Version Francaise

Intitulé du Sujet de Thèse: Development of novel broad-spectrum antivirals targeting *Enterovirus* capsid through medicinal chemistry and structure-guided design

Laboratoire : Institut de Chimie Radicalaire (ICR), CNRS UMR 7273, Aix-Marseille Université
Equipe: Pharmacochimie Radicalaire (PCR)

Directeur de thèse HDR (100%) : Thierry TERME

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Subject / Objective

Enteroviruses represent a persistent global public health threat, being responsible for a wide spectrum of diseases ranging from mild infections to severe complications such as neurological disorders, myocarditis, and ocular infections. The recent emergence of more virulent variants, notably EV-A71 and EV-D68, associated with severe neurological manifestations, highlights the urgent need for the development of new therapeutic strategies. To date, no specific antiviral targeting enteroviruses is available in clinical practice.

This PhD project aims to develop new antiviral inhibitors targeting the viral capsid protein VP1, a key component involved in viral attachment and entry into host cells. The conserved hydrophobic pockets of this protein represent a strategic opportunity for the design of broad-spectrum antivirals.

Building on previous work conducted in the laboratory, which led to the synthesis and evaluation of more than 400 compounds, this project seeks to optimize initial "hit" molecules displaying micromolar to submicromolar antiviral activity to identify new "lead" candidates **[1–9].**

The project will rely on a multidisciplinary strategy integrating computer-aided drug design, innovative medicinal chemistry approaches (including radical photocatalysis) **[10]**, in vitro biological evaluation, and pharmacokinetic optimization (ADMET studies and formulation strategies). The goal is to identify broad-spectrum drug candidates targeting enteroviruses and polioviruses, paving the way for future preclinical development.

Figure 1 – Overall schematic of the research project

Scientific Contribution and Innovation

This PhD project will:
- Contribute to the development of broad-spectrum antiviral agents.
- Implement a unique multidisciplinary approach combining medicinal chemistry, biology, and molecular modelling.
- Address a major European public health priority related to emerging viral infections.
- Potentially lead to the filing of a patent for a promising lead compound.

Skills Developed by the PhD Candidate

- Advanced medicinal chemistry
- Innovative organic synthesis
- Molecular modelling and computer-assisted drug design
- Structural analysis of ligand–target interactions
- Translational drug discovery approaches

Références Bibliographiques associées au projet

1. Roche M et al. Synthesis, biological activity, structure-activity relationship of 4,5-dimethoxybenzene derivatives inhibitor of rhinovirus 14. Eur. J. Med. **2014**, 76, 445
2. Lacroix C, Roche M et al. A novel benzonitrile analogue inhibits rhinovirus replication. J Antimicrob Chemother. **2014**, 69, 2723.
3. Da Costa L, Roche M et al. VP1 crystal structure-guided exploration, optimization of 4,5-dimethoxybenzene-based inhibitors of rhinovirus 14 Eur. J. Med. Chem. **2016**, 115, 453.
4. Da Costa L, Roche M et al. Heterocyclic pharmacochemistry of rhinovirus antiviral agents: A combined computational and experimental study. Eur. J. Med. Chem. **2017**, 140, 528.
5. Da Costa L, Roche M et al. Structure-Based Drug Design of Potent Pyrazole Derivatives against Rhinovirus Replication. J. Med. Chem. **2018**, 61, 18, 8402.
6. Roux, H, Roche et al. From the "One Molecule – One Target – One Disease" Concept towards looking for Multi-Target Therapeutics for Treating Non-Polio Enterovirus (NPEV) Infections. Pharmaceuticals. **2024**, 17, 9, 1218.
7. Roux, H, Roche M et al, New Potent EV-A71 Antivirals Targeting Capsid. Eur. J. Med. Chem. **2024**, 276, 116658.
8. Roux, H, Roche M et al. Design and Synthesis of Novel Thioether Analogs as Promising Antiviral Agents: Evaluation of In Vitro Activity against Enteroviruses of Interest. Eur. J. Med. Chem. **2025**, 288, 117395
9. Roux, H, Roche M et al. Non-Polio Enterovirus Inhibitors: Scaffold, Targets, and Potency, What's New? ACS Infect. Dis. **2025,** 11, 1, 21.
10. Zhao, Y, Broggi. J et al Switching from single to simultaneous free radical and anionic polymerization with enamine-based organic electron donors. Angew. Chem. Int. Ed., **2021**, 60, 19389.

English version

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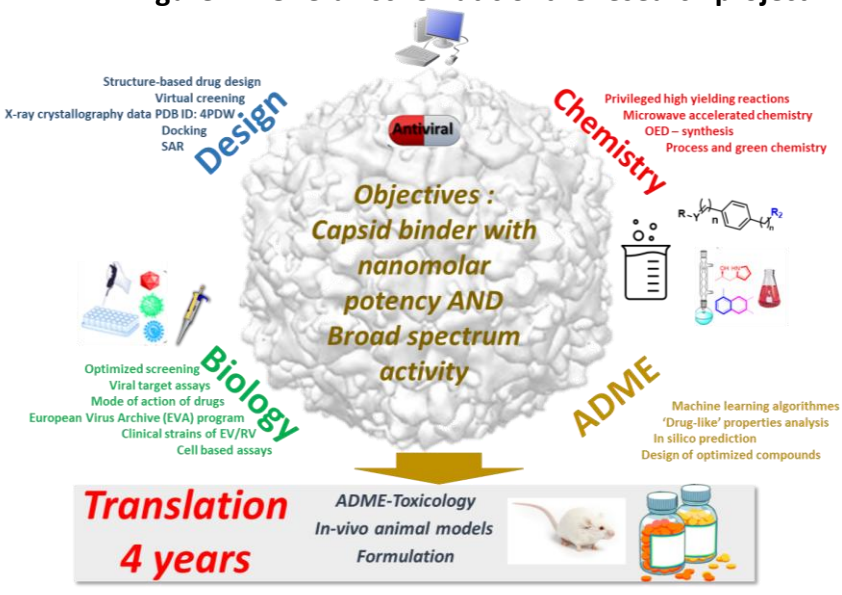

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