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Synthesis and Bioevaluation of 5-Chloro-4-(1,3-Oxazol-5-yl)-1*H*-Pyrrole-3-Carboxyamides as Antimicrobial Agents

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Abstract: This investigation deals with the design and synthesis of new derivatives of pyrrole consisting of modifying atoms of chlorine, amide, and 1,3-oxazole fragments. These compounds can be interesting in the context of research of new antimicrobial agents. Ethyl 5-chloro-4-formyl-1H-pyrrole-3-carboxylates were used as a key substrate for further transformation into target compounds. This process was realized as a direct transformation of an aldehyde fragment into a 1,3-oxazole cycle by van Leusen's reaction followed by hydrolysis of an ester group, which finally converted a reactant into the corresponding pyrrole-3-carboxylic acid. This acid has been found to be an efficient construction block for the further development of antimicrobial agents. The preparative potential of these compounds has been verified by way of their transformation into a series of carbamides through consecutive reactions with thionyl chloride and alkyl-, aryl, and heterylamines under mild reaction conditions. According to bio screening results, the following two compounds have been chosen as those exhibiting a high anti-staphylococcus activity: 1-butyl-5-chloro-2-methyl-4-(1,3-oxazol-5-yl)-N-[(1,3-thiazol-2-yl]-1*H*-pyrrole-3-carboxamide and 1-butyl-5-chloro-N-[(3-dimethylaminosulfonyl)phenyl]-2-methyl-4-(1,3-oxazol-5-yl)-1*H*-pyrrole-3-carboxamide (MIC=7.8 μg/ml), while another one – 5-chloro-N-(4-chlorophenyl)-4-(1,3-oxazol-5-yl)-2-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide was selected as a compound exhibiting high antifungal activity (MIC=7.8 μg/ml) against the reference strains *Candida albicans* ATCC 885/653 and *Aspergillus niger* K9.

Keywords: ethyl 5-chloro-4-formyl-1H-pyrrole-3-carboxylates; van Leusen's reaction; toluenesulfonylmethyl isocyanide; 5-chloro-4-(1,3-oxazol-5-yl)-1H-pyrrole-3-carboxamides, antibacterial activity; antifungal activity.

1. Introduction

It is known that the derivatives of pyrrole can be used as key structural components of a significant array of natural and synthetic substances, and today they are involved in various syntheses as prospective scaffolds for the development of various bioactive compounds possessing a high pharmaceutical profile [1-7]. Several original structures with antibacterial [8-11], antifungal [12-14], antiviral [15-16], anti-inflammatory [17-19], anticancer [20-22], antimalarial [23, 24], and other therapeutic effects [2] have been developed as a result of systematic synthetic and biomedical investigations.

The character of the influence of the heterocycle's functional substitutes on its bioactivity can be retrieved from the structure/activity dependence analyzed across a series of polysubstituted pyrroles. In particular, it was found that haloids, amide fragments present in the pyrrole nucleus would seriously influence the pharmaceutical properties of the compounds. It can be clearly shown with the example of the bromine-pyrrole alkaloids including the oroidin analogs hymenidin (I,II) [25,26], dispacamide B (III) and dispacamide D (IV) [27,28], bromopyrrolohomoarginin (V) [27,29], anticancer medication sunitinib (VI) [30-32], antimicrobial agents AZD5099 (VII) [33] and (VIII) [34] (Figure 1).

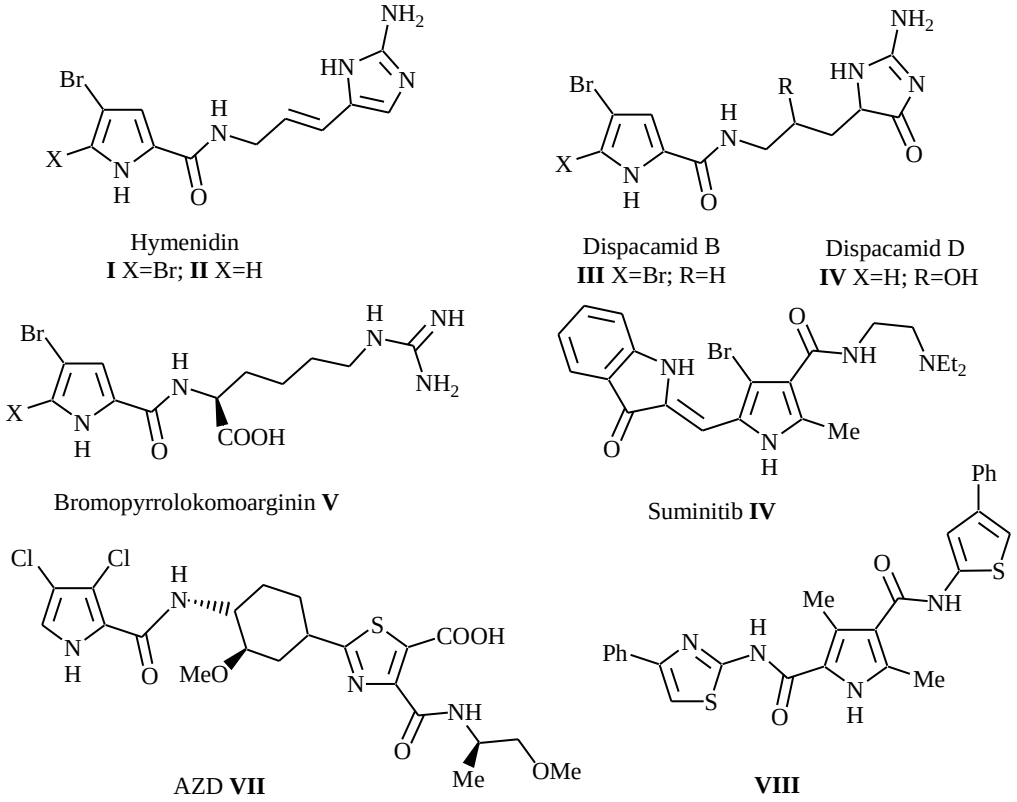


Figure 1. Some examples of the bioactive pyrroles functionalized with the haloid atoms and amide groups.

