CHEMIJA. 2017. Vol. 28. No. 1. P. 64–73

Synthesis, transformation and antibacterial activity of new *N,N*-disubstituted 2-aminothiazole derivatives

Birutė Grybaitė,

Ilona Jonuškienė,

Rita Vaickelionienė,

Vytautas Mickevičius*

Department of Organic Chemistry,
Kaunas University of Technology,
Radvilėnų Road 19,
LT-50254 Kaunas, Lithuania

A series of novel *N,N*-disubstituted 2-aminothiazole derivatives were synthesized by the Hantzsch reaction from 3-[(1-naphthyl)carbamothioylamino]propanoic acid and α-halocarbonyl compounds. With the help of various chemical transformations of the obtained compounds, new variously functionalized 2-aminothiazole derivatives were synthesized. Some of them were tested for their antibacterial properties against gram-negative non-spore-forming rods of *Rhizobium radiobacter*.

Keywords: thiazole, 4-quinolone, biological activity, pharmaceuticals

INTRODUCTION

Many heterocycles play a vital role in the biological process and are widely found in nature, particularly in nucleic acid, alkaloids, anthocyanins and flavours; some vitamins, proteins, hormones contain an aromatic heterocyclic system [1]. Various biological activities are associated with some substituted thiazoles [2–5]. The thiazole ring is a constituent of medicinal agents, agrochemicals, and dyes. Thiazole found application in drug development for the treatment of different diseases, for example, allergies [6], hypertension [7], fungal infections [8], schizophrenia [9]. Pharmaceuticals containing a thiazole fragment also show antiinflamatory [10], anti-HIV [11], hypnotic [12], analgesic [13], and fibrinogen receptor antagonists with antithrombotic [14] activities. This moiety occurs in some antibiotics like penicillin, micrococcin [15], and LFF571 [16]. Furthermore, it is known that a naphthyl-substituted thiazole inhibits the allosteric cysteine in the p10 subunit of caspase-5 [17]. Thiazole dyes are used for dying cotton, even for quasi-solid-state dye-sensitized solar cells (DSSCs) [18]. A thiazole-based vulcanization accelerator is important in rubber industry [19]. 4-Quinolone derivatives are used as antidiabetic [20], anticancer [21, 22], and antiviral agents [23]. Due to the importance of the mentioned compounds, a series of thiazole derivatives were synthesized and tested for their *in vitro* antimicrobial properties against the gram-negative bacteria strain *Rhizobium radiobacter*.

EXPERIMENTAL

TLC was performed with Merck Silica gel 60 F254 (Kieselgel 60 F254) silica gel plates. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Ascend 400 (^{1}H 400 MHz, ^{13}C 101 MHz) and Bruker Ascend (^{1}H 700 MHz, ^{13}C 176 MHz) spectrometers. Chemical shifts are expressed as δ, ppm relative to TMS. IR spectra (ν, cm^{-1}) were recorded on a PERKIN ELMER Spectrum Bx FT-IR spectrometer using KBr tablets. Elemental analyses were performed with a CE-440 elemental analyzer. Melting points were determined with a B-540 Melting Point Analyzer (Buchi Corporation, USA) and are uncorrected.

3-[Naphthalen-1-yl(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)amino]propanoic acid (2). Method A. To a solution of compound **1** (1.37 g, 5 mmol) and sodium carbonate (1.69 g, 16 mmol) in water (20 mL), monochloroacetic acid (1.04 g, 11 mmol) was added. The mixture was allowed to reflux for 4 h. Upon completion of the reaction (TLC), the reaction mixture was cooled down to r. t. and acidified with acetic acid to pH 6. The formed solid was

---

* Corresponding author. E-mail: Vytautas.Mickevicius@ktu.lt

filtered off, washed with water and dried. Purification was performed by dissolving crystals in 5% aqueous sodium carbonate, filtering, and acidifying the filtrate with acetic acid to pH 6 to give **2** as a white solid, yield 56%, 0.84 g, m. p. 101–102 °C.

Method B. To a solution of compound **1** (1.37 g, 5 mmol) and sodium acetate (0.82 g, 10 mmol) in 2-propanol (10 mL), monochloroacetic acid (1.04 g, 11 mmol) was added, and the mixture was refluxed for 4 h. Upon completion of the reaction (TLC), the reaction mixture was diluted with water, cooled down, and the formed precipitate was filtered off, washed with water, dried. Purification was performed as in the method A to give **2** as a white solid, yield 84%, 1.32 g, m. p. 101–102 °C.

^{1}H NMR (700 MHz, DMSO-d_6) δ: 2.66 (t, 2H, J = 7.4 Hz, CH_2CO); 3.91 (s, 2H, SCH_2); 4.57–4.63 (m, 2H, NCH_2); 7.53–8.15 (m, 7H, H_{Ar}); 12.40 (br s, 1H, COOH).

^{13}C NMR (176 MHz, DMSO-d_6) δ: 32.20 ($\underline{C}H_2CO$); 40.65 (SCH_2); 49.96 (NCH_2); 121.82; 125.76, 127.05, 127.68, 128.05, 128.83, 129.02, 130.39, 134.25; 136.07 (C_{Ar}); 171.96 (COOH); 184.20 (C=O); 187.09 (C=N).

IR (KBr), ν, cm^{-1}: 3472 (OH); 1716 (C=O); 1547 (C=N).

Calcd. for $C_{16}H_{14}N_2O_3S$, %: C 61.13; H 4.49; N 8.91. Found, %: C 61.35; H 4.48; N 8.87.

General synthetic procedure for 3–7. A mixture of compound **2** (0.47 g, 1.5 mmol), the corresponding aldehyde (2.5 mmol), sodium carbonate (0.48 g, 4.5 mmol), and water (30 mL) was refluxed for 3 h. The cooled reaction mixture was acidified with acetic acid to pH 6, the formed solid was filtered off, washed with water, dried. Purification was performed by dissolving crystals in 5% aqueous sodium carbonate, filtering and acidifying the filtrate with acetic acid to pH 6 to give **3–7** as solids: **3** – yield 69%, 0.46 g, m. p. 144–145 °C, **4** – yield 41%, 0.26 g, m. p. 151–152 °C, **5** – yield 55%, 0.42 g, m. p. 167–168 °C, **6** – yield 42%, 0.3 g, m. p. 258–259 °C, **7** – yield 60%, 0.42 g, 191–192 °C.

3-{[(5*Z*)-5-(4-Fluorobenzylidene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl](naphthalen-1-yl)amino}propanoic acid (3)

^{1}H NMR (700 MHz, DMSO-d_6) δ: 2.71–2.75 (m, 2H, CH_2CO); 4.00–4.04 and 4.71–4.75 (m, 2H, NCH_2); 7.18–8.20 (m, 12H, H_{Ar}+CH), 12.48 (br s, 1H, COOH).

^{13}C NMR (176 MHz, DMSO-d_6) δ: 32.15 ($\underline{C}H_2CO$); 49.91 (NCH_2); 121.57, 121.78, 123.99, 125.62, 125.89, 126.83, 127.26, 127.96, 127.99, 128.33, 128.91, 129.67, 130.84, 131.76, 131.81, 134.27, 136.67, 143.79 (C_{Ar}+S$\underline{C}$=$\underline{C}$H); 171.92 (COOH); 177.20 (C=O); 179.52 (C=N).

IR (KBr), ν, cm^{-1}: 3059 (OH); 1731 (C=O); 1531 (C=N).

Calcd. for $C_{23}H_{17}FN_2O_3S$, %: C 65.70; H 4.08; N 6.66. Found, %: C 65.49; H 4.10; N 6.69.

3-{[(5*Z*)-5-(4-Chlorobenzylidene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl](naphthalen-1-yl)amino}propanoic acid (4)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.64–2.69 (m, 2H, CH_2CO); 3.95–4.03 and 4.67–4.73 (2m, 2H, NCH_2); 7.31–8.17 (m, 12H, H_{Ar}+CH).

