

# Synthesis and antibacterial evaluation of novel 1-(2,6-diethylphenyl)-5-oxopyrrolidine derivatives

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Synthesis of 1-(2,6-diethylphenyl)-5-oxopyrrolidine derivatives containing hydrazone, semi/thiosemicarbazide and azole moieties is described. For this purpose, the appropriate hydrazide was treated with aromatic aldehydes, ketones and phenyl iso(thio)cyanates to obtain the desired outcome. The synthesized target compounds were evaluated for their antibacterial properties. The antibacterial screening revealed promising compounds with a pyrazole and thiosemicarbazide moieties in the molecule, which in some cases appeared to be 4 times more effective than *Ampicillin*.

**Keywords:** 5-oxopyrrolidines, hydrazones, azoles, antibacterial activity

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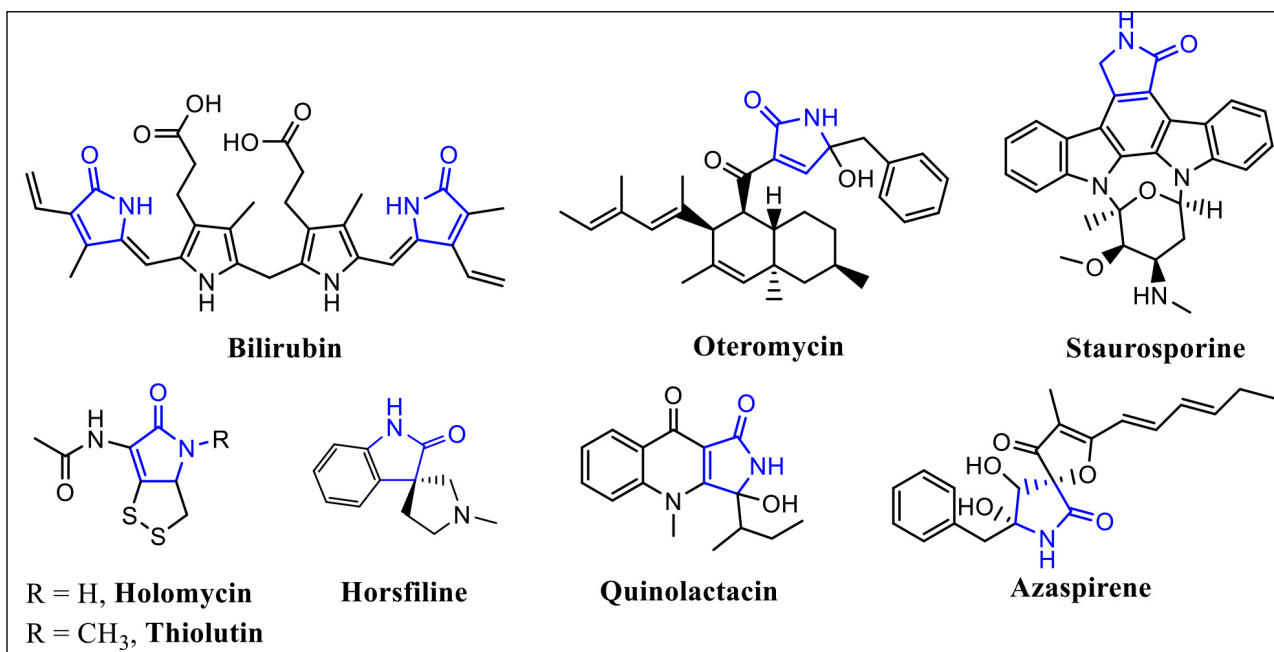
## INTRODUCTION

Pyrrolidinone nucleus is one of the most important heterocyclic rings which indicates remarkable pharmaceutical properties and is versatile for designing efficient agents. 2-Pyrrolidinone cycle is a common constituent of abundant natural products such as bilirubins, oteromycin, staurosporine, horsfiline, salinosporamide A, holomycin, thiolutin, quinolactacin C, azaspirene (Fig. 1) and others [1], which participate in the living processes of the organisms or show various biological activities.

As an example, holomycin and thiolutin can be presented. They are probably best-known representatives of the dithiopyrrolone compounds, which display bacteriostatic activity against both gram-positive and gram-negative bacteria [2]. The dithiopyrrolones exhibit a very broad-spectrum antibiotic activity and potent antiangiogenic effects [3].

Many substituted 2-pyrrolidinones are synthesized over a long period of their research, and abundance of the synthetic ones demonstrate a wide variety of healing properties such as anti-HIV [4–6], antiarrhythmic, hypotensive, antihypertensive [7, 8], anticancer and antitumour [9–13],

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**Fig. 1.** Substances of natural origin having a 2-pyrrolidinone moiety in the structure (coloured online)

anti-inflammatory [14], anti-obesity [15], antiepileptic [16], antimicrobial [17], are used as antagonist of ETB [18], and others [19–23]. This moiety is a component of many synthetic pharmaceuticals (levetiracetam, medication for treatment epilepsy, pramiracetam, known as Pramistar, is a central nervous system stimulant and nootropic agent, doxapram hydrochloride, marketed as Dopram (Fig. 2), stimulex or respiram is a respiratory stimulant, ethosuximide is a succinimide anticonvulsant) widely used for the treatment of various diseases.

On the other hand, pyrrolidinones found application not only in medicine. They also find industrial application. One of the examples of the industrial usage is poly (vinyl)pyrrolidone (PVP) which represents a significant class of water-soluble polymers and is used for different purposes ranging

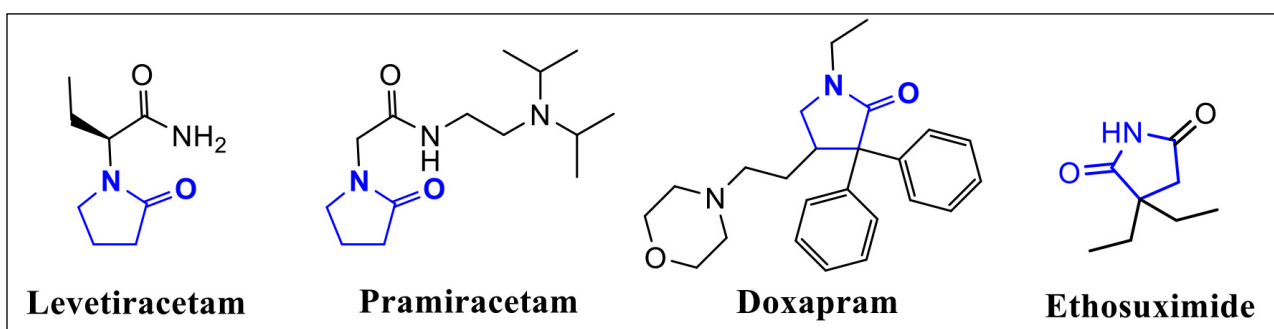
from pharmacological areas (as binders in tablets) to nanoparticles and membranes for water purification [24].

