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Synthesis and antiarrhythmic activity of novel 1,4-dihydropyridine-coumarin hybrid molecules

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Abstract

One of the urgent tasks of modern pharmaceutical science is the search for new highly effective drugs that have both natural and synthetic origin. Among the biologically active substances, coumarin derivatives (2*H*-chromen-2-one) are very important in practice. In the course of the long-term researches of the physicochemical and pharmacological properties of numerous natural and synthetic coumarin derivatives, we have shown that this group of substances has a sufficiently wide spectrum of biological action, including anti-HIV, antihypertensive, anticoagulant, antiarrhythmic, anticancer, immunomodulating and antiviral activity. On the other hand, amlodipine, which is an important blocker of calcium channels from the 1,4-dihydropyridine group, is widely used for the treatment of hypertension, angina and other cardiovascular diseases.

Over the last few years, with the development of pharmaceutical chemistry, the hybrid approach to the development of new highly active hybrid drugs has received considerable attention because it has allowed the synthesis of a number of hybrid substances with improved biological activity with respect to the parent compounds. Thus, the development of methods for the synthesis of hybrid molecules covering two pharmacophores in one molecular scaffold is a well-known approach to the synthesis of more effective drugs.

We synthesized a series of novel 1,4-dihydropyridine-coumarin hybrid molecules by the acylation reaction with the water-removing reagent *N,N'*-dicyclohexylcarbodiimide and the catalyst 4-dimethylamino-pyridine using this approach. The structure of synthesized compounds was completely established by the data of modern spectral methods (IR, NMR spectroscopy and mass spectrometry). In the study of the antiarrhythmic activity of the synthesized compounds on the model of arrhythmias caused by the intravenous administration of calcium chloride (300 mg/kg) to rats, we showed that 4-(2-chlorophenyl)-3-(ethoxy-carbonyl)-5-(methoxycarbonyl)-6-methyl-2-[[2-[*N*-((7-methoxy-2-oxo-2*H*-chromen-4-yl)acetyl)-amino]-ethoxy]methyl]-1,4-dihydropyridine, 4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-2-[[2-[*N*-(2-oxo-2*H*-chromen-7-yl)oxy]-1-oxoethyl]amino]ethoxy]methyl]-1,4-dihydropyridine and 4-(2-chlorophenyl)(2-oxo-2*H*-chromen-7-yl)oxy]-1-oxoethyl]amino]ethoxy]methyl]-1,4-dihydropyridine (ED_{50} = 0.70-1.26) have the most pronounced antiarrhythmic activity.

It is established that according to Hodge and Sterner classification they are practically nontoxic compounds and their antiarrhythmic index (AI = LD_{50}/ED_{50}) significantly exceeds the AI of the known drug verapamil. The revealed properties allow us to recommend them for clinical trials as a new relatively safe calcium channel blocker with pronounced antiarrhythmic action for the purpose of further introduction in medical practice.

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