English – Article abstract

Design and synthesis of new asymmetrical derivatives of 1, 4-dihydropyridine with constant 4-pyridylmethyl ester in C_3 position and Alkyl esters in C_5 position and evaluation of their calcium channel blocking and cytotoxicity activities

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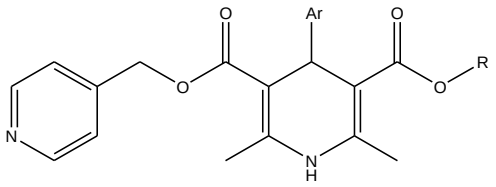
Introduction and Objectives: Considering the importance of cancer cells' resistance to chemotherapy (MDR or Multi Drug Resistance) many studies have been done to overcome it. One of the major mechanisms of MDR is increaseing of p-glycoprotein in cell membrane that called typical MDR. Atypical type of MDR is due to changed activity or level of topoisomerase II. Recently, Dihydropyridines that are known as calcium channel blockers are recognized as new molecules that have MDR reversing activities by both inhibiting p-glycoprotein and effect on topoisomerase II. Also it's found recently that they have the intrinsic cytotoxicity activities. Therefore in this study the dihydroprydine molecules were designed to have more cytotoxicity properties. Beside the calcium channel blocking activities were count as a side-effect and it's tried to minimize these effects in our designs.

Method: The molecules were synthesized by a modified Hanzsch reaction. The sixteen molecules were had a constant pyridyl group in C_3 position of the dihydropyridine ring and Aryl acetate group in C_5. Also the C_4 position was substituted by Nitrophenyl and Nitro-imidazolyl groups.



Ar = 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl and nitroimidazol

R = methyl, ethyl, isopropyl and t-butyl

After confirming the structures they were evaluated for their cytotoxicity and calcium channel blocking activities. The cytotoxicity activities were evaluated by MTT assay in four cell lines which were HL-60, LS180, MCF-7 and K562. Also their calcium channel blocking activities were measured by using guinea pig ileum as a human vascular model.

Result and Discussion: All the molecules synthesized successfully and were confirmed by Ft-IR, Mass spectrometry and ^{1}H-NMR.

The molecules were shown reasonable facts for having cytotoxicity and calcium channel blocking activities. Each molecule which had a larger group in C_5 position was shown the cytotoxicity activity the better. Also all molecules whit 4-nitrophenyl or nitroimidazol in C_3 position had a weak or intermediate effect in blocking of calcium channels and because of our purpose this fact is demonstrated 4I the most efficient agent for being a reasonable drug candidate for other research.

Keywords: 1, 4-dihydropyridines, resistance to chemotherapy, modified Hauntzsh synthesis, p-glycoprotein inhibitor, cytotoxicity, calcium channel blocker