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## "Chemical Tools for Investigating Histone Deacetylase (HDAC) Enzymes"

by Prof. Christian A. OLSEN

[Center for Biopharmaceuticals and Department for Drug Design and Pharmacology](#), Faculty of Health and Medical Sciences, University of Copenhagen

on: **Wednesday, June 10<sup>th</sup>, 16:00.**

Host: Prof. Nuno MAULIDE, Dept. of Organic Chemistry

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**ABSTRACT:** Histone deacetylases (HDACs) are validated targets for treatment of certain cancer types and play numerous regulatory roles in biology, ranging from epigenetics to metabolism. Small molecules are highly important as tool compounds to probe these mechanisms as well as for the development of new medicines. Therefore, detailed mechanistic information and precise characterization of the enzyme substrate preference as well as the chemical probes used to investigate the effects of HDAC enzymes are vital.

Through profiling of both sirtuins and zinc-dependent HDACs, we have developed efficient assay formats for probe characterization and discovered enzymatic activities against novel acyllysine posttranslational modifications (PTMs).

Furthermore, we have interrogated Nature's arsenal of macrocyclic non-ribosomal peptide HDAC inhibitors by chemical synthesis and evaluation of more than 30 natural products and analogs. This furnished surprising trends in binding affinities for the various macrocycles, which were then exploited for design of highly potent class I and IIb HDAC inhibitors. Furthermore, thorough kinetic investigation revealed unexpected inhibition kinetics of important tool compounds as well as the approved drug Istodax (romidepsin). **This work provides novel inhibitors with varying potencies, selectivity profiles, and mechanisms of inhibition and, importantly, affords insight regarding known tools compounds that will improve interpretation of their effects in biology and medicine.**

**RESEARCH PROFILE:** Christian A. Olsen is a professor in the Center for Biopharmaceuticals and Department of Drug Design and Pharmacology at University of Copenhagen. He received his M.Sc. from The Technical University of Denmark in 2000 and his Ph.D. from The Danish University of Pharmaceutical Sciences in 2004. He did his postdoctoral fellowship with Prof. Ghadiri at The Scripps Research Institute. In 2010 he became a Lundbeck Foundation Fellow and in 2016 he was awarded the ERC Consolidator grant. **His research interests include foldamers, macrocyclic peptide-based HDAC inhibitors and quorum sensing modulators, as well as investigation of protein lysine acylation.**

Contact: Doctoral Program MolTag, Dept. of Pharmaceutical Chemistry, University of Vienna; <http://moltag.univie.ac.at/>, [Office.moltag@univie.ac.at](mailto:Office.moltag@univie.ac.at)

