Universität Zürich[UZH]

Institut für Biochemie

PhD/traineeship position

Design and synthesis of epitranscriptomic protein ligands

Subject Areas: Organic Chemistry/Medicinal Chemistry

Group: Prof Dr. Amedeo Caflisch Y44 L 66 / Fon: +41 44 635 5521 / caflisch@bioc.uzh.ch

Starting date: July 2021 or later

Contact: Frantisek Zalesak, f.zalesak01@gmail.com

Epitranscriptomics gathers all RNA modifications, which do not alter the nucleotide sequence. Among these modifications, several of them are involved in gene expression and play a key role in diseases such as cancer. m^6A is the most prevalent RNA modification (over 160 reported so far) and became the focus of extensive research in the past years.

Currently, the role of m^6A in biological processes and particularly in diseases remain elusive. Therefore, the Caflisch group identified several hits of m^6A interacting proteins, by computer-based methods, in order to develop small molecules able to bind these proteins and unravel their role. One of these hits has been successfully optimized to a low nanomolar inhibitor with favorable ADMET properties. However, there are several other hits waiting for an enthusiastic organic synthesis student to start a medicinal chemistry hit-to-lead campaign. The 30 crystal structures of the m^6A writer enzyme complexes solved in house will be used for protein structure-based hit optimization.

In this project, you will combine retrosynthesis of one of the hit molecules, design of modifications through 3D software visualization of the protein-hit complex and synthesis of the planned derivatives. The aim is to obtain potency improvement while, as far as possible, consider ADMET properties to achieve a lead molecule. The different synthesized compounds will be evaluated in biochemical/biophysical assays and if relevant in cell based experiments.