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

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Abstract

Phosphoinositide-3-kinase α (PI3Kα) is emerged as a potential target for anticancer drug design and development. Derivatives of *N*-substituted-6-chloro-4-hydroxy-2-quinolone-3-carboxamide (**35a-r**) were synthesized and characterized by FT-IR and NMR (^{1}H and ^{13}C). The series exhibited selective inhibitory activity against human epithelial colorectal adenocarcinoma (Caco-2) and colon carcinoma (HCT-116) cell lines. Compounds functionalized with benzyl motif (**35a**) (IC_{50} = 13.8 µM) or *p*-methoxyphenyl (**35e**) (IC_{50} = 14.1 µM) showed higher inhibitory activity against Caco-2 interrogating that elongation of carboxamide link might orientate the analogue deeply in the binding domain. Analogues tailored with *m*-COOH (**35l**) (IC_{50} = 3.3 µM), *o*-F (**35m**) (IC_{50} = 5.3 µM), and *p*-F (**35o**) (IC_{50} = 4.9 µM) exerted higher activity against HCT-116 implying that H-bond mediates ligand/PI3Kα interaction. The biological testing of **35j** (IC_{50} = 8.9 µM), **35l** (IC_{50} = 3.3 µM), **35m** (IC_{50} = 5.3 µM), **35o** (IC_{50} = 4.9 µM), and **35r** (IC_{50} = 10.5 µM) against HCT-116 reveal selective targeting of mutant (MUT) (H1047R) PI3Kα. The induced-fit docking (IFD) studies against PI3Kαs shows that the series occupies PI3Kα kinase domain and form H-bonds with key binding residues.

Keywords: Cancer , Selective PI3Kα inhibitors , anti cancer agent.