

Preface

The serine protease thrombin plays a central role in hemostasis and thrombosis. In addition to its critical function in the coagulation cascade, thrombin also takes part in multiple enzymatic and cellular events such as platelet and endothelial cell activation, induction of fibroblast and smooth muscle cell proliferation and migration, and regulation of neuronal differentiation and growth. By virtue of its multifunctional role, regulation of thrombin production and/or its action offers therapeutic potential in various disease states. An explosive growth in research activities occurred in the discovery and development of agents that control the generation and/or action of thrombin from both industry and academia during the mid 1980s and early 1990s.

Research into peptide based thrombin inhibitors as potential antithrombotics is now well into its third decade. Recent X-ray structure determination of the free enzyme as well as inhibitor bound enzyme complexes have significantly aided the understanding of the structure and the drug design processes of small molecule inhibitors of this enzyme. This Symposium-in-Print comprises a review on thrombin active-site inhibitors followed by a series of articles providing detailed summaries of small molecule thrombin inhibitors contributed by a range of investigators active in this area.

As can be seen from this Symposium, there exists to date a number of potent inhibitors of thrombin. The majority of these inhibitors show excellent activity in animal models of thrombosis; yet, the challenge lies in the development of orally-active, safe thrombin inhibitors with an adequate duration of action that inhibit thrombosis without imposing significant hemostatic burden. Continued commitment from the pharmaceutical industry and academia in this area of science will produce an effective therapy in the secondary prevention of myocardial infarction, thromboembolism and stroke.

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