

Synthesis and biological activity evaluation *in silico* of bis(4-hydroxy-6H-1,3-oxazin-6-one) derivatives and the products of their alcoholysis

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INTRODUCTION & AIM

Bis(1,3-oxazin-6-one) derivatives (figure 1, figure 2) are a poorly studied class of compounds that are promising for research, as their mono-analogues are pharmacologically active substances [1] and key reagents for the synthesis of heterocyclic and acyclic compounds [2]. Therefore, the aim of this work was to obtain bis(4-hydroxy-6H-1,3-oxazin-6-ones), study their ethanolysis reaction, prove the structure of the target compounds and evaluate their pharmacological potential *in silico*.

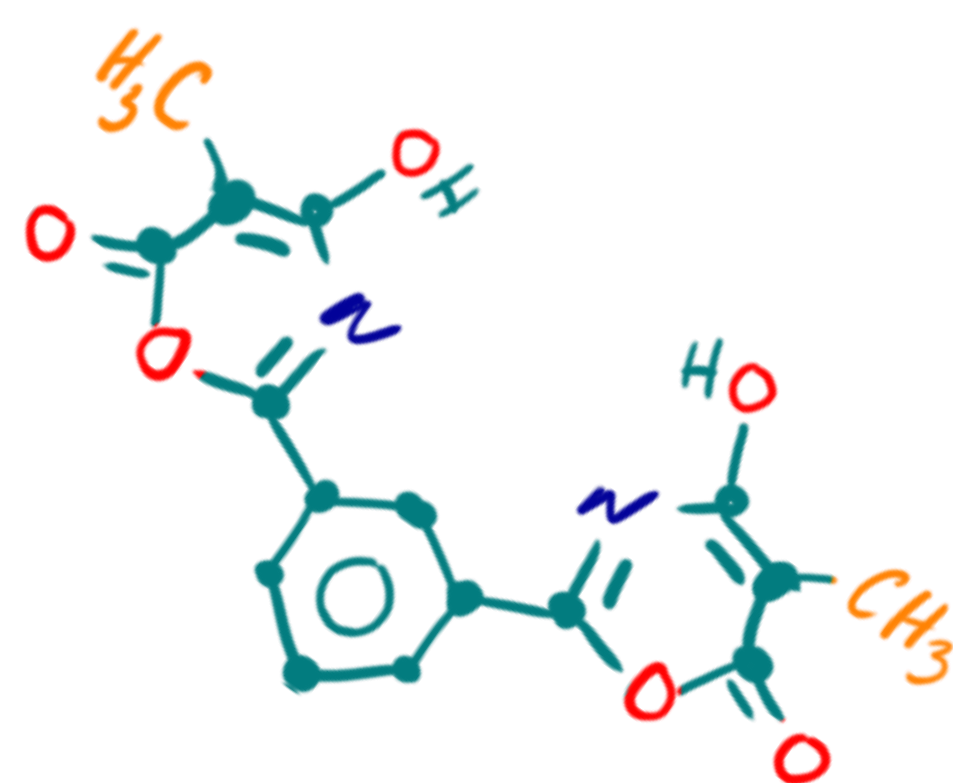


Figure 1. 2,2'-(benzene-1,3-diyl)bis(4-hydroxy-5-methyl-6H-1,3-oxazine-6-one)

