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New low molecular weight heterocyclic compounds with antiviral activity

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pharmaceuticals MDPI

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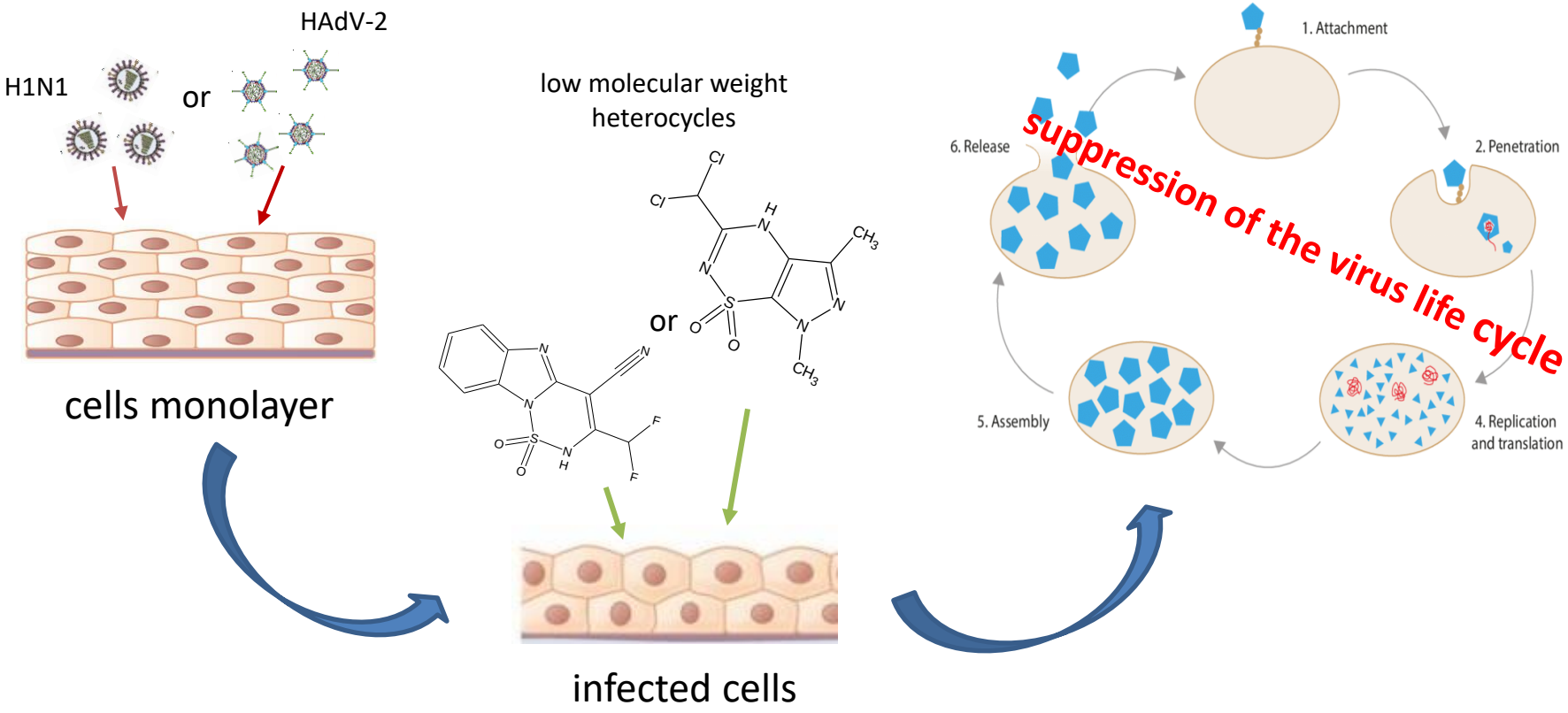
New low molecular weight heterocyclic compounds with antiviral activity



Abstract:

Development of an effective antiviral drug is typically followed by expansion of the successful strategy with numerous chemical variations of compounds providing improvements in parameters including affinity, solubility, lipophilicity, pharmacology, toxicity, drug resistance profiles etc. The aim of this study was to investigate the antiviral properties of newly synthesized fluorine-, chlorine-, and bromine-containing heterocyclic compounds against adeno-, herpes- and influenza viruses. Cytotoxicity and antiviral efficacy of compounds was determined using a tetrazolium-based colorimetric and yield reduction assays, respectively. It should be noted that viability results were dependent on the type of used cells. It was found that compound 5,7-dimethyl-4,7-dihydropyrazolo[4,3-e][1,2,4]thiadiazine1,1-dioxide with 3-(difluoromethyl), 3-(dichloromethyl) or 3-(bromodifluoromethyl) substituents (1784, 1779 and 1753, respectively) inhibited HAdV-2 development of virus cytopathic effect on cells up to 79% and decreased infectious titer of virus obtained *de novo* by 1-5 $\log_{10}TCID_{50}$/ml. Also, significant antiinfluenza and antiadenoviral activity was observed for compound 3-(difluoromethyl)-2H-benzo[4,5]imidazole[1,2-b][1,2,6]thiadiazine-4-carbonitrile 1,1-dioxide, that decreased viruses reproduction up to 76%. Obtained data indicate that synthesized compounds may be promising antiviral agent. Furthermore, we showed that incorporation of the fluorine or chlorine atoms in molecule of compound significantly impact on its cytotoxicity and antiviral potency.

Keywords: antiviral potential; cytotoxicity; HAdV-5; heterocyclic compounds; IAV

Introduction

Viral diseases are one of the most important medical and social problems of the 21st century and occupy the first place among the causes of morbidity in the world (Adamson C., 2021). Treatment of patients with virus infection is not an easy task. The reasons for this are the complex strategy of parasitism, the opportunistic properties of pathogens, the multiple organ lesions, the presence of numerous complications, and the multifactorial nature of some lesions (De Clercq E., 2016). Antiviral compounds with broad-spectrum activity against different virus genotypes or subtypes are still very necessary, because the effectiveness of most antiviral drugs is limited to only certain viral strains (Zhang D.-J., 2014).

Despite the rapid advancement of pharmaceutical and biotechnological approaches, the development of successful antiviral treatments remains a challenge (De Clercq E., 2016), since:

- potent antiviral drugs that counteract the highly variable nature of virus genomes are still required, because emerging drug resistance mutations remain a major cause of treatment failure
- it is difficult to eradicate viral reservoirs using antiviral agents, because DNA viruses and retroviruses can integrate their genomes into human genomes
- it remains a challenge to rapidly develop antiviral drugs and vaccines against emerging infectious diseases, calling for a joint effort between scientific and industrial partners
- it is a challenge to pursue effective, low-toxicity, and well-tolerated drugs that enhance patient compliance and drug administration
- efficient antiviral treatments against viral coinfections
- access to and delivery of costly new therapies are becoming increasingly problematic in resource-limited settings

Introduction

Low molecular weight heterocycles are among the most common objects of modern bioorganic and medical chemistry, and are widely used in antiviral therapy. (De A., 2021; Tran T.N., 2022)

Any pharmacophore element necessary for the interaction of the pharmacophore with the active sites of target molecules can be introduced into their structure

Heterocycles-target interactions are determined by a number of non-covalent interactions, including hydrogen bonding, van der Waals forces, and π effects. Bonds between lone pairs of amino acid residues and the heterocyclic ring play a significant role in molecular binding to the target.

The **aim** of this study was to investigate the antiviral properties of newly synthesized fluorine-, chlorine-, and bromine-containing low molecular weight heterocyclic compounds against different type of viruses.