^{13}C NMR (101 MHz, DMSO-d_6) δ: 32.59 ($\underline{C}H_2CO$); 50.32 (NCH_2); 121.76, 125.87, 127.23, 127.97, 128.88, 129.06, 129.19, 129.31, 129.36, 129.85, 130.79, 131.01, 131.32, 132.63, 134.24, 134.27, 135.65, 137.73 (C_{Ar}+S$\underline{C}$=$\underline{C}$H); 172.11 (COOH); 176.97 (C=O); 179.45 (C=N).

IR (KBr), ν, cm^{-1}: 3376 (OH); 1725 (C=O); 1534 (C=N).

Calcd. for $C_{23}H_{17}ClN_2O_3S$, %: C 63.23; H 3.92; N 6.41. Found, %: C 63.35; H 3.94; N 6.62.

3-{[(5*Z*)-5-(4-Bromobenzylidene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl](naphthalen-1-yl)amino}propanoic acid (5)

^{1}H NMR (700 MHz, DMSO-d_6) δ: 2.69–2.77 (m, 2H, CH_2CO); 3.99–4.03 and 4.71–4.75 (m, 2H, NCH_2); 7.27–8.20 (m, 12H, H_{Ar}+CH), 12.48 (br s, 1H, COOH).

^{13}C NMR (176 MHz, DMSO-d_6) δ: 32.11 ($\underline{C}H_2CO$); 49.96 (NCH_2); 121.77, 123.19, 123.98, 125.90, 127.28, 127.99, 128.35, 128.91, 129.04, 129.53, 129.90, 130.87, 131.23, 132.17, 132.76, 134.27, 136.61, 143.78 (C_{Ar}+S$\underline{C}$=$\underline{C}$H); 171.88 (COOH); 177.09 (C=O); 179.45 (C=N).

IR (KBr), ν, cm^{-1}: 3059 (OH); 1704 (C=O); 1531 (C=N).

Calcd. for $C_{23}H_{17}BrN_2O_3S$, %: C 57.39; H 3.56; N 5.82. Found, %: C 57.57; H 3.54; N 5.79.

3-{Naphthalen-1-yl[(5*Z*)-5-(4-nitrobenzylidene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl]amino}propanoic acid (6)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.63–2.77 (m, 2H, CH_2CO); 3.99–4.79 (m, 2H, NCH_2); 6.50–8.32 (m, 12H, H_{Ar}+CH); 12.40 (br s, 1H, COOH).

^{13}C NMR (101 MHz, DMSO-d_6) δ: 22.97 ($\underline{C}H_2CO$); 47.69 (NCH_2); 124.61, 129.62, 130.58, 132.19, 135.14, 137.06, 139.35, 139.75, 141.02, 141.69, 142.64, 143.96, 146.31, 147.10, 147.24, 149.32, 150.41, 154.50 (C_{Ar}+S$\underline{C}$=$\underline{C}$H); 172.02 (COOH); 176.36 (C=O); 179.58 (C=N).

IR (KBr), ν, cm^{-1}: 3374 (OH); 1699 (C=O); 1519 (C=N).

Calcd. for $C_{23}H_{17}N_3O_5S$, %: C 61.74; H 3.83; N 9.39. Found, %: C 61.88; H 3.81; N 9.42.

3-(Naphthalen-1-yl{4-oxo-5-[(*Z*)-2-phenylethenyl]-4,5-dihidro-1,3-thiazol-2-yl}amino)propanoic acid (7)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.72 (t, 2H, J = 7.4 Hz, CH_2CO); 3.97–4.03 and 4.63–4.73 (2m, 2H, NCH_2); 6.77–8.25 (m, 15H, H_{Ar}+3CH); 12.44 (br s, 1H, COOH).

^{13}C NMR (101 MHz, DMSO-d_6) δ: 32.12 ($\underline{C}H_2CO$); 45.81 (NCH_2); 49.57 (SCH); 115.65, 121.38, 125.03, 125.89, 127.58, 127.97, 128.68, 128.76, 129.18, 130.60, 131.53, 134.34, 135.76, 139.24, 141.97, 144.94, 148.06, 149.44 (C_{Ar}+S$\underline{C}$=$\underline{C}$H–$\underline{C}$H=$\underline{C}$H); 171.96 (COOH); 176.66 (C=O); 179.38 (C=N).

IR (KBr), ν, cm^{-1}: 3376 (OH); 1708 (C=O); 1526 (C=N).

Calcd. for $C_{23}H_{17}N_3O_5S$, %: C 69.21; H 4.84; N 6.73. Found, %: C 69.31; H 4.83; N 6.70.

3,3’-[(5*Z*,5*Z*’)-(1,4-Phenylbis(methanyliden))bis(4-oxo-4,5-dihydrothiazol-2-yl-5-yliden)bis(naphthalen-1-ylazanediyl)]dipropanoic acid (8)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.66–2.69 and 3.41–3.46 (2 m, 4H, CH_2CO); 3.99–4.67 (m, 4H, NCH_2); 6.50–8.11 (m, 20H, H_{Ar}+2CH); 12.56 (br s, 1H, COOH).

^{13}C NMR (101 MHz, DMSO-d_6) δ: 33.31 ($\underline{C}H_2CO$); 57.63 (NCH_2); 117.71, 121.57, 123.96, 126.94, 127.94, 129.39, 130.12, 132.82, 134.04, 138.60, 140.30, 141.46, 145.60, 147.68, 149.64, 152.08, 154.27, 157.93 (C_{Ar}+S$\underline{C}$=$\underline{C}$H); 172.02 (COOH); 176.38 (C=O); 179.06 (C=N).

IR (KBr), ν, cm^{-1}: 3401 (OH); 1738, 1699 (C=O); 1527 (C=N).

Calcd. for $C_{40}H_{30}N_4O_6S_2$, %: C 66.10; H 4.16; N 7.71. Found, %: C 66.13; H 4.15; N 7.67.

3-[(4,5-Dioxo-4,5-dihydro-1,3-thiazol-2-yl)(naphthalen-1-yl)amino]propanoic acid (9). To a solution of thioureido acid **1** (2 g, 7.3 mmol) in acetone (30 mL), pyridine was added dropwise (1.73 g, 22 mmol) and then oxalyl chloride (1.02 g, 8 mmol) was poured in. The mixture was stirred at room temperature for 4 h. Upon completion of the reaction (TLC), the formed precipitate was filtered off, washed with acetone, ether, dissolved in water (50 mL) and filtered off. To the obtained filtrate, sodium acetate (1.26 g, 15 mmol) was added, and the mixture was heated to boiling. After cooling it down, the formed crystals were filtered off, washed with water and dried. Purification was performed by dissolving crystals in 5% aqueous sodium carbonate, filtering and acidifying the filtrate with acetic acid to pH 6 to give **9** as a white solid, yield 36%, 0.86 g, m. p. 265–266 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.80–2.87 and 3.00–3.09 (m, 2H, CH_2CO); 3.85-3.91 and 3.99–4.06 (m, 2H, NCH_2); 7.52–8.03 (m, 7H, H_{Ar}); 12.43 (s, 1H, COOH).

^{13}C NMR (101 MHz, DMSO-d_6) δ: 30.52 ($\underline{C}H_2CO$); 48.68 (NCH_2); 122.99, 125.26, 126.09, 126.47, 126.98, 128.20, 128.41, 128.66, 134.12, 141.67 (C_{Ar}); 167.24 (C=N); 172.47, 179.97, 181.33 (3C=O).

IR (KBr), ν, cm^{-1}: 3054 (OH); 1711 (C=O); 1576 (C=N).

Calcd. for $C_{16}H_{12}N_2O_4S$, %: C 58.53; H 3.68; N 8.53. Found, %: C 58.30; H 3.67; N 8.57.

