Targeting the PI3K/AKT/mTOR signaling pathway in cancer by new quinoline/chalcone hybrids

Amer A. Abd El-Hafeez¹,²,³, Heba A. Hassan⁴, Sammar H. Abbas⁴, Toru Hosoi¹, Koichiro Ozawa¹, Mai E. Shoman⁴

¹Pharmacotherapy Department, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan, ²Global Career Design Center, Hiroshima University, Hiroshima, Japan, ³Pharmacology and Experimental Oncology Unit, Cancer Biology Department, National Cancer Institute, Cairo University, Cairo, Egypt, ⁴Medicinal Chemistry Department, Faculty of Pharmacy, Minia University, Minia, Egypt

Background: Growing research studies have been directed towards quinoline and chalcone optimization and incorporation into chemotherapeutic agents. Herein, our current research is directed onto more potent anticancer agents targeting PI3K pathway using quinoline and chalcone scaffolds.

Materials and methods: A series of quinoline-chalcone analogues was designed as potential anti-cancer agents, synthesized and evaluated by sulforhodamine B (SRB), Bromodeoxyuridine (5-bromo-2-deoxyuridine, BrdU) incorporation, and trypan blue exclusion assays. Molecular docking of the synthesized compounds was done on MOE 2014 program. PI3K activity assay was performed using PI3K ELISA Kit. Cell cycle and apoptosis analyses were carried out by flow cytometry. To elucidate antitumor mechanisms of the potent compounds, expression and activation status of cell cycle/apoptosis regulators, as well as PI3K/AKT/mTOR, were thoroughly analyzed by immunoblotting.

Results: Three different cytotoxic assays revealed that compounds experienced promising activity with 9i and 9j being most potent (IC₅₀ = 1.91-5.29 µM against A549 and K-562 cells). No resistance to both compounds was observed after thirty days of exposure to 10% of their IC₅₀. Docking analysis of 9i and 9j showed a possible formation of H-bonding with the valine residues in the active site of different PI3K isoforms. Moreover, the two compounds inhibited PI3K with IC₅₀ of 0.17-0.84 µM. Meanwhile, Western blotting analysis revealed that 9i and 9j inhibited the phosphorylation of PI3K, AKT, mTOR, as well as GSK-3β in both A549 and K-562 cells. Furthermore, 9i and 9j induced G₂/M cell cycle arrest and apoptosis in both A549 and K-562 cells. G₂/M arrest by 9i and 9j might be attributed to possibly via downregulation of Cdc2-cyclin B1 complex and upregulation of p21, regardless of p53 status in the cells. The apoptotic pathway induction might be related to Bcl-2 downregulation, Bax upregulation, and caspase 3 and 9 activation. The induction of G₂/M cell cycle arrest and apoptosis correlated with the inhibition of PI3K/AKT/mTOR pathway.

Conclusion: Together, our findings indicate the antitumor potential of quinoline-chalcone derivatives by targeting PI3K/AKT/mTOR pathway.

Keywords: Quinoline-chalcone analogues, PI3K pathway, cancer