CHEMIJA. 2014. Vol. 25. No. 2. P. 107–114

Synthesis and antibacterial activity of *N*-carboxyethyl-*N*-(4-hydroxyphenyl)-2-aminothiazoles and dihydrothiazolones

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New 2-aminothiazole and 2-aminodihydrothiazole derivatives with carboxyethyl, aromatic, and heterocyclic moieties were synthesized from *N*-(4-hydroxyphenyl)-*N*-thiocarbamoyl-β-alanine as a starting material. This thioureido derivative was found to be a useful intermediate for the synthesis of various substituted thiazole derivatives. The structure of the new compounds was confirmed by chemical and spectroscopic methods. Antibacterial evaluation of synthesized compounds was explored against *Rhizobium radiobacter*. It was found that among all synthesized compounds, the highest antibacterial activity was exhibited by compound 3-[{5-[(2*E*)-3-(4-chlorophenyl)prop-2-enoyl]-4-methyl-1,3-thiazol-2-yl}(4-hydroxyphenyl)amino]propanoic acid at 75–1 000 μg/ml concentrations.

Key words: *N*-thiocarbamoyl-β-alanine, aminothiazole, dihydrothiazole, condensation, chalcone, antibacterial activity

INTRODUCTION

β-Amino acids and their fragments are found in biologically active compounds such as peptides, depsipeptides, lactones, alkaloids; also, in a free form they show interesting pharmacological effects [1, 2]. β-Lactame antibiotics penicillins, cephalosporins comprise the largest therapeutic class of antibiotics. *N*-substituted β-amino acids are used for the synthesis of heterocyclic compounds such as dihydrouracils and their 2-thioanalogues [3–6], quinolinones [7, 8], tetrahydropyridones [9, 10], quinazolinones [11, 12] benzodiazepinones [13]. A thiazole ring is naturally found in vitamin B_1 (thiamine). Thiamine is a water-soluble vitamin, and it helps in the normal functioning of the nervous system by its role in the synthesis of neurotransmitters such as acetylcholine [14]. Thiazoles and their derivatives are found to be associated with various biological activities such as antibacterial [15–17], fungicidal [18], analgesic and anti-inflammatory [19, 20], antihypertensive [21, 22], anti-HIV [23, 24], antitumor [25], antioxidant [26], herbicidal, insecticidal [27, 28], pseudomonal infection [29].

The aim of this work was to synthesize new potentially biologically active compounds containing *N*-substituted β-amino acids and thiazole moieties.

RESULTS AND DISCUSSION

Chemistry

One of the widely used methods of thiazole ring synthesis is the Hantzsch method. The starting compound *N*-(4-hydroxyphenyl)-*N*-thiocarbamoyl-β-alanine (**1**) was prepared by the published procedure [5]. The new substituted dihydrothiazoles **2–6** were synthesized as shown in Scheme 1. Firstly, we investigated the reaction of compound **1** with monochloroacetic acid with the purpose to find the optimal synthesis conditions. This reaction was performed in water using various types of bases (NaOH, Na_2CO_3, CH_3COONa) or without them. In all cases, the

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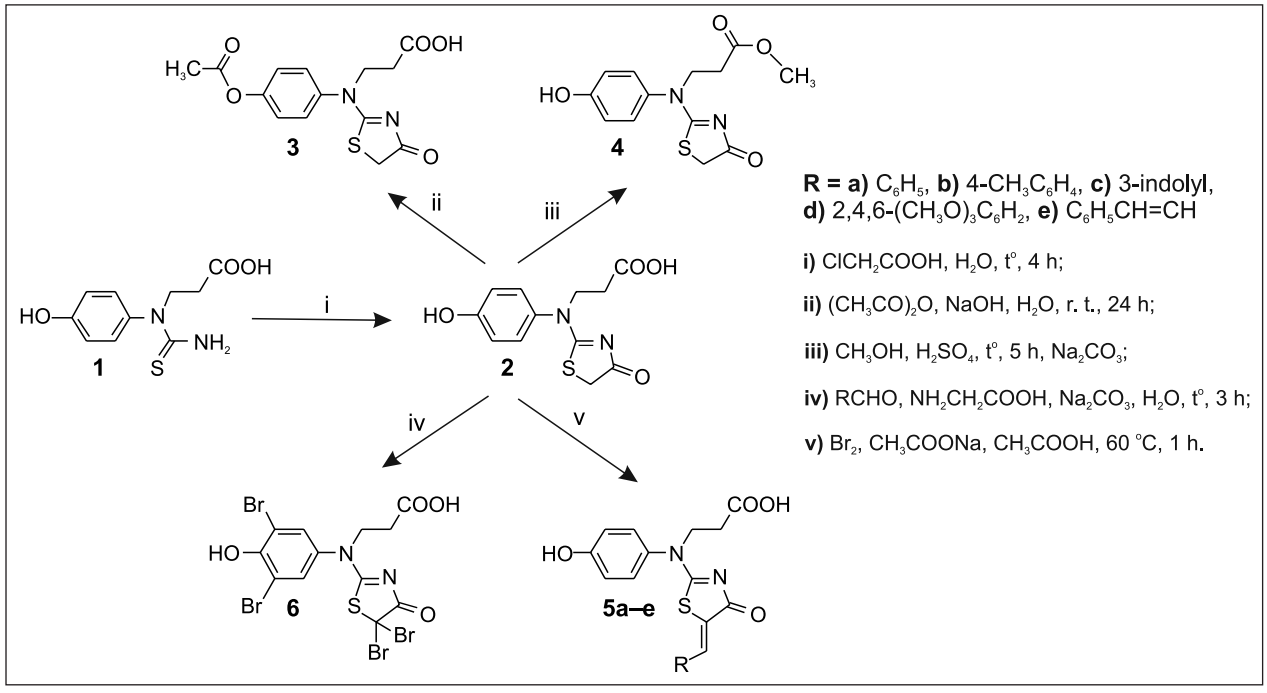


Scheme 1. Synthesis of substituted aminothiazolones 2–6

reaction was carried out for four hours at a mixture boiling temperature. As can be seen from the experimental data, the base basicity practically had no effect. After reaction without the base, sodium acetate must be added to the reaction mixture. The structure of compound **2** was confirmed by ^{1}H, ^{13}C NMR spectrum data. In the ^{1}H NMR spectrum of compound **2**, a singlet at 3.89 ppm shows CH_2 group protons of a newly formed thiazolone ring; this singlet was not visible in the spectrum of the initial compound **1**. In the ^{13}C NMR spectrum of this compound, two signals at 183.8 ppm (CO) and 187.1 ppm (C=N) characterictic of the thiazolone ring were observed.

