International Conference on Natural Products and Physiologically Active Substances (ICNPAS-2004)
September 12-17, 2004, Novosibirsk, Russia
Poster Presentation

Inclusion Complexes of Glycyrrhizinic Acid with Anti Arrhythmic Drugs, Nifedipine and Lappaconitine

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Complexation of anti arrhythmic drugs lappaconitine and nifedipine with pharmaceutically acceptable complexing agent, glycyrrhizinic acid (GA), was investigated in light of recently discovered influence of GA on its therapeutic activity. NMR and UV-Vis spectroscopy were applied to establish that lappaconitine forms stable 1:1 complex with GA at wide range of reagents concentrations, from 1 μM to 5 mM. Computer simulation of the experimental data allows to calculate the stability constant of this complex, $K = 2.0 \times 10^5$ M^{-1}, in 20% methanol or DMSO aqueous solutions. The stability constant decreases about one order in pure methanol. The complex of lappaconitine hydrobromide (the generic name of the latter is "allapinin") is two orders less stable as compared to pure lappaconitine.

The photoinduced electron transfer reaction of lappaconitine with amino acid tyrosine was investigated to determine the influence of complexation on the reactivity of lappaconitine. The observed decrease of the reactivity in the presence of GA is in accordance with the recent finding of increasing of lappaconitine therapeutic activity in the presence of glycyrrhizinic acid.

It was established, that the structure of GA-nifedipine complex depends on the concentration of GA. The complex formation was detected only with concentration above 0.05 mM. In the range 0.05 – 1 mM of GA nifedipine forms inclusion complex with dimer of GA with stability constant $K_S = 1.2 \times 10^5$ M^{-1}. At the concentration > 1 mM, GA forms more complex associates.

This work was supported by RFBR grant 04-03-32449 and has been carried out in the frame of interdisciplinary integration project of SB RAS № 146 "Drugs and prophylactics design for medical purposes. Fundamentals and implementation."