Optimization of 4-Hydroxy-2-Quinolone-3-Carboxamide Core Nucleus Targeting PI3Kα Inhibition

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Abstract

Phosphatidylinositol 3-kinase alpha (PI3Kα) has emerged as a hot target for anticancer drug design. A series of *N*-substituted-4-hydroxy-6-nitro-2-quinolone-3-carboxamides were designed and synthesized as PI3Kα inhibitors employing structure-based drug design and molecular docking. The identity of core nucleus of this series as well as the synthesized derivatives were characterized using (^{1}H and ^{13}C) NMR analysis technique. Biological studies in human colon carcinoma (HCT116) cell line showed that the analogues (**28**, **30**-**36**) inhibited cell proliferation. Promising PI3Kα inhibitory activity was exhibited for analogues bearing H-bond acceptor and small hydrophobic moieties on *p*-position (**31**) (IC_{50} = 0.704 mM). Derivatives tailored with *p*-H-bond donor and/or acceptor (**34**) and small hydrophobic moiety (**35**) were inactive. Elongation the carboxamide motif by $–CH_2$ (**32**) (IC_{50} = 5.89 mM) and NH (**33**) (IC_{50} = 0.734 mM) potentiates the inhibitory activity implying that a steric factor pushes the compound deeply into the binding cleft. The activity of **33** suggests that H-bond acceptor drives ligand/PI3Kα complex formation. The activity of **36** (IC_{50} = 4.95 mM) infers that bulky

m-substituent impedes the proper orientation of ligand in the kinase domain. Glide 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.