Some chemical transformations of compound **2** were investigated. Compound **3** was obtained by acylation of 3-[(4-hydroxyphenyl)(4-oxo-4,5-dihydro-1,3-thiazol-2-yl) amino]propanoic acid (**2**) witch acetic anhydride. The reaction was carried out in water in the presence of sodium hydroxide for 24 h at room temperature. Heating dihydrothiazolone **2** in methanol for 5 h at 80 °C with a catalytic amount of H_2SO_4, compound **4** was obtained. The structure of compounds **3** and **4** was confirmed by ^{1}H NMR spectrum data. Intense singlets at 2.03 (compound **3**) and 3.30 (compound **4**) ppm were classified as methyl group signals.

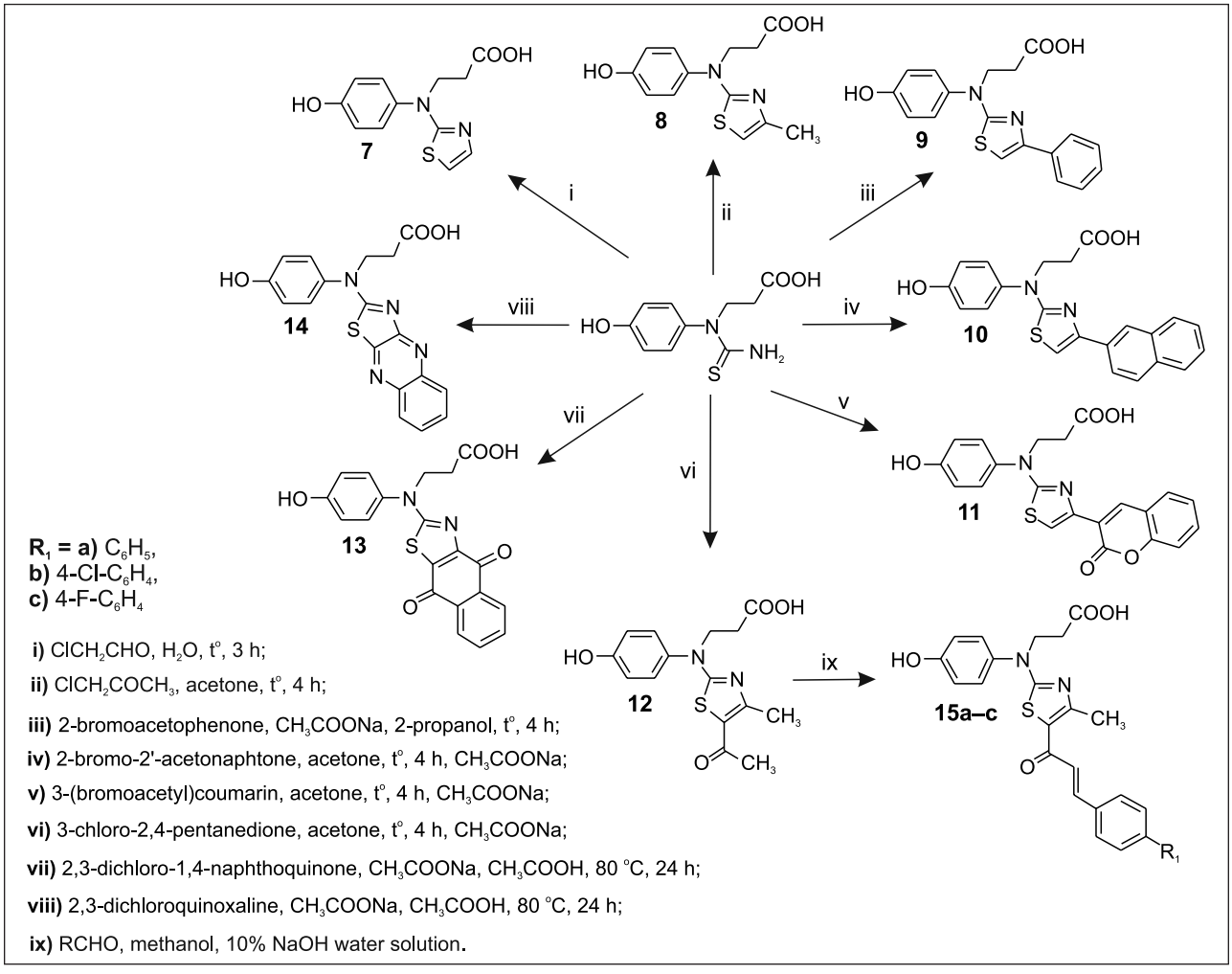
The methylene group in the thiazolone ring easily participates in condensation reactions with aromatic aldehydes. All these reactions were performed in water in the presence of sodium carbonate, and glycine was used as a bifunctional catalyst [30] which gives a single isomer (*Z*).

The formed salt was transferred to acids by acidifying the reaction mixture with acetic acid to pH 6. Analyzing ^{1}H, ^{13}C NMR spectra of compounds **5a–e** in the aromatics region revealed additional signals assigned to the connected phenyl ring. Also, their ^{1}H NMR spectra show that there are no thiazolone ring methylene group signals which can be seen in the spectrum of compound **2**. Bromination of compound **2** was performed in acetic acid at 60 °C and room temperature, which resulted in the same 3-[(3,5-dibromo-4-hydroxyphenyl)(5,5-dibromo-4-oxo-4,5-dihydro-1,3-thiazol-2-yl)amino]propanoic acid (**6**).

At the second stage of this work, the new substituted thiazoles **7–12** were synthesized as shown in Scheme 2. 3-[(4-Hydroxyphenyl)(1,3-thiazol-2-yl)amino]propanoic acid (**7**) was obtained from thioureido acid **1** and chloroacetaldehyde in a water solution. This reaction was performed at 50 °C because at higher temperatures resin products were formed. The ^{1}H NMR spectra of compound **7** exhibited two duplets – at 6.38 ppm and 6.79 ppm (SCH and NCH, respectively) for the newly formed thiazole cycle, while the signal originating from NH_2 disappeared. Also the new resonances at 107.9 ppm and 139.8 ppm in the ^{13}C NMR spectrum are typical of the NCH and SCH fragments of a thiazole ring. The substituted thiazoles **8–12** were synthesized from thioureido acid **1** and various haloketones in organic solvents – acetone or 2-propanol – at reflux. In all reactions, sodium acetate was used for aminothiazolium halide transfer into the base.