The increasing focus on the synthesis of pyrrolidinone derivatives and the study of their biological properties encouraged us to extend the works in the synthesis and investigations of functionalized 2-pyrrolidinone derivatives [25–28] with aromatic and heterocyclic moieties in the structure.

## EXPERIMENTAL

### General procedures

Reagents and solvents were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used without further purification. The reaction course and purity of the synthesized compounds were monitored



**Fig. 2.** Medications with 2-pyrrolidinone core (coloured online)

by TLC using aluminium plates pre-coated with Silica gel with F254 nm (Merck KGaA, Darmstadt, Germany). Melting points were determined with a B-540 melting point analyser (Büchi Corporation, New Castle, DE, USA) and are uncorrected. IR spectra ( $\nu$ ,  $\text{cm}^{-1}$ ) were recorded on a Perkin-Elmer Spectrum BX FT-IR spectrometer (Perkin-Elmer Inc., Waltham, MA, USA) using KBr pellets. NMR spectra were recorded on a Bruker Avance III (400, 101 MHz) spectrometer (Bruker Bio-Spin AG, Fällanden, Switzerland). Chemical shifts were reported in ( $\delta$ ) ppm relative to tetramethylsilane (TMS) with the residual solvent as internal reference (DMSO- $d_6$ ,  $\delta = 2.50$  ppm for  $^1\text{H}$  and  $\delta = 39.5$  ppm for  $^{13}\text{C}$ ). Data are reported as follows: chemical shift, multiplicity, coupling constant [Hz], integration and assignment. Mass spectra were obtained on a Bruker maXis UHR-TOF mass spectrometer (Bruker Daltonics, Bremen, Germany) with ESI ionization.

### Synthesis

**1-(2,6-Diethylphenyl)-5-oxopyrrolidine-3-carbohydrazide (1).** Synthesized from 2,6-diethylaniline according to the known method [29]. White powder, yield 12.54 g (67%), m. p. 161.5–163.5°C (from 1,4-dioxane); IR (KBr):  $\nu$  ( $\text{cm}^{-1}$ ): 3326 (NH), 3180 ( $\text{NH}_2$ ), 1678, 1631 (C=O);  $^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$ : 1.08–1.18 (m, 6H,  $2\text{CH}_3$ ), 2.41–2.50 (m, 4H,  $2\text{CH}_2$ ), 2.54–2.68 (m, 2H,  $\text{CH}_2\text{CO}$ ), 3.21–3.32 (m, 1H, CH), 3.56 (dd,  $J = 9.7, 6.1$  Hz, 1H,  $\text{NCH}_2$ ), 3.66 (t,  $J = 9.2$  Hz, 1H,  $\text{NCH}_2$ ), 4.30, 4.44 (2s, 2H,  $\text{NH}_2$ ), 7.15 (d,  $J = 7.6$  Hz, 2H,  $\text{H}_{\text{arom}}$ ), 7.21–7.31 (m, 1H,  $\text{H}_{\text{arom}}$ ), 9.24 (s, 1H, NH);  $^{13}\text{C-NMR}$  (101 MHz, DMSO- $d_6$ )  $\delta$ : 14.7, 14.8 ( $2\text{CH}_3$ ), 23.3, 23.5 ( $2\text{CH}_2$ ), 33.8 ( $\text{CH}_2\text{CO}$ ), 35.3 (CH), 52.2 ( $\text{NCH}_2$ ), 126.3, 126.5, 128.3, 134.7, 141.7, 142.1 ( $\text{C}_{\text{arom}}$ ), 171.7, 172.4 (C=O); Anal. calcd. for  $\text{C}_{15}\text{H}_{22}\text{N}_3\text{O}_2$  m/z %: 276.1712 [ $\text{M} + \text{H}$ ] $^+$ , found HRMS (ESI), m/z %: 276.1706 [ $\text{M} + \text{H}$ ] $^+$  (100%).

**General procedure for the preparation of hydrazones 2–5.** To a solution of acid hydrazide **1** (0.5 g, 1.8 mmol) in 2-propanol (20 mL), the corresponding aromatic aldehyde (2.7 mmol) was added and the mixture was heated at reflux for 1.5 h, then cooled down, the solvent was removed under reduced pressure, and the residue diluted with diethyl ether (10 mL). The formed crystalline solid was filtered off, washed with diethyl ether (**2–4**). In case **5** after completion of the reaction, the formed

crystalline solid was filtered off and washed with diethyl ether.

**N<sup>1</sup>-Benzylidene-1-(2,6-diethylphenyl)-5-oxopyrrolidine-3-carbohydrazide (2).** White powder, yield 0.58 g (89%), m. p. 133–134°C (from 2-propanol); IR (KBr):  $\nu$  ( $\text{cm}^{-1}$ ): 3157 (NH), 1696, 1665 ( $2\text{C}=\text{O}$ ), 1620 (CH=N);  $^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$ : (a mixture of Z/E isomers, 0.65/0.35): 1.03–1.23 (m, 6H,  $2\text{CH}_3$ ), 2.39–2.48 (m, 2H,  $\text{CH}_2$ ), 2.50–2.57 (m, 2H,  $\text{CH}_2$ , overlaps with the residual signal of DMSO- $d_6$ ), 2.65–2.86 (m, 2H,  $\text{CH}_2\text{CO}$ ), 3.41–3.49 (m, 0.4(1H), CH), 3.62–3.73 (m, 1H,  $\text{NCH}_2$ ), 3.76 (t,  $J = 9.2$  Hz, 0.4(1H),  $\text{NCH}_2$ ), 3.89 (t,  $J = 9.4$  Hz, 0.6(1H),  $\text{NCH}_2$ ), 4.14–4.24 (m, 0.6(1H), CH), 7.05–7.21 (m, 2H,  $\text{H}_{\text{arom}}$ ), 7.22–7.32 (m, 1H,  $\text{H}_{\text{arom}}$ ), 7.32–7.52 (m, 3H,  $\text{H}_{\text{arom}}$ ), 7.58–7.78 (m, 2H,  $\text{H}_{\text{arom}}$ ), 8.03, 8.22 (2s, 1H, CH=N), 11.58, 11.63 (2s, 1H, NH);  $^{13}\text{C-NMR}$  (101 MHz, DMSO- $d_6$ )  $\delta$ : 14.7, 14.8, 14.9, 23.4, 23.5, 32.9, 33.8, 34.1, 36.1, 51.8, 52.0, 126.3, 126.4, 126.5, 126.8, 127.1, 128.3, 128.8, 129.9, 130.1, 134.1, 134.6, 134.7, 141.8, 142.0, 142.2, 143.6, 147.0, 168.9, 172.3, 172.5, 173.8; Anal. calcd. for  $\text{C}_{22}\text{H}_{26}\text{N}_3\text{O}_2$ , m/z %: 364.2025 [ $\text{M} + \text{H}$ ] $^+$ , found HRMS (ESI), m/z %: 364.2025 [ $\text{M} + \text{H}$ ] $^+$  (100%).

