SCIENCES & BIOENGINEERING SCIENCES

The Research Group

Organic Chemistry

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

Olivier VAN DER POORTEN

to obtain the degree of Doctor in Sciences

Title of the PhD thesis:

Side chain constrained aromatic amino acids for use in peptide turn mimicry and cell-penetrating oligomers

Promotor:

Prof. Steven Ballet

The defense will take place on

Thursday March 29, 2018 at 17h00

in Auditorium E.0.12 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. Wim Versées (chairman)
Prof. Frederik Tielens (secretary)
Prof. Em. Dirk Tourwé
Prof. Mette Rosenkilde (Univ. of Copenhagen)
Prof. Sandrine Ongeri (Univ. Paris Sud)

Curriculum vitae

Olivier Van der Poorten (°1989) graduated as Master of Science in Chemistry – Molecular and Macromolecular Design – from the Vrije Universiteit Brussel (VUB) in 2013. Next, he obtained a VLAIO doctoral grant with a research focus on conformationally constrained amino acids and cell-penetrating oligomers. During his doctoral thesis, he performed a three- and four-month research stay at the Universities of Montpellier, France and Montréal, Canada, respectively. His research has led to 6 first author publications in international peer reviewed journals (11 publications in total). He supervised three MSc and two Bachelor dissertations, and presented his work at (inter)national conferences by oral talks and poster presentations.

Abstract of the PhD research

Since almost all peptide-binding G protein-coupled receptors are implicated in disease pathology, there is a need to develop tools that allow the efficient design of peptide-like and small molecule ligands for these receptors. In the past many linear peptides have been rigidified to favor their bioactive conformation, mainly via macrocyclization of the backbone and/or the side chains. This continues to be a reliable and efficient strategy for optimizing the overall properties of potential therapeutic peptides. However, these macrocyclization strategies only provide the medicinal chemist with control of the Φ and Ψ dihedral angles of the peptide backbone and not so-called "χ-space". Next to the advantages of controlled peptide backbone dihedral angles for improving potency, selectivity, and metabolic stability, the orientation of side chain pharmacophoric groups, which is determined by the χ-space, is at least equally important for favorable biological recognition events. The use of unnatural amino acids has been central to the success of peptide drugs since the biological activity of a peptide is determined not only by its secondary structure, but also by the 3D orientation of key side chain functional groups which constitute the pharmacophore elements of the peptide ligand. Introduction of cyclic constrained aromatic amino acids in peptide ligands provides a valuable tool for controlling χ dihedral angles and thus for presenting specific topologies. This doctoral thesis focused on unnatural amino acids that are constrained via cyclization of the amino acid side chain to the peptide backbone. Constraining the side chain dihedral angles (χ angles) may limit the number of low energy conformations and lead to more potent, receptor (sub)type selective and enzymatically stable peptide ligands. The described cyclic constrained aromatic amino acids present an additional feature to control χ dihedral angles and can be regarded as additional tools to modulate receptor selectivity and activity, but they also provide a way to enhance proteolytic stability and bioavailability of lead peptides.

To apply χ-space screening, various conformationally constrained aromatic amino acids were synthesized in this thesis via different synthetic pathways, such as a Pictet-Spengler reaction, a reductive amination of 2'-formyl-Phe/2'-formyl-Trp derivatives and intramolecular lactam formation, *N*-acyliminium ion cyclizations of an oxazolidinone precursor, an intramolecular Cu(I)-catalyzed Goldberg amidation reaction, and an Ugi-4CR – Ullmann cross-coupling sequence. These constrained building blocks were successfully incorporated in various bioactive peptide sequences (e.g. opioids, melanocortin, angiotensin II, etc.) and non-cationic and amphipathic cell-penetrating oligomers as new vectors for intracellular delivery of bioactive cargoes.