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

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Abstract

The oncogenic potential of phosphoinositide-3-kinase α (PI3Kα) has been rated as a promising target for anticancer drug design and development. A series of *N*-substituted- 6-fluoro-4-hydroxy-2-quinolone-3-carboxamides (**41a-f**) was synthesized and characterized by FT-IR and NMR (^{1}H and ^{13}C). The derivatives exhibited an inhibitory activity against human colon carcinoma (HCT-116) cell line.

Compound tailored with *o*-F showed higher inhibitory activity suggesting that H-bond interaction mediates ligand/ PI3Kα on *o*-position. Attaching *m*-F or *p*-F moiety on the aromatic side decreased the potency deducing that *o*-H-Bond acceptor moderated ligand/PI3Kα interaction. Unsubstituted aromatic motif enhanced the activity referring that aromatic nucleus orientates the ligand properly in the kinase domain. Elongating the carboxamide linkage with one carbon placed the ligand deeply in the

binding domain. Introducing *p*-OCH_3 decreased the activity suggesting that steric effect impedes the proper orientation in the binding domain.

Glide docking studies against PI3Kα displays that the derivatives fit PI3Kα kinase pocket and form H-bond with key binding residue.