Objects and methods

Compounds:

Fluorine-, chlorine-, and bromine-containing heterocycles

Cell cultures:

- Vero cells (african green monkey kidneys)
- MDCK cells (dog kidneys)

Viruses:

- Influenza virus type A (IAV), H1N1, strain A/FM/1/47
- Human adenovirus type 2 (HAdV-2)
- Herpes simplex virus type 1 (HSV-1)

Methods:

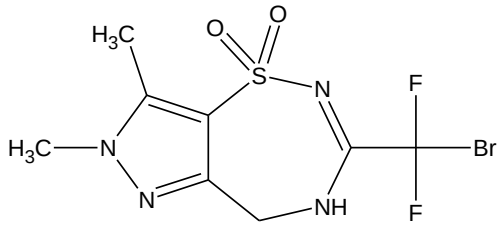
- Cytotoxicity of compounds was determined using a tetrazolium-based colorimetric assay.
- Antiviral efficacy of compounds against IAV and HAdV-2 was estimated by inhibition of the development of viruses cytopathic effect on cells and the reduction of virus infectivity.

Results and discussion

Compounds structure

1794

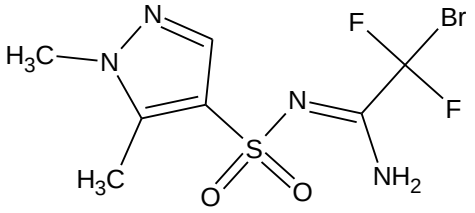
MW 343.1496



6-(brominedifluoromethyl)-2,3-dimethyl-7,8-dihydro-2H-pyrazolo[3,4-f][1,2,4]thiadiazepine 4,4-dioxide

