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Molecular dynamics simulation of the human estrogen receptor alpha: contribution to the pharmacophore of the agonists

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Abstract

Human estrogen receptor alpha (View the MathML source) is one of the most studied targets for in silico screening of bioactive compounds. The estrogenic activity of a vast number of chemicals has been studied for their potentially adverse effects on the hormone regulation of the endocrine system. The commonly accepted presentation of the View the MathML source agonist pharmacophore includes terminal phenolic groups and a hydrophobic rigid backbone. In this study we report on molecular dynamics (MD) simulations of View the MathML source to get a deeper structural insight into the agonist–receptor interactions and the pharmacophore pattern of compounds with agonistic activity. We rely on a crystallographic structure of a complex of View the MathML source (PDB ID 2P15) with an agonist of picomolar affinity. As the X-ray structure has a mutation next to a key structural element for View the MathML source agonistic activity (helix H12, Y537S), a series of MD simulations have been performed on the mutated and on the wild type receptor to prove the stability of the agonist–receptor interactions. No significant difference in the ligand–protein interactions has been detected between the studied proteins implying that the Y537S mutant structure can be used for refinement of the pharmacophore model of the View the MathML source agonists. The results suggest that the pharmacophore of compounds with View the MathML source agonistic activity can be extended by a feature that occupies a free hydrophobic region of the binding pocket. The extended pharmacophore model has been evaluated by a pharmacophore-based virtual screening of databases of View the MathML source binders and decoys. The results also imply that MD simulations are a powerful in silico tool for both protein dynamics and structure investigation, especially when mutations are available that can potentially disturb the protein structure and functions.

Mathematics and Computers in Simulation (http://www.sciencedirect.com/science/article/pii/S0378475415001354)

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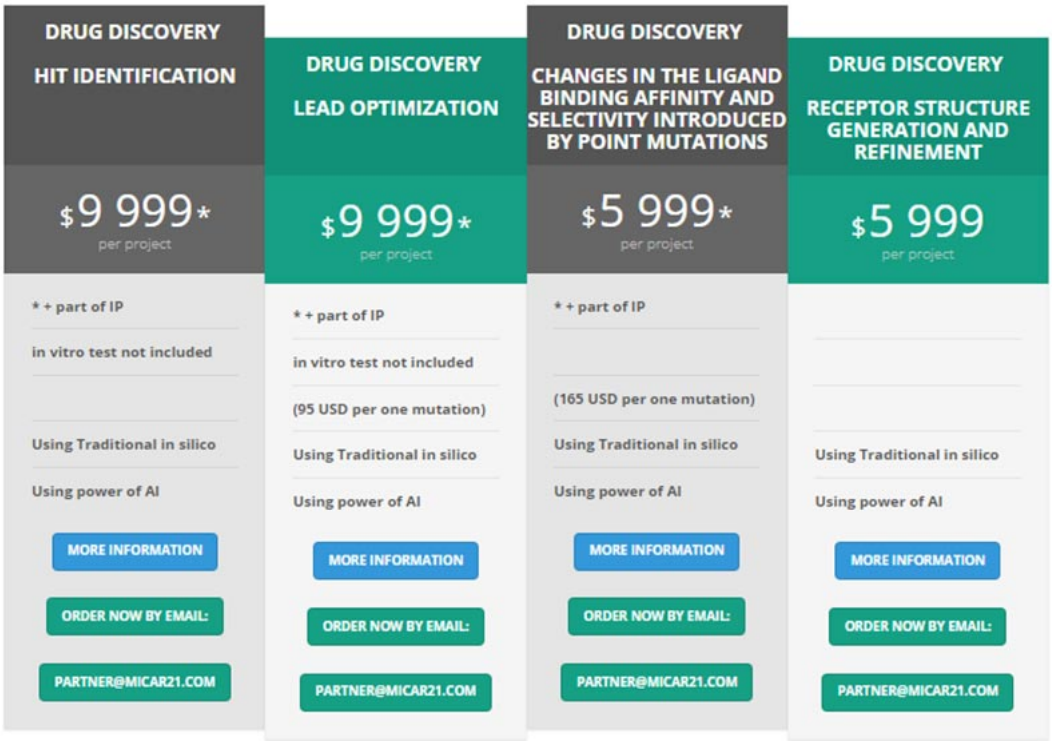

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