**N<sup>1</sup>-(4-Chlorobenzylidene)-1-(2,6-diethylphenyl)-5-oxopyrrolidine-3-carbohydrazide (3).** White powder, yield 0.55 g (77%), m. p. 171–173°C (from 2-propanol); IR (KBr):  $\nu$  ( $\text{cm}^{-1}$ ): 3184 (NH), 1670 ( $2\text{C}=\text{O}$ ), 1608 (CH=N);  $^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$ : (a mixture of Z/E isomers, 0.65/0.35): 1.05–1.21 (m, 6H,  $2\text{CH}_3$ ), 2.40–2.55 (m, 4H,  $2\text{CH}_2$ , overlaps with the residual signal of DMSO- $d_6$ ), 2.64–2.84 (m, 2H,  $\text{CH}_2\text{CO}$ ), 3.39–3.52 (m, 0.35(1H), CH), 3.62–3.71 (m, 1H,  $\text{NCH}_2$ ), 3.72 (t,  $J = 9.2$  Hz, 0.35(1H),  $\text{NCH}_2$ ), 3.87 (t,  $J = 9.4$  Hz, 0.65(1H),  $\text{NCH}_2$ ), 4.11–4.26 (m, 0.65(1H), CH), 7.09–7.21 (m, 2H,  $\text{H}_{\text{arom}}$ ), 7.22–7.32 (m, 1H,  $\text{H}_{\text{arom}}$ ), 7.43–7.57 (m, 2H,  $\text{H}_{\text{arom}}$ ), 7.66–7.77 (m, 2H,  $\text{H}_{\text{arom}}$ ), 8.02, 8.20 (2s, 1H, CH=N), 11.64, 11.69 (2s, 1H, NH);  $^{13}\text{C-NMR}$  (101 MHz, DMSO- $d_6$ )  $\delta$ : 14.7, 14.8, 14.9, 23.4, 23.5, 32.9, 33.7, 33.9, 36.0, 51.7, 52.0, 126.3, 126.4, 126.5, 128.3, 128.5, 128.7, 128.9, 133.1, 134.3, 134.6, 134.7, 141.7, 141.8, 142.0, 142.2, 142.3, 145.6, 169.0, 172.2, 172.4, 174.0; Anal. calcd. for  $\text{C}_{22}\text{H}_{25}\text{ClN}_3\text{O}_2$  m/z %: 398.1635 [ $\text{M} + \text{H}$ ] $^+$ , found HRMS (ESI), m/z %: 398.1636 [ $\text{M} + \text{H}$ ] $^+$  (100%), 400.1638 [ $\text{M} + \text{H} + 2$ ] $^+$  (31%).

**N<sup>1</sup>-(4-Bromobenzylidene)-1-(2,6-diethylphenyl)-5-oxopyrrolidine-3-carbohydrazide (4).** White powder, yield 0.49 g (62%), m. p. 124–126°C

(from 2-propanol); IR (KBr):  $\nu$  ( $\text{cm}^{-1}$ ): 3161 (NH), 1665 (2C=O), 1611 (CH=N);  $^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$ : (a mixture of Z/E isomers, 0.65/0.35): 1.06–1.22 (m, 6H, 2CH<sub>3</sub>), 2.42–2.48 (m, 2H, 2CH<sub>2</sub> overlaps with the residual signal of DMSO- $d_6$ ), 2.50–2.57 (m, 2H, 2CH<sub>2</sub> overlaps with the residual signal of DMSO- $d_6$ ), 2.64–2.84 (m, 2H, CH<sub>2</sub>CO), 3.39–3.50 (m, 0.35(1H), CH), 3.62–3.72 (m, 1H, NCH<sub>2</sub>), 3.76 (t,  $J = 9.2$  Hz, 0.35(1H), NCH<sub>2</sub>), 3.87 (t,  $J = 9.4$  Hz, 0.65(1H), NCH<sub>2</sub>), 4.13–4.25 (m, 0.65(1H), CH), 7.09–7.32 (m, 3H, H<sub>arom</sub>), 7.50–7.80 (m, 4H, H<sub>arom</sub>), 8.00, 8.19 (2s, 1H, CH=N), 11.64, 11.69 (2s, 1H, NH);  $^{13}\text{C-NMR}$  (101 MHz, DMSO- $d_6$ )  $\delta$ : 14.7, 14.8, 14.9, 23.4, 23.5, 32.9, 33.7, 33.9, 36.0, 51.7, 52.0, 123.1, 123.3, 126.3, 126.4, 126.5, 128.3, 128.7, 129.0, 131.8, 133.4, 133.5, 134.6, 134.7, 141.7, 141.8, 142.0, 142.2, 142.4, 145.7, 169.0, 172.2, 172.4, 174.0; Anal. calcd. for C<sub>22</sub>H<sub>25</sub>BrN<sub>3</sub>O<sub>2</sub> m/z %: 442.1130 [M + H]<sup>+</sup>, found HRMS (ESI), m/z %: 442.1158 [M + H]<sup>+</sup> (100%), 444.1161 [M + H + 2]<sup>+</sup> (98%).

**N<sup>2</sup>-(4-Nitrobenzylidene)-1-(2,6-diethylphenyl)-5-oxopyrrolidine-3-carbohydrazide (5).** Light yellow powder, yield 0.61 g (83%), m. p. 206–207°C (from 2-propanol); IR (KBr):  $\nu$  ( $\text{cm}^{-1}$ ): 3188 (NH), 1668 (2C=O), 1617 (CH=N);  $^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$ : (a mixture of Z/E isomers, 0.6/0.4): 1.06–1.21 (m, 6H, 2CH<sub>3</sub>), 2.41–2.48 (m, 2H, 2CH<sub>2</sub>), 2.50–2.55 (m, 2H, 2CH<sub>2</sub>), 2.65–2.85 (m, 2H, CH<sub>2</sub>CO), 3.43–3.55 (m, 0.4(1H), CH), 3.63–3.73 (m, 1H, NCH<sub>2</sub>), 3.77 (t,  $J = 9.2$  Hz, 0.4(1H), NCH<sub>2</sub>), 3.89 (t,  $J = 9.4$  Hz, 0.6(1H), NCH<sub>2</sub>), 4.15–4.29 (m, 0.6(1H), CH), 7.08–7.22 (m, 2H, H<sub>arom</sub>), 7.22–7.31 (m, 1H, H<sub>arom</sub>), 7.96 (t,  $J = 9.2$  Hz, 2H, NCH<sub>2</sub>), 8.12 (s, 0.6(1H), CH=N), 8.17–8.52 (m, 2H, H<sub>arom</sub> + 0.4(1H), CH=N), 11.87, 11.92 (2s, 1H, NH);  $^{13}\text{C-NMR}$  (101 MHz, DMSO- $d_6$ )  $\delta$ : 14.7, 14.8, 14.9, 23.4, 23.5, 32.9, 33.7, 36.1, 51.6, 51.9, 124.0, 126.3, 126.4, 126.5, 127.8, 128.0, 128.3, 128.4, 134.6, 134.7, 140.4, 140.5, 141.2, 141.7, 141.8, 142.0, 142.2, 144.5, 147.7, 147.9, 169.4, 172.2, 172.4, 174.4; Anal. calcd. for C<sub>22</sub>H<sub>25</sub>N<sub>4</sub>O<sub>4</sub> m/z %: 409.1876 [M + H]<sup>+</sup>, found HRMS (ESI), m/z %: 409.1874 [M + H]<sup>+</sup> (100%).

