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# THE SYNTHESIS AND THE ANTIMICROBIAL ACTIVITY OF THE SUBSTITUTED ARYL AMIDES OF 3-ARYLMETHYL-2,4-DIOXO-1,3,7-TRIAZASPIRO[4.4]NONANE-7-CARBOXYLIC ACIDS

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*By the interaction of the substituted aryl isocyanates with the series of 3-arylmethyl-1,3,7-triazaspiro[4.4]nonane-2,4-diones in the propanol-2 medium the series of the substituted aryl amides of 3-arylmethyl-2,4-dioxo-1,3,7-triazaspiro[4.4]nonane-7-carboxylic acids have been obtained. The structure of the products obtained has been confirmed by the instrumental methods of the analysis, such as $^{1}H$, $^{13}C$ NMR- and chromato-mass spectrometry. The $^{1}H$ NMR-spectra of all of the substances obtained contain the signal of the methylene group of the arylmethyl fragment at 4.5 ppm as a singlet; the number and splitting of the signal in the range of the aromatic protons resonance well corresponds with the substitution in the aromatic part of the molecule; the protons of the NHCO urea fragment with the signal of the NH at position 1 are observed as two singlet signals at 7.4-8.2 and 8.9 ppm. The $^{13}C$ NMR-spectra of all compounds obtained contain four signals at 35, 45, 54 and 65 ppm of the pyrrolidine cycle of the molecules; three signals of the carbonyl groups carbon atoms are observed at 154, 155 and 174 ppm. The LC-MS spectra of the target compounds contain the peaks of $[M+H]^+$ ions, which masses are in good accordance with the structures proposed. The results of the antimicrobial activity screening show the ability of the compounds synthesized to inhibit the growth of the Candida albicans fungi strain. The gram-positive microorganisms such as the strains of Staphylococcus aureus and Bacillus subtilis are found to be sensitive to the compounds containing the methyl groups as substituents in the arylmethyl fragments of the molecule.*

Since bacteria may cause pneumonia [3], meningitis [5], osteomyelitis [9], endocarditis [4], sepsis [5], and the purulent inflammatory diseases the development of the novel antibacterial drugs is an important approach to treat and control infections. It is known that derivatives of 3-arylmethyl-1,3,7-triazospiro[4.4]nonane-2,4-dione (compounds of the general formula 1) and their *N*-benzoyl derivatives exhibit the moderate antimicrobial activity against the strains of gram-positive and gram-negative bacteria, as well as against fungi [3]. Therefore, the aim of our work was to develop the novel antimicrobial substances with the similar structure from aryl amides of the series of 3-arylmethyl-2,4-dioxo-1,3,7-triazospiro[4.4]nonane-7-carboxylic acids.

**Experimental Part**

**Chemical Part**

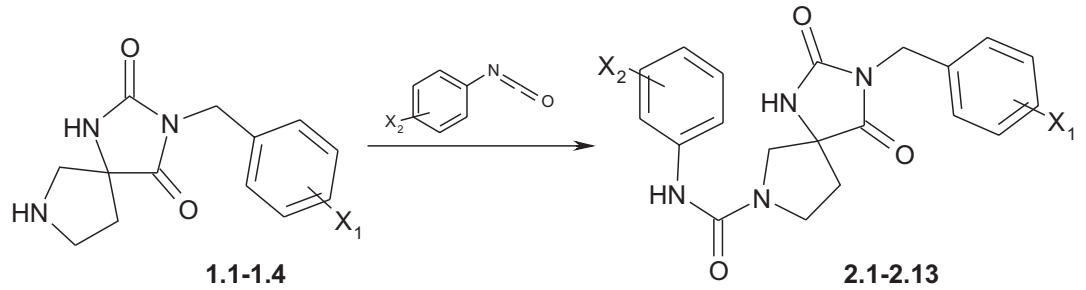
All solvents and reagents were obtained from the commercial sources. The NMR-spectra were recorded with a Bruker 170 Avance 500 spectrometer at 500 MHz for NMR $^{1}H$-spectra and at 125 MHz for NMR $^{13}C$-spectra, the solvent was DMSO-$d_6$; TMS was used as an internal standard. Chromato-mass spectra were recorded using an Agilent 1100 HPLC device equipped with a diode matrix detector and a mass-spectrometer (Agilent LC-MSD SL); a Zorbax SB-C18 column (4.6×15 mm) and an atmospheric pressure chemical ionization (APCI) were used for the analyses. The TLC was performed on the aluminium plates covered with a silica gel (Merck, Kiesgel 60 F-254). The melting points were measured with a Kofler melting point apparatus and were not corrected.

