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Synthesis and Study of Antimicrobial Activity of 2-Dithiocarbamate-*N*-(9,10-Dioxo-9,10-Dihydroanthracenyl)Acetamides

Viktor Zvarych [1], Maryna Stasevych [1,*], Volodymyr Novikov [1], Mykhailo Vovk [2]

[1] Department of Technology of Biologically Active Substances, Pharmacy, and Biotechnology, Lviv Polytechnic National University, 13, 79013 Lviv, Ukraine
[2] Department of Mechanism of Organic Reactions, Institute of Organic Chemistry of National Academy of Sciences of Ukraine, 02660 Kyiv, Ukraine
* Correspondence: maryna.v.stasevych@lpnu.ua;

Scopus Author ID 8636372500
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Abstract: The global emergence and dissemination of multidrug-resistant fungal and bacterial pathogens is a serious public health threat. The development of novel highly active antimicrobial compounds simultaneously targeting several targets in bacterial or fungal pathogens could help to fight antimicrobial resistance. The four-component one-pot two-step facile synthesis of a new 2-dithiocarbamate-N-(9,10-dioxo-9,10-dihydroanthracenyl)acetamides 3a-n by the interaction of 2-chloro-*N*-(9,10-dioxo-9,10-dihydroanthracenyl)acetamide 1 or 2 with a series of *in situ* generated potassium salt of dithiocarbamic acids in DMF-H_2O is presented. Evaluation of the antimicrobial activity of the synthesized compounds against bacteria strains *Escherichia coli B-906, Staphylococcus aureus 209-P, Mycobacterium luteumB-917*, and fungi *Candida tenuis VKM Y-70, Aspergillus niger VKM F-1119* has been carried out by the diffusion in agar method and by the serial dilution technique. It has been established that synthesized compounds 3a, 3i, 3j have the good antibacterial activity against strain *M. luteum* at a concentration of 0.5% and the dithiocarbamates 3b, 3i, 3j, 3n demonstrate antifungal effect against *C. tenuis* at *the* same concentration. The results of the serial dilution technique showed that compound 3j has high antibacterial action at MIC 3.9 μg/ml.

Keywords: 2-chloro-*N*-(9,10-dioxo-9,10-dihydroanthracenyl)acetamide; dithiocarbamates; *in vitro* study; antibacterial activity; antifungal activity.

1. Introduction

The global emergence and dissemination of multidrug-resistant (MDR) *Mycobacterium tuberculosis*, *Staphylococcus aureus*, and non-fermentative Gram-negative bacilli such as *Pseudomonas aeruginosa* is an increasingly important global public health concern [1-2]. Moreover, lack of active antifungal agents, rising antifungal resistance, and emergence of MDR fungal pathogens is a serious public health threat [3-9]. MDR organisms generated in clinical or veterinarian sectors can persist in the environment, are capable of colonizing hosts, and then spread outside primary sites (farms, hospitals). Once the colonized host immune system is impaired, MDR fungal and bacterial pathogens can cause devastating infections that are often non-responsive to standard and even last-line treatment options. Therefore, the development of novel highly active antimicrobial compounds simultaneously targeting several targets in bacterial or fungal pathogens could help to fight antimicrobial resistance.

Dithiocarbamates are valuable synthetic products [10] and are a class of perspective compounds with different types of biological activities. In particular, antibacterial and antifungal agents [11-18] were found among them. The functionalization of dithiocarbamates with biophore fragments has proven to be especially useful in creating combinatorial libraries for rapid screening [19] and drug design [20-22].

From the other side, the anthraquinone core is one of the key quinone molecular platforms, which has a strong synthetic, applied, and pharmacological potential [23-24]. The substances with a high antimicrobial effect were revealed among anthraquinone derivatives of both natural and synthetic origin [25-30].

In the context of the above, the aim of our work was the synthesis of a new hybrid anthraquinone-dithiocarbamate derivatives and the investigation of their antibacterial and antifungal properties for identifying potential antimicrobial agents among them.

2. Materials and Methods

2.1. Materials.

All chemicals were of reagent grade and used without further purification. The solvents were purified according to the standard procedures [31]. The initial 2-chloroacetamides **1,2** were prepared from 1-amino-9,10-dioxo-9,10-dihydroanthracene (Sigma-Aldrich) and 2-amino-9,10-dioxo-9,10-dihydroanthracene (Sigma-Aldrich) according to the method described in [26].

