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Design and synthesis of the O'nyong-nyong virus capsid protease inhibitors

ABSTRACT

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The O'nyong-nyong virus (ONNV) is an arbovirus belonging to the *Togaviridae* family *Alphavirus* genus. The main vectors responsible for ONNV transfer are mosquitoes of the *Anopheles* genus, *A. gambiae* and *A. funestus*. The disease caused by ONNV infection in humans is called O'nyong-nyong fever. This virus was first isolated in 1959 in Gulu (Uganda) and its name means '*severe joint pain*'. Over the following years ONNV reached Kenya, Tanzania, Malawi, Mozambique, the Democratic Republic of the Congo, Cameroon and Senegal, causing two large epidemics, resulting in over 3 million confirmed infections. The only confirmed ONNV infection outside the African continent was reported in 2013 in Germany.

The capsid protease (CP) of the O'nyong-nyong virus is a serine protease that plays a crucial role in the viral replication cycle. It is responsible for the process of autoproteolytic maturation of the structural polyprotein, which leads to the release of mature capsid protein C, as well as to the formation of other functional structural proteins responsible for the building of new virions as a consequence of further transformations.

The main goal of this dissertation was to design, synthesize and perform an enzymatic tests of the first phosphonic inhibitors and low-molecular activity-based probes of the CP ONNV, compounds belonging to the group of diaryl esters of 1-amino-alkanophosphonic acids. The remaining research works present the synthesis and characterization of new peptidyl substrates specific for the CP ONNV. The dissertation is complemented by the development of a kinetic test used to evaluate the activity of the CP ONNV and its inhibitors.

The research results allowed to determine the optimal structure of the side chain and the optimal ester group of diaryl esters of 1-aminoalkanophosphonic acid, and also identified the structure with the highest inhibitory potential, which was confirmed by enzymatic kinetic assays. This dissertation presents for the first time the effective methods

for the synthesis of phosphonic analogues of tryptophan using the α-amidoalkylation reaction in the presence of acid catalysts.

The presented results are the first comprehensive studies focusing on the development of substrates, inhibitors, and low-molecular activity-based probes with confirmed activity and specificity towards the O'nyong-nyong virus capsid protease. They constitute a solid foundation and provide a new direction for further research and the design of compounds with antiviral properties directed against the O'nyong-nyong virus as well as other representatives of the *Alphavirus* genus, which may become an effective tool against these virial infections in the future.