**The substituted 3-arylmethyl-1,3,7-triazaspiro[4.4]nonane-2,4-diones (1.1-1.4)** were obtained according to the methods previously reported [3].

**The general method for the synthesis of the substituted aryl amides of 3-arylmethyl-2,4-dioxo-1,3,7-triazaspiro[4.4]nonane-7-carboxylic acids (2.1-2.13).** Dissolve 1.2 mmol of the corresponding 3-arylmethyl-1,3,7-triazaspiro[4.4]nonane-2,4-dione (**1.1-1.4**) in 3-4 ml of 2-propanol, and then add 1.44 mmol of the substituted aryl isocyanate. Stir the reaction mixture at room temperature for 12 h. Then filter the precipitate formed and wash with 2-propanol. Recrystallize the purified compounds from ethanol.

**Microbiological Experiment**

The microbiological experiment was performed by the Microorganism Biochemistry and Nutrient Media Laboratory of the Mechnikov Institute of Microbiology and Immunology of the NAMS of Ukraine. According to the WHO recommendations to estimate the activity of the compounds tested the following strains of microorganisms were used: *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Proteus vulgaris* ATCC 4636, *Bacillus subtilis* ATCC 6633, *Candida albicans* ATCC653/885.



**1.1-1.4** **2.1-2.13**

**1.1** $X_1$=H; **1.2** $X_1$=4-Me; **1.3** $X_1$=2,5-diMe; **1.4** $X_1$=3-Me; **2.1** $X_1$=H, $X_2$=H; **2.2** $X_1$=4-Me, $X_2$=H; **2.3** $X_1$=2,5-diMe, $X_2$=H; **2.4** $X_1$=3-Me, $X_2$=H; **2.5** $X_1$=3-Me, $X_2$=2,5-diMe; **2.6** $X_1$=3-Me, $X_2$=2-Cl; **2.7** $X_1$=3-Me, $X_2$=3-OMe; **2.8** $X_1$=4-Me, $X_2$=2,5-diMe; **2.9** $X_1$=4-Me, $X_2$=2-Cl; **2.10** $X_1$=4-Me, $X_2$=3-OMe; **2.11** $X_1$=2,5-diMe, $X_2$=3-Me; **2.12** $X_1$=2,5-diMe, $X_2$=3-Cl; **2.13** $X_1$=H, $X_2$=3-OMe.

Scheme. The synthesis of the substituted aryl amides of 3-arylmethyl-2,4-dioxo-1,3,7-triazospiro[4.4]nonane-7-carboxylic acids **2.1-2.13**.

The inoculum suspension was prepared using a Densi-La-Meter apparatus (made by PLIVA-Lachema, Czech Republic; with the wavelength of 540 nm). The suspension was prepared according to the instruction for the apparatus and the Information letter about innovation in the healthcare system No.163-2006 "Standardization of microbial suspension preparation" (Kyiv). The cultures were synchronized using low temperature conditions (4°C). The inoculum density was 107 cells in 1 ml of the medium and was determined by comparing with McFarland standard [8]. The 18 to 24-hour old culture of the microorganism was used for the test. Mueller-Hinton agar was used for bacteria. The strain of *Candida albicans* was cultivated using Sabouraud agar. The experiment was performed using the agar "well" diffusion method [7]. The compounds studied were introduced as 0.3 ml DMSO solution (with the concentration of 100 μg/ml) aliquots. The standards were introduced as the solution in DMSO (30 μg/lm) for Metronidazole and as the water solution (30 μg/lm) for Synthomycine.

**Results and Discussion**

The synthesis of the compounds for the antimicrobial activity screening was performed according to Scheme. The starting secondary amines 1 [6] were introduced into the reaction with aryl isocyanates in the 2-propanol medium. The products **2** were precipitated as white amorphous solids.

The structures of the compounds obtained were confirmed using $^1$H, $^{13}$C NMR- and chromato-mass spectrometric methods. The data of the instrumental analyses and the melting points for compounds **2** are listed in Tab. 1.

