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Synthesis and heterocyclization of *N*-[4-(1,3-benzothiazol-2-yl)phenyl]-β-alanines

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Novel derivatives of 2-phenyl substituted benzothiazole containing different moieties, such as β-alanine, carboxyethyl-β-alanine, dihydropyrimidinedione, dihydropyrimidinone-2-thione, or hydrothiazole, as well as one or two halogen atoms on the benzene ring were synthesized.

Key words: β-alanine, benzothiazole, dihydropyrimidinedione, hydrothiazole, halogenation

INTRODUCTION

Benzothiazole derivatives are an attractive class of biologically active molecules. Among them, 2-phenyl substituted benzothiazoles are of particular interest since many of them have been reported to possess antitumor [1–6] and antimicrobial [7] activities. Halogen-containing derivatives of 2-(4-aminophenyl)benzothiazole were shown to be useful as probes for detecting β-amyloid plaques in Alzheimer's disease [8].

On the other hand, *N*-substituted β-amino acids, their salts, and hydrazides display growth regulating properties [9, 10]. Sceletons of some of them are often encounted in natural biologically active compounds. *N*-Substituted β-amino acids undergo cyclization to heterocyclic compounds, such as derivatives of imidazole, pyridine, quinolinone, pyrimidine, and azepine [11–15].

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RESULTS AND DISCUSSION

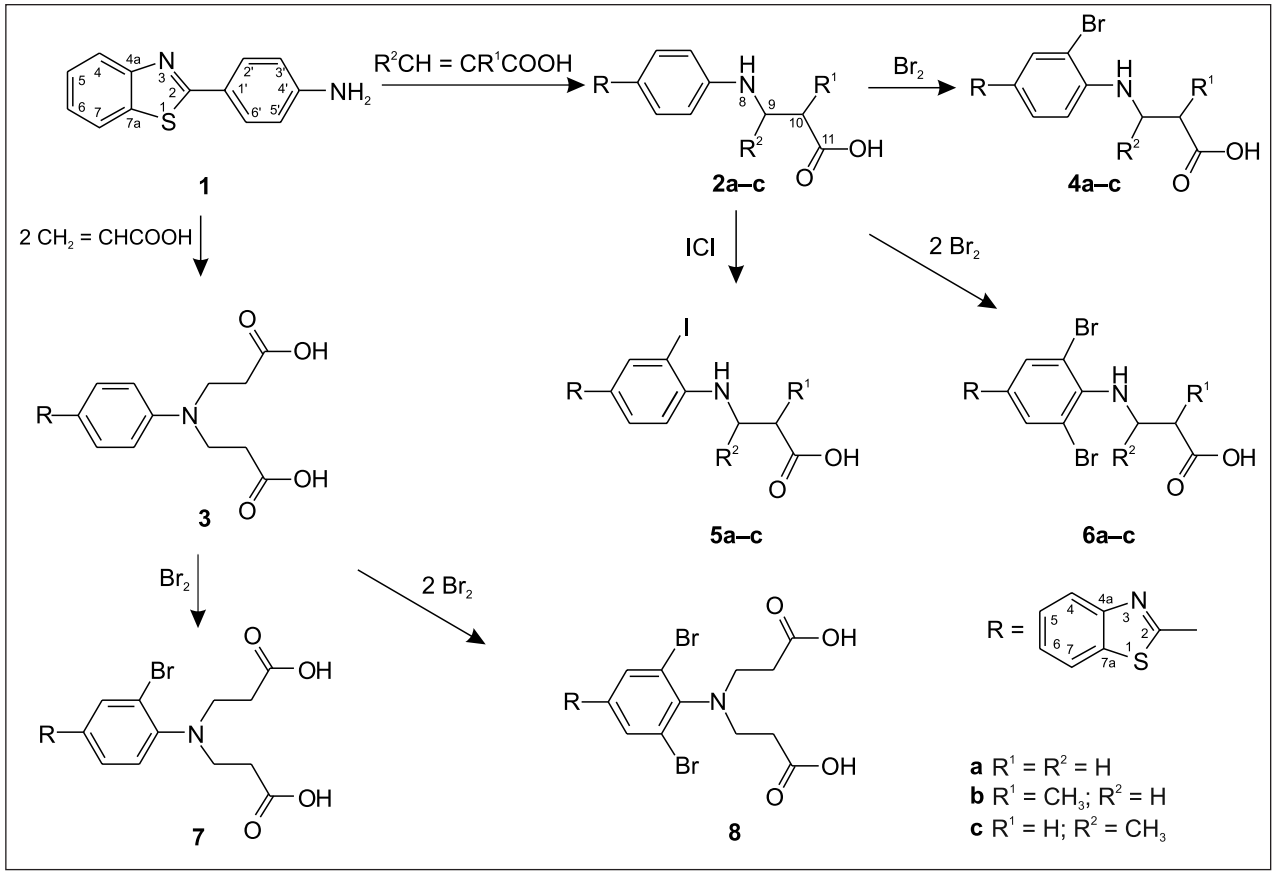
Herein, we report the synthesis of *N*-substituted β-amino acids containing benzothiazole moiety, their halogenization, and cyclization to the derivatives of hydropyrimidinedione and hydrothiazole.

