PHD POSITION

New photo-generated diazonia derivatives, their photophysics and biological applications.

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Context The synthesis of novel polycyclic-aromatic and poly-heteroaromatic compounds is a very challenging issue in modern synthetic chemistry. As a general statement, the synthesis of such extended polyaromatics is rarely an easy task: protocols used for the creation of carbon-carbon bounds and the aromatization of the structure generally involve harsh conditions, hazardous reagents and most often operate with moderate to low (or very low) yields. **Thus, the development of milder, more efficient and environmentally friendly approaches is a fundamental objective to further expand the scope of that chemistry.**

Poly-heteroaromatic ligands interacting with G-quadruplex (G4) have attracted great attention as potential anticancer therapies or in molecular probe applications.[1] G4s are well-known nucleic acid secondary structures found for example in the telomere region of the chromosomes. They have major implications for many pharmacological and biological events, including the proliferation of cancer cells while they are involved, together with the telomerases, in the lengthening of the telomeres. Reported G4s linkers[2] show enticing features such as: (i) an extended aromatic core maximizing pi-stacking interactions between the guanines of the G-quartet planes and aromatic rings of the ligand, (ii) positive charges capable of interacting with the negative charges of the phosphates of the DNA backbone, (iii) functionalized side chains for additional interactions with the nucleic bases at the loops or grooves formed by the winding of the DNA.

For several years, we have been developing synthesis routes for inherently chiral helicene-like polyaromatic compounds, such as water-soluble compound **1a** accessible at gram scale as pure enantiomer (Figure 1).[3] Very recently,[4] we discovered that **1a** undergoes a photochemical cyclization in water affording the new compound **2** which presents a good water solubility despite its extended poly-heteroaromatic skeleton. According to its structure, 2 constitutes a new member of the diazonia family of molecules.[5] We demonstrated in a preliminary study that **2** binds efficiently to DNA (K_d> 20 µM with *ds*-DNA). More interestingly, it possesses a remarkable selectivity to G4 motives (K_d <2µM with Tel-22, K^+ for example). Meanwhile, the molecule from which it is derived (**1a**) has no particular affinity for these biomolecules. At the same time, we have shown that compound **2** is a very effective photosensitizer. The singlet oxygen quantum yield measured in water is 0.6 ranging **2** among the best photosensitizers used in cancers dynamic phototherapy (PDT) up today.[6]

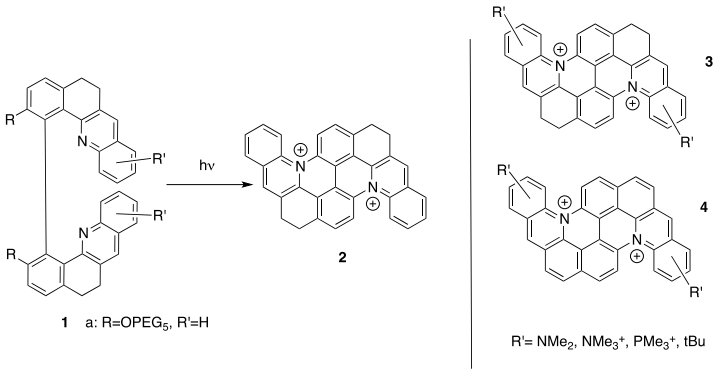

Figure 1 : Photochemical synthesis of diazonia **2** and targeted new compounds **3** and **4** .

Description of the project In continuity of these preliminary results, we propose a PhD project presenting several objectives:

- On a synthetic point of view, it will explore the versatility of the proposed approach to generate a whole family of diazonia compounds with various substitutions motifs either aimed at tuning their

spectroscopic properties (electron donating or withdrawing substituents, side aromatic groups, etc.) or their bioavailability (introduction of cationic chains, see 3 and 4 Fig. 1)

- On an applicative point of view, advantage will be taken of this photoinduced transformation to propose an innovative modality of cancer treatment. The proposed therapeutic mechanism proceeds in two steps. The first step corresponds to the penetration into the cell of a non-toxic pro-drug (1 shown in Figure 1). Once the target is reached, irradiation will liberate active diazonia compounds (2, 3 or 4 in Figure 1) with two toxicity pathways for the cell: PDT and G4 stabilization. Noteworthy, the molecules that are the subject of our study have a luminescence allowing following their intracellular location by imaging.

Profile and skills required The candidate should have a good knowledge of organic synthesis and heterocyclic chemistry and show a real motivation for photophysical measurements. The candidate will be encourage to participate and closely follow the biological studies which will be conducted in collaboration of several teams in Lyon (Dr. Yann Leverrier, Pr. Renaud Mahieux) and abroad (Pr. Nasim Sabouri and Dr. Marco Deiana in Umea Swenden).

1 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> 2 S. Asamitsu et al. Chem. Eur. J. 2019, 25, 417 <doi: 10.1002/chem.201802691>; S. Asamitsu Molecules 2019, 24, 429. <doi: 10.3390/molecules24030429>; Chilka P. Molecules 2019, 24, 752. <doi: 10.3390/molecules24040752> 3 L. Guy et al. Journal of Organic Chemistry, 2019, 84 (17), 10870. <doi: 10.1021/acs.joc.9b01465> <hal-02316017>; L. Jierry, L. Guy, et al. Organic Letters, 2011, 14 (1), 288. <doi: 10.1021/ol202799j> ⟨hal-01898650⟩ 4 To be submitted 5 D. Sucunza et al. Journal of Organic Chemistry, 2016, 81(21), 10126 <doi: 10.1021/acs.joc.6b01092> 6 Bonnett, R. Chemical Society Reviews 1995, 24(1), 19 <doi:10.1021/jp5088515>