Naphthoquinone and quinoxaline-fused thiazoles **13** and **14** were synthesized by the interaction of compound **1** with 2,3-dichloro-1,4-naphthoquinone or 2,3-dichloroquinoxaline by stirring it in glacial acetic acid at 70–80 °C in the presence of sodium acetate for 24 h.

Using the well known aldol condensation (Claisen-Schmidt condensation) reaction chalkones **15a–c** were synthesized from compound **12** by the published procedure [31] and compounds were produced with an (*E*) configuration.



Scheme 2. Synthesis of substituted aminothiazoles 7–15

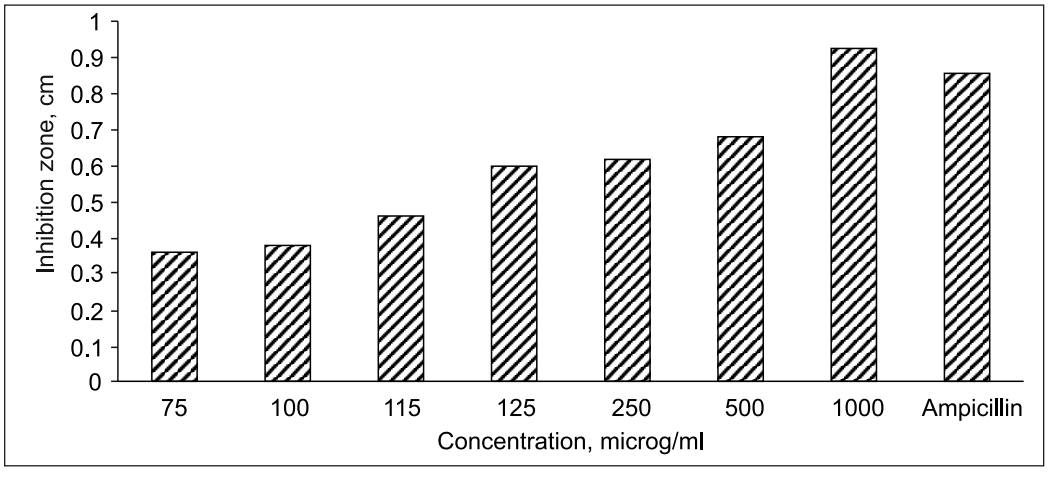


Figure. Antibacterial activity (75–1 000 μg/ml) of compound **15b** against *Rhizobium radiobacter*

Antibacterial activity

It was found that compounds **6, 10, 12** and **15a–c** exhibited antibacterial activity against *Rhizobium radiobacter* at 1 000 μg/ml concentration, however, compounds **5a, 5b, 5c, 5e, 7, 9, 11,** and **14** did not show antibacterial activity against the tested microorganism. The thiazoles with chalcone moiety displayed better potential antibacterial activity. Among all synthesized compounds, the highest antibacterial activity was exhibited by compound **15b** containing a chloro atom in a chalcone fragment in comparison with the activity of thiazoles containing phenylprop-2-enoyl- or (4-fluorophenyl) prop-2-enoyl substituents (Figure). Compound **15c** exhibited lower antibacterial activity at 500–1 000 μg/ml and the one for compound **15a** was lower at 1 000 μg/ml concentration.

EXPERIMENTAL

TLC was performed with Merch, Silica gel 60 F_{254} (Kieselgel 60 F_{254}) silica gel plates. The ^{1}H and ^{13}C NMR spectra were recorded on Varian Unity Inova (^{1}H 300 MHz, ^{13}C 75 MHz) and Bruker BioSpin GmbH (^{1}H 400 MHz, ^{13}C 100 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 (Büchi Corporation, USA) and are uncorrected.

3-[(4-Hydroxyphenyl)(4-oxo-4,5-dihydro-1,3-thiazol-2-yl) amino]propanoic acid (2)

Method A. *N*-(4-Hydroxyphenyl)-*N*-thiocarbamoyl-β-alanine (**1**) (1.20 g, 5 mmol), sodium carbonate (1.17 g, 11 mmol) were dissolved in water (10 ml), then chloroacetic acid (1.04 g, 11 mmol) was added, and the reaction mixture was refluxed for 4 h. After cooling to room temperature, the mixture was acidified with acetic acid to pH 6. The precipitate was filtered and washed with water. Yield 0.89 g (63%).

Method B. Thioureido acid **1** (1.20 g, 5 mmol) and sodium acetate (0.90 g, 11 mmol) were dissolved in water (10 ml), then chloroacetic acid (1.04 g, 11 mmol) was added, and the reaction mixture was refluxed for 4 h. After cooling to room temperature, the precipitate was filtered and washed with water. Yield 0.94 g (67%).

Method C. Thioureido acid **1** (1.20 g, 5 mmol), sodium hydroxide (0.44 g, 11 mmol) were dissolved in water (10 ml), then chloroacetic acid (1.04 g, 11 mmol) was added, and the reaction mixture was refluxed for 4 h. After cooling to room temperature, the precipitate was filtered and washed with water. Yield 0.84 g (60%).

Method D. Thioureido acid **1** (1.20 g, 5 mmol) was dissolved in water (10 ml), then chloroacetic acid (1.04 g, 11 mmol) was added, and the reaction mixture was refluxed for 4 h. After cooling to room temperature, the precipitate was filtered and washed with water. Yield 0.90 g (64%), m. p. 205–206 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.53 (t, 2H, J = 7.5 Hz, CH_2CO), 3.89 (s, 2H, SCH_2), 4.09 (t, 2H, J = 7.4 Hz, NCH_2), 6.85 (d, 2H, J = 8.7 Hz, H_{Ar}), 7.23 (d, 2H, J = 8.7 Hz, H_{Ar}), 10.24 (br. s, 1H, OH), 12.08 (br. s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 32.0 ($\underline{C}H_2CO$), 40.6 (SCH_2), 50.0 (NCH_2), 116.2, 129.4, 131.3, 158.3 (C_{Ar}), 172.1, 183.8, 187.1 (COOH, CO, C=N). IR (KBr), ν, cm^{-1}: 3 282, 3 201 (OH), 1 713, 1 648 (CO), 1 528 (C=N). Found, %: C, 51.53; H, 4.38; N, 10.26. Anal. calcd. for $C_{12}H_{12}N_2O_4S$, %: C, 51.42; H, 4.32; N, 9.99.

