CREATION OF NOVEL CARDIOPROTECTIVE AGENTS ON THE BASIS OF LINKED BIAROMATIC PHARMACOPHORE

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Cardiovascular diseases (CVD) are the leading cause of death in the world. CVDs are especially widespread in Russia, where they occupy 45-60% in the mortality structure. It is actual to create new cardioprotective agents with high efficiency, complex mechanism of action and with modern safety profile.

The concept of creating multitarget cardioprotective agents based on a pharmacophore model, which includes two aromatic nuclei linked by a linear linker is developing in Zakusov Institute of Pharmacology. This model describes a large number of known agents for the treatment of CVD of various classes. Using this model, we have designed and synthesized a group of bis-(alkoxyphenyl)- triazaalkanes. Compounds of this series have shown pronounced cardioprotective properties in *in vivo* models of arrhythmia and ischemia [1].

Based on the results of structure-activity relationship, compound ALM-802 (Arkadin) was selected for further development, which had the maximum severity of effects in all models of arrhythmia and ischemia at doses of 1–2 mg/kg (iv). When studying the mechanism of action of ALM-802, it was found that it blocks both sodium and potassium current, and also blocks ryanodine (RyR2) receptors. The relatively low acute toxicity (LD50 = 119 mg/kg, mice, i.p.) and the positive pharmacokinetic characteristics of ALM-802 indicate the prospects for the development of this drug as a new cardioprotective agent.

References

- [1] G.V. Mokrov, A.M. Likhoshershtov, V.V. Barchukov et al., Pharm. Chem.J. 2019, 53(6), 500-506.