Hepatitis C virus (HCV) is an 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. In USA alone, there are 175,000 cases of newly documented hepatitis C infections per year, and the number of HCV carriers has been estimated to be 4 millions. Unlike hepatitis B, which is associated with chronicity in approximately 5% of adult infections, more than 80% of HCV-infected individuals develop chronic hepatitis. Moreover, a significant proportion of individuals (20-50%) is at risk of developing cirrhosis and hepatocellular carcinoma. The known modes of HCV transmission are transfusion (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 date, IFN-alpha monotherapy and, more recently, combination therapy of ribivarin 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. For instance, the recent solution of the tertiary structure of an NS3 fragment complexed with a synthetic NS4 cofactor peptide, which appears to be an integral component of the proteinase structure, allows a rational approach to the design of protease inhibitors for this region.

In this work we used molecular modeling methods to derive QSAR for a series of inhibitors such as nucleoside analogues known to be active in the replication of the HCV viruses and for a series of protease inhibitors. In the next step we designed new inhibitors for the HCV using computer models of the receptors and rational structure-based molecular design methods. In addition, we applied computer assisted combinatorial chemistry approaches to design and optimize virtual libraries of enzyme inhibitors and performed *in silico* screening and scoring of these drug candidates.