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Search for new antithrombotic compounds among sulfur-containing acetamide derivatives of 9,10-anthraquinone

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Thrombotic complications, both venous and arterial, are often a key factor determining the course and result of pathologies of the cardiovascular system, as well as cancer, which together share the first place among the causes of death, both in Ukraine and in the world. Commonly used antiplatelet and anticoagulant drugs affect the process of platelet aggregation and the activation of factors of the blood coagulation system. However, their effectiveness often does not satisfy clinicians. In addition, the presence of side

effects of these drugs from the gastrointestinal tract limits their use in some categories of patients. Antiplatelet therapy is often accompanied by side effects such as resistance to their action, increased risk of uncontrolled bleeding, as well as the development of serious systemic complications. And, along with all of this, high cost of such medicines leads to necessity of further research to find perspective more effective and safe substances, and development on their basis of new antithrombotic drugs. Earlier, among the derivatives of 9,10-anthraquinone, compounds with antiaggregatory activity have already been found. In particular, it was found that mitoxantrone and bisanthrene as derivatives of amino-9,10-anthraquinone inhibited platelet aggregation induced by the action of both adenosine diphosphate (ADP) and collagen. A number of anthra[2,1-*d*]isothiazole-3,6,11-trione derivatives effectively inhibited ADP-dependent platelet aggregation in human plasma with an IC_{50} value of up to 10 μm. 3-Alkylaminopropoxy-9,10-anthraquinone derivatives selectively inhibited platelet cyclooxygenase – enzyme involved in the synthesis of thromboxane A2, one of the key mediators of the platelet aggregation process. Glycoside and dithiocarbamate derivatives of anthraquinones also have shown antithrombotic activity.

Aim. The search for new promising substances with antiplatelet action among new sulfur-containing derivatives of 9,10-anthraquinone.

Materials and research methods. The effect of the studied compounds on the platelet aggregation was assessed *in vitro* using a photo-optical aggregometer AT-02 (Medtech, Russia). Platelet-rich plasma (PRP) and platelet-poor plasma (PPP) were prepared from the citrated rabbit blood following the standard procedure. Before the assessment, the platelet count in PRP was adjusted with PPP to about $(230\text{-}250)\times10^3$ cells/μL. The PRP suspension was incubated with the studied compounds (final concentration was 50 μmol/L) or with 0.5% dimethylsulphoxide (DMSO) alone for 3 minutes. The aggregation was induced by adding ADP in the final concentration of 5 μmol/L, and the change of light transmission was monitored for 7 minutes, measuring the maximal increase after the addition of the inducer. In each experiment, all samples were tested in triplicate.

Results. It has been found that the investigated *N*-acyl sulfide derivatives of 9,10-anthraquinone at the studied concentration did not cause spontaneous platelet aggregation. Three *N*-acyl sulfide derivatives of 9,10-anthraquinone exhibited antiaggregation activity, reducing the maximum degree of platelet aggregation by 20-30%. According to the results obtained, the most pronounced inhibitory effect is inherent in the acylmercaptoethanol derivative of 9,10-anthraquinone. It was found that the replacement of the hydroxy group in the alkyl fragment of the sulfide residue by a

carboxyl group leads to a decrease in antiaggregation potential, and the displacement of the acylthioethanol substituent from the position 1 to position 2 of the 9,10-anthraquinone ring also leads to a similar result. Replacement of a thioalkyl hydroxyl fragment by a thioaromatic one with a carboxyl group does not show any effect on antiaggregation activity.

Conclusions. As a result of the studies, three sulfide acetamide derivatives of 9,10-anthraquinone were identified, which exhibit antiaggregatory activity in *in vitro* experiments on rabbit PRP at a concentration of 50 μM and inhibited ADP-dependent aggregation by 20-30%, which creates the prospect of further research in this direction.