Supporting Information

Wang et al. 10.1073/pnas.1016793108

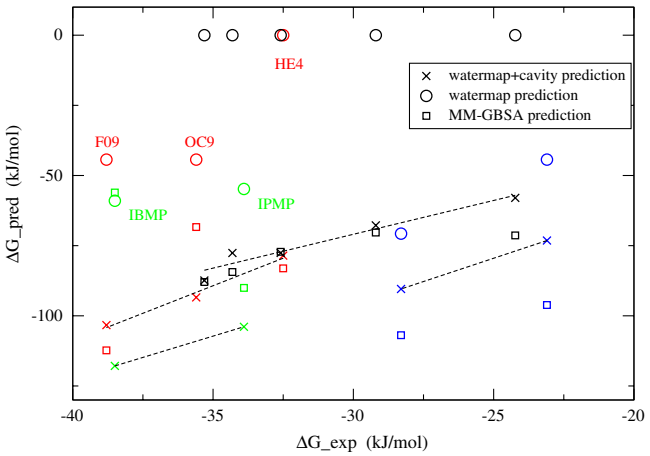


Fig. S1. The Watermap, Watermap+cavity, and MM-GBSA predictions for the binding affinities of different ligands to the MUP receptor versus the experimental data. The Watermap predictions are displayed as circles, Watermap+cavity predictions are displayed as crosses, and MM-GBSA predictions are displayed as rectangles. The ligands belonging to different groups are indicated by different colors. Whereas the Watermap and MM-GBSA predictions fail to rank-order most of the congeneric ligands, Watermap+cavity predictions correctly rank-order all the congeneric ligands in each group.

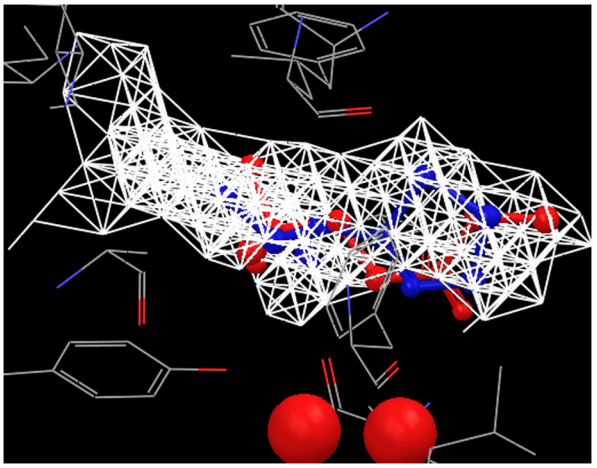


Fig. S2. Ligands LTL (red) and TZL (blue) binding to the MUP receptor. Large portions of the ligand atoms are located in the dry cavity region.

Table S1. Data for the Watermap and cavity contributions to the binding affinities for different ligands binding to MUP receptor

Binding affinities	PE9	HE2	HE4	OC9	F09	IBMP	IPMP	SBT	PT	IPT	ET	MT
Exp	−23.1	−28.3	−32.5	−35.6	−38.8	−38.5	−33.9	−35.3	−34.3	−32.6	−29.2	−24.2
WaterMap	−44.4	−70.7	0.0	−44.4	−44.4	−59.0	54.8	0.0	0.0	0.0	0.0	0.0
Cavity	−28.8	−19.7	−78.6	−49.1	−59.0	−58.9	−49.1	−87.4	−77.6	−77.6	−67.8	−58.8
Total	−73.2	−90.4	−78.6	−93.5	−103.4	−117.9	−103.9	−87.4	−77.6	−77.6	−67.8	−58.8
MM-GBSA	−96.2	−106.9	−83.1	−68.4	−112.3	−56.1	−90.0	−88.0	−84.4	−77.2	−70.3	−71.3

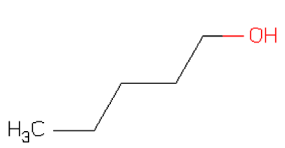
Note1: Free energies in kJ/mol. For ligand PE9, the PDB structure (PDB ID 1ZND) contains two ligands (with two binding modes). However, experimental ITC data indicate a binding stoichiometry of approximately 1 for PE9 (1), so only the binding mode with stronger binding affinity was analyzed. The predicted binding affinities for the two binding modes agree with experimental data.

