Insights into Docking and Scoring Neuronal α4β2 Nicotinic Receptor Agonists Using Molecular Dynamics Simulations and QM/MM Calculations

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Abstract: A combined quantum mechanical (QM)-polarized docking and molecular dynamics approach to study the binding mode and to predict the binding affinity of ligands acting at the α4β2-nAChR is presented. The results obtained in this study indicate that the quantum mechanical/molecular mechanics docking protocol well describes the charge-driven interactions occurring in the binding of nicotinic agonists, and it is able to represent the polarization effects on the ligand exerted by the surrounding atoms of the receptor at the binding site. This makes it possible to properly score agonists of α4β2-nAChR and to reproduce the experimental binding affinity data with good accuracy, within a mean error of 2.2 kcal/mol. Moreover, applying the QM-polarized docking to an ensemble of nAChR conformations obtained from MD simulations enabled us to accurately capture nAChR-ligand induced-fit effects.

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