3-{[(5*Z*)-5-[2-(4-Chlorophenyl)hydrazinylidene]-4-oxo-4,5-dihydro-1,3-thiazol-2-yl](naphthalen-1-yl)amino}propanoic acid (10). To a cooled (0 °C) mixture of the solution of compound **2** (0.3 g, 0.95 mmol) in aqueous sodium carbonate (0.1 g, 0.95 mmol/10 mL of water) the cooled (0 °C) diazonium salt solution was poured with vigorous stirring. The formed solid was filtered off, washed with water, dried. Purification was performed by dissolving crystals in 5% aqueous sodium carbonate, filtering and acidifying the filtrate with acetic acid to pH 6 to give **10** as a red solid, yield 49%, 0.21 g, m. p. 180–181 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.65–2.76 (m, 2H, CH_2CO); 4.00–4.08 and 4.57–4.71 (m, 2H, NCH_2); 7.08–8.19 (m, 11H, H_{Ar}); 10.18 (s, 1H, NH); 12.03 (br s, 1H, COOH).

^{13}C NMR (101 MHz, DMSO-d_6) δ: 32.48 ($\underline{C}H_2CO$); 52.81 (NCH_2); 115.69, 122.20; 126.18, 126.23, 127.73, 128.83, 129.33, 129.36, 129.87, 130.87, 131.38, 134.60, 135.78, 136.52, 143.09, 147.30, 158.73 (C_{Ar}+C=NNH); 172.27 (COOH); 175.89 (C=O); 179.65 (C=N).

IR (KBr), ν, cm^{-1}: 3057 (OH); 1720 (C=O); 1532 (C=N).

Calcd. for $C_{22}H_{17}ClN_4O_3S$, %: C 58.34; H 3.78; N 12.37. Found, %: C 58.54; H 3.80; N 12.42.

3-[Naphthalen-1-yl(1,3-thiazol-2-yl)amino]propanoic acid (11). A mixture of compound **1** (1.37 g, 5 mmol), chloroacetaldehyde 50% aqueous solution (1.05 mL, 7.5 mmol), sodium carbonate (1.69 g, 16 mmol) and water (20 mL) was refluxed for 3 h. Upon completion of the reaction (TLC), the reaction mixture was cooled down and acidified with diluted acetic acid to pH 6. The formed solid was filtered off, washed with water and dried. Purification was performed by dissolving crystals in 5% aqueous sodium carbonate, filtering and acidifying the filtrate with acetic acid to pH 6 to give **7** as a white solid, yield 47%, 0.7 g, m. p. 134–135 °C.

^{1}H NMR (700 MHz, DMSO-d_6) δ: 2.69 (t, 2H, J = 7.4 Hz, CH_2CO); 4.01–4.45 (m, 2H, NCH_2); 6.66 (d, 1H, J = 3.6 Hz, SCH); 7.20 (d, 1H, J = 3.6 Hz, NCH); 7.52–8.07 (m, 7H, H_{Ar}); 12.23 (br s, 1H, COOH).

^{13}C NMR (176 MHz, DMSO-d_6) δ: 32.62 ($\underline{C}H_2CO$); 48.80 (NCH_2); 108.53 (SCH); 139.16 (NCH); 122.39, 126.50, 126.70, 127.12, 127.28, 128.76, 128.89, 129.82, 134.85, 140.76 (C_{Ar}+S$\underline{C}$H=$\underline{C}$HN); 170.72 (C=N); 172.61 (COOH).

IR (KBr), ν, cm^{-1}: 3425 (OH); 3118 (C–H); 1715 (C=O); 1517 (C=N).

Calcd. for $C_{16}H_{14}N_2O_2S$, %: C 64.41; H 4.73; N 9.39. Found, %: C 64.57; H 4.74; N 9.42.

3-[(4-Methyl-1,3-thiazol-2-yl)(naphthalen-1-yl)amino]propanoic acid (12). To a solution of compound **1** (1.37 g, 5 mmol) and sodium carbonate (1.66 g, 16 mmol) in water (20 mL), chloroacetone (0.7 g, 7.5 mmol) was added dropwise. The solution was allowed to reflux for 4 h. Upon completion of the reaction (TLC), the reaction mixture was cooled down and acidified with diluted acetic acid to pH 6. The formed solid was filtered off, washed with water, dried and purified by dissolving crystals in 5% aqueous sodium carbonate, filtering and acidifying the filtrate with acetic acid to pH 6 to give **8** as a white solid, yield 62%, 0.96 g, m. p. 149–150 °C.

^{1}H NMR (700 MHz, DMSO-d_6) δ: 2.18 (s, 3H, CH_3); 2.64 (t, 2H, J = 7.4 Hz, CH_2CO); 3.95–4.40 (m, 2H, NCH_2); 6.19 (s, 1H, SCH); 7.52–8.05 (m, 7H, H_{Ar}).

^{13}C NMR (176 MHz, DMSO-d_6) δ: 17.47 (CH_3); 32.84 ($\underline{C}H_2CO$); 48.75 (NCH_2); 102.41 (SCH); 122.42, 126.41, 126.62, 127.18, 127.24, 128.69, 128.79, 129.94, 134.79, 140.47 (C_{Ar}+SCH); 148.32 (CCH_3); 169.83 (C=N); 172.71 (COOH).

IR (KBr), ν, cm^{-1}: 3436 (OH); 1719 (C=O); 1517 (C=N).

Calcd. for $C_{17}H_{16}N_2O_2S$, %: C 65.36; H 5.16; N 8.97. Found, %: C 65.49; H 5.17; N 8.95.

General synthetic procedure for 13–17. To a solution of compound **1** (0.7 g, 2.5 mmol) in acetone (10 mL), haloketone (3.1 mmol) was added, and the mixture was refluxed for 2 h. Upon completion of the reaction (TLC), the mixture was cooled down, and the formed aminothiazolium bromide was filtered off, washed with acetone, dried and transferred into the base by refluxing in 2.5% aqueous sodium acetate (0.5 g/20 mL), cooling the solution and filtering off the formed solid to give **13** as a white solid, yield 74%, 0.66 g, m. p. 162–163 °C, **14** as a white solid, yield 54%, 0.74 g, m. p. 197–198 °C, **15** as a white solid, yield 92%, 1.10 g, m. p. 157–158 °C, **16** as a white solid, yield 77%, 0.98 g, m. p. 189–190 °C, **17** as a white solid, yield 64%, 0.84 g, m. p. 181–182 °C.

3-[(4-Phenyl-1,3-thiazol-2-yl)(naphthalen-1-yl)amino]propanoic acid (13)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.77 (t, 2H, *J* = 7.2 Hz, CH_2CO); 3.95–4.70 (m, 2H, NCH_2); 7.09 (s, 1H, SCH); 7.08–8.13 (m, 12H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-d_6) δ: 32.61 ($\underline{C}H_2CO$); 48.84 (NCH_2); 103.26, 122.36, 125.77, 126.47, 126.75, 127.26, 127.37, 127.61, 128.02, 128.31, 128.57, 128.78, 129.10, 129.76, 134.50, 134.82, 140.31, 150.03 (C_{Ar}+S–$\underline{C}H{=}\underline{C}$); 169.97 (C=N); 172.63 (COOH).

IR (KBr), ν, cm^{-1}: 3055 (OH); 1736 (C=O); 1534 (C=N).

Calcd. for $C_{22}H_{18}N_2O_2S$, %: C 70.19; H 5.35; N 6.54. Found, %: C 70.14; H 5.37; N 6.51.

3-{[4-(4-Bromophenyl)-1,3-thiazol-2-yl](naphthalen-1-yl)amino}propanoic acid (14)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.75 (t, 2H, *J* = 7.3 Hz, CH_2CO); 3.95–4.18 and 4.36–4.61 (m, 2H, NCH_2); 7.17 (s, 1H, SCH); 7.55–8.09 (m, 11H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-d_6) δ: 32.60 ($\underline{C}H_2CO$); 48.77 (NCH_2); 104.10, 122.36, 126.48, 126.76, 126.94, 127.28, 127.39, 127.73, 128.78, 129.12, 129.75, 129.96, 131.36, 131.50, 134.82, 140.25, 149.06 (C_{Ar} + S–$\underline{C}H{=}\underline{C}$); 170.09 (C=N); 172.63 (COOH).

