Structure Determination of Peptides and Peptidotriazoles by MD Simulations

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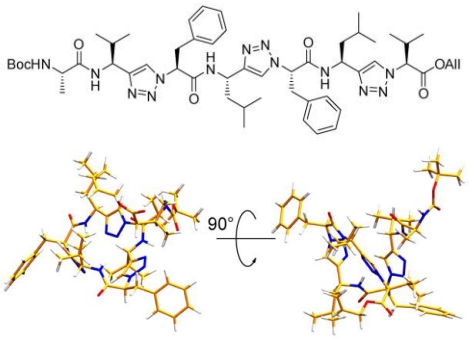

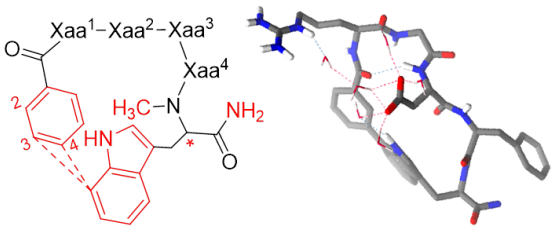

	Xaa[1-4]	*	connection
1	RGDF	D	7-4
2	RGD	L	7-4
3	RGDF	D	7-3

Specific protein-protein interactions are important targets in pharmaceutical research. Therefore, peptides and peptide like small molecules so called peptidomimetics are of special interest. It has been thoroughly shown that 1,4-disubstituted 1*H*-1,2,3-triazoles are potent isosteric replacements for proteolytically labile *trans* peptide bonds. Moreover, the isosteric replacement of the amide bonds can although stabilize or force secondary structure elements. We investigated an MD-based in solution conformational analysis on peptidotriazolamers, hybrid foldamers with features of peptides and triazolamers, containing alternation of amide bonds and 1,4-disubstituted 1*H*-1,2,3-triazoles with conservation of the amino acid side chains. [1] The simulations were based on the specific molecular mechanics force-field parameterization TZLff that we recently published. [2] Conformational properties of a given sequence for a homochiral (Fig. left), a heterochiral and a homochiral equivalent where every second former amino acid has been exchanged by glycine, were analyzed in DMSO as well as in Water. [1]

In a second project, we elucidated the conformation of cyclic peptides containing the RGD (Arg, Gly, Asp; Fig. right) motive being the recognition sequence for integrins. The RGD sequence naturally occurs in extracellular matrix (ECM) proteins, such as vitronectin and fibronectin, playing a crucial role in the bidirectional cell signalling. The integrin ECM interaction turned out to be a promising target in the fields of cancer treatment, radiotherapy and surface coating of implants. In our study, we found an explanation for multiple NMR data sets in DMSO as well the difference in biological activity in aqueous media. [3]

[1] D. C. Schröder et al., *Front Chem*, **2019**, *7*.
[2] A. Marion et al., *J. Chem. Inf. Model.*, **2018**, *58*, 90–110.
[3] I. Kemker, C. Schnepel, D.C. Schröder et al., *J. Med. Chem.*, **2019**, *62*, 7417-7430.

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