2.2. Chemistry.

Melting points were measured on a Boetius melting point-device and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in DMSO-d_6 solutions on a Varian Mercury-400 spectrometer with TMS as an internal standard. Mass spectra were recorded on an Agilent 1100 Series G1956BLC/MSD SL LCMS system using electrospray ionization at atmospheric pressure (70 eV). Elemental analysis was performed on a PerkinElmer CHN-analyzer Series 2400. The individuality of the obtained compounds was monitored by TLC on Silufol UV-254 plates.

General procedure for the synthesis of 2-dithiocarbamate-*N*-(9,10-dioxo-9,10-dihydroanthracenyl)acetamides 3a-n. To 1 ml of water, 0.103 g (1.87 mmol) of KOH, 10 ml of dimethylformamide, 1.87 mmol of the corresponding secondary amine, and 0.12 ml (1.87 mmol) of carbon disulfide were successively added and stirred at room temperature for 1 h (with dicyclohexylamine 12 h). Than 0.5 g (1.70 mmol) of 2-chloro-*N*-acetamide **1** or **2** in 40 ml of dimethylformamide was added to the mixture, and stirred for 1 h. Then it was heated at 70 °C for 5 hours. The reaction mixture was cooled, and 150 ml of water was added. The precipitate formed was filtered off, washed with water and dried.

2-((9,10-Dioxo-9,10-dihydroanthracen-1-yl)amino)-2-oxoethyl azepane-1-carbodithioate 3a. Yield 74%; m.p.: 184 ºC (decomposition). ^{1}H NMR: δ = 12.48 (br. s, 1H, NH), 8.95 (dd, 1H, *J* = 17.1, 8.0 Hz, CHar), 8.19-8.07 (m, 2H, CH_{ar}), 7.94-7.81 (m, 4H, CH_{ar}), 4.34 (s, 2H, CH_2), 4.16-4.06 (m, 4H, CH_2), 2.04-1.88 (m, 2H, CH_2), 1.81-1.71 (m, 2H, CH_2), 1.64-1.44 (m, 4H, CH_2). ^{13}C NMR: δ = 193.51 (C=S), 186.64, 182.45, 167.82 (C=O), 141.43, 136.16, 135.10, 134.31, 134.02, 132.76, 127.25, 126.92, 125.66, 122.49, 118.31 (C_{ar}), 55.96, 53.38, 41.42, 27.95, 27.29, 26.47, 25.91 (CH_2). LC-MS: *m/z* = 439 [M+1] (100%). Anal. Calcd.

for $C_{23}H_{22}N_2O_3S_2$, %: C 62.99; H 5.06; N 6.39; S 14.62. Found, %: C 63.03; H 5.01; N 6.43; S 14.69.

2-((9,10-Dioxo-9,10-dihydroanthracen-1-yl)amino)-2-oxoethyl dibenzylcarbamodithioate 3b. Yield 75%; m.p.: 195 ºC (decomposition). ^{1}H NMR: δ = 12.64 (br. s, 1H, NH), 9.01 (d, 1H, *J* = 8.3 Hz, CH_{ar}), 8.12 (m, 2H, CH_{ar}), 7.96-7.85 (m, 4H, CH_{ar}), 7.41-7.07 (m, 10H, CH_{ar}), 5.32-5.23 (m, 4H, CH_2), 4.40 (s, 2H, CH_2). ^{13}C NMR: δ = 197.03 (C=S), 186.77, 182.48, 167.57 (C=O), 141.45, 136.38, 135.70, 135.30, 135.22, 135.10, 134.26, 133.83, 132.65, 129.38, 128.82, 128.27, 127.76, 127.55, 126.92, 125.46, 122.57, 118.05 (C_{ar}), 57.72, 55.46, 42.09 (CH_2). LC-MS: *m/z* = 537 [M+1] (100%). Anal. Calcd. for $C_{31}H_{24}N_2O_3S_2$, %: C 69.38; H 4.51; N 5.22; S 11.95. Found, %: C 69.43; H 4.46; N 5.27; S 11.91.