IR (KBr), ν, cm^{-1}: 3051 (OH); 1705 (C=O); 1537 (C=N).

Calcd. for $C_{22}H_{17}BrN_2O_2S$, %: C 58.28; H 3.78; N 6.18. Found %: C 58.09; H 3.76; N 6.20.

3-{[4-(4-Cyanophenyl)-1,3-thiazol-2-yl](naphthalen-1-yl)amino}propanoic acid (15)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.76 (t, 2H, *J* = 7.4 Hz, CH_2CO); 4.01–4.16 and 4.46–4.60 (m, 2H, NCH_2); 7.41 (s, 1H, SCH); 7.56–8.09 (m, 11H, H_{Ar}); 12.38 (br s, 1H, COOH).

^{13}C NMR (101 MHz, DMSO-d_6) δ: 32.66 ($\underline{C}H_2CO$); 48.88 (NCH_2); 107.08, 109.59, 129.12, 122.33, 126.33, 126.53, 126.84, 127.34, 127.49, 128.85, 129.94, 129.71, 132.71, 134.86, 138.78, 140.18, 148.60 (C_{Ar}+S–$\underline{C}H{=}\underline{C}$); 170.23 (C=N); 172.73 (COOH).

IR (KBr), ν, cm^{-1}: 3050 (OH); 1708 (C=O); 1536 (C=N).

Calcd. for $C_{22}H_{17}N_3O_2S$, %: C 69.15; H 4.29; N 10.52. Found, %: C 69.06; H 4.27; N 10.47.

3-{[4-(4-Nitrophenyl)-1,3-thiazol-2-yl](naphthalen-1-yl)amino}propanoic acid (16)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.76 (t, 2H, *J* = 7.4 Hz, CH_2CO); 4.02–4.18 and 4.47–4.62 (m, 2H, NCH_2); 7.49 (s, 1H, SCH); 7.56–8.29 (m, 11H, H_{Ar}); 12.36 (br s, 1H, COOH).

^{13}C NMR (101 MHz, DMSO-d_6) δ: 32.62 ($\underline{C}H_2CO$); 48.81 (NCH_2); 108.12, 122.32, 124.14, 126.54, 126.86, 127.37, 127.52, 128.86, 129.29, 129.70, 134.87, 140.09, 140.69, 146.26, 148.31 (C_{Ar}+S–$\underline{C}H{=}\underline{C}$); 170.38 (C=N); 172.70 (COOH).

IR (KBr), ν, cm^{-1}: 3050 (OH); 1712 (C=O); 1533 (C=N).

Calcd. for $C_{22}H_{17}N_3O_4S$, %: C 63.00; H 4.09; N 10.02. Found, %: C 63.22; H 4.09; N 9.99.

3-[Naphthalen-1-yl(4-naphthalen-1,3-thiazol-2-yl)amino]propanoic acid (17)

^{1}H NMR (700 MHz, DMSO-d_6) δ: 2.80 (t, 2H, *J* = 7.3 Hz, CH_2CO); 4.03–4.70 (m, 2H, NCH_2); 7.25 (s, 1H, SCH); 7.48–8.11 (m, 14H, H_{Ar}).

^{13}C NMR (176 MHz, DMSO-d_6) δ: 32.69 ($\underline{C}H_2CO$); 48.74 (NCH_2); 104.15, 122.41, 124.19, 124.28, 126.03, 126.48, 126.53, 126.81, 127.39, 127.45, 127.64, 128.11, 128.19, 128.83, 129.19, 129.84, 132.06, 132.53, 133.19, 134.87, 140.26, 150.09 (C_{Ar}+S–$\underline{C}H{=}\underline{C}$); 170.18 (C=N); 172.75 (COOH).

IR (KBr), ν, cm^{-1}: 3435 (OH); 1709 (C=O); 1533 (C=N).

Calcd. for $C_{26}H_{20}N_2O_2S$, %: C 73.56; H 4.75; N 6.60. Found, %: C 73.61; H 4.76; N 6.58.

General synthetic procedure for 18 and 19. A mixture of the corresponding compound **15** or **16** (1.6 mmol) and Eaton's reagent (7 mL) was stirred at 80 °C for 1 h. The cooled reaction mixture was diluted with water (10 mL) and neutralized with 10% aqueous sodium hydroxide to pH 8. The formed solid was filtered off, washed with water, dried. The obtained quinolinones were recrystallized from methanol to give **18** as a light orange solid, yield 92%, 0.56 g, m. p. 234–235 °C, and **19** as a light brown solid, yield 88%, 0.56 g, m. p. 180–181 °C.

4-[2-(4-Oxo-3,4-dihydrobenzo[*h*]quinolin-1(*2H*)-yl)-1,3-thiazol-4-yl]benzonitrile (18)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.90 (t, 2H, *J* = 7.5 Hz, CH_2CO); 4.65 (t, 2H, *J* = 7.5 Hz, NCH_2); 7.19 (s, 1H, CH) 7.38–8.06 (m, 10H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-d_6) δ: 36.87 ($\underline{C}H_2CO$); 51.36 (NCH_2); 105.09, 108.18, 121.98, 123.90, 125.50, 125.69, 126.47, 126.69, 127.04, 128.02, 128.81, 129.43, 129.98, 133.27, 134.77, 136.66, 145.43, 149.50, 167.55 (C_{Ar}+S$\underline{C}H{=}\underline{C}$); 168.92 (C=N); 194.00 (C=O).

IR (KBr), ν, cm^{-1}: 1705 (C=O); 1537 (C=N).

Calcd. for $C_{23}H_{15}N_3OS$, %: C 72.42; H 3.96; N 11.02. Found, %: C 72.48; H 3.95; N 10.99.

1-[4-(4-Nitrophenyl)-1,3-thiazol-2-yl]-2,3-dihydrobenzo[*h*]quinolin-4(*1H*)-one (19)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.91 (t, 2H, *J* = 7.5 Hz, CH_2CO); 4.67 (t, 2H, *J* = 7.5 Hz, NCH_2); 7.19 (s, 1H, CH) 7.56–8.27 (m, 10H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-d_6) δ: 36.93 ($\underline{C}H_2CO$); 47.91 (NCH_2); 121.98, 123.34, 123.99, 124.21, 124.37, 125.77, 126.53, 126.64, 126.82, 127.13, 128.85, 129.47, 136.70, 140.14, 145.18, 146.44, 148.08, 164.99 (C_{Ar}+ S$\underline{C}H{=}\underline{C}$); 174.16 (C=N); 193.93 (C=O).

IR (KBr), ν, cm^{-1}: 1688 (C=O); 1568 (C=N).

Calcd. for $C_{22}H_{15}N_3O_3S$, %: C 65.82; H 3.77; N 10.47. Found, %: C 65.75; H 3.75; N 10.50.

3-[(5-Acetyl-4-methyl-1,3-thiazol-2-yl)(naphthalen-1-yl)amino]propanoic acid (20). A mixture of compound **16** (4.12 g, 1.5 mmol), 3-chloro-2,4-pentanedione (2.42, 1.8 mmol) and acetone (20 mL) was refluxed for 4 h. Upon completion of the reaction (TLC), the reaction mixture was cooled down, diluted with water (40 mL), and sodium acetate was added (3 g, 3.6 mmol). The formed solid was filtered off, washed with water and dried. Purification was performed by dissolving crystals in 5 aqueous sodium carbonate, filtering and acidifying the filtrate with acetic acid to pH 6 and then recrystallizing from 2-propanol to give **20** as a white solid, yield 93%, 4.96 g, m. p. 185–186 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.24 (s, 3H, $OCCH_3$); 2.52 (s, 3H, CCH_3); 2.69–2.77 and 2.93–3.03 (m, 2H, CH_2CO); 3.61–3.69 and 3.84–3.94 (m, 2H, NCH_2); 7.52–8.10 (m, 7H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-d_6) δ: 18.58 ($C\underline{C}H_3$); 29.48 ($CO\underline{C}H_3$); 31.21 ($\underline{C}H_2CO$); 45.39 (NCH_2); 121.97 ($\underline{C}CH_3$); 122.98, 125.07, 125.87, 126.32, 126.72, 127.79, 128.24, 129.78, 133.99, 138.76 (C_{Ar}); 152.65 ($S\underline{C}$=C); 170.86 (C=N); 171.07 (COOH); 188.62 ($\underline{C}OCH_3$).