3-{[4-(Acetyloxy)phenyl](4-oxo-4,5-dihydro-1,3-thiazol-2-yl)amino}propanoic acid (3)

3-[(4-Hydroxyphenyl)(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)amino]propanoic acid (**2**) (1.40 g, 5 mmol), sodium hydroxide (0.60 g, 15 mmol) were dissolved in water. Then acetic anhydride (1 ml, 10 mmol) was added dropwise, and the mixture was stirred at room temperature for 24 h. The solvent was evaporated with a rotary evaporator. Yield 1.24 g (77%), m. p. 198–199 °C (from water). ^{1}H NMR (400 MHz, CD_3OD, δ, ppm): 2.03 (s, 3H, CCH_3), 2.50 (t, 2H, J = 7.4 Hz, CH_2CO), 3.84 (s, 2H, SCH_2), 4.20 (t, 2H, J = 7.4 Hz, NCH_2), 6.88–7.20 (m, 4H, H_{Ar}). IR (KBr), ν, cm^{-1}: 3 438 (OH), 1 706, 1 698, 1 640 (CO), 1 560 (C=N), 1 021 (C-O-C). Found, %: C, 52.23; H, 4.38; N, 8.59. Anal. calcd. for $C_{14}H_{14}N_2O_5S$, %: C, 52.17; H, 4.38; N, 8.69.

Methyl 3-[(4-hydroxyphenyl)(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)amino]propanoate (4)

Thiazolone derivative **2** (0.70 g, 2.5 mmol), methanol (30 ml), and the catalytic amount of concentrated sulfuric acid (10 drops) were refluxed of 6 h. Then 60 ml of sodium carbonate (15%) was added to neutralize H_2SO_4. The liquid phase was evaporated with a rotary evaporator, and the precipitate was purified by chromatography on a silica gel 60 column (acetone : hexane 1 : 1). Yield 0.47 g (64%), m. p. 115–116 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.70 (t, 2H, J = 7.2 Hz, CH_2CO), 3.60 (s, 3H, OCH_3), 3.87 (s, 2H, SCH_2), 4.27 (t, 2H, J = 7.2 Hz, NCH_2), 6.99 (d, 2H, J = 8.8 Hz, H_{Ar}), 7.11 (d, 2H, J = 8.8 Hz, H_{Ar}), 8.24 (br. s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 32.3 ($\underline{C}H_2CO$), 41.1 (SCH_2), 50.8 (NCH_2), 52.1 ($COO\underline{C}H_3$), 117.1, 129.0, 131.8, 158.29 (C_{Ar}), 171.4, 185.6, 189.1 ($\underline{C}OOCH_3$, CO, C=N). IR (KBr), ν, cm^{-1}: 3 251 (OH), 1 745 (CO), 1 579 (C=N). Found, %: C, 53.01; H, 4.69; N, 9.46. Anal. calcd. for $C_{13}H_{14}N_2O_4S$, %: C, 53.05; H, 4.79; N, 9.52.

General method of synthesis of compounds 5a–e

A mixture of compound **2** (1.40 g, 5 mmol), the corresponding aldehyde (6 mmol), sodium carbonate (1.59 g, 15 mmol), glycine (0.38 g, 5 mmol), and water (30 ml) was refluxed for 3 h. Then the reaction mixture was acidified with acetic acid to pH 6. The precipitate was filtered and washed with water. Purification was performed by dissolving crystals in 15% aqueous sodium carbonate, filtering, and acidifying the filtrate with acetic acid to pH 6.

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

Yield 1.40 g (76%), m. p. 218–219 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.59 (t, 2H, J = 7.3 Hz, CH_2CO), 4.21 (t, 2H, J = 7.3 Hz, NCH_2), 6.87–7.49 (m, 9H, H_{Ar}), 7.62 (s, 1H, CH), 11.25 (br. s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 32.0 ($\underline{C}H_2CO$), 50.0 (NCH_2), 116.4, 129.3, 129.4, 129.5, 129.6, 129.8, 130.2, 130.9, 133.8, 158.6 (C_{Ar}, S-$\underline{C}$=$\underline{C}$H), 172.0, 176.9, 179.7 (COOH, CO, C=N). IR (KBr), ν, cm^{-1}: 3 650, 3 156 (OH), 1 728, 1 663 (C=O), 1 514 (C=N), 1 347 (C-S). Found, %: C, 61.85; H, 4.42; N, 7.69. Anal. calcd. for $C_{19}H_{16}N_2O_4S$, %: C, 61.94; H, 4.38; N, 7.60.

3-{(4-Hydroxyphenyl)[(5Z)-5-(4-methylbenzylidene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl]amino}propanoic acid (5b)

Yield 1.76 g (92%), m. p. 225–226 °C. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.29 (s, 3H, CH_3), 2.60 (t, 2H, *J* = 7.4 Hz, CH_2CO), 4.20 (t, 2H, *J* = 7.3 Hz, NCH_2), 6.87–7.37 (m, 8H, H_{Ar}), 7.59 (s, 1H, CH), 10.12 (br. s, 1H, OH), 12.38 (br. s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 21.1 ($\underline{C}H_3$), 31.9 ($\underline{C}H_2CO$), 49.9 (NCH_2), 116.3, 127.8, 128.3, 129.5, 129.6, 129.9, 130.3, 131.0, 139.9, 158.5 (C_{Ar}, S-$\underline{C}$=$\underline{C}$H), 172.0, 176.8, 179.8 (COOH, CO, C=N). IR (KBr), ν, cm^{-1}: 3 849, 3 305 (OH), 1 699, 1 645 (CO), 1 515 (C=N), 1 362 (C-S). Found, %: C, 62.93; H, 4.65; N, 7.28. Anal. calcd. for $C_{20}H_{18}N_2O_4S$, %: C, 62.81; H, 4.74; N, 7.33.

