The high specificity of blood coagulation proteases has been attributed not only to residues surrounding the active site but also to other surface domains that are involved in recognizing and interacting with macromolecular substrates and inhibitors. Specific blood coagulation inhibitors obtained from exogenous sources such as bloodsucking salivary glands and snake venom have been identified. Some of these inhibitors interact with exosites on coagulation enzymes. Two examples discussed in this short revision. Both rojaracin is a snake venom-derived protein that binds to thrombin exosites 1 and 2. Complex formation impairs several exosite-dependent activities of thrombin including fibrinogen cleavage and platelet activation. Bothrojaracinal also interacts with proexosite 1 on prothrombin thus decreasing the zymogen activation by the prothrombinase complex (FXa/FVa). Ixolaris is a two Kunitz salivary gland inhibitor that is homologous to tissue factor pathway inhibitor. Recently, it was demonstrated that ixolaris binds to heparin-binding exosite of FXa, thus impairing the recognition of prothrombin by the enzyme. In addition, ixolaris interacts with FX possibly through the heparin-binding proexosite. Differently from FX, the ixolaris-FX complex is not recognized as a substrate by the intrinsic tenase complex (FXa/FVIIa). We conclude that these inhibitors may serve as tools for the study of coagulation exosites as well as prototypes for new anticoagulant drugs.

Keywords
blood coagulation, serine proteases, exosites, exogenous inhibitors.