According to the data of Tab. 1 in the $^1$H NMR-spectra of compounds **2** the multiplet signals at 2.0-2.4, 3.5-3.6 and 3.6-3.8 ppm produced by the resonance of methylene

Table 1

The data of $^1$H, $^{13}$C NMR-, chromato-mass spectra and the melting points for the substituted aryl amides of 3-arylmethyl-2,4-dioxo-1,3,7-triazospiro[4.4]nonane-7-carboxylic acids **2.1**-**2.13**

| No. | M. p., °C | $^1$H NMR, δ, ppm (*J*, Hz) | $^{13}$C NMR, δ, ppm | $[M+H]^+$ |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |
| **2.1** | 227-228 | 2.04-2.16 (1H, m) and 2.25-2.38 (1H, m, 9-$CH_2$); 3.55-3.66 (2H, m) and 3.67-3.77 (2H, m, 6,8-$CH_2$); 4.59 (2H, s, $CH_2$); 6.94 (1H, t, *J* = 6.8, H-4 Ar′); 7.19-7.31 (5H, m, H-2,3,4,5,6 Ar); 7.35 (2H, t, *J* = 6.8, H-3,5 Ar′); 7.52 (2H, d, *J* = 7.7, H-2,6 Ar′); 8.25 (1H, s, NHCO); 8.93 (1H, s, 1-NH). | 35.5; 41.8; 45.3; 54.5; 65.8; 120.1; 122.4; 127.8; 128.0; 128.8; 129.1; 137.2; 140.8; 154.2; 156.0; 174.7 | 365.2 |
| **2.2** | 259-260 | 2.03-2.13 (1H, m) and 2.23-2.35 (4H, m, 9-$CH_2$, $CH_3$); 3.54-3.65 (2H, m) and 3.66-3.75 (2H, m, 6,8-$CH_2$); 4.52 (2H, s, $CH_2$); 6.93 (1H, t, *J* = 7.3 H-4 Ar′); 7.15 (4H, s, H-2,3,5,6 Ar); 7.23 (2H, t, *J* = 7.8 H-3,5 Ar′); 7.51 (2H, d, *J* = 7.8 H-2,6 Ar′); 8.24 (1H, s, NHCO); 8.90 (1H, s, 1-NH) | 21.2; 35.4; 41.6; 45.2; 54.5; 65.8; 120.0; 122.3; 127.9; 128.8; 129.7; 134.2; 137.2; 140.8; 154.2; 156.0; 174.7 | 379.2 |
| **2.3** | 216-217 | 2.07-2.18 (1H, m) and 2.20-2.38 (7H, m, 9-$CH_2$, 2,5-$CH_3$); 3.57-3.66 (2H, m) and 3.67-3.75 (2H, m, 6,8-$CH_2$); 4.52 (2H, s, $CH_2$); 6.85 (1H, s, H-6 Ar); 6.94 (1H, t, *J* = 7.2) and 6.98 (1H, d, *J* = 7.5), and 7.06 (1H, d, *J* = 7.5 H-3,4 Ar, H-4 Ar′); 7.23 (2H, t, *J* = 7.7 H-3,5 Ar′); 7.51 (2H, d, *J* = 7.9 H-2,6 Ar′); 8.25 (1H, s, NHCO); 8.90 (1H, s, 1-NH) | 18.9; 21.3; 35.6; 45.2; 54.5; 65.8; 120.1; 122.3; 127.8; 128.4; 128.8; 130.7; 132.8; 134.6; 135.4; 140.8; 154.2; 156.1; 174.8 | 393.2 |
| **2.4** | 245-247 | 2.04-2.14 (1H, m) and 2.24-2.36 (4H, m, 9-$CH_2$, $CH_3$); 3.53-3.64 (2H, m) and 3.65-3.74 (2H, m, 6,8-$CH_2$); 4.52 (2H, s, $CH_2$); 6.93 (1H, t, *J* = 7.2) and 6.99-7.12 (3H, m), and 7.22 (3H, t, *J* = 7.5, H-2,4,5,6 Ar, H-3,4,5 Ar′); 7.50 (2H, d, *J* = 7.9 H-2,6 Ar′); 8.24 (1H, s, NHCO); 8.90 (1H, s, 1-NH) | 21.4; 35.4; 41.7; 45.1; 54.4; 65.6; 119.9; 122.2; 124.7; 128.3; 128.5; 128.7; 129.0; 137.0; 138.2; 140.7; 154.1; 155.9; 174.6 | 379.2 |