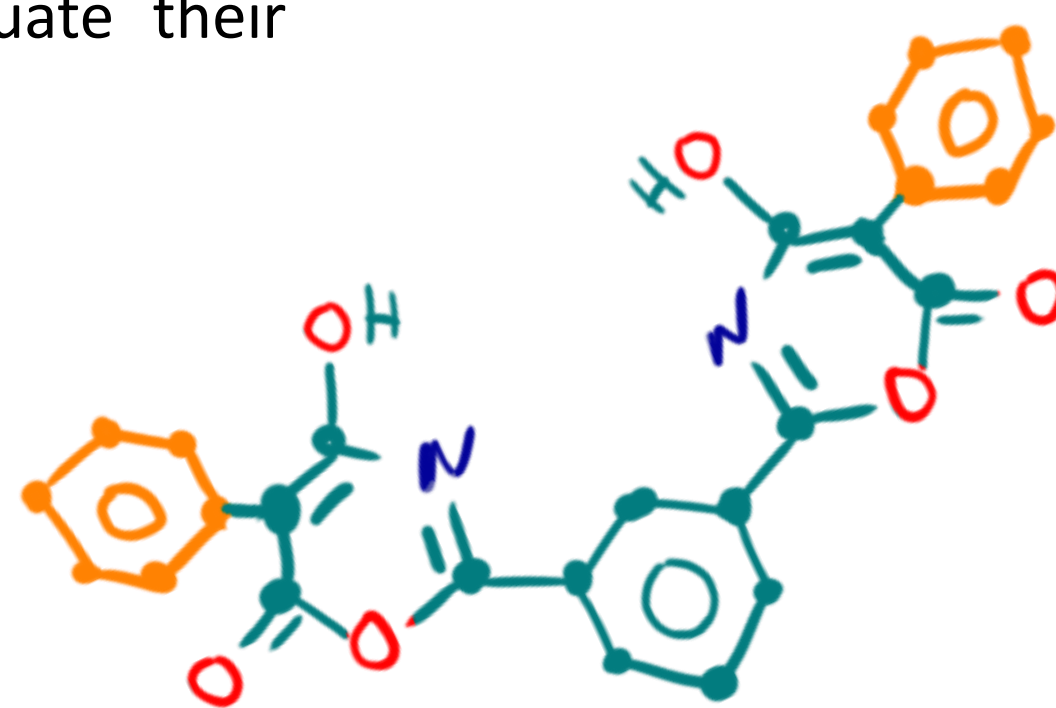
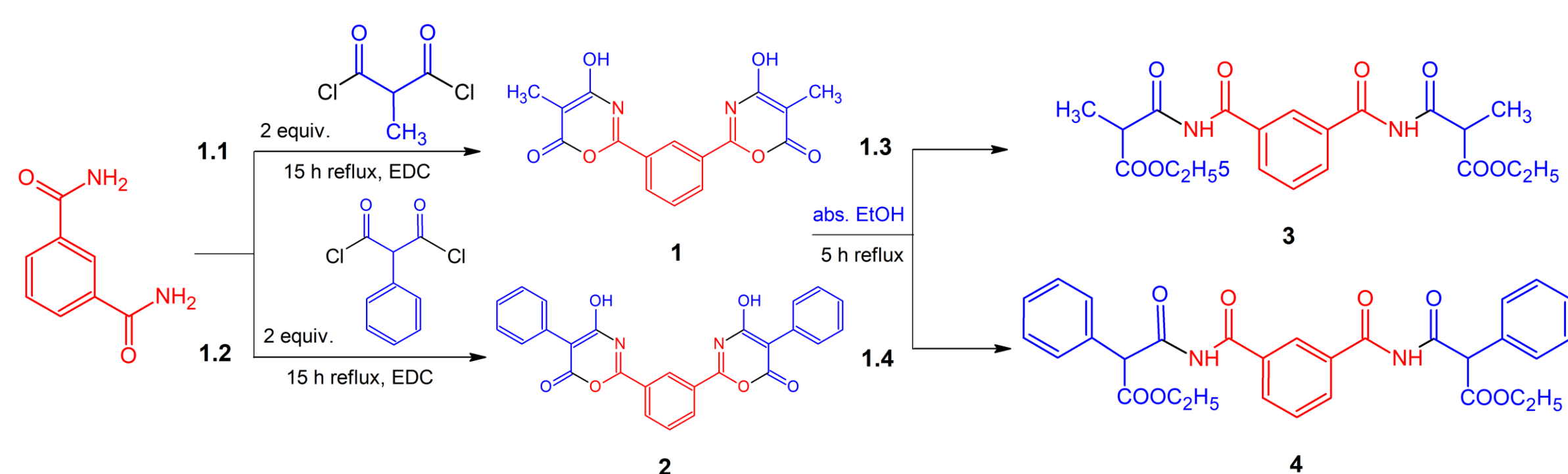


Figure 2. 2,2'-(benzene-1,3-diyl)bis(4-hydroxy-5-phenyl-6H-1,3-oxazine-6-one)