**1-(2,6-Diethylphenyl)-4-(3,5-dimethyl-1H-pyrazole-1-carbonyl)pyrrolidin-2-one (6).** To a solution of acid hydrazide **1** (0.5 g, 1.8 mmol) in 2-propanol (10 mL), pentane-2,4-dione (0.54 g, 5.4 mmol) and hydrochloric acid (0.05 mL) was added and the mixture was heated at reflux for 2 h. Afterwards, the mixture was cooled down, the solvent was removed under reduced pressure, the resi-

due mixed with water (50 mL) and heated to its boiling point. After cooling the formed crystalline solid was filtered off, washed with diethyl ether. White powder, yield 0.48 g (79%), m. p. 139–141°C (from ethanol); IR (KBr):  $\nu$  ( $\text{cm}^{-1}$ ): 1721, 1700 (C=O), 1585 (C=N);  $^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$ : 1.07 (t,  $J = 7.5$  Hz, 3H, CH<sub>3</sub>), 1.16 (t,  $J = 7.5$  Hz, 3H, CH<sub>3</sub>), 2.18 (s, 3H, CH<sub>3</sub>C), 2.37–2.51 (m, 7H, CH<sub>3</sub>C + 2CH<sub>2</sub>CH<sub>3</sub>), 2.73–2.90 (m, 2H, CH<sub>2</sub>CO), 3.70 (dd,  $J = 10.2, 5.3$ , 1H, NCH<sub>2</sub>), 3.93 (t,  $J = 9.5$  Hz, 1H, NCH<sub>2</sub>), 4.52–4.65 (m, 1H, CH), 6.23 (s, 1H, CH<sub>pyr</sub>), 7.15 (t,  $J = 8.2$  Hz, 2H, H<sub>arom</sub>), 7.27 (t,  $J = 7.6$  Hz, 1H, H<sub>arom</sub>);  $^{13}\text{C-NMR}$  (101 MHz, DMSO- $d_6$ )  $\delta$ : 13.5, 14.1, 14.7, 14.8 (CH<sub>3</sub>), 23.4, 23.5 (CH<sub>2</sub>), 33.2 (CH<sub>2</sub>CO), 36.7 (CH), 51.8 (NCH<sub>2</sub>), 111.6, 126.4, 126.5, 128.4, 134.5, 141.9, 142.0, 143.8, 152.2 (C<sub>arom</sub>), 171.9, 172.9 (C=O); Anal. calcd. for C<sub>20</sub>H<sub>26</sub>N<sub>3</sub>O<sub>2</sub> m/z %: 340.2025 [M + H]<sup>+</sup>, found HRMS (ESI), m/z %: 340.2020 [M + H]<sup>+</sup> (100%).

**1-(2,6-Diethylphenyl)-N-(2,5-dimethyl-1H-pyrrol-1-yl)-5-oxopyrrolidine-3-carboxamide (7).** To a solution of acid hydrazide **1** (0.5 g, 1.8 mmol) in 2-propanol (10 mL), hexane-2,5-dione (0.62 g, 5.4 mmol) and acetic acid (0.05 mL) was added and the mixture was heated at reflux for 4 h. Afterwards, the mixture was cooled down, part of the solvent was removed under reduced pressure, the residue mixed with water (50 mL) and heated to its boiling point. After cooling the formed crystalline solid was filtered off and washed with water. Light brown powder, yield 0.59 g (92%), m. p. 116–117°C (from ethanol); IR (KBr):  $\nu$  ( $\text{cm}^{-1}$ ): 3233 (NH), 1734, 1674 (2C=O);  $^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$ : 1.09 (t,  $J = 7.5$  Hz, 3H, CH<sub>3</sub>), 1.17 (t,  $J = 7.5$  Hz, 3H, CH<sub>3</sub>), 1.99 (s, 3H, CH<sub>3</sub>C), 2.02 (s, 3H, CH<sub>3</sub>C), 2.43–2.50 (m, 4H, CH<sub>2</sub>), 2.69 (dd,  $J = 16.8, 5.7$  Hz, 1H, CH<sub>2</sub>CO), 2.86 (dd,  $J = 16.8, 9.6$  Hz, 1H, CH<sub>2</sub>CO), 3.51–3.62 (m, 1H, CH), 3.68 (dd,  $J = 9.7, 4.9$  Hz, 1H, NCH<sub>2</sub>), 3.88 (t,  $J = 9.2$  Hz, 1H, NCH<sub>2</sub>), 5.66 (s, 2H, 2CH<sub>pyr</sub>), 7.13–7.21 (m, 2H, H<sub>arom</sub>), 7.28 (t,  $J = 7.6$  Hz, 1H, H<sub>arom</sub>), 10.89 (s, 1H, NH);  $^{13}\text{C-NMR}$  (101 MHz, DMSO- $d_6$ )  $\delta$ : 10.9 (2C-CH<sub>3</sub>), 14.7, 14.9 (2CH<sub>3</sub>), 23.3, 23.4 (2CH<sub>2</sub>), 33.5 (CH<sub>2</sub>CO), 35.0 (CH), 52.0 (NCH<sub>2</sub>), 103.1 (CH<sub>3</sub>C=CH-CH=CCH<sub>3</sub>), 126.3, 126.5, 126.7, 126.8, 128.4, 134.5, 141.8, 142.2 (C<sub>arom</sub>), 172.1, 172.2 (2C=O); Anal. calcd. for C<sub>21</sub>H<sub>28</sub>N<sub>3</sub>O<sub>2</sub> m/z %: 354.2181 [M + H]<sup>+</sup>, found HRMS (ESI), m/z %: 354.2176 [M + H]<sup>+</sup> (100%).

**General procedure for the preparation of semi- and thiosemicarbazides 8 and 9.** To a solution of acid hydrazide **1** (1.98 g, 7.2 mmol) in methanol

(150 mL), phenyl isocyanate (1.12 g, 9.4 mmol) or phenyl isothiocyanate (0.97 g, 7.2 mmol) was added and the mixture was refluxed for 2 h. After completion of the reaction in the case of **8** a part of the solvent was removed under reduced pressure, the obtained crystalline solid was filtered off, washed with diethyl ether, and in the case of **9** after cooling of the reaction mixture, the resulting precipitate was filtered off and washed with diethyl ether.

