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The anti-herpetic activity of fluorine-containing compounds based on β-D-glucopyranose

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Abstract: The diseases caused by Herpes Simplex Virus 1 (HSV-1) are widely spread. The shortage of antiviral compounds due to their high toxicity and emergence of resistant viruses is a major problem in the treatment of patients. This work is related to the determination of the antiviral activity of new fluorine containing derivatives against HSV-1.

Cytotoxicity and anti-herpetic activity of compounds **10S-25** (1-S-thio-(1- methylsulfonyl-2-difluoromethyl-vinyl)-2,3,4,6,-tetra-O-acetyl-β-D-glucopyranose) and **10S-27** 1-(β-D-glucopyranosyl)-4-(hexafluoropropyl)-5-tosyl-1H-1,2,3-triazole) were studied using MTT assay. To sort the compounds, four experimental procedures were used: co-incubation of compounds and HSV-1, addition of compounds during virus adsorption and penetration, addition of compounds post-infection. The antiviral activity was assessed using real-time PCR and virus yield reduction assay.

Compounds **10S-25** and **10S-27** demonstrated high toxicity for cells and their IC_{50} values were 13 and 250 μg/ml, respectively. It was determined, that only **10S-27** inhibited the formation CPE of the HSV-1 (EC_{50} value - 48 μg/ml). The absence of virucidal activity and prevention of the adsorption and penetration of HSV-1 into cells were shown for this compound. But in the presence of **10S-27** in higher concentration, HSV-1 DNA replication was inhibited and the viral DNA copy number was reduced to 38 %. Moreover, it was found that **10S-27** in concentrations 4 - 150 μg/ml reduced the titer of the virus obtained *de novo* by 39 - 98%. Taken together, our results showed that **10S-27** possesses an anti-HSV-1 activity at non-toxic concentrations with multiple mechanisms, but further investigation is needed to explore this action in detail.

Keywords: fluorine-containing compounds; herpes simplex virus 1; antiviral activity

Introduction

- Worldwide, an estimated 66 percent of the population has herpes simplex virus type 1 (HSV-1) infection. HSV-1 is typically transmitted from person to person via infected oral secretions during close contact. After initial infection, HSV-1 establishes chronic infection in neural ganglia and reactivates to mucosa and skin. Although infections are frequently asymptomatic, they can produce a variety of signs and symptoms. These include recurrent oral or perioral lesions ("cold sores"), skin and mucous membrane lesions, including genital lesions, ocular infections (eg, herpetic keratitis), and serious systemic illnesses such as encephalitis and neonatal disease involving multiple organs.
- Due to their high chemical and biological stability, fluorinated derivatives are prevalent building blocks in medicinal chemistry. The heterocyclic core of such compounds is stable to acidic and alkaline hydrolysis, to the action of reducing and oxidizing agents, and to the metabolic degradation by enzymes.
- For a large quantity of the fluorine-containing derivatives antiviral and antitumor biological activity was shown. That is why the synthesis of the new fluorinated compounds and the studying of the mechanisms of their action are promising for the development of efficient antiviral drugs of our time, as these compounds are characterized by significant bioavailability and rapid metabolism, high lipophilicity, adsorption and transport of the molecule *in vivo*, which leads to an improvement in their therapeutic effect and pharmacological activity.

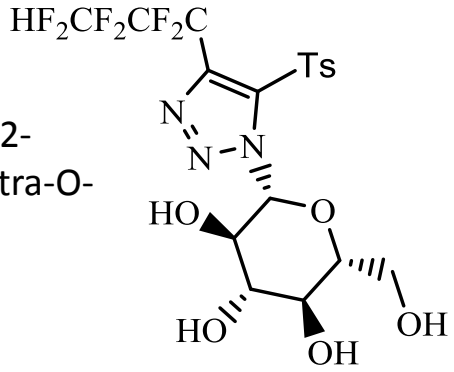
Results

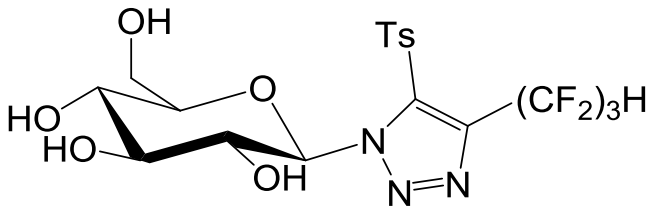
Test compounds

Novel fluorine-containing compounds synthesized in the Institute of Organic Chemistry of the NAS of Ukraine were studied:

10S-25

(1-S-thio-(1- methylsulfonyl-2-difluoromethyl-vinyl)-2,3,4,6,-tetra-O-acetyl-β-D-glucopyranose)





10S-27

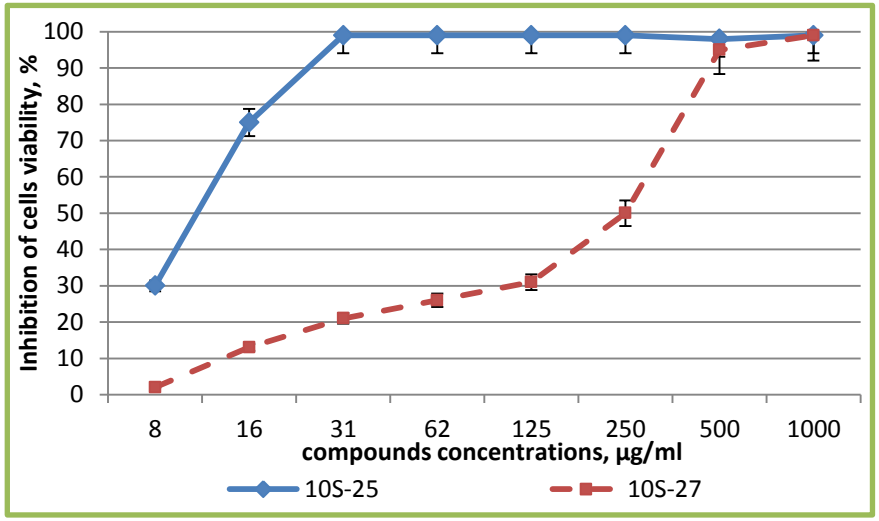
1-(β-D-glucopyranosyl)-4-(hexafluoropropyl)-5-tosyl-1H-1,2,3-triazole)

Cytotoxicity of test compounds

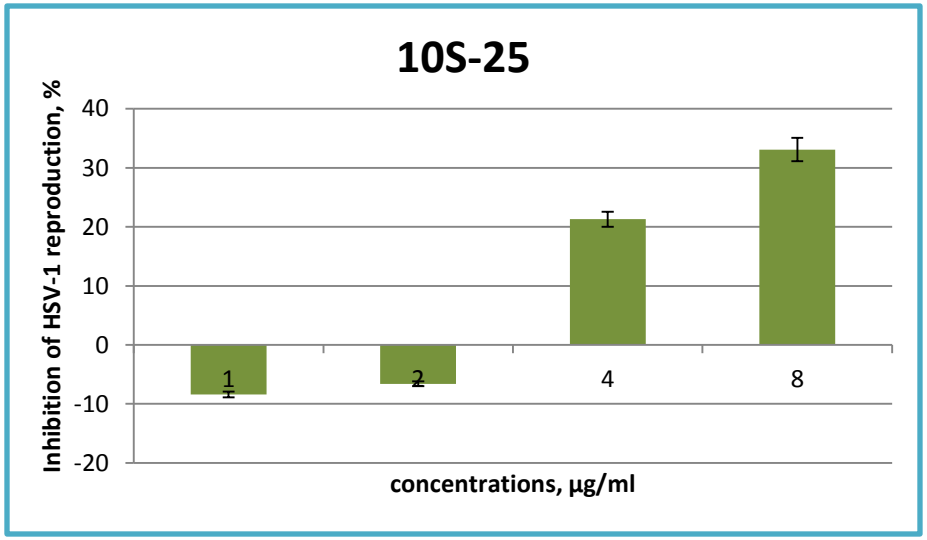
MTT-assay was used for the analysis of cell viability.