*Continuation of Table 1*

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| **2.5** | 196-198 | 2.04-2.18 (4H, m) and 2.19-2.36 (7H, m, 9-$CH_2$, 3-$CH_3$, 2′,5′-$CH_3$); 3.51-3.63 (2H, m) and 3.65-3.73 (2H, m, 6,8-$CH_2$); 4.53 (2H, s, $CH_2$); 6.84 (1H, d, *J* = 7.5 H-4 Ar′); 7.00-7.13 (5H, m, H-2,4,6 Ar, H-3,6 Ar′); 7.22 (1H, t, *J* = 7.5, H-5 Ar); 7.62 (1H, s, NHCO); 8.92 (1H, s, 1-NH) | 17.9; 21.0; 21.4; 35.5; 41.7; 45.1; 54.4; 65.7; 124.7; 125.6; 126.8; 128.3; 128.5; 129.0; 130.0; 130.3; 135.1; 135.4; 137.0; 137.7; 138.2; 154.7; 155.9; 174.7 | 407.2 |
| **2.6** | 167-168 | 2.02-2.18 (1H, m) and 2.23-2.38 (4H, m, 9-$CH_2$, 3-$CH_3$); 3.52-3.66 (2H, m) and 3.67-3.78 (2H, m, 6,8-$CH_2$); 4.53 (2H, s, $CH_2$); 7.00-7.15 (4H, m) and 7.22 (1H, t, *J* = 7.5), and 7.28 (1H, t, *J* = 7.7), and 7.45 (1H, d, *J* = 7.9), and 7.65 (1H, d, *J* = 8.0 H-2,4,5,6 Ar, H-3,4,5,6 Ar′); 7.82 (1H, s, NHCO); 8.91 (1H, s, 1-NH) | 21.4; 35.4; 41.7; 45.1; 54.3; 65.7; 124.7; 125.7; 126.5; 127.4; 127.7; 128.3; 128.5; 129.0; 129.6; 136.5; 137.0; 138.2; 153.8; 155.9; 174.6 | 413.0 |
| **2.7** | 186-187 | 2.03-2.15 (1H, m) and 2.24-2.38 (4H, m, 9-$CH_2$, 3-$CH_3$); 3.53-3.64 (2H, m) and 3.65-3.75 (5H, m, $OCH_3$,6,8-$CH_2$); 4.52 (2H, s, $CH_2$); 6.47-6.55 (1H, m, H-4 Ar′); 7.00-7.16 (5H, m) and 7.18-7.26 (2H, m, H-2,4,5,6 Ar, H-2,5,6 Ar′); 7.82 (1H, s, NHCO); 8.91 (1H, s, 1-NH) | 21.4; 35.4; 41.7; 45.1; 54.4; 55.3; 65.6; 105.5; 107.7; 112.1; 124.7; 128.3; 128.5; 129.0; 129.5; 137.0; 138.2; 142.0; 154.0; 155.9; 159.8; 174.6 | 409.2 |
| **2.8** | 215-216 | 2.00-2.18 (4H, m) and 2.19-2.38 (7H, m, 9-$CH_2$, 2′,5′-$CH_3$, 4-$CH_3$); 3.48-3.77 (4H, m, 6,8-$CH_2$); 4.54 (2H, s, $CH_2$); 6.84 (1H, d, *J* = 6.8) and 7.04 (1H, d, *J* = 6.4), and 7.15 (5H, s, H-2,3,5,6 Ar, H-3,4,6 Ar′); 7.40 (1H, s, NHCO); 8.63 (1H, s, 1-NH) | 17.9; 21.0; 21.1; 35.5; 41.5; 45.1; 54.4; 65.7; 125.6; 126.8; 127.8; 129.6; 130.0; 130.3; 134.1; 135.1; 137.1; 137.7; 154.7; 155.9; 174.7 | 407.2 |