**2-(1-(2,6-Diethylphenyl)-5-oxopyrrolidine-3-carbonyl)-N-phenylhydrazine-1-carboxamide (8)**. White powder, yield 2.07 g (73%), m. p. 180–182°C (from 1,4-dioxane); IR (KBr):  $\nu$  (cm<sup>-1</sup>): 3348, 3297, 3252 (3NH), 1743, 1722, 1661 (3C=O); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$ : 1.09 (t,  $J$  = 7.6 Hz, 3H, CH<sub>3</sub>), 1.15 (t,  $J$  = 7.5 Hz, 3H, CH<sub>3</sub>), 2.38–2.50 (m, 4H, 2CH<sub>2</sub>), 2.61 (dd,  $J$  = 16.8, 6.2 Hz, 1H, CH<sub>2</sub>CO), 2.76 (dd,  $J$  = 16.8, 9.7 Hz, 1H, CH<sub>2</sub>CO), 3.35–3.48 (m, 1H, CH), 3.61–3.67 (m, 1H, NCH<sub>2</sub>), 3.75 (t,  $J$  = 9.1 Hz, 1H, NCH<sub>2</sub>), 6.96 (t,  $J$  = 7.3, 1H, H<sub>arom</sub>), 7.08–7.35 (m, 5H, H<sub>arom</sub>), 7.46 (d,  $J$  = 8.9 Hz, 2H, H<sub>arom</sub>), 8.11, 8.40, 8.79, 8.98, 9.24, 9.91 (6s, 3H, NH); <sup>13</sup>C-NMR (101 MHz, DMSO-d<sub>6</sub>)  $\delta$ : 14.7, 14.9 (2CH<sub>3</sub>), 23.3, 23.5 (2CH<sub>2</sub>), 33.6 (CH<sub>2</sub>CO), 34.8 (CH), 52.0 (NCH<sub>2</sub>), 118.5, 122.0, 126.3, 126.5, 128.3, 128.7, 134.6, 139.6, 141.8, 142.2 (C<sub>arom</sub>), 155.3, 172.3, 172.8 (3C=O); Anal. calcd. for C<sub>22</sub>H<sub>27</sub>N<sub>4</sub>O<sub>3</sub> m/z %: 395.2083 [M + H]<sup>+</sup>, found HRMS (ESI), m/z %: 395.2078 [M + H]<sup>+</sup> (100%).

**2-(2-(1-(2,6-Diethylphenyl)-5-oxopyrrolidine-3-carbonyl)hydrazinyl)-N-phenylethanethioamide (9)**. White powder, yield 2.22 g (75%), m. p. 170–172°C (from 1,4-dioxane); IR (KBr):  $\nu$  (cm<sup>-1</sup>): 3149 (NH), 1710, 1682 (2C=O), 1185 (C=S); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$ : 1.13 (dt,  $J$  = 15.1, 7.5 Hz, 6H, 2CH<sub>3</sub>), 2.42–2.50 (m, 4H, 2CH<sub>2</sub>), 2.65 (dd,  $J$  = 16.9, 5.8 Hz, 1H, CH<sub>2</sub>CO), 2.77 (dd,  $J$  = 16.9, 9.7 Hz, 1H, CH<sub>2</sub>CO), 3.39–3.49 (m, 1H, CH), 3.66–3.79 (m, 2H, NCH<sub>2</sub>), 7.13–7.19 (m, 3H, H<sub>arom</sub>), 7.26–7.30 (m, 1H, H<sub>arom</sub>), 7.34 (t,  $J$  = 7.8 Hz, 2H, H<sub>arom</sub>), 7.38–7.49 (m, 2H, H<sub>arom</sub>), 9.60 (s, 1H, NH), 9.67 (br s, 1H, NH), 10.08, 10.17 (2s, 1H, NH); <sup>13</sup>C-NMR (101 MHz, DMSO-d<sub>6</sub>)  $\delta$ : 14.7, 14.9 (2CH<sub>3</sub>), 23.4, 23.5 (2CH<sub>2</sub>), 33.6 (CH<sub>2</sub>CO), 35.1 (CH), 51.9 (NCH<sub>2</sub>), 125.2, 126.0, 126.3, 126.5, 128.2, 128.4, 134.7, 139.1, 141.7, 142.2 (C<sub>arom</sub>), 172.3, 172.6 (2C=O), 181.2 (C=S); Anal. calcd. for C<sub>22</sub>H<sub>26</sub>N<sub>4</sub>O<sub>2</sub>S m/z %:

411.1854 [M + H]<sup>+</sup>, found HRMS (ESI), m/z %: 411.1849 [M + H]<sup>+</sup> (100%).

**General procedure for the preparation of triazole derivatives 10 and 11**. A solution of the corresponding compound **8** or **9** (2.5 mmol) in 4% aqueous sodium hydroxide (**8** – 25 mL, **9** – 35 mL) was heated at reflux for 10 (**8**) or 3 (**9**) h. After completion of the reaction, the reaction mixture was cooled down, diluted with water (50 mL), placed in an ice-water bath and acidified with hydrochloric acid to pH 2. The obtained crystalline solid was filtered off and washed with water.

**5-(1-(2,6-Diethylphenyl)-5-oxopyrrolidin-3-yl)-4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-one (10)**. Light yellow powder, yield 0.55 g (59%), m. p. 220–222°C (from 1,4-dioxane); IR (KBr):  $\nu$  (cm<sup>-1</sup>): 3194 (NH), 1674 (2C=O); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$ : 1.01–1.15 (m, 6H, 2CH<sub>3</sub>), 2.31–2.47 (m, 4H, 2CH<sub>2</sub>), 2.55–2.66 (m, 1H, CH<sub>2</sub>CO), 2.76 (dd, 1H,  $J$  = 16.6, 6.1 Hz, CH<sub>2</sub>CO), 3.39–3.59 (m, 2H, NCH<sub>2</sub>), 3.71–3.82 (m, 1H, CH), 7.06–7.26 (m, 3H, H<sub>arom</sub>), 7.28–7.68 (m, 5H, H<sub>arom</sub>), 11.90 (s, 1H, NH); <sup>13</sup>C-NMR (101 MHz, DMSO-d<sub>6</sub>)  $\delta$ : 14.6, 14.7, 14.8 (2CH<sub>3</sub>), 23.3, 23.4 (2CH<sub>2</sub>), 29.2 (CH<sub>2</sub>CO), 33.3, 33.4 (CH), 51.7, 51.8 (NCH<sub>2</sub>), 126.4, 126.5, 127.7, 128.4, 128.9, 129.6, 132.7, 134.3, 141.8, 142.0, 147.4 (C<sub>arom</sub>), 154.7, 171.9 (2C=O); Anal. calcd. for C<sub>22</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub> m/z %: 377.1977 [M + H]<sup>+</sup>, found HRMS (ESI), m/z %: 377.1972 [M + H]<sup>+</sup> (100%).

