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Synthesis and evaluation of antimicrobial activity of some new 3-(pyrrol-4-yl)acrylamide derivatives

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A B S T R A C T

A series of new derivatives of 3-(pyrrol-4-yl)acrylamides **3a-l** with the pyrrole nucleus functionalized by chlorine atoms and ester group, have been synthesized by simple preparative methods from the available esters of 5-chloro-4-formylpyrrol-3-carboxylic acids **1a-e**. At first, 3-(pyrrol-4-yl)acrylic acids **2a-e** were synthesized by the Knoevenagel's reaction between malonic acid and the esters **1a-e**. Then the target compounds were obtained with a high yield in the reactions between chloroanhydrides of the synthesized acrylic acids and aromatic or aliphatic amines in the boiling benzene. The structure of all obtained compounds was confirmed by elemental analysis, IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy, and additionally checked by the mass-spectrometry. Then the antimicrobial activity of all amides was tested *in vitro* on some gram-positive and gram-negative bacteria and fungi. It has been found that the gram-negative bacteria are resistant against the synthesized chemicals, while the gram-positive bacteria are sensitive to the amides **3c, e, f, g, i.** The highest activity against *Staphylococcus aureus* MR and *Staphylococcus epidermidis* MS was registered for the amide **3f**, and the retardation area diameter for this amide was greater than that for the control drugs.

1. Introduction

It is reported by WHS that a microbial resistance is one of the most challenging global threats to public health.[1] As a bacterial multi-resistance grows in various strains of gram-positive bacteria including the methicillin-resistant bacteria of the genus *Staphylococcus*, penicillin-resistant bacteria of the genus *Streptococcus*, and vancomycin-resistant *Enterococcus*,[2] the search for new effective antibacterial compounds becomes more and more topical. Besides such bacterial resistance, a fungal resistance also grows rapidly in many fungal pathogens, which brings new challenges for the health protection system.[3] That is why, the construction of new anti-germ compounds, including those based on the heterocyclic molecules, keeps its topicality.

In the framework of the development of the highly efficient antimicrobial agents based on the polyfunctional and condensed pyrrole systems,[4-6] this work represents the results of the investigation of some previously unknown amides of acrylic acid consisting a functionalized pyrrole fragment in the alkenylic part of the molecule. Even though the information related to this type of compounds is very scarce,[7-9] special attention should be given to the recently published method of synthesis of such compounds that is based on the Ru(0)-catalyzed alkenization in the β-position of α-iminofunctionalized pyrroles[10]. Amides of 3-pyrrolylsubstituted acrylic acids are used in this method because they are in fact heteroanalogs of cinnamic acid amides known as active antimicrobial agents.[11-15] On the other hand, another type of benzoanalogs of the above unknown amides, derivatives of indolyl-3-acrylamides are known as pharmaceutically active chemicals. For instance,

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they can be used as the inhibitors of hepatitis C virus (HCV),[16] human immune deficit virus (HIV),[17] human deacylglycerol acyltransferase-2 (DGAT-2),[18] and also as antiproliferation agents.[19,20]

Since the pyrrole scaffold is important for the construction of various bioactive compounds,[21-23] the synthetically potent formyl and ester groups, and a chlorine atom as a pharmacophoric substitute should be present in the basic pyrrole substrates to be transformed into further pharmaceutical agents. It should be emphasized that the pharmaceutical effectiveness of organic compounds increases if they consist of chlorine.[24,25] This effect is based on the improved absorption,[26] and allocation of the biotargets in the hydrophobic 'pockets'[27]. A series of esters of 5-chloro-4-formylpyrrol-3-carboxylic acids **1a-e** recently synthesized by us[28] and the authors of[29] completely satisfies the above requirements and that is why these compounds were used for the synthesis of the target pyrrolacrylamides. As shown before, the compounds of class **1** can be effectively used as synthetic units in construction of some pyrrol[2,3-*b*]quinoline[30] and pyrrol[3,4-*b*;3',4'-*d*]pyridine[31] systems.

2. Results and Discussion

2.1 Synthesis and spectra characteristics

We have developed a preparative simple method of synthesis in which the esters of 5-chloro-4-formylpyrrol-3-carboxylic acids **1a-e** are transformed in the corresponding acrylamides (**Fig**. **1**). At the first stage, the compounds **1a-e** interact with malonic acid by the Knoevenagel reaction and form the respective 3-(pyrrol-4-yl)acrylic acids **2a-e** which yields 86-93 %. Their IR spectra reveal the medium intensity absorbance bands corresponding to the groups C=C (1639-1645 sm^{-1}), carboxylic C=O (1700-1710 sm^{-1}), carboxylatic C=O (1720-1730 sm^{-1}), and wider absorbance bands of the carboxylic O-H (2524-2832 sm^{-1}). The peaks related to the pyrrole-like derivatives, the carboxylic group singlets at 12.15-12.25 ppm, and the doublets of C^2H= and C^3H= protons in the ranges 6.38-6.50 and 7.98-8.04 ppm respectively were found in the ^{1}H-NMR spectra of the above compounds recorded for J = 16.0 Hz. It is a proof of the *trans*-configuration of a pyrrole fragment and a carboxylic group in the regard of a double bond.

At the second stage, chloroanhydrides of the acids **2a-e** were synthesized by a 4 h long boiling of the respective acids in a benzene solution of excessive thionyl chloride. Further, the raw uncleaned chloroanhydrides reacted with aromatic or aliphatic amines in a boiling acetonitrile solution of triethylamine. This process lasted during 3 h. As a result the amides **3a-l** of 3-(pyrrol-4-yl)acrylic acid were obtained with yields 72-94% (**Table 1**). Even though a pyrrole fragment of the intermediate chloroanhydrides consists of an electrophilic ester group, the reactions with substituted anilines and more basic aliphatic amines remain regioselective and involve only chlorocarbonyl function.

