Development of Potent Hepatitis C Virus NS5A Inhibitors

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Hepatitis C virus (HCV) infection is a life-threatening disease spread worldwide, often leading to serious ailments such as liver cirrhosis followed eventually by hepatocellular carcinoma. HCV gene products consist of structural and nonstructural proteins. Especially, several non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B) involved in theHCV reproduction process are of great importance for new therapeutic target identification. However, current standard of anti-HCV therapy has been the combination of pegylated interferon-α with ribavirin (Peg-IFN/RBV), until a recent addition of the HCV protease inhibitors, Boceprevier and Telaprevir. However, even with the protease inhibitors, sustained virologic response for genotype 1 is still about 60~80%. Therefore development of effective anti-HCV drug candidates is urgently needed. Recently NS5A has been a hotly pursued target for the HCV drug discovery and new inhibitor structures have emerged as promising therapeutic alternatives to existing treatments. Here we report the discovery of a series of extremely potent HCV NS5A inhibitors[1] based on the benzidine prolinamide skeleton.[2] Taking a simple synthetic route, we developed a novel inhibitor structure, which allows for easy modification, and facile optimization. Through our optimization process, we identified a series of inhibitors that exhibit sub-nano molar anti-HCV activities. Several interesting compounds were further evaluated with other pharmacological studies. Especially, our inhibitors have been found to be nontoxic and are anticipated to be effective HCV drug candidates.

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