IR (KBr), ν, cm^{-1}: 3420 (OH); 1737, 1677 (C=O); 1576 (C=N).

Calcd. for $C_{19}H_{18}N_2O_3S$, %; C 64.39; H 5.12; N 7.90. Found, %: C 64.45; H 5.13; N 7.92.

General synthetic procedure for 21–23. To a solution of compound **20** (0.5 g, 1.4 mmol) in 10% NaOH (10 mL) 2-propanol (15 mL) was poured. The prepared solution was kept at 8 °C for 30 min, and then the appropriate aldehyde (1.54 mmol) was added dropwise. The reaction mixture was kept at 8 °C for 72 h, diluted with water (10 mL) and acidified with 30% acetic acid to pH 6. The formed precipitate was filtered off, washed with water and dried. Purification was performed by dissolving crystals in 5% aqueous sodium carbonate, filtering and acidifying the filtrate with acetic acid to pH 6 to give as light brown solids: **21** – yield 58%, 0.36 g, m. p. 87–88 °C, **22** – yield 55%, 0.37 g, m. p. 143–144 °C, and **23** – yield 68%, 0.44 g, m. p. 104–105 °C.

_N_-{4-Methyl-5-[(_E_)-3-phenyl-2-propenoyl]-1,3-thiazol-2-yl}-_N_-(1-naphthyl)-β-alanine (21)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.53 (s, 3H, CCH_3); 2.66–2.71 (m, 2H, CH_2CO); 3.97–4.07 and 4.46–4.58 (m, 2H, NCH_2); 7.12–8.12 (m, 14H, H_{Ar}+2CH).

^{13}C NMR (101 MHz, DMSO-d_6) δ: 18.59 ($C\underline{C}H_3$); 32.49 ($\underline{C}H_2CO$); 48.33 (NCH_2); 121.98 ($\underline{C}CH_3$); 122.92, 123.13, 124.52, 126.44, 126.91, 127.07, 127.67, 128.51, 128.87, 129.00, 129.62, 134.42, 134.82, 139.12, 141.70, 142.80 (C_{Ar}); 157.32 ($S\underline{C}$=C); 171.10 (C=N); 172.32 (COOH); 188.68 ($CH\underline{C}O$).

IR (KBr), ν, cm^{-1}: 3057 (OH); 1727 (C=O); 1631 (C=O); 1576 (C=N).

Calcd. for $C_{26}H_{22}N_2O_3S$, %; C 70.57; H 5.01; N 6.33. Found, %: C 70.49; H 4.99; N 6.30.

_N_-{5-[(_E_)-3-(4-Chlorophenyl)-2-propenoyl]-4-methyl-1,3-thiazol-2-yl}-_N_-(1-naphthyl)-β-alanine (22)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.52 (s, 3H, CCH_3); 2.64 (s, 2H, CH_2CO); 3.93–4.04 and 4.41–4.52 (m, 2H, NCH_2); 7.40–8.09 (m, 13H, H_{Ar}+2CH).

^{13}C NMR (101 MHz, DMSO-d_6) δ: 18.58 ($C\underline{C}H_3$); 33.36 ($\underline{C}H_2CO$); 48.95 (NCH_2); 122.00 ($\underline{C}CH_3$); 122.59, 122.93, 125.34, 126.42, 126.86, 127.06, 127.60, 128.85, 129.02, 129.50, 130.23, 133.42, 134.76, 139.17, 140.16, 141.71 (C_{Ar}); 157.41 ($S\underline{C}$=C); 171.07 (C=N); 172.75 (COOH); 188.59 ($CH\underline{C}O$).

IR (KBr), ν, cm^{-1}: 3058 (OH); 1723 (C=O); 1637 (C=O); 1556 (C=N).

Calcd. for $C_{26}H_{21}ClN_2O_3S$, %; C 64.47; H 4.44; N 5.87. Found, %: C 64.55; H 4.44; N 5.89.

_N_-{5-[(_E_)-3-(4-Fluorophenyl)-2-propenoyl]-4-methyl-1,3-thiazol-2-yl}-_N_-(1-naphthyl)-β-alanine (23)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.53 (s, 3H, CCH_3); 2.65 (s, 2H, CH_2CO); 3.98–4.08 and 4.47–4.58 (m, 2H, NCH_2); 7.07–8.12 (m, 13H, H_{Ar}+2CH).

^{13}C NMR (101 MHz, DMSO-d_6) δ: 18.58 ($C\underline{C}H_3$); 33.36 ($\underline{C}H_2CO$); 48.95 (NCH_2); 115.94 ($\underline{C}CH_3$); 121.98, 122.81, 123.14, 124.43, 126.44, 126.91, 127.07, 127.67, 128.87, 129.00, 129.62, 130.84, 130.92, 134.78, 139.12, 140.51 (C_{Ar}); 157.31 ($S\underline{C}$=C); 171.10 (C=N); 172.31 (COOH); 188.67 ($CH\underline{C}O$).

IR (KBr), ν, cm^{-1}: 3057 (OH); 1729 (C=O); 1638 (C=O); 1509 (C=N).

Calcd. for $C_{26}H_{21}FN_2O_3S$, %; C 67.81; H 4.60; N 6.08. Found, %: C 67.89; H 4.61; N 6.09.

_N_-(1-Naphthyl)-_N_-{4-[(_E_)-2-phenylethyl]-5-[(_E_)-3-phenyl-2-propenoyl]-1,3-thiazol-2-yl}-β-alanine (24). To a solution of compound **20** (0.9 g, 2.5 mmol) in 10% NaOH (10 mL) 2-propanol (10 mL) was poured and then benzaldehyde (0.8 g, 7.5 mmol) was added dropwise. The reaction mixture was heated under reflux for 4 h, then diluted with water (10 mL) and acidified with 30% acetic acid to pH 6. The formed precipitate was filtered off, washed with water, dried and purified by column chromatography. Eluent – chloroform : methanol 100 : 5; R_f = 0.58. Orange solid, yield 89%, 1.2 g, m. p. 104–105 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.75 (t, 2H, J = 7.5 Hz, CH_2CO); 4.09–4.16 and 4.65–4.72 (m, 2H, NCH_2); 6.98–8.14 (m, 21H, H_{Ar}+4CH).

^{13}C NMR (101 MHz, DMSO-d_6) δ: 32.56 ($\underline{C}H_2CO$); 48.52 (NCH_2); 121.74 ($\underline{C}CH$); 122.02, 122.64, 123.92, 125.68, 126.40, 127.23, 127.64, 128.65, 128.94, 129.03, 129.11, 130.26, 130.45, 131.35, 134.95, 136.33, 136.66, 137.02, 138.09, 139.03, 139.82, 142.37 (C_{Ar}); 156.54 ($S\underline{C}$=C); 170.35 (C=N); 172.48 (COOH); 180.45 ($CH\underline{C}O$).

IR (KBr), ν, cm^{-1}: 3058 (OH); 1711 (C=O); 1642 (C=O); 1519 (C=N).

Calcd. for $C_{33}H_{26}N_2O_3S$, %; C 74.69; H 4.94; N 5.28. Found, %: C 74.75; H 4.96; N 5.25.

RESULTS AND DISCUSSION

Compounds bearing a thiazolone moiety possess a wide variety of biological activities [24, 25]. Our previous study data and literature review prompted the development of novel compounds with thiazolone and carboxyalkyl fragments in the structure the aim of which was evaluation of the biological properties of newly synthesized compounds.

