

Project Sphinx

Impairing *Aedes aegypti* olfactory system





Olfactory system

Near cuticle (neutral pH):
 $OM + OBP \rightarrow OM-OBP$

Close to dendrite membrane (low pH):
 $OM-OBP + OR-ORCO \rightarrow OM-OR-ORCO + OBP$

acidic pH



Molecular modeling approach

Homology modeling

- BLAST, Prime
- Ramachandran plot
- Docking

Structure-based virtual screening

- ZINC
- DB filtering
- 100K molecules
- Ranking: consensus

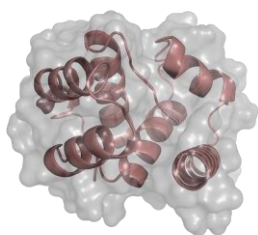
Binding free energy estimation

- MM-GBSA (Prime)
- MM-PBSA (AMBER)

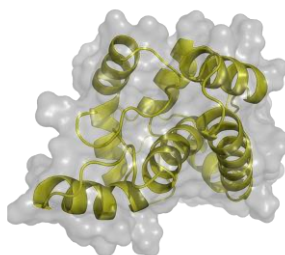
Efficacy tests

- 5 substances

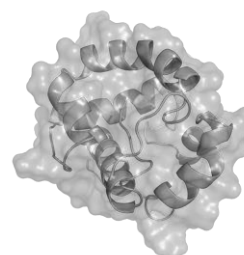
Results: OBP homology modeling



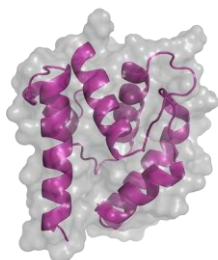
Q0C747



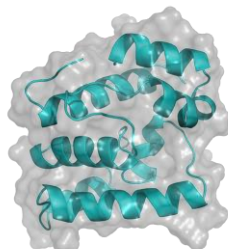
Q1DGM9



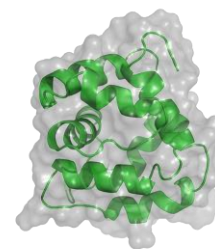
Q6Y2R8



Q16MA2

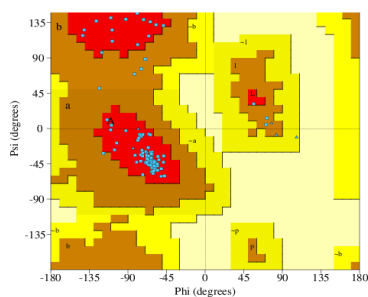


Q17HN6

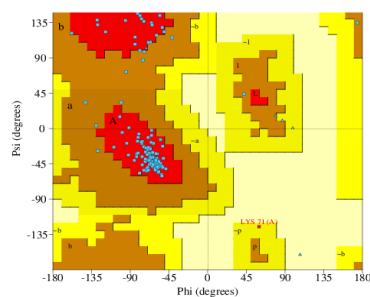


Q177B9

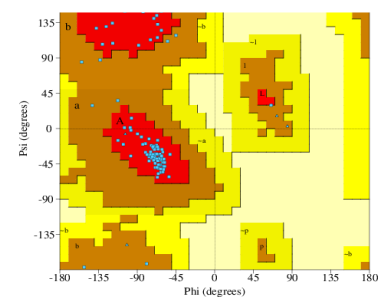
Results: Ramachandran plots



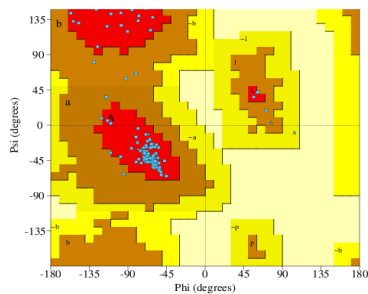
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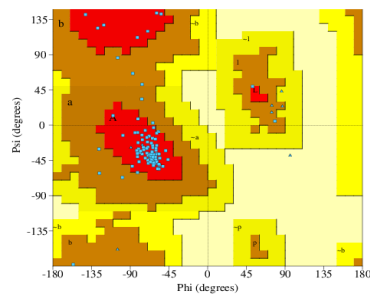
Q1DGM9