2-((9,10-Dioxo-9,10-dihydroanthracen-1-yl)amino)-2-oxoethyl dibutylcarbamodithioate 3c. Yield 92%; m.p.: 197 ºC (decomposition). ^{1}H NMR: δ = 12.49 (br. s, 1H, NH), 8.95 (dd, 1H, *J* = 15.0, 8.2 Hz, CH_{ar}), 8.18-8.07 (m, 3H, CH_{ar}), 7.97-7.81 (m, 3H, CH_{ar}), 4.34 (d, 2H, *J* = 9.2 Hz, CH_2), 3.90 (s, 4H, CH_2), 1.91-1.78 (m, 2H, CH_2), 1.67-1.54 (m, 3H, CH_2), 1.50-1.38 (m, 2H, CH_2), 1.27-1.17 (m, 1H, CH_2), 1.00 (t, 3H, *J* = 7.4 Hz, CH_3), 0.77 (t, 3H, *J* = 6.9 Hz, CH_3). ^{13}C NMR: δ = 193.89 (C=S), 186.78, 182.51, 167.70 (C=O), 141.28, 136.25, 136.20, 135.18, 134.27, 134.00, 132.69, 127.38, 127.28, 126.91, 125.58, 122.49, 118.33 (C_{ar}), 57.19, 55.33, 41.79, 29.50, 28.27, 20.09, 19.93 (CH_2), 14.15, 14.09 (CH_3). LC-MS: *m/z* = 470 [M+1] (100%). Anal. Calcd. for $C_{25}H_{28}N_2O_3S_2$, %: C 64.08; H 6.02; N 5.98; S 13.68. Found, %: C 64.02; H 6.06; N 5.93; S 13.75.

2-((9,10-Dioxo-9,10-dihydroanthracen-1-yl)amino)-2-oxoethyl dipropylcarbamodithioate 3d. Yield 69%; m.p.: 199 ºC (decomposition). ^{1}H NMR: δ = 12.49 (br. s, 1H, NH), 8.95 (d, 1H, *J* = 8.0 Hz, CH_{ar}), 8.09 (d, 2H, *J* = 6.7 Hz, CH_{ar}), 7.90-7.86 (m, 4H, CH_{ar}), 4.33 (d, 2H, *J* = 6.7 Hz, CH_2), 3.90-3.85 (m, 4H, CH_2), 1.92-1.85 (m, 2H, CH_2), 1.69-1.62 (m, 2H, CH_2), 1.02 (t, 3H, *J* = 6.9 Hz, CH_3), 0.80 (t, 3H, *J* = 7.1 Hz, CH_3). ^{13}C NMR: δ = 193.25 (C=S), 186.66, 182.52, 167.71 (C=O), 141.37, 136.20, 135.16, 134.29, 134.01, 132.71, 127.39, 127.22, 126.92, 125.58, 122.50, 118.36 (C_{ar}), 57.09, 54.68, 41.79, 20.88, 19.47 (CH_2), 11.57, 11.37 (CH_3). LC-MS: *m/z* = 442 [M+1] (100%). Anal. Calcd. for $C_{23}H_{24}N_2O_3S_2$, %: C 62.70; H 5.49; N 6.36; S 14.55. Found, %: C 62.76; H 5.42; N 6.31; S 14.62.

2-((9,10-Dioxo-9,10-dihydroanthracen-1-yl)amino)-2-oxoethyl dicyclohexylcarbamodithioate 3e. Yield 71%; m.p.: 243 ºC (decomposition). ^{1}H NMR: δ = 12.45 (br. s, 1H, NH), 8.94 (dd, 1H, *J* = 24.2, 7.3 Hz, CH_{ar}), 8.16-8.05 (m, 2H, CH_{ar}), 7.89-7.81 (m, 3H, CH_{ar}), 4.33 (s, 2H, CH_2), 4.29-4.22 (m, 4H, CH_2), 2.05-1.15 (m, 20H, CH_2). ^{13}C NMR: δ = 193.89 (C=S), 186.74, 182.46, 167.69 (C=O), 141.28, 136.20, 135.18, 135.13, 134.23, 133.96, 132.70, 132.65, 127.37, 126.90, 125.56, 125.49, 122.49, 118.26 (C_{ar}), 56.46 (CH), 41.80, 35.10, 26.01, 24.73 (CH_2). LC-MS: *m/z* = 522 [M+1] (100%). Anal. Calcd. for $C_{29}H_{32}N_2O_3S_2$, %: C 66.89; H 6.19; N 5.38; S 12.31. Found, %: C 66.94; H 6.15; N 5.43; S 12.39.

2-((9,10-Dioxo-9,10-dihydroanthracen-1-yl)amino)-2-oxoethyl diethylcarbamodithioate 3f. Yield 78%; m.p.: 201 ºC (decomposition). ^{1}H NMR: δ = 12.57 (br. s, 1H, NH), 9.00 (m, 1H, CH_{ar}), 8.16 (m, 2H, CH_{ar}), 7.93 (m, 4H, CH_{ar}), 4.33 (d, 2H, *J* = 6.7 Hz, CH_2), 3.97 (m, 4H, CH_2), 1.42 (t, 3H, *J* = 7.0 Hz, CH_3), 1.14 (t, 3H, *J* = 7.1 Hz, CH_3). ^{13}C NMR: δ = 192.72 (C=S), 186.62, 182.45, 167.78 (C=O), 141.40, 136.15, 135.13, 134.30, 134.00, 132.75, 127.27, 126.92, 125.66, 122.49, 118.32 (C_{ar}), 50.13, 47.50, 41.40 (CH_2), 12.92, 11.68 (CH_3). LC-MS: *m/z* = 414 [M+1] (100%). Anal. Calcd. for $C_{21}H_{20}N_2O_3S_2$, %: C 61.14; H 4.89; N 6.79; S 15.54. Found, %: C 61.20; H 4.81; N 6.83; S 15.61.