3-{(4-Hydroxyphenyl)[(5*Z*)-5-(1*H*-indol-3-ylmethylidene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl]amino}propanoic acid (5c)

Yield 1.43 g (70%), m. p. 158–159 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.41 (t, 2H, *J* = 7.4 Hz, CH_2CO), 4.15 (t, 2H, *J* = 7.4 Hz, NCH_2), 6.87–7.81 (m, 9H, H_{Ar}), 7.85 (1H, s, CH), 8.27 (1H, s, NH), 9.29 (1H, s, OH), 11.99 (1H, s, COOH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 34.7 ($\underline{C}H_2CO$), 51.5 (NCH_2), 110.9, 112.5, 116.5, 118.2, 120.7, 121.9, 122.8, 123.4, 126.9, 127.5, 129.5, 131.2, 136.4, 159.1 (C_{Ar}, S-$\underline{C}$=$\underline{C}$H), 173.5, 175.3, 180.3 (COOH, CO, C=N). IR (KBr), ν, cm^{-1}: 3 855, 3 243 (OH), 1 703, 1 662 (CO), 1 538 (C=N), 1 363 (C-S). Found, %: C, 62.08; H, 4.15; N, 10.24. Anal. calcd. for $C_{21}H_{17}N_3O_4S$, %: C, 61.90; H, 4.21; N, 10.31.

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

Yield 2.09 g (91%), m. p. 225–226 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.57 (t, 2H, *J* = 7.4 Hz, CH_2CO), 3.70, 3.79 (2s, 9H, OCH_3), 4.14 (t, 2H, *J* = 7.4 Hz, NCH_2), 6.21 (s, 1H, H_{Ar}), 6.86 (d, 2H, *J* = 8.7 Hz, H_{Ar}), 7.28 (d, 2H, *J* = 8.7 Hz, H_{Ar}), 7.68 (s, 1H, CH), 10.20 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 32.0 ($\underline{C}H_2CO$), 49.1 (NCH_2), 55.5, 55.6 (CH_3), 90.9, 103.9, 116.1, 123.3, 128.9, 129.6, 131.2, 158.2, 159.2, 163.2 (C_{Ar}, S-$\underline{C}$=$\underline{C}$H), 172.1, 177.3, 180.3 (COOH, CO, C=N). IR (KBr), ν, cm^{-1}: 3 847, 3 269 (OH), 1 727, 1 682 (CO), 1 519 (C=N), 1 320 (C-S), 1 296, 1 271 (CH_3-O). Found, %: C, 57.52; H, 4.79; N, 6.35. Anal. calcd. for $C_{22}H_{22}N_2O_7S$, %: C, 57.63; H, 4.84; N, 6.11.

3-[(4-Hydroxyphenyl)-4-oxo-5-(3-phenylprop-2-en-1-ylidene)-4,5-dihydro-1,3-thiazol-2-yl}amino]propanoic acid (5e)

Yield 1.71 g (87%), m. p. 187–188 °C. ^{1}H NMR (700 MHz, DMSO-d_6, δ, ppm): 2.46 (t, 2H, *J* = 7.4 Hz, CH_2CO), 4.13 (t, 2H, *J* = 7.5 Hz, NCH_2), 6.86 (m, 1H, CH=C$\underline{H}$-CH=), 6.85–8.59 (m, 9H, H_{Ar}), 7.10 (d, 1H, *J* = 15.2 Hz, C$\underline{H}$=CH-CH=), 7.25 (d, 1H, *J* = 11.3 Hz, CH=CH-C$\underline{H}$=), 10.26 (br. s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 33.4 ($\underline{C}H_2CO$), 50.6 (NCH_2), 116.4, 125.2, 127.6, 128.8, 129.2, 129.5, 129.8, 131.2, 132.1, 135.9, 141.5, 158.8 (C_{Ar}, $\underline{C}$H=$\underline{C}$H-$\underline{C}$H=), 173.1, 176.0, 179.3 (COOH, CO, C=N). IR (KBr), ν, cm^{-1}: 3 866 (OH), 1 720, 1 667 (CO), 1 511 (C=N), 1 355 (C-S). Found, %: C, 63.79; H, 4.67; N, 7.21. Anal. calcd. for $C_{21}H_{18}N_2O_4S$, %: C, 63.95; H, 4.60; N, 7.10.

3-[(3,5-Dibromo-4-hydroxyphenyl)(5,5-dibromo-4-oxo-4,5-dihydro-1,3-thiazol-2-yl)amino]propanoic acid (6)

Compound **2** (0.70 g, 2.5 mmol) and sodium acetate (0.82 g, 10 mmol) were dissolved in 10 ml of acetic acid. Then bromine (1.60 g, 10 mmol in 5 ml of acetic acid) was slowly added dropwise, and the mixture was heated (60 °C) for 1 h. After cooling to room temperature, the mixture was diluted with water (30 ml), the precipitate was filtered and crystallized from 2-propanol. Yield 1.03 g (69%), decomposition at 92–93 °C (2-propanol). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.62 (t, 2H, *J* = 7.3 Hz, CH_2CO), 4.20 (t, 2H, *J* = 7.3 Hz, NCH_2), 7.86 (s, 2H, H_{Ar}), 10.74 (br. s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 32.0 ($\underline{C}H_2CO$), 50.1 (NCH_2), 52.0 (S$\underline{C}Br_2CO$), 111.8, 131.3, 132.0, 152.9 (C_{Ar}), 172.0, 176.0, 180.1 (COOH, CO, C=N). IR (KBr), ν, cm^{-1}: 3 614, 3 059 (OH), 1 721, 1 697 (CO), 1 544 (C=N), 1 354 (C-S). Found, %: C, 24.11; H, 1.30; N, 4.62. Anal. calcd. for $C_{12}H_8Br_4N_2O_4S$, %: C, 24.19; H, 1.35; N, 4.70.

3-[(4-Hydroxyphenyl)(1,3-thiazol-2-yl)amino]propanoic acid (7)

A mixture of thioureido acid **1** (1.20 g, 5 mmol), chloroacetaldehyde 50% aqueous solution (3.5 ml, 10 mmol) and water (20 ml) was refluxed for 2 h. Then sodium acetate (0.82 g, 10 mmol) was added, and the mixture was stirred for 5 min at room temperature. The precipitate was filtered and washed with water. Purification was performed by dissolving crystals in 15% aqueous sodium carbonate, filtering and acidifying the filtrate with acetic acid to pH 6. Yield 0.61 g (46%), m. p. 145–146 °C. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.55 (t, 2H, *J* = 7.4 Hz, CH_2CO), 3.99 (t, 2H, *J* = 7.5 Hz, NCH_2), 6.38 (d, 1H, *J* = 3.6 Hz, SCH), 6.79 (d, 1H, *J* = 3.6 Hz, NCH), 6.82–7.20 (m, 4H, H_{Ar}), 9.76 (br. s, 1H, OH), 12.19 (br. s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 32.4 ($\underline{C}H_2CO$), 48.1 (NCH_2), 107.9 (NCH), 116.6, 129.1, 135.8, 139.8, 157.0 (C_{Ar}, SCH), 170.0, 172.5 (COOH, C=N). IR (KBr), ν, cm^{-1}: 3 653, 3 325 (OH), 3 116 (C-H), 1 682 (CO), 1 517 (C=N). Found, %: C, 54.46; H, 4.30; N, 10.31. Anal. calcd. for $C_{12}H_{12}N_2O_3S$, %: C, 54.53; H, 4.58; N, 10.60.

