Proposition de thèse 2019 – Equipe CASYEN Andrioletti

Title: Synthèse de nouveaux agents théranostiques fluorescents type BODIPY à base de platine et d'or.

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

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

Main context: "Theranostic" is a contraction between "therapy" and "diagnostic". Initially, theranostic agents were composed of a probe associated to a specific disease marker. They helped the specialists to determine the best treatment (therapy) according to the type of disease diagnosed thanks to these theranostic agents. Now, theranostic agents are built-in with a therapeutic agent and 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.

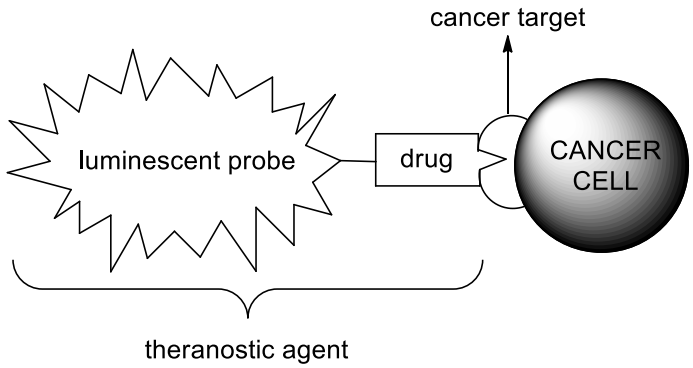

Figure 1 Theranostic agent

Project: In the first part of this project, we want to develop a theranostic agent composed of a BODIPY (Boron DIPYrromethene) as the imaging probe and a metal-based drug. BODIPYs are fluorescent dyes composed of a dipyrromethene core complexed with a disubstituted boron center (BF_2 in our case) (**Figure 2**). In our group, we have developed some expertise in the design and in the preparation of novel BODIPY structures[1,2] that will be of great help in this project.

[1] Guérin, C.; Jean-Gérard, L.; Octobre, G.; Pascale, 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.

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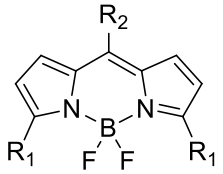
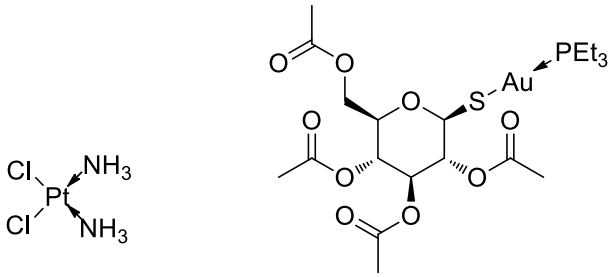


Figure 2 BODIPY structure

The metal-based drug could be composed of platinum or gold. Cisplatin (**Figure 3**) is one of the most widely used anticancer drugs. However, regarding its severe side effects, some derivatives are required. Within this project, we ought to synthesize novel platinum drugs grafted to a fluorescent BODIPY structure.



cisplatin auranofin

Figure 3 Structures of cisplatin and auranofin

In contrary to platinum, gold anti-inflammatory drugs like auranofin (**Figure 3**) are still in clinical trials for the treatment of cancer, but they are very promising because these drugs should limit the inflammation phenomena usually caused by classical anticancer drugs. As such, gold-BODIPY complexes will be studied as potential new theranostic agents. (All the synthesized metal-BODIPY molecules will be fully characterized using classical analysis like NMR, mass spectroscopy and also fluorescence spectroscopy.)

BODIPYs are known to be excellent photodynamic agents and have been studied as ideal candidates for photodynamic therapy (PDT). PDT consists in generating singlet oxygen ($^1O_2$) from triplet oxygen ($^3O_2$) using a photosensitizer and light. The $^1O_2$ generated thus kills nearby cancer cells.
To be a good PDT agent, the BODIPY needs to be structurally modified to allow for the generation of triplet excited states by intersystem crossing (ISC). The most common way to do that is to introduce heavy atoms (known as the “heavy atom effect”).
The metal-BODIPY theranostic agents prepared above might be promising candidates for PDT and will thus be tested. Precedents in the literature describing some BODIPYs as good theranostic agents and photosensitizers are very encouraging.

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 specialized in the clinical evaluation of the different molecules synthesized will also be part of the PhD.

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