SCIENCES & BIOENGINEERING SCIENCES

The Research Group

Organic Chemistry

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

Steven VERLINDEN

to obtain the degree of Doctor of Sciences

Title of the PhD thesis:

The 1,3-diyne linker as a tunable tool for peptide macrocyclization and secondary structure stabilization

Promotors:

Prof. dr. Steven Ballet
Prof. dr. Guido Verniest

The defence will take place on

Tuesday April 23rd 2019 at 17:30h

in Auditorium E.0.04 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. dr. Jo Van Ginderachter (chairman)
Prof. dr. Ulrich Hennecke (secretary)
Prof. dr. Mercedes Alonso (co-promotor)
Dr. Freija De Vleesschouwer
Prof. dr. Annemieke Madder (Univ. Gent)
Prof. dr. Christian Olsen (Univ. of Copenhagen)

Curriculum vitae

Steven Verlinden (°1990) graduated as Master of Science in Chemistry – molecular and macromolecular design – from Vrije Universiteit Brussel (VUB) in 2014. Next, he was appointed as a teaching assistant at the Chemistry Department combined with a doctoral research. His research focused to the development of a novel peptide macrocyclization strategy and led to 4 manuscripts in international, peer-reviewed journals.

Abstract of the PhD research

Peptide macrocyclization has shown to be a valuable strategy in peptide drug development. Macrocyclic peptides overcome several drawbacks of native linear peptides and can increase target selectivity, (oral) bioavailability and metabolic stability. The goal of this project was to develop a new, tuneable macrocyclization tool for peptides, which makes use of an intramolecular oxidative alkyne alkyne coupling. After insertion into the macrocyclic peptide structure, the resulting 1,3-diyne linkage can be further transformed into a heterocycle-bearing bridging unit to modulate the bioactivity and/or polarity of the resulting compounds. With this new method, the toolbox of peptide macrocyclization chemistry expands.

After having optimized the alkyne alkyne coupling reaction between two amino acids in an intermolecular fashion, the intramolecular version of this oxidative coupling was developed and resulted in the synthesis of novel macrocyclic tetrapeptides. NMR studies were performed to gain insight into the secondary structure of the cyclic peptides and on the influence of the 1,3-diyne linker as a constraining element, as for example compared to a less rigid saturated hydrocarbon linker.

Treatment of the prepared 1,3-diyne tethered tetrapeptides with (bis)nucleophiles led to the formation of novel heterocycle-tethered tetrapeptides. In a final stage, the 1,3-diyne linker was used for the stabilization of short α-helical peptide sequences bridged at positions *i*,*i*+7. The influence of the configuration of the linking amino acids on the secondary structure of the stapled peptides was investigated by CD and NMR analysis. The synthesis of these 1,3-diyne stapled α-helical peptides is of particular interest in peptide drug development, since protein-protein interactions are often occurring through key helical domains, and these are critical for the control and modulation of many biological systems.