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 nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B) involved in the HCV 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, Boceprevir 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 based on the benzidine prolinamide skeleton. 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.

REFERENCES