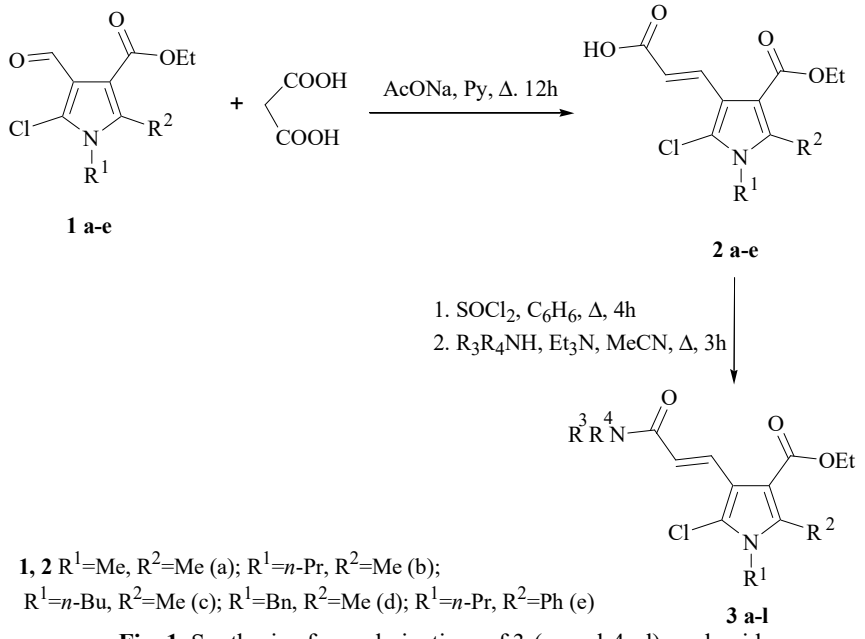
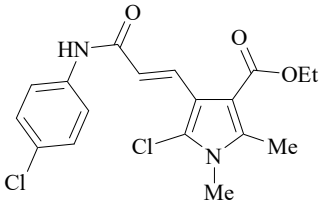
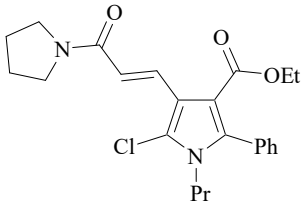
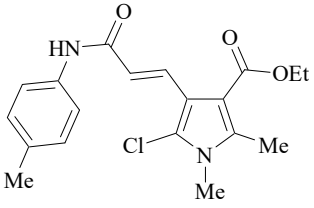
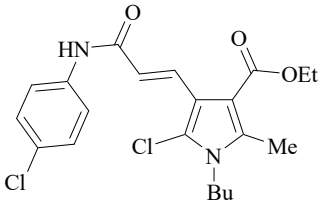
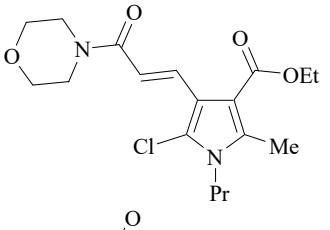
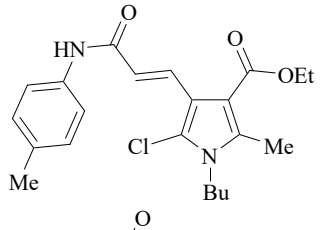
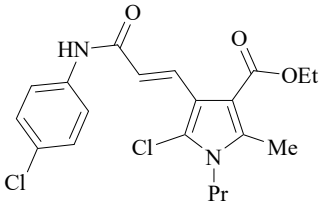
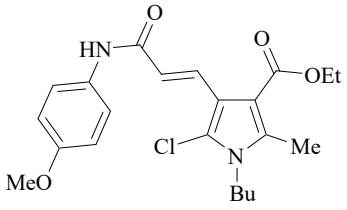
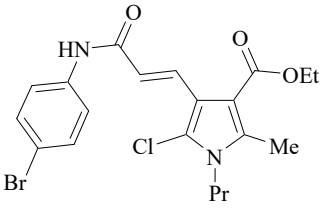
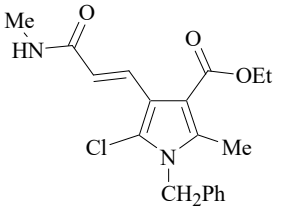
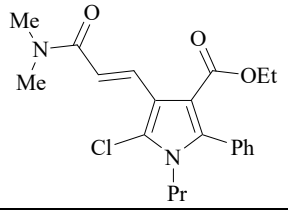
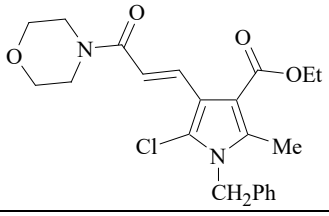


Fig. 1. Synthesis of new derivatives of 3-(pyrrol-4-yl)acrylamides

Table 1. Structure of synthesized compounds

Compound	Structure	Compound	Structure
3 a		**3g**	
3 b		**3h**	
3c		**3 i**	
3d		**3j**	
3e		**3k**	
3f		**3l**	

Structural composition of the amides **3a-l** was confirmed by their spectral characteristics. For instance, the absorption bands of the valent asymmetric oscillations of bonds C=C (1634-1649 sm^{-1}), amide C=O (1665-1676 sm^{-1}), and ester C=O (1720-1728 sm^{-1}) were found in their IR spectra. The NH absorption band of monosubstituted amides **3a, b, d, e, h-k** was registered at 3240-3254 sm^{-1}. The doublet peaks of C^2H= and C^3H= protons were registered in the ^1H-NMR spectra of synthesized compounds **3a-l** at 6.73-7.19 and 7.94-8.23 ppm for J = 16.0 Hz. Thus, the introduction of aromatic amines in the structure of compounds **3** does not cause any changes in the shift of the C^3H= protons, and leads to a weak-field shift of the C^2H= protons on average by 0.3 ppm on average as compared to acids **2**. On the contrary, the similar effect caused by the introduction of cycloalkylamino groups (compounds **3c, f, g**) is more significant, and it causes a shift of the abovementioned protons towards a weaker field by 0.6-0.7 ppm.

