ISSN 1993-6842 (on-line); ISSN 0233-7657 (print)
Biopolymers and Cell. 2022. Vol. 38. N 1. P 48–57
doi: http://dx.doi.org/10.7124/bc.000A72

UDC: 615.28:547.29`746`852.057

Synthesis and biological evaluation of *O*-acyloximes of 5-chloro-4-formyl- 1*H*-pyrrol-3-carboxylates as antimicrobial agents

A. M. Grozav[1], V. O. Chornous[1], I. V. Diichuk[1], S. V. Kemskyi[2], N. D. Yakovychuk[1], M. Z. Fedoriv[3], M. V. Vovk[2]

[1] Higher State Educational Establishment of Ukraine «Bukovinian State Medical University»
2, Theatralna sq., Chernivtsi, Ukraine, 58002

[2] Institute of Organic Chemistry, NAS of Ukraine
5, Murmanska Str., Kyiv, Ukraine, 02660

[3] Ivano-Frankivsk National Medical University
2, Halytska Str., Ivano-Frankivsk, Ukraine, 76018
hrozav.alina@bsmu.edu.ua

Aim. Elaboration of effective methods for the synthesis of the polysubstituted oximes with the *O*-acyloxime groups and investigation of their antibacterial and antifungal activity. **Methods.** Organic synthesis, analytical and spectral methods, pharmaceutical screening. **Results.** A series of new *O*-acyloximes of 4-formylpyrroles has been synthesized, and the screening of their antibacterial and antifungal activity was performed. It was found that the synthesized compounds exhibit antimicrobial activity, and their minimum inhibitory concentration (MIC) is ranged between 7.81 and 125 μg/mL. A comparatively high antibacterial activity has been registered for some synthesized compounds against the gram-negative bacteria of the genus *Proteus* (MIC=7.8-62.5 μg/mL). **Conclusions.** The most active antibacterial *O*-acyloximes were identified among the array of the synthesized substances, and the MIC of the compound **10** consisting of an *m*-nitrobenzoilic fragment against the bacterial test strains *Proteus aeruginosa ATCC 27853* and *Proteus mirabilis ATCC 410* was 15.625 μg/mL. In the case of the latter strain, this value is close to the MIC value of the control drug. The MIC of the compound **9** against the bacterial strain *Proteus mirabilis ATCC 410* was 7.81 μg/mL, which is greater than the corresponding control MIC.

K e y w o r d s: oximes of 4-formylpyrroles, acylation, *O*-acyloximes, antimicrobial activity

Introduction

O-acyloximes are the representatives of the important series of the derivatives of carbonyl compounds that are used as the molecular platforms for the design of some pharmaceuti-

cally active agents [1, 2] and as the target compounds exhibiting a distinct biologic activity. In the latter context, the following agents can be mentioned: inhibitors of the N-end kinases [3], selective covalent inhibitors of serine hydrolase [4], the antioxidant [5], anti-inflammatory [6] and herbicide [7] agents. Special attention is also paid to the *O*-acyloximes exhibiting high antibacterial and antifungal activity. For instance, it was found that the antibacterial activity of aroyloxime **I** against the bacteria *E. coli* and *P. aeruginosa* was close to the activity of streptomycin [5], whereas its fungicide efficiency against *A. flavus* was higher than that of the antifungal medication fluconazole. The antimicrobial screening of the acyloxime of benzaldehyde **II** regarding the strains of *S. aureus* and *E.coli* proved that its activity was close to the activity of the test drug bromheramin [8]. The bacteriostatic activity of the *O*-aroyloxime **III** concerning *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* was sufficient to stop their proliferation, and its MIC was 1.562 μg/mL that is close to the efficiency of penicillin [9].

As seen from the published scientific papers, only the derivatives of simple pyrrole-2- and 3-carbaldehydes with an *O*-acylated oxime fragment were investigated previously. Among them, there are the inhibitors of the lipoprotein-associated phospholipase A2 [10], the BODIPY-based photoelectronic platforms for the transportation of valproic acid (VPA) known as an inhibitor of histone diacetylase and an inductor of the tumor cell apoptosis [11]. Many *O*-acyloximes are used also as synthetic blocks in the designing of the condensed pyrrole-containing systems [12, 13].

However, further structural modification of functionalized pyrroles by the acyloxime fragment seems reasonable. This assumption is based on the fact that such pyrroles are the key components of a wide array of important natural and synthetic compounds used as a promising scaffold for further transformation into various bioactive agents [14–16].

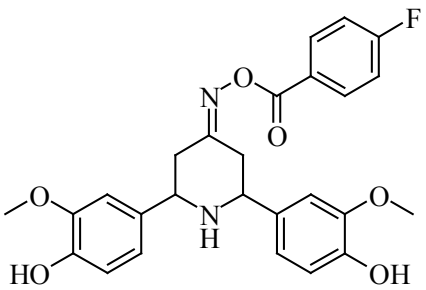
A wide-scale proliferation of tuberculosis bacteria, Staphylococcus aureus, and non-fermenting gram-positive germs of multidrug resistance is one of the most acute problems in today's public health system [17–19]. Besides, the lack of efficacious antifungal drugs and the rising resistance of the fungal pathogens also require intense counter-efforts [20–22]. That is why, the research and development of new highly active wide-range antimicrobial/antifungal agents seem a promising direction to address the problem of germ multidrug resistance.

