

Virology

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

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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 and sime previrto 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 compounds display 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.

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