PROPOSITION SUJET DE THESE 2019-2022
PhD PROPOSAL 2019-2022

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Synthesis and conformational studies of constrained fluorinated nucleosides.

Synthèse et étude conformationnelle de nucléosides fluorés à conformation contrainte.

Keywords: nucleosides, electrochemistry, photoredox catalysis, fluorine, NMR, biological studies.

CONTEXT: Modified nucleosides and oligonucleotides are relevant compounds for the development of antisense therapies against various diseases including diabetes, cancers, some viral infections or the amyotrophic lateral sclerosis. The interest of the scientific community for these molecules has resulted in the generation of drug-candidates in clinical development[1] while some of them are already commercialized (Fomivirsen, Mipomersen, Nusinersen, Eteplirsen). The main benefit brought by modified nucleosides is a higher stability in biological media when their natural counterparts (Figure 1a) are efficiently degraded by nucleases making their pharmacokinetic properties limited. A strategy to access modified nucleosides/oligonucleotides relies on the *freezing* of the furanose ring conformation. The introduction of a new cycle to the furanose residue constitutes a frequently explored approach to provide « Locked Nucleic Acids (LNAs) and « Bridged Nucleic Acids » (BNAs) (Figure 1b).[2] Such conformational locking disturbs the recognitions by enzymes like nuclease then slowing degradation processes. Another promising but underexplored approach aims to synthesize « Constrained Nucleic Acids » (CNAs) for which the conformation is constrained by spiro moieties (Figure 1c). [3] Indeed, recent studies supported by structural analyses (NMR, X-rays, molecular mechanics calculations) have demonstrated that the presence of 5 and 6 membered spiro cycle could improve significantly the thermal stability of oligonucleotides.[3d] Additionally, the introduction of polar residues and heteroatoms onto the spiro scaffold was suspected to be a crucial optimization step in order to access to better clinical candidates. In the meantime, some spiro nucleosides have displayed significant antiviral activities against human coronavirus while displaying high selectivity and no cytotoxicity.[3b] Consequently, several elegant syntheses of spiro nucleosides[3] have been described in the literature. However, most of these approaches require numerous synthetic steps, the use of cryogenic conditions, expensive catalysts and only provide poor structural diversity. These high cost and complexity issues constitute the main barriers to large-scale developments. By considering the

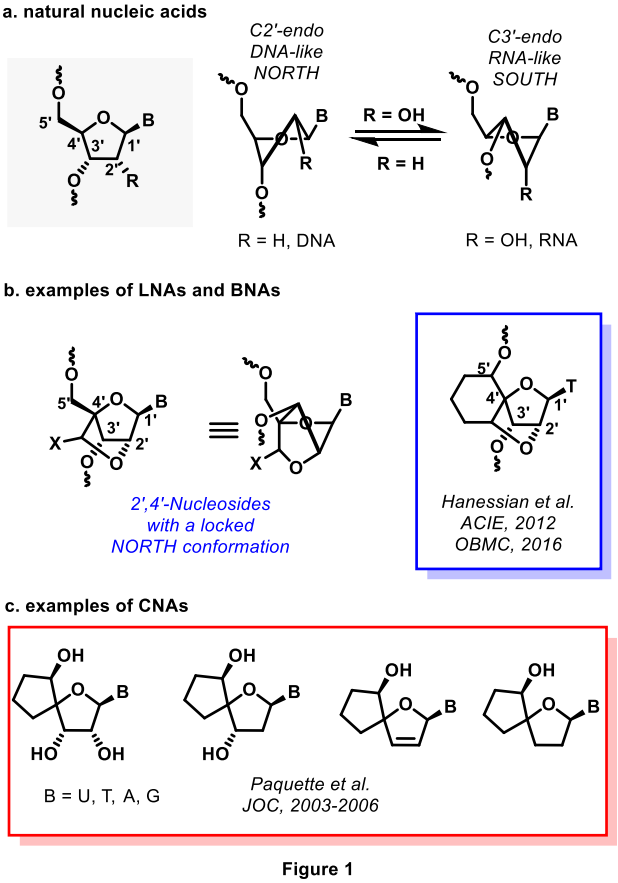

Figure 1

[1] Swayze, E. E.; Bhat, B. The Medicinal Chemistry of Oligonucleotides. In *Antisense Drug Technology: Principles, Strategies and Applications*, 2nd ed.; Crooke, S. T., Ed.; CRC Press: Boca Raton, FL, 2007; pp 143-182.