Note 2: Ligands PE9 and HE2 bind in a similar orientation whereas ligands HE4, OC9, and F09 bind in an alternate orientation. So they are considered as two groups (1).

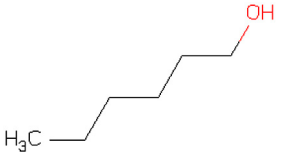
Note 3: For SBT series of ligands, PDB structures are only available for SBT/MUP complex, and structures of other ligands were obtained by removing the appropriate carbon atoms from SBT.

1 Malham R, et al. (2005) Strong solute-solute dispersive interactions in a protein–ligand complex. *J Am Chem Soc* 127:17061–17067.

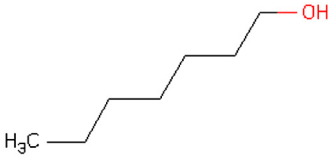
Table S2. The structure of the ligands and their associated PDB ID



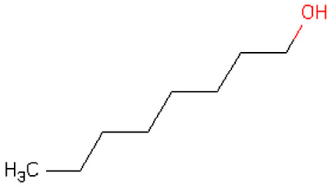
PE9:1ZND



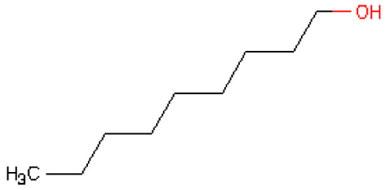
HE2:1ZNE



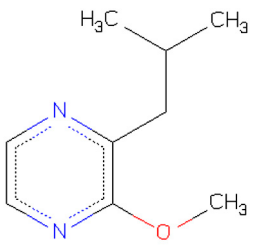
HE4:1ZNG



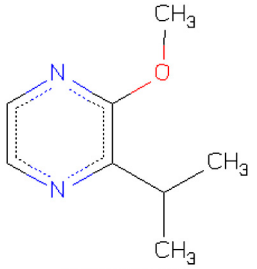
OC9:1ZNH



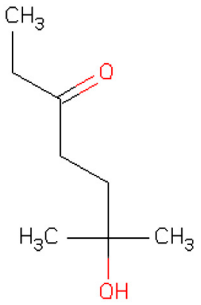
F09:1ZNK



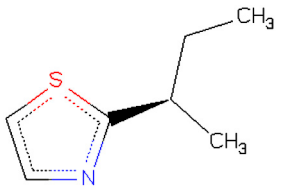
IBMP:1QY1 (PRZ)



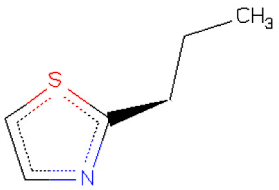
IPMP:1QY2 (IPZ)



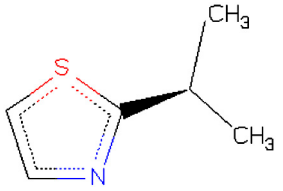
LTL:1I05 (HMH)



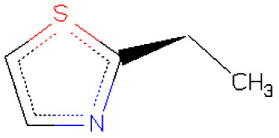
TZL:1I06 (SBT)



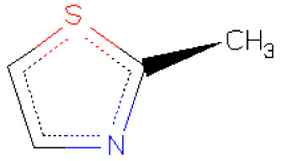
PT



IPT

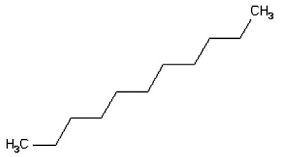


ET



MT

DKA:1WBE



UND:1Y9L