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EDITORIAL

Editorial to the Special Issue *Foldamers*

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Nature makes extensive use of proteins as important effector molecules. They are composed of 22 genetically encoded building blocks (including selenocysteine and pyrrolysine). Most proteins fold into well-defined three-dimensional structures and this folding is crucial for their function. As we do not yet know a general folding code based on the chemical and physical rules that control the formation of protein structures, the design or prediction of a folded protein structure is still a challenge.

Biopolymers, such as proteins or RNA, however, are not the only molecules that are able to adopt folded structures. During the past decade, an increasing number of publications appeared describing man-made molecular systems able to adopt discrete and predictable three-dimensional structures. Sam Gellman, one of the pioneers in the field, coined the term *foldamer* for "any polymer with a strong tendency to adopt a specific compact conformation" (Gellman 1998) and such artificial folded molecular structures can be designed in many different ways from many different building blocks. Some of them have some resemblance to natural peptides and proteins, as they are composed of amino acids. These amino acids often exert conformational bias leading, e.g. to helical structures, such as C^{α}-disubstituted amino acids, *N*-methyl amino acids, β-amino acids, γ-amino acids, and hybrid structures thereof. Others, like aminoxy acids, hydrazino acids, carbamates, and ureas, but also aromatic oligoamides or oligomers of aromatic heterocycles have to be mentioned in this context, too.

Such structurally diverse oligomers were shown to adopt various helix types, strand-like conformations, or turns. They have high potential for application in a therapeutic context or in materials chemistry. Some representatives have been proven to display biological activity even without resembling naturally occurring counterparts. Others may be "decorated" with pharmacophores for applications in Medicinal Chemistry. These compounds may display novel and favorable metabolic profiles and possibly bridge the gap in molecular weight between small molecule drugs and protein-based drugs.

This special issue of Amino Acids is devoted to *foldamers*. The idea of preparing such a compilation originated in the frame of the European Cooperation in Science and Technology (COST) Action CM0803 *Foldamers*: *Building Blocks, Structure, and Function* with scientific meetings held in 2009 and 2010 at Szeged, Bordeaux, and Bologna. Research groups from 14 European member states cooperate in this network. Contributions by the participating scientists and international guests nucleated this Special Issue *Foldamers*.

The scope of the topics in this special issue ranges from the stereoselective synthesis of novel building blocks for foldamer synthesis over functional studies on non-natural peptides as gelators and sensors to longer peptides, hybrid peptides, and hybrid peptoids with interesting structural and functional features.

The section on building block synthesis starts with an original paper communicated by De Kimpe and colleagues (Žukauskaitė et al. 2011) on monomers containing three- and four-membered nitrogen heterocycles. Fustero et al. (2011) report on the stereoselective synthesis of quaternary α-amino acids and fluorinated analogues. Tolomelli et al. (2011) provide details on the synthesis of novel 3,4-dehydro-β-proline derivatives by ring-closing metathesis, while Declerck and Aitken (2011) describe a synthetic route to all four stereoisomers of the constrained foldamer building

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block Boc-2-aminocyclobutanecarboxylic acid. Szakonyi and Fülöp (2011) review the role of the chiral pool as a source for enantiomerically pure terpene-based β-amino acids also providing information on pharmaceutical relevance and potential applications.

Tomasini and co-workers were able to show that small peptides composed of non-natural amino acids act as gelators in the presence of metal ions (Castellucci et al. 2011). Granja and co-workers report on the design and synthesis of self-assembling cyclic hexapeptides that contain three γ-amino acids. These supramolecular assemblies might find application as metal-ion sensors or molecular rotors (Pérez-Alvite et al. 2011).

Reproducible and robust structure formation is a major cornerstone in foldamer chemistry. The bottom-up approach in foldamer chemistry aims at the discovery of novel secondary structures that can subsequently be transformed into molecules with a specific function. Toniolo and co-workers (Crisma et al. 2011) discovered that homochiral hexapeptide esters synthesized from C^{α}-ethyl, C^{α}-*n*-pentylglycine adopt fully extended helical structures (2.0_5-helix). Simone et al. (2011) address the synthesis of branched sugar-based amino acids (SAA) and of oligomers derived from them. Octameric peptoid macrocycles containing alternating α- and β-amino acids with chiral and achiral *N*-alkyl substituents were synthesized and structurally characterized by Edwards and colleagues (De Santis et al. 2011). Likewise, Ortuño and colleagues studied the synthesis and conformational parameters of hybrid γ,γ-peptides composed of *cis*-4-amino-L-proline and different stereoisomers of 3-amino-2,2-dimethylcyclobutane-1-carboxylic acid in alternating positions (Gutiérrez-Abad et al. 2011). Alezra and colleagues review peptidomimetic oligomers that contain γ-amino acids or aminoxy acids, covering γ-peptides, hybrid α,γ-peptides, hybrid β,γ-peptides and oligoureas (Bouillère et al. 2011). Details on biological properties and applications are also given. Pilsl and Reiser (2011) summarize the state of the art concerning hybrid α/β-peptide foldamers covering structural features and biological properties, such as protein surface recognition and HIV cell entry inhibition.

In top-down approaches Sewald and colleagues studied the synthesis and antifreeze properties of glycopeptides (Nagel et al. 2011), while Koksch and colleagues investigated the consequences of the iso-atomic replacement of two α-amino acids in an α-helical coiled coil by a β- and a γ-amino acid, especially with respect to conformation and association (RezaeiAraghi et al. 2011).

The potential of helix mimicking foldamers to interfere with protein–protein interaction is finally reviewed by Edwards and Wilson (2011) clearly highlighting the impressive advances that have been achieved with foldamers in a biological context.

The collection of articles in this Special Issue *Foldamers* reflects many of the facets of current foldamer research, the recent advances, and the promising perspectives. I hope the readers will find this collection of publications informative and stimulating.

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