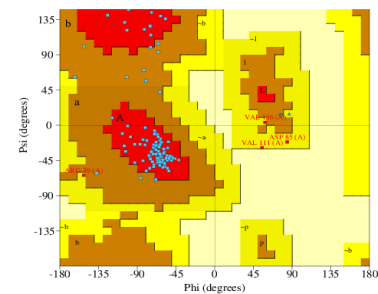
Q6Y2R8



Q16MA2

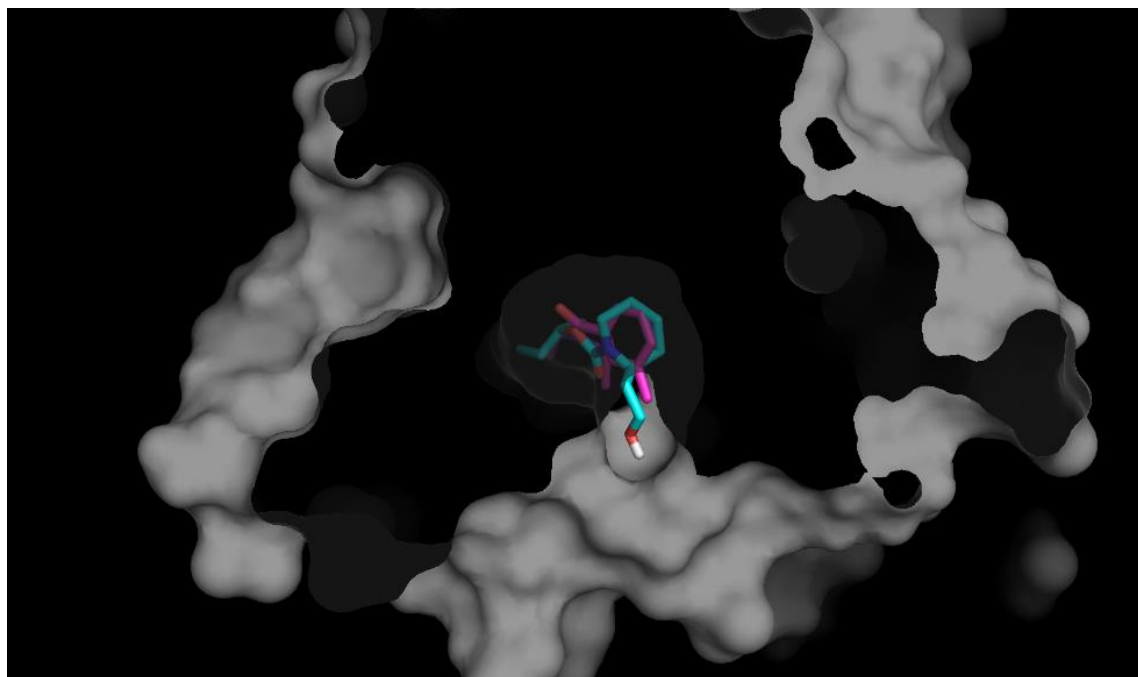


Q17HN6



Q177B9

Results: Docking of repellents



DEET (pink); icaridin (cyano)

Results: Virtual screening (GScore, Kcal/mol)

Substance	Q6Y2R8	Q16MA2	Q177B9	Q1DGM9	Q17HN6	Q0C747
DEET	-4.460	-3.429	-5.935	-4.959	-5.583	-3.719
Icaridin	-9.462	-4.763	-5.021	-5.020	-5.401	-5.586
CH000005	-9.406	-7.558	-8.585	-6.607	-6.705	-8.449
CH000006	-9.074	-7.689	-8.329	-6.875	-6.976	-6.453
CH000015	-8.067	-7.006	-7.635	-5.531	-6.157	-6.223
CH000027	-7.367	-8.383	-8.729	-5.454	-6.012	-8.970
CH000029	-7.337	-6.977	-7.769	-4.902	-6.169	-7.001
CH000040	-6.841	-7.811	-8.353	-6.796	-6.475	-8.705
CH000041	-6.829	-7.620	-7.915	-6.922	-5.941	-8.188

Results: Binding free energy (in Kcal/mol)

	MM-PBSA	MM-GBSA					
Molecule	Q6Y2R8	Q6Y2R8	Q16MA2	Q177B9	Q1DGM9	Q17HN6	Q0C747
CH000005	-80,45	-47,63	-48,29	-53,97	-51,51	-30,68	-49,02
CH000006	-86,37	-47,66	-40,77	-59,28	-52,15	-42,23	-51,32
CH000015	-81,63	-43,18	-47,98	-54,71	-44,85	-43,98	-46,33
CH000027	-75,58	-49,60	-43,18	-55,01	-42,28	-43,81	-48,34
CH000029	-81,28	-50,89	-58,37	-66,16	-44,20	-44,24	-55,42
CH000040	-105,10	-46,98	-45,69	-56,63	-50,70	-29,71	-49,82
CH000041	-87,76	-42,12	-40,50	-58,25	-40,95	-41,32	-51,08



Status

- *In silico* toxicity – OK
- Repellency tests – ongoing



Food for thought

- Are all these OBP really critical for host seeking?
⇒ If tests above can't answer: OBP KO?
- Experimental binding free energy?
⇒ OBP heterologous expression & purification, uITC?

Special thanks



Prof. Dr. Rafael V. C. Guido





Thank you!



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