STUDY OF COUMARINS WITH IMPROVED SOLUBILITY TO INHIBIT FXIIa, AN EMERGING TARGET IN THROMBOSIS RESEARCH
Bouckaert, Charlotte; Vancraeynest, Christelle; Dolušić, Eduard; Frédérick, Raphaël; Pochet, Lionel

Publication date: 2012

Document Version
Early version, also known as pre-print

Link to publication

Citation for published version (HARVARD):

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.
STUDY OF COUMARINS WITH IMPROVED SOLUBILITY TO INHIBIT FXIIa, AN EMERGING TARGET IN THROMBOSIS RESEARCH.

Charlotte Bouckaert, Christelle Vancraeynest, Eduard Dolušić, Raphaël Frédérick, Lionel Pochet
Namur Medecine & Drug Innovation Center (NAMEDIC-NARILIS), University of Namur, rue de Bruxelles 61, 5000 Namur, Belgium

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 nonpeptidic and selective inhibitors of FXIIa described in literature\(^4\). However, their low solubility and poor pharmacokinetics resulted in a lack of activity in \textit{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](image)

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.