**5-(1-(2,6-Diethylphenyl)-5-oxopyrrolidin-3-yl)-4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-thione (11)**. White powder, yield 0.75 g (76%), m. p. 241–242°C (from 1,4-dioxane); IR (KBr):  $\nu$  (cm<sup>-1</sup>): 3446 (NH), 1658 (C=O), 1589, 1569 (C=N<sub>triazole ring</sub>), 1310 (C=S); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$ : 1.02 (t,  $J$  = 7.5 Hz, 3H, CH<sub>3</sub>), 1.07 (t,  $J$  = 7.5 Hz, 3H, CH<sub>3</sub>), 2.25–2.45 (m, 4H, 2CH<sub>2</sub>), 2.59 (dd,  $J$  = 16.7, 9.2 Hz, 1H, CH<sub>2</sub>CO), 2.78 (dd,  $J$  = 16.6, 6.4 Hz, 1H, CH<sub>2</sub>CO), 3.48 (d,  $J$  = 8.3 Hz, 1H, NCH<sub>2</sub>), 3.51 (d,  $J$  = 8.2 Hz, 1H, NCH<sub>2</sub>), 3.66–3.75 (m, 1H, CH), 7.02–7.23 (m, 2H, H<sub>arom</sub>), 7.25 (t,  $J$  = 7.6 Hz, 1H, H<sub>arom</sub>), 7.44–7.65 (m, 5H, H<sub>arom</sub>), 13.90 (s, 1H, NH); <sup>13</sup>C-NMR (101 MHz, DMSO-d<sub>6</sub>)  $\delta$ : 14.7, 14.8 (2CH<sub>3</sub>), 23.3, 23.4 (2CH<sub>2</sub>), 29.0 (CH<sub>2</sub>CO), 33.9 (CH), 52.0 (NCH<sub>2</sub>), 126.4, 126.5, 128.4, 128.5, 129.6, 129.7, 133.5, 134.2, 141.8, 142.0, 153.0 (C<sub>arom</sub>), 168.5 (C=S), 171.6 (C=O); Anal. calcd. for C<sub>22</sub>H<sub>24</sub>N<sub>4</sub>OS m/z %: 393.1749 [M + H]<sup>+</sup>, found HRMS (ESI), m/z %: 393.1755 [M + H]<sup>+</sup> (100%).

**1-(2,6-Diethylphenyl)-4-(5-(phenylamino)-1,3,4-thiadiazol-2-yl)pyrrolidin-2-one (12).** A solution of compound **9** (0.7 g, 1.7 mmol) in concentrated sulphuric acid (10 mL) was heated at reflux for 2 h, then cooled down in an ice-water bath, diluted with water (50 mL) and neutralized with ammonium hydroxide to pH 7. The formed solid was filtered off and washed with water. White powder, yield 0.53 g (80%), m. p. 120–122°C (from 1,4-dioxane); IR (KBr):  $\nu$  (cm<sup>-1</sup>): 3230, 3046 (NH), 1693 (C=O), 1603, 1572 (C=N); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$ : 1.04 (t,  $J$  = 7.5 Hz, 3H, CH<sub>3</sub>), 1.16 (t,  $J$  = 7.5 Hz, 3H, CH<sub>3</sub>), 2.33–2.43 (m, 2H, 2CH<sub>2</sub>), 2.47–2.53 (m, 2H, 2CH<sub>2</sub>, overlaps with the residual peak of DMSO-d<sub>6</sub>), 2.87 (dd,  $J$  = 16.6, 6.4 Hz, 1H, CH<sub>2</sub>CO), 3.01 (dd,  $J$  = 16.6, 8.9 Hz, 1H, CH<sub>2</sub>CO), 3.75 (dd,  $J$  = 10.0, 5.3 Hz, 1H, NCH<sub>2</sub>), 4.00 (d,  $J$  = 7.9 Hz, 1H, NCH<sub>2</sub>), 4.03 (d,  $J$  = 8.0 Hz, 1H, NCH<sub>2</sub>), 4.16–4.29 (m, 1H, CH), 7.00 (t,  $J$  = 7.4, 1H, H<sub>arom</sub>), 7.09–7.19 (m, 2H, H<sub>arom</sub>), 7.27 (t,  $J$  = 7.6, 1H, H<sub>arom</sub>), 7.35 (t,  $J$  = 8.0 Hz, 2H, H<sub>arom</sub>), 7.62 (d,  $J$  = 7.9 Hz, 2H, H<sub>arom</sub>), 10.36 (s, 1H, NH); <sup>13</sup>C-NMR (101 MHz, DMSO-d<sub>6</sub>)  $\delta$ : 14.6, 14.9 (2CH<sub>3</sub>), 23.5 (2CH<sub>2</sub>), 33.3 (CH<sub>2</sub>CO), 36.1 (CH), 54.7 (NCH<sub>2</sub>), 117.3, 121.8, 126.3, 126.5, 128.4, 129.1, 134.5, 140.7, 141.9, 142.1 (C<sub>arom</sub>), 160.6, 164.6 (2C=N), 172.1 (C=O); Anal. calcd. for C<sub>22</sub>H<sub>24</sub>N<sub>4</sub>O S m/z %: 393.1749 [M + H]<sup>+</sup>, found HRMS (ESI), m/z %: 393.1748 [M + H]<sup>+</sup> (100%).

## Biology

### Bacteria strains and culturing conditions.

#### The inhibitory and bactericidal activity evaluation of compounds

The antibacterial properties were evaluated against gram-positive cocci *Staphylococcus aureus* (ATCC 9144), gram-positive rods *Listeria monocytogenes* (ATCC 19111) and *Bacillus cereus* (ATCC 11778), and gram-negative rods *Escherichia coli* (ATCC 8739) by the broth and spread-plate methods [30]. The most important test results displaying the minimum inhibition concentration (MIC,  $\mu$ g/mL) and the minimum bactericidal concentration (MBC,  $\mu$ g/mL) values are presented in the Table. A broad-spectrum antibiotic *Ampicillin* was used as a positive control for *S. aureus*, *L. monocytogenes*, *B. cereus* and *E. coli*. The *in vitro* antibacterial activity (MIC and MBC) of the antibiotic was 125  $\mu$ g/mL for *B. cereus* and 62.5  $\mu$ g/mL for the rest strains.

## RESULTS AND DISCUSSION

### Chemistry

Acid hydrazide **1** was used as a precursor for various chemical transformations (Scheme) to obtain a series of compounds containing hydrazone, semi- or thiosemicarbazide and azole scaffolds.

