Synthesis and Antimicrobial Studies of N-Hydroxy-2-(9-oxoacridin-10(9H)-yl)acetamide Derivatives

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Introduction

Emerging pathogen resistance is a global health, agricultural and food industry problem. In October 2020, the World Health Organization declared the resistance of microorganisms to antimicrobial drugs one of the global threats to human health [1]. Therefore, a large number of scientific groups are engaged in the search for new, antibacterial drugs. Such drugs include compounds containing structural fragments of hydroxamic acids and acridine-9(10H)-one (acridone).

Acridne derivatives are known for their biological activity against gram-positive and gram-negative strains of microorganisms [2-4].

At the same time, compounds containing a structural fragment of hydroxamic acid (HA), as well as their derivatives, exhibit a wide range of biological activity with low toxicity [5]. Due to their ability to chelate metal ions they exhibit the ability to inhibit metalloproteases and other enzymes, such as 5-lipoxygenase, urease or ribonucleotide reductase, due to which they exhibit antibacterial, antifungal and anti-inflammatory activity [6].

In this work, we report about the efficient synthesis of two new hydroxamic acids containing structural fragments of acridone and the study of their antimicrobial activity against five pathogenic bacterial and one fungal strains of microorganisms.

Antimicrobial activity

Synthesized compounds and compounds that we described earlier [7] (Figure 1) were tested in vitro for antimicrobial activity against three Gram-negative (*Pseudomonas aeruginosa, Escherichia coli* and *Proteus vulgaris*) and two Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*), as well as antifungal activity against one fungal strain (*Candida albicans*) by agar diffusion method.

The compounds were screened at the concentrations of 20 mg/mL and 10 mg/mL in DMSO using Rivanol as standard by measuring the average zone inhibition in mm.

Table 1. Antimicrobial activity of synthesized compounds.

Compounds	C, mg/ml	E. coli (ATCC 25922)	Ps. aeruginosa (ATCC 27853)	Pr. vulgaris (ATCC 4636)	S. aureus (ATCC 25923)	B. subtilis (ATCC 6633)	Candida albicans (NCTC 2625)
2a	10	10.5	11.0	12.8	8.5	9.0	12.3
	20	9.5	11.5	10.4	9.0	11.0	13.6
2b	10	9.5	11.0	16.6	9.0	18.2	12.5
	20	10.0	11.8	17.6	10.0	25.2	13.0
3	10	8.0	8.0	8.0	9.0	8.0	8.5
	20	9.0	9.0	8.0	9.0	8.0	9.0
4	10	10.0	10.0	8.0	12.5	8.0	11.0
	20*	-	-	-	-	-	-
Rivanol	10	12.7	12.0	12.5	17.0	14.3	13.5
DMSO	-	8.5	9.5	9.5	9.0	7.0	0

* Non-soluble in DMSO at the room temperature.

Almost all the presented compounds do not show antimicrobial activity, except for compound **2b** which shows good inhibitory activity against *Proteus vulgaris* and *Bacillus subtilis*. It is also worth noting the fact that the activity of compound **2a** against *Proteus vulgaris* increases slightly increases upon dilution.

Conclusion

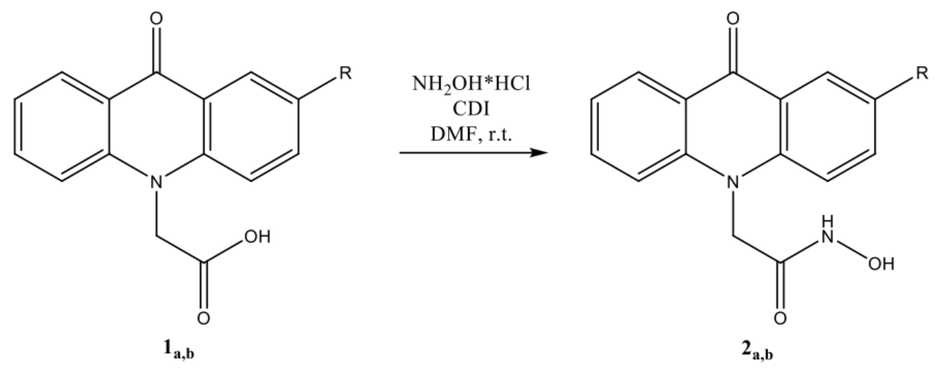
In summary, we have reported on the synthesis of new hydroxamic acids based on acridine-9(10H)-one, which were in high yields using CDI, hydroxylamine hydrochloride and DMF as solvent at room temperature. For prepared compounds was studied of antimicrobial activity against three Gram-negative (*Pseudomonas aeruginosa, Escherichia coli* and *Proteus vulgaris*) and two Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and one fungal pathogen strain (*Candida albicans*). Compound **2b** shows good antibacterial activity against *Proteus vulgaris* and *Bacillus subtilis*. The obtained compounds were characterized by spectrochemical methods, *vis* FT-IR, NMR and Mass-spectrometry.