| **2.9** | 185-186 | 2.01-2.17 (1H, m) and 2.20-2.37 (4H, m, 9-$CH_2$, 4-$CH_3$); 3.52-3.77 (4H, m, 6,8-$CH_2$); 4.54 (2H, s, $CH_2$); 7.07-7.18 (5H, m) and 7.28 (1H, t, *J* = 7.7), and 7.45 (1H, d, *J* = 8.0), and 7.66 (1H, d, *J* = 8.0 H-2,3,5,6 Ar, H-3,4,5,6 Ar′); 7.81 (1H, s, NHCO); 8.90 (1H, s, 1-NH) | 21.1; 35.4; 41.5; 45.1; 54.3; 65.6; 125.7; 126.4; 127.4; 127.7; 127.8; 129.6; 129.6; 134.1; 136.5; 137.1; 153.8; 155.9; 174.5 | 413.2 |
| **2.10** | 206-207 | 2.00-2.14 (1H, m) and 2.19-2.36 (4H, m, 9-$CH_2$, 4-$CH_3$); 3.52-3.73 (7H, m, 6,8-$CH_2$, $OCH_3$); 4.51 (2H, s, $CH_2$); 6.51 (1H, d, *J* = 6.9 H-4 Ar′); 7.06-7.18 (6H, m) and 7.19-7.22 (1H, m, H-2,3,5,6 Ar, H-2,5,6 Ar′); 8.21 (1H, s, NHCO); 8.89 (1H, s, 1-NH) | 21.1; 25.9; 35.3; 41.5; 45.1; 54.4; 55.32; 65.6; 105.5; 107.7; 112.1; 127.8; 129.5; 129.6; 134.1; 137.1; 142.0; 154.0; 155.9; 159.8; 174.5 | 409.2 |
| **2.11** | 236-237 | 2.05-2.18 (1H, m) and 2.20-2.38 (7H, m, 9-$CH_2$, 2,5-$CH_3$); 3.54-3.77 (7H, m, 6,8-$CH_2$, $OCH_3$); 4.51 (2H, s, $CH_2$); 6.48-6.55 (1H, m) and 6.84 (1H, s), and 6.93-7.01 (1H, m), and 7.02-7.08 (1H, m), and 7.09-7.16 (2H, m), and 7.22 (1H, m, H-3,4,6 Ar, H-2,4,5,6 Ar′); 8.25 (1H, s, NHCO); 8.92 (1H, s, 1-NH). | 18.8; 21.2; 25.9; 35.4; 45.1; 54.4; 55.3; 65.6; 105.5; 107.7; 112.1; 127.7; 128.3; 129.5; 130.6; 132.7; 134.5; 135.3; 142.0; 154.0; 156.0; 159.8; 174.7 | 423.2 |
| **2.12** | 172-173 | 2.08-2.19 (1H, m) and 2.21-2.41 (7H, m, 9-$CH_2$, 2,5-$CH_3$); 3.57-3.79 (7H, m, 6,8-$CH_2$, 3′-$CH_3$); 4.51 (2H, s, $CH_2$); 6.84 (1H, c) and 6.97 (1H, d, *J* = 7.5), and 7.05 (1H, d, *J* = 7.6), and 7.12 (1H, t, *J* = 7.6), and 7.29 (1H, t, *J* = 7.7), and 7.45 (1H, d, *J* = 8.0), and 7.66 (1H, d, *J* = 8.0 H-3,4,6 Ar, H-3,4,5,6 Ar′); 7.85 (1H, s, NHCO); 8.91 (1H, s, 1-NH) | 18.8; 21.2; 25.9; 35.5; 45.1; 54.3; 65.7; 125.7; 126.5; 127.4; 127.7; 127.7; 128.3; 129.6; 130.6; 132.7; 134.5; 135.3; 136.6; 153.9; 156.0; 174.4 | 427.2 |
| **2.13** | 163-164 | 2.01-2.17 (1H, m) and 2.22-2.38 (1H, m, 9-$CH_2$); 3.54-3.65 (2H, m) and 3.67-3.74 (5H, m, 6,8-$CH_2$, $OCH_3$); 4.57 (2H, s, $CH_2$); 6.48-6.54 (1H, m, H-4 Ar′); 7.07-7.15 (2H, m) and 7.18-7.31 (4H, m) and 7.32-7.38 (2H, m, H-2,3,4,5,6 Ar, H-2,5,6 Ar′); 8.22 (1H, s, NHCO); 8.92 (1H, s, 1-NH) | 35.3; 41.7; 45.1; 54.4; 55.3; 65.7; 105.5; 107.7; 112.1; 127.6; 127.9; 129.0; 129.5; 137.0; 142.0; 154.0; 155.9; 159.8; 174.6 | 395.2 |

