Marcin Sieńczyk, J Antivir Antiretrovir 2014, 6:2
http://dx.doi.org/10.4172/1948-5964.S1.021

OMICS Group Conferences
Accelerating Scientific Discovery

4th World Congress on
Virology

October 06-08, 2014 Hilton San Antonio Airport, TX, USA

Targeting hepatitis C NS3/4A protease with phosphonic-type inhibitors

Marcin Sieńczyk
Wroclaw University of Technology, Poland

Hepatitis C virus (HCV, HVC) is a small, enveloped, positive-sense single-stranded RNA virus of the Flaviviridae family. HCV can cause acute or chronic infection. An acute HCV infection is usually asymptomatic and is very rarely associated with life-threatening disease. About 15–45% of infected individuals spontaneously clear the virus within 6 months post infection without any treatment. The remaining 55–85% develop a chronic infection where the risk of liver cirrhosis is 15–30% within 20 years. It has been estimated that 130–150 million people live with chronic hepatitis C infectionworldwide and 350 000 to 500 000 people die each year from HCV-related liver diseases.

Since no effective vaccine for HCV is available, several potential molecular targets for anti-HCV therapy have been identified where a protease, which is a part of the bifunctional nonstructural protein 3 (NS3/4A), is one of the most well-studied. The proof-of-concept that the inhibition of NS3/4A protease leads to the reduction of plasma HCV RNA loads was established in 2003 with ciluprevir. In the next years several novel inhibitors of NS3/4A protease have been developed resulting in the introduction of telaprevir, boceprevir andsimeprevirto the market which are now used in combination with the standard therapy (pegylated interferon-α and ribavirin) for the treatment of HCV genotype 1.

All of already approved for the treatment of HCV infection compoundsdisplay a reversible-type of inhibition and their activity relies on an extensive interaction with P4-P1 binding sites of NS3/4A protease. The major problem associated with the anti-HCV therapy based on the inhibition of NS3/4A protease is the appearance of inhibitor-resistant mutant strains which limits the efficiency of the overall treatment.

Here we report the development of α-aminoalkylphosphonatediaryl- and difluoroalkylesters as well as their peptidyl derivatives as 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. Moreover, even for two serine proteases of similar substrate recognition profile,a selective and potent phosphonic inhibitor may be developed. Considering the stability in human plasma, irreversible mode of action and low toxicity α-aminoalkylphosphonates represent an interesting class of inhibitors for novel anti-HCV agents development.

marcin.sienczyk@pwr.edu.pl