Design, Synthesis, and Biological Evaluation of *N*-Substituted-4-Hydroxy-6-Methyl-2-Quinolone-3-Carboxamides as PI3Kα Inhibitors

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Abstract

Phosphatidylinositol 3-kinase alpha (PI3Kα) has been highlighted as a hot target for anticancer drug design. A series of *N*-substituted-4-hydroxy-6-methyl-2-quinolone-3-carboxamides was designed and synthesized as possible PI3Kα inhibitors recruiting structure-based drug design and molecular docking. The identity of the core nucleus and synthesized derivatives was characterized using (^{1}H and ^{13}C) NMR analysis technique.

Biological studies in human colon carcinoma (HCT116) cell line showed that the analogues **37**, **39-45** exhibited distinct antiproliferative activity against PI3Kα. Compound tailored with hydrazide motif (**42**) exhibited higher inhibitory activity (IC_{50} = 0.323 mM) suggesting that H-bond interaction improves the binding affinity. Compound tailored with *o*-COOH and *p*-CH_3 (**45**) showed high activity (IC_{50} = 0.567

mM) implying that H-bond and hydrophobic interaction on the *o*-and *p*-positions elicit the activity.

Compounds **39** and **41** displayed comparable antiproliferative activity (IC_{50} = 0.849 and 0.811 mM) inferring that similar binding conformation is generated in the kinase domain. The loss of activity of compounds **43** and **44** indicates that *p*-H-bond acceptor and/or donor doesn't mediate ligand/PI3Kα complex formation. Conversely, the activity of **40** (IC_{50} = 1.54 mM) suggests that *p*-OCH_3 accommodates a tight hydrophobic cleft and confirms the absence of H-bond acceptor on *p*-position.

The Induced-fit docking studies against PI3Kα demonstrated that the derivatives accommodate PI3Kα kinase catalytic domain and form H-bonding with the key binding residues. Our results suggest that further optimization of this series would be beneficial for colon cancer treatment.