Optimization and Synthesis of Benzoin Derivatives as PI3Kα Inhibitors

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Abstract

The oncogenic potential of PI3Kα emerged it as a promising target for anticancer drug design. This work describes our continued efforts to functionalize the core structure of 2-Hydroxy-1,2-bis(4-methoxyphenyl)ethanone (*p*-anisoin) as PI3Kα inhibitor. A series of 2-Hydroxy-1,2-bis(4-methoxyphenyl)ethanone derivatives were identified as potential PI3Kα inhibitors. The biological data demonstrated that the synthesized molecules could be inhibited PI3Kα activity in human colon carcinoma (HCT-116) cell line and exerted comparable inhibitory activity. The substituted analogues showed higher inhibitory activity compared to that of unsubstituted core structure suggesting that substitution is essential to elicit the biological activity. The *p*-tailored derivatives such as (*p*-NO_2 and *p*-Cl) exerted relatively higher inhibitory activity comparing with that of *p*-F implying that the steric effect directs the proper orientation of the prospective ligands in the kinase domain. On the other hand, *o*- and *m*-F exhibited similar potency against PI3Kα activity suggesting that a tight binding subunit prohibits

the orientation of bulky groups on the *o*- and *m*-position. Glide docking identifies S773, K802, Y836, and V851 as key binding residues and suggests that aromatic (π-π stacking) interaction mediates ligand-protein complex formation.