Depending on the ratio of the reacting substances, heating of 2-(4-aminophenyl)benzothiazole (**1**), which was obtained by condensation of 2-aminothiophenol with

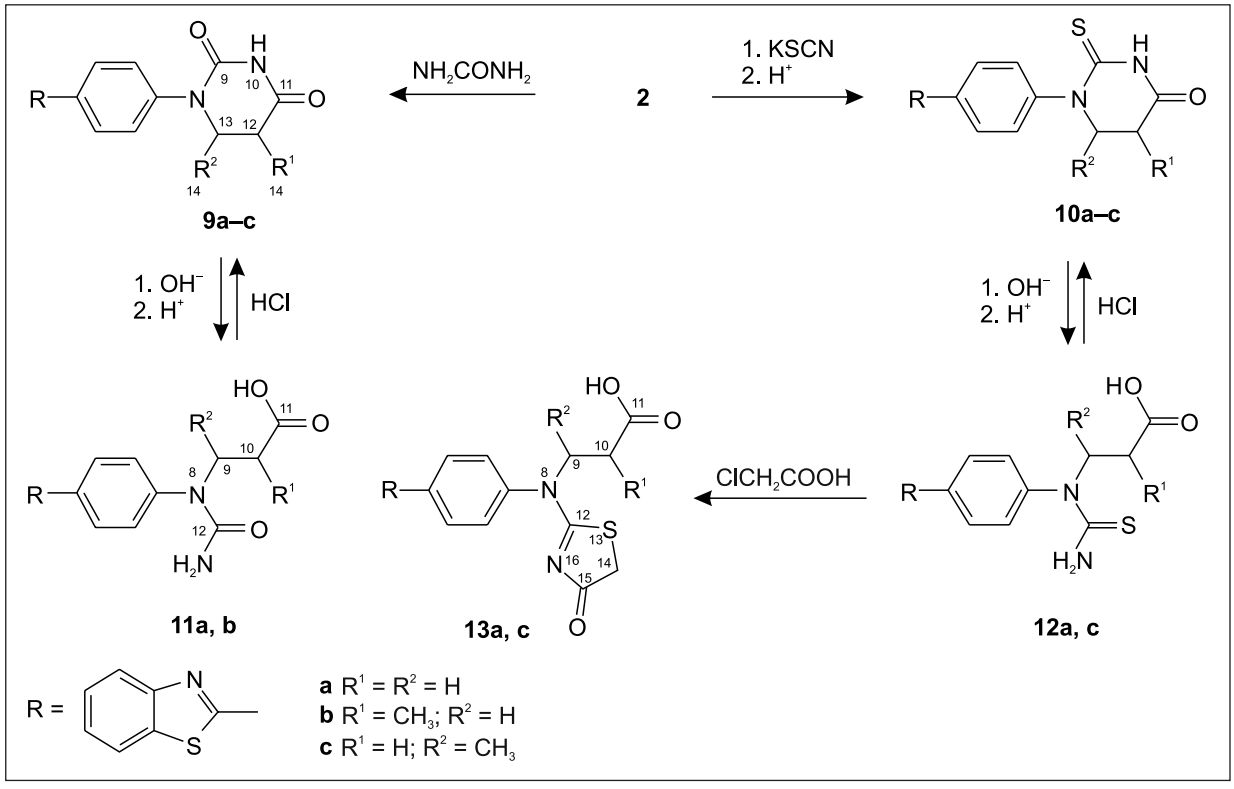
4-aminobenzoic acid, with acrylic acid provided products of mono- and diaddition, i. e. *N*-[4-(1,3-benzothiazol-2-yl) phenyl]-β-alanine (**2a**) and *N*-[4-(1,3-benzothiazol-2-yl) phenyl-*N*-(2-carboxyethyl)-β-alanine (**3**) (Scheme 1). Only monoacids **2b**, **c** were obtained in the reaction of amine **1** with methacrylic or crotonic acids. In the ^{1}H NMR spectrum of **2c**, a double set of resonances are observed for the methylene group at 2.37 ppm and 2.57 ppm and the ones for the NH group are at 3.35 ppm and 6.37 ppm. Aromatic protons 2', 3', 5', and 6' gave rise to a double set of resonances in the range of 6.69–7.90 ppm. Water-acetone solutions of **2** and **3** possess fluorescent properties.

