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Approach to the synthesis of new bis(6-hydroxypyrimidin-4(3H)-ones) with an aromatic bridging fragment

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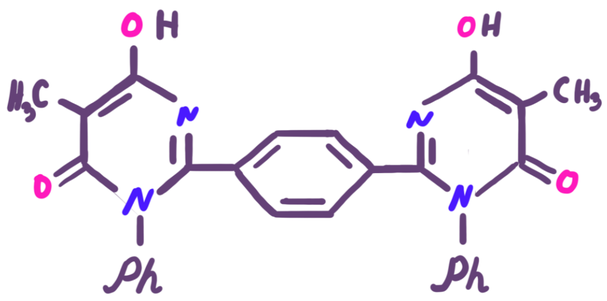
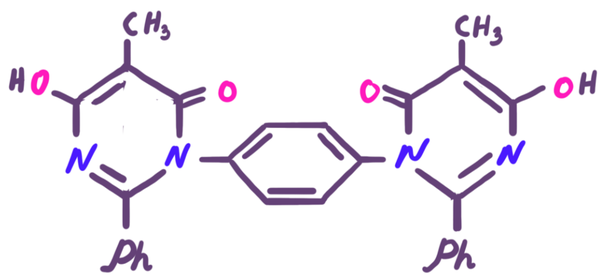
INTRODUCTION & AIM

Among the 5-substituted-6-hydroxy-2,3-diarylpyrimidine-4(3H)-ones derivatives there are compounds with reported anti-inflammatory activities and analgesic activity [1,2]. Various reports in the patent and scientific literature have revealed that bis(pyrimidine) derivatives exhibit antitumor and antimicrobial activity [3]. Therefore, the aim of our work was the synthesis of new derivatives of bis(6-hydroxypyrimidin-4(3H)-one) with aromatic linker – 2,2'-(1,4-phenylene)bis(6-hydroxy-5-methyl-3-phenylpyrimidin-4(3H)-one) (**1**) and 3,3'-(1,4-phenylene)bis(6-hydroxy-5-methyl-2-phenylpyrimidin-4(3H)-one) (**2**). Proof of structure and assessment of the biological activity through in silico analysis.



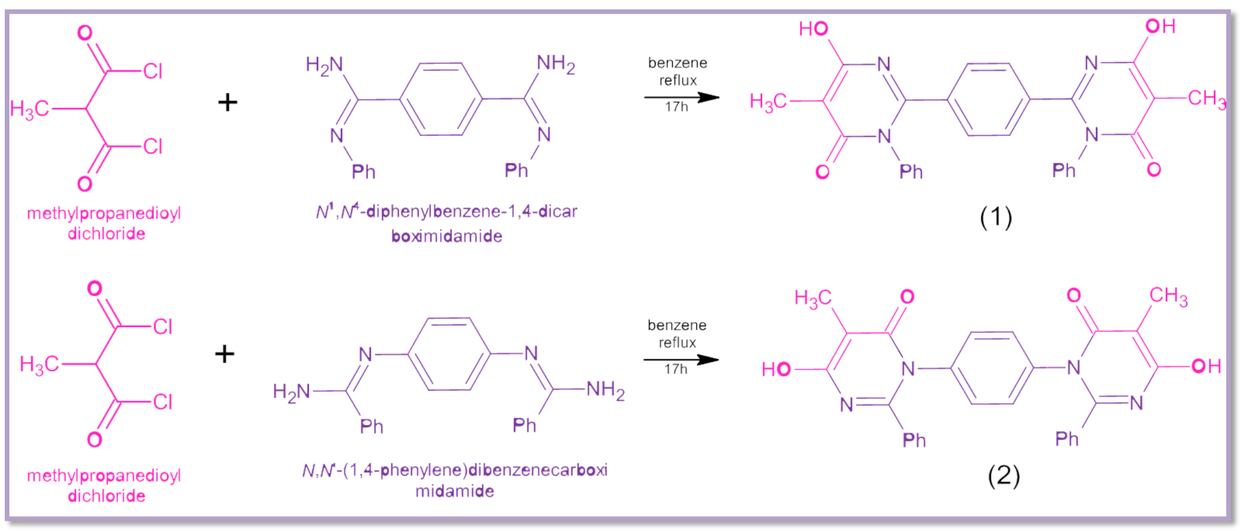
2,2'-(1,4-phenylene)bis(6-hydroxy-5-methyl-3-phenylpyrimidin-4(3H)-one) (1)



3,3'-(1,4-phenylene)bis(6-hydroxy-5-methyl-2-phenylpyrimidin-4(3H)-one) (2)

METHOD

- Target compounds **1** and **2** were obtained via interaction methylmalonyldichloride with the corresponding carboximidamide in boiling benzene medium for 17 h. (Scheme1).