2.2 Antimicrobial activity

The 10 μg/ml solutions of synthesized amides **3a-l** have been evaluated for antimicrobial activity on some archive strains and clinical isolates of antibiotic-sensitive (MS) and antibiotic-resistant (MR) microorganisms including gram-positive *Staphylococcus aureus* MR and MS, *Staphylococcus haemolyticus* MR, *Staphylococcus epidermidis* MS, *Bacillus subtilis,*

Streptococcus pyogenes, Streptococcus oralis, Streptococcus gordonii; gram-negative *Klebsiella pneumonniae* and *Escherichia coli* ATCC 35218, and fungi *Candida albicans* and *Candida tropicalis.* Chlorhexidine[32] and Decamethoxin (Dekasan)[33] were used as the control antiseptic and disinfection agents revealing activity against bacteria and fungi.

It was found that the gram-negative bacteria *Klebsiella pneumonniae* and *Escherichia coli* are not sensitive to the studied amides **3a-l.** In contrary, the gram-positive bacteria were found sensitive to the amides **3c, e, f, g, i** (**Tabl**e **2**). In particular, *Staphylococcus aureus* MS, *Streptococcus pyogenes* and *Streptococcus gordonii* are sensitive to the amides **3g** and **3f**, *Staphylococcus aureus* MR, *Staphylococcus haemolyticus* MR and *Staphylococcus epidermidis* MS – to the amides **3c, f, g,** *Bacillus subtilis* – to the amides **3f, g, i,** and *Streptococcus oralis* – to the amides **3 e, f, g.** Some antifungal activity has been found in the amides **3c, f, g,** in particular, the amide **3c** retards the proliferation of *Candida albicans,* and the compounds **3 c, f, g** – *Candida tropicalis*.

Basing on these results, we can emphasize the antistaphylococcus activity of the amide **3f** against *Staphylococcus aureus* MR and *Staphylococcus epidermidis* MS, for which the retardation area diameter was 14.65 mm, which is greater than that for the control agents. Such a notable antibacterial effect can be caused by the strong electrondonoring dimethylamino group of the amide fragment, which increases a lypophility of the molecule[34]. Taking into account the natural resistance of staphylococcus bacteria against many drugs, a deeper study of the amide **3f** will be taken.

Table. 2. Antimicrobial activity of the synthesized compounds

Name of bacteria (fungus)	3c	3e	3f	3g	3i	C[1]	C[2]
Staphylococcus aureus MS	-	-	7.14 ±0.25	8.80 ±1.10	-	11.90 ±0.19	14.29 ±0.21
Staphylococcus aureus MR	11.64 ±0.63	-	14.56 ±0.20	14.00 ±0.46	-	12.00 ±1.17	13.65 ±0.25
Staphylococcus haemolyticus MR	4.92 ±0.36	-	10.21 ±0.77	8.35 ±0.47	-	13.50 ±0.45	15.81 ±0.77
Staphylococcus epidermidis MS	6.64 ±0.43	-	14.65 ±0.35	13.16 ±0.22	-	14.50 ±0.17	13.87 ±1.10
Bacillus subtilis	-	-	12.11 ±0.30	11.65 ±0.36	12.68 ±1.33	20,96 ±0,68	23.08 ±0.42
Streptococcus pyogenes	-	-	6.46 ±0.19	5.42 ±0.31	-	11.96 ±0,86	14.25 ±0.78
Streptococcus oralis	-	13.3 ±0.73	12.73 ±1.16	13.39 ±0.88	-	20.25 ±0.23	16.39 ±0.64
Streptococcus gordonii	-	-	6.66 ±0.55	6.73 ±0.95	-	16.23 ±0.56	15.22 ±0.59
Candida albicans	5.30 ±0.52	-	-	-	-	11.71 ±0.39	10.20 ±0.36
Candida tropicalis	5.71 ±0.66	-	5.32 ±0.28	5.73 ±0.66	-	6.38 ±0.17	11.69 ±0.36

C^1 – 0.05% solution of chlorhexidine (by PJSC Pharmaceutical factory «Viola»)
C^2 –0.02% solution of Dekasan (by LLC «YuriyaPharm»)

3. Conclusions

It can be concluded that an efficient method of synthesis of new antimicrobial active 3-(pyrrol-4-yl)acrylamides has been developed. These products consist of biophoric chlorine atoms and an easily modifiable ester group in the pyrrole cycle. This method is very promising as it involves readily available reactants, easy procedures of synthesis, and ensures high yields of intermediate and final compounds. Structural composition of the synthesized products was confirmed by IR-, ^{1}H (^{13}C)-NMR-spectroscopy, mass spectrometry, and elemental analysis. As seen from the evaluation of antimicrobial properties of the synthesized amides, the compounds **3c, e, f, g, i** are highly efficient against gram-positive bacteria. Special attention should be given to the compound **3f** because its activity against *Staphylococcus aureus* MR and *Staphylococcus epidermidis* MS is greater than that of the control drugs. As seen from the antimicrobial activity investigation, the obtained 3-(pyrrol-4-yl)acrylamides deserve further study as prospective antigerm agents.

4. Experimental

4.1. Materials and Methods

All chemicals were of analytical grade and commercially available. When performing the synthetic part of the work, the reagents of the company Merck (Germany) and Sigma-Aldrich (USA) were used. All reagents and solvents were used

without further purification and drying. All the melting points were determined in an open capillary and left uncorrected. IR spectra were recorded on Bruker Vertex 70 FT-IR spectrometer for samples in KBr pellets. ^{1}H-NMR spectra were acquired in pulse Fourier transform mode on a Varian VXR-400 spectrometer (400 MHz) in DMSO-d_6 (compounds **2 a-e**) or $CDCl_3$ (compounds **3 a-l**), while ^{13}C-NMR spectra of all compounds were recorded on a Bruker Avance DRX-500 spectrometer. The solvent signal (DMSO-d6: 2.49 ppm for $_1$H nuclei, 39.5 ppm for ^{13}C nuclei; $CDCl_3$: 7.26 ppm for ^{1}H nuclei) served as the internal standard. Mass spectra were recorded on an Agilent LC/MSD SL mass spectrometer; column: Zorbax SB-C18, 4.6 × 15 mm, 1.8 μm (PN 82 (c)75-932); DMSO solvent, atmospheric pressure electrospray ionization. Elemental analysis was performed on a Perkin Elmer 2400 CHN-analyzer. Melting points were determined on a Kofler bench and left uncorrected.