Treatment of acids **2** with an equimolar amount of bromine in acetic acid at room temperature resulted in formation of *N*-[4-(1,3-benzothiazol-2-yl)-2-bromophenyl]-β-alanine (**4a**) and its methyl homologues **4b**, **c**. Reaction of **2** with ICl in acetic acid gave iodine derivatives **5**. In the ^{1}H NMR spectrum of **5a**, two sets of triplets are observed for the protons of the CH_2CO group (2.54 ppm and 2.61 ppm) and the CH_2NH group (3.36 ppm and 3.48 ppm). Aromatic protons 5' and 6' gave rise to a double set of singlets in the range of 6.72–6.78 ppm and 7.82–7.88 ppm, respectively. Dibromo derivatives **6** were obtained by using a double amount of bromine at elevated temperature. However, attempts to obtain analogous diiodine derivatives failed. It should be noted that iodine derivatives **5** became black at elevated temperature. Bromination of diacid **3** provided mono- **7** and dibromo acids **8**. Halogenization of **2** and **3** took place at the *o*-position of the phenylene radical in respect to the amino group. The ^{1}H NMR spectra of bromo derivatives **4** display three signal groups attributed to the benzene ring. The least deshielded dublet observed in the range of 6.8–7.6 ppm has been ascribed to H-5' Ar proton, which is at the *o*-position to H-6' Ar. H-6' Ar proton, which feels *o*- and *m*- influence of H-5' Ar and H-2' Ar protons, resonated as two dublets in the region of 7.8–7.9 ppm. The signal of the most deshielded proton H-2' Ar, which is at the *m*-position to H-5' Ar, is observed in the region of 8.1–8.2 ppm. The ^{1}H NMR spectra of **3**, **7** and **8** show characteristic triplets of the CH_2CO group in the range of 2.42–2.47 ppm and the ones of the CH_2N group at 3.38–3.66 ppm. The hydrogens of the OH group gave rise to singlets in the range of 12.19–12.33 ppm. The resonances ascribed to H-3', 5' Ar and H-2', 6' Ar are observed as a double set of resonances in the 6.71–6.80 ppm and 7.82–7.87 ppm regions, respectively, of the ^{1}H NMR spectrum for **3**. In the ^{13}C NMR spectra of **3**, **7** and **8**, CO group carbons resonated at 174.06 ppm (**3**), 172.99 (**7**), and 176.05 (**8**).

Reaction of **2** with carbamide in acetic acid at elevated temperature with the subsequent treatment with HCl at reflux temperature provided 1-[4-(1,3-benzothiazol-2-yl)phenyl]dihydro-2,4(1*H*,3*H*)-pyrimidinedione (**9a**) and its 5- and 6-methyl homologues **9b**, **c** (Scheme 2). When potassium



Scheme 1. Synthesis of *N*-[4-(1,3-benzothiazol-2-yl)phenyl]-β-alanines



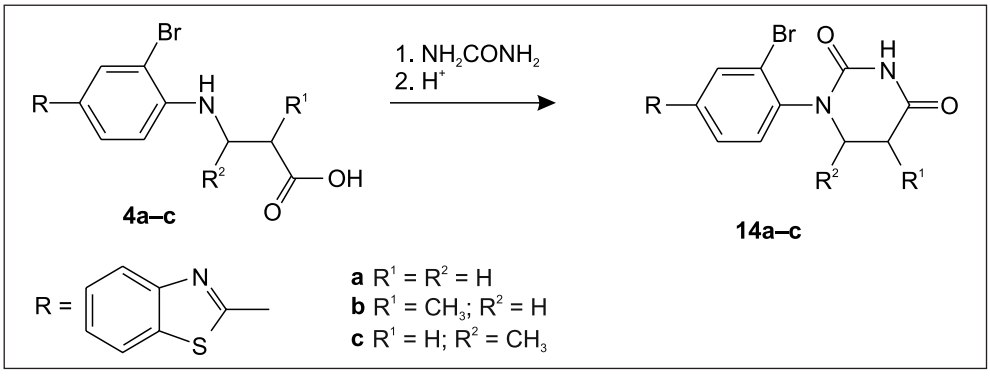
Scheme 2. Cyclization of *N*-[4-(1,3-benzothiazol-2-yl)phenyl]-β-alanines