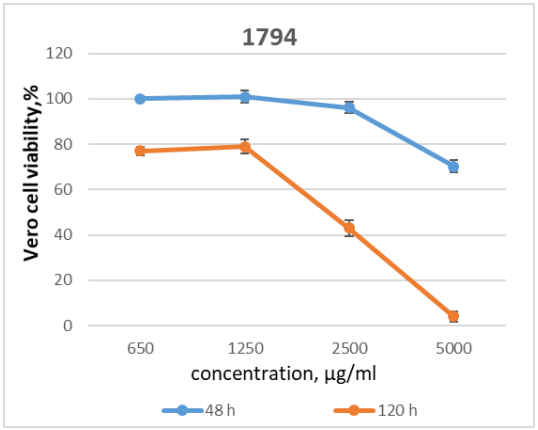
1797

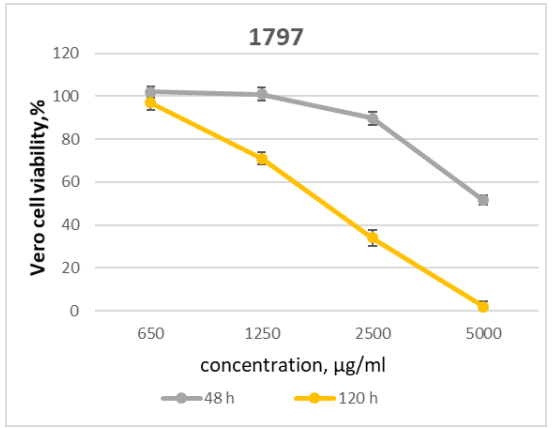
MW 331.1389

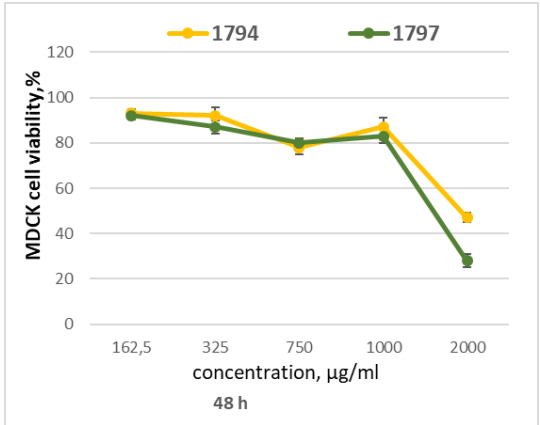


2-bromo-N'-((1,5-dimethyl-1H-pyrazol-4-yl)sulfonyl)-2,2-difluoroacetimidamide

Cell cytotoxic effect of the compounds





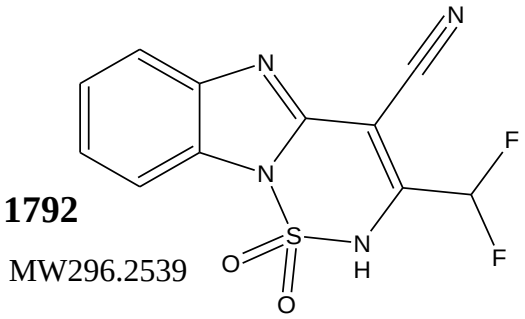


Antiviral activity of the compounds

Antiviral effect of compounds against adeno-, herpes- and influenza viruses was not detected, as inhibition of the development of viruses cytopathic effect on cells and the reduction of viruses infectious titer did not exceed 10% and 0.8 $\log_{10}TCID_{50}$/ml, respectively.

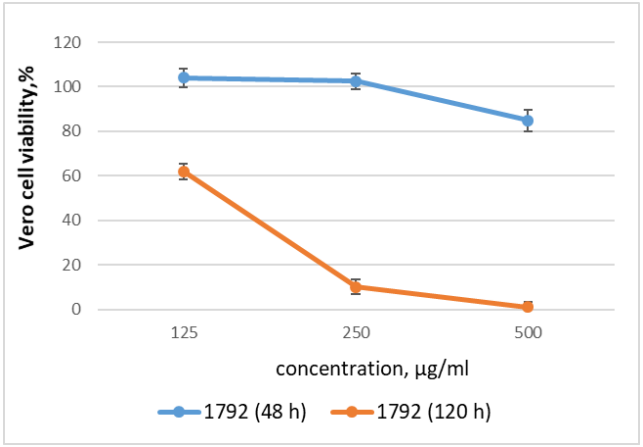
Results and discussion

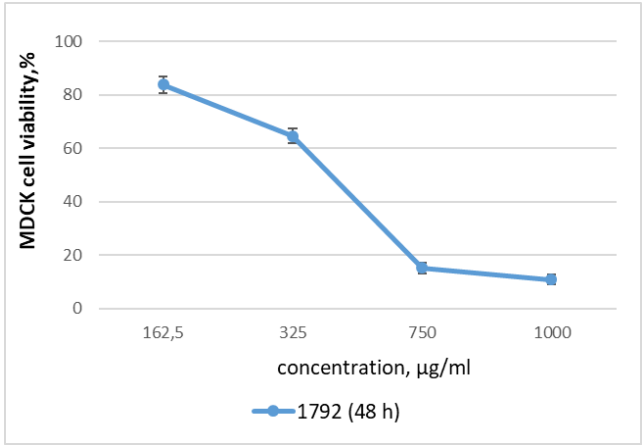
Compound structure



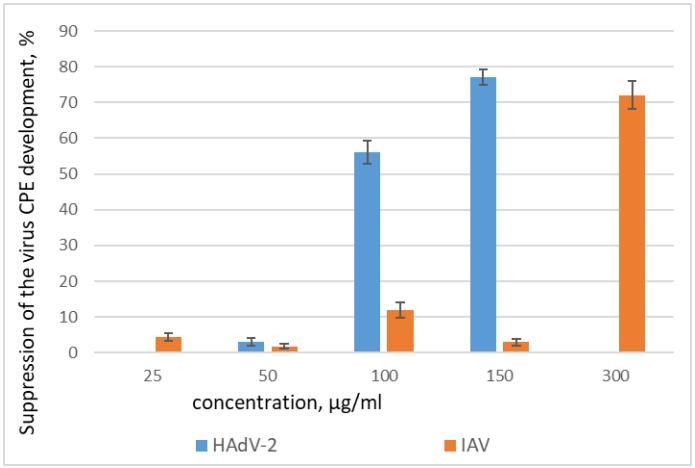
3-(difluoromethyl)-2H-benzo[4,5]imidazo[1,2-b][1,2,6]thiadiazine-4-carbonitrile 1,1-dioxide