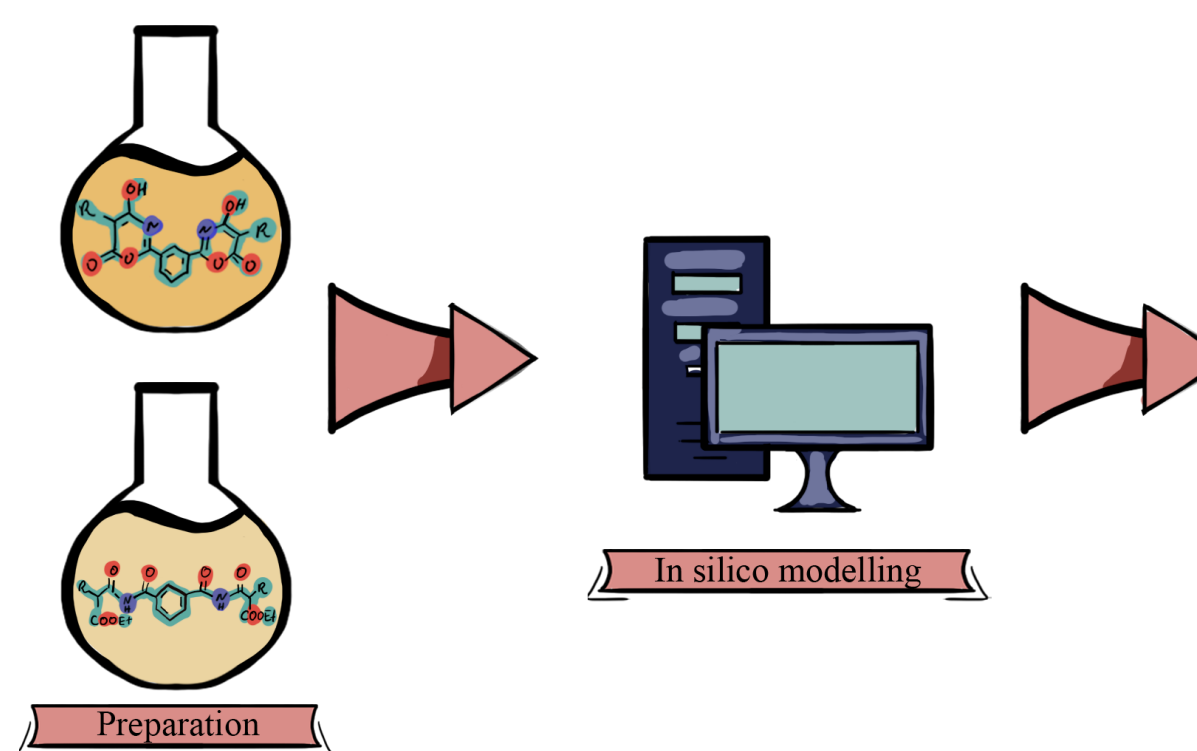
METHOD



Scheme 1. Interaction of benzene-1,3-dicarboxamide with malonyl chlorides, followed by ethanolysis of products 1 and 2

Yields of the compounds:

- 2,2'-(benzene-1,3-diyl)bis(4-hydroxy-5-methyl-6H-1,3-oxazine-6-one) (1) – 90%
- 2,2'-(benzene-1,3-diyl)bis(4-hydroxy-5-phenyl-6H-1,3-oxazine-6-one) (2) – 90%
- Diethyl 3,3'-(isophthaloylbis(azandiylloxy))bis(3-oxo-2-methylpropanoate) (3) – 93%
- Diethyl 3,3'-(isophthaloylbis(azandiylloxy))bis(3-oxo-2-phenylpropanoate) (4) – 89%



CONCLUSION

This paper presents the results of synthesis and *in silico* evaluation of biological activity of bis(4-hydroxy-6H-1,3-oxazin-6-one) derivatives and their ethanolysis products. According to *in silico* biological activity screening bis(1,3-oxazin-6-ones) show antitumor activity with high probability, and ethyl esters of N-acylmalonamic acids demonstrate promising high anxiolytic, antieczematous, fibrinolytic activity. All of the obtained substances are practically non-toxic compounds.

RESULTS & DISCUSSION

The interaction of benzene-1,3-dicarboxamide and substituted malonyl chloride in a 1:2 ratio led to the formation of bis(4-hydroxy-6H-1,3-oxazin-6-ones) (1, 2) after 15 hours of refluxing with a yield of 90%. Further treatment of the latter with ethanol at boiling point resulted in the formation of acyclic ethyl esters of N-acylmalonamic acids (3, 4) with yields of 93% and 89%, respectively. The slight difference in the yield is due to the nature of the substituent at the C₅ position of the oxazine ring. The structure of the obtained compounds was confirmed by NMR spectroscopy on the ¹H and ¹³C nuclei (figures 3, 4).