groups at positions 9, 6 and 8 of 2,4-dioxo-1,3,7-triazospiro[4.4]nonane skeleton are present; the methylene group of the arylmethyl substituent at position 3 is observed as the singlet signal at 4.5 ppm. The number and the multiplicity of the signals in the range of the aromatic protons resonance correlate well with the substitution pattern for each compound **2**. The signals of the protons of the NHCO urea fragment and the NH-group at position 1 are observed as two singlet signals at 7.4-8.2 and 8.9 ppm. The $^{13}C$ NMR-spectra of compounds **2** contain the signals of the carbon atoms at positions 6, 7 and 9 at 35, 45 and 54 ppm, the bridgehead carbon atom at position 5 produces the typical low intensity signal at 65 ppm, the carbon atom of the methylene group of the arylmethyl substituent gives the signal at 41 ppm; the aromatic carbon atoms resonate in the range 120-140 ppm, while the signals of the carbonyl carbon atoms at positions 1 and 3 of 2,4-dioxo-1,3,7-triazospiro[4.4]nonane skeleton and the signal of NHCO are present at 154, 174 and 155 ppm, respectively.

Table 2

The antimicrobial activity of the substituted aryl amides of 3-arylmethyl-2,4-dioxo-1,3,7-triazaspiro[4.4]nonane-7-carboxylic acids **2**

| No. | The growth inhibition zone diameter*, mm | | | | | |
|---|---|---|---|---|---|---|
| | *Gram "+" bacteria* | | *Gram "-" bacteria* | | | *Fungi* |
| | *S. a.* | *B. c.* | *E. c.* | *P. v.* | *P. a.* | *C. a.*** |
| **Metronidazole** | 14 | 16 | 14 | 0 | 0 | 14 |
| **Synthomycine** | 14 | 17 | 17 | 17 | 17 | 0 |
| **2.1** | 18 | 17 | 18 | 16 | 16 | 25 |
| **2.2** | 18 | 16 | 18 | 17 | 16 | 25 |
| **2.3** | 21 | 23 | 16 | 15 | 15 | 17 |
| **2.4** | 20 | 21 | 17 | 14 | 15 | 17 |
| **2.5** | 13 | 18 | 17 | 19 | 17 | 20 |
| **2.6** | 15 | 17 | 16 | 20 | 19 | 17 |
| **2.7** | 16 | 16 | 16 | 17 | 17 | 18 |
| **2.8** | 19 | 18 | 15 | 17 | 18 | 16 |
| **2.9** | 18 | 15 | 17 | 16 | 15 | 19 |
| **2.10** | 18 | 18 | 16 | 16 | 15 | 20 |
| **2.11** | 16 | 18 | 16 | 16 | 14 | 19 |
| **2.12** | 14 | 16 | 17 | 15 | 15 | 20 |
| **2.13** | 15 | 14 | 18 | 16 | 15 | 20 |

Note: * – the average value for 3 experiments; ** – the test strains are given in the experimental part.

The study of the antimicrobial activity for the compounds synthesized was performed using the agar "well" diffusion method. The standard test-strains of gram-positive and gram-negative bacteria, as well as fungi were used according to the international standards [1, 2]. The results of the antibacterial activity screening are presented in Tab. 2.

As it is presented in Tab. 2, almost all compounds tested exhibit the antimicrobial activity against the strains of gram-positive and gram-negative bacteria, as well as against fungi. The fungi of *Candida albicans* appeared to be the most sensitive for compounds **2**, the diameters of the growth inhibition zones in some cases exceeded 20 mm. It should be also mentioned that methyl substitution in the arylmethyl fragment increases the antimicrobial activity against gram-positive bacteria, and it is typical for compounds **2.3** and **2.4.**

CONCLUSIONS

Using the methodology of the liquid phase combinatorial synthesis the chemical diversity of the available 3-arylmethyl-1,3,7-triazaspiro[4.4]nionane-2,4-diones has been enlarged by the synthesis of the series of novel aryl amides of 3-arylmethyl-2,4-dioxo-1,3,7-triazaspiro [4.4]nonane-7-carboxylic acids. The antimicrobial activity of the compounds obtained has been studied. According to the results of the microbiological screening it has been found that they mostly inhibited the growth of the *Candida albicans* fungi strain.