Therefore, our investigation was planned in the framework of the search for new antimicrobial agents. It dealt with the elaboration of the effective methods of synthesis of the polysubstituted pyrroles with the *O*-acyloxime group and the study of their antibacterial and antifungal properties.

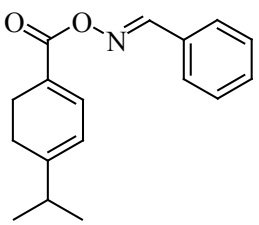
Materials and Methods

Chemistry

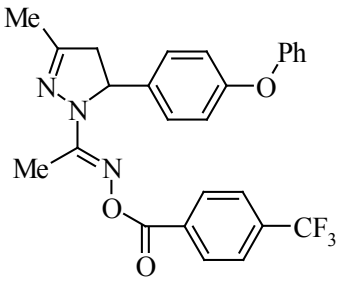
Melting points were measured on a Kofler melting point-device and are uncorrected. IR spectra were recorded on Bruker Vertex 70 FT-IR spectrometer for samples in KBr pellets. ^{1}H NMR spectra were acquired in pulsed Fourier transform mode on a Varian VXR-400 spectrometer (400 MHz), whereas ^{13}CNMR



I



II



III

spectra were acquired on a Bruker Avance DRX-500 spectrometer (125 MHz), using DMSO-d_6 as a solvent. Mass spectra were recorded on an Agilent LC/MSD SL chromatograph equipped with Zorbax SB-C_{18} column (4.6x15mm), particle size 1.8 μm (PN 82(c)75-932), solvent DMSO, electrospray ionization at atmospheric pressure. Elemental analysis was performed on a PerkinElmer 2400 CHN Analyzer. The individuality of the obtained compounds was monitored by TLC on Silutol UV-254 plates.

Common experimental methods (Method 1). A mixture of 5 mmol of the corresponding carboxylic acid, 0.81 g (5 mmol) of 1,1-carbodiimidazole (CDI) and 100 mg of 4-dimethylenaminepyridine (DMAP) was added to a solution of 5 mmol of the oxime **1** in 10 mL of methylene chloride. The system was stirred at room temperature for 10 h, then the solvent was vacuum evaporated, and 10 mL of water were added to the remaining solid residue. The sediment was filtered out, dried and recrystallized from the 70% ethanol.

(Method 2). 0.89 g (7.5 mmol) of thionyl chloride were added to a solution of 5 mmol of the corresponding carboxylic acid in 10 mL of toluene, and then the mixture was boiled for 1 h. The solvent was vacuum evaporated, and 10 mL of acetonitrile, 5 mmol of the oxime **1** and 0.51 g (5 mmol) of triethylamine were added to the solid residue. The mixture was boiled for 1 h, and then the solvent was vacuum evaporated. Finally, 10 mL of water were added to the residue, and then the sediment was filtered out, dried and recrystallized from the 70% ethanol.

Ethyl 4-{[(acetyloxy)imino]methyl}-5-chloro-2-methyl-1H-pyrrole-3-carboxylate (2). Yield 89%, mp 170 °C. ^{1}H NMR (400 MHz, DMSO-d^6), δ, ppm: 1.24 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 2.15 (s, 3H, $C(O)CH_3$), 2.35 (s, 3H, 2-CH_3), 4.17 (q, 2H, J = 7.2 Hz, OCH_2CH_3), 8.73 (s, 1H, CH), 12.57 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d^6), δ, ppm: 13.4, 14.6, 19.9, 60.0, 109.9, 110.9, 114.8, 136.6, 151.2, 164.0, 169.1. Anal. Calcd for $C_{11}H_{13}ClN_2O_4$, %: C, 48.45; H, 4.81; N, 10.27. Found, %: C, 48.56; H, 4.91; N, 10.38.

Ethyl 5-chloro-4-({[(4-methyoxybenzoyl) oxy]imino}methyl)-2-methyl-1H-pyrrole-3-carboxylate (3). Yield 92%, mp 174 °C. ^{1}H NMR (400 MHz, DMSO-d^6), δ, ppm: 1.27 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 2.39 (s, 3H, 2-CH_3), 3.84 (s, 3H, OCH_3), 4.20 (k, 2H, J = 7.2 Hz, OCH_2CH_3), 7.07 (d, 2H, J = 8.0 Hz, Ar), 7.98

(d, 2H, *J* = 8.0 Hz, Ar), 8.95 (s, 1H, CH), 12.60 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d^6), δ, ppm: 13.4, 14.6, 40.4, 56.0, 60.1, 110.0, 110.1, 114.7, 115.1, 120.8, 131.8, 136.6, 152.4, 163.3, 163.8. Anal. Calcd for $C_{17}H_{17}ClN_2O_5$, %: C, 55.97; H, 4.70; N, 7.68. Found, %: C, 55.81; H, 4.64; N, 7.77.