4.2. General procedure

*General procedure for the synthesis of 3-[2-chloro-4-(ethoxycarbonyl)-1H-pyrrol-3-yl]acrylic acids (***2a-e***).* A solution of sodium acetate (4.08 g, 30 mmol) in 5 ml of ethanol was added to a suspension of ethyl 5-chloro-4-formylpyrrol-3-carboxylate **1a-e** (10 mmol) and malonic acid (1.04 g, 10 mmol) in 25 ml of pyridine. The mixture was boiled for 24 h, then cooled and poured into 100 mL of a 1N HCl. The sediment was filtered, washed by 50 mL of water, dried and recrystallized from a 70 % aqueous solution of ethanol.

General procedure for the synthesis of ethyl 1-R^1,2-R^2- 5-chloro-4-{[3-(4-R^3R^4-amino)]-3-oxoprop-1-enyl}-1H-pyrrole-3-carboxylates (**3a-l**). 0.89 g (7.5 mmol) of thionylchloride were added to a suspension of 3-[2-chloro-4-(ethoxycarbonyl)-1*H*-pyrrol-3-yl]acrylic acid **2a-e** (5 mmol) in 25 mL of benzene and boiled for 4 h. After evaporation of the solvent, the dry residue was dissolved in 20 mL of acetonitrile. Then 5 mmol of the corresponding amine and 0.51 g (5 mmol) of triethylamine were added to the solution. The mixture was boiled for 3 h, cooled and filtered. Acetonitrile was evaporated and the sediment was recrystallized from a 70 % aqueous solution of ethanol.

4.3 Physical and Spectral Data

*4.3.1 3-[2-Chloro-4-(ethoxycarbonyl)-1,5-dimethyl-1-propyl-1H-pyrrol-3-yl]acrylic acid (***2a***).* Yield 86 % (2.34 g), white solid, m. p. 169-171 ºC; IR (KBr, sm^{-1}): 1637(C=C), 1705(C=O), 1722(C=O), 2524-2808 (OH); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 1.27 (3H, t, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 2.44 (3H, s, CH_3), 3.50 (3H, s, NCH_3), 4.21 (2H, k, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 6.38 (1H, d, *J* = 16.0 Hz, CH), 7.98 (1H, d, *J* = 16.0 Hz, CH), 12.15 (1H, s, CO_2H). ^{13}C-NMR (125.7 MHz, DMSO-d_6) δ (ppm): 12.3, 14.5, 31.4, 60.0, 110.3, 114.1, 117.9, 118.0, 136.1, 136.4, 164.2, 168.6. MS, *m*/*z* ($I_{отн}$, %): 272 $[M-H]^+$ (100). Anal. Calcd. for $C_{12}H_{14}ClNO_4$ (%): C, 53.05; H, 5.19; N, 5.16. Found: C, 49.92; H, 5.31; N, 5.29.

*4.3.2 3-[2-Chloro-4-(ethoxycarbonyl)-5-methyl-1-propyl-1H-pyrrol-3-yl]acrylic acid (***2b***).* Yield 92% (2.86 g), white solid, m. p. 154-155 ºC; IR (KBr, sm^{-1}): 1639(C=C), 1705(C=O), 1724(C=O), 2536-2810(OH); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 0.86 (3H, t, *J* = 7.2 Hz, $NCH_2CH_2\underline{CH_3}$), 1.28 (3H, t, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 1.47-1.68 (2H, m, $NCH_2\underline{CH_2}CH_3$), 2.46 (3H, s, CH_3), 3.92 (2H, t, *J* = 7.2 Hz, NCH_2), 4.20 (2H, k, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 6.40 (1H, d, *J* = 16.0 Hz, CH), 7.98 (1H, d, *J* = 16.0 Hz, CH), 12.19 (1H, s, CO_2H). ^{13}C-NMR (125.7 MHz, DMSO-d_6) δ (ppm): 11.2, 12.1, 14.6, 23.0, 45.8, 60.1, 110.7, 114.4, 117.4, 118.2, 136.1, 136.8, 164.2, 168.5. MS, *m*/*z* ($I_{отн}$, %): 310 $[M-H]^+$ (100). Anal. Calcd. for $C_{14}H_{18}ClNO_4$ (%): C, 56.10; H, 6.05; N, 4.67. Found: C, 56.23; H, 5.98; N, 4.54.

*4.3.3 3-[1-Butyl-2-chloro-4-(ethoxycarbonyl)-5-methyl-1H-pyrrol-3-yl]acrylic acid (***2c***).* Yield 93% (2.92 g), white solid, m. p. 147-148 ºC; IR (KBr, sm^{-1}): 1642(C=C), 1708(C=O), 1727(C=O), 2540-2812(OH); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 0.89 (3H, t, *J* = 7.2 Hz, $N(CH_2)_3\underline{CH_3}$), 1.21-1.39 (5H, m, CH_2 + $OCH_2\underline{CH_3}$), 1.49-1.61 (2H, m, CH_2), 2.46 (3H, s, CH_3), 3.94 (2H, t, *J* = 7.2 Hz, NCH_2), 4.20 (2H, k, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 6.40 (1H, d, *J* = 16.0 Hz, CH), 7.98 (1H, d, *J* = 16.0 Hz, CH), 12.20 (1H, s, CO_2H). ^{13}C-NMR (125.7 MHz, DMSO-d_6) δ (ppm): 12.1, 13.9, 14.6, 19.7, 31.7, 44.2, 60.1, 110.1, 114.4, 117.4, 118.2, 136.1, 136.7, 164.2, 168.4. MS, *m*/*z* ($I_{отн}$, %): 314 $[M-H]^+$ (100). Anal. Calcd. for $C_{15}H_{20}ClNO_4$ (%): C, 57.42; H, 6.42; N, 4.46. Found: C, 57.29; H, 6.49; N, 4.50 .