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**СИНТЕЗ ТА АНТИМІКРОБНА АКТИВНІСТЬ ЗАМІЩЕНИХ АРИЛАМІДІВ 3-АРИЛМЕТИЛ-2,4-ДІОКСО-1,3,7-ТРИАЗАСПІРО[4.4]НОНАН-7-КАРБОНОВИХ КИСЛОТ**

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***Ключові слова**: гідантоїн; сечовина; піролідон; антибактеріальні засоби*

*Реакцією взаємодії заміщених арилізоціонатів та ряду 3-арилметил-1,3,7-триазаспіро[4.4] нонан-2,4-діонів у середовищі пропанолу-2 було отримано ряд заміщених ариламідів 3-арилметил-2,4-діоксо-1,3,7-триазаспіро[4.4]нонан-7-карбонових кислот. Будову продуктів реакції було підтверджено інструментальними методами аналізу, такими як: $^{1}$H, $^{13}$C ЯМР- та хромато-мас-спектроскопія. У всіх $^{1}$H ЯМР-спектрах досліджуваних зразків спостерігається синглетний сигнал при 4,5 м.ч., що відповідає метиленовій групі арилметильного фрагменту, кількість та мультиплетність сигналів в ароматичній частині спектрів залежить від замісників у кожному конкретному випадку; протони сечовинного фрагменту NHCO та NH-групи в положенні 1 проявляються у вигляді синглетів при 7,4-8,2 та 8,9 м.ч. відповідно. У $^{13}$C ЯМР-спектрах всіх отриманих сполук спостерігаються чотири сигнали при 35, 45, 54 та 65 м.ч., що відповідають піролідиновому фрагменту молекул, також для кожної з отриманих молекул*

*характерними є три сигнали при 154, 155 та 174 м.ч., що відповідають атомам Карбону карбонільних груп. На LC-MS спектрах отриманих речовин спостерігаються $[M+H]^+$ іони, маса яких відповідає масам заявлених структур. Результати мікробіологічного скринінгу показують наявність чутливості мікроорганізмів штаму Candida albicans до синтезованих речовин. Також спостерігається чутливість грампозитивних мікроорганізмів штамів Staphylococcus aureus та Bacillus subtilis до зразків, що містять метильні групи в арилметильному фрагменті досліджуваних молекул.*

**СИНТЕЗ И ПРОТИВОМИКРОБНАЯ АКТИВНОСТЬ ЗАМЕЩЕННЫХ АРИЛАМИДОВ 3-АРИЛМЕТИЛ-2,4-ДИОКСО-1,3,7-ТРИАЗАСПИРО[4.4]НОНАН-7-КАРБОНОВЫХ КИСЛОТ**

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***Ключевые слова:*** *гидантоин; мочевина; пирролидон; антибактериальные средства*

*Реакцией взаимодействия замещенных арилизоцианатов и ряда 3-арилметил-1,3,7-триазаспиро[4.4]нонан-2,4-дионов в среде пропанола-2 был получен ряд ариламидов 3-арилметил-2,4-диоксо-1,3,7-триазаспиро[4.4]нонан-7-карбоновых кислот. Строение продуктов реакции было подтверждено инструментальными методами анализа, такими как: $^{1}H$, $^{13}C$ ЯМР- и хромато-масс-спектроскопия. На всех $^{1}H$ ЯМР-спектрах исследуемых образцов наблюдается синглетный сигнал при 4,5 м.д., что соответствует метиленовой группе арилметильного фрагмента, количество и мультиплетность сигналов в ароматической части спектров зависит от заместителей в каждом конкретном случае; протоны мочевинного фрагмента NHCO и NH-группы в положении 1 проявляются в виде синглетов при 7,4-8,2 и 8,9 м.д. соответственно. В $^{13}C$ ЯМР-спектрах всех полученных соединений наблюдаются четыре сигнала при 35, 45, 54 и 65 м.д., которые соответствуют пирролидиновому фрагменту молекул, также для каждой из полученных молекул характерны три сигнала при 154, 155 и 174 м.д., которые соответствуют атомам углерода карбонильных групп. На LC-MS спектрах полученных веществ наблюдаются $[M+H]^+$ ионы, масса которых соответствует массам заявленных структур. Результаты микробиологического скрининга показывают наличие чувствительности микроорганизмов штамма Candida albicans к синтезированным веществам. Также наблюдается чувствительность граммположительных микроорганизмов штаммов Staphylococcus aureus и Bacillus subtilis к образцам, которые содержат метильные группы в арилметильном фрагменте исследуемых молекул.*

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