Along with the acyclic amide group, the bioactivity of the pyrrole derivatives is also significantly influenced by its isostructural heterocyclic analogs – 1,3-oxazoles known as representatives of systems exhibiting a clear pharmacophoric effect [35-47]. Chlorinated phenylpyrrolyloxazoles known as phorbazoles (IX-XII) can be mentioned as such derivatives (Figure 2). They were isolated from the sea sponge *Phorbas aff clathata* [38], and their carcinostatic activity was reported in [39].

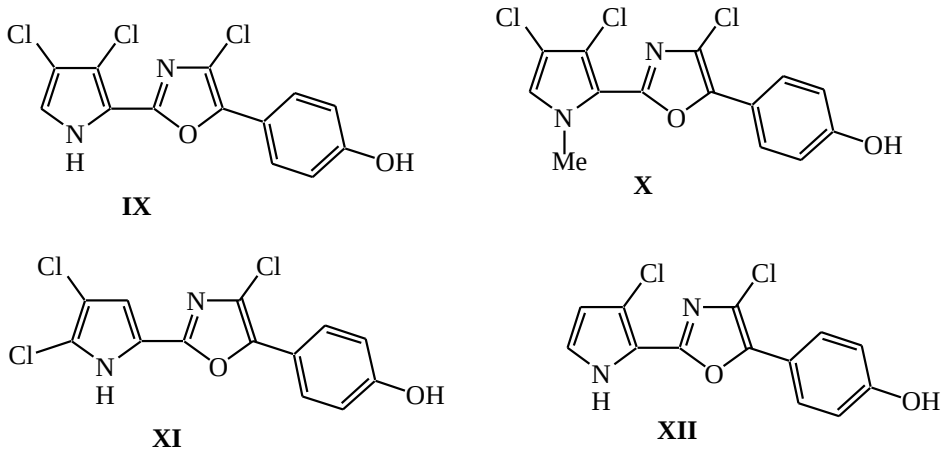


Figure 2. Structures of phorbazoles IX-XII.

In addition to the abovementioned natural phorbazoles where both cycles are bonded by the combination $C^2_{pyrrole}$-$C^2_{oxazole}$, heterocyclic ensembles formed by the bond $C^2_{pyrrole}$–$C^5_{oxazole}$ and acting as inhibitors of the hydrolase of fatty acid amides [40] or as selective ligands for the dopamine D4 receptor [41] were described.

In this context, it seems reasonable to investigate the design and synthesis of new pyrrole derivatives with exofunctional chlorine atoms, amide, and 1,3-oxazole fragments as promising bioactive compounds. Since the problem of microbial infection control is of top medical importance today [42-43], major efforts should be directed towards the evaluation of antibacterial and antifungal properties of these substances.

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 [44]. The initial ethyl 5-chloro-4-formylpyrrole-3-carboxylates 1a-f were prepared from ethyl 2-methyl-5-oxo-4,5-dihydropyrrole-3-carboxylates [45] according to the method described in [46].

2.2. 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), while ^{13}CNMR spectra were acquired on a Bruker Avance DRX-500 spectrometer (125 MHz), using DMSO-d_6 as 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.

General procedure for the synthesis of methyl (2 a-f) and ethyl (3 a-f) 1-alkyl-5-chloro-2-methyl(phenyl)-4-(1,3-oxazol-5-yl)-1*H*-pyrrole-3-carboxylates.

1.95 g (10 mmole) of toluenesulfonylmethyl isocyanide and 4.14 g of potassium carbonate were added to the solution of 10 mmole of 1 a-f aldehyde in 20 ml of dehydrated methanol. The mixture was boiled for 4 hours, and then the solvent was vacuum-evaporated. Finally, 20 ml of water were added to the dry residue; the sediment was filtered out and dried.

General procedure for the synthesis of 1-alkyl-5-chloro-2- methyl(phenyl)-4-(1,3-oxazol-5-yl)-1*H*-pyrrole-3-carboxylic acides (4 a-f).

0.70 g (12.5 mmole) of KOH was added to the solution of 5 mmole of a mixture of carboxylates 2a-f and 3a-f in the 1:1 mixture dioxane-water. The mixture was boiled for 3 hours, then the solvent was vacuum-evaporated, 20 ml of water were added to the dry residue, and the sediment was filtered out. The filtrate was acidified by a 10 % solution of hydrochloric acid up to pH=5. Then the newly formed sediment was filtered out, dried, and crystallized from the 50 % aqueous solution of acetic acid.

5-Chloro-1,2-dimethyl-4-(1,3-oxazol-5-yl)-1*H*-pyrrole-3-carboxylic acid (4 a).