thiocyanate was used instead of carbamide, 1-[4-(1,3-benzothiazol-2-yl)phenyl]dihydro-4(1*H*,3*H*)-pyrimidinone-2-thione (**10a**) and its homologues **10b**, **c** were obtained. In the ^{1}H NMR spectra of hydropyrimidinediones **9** and **10**, protons of the amide group resonated in the range of 10.5–11.5 ppm due to the deshielding effect of adjacent C=O and C=S groups. In the ^{13}C NMR spectra, C=O group carbons resonated in the range of 151–152 ppm, and the resonances in the 176–180 ppm region have been attributed to C=S group carbons.

Dihydropyrimidinediones as well as dihydropyrimidinonethiones undergo hydrolysis under the influence of alkali forming derivatives of ureido acids [11], which cyclize back to dihydropyrimidine derivatives under treatment with strong acids. Thus, when **9** and **10** were dissolved in 10% aqueous NaOH solution, and the obtained solutions were subsequently acidified with acetic acid, *N*-[4-(1,3-benzothiazol-2-yl)phenyl]-*N*-carbamoyl-β-alanine (**11a**) and its methyl homologues **11b**, **c** as well as their thio analogues **12** were obtained.

Heating at reflux temperature of **12a**, **c** with chloroacetic acid in acetic acid [16], in the presence of sodium acetate, provided 4-thiazolone derivatives of *N*-aryl-β-alanines **13a**, **c**. In their ^{1}H NMR spectra, a singlet at 2.12 ppm has been ascribed to the protons of the methylene group in the thiazolone ring, whereas carbons of the carbonyl group in the thiazolone moiety resonate in the range of 180–184 ppm in the ^{13}C NMR spectra.

Hydropyrimidinediones **14** were obtained in 70% yield in the reaction of bromo derivatives of amino acids **4** with carbamide in acetic acid with the subsequent addition of HCl (Scheme 3).



Scheme 3. Synthesis of halogen-containing dihydropyrimidinediones

EXPERIMENTAL

Melting points were determined with an automatic APA1 melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a *Varian Unity Inova* (300 MHz, 75 MHz) Spectrometer operating in the Fourier transform mode. Chemical shifts (δ) are reported in parts per million (ppm) calibrated from TMS (0 ppm) as an internal standard for ^{1}H NMR, and DMSO-d_6 (39.50 ppm) for ^{13}C NMR. Mass spectra were obtained on a Waters (Micromas) ZQ 2000 Spectrometer, using the chemical ionization mode (25 V). Elemental analyses (C, H, N) were performed with an Elemental Analyzer CE-440. The monitoring of the reaction course and the purity of the synthesized compounds were carried out using TLC on Alugram SIL G/UV$_{254}$ plates.

2-(4-Aminophenyl)benzothiazole (1) was synthesized as described previously [6]. M. p. 149–150 °C.

