Methoxylated Derivatives of *N*-Substituted-4-Hydroxy-2-Quinolone-3-Carboxamides as PI3Kα Inhibitors

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Abstract

Phosphatidylinositol 3-kinase α (PI3Kα) has been highlighted as a hot target for anticancer drug design. A series of *N*-substituted-4-hydroxy-6-methoxy-2-quinolone-3-carboxamides was designed and synthesized as potential PI3Kα inhibitors employing structure-based drug design and molecular docking approach. The synthesized compounds were characterized using FT-IR and (^{1}H and ^{13}C) NMR analysis technique.

Biological studies in human colon carcinoma (HCT116) cell line showed that the analogues **28**, **30-35** exhibited antiproliferative activity against PI3Kα. Compound tailored with *p*-OH (**33**) exerted promising activity interrogating that H-bond acceptor and/or donor mediates ligand/PI3Kα complex formation. Extension of the carboxamide linkage with one carbon (**34**) enhanced the activity implying that **34** orientated deeply in the binding pocket.

The Induced-fit 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.