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Structure guided design and synthesis of SAR107375A, aselective and potent dual thrombin and factor Xa inhibitor

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Oral treatment through direct inhibition of the main serine proteases of the coagulation cascade appears one of the most promising strategies to substitute anti-vitamin K long term treatment in the field of cardiovascular diseases. In that particular context, SAR107375 is a novel oral and intravenous anticoagulant, inhibiting both factors Xa and thrombin activities. Despite important efforts in various research laboratories, it remained very challenging to identify dual inhibitors of these two key enzymes of the coagulation cascade with sufficient oral bioavailability in animals. SAR107375 resulted from a rational optimization process. Starting from compound with low factor Xa and modest anti-thrombin inhibitory activities (IC50's of 3.5 and 0.39 μM, respectively), structure-based optimization of a neutral P1 fragment and fine tuning of P2 and P3–P4 residues considerably allowed improvements of both activities.Indeed, during the course of this chemical optimization, we solved a number of thrombin and factor Xa crystal structures in complex with inhibitors and the main guiding principles will be illustrated in order to obtain dual inhibition through the detailed analysis of those complexes. The discovery of development candidate SAR107375 may help to demonstrate the expected beneficial effects in patients from combining inhibition of both factor Xa and thrombin in one single molecule.

Biography

Jerome Meneyrol has completed his PhD at the age of 27 years from Paris 5 University and postdoctoral studies from Newcastle University. He is the Associate Director of Medicinal Chemistry for Early to Candidate (E2C), a Sanofi R&D organization. He has published 5 papers in reputed journals and 1 patent. Moreover, he has contributed to the identification of 2 preclinical candidates in the thrombosis and cancer fields.

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