Title: A Novel Quinazoline Inhibits Hsp90 Protein, EGFR and Induces Apoptosis in Leukemia Cells

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Abstract

The objective of the first part of this study was to investigate the Hsp90 protein possible activity of a novel quinazoline Her2/EGFR inhibitor (Compound No. 1:
4-(2-(4-Oxo-2-thioxo-1,4-dihydroquinazolin-3(2H)-yl)ethyl)benzenesulfonamide) previously synthesized by a collaborating group. Heat shock protein 90 (Hsp90) has a central role in regulation of several client proteins involved in cancers [1,2]. Several Hsp90 inhibitors of the natural or synthetic origin displayed potent anticancer activity [3,4]. Accordingly, Hsp90 emerged as an attractive target in the design of anticancer agents. To evaluate the binding mode of compound No. 1 into the ATPase site of Hsp90, a comparative molecular docking study was performed using AutoDock 4.2. The results of this studywas compared with that of the co-crystallized ligand (ATI-13387X, Onalespib). The energy minimization process of the chemical structures of No. 1 was done following our previous report [5]. The results of the docking study revealed that No. 1 fit nicely into the ATPase site, and it displayed a binding free energy (ΔGb) of -7.21 kcal/mol and inhibition constant (Ki) of 5.19 µM to Hsp90, compared to ΔGb of -7.90 kcal/mol and Ki of 1.62 µM for ATI-13387X. Furthermore, to confirm this result, the surface plasmon resonance (SPR) was devised to test the Hsp90 inhibition activity of No.1, which was 51 nM compared to Radicicol and 17AAG (1.8 nM, and 360 nM; respectively). Overall, compound No. 1 exhibited promising Hsp90 inhibiting activity.
The second part of the study focused on the effect of No. 1, Dinaciclib and their combinationsin HL-60 leukemia cells. The combination showed synergistic EGFR inhibition effect in HL-60 cells. Moreover, No. 1, Dinaciclib and their combination caused a significant increase in the Sub-G1 compared to control and doxorubicin (24h), at the expense of S and G2/M cell cycle phases. Cyclin D3, was consequently inhibited by each of the two drugs, and synergistically by their combination in HL-60 cells. Furthermore, each of the two drugs downregulated Survivin, which was synergistically inhibited by the combination. In conclusion, compound No.1, Dinaciclib and their combinations showed synergestic EGFR inhibition; and pro-apoptoticeffect in HL-60 cells.This project was funded by the deanship of scientific research, Umm Alqura University, KSA (DSR: 15-MED-3-1-0060).

Keywords: Novelquinazoline EGFR inhibitor, Hsp90 protein, Leukemia cells.

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