

Computer-assisted design of new, potential HCV inhibitors

Sabrina Pricl^{1,*} Maurizio Fermeglia¹, Marco Ferrone¹, Stefano Manfredini²,
Angela Angusti², Roberto Di Santo³, Vladimir Frecer^{4,5}, Stanislav Miertuš⁴

¹*Computer-Aided Systems Laboratory, Department of Chemical Engineering -
DICAMP, University of Trieste, Piazzale Europa 1, I-34127 Trieste, Italy*

²*Department of Pharmaceutical Sciences, University of Ferrara,
Via Fossato di Mortara 19, I-44100 Ferrara, Italy*

³*“Istituto Pasteur-Fondazione Cenci Bolognetti”-Dipartimento di Studi Farmaceutici,
Facoltà di Farmacia, Università di Roma “La Sapienza”, Piazzale Aldo Moro 5,
I-00185 Roma, Italy*

⁴*International Centre for Science and High Technology, UNIDO, AREA Science Park,
I-34012 Trieste, Italy*

⁵*Cancer Research Institute, Slovak Academy of Sciences, SK-83391 Bratislava, Slovakia*

Hepatitis C (HCV) is a RNA virus with a genomic size of 9.4 kb. Since the advent of serological essays for HCV in 1990, it has been shown to be the major etiological agent for post-transfusion and sporadic non-A, non-B hepatitis worldwide. Unlike hepatitis B, which is associated with chronicity **only** in approximately 5% of adult infections, more than 80% of HCV-infected individuals develop chronic hepatitis. Moreover, a significant proportion of individuals (20-50%) are at risk of developing cirrhosis and hepatocellular carcinoma. The known modes of HCV transmissions are transfusions (including contaminated immunoglobulin preparations), occupational exposure and intravenous drug abuse.

HCV is a single stranded RNA virus within the *Flaviviridae* family. The structural proteins (E1 and E2) are encoded at the 5' end, followed by the non-structural proteins (NS2 to NS5B) that have various functions, including a helicase or protease (NS3), and a RNA polymerase (NS5).

To **this** date, IFN- α monotherapy and, more recently, combination therapy of ribavarin **ribavirin?** plus intron-A (Rebetron) are the only FDA approved agents that have demonstrated efficacy in the treatment of HCV infections. However, several steps in the HCV replicative pathway can be the targets for selective antiviral interventions.

In this work we present the results obtained **by** a combined effort of **structure-based molecular design, synthesis and testing of** new potential inhibitors of different enzymatic targets **of HCV**. In particular, **a variety of** computational techniques, ranging from molecular mechanics/dynamics, free energy **perturbation method** and QSAR **techniques** have been employed to design **effective** antiviral agents specific to HCV **derived from** nucleotide, **pseudopeptide** or diketoacid moieties.

* Presenting author. E-mail: sabrinap@dicamp.units.it; Web-site: <http://www.caslab.units.it>