Scheme 1.

- The structure of the obtained compounds **1** and **2** was reliably proven by 1H NMR spectroscopy and High-Resolution Mass Spectrometry (HRMS-ESI) data.
- Prediction of biological activity spectra was carried out using web resources: GUSAR, PASS Online, AntiHIV-Pred and CLC Pred.

RESULTS & DISCUSSION

Target compounds – 2,2'-(1,4-phenylene)bis(6-hydroxy-5-methyl-3-phenylpyrimidin-4(3H)-one) (**1**) and 3,3'-(1,4-phenylene)bis(6-hydroxy-5-methyl-2-phenylpyrimidin-4(3H)-one) (**2**) were obtained in 36 % and 42 % yield accordingly. The structure of the obtained compounds was reliably proven by ^{1}H NMR spectroscopy and High-Resolution Mass Spectrometry (HRMS-ESI) data (Fig. 1 and 2).

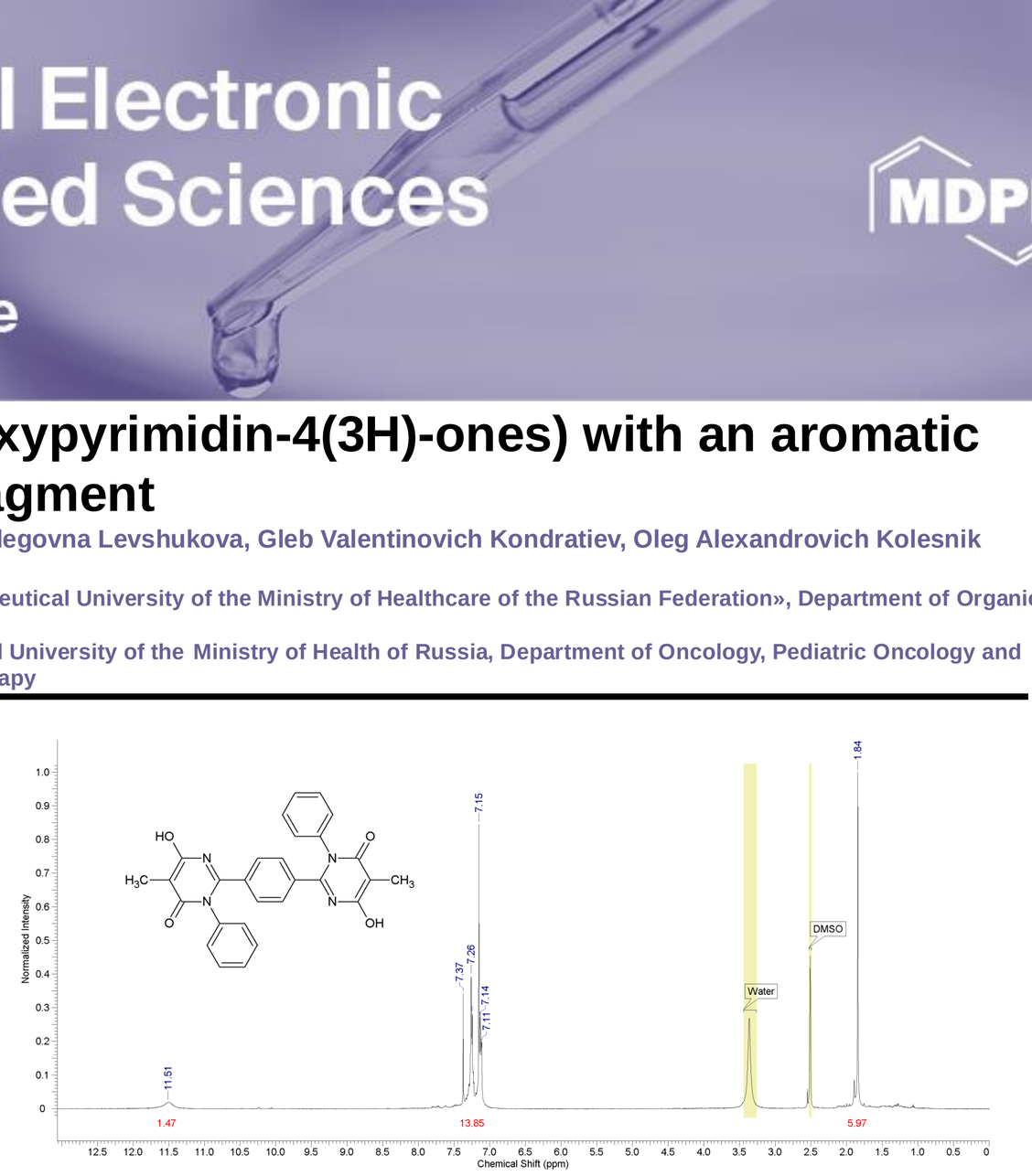


Figure 1. 1H-NMR spectra of compound 1

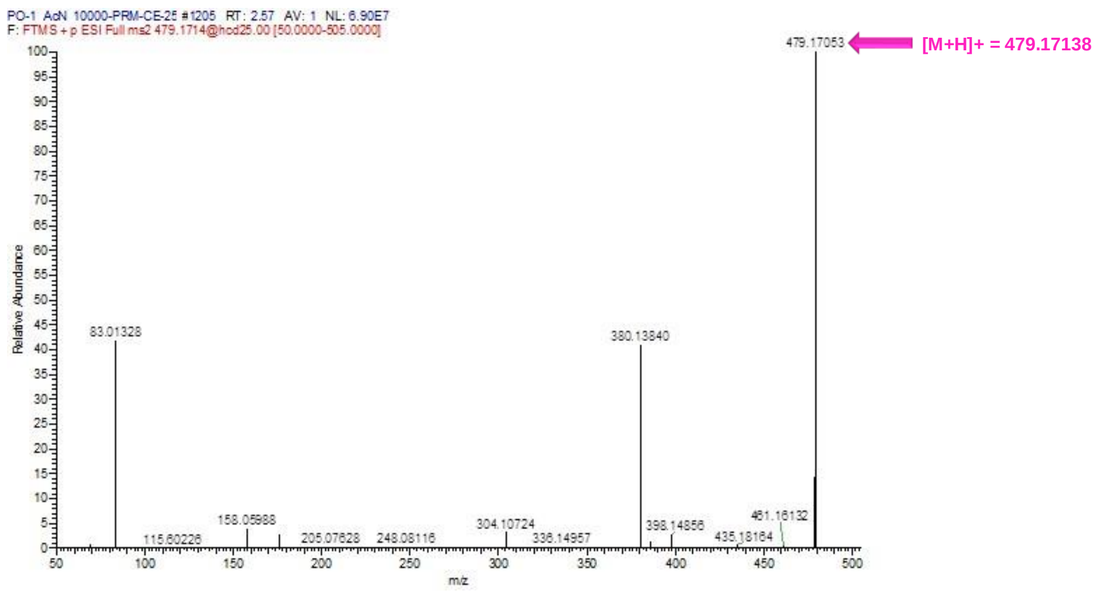
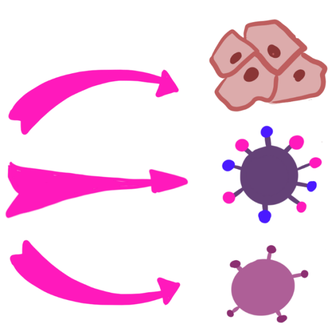


Figure 2. High-Resolution Mass spectra of compound 1

According to the results of in silico screening, compounds **1** and **2** potentially exhibit antitumor activity against cisplastin-resistant ovarian carcinoma and diffuse large B-cell lymphoma activated B-cell type, and also with a high probability antiviral activity against Dengue virus type 2 and SARS-CoV-2. It is noted that they can effectively inhibit reverse transcriptase (HIV-1).



