Optimization of *N*-Substituted-6-chloro-4-hydroxy-2-Quinolone-3-Carboxamides as PI3Kα Inhibitors

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Abstract

Phosphoinositide 3-Kinase α (PI3Kα) has appeared as a promising target for design and synthesis of new anti-cancer agents. A series of *N*-substituted-6-chloro-4-hydroxy-2-quinolone-3-carboxamides (**33-48**) was synthesized and characterized using FT-IR, ^{1}H and ^{13}C-NMR. The derivatives exerted selective anti-proliferative activity in human epithelial colorectal adenocarcinoma (Caco-2) and colon carcinoma (HCT-116) cell lines. Compounds (**36)** (Caco-2 IC_{50} = 268 µM, HCT-116 IC_{50} = 72µM), **37** (Caco-2 IC_{50} = >300 µM, HCT-116 IC_{50} = 100 µM), **44** (Caco-2 IC_{50} = >300 µM, HCT-116 IC_{50} = 109 µM), and **45** (Caco-2 IC_{50} = >300 µM, HCT-116 IC_{50} = 103 µM) showed selective inhibitory effect in HCT-116 cell line. The induced-fit docking (IFD) results showed that the series accommodate PI3Kα kinase domain and make H-bond with Ser 774, Lys 802, Asp 810, Tyr 835, Tyr 836, Glu 849, Ile 932, and Asp 933 of mutant PI3Kα.

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