One of the most convenient methods of thiazole ring formation is the Hantzsh type reaction. In this work, the reaction of thioureido acid **1** with monochloroacetic acid was performed. The acidic fragment in the molecule of compound **1** enables the reaction to proceed in water, using sodium carbonate as a base, and without the addition of any solvents. The investigation showed that the higher yield of the target compound – 3-[naphthalen-1-yl(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)amino]propanoic acid **(2)** – was obtained using the weaker bases (sodium acetate) and carrying out the reaction in 2-propanol.

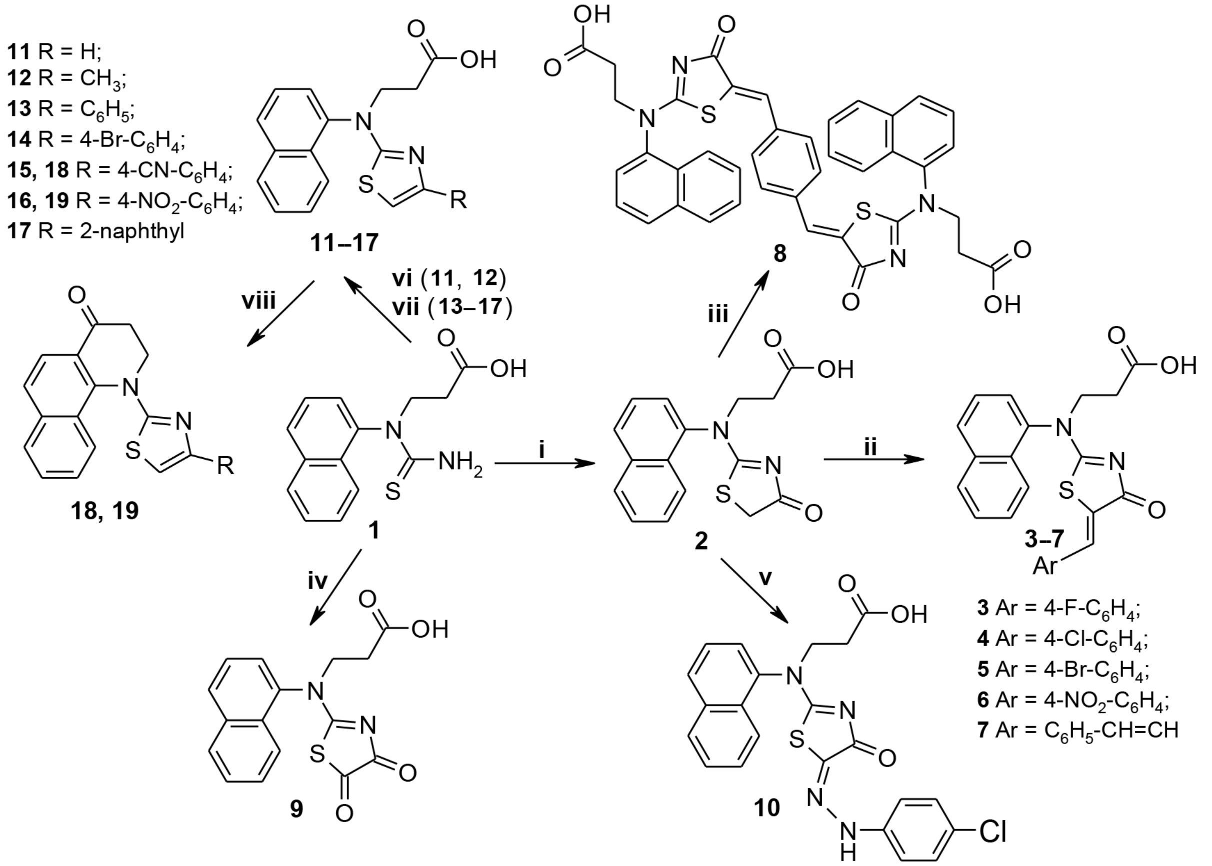
In the ^{1}H NMR spectrum of compound **2**, the signals ascribed to CH_2CO, NCH_2 and SCH_2 groups of protons are observed at 2.66, in the range of 4.57–4.63 and 3.91 ppm, respectively. The singlet at 12.40 ppm indicates the existence of a COOH group. In the ^{13}C NMR spectrum of this compound, the COOH, C=O and C=N groups of carbons gave rise to peaks at 171.96, 184.20 and 187.09 ppm, respectively.

The methylene group in the thiazolone ring easily participates in condensation reactions. Using this feature, the condensation of compound **2** with various carbaldehydes was investigated (Scheme 1). The reactions were performed in water in the presence of sodium carbonate and gave a single isomer (*Z*) [26]. The desired products **3–7** were isolated from the reaction mixtures by acidifying them with acetic acid to pH 6. In the same way, compound **8** was synthesized from dihydrothiazolone **2** and terephthaldehyde.

The interaction of oxalyl chloride and thioureido acid **1** in acetone, in the presence of catalytic amount of pyridine, gave 3-[(4,5-dioxo-4,5-dihydro-1,3-thiazol-2-yl)(naphthalen-1-yl)amino]propanoic acid **(9)**. The spectral lines at 179.97 and 181.33 ppm (2C=O) in the ^{13}C NMR spectrum is a reasonable evidence of the formed structure.

The coupling reaction between compound **2** and the appropriate diazonium salt was carried out. The reaction took place at the 5-position of the thiazolone ring and afforded the coloured thiazolone derivative – 3-({5-[2-(4-chlorophenyl)hydrazono]-4-oxo-4,5-dihydrothiazol-2-yl}(naphthalen-1-yl)amino)propanoic acid **(10)**.

The comparison of the ^{1}H NMR of the formed compound **10** with the initial one showed the increase in signals



i: $ClCH_2COOH$, CH_3COONa, 2-propanol, t°, 4 h; **ii:** ArCHO, Na_2CO_3, water, t°, 3 h, CH_3COOH to pH 6; **iii:** OHC-C_6H_4-CHO, Na_2CO_3, water, t°, 3 h, CH_3COOH to pH 6; **iv:** oxalyl chloride, acetone, pyridine, rt, 4 h; **v:** Cl-C_6H_4-$N^+{\equiv}NCl^-$, 0 °C, stirring; **vi:** 50% $ClCH_2CHO$ or $ClCH_2COCH_3$, Na_2CO_3, water, t°, 3 or 4 h, CH_3COOH to pH 6; **vii:** haloketone, acetone, 90 °C, 2 h, CH_3COONa; **viii:** Eaton's reagent, 80 °C, 1 h, NaOH to pH 8

Scheme 1. Synthesis of thiazole and thiazolone derivatives of aromatic protons and the arised singlet at 10.18 ppm, which was attributed to the NH group proton.

The interaction of thioureido acid **1** with chloroacetaldehyde gave 3-[naphthalene-1-yl(1,3-thiazol-2-yl)amino]propanoic acid **(11)**, and the reaction with chloroacetone afforded 3-[(4-methyl-1,3-thiazol-2-yl)(naphthalene-1-yl)amino] propanoic acid **(12)**. In the NMR spectra of compound **11** doublets at 6.66 and 7.20 ppm (SCH, NCH, ^{1}H NMR) and the resonance lines at 108.53 and 139.16 ppm (SCH, NCH, ^{13}C NMR) are the evidences of thiazole heterocycle formation. In the ^{1}H NMR spectrum of compound **12**, the additional singlet at 2.18 ppm was assigned to the CH_3 protons.

The reaction of the corresponding halocarbonyl compound with thioureido acid **1** was performed in acetone for 2 h. In order to obtain purer target compounds, the formed *N,N*-disubstituted β-alanine hydrobromides were separated from the reaction mixtures and then converted into insoluble bases by treating them with the aqueous sodium acetate.

