University of Naples Federico II
Department of Pharmacy
Doctoral Course in Pharmaceutical Sciences XL Cycle

Title: Design and Synthesis Studies of New Therapeutic Agents for Acute and Chronic Viral Infections

The project is developed in the contest of a large European consortium belong the Horizon Europe framework program, titled "Antiviral Therapeutics for Rapid Response Against Pandemic Infectious Diseases-Avithrapid"*

Human evolution has been punctuated by pandemics caused by viruses that have profoundly influenced its course. A relevant example is the most recent COVID-19 pandemic, which has caused more than 7,000,000 deaths and incalculable economic damage. Due to these catastrophic events, the scientific community and society have recognized the importance of developing new therapeutic agents capable of blocking the replication of viruses and their transmission. While in the past antiviral therapies focused on the search for a single therapeutic agent for a single virus, today, considering recent experiences, efforts are being made to develop antivirals capable of inhibiting families of viruses, such as Flaviviruses and Coronaviruses (1,2), to create an arsenal of drugs available for current infections and for possible future emerging pandemics. The strategies for "Antiviral Drug Discovery" have therefore evolved. In particular, the preliminary study of the structural similarities of viral enzymes essential for replication has a primary importance in designing new agents. Essential viral enzymes that are highly conserved across various families, that have no human analogs, are preferred to obtain broad-spectrum agents with high selectivity and low toxicity for the host. This project is based on the design of molecules capable of interacting with essential viral enzymes highly conserved in different families. The design will be followed by a careful analysis of the synthetic feasibility of these molecules and their potential production on a multigram scale. The synthetic procedures will utilize all modern organic synthesis techniques with particular attention to green chemistry, organocatalysis, solid-phase synthesis, the use of supported reagents, flow chemistry, and microwave-assisted processes. Furthermore, the syntheses will include optimization and characterization studies of byproducts for the most promising molecules that require scale-up. Structural characterization will be conducted using modern analytical techniques such as NMR, UPLC-MS, and HPLC MS-MS. The project involves collaborations with other partner laboratories responsible for enzymatic and antiviral tests in BSL3-4 facilities, as well as for ADME-PK studies to support in vivo experiments on animal models for proof-of-concept efficacy, and acute and chronic toxicity studies conducted in OSR BSL3-4 animal facilities. Furthermore, IRCSS, big pharma e international research center responsible of clinical trial are part of the consortium. Finally, stability and formulation studies will be an integral part of progressing the preclinical candidate to the advanced stages of development. The project is fully integrated in the AVITHRAPID activities carried out in the WP1.

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1) Targeting SARS-CoV-2 proteases and polymerase for COVID-19 treatment: state of the art and future opportunities. Cannalire, R., Carmen Cerchia,C., Beccari,A.R., Di Leva, F.S., Summa,V. J. Med. Chem. 2022, 65, 4, 2716–2746. doi.org/10.1021/acs.jmedchem.0c01140

2) Broad-spectrum coronavirus 3C-like protease peptidomimetic inhibitors effectively block SARS-CoV-2 replication in cells: Design, synthesis, biological evaluation, and X-ray structure determination. Stefanelli, I.; Corona, A.; Cerchia, C.; Cassese, E.; Improta, S. Costanzi, E.; Pelliccia, S.; Morasso, S.; Esposito, F.; Paulis, A.; Scognamiglio, S.; Di Leva, F. S.; Storici, P.; Brindisi, M.; Tramontano, E.; Cannalire, R.; Summa, V. Eur. J. Med. Chem. - ISSN 1768-3254. - 253:(2023), p. 115311. [DOI: 10.1016/j.ejmech.2023.115311]

*https://avithrapid.eu/