SCIENCES & BIOENGINEERING SCIENCES

The Research Group
Organic Chemistry

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

Debora Iaculli

to obtain the degree of Doctor of Sciences

Title of the PhD thesis:

Design and development of Pannexin1 and Connexin43 (hemi)channel peptide inhibitors

Promotor:
Prof. dr. Steven Ballet (VUB)

The defence will take place on

Monday, March 24, 2025 at 5 p.m. in auditorium I.2.01

Members of the jury

Prof. dr. Ann Massie (VUB, chair)
Prof. dr. Charlotte Martin (VUB, secretary)
Prof. dr. Ulrich Hennecke (VUB)
Prof. dr. Marc Vendrell (The University of Edinburgh, UK)
Prof. dr. Stéphane P. Vincent (UNamur)

Curriculum vitae

Debora Iaculli obtained her bachelor and master degrees in Chemistry at the University of Bologna, Italy. In 2020, she joined the Research Group of Organic Chemistry (ORGC) at VUB as a PhD student on the European FET project PANACHE. During her PhD, she co-authored four publications in peer-reviewed journals (two as first author). She communicated her work through seven poster and two oral presentations at international conferences, and was awarded with a poster prize at the 13th IPS in Brisbane (2023). Debora supervised three master students, other than assisting multiple courses.

Abstract of the PhD research

Membrane-bound channel-forming proteins are essential in mediating cellular communication and their modulation offers an opportunity for the development of new drugs. Among such proteins, Connexin43 (Cx43) and Pannexin1 (Panx1) are key players in both "healthy" physiological intercellular communication as well as communication related to pathological states. Selective modulation of Cx43 and Panx1 activity represents thus a potential therapeutical approach. A handful of modulators of Panx1 and Cx43 (hemi)channel activity were already known (e.g. ^{10}Panx1 and CT10, respectively), although they possessed some drawbacks such as a lack of selectivity, proteolytic instability or an inhibition of physiological communication other than pathological activity. This study aimed to develop a new generation of connexin and pannexin (hemi)channel inhibitors as potential drug candidates in the treatment of cardiac and hepatic inflammatory diseases. Among known modulators, peptide mimetics which mimic portions of the native sequences of Cx43 and Panx1 were of particular interest as they have shown promising inhibitory activity both by *in vitro* and *in vivo* experiments. Hence, the identification of new peptide inhibitors of Cx43 and Panx1 was reached by synthesizing peptide mimetics of the primary sequence of the two proteins and testing them for *in vitro* inhibition of ATP release, a significant indicator of (hemi)channel activity. To overcome some of the aforementioned limitations, a series of chemical strategies was used to conformationally and proteolytically stabilize the identified lead peptides. Among these strategies, the use of D-amino acids and cyclization through disulfide or triazole tethers resulted in compounds with half-lives exceeding 24 hours. Multiple Panx1-derived compounds were found to reduce ATP release at concentrations ranging from 1 to 300 µM, with some of them showing promising anti-inflammatory potential *in vitro*. Proteolytically stable compounds based on the lead CT10 showed activity at even lower concentrations (100 nM). Preliminary *in vivo* experiments revealed the therapeutic potential of the peptides.