



PhD Thesis (2024-2027):

Enzyme-directed photocatalytic assembling of inhibitors for drug discovery **(Laboratory COBRA, UMR 6014, CNRS, University of Rouen Normandy)**

Key words: Drug discovery, Photochemistry, Organic chemistry, Bioconjugation, Enzyme-guided synthesis.

Funding: Institutional funding (University of Rouen Normandy)

Expected starting date: December 1st, 2024

Gross salary: 2250 €

Project overview: Kinetic target-guided synthesis (KTGS) is a fragment-based drug discovery (FBDD) approach in which the protein of interest (POI) is able to both select good binders and promote their linking through irreversible bond formation, in a single-step process.¹ In situ click chemistry, pioneered by Sharpless and colleagues, is the most used KTGS reaction for the identification of multisite ligands. However, this strategy requires significant entropic contributions to overcome high activation barriers, which can result in a long incubation time (up to several days), when tolerated by proteins, to counterbalance its low reactivity.²

Based on this observation, we investigated for the first time the use of a photochemical transformation as a complementary ligation approach, to accelerate KTGS reactions to an unprecedented level (Photo-KTGS).³ This research program aims to combine bioconjugation with Photo-KTGS to develop new reactions with no background activity.

Candidate profile: We are looking for highly motivated candidates with a strong interest in working at the interface of chemistry and biology. This multidisciplinary project will involve organic synthesis, bioconjugation, LC-MS/MS analyses, and enzymatic assays. Experience in bioconjugation or protein purification would be a plus.

Application procedure: A detailed curriculum vitae, a short research summary, and two contacts able to provide a recommendation letter have to be sent to:

cyrille.sabot@univ-rouen.fr & pierre-yves.renard@univ-rouen.fr.

¹ E. Oueis, C. Sabot, P. Y. Renard, *Chem. Commun. (Camb.)* **2015**, *51*, 12158–12169.

² A. Lossouarn, P.-Y. Renard, C. Sabot, *Bioconjugate Chem.* **2021**, *32*, 1, 63–7.

³ C. Puteaux, I. Toubia, L. Truong, M. Hubert-Roux, L. Bailly, H. Oulyadi, P.-Y. Renard, C. Sabot, *Angew Chem. Int. Ed.* **2024** (<https://doi.org/10.1002/anie.202407888>).