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[3] (a) Dong, S.; Paquette, L. A. *J. Org. Chem*. **2006**, *71*, 1647. (b) Paquette, L. A.; Kahane, A. L.; Seekamp, C. K. *J. Org. Chem*. **2004**, *69*, 5555. (c) Paquette, L. A.; Seekamp, C. K.; Kahane, A. L. *J. Org. Chem*. **2003**, *68*, 8614. (d) Hanessian, S.; Schroeder, B. R.; Giacometti, R. D.; Merner, B. L.; ØStergaard, M.; Swayze, E. E.; Seth, P. P. *Angew. Chem. Int. Ed*. **2012**, *51*, 11242. (e) Giacometti, R. D.; Salinas, J. C.; ØStergaard, M. E; Swayze, E. E.; Seth, P. P.; Hanessian, S. *Org. Biomol. Chem*., **2016**, *14*, 2034.

high therapeutic potential of these compounds, the emergence of original, easy and direct strategy to access CNAs is yet highly appealing. A method providing a broad structural modularity (notably by the efficient introduction of polar residues) would be particularly useful.

PROJECT: The group of M. Médebielle (ICBMS) is involved in the development of redox processes to access fluorinated derivatives with strong interest in fine chemistry and therapeutics. [4] To achieve this goal, electrochemical and photocatalytic strategies are extensively explored. [5] Based on previous achievements,[4b] we envision to set up a new synthetic route to spiro nucleosides relying on electrochemical or photoredox-catalysed cyclizations between various fluorinated enones and nucleosides bearing an exo-cyclic olefin (Figure 2). Preliminary results have established the feasibility of this radical tandem cyclization to build spiro compounds derived from simple carbohydrates (unpublished results).

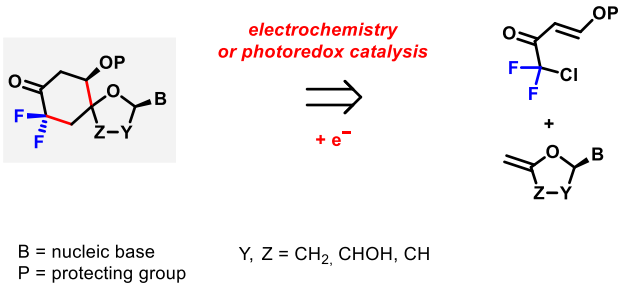

Figure 2

The present project would involve several steps of development:

- The implementation of a direct and simple access to the substrates:
  - Nucleosides with an exocyclic olefin derived from natural uridine, thymidine, adenine, guanine and cytosine but also with modified nucleic bases and furanose cycles.
  - *Gem*-difluoroenones with different stereoelectronic properties.

- Electrochemical studies (determination of the redox potentials of the substrates based on cyclic voltammetry experiments)

- The development of a reliable synthesis by a) electrochemistry or b) photoredox catalysis of the target molecules on a preparative scale.

- Extensive investigations would be done to determine the influence of the structural modifications to the conformation. Notably, NMR studies would be conducted in collaboration with a group at the Institut des Sciences Analytiques (ISA - UCBL).

- The synthesized nucleosides will be converted into oligonucleotides at the MacGill University (Canada) to investigate their biological activity.

- In conclusion, this proposal involves the development of original synthetic methodologies and the use of conformational studies to rationalize the preparation of biologically active molecules. It then constitutes a long-term project including several aspects of molecular sciences.

FORMATION: the candidate will receive a solid formation in organic synthesis with a strong emphasis onto the development of radical-based redox processes. He/she will be confronted to essentials technics of modern organic chemistry that are electrosynthesis and photoredox catalysis. Moreover, he/she will be pushed to investigate the stereoelectronic behaviour of the synthesized compounds by specific analytic methods (cyclic voltammetry, NMR conformational studies…). The candidate will have the opportunity to study the bioactivity of the prepared molecules during short stays in Canada (2 x 3 months).

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