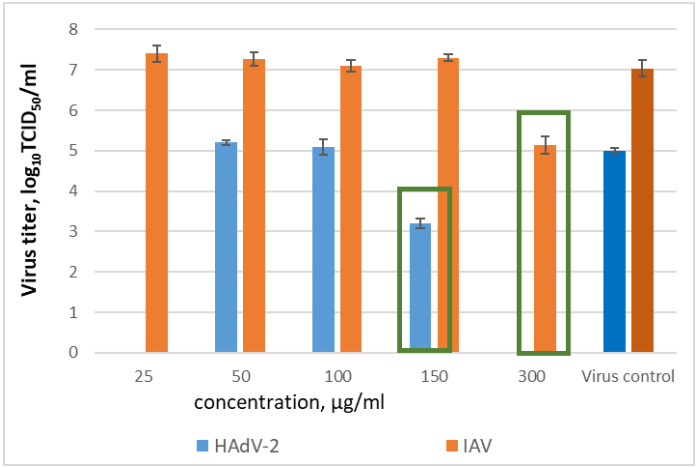
Cytotoxicity of the compound





Antiviral activity of the compound

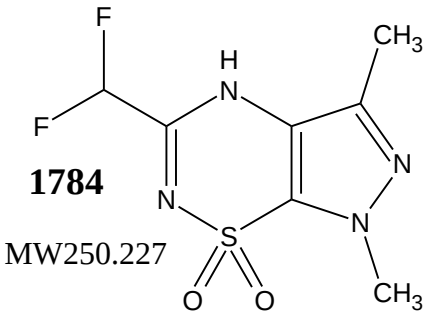




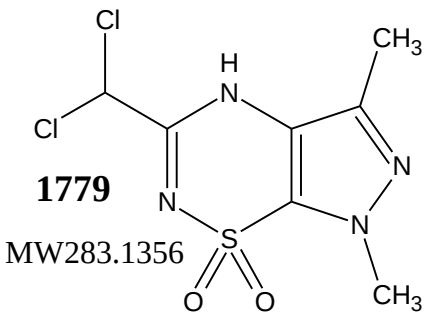
Compound inhibited HAdV-2 and IAV reproduction up to 76% and decreased infectious titer of viruses obtained *de novo* by 2 $\log_{10}TCID_{50}$/ml.

Results and discussion

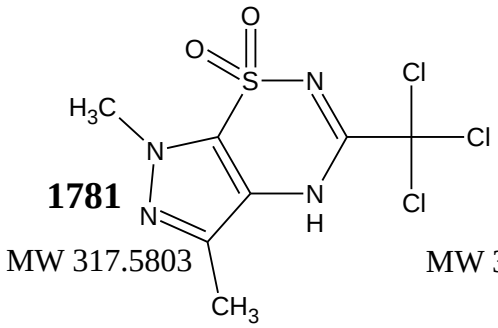
Compounds structure



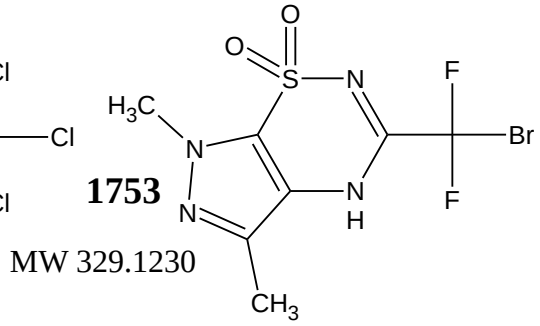
3-(difluoromethyl)-5,7-dimethyl-4,7-dihydropyrazolo[4,3-e][1,2,4]thiadiazine 1,1-dioxide



3-(dichloromethyl)-5,7-dimethyl-4,7-dihydropyrazolo[4,3-e][1,2,4]thiadiazine 1,1-dioxide