Yield 87 %; m.p.: 200-202 °C. ^{1}H NMR: δ = 12.13 (br.s, 1H, COOH), 8.36 (s, 1H, CH), 7.16 (s, 1H, CH), 4.04 (s, 3H, CH_3), 2.42 (s, 3H, CH_3). ^{13}C NMR: δ = 164.5 (COOH), 151.1 (CH), 143.8, 136.1, 124.3 (CH), 116.1, 110.6, 106.8, 30.9 (CH_3), 10.7 (CH_3). LC-MS: m/z =

241 [M+1] (100%). Anal. Calcd. for $C_{10}H_9ClN_2O_3$, %: C 49.91; H 3.77; N 11.64. Found, %: C 50.18; H 3.88; N 11.50.

5-Chloro-2-methyl-4-(1,3-oxazol-5-yl)-1-propyl-1*H*-pyrrole-3-carboxylic acid (4 b).

Yield 82 %; m.p.: 135-136 °C. ^{1}H NMR: δ = 12.13 (br.s, 1H, COOH), 8.36 (s, 1H, CH), 7.17 (s, 1H, CH), 3.93 (t, 2H, *J*=7.2 Hz, CH_2), 2.42 (s, 3H, CH_3), 1.67 (q, 2H, *J*=7.2 Hz, CH_2), 0.89 (t, 3H, *J*=7.2 Hz, CH_3). ^{13}C NMR: δ = 164.7 (COOH), 151.3 (CH), 143.9, 135.8, 124.6 (CH), 116.0, 111.1, 107.4, 45.5 (CH_2), 22.8 (CH_2), 11.4 (CH_3), 11.8 (CH_3). LC-MS: m/z = 269 [M+1] (100%). Anal. Calcd. for $C_{12}H_{13}ClN_2O_3$, %: C 53.64; H 4.88; N 10.43. Found, %: C 53.88; H 4.99; N 10.57.

1-Butyl-5-chloro-2-methyl-4-(1,3-oxazol-5-yl)-1*H*-pyrrole-3-carboxylic acid (4 c).

Yield 84 %; m.p.: 118-119°C. ^{1}H NMR: δ = 12.11 (br.s, 1H, COOH), 8.33 (s, 1H, CH), 7.16 (s, 1H, CH), 3.98 (t, 2H, *J*=7.2 Hz, CH_2), 2.44 (s, 3H, CH_3), 1.60 (q, 2H, *J*=7.2 Hz, CH_2), 1.33 (q, 2H, *J*=7.2 Hz, CH_2), 0.96 (t, 3H, *J*=7.2 Hz, CH_3). ^{13}C NMR: δ = 164.9 (COOH), 151.5 (CH), 144.1, 135.9, 124.6 (CH), 116.1, 111.3, 107.5, 44.0 (CH_2), 31.6 (CH_2), 19.4 (CH_2), 13.6 (CH_3), 11.5 (CH_3). LC-MS: m/z = 283 [M+1] (100%). Anal. Calcd. for $C_{13}H_{15}ClN_2O_3$, %: C 55.23; H 5.35; N 9.91. Found, %: C 54.98; H 5.26; N 10.07.

1-Benzyl-5-chloro-2-methyl-4-(1,3-oxazol-5-yl)-1*H*-pyrrole-3-carboxylic acid (4 d).

Yield 82 %; m.p.: 158-159°C. ^{1}H NMR: δ = 11.93 (br.s, 1H, COOH), 8.34 (s, 1H, CH), 7.39-7.22 (m, 3H, CH_{ar}), 7.21 (s, 1H, CH), 7.05 (d, 2H, CH_{ar}), 5.30 (s, 2H, CH_2), 2.45 (s, 3H, CH_3). ^{13}C NMR: δ = 164.8 (COOH), 151.5 (CH), 143.9, 136.4, 136.2, 129.2 (2 CH), 127.8 (CH), 126.1 (2 CH), 124.9 (CH), 117.7, 116.1, 107.8, 47.2 (CH_2), 11.8 (CH_3). LC-MS: m/z = 317 [M+1] (100%). Anal. Calcd. for $C_{16}H_{13}ClN_2O_3$, %: C 60.67; H 4.14; N 8.84. Found, %: C 60.38; H 4.06; N 9.01.

5-Chloro-1-methyl-4-(1,3-oxazol-5-yl)-2-phenyl-1*H*-pyrrole-3-carboxylic acid (4 e).

Yield 85 %; m.p.: 228-230 °C. ^{1}H NMR: δ = 11.88 (br.s, 1H, COOH), 8.38 (s, 1H, CH), 7.48-7.39 (m, 5H, CH_{ar}), 7.26 (s, 1H, CH), 3.38 (s, 3H, CH_3). ^{13}C NMR: δ = 163.8 (COOH), 151.2 (CH), 143.9, 137.7, 130.8, 130.8 (2 CH), 128.7 (CH), 128.1 (2 CH), 124.6 (CH), 117.8, 112.7, 107.8, 32.6 (CH_3). LC-MS: m/z = 303 [M+1] (100%). Anal. Calcd. for $C_{15}H_{11}ClN_2O_3$, %: C 59.52; H 3.66; N 11.71. Found, %: C 59.78; H 3.77; N 11.60.

5-Chloro-4-(1,3-oxazol-5-yl)-2-phenyl-1-propyl-1*H*-pyrrole-3-carboxylic acid (4 f).

