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Assessment of quantum optimized $mGlu_1R$ in virtual screening

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The mGlu1 and mGlu5 receptors (metabotropic glutamate receptor 1 and 5) are considered promising therapeutic targets to treat diseases including chronic pain, schizophrenia, Alzheimer's disease, anxiety, and autism [1-3]. However, the development of selective small-molecule ligands that might serve as drug candidates for these receptors has been hampered by the conservation of the orthosteric (glutamate) binding site. This can be overcome by using allosteric modulators that act at alternative binding sites; i.e., within the 7TM domain of the receptors [1].

In this study the potential of 23 quantum optimized (ONIOM method) conformations of $mGlu_1R$ in virtual screening was tested. The active site was tuned on structures of thirteen known allosteric modulators (2.4 nM < IC50 > 10000 nM) as well as modeled using 10 different calculation methods (7 different DFT method, 3 different basis sets). Each resulting conformation was evaluated by docking the test set (195 active and 14465 non-active molecules) and several performance metrics was calculated: ROC AUC, BEDROC. Interestingly, the best discriminative model was obtained by optimizing the complex of receptor with CHEMBL565934, for which the experimentally determined affinity was 210 nM.

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