*4.3.4 3-[1-Benzyl-2-chloro-4-(ethoxycarbonyl)-5-methyl-1H-pyrrol-3-yl]acrylic acid (***2d***).* Yield 88% (2.80 g), white solid, m. p. 188-190 ºC; IR (KBr, sm^{-1}): 1645(C=C), 1706(C=O), 1725(C=O), 2531-2823(OH); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 1.28 (3H, t, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 2.41 (3H, s, CH_3), 4.22 (2H, k, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 5.30 (2H, s, $\underline{CH_2}Ph$), 6.43 (1H, d, *J* = 16.0 Hz, CH), 7.01 (2H, d, *J* = 7.2 Hz, Ph), 7.23-7.40 (3H, m, Ph), 8.04 (1H, d, *J* = 16.0 Hz, CH), 12.25 (1H, s, CO_2H). ^{13}C-NMR (125.7 MHz, DMSO-d_6) δ (ppm): 12.3, 14.5, 47.4, 60.2, 111.2, 114.7, 118.0, 118.7, 126.3 (2C), 128.0. 129.3 (2C), 136.0, 136.3, 137.3, 164.2, 168.4. MS, *m*/*z* ($I_{отн}$, %): 318 $[M-H]^+$ (100). Anal. Calcd. for $C_{18}H_{18}ClNO_4$ (%): C, 62.16; H, 5.22; N, 4.03. Found: C, 62.33; H, 5.17; N, 3.94.

*4.3.5 3-[2-Chloro-4-(ethoxycarbonyl)-5-phenyl-1-propyl-1H-pyrrol-3-yl]acrylic acid (***2e***).* Yield 85% (3.08 g), white solid, m. p. 162-164 ºC; IR (KBr, sm^{-1}): 1639(C=C), 1710(C=O), 1730(C=O), 2525-2832(OH); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 0.63 (3H, t, *J* = 7.2 Hz, $NCH_2CH_2\underline{CH_3}$), 0.78 (3H, t, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 1.37-1.54 (2H, m, $NCH_2\underline{CH_2}CH_3$), 3.70 (3H, t, *J* = 7.2 Hz, $N\underline{CH_2}$), 3.89 (2H, k, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 6.50 (1H, d, *J* = 16.0 Hz, CH), 7.31-7.48 (5H, m, Ph), 7.98 (1H, d, *J* = 16.0 Hz, CH), 12.25 (1H, s, CO_2H). ^{13}C-NMR (125.7 MHz, DMSO-d_6) δ (ppm): 11.1, 13.8, 23.2, 46.7,

59.8, 112.3, 114.9, 118.8, 118.9, 126.5 (2C), 129.3. 130.8 (2C), 131.4, 135.3, 139.1, 163.6, 168.4. MS, *m/z* ($I_{отн}$, %): 362 $[M-H]^+$ (100). Anal. Calcd. for $C_{19}H_{20}ClNO_4$ (%): C, 63.07; H, 5.57; N, 3.81. Found: C, 63.22; H, 5.63; N, 3.69.

*4.3.6 Ethyl 5-choro-4-{3-[(4-chlorophenyl)amino]-3-oxoprop-1-enyl}-1,2-dimethyl-1H-pyrrole-3-carboxylate (**3a**).* Yield 83% (1.59 g), white solid, m. p. 197-199 ºC; IR (KBr, sm^{-1}): 1638(C=C), 1665(C=O), 1720(C=O), 3248(N-H); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.38 (3H, t, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 2.50 (3H, s, CH_3), 3.50 (3H, s, NCH_3), 4.30 (2H, k, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 6.73 (1H, d, *J* = 16.0 Hz, CH), 7.24 (2H, d, *J* = 8.4 Hz, Ar-H), 7.57 (2H, d, *J* = 8.4 Hz, Ar-H), 7.20 (1H, t, *J* = 8.4 Hz, NH), 8.04 (1H, d, *J* = 16.0 Hz, CH). ^{13}C-NMR (125.7 MHz, DMSO-d6) δ (ppm): 12.2, 14.4, 31.0, 60.2, 111.1, 114.9, 118.2, 120.4, 121.0, 128.6, 128.7 (2C), 128.9 (2C), 133.8, 136.6, 137.1, 164.8. MS, *m/z* ($I_{отн}$, %): 382 $[M-H]^+$ (100). Anal. Calcd. for $C_{18}H_{18}Cl_2N_2O_3$ (%): C, 56.71; H, 4.76; N, 7.35. Found: C, 56.65; H, 4.82; N, 7.46.

4.3.7. Ethyl 5-choro-4-{3-[(4-methylphenyl)amino]-3-oxoprop-1-enyl}-1,2-dimethyl-1H-pyrrole-3-carboxylate (**3b**). Yield 81% (1.46 g), white solid, m. p. 176-178 ºC; IR (KBr, sm^{-1}): 1642(C=C), 1670(C=O), 1725(C=O), 3243(N-H); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.40 (3H, t, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 2.32 (3H, s, CH_3), 2.52 (3H, s, CH_3), 3.52 (3H, s, NCH_3), 4.32 (2H, k, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 6.74 (1H, d, *J* = 16.0 Hz, CH), 7.12 (2H, d, *J* = 8 Hz, Ar-H), 7.47-7.55 (3H, m, Ar-H + NH), 8.09 (1H, d, *J* = 16.0 Hz, CH). ^{13}C-NMR (125.7 MHz, DMSO-d6) δ (ppm): 11.6, 14.0, 20.4, 30.4, 59.6, 110.7, 114.8, 117.0, 119.1, 120.9, 127.9 (2C), 128.1 (2C), 132.2, 132.9, 135.1, 136.2, 164.4. MS, *m/z* ($I_{отн}$, %): 361 $[M-H]^+$ (100). Anal. Calcd. for $C_{19}H_{21}ClN_2O_3$ (%): C, 63.24; H, 5.87; N, 7.76. Found: C, 63.39; H, 5.92; N, 7.63