Yield 86 %; m.p.: 205-207 °C. ^{1}H NMR: δ = 11.94 (br.s, 1H, COOH), 8.41 (s, 1H, CH), 7.48-7.36 (m, 5H, CH_{ar}), 7.28 (s, 1H, CH), 3.75 (t, 2H, *J*=7.2 Hz, CH_2), 1.48 (q, 2H, *J*=7.2 Hz, CH_2), 0.65 (t, 3H, *J*=7.2 Hz, CH_3). ^{13}C NMR: δ = 163.97 (COOH), 157.5 (CH), 143.7, 137.6, 130.9, 130.6 (2 CH), 128.8 (CH), 128.0 (2 CH), 124.7 (CH), 117.1, 110.9, 107.9, 46.4, 22.9 (CH_2), 10.6 (CH_3). LC-MS: m/z = 331 [M+1] (100%). Anal. Calcd. for $C_{17}H_{15}ClN_2O_3$, %: C 61.73; H 4.57; N 8.47. Found, %: C 61.93; H 4.68; N 8.59.

General procedure for the synthesis of 1-alkyl-5-chloro-2-methyl(phenyl)-4-(1,3-oxazol-5-yl)-1*H*-pyrrole-3-carboxamides (5 a-k).

0.71 g (6 mmole) of thionylchloride was dripped to the solution of 3 mmole of the acid 4 a-f in 10 ml of dehydrated dichloromethane and boiled for 1 hour. The solvent was vacuum-evaporated, and then 10 ml of dehydrated tetrahydrofuran, 3 mmole of the corresponding amine, and 0.3 g (3 mmole) of triethylamine were added to the dry residue. This mixture was boiled for 2 hours, the solvent was vacuum-evaporated, and the dry residue was dissolved in the 50% solution of sodium bicarbonate. Finally, the sediment was filtered out, dried, and crystallized from the 70 % aqueous solution of ethanol.

5-[2-Chloro-1,5-dimethyl-4-(pyrrolidin-1-ylcarbonyl)-1*H*-pyrrole-3-yl]-1,3-oxazole (5a). Yield 80 %; m.p.: 108-110 °C. ^{1}H NMR: δ = 8.31 (s, 1H, CH), 7.13 (s, 1H, CH), 3.51 (s, 3H, CH_3), 3.43 (t, 2H, *J*=6.8 Hz, CH_2), 2.99 (t, 2H, *J*=6.8 Hz, CH_2), 2.17 (s, 3H, CH_3), 1.83-1.78 (m, 2H, CH_2), 1.72-1.67 (m, 2H, CH_2). ^{13}C NMR: δ = 162.1 (C=O), 150.3 (CH), 144.9, 127.8, 121.0 (CH), 115.6, 112.5, 104.6, 47.4 (CH_2), 45.2 (CH_2), 30.9 (CH_3), 25.3 (CH_2), 24.1 (CH_2), 10.9 (CH_3). LC-MS: m/z = 294 [M+1] (100%). Anal. Calcd. for $C_{14}H_{16}ClN_3O_2$, %: C 57.24; H 5.49; N 14.30. Found, %: C 57.50; H 5.58; N 14.18.

5-[2-Chloro-1-methyl-5-phenyl-4-(pyrrolidin-1-ylcarbonyl)-1*H*-pyrrole-3-yl]-1,3-oxazole (5b)

Yield 81 %; m.p.: 138-140 °C. ^{1}H NMR: δ = 8.37 (s, 1H, CH), 7.51-7.39 (m, 5H, CH_{ar}), 7.21 (s, 1H, CH), 3.59 (s, 3H, CH_3), 3.28-3.24 (m, 2H, CH_2), 2.89-2.85 (m, 2H, CH_2), 1.67-1.62 (m, 2H, CH_2), 1.52-1.47 (m, 2H, CH_2). ^{13}C NMR: δ = 164.0 (C=O), 151.3 (CH), 144.9, 131.3, 130.5, 129.7 (2 CH), 129.1 (2 CH), 128.9 (CH), 121.9 (CH), 117.5, 115.6, 106.0, 47.7 (CH_2), 45.5 (CH_2), 34.9 (CH_3), 25.6 (CH_2), 24.4 (CH_2). LC-MS: m/z = 356 [M+1] (100%). Anal. Calcd. for $C_{19}H_{18}ClN_3O_2$, %: C 64.14; H 5.10; N 11.81. Found, %: C 63.90; H 4.98; N 12.00.

1-{[5-Chloro-1-methyl-4-(1,3-oxazol-5-yl)-2-phenyl-1*H*-pyrrole-3-yl]carbonyl}piperidine (5c).

Yield 82 %; m.p.: 145-146 °C. ^{1}H NMR: δ = 8.39 (s, 1H, CH), 7.49-7.38 (m, 5H, CH_{ar}), 7.20 (s, 1H, CH), 3.54 (s, 3H, CH_3), 3.49-3.45 (m, 2H, CH_2), 3.04-3.00 (m, 2H, CH_2), 1.36-1.21 (m, 4H, CH_2), 0.99-0.96 (m, 1H, CH), 0.68-0.63 (m, 1H, CH). ^{13}C NMR: δ = 164.0 (C=O), 154.3 (CH), 144.8, 131.1, 130.4, 129.9 (2 CH), 129.0 (2 CH), 128.9 (CH), 122.1 (CH), 116.1, 115.7, 106.4, 47.5 (CH_2), 45.1 (CH_2), 32.9 (CH_3), 25.6 (CH_2), 25.3 (CH_2), 24.3 (CH_2). LC-MS: m/z = 370 [M+1] (100%). Anal. Calcd. for $C_{20}H_{20}ClN_3O_2$, %: C 64.95; H 5.45; N 11.36. Found, %: C 65.10; H 5.38; N 11.50.

