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Antiviral activity of fluorinated compounds against DNA- and RNA-containing viruses

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Viral infections occupy an important place in human infectious pathology, as one of the most common and poorly controlled infections. At present, Influenza A virus (IAV) and Epstein-Barr virus (EBV) cause different infections, thereby imposing a huge toll on both human health and the economy worldwide. Therefore, screening new effective drugs is an urgent and important problem.

Our study aimed to determine cytotoxicity and antiviral effect of fluorinated compounds against the Influenza A virus and Epstein-Barr virus. The cytotoxicity was studied in two cell lines by MTT assay. The cytotoxicity of the compounds the rate was 41 – 990 μg/ml in the B95-8 cell culture, which produces EBV, and 200 – 478 μg/ml in MDCK cells.

Compounds **10S-47** and **10S-49** were able to inhibit reproduction of IAV with EC_{50} of 38 μg/ml and 50 μg/ml, respectively. It was shown that fluorinated compounds showed low effectiveness against the Epstein-Barr virus, and inhibited the reproduction of the virus at 20% in the concentration range of 1 – 100 μg/ml. Also, we studied the potency of compound **10S-47** to make an apoptosis induction because it exhibited a significant cytotoxic effect on the growth of transformed cells. It was established that for compound **10S-47** at 40 mg/ml, the percentage of apoptotic cells exceeded the control and was 10%.

Keywords: Influenza A virus , Epstein-Barr virus , Antiviral activity

Introduction

VIRUSES

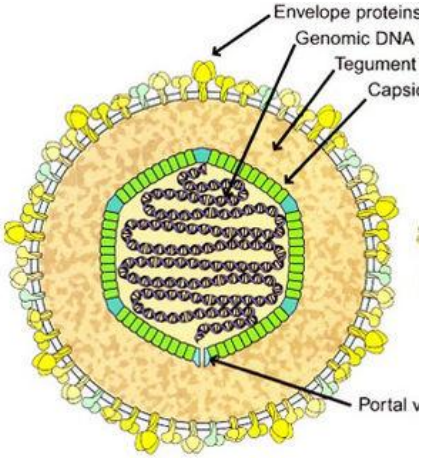
DNA-containing virus

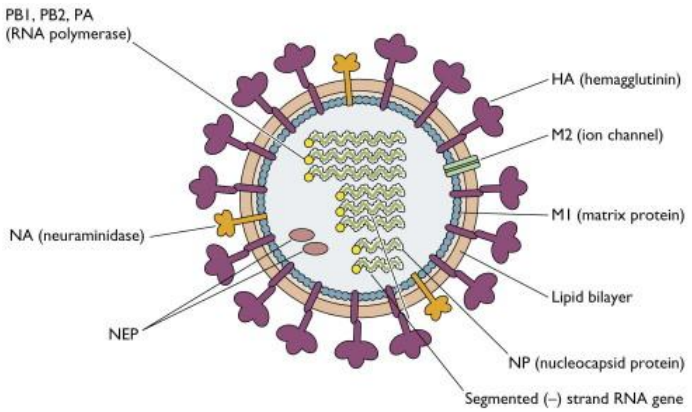
The EBV is one of the world's most disseminated viruses and has been associated with a post-transplant lymphoproliferative disease, together with several cancers including Burkitt's lymphoma, gastric cancer, Hodgkin's lymphoma, lung carcinoma, nasopharyngeal carcinoma. EBV is a member of the *Herpesviridae* family, more specifically, belonging to the *Gammaherpesvirinae* subfamily.

RNA-containing virus

Infuenza viruses cause acute respiratory infection responsible for seasonal epidemics and pandemics

Influenza viruses are members of the family *Orthomyxoviridae*. This family represents enveloped viruses the genome of which consists of segmented negative-sense single-strand RNA segments.

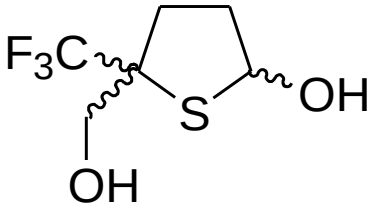




Chemical compounds

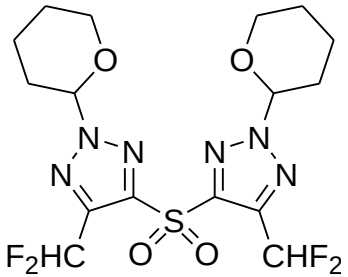
(*2RS,5SR*)-2-Hydroxy-5-hydroxymethyl-5-(trifluoromethyl)tetrahydrothiophene and (*2SR,5SR*)-2-hydroxy-5-hydroxymethyl-5-(trifluoromethyl)-tetrahydrothiophene*