Table. Minimum inhibitory (MIC) and minimum bactericidal (MBC) concentrations values for the tested compounds 1–12

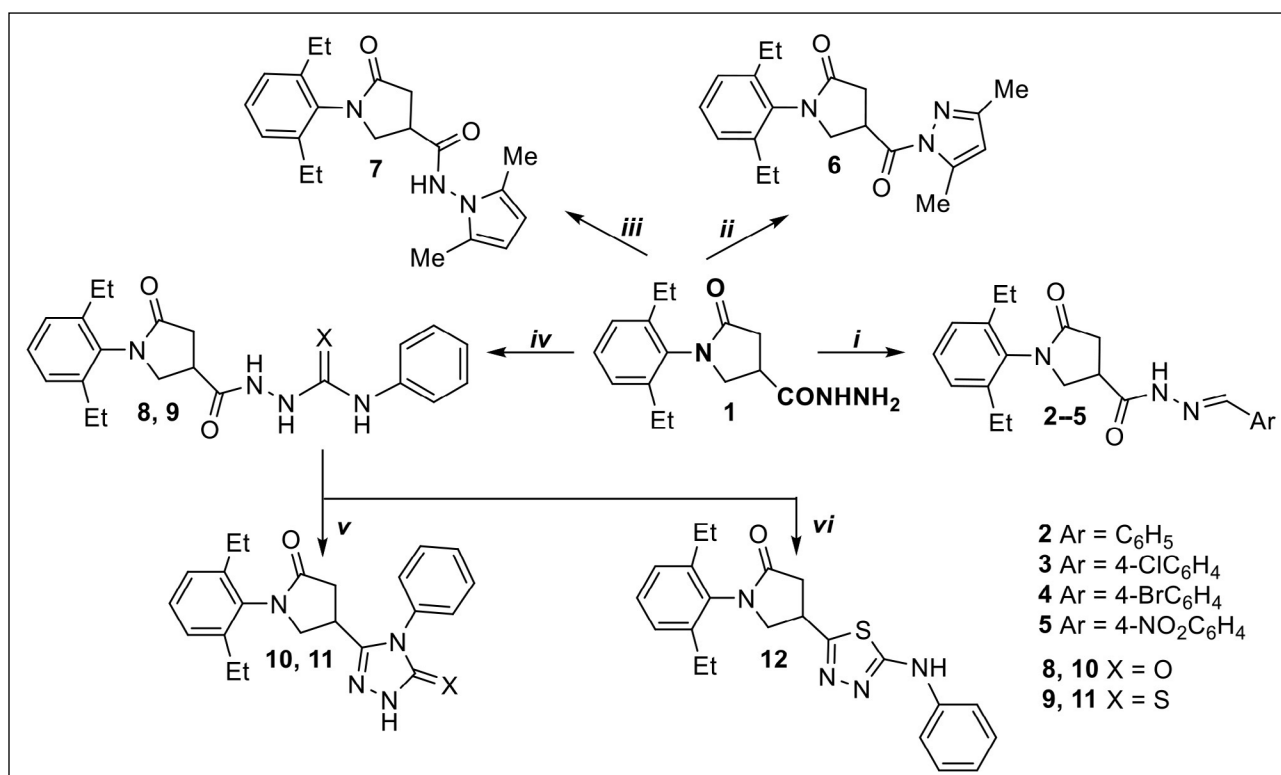
Compounds	Bacteria strains							
	<i>S. aureus</i>		<i>E. coli</i>		<i>B. cereus</i>		<i>L. monocytogenes</i>	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
	$\mu$ g/mL							
1	15.63	31.25	31.25	62.5	125	250	15.63	31.25
2	62.5	125	125	125	500	500	31.25	62.5
3	250	500	62.5	125	500	500	31.25	62.5
4	125	250	125	250	500	500	31.25	62.5
5	31.25	31.25	125	15.63	500	500	31.25	62.5
6	15.63	31.25	15.63	15.63	31.25	62.5	15.63	31.25
7	31.25	62.5	15.63	62.5	31.25	62.5	31.25	62.5
8	15.63	31.25	31.25	31.25	31.25	62.5	31.25	62.5
9	15.63	31.25	15.63	125	31.25	62.5	15.63	31.25
10	31.25	62.5	62.5	62.5	62.5	125	31.25	62.5
11	31.25	62.5	31.25	62.5	62.5	125	62.5	125
12	62.5	125	31.25		31.25	62.5	31.25	62.5
C		62.5			125		62.5	

C is control *Ampicillin*, whose MIC and MBC for *S. aureus*, *E. coli* and *L. monocytogenes* is 62.5  $\mu$ g/mL and for *B. cereus* 125  $\mu$ g/mL.

Condensation of acid hydrazide with aromatic aldehydes in 2-propanol at reflux gave hydrazones **2–5** in 62–89% yield. The restricted rotation around the CONH led to the formation in an isomeric mixture of hydrazones where *Z* isomer predominates. Most of the resulting hydrazones show double sets of resonances for the N=CH and CONH fragment protons with an intensity ratio of 0.65:0.35 ( $^1\text{H}$  NMR), while the intensity ratio for derivative with *p*-nitrophenyl substituent in the structure was 0.6:0.4. No formation of geometrical isomers was observed.

An action of hydrazides **1** with pentane-2,4-dione catalyzed by hydrochloric acid led to the formation of 1-(2,6-diethylphenyl)-4-(3,5-dimethyl-1H-pyrazole-1-carbonyl)pyrrolidin-2-one (**6**). The formed 3,5-dimethylpyrazole moiety was identified as a singlet at 6.23 ( $\text{CH}_{\text{pyr}}$ ) ppm as well as a singlet at 2.18 ( $\text{C-CH}_3$ ) and a multiplet in a range of 2.37–2.51 ( $\text{C-CH}_3 + 2\text{CH}_2\text{CH}_3$ ) ppm integrated for 7 protons. 2,5-Dimethylpyrrole **7** was prepared by condensation of **1** with hexane-2,5-

dione. The reaction was carried out in 2-propanol and catalyzed by acetic acid. In the NMR spectra for **7**, the proton peaks of  $2\text{CH}_3$  at approx. 2.0 ppm (10.9 ppm,  $^{13}\text{C}$ ) and a singlet at 5.66 ppm integrated for two protons of the =CH–CH= fragment (103.1 ppm,  $^{13}\text{C}$ ) have confirmed the formation of a five-membered pyrrole cycle. Heating the reaction mixture of compounds **1** with phenyl isocyanate or phenyl isothiocyanate at reflux in methanol gave semicarbazide **8** and thiosemicarbazide **9**. The ring closure successfully proceeded in the basic medium and afforded triazolone **10** or triazolethione **11**. The analysis of the NMR spectra of semicarbazide **8** and thiosemicarbazide **9** clearly prove the formation of the target fragment. Six singlets in a range of 8.11–9.91 ppm, integrated for three protons, represent three NH groups. The additional resonance line at 155.3 ppm in the  $^{13}\text{C}$  NMR spectrum of derivative **8** indicated the existence of the additional carbonyl group in the target molecule.



