SCIENCES & BIOENGINEERING SCIENCES

The Research Group

Organic Chemistry

has the honor to invite you to the public defense of the Joint PhD thesis of

Tom WILLEMSE

to obtain the degree of Doctor of Sciences

Joint PhD with the University of Antwerp

Title of the PhD thesis:

Peptide diversification: Palladium-catalyzed derivatization of peptidic lead compounds in aqueous media

Promotors:

Prof. Steven Ballet
Prof. Bert Maes (UA)

The defense will take place on

Friday February 23rd 2018 at 17:00 h

in Auditorium D.2.01 at the campus Humanities, Sciences and Engineering of the Vrije Universiteit Brussel, Pleinlaan 2 - 1050 Elsene, and will be followed by a reception.

Members of the jury:

Prof. Dominique Maes (chair)
Prof. Pieter Van Der Veken (secretary, UA)
Dr. Wim Schepens
(industrial promotor, Janssen Pharmaceutica)
Prof. Guido Verniest
Prof. Em. Dirk Tourwé
Prof. Frédéric Bihel (Univ. De Strasbourg)
Prof. Norbert Sewald (Bielefeld Univ.)

Curriculum vitae

Tom Willemse (28/03/1989) graduated as Master of Science in Chemistry - Molecular and macromolecular design - from the Vrije Universiteit Brussel (VUB) in 2012. Next, he obtained an IWT-Baekeland scholarship for research towards transition metal-catalyzed reactions for diversification of peptide substrates. His research was funded by the Agency for Innovation by Science and Technology in Flanders (IWT) and Janssen Pharmaceutica, under supervision of promotors Prof. Steven Ballet (VUB), Prof Bert Maes (UA) and Dr. Wim Schepens (Janssen Pharmaceutica). During his doctoral thesis, he stayed for four months at the University of Saint-Andrews and his research has led to 4 first author and 2 coauthor publications, and submitted manuscripts in international peer-reviewed journals. He supervised a Master thesis and two Bachelor theses and presented his work at (inter)national conferences by oral talks and poster presentations.

Abstract of the PhD research

Peptides and proteins play a key role in the control and modulation of many biological processes. However, the use of natural peptides as potential therapeutics is often hampered by several inherent drawbacks of these products. In general, these molecules possess low oral bioavailability, limited resistance to proteolytic enzymes, high conformational flexibility and low capacity to cross cell membranes. Nevertheless, in comparison to traditional “small molecules”, they exert an enhanced specificity and allow mimicking of complex mechanisms, such as protein-protein interactions. Over the last two decades a remarkable progress has been realized, which resulted in lowered production costs related of therapeutic peptides. Moreover, solutions to overcome these drawbacks have been proposed by means of the development of numerous chemical transformations that allow to modify the peptide chain via bioorthogonal reactions. An example of these transformations is the palladium-catalyzed Suzuki-Miyaura reaction that typically employs mild reaction conditions and thus is broadly applicable in peptide chemistry. This includes the use of environmentally benign boron compounds and a compatibility for diverse functional groups in an aqueous environment.

Via selective introduction of a halogen atom as a “derivatization handle” on the side chain of aromatic amino acids (phenylalanine and tryptophan in this work) it is possible to generate numerous non-natural amino acid residues. We acquired synthetically useful quantities of halogenated tryptophans via enzymatic biotransformation, that are otherwise not straightforwardly prepared in an enantioselective manner. These substrates, along with the commercially available halophenylalanines, served as the starting materials for diversification of amino acids and more complex substrates (di- up to decapeptides) via the Suzuki-Miyaura reaction. After thorough evaluation and optimization of several reaction parameters, we defined optimal conditions that allowed us to synthesize modified, biologically active peptides both in aqueous environment and on solid support.

This optimized methodology was applied for the synthesis of a library of analogues of opioid tetrapeptides. Dependent on the size and position of the substituent on the modified amino acid in the peptide, high affinities for both the mu and delta opioid G protein-coupled receptors (GPCRs) could be achieved. Furthermore, during *in vivo* studies a highly desirable antinociceptive effect was observed after injection of these analogues in mice. In addition to the synthesis of modified peptides we could, again via the Suzuki-Miyaura cross-coupling, also gain access to cyclized peptides that are known to improve the stability against proteolytic degradation. Via this approach we realized the synthesis of various cyclic peptides that can be applied for both the synthesis of novel therapeutic peptides and as a vector to transport other biologically active ligands through cellular membranes.