2-((9,10-Dioxo-9,10-dihydroanthracen-1-yl)amino)-2-oxoethyl 1*H*-imidazole-1-carbodithioate 3g. Yield 75%; m.p.: 187 ºC (decomposition). ^{1}H NMR: δ = 12.32 (br. s, 1H, NH), 8.90-8.80 (m, 1H, CH_{ar}), 8.08-7.95 (m, 3H, CH_{ar}+imidazole), 7.88-7.62 (m, 6H, CH_{ar}+imidazole), 4.39 (d, 2H, *J* = 7.3 Hz, CH_2). ^{13}C NMR: δ = 194.17 (C=S), 186.70, 182.30, 167.55 (C=O), 141.29, 140.74, 136.07, 135.09, 134.27, 133.93, 132.69, 127.49, 127.35, 126.87, 125.81, 125.72, 122.95, 122.46, 118.36 (C_{ar}), 44.06 (CH_2). LC-MS: *m/z* = 408 [M+1] (100%). Anal. Calcd. for $C_{20}H_{13}N_3O_3S_2$, %: C 58.96; H 3.22; N 10.31; S 15.74. Found, %: C 58.91; H 3.25; N 10.35; S 15.69.

2-((9,10-Dioxo-9,10-dihydroanthracen-1-yl)amino)-2-oxoethyl morpholine-4-carbodithioate 3h. Yield 89%; m.p.: 226 ºC (decomposition). ^{1}H NMR: δ = 12.50 (br. s, 1H, NH), 8.99-8.94 (m, 1H, CH_{ar}), 8.18-8.10 (m, 2H, CH_{ar}), 7.89 (m, 4H, CH_{ar}), 4.37 (d, 2H, *J* = 17.2 Hz, CH_2), 4.21-4.16 (m, 4H, CH_2), 3.81-3.70 (m, 4H, CH_2). ^{13}C NMR: δ = 194.15 (C=S), 186.89, 182.64, 162.77 (C=O), 136.24, 135.21, 132.81, 127.32, 126.98, 125.59, 125.51, 122.57 (C_{ar}), 66.10, 66.02, 52.21, 51.27, 42.07 (CH_2). LC-MS: *m/z* = 428 [M+1] (100%). Anal. Calcd. for $C_{21}H_{18}N_2O_4S_2$, %: C 59.14; H 4.25; N 6.57; S 15.03. Found, %: C 59.18; H 4.21; N 6.62; S 15.09.

2-((9,10-Dioxo-9,10-dihydroanthracen-1-yl)amino)-2-oxoethyl pyrrolidine-1-carbodithioate 3i. Yield 80%; m.p.: 210 ºC (decomposition). ^{1}H NMR: δ = 12.40 (br. s, 1H, NH), 8.98-8.88 (m, 1H, CH_{ar}), 8.24-8.08 (m, 2H, CH_{ar}), 8.00-7.80 (m, 4H, CH_{ar}), 4.38 (s, 2H, CH_2), 3.94-3.76 (m, 4H, CH_2), 2.19-2.09 (m, 2H, CH_2), 2.04-1.92 (m, 2H, CH_2). ^{13}C NMR: δ = 189.81 (C=S), 186.70, 182.45, 167.68 (C=O), 141.38, 136.06, 135.09, 134.39, 134.13, 132.83, 127.27, 126.92, 125.81, 122.53, 118.56 (C_{ar}), 55.90, 51.35, 39.75, 26.21, 24.32 (CH_2). LC-MS: *m/z* = 412 [M+1] (100%). Anal. Calcd. for $C_{21}H_{18}N_2O_3S_2$, %: C 61.44; H 4.42; N 6.82; S 15.62. Found, %: C 61.49; H 4.37; N 6.76; S 15.69.

