Combining docking-based comparative intermolecular contacts analysis and k-nearest neighbor correlation for the discovery of new check point kinase 1 inhibitors

Abstract
Check point kinase 1 (Chk1) is an important protein in G2 phase checkpoint arrest required by cancer cells to maintain cell cycle and to prevent cell death. Therefore, Chk1 inhibitors should have potential as anti-cancer therapeutics. Docking-based comparative intermolecular contacts analysis (dbCICA) is a new three-dimensional quantitative structure activity relationship method that depends on the quality and number of contact points between docked ligands and binding pocket amino acid residues. In this presented work we implemented a novel combination of k-nearest neighbor/genetic function algorithm modeling coupled with dbCICA to select critical ligand-Chk1 contacts capable of explaining anti-Chk1 bioactivity among a long list of inhibitors. The finest set of contacts were translated into two valid pharmacophore hypotheses that were used as 3D search queries to screen the National Cancer Institute's structural database for new Chk1 inhibitors. Three potent Chk1 inhibitors were discovered with IC50 values ranging from 2.4 to 69.7 μM.