5-Chloro-2-methyl-N-methyl-4-(1,3-oxazol-5-yl)-1-propyl-1*H*-pyrrole-3-carboxamide (5d).

Yield 83 %; m.p.: 112-113 °C. ^{1}H NMR: δ = 8.32 (s, 1H, CH), 7.66 (s, 1H, NH), 7.16 (s, 1H, CH), 3.90 (t, 2H, *J*=7.6 Hz, CH_2), 2.67 (d, 3H, *J*=4.4 Hz, CH_3), 2.29 (s, 3H, CH_3), 1.63 (q, 2H, *J*=7.6 Hz, CH_2), 0.91 (t, 3H, *J*=7.6 Hz, CH_3). ^{13}C NMR: δ = 164.6 (C=O), 150.4 (CH), 144.4, 129.1, 122.8 (CH), 116.3, 112.9, 105.7, 45.3 (CH_2), 25.3 (CH_3), 22.9 (CH_2), 10.9 (CH_3), 10.8 (CH_3). LC-MS: m/z = 282 [M+1] (100%). Anal. Calcd. for $C_{13}H_{16}ClN_3O_2$, %: C 55.42; H 5.72; N 14.91. Found, %: C 55.15; H 5.60; N 15.06.

4-({[5-Chloro-2-methyl-4-(1,3-oxazol-5-yl)-1-propyl-1*H*-pyrrole-3-yl]carbonyl}amino)benzoic acid (5e).

Yield 82 %; m.p.: 180-182 °C. ^{1}H NMR: δ = 12.34 (br.s, 1H, COOH), 10.22 (s, 1H, NH), 8.31 (s, 1H, CH), 7.89 (d, 2H, *J*=8.4 Hz, CH_{ar}), 7.73 (d, 2H, *J*=8.4 Hz, CH_{ar}), 7.21 (s, 1H, CH), 3.95 (t, 2H, *J*=7.6 Hz, CH_2), 2.36 (s, 3H, CH_3), 1.67 (q, 2H, *J*=7.6 Hz, CH_2), 0.93 (t, 3H, *J*=7.6 Hz, CH_3). ^{13}C NMR: δ = 167.4 (COOH), 163.6 (C=O), 151.3 (CH), 144.7, 143.8, 130.9, 130.7 (2CH), 125.7, 123.0 (CH), 119.0 (2CH), 116.4, 113.9, 106.5, 45.9 (CH_2), 23.4 (CH_2), 11.4 (CH_3), 11.3 (CH_3). LC-MS: m/z = 388 [M+1] (100%). Anal. Calcd. for $C_{19}H_{18}ClN_3O_4$, %: C 58.84; H 4.68; N 10.83. Found, %: C 59.10; H 4.79; N 11.00.

5-Chloro-N-(2-hydroxyethyl)-4-(1,3-oxazol-5-yl)-2-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide (5f).

Yield 82 %; m.p.: 133-134 °C. ^{1}H NMR: δ = 8.37 (s, 1H, CH), 7.66 (b. s, 1H, NH), 7.47-7.40 (m, 5H, CH_{ar}), 7.26 (s, 1H, CH), 4.97 (b. s, 1H, OH), 3.84 (q, 2H, *J*=7.2 Hz, CH_2), 3.19-3.15 (m, 2H, CH_2), 3.07-3.04 (m, 2H, CH_2), 1.48 (q, 2H, *J*=7.2 Hz, CH_2), 0.67 (t, 3H, *J*=7.2

Hz, CH_3). ^{13}C NMR: δ = 164.4 (C=O), 151.3 (CH), 144.7, 132.6, 130.6 (2 CH), 130.5, 129.1 (CH), 128.9 (2 CH), 123.0 (CH), 118.9, 114.8, 106.9, 59.8 (CH_2), 49.5 (CH_2), 41.9 (CH_2), 23.5 (CH_2), 11.1 (CH_3). LC-MS: m/z = 374 [M+1] (100%). Anal. Calcd. for $C_{19}H_{20}ClN_3O_3$, %: C 61.04; H 5.39; N 11.24. Found, %: C 60.85; H 5.50; N 11.40.

5-Chloro-N-(4-methylphenyl)-4-(1,3-oxazol-5-yl)-2-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide (5g).

Yield 84 %; m.p.: 162-163 °C. ^1H NMR: 9.79 (s, 1H, NH), 8.34 (s, 1H, CH), 7.45-7.33 (m, 6H, CH_{ar}+CH), 7.30 (d, 2H, *J*=6.4 Hz, CH_{ar}), 7.25 (s, 1H, CH), 7.00 (d, 2H, *J*=6.4 Hz, CH_{ar}), 3.86 (t, 2H, *J*=7.6 Hz, CH_2), 2.47 (s, 3H, CH_3), 1.51 (q, 2H, *J*=7.2 Hz, CH_2), 0.67 (t, 3H, *J*=7.6 Hz, CH_3). ^{13}C NMR: δ = 162.3 (C=O), 151.0 (CH), 144.2, 136.5, 132.5, 132.3, 131.2(2 CH), 130.2 (2 CH), 128.8 (CH), 128.4 (2 CH), 122.1 (CH), 119.4 (2 CH), 118.4, 114.5, 113.9, 106.6, 46.1 (CH_2), 23.1 (CH_2), 20.3 (CH_3), 10.6 (CH_3). LC-MS: m/z = 388 [M+1] (100%). Anal. Calcd. for $C_{24}H_{22}ClN_3O_2$, %: C 68.65; H 5.28; N 10.01. Found, %: C 68.90; H 5.19; N 9.89.