3-[(4-Hydroxyphenyl)(4-methyl-1,3-thiazol-2-yl)amino]propanoic acid (8)

Thioureido acid **1** (1.20 g, 5 mmol), chloroacetone (0.70 ml, 6 mmol), and acetone (15 ml) were refluxed for 4 h. Then the reaction mixture was diluted with water (30 ml), and sodium acetate (0.82 g, 10 mmol) was added. After stirring for 10 min at room temperature, the precipitate was filtered and washed with water. Yield 0.81 g (58%), m. p. 146–147 °C. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.13 (s, 3H, CH_3), 2.64 (t, 2H, *J* = 7.3 Hz,

CH_2CO), 4.15 (t, 2H, J = 7.3 Hz, NCH_2), 6.28 (s, 1H, SCH), 7.26–7.47 (m, 4H, H_{Ar}), 9.86 (br. s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 17.3 (CH_3), 32.4 ($\underline{C}H_2CO$), 48.3 (NCH_2), 102.7, 126.7, 127.1, 130.0, 144.5, 157.3 (C_{Ar}, SCH, $\underline{C}CH_3$), 170.2, 172.6 (COOH, C=N). IR (KBr), ν, cm^{-1}: 3 167 (OH), 1 725 (CO), 1 513 (C=N). Found, %: C, 56.04; H, 4.98; N, 10.02. Anal. calcd. for $C_{13}H_{14}N_2O_3S$, %: C, 56.10; H, 5.07; N, 10.07.

3-[(4-Hydroxyphenyl)(4-phenyl-1,3-thiazol-2-yl)amino] propanoic acid (9)

Thioureido acid **1** (1.20 g, 5 mmol), 2-bromoacetophenone (1.16 g, 6 mmol), and sodium acetate (0.57 g, 7 mmol) were refluxed in 2-propanol (10 ml) for 4 h. Then the reaction mixture was diluted with water (40 ml). The formed precipitate was purified in the same way as compounds **5a–d**. Yield 1.26 g (74%), m. p. 174–175 °C. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.65 (t, 2H, J = 7.3 Hz, CH_2CO), 4.11 (t, 2H, J = 7.3 Hz, NCH_2), 6.83–7.87 (m, 9H, H_{Ar}), 7.07 (s, 1H, S-CH), 9.77 (br. s, 1H, OH), 12.28 (br. s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 32.4 ($\underline{C}H_2CO$), 48.5 (NCH_2), 102.6, 116.6, 125.7, 127.5, 128.6, 129.1, 134.8, 135.8, 150.4, 157.0 (C_{Ar}, S$\underline{C}$H=$\underline{C}$), 170.1, 172.8 (COOH, C=N). IR (KBr), ν, cm^{-1}: 3 149, 3 111 (OH), 1 706 (CO), 1 513 (C=N). Found, %: C, 63.81; H, 4.84; N, 8.12. Anal. calcd. for $C_{18}H_{16}N_2O_3S$, %: C, 63.51; H, 4.74; N, 8.23.

3-{(4-Hydroxyphenyl)[4-(naphthalen-2-yl)-1,3-thiazol-2-yl]amino}propanoic acid (10)

A mixture of thioureido acid (0.60 g, 2.5 mmol) and 2-bromo-2'-acetonaphtone (0.75 g, 3 mmol) was refluxed for 4 h in acetone (10 ml). Then a solution of sodium acetate (0.98 g, 12 mmol) in water (40 ml) was added. The precipitate was filtered and washed with water. In this purification process, KOH 10% aqueous solution was used (the same technique as for compounds **5a–d**). Yield 0.77 g (79 %), m. p. 201–202 °C. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.68 (t, 2H, J = 7.2 Hz, CH_2CO), 4.19 (t, 2H, J = 7.2 Hz, NCH_2), 6.81–8.07 (m, 11H, H_{Ar}), 8.40 (s, 1H, S-CH), 11.06 (br. s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 32.6 ($\underline{C}H_2CO$), 48.4 (NCH_2), 103.5, 116.6, 124.1, 124.2, 126.0, 126.4, 127.6, 128.1, 128.2, 129.2, 132.3, 132.5, 133.2, 135.7, 150.4, 157.1 (C_{Ar}, S$\underline{C}$H=$\underline{C}$), 170.4, 172.9 (COOH, C=N). IR (KBr), ν, cm^{-1}: 3 821, 3 323 (OH), 1 703 (CO), 1 511 (C=N). Found, %: C, 67.53; H, 4.60; N, 7.08. Anal. calcd. for $C_{22}H_{18}N_2O_3S$, %: C, 67.68; H, 4.65; N, 7.17.

3-{(4-Hydroxyphenyl)[4-(2-oxo-2*H*-chromen-3-yl)-1,3-thiazol-2-yl]amino}propanoic acid (11)

Thioureido acid **1** (0.60 g, 2.5 mmol), 3-(bromoacetyl) coumarin (0.80 g, 3 mmol) were refluxed for 4 h in acetone (10 ml). Then a solution of sodium acetate (0.98 g, 12 mmol) in water (40 ml) was added. The formed crystals were purified in the same way as compound **10**. Yield 0.65 g (64%), decomposition at 185–186 °C. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.63 (t, 2H, J = 7.2 Hz, CH_2CO), 4.16 (t, 2H, J = 7.2 Hz, NCH_2), 6.86–7.89 (m, 9H, H_{Ar}), 8.64 (s, 1H, SCH), 11.07 (br. s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 32.5 ($\underline{C}H_2CO$), 48.3 (NCH_2), 109.7, 115.9, 116.7, 119.3, 120.5, 124.8, 128.9, 129.2, 131.6, 135.4, 138.4, 143.9, 152.3, 157.2, 158.8 (C_{Ar}, S$\underline{C}$H=$\underline{C}$), 169.6, 172.8 (COOH, C=N). IR (KBr), ν, cm^{-1}: 3 856, 3 151 (OH), 1 703, 1 698 (CO), 1 513 (C=N). Found, %: C, 61.64; H, 3.87; N, 6.82. Anal. calcd. for $C_{21}H_{16}N_2O_5S$, %: C, 61.76; H, 3.95; N, 6.86.