4.3.8 Ethyl 5-choro-2-methyl-4-[3-morpholin-4-yl-3-oxoprop-1-enyl]-1-propyl-1H-pyrrole-3-carboxylate (**3c**). Yield 77% (1.42 g), white solid, m. p. 112-113 ºC; IR (KBr, sm^{-1}): 1642(C=C), 1670(C=O), 1725(C=O); H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.93 (3H, t, *J* = 7.2 Hz, $NCH_2CH_2\underline{CH_3}$), 1.36 (3H, t, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 1.62-1.73 (2H, m, $NCH_2\underline{CH_2}CH_3$), 2.50 (3H, s, CH_3), 3.59-3.81 (8H, m, morpholin), 4.32 (2H, k, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 6.99 (1H, d, *J* = 16.0 Hz, CH), 7.98 (1H, d, *J* = 16.0 Hz, CH). ^{13}C-NMR (125.7 MHz, DMSO-d6) δ (ppm): 11.0, 11.9, 14.4, 23.2, 43.4 (2C), 45.7, 60.0, 66.9 (2C), 111.3, 115.5, 116.6, 117.0, 128.7, 136.0, 164.9, 166.6. MS, *m/z* ($I_{отн}$, %): 369 $[M-H]^+$ (100). Anal. Calcd. for $C_{18}H_{25}ClN_2O_4$ (%): C, 58.61; H, 6.83; N, 7.59. Found: C, 58.73; H, 6.76; N, 7.41

4.3.9 Ethyl 5-choro-4-{3-[(4-chlorophenyl)amino]-3-oxoprop-1-enyl}-2-methyl-1-propyl-1H-pyrrole-3-carboxylate (**3d**). Yield 84% (1.72 g), white solid, m. p. 158-160 ºC; IR (KBr, sm^{-1}): 1646(C=C), 1673(C=O), 1728(C=O), 3250(N-H); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.96 (3H, t, *J* = 7.2 Hz, $NCH_2CH_2\underline{CH_3}$), 1.39 (3H, t, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 1.61-1.74 (2H, m, $NCH_2\underline{CH_2}CH_3$), 2.52 (3H, s, CH_3), 3.87 (2H, t, *J* = 7.2 Hz, $N\underline{CH_2}CH_2CH_3$), 4.31 (2H, k, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 6.77 (1H, d, *J* = 16.0 Hz, CH), 7.25 (2H, d, *J* = 8.4 Hz, Ar-H), 7.59 (2H, d, *J* = 8.4 Hz, Ar-H), 7.83 (1H, t, *J* = 5.4 Hz, NH), 8.10 (1H, d, *J* = 16.0 Hz, CH). ^{13}C-NMR (125.7 MHz, DMSO-d6) δ (ppm): 10.6, 11.6, 14.0, 22.8, 45.4, 59.7, 111.4, 114.6, 117.3, 119.8, 120.6, 128.2 (2C), 128.5 (2C), 133.6. 133.7, 135.7, 136.6, 164.6. MS, *m/z* ($I_{отн}$, %): 410 $[M-H]^+$ (100). Anal. Calcd. for $C_{20}H_{22}Cl_2N_2O_3$ (%): C, 58.69; H, 5.42; N, 6.84. Found: C, 58.71; H, 5.37; N, 6.78 .

4.3.10 Ethyl 4-{3-[(4-bromophenyl)amino]-3-oxoprop-1-enyl}-5-choro-2-methyl-1-propyl-1H-pyrrole-3-carboxylate (**3e**). Yield 89% (2.02 g), white solid, m. p. 164-165 ºC; IR (KBr, sm^{-1}): 1649(C=C), 1676(C=O), 1726(C=O), 3254(N-H); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.97 (3H, t, *J* = 7.2 Hz, $NCH_2CH_2\underline{CH_3}$), 1.40 (3H, t, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 1.63-1.77 (2H, m, $NCH_2\underline{CH_2}CH_3$), 2.53 (3H, s, CH_3), 3.89 (2H, t, *J* = 7.2 Hz, NCH_2), 4.34 (2H, k, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 6.75 (1H, d, *J* = 16.0 Hz, CH), 7.41 (2H, d, *J* = 8.4 Hz, Ar-H), 7.54 (2H, d, *J* = 8.4 Hz, Ar-H), 7.63 (1H, t, *J* = 5.4 Hz, NH), 8.12 (1H, d, *J* = 16.0 Hz, CH). ^{13}C-NMR (125.7 MHz, DMSO-d6) δ (ppm): 10.6, 11.6, 14.0, 22.8, 45.4, 59.7, 110.9, 114.6, 116.0, 117.3, 119.8, 121.0, 131.2 (2C), 131.6 (2C), 133.7, 135.7, 137.1, 164.4. MS, *m/z* ($I_{отн}$, %): 454 $[M-H]^+$ (100). Anal. Calcd. for $C_{20}H_{22}BrClN_2O_3$ (%): C, 52.94; H, 4.89; N, 6.17. Found: C, 53.11; H, 4.81; N, 6.09

4.3.11 Ethyl 5-choro-4-[3-(dimethylamino)-3-oxoprop-1-enyl]-2-methyl-1-propyl-1H-pyrrole-3-carboxylate (**3f**). Yield 82% (1.64 g), white solid, m. p. 173-174 ºC; IR (KBr, sm^{-1}): 1639(C=C), 1670(C=O), 1721(C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.73 (3H, t, *J* = 7.2 Hz, $NCH_2CH_2\underline{CH_3}$), 0.96 (3H, t, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 1.49-1.30 (2H, m, $NCH_2\underline{CH_2}CH_3$), 3.05 (3H, s, NCH_3), 3.15 (3H, s, NCH_3), 3.71 (2H, t, *J* = 7.2 Hz, NCH_2), 4.01 (2H, k, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 7.19 (1H, d, *J* = 16.0 Hz, CH), 7.21-7.29 (2H, m, Ph), 7.32-7.44 (3H, m, Ph), 7.94 (1H, d, *J* = 16.0 Hz, CH). ^{13}C-NMR (125.7 MHz, DMSO-d6) δ (ppm): 10.9, 13.8, 23.6, 32.9, 35.9, 46.5, 59.9, 112.7, 116.2, 118.3, 118.6, 128.1 (2C), 128.7, 130.5 (2C), 131.7, 132.8, 138.6, 164.3, 167.6. MS, *m/z* ($I_{отн}$, %): 399 $[M-H]^+$ (100). Anal. Calcd. for $C_{21}H_{25}ClN_2O_3$ (%): C, 64.86; H, 6.48; N, 7.20. Found: C, 64.79; H, 6.54; N, 7.33 .