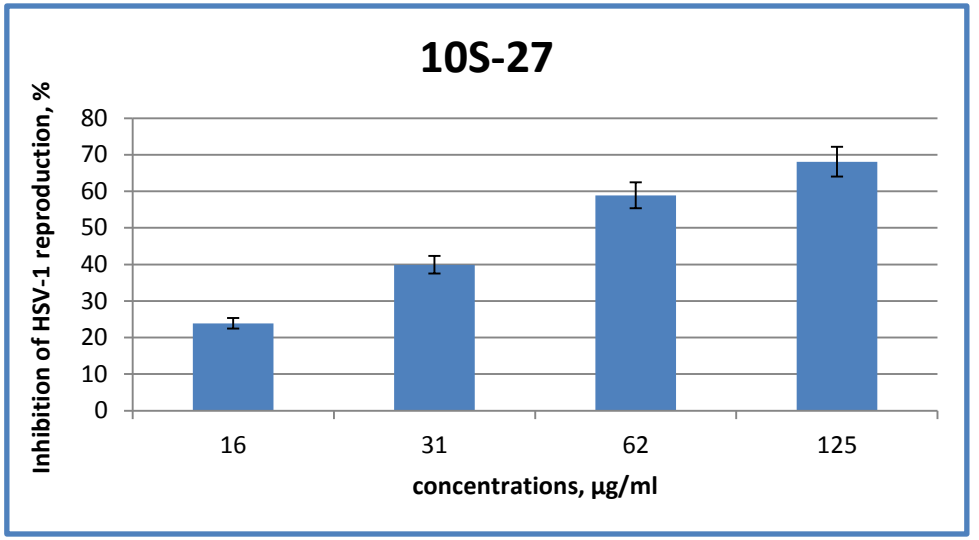
Inoculated cell culture MDBK (bovine kidney) were used for this procedure.

IC_{50} values were 13 and 250 μg/ml, respectively, for **10S-25** and **10S-27**.



Antiviral activity of tested compounds
(was determined by MTT-test)

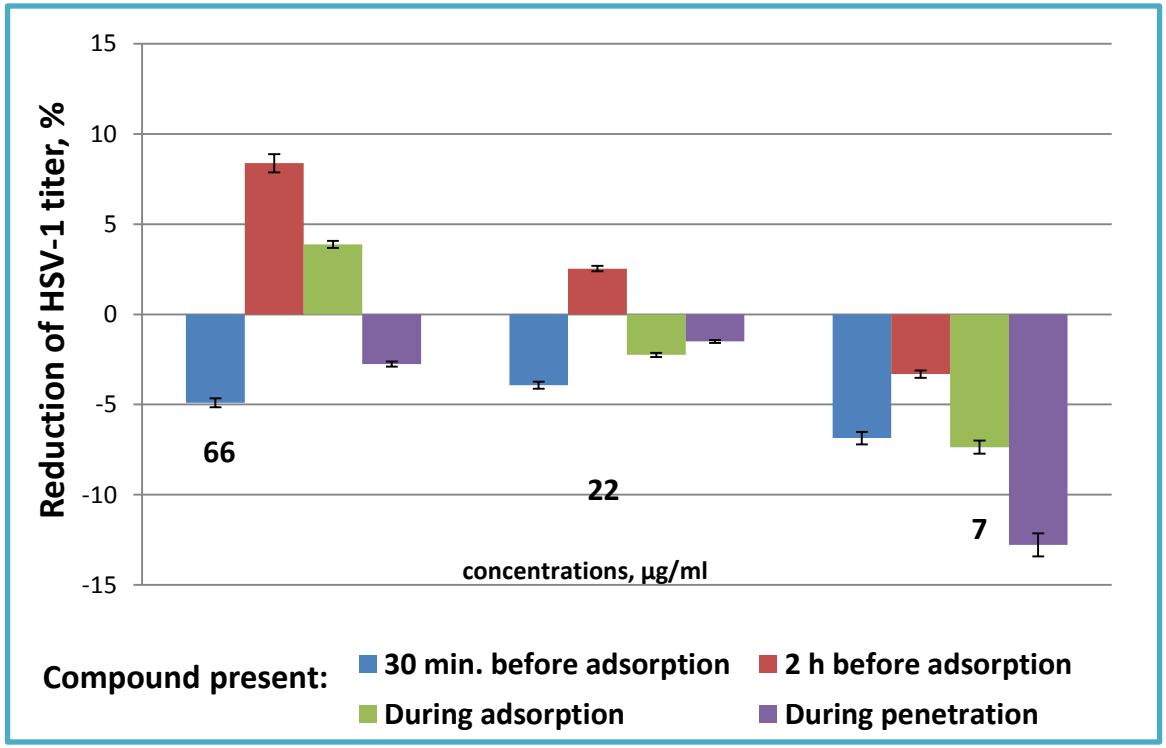




It was founded, that only **10S-27** inhibited the HSV-1 reproduction significantly (EC_{50} value - 48 µg/ml).

