

## Design of photo-activable molecules for new therapeutic strategies (Vers de nouvelles thérapies combinées à l'aide de molécules photo-activables)

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**Summary** -- In this project, we aim to develop an efficient approach for the synthesis of water-soluble polyheteroaromatic derivatives capable of photo-converting and releasing several molecules with biological activities. By optimizing the photo-physics of these heteroaromatics, we anticipate biological applications in which these new biologically inactive derivatives will be designed to be activated in vivo and will have multiple therapeutic actions, including the activation of G-quadruplexes and the generation of singlet oxygen.

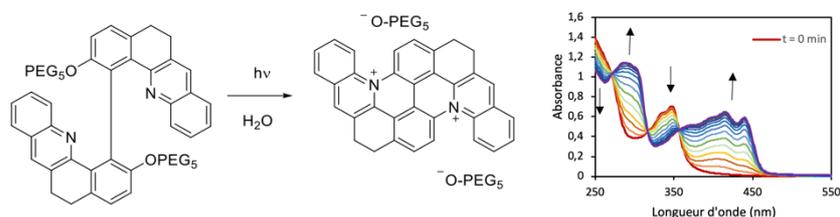
Managing the number of cancer patients is putting public health systems under considerable pressure. Today's cancer treatments (chemotherapy and radiotherapy) are highly invasive because they are poorly targeted, leading to numerous undesirable side-effects and a deterioration in patients' quality of life. This project proposes an original approach to therapy derived from dynamic phototherapy (activation by light).

In human cells, the ends of chromosomes are made up of repeated DNA sequences ending single stranded DNA called a "telomere", in which two conformations are known the G-quadruplex and the T-loop. The shortening the telomeres leads to cell death and is counterbalanced by the action of telomerases, whose role is to allow elongation and conservation of telomere size. On the other hand, this senescence is a very powerful anti-tumour mechanism because it limits cell proliferation. Since the recent discovery of the role of G-quadruplexes (or G4), targeting these motifs with small organic molecules has become a promising therapeutic strategy in the treatment of cancer and certain viruses that base their cellular action on overexpression of telomerase.<sup>1</sup>

The molecules able to achieve this objective have structural similarities with molecules developed in the Supramolecular Chemistry and Biological Chemistry axis of the Laboratoire de Chimie at ENS Lyon. The possibility of generating a photocyclisation reaction under controlled light irradiation conditions was demonstrated (see Figure 1) and leads in a single step to an extended polyheteroaromatic compound, a new member in the azonia family. This compound exhibits a degree of aromatic delocalisation that is difficult to achieve using conventional synthesis methods, while retaining good water solubility.

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<sup>1</sup> G.W. Collie et al. Chem. Soc. Rev., 2011, 40, 5867 <doi: 10.1039/c1cs15067g> ; Shivalingam, A. et al. Nat. Commun. 2015, 6:8178 <doi: 10.1038/ncomms9178>

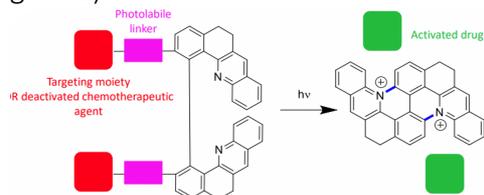


**Figure 1:** Evolution of the UV-visible spectrum during cyclisation ( $c = 35 \mu\text{M}$ ) by continuous excitation at 350 nm in water.

The interaction efficiency of the diazonia product with G4 units was measured and found to be similar to that of CX-5461, a G4 stabilizer in clinical trials for cancer therapies. At the same time, the singlet oxygen generation quantum yield of 0.55 places this new diazonia among the best photosensitizers to date used in photodynamic therapy (PDT) of cancers.

This background and the preliminary results presented above are the basis of this project.<sup>2</sup>

The synthetic aspect is at the heart of this thesis project, the aim being to explore the versatility of the proposed approach to generate a whole family of pro-drugs with various substitution motifs for (i) targeting cellular organelles, (ii) liberating a drug, or (iii) promoting internalization (as schematically proposed in Figure 2).



**Figure 2:** New pro-drugs under consideration

From an application point of view, we will test the hypothesis that this photo-induced transformation could be an innovative way of treating cancer. This study will be carried out by biologists either at cell level (Umea University Sweden M. Deiana, N. Sabouri) or on spheroid tumour models (Ecole Centrale de Lyon/ILM M. Frénéa-Robin, C. Rivière).

**Candidate profile** -- We are looking for a candidate with a master's degree in chemistry with a strong interest in making functional molecular systems to study their physico-chemical properties. Knowledge of synthetic chemistry is a must, and knowledge of in photochemistry would be a clear advantage for this project. The candidate will learn to work independently and in a multidisciplinary setting in collaboration with photophysicists and biologists. Good oral and written communication skills and English proficiency would be a plus for the dissemination of the results (publications, conferences...).

<sup>2</sup> Guy et al *Nanoscale*, 2021,**13**, 13795-13808 <doi: 10.1039/D1NR02855C>