10S-45



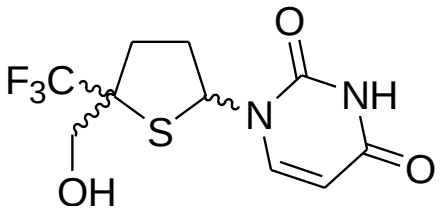
Bis(5-difluoromethyl-2-(tetrahydropyran-2-yl)-2*H*-triazole-4-yl)sulfone

10S-47



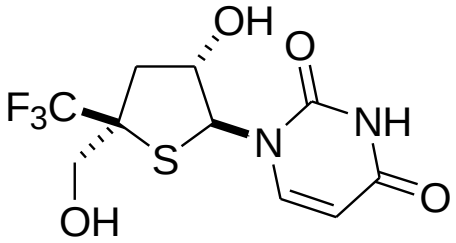
(*2RS,5SR*)-2-(2,4-Dioxopyrimidine-1-yl)-5-hydroxymethyl-5-(trifluoromethyl)tetrahydrothiophene and (*2SR,5SR*)-2-(2,4-dioxopyrimidine-1-yl)-5-hydroxymethyl-5-(trifluoromethyl)-tetrahydrothiophene*

10S-46



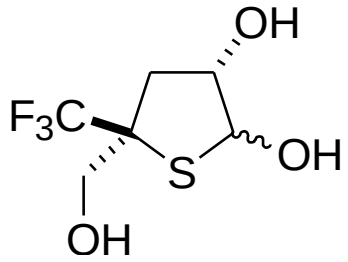
(*2RS,3RS,4RS*)-2-(2,4-Dioxopyrimidine-1-yl)-3-hydroxy-5-hydroxymethyl-5-(trifluoromethyl)-tetrahydrothiophene

10S-48



(*2SR,3SR,5SR*)-2,3-Dihydroxy-5-hydroxymethyl-5-(trifluoromethyl)-tetrahydrothiophene and (*2RS,3SR,5SR*)-2,3-Dihydroxy-5-hydroxymethyl-5-(trifluoromethyl)-tetrahydrothiophene*

10S-49

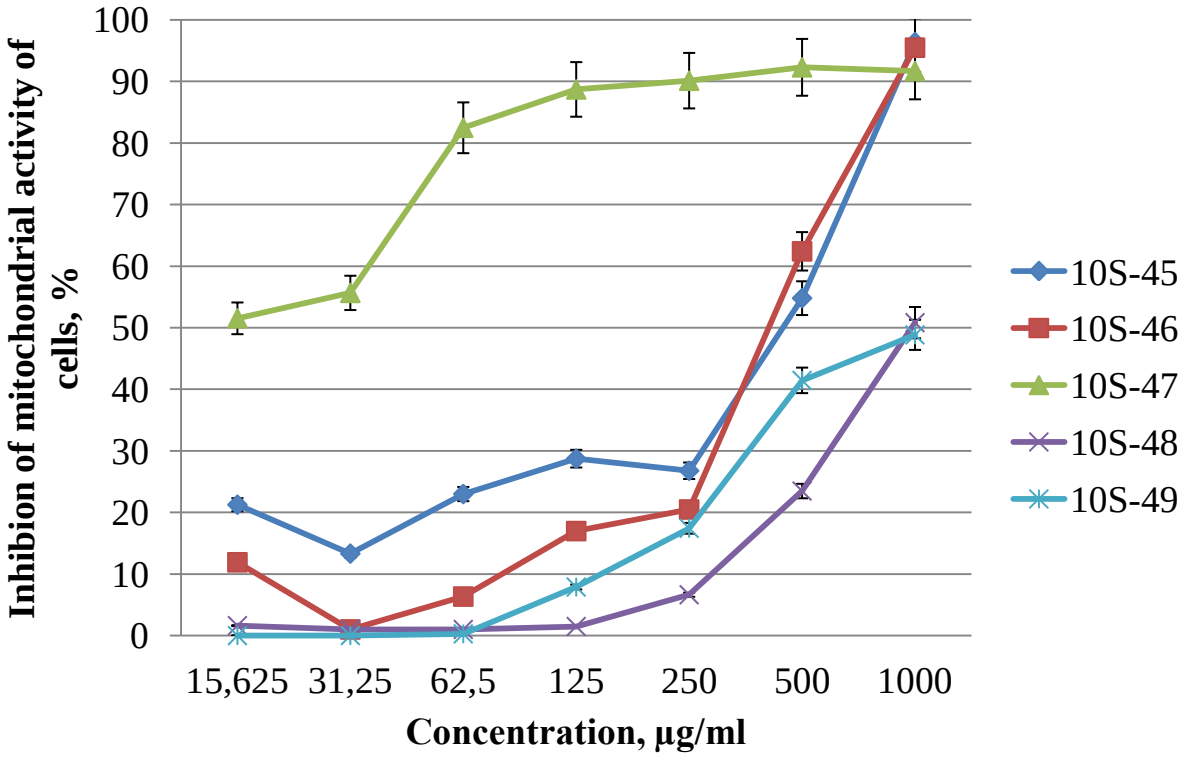


All studied compounds were synthesized in Institute of Organic Chemistry of NAS of Ukraine.

