

Proposition de thèse 2020 – Equipe CASYEN Andrioletti

Title: Synthèse de nouveaux agents théranostiques fluorescents type BODIPY à base de carbènes métalliques.

Design and synthesis of new theranostic metal-carbene complexes with a built-in fluorescent BODIPY dye.

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Key words: anti-cancer drugs, theranostic agents, carbene synthesis, multi-step organic and organometallic synthesis, fluorescence.

Main context: “Theranostic” is a contraction between “therapy” and “diagnostic”. Theranostic agents are built-in with a therapeutic agent covalently linked to a luminescent molecule to allow for a real-time monitoring of the drug delivery and its release at the targeted cells (**Figure 1**). Today, the idea is to track the anticancer drugs in the organism, to follow their distribution and to monitor the response of the organism to the treatment.

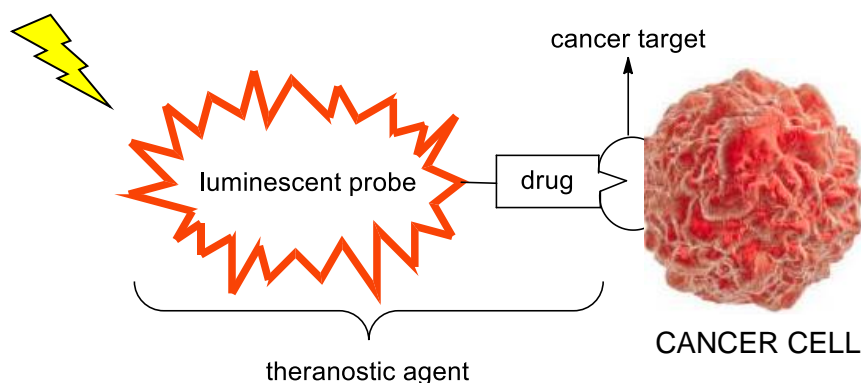


Figure 1 Theranostic agent

Cisplatin (**Figure 2**) and its derivatives are among the most widely used anticancer drugs. However, regarding their severe side effects, some derivatives are required. In contrary to platinum, gold anti-inflammatory drugs like auranofin (**Figure 2**) are still in clinical trials for the treatment of cancer, but they are very promising because these drugs limit the inflammation phenomena usually caused by classical anticancer drugs.

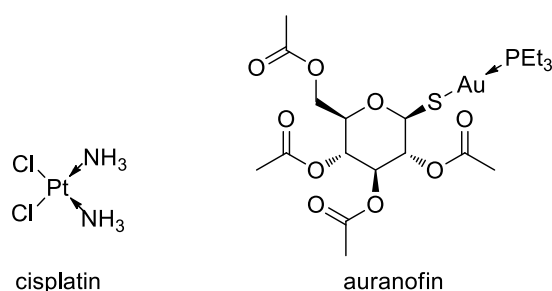


Figure 2 Structures of cisplatin and auranofin

Research project: In this project, we want to develop a theranostic agent comprising a BODIPY (BORon DIPYrromethene) as the imaging probe and a metal-based drug composed of gold- or ruthenium-carbene.

BODIPYs are fluorescent dyes composed of a dipyrromethene core complexed with a disubstituted boron center (BF₂ in our case) (**Figure 3**). In our group, we have developed an acknowledged expertise in the design and in the preparation of novel BODIPY structures^{1,2} that will be beneficial for the development of this project.

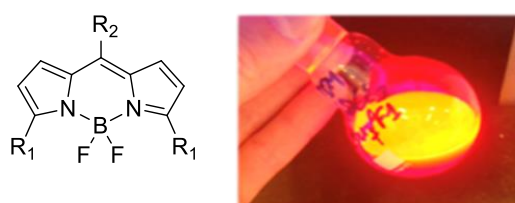


Figure 3 BODIPY structure and example of fluorescence

The research project will be divided in two parts:

- Firstly, we will synthesize various BODIPY molecules with the metal carbenes inserted at the positions R₁. The fluorescence of all these molecules will be studied in detail to provide rapidly some interesting publishable results. (All the synthesized fluorophores will be fully characterized using classical analyses like NMR, mass spectroscopy and also fluorescence spectroscopy.)
- Secondly, depending on the observations obtained in the first part, the metal will be functionalized by strategic groups to obtain a positive therapeutic response.

This PhD proposal requires a highly-motivated candidate willing to perform multi-step synthesis towards the development of new metallic-BODIPY theranostic agents. Partnership with laboratories or companies specialized in the clinical evaluation of the different molecules synthesized will also be part of the PhD. After these 3 years, the future PhD holder will have gained knowledge in the design and synthesis of organic and organometallic dyes as well as in the analyses of the photophysical characterizations and some applications in the biomedical field.

¹ Guérin, C.; Jean-Gérard, L.; Octobre, G.; Pascal, S.; Maury, O.; Pilet, G.; Ledoux, A.; Andrioletti, B. *RSC Adv.* **2015**, *5*, 76432-76345.

² Jean-Gérard, L.; Vasseur, W.; Scherninski, F.; Andrioletti, B. *Chem. Commun.* **2018**, *54*, 12914-12929.