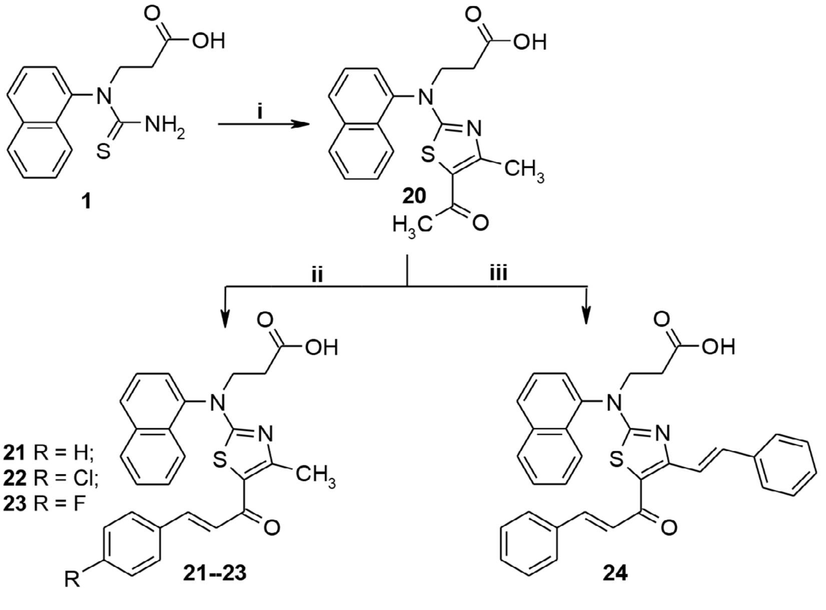
The formation of 4-substituted thiazoles was proven by comparing the NMR spectra of the newly synthesized compounds with the spectrum of **11**. In the ^{1}H NMR spectra of compounds **13–17**, signals of the NCH group protons are absent and the spectral lines of 4-C of the thiazole ring in the ^{13}C NMR spectra are observed in a weaker magnetic field, i. e. in the range of 148.31–150.09 ppm in comparison with the 139.16 ppm of **11**.

Some of the synthesized *N*-carboxyethyl-*N*-substituted aminothiazoles were used for the synthesis of quinolone-type compounds. As is known, such compounds can be prepared by heating *N*-aryl-β-alanines with strong dehydrating agents such as polyphosphoric acid or phosphorus pentoxide [27]. In such case, Eaton's reagent appeared to be a superior agent in the cyclization of compounds **15** and **16** containing a carboxyalkyl fragment. The reactions were carried out at 80 °C for 1 h. The reaction mixtures were afterwards diluted with water and neutralized with the 10% NaOH aqueous solution. Notably informative are the ^{13}C NMR spectra of the synthesized compounds **18** and **19**. For example, characteristic spectral resonances of the methylene groups of product **18** occur in lower magnetic fields in comparison with the initial compound **15**, and at 194.0 ppm there is visible a spectral line assigned to the C=O group of the newly formed heterocyclic fragment.

Chalcones are natural products belonging to flavonoids and are considered as intermediates in the biosynthesis of flavonoids. The α, β-unsaturated ketone moiety of chalcones is found in various biologically active compounds. Therefore, natural or synthetic chalcone derivatives exhibit diverse pharmacological activities [28–30].

For the synthesis of chalkones, the 3-[(5-acetyl-4-methyl-1,3-thiazol-2-yl)(naphthalen-1-yl)amino]propanoic acid **(20)** from thioureido acid **1** and 3-chloro-2,4-pentanedione was primarily prepared (Scheme 2). Two singlets at 2.24 ($OCC\underline{H}_3$) and 2.52 ($CC\underline{H}_3$) ppm in the ^{1}H NMR spectrum of compound **20** and the resonance lines at 18.58 ($C\underline{C}H_3$), 29.48 ($OC\underline{C}H_3$), 121.97 ($\underline{C}CH_3$) and 152.65 ($S\underline{C}=C$) ppm in the ^{13}C NMR prove the formation of a 5-acetyl-4-methylthiazole fragment.

Chalkones **21–23** were synthesized by the interaction of compound **20** with the appropriate aldehyde. The reaction was carried out at 8 °C for 72 h, and the desired product from the reaction mixture was separated by diluting it with water



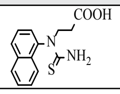
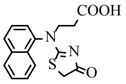
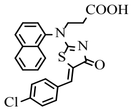
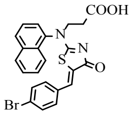
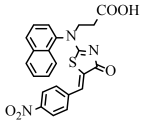
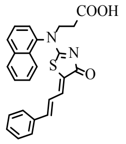
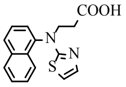
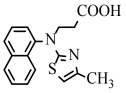
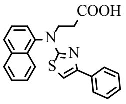
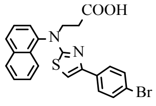
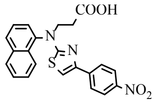
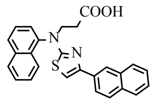
i: 3-chloro-2,4-pentanedione, acetone, t°, 4 h, water, CH_3COONa; **ii:** 10% NaOH, 2-propanol, 8 °C, 30 min, aromatic aldehyde, 8 °C, 72 h, water, 30% CH_3COOH to pH 6; **iii:** 10% NaOH, 2-propanol, benzaldehyde, t°, 4 h, water, 30% CH_3COOH to pH 6

Scheme 2. Synthesis and transformations of 3-[(5-acetyl-4-methyl-1,3-thiazol-2-yl)(naphthalen-1-yl)amino] propanoic acid (**20**) and acidifying with acetic acid to pH 6. The condensation of **20** with the aldehyde under reflux afforded compound **24**. For example, the increase of the signals in the aromatic region of the ^{1}H NMR spectrum of compound **21** in comparison with the same spectrum of the initial compound **20** and the resonance peak at 188.68 ppm in the ^{13}C NMR show a chalkone fragment in molecule **21**. The comparison of the ^{1}H NMR spectrum of compound **24** with the spectrum of **20** showed the absence of the characteristic singlets at 2.24 (OCC$\underline{H}_3$) and 2.52 (CC$\underline{H}_3$) ppm, but an increase in the signals of aromatic protons and four protons of two CH=CH groups is visible.

Evaluation of antibacterial activity of some of aminothiazole derivatives

The synthesized compounds **1, 2, 4–7** and **11–14, 16** and **17** were evaluated for their antibacterial properties (Table)

Table. The inhibition zone diameters of some synthesized compounds

Compound		Concentration of the solution, μg/mL						
No.	Structural formula	1000	500	250	125	50	25	12.5
		The diameters of inhibition zone, cm						
1		2.6	3.2	2.8	1.0	+	+	+
2		4.0	2.4	2.6	2.2	+	+	+
4		5.4	4.8	3.8	3.2	+	+	+
5		6.3	3.8	1.8	0.6	+	+	+
6		6.8	5.0	3.6	2.8	2.0	1.6	+
7		4.4	3.8	3.0	1.6	+	+	+
11		6.2	4.0	3.8	0.8	+	+	+
12		3.4	3.6	2.0	1.8	+	+	+
13		2.8	3.6	2.4	2.4	+	+	+
14		6.2	2.2	1.2	1.0	+	+	+
16		3.7	0.8	0.3	+	+	+	+
17		3.6	4.0	2.4	2.2	+	+	+
Ampicillin						4.6		

[+] The compound did not exhibit antibacterial activity.

against gram-negative non-spore forming rods of *Rhizobium radiobacter* which causes the crown gall bacterial infection – a bacterial disease of plants, especially fruit bushes and trees, characterized by large tumorlike galls on the roots and lower trunk. This bacterial infection produces galls on any part of the plant stem or roots, but usually where the root and stem join. The crown gall bacteria reside in the soil. Blown by the wind or moistened by rain, they cause the formation of galls. The tissue near the gall is crushed. If the vascular tissue is crushed, wilting can result from the restricted water movement. Crown gall is a very common disease affecting various herbaceous and woody plants.

The evaluation of the antibacterial activity was performed at the Laboratory of Biotechnology of the Kaunas University of Technology (Lithuania). The growth of bacteria and the antibacterial activity were determined using the Luria-Bertani (LB) nutrition medium. The following concentrations of solutions in dimethyl sulfoxide of the synthesized compounds were prepared: 1000, 500, 250, 125, 50, 25 and 12.5 μg/mL. The test microorganisms (50 μL) were added to an agar plate containing the LB growth medium and then covered with sterile paper discs. 25 μL of solution of the investigated compound was added dropwise to each disc and incubated at 37 °C for 24 h. After the incubation period, the diameters of the inhibition zone were measured. Ampicillin (50 μg/mL) was used as the positive control.

