1B1a New Quinoline/Chalcone Hybrids induce G_2/M cell cycle arrest and apoptosis in A549 and K-562 cells via PI3K/AKt/mTOR pathway inhibition

Amer Ali Abd El-Hafeez[1, 2, 3], Heba A. Hassan[4], Sammar H. Abbas[4], Toru Hosoi[1], Koichiro Ozawa[1], Mai E. Shoman[4]

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

Background: PI3K/AKT/mTOR cascade is one of the most important commonly activated pathways in lung cancer and leukemia. Herein, our current research is directed onto more potent anticancer agents targeting PI3K pathway using quinoline and chalcone scaffolds.

Methods: A series of quinoline-chalcone analogues was designed as potential anti-cancer agents, synthesized and evaluated by SRB and BrdU incorporation assays. 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: Different cytotoxic assays revealed that compounds experienced promising activity with **9i** and **9j** being most potent (IC_{50} = 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 IC_{50}. 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 IC_{50} 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 G_2/M cell cycle arrest and apoptosis in both A549 and K-562cells. G_2/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 G_2/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.

Key words
Quinoline, chalcone, PI3K pathway