Ethyl 5-chloro-4-({[(cyclobutylcarbonyl) oxy]imino}methyl)-1,2-dimethyl-1H-pyrrole-3-carboxylate (4). Yield 85%, mp 71 °C. ^{1}H NMR (400 MHz, DMSO-d^6), δ, ppm: 1.26 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3), 1.79-1.88 (m, 1H, *cyclo*-C_4H_9), 1.93-2.00 (m, 1H, *cyclo*-C_4H_9), 2.19-2.26 (m, 4H, *cyclo*-C_4H_9), 2.47 (s, 3H, 2-CH_3), 3.37-3.42 (m, 1H, *cyclo*-C_4H_9), 3.53 (s, 3H, NCH_3), 4.20 (q, 2H, *J* = 7.2 Hz, OCH_2CH_3), 8.74 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d^6), δ, ppm: 13.1, 13.3, 19.8, 28.2, 30.7, 41.6, 60.7, 114.9, 117.6, 127.5, 144.8, 150.8, 162.8, 171.3. Anal. Calcd for $C_{15}H_{19}ClN_2O_4$, %: C, 55.13; H, 5.86; N, 8.57. Found, %: C, 55.33; H, 5.96; N, 8.43.

Ethyl 5-chloro-1,2-dimethyl-4-{[(octanoyloxy)imino]methyl}-1H-pyrrole-3-carboxylate (5). Yield 86%, mp 44 °C. ^{1}H NMR (400 MHz, DMSO-d^6), δ, ppm: 0.84 (m, 5H, CH_3CH_2), 1.14-1.25 (m, 19 H, $8CH_2$ + OCH_2CH_3), 1.47-1.58 (m, 2 H, CH_2), 2.45 (s, 3H, 2-CH_3), 3.55 (s, 3H, NCH_3), 4.21 (q, 2H, *J* = 7.2 Hz, OCH_2CH_3), 8.68 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d^6), δ, ppm: 12.2, 14.3, 14.5, 22.6, 24.9, 28.9, 29.1, 29.2, 29.3, 29.5, 29.4, 31.8, 32.5, 34.1, 60.2, 109.6, 110.6, 117.7, 137.7, 151.3, 163.9, 171.3. Anal. Calcd for $C_{22}H_{35}ClN_2O_4$, %: C, 61.89; H, 8.26; N, 6.56. Found, %: C, 62.09; H, 6.47; N, 6.65.

Ethyl 5-chloro-1,2-dimethyl-4-({[(4-methylbenzoyl)oxy]imino}methyl)-1H-pyrrole-3-carboxylate (6). Yield 90%, mp 124 °C. ^{1}H NMR (400 MHz, DMSO-d^6), δ, ppm: 1.28 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3), 2.40 (s, 3H, 2-CH_3), 3.34 (s, 3H, NCH_3), 3.57 (s, 3H, CH_3), 4.23 (q, 2H, *J* = 7.2 Hz, OCH_2CH_3), 7.38 (d, 2H, *J* = 8.0 Hz, Ar), 7.93 (d, 2H, *J* = 8.0 Hz, Ar), 8.98 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d^6), δ, ppm: 12.3, 14.6, 21.7, 31.7, 39.7, 40.5, 60.4, 109.6, 110.7, 129.7, 129.9, 137.8, 144.5, 152.6, 163.6, 163.9. Anal. Calcd for $C_{18}H_{19}ClN_2O_4$, %: C, 59.59; H, 5.8; N, 7.72. Found, %: C, 59.64; H, 5.20; N, 7.65.

Ethyl 4-{[(benzoyloxy)imino]methyl}5-chloro-1-ethyl-2-methyl-1H-pyrrole-3-carboxylate (7). Yield 90%, mp 104 °C. ^{1}H NMR (400 MHz, DMSO-d^6), δ, ppm: 1.24 (m, 6H, OCH_2CH_3 + NCH_2CH_3), 2.48 (s, 3H, 2-CH_3), 4.05 (q, 2H, *J* = 7.2 Hz, NCH_2CH_3), 4.22 (q, 2H, *J* = 7.2 Hz,OCH_2CH_3), 7.53-7.58 (m, 2H, Ar), 7.6-7.71 (m, 1H, Ar), 8.03 (d, 2H, *J* = = 6.0 Hz, Ar), 8.98 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d^6), δ, ppm: 11.9, 14.5, 15.1, 40.1, 60.3, 111.0, 114.2, 117.2, 128.8, 129.4, 129.6, 134.1, 136.9, 152.8, 163.5, 163.9. Anal. Calcd for $C_{18}H_{19}ClN_2O_4$, %: C, 59.59; H, 5.28; N, 7.72. Found, %: C, 59.69; H, 5.39; N, 7.81.

Ethyl 4-({[(3-fluorobenzoyl)oxy]imino}methyl)-5-chloro-1-ethyl-2-methyl-1H-pyrrole-3-carboxylate (8). Yield 92%, mp 97 °C. ^{1}H NMR (400 MHz, DMSO-d^6), δ, ppm: 1.19-128 (m, 6H, OCH_2CH_3 + NCH_2CH_3), 4.04 (q, 2H, *J* = 7.2 Hz, NCH_2CH_3), 4.20 (q, 2H, *J* = 7.2 Hz, OCH_2CH_3), 7.33-7.41 (m, 2H, Ar), 7.67-7.73 (m, 1H, Ar), 7.91-7.96 (m, 1H, Ar), 8.93 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d^6), δ, ppm: 11.5, 11.9, 14.5, 15.1, 60.4, 109.7, 111.0, 117.3, 117.6, 125.3, 132.1, 135.9, 137.0, 153.1, 160.2, 161.6, 162.2, 163.8. Anal. Calcd

for $C_{18}H_{18}ClFN_2O_4$, %: C, 56.77; H, 4.76; N, 7.36. Found, %: C, 56.92; H, 4.87; N, 7.49.