Some of the test compounds, including quinolones, were inactive against the *Rhizobium radiobacter* strain at all. Also, it should be noted that the solutions of 50, 25 and 12.5 μg/mL concentrations did not inhibit the growth of this strain of bacteria. Only compound **6** showed a moderate inhibition at the concentrations of 50 and 25 μg/mL.

The evaluation of the antibacterial activity against *Rhizobium radiobacter* revealed that the most active appeared to be two thiazolones, i. e. 3-{[(5*Z*)-5-(4-chlorobenzylidene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl](naphthalen-1-yl)amino}propanoic acid **(4)** and 3-{naphthalen-1-yl[(5*Z*)-5-(4-nitrobenzylidene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl]amino}propanoic acid **(6)**, which strongly differ from all the other test compounds.

Received 7 November 2016
Accepted 7 December 2016

References

1. S. J. Kashyap, P. K. Sharma, V. K. Garg, R. Dudhe, N. Kumar, *J. Adv. Sci. Res.*, **2**, 18 (2011).
2. S. Nadeem, M. Faiz Arshad, W. Ahsan, M. Shamsher Alam, *Int. J. Pharm. Sci. Drug. Res.*, **1(3)**, 136 (2009).
3. V. Mickevičius, A. Voskienė, I. Jonuškienė, et al., *Molecules*, **18(12)**, 15000 (2013).
4. R. Vaickelionienė, V. Mickevičius, G. Vaickelionis, M. Stasevych, O. Komarovska-Porokhnyavets, V. Novikov, *Arkivoc*, **v**, 303 (2015).
5. R. Vaickelioniene, K. Mickeviciene, K. Anusevicius, J. Siugzdaite, K. Kantminiene, V. Mickevicius, *Heterocycles*, **91(4)**, 747 (2015).
6. K. D. Hargrave, F. K. Hess, J. T. Oliver, *J. Med. Chem.*, **26**, 1158 (1983).
7. W. C. Patt, H. W. Hamilton, M. D. Taylor, et al., *J. Med. Chem.*, **35(14)**, 2562 (1992).
8. B. Narayana, K. K. Vijaya Raj, B. V. Ashalata, N. S. Kumari, B. K. Sarojini, *Eur. J. Med. Chem.*, **39**, 867 (2004).
9. J. C. Jean, L. D. Wise, B. W. Caprathe, H. Tecle, S. Bergmeier, *J. Med. Chem.*, **33**, 311 (1990).
10. R. N. Sharma, F. P. Xavier, K. K. Vasu, S. C. Chaturvedi, S. S. Pancholi, *J. Enzyme Inhib. Med. Chem.*, **24(3)**, 890 (2009).
11. P. Bhattacharya, J. T. Leonard, K. Roy, *Bioorg. Med. Chem.*, **13(4)**, 1159 (2005).
12. N. G. Ergenc, N. S. Capan, S. Gunay, M. Ozkirimli Gungor, S. Ozbey, E. Kendi, *Arch. Pharm. Pharm. Med. Chem.*, **332**, 343 (1999).
13. J. S. Cartner, S. Kramer, J. J. Talley, T. Penning, P. Collins, *Bioorg. Med. Chem. Lett.*, **9**, 1171 (1999).
14. A. Badore, M. F. Bordes, P. de Cointet, et al., *J. Med. Chem.*, **40**, 3393 (1997).
15. M. J. Rogers, E. Cundliffe, T. F. Mccutchan, *Antimicrob. Agents Chemother.*, **42(3)**, 715 (1966).
16. M. J. LaMarche, J. A. Leeds, A. Amaral, et al., *J. Med. Chem.*, **55(5)**, 2376 (2012).
17. J. Gao, J. A. Wells, *Chem. Biol. Drug Des.*, **79(2)**, 209 (2012).
18. W. Zhang, Q. Feng, Z. S. Wang, G. Zhou, *Chem. Asian J.*, **8(5)**, 939 (2013).
19. M.D. Najib Alam, S. K. Mandal, S. Ch. Debnath, *Rubber Chem. Technol.*, **85(1)**, 120 (2012).
20. D. Edmont, R. Rocher, C. Plisson, J. Chenault, *Bioorg. Med. Chem. Lett.*, **10**, 1831 (2000).
21. Y. Xia, Z.-Y. Yang, P. Xia, et al., *Bioorg. Med. Chem. Lett.*, **13**, 2891 (2003).
22. S. Nakamura, M. Kozuka, K. F. Bastow, et al., *Bioorg. Med. Chem.*, **13**, 4396 (2005).
23. B. d'A. Lucero, C. R. B. Gomes, I. C. De P. P. Frugulhetti, et al., *Bioorg. Med. Chem. Lett.*, **16**, 1010 (2006).
24. P. N. Kalaria, J. A. Makawana, Sh. P. Satasia, D. K. Raval, H.-L. Zhu, *Med. Chem. Commun.*, **5**, 1555 (2014).
25. X. Liu, L. Deng, H. Song, H. Jia, R. Wang, *Org. Lett.*, **13(6)**, 1494 (2011).
26. M. M. Chowdhry, D. M. P. Mingos, A. J. P. White, D. J. Williams, *J. Chem. Soc., Perkin Trans.* **1**, 3495 (2000).
27. C. Huang, J. H. Guo, H. M. Fu, M. L. Yuan, L. J. Yang, *Tetrahedron Lett.*, **56**, 3777 (2015).
28. S. Vogel, S. Ohmayer, G. Brunner, J. Heilmann, *Bioorg. Med. Chem.*, **16**, 4286 (2008).
29. N. J. Lawerence, R. P. Patterson, L.-L. Ooi, D. Cook, S. Ducki, *Bioorg. Med. Chem. Lett.*, **16**, 5844 (2006).
30. C.-T. Hsieh, T.-J. Hsieh, M. El-Shazly, et al., *Bioorg. Med. Chem. Lett.*, **22**, 3912 (2012).

Birutė Grybaitė, Ilona Jonuškienė, Rita Vaickelionienė, Vytautas Mickevičius

NAUJŲ *N,N*-DIPAKEISTŲJŲ 2-AMINOTIAZOLO DARINIŲ SINTEZĖ IR ANTIBAKTERINIS AKTYVUMAS

Santrauka

N-(1-naftil)-N-tiokarbamoil-β-alaniną veikiant skirtingais halogenketonais susintetinti pakeistieji aminotiazolai, o dėl monochloracto rūgšties poveikio gautas tiazolono darinys. Ištirta šio junginio kondensacija su aromatiniais aldehidais, diazonio druska. Tioureidorūgštį veikiant 3-chlor-2,4-pentandionu gauta 3-[(5-acetil-4-metil-1,3-tiazol-2-il)(naftalen-1-il)amino]propano rūgštis panaudota chalkono dariniams sintetinti. Nustatyta, kad naudojant tuos pačius reagentus kaip ir chalkonų sintezei, tačiau reakciją vykdant virimo temperatūroje, kondensacijoje dalyvauja ne tik tiazolo fragmente esanti acetilgrupė, bet ir metilgrupė. Atlikti dalies susintetintų junginių antibakterinio poveikio *Rhizobium radiobacter* padermės bakterijoms tyrimai ir nustatyti aktyviausi junginiai – tiazolono dariniai 3-{[(5Z)-5-(4-chlorbenziliden)-4-okso-4,5-dihidro-1,3-tiazol-2-il](naftalen-1-il)amino}propano rūgštis (**4**) ir 3-{naftalen-1-il[(5Z)-5-(4-nitrobenziliden)-4-okso-4,5-dihidro-1,3-tiazol-2-il]amino}propano rūgštis (**6**), kuri savo biologiniu aktyvumu ryškiai skiriasi nuo kitų tirtų junginių.