SCIENCES & BIOENGINEERING SCIENCES

The Research Group

Organic Chemistry

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

Jolien De Neve

to obtain the degree of Doctor of Sciences

Title of the PhD thesis:

G protein signaling-biased μ-opioid receptor agonists and their incorporation in multitarget ligands containing non-opioid pharmacophores for improved pain therapy

Promotor:
Prof. Dr. Steven Ballet

The defence will take place on

Wednesday, September 25, 2024 at 5.00 p.m. in auditorium I.0.01

Members of the jury

Prof. Dr. Frank De Proft (VUB, chair)
Prof. Dr. Ulrich Hennecke (VUB, secretary)
Prof. Dr. Dimitri De Bundel (VUB)
Prof. Dr. Freija De Vleeschouwer (VUB)
Dr. Frédéric Simonin (Université de Strasbourg, France)
Dr. Maud Larregola (CY Cergy Paris Université, France)

Curriculum vitae

Jolien De Neve (°1996) obtained her Master's degree in Chemistry (Specialization Organic and Medicinal Chemistry) at the Vrije Universiteit Brussel in 2019. After graduating, she started her PhD in the Research Group of Organic Chemistry with a FWO scholarship. Her research resulted in three published peer-reviewed papers as a first author and two published peer-reviewed papers as a co-author. She presented her work at national and international conferences & meetings, and received a poster award at MOCS in Blankenberge (2019). During her PhD, Jolien supervised three master and two bachelor students, next to having coordinated many practical sessions.

Abstract of the PhD research

The development of safer analgesics is a main challenge in contemporary medicine. Moderate to severe pain is still treated with the "gold standard" opioids, such as morphine and fentanyl. Nonetheless, short- and long-term use of these drugs leads to adverse effects, such as respiratory depression, constipation, tolerance, physical dependence, and sedation. Respiratory depression in particular underpins the opioid crisis in both the USA and Europe, causing many deaths across these continents. The pharmacological action of opioids is mediated by the opioid receptors, among which the μ-opioid receptor (MOP) has proven to be most important in terms of analgesia, but unfortunately activation of this receptor also leads to most side effects. In this work, two strategies were developed to overcome the latter. One strategy consists of the design of molecules inducing G protein-biased signaling at MOP. Biased MOP agonists have been suggested to attenuate the detrimental effects of opioids. Additionally, partial agonism at MOP also results in a favorable side effect profile. In this context, different MOP-targeting peptidomimetic ligands containing *N*-alkylated and constrained amino acids were designed, giving way biased and/or partial MOP agonists, as determined by *in vitro* pharmacological evaluation. A second strategy aims at the development of opioid/non-opioid hybrids, wherein the non-opioid receptor systems are also involved in pain signaling. These hybrids induce enhanced analgesia or alleviate side effects through an additive or even synergistic effect between the opioid and non-opioid pharmacophore. In this work, a focus was placed on the development of opioid-neuropeptide FF and opioid-neurotensin hybrids. After *in vitro* and *in vivo* evaluation of a series of OPFF peptides, two lead peptides, **DP32** and **DP50**, displayed a favorable profile. Importantly, the most dangerous side effect, respiratory depression, was not observed when testing these peptidomimetics. *In vitro* evaluation of a new OPNT series, on the other hand, resulted in promising lead compounds with high affinity for MOP and the NTS2 receptor, showcasing a half-life superior to 48 h. **SBL-OPNT-13** and **-18** displayed low β-arrestin-2 recruitment, but favorable partial G protein signaling at MOP. *In vivo* evaluation of these compounds showed an analgesic effect stronger than morphine in an acute tail beam pain model. Altogether, several lead compounds with highly promising profiles were unraveled in this work. Their further preclinical validation will demonstrate if they represent a gateway towards safer analgesics.