Editorial

Peptaibiotics

In the past, peptaibiotics (peptide antibiotics heavily based on α-aminoisobutyric acid (Aib)) were detected, rather incidentally, on the search for new active compounds of this type. Nowadays, the exploitation of the unique Aib residue as the marker amino acid and its detection by applying a variety of specific and sensitive gas- and liquid-chromatographic techniques, advantageously coupled to mass spectrometry, make the rapid screening of fungi for the production of peptaibiotics a realistic experimental effort.

Effective separation of a number of peptide components by state-of-the-art analytical techniques, such as highly effective reversed-phase stationary phases along with optimized gradient elution and sophisticated HPLC instruments, and on-line sequencing using electrospray-ionization (ESI) ion-trap tandem mass spectrometry (MS), ESI triple-quadrupol MS/MS, or matrix-assisted-laser-desorption-ionization time-of-flight (MALDI-TOF) MS or *Fourier* transform ion cyclotron resonance (FTICR) allow the sequencing of complex mixtures of peptaibiotics. Also, MS techniques make sequencing possible of overlapping peaks by selecting appropriate precursor and product ions. Applying them to fungi or suitable extracts, the entirety of Aib-containing peptides is often determined. This approach is termed '*peptaibiomics*', in analogy to other '*-omics*'. Besides *Trichoderma,* an abundance of other genera of filamentous fungi is recognized to produce peptaibiotics. Use of some of these fungi for the biocontrol of plant pathogens is of major practical relevance and the subject of intensive investigations.

New constituents and bioactivities of peptaibiotics have been recognized. The long-waited for occurrence of the Aib cyclic analogue 1-aminocyclopropane-1-carboxylic acid (Ac_3c) has recently been detected in neoefrapeptins and acretocins. Notably, model peptides containing Ac_3c have been synthesized two decades ago for 3D-structural studies. Some peptaibols induce pigment formation and cytodifferentiation in *Phoma destructiva*, an effect that is correlated with the induction of hypothermia and neuroleptic effects in rodents. Rather weak effects against plant viruses have been reported. However, inhibition of HIV-1 integrase by integramides, peptaibiotics rich on Aib as well as (*R*)- and (*S*)-Iva (isovaline), have recently attracted much attention and certainly will boost interest in peptaibiotics.

The total chemical synthesis of peptaibiotics is now feasible *via* the solution or the solid-phase strategy, or a variety of their combinations by taking advantage not only of the modern protecting groups of the terminal and side-chain functionalities, but, in particular, of effective *C*-activation reagents for the difficult coupling between the two *C*(α)-tetrasubstituted α-amino residues Aib and Iva. The intriguing azirine/oxazolone

method is also appropriate for the introduction of Aib and Iva. Furthermore, these methodologies allow the preparation of a variety of analogues, some of them characterized by useful spectroscopic probes. The total chemical synthesis of labeled analogues is an attractive alternative because peptaibiotics contain only very few functional groups that can be modified by chemical reagents.

Precise determination of the 3D structures of peptaibiotics in solution is achieved by the combined application of the FT-IR absorption, CD, and ^{1}H-NMR techniques. Indirect information on conformation is also extracted from fluorescence and EPR studies of appropriately bis-labeled analogues. The extremely high crystallinity of the Aib-rich peptides allows the solution of the X-ray diffraction structures of peptaibiotics and some of their informative, short-length, synthetic intermediates.

Investigations by NMR, fluorescence, and EPR techniques, particularly on appropriately mono-labeled peptaibiotic analogues, shed light on their conformation in membrane-mimetic environments and actual membranes. Valuable indications on the orientation, immersion depth, and extent of self-aggregation of the peptaibiotic molecules in these media are also obtained. The detailed knowledge of all these properties is a prerequisite for the construction of models describing the unique transmembrane channel-forming properties of peptaibiotics of sufficient main-chain length.

Finally, evidence has been gathered that some peptaibiotics form fluorescent complexes with selected metal cations and increase the permeability of lipid bilayers for the delivery of substrates into vesicular nanoreactors for biocatalysis experiments.

To summarize, this Topical Issue of *Chemistry & Biodiversity* provides an excellent overview on the status of contemporary studies of peptaibiotics, covering aspects ranging from the search for novel bioactive compounds and their biosynthetic aspects to the total chemical synthesis and exploitation of X-ray diffraction and various spectroscopic techniques, to considerations of their membrane-modifying properties, including mechanisms of transmembrane channel formation through peptide self-association.

The articles compiled in this Issue represent also a legitimation of the long-standing interest of the Guest Editors and their co-workers and collaborators in the field of natural and synthetic Aib-rich peptides, and are an appropriate tribute to the pioneers of the research in peptaibiotics.

Last but not least, the Guest Editors would like to express their sincere appreciation to Dr. *M. Volkan Kisakürek* for his continuous support and encouragement, and his extremely careful and highly professional handling and editing of the contributions.

Claudio Toniolo *Hans Brückner*