Ethyl 5-chloro-2-methy-1-propyl-4-[({[4-(pyrrolidin-1-ylsulfonyl)benzoyl]oxy}imino) methyl]-1H-pyrrole-3-carboxylate (9). Yield 88%, mp 165 °C. ^{1}H NMR (400 MHz, DMSO-d^6), δ, ppm: 0.91 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3), 1.30 (t, 3H, *J* = 7.2 Hz, $CH_2CH_2CH_3$), 1.70 (m, 4H, pyrrolidin), 2.53 (s, 3H, 2-CH_3), 3.21 (m, 4H, pyrrolidin), 4.01 (t, 2H, *J* = 7.2 Hz, $NCH_2CH_2CH_3$), 4.26 (q, 2H, *J* = 7.2 Hz, OCH_2CH_3), 7.98 (d, 2H, *J* = = 8.0 Hz, Ar), 8.25 (d, 2H, *J* = 8.0 Hz, Ar), 9.03 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d^6), δ, ppm: 10.7, 11.7, 14.1, 22.7, 24.8, 45.5, 48.0, 60.7, 103.9, 117.2, 126.1, 127.5, 130.2, 136.9, 139.1, 143.6, 152.8, 162.1, 163.2. Anal. Calcd for $C_{23}H_{28}ClN_3O_6S$, %: C, 54.17; H, 5.53; N, 8.24. Found, %: C, 53.97; H, 5.61; N, 8.32.

Ethyl 1-butyl-5-chloro-2-methyl-4-({[(3-nitrobenzoyl)oxy]imino}methyl)-1H-pyrrole-3-carboxylate (10). Yield 94%, mp 111 °C. ^{1}H NMR (400 MHz, DMSO-d^6), δ, ppm: 0.91 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3), 1.28-1.35 (m, 5H, $CH_2CH_2CH_2CH_3$), 1.52-1.64 (m, 2H, $CH_2CH_2CH_2CH_3$), 4.00 (t, *J* = 7.2 Hz, $NCH_2CH_2CH_2CH_3$), 4.23 (q, 2H, *J* = 7.2 Hz, OCH_2CH_3), 7.86 (m, 1H, Ar), 8.43 (d, 1H, *J* = 8.0 Hz, Ar), 8.51 (d, 1H, *J* = 8.0 Hz, Ar), 8.68 (s, 1H, Ar), 9.04 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d^6), δ, ppm: 11.6, 13.5, 14.1, 19.2, 31.2, 43.9, 59.9, 109.1, 110.6, 117.3, 123.6, 127.9, 129.9, 130.8, 135.3, 136.7, 147.9, 152.9, 161.4, 163.4. Anal. Calcd for $C_{20}H_{22}ClN_3O_6$, %: C, 55.11; H, 5.09; N, 9.64. Found, %: C, 55.30; H, 5.17; N, 9.58.

Ethyl 1-butyl-5-chloro-4-[({[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetyl]oxy}imino) methyl]-2-methyl-1H-pyrrole-3-carboxylate (11). Yield 94%, mp 126 °C. ^{1}H NMR (400 MHz, DMSO-d^6), δ, ppm: 0.89 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3), 1.23-1.33 (m, 5H, $CH_2CH_2CH_2CH_3$), 1.54-1.62 (m, 2H, $CH_2CH_2CH_2CH_3$), 3.98 (t, 2H, *J* = 7.2 Hz, $NCH_2CH_2CH_2CH_3$), 4.21 (q, 2H, *J* = 7.2 Hz, OCH_2CH_3), 4.68 (s, 2H, NCH_2), 7.88-7.96 (m, 4H, Ar), 8.83 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d^6), δ, ppm: 11.5, 13.5, 14.1, 19.2, 31.2, 38.3, 40.0, 43.9, 59.9, 94.5, 108.8, 110.6, 117.3, 123.5, 131.3, 134.9, 136.9, 152.2, 163.6, 166.2, 167.1. Anal. Calcd for $C_{23}H_{24}ClN_3O_6$, %: C, 58.29; H, 5.10; N, 8.87. Found, %: C, 58.41; H, 5.18; N, 8.93.

Ethyl 1-benzyl-4-({[(4-bromobenzoyl)oxy] imino}methyl)-5-chloro-2-methyl-1H-pyrrole-3-carboxylate (12). Yield 92%, mp 109 °C. ^{1}H NMR (400 MHz, DMSO-d^6), δ, ppm: 1.28 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3), 2.45 (s, 3H, 2-CH_3), 4.24 (q, 2H, *J* = 7.2 Hz, OCH_2CH_3), 5.35 (s, 2H, CH_2Ph), 7.04 (d, 2H, *J* = 8.0 Hz, Ar), 7.28-7.39 (m, 3H, Ar), 7.77 (d, 2H, *J* = 8.0 Hz, Ar), 7.96 (d, 2H, *J* = 8.0 Hz, Ar), 9.0 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d^6), δ, ppm: 13.3, 14.3, 45.6, 60.6, 105.6, 118.2, 127.5, 127.6, 127.6, 127.7, 128.6, 128.7, 131.6, 131.7, 143.9, 155.6, 161.8, 163.1. Anal. Calcd for $C_{23}H_{20}BrClN_2O_4$, %: C, 54.84; H, 4.00; N, 5.56. Found, %: C, 54.77; H, 4.08; N, 5.66.

