Discovery of potent and selective Direct Antiviral Agents (DAA).

The recent Covid-19 pandemic unfortunately proved the devastating consequences of highly transmittable viral infection causing more than 750.000.000 infection and 7.000.000 deaths and a socioeconomic disaster. The pandemic made aware the scientific and non-scientific community about the relevance to study the viruses, their pathogenicity and transmissibility and more importantly the necessity to develop new antivirals to block the infection and transmission. In particular, it is fundamental develop Drug Discovery strategies to inhibit several classes of viruses (ie flavi viruses, corona viruses etc) to be ready for the next pandemic. All viruses have special proteins essential for their replication. These are the ideal targets for antivirals development because these proteins do not have any homologues in man. Developing antivirals acting against these essential viral enzymes result in blocking the viral replication. The selective mode of action has also a consequence to have a very clean safety profile of these drugs. The present project is based on the design and synthesis of new molecules able to inhibit the essential viral targets like proteases, helicase, polymerases etc in the active, allosteric and PPI binding sites. The selection of the target will be focused on the one with high homology to have a pan-virus profile of the new inhibitors. Similar to what has been done for the corona viruses protease (1,2). The project includes several aspects of the drug discovery process, starting from the design and synthesis utilizing all modern techniques including green chemistry to prepare the compounds. All modern technique for their characterizations and purifications, enzymatic assays and antiviral assays in BLS3 labs of project partners to assess their antiviral potency and profiles, scale up of the most promising compounds to support all ADME experiments and the efficacy proof of concept in relevant animal models, acute and chronic toxicity conducted in the animal facility BLS3 of OSR . Finally, studies of stability and formulation will be integral part of the project in order to guarantee the transfer of the molecules to the next level of development.

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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. EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY. - ISSN 1768-3254. - 253:(2023), p. 115311. [DOI: 10.1016/j.ejmech.2023.115311]