Ma'mon Hatmal

Medical Laboratory Sciences Dept, The Hashemite University

Combining Stochastic Deformation/Relaxation and Intermolecular Contacts Analysis as a Novel Approach for Pharmacophore Modeling Based on X-Ray or Homology-Modeled Ligand-Receptor complexes .

Abstract

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 structureor form homology modeled structure within reasonable time scale. Homology modeling were used to obtain three-dimensional coordinates for proteins. In an attempt to evaluate the quality of Akt3 homology models, a number of homology structures were scanned for potential binding cavities. Subsequently, a group of inhibitors were docked into each of the proposed binding sites via four different scoring functions.

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 different enzymes (x-ray or homology modeled structures) to search for new inhibitors from the national cancer institute list of compounds. The process culminated in new inhibitory leads of low micromolar IC50s.