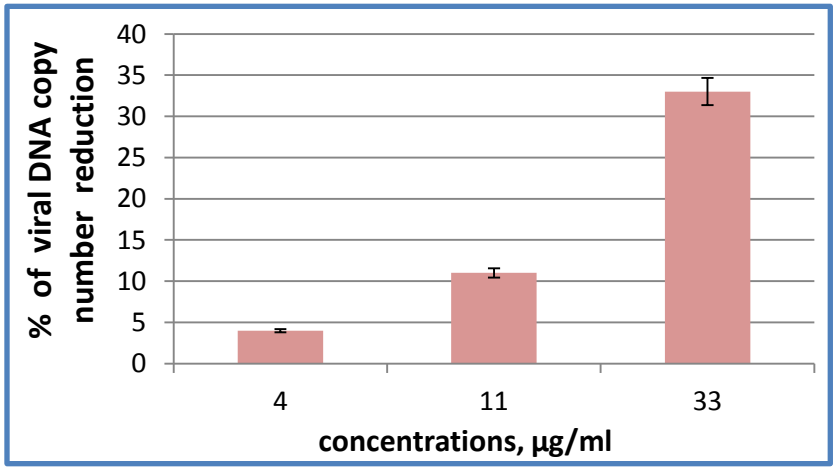
To determine a stage of the HSV-1 infection inhibited by the **10S-27** the virus and cells were treated with the compound at various times before and after the HSV-1 infections. The titer of the virus synthesized *de novo* was studied by the plaque method, based on the formation of necrotic sites in the infected cells due to the reproduction of the virus.

Dependence of antiviral activity of the 10S-27 compound on the treatment schedule

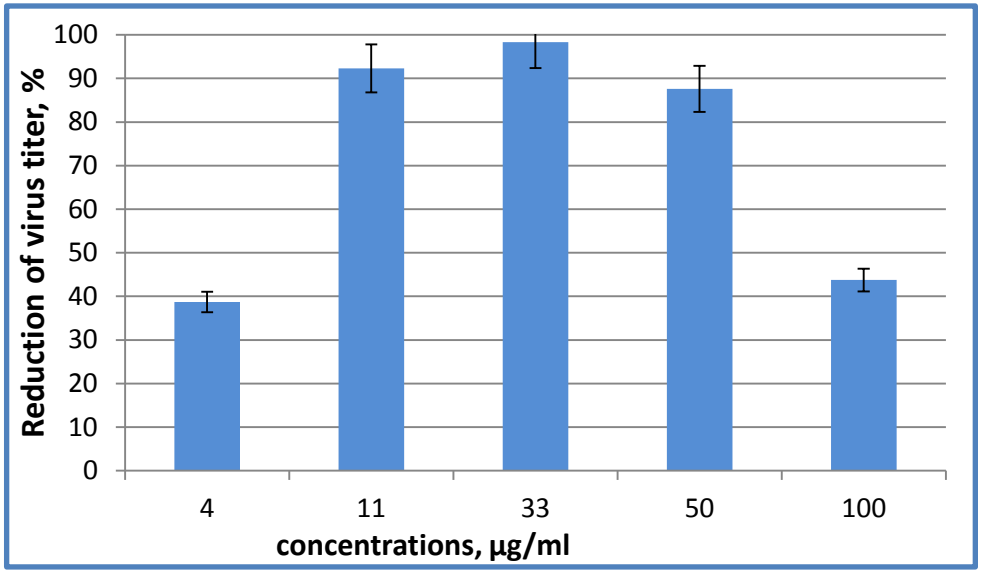


The antiviral activity assessed via real-time PCR and infectious virus yield reduction assay demonstrated the inhibitory effect of the compound at the late stage of the HSV-1 reproduction. It was found that compound **10S-27** at the concentrations of 11-50 µg/ml considerably reduces the titer of virus obtained *de novo* and inhibited HSV-1 plaque formation by 87-98%.

Effect of the 10S-27 on HSV-1 DNA synthesis



Influence of the compound on virus synthesized *de novo*



Discussion

- Compound 1-S-thio-(1- methylsulfonyl-2-difluoromethyl-vinyl)-2,3,4,6,-tetra-O-acetyl-β-D-glucopyranose showed low antiviral activity.

- Compound 1-(β-D-glucopyranosyl)-4-(hexafluoropropyl)-5-tosyl-1H-1,2,3-triazole) affect the viral DNA and significantly inhibited the HSV-1 titer synthesized *de novo*. Although virus offspring are formed, virus particles are not complete, and they are not able to cause an infection process.

Conclusions:

The 1-(β-D-glucopyranosyl)-4-(hexafluoropropyl)-5-tosyl-1H-1,2,3-triazole) possesses significant anti-HSV-1 activity, which is realized via multiple mechanisms. The compound inhibits the viral DNA replication and infectivity of viral progeny, which is probably caused by decreasing protein synthesis or capsid assembly.