19ème Congrès du Groupe Français des Peptides et des Protéines
17-22 mai 2015
Portbail, Normandie, France

Modified peptides for non-covalent and covalent recognition of biological targets

Abhishek Iyer, Yara Ruiz, Lieselot Carrette, Kurt Hoogewijs, Willem Vannecke and Annemieke Madder

Organic and Biomimetic Chemistry Research Group, Department of Organic Chemistry, Ghent University, Krijgslaan 281 S4, B-9000 Gent, Belgium, annemieke.madder@ugent.be

The study of DNA-protein interactions, important for many cellular processes, has so far not allowed unraveling the exact mechanism behind their unique selectivity and affinity. We have been studying these interactions through the use of DNA binding protein mimics.[1] Next to an earlier described non-covalent GCN4 mimicking peptide dimer as standard;[2] a new type of steroid-based dipodal DNA binders has been investigated.[3] Though synthetically challenging in view of the close distance between two peptide chains immobilized on the steroid template, improved properties in terms of binding, biostability and bio-availability have been observed. In a subsequent attempt to further reduce the size of the synthetic DNA binders, we have been looking into existing stapling methods to enhance the DNA binding potential of a single chain peptide containing the binding region of the GCN4 protein. Two selectively positioned, non-binding amino acids on the GCN4 peptide were replaced by Cysteine residues and covalently connected using bisalkylators resulting in stapled peptides. Unlike the synthetic bZip peptides where α helicity is induced via a dimeric structure, we here stabilize a single α helix via peptide stapling. CD analysis of the peptides has shown improvement in helicity. Subsequently, the DNA binding of the peptides to the CRE binding site was studied by Gel electrophoresis.[4]

In a further study, synthetic miniaturized peptides were modified with furan moieties, which trigger crosslinking upon oxidation into a reactive ketobutenal[5] and allow the conversion of transient supramolecular interactions into stable covalently bound complexes. Proximity being a prerequisite for this novel selective DNA-peptide crosslinking methodology, it allows for distance probing to interacting functionalities and offers further opportunities for therapeutic developments.[6] The furan-oxidation based crosslink methodology was then transferred to and applied on the peptide-protein interface and some examples thereof will be discussed.

1. Carrette L.L.G., Madder A. *et. al. Drug. Discov. Today: Tech.* **2010**, *7*, 115.
2. Ueno M., *et. al.*, *J. Amer. Chem. Soc.* **1993**, *115*, 125752.
3. Verzele D., Madder A., *Eur. J. Org. Chem.* **2013**, *4*, 673.
4. Iyer A., Madder A., *Org. Biomol. Chem.* **2015**, *accepted.*
5. Op de Beeck, M., Madder, A., *J. Amer. Chem. Soc.* **2011**, *133*, 796.
6. Carrette L.L.G., Madder A. *et. al. Bioconj. Chem.* **2013**, *24(12),* 2008.