SAPIENZA
UNIVERSITÀ DI ROMA

Dipartimento di Chimica
e Tecnologie del Farmaco

AVVISO DI CONFERENZA

Si comunica che Lunedì 18 Dicembre, alle ore 10:00, nell'Aula D del plesso Tecce. dell'Università La Sapienza il

Prof. Karl-Heinz Altmann

(ETH Zürich, Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, Zürich, Switzerland "), terrà una conferenza dal titolo:

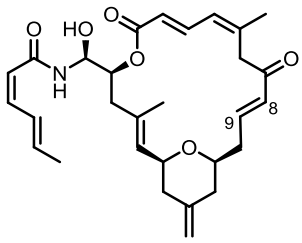
"Total Synthesis and Functional Exploration of Bioactive Natural Macrocycles"

La S.V. è invitata ad intervenire.

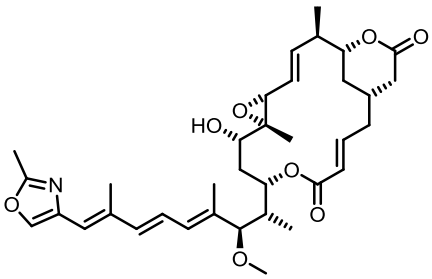
Il Direttore
Prof. Bruno Botta

ABSTRACT

*Macrocyclic secondary metabolites are a diverse group of bioactive natural products and many of these compounds have been, and continue to be important leads for drug discovery and development. This contribution will discuss selected aspects of the synthetic chemistry, medicinal chemistry and chemical biology of two macrocyclic natural products, the marine macrolide zampanolide (**1**) and the bacterial toxin rhizoxin F (**2**). (-)-Zampanolide (1) is a microtubule-stabilizing agent (MSA), while rhizoxin F (**2**) is a tubulin polymerization inhibitor; both compounds are potent inhibitors of human cancer cell proliferation in vitro.*



1



2

*We have developed efficient modular total syntheses for both of the above natural products. For **1**, macrocyclic ring-closure was based on an intramolecular Horner-Wittig-Emmons reaction between C8 and C9, which proceeded in high yield and with excellent selectivity. The same overall approach was employed in the synthesis of analogs of **1** for SAR studies. A high resolution crystal structure of the complex of **1** with tubulin has provided fundamentally new insights into the molecular mechanism of MSA-induced tubulin assembly. **2** was prepared via ring-closing alkyne metathesis (RCAM) as one of the key steps, followed by elaboration of the side chain. The crystal structure of tubulin-bound **2** has revealed a new ligand binding site on β-tubulin.*