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Design and synthesis of the West Nile Virus NS2B/NS3 protease

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West Nile Virus (WNV) is a member of the flavivirus genus and belongs to the Flaviviridaefamily. For the first time WNV was isolated from human in 1937 in the West Nile district of Uganda. In 1953 it was identified in birds of the Nile delta region. Until 1997 WNV was not considered as pathogenic to birds when a more virulent strain appeared in Israel and caused death of various bird species with signs of encephalitis and paralysis. In 1999 apathogenic WNV strain was brought to New York leading to a dramatic outbreak which started to spread throughout the USA, Canadain the following years reaching northern countries of South America. Later the largest outbreaks of WNV appeared in Greece, Israel, Romania and Russia.

Although the lifecycle of WNV involves the transmission of virus between birds and mosquitoes, various mammalian species, including human and horses, can be infected. WNV is transmitted to people through the bites of infected mosquitoes, however about 80% of infected individuals do not show any symptoms of the disease. In cases where the symptoms occur, WNV can cause a fatal neurological disease. Unfortunately, no vaccinenoreffective treatment are available currently.

A viral trypsin-like serine protease: NS2B/NS3 has been considered as an attractive target for the development of novel anti-WNV agents. The primary function of this protease is the cleavage of viral polyproteinreleasing structural and non-structural viral proteins essential for virus replication and the assembly of new virus particles. An inactivation of NS2B/NS3 protease blocks the replication of the virus. Although severalNS2B/NS3 protease inhibitors have been described already, most of them are peptide aldehydes thus due to the high reactivity their application in vivois limited.

Herein we present a series of α -aminoalkylphosphonatediaryl esters as potent inhibitors of WNV NS2B/NS3 protease. These compounds represent a class of irreversible inhibitors that specifically and exclusively react with the active site serine residue of the protease leading to the formation of a stable, slow-hydrolyzing complex. One of the major advantage of α -aminoalkylphosphonatediaryl esters is lack of reactivity with cysteine, aspartyl and metalloproteasesas well as good stability in buffer and human plasma. In this work we presented a series of phosphonic analogues of lysine and arginine which could be considered as the promising starting templates for further structure optimization.

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