Evaluation of new antihypertensive drugs designed in silico using Thermolysin as a target

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The search for new therapies for the treatment of Arterial hypertension is a major concern in the scientific community. Here, we employ a computational biochemistry protocol to evaluate the performance of six compounds (Lig783, Lig1022, Lig1392, Lig2177, Lig3444 and Lig6199) to act as antihypertensive agents. This protocol consists of Docking experiments, efficiency calculations of ligands, molecular dynamics simulations, free energy, pharmacological and toxicological properties predictions (ADME-Tox) of the six ligands against Thermolysin. Our results show that the docked structures had an adequate orientation in the pocket of the Thermolysin enzymes, reproducing the X-ray crystal structure of Inhibitor-Thermolysin complexes in an acceptable way. The most promising candidates to act as antihypertensive agents among the series are Lig2177 and Lig3444. These compounds form the most stable ligand-Thermolysin complexes according to their binding free energy values obtained in the docking experiments as well as MM-GBSA decomposition analysis calculations. They present the lowest values of Ki, indicating that these ligands bind strongly to Thermolysin. Lig2177 was oriented in the pocket of Thermolysin in such a way that both OH of the dihydroxyl-amino groups to establish hydrogen bond interactions with Glu146 and Glu166. In the same way, Lig3444 interacts with Asp150, Glu143 and Tyr157. Additionally, Lig2177 and Lig3444 fulfill all the requirements established by Lipinski Veber and Pfizer 3/75 rules, indicating that these compounds could be safe compounds to be used as antihypertensive agents. We are confident that our computational biochemistry protocol can be used to evaluate and predict the behavior of a broad range of compounds designed in silicoagainst a protein target.

ADME-Tox

Antihypertensive

Ligand efficiency

MM-GBSA

Molecular dynamics

antihypertensive agent

lig 1022

lig 1392

lig 2177

lig 3444

lig 6199

lig 783

thermolysin

unclassified drug

Article

computer model

crystal structure

drug targeting

human

molecular docking

X ray crystallography