Design, Synthesis and Biological Evaluation of Benzoin Schiff's Bases as Antitumor Agents.

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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.In an effort to develop new PI3Kαinhibitors, we recruited structure-based drug design (SBDD)to functionalize the core structure of benzoin and to explore the structural basis of binding of the prospective molecules in the kinase domains of native PI3Kα. We successfully identified a new series of 1,2-diphenylimino ethanol as PI3Kα inhibitors. The biological data showed that the synthesized molecules inhibited PI3Kα activity in human colon adenocarcinoma (HCT-116) cell line. Substituted derivatives exhibited higher inhibitory activity compared to those of non-substituted core structures. Potent inhibitory activity was exhibited for *m*-F, *m*-CF_3, and *m*-CH_3 substituent indicating that hydrophobic and/or hydrogen bond-acceptor mediate(s) drug-receptor interaction. It's worth noting that *m*-electronwithdrawing group such as (*m*-F and *m*-CF_3) exhibited higher potency than that of *m*-electrondonating group (*m*-CH_3). This could be due to the H-bond formation between the fluoro moiety and backbones of key binding residues. On the other hand, the *p*-substituent such as *p*-F, *p*-CH_3, *p*-OH, *p*-OCH_3, and *p*-SCH_3 exhibited comparable inhibitory activity. Noting that *p*-CH_3 and *p*-OH exerted similar inhibitory activity and this might be due to the isosteric effect. Additionally, *p*-OCH_3

and *p*-SCH_3 showed comparable inhibitory activity and this is an additional proof for the isosteric effect. Noting that the activity of the *p*-substituents illustrates that bulkier group such as *p*-OCH_3 and *p*-SCH_3 are not favored and this might be due to the tight size of the hydrophobic pocket that prefers small size functionalities. And, the activity of the *p*-F implies that size and/or H-bond acceptor is required to elicit an activity. Remarkably, the fluoro moiety at *o*-position exhibited comparable inhibitory activity to *p*-F derivative and this suggests that small size functionality is also favored at *m*-site. Non-substituted derivative showed lower activity implying that tailoring the core structure is preferred for activity. Glide docking identifiesSer774, Lys802, and Asp933 as key binding residues and suggests that aromatic (π-π stacking) interaction mediates complex formation.