World Academy of Science, Engineering and Technology
International Journal of Biomedical and Biological Engineering
Vol:8, No:11, 2014

Insight into the Binding Theme of CA-074Me to Cathepsin B: Molecular Dynamics Simulations and Scaffold Hopping to Identify Potential Analogues as Anti-Neurodegenerative Diseases

Authors : Tivani Phosa Mashamba-Thompson, Mahmoud E. S. Soliman

Abstract : To date, the cause of neurodegeneration is not well understood and diseases that stem from neurodegeneration currently have no known cures. Cathepsin B (CB) enzyme is known to be involved in the production of peptide neurotransmitters and toxic peptides in neurodegenerative diseases (NDs). CA-074Me is a membrane-permeable irreversible selective cathepsin B (CB) inhibitor as confirmed by in vivo studies. Due to the lack of the crystal structure, the binding mode of CA-074Me with the human CB at molecular level has not been previously reported. The main aim of this study is to gain an insight into the binding mode of CB CA-074Me to human CB using various computational tools. Herein, molecular dynamics simulations, binding free energy calculations and per-residue energy decomposition analysis were employed to accomplish the aim of the study. Another objective was to identify novel CB inhibitors based on the structure of CA-074Me using fragment based drug design using scaffold hoping drug design approach. Results showed that two of the designed ligands (hit 1 and hit 2) were found to have better binding affinities than the prototype inhibitor, CA-074Me, by ~2-3 kcal/mol. Per-residue energy decomposition showed that amino acid residues Cys29, Gly196, His197 and Val174 contributed the most towards the binding. The Van der Waals binding forces were found to be the major component of the binding interactions. The findings of this study should assist medicinal chemist towards the design of potential irreversible CB inhibitors.

Keywords : cathepsin B, scaffold hopping, docking, molecular dynamics, binding-free energy, neurodegerative diseases
Conference Title : ICBBS 2014 : International Conference on Bioinformatics and Biomedical Science
Conference Location : Madrid, Spain
Conference Dates : November 10-11, 2014