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Original Article

Synthesis and in vitro dual calcium channel antagonist-agonist activity of some 1, 4-Dihydo-2,6-dimethyl-3-nitro and cyano-4-(1-methyl-5-nitro-1H-imidazol-2-yl)-5-pyridinecarboxylates

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Abstract:

ABSTRACT
Background and purpose of the study: The vasorelaxant action of the dihydropyridines (DHPs) provides many useful clinical indications. However, their negative effects on cardiac contractility is still of a great concern especially in patients with heart failure. Design and synthesis of dual action compounds, i. e. smooth muscle calcium channel antagonist/cardiac muscle calcium channel agonist provides better and safer compounds particularly in patients with compromised cardiac contractility. In the present study, dual cardioselective Ca2+ channel agonists / vascular selective smooth muscle Ca2+ channel antagonists as third generation of DHP drugs were synthesized by a reported method.
Methods: Synthetic procedure involved condensation of isopropyl-3-aminocrotonate with nitroacetone and 1-methyl-5-nitroimidazole2-carboxaldehyde and condensation of alkylacetoacetates with 3-aminocrotonitryl and 1-methyl-5-nitro-1H-imidazole-2-carbaldehyde for the preparation of 1,4-Dihydo-2,6-dimethyl-3-nitro and cyano-4-(1-methyl-5-nitro-1H-imidazol-2-yl)-5-pyridinecarboxylates, respectively. The in vitro effects of the synthesized compounds were evaluated on longitudal Smooth Muscle (GPILSM) and Guinea Pig Left Atrium (GPLA) preparations and finally, their conformations and structure-activity relationships were assessed.
Results and major conclusion: All compounds showed calcium channel antagonist activity on isolated guinea pig ileum and some of them showed calcium channel agonist effects (or positive inotropic effect instead of calcium channel agonist effect) on isolated guinea-pig left atrium. QSAR and conformational analyses showed that conformation and charge of aryl substituents at C4 position have a main role in antagonistic activity while carbonyl group at C5 position plays an important role in agonistic effects.

Keywords:

Keywords: Calcium channel antagonist-agonist activity, Dihydropyridines, QSAR

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