PhD position available in Organic Chemistry / Medicinal Chemistry

Synthesis of fluorinated Angiotensin II analogs as constrained biased ligands for cardioprotective activity

Institution: CY Cergy Paris Université
Doctoral School: Science and Engineering (n°417)
Research Unit: BioCIS, *Equipe de Chimie Biologie* – UMR-CNRS-8076
PhD Supervisors: *Dr Simon GONZALEZ, Prof. Grégory CHAUME*
PhD duration: 3 years – Starting between October 2025 and January 2026
Funding: ANR JCJC 2025
Application Deadline: Open until filled

Context and Project Objectives:
Cardiovascular diseases, one of the leading causes of death worldwide, are closely linked to **hypertension**, a major risk factor associated with the Renin-Angiotensin System (RAS) and its key effector, **angiotensin II (Ang II)**.[1] This octapeptide acts on a G protein-coupled receptor, AT_1R, triggering adverse effects through Gq protein recruitment. However, certain **Ang II** analogs, known as **biased ligands**, can selectively recruit beta-arrestin2, inducing **cardioprotective effects**.[2] Developing such biased analogs offers a *promising strategy for antihypertensive therapies*. Recent studies have highlighted the importance of **Ang II** C-terminal region — in particular its **size and flexibility** — for biased signaling.[3] We previously showed that fluoroalkyl groups significantly influence peptide structure and physicochemical properties.[4] Based on this, we aim to introduce tri- and difluoromethylated (**Tfm** and **Dfm**) amino acids into **Ang II** analogs to obtain more stable and efficient beta-arrestin2-biased ligands. These analogs will be assessed by collaborators for functional selectivity (Inserm) and docking studies within the receptor binding pocket (BioCIS, Saclay).

Job Description:
In this interdisciplinary and challenging project, the PhD student will be responsible for **synthesizing fluorinated constrained amino acids** (derived from Phe and Pro, varying the fluoroalkyl group and its position) and **incorporating them into the Ang II peptide sequence**. Preliminary results have helped define the synthetic conditions to access cyclic trifluoromethylated analogs,[5] and the laboratory has solid expertise in handling fluorinated amino acids in demanding peptide syntheses.[4] The student will work in a dynamic and collaborative environment, within a young team skilled in amino acid and peptide synthesis, bioactive peptide design, structural analysis, biological evaluation (with potential mobility to Inserm, Toulouse), and molecular modelling. Based at the BioCIS laboratory, the PhD candidate will interact closely with collaborators and contribute to the project's progress.

Candidate's Requirements*:*
The ideal candidate should be highly motivated to work at the interface between chemistry and biology. A Master's degree in Chemistry (or an equivalent qualification) is required, along with strong theoretical and practical knowledge in organic synthesis and in the characterisation of organic compounds. Prior experience in fluorine chemistry and/or peptide chemistry will be considered as an asset, as well as a good level of English.

To apply: send CV, cover letter, reference letter(s) and Master degree marks/evaluation to *simon.gonzalez1@cyu.fr*.

References:

[1] Joseph, P., *et al.*, *Circ. Res.* **2017**, 121, 677.
[2] Delaitre, C., *et al.*, *Int. J. Mol. Sci.* **2021,** *22*, 6738.
[3] Wingler, L. M., *et al.*, *Science* **2020,** *367*, 888.
[4] Chaume, G., *et al.*, *J. Org. Chem.* **2017,** *82*, 13602.
[5] Loisons, L., *et al.*, In *37th European Peptide Symposium*, Florence, Italy, **2024**; p https://doi.org/10.17952/37EPS.2024.P2024.