2-((9,10-Dioxo-9,10-dihydroanthracen-2-yl)amino)-2-oxoethyl azepane-1-carbodithioate 3j. Yield 90%; m.p.: 175 ºC (decomposition). ^{1}H NMR: δ = 10.82 (br. s, 1H, NH), 8.41-8.39 (m, 1H, CH_{ar}), 8.14-8.10 (m, 3H, CH_{ar}), 8.01 (d, 1H, *J* = 8.4 Hz, CH_{ar}), 7.88-7.85 (m, 2H, CH_{ar}), 4.31 (s, 2H, CH_2), 4.13-4.09 (m, 2H, CH_2), 3.97-3.92 (m, 2H, CH_2), 1.84-1.74 (m, 4H, CH_2), 1.53-1.49 (m, 4H, CH_2). ^{13}C NMR: δ = 194.39 (C=S), 182.79, 181.70, 166.93 (C=O), 144.88, 134.96, 134.62, 134.56, 133.54, 133.50, 128.93, 128.41, 127.15, 127.07, 124.14, 116.25 (C_{ar}), 55.69, 53.12, 41.80, 27.25, 26.57, 26.39, 25.99 (CH_2). LC-MS: *m/z* = 440 [M+1] (100%). Anal. Calcd. for $C_{23}H_{22}N_2O_3S_2$, %: C 62.99; H 5.06; N 6.39; S 14.62. Found, %: C 62.92; H 5.11; N 6.31; S 14.54.

2-((9,10-Dioxo-9,10-dihydroanthracen-2-yl)amino)-2-oxoethyl diethylcarbamodithioate 3k. Yield 79%; m.p.: 210 ºC (decomposition). ^{1}H NMR: δ = 10.76 (br. s, 1H, NH), 8.43-8.41 (m, 1H, CH_{ar}), 8.17-8.15 (m, 2H, CH_{ar}), 8.14-8.13 (m, 1H, CH_{ar}), 8.04 (d, 1H, *J* = 8.5 Hz, CH_{ar}), 7.89-7.86 (m, 2H, CH_{ar}), 4.32 (s, 2H, CH_2), 3.98-3.83 (m, 4H, CH_2), 1.24 (s, 6H, CH_3). ^{13}C NMR: δ = 193.62 (C=S), 182.81, 181.72, 166.95 (C=O), 144.89, 134.98, 134.64, 134.59, 133.55, 133.52, 128.96, 128.42, 127.16, 127.08, 124.14, 116.24 (C_{ar}), 49.84, 47.28, 41.80 (CH_2), 12.91, 11.82 (CH_3). LC-MS: *m/z* = 414 [M+1] (100%). Anal. Calcd. for $C_{21}H_{20}N_2O_3S_2$, %: C 61.14; H 4.89; N 6.79; S 15.54. Found, %: C 61.19; H 4.95; N 6.83; S 15.48.

2-((9,10-Dioxo-9,10-dihydroanthracen-2-yl)amino)-2-oxoethyl 4-methylpiperazine-1-carbodithioate 3l. Yield 80%; m.p.: 147 ºC (decomposition). ^{1}H NMR: δ = 10.91 (br. s, 1H, NH), 8.37-8.35 (m, 1H, CH_{ar}), 8.09-8.04 (m, 3H, CH_{ar}), 7.99 (d, 1H, *J* = 7.9 Hz, CH_{ar}), 7.83-7.81 (m, 2H, CH_{ar}), 4.32 (d, 2H, *J* = 11.9 Hz, CH_2), 4.17-3.93 (m, 4H, CH_2), 2.41-2.39 (m, 4H,

CH_2), 2.20 (s, 3H, CH_3). ^{13}C NMR: δ = 194.93 (C=S), 182.72, 181.62, 166.86 (C=O), 144.87, 134.89, 134.55, 134.49, 133.48, 128.85, 128.35, 127.10, 127.02, 124.10, 116.23 (C_{ar}), 54.45, 54.43, 51.54, 50.21 (CH_2), 45.55 (CH_3), 41.91 (CH_2). LC-MS: *m/z* = 441 [M+1] (100%). Anal. Calcd. for $C_{22}H_{21}N_3O_3S_2$, %: C 60.12; H 4.82; N 9.56; S 14.59. Found, %: C 60.18; H 4.76; N 9.59; S 14.62.

