Design, Synthesis, and Biological Evaluation of *N*-Substituted-4-Hydroxy-8-Methoxy-2-Quinolone-3-Carboxamides as PI3Kα Inhibitors

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Abstract

Phosphoinositide-3-kinase α (PI3Kα) has been intensively investigated as a promising target for anticancer drug design and development. A series of *N*-substituted-4-hydroxy-8-methoxy-2-quinolone-3-carboxamides (**41a-h**) was synthesized and characterized by FT-IR and NMR (^{1}H and ^{13}C). The prospective compounds inhibited the proliferation of human colon carcinoma (HCT-116) cell line. Compound functionalized with *p*-OH (**41f**) (IC_{50} = 218 µM) showed promising activity implying that H-bond acceptor and/or donor mediates ligand/PI3Kα complex formation. Compounds tailored with *o*- (**41c**) (IC_{50} = 231 µM) and *p*-F (**41e**) (IC_{50}= 238µM) exerted higher activity interrogating H-bond acceptor drives ligand/PI3Kα interaction. The induced-fit docking (IFD) against PI3Kα demonstrates that the series accommodates PI3Kα kinase binding pocket and form H-bonds with key binding residues.