Ecole Doctorale des Sciences Fondamentales

Title of the thesis: Development of original analgesic agents based on protein-protein interactions inhibition.

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Summary :

The design of molecules aimed at targeting Protein-Protein Interactions (PPI) is an emerging field in medicinal chemistry. The objective of this project is to conceive original analgesic agents, based on this innovative approach. It relies on expertise developed by the «Peptoid»[1,2] and « CESMA »[3] research groups of the Institute of Chemistry of Clermont-Ferrand (ICCF).

The goal of the project is to design and synthesise protein-protein interactions inhibitors using a peptidomimetic approach, notably peptoid oligomers. Peptoids are a class of peptidomimetics composed of *N*-substituted glycines monomers. They present key advantages over peptides, including a greater metabolic stability and better cell permeability. Expertise of the «Peptoid» group on the folding of this family of compounds will be used to control the conformation of the synthesised oligomers.

One part of the project will focus on the interaction between the PDZ protein, PSD-95, and the serotonin receptor 5-HT_{2A}. It was shown recently that a nonapeptide related to the C-terminus of 5-HT_{2A} is able to inhibit the targeting interaction and that this inhibition is accompanied by an analgesic effect in mice suffering from neuropathic pain.

The ability of the molecules to interact with PSD-95 will be assessed by HSQC $^{1}H/^{15}N$ NMR experiments and the analgesic properties of the most promising inhibitors will be evaluated in vivo as part of a collaboration with the team of Prof. Courteix of Neurodol Institute.

[1] C. Caumes, O. Roy, S. Faure, C. Taillefumier *J. Am. Chem. Soc.* **2012**, *134*, 9553-9556.
[2] G. Angelici, N. Bhattacharjee, O. Roy, S. Faure, C. Didierjean, L. Jouffret, F. Jolibois, L. Perrin, C. Taillefumier *Chem. Commun.* **2016**, *52*, 4573-4576.
[3] A. Vogrig, L. Dorr, N. Bouzidi, B. Boucherle, A.-S. Wattiez, E. Cassier, G. Vallon, I. Ripoche, I. Abrunhosa-Thomas, P. Marin, L. Nauton, V. Thery, C. Courteix, L.-Y., Lian, S. Ducki *ACS Chem. Biol*. **2013**, *8*, 2209–2216.

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