Methodology

Within the applied procedure, 4 mmol of CDI was added to a solution consisting of 4 mmol of **1** in 10 ml DMF and stirred for 15 min at room temperature. To the resulting solution, 8 mmol of hydroxylamine hydrochloride was added. The mixture was stirred for 24 hours at room temperature. After completion of the reaction, the mixture was poured into water, the precipitate was filtered, washed and dried at 105 ^oC.

The products were purified by recrystallization from DMF.

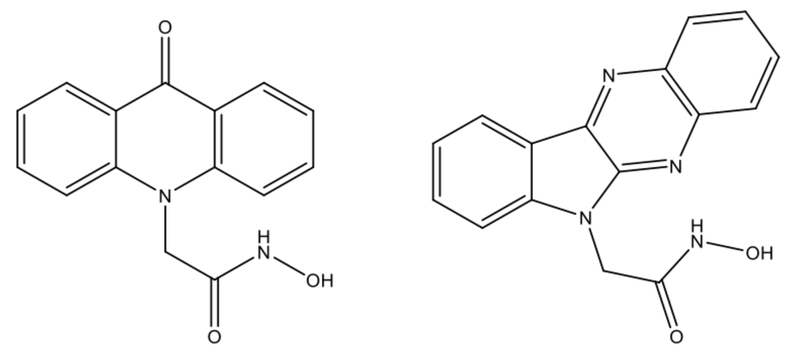
Antimicrobial activity was studied by the agar-disk diffusion method



$1_{a,b}$ $2_{a,b}$

2_a: R = CH_3
2_b: R = F

Scheme 1. Synthesis of Hydroxamic Acids **2**



3 **4**

Figure 1. Structure of: **3** – N-hydroxy-2-(9-oxoacridin-10(9H)-yl)acetamide; **4** – N-hydroxy-2-(6H-indolo[2,3-b]quinoxalin-6-yl)acetamide.

References

[1] WHO Antimicrobial Resistanse. Available online: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance (accessed on 13 October 2022)

[2] Aarjane, M., Slassi, S., Tazi, B., Maouloula. M., Amine Novel series of acridone-1,2,3-triazole derivatives: microwave-assisted synthesis, DFT study and antibacterial activities. *J Chem Sci, 131, 85.*, 2019. doi: 10.1007/s12039-019-1653-2.

[3] Aarjane, M., Aouidate, A., Slassi, S., Amine, A. Synthesis, antibacterial evaluation, in silico ADMET and molecular docking studies of new N-acylhydrazone derivatives from acridone. *Arab J Chem , 13, 6236-6245.*, 2020. doi: 10.1016/j.arabjc.2020.05.034.

[4] Markovich, Y.D., Kudryavtseva, T.N., Bogatyrev, K.V., et al. Synthesis of 2-(4-methyl-1,3-thiazol-5-yl)ethyl esters of acridone carboxylic acids and evaluation of their antibacterial activity. *Russ Chem Bull , 63, 1153–1158.*, 2014. doi: 10.1007/s11172-014-0564-0

[5] Jahangirian, H., Saleh, B., Kalantari, K., Rafiee-Moghaddam R., Nikpey, B., Jahangirian, S., Webster, T.J. Enzymatic Synthesis of Ricinoleyl Hydroxamic Acid Based on Commercial Castor Oil, Cytotoxicity Properties and Application as a New Anticancer Agent. *Int J Nanomedicine , 15, 2935-2945.*, 2020. doi: 10.2147/IJN.S223796

[6] Laronha, H., Carpinteiro, I.; Portugal, J.; Azul, A.; Polido, M.; Petrova, K.T.; Salema-Oom, M., Caldeira, J. Challenges in Matrix Metalloproteinases Inhibition. *Bio,olecules , 10, 717.*, 2020. doi: 10.3390/biom10050717

[7] Melnichenko, V.E., Kudryavtseva, T.N., Lamanov, A.Y., Vanina, A.S., Grekhnyova, E.V. Synthesis of several new hydroxamic acids containing heterocyclic fragment. *CDC , 35, 100759.*, 2021. 100759. doi: 10.1016/j.cdc.2021.100759.