Aix*Marseille université | Ecole Doctorale des Sciences Chimiques ED250 | Contrats Doctoraux **2020**

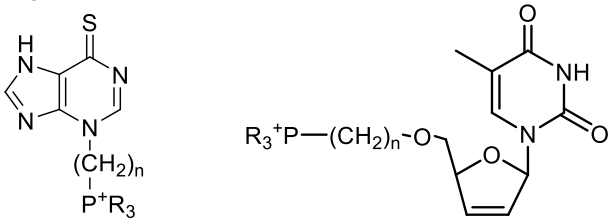
Title : Nucleoside and nucleobase phosphonium derivatives as antibiotics and biofilm inhibitors.

Laboratoire : CINaM – CNRS UMR 7325 (Dir. Pr. Pierre Muller)
PhD Supervisor: Dr. Michel Camplo (michel.camplo@univ-amu.fr, phone: 06 17 24 81 75)
Keywords: nucleosides, antibiotics, phosphonium ionic liquids.

Project description:

Our team is developing molecules derived from phosphonium ionic liquids[1] particularly efficient (CMI = 0.5 mg/L) against *Staphylococcus aureus* a bacteria responsible for a large part of nosocomial infections. Some of these molecules displayed fluorescent properties that could allow us to understand their bacterial penetration mechanism. However, although these drugs can be used as biomaterials for surface treatment, they cannot be developed as *in vivo* antibiotic mainly because of their toxicity. One possible way to reduce this cytotoxicity will be to couple these ionic liquids to commercially available drugs. Among them nucleobase and nucleoside analogue drugs (NNADs) that have already proved antibacterial properties[2] could represent a valuable approach. Indeed, the antibacterial potential of NNADS has not been fully exploited yet but it is likely that these molecules possess a different mechanism of action than our phosphonium liquid ionic and therefore might have a synergistic effect on bacteria.

The purpose of this project is to combine the NNADs with phosphonium ionic liquids to make a new class of molecules capable to inhibit the bacterial growth by different mechanism of action. Such molecules (examples below) would be derived from both cyclic and acyclic nucleosides which are commercially approved drugs.



Mercaptopurine and Stavudine derivatives

Moreover this amphiphilic molecules are susceptible to self assembled to form nano-object which could be of interest for delivering. These molecules will be designed in regards to their biological potential, their physicochemical properties as well as their feasibility for appropriate and straightforward synthesis that will be discussed with the candidates.

Study context:

The world health organization raises alarm regularly about the emergence of new bacterial resistances to today's antibiotics suggesting that action must be taken urgently to develop new antibacterial agents.[3] It is hoping that the new class of molecules that we described in this project will fulfill these goals and reinforce the existing therapeutic arsenal.

Application terms:

The candidate should send a CV together with a motivation letter to Dr Michel Camplo.

References:

1- (a) Brunel, F., Lautard, C., Garzino, F., di Giorgio, C., Raimundo, J-M., Bolla, J-M. and Camplo, M. Antibacterial activities of mono-, di- and tri-substituted triphenylamine-based phosphonium ionic liquids.. *Bioorg Med Chem Lett Aug* Mar 1; 28(5): 926-929 (2018) b) Brunel, F., Lautard, C., Garzino, F., Giorgio, S., Raimundo, J-M., Bolla, J-M. and Camplo, M. Antibacterial activities of fluorescent nano assembled triphenylamine phosphonium ionic liquids. *Bioorg Med Chem Lett* Aug 20; 26(15):3770-3 (2016) c) Raimundo, JM et al. EP 3590343 A1 20200108 (2020).
2- (a) Yssel, A.E.J., Vanderleyden, J. and Steenackers, H.P. Repurposing of nucleoside and nucleobase-derivative drugs as antibiotics and biofilms inhibitors. *J.Antimicrob. Chemother*. 72, 2156-2170 (2017); (b) Serpi, M., Ferrari, V. and Pertusati, F. Nucleoside derived antibiotics to fight microbial drug resistance : new utilities for an established class of drugs. *J. Med.Chem.* 59, 10343-10382 (2016).
3- (a) Antimicrobial resistance: global report on surveillance. World Health Organization, (2014). (b) O'Neill, J. Tackling Drug-Resistant infections globally: Final report and recommendations (2016).