4.3.12 Ethyl 5-choro-4-[3-oxo-3-pyrrolidin-1-ylprop-1-enyl]-2-phenyl-1-propyl-1H-pyrrole-3-carboxylate (**3g**). Yield 72% (1.48 g), white solid, m. p. 139-140 ºC; IR (KBr, sm^{-1}): 1634 (C=C), 1669(C=O), 1720(C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.72 (3H, t, *J* = 7.2 Hz, $NCH_2CH_2\underline{CH_3}$), 0.97 (3H, t, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 1.50-1.59 (2H, m, $NCH_2\underline{CH_2}CH_3$), 1.81-1.99 (4H, m, $2CH_{2\text{pyrrolidin}}$), 3.52-3.65 (4H, m, $2CH_{2\text{pyrrolidin}}$), 3.70 (2H, t, *J* = 7.2 Hz, NCH_2), 4.03 (2H, k, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 7.03 (1H, d, *J* = 16.0 Hz, CH), 7.21-7.30 (2H, m, Ar-H), 7.35-7.43 (3H, m, Ar-H), 7.97 (1H, d, *J* = 16.0 Hz, CH). ^{13}C-NMR (125.7 MHz, DMSO-d6) δ (ppm): 10.9, 13.8, 23.5, 24.4, 26.1, 45.8, 46.4, 46.6, 59.9, 113.4, 116.2, 118.6, 119.8, 128.1 (2C), 128.7, 130.5 (2C), 131.7, 132.1, 138.6, 164.2, 165.6. MS, *m/z* ($I_{отн}$, %): 415 $[M-H]^+$ (100). Anal. Calcd. for $C_{23}H_{27}ClN_3O_3$ (%): C, 66.58; H, 6.56; N, 6.75. Found: C, 66.43; H, 6.68; N, 6.86 .

4.3.13 Ethyl 1-butyl-5-choro-4-{3-[(4-chlorophenyl)amino]-3-oxoprop-1-enyl}-2-methyl-1H-pyrrole-3-carboxylate (**3h**). Yield 75% (1.54 g), white solid, m. p. 123-125 ºC; IR (KBr, sm^{-1}): 1648(C=C), 1676(C=O), 1724(C=O), 3240(N-H); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.98 (3H, t, *J* = 7.2 Hz, $N(CH_2)_3\underline{CH_3}$), 1.34-1.45 (5H, m, CH_2 + $OCH_2\underline{CH_3}$), 1.61-1.69 (2H, m, CH_2), 2.52 (3H, s, CH_3), 3.91 (2H, t, *J* = 7.2 Hz, NCH_2), 4.31 (2H, k, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 6.73 (1H, d, *J* = 16.0 Hz, CH), 7.04 (2H, d, *J* = 8.4 Hz, Ar-H), 7.43 (1H, t, *J* = 5.4 Hz, NH), 7.58 (2H, d, *J* = 8.4 Hz, Ar-H), 8.23 (1H, d, *J* = 16.0 Hz, CH). ^{13}C-NMR (125.7 MHz, DMSO-d6) δ (ppm): 12.1, 13.7, 14.5, 19.9, 31.9, 44.1, 60.1, 111.6, 115.2, 118.0, 120.1, 128.9, 128.9 (2C), 129.6 (2C), 134.0. 136.2, 136.7, 137.9, 164.7. MS, *m*/*z* ($I_{отн}$, %): 410 $[M-H]^+$ (100). Anal. Calcd. for $C_{21}H_{24}Cl_2N_2O_3$ (%): C, 59.58; H, 5.71; N, 6.62. Found: C, 59.71; H, 5.63; N, 6.50 .

4.3.14 Ethyl 1-butyl-5-choro-2-methyl-4-{3-[(4-methylphenyl)amino]-3-oxoprop-1-enyl}-1H-pyrrole-3-carboxylate (**3i**). Yield 85% (1.71 g), white solid, m. p. 137-138 ºC; IR (KBr, sm^{-1}): 1645(C=C), 1666(C=O), 1722(C=O), 3244(N-H); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.98 (3H, t, *J* = 7.2 Hz, $N(CH_2)_3\underline{CH_3}$), 1.30-1.45 (5H, m, CH_2 + $OCH_2\underline{CH_3}$), 1.61-1.68 (2H, m, CH_2), 2.23 (3H, s, CH_3), 2.53 (3H, s, CH_3), 3.92 (2H, t, *J* = 7.2 Hz, NCH_2), 4.33 (2H, k, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 6.73 (1H, d, *J* = 16.0 Hz, CH), 7.12 (2H, d, *J* = 8.4 Hz, Ar-H), 7.42-7.54 (3H, m, NH + Ar-H), 8.10 (1H, d, *J* = 16.0 Hz, CH). ^{13}C-NMR (125.7 MHz, DMSO-d6) δ (ppm): 11.9, 13.7, 14.5, 19.9, 20.9, 32.0, 44.2, 60.1, 111.5, 115.0, 119.8, 120.9, 129.3 (2C), 129.6 (2C), 132.9, 132.1, 133.8, 134.2, 136.1, 164.9. MS, *m*/*z* ($I_{отн}$, %): 403 $[M-H]^+$ (100). Anal. Calcd. for $C_{22}H_{27}ClN_2O_3$ (%): C, 65.58; H, 6.75; N, 6.95. Found: C, 65.71; H, 6.69; N, 6.87.

