

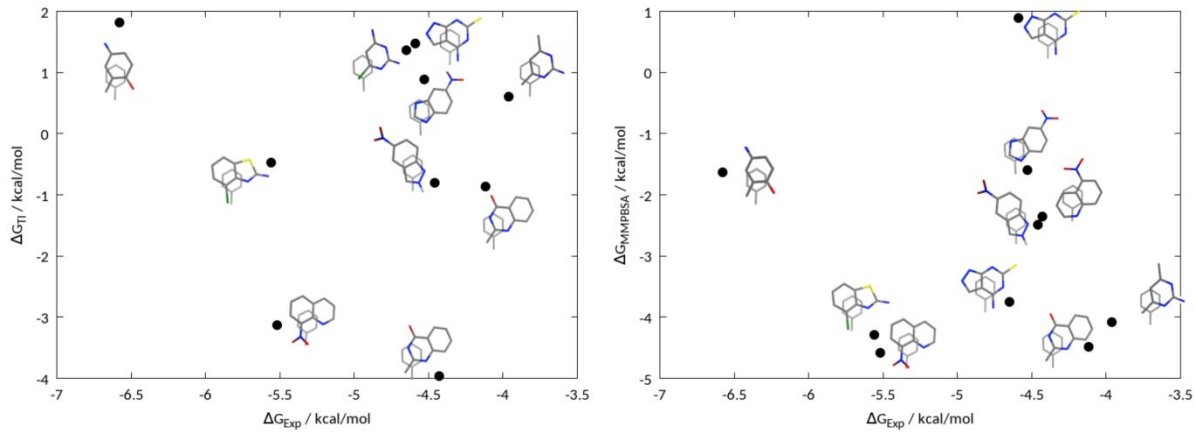

Figure S3: Correlation of free energies and the experimental binding energies. The free energies are calculated using TI (left) and MMPBSA (right). We have performed MM-GBSA as well as TI studies on the experimental data set using MOE and AMBER19. For the TI calculations we used 11 lambda windows with a simulation time of 100 ns per window. When using MMPBSA we find once more, that the best stacking ligand is by far not ranked in the top compounds. However, it is far better ranked compared to vacuum stacking interactions. Overall the correlation is -0.12 and improves solely to 0.21 by neglecting 4LLP.

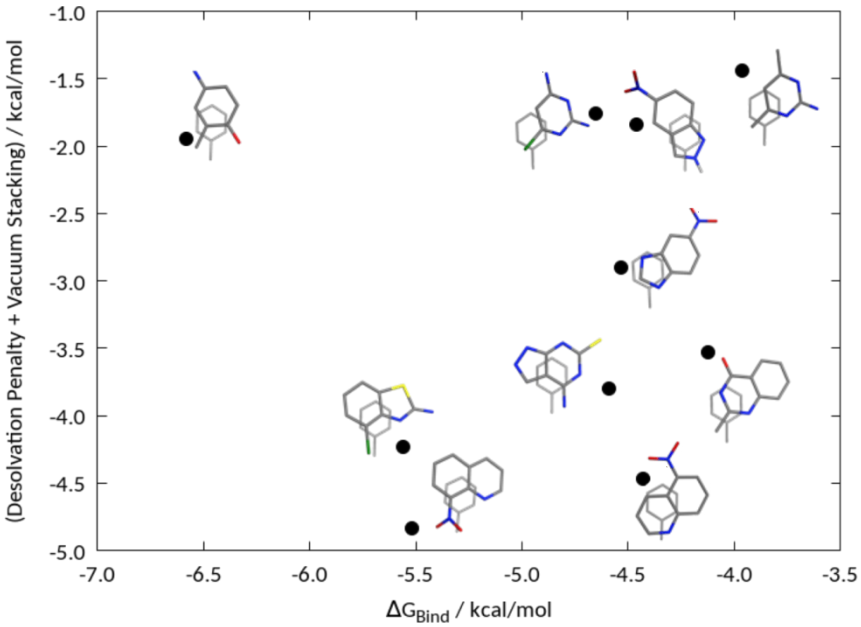

Figure S4: Correlation of the sum of the desolvation penalty and the vacuum stacking interactions with the experimental binding free energy. The vacuum stacking interactions are the more dominant interaction in this sum, therefore the correlation vanished compared to the desolvation penalty alone.