Antimicrobial activity

A micromethod of the double serial dilutions in the liquid nutrient medium [23] has been employed for the determination of the antibacterial and antifungal activity of the synthesized compounds. The minimal inhibition concentration (MIC) against the reference bacterial

strains (*Proteus mirabilis ATCC 410, Proteus aeruginosa ATCC* 27853*, Proteus vulgaris ATCC 4636, Klebsiella pneumoniae ATCC 13883, Staphylococcus epidermidis ATCC* 12228*, Corynebacterium xerosis ATCC* 373, *Enterococcus faecalis ATCC 6783*) and the fungi (*Candida albicans ATCC 885/653* and *Aspergillus amstelodami K12*) was found for the compounds **2-12** synthesized in this work.

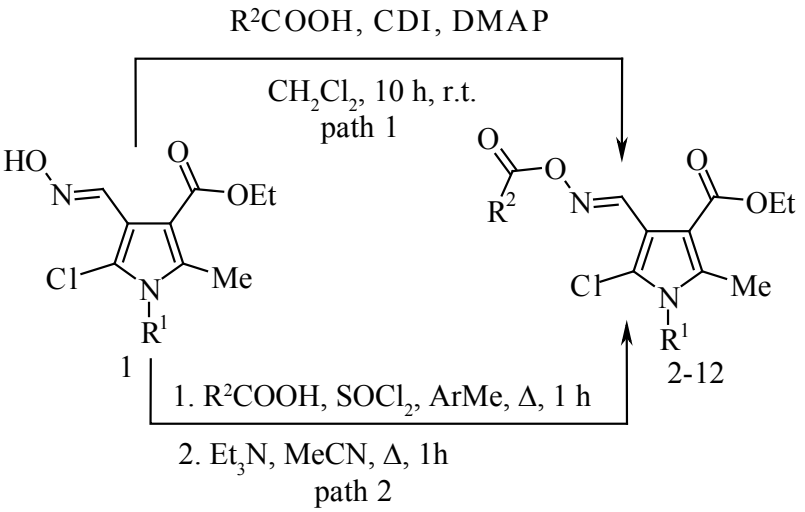
The 1000 μg/ml DMSO solutions of all the compounds to be researched were prepared and then involved in experiments according to the serial dilutions micromethod. All the experiments were repeated three times until the relevant and not-contradictory data were obtained. DMSO was used as a reference system, whereas Decasan was used as a control drug in the investigation of antimicrobial efficiency.

