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Synthesis and Antimicrobial Studies of N-Hydroxy-2-(9-Oxoacridin-10(9H)-yl)Acetamide Derivatives†

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Abstract: In this paper, we reported the synthesis of new hydroxamic acids, containing a heteroaromatic fragment of acridine-9(10H)-one. These compounds were prepared by the interaction of corresponding carboxylic acid with hydroxylamine hydrochloride in the presence of CDI in DMF solution. The structure of obtained compounds was confirmed by IR, Mass-spectrometry, ^{1}H and ^{13}C NMR analyzed methods. Obtained compounds were screened for their in vitro antimicrobial activity against five bacterial and one fungal pathogens. Some synthesized compounds showed high efficiency against the gram-positive strain *Bacillus subtilis* and gram-negative strain *Proteus vulgaris*.

Keywords: acridine-9(10H)-one; hydroxamic acid; hydroxylamine; antimicrobial activity

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1. 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 as 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(10*H*)-one (acridone).

Acridine derivatives are known for their biological activity against gram-positive and gram-negative strains of microorganisms [2–5]. For example, it has been described in the work [6] that various oxoazole derivatives of acridone exhibit high activity against gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris*) and gram-positive strains (*Staphylococcus aureus*, *Bacillus subtilis*), commensurate with known antibiotic ofloxacin. And in relation to the fungal strain of *Candida albicans*, it is more active than ofloxacin. Also, among the derivatives of acridone there are compounds with anticancer activity. In particular, N-[2-(diethylamino)ethyl]-4-nitro-9-oxo- 9,10-dihydroacridine-1-carboxamide showed activity against breast adenocarcinoma MCF-7 [7].

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 [8]. 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 [9–13].

In this work, we report on 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.

2. Materials and Methods

2.1. Instrumentation and Chemicals

All the chemicals were obtained from Sigma Aldrich and used without further purification unless otherwise specified. Melting point ranges of solid compounds were determined with the open capillary method on the Electrothermal IA 9100. Progress of the reaction was monitored by TLC using Merck silica gel 60 F254 precoated on aluminium-backed plates. FSM-1201 was used to record FTIR spectra using KBr pellets. 1H nuclear magnetic resonance spectra of compounds have been recorded on Brucker AV-600 spectrometer using DMSO-d6 as solvent and TMS was chosen as an internal standard and chemical shifts were expressed as δ values (ppm). Mass spectra were recorded using ACQUITY SQD. Elemental analysis was performed on Perkin Elmer 2400 CHN-analyzer. The results of the elemental analysis were within ±0.4% of the theoretical values. Antimicrobial activity was studied by the agar-disk diffusion method.

2.2. General Procedure for the Synthesis of Hydroxamic Acids 2

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 h at room temperature. After completion of the reaction, the mixture was poured into water, the precipitate was filtered, washed and dried at 105 °C. The products were purified by recrystallization from DMF.

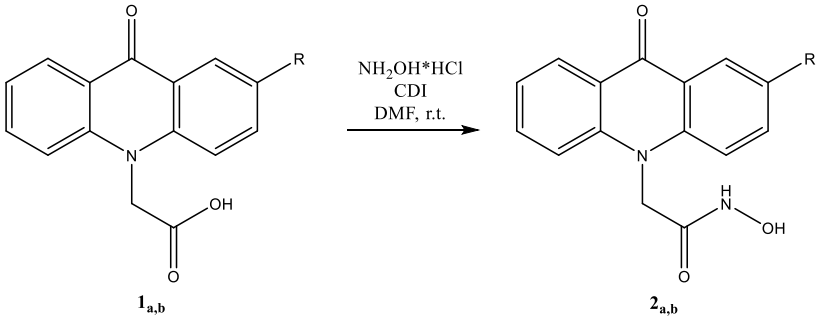
N-hydroxy-2-(2-methyl-9-oxoacridin-10(9H)-yl)acetamide: Light yellow solid; m.p. 203–206 °C; FT-IR (KBr) ν_{max} (cm^{-1}): 3204 (N-H_{amide}), 1658 (C = O_{amide}), 1638 (C = O_{Ar}), 1614 (C-N); ^{1}H NMR (DMSO-d6, 600 MHz): Shift = 11.03 (s, 1 H), 9.11 (s, 1 H), 8.35 (dd, J = 8.0, 1.5 Hz, 1 H), 8.14 (s, 1 H), 7.77–7.81 (m, 1 H), 7.64 (d, J = 8.6 Hz, 2 H), 7.55–7.59 (m, 1 H), 7.33 (t, J = 7.4 Hz, 1 H), 5.10 (s, 2 H), 2.44 ppm (s, 3 H); ^{13}C NMR (DMSO-d6, 151 MHz): Shift = 142.8, 141.1, 135.7, 134.3, 131.1, 127.0, 126.2, 122.1, 121.7, 116.4, 116.3, 47.1, 20.7; EI-MS: 283[M^{+}]. Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92; O, 17.00 Found: C, 68.32; H, 4.89; N, 10.05; O, 16.74.

