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*Article*

# Potency- and Selectivity-Enhancing Mutations of Conotoxins for Nicotinic Acetylcholine Receptors can be Predicted Using Accurate Free-Energy Calculations

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**Table S1.** Comparison of FEP affinity predictions for LsIA mutations using OPLS3e and OPLS4 forcefields

| LsIA Mutation | Experimental ΔΔG at Ls-AchBP (kcal/mol) | OPLS3e Predicted ΔΔG (kcal/mol) | OPLS4 Predicted ΔΔG (kcal/mol) |
|---|---|---|---|
| R10M | 0.51 | -0.70 ± 0.22 | -2.72 ± 0.18 |
| R10F | -0.38 | -0.82 ± 0.07 | -2.81 ± 0.34 |
| N12Q | 1.45 | 1.57 ± 0.30 | 1.25 ± 0.11 |

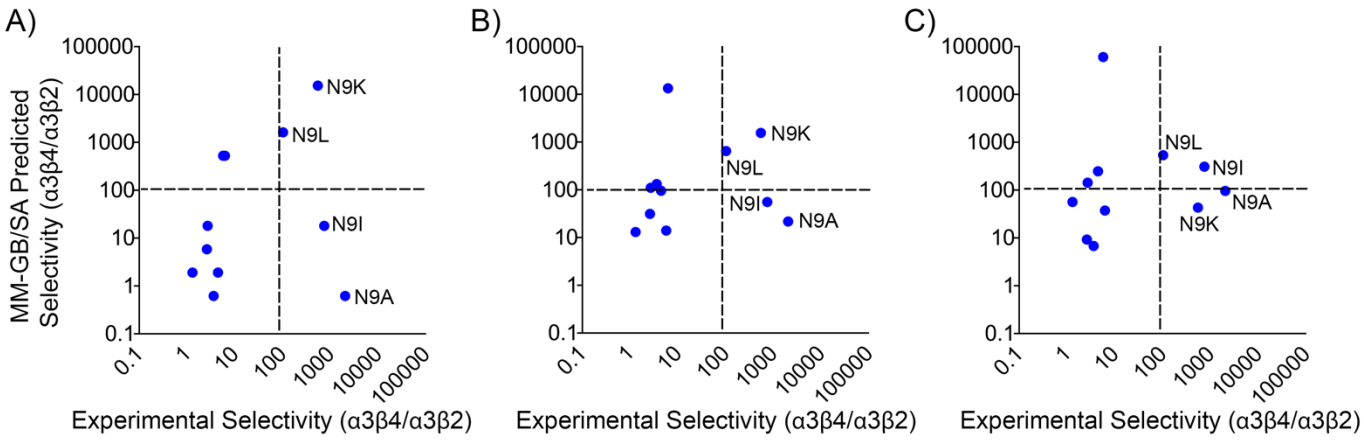


**Figure S1**. MM-GB/SA selectivity predictions for LvIA mutants using different nAChR conformations. The accuracy of MM/GB-SA at classifying LvIA mutants as selective or not was measured using α3β2 and α3β4 nAChR conformations **(A)** prior to MD refinement **(B)** extracted from the respective simulation frames after 5 ns of MD refinement **(C)** extracted from the final frames of the respective WT LvIA FEP trajectories. The four mutants which are experimentally verified to be greater than 100X selective are labeled.

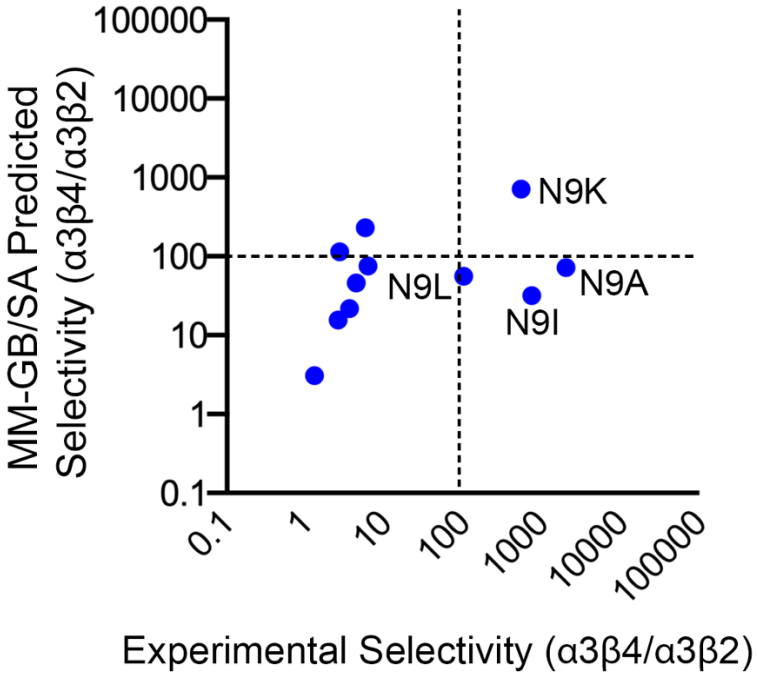


**Figure S2.** Performance of MM/GB-SA using an ensemble of conformations. The selecitives of eleven LvIA mutants were computed with MM/GB-SA using ten, evenly spaced frames from a 25 ns MD trajectory. The four mutants which are experimentally verified to be greater than 100X selective are labeled.