5-Chloro-N-(4-chlorophenyl)-4-(1,3-oxazol-5-yl)-2-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide (5h)

Yield 85 %; m.p.: 131-132°C. ^1H NMR: δ = 10.06 (s, 1H, NH), 8.36 (s, 1H, CH), 7.54-7.40 (m, 7H, CH_{ar}), 7.31-7.26 (m, 3H, CH_{ar}+CH), 3.89 (t, 2H, *J*=6.8 Hz, CH_2), 1.53 (q, 2H, *J*=6.8 Hz, CH_2), 0.71 (t, 3H, *J*=6.8 Hz, CH_3). ^{13}C NMR: δ = 162.4 (C=O), 151.5 (CH), 144.6, 138.4, 132.3, 132.1, 131.3, 130.7 (2CH), 130.3 (CH), 129.3 (2CH), 128.9 (2CH), 127.4, 122.9 (CH), 118.4 (2CH), 115.1, 107.1, 40.6 (CH_2), 23.5 (CH_2), 11.1 (CH_3). LC-MS: m/z = 441 [M+1] (100%). Anal. Calcd. for $C_{23}H_{19}Cl_2N_3O_2$, %: C 62.74; H 4.35; N 9.54. Found, %: C 62.95; H 4.26; N 9.67.

1-Butyl-5-chloro-N-[(3-dimethylaminosulfonyl)phenyl]-2-methyl-4-(1,3-oxazol-5-yl)-1*H*-pyrrole-3-carboxamide (5i).

Yield 85 %; m.p.: 170-172°C. ^1H NMR: δ = 10.23 (s, 1H, NH), 8.30 (s, 1H, CH), 8.10 (s, 1H, CH_{ar}), 7.91 (d, 1H, *J*=7.6 Hz, CH_{ar}), 7.58 (t, 1H, *J*=7.6 Hz, CH_{ar}), 7.40 (d, 1H, *J*=7.6 Hz, CH_{ar}), 7.22 (s, 1H, CH), 4.00 (t, 2H, *J*=7.2 Hz, CH_2), 2.63 (s, 6H, 2 CH_3), 2.38 (s, 3H, CH_3), 1.63 (q, 2H, *J*=7.2 Hz, CH_2), 1.36 (q, 2H, *J*=7.2 Hz, CH_2), 0.97 (t, 3H, *J*=7.2 Hz, CH_3). ^{13}C NMR: δ = 163.2 (C=O), 150.8 (CH), 144.2, 140.0, 135.2, 130.5, 129.6 (CH), 123.1 (CH), 122.7 (CH), 121.8 (CH), 117.7, 115.7 (CH), 113.4, 106.0, 47.7 (CH_2), 39.5 (2CH_3), 31.7 (CH_2), 19.3 (CH_2), 13.6 (CH_3), 10.8 (CH_3). LC-MS: m/z = 465 [M+1] (100%). Anal. Calcd. for $C_{21}H_{25}ClN_4O_4S$, %: C 54.25; H 5.42; N 12.05. Found, %: C 53.98; H 5.50; N 11.97.

1-Butyl-5-chloro-2-methyl-4-(1,3-oxazol-5-yl)-N-[(1,3-thiazol-2-yl]-1*H*-pyrrole-3-carboxamide (5j).

Yield 80 %; m.p.: 110-111°C. ^1H NMR: δ = 12.00 (s, 1H, NH), 8.33 (s, 1H, CH), 7.47 (s, 1H, CH), 7.22 (s, 1H, CH), 7.19 (s, 1H, CH), 3.99 (t, 2H, *J*=7.2 Hz, CH_2), 2.37 (s, 3H, CH_3), 1.64 (q, 2H, *J*=7.2 Hz, CH_2), 1.34 (q, 2H, *J*=7.2 Hz, CH_2), 0.93 (t, 3H, *J*=7.2 Hz, CH_3). ^{13}C NMR: δ = 162.8 (C=O), 158.6, 151.3 (CH), 144.5, 138.1 (CH), 132.0, 123.3 (CH), 114.3, 114.1, 113.8 (CH), 106.8, 44.1 (CH_2), 32.3 (CH_2), 19.7 (CH_2), 15.0 (CH_3), 11.3 (CH_3). LC-MS: m/z = 365 [M+1] (100%). Anal. Calcd. for $C_{16}H_{17}ClN_4O_2S$, %: C 52.67; H 4.70; N 15.36. Found, %: C 52.88; H 4.60; N 15.47.

1-Benzyl-5-chloro-N-(2-hydroxyethyl)2-methyl-4-(1,3-oxazol-5-yl)-1*H*-pyrrole-3-carboxamide (5k).