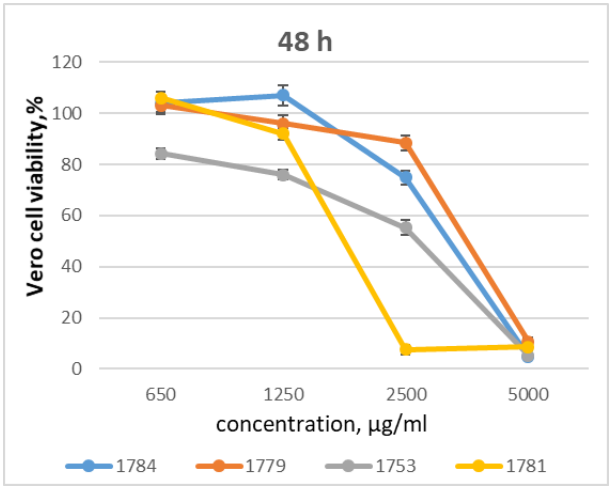


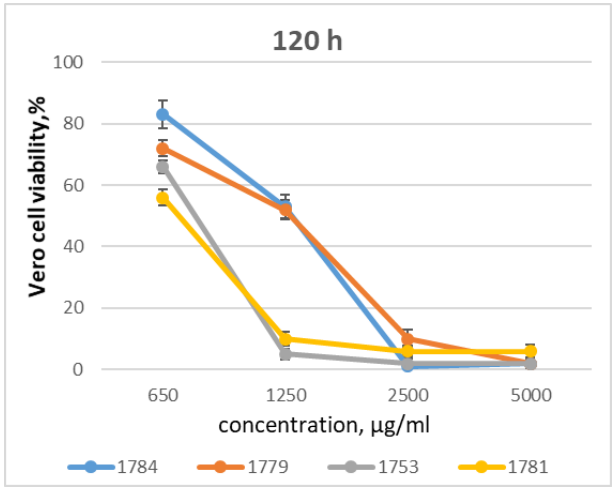
3-(trichloromethyl)-5,7-dimethyl-4,7-dihydropyrazolo[4,3-e][1,2,4]thiadiazine 1,1-dioxide

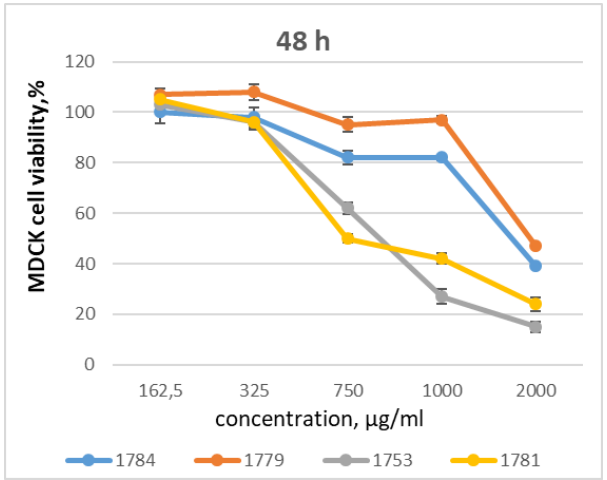


3-(bromodifluoromethyl)-5,7-dimethyl-4,7-dihydropyrazolo[4,3-e][1,2,4]thiadiazine 1,1-dioxide

