Master 2 internship in Grenoble

Diaziridines synthesis for chemoselective methionine bioconjugation

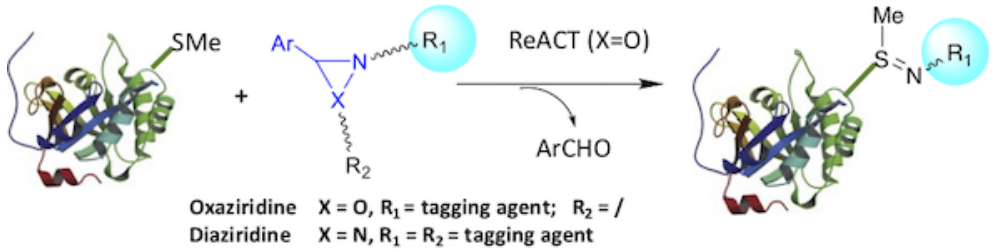
Département de Chimie Moléculaire (DCM)

Team : SERCO "Synthèse et Réactivité en Chimie Organique"

Context

Chemical modification of native amino acids (lysine, cysteine, and to a lesser extent tyrosine) is largely used for protein bioconjugation, however selectivity control is an issue. An emerging trend is to target less frequently occurring amino acids such as methionine (Met).[1] Met is naturally scare (2.5%) and its expression at specific positions on the surface of a protein is possible by site-directed mutagenesis.

The ReACT methodology, involving a chemoselective reaction of Met with oxaziridines has recently become a method of choice to target Met residues in protein bioconjugation.[2] However, it suffers from an unproductive *O*-transfer pathway competing with the desired *N*-transfer. In this project, we propose to study the potential of diaziridines as sulfur imidation agents acting through selective *N*-transfer process.



Objectives

The objective of the internship is to develop the synthesis of original diaziridines and to explore their potential in sulfur imidation reactions with the aim to develop new tools for the chemoselective bioconjugation of peptides / proteins containing at least one methionine residue. The reactivity of diaziridines with methionines will be investigated and compared to that of oxaziridines recently used in the ReACT (Redox Active Chemical Tagging) methodology. We will specifically target symmetrical diaziridines carrying an azide or alkyne function that will serve as a functional handle to conjugate proteins with various labels or biomolecules (carbohydrates, lipids) through click chemistry. Such selective transformations are expected to represent a new method to modulate the biological and physicochemical properties of proteins.

Competences: Classical methods of organic synthesis, NMR and other spectroscopic analytical methods.

Candidate's profile

The candidate must be endowed with good knowledge of organic chemistry and interest in chemical biology. He/she will be expected to acquire a good knowledge of the literature related to this project and to harness it for the benefits of the project.

Application

Applicants are invited to submit a full CV, a motivation letter, and academic transcripts for the last 2-3 years by email to Sandrine Py (sandrine.py@univ-grenoble-alpes.fr).

Deadline for application: 01/12/2024 – **Internship**: 6 months, starting January or February

[1] N.L. Kjærsgaard, T.B. Nielsen, K.V. Gothelf, Chemical Conjugation to Less Targeted Proteinogenic Amino Acids, ChemBioChem. 23 (2022) e202200245. https://doi.org/10.1002/cbic.202200245.

[2] S. Lin, X. Yang, S. Jia, A.M. Weeks, M. Hornsby, P.S. Lee, R.V. Nichiporuk, A.T. Iavarone, J.A. Wells, F.D. Toste, C.J. Chang, Redox-based reagents for chemoselective methionine bioconjugation, Science. 355 (2017) 597–602. https://doi.org/10.1126/science.aal3316.