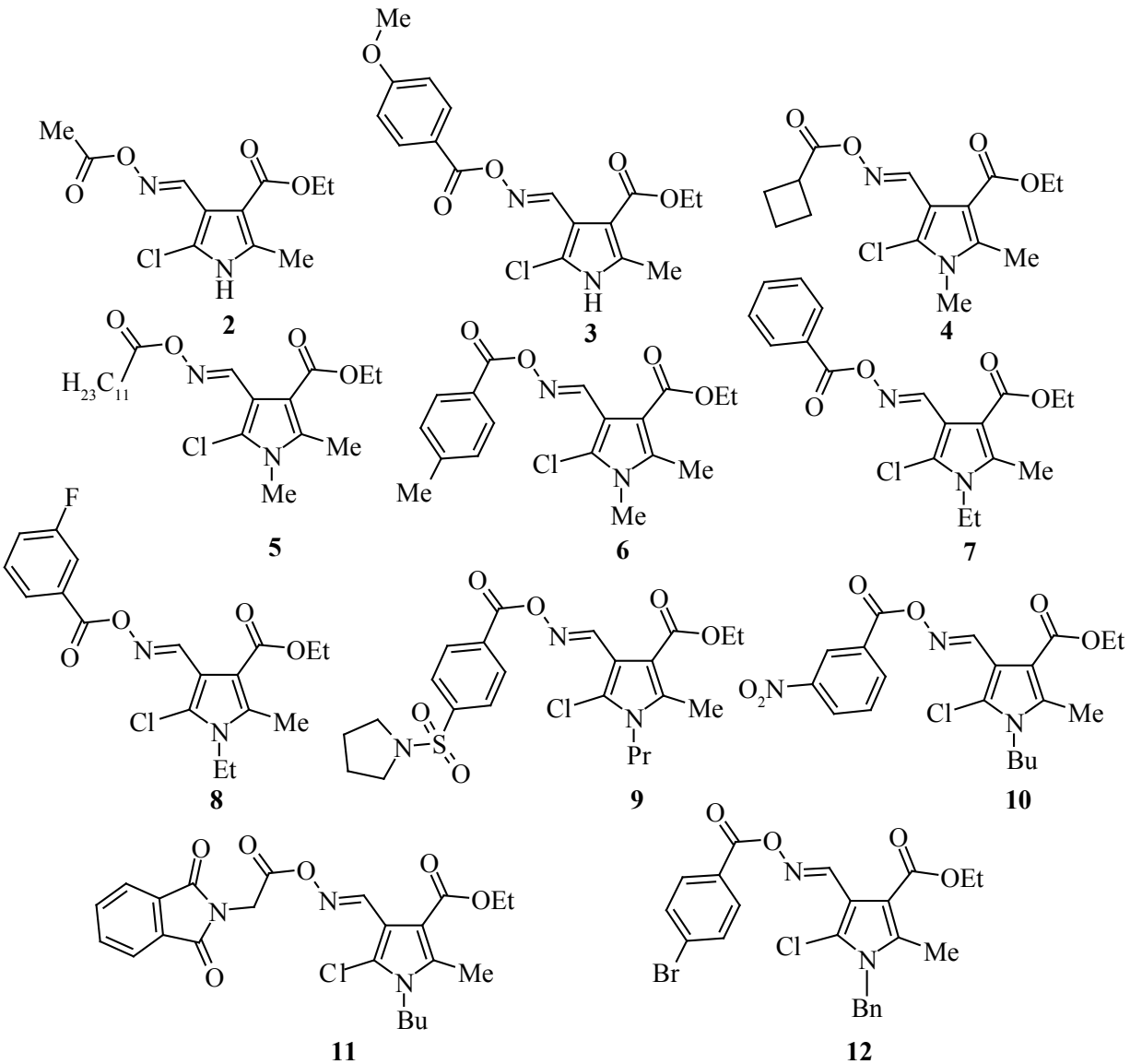
Results and Discussion

Chemistry

This investigation was aimed at the elaboration of effective methods of the synthesis of new *O*-acyloximes of pyrrol-4-carbaldehydes with an additional functionalization by the etoxycarbonile group in the 3rd position and by chlorine – in the 5th position. Besides, all synthesized compounds were checked for their possible application as antimicrobial agents. Two preparatively convenient methods of acylation of the previously synthesized oximes of 4-formylpyrroles **1** [24] were applied to obtain the target compounds. The first of them implied an acylation by carboxylic acids in the presence of carbodiimydazole (CDI) and 4-dimethylaminopyridine (DMAP). It was shown that the *O*-acyloximes **2, 5, 6, 8, 10, 11** were synthesized with the yields of 86-94 % after the 10-hour stirring of corresponding reactants in dichloromethane at room temperature. According to the second method, the acylation was performed *in situ* by chloranhydrides of carboxylic acids interacting in boiling toluene with the oximes **1** in the presence of triethylamine acting as a base and leading to the O-acyloximes **3, 4, 7, 9, 12** with the yields of 85-92 %.

The structures of the synthesized compounds **2-12** were confirmed by NMR ^{1}H, ^{13}C and chromato-mass spectra. In particular, the singlets of the azomethine group protons are present in the NMR spectra in the range 8.68-9.05 m.n. along with the specific signals of the substitutes R^1 and R^2.





Antimicrobial activity

As seen from the results of bioscreening of the *O*-acyloximes **2-12**, they exhibit some antimicrobial activity, and their MIC is ranged between 7.81-125 μg/mL (Table 1). It is also clear that their antifungal activity is lesser than the antibacterial efficiency, and this activity does not depend on the structure of acylic oxime fragment (MIC=31.25-62.5 μg/mL). Unlike the antifungal activity of the compounds, their antibacterial effect differs significantly depending on the type of germs and

the structure of acyloxime. For instance, a high antibacterial effect was determined against the gram-negative bacteria of the genus *Proteus* (MIC=7.8-62.5 μg/mL). The MIC of the compound **10** consisting of an *m*-nitrobenzoilic fragment against the test strains of bacteria *Proteus aeruginosa ATCC* and *27853 Proteus mirabilis ATCC 410* was 15.625 mg/mL. This value is close to the activity of the test antibacterial compound. The MIC of the compound **9** against the test strain *Proteus mirabilis ATCC 410* was 7.81 mg/mL, which is higher than the control value. Taking into consideration the noticeable antibiotic resistance of these strains [25], the abovementioned results seem important for further detailed investigations in this direction.

Conclusions

The preparatively convenient methods for the synthesis of *O*-acyloximes of pyrrol-4-carbaldehydes **2-12** with an additional functionalization in the 3rd position by an etoxycarbonile group and in the 5th position – by chlorine are proposed and discussed. As seen from the bioscreening data, the target compounds show quite high antimicrobial activity against the gram-negative bacteria of the genus *Proteus* (MIC=7.8-62.5 mg/mL). It has been found that the MIC of the compound **10**, consisting of an *m*-nitrobenzoilic fragment, against the test strain of bacteria *Proteus aeruginosa ATCC* and *27853 Proteus mirabilis ATCC 410* was 15.625 mg/mL. For the latter strain, this value is close to the activity of the control drug.