Cytotoxicity of the compounds

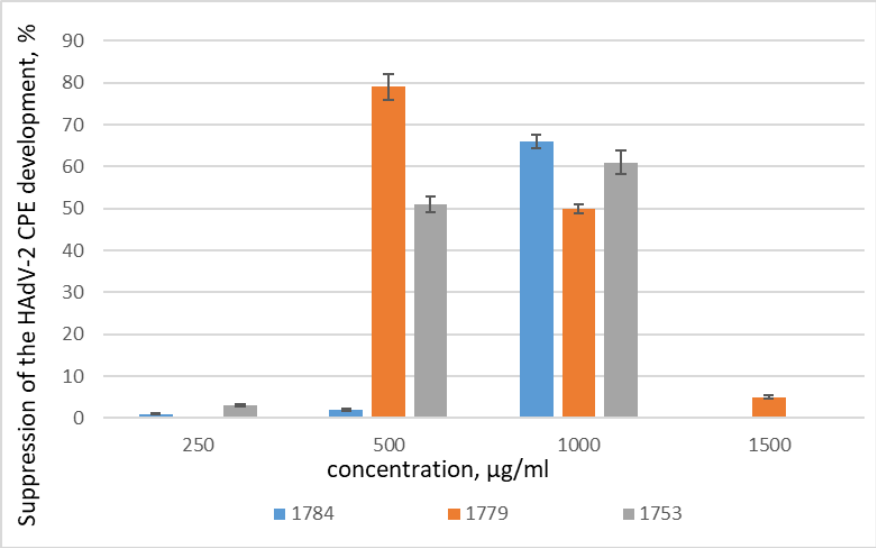


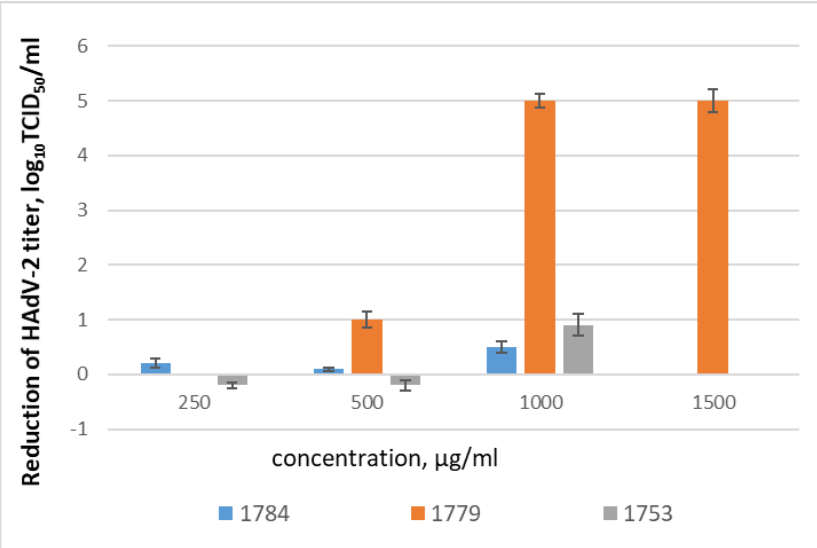




Results and discussion

Antiviral activity of the compounds





- Among the tested compounds in the group of thiadiazines, only compound 1779 reduced adenovirus reproduction by 79% and completely blocked the formation of full-fledged and infectious progeny of the virus. Indicating that incorporation of 3-(difluoromethyl), 3-(bromodifluoromethyl) or 3-(trichloromethyl) substituents in the molecule 5,7-dimethyl-4,7-dihydropyrazolo[4,3-e][1,2,4]thiadiazine1,1-dioxide leads to decreasing of its antiviral activity.
- None of the synthesized compounds from the group of thiadiazines demonstrated antiviral activity against IAV and HSV-1.

Conclusions:

- Seven fluorine-, chlorine-, and bromine-containing heterocyclic compounds were synthesized and their antiviral activities against DNA and RNA viruses were evaluated *in vitro*. Among them «leader structures» were found characterized by a high level of inhibitory activity and significant selectivity for adenovirus and influenza virus (3-(difluoromethyl)-2H-benzo[4,5]imidazo[1,2-b][1,2,6]thiadiazine-4-carbonitrile 1,1-dioxide and 3-(dichloromethyl)-5,7-dimethyl-4,7-dihydropyrazolo[4,3-e][1,2,4]thiadiazine 1,1-dioxide).

- The structure-activity relationship for synthesized thiadiazines is analyzed. It was shown that incorporation exactly the dichloromethyl group in third position of the molecule 5,7-dimethyl-4,7-dihydropyrazolo[4,3-e][1,2,4]thiadiazine 1,1-dioxide significantly impact on compound cytotoxicity and increases its antiviral potency.

Obtained data indicate that compounds 1779 and 1792 may be promising antiviral agent.

References

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Acknowledgments

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