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Gabaergic insecticides exploration: characterization of one GABA receptor binding site. A

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The insect $GABA_A$ receptor (RDL) is an important protein target for natural and artificial insecticides that act by blocking the channel and inhibiting the ions flux through it. We aim to characterize the non-competitive antagonists II (NCA-II) binding site, to develop tools that allow us to obtain new insecticidal compounds that share this same blocking site. This site is targeted by isoxazolines, being Fluralaner a canonical representative of this chemical class. We pretend to evaluate whether these compounds could interact with the membrane where the receptor is embedded and module it. Different 3D models of the *Aedes aegypti* homopentamer RDL were developed in our group by homology modelling, due to the fact that there is no available crystallographic structure of the receptor. Distinct templates corresponding to different conformational states of the channel were used. We have evaluated the performance of the models by molecular docking assays of Fluralaner, in order to determine which of them is capable of replicating the Fluralaner binding pose. The model obtained from the 3RHW template (PDB ID 3RHW), which has an open channel conformation, was the one that best replicated both the interactions reported by biochemical assays, as well as the spatial orientation of the Fluralaner molecule at the receptor blocking site. These molecular docking assays of the Fluralaner at the NCA-II site allowed us to select a model of the *Aedes aegypti* $GABA_A$ receptor that reproduces that reported by previous works. We performed ALL ATOM detail Molecular Dynamics simulations to characterize the membrane-receptor-ligand interactions, which allowed us to validate the selected model since the interactions between the Fluranaler and the rest of the system components were as expected.

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