***N*-[4-(1,3-Benzothiazol-2-yl)phenyl]-β-alanine (2a)**. A mixture of amine **1** (4.52 g, 20 mmol), acrylic acid (1.49 ml, 22 mmol), and toluene (20 ml) was heated at reflux temperature for 6 h. Afterwards, it was cooled to room temperature, the precipitate formed was filtered off and dissolved in 10% aqueous NaOH solution (20 ml), unreacted amine was extracted with diethyl ether (2 × 10 ml), and acetic acid was added to the aqueous layer to pH 4. The crystals formed were filtered off and crystallized from isopropyl alcohol. Yield 3.39 g (57%). M. p. 188–189 °C. ^{1}H NMR (DMSO-d_6) δ: 2.56 (t, 2H, *J* = 6.9 Hz, CH_2CO); 3.36 (q, 2H, *J* = 6.9 Hz, *J* = 12.3 Hz, $\underline{CH_2}NH$); 6.52 (t, 1H, *J* = 5.1 Hz, NH); 6.72 (d, 2H, *J* = 8.7 Hz, H-3',5' Ar); 7.36 (dt, 1H, *J* = 1.5 Hz, *J* = 8.5 Hz, H-6 Ar); 7.68 (dt, 1H, *J* = 1.5 Hz, *J* = 8.5 Hz, H-5 Ar); 7.83 (d, 2H, *J* = 8.7 Hz, H-2',6' Ar); 7.92 (dd, 1H, *J* = 1.1 Hz, *J* = 8.5 Hz, H-4 Ar); 8.04 (dd, 1H, *J* = 1.1 Hz, *J* = 8.5 Hz, H-7 Ar), 12.28 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 33.81 (C-10); 38.51 (C-9); 111.75 (C-3',5'); 120.10 (C-1'); 121.70 (C-6); 121.81 (C-5); 124.26 (C-4); 126.23 (C-7); 128.63 (C-2',6'); 133.66 (C-7a); 151.33 (C-4'); 153.85 (C-4a); 167.95 (C-2); 173.23 (C-11). ^{13}C NMR, DEPT-45, (DMSO-d_6) δ: 114.30 (C-3',5'); 122.46 (C-6); 122.25 (C-5); 125.00 (C-4); 126.91 (C-7); 129.48 (C-2', 6'). MS (CI, 20 V), *m/z* (%): 299 $[M+H]^+$ (100). Anal. calcd. for $C_{16}H_{14}N_2O_2S$, %: C, 64.41; H, 4.73; N, 9.39. Found, %: C, 64.32; H, 4.64; N, 9.18.

***N*-[4-(1,3-Benzothiazol-2-yl)phenyl-α-methyl-β-alanine (2b)**. A mixture of amine **1** (2.26 g, 10 mmol), methacrylic acid (4.24 ml, 50 mmol), and toluene (10 ml) was heated at 90 °C for 20 h. Afterwards, it was cooled to room temperature, the precipitate formed was filtered off and dissolved in 10% aqueous NaOH solution (20 ml), and acetic acid was added to pH 4. The crystals formed were filtered off and crystallized from isopropyl alcohol. Yield 3.00 g (96%). M. p. 107–108 °C. ^{1}H NMR (DMSO-d_6) δ: 1.17 (d, 3H, *J* = 6.6 Hz, CH_3); 2.64–2.73 (m, 1H, CH); 3.15 (dd, 1H, *J* = 6.6 Hz, *J* = 13.2 Hz, CH_2); 3.43 (dd, 1H, *J* = 6.6 Hz, *J* = 13.2 Hz, CH_2); 6.57 (t, 1H, *J* = 5.1 Hz, NH); 6.72 (d, 2H, *J* = 8.7 Hz, H-3',5' Ar); 7.34 (t, 1H, *J* = 7.8 Hz, H-6 Ar); 7.46 (t, 1H, *J* = 7.8 Hz, H-5 Ar); 7.80 (d, 2H, *J* = 8.7 Hz, H-2',6' Ar); 7.93 (d, 1H, *J* = 7.8 Hz, H-4 Ar); 8.01 (d, 1H, *J* = 7.8 Hz, H-7 Ar), 12.30 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 14.89 (C-12); 38.56 (C-10); 45.40 (C-9); 111.76 (C-3',5'); 119.01 (C–1'); 120.1 (C-6); 121.65 (C-5); 124.74 (C-4); 126.08 (C-7); 128.57 (C-2',6'); 133.62 (C-7a); 151.30 (C-4'); 153.80 (C-4a); 167.85 (C-2); 175.94 (C-11). MS (CI, 20 V), *m/z* (%): 313 $[M+H]^+$ (70). Anal. calcd. for $C_{17}H_{16}N_2O_2S$, %: C, 65.36; H, 5.16; N, 8.97. Found, %: C, 65.10; H, 4.95; N, 9.28.

***N*-[4-(1,3-Benzothiazol-2-yl)phenyl-β-methyl-β-alanine (2c)**. A mixture of amine **1** (4.52 g, 20 mmol), crotonic acid (2.2 g, 26 mmol), and toluene (20 ml) was heated at reflux temperature for 20 h. The crystals formed were isolated according to the same procedure as **2a**. Yield 2.46 g (39%). M. p. 134–135 °C (isopropyl alcohol). ^{1}H NMR (DMSO-d_6) δ: 1.22 (d, 3H, *J* = 6.6 Hz, CH_3); 2.37 (dd, 1H, *J* = 7.2 Hz, *J* = 15.3 Hz, CH_