Helmholtz-Institute for Pharmaceutical Research Saarland
HELMHOLTZ ZENTRUM FÜR INFEKTIONSFORSCHUNG
UNIVERSITÄT DES SAARLANDES

Prof. Dr. Karl-Heinz Altmann

Department of Chemistry and Applied Biosciences,
ETH Zürich

will give a presentation entitled

“Total Synthesis and Functional Exploration of Bioactive Natural Macrocycles“

Tuesday, April 19, 2016, at 17:00 s.t.
in Blg E8.1, Seminar Room (Ground Floor)

Host: Prof. Dr. Rolf Müller

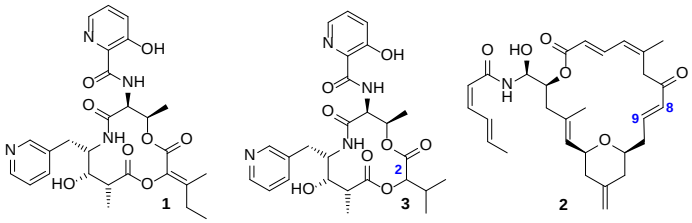
There is opportunity to talk with the speaker before the talk.
There will be a follow-up session (Nachsitzung).

For details and for making appointments please contact: Christina Decker, 0681-98806-3001 or per email: office.mueller@helmholtz-hzi.de

Guests are welcome!

Abstract

Macrocyclic secondary metabolites form a diverse group of bioactive natural products, of which many have proven to be important leads for drug discovery and development. This contribution will discuss selected aspects of the synthetic chemistry and biological activity of two macrocyclic natural products, namely the bacterial cyclo-depsipeptide pyridomycin (1) and the marine macrolide (-)-zampanolide (2). Pyridomycin (1) was first isolated from Streptomyces albidofuscus in 1954 and it exhibits significant in vitro activity against Mycobacterium tuberculosis.[1] The molecular target of 1 has recently been revealed as the enoyl-ACP reductase InhA, which is also the target of the clinical anti-TB drug isoniazid.[2] (-)-Zampanolide (2) is a microtubule-stabilizing agent (MSA)[3] and as such is a potent inhibitor of human cancer cell proliferation in vitro.



Our exploration of the biology and medicinal chemistry of pyridomycin (1) has focused on the de novo synthesis of analogs of type 3. Remarkably, although lacking an enol ester moiety, (2R)-3 retained most of the anti-tubercular activity of 1, while (2S)-3 was significantly less active. Based on these findings we have investigated additional analogs derived from (2R)-3, whose synthesis, binding to InhA and antibacterial activity will be discussed in this presentation. As for (-)-zampanolide (2), we have developed an efficient modular total synthesis for this natural product, based on macrocyclic ring-closure by an intramolecular Horner-Wittig-Emmons reaction between C8 and C9. The high resolution crystal structure of the complex of 2 with tubulin has provided fundamentally new insights into the molecular mechanism of MSA-induced tubulin assembly.

[1] Kuroya, M.; et al. J. Antibiot., Ser. A 1954, 7, 58.
[2] Hartkoorn, R. C.; et al. EMBO Mol. Med. 2012, 4, 1032.
[3] Field, J. J.; et al. J. Med. Chem. 2009, 52, 7328.

CV

Karl-Heinz Altmann has been a professor of Pharmaceutical Sciences at the Institute of Pharmaceutical Sciences of the ETH Zürich since July 1st, 2003.
Professor Altmann studied chemistry at the Johannes-Gutenberg University in Mainz, from where he graduated with a diploma in 1983. His subsequent Ph. D. work in the area of peptide chemistry was performed at the University of Basel from 1984-1986. Karl-Heinz Altman then spent two and a half years as a post-doctoral associate at Cornell University, Ithaca, NY, which was followed by a one year stay as a master assistant at the University of Lausanne. In Sept. 1990 Karl-Heinz Altmann joined Ciba-Geigy's Central Research Laboratories in Basel, where he worked on the design and synthesis of modified nucleosides as potential building blocks for antisense therapeutics until 1996. In 1997 he moved to Oncology Research within Novartis Pharma AG, which had been formed through the merger between Sandoz and Ciba- Geigy. After four years as a project leader in Oncology Research Karl-Heinz Altmann was appointed the Novartis Senior Chemistry Expert in 2000. From Jan. 2003 until his move to the ETH, he was the acting Global Head of Chemistry of the Novartis Institutes for BioMedical Research.
In 1998 Karl-Heinz Altmann received the "Novartis Leading Scientist Award", an important internal science award of Novartis Pharma AG.
Prof. Altmann's research interests are at the interface between chemistry and biology, with a particular focus on the chemical synthesis and the biological and pharmacological profiling of biologically active natural products and their synthetic and semi-synthetic analogs. This research on one hand aims at the understanding of the mechanism of action of such molecules and the elucidation of the structural requirements for biological activity. On the other hand, it tries to assess the therapeutic potential of such compounds with the ultimate goal to discover new therapeutics for clinical applications.