Probing the activity of diketoacis as HCV NS5B polymerase inhibitors via detailed molecular modeling

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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. In USA alone, there are 175 000 cases of newly documented hepatitis C 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 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 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, development of inhibitors targeting the HCV polymerase activity has been explored and, only recently, approximately 200 compounds including alkyl-, phenyl-, pyrrole- and thiophene-substituted diketoacids have been evaluated in the HCV NS5 polymerase essay. Interestingly, some of the diketoacids also inhibits hepatitis B virus polymerase, and HIV reverse transcriptase.[1]

Under these perspectives, in this work we used molecular modeling methods to derive QSARs for diketoacids analogues already synthesized and known as active in the replication of the HIV viruses,[2] to carry out design of new, potential inhibitors for the HCV using computer models of the receptors and rational structure-based molecular design methods, and to apply computer assisted combinatorial chemistry approaches to design and optimize virtual libraries of enzyme inhibitors and perform *in silico* screening and scoring of the drug candidates.

References

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