Table 1. **Antimicrobial activity of 5-chloro-4-({[alkyl(aryl)oxyimino]methyl})-1*H*-pyrrol-3-carboxylates 2-12**

№	*P. mirabilis ATCC 410*	*P. aeruginosa ATCC* 27853	*P. vulgaris ATCC 4636*	*Kl. pneumoniae ATCC 13883*	*S. epidermidis ATCC* 12228	*C. xerosis ATCC* 373	*E. faecalis ATCC 6783*	*A. amstelodam K12*	*C. albicans ATCC 885/653*
	MIK								
2	62.5	31.25	31.25	15.625	15.625	62.5	62.5	62.5	62.5
3	62.5	31.25	31.25	31.25	62.5	31.25	62.5	31.25	62.5
4	62.5	31.25	31.25	31.25	15.625	31.25	62.5	31.25	62.5
5	62.5	31.25	31.25	125	62.5	31.25	62.5	31.25	62.5
6	62.5	31.25	31.25	62.5	15.625	31.25	31.25	31.25	62.5
7	125	62.5	15.625	31.25	15.625	62.5	62.5	31.25	62.5
8	62.5	62,5	62.5	31.25	31.25	62.5	62.5	31.25	62.5
9	7.81	31.25	31.25	62.5	31.25	31.25	31.25	62.5	62.5
10	15.625	15.625	31.25	125	62.5	31.25	62.5	62.5	62.5
11	62.5	31.25	31.25	62.5	31.25	31.25	31.25	31.25	62.5
12	62.5	31.25	31.25	125	62.5	31.25	62.5	62.5	62.5
DMSO*	+	+	+	+	+	+	+	+	+
Ctrl**	15.625	31.25	15.625	3.9	3.9	15.625	3.9	62.5	7.81

* proliferation of bacteria detected

** Decasan (a solution consisting of 0.2 mg/mL of decamethoxin) made by "Yuria-Pharm" was used as the control drugs

Regarding the compound **9**, its MIC for the test strain *Proteus mirabilis ATCC 410* was 7.81 mg/mL, which is higher than the control activity.

REFERENCES

1. *Rykaczewski KA, Wearing ER, Blackmun DE, Schindler CS.* Reactivity of oximes for diverse methodologies and synthetic applications. *Nat Synths.* 2022; **1**: 24–36.
2. *Vessally E, Saeidian H, Hosseinian A, Edjlali L, Bekhradni A.* A review on synthetic applications of oxime esters. *Curr Org Chem.* 2016; **21** (3): 249–71.
3. *Koch P, Gehringer M, Laufer SA.* Inhibitors of c-Jun N-terminal kinases – an update. *J Med Chem.* 2014; **58** (1): 72–95.
4. *Bachovchin DA, Wolfe MR, Masuda K, Brown SJ, Spicer TP, Fernandez-Vega V, Chase P, Hodder PS, Rosen H, Cravatt BF.* Oxime esters as selective, covalent inhibitors of the serine hydrolase retinoblastoma-binding protein 9 (RBBP9). *Bioorg Med Chem Lett.* 2010; **29**(7): 2254–8.
5. *Harini ST, Kumar HV, Rangaswamy J, Naik N.* Synthesis, antioxidant and antimicrobial activity of novel vanillin derived piperidin-4-one oxime esters: Preponderant role of the phenyl ester substituents on the piperidin-4-one oxime core. *Bioorg Med Chem Lett.* 2012; **16** (22): 7588–92.
6. *Abdel-Hafez EMN, Abuo-Rahma GEAA, Abdel-Aziz M, Radwan MF, Farag HH.* Design, synthesis and biological investigation of certain pyrazole-3-carboxylic acid derivatives as novel carriers for nitric oxide. *Bioorg Med Chem.* 2009; **17**(11): 3829–37.
7. *Hu Q, Lin GS, Duan WG, Huang M, Lei F-H.* Synthesis and biological activity of novel (Z)- and (E)-verbenone oxime esters. *Molecules.* 2017; **22**(10): 1678–94.
8. *Gao Y, Song J, Shang S, Wang D, Li J.* Synthesis and antibacterial activity of oxime esters from dihydrocumic acid. *Bioresources.* 2021; **7**(3): 4150–60.
9. *Liu X-H, Zhi L, Song B, Xu H.* Synthesis, characterization and antibacterial activity of new 5-aryl pyrazole oxime ester derivatives. *Chem Res Chinese universities.* 2008;**24** (4): 454–8.
10. *Jeong HJ, Park Y-D, Park H-Y, Jeong IY, Jeonga T-S, Leea WS.* Potent inhibitors of lipoprotein-associated phos-pholipase A2: Benzaldehyde O-heterocycle-4-carbonyloxime. *Bioorg Med Chem Lett.* 2006; **16**(21): 5576–9.
11. *Sambath K, Zhao T, Wan Z, Zhang Y.* Photouncaging of BODIPY oxime ester for histone deacetylases induced apoptosis in tumor cells. *Chem Commun.* 2019; **55**(94): 14162–5.
12. *Shao N, Li J, Zhu H, Zhang S, Zou H.* Functionalized N-containing heterocyclic scaffolds derived from N-substituted pyrroles via inter- and intramolecular annulations. *Tetrahedron.* 2018; **74** (42): 6088–94.
13. *Zhang Z, Li J, Zhang G, Ma N, Liu Q, Liu T.* Iron-catalyzed intramolecular C(sp2)–Ncyclization of 1-(N-arylpyrrol-2-yl)ethanone O-acetyl oximes toward pyrrolo[1,2-a]quinoxaline derivatives. *Org Chem.* 2015; **80** (13): 6875–84.
14. *Abd El-Hameed RH, Sayed AI, Ali SM, Mosa MA, Khoder ZM, Fatahala SS.* Synthesis of novel pyrroles and fused pyrroles as antifungal and antibacterial agents. *J Enzyme Inhib Med Chem.* 2021; **36** (1): 2183–98.
15. *Petri GL, Spanò V, Spatola R, Holl R, Raimondi MV, Barraja P, Montalbano A.* Bioactive pyrrole-based com-pounds with target selectivity. *Eur J Med Chem.* 2020; **208**: 112783.
16. *Bianco MCAD, Marinho DILF, Hoelz LVB, Bastos MM, Boechat N.* Pyrroles as privileged scaffolds in the search for new potential HIV inhibitors. *Pharmaceuticals.* 2021; **14**(9): 893.
17. *Klemm EJ, Wong VK, Dougan G.* Emergence of dominant multidrug-resistant bacterial clades: Lessons from history and whole-genome sequencing. *Proc Natl Acad Sci USA.* 2018; **115**(51): 12872–77.
18. *Hawkey PM, Warren RE, Livermore DM, McNulty CAM, Enoch DA, Otter JA, Wilson APR.* Treatment of infections caused by multidrug-resistant gram-negative bacteria: report of the british society for antimicrobial chemo-therapy/healthcare infection society/british infection association joint working party. *J Antimicrob Chemother.* 2018; **73**(Suppl_3): iii2–iii78.