4.3.15 Ethyl 1-butyl-5-choro-4-{3-[(4-methoxyphenyl)amino]-3-oxoprop-1-enyl}-2-methyl-1H-pyrrole-3-carboxylate (**3j**). Yield 89% (1.86 g), white solid, m. p. 132-134 ºC; IR (KBr, sm^{-1}): 1644(C=C), 1665(C=O), 1727(C=O), 3251(N-H); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.98 (3H, t, *J* = 7.2 Hz, $N(CH_2)_3\underline{CH_3}$), 1.33-1.44 (5H, m, CH_2 + $OCH_2\underline{CH_3}$), 1.61-1.72 (2H, m, CH_2), 2.53 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 3.92 (2H, t, *J* = 7.2 Hz, NCH_2), 4.33 (2H, k, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 6.74 (1H, d, *J* = 16.0 Hz, CH), 6.87 (2H, d, *J* = 8.8 Hz, Ar-H), 7.28 (1H, t, *J* = 5.4 Hz, NH), 7.53 (2H, d, *J* = 8.8 Hz, Ar-H), 8.09 (1H, d, *J* = 16.0 Hz, CH). ^{13}C-NMR (125.7 MHz, DMSO-d6) δ (ppm): 11.9, 13.7, 14.5, 19.9, 32.0, 44.1, 55.5, 60.1, 111.4, 113.9 (2C), 114.1 (2C), 115.1, 117.3, 120.8, 121.5, 131.9, 133.3, 136.0, 156.9, 164.9. MS, *m*/*z* ($I_{отн}$, %): 419 $[M-H]^+$ (100). Anal. Calcd. for $C_{22}H_{27}ClN_2O_4$ (%): C, 63.08; H, 6.50; N, 6.99. Found: C, 63.23; H, 6.42; N, 6.88 .

4.3.16 Ethyl 1-benzyl-5-choro-2-methyl-4-[3-(methylamino)-3-oxoprop-1-enyl]-1H-pyrrole-3-carboxylate (**3k**). Yield 94% (1.70 g), white solid, m. p. 171-173 ºC; IR (KBr, sm^{-1}): 1640(C=C), 1667(C=O), 1724(C=O), 3254(N-H); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.36 (3H, t, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 2.41 (3H, s, CH_3), 2.89 (3H, d, *J* = 4.8 Hz, NCH_3), 4.33 (2H, k, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 5.31 (2H, s, $\underline{CH_2}Ph$), 5.96 (1H, t, *J* = 5.4 Hz, NH), 6.76 (1H, d, *J* = 16.0 Hz, CH), 6.92-6.99 (2H, m, Ph), 7.25-7.32 (3H, m, Ph), 7.96 (1H, d, *J* = 16.0 Hz, CH). ^{13}C-NMR (125.7 MHz, DMSO-d6) δ (ppm): 12.4, 14.4, 26.4, 47.4, 60.2, 111.8, 115.4, 117.2, 121.1, 125.9 (2C), 127.8, 129.0 (2C), 132.1, 135.5, 136.6, 164.8, 167,5. MS, *m*/*z* ($I_{отн}$, %): 361 $[M-H]^+$ (100). Anal. Calcd. for $C_{19}H_{21}ClN_2O_3$ (%): C, 63.24; H, 5.87; N, 7.76. Found: C, 63.38; H, 5.80; N, 7.64

4.3.17 Ethyl 1-benzyl-5-choro-2-methyl-4-[3-morpholin-4-yl-3-oxoprop-1-enyl]-1H-pyrrole-3-carboxylate (**3l**). Yield 79% (1.65 g), white solid, m. p. 126-127 ºC; IR (KBr, sm^{-1}): 1642(C=C), 1673(C=O), 1725(C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.38 (3H, t, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 2.45 (3H, s, CH_3), 3.59-3.81 (8H, m, morpholin), 4.32 (2H, k, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 5.20 (2H, s, CH_2Ph), 6.93-7.09 (3H, m, CH + Ph), 7.27-7.36 (3H, m, Ph), 8.04 (1H, d, *J* = 16.0 Hz, CH). ^{13}C-NMR (125.7 MHz, DMSO-d6) δ (ppm): 12.1, 14.4, 44.1 (2C), 47.4, 60.2, 66.9 (2C), 111.8, 115.9, 117.1, 117.4, 125.9 (2C), 127.8, 128.9 (2C), 134.4, 135.5, 136.7, 164.8, 166.6. MS, *m*/*z* ($I_{отн}$, %): 417 $[M-H]^+$ (100). Anal. Calcd. for $C_{22}H_{25}ClN_2O_4$ (%): C, 63.38; H, 6.04; N, 6.72. Found: C, 63.50; H, 6.11; N, 6.59.

4.4 Antimicrobial activity

A micromethod of diffusion into agar was used to evaluate an antimicrobial activity of the synthesized compounds. Nutritional agar was placed in the Petri bowls, and a series of 4.0 mm holes was made in it. Then the agar was uniformly populated with the standard suspensions of test-cultures with the concentration 1×10^7 CFU/mL. 20 μL of a 10 mg/mL solution of the studied compounds in a mixture DMSO/ethanol/ water (1:2:1) were added to each hole to evaluate their antimicrobial activity. To do that, a diameter of the bacterial colony's retardation area was measured 24 h after the addition of a compound by taking digital images of the colonies followed by their analysis performed by the software UTHSCSA ImageTool 3.0 (The University of Texas Health Science Center in San Antonio, ©1995-2002). Then the results were additionally processed using variational statistics methods. No retardation of the colony's growth was found in the control holes treated with a pure mixture DMSO/ethanol/ water (1:2:1).

In the above study, some archival strains and clinical isolates of the antibiotic sensitive and resistant microbes were involved. They were identified by their morphological, cultural features, and using the biochemical tests «STAPHYtest 16», «ENTEROtest 24», «STREPTOTtest 16» (by Lachema, Czechia), test-systems VITEK 2 GP and VITEK 2 YST (by Biomerieux, France) on the analyzer VITEK 2 Compact.

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