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

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Abstract

Phosphoinositide 3-Kinase α (PI3Kα) has been defined as a substantial target for the design and development of anticancer agents. A series of Nitrated N-Substituted-4-Hydroxy -2-Quinolone-3-Carboxamides (**50**-**69**) was synthesized and characterized using FT-IR, ^{1}H and ^{13}C-NMR, and elemental analysis. The derivatives displayed distinct inhibitory activity in human epithelial colorectal adenocarcinoma (Caco-2) and colon carcinoma (HCT-116) cell lines. Compound **(64)** shows a significant anti-proliferative effect against Caco-2 (IC_{50} = 60.57 µM) while **(61)** was the most effective against HCT-116 (IC_{50} = 22.95 µM). Compounds (**60)** (Caco-2 IC_{50} = 94.12 µM, HCT-116 IC_{50} = 39.08 µM), **61** (Caco-2 IC_{50} = 84.01 µM, HCT-116 IC_{50} = 22.95 µM), **62** (Caco-2 IC_{50} = 235.77 µM, HCT-116 IC_{50} = 43.68 µM), and **65** (Caco-2 IC_{50} = 199.26 µM, HCT-116 IC_{50} = 51.39 µM) exerted distinguishable inhibitory selective effect in HCT-116 cell line. The induced-fit docking (IFD) studies demonstrated that the derivatives occupy PI3Kα kinase domain and bind to the backbones of key binding residues.

Keywords: Cancer, PI3Kα inhibitors, kinase domain, Caco-2, HCT-116.