*****These samples are mixtures of diastereomers, so the names of each component are given using stereochemical descriptors according to the R, S-nomenclature.

Study of the cytotoxicity and anti-EBV action of the fluorinated compounds **10S-45**, **10S-46**, 1**0S-47**, **10S-48**, and **10S-49** were performed with B95-8 cell line, which produces EBV, as an chronic infection model.

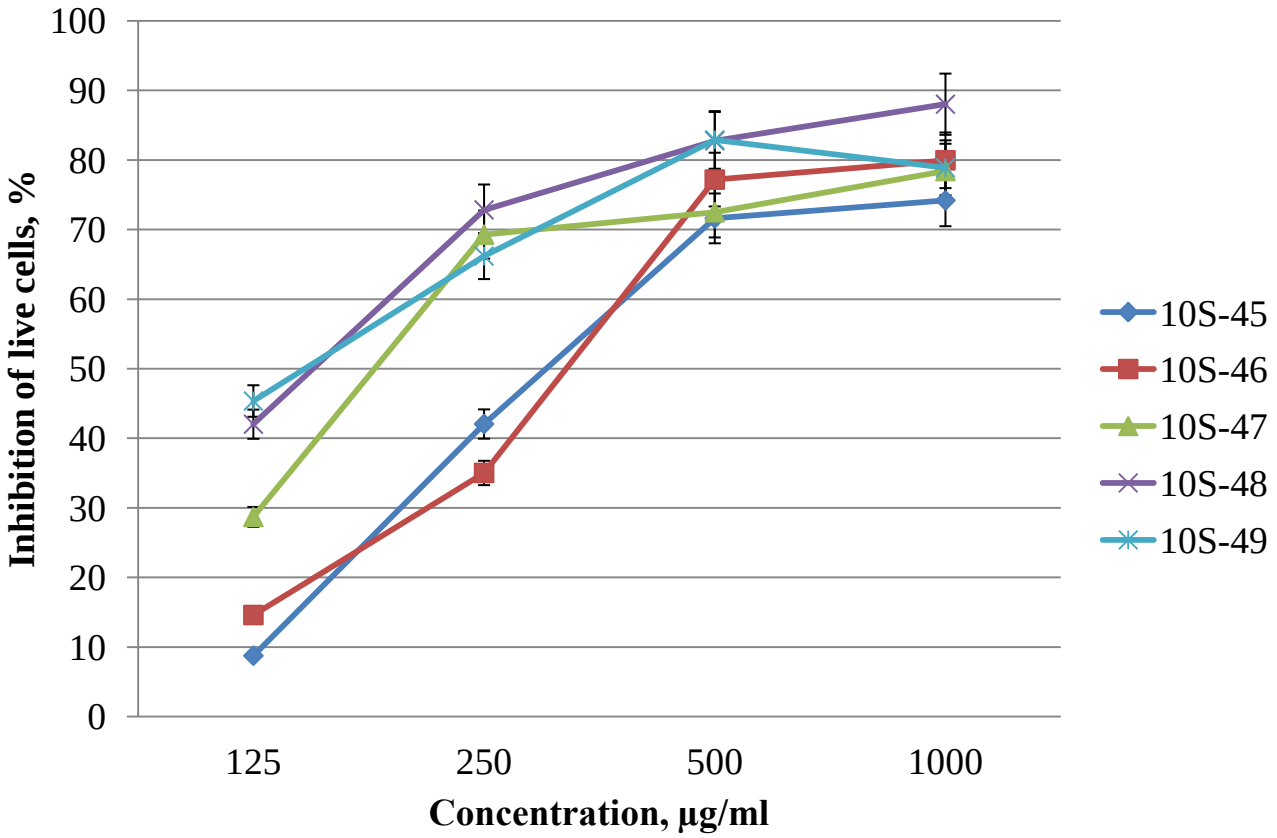
The cytotoxicity of compounds was determined by MTT-method, CC_{50} were in the range 41 – 990 μg/ml. The antiviral activity of the compounds was determined by RT-PCR. It was shown that only **10S-48** and **10S-49** compounds inhibit EBV reproduction, percentage of inhibition of synthesis of viral DNA was in range from 1 to 7. This data do not allow us to assign this class of compounds to promising anti-EBV agents.



