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Design and synthesis of selective, irreversible inhibitors of HAT protease: Promising drug target for influenza treatment

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The HAT protease also known as TMPRSS11D or airway trypsin-like protease is a member of the serine protease family. In humans, HAT is responsible for several biologically important processes including modulation of urokinase-type plasminogen activator receptor and fibrinogen processing. Moreover elevated level of HAT has been reported for patients suffering from chronic skin diseases (such as psoriasis) and respiratory tract dysfunction. Additionally, HAT was found to cleave the surface glycoprotein hemagglutinin of the influenza virus. Without this process, virus particles can not enter the host cell and start replication process, thus enzymes responsible for this cleavage are considered as promising drug targets for influenza treatment. The main objective of our research was the design and synthesis of selective, irreversible, active site-directed inhibitors of HAT protease. The target compounds belong to the group of phosphonic analogues of amino acids containing various, structurally diverse ester groups. These compounds are known as highly specific and irreversible inhibitors of serine proteases and have been successfully used as inhibitors of many physiologically important serine proteases such as thrombin, human neutrophil elastase, cathepsin G, proteinase 3, and dipeptidyl peptidase IV. Since the complete biological and physiological functions of HAT protease are yet to be discovered, the development of potent and specific inhibitors might provide very useful tools to study the HAT. Some recent reports consider HAT protease as a promising therapeutic target which inactivation could potentially limit the influenza virus infection hence the development of specific inhibitors might lead to a new class of antiviral agents.

Biography

Marcin Skorenski is PhD student at Wroclaw University of Technology, Faculty of Chemistry, Division of Medicinal Chemistry and Microbiology. His research is focused on the development of low molecular weight compounds designed to target proteases involved in the pathogenesis of viral infections (hepatitis C virus (HCV), West Nile virus (WNV) and herpes viruses, influenza). He is a Co-author of 5 papers, 14 patents and more than 10 pending patent applications.

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