Marcin Sienczyk et al., J Antivir Antiretrovir 2016, 8:5(Suppl)
http://dx.doi.org/10.4172/1948-5964.C1.033

Development of novel inhibitors targeting NS3/4A protease of hepatitis C virus

Marcin Sienczyk, Marcin Skorenski and **Jozef Oleksyszyn**
Wroclaw University of Technology, Poland

Currently about 130-150 million people live with chronic hepatitis C virus infection worldwide of which many patients remain asymptomatic with a high chance of developing liver cirrhosis. One of the developed anti-HCV therapies target a serine protease crucial for viral replication-the bifunctional non-structural protein 3 (NS3/4A) of two separate functional activities: Serine protease and NTPase/RNA helicase activity. Moreover, due to its ability to destroy several important cellular proteins NS3/4A is able to block innate immune pathways and modulate growth factor signaling pathways. All of already approved for the treatment of HCV infection compounds display a reversible-type of inhibition. Nevertheless, the appearance of the inhibitor-resistant mutant strains limits the efficiency of the overall treatment. Irreversible protease inhibitors, such as α-aminophosphonic inhibitors, therefore, might represent a new therapeutic option. These compounds strike a balance between reactivity and chemical stability. Their mechanism of action relies on the phosphonylation of a serine residue which leads to the formation of an irreversible covalent complex. Here we report the design and biological evaluation of highly potent, active site-directed and irreversible inhibitors of HCV NS3/4A protease. One of the advantages of α-aminophosphonic inhibitors is their specificity of action toward serine proteases and lack of reactivity with cysteine, aspartyl and metalloproteinases. Considering high stability in human plasma, irreversible mechanism of action and low toxicity α-aminoalkylphosphonates represent an interesting class of inhibitors for novel antiviral agents' development.

Biography

Marcin Sienczyk was graduated in the Molecular Biotechnology and Biocatalysis program in 2002 from Wroclaw University of Technology and obtained his PhD in Medicinal Chemistry. In 2015 he was awarded Habilitation (DSc) in Biotechnology. He currently holds the position of Assistant Professor at Wroclaw University of Science and Technology. His research is focused on the development of compounds designed to target proteases involved in the pathogenesis of various diseases including cancer, bacterial or viral infections. He is a co-author of more than 40 papers, 14 patents and more than 25 pending patent applications.

marcin.sienczyk@pwr.edu.pl

Notes: