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## ENZYMOMOLOGY AND MOLECULAR BIOLOGY

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**Inhibition of the RNA-dependent RNA polymerase activity of *Flavivirus* NS5 by heterocyclic compounds**Giuseppe Manfroni<sup>1</sup>, Rolando Cannalire<sup>1</sup>, Eloise Mastrangelo<sup>2</sup>, Gilles Querat<sup>3</sup> and Violetta Cecchetti<sup>1</sup><sup>1</sup>Università degli Studi di Perugia, Italy<sup>2</sup>Consiglio Nazionale delle Ricerche, Italy<sup>3</sup>Aix-Marseille University, France

Among more than 70 related members of *Flavivirus* genus, Dengue virus (DENV), West Nile virus (WNV), Japanese encephalitis virus (JEV), Yellow fever virus (YFV) and Zika virus (ZV) are considered (re)-emerging pathogens that were originally endemic in the tropical regions but recently are spreading also in a wider geographic area. Indeed, there are several environmental, demographic and ecological factors that promote the worldwide diffusion of known and/or novel *flaviviruses*. *Flaviviruses* can produce from mild flu-like symptoms to hemorrhagic fevers, hepatitis and neuropathies, such as encephalopathy, meningitis and microcephaly in human embryos depending on the infective agents. Vaccines are available against YFV, JEV, TBEV and more recently against DENV but the coverage is far from being complete. Moreover, the lack of an effective and specific therapy further worsens the scenario. The RNA-dependent RNA polymerase (RdRp) of the non-structural NS5 protein is one of the most favored targets to find new potential anti-*Flavivirus* drugs. With the aim to find new inhibitors of the RdRp we undertook a research program exploiting, consecutively, two different approaches: i) A virtual screening carried out on the NS5 polymerase domain (DENV RdRp, 2J7U) followed by a biochemical validation on the isolate target, and ii) a direct biochemical screening carried out on DENV NS5 polymerase with the intent to not exclude any potential hit compounds eventually missed during the *in silico* procedures. Both these approaches were realized using an in-house library of about 200, published and unpublished, compounds previously designed and synthesized as HCV NS5B inhibitors. To validate the potential of the identified hits, an anti-viral activity against a panel of *Flavivirus* was evaluated. The two strategies led us to identify new RdRp inhibitors able to reduce the polymerase activity in the low micromolar range. In particular, the *in silico* procedure (i) was fruitful for the identification of a pyridobenzothiazole which was extensively characterized with biochemical and structural studies; the second approach (ii) led us to identify functionalized 2,1-benzothiazines with promising anti-RdRp activity, not emerged as hit compounds during the *in silico* studies (Figure 1). Also in this case, a representative compound derived from a chemical optimization was better characterized in biochemical and virological assays. The strategy applied in this study led us to identify new promising inhibitors of the NS5 polymerase, worthy of further optimization with the final aim to discover anti-*Flavivirus* agents.

**Biography**

Giuseppe Manfroni has graduated in Pharmaceutical Chemistry and Technology (2001) and received his PhD in Medicinal Chemistry (2006) from the University of Perugia (Italy). From 2006 to 2008, he worked as a Post-doctoral Researcher at the University of Perugia. From 2008 to date, he is an Assistant Professor in the Department of Pharmaceutical Sciences and is a Lecturer in Pharmaceutical Analysis. He has spent short periods as a Visiting PhD Student at Rega Institute for Medical Research (Leuven, Belgium) and at the Molecular Modeling Laboratory (University of Perugia) under the supervision of Professor Johan Neyts and Professor Gabriele Cruciani, respectively. He is the author of 40 papers and his research is mainly focused on Medicinal Chemistry of antiviral (HIV, HCV, and *Flavivirus*), antitumor and anti-inflammatory (p38 inhibitors) agents. He is an expert in the synthesis of heterocyclic compounds and microwave assisted synthesis.

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