3-[(5-Acetyl-4-methyl-1,3-thiazol-2-yl)(4-hydroxyphenyl) amino]propanoic acid (12)

A mixture of thioureido acid **1** (0.60 g, 2.5 mmol), 3-chloro-2,4-pentanedione (0.68 ml, 6 mmol), and acetone (20 ml) was refluxed for 4 h and diluted with water (40 ml). Then the reaction mixture was cooled to room temperature, and sodium acetate (0.99 g, 12 mmol) was added. After 5 min of stirring, the precipitate was filtered and purified in the same way as compounds **5a–d**. Yield 0.44 g (55%), m. p. 178–179 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.28 (s, 3H, $OCCH_3$), 2.48 (s, 3H, CCH_3), 2.55 (t, 2H, J = 7.3 Hz, CH_2CO), 4.07 (t, 2H, J = 7.3 Hz, NCH_2), 6.87 (d, 2H, J = 8.7 Hz, H_{Ar}), 7.20 (d, 2H, J = 8.7 Hz, H_{Ar}), 9.88 (br. s, 1H, OH), 12.32 (br. s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 18.6 ($C\underline{C}H_3$), 29.6 ($CO\underline{C}H_3$), 32.3 ($\underline{C}H_2CO$), 48.0 (NCH_2), 116.3, 122.4, 128.9, 134.5, 157.6, 157.7 (C_{Ar}, $\underline{C}CH_3$, S$\underline{C}$=C), 171.4, 172.5, 188.7 (COOH, C=N, $\underline{C}OCH_3$). IR (KBr), ν, cm^{-1}: 3 886, 3 301 (OH), 1 705, 1 654 (CO), 1 512 (C=N). Found, %: C, 56.43; H, 4.96; N, 8.60. Anal. calcd. for $C_{15}H_{16}N_2O_4S$, %: C, 56.24; H, 5.03; N, 8.74.

3-[(4,9-Dioxo-4,9-dihydronaphtho[2,3-*d*][1,3]thiazol-2-yl)(4-hydroxyphenyl)amino]propanoic acid (13)

A mixture of thioureido acid **1** (2.40 g, 10 mmol), 2,3-dichloro-1,4-naphthoquinone (2.72 g, 12 mmol), sodium acetate (1.50 g, 18 mmol), and acetic acid (50 ml) was stirred at 80 °C for 24 h. The chilled reaction mixture was diluted with water (150 ml). Purification was performed by dissolving the compound crystals in 10% aqueous KOH (250 ml), filtering, and acidifying the filtrate with acetic acid to pH 6. Yield 2.17 g (55%), m. p. 226–227 °C. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.66 (t, 2H, J = 7.2 Hz, CH_2CO), 4.28 (t, 2H, J = 7.1 Hz, NCH_2), 6.82–8.05 (m, 8H, H_{Ar}), 10.05 (br. s, 1H, OH), 12.39 (br. s, 1H, COOH). IR (KBr), ν, cm^{-1}: 3 184 (OH), 1 714, 1 637, 1 619 (CO), 1 513 (C=N). Found, %: C, 60.79; H, 3.52; N, 7.02. Anal. calcd. for $C_{20}H_{14}N_2O_5S$, %: C, 60.91; H, 3.58; N, 7.10.

3-[(4-Hydroxyphenyl)([1,3]thiazolo[4,5-*b*]quinoxalin-2-yl)amino]propanoic acid (14)

In acetic acid (20 ml), thioureido acid **1** (0.60 g, 2.5 mmol), 2,3-dichloroquinoxaline (0.60 g, 3 mmol) and sodium acetate (0.49 g, 6 mmol) were stirred at 80 °C for 24 h. The crystals were precipitated by diluting the reaction mixture with water (60 ml). The purification process was same as for compound **10** and repeated 2 times. Yield 0.59 g (64%), m. p. 175–176 °C. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.69 (t, 2H, J = 7.2 Hz, CH_2CO), 4.28 (t, 2H, J = 7.0 Hz, NCH_2), 6.90–7.96 (m, 8H,

H_{Ar}), 10.05 (br. s, 1H, OH), 12.24 (br. s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 31.9 ($\underline{C}H_2CO$), 48.8 (NCH_2), 116.8, 127.0, 127.6, 128.0, 129.1, 129.5, 132.6, 138.1, 140.7, 154.2, 158.3, 158.7 (C_{Ar}, C=N), 170.5, 172.2 (COOH, S-C=N). IR (KBr), ν, cm^{-1}: 3 886, 3 060 (OH), 1 716 (CO), 1 610, 1 593, 1 514 (C=N). Found, %: C, 58.87; H, 3.68; N, 15.23. Anal. calcd. for $C_{18}H_{14}N_4O_3S$, %: C, 59.01; H, 3.85; N, 15.29.

General method of synthesis of compounds 15a–c

Compound **12** (0.50 g, 1.6 mmol) in methanol (5 ml) was added dropwise to a cooled solution (0 °C) of corresponding aromatic aldehydes (1.6 mmol) in 10% NaOH water solution (5 ml). The solution was stirred at 0 °C for 1.5 h and then at room temperature for 24 h. Then reaction mixture was diluted with water, acidified with acetic acid to pH 6. The precipitate was filtered and purified in the same way as compound **10**.

3-[(4-Hydroxyphenyl){4-methyl-5-[(2*E*)-3-phenylprop-2-enoyl]-1,3-thiazol-2-yl}amino]propanoic acid (15a)

Yield 0.48 g (73%), m. p. 121–122 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.57 (t, 2H, *J* = 7.4 Hz, CH_2CO), 2.60 (s, 3H, CH_3), 4.10 (t, 2H, *J* = 7.3 Hz, NCH_2), 6.88–7.72 (m, 9H, H_{Ar}), 7.20 (d, 1H, *J* = 15.5 Hz, CO-C$\underline{H}$=CH), 7.53 (d, 1H, *J* = 15.4 Hz, CO-CH=C$\underline{H}$), 10.05 (br. s, 1H, OH), 12.29 (br. s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 19.2 (CH_3), 32.3 ($\underline{C}H_2CO$), 48.2 (NCH_2), 116.8, 122.2, 124.7, 128.6, 128.9, 129.0, 130.3, 134.4, 134.5, 141.6, 157.7, 159.1 (C_{Ar}, $\underline{C}CH_3$, $\underline{C}$-CO-$\underline{C}$H=$\underline{C}$H), 171.7, 172.4, 180.3 (COOH, CO, C=N). IR (KBr), ν, cm^{-1}: 3 179 (OH), 1 713, 1 639 (CO), 1 514 (C=N), 1 332 (C-S). Found, %: C, 64.73; H, 4.89; N, 6.78. Anal. calcd. for $C_{22}H_{20}N_2O_4S$, %: C, 64.69; H, 4.94; N, 6.86.

