Progress in the Design and Development of Phosphoinositide-3-Kinase (PI3Kα) Inhibitors

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ABSTRACT

Background: The phosphatidylinositol 3-kinase (PI3Kα) has been spotlighted as a potential oncogene and therapeutic target for anticancer drug design.

Objective: Target compounds were designed employing ligand- and structure-based drug design approaches to address the effect of the compounds' backbones and functionalities on their biological activity.

Methods: Synthesis of the targeted compounds, biological evaluation tests against human cancer cell lines, and molecular docking studies.

Results: Fortunately, 20 novel series of diverse scaffolds were prepared and characterized by means of FT-IR, ^{1}H and ^{13}C NMR, HRMS, and elemental analysis. In addition, the identity of one core nucleus was successfully interpreted with the aid of X-ray crystallography. Biological activity of prepared compounds was investigated *in vitro* against human cancer cell lines. Results that these compounds inhibit cell proliferation and induce apoptosis through an increase in caspase-3 activity and a decrease in DNA cellular content. Furthermore, ligand-based pharmacophore modeling showed that the newly synthesized analogues match PI3Kα inhibitors fingerprint and the molecular docking studies against PI3Kα revealed that the analogues fit PI3Kα kinase catalytic domain and form H-bonding with key binding residues.

Conclusion: The harvested series exhibited a potential PI3Kα inhibitory activity in human cancer cell lines.