



## Impact of the template conformational state on pLGICs homology models applicability for virtual screening: a case study on the insect GABA receptor

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Pentameric ligand-gated ion channels (pLGICs) constitute a large family of transmembrane proteins that includes the  $\gamma$ -aminobutyric acid receptors (GABA-R). The RDL receptor (RDL-R) is the main GABA-R in the insect nervous system and it is one of the most relevant targets for insecticides. Due to the difficulties related to pLGICs crystallization, many studies have used homology modeling to obtain their structures and to perform docking-based virtual screening (VS). However, the impact that the template conformational state could exert on the model VS performance has not been studied in detail. The aim of this work was to obtain RDL-R homology models in different conformational states and to evaluate their performance in a retrospective VS of channel-blocker insecticides. Fifteen RDL-R models were obtained, based on different pLGICs templates in three conformational states: closed, open and desensitized. With these models, molecular docking assays were performed with active ligands and decoys. To evaluate the VS performance, the area under the ROC curve and the BEDROC score were calculated. Besides, molecular dynamics simulations (MDS) were performed for the best models among each of the conformational states in complex with the insecticide fipronil. VS performance parameters showed variations according to the conformational state of the templates. These parameters were correlated with different variables to analyze which were the determinant factors for a good VS performance. The solvent-accessible area and volume and the pore diameter explained the differences in VS performance. The best results were obtained for a model based on a closed template. MDS confirmed that the expected interactions between the binding site and fipronil were present only in that model. Different templates should be explored to obtain accurate RDL homology models, particularly focusing on the template conformational state. The model that presented the best performance is suitable for a prospective VS.