DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL PI3K ALPHA INHIBITORS.

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Abstract

Phosphatidylinositol 3-kinase alpha (PI3Kα) phosphorylates the hydroxyl group at position 3 on the inositol ring to form phosphatidylinositol 3, 4 ,5-trisphosphate, a second messenger, which induces the PI3K mediated signaling pathway and the downstream components; protein kinase B (Akt) and mammalian target of rapamycin (mTOR).

PI3Kα, is mutated, amplified, and overexpressed in numerous and diverse human cancers. Therefore, targeting PI3Kα is promising for cancer treatment.

In this work, we recruited ligand- and structure-based drug design approaches to design and synthesize novel selective PI3Kα inhibitors. Successfully, we synthesize a series of twenty derivatives of 1,2-dihydroquinoline-3-carboxamides. Chemical modifications on the carboxamide side chain were applied to derive the structural activity relationship (SAR). We found that *para*-substitution on the phenyl ring having H-bond donor/acceptor, showed high inhibitory activity in colorectal adenocarcenoma cell lines

(Caco II**)**. Compounds **52** and **51** exhibited high inhibitory activity with IC_{50} values 154 and 189 ng/ul, respectively.

We suggest to optimize the scaffold of our verified compounds to get better activity and selectivity against a panel of kinase proteins.