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Amides of antiviral drug oseltamivir with antioxidant active aminoacids: Synthesis and biological activities

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Introduction

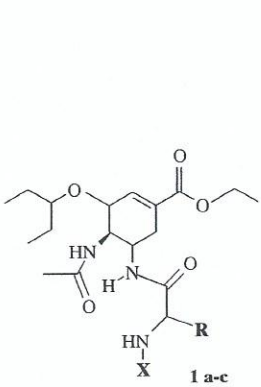
Annually, influenza infects approximately 600,000,000 people and causes epidemics and pandemics all over the world [1]. Influenza viruses belong to the family *Orthomyxoviridae* and have negative-sense, single-stranded RNA genome [2]. According to the antigenic difference in their nucleoproteins and matrix proteins, the viruses are divided into three genera: A, B and C [3]. To date, two strategies for combating influenza: vaccines and drugs are applied. The rapidly spreading influenza viruses and their mutation lead to limitation of protection through vaccination; therefore there is a great need to develop novel anti-influenza drugs.

Currently, four antiviral drugs have been approved by the Food and Drug Administration: aminoadamantanes (rimantadine and amantadin), known as M2 channel blockers and neuraminidase inhibitors (Zanamivir [Relenza] and Oseltamivir [Tamiflu]), belonging to the second generation anti-flu agents. Lately, the majority of research efforts are focused on the influenza neuraminidase, that is essential for virus replication and infectivity. This enzyme has become an attractive target for the development of new neuraminidase inhibitors, which have activity against both influenza viral types A and B.

Many investigators have shown that oxidative stress is important in the pathogenesis of pulmonary damage during influenza virus infections. Therefore, antioxidant could be one potential approach to chemotherapy for human influenza infection. The application of combination therapy of antioxidants with antiviral drugs could reduce the complications and lethal effects, caused by an influenza virus [4].

Results and Discussion

In our study, antiviral drug oseltamivir (Os) was conjugated to antioxidant active amino acid derivatives of cysteine, histidine and tyrosine, in order to indicate a possible advantage of chemically combining the two treatments during severe influenza infection. The C-terminus of the amino acids was converted to amide (**1a-c**) using EDC/ HOBt method (**Fig. 1a**). Initially, we evaluated the antioxidative activities (% RSA) of oseltamivir amides (**1a-c**) by use of the 1, 1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging test [5]. The effect of the tested activities was illustrated in **Fig. 1b**. The results were expressed as: % RSA = [Abs516 nm (t=0)-Abs516nm (t=t')]/Abs516 nm (t=0) x 100. It was established that conversion of amino acid derivatives into their Os analogues significantly decreased the DPPH scavenging abilities compared with positive control like *N*-Acetyl cysteine (ACC).

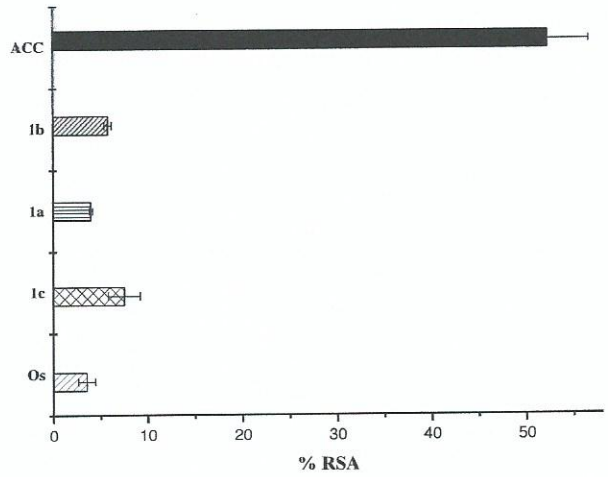


1a) Acetyl-Cys-**Os**

1b) Fmoc-Tyr(ᵗBu)-**Os**

1c) Boc-His(Dnp)-**Os**

a



b

Fig. 1.

Although DPPH assay has been widely used to conveniently test for determination of the free radical scavenging activity of compounds, the method is only chemical relevance and the system used is a homogenous solution. It has been known that the antioxidant activity in homogenous solutions may not parallel that in heterogeneous media (e.g. human red blood cells). Therefore, to evaluate the influence of microenvironment on antioxidative effect, the tested amides will be investigated in other antioxidant model.

Acknowledgments

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