Yield 82 %; m.p.: 122-123 °C. ^1H NMR: δ = 8.34 (s, 1H, CH), 7.77 (t, 1H, *J*=5.6 Hz, NH), 7.36 (t, 2H, *J*=7.6 Hz, CH_{ar}), 7.29 (t, 1H, *J*=7.6 Hz, CH_{ar}), 7.23 (s, 1H, CH), 7.07 (d, 2H,

J=7.6 Hz, CH_{ar}), 5.26 (s, 2H, CH_2), 4.64 (t, 1H, *J*=5.4 Hz, OH), 3.45 (q, 2H, *J*=5.4 Hz, CH_2), 3.24 (q, 2H, *J*=5.4 Hz, CH_2), 2.24 (s, 3H, CH_3). ^{13}C NMR: δ = 164.0 (C=O), 150.7 (CH), 144.2, 136.5, 129.8, 128.7 (2 CH), 127.2 (CH), 126.3 (2 CH), 122.8 (CH), 116.6, 113.4, 106.0, 58.9 (CH_2), 46.9 (CH_2), 41.7 (CH_2), 11.2 (CH_3). LC-MS: m/z = 360 [M+1] (100%). Anal. Calcd. for $C_{18}H_{18}ClN_3O_3$, %: C 60.09; H 5.04; N 11.68. Found, %: C 59.85; H 4.93; N 11.50.

2.3. Antimicrobial activity.

A micro method of the double serial dilutions in the liquid nutrient medium [46] 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 (*Staphylococcus aureus 25923 F 49, Escherichia coli ATCC 25922, Bacillus cereus ATCC 11778, Bacillus subtilis ATCC 6633, Proteus vulgaris 4636, Enterococcus faecalis ATCC 29212*) and the fungi (*Candida albicans ATCC 885/653* and *Aspergillus niger K9*) was found for the carbamides 5a-k 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 micro method. All the experiments were repeated three times until the relevant and not-contradictory data were obtained.

3. Results and Discussion

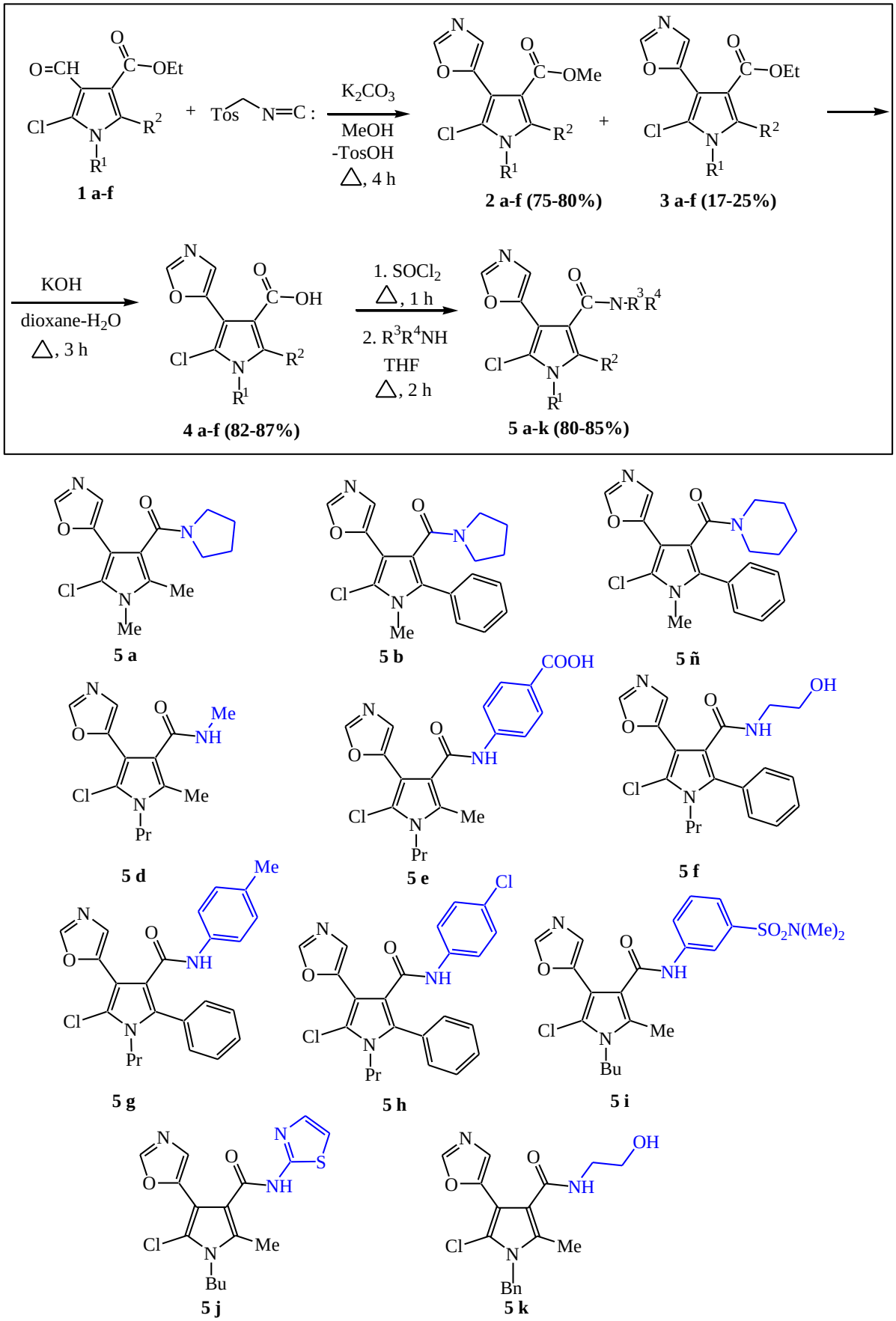
3.1. Chemistry.

