Research & Reviews: Journal of Medicinal Chemistry

Extended Abstract
Vol. 6, Iss. 2
2019

Advanced Chemistry 2019: Peptidyl derivatives of diaryl 1-aminoalkylphosphonates as a new potential antibacterial and antiviral agent - Jozef Oleksyszyn

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Statement of the Problem: The bacterial and viral infections are still serious health risk around the world. There is a need for new antibacterial and antiviral agent development. Peptidyl derivatives of diaryl 1-aminoalkylphosphonates are potent, irreversible and selective inhibitors of serine proteases including bacterial and viral serine proteases. The activities of these enzymes are crucial for survival of bacteria and in life cycle of certain viruses. Effective inhibitors of these enzymes could be a next generation of antibacterial and antiviral agents. Methodology & Theoretical Orientation: Applying the described earlier methodologies we have design and synthesized several new inhibitors for bacterial and viral serine proteases including chymotrypsin-like serine protease from Staphylococcus aureus SplA and SplB (1, 2), endoproteinase GluC (V8 proteinase) (3), subtilisin-like protease SufA from Finegoldia magna (4), protease CtHtrA from Chlamydia trachomatis (5) and viral protease NS3/4A of hepatitis C virus and N2B/NS3 protease from west Nile virus. Conclusion & Significance: Some of these inhibitors showed excellent activity in vitro and for inhibitors of serine protease from Chlamydia trachomatis the significant activity in vivo was observed. In general more in vivo studies are required.

Diaryl α-aminoalkylphosphonates and their peptidyl extensions (in short, peptidyl diaryl phosphonates) are well-known, powerful and selective mechanisms based on serine protease inhibitors. Due to the steric and electronic resemblance of the phosphorus moiety to the transition state of the peptide bond hydrolysis, the diaryl phosphonate esters are classified as analogous to the transition state. However, their mode of action is more complex than that presented by other phosphorus-containing pseudopeptides, and with an irreversible transesterification of the hydroxyl group of the active site serine, and the formation of a covalent enzyme-inhibitory bond. A phenol molecule of the accompanying release. During aging, the second phenol residue is also hydrolyzed to produce the final form of phosphorylated enzyme and therefore inactivated.

The potency, selectivity and specificity of the peptidyl diaryl phosphidates can be conveniently regulated by three complementary adjustments to their structural properties. Basically, the structure and configuration of the side chain substituent P1 should match the S1 binding pocket of the target enzyme. At the earliest stage of phosphonate development, it has been stated that effective binding, the absolute configuration of the α carbon of the aminophoshonate moiety is preferentially (R) which correlates to the configuration (S) of the acid homologs. Oleksyszyn and Powers used 31P NMR to show that a diastereoisomer of a peptidyl diphenyl phosphonate reacted more quickly. This was confirmed by solving the crystal structures of the serine protease - phosphonate complexes and obtaining enantiomeric phosphonates which exhibit high activity of (R) configuration. Second, the structure and reactivity of the leaving groups can be modified by appropriate substitution of the phenyl rings.

These modifications modulate the electrophilic properties of the phosphorus atom by electron withdrawal / donation effects. Initial binding on active sites within contacts, for example, for example, p-SMe, improvements to the specificity of inhibitors, assumes that added groups or functionality. Finally, the Sn-S2 region, which tightens the interactions within the N-terminal end of the basic aminophosphonate structure, can be extended by providing amino acids or peptides to extended derivatives. These peptidyl diastereoisomeric products are easily separated by chromatography. The aminophosphonate part of the configuration (R) is largely attributed to the epimer, which is more reactive with its enzymatic target.

Antivirals are a class of drugs used to treat viral infections. Most viral infections resolve spontaneously in immunocompetent individuals. The goal of antiviral

This work is partly presented on 2nd European Congress on Advanced Chemistry on May 09-10, 2019 held at Stockholm, Sweden

therapy is to minimize symptoms and infectivity as well as shorten the duration of illness. These drugs work at different stages of the viral replication of the cycle. Currently, antiviral therapy is only available for a limited number of infections. Most antivirals are currently used to treat HIV, herpes viruses, hepatitis B and C viruses and influenza A and B viruses. Because viruses are parasites in the intracellular mandatory, it is difficult to find drug targets that interfere with viral replication and even harming the host cells. Unlike other antimicrobials, antiviral drugs do not deactivate or destroy the microbe. the virus) but act by inhibiting replication. In this way, they prevent the viral load from increasing to a point where it can cause pathogenesis, which causes the body's innate immune mechanisms to neutralize the virus. This learning card provides an overview of the most commonly used antiviral agents. For more information on antiretroviral agents used in the treatment of HIV, known as highly active antiretroviral therapy (HAART), see Treatment of HIV