2-((9,10-Dioxo-9,10-dihydroanthracen-2-yl)amino)-2-oxoethyl morpholine-4-carbodithioate 3m. Yield 78%; m.p.: 232 ºC (decomposition). ^1H NMR: δ = 10.88 (br. s, 1H, NH), 8.42-8.38 (m, 1H, CH_{ar}), 8.16-8.09 (m, 3H, CH_{ar}), 8.02 (d, 1H, *J* = 8.4 Hz, CH_{ar}), 7.90-7.84 (m, 2H, CH_{ar}), 4.35 (s, 2H, CH_2), 4.20-4.01 (m, 4H, CH_2), 3.71-3.68 (m, 4H, CH_2). ^{13}C NMR: δ = 195.36 (C=S), 182.81, 181.73, 166.80 (C=O), 144.86, 134.98, 134.63, 134.60, 133.56, 128.96, 128.46, 127.16, 127.09, 124.16, 116.27 (C_{ar}), 66.06, 51.91, 51.03, 41.60 (CH_2). LC-MS: *m/z* = 428 [M+1] (100%). Anal. Calcd. for $C_{21}H_{18}N_2O_4S_2$, %: C 59.14; H 4.25; N 6.57; S 15.03. Found, %: C 59.19; H 4.19; N 6.59; S 15.00.

2-((9,10-Dioxo-9,10-dihydroanthracen-2-yl)amino)-2-oxoethyl pyrrolidine-1-carbodithioate 3n. Yield 95%; m.p.: 206 ºC (decomposition). ^1H NMR: δ = 10.84 (br. s, 1H, NH), 8.40 (s, 1H, CH_{ar}), 8.16-8.11 (m, 3H, CH_{ar}), 8.04-8.01 (m, 1H, CH_{ar}), 7.89-7.86 (m, 2H, CH_{ar}), 4.32 (s, 2H, CH_2), 3.77 (t, 2H, *J* = 6.7 Hz, CH_2), 3.69 (t, 2H, *J* = 6.7 Hz, CH_2), 2.08-2.03 (m, 2H, CH_2), 1.95-1.91 (m, 2H, CH_2). ^{13}C NMR: δ = 193.49 (C=S), 182.19, 181.69, 166.87 (C=O), 138.59, 135.11, 133.69, 133.42, 133.34, 132.12, 130.42, 128.11, 127.42 (C_{ar}), 57.39, 51.48, 41.81, 26.55, 24.12 (CH_2). LC-MS: *m/z* = 412 [M+1] (100%). Anal. Calcd. for $C_{21}H_{18}N_2O_3S_2$, %: C 61.44; H 4.42; N 6.82; S 15.62. Found, %: C 61.39; H, 4.48; N 6.85; S 15.59.

2.3. Antimicrobial activity.

2.3.1. Methodology of the diffusion method.

Antibacterial activity of compounds was evaluated by diffusion in peptone on nutrient medium (meat-extract agar for bacteria; wort agar for fungi). The microbial loading was 10^9 cells (spores)/cm^3. The required incubation periods were as follows: 24 h at 35 °C for bacteria and 48–72 h at 28–30 °C for fungi. The results were recorded by measuring the zones surrounding the disk. Control disk contained Vancomycin (for bacteria) or Nystatin (for fungi) as a standard.