**Reagents and conditions:** *i* ArCHO, 2-PrOH,  $\Delta$ , 1.5 h, solvent was removed under reduced pressure, Et<sub>2</sub>O; *ii* pentane-2,4-dione, 2-PrOH, HCl,  $\Delta$ , 2 h, reduced pressure, water; *iii* hexane-2,5-dione, 2-PrOH, AcOH,  $\Delta$ , 4 h, reduced pressure, water; *iv* phenyl isocyanate (**8**) or phenyl isothiocyanate (**9**), MeOH,  $\Delta$ , 2 h, reduced pressure; *v* semicarbazide or thiosemicarbazide, 4% NaOH,  $\Delta$ , 10 (**8**) or 3 (**9**) h, water, ice-water bath, HCl to pH 2; *vi* conc. H<sub>2</sub>SO<sub>4</sub>,  $\Delta$ , 2 h, ice-water bath, NH<sub>4</sub>OH to pH 7.

**Scheme.** Synthesis of 1-(2,6-diethylphenyl)-5-oxopyrrolidine derivatives **2–12**

The characteristic resonance line which appears at 181.2 ppm in the  $^{13}\text{C}$  NMR spectrum of thiosemicarbazide **9** confirms the presence of the C=S group. The NMR of cyclic derivatives **10** and **11** showed exclusively representative signals of NH, carbonyl and thiocarbonyl groups of the formed triazolone or triazolethione. It should be noted that cyclization of thiosemicarbazide **9** was also successful in a strong acidic medium and provided heterocyclic derivative – 2,5-disubstituted thiadiazole **12** as expected.

## Biology

### Growth inhibition and bactericidal effect of the synthesized compounds

The synthesized target compounds **1–12** were screened for their antibacterial activity. The data of the antibacterial evaluation have revealed that most of the synthesized compounds were twice more effective than the control antibiotic ampicillin (Table). It has been found that compound **6** containing the pyrazole fragment in the molecule and compound **9** with the thiosemicarbazide fragment in the structure showed the strongest effect against three tested pathogens, with the MIC value of 15.63  $\mu\text{g}/\text{mL}$  and MBC of 31.25  $\mu\text{g}/\text{mL}$  (**6**, MBC for *E. coli* 15.63  $\mu\text{g}/\text{mL}$ ). Pyrazole **6** and thiosemicarbazide **9** derivatives demonstrated a slightly weaker inhibitory and bactericidal influence on *B. cereus*. The inhibition concentration of these compounds was 31.25, and the bactericidal concentration appeared to be 62.5  $\mu\text{g}/\text{mL}$ .

It should be noted that the synthesized hydrazones in most cases have been demonstrated to possess weak to moderate antibacterial properties (MIC and MBC ranging from 125 to 500  $\mu\text{g}/\text{mL}$ ). Only two cases should be distinguished: an inhibitory activity of hydrazones **2–5** against *L. monocytogenes* was twice as strong as that of ampicillin. Hydrazone **5** had a similar effect against the strain of *S. aureus*. That concentration also appeared to be bactericidal for this strain. It was also found that *L. monocytogenes* was the most sensitive to the action of all synthesized compounds.

Correlations between the chemical structure of compound and its activity are important for the development of pharmacological agents, agro protectors, plant protection products, as well as for the investigation of toxicity and the mutagenic

and carcinogenic potential. Practical importance is attached to these studies because the results can be used to predict the activity of untested compounds.

Biological activity of the synthesized compounds is closely related to the presence of azole or semi/thiosemicarbazide substituents in the molecules. The above-mentioned compounds showed a much stronger antibacterial potency in comparison with those of derivatives with the hydrazone fragment. Obviously, the introduction of the carbothio moiety into the molecule had a major effect on the enhancement of the antibacterial properties of the compound. Thiosemicarbazide **9** demonstrated stronger antibacterial properties in comparison with compound **8** containing a carbonyl fragment.

The antibacterial activity of compounds **8** and **9** appeared to be much wider than those of their cyclic derivatives **10** and **11**. Compounds **8** and **9** were more effective against all test-strains than triazoles **10** and **11**. The broader and increased biological properties of semi/thiosemicarbazides are predetermined by the presence of several NH groups.

The analysis of the results revealed that among the azoles, pyrazole derivative fully inhibited bacteria growth rate and killed test-bacteria strains at the lowest concentrations.

## CONCLUSIONS

In conclusion, a series of new (2,6-diethylphenyl)-5-oxopyrrolidine derivatives were synthesized and evaluated for their antibacterial properties. The antibacterial screening has demonstrated that the above properties of the synthesized compounds are closely related to the presence of the hydrazide, azole and thiosemicarbazide substituents in the molecules, which in some cases increased the biological effect up to 4 times (15.63  $\mu\text{g}/\text{mL}$ ) in comparison with that of the control ampicillin (62.5  $\mu\text{g}/\text{mL}$ ).

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### NAUJŲ 1-(2,6-DIETILFENIL)-5-OKSOPIROLIDINO DARINIŲ SINTEZĖ IR ANTIBAKTERINIS TYRIMAS

#### Santrauka

Darbe pateikta 1-(2,6-dietilfenil)-5-oksopirolidino darinių su hidrazono, semi/tiosemikarbazido ir azolų fragmentais molekulėje sintezė bei biologinio tyrimo rezultatai. Minėti junginiai gauti atitinkamą hidrazidą veikiant aromatiniais aldehidais, diketonais ir fenilizo(tio)cianatais. Susintetinti junginiai identifikuoti remiantis  $^1\text{H}$ ,  $^{13}\text{C}$  BMR, IR, masių spektroskopijos ir elementinės analizės duomenimis. Ištirtas susintetintų junginių antibakterinis aktyvumas prieš *Staphylococcus aureus*, *Escherichia coli*, *Bacillus cereus* ir *Listeria monocytogenes* bakterijų padermės. Kontrolėi pasirinktas antibiotikas ampicilinas, kurio antibakterinis aktyvumas (MIK ir MBK) prieš *B. cereus* yra 125  $\mu\text{g/mL}$  ir 62,5  $\mu\text{g/mL}$  prieš kitas tyrime naudotas bakterijas. Iš darbe gautų junginių stipriausiai antibakteriškai veikė pirazolo ir tiosemikarbazido dariniai. Jų minimali slopinamoji koncentracija net keturis kartus mažesnė, palyginti su kontroliniu ampicilinu. Jautriausia junginių poveikiui buvo *L. monocytogenes* bakterijų padermė, šiek tiek atsparesnė – *S. aureus*.

Susintetintų junginių biologinis aktyvumas glaudžiai siejasi su azolo ir semi/tiosemikarbazido fragmentais junginio struktūroje. Šie dariniai yra gerokai aktyvesni negu hidrazonai. Akivaizdu, kad tiosemikarbazido molekulėje esantis karbotiofragmentas gerokai sustiprina junginio priešbakterinį poveikį. Taip pat reikia paminėti, kad iš semi/tiosemikarbazidų gautų ciklinių darinių biologinės savybės yra silpnesnės. Stipresnės semi/tiosemikarbazidų antibakterinės savybės ir platesnį jų poveikio spektrą lemia junginio molekulėje esančios kelios NH grupės.