Cisplastin-resistant ovarian carcinoma and diffuse large B-cell lymphoma

Dengue virus type 2 and SARS-CoV-2

HIV-1

The predicted values of acute toxicity in rats (LD_{50})		
Compound	**The intravenous route of administration**	**The oral route of administration**
1	314 mg/kg	1525 mg/kg
2	309 mg/kg	1611 mg/kg

CONCLUSION

New derivatives of bis(6-hydroxypyrimidine-4(3H)-one) **1** and **2** were obtained, the structure of which was proved using 1H NMR spectroscopy and High-Resolution Mass Spectrometry (HRMS-ESI) data. According to the results of screening *in silico* for obtained compounds **1** and **2**, antitumor activity against cisplastin-resistant ovarian carcinoma and diffuse large B-cell lymphoma activated B-cell type, antiviral activity against Dengue virus type 2, SARS-CoV-2 and HIV-1 were found.

FUTURE WORK / REFERENCES

1. Kuvaeva E.V., Kolesnik D.A., Levshukova P.O., Ivkin D.YU., Yakovlev I.P. Sintez i ocenka anal'geziruyushchej aktivnosti novogo 5-butil-1,2-difenil-6-okso-1,6-digidropirimidin-4-olyata natriya. Voprosy biologicheskoj, medicinskoj i farmacevticheskoj khimii. 2021;24(6):15−21. https://doi.org/10.29296/25877313-2021-06-00.

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