Targeted Fluoro Positioning for the Discovery of a Potent and Highly Selective Matrix Metalloproteinase Inhibitor

The group of Professor Rainer Riedl

Invited for this month's cover picture is the group of Professor Rainer Riedl from the Institute of Chemistry and Biotechnology at the Zurich University of Applied Sciences (ZHAW), Switzerland. The cover picture depicts the structure-based design of a drug-like small molecule inhibitor of matrix metalloproteinase-13 (MMP-13) with a combined dual binding motif. The targeted introduction of a single fluoro atom was of vital importance for the optimization of the inhibitor. For more details, read the full text of the Communication at 10.1002/open.201600158.

What advice can you give to students interested in your field or chemistry in general?

Enjoy the structural interplay between chemistry and biology! As an organic chemist, you have the tools to create novel small molecules to interact with biological macromolecules, manipulate biological processes, and decipher the underlying molecular principles of diseases. This can ultimately give you the power to treat these indications and help patients.

What are the main challenges in the broad area of your research?

Drug discovery is a very challenging endeavor, as multiple parameters of the drug molecule have to be tuned in order to get the optimal candidate for the treatment of a disease. The discovery of novel chemical scaffolds represents one of the first big hurdles in a drug discovery program. Here, the *de novo* design of novel scaffolds is a very attractive and rewarding alternative to high-throughput screens. This needs detailed structural understanding of the biological target molecule and a lot of creative thinking about appropriate small molecule counterparts and their synthetic manipulation.

What future opportunities do you see (in the light of the results presented in this paper)?

As matrix metalloproteinases are validated therapeutic targets, but the development of marketed drugs has been hampered so far, the presented design approach could serve as an inspiration for future drug discovery and development campaigns in this field. Merging two binding motifs in one inhibitor molecule could also be exploited in the search for new modulators of other target proteins.

What other topics are you working on at the moment?

We are working on several aspects of medicinal chemistry. This includes, amongst others, the *de novo* design of drug-like small molecules, natural products, and the synthesis of peptidomimetics. Together with our academic and industrial partners, we are collaborating on drug discovery and development projects for a variety of indications. Currently, we have a strong focus on infectious diseases stretching from antibiotics to parasitic infections, but also diabetes and cancer are indications in our project portfolio.

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