BACE1 Inhibitor - from 12 mg to 7 kg: A Great Mix of Challenges, "Surprises" & Achievements

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Fine tuning of molecular properties for the optimal profile of clinical candidate molecules comes at the expense of structural complexity. In the highly competitive field of BACE1 inhibitors innovation came with a single fluorine atom in a defined and complex stereochemical arrangement which made the difference of hitting the sweet spot for drug-likeness. While the initial synthesis within Medicinal Chemistry was a heroic effort obtaining the first 12 mg proving the quality of the design – it posed an enormous challenge onto process research to provide material on larger scale. State of the art organic synthesis in conjunction with thorough analytics and modern in-line analysis tools finally enabled the production of 7 kg API – not without a number of "surprises" being encountered, addressed and successfully removed.

It will be demonstrated how a 16 step sequence with overall 0.06% yield could be turned into an efficient 10 step route with 3.5% yield and thereby increasing the efficiency by 58-fold.

[1] H. Hilpert, R. Humm, T. Muser, C. Schnider, R. Wermuth, T. Woltering, *PCT Int. Appl.*, WO**2014**166906 A1.
[2] W. Haap, T. Woltering, *PCT Int. Appl.*, WO**2017**148878 A1.