

## PhD Proposal

# Synthesis and characterization of hemiindigoids as water-operable photoswitches and isomer-dependent acetylcholinesterase inhibitors

<b>Funding:</b>	PEPR LUMA
<b>Directors:</b>	Dr Romain Haudecoeur (DPM) & Prof. Frédérique Loiseau (DCM)
<b>Doctoral school:</b>	EDCSV, University Grenoble Alpes
<b>Location:</b>	Grenoble
<b>Specialty:</b>	Chemistry-Biology
<b>Expected start date:</b>	Between October 1, 2025 and December 1, 2025

This PhD thesis is part of HELIOPHORE project,<sup>1</sup> a national collaborative program supported by PEPR LUMA, involving four laboratories with complementary expertise, from theoretical chemistry to animal biology. The HELIOPHORE project aims at applying hemiindigoid-based photoswitching compounds to photopharmacology by (1) deciphering the photoswitching properties of these systems in water and physiological media through systematic series of molecules studied both experimentally and theoretically, a blind spot of the existing studies; (2) designing hemiindigoid-based inhibitors of acetylcholinesterase (AChE), an enzyme involved in Alzheimer's disease (AD), with isomer-dependent activity, by relying on a very encouraging preliminary prototype; (3) translating the *in vitro* potential to *in vivo* outcomes through a progressive pipeline of assays involving complex biological media, human cells, zebrafish larvae and transgenic AD mice, with a constant focus on the dark-vs.-light activity.

The PhD student will be the primary contributor for chemical synthesis and photophysical characterizations within the project, by joining two adjacent laboratories of the Grenoble chemistry site, DPM<sup>2</sup> and DCM.<sup>3</sup> The role of the candidate will be (1) to design and synthesize series of compounds by mobilizing heterocyclic chemistry already partly developed (DPM); (2) to study the photochromic properties of the compounds in various solvents, especially by measuring key parameters such as photostationary states, thermal half-lives and quantum yields (DPM and DCM); (3) to perform the first step of biochemical evaluations by assessing the isomer-specific activity of the compounds over isolated human AChE and related enzymes, as a go-no go test for further *in vitro*, *in vivo* and preclinical assays led by biologist partners (DPM).

The candidate must hold a Master's degree in Chemistry, preferably in Organic Chemistry or Chemical Biology, and have a solid laboratory experience in chemical synthesis. Strong motivation, open-mindedness, ability to take initiative and work autonomously, and a willingness to learn beyond the initial discipline are important prerequisites for this thesis, which lies at the interface of organic chemistry, photophysical chemistry, and biochemistry. A knowledge of spectroscopic and photochemical techniques would be appreciated but is not mandatory.

**To apply, please send a complete application file including a CV, academic bachelor and master transcripts, a motivation letter, and letters of recommendation or reference names, to the following addresses: [Romain.Haudecoeur@univ-grenoble-alpes.fr](mailto:Romain.Haudecoeur@univ-grenoble-alpes.fr) & [Frederique.Loiseau@univ-grenoble-alpes.fr](mailto:Frederique.Loiseau@univ-grenoble-alpes.fr) as soon as possible.**

<sup>1</sup><https://www.pepr-luma.fr/projet/heliophore/>

<sup>2</sup><https://dpm.univ-grenoble-alpes.fr/>

<sup>3</sup><https://dcm.univ-grenoble-alpes.fr/>