CC_{50} (μg/ml)	Compounds
433	10S-45
479	10S-46
41	10S-47
990	10S-48
801	10S-49

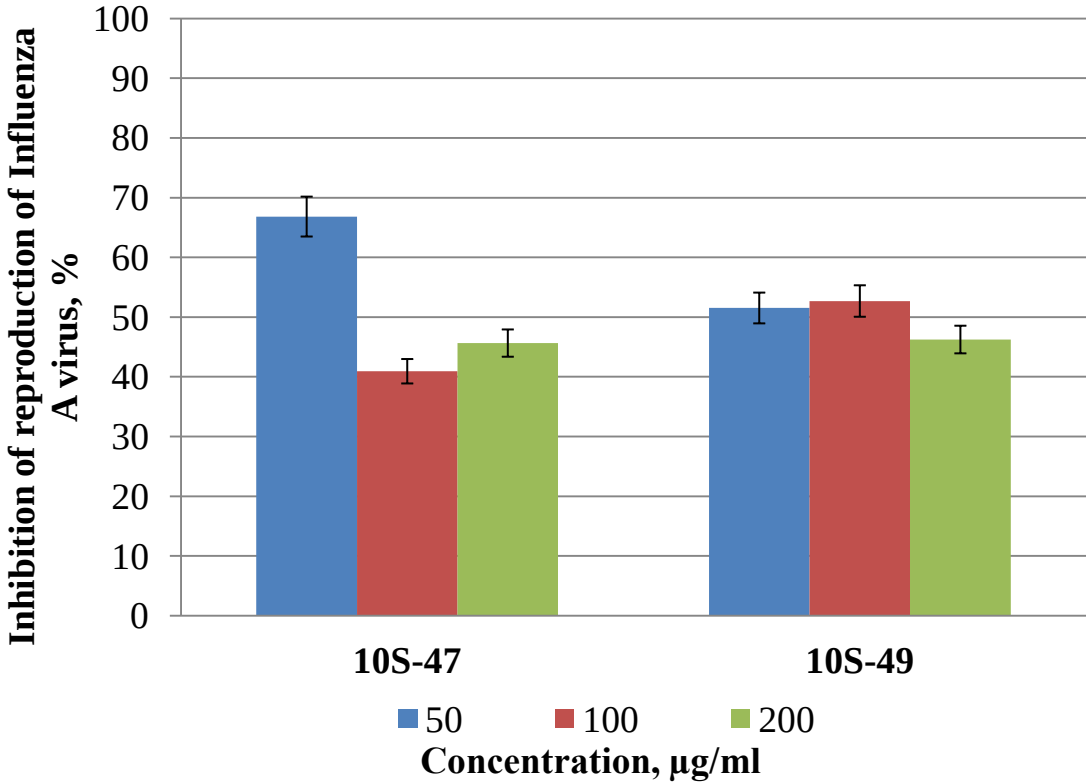
Study of the cytotoxicity and antiviral action against influenza A virus H1N1 A/FM/1/47 of the fluorinated compounds **10S-45**, **10S-46**, 1**0S-47**, **10S-48**, and **10S-49** were performed with MDCK cell line, as classical culture model for IAV infection.

It was determined that all studied compounds at maximum concentration (500 – 1000 µg/ml) inhibit mitochondrial activity of cells in the range 80 – 90%. Another studied concentration do not cause significant cytotoxicity effect on MDCK cell culture.



CC_{50} (µg/ml)	Compounds
478	10S-45
451	10S-46
200	10S-47
298	10S-48
320	10S-49

Antiviral activity was assessed by crystal violet straining and percent of viral inhibition was calculated. It was established that compound **10S-47** at concentrations (50, 100, and 200 µg/ml) inhibited virus replication for 67%, 41, and 46%, respectively. The compound **10S-49** inhibit reproduction of the IAV in mentioned above concentrations for 52%, 53%, and 46%. It was determined that EC_{50} (effective concentration inhibiting reproduction of the virus by 50%) were 38 µg/ml and 50 µg/ml, for **10S-47** and **10S-49**, respectively. Another compouds shown low antiviral activity in the range 4 – 30%.



Compounds	Selective Index
10S-45	-
10S-46	-
10S-47	5
10S-48	-
10S-49	6

Conclusion

Taken together, our results showed that the fluorinated compounds **10S-45**, **10S-46**, **10S-47**, **10S-48**, and **10S-49** possess the antiviral activity. The **10S-47** and **10S-49** showed significant antiviral activity against influenza A virus for 67%. Whereas compounds **10S-45-49** do not inhibit reproduction of Epstein-Barr virus.

Obtained and analyzed data let to relate the compounds **10S-47** and **10S-49** to a perspective anti-IAV agents, that can be used in further research on antitumor action.