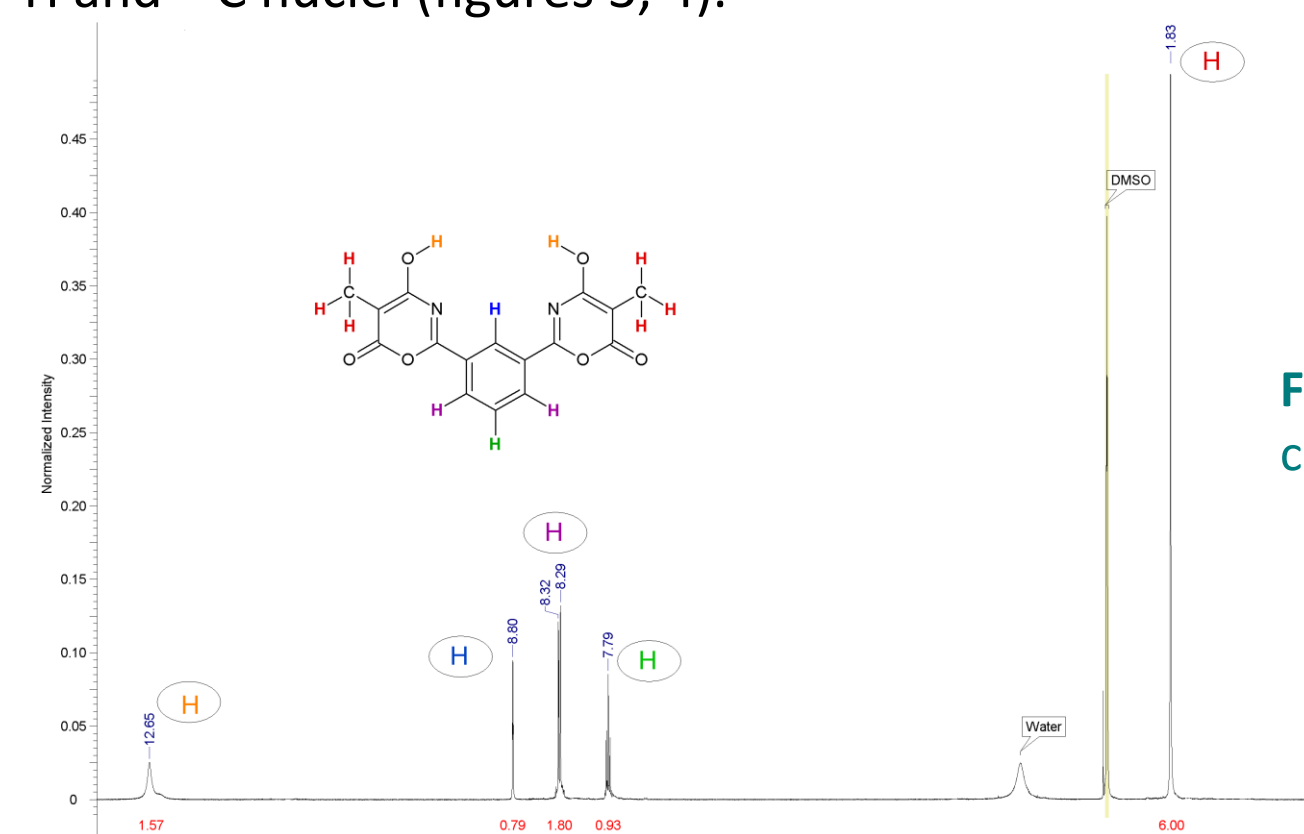


Figure 3. ¹H NMR spectrum of compound 1

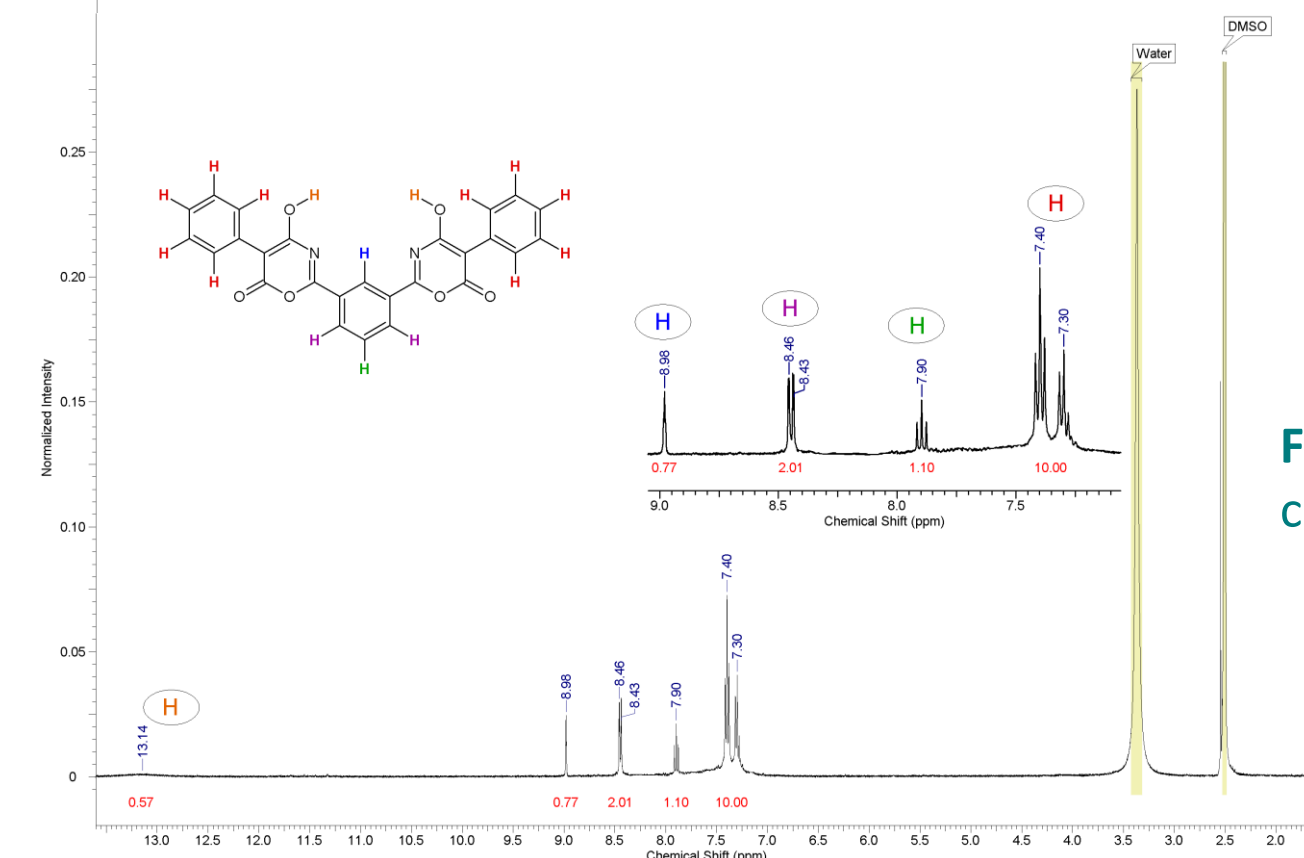


Figure 4. ¹H NMR spectrum of compound 2

For compounds 1-4 the biological activity and acute toxicity based on the classification of chemical compounds by the OECD Project were determined using the PASS online and GUSAR web-resources, *in silico* (figure 5).

Biological activity prediction

Compound	Activity	Pa
1,2	Antitumor	0,7
3,4	Anxiolytic	0,9
	Antieczematous	0,8
	Fibrinolytic	0,7

Rat acute toxicity prediction

Compound	Rat intravenous route of administration LD50 (mg/kg)	Rat oral route of administration LD50 (mg/kg)
1	135	2055
2	143	3533
3	214	1647
4	238	2008

Figure 5. Results of *in silico* screening of biological activity and acute toxicity

FUTURE WORK

This work could be the starting point for studying the reactions of bis(4-hydroxy-6H-1,3-oxazin-6-ones) with other O- and N-nucleophiles, such as water, hydrazine, and phenylhydrazine in order to obtain new molecules with potentially new characteristics.