19. *Sharma D, Sharma S, Sharma J.* Potential strategies for the management of drug-resistant tuberculosis. *J Glob Antimicrob Resist.* 2020; **22**: 210–4.
20. *Morel CM, Lindahl O, Harbarth S, de Kraker MEA, Edwards S, Hollis A.* Industry incentives and antibiotic resistance: an introduction to the antibiotic susceptibility bonus. *J Antibiot.* 2020; **73**(7): 421–8.
21. *Murray AK.* The novel coronavirus COVID-19 outbreak: Global implications for antimicrobial resistance. *Front Microbiol.* 2020; **11**: 1020.
22. *Kishida N, Nishiura H.* Accelerating reductions in antimicrobial resistance: Evaluating the effectiveness of an intervention program implemented by an infectious disease consultant. *Int J Infect Dis.* 2020; **93**: 175–81.
23. *Yakovychuk ND, Deyneka SY, Grozav AM, Humenna AV, Popovych VB, Djuiriak VS.* Antifungal activity of 5-(2-nitrovinyl) imidazoles and their derivatives against the causative agents of vulvovaginal candidiasis. *Reg Mech Biosyst.* 2018; **9** (3), 369–73.
24. *Grozav AM, Fedoriv MZ, Chornous VO, Kemskyi SV, Vovk MV.* Synthesis of 4-amino-5-chloro-2,6-dihydropyrrolo[3,4-d]pyridazin-1-ones. *Vopr Khim Khim Tekhnol.* 2020; **5**: 11–7.
25. *Girlich D, Bonnin RA, Dortet L, Naas T.* Genetics of acquired antibiotic resistance genes in Proteus spp. *Front Microbiol.* 2020; **11**: 256.

Синтез та біологічна оцінка *O*-ацилоксимів 5-хлоро-4-форміл-1*H*-пірол-3-карбоксилатів як протимікробних агентів

А. М. Грозав, В. О. Чорноус, І. В. Дійчук, С. В. Кемський, Н. Д. Яковичук, М. З. Федорів, М. В. Вовк

Мета. Розробка зручних методів синтезу та вивчення протибактеріальних і протигрибкових властивостей полізаміщених піролів із *O*-ацилоксимними угрупованнями. Методи: органічний синтез, аналітичні та спектральні методи, фармакологічний скринінг. **Результати.** Синтезовано ряд нових *O*-ацилоксимів 4-формілпіролів, для яких проведено скриніг відносно низки тест-штамів грампозитивних і грамнегативних бактерій та грибів. Отримані результати свідчать, що тестовані сполуки проявляють протимікробну активність, їх мінімальна інгібуюча концентрація знаходиться в діапазоні 7.81-125 мкг/мл. Виявлено високий протибактеріальний ефект деяких сполук відносно грамнегативної бактерії роду *Proteus* (MIC=7.8-62.5 мкг/мл). **Висновки.** Проведені дослідження дозволили серед синтезованих *O*-ацилоксимів виділити сполуки з високою протибактеріальною активністю. При тестуванні сполуки **10,** яка містить *м*-нітробензоїльний фрагмент, відносно тест-штамів бактерії *Proteus aeruginosa ATCC 27853* та *Proteus mirabilis ATCC 410* MIC=15.625 мкг/мл, що у випадку останнього штаму знаходиться на рівні контролю. При тестуванні сполуки **9** відносно тест-штаму бактерії *Proteus mirabilis ATCC 410* мінімальна інгібуюча концентрація склала 7.81 мкг/мл, що перевищує рівень контролю.

Ключові слова: оксими 4-формілпіролів, ацилювання, *O*-ацилоксими, протимікробна активність

Received 15.01.2022