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.

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. Indeed, it was demonstrated that FXII deficiency or inhibition protects against thrombosis without causing spontaneous bleeding in mice3.

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. 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.

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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Factor XIIa
Medicine & Life Sciences
Factor XIIa inhibitor
Medicine & Life Sciences
Thrombosis
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Serine Proteases
Medicine & Life Sciences
Coumarins
Medicine & Life Sciences
Solubility
Medicine & Life Sciences
Hemorrhage
Medicine & Life Sciences
Hemostatics
Medicine & Life Sciences

Projects
Projects per year
2001 → 2006

COUMARINE: Conception and synthesis of inhibitors of serine proteases
MASEREEL, B., POCHET, L., FREDERICK, R. & ROBERT, S.
1/01/01 → 1/02/06
Project: PHD

Equipment
Physical Chemistry and characterization(PC2)
Johan Wouters (Manager) & Carmela Aprile (Manager)
Technological Platform Physical Chemistry and characterization
Facility/equipment: Technological Platform
Annual One-Day Symposium on Medicinal Chemistry of SRC & KVCV (Medchem 2012)
Eduard Dolusic (Contributor)
30 Nov 2012
Activity: Participating in or organising an event types Participation in conference

Student Theses

Conception, synthèse et évaluation biologique de coumarines en tant qu'inhibiteurs de protéases à sérine
Author: Pochet, L., 2000
Supervisor: Masereel, B. (Supervisor)
Student thesis: Doc types Doctor of Sciences

Etude du mode de liaison de composés coumariniques, inhibiteurs de thrombine
Author: De Ruyck, J., 2004
Supervisor: Durant, F. (Supervisor)
Student thesis: Master types Master in Chemistry

Evaluation biologique de coumarines en tant qu'inhibiteurs de protéases à sérine de la cascade de la coagulation
Author: Robert, S. H., 2004
Supervisor: Masereel, B. (Supervisor) & Pochet, L. (Co-Supervisor)
Student thesis: Master types Master in Biology

Cite this

Coumarin, sulphonated coumarin, and biscoumarin compounds were examined for their effects on suppressing the adipocyte differentiation in 3T3-L1 cells. Many of them inhibited the adipocyte differentiation in a dose dependent manner, amongst them compounds (7), (28), and (33) significantly suppressed the adipogenic differentiation, and also exhibited lipolytic effect on mature adipocytes. The active compounds potentially imitate the AMP-activated protein kinase (AMPK) ligands, therefore, binding of these compounds with AMPK possibly shuts down the anabolic pathways.

Charlotte Bouckaert, Christelle Vancraeynest, Eduard Dolušić, Raphaël Frédérick, Lionel Pochet. Namur Research Institute for Life Sciences. Department of Pharmacy. Research output: Contribution to conference › Poster. 16 Downloads (Pure). Overview. Coumarin-based ion receptors, fluorescent probes, and biological stains are growing quickly and have extensive applications to monitor timely enzyme activity, complex biological events, as well as accurate pharmacological and pharmacokinetic properties in living cells [26, 27]. The above coumarins have also been found to inhibit multiplication of bacteria, fungi, and viruses [111] and demonstrated anti-allergy [112], anti-inflammation [113], and immunosuppression activities [114]. Table 1 also shows the importance of a number of families containing coumarins in human nutrition. Rutaceae also proved to contain a great number of coumarins with nutritional and economic interest, particularly the citrus and some other fruits such as Bael [115]. 135 FX and FXII have not been employed to target nanomaterials to atherosclerosis or thrombosis though.

The Choice of Targets and Ligands for Site-Specific Delivery of Nanomedicine to Atherosclerosis. Article. Coagulation factor XII (FXII) inhibitors are of interest for the study of the protease in the intrinsic coagulation pathway, for the suppression of contact activation in blood coagulation assays, and they have potential application in antithrombotic therapy. However, synthetic FXII inhibitors developed to date have weak binding affinity and/or poor selectivity. Here we review data on the role of factor XI and factor XII in thrombosis, and results of pre-clinical and human trials for therapies targeting these proteins. This article is protected by copyright. All rights reserved.