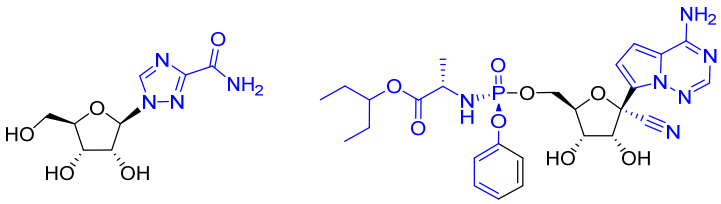
PhD Fellowship CNRS – Région Pays de la Loire
(3-years contract from 2022, october)

Synthesis of new inhibitors of proteic targets fighting emerging viral diseases

Since the beginning of the COVID-19 pandemic, there have been more than 6 million deaths in the world. The current pandemic reminds us of our vulnerability to viruses, especially emerging RNA viruses (SARS-CoV, MERS, SARS-CoV-2, Zika, Dengue, Chikungunya, Ebola, etc.). As examplified by nucleosides such as remdesevir or ribavirin, this family of compounds represents in this fight, more than half of the antivirals on the market. In this context, our research program plans to design and evaluate new antivirals against these viruses emerging. The objective of this PhD thesis is part of a rational approach for the design and the development of original nucleoside analogues within a national GAVO program (Generation of Original Antivirals). In support of this work, the biological evaluation of these analogues originals on a large panel of viruses, will be carried out by a consortium of virologists and biologists (ViroCrib, INSB-CNRS).



Ribavirine
Herpès, Adénovirus

Remdesivir
Virus Ebola

Based on the model of C-nucleoside Remdesivir and based on the expertise of our team on the synthesis of nucleoside analogues,[1] the work of the PhD student will be focused on the development of the 1 'position of natural nucleosides to lead to a generation of new antivirals. For this, one of the objectives in this first phase of the PhD thesis will aim to provide a variety of original chemical modifications, from key saccharide precursors having teir synthesis already validated in our hand.1

Thus, via this synthesis strategy that we master, a series of C-nucleosides comprising original nucleobases will be targeted in order to evaluate new original analogs of remdesivir, not accessible by current synthetic strategies. The inhibitory activity of new nucleoside candidates against viral strains available on the platforms of the ViroCrib consortium, will be evaluated in parallel with the synthesis to establish relevant pharmacomodulation elements. These results can be analyzed and interpreted within the GAVO consortium thanks to the contribution of bioinformaticians specialized in the targeted protein of interest. [2] On the other hand, the introduction of relevant functional groups in position 5' du ribose will complete this PhD thesis project and will also aim to produce prodrugs of nucleosides as new and more efficient derivatives, in order to consider their evaluation *in cellulo* or *in vivo*.

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[1] Synthesis of novel *C*-nucleoside analogues bearing an anomeric cyano and a 1,2,3-triazole nucleobase as potential antiviral agents. Sierocki P. ; Gaillard, K. ; Arellano Reyes, R.A. ; Donnart, C. ; Lambert, E. ; Grosse, S. ; Arzel, L. ; Tessier, A. ; Guillemeont, J. ; Mathé-Allainmat, M. ; Lebreton, J. *Org. Biomol. Chem.* **2022**, *20*, 2715-2728. DOI : 10.1039/D1OB02451E

[2] Autophagy and evasion of immune system by SARS-CoV-2. Structural features of the Non-structural protein 6 from Wild Type and Omicron viral strains interacting with a model lipid bilayer. Bignon, E. ; Marazzi, M. ; Grandemange, S. ; Monari, A. BioRxiv *2022*, DOI : 10.1101/2022.01.05.475107.