Synthesis and Biological Evaluation of *N*-Substituted-4-Hydroxy-8-Methyl-2-Quinolone-3-Carboxamide Derivatives as PI3Kα Inhibitors

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Abstract

Phosphoinositide-3-kinase α (PI3Kα) has emerged as a potential target for anticancer drug design and development. A series of *N*-substituted-4-hydroxy-8-methyl-2-quinolone-3-carboxamides (**41a-h**) was synthesized and characterized by FT-IR and NMR (^{1}H and ^{13}C). The derivatives inhibited the proliferation of human colon carcinoma (HCT-116) cell line. Analogues functionalized with *m*-CF_3 (**41c**) (IC_{50} = 118 µM) and *p*-CF_3 (**41d**) (IC_{50} = 89 µM) showed promising activity implying that hydrophobic interaction guides ligand/PI3Kα complex formation. The induced-fit docking (IFD) against PI3Kα demonstrates that the series occupiesPI3Kα kinase and H-bond with key binding residue.