2.3.2. Methodology of the serial dilution method.

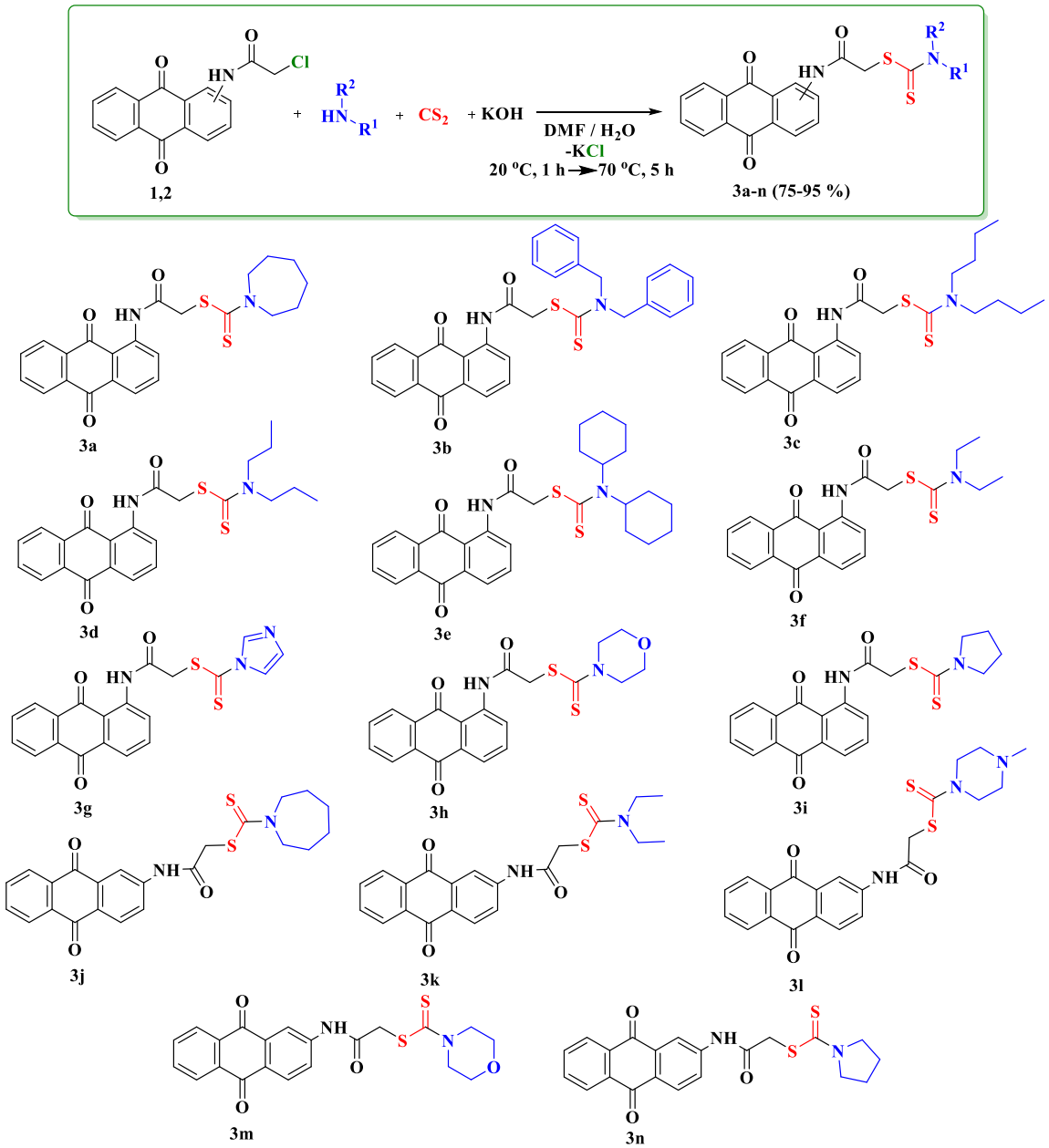
Testing was performed in a flat-bottomed 96-well tissue culture plate. The tested compounds were dissolved in dimethyl sulfoxide (DMSO) to the necessary concentration. The exact volume of the solution of compounds was brought in a nutrient medium. The inoculum of bacteria and fungi was in a nutrient medium (meat-extract agar for bacteria; wort agar for fungi). The duration of incubation was 24–72 h at 37 °C for bacteria and 30 °C for fungi. The results were estimated according to the presence or absence of microorganism growth.

3. Results and Discussion

3.1. Chemistry.

In continuation of our research on the molecular design and the search of new biologically active derivatives of 9,10-anthracenedione [32-36], the new 2-((9,10-dioxo-9,10-

dihydroanthracenyl)amino)-2-oxoethyl-carbodithioates 3a-n were synthesized by the four-component one-pot two-step reaction of 2-chloro-*N*-(9,10-dioxo-9,10-dihydroanthracenyl)acetamide 1 or 2 with a series of *in situ* generated potassium salt of dithiocarbamic acids in DMF-H_2O medium at heating for 5 h (Scheme 1).



Scheme 1. Synthesis of 2-((9,10-dioxo-9,10-dihydroanthracenyl)amino)-2-oxoethyl-carbodithioates 3a-n.

The structure of the synthesized 9,10-dioxoanthracenyldithiocarbamates 3a-n is clearly confirmed by the results of the NMR study. In particular, the ^{1}H NMR spectra of dithiocarbamates 3a-n contain the resonance signals of the CH_2 group of the oxoethyl fragment represented as a doublet of two protons at the range of 4.31-4.39 ppm. The proton of the secondary amino group, depending on the substitution position in the 9,10-anthracenedione fragment, is characterized by a broad singlet signal at the range of 12.40-12.64 ppm for 3a-i and 10.76-10.91 ppm for 3j-n. The dithiocarbamate substituent in the ^{13}C NMR spectra is represented by a signal of thiocarbonyl carbon in a weaker field in the range of 189.81-197.03 ppm, while the signals of two carbonyl groups of anthracene ring hydrocarbons are located at the range of 181.62-186.89 ppm.

3.2 Investigation of antimicrobial activity.

Antibacterial and antifungal activities of the synthesized dithiocarbamates **3a-n** were evaluated *in vitro* against the strains of *Escherichia coli B-906, Staphylococcus aureus 209-P, Mycobacterium luteumB-917, Candida tenuis VKM Y-70,* and *Aspergillus niger VKM F-1119* by the diffusion technique [37] and by the serial dilution technique (determination of minimal inhibition concentrations MIC) [38]. Antibacterial agent Vancomycin and antifungal agent Nystatin were used as control (C).