We recently synthesized [47] ethyl 5-chloro-4-formyl-1*H*-pyrrole-3-carboxylates 1a-f with the two functional groups, which are easily available for further structural modifications: aldehyde and ester were used as a basic substrate for obtaining the target products. First, an aldehyde fragment of the compound 1a-f was transformed in the 1,3-oxazolyl cycle by van Leusen's reaction using tosylmethylisocyanind (TosMIC) as an equivalent of the three-atom synthon [C-N=C] [7]. For the studied compounds, this process runs with some peculiarities: it takes place in the boiling methanol solution of K_2CO_3 acting as a base, and a partial methanolysis of the etoxycarbonile group occurs along with the oxazole cycle construction as seen from the NMR ^{1}H spectroscopy and mass-spectrometry results, the products obtained after the above transformation was, in fact, a mixture of methylcarboxylates 2a-f and ethylcarboxylates 3a-f with an approximate ratio of 3-4:1.

At the next stage, a mixture of the esters 2a-f and 3a-f have been hydrolyzed by KOH in the boiling water-dioxane solution, which resulted in obtaining of 5-chloro-4-(1,3-oxazol-5-yl)-1*H*-pyrrole-3-carboxylic 4a-f acids with the yield 82-87 %. Some H^5 (8.41-8.33 ppm) and H^2 (7.28 -7.16 ppm) proton wide singlets of the oxazole cycle can be seen together with the typical R^1 and R^2 substituents signals in the ^{1}H NMR spectra of these compounds. The oxazole carbon atoms have been registered within the ranges 151.53-151.08 ppm and 124.92-124.32 ppm in the ^{13}C NMR spectra.

The acids containing the pharmacophore pyrrole and 1,3-oxazole nuclei are new building blocks for the design of the bio perspective compounds. Their preparative potential has been investigated at the third stage of our work through the example of a synthesis of the carboxamides 5a-k. The acids 4a-f were sequentially treated by thionylchloride, alkyl-, aryl- and heterylamines under mild reaction conditions ensuring the yields of 80-85 % (see Scheme

1). A composition of all obtained amides was confirmed by the results of ^{1}H (^{13}C) NMR and mass spectrometry.



Scheme 1. Synthesis of 5-chloro-4-(1,3-oxazolyl-5-yl)-1*H*-pyrrole-3-carboxamides 5a-k.

3.2 Investigation of antimicrobial activity.

The antibacterial and antifungal activities of the carboxamides 5a-k have been evaluated *in vitro* using the double serial dilution method against the test-strains of some gram-positive and gram-negative bacteria and fungi (Table 1). All the test microorganisms showed sensitivity to the synthesized carboxamides 5a-k, while their minimum inhibition concentrations (MIC) were ranged between 7.8-500 µg/ml proving good antimicrobial activity of this class of carboxamides.

It should be emphasized that *S. aureus* is a pathogen with a natural resistance to many antimicrobial agents [48]. However, some of our carboxamides have proven a high activity against these microbes (MIC = 7.8-31.2 µg/ml), and the best antistaphylococcal activity was found for the amides 5j, 5i (MIC=7.8 µg/ml, same as the activity of the reference medicine). As seen from the antifungal activity analysis, all synthesized compounds, but the compound 5g showed a clear effect against the strains of *C. albicans* and *A. niger*. It should also be taken into account that the MIC of the amide 5h against *C. albicans* (7.8 µg/ml) is equal to that of the reference medicine "Clotrimazole".

Table 1. Antibacterial and antifungal activities of the synthesized compounds.

Compound	Cultures of microorganisms / MIC, µg/ml							
	S. aureus	***E. coli***	***B. cereus***	***B. subtilis***	***E. faecalis***	***P. vulgaris***	***C. albicans***	***A. niger***
5 a	31.2	31.2	62.5	62.5	62.5	62.5	15.6	15.6
5 b	31.2	62.5	62.5	62.5	125	62.5	31.2	31.2
5 c	31.2	62.5	62.5	62.5	62.5	62.5	31.2	31.2
5 d	15.6	62.5	62.5	62.5	125	62.5	31.2	31.2
5 e	31.2	31.2	62.5	62.5	125	62.5	15.6	15.6
5 f	31.2	31.2	62.5	62.5	125	62.5	15.6	15.6
5 g	500	250	250	500	500	62.5	250	250
5 h	31.2	125	125	125	125	62.5	7.8	7.8
5 j	7.8	62.5	62.5	62.5	62.5	62.5	31.2	31.2
5 i	7.8	31.2	250	62.5	62.5	62.5	15.6	31.2
5 k	15.6	31.2	62.5	62.5	62.5	62.5	31.2	31.2
Control*	7.8	3.9	3.9	3.9	1.9	3.9	7.8	0.9

*Doxycycline was used as a reference for the evaluation of the antibacterial activity [49], and Clotrimazole was used as a reference in the antifungal activity determination series [50].

4. Conclusions

A small library of 5-chloro-4-(1,3-oxazol-5-yl)-1*H*-pyrrole-3-carboxamides has been synthesized through the structural modification of the aldehyde and ester groups of ethyl 5-chloro-4-formyl-1*H*-pyrrole-3-carboxylates. The synthesized compounds can be considered as perspective objects for further synthesis of new antimicrobial agents. According to the bio screening results, the amides 5 j, i can be highlighted as the agents with high antistaphylococcal activity against the test strain *S. aureus*, while the amide 5 h exhibits high antifungal activity against the test strains *C. albicans* and *A. niger*.

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Conflicts of Interest

The authors declare no conflict of interest.

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