Molecular Simulations to Design new Drugs Against Heart Failure

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We report new in silico designed, more efficient, and less toxic molecules against heart failure, based on the leading drug Entresto, which is a combination of Sacubitril/Valsartan. DFT calculations (B3LYP/6-31+G(d)) were performed using Gaussian09 to evaluate all molecules chemical reactivity. Likewise, a pharmacophore proposal was made with Pharmit, and virtual screening in the Zinc database. Also, molecular docking with AutoDock4 and the ADMET properties of the proposed and reference molecules were calculated. In addition, molecular dynamics were performed with the Gromacs program to study the stability of the proposed ligands at the active site. We report two new molecules designed from Valsartan that are predicted to be less toxic and with better binding energies to the biological target AT1. The dynamics results indicate stability in the active site during 20 ns. We also report molecules designed from Sacubitril, the two that show improved binding energies to the biological target neprilysin, are less toxic and remain stable in the active site during the molecular simulation. In short, new molecules have been designed with less toxicity, and an increase in affinity to biological targets compared to the leading drugs. *Keywords:* Heart failure, molecular simulations, in silico drug design, pharmacophore, DFT electronic calculations, Docking, Molecular Dynamics

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