3-[{5-[(2*E*)-3-(4-Chlorophenyl)prop-2-enoyl]-4-methyl-1,3-thiazol-2-yl}(4-hydroxyphenyl)amino]propanoic acid (15b)

Yield 0.45 g (63%), m. p. 134–135 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.57 (t, 2H, *J* = 7.4 Hz, CH_2CO), 2.60 (s, 3H, CH_3), 4.10 (t, 2H, *J* = 7.3 Hz, NCH_2), 6.89–7.78 (m, 8H, H_{Ar}), 7.21 (d, 1H, *J* = 15.5 Hz, CO-C$\underline{H}$=CH), 7.52 (d, 1H, *J* = 15.4 Hz, CO-CH=C$\underline{H}$), 10.89 (br. s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 19.14 (CH_3), 32.4 ($\underline{C}H_2CO$), 48.2 (NCH_2), 116.8, 122.1, 125.5, 128.9, 129.0, 130.3, 133.5, 134.4, 134.7, 140.1, 157.7, 159.4 (C_{Ar}, $\underline{C}CH_3$, $\underline{C}$-CO-$\underline{C}$H=$\underline{C}$H), 171.8, 172.5, 180.0 (COOH, CO, C=N). IR (KBr), ν, cm^{-1}: 3 180 (OH), 1 712, 1 639 (CO), 1 514 (C=N), 1 330 (C-S). Found, %: C, 59.61; H, 4.29; N, 6.27. Anal. calcd. for $C_{22}H_{19}ClN_2O_4S$, %: C, 59.66; H, 4.32; N, 6.32.

3-[{5-[(2*E*)-3-(4-Fluorophenyl)prop-2-enoyl]-4-methyl-1,3-thiazol-2-yl}(4-hydroxyphenyl)amino]propanoic acid (15c)

Yield 0.53 g (77%), m. p. 129–130 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.54 (t, 2H, *J* = 7.3 Hz, CH_2CO), 2.59 (s, 3H, CH_3), 4.09 (t, 2H, *J* = 7.4 Hz, NCH_2), 6.88–7.82 (m, 8H, H_{Ar}), 7.15 (d, 1H, *J* = 15.5 Hz, CO-C$\underline{H}$=CH), 7.52 (d, 1H, *J* = 15.4 Hz, CO-CH=C$\underline{H}$), 10.82 (br. s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 19.1 (CH_3), 32.6 ($\underline{C}H_2CO$), 48.4 (NCH_2), 115.8, 116.0, 116.8, 122.1, 124.6, 128.9, 130.9, 130.9, 134.4, 140.3, 157.7, 159.2 (C_{Ar}, $\underline{C}CH_3$, $\underline{C}$-CO-$\underline{C}$H=$\underline{C}$H), 171.7, 172.6, 180.1 (COOH, CO, C=N). IR (KBr), ν, cm^{-1}: 3 180 (OH), 1 716, 1 640 (CO), 1 510 (C=N), 1 330 (C-S). Found, %: C, 61.87; H, 4.41; N, 6.50. Anal. calcd. for $C_{22}H_{19}FN_2O_4S$, %: C, 61.96; H, 4.49; N, 6.57.

Microbiology

Some of the synthesized thiazole derivatives (**5a, 5b, 5c, 5e, 6, 7, 9, 10, 11, 12, 14, 15a, 15b,** and **15c**) were evaluated for their antibacterial activity against *Rhizobium radiobacter* by use of the diffusion technique [32, 33]. The microbial agent *Rhizobium radiobacter* was commercially available from the German Collection of Microorganisms and Cell Cultures (DSMZ). The zone of inhibition of bacterial growth was investigated. The main solutions (1 mg/ml) of the synthesized compounds were prepared in DMSO and diluted to different concentrations (50, 75, 100, 115, 250, 500, 1 000 μg/ml) with DMSO. Cultures of *Rhizobium radiobacter* were cultivated in Petri dishes for 24 h at 37 °C on Luria-Bertani (LB) agar medium. A bacterial suspension was prepared from cultivated bacterial cultures and 100 μl inoculum containing bacterial cells (10^8 CFU/ml) was spread over the LB agar medium. Filter paper disks were prepared by adding 25 μl of each compound solution and then disks were placed on the LB agar medium. Ampicillin (50 μg/ml) was used as the positive control, and DMSO was used as the negative control. The Petri dishes were incubated for 24 h at 37 °C and zones of inhibition were then ascertained for each sample.

CONCLUSIONS

The *N*-(4-hydroxyphenyl)-*N*-thiocarbamoyl-β-alanine was used for the first time for the synthesis of potentially biologically active 2-aminothiazole derivatives. It was shown that various *N*-carboxyethylaminodihydrothiazolones, *N*-carboxyethylaminothiazoles with aliphatic, aromatic or heterocyclic substituents can be synthesized by the proposed methods. It was found that the highest antibacterial activity against *Rhizobium radiobacter* was exhibited by thiazoles with chalcone moiety.

Received 13 December 2013
Accepted 9 January 2014

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N-(4-HIDROKSIFENIL)-*N*-KARBOKSIETIL-2-AMINOTIAZOLŲ IR DIHIDROTIAZOLONŲ SINTEZĖ BEI ANTIBAKTERINIS AKTYVUMAS

S a n t r a u k a

Iš *N*-(4-hidroksifenil)-*N*-tiokarbamoil-β-alanino susintetinti nauji 2-aminotiazolų ir 2-aminodihidrotiazolų dariniai, turintys karboksietilinį, aromatinį, heterociklinį fragmentus. Konstatuota, kad *N*-aril-*N*-tiokarbamoil-β-alaninai yra tinkami tarpiniai junginiai sintetinant įvairiai pakeistus tiazolo darinius. Naujai susintetintų junginių struktūra patvirtinta cheminiais ir spektroskopiniais metodais. Atlikus dalies susintetintų junginių antibakterinio aktyvumo tyrimus, nustatyta, kad didžiausiu aktyvumu pasižymėjo tiazolo dariniai, turintys chalkono fragmentą.