Pharmacophore-Based Screening and Identification of Novel Phosphoinositide 3-Kinase (PI3Kα) Inhibitors.

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Abstract

Phosphoinositide 3-kinases (PI3Ks) and their phosphatidylinositol 3,4,5 triphosphate (PIP_3) products regulate a variety of cellular processes. Of these, PI3Kα is an attractive target for anticancer drug design. Mutation in the kinase domain of PI3Kα (H1047R) alters the position and the mobility of the activation loop resulting in conformational changes in the binding domain and gain of function. In an effort to develop new inhibitors, we created a pharmacophore model based on the scaffolds of twelve selective PI3Kα inhibitors. Pharmacophore searching against the national cancer institute identified 87,859 as hits. Induced fit docking (IFD) study was applied to explore the structural basis of binding for hit molecules in the kinase domains of native and mutant PI3Kα.

We functionalized the hydroxyl moiety of the lead PI3Kα inhibitor 2-hydroxy-1,2-diphenylethanone using structural- based drug design and Glide docking. We identified a novel series of 2-oxo-1,2-diphenylethyl benzoate as PI3Kα inhibitors. Glide docking identified Gln859 as selective key binding residue. The biological study showed that the

verified molecules inhibited PI3Kα activity in human colon adenocarcinoma Caco-II cell line. Potent inhibitory activity was exhibited for *p*-chloro and *p*-nitro substituent indicating that hydrophobic and/or hydrogen bond-acceptor mediate(s) drug-receptor interaction. Tailoring the benzoate with fluoro moiety at *o*-, *m*-, and *p*- position suggested that small size functionality is favored at *o*- or *m*-sites. Non-substituted benzoate showed lower activity implying that tailored benzoate is preferred for activity. The IC_{50} accounts for 71% of binding affinity values in mutant (H1047R) active domain.