SAR STUDIES ON INDOLYL DIKETO ACID DERIVATIVES AS HCV RNA-DEPENDENT RNA POLYMERASE INHIBITORS

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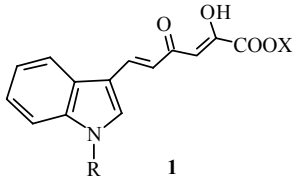
Hepatitis C virus (HCV) is a RNA virus of the *Flaviviridae* family. Since the advent of serological assays for HCV in 1990, it has been shown to be the major etiological agent for post-transfusion and sporadic non-A, non-B hepatitis worldwide. Further, it is estimated that the 3% of the world's population, or about 170 million people, are seropositive for HCV. Unlike hepatitis B, which is associated with chronicity in approximately 5% of adult infections, more than 80% of HCV-infected individuals develop chronic hepatitis. Chronic hepatitis C can lead to cirrhosis and end-stage liver disease in 20-30% of the patients and, among these, 1-4 % may develop hepatocellular carcinoma. The currently approved therapeutic protocol includes a combination of pegylated interferon and ribavirin. However, these regimens have limited efficacy (10-40% of the patients) and significant side effects, causing up to 20% of the patients to discontinue the therapy. As a result, there is an urgent need for developing safe and effective antiviral agents. In the last decade the development of inhibitors targeting the HCV NS5B polymerase (RdRp) has attracted the attention of investigators worldwide. Specific inhibitors for HCV RdRp were however not identified until recently. These include nucleoside analogues and various non-nucleosides from different chemical classes. Belonging to the latter group, over 200 compounds including alkyl-, phenyl-, pyrrole- and thiophene-substituted diketo acids (DKAs) were evaluated by Merck Company in the HCV NS5B polymerase assay: of these, several compounds demonstrated low micromolar IC_{50} values. Pursuing our studies on DKAs as inhibitors of viral and human polymerases, we recently designed and synthesized indolyl-2,4-dioxo-5-hexenoic acids **1** as HCV RdRp inhibitors [1]. A number of derivatives **1** showed interesting activity against recombinant HCV RdRp at micromolar concentrations. QSAR studies are ongoing to elucidate the binding mode of these inhibitors to the biological target.



1

R = CH_2CH_3, $CH_2CH_2CH_3$, C_6H_4CN, C_6H_4OH
X = H, CH_2CH_3

[1] R. Di Santo, R. Costi, A. Roux, S. Pricl et al. *J. Med Chem.* submitted.