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Synthesis of novel asymmetrical 1, 4-dihydropyridine derivatives and evaluation of their calcium channel blocking and cytotoxic activities

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Background and Aims: Multiple drug resistance (MDR) is defined as a resistance of tumor cells to drugs used in chemotherapy. P-Gp mediated MDR is one of the main mechanisms called as typical MDR. Some types of atypical MDR are related to altered topoisomerase II levels or their activity. Dihydropyridine (DHP) derivatives are one of the first classes of drugs that are identified as MDR inhibitors being effective on both typical and atypical MDR. In the present study, new DHPs were designed with the aim of increased cytotoxic properties. In this case, calcium channel blocking activities regarded as a side-effect and we tried to minimize this effect in our designs.
Methods: Reaction of 4-pyridylmethanol & 2, 2, 6-trimethyl-4-H 1, 3dioxin-4-one afforded the corresponding 4-pyridyl methyl-3-oxobutanoate. Subsequent reaction of 4-pyridyl methyl-3-oxobutanoate with related aldehyde and alkyl 3-aminocrotonate afforded final 1, 4-dihydropyridines by modified Hantzsch method. The cytotoxic activities were evaluated by MTT assay in four cell lines which were HL-60, LS180, MCF-7 and K562 and compared with cisplatin as standard cytotoxic agent. Moreover DHPs were evaluated as calcium-channel antagonists using high potassium ion concentration in guinea-pig ileal longitudinal smooth muscle (GPILSM).
Results: Sixteen compounds were synthesized and their structures confirmed by FT-IR, Mass spectrometry and 1H-NMR. Calcium channel blocking activities and cytotoxic effects were reported as IC50 values.
Conclusions: Molecules bearing 4-nitrophenyl or 5-nitroimidazole moieties in C4 position of a DHP ring had a weak or moderate calcium channel antagonist activities. Molecules possessing larger groups in C5 position were found to be more cytotoxic. 3-(4-pyridyl) methyl 5-isopropyl 2, 6-dimethyl 4-(4-nitro) phenyl 1, 4-dihydropyridine 3, 5 dicarboxylate showed the highest cytotoxic activity and at the same time, the least calcium channel blocking activity. This compound may be an efficient agent as a reasonable lead compound candidate for future studies.

Keywords: 1, 4-dihydropyridines; Modified Hantzsch method; Cytotoxicity; Calcium channel blocker