The bacterial strains of *E. coli* and *S. aureus* appeared to be insensitive to the action of the dithiocarbamate derivatives of 2-chloro-*N*-acetamides 3a-n investigated by the diffusion technique in agar at concentrations of 0.1 and 0.5% (Table 1). Dithiocarbamates 3a, 3i, and 3j showed their antibacterial effect against the bacteria *M. luteum* at a concentration of 0.5% with a diameter of the inhibition zone d = 19, 20, and 18 mm, respectively. The test culture of *C. tenuis* appeared to be sensitive to the derivatives 3a, 3i, 3j, and 3n at a concentration of 0.5% (the diameters of the growth inhibition zone were 17-26 mm). The strain *S. aureus* to be low sensitive to the action of compound 3n at concentrations of 0.1 and 0.5% (Table 1).

Table 1. Antibacterial and antifungal activities of the synthesized compounds determined by the diffusion technique.*

Compound	Concentration, %	Inhibition diameter of microorganism growth, mm				
		Bactericidal activity			Fungicidal activity	
		E. coli	*S. aureus*	*M. luteum*	*C. tenuis*	*A. niger*
3a	0.5	0	0	**19.0**	17.0	7.0
	0.1	0	0	12.0	10.0	0
3b	0.5	0	0	15.0	**19.0**	7.0
	0.1	0	0	10.0	10,0	0
3c	0.5	0	0	12.0	0	9.0
	0.1	0	0	0	0	7.0
3f	0.5	0	0	10,0	15.0	7.0
	0.1	0	0	0	8.0	0
3i	0.5	0	0	**20.0**	**20.0**	7.0
	0.1	0	0	13.0	14.0	0
3j	0.5	0	0	**18.0**	**20.0**	15.0
	0.1	0	0	10.0	15.0	7.0
3l	0.5	0	0	10.0	0	7.0
	0.1	0	0	0	0	0
3m	0.5	0	0	12.0	17.0	15.0
	0.1	0	0	0	15.0	7.0
3n	0.5	0	12.0	15.0	**26.0**	15.0
	0.1	0	9.0	10.0	17.0	7.0
Control	0.5	14.0	15.0	18.0	19.0	20.0

* only compounds with positive results are included in the table

Table 2. Antibacterial and antifungal activities of the synthesized compounds determined by the serial dilution technique.*

Compound	Cultures of microorganisms / MIC, μg/ml				
	E. coli	*S. aureus*	*M. luteum*	*C. tenuis*	*A. niger*
3a	+	+	250.0	62.5	125.0
3i	+	125.0	62.5	500.0	500.0
3j	125.0	125.0	3.9	125.0	62.5
3n	250.0	250.0	31.2	500.0	250.0
Control	31.2	62.5	7.8	31.2	7.8

"+" – growth of microorganisms

* only compounds with positive results are included in the table

An *in vitro* studies of the antibacterial and antifungal effect using the serial dilution technique showed the following (Table 2). The test culture of bacteria *M. luteum* was highly

sensitive to the dithiocarbamate 3j with MIC = 3.9 μg/ml. Dithiocarbamate 3n caused an antibacterial effect against the strain of *M. luteum* at a concentration two times lower (MIC = 31.2 μg/ml) than its isomeric analog 3i (MIC = 62.5 μg/ml). The compounds 3i, 3j, and 3n showed the antibacterial effect against strains of bacteria *E. coli* and *S. aureus* with MIC 125-250 μg/ml. Strains of fungi *C. tenuis* and *A.niger* to be sensitive to the action of the dithiocarbamate derivatives 3a, 3i, 3j, and 3n at MIC 62.5-500 μg/ml.

4. Conclusions

Therefore, in this work, we carried out the four-component one-pot two-step facile synthesis of a new 2-dithiocarbamate-*N*-(9,10-dioxo-9,10-dihydroanthracenyl)acetamides 3a-n and their antibacterial and antifungal effects were investigated. The outcomes of our *in vitro* antimicrobial screening revealed the compounds with good antibacterial activity against strain *M. luteum* and antifungal effect against *C. tenuis*. The dithiocarbamate 3j showed higher antibacterial action at MIC 3.9 μg/ml in comparison with control. The obtained results show the perspective of further in-depth investigations of selected dithiocarbamates as antimicrobial agents.

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Conflicts of Interest

The authors declare no conflict of interest.

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