2-(2-fluoro-9-oxoacridin-10(9H)-yl)-N-hydroxyacetamide: Light yellow solid; m.p. 218–220 °C; FT-IR (KBr) ν_{max} (cm^{-1}): 3213 (N-H_{amide}), 1669 (C = O_{amide}), 1616 (C-N_{Ar}); ^{1}H NMR (DMSO-d6, 600 MHz): Shift = 11.04 (s, 1 H), 9.14 (br. s., 1 H), 8.34 (dd, J = 8.0, 1.5 Hz, 1 H), 7.98 (dd, J = 8.7, 2.3 Hz, 1 H), 7.83 (td, J = 7.8, 1.6 Hz, 1 H), 7.73–7.77 (m, 2 H), 7.66 (d, J = 8.7 Hz, 1 H), 7.36 (t, J = 7.4 Hz, 1 H), 5.14 ppm (s, 2 H); ^{13}C NMR (DMSO-d6, 151 MHz): Shift = 176.5, 164.5, 158.4, 156.8, 142.8, 139.8, 134.7, 127.0, 122.8, 122.2, 121.4, 119.4, 116.4, 110.8, 47.6 ppm; EI-MS: 287[M^{+}]. Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 62.94; H, 3.87; F, 6.64; N, 9.79; O, 16.77 Found: C, 63.12; H, 3.68; N, 10.13.

3. Results and Discussion

3.1. Synthesis and Characterization

Previously we reported on the synthesis of hydroxamic acids containing acridone fragments by aminolysis reaction of the corresponding butyl esters in a DMF/BuOH solvent mixture in the presence of BuONa [14]. However, this method of the synthesis of hydroxamic acids turned out to be ineffective in the presence of a substitute in the aromatic ring of acridone. Therefore, for preparing the compounds **2** we carried out the reaction of the corresponding carboxylic acids with hydroxylamine hydrochloride in DMF with CDI at room temperature for 24 h (Scheme 1).



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

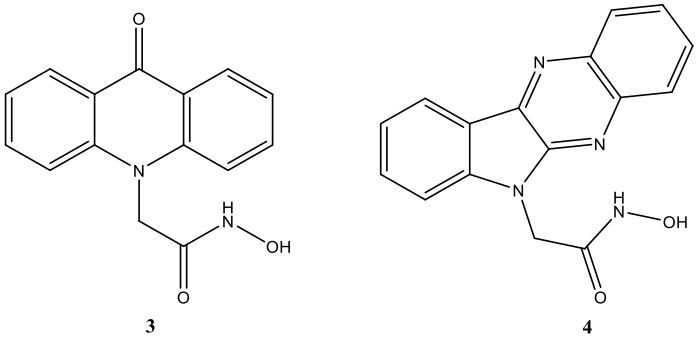
2_a: R = CH_3
2_b: R = F

Scheme 1. Synthesis of compounds **2.**

Synthesized compounds are light yellow solids, non-soluble in water and poorly soluble in most organic solvents.

3.2. Antimicrobial Activity

Synthesized compounds and compounds that we described earlier [14] (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 (Table 1).



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.

Table 1. Antimicrobial activity of synthesized compounds.

Compounds	C, mg/mL	*E. coli* (ATCC 25,922)	*Ps. aeruginosa* (ATCC 27,853)	*Pr. vulgaris* (ATCC 4636)	*S. aureus* (ATCC 25,923)	*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.

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.

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.

4. Conclusions

In summary, we have reported on the synthesis of new hydroxamic acids based on acridine-9(10*H*)-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*), 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.

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