STUDY OF COUMARINS WITH IMPROVED SOLUBILITY TO INHIBIT FXIIa, AN EMERGING TARGET IN THROMBOSIS RESEARCH

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STUDY OF COUMARINS WITH IMPROVED SOLUBILITY TO INHIBIT FXIIa, AN EMERGING TARGET IN THROMBOSIS RESEARCH.

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Thrombotic diseases, in which a deregulated haemostatic activity occurs, remain a major concern in medicine. Anticoagulants are part of the strategies to address these disorders. However current available drugs are still associated with risk of severe bleeding complications and thus, novel antithrombotics are required[1].

In this perspective, coagulation factor XIIa (FXIIa), a serine protease implicated in the coagulation cascade, recently emerged as a promising target in the development of such agents[2]. Indeed, it was demonstrated that FXII deficiency or inhibition protects against thrombosis without causing spontaneous bleeding in mice[3].

Based on these considerations, the aim of our project is to develop novel selective FXIIa inhibitors to detail the exact role of this enzyme in thrombotic diseases. These compounds could also be a good starting point for the development of new antithrombotic drugs.

The 3-carboxamide coumarins (figure 1) are to date the only nonpetidic and selective inhibitors of FXIIa described in literature[4]. However, their low solubility and poor pharmacokinetics resulted in a lack of activity in *in vivo* models of thrombosis. As consequence, we need to improve these characteristics while keeping the selectivity and potency towards FXIIa.

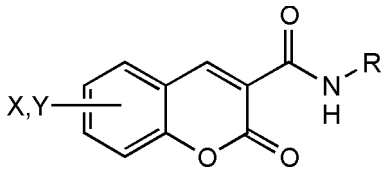

Figure 1 : 3-carboxamide coumarin scaffold

In this work, we first synthesized new coumarins with improved solubility. Their inhibition potency was then measured on FXIIa and finally, their stability was evaluated.

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