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COMBINING STOCHASTIC DEFORMATION/RELAXATION AND INTERMOLECULAR CONTACTS ANALYSIS AS A NOVEL APPROACH FOR PHARMACOPHORE MODELING BASED ON X-RAY OR HOMOLOGY-MODELLED LIGAND-RECEPTOR COMPLEXES

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We previously combined molecular dynamics (classical or simulated annealing) with ligand-receptor contacts analysis as means to extract valid pharmacophore model(s) from single ligand-receptor complexes. However, molecular dynamics methods are computationally expensive and time consuming. Here we describe a novel method for extracting valid pharmacophore model(s) from a single crystallographic structure or form homology modelled structure within reasonable time scale. The new method is based on ligand-receptor contacts analysis following energy relaxation of predetermined set of randomly deformed complexes generated from the targeted crystallographic structure. Ligand-receptor contacts maintained across many deformed/relaxed structures are assumed to be critical and used to guide pharmacophore development. This methodology was implemented to develop valid pharmacophore models for different enzymes (i.e., PI3K-γ, and Akt3). The resulting pharmacophore models were validated by receiver operating characteristic (ROC) analysis against inhibitors extracted from CHEMBL database. Additionally, we implemented pharmacophores extracted from PI3K-γ to search for new inhibitors from the national cancer institute list of compounds. The process culminated in new PI3K-γ/mTOR inhibitory leads of low micromolar IC50s.

Biography

Dr. Ma'mon Hatmal has a PhD in Philosophy of Biochemistry and Molecular Biology with Honors from the University of Southern California (USC), USA (2012). He is now an assistant professor and a researcher at the Hashemite University/ Jordan. He was a Fulbright post-doctoral researcher at USC, USA (2017). He received many awards for his performance and research (i.e., Philadelphia University International award for best scientific software). His current research interests focus mainly on bioinformatics, in particular computer-aided molecular design and discovery towards new bioactive compounds, and computational prediction of 3D structures of biological macromolecules. He published couple of novel approaches of combining molecular dynamics (classical, simulated annealing, and stochastic deformation/relaxation) with contact analysis to extract valid pharmacophore model(s) from a single crystallographic structure within a reasonable time scale, these approaches culminated in new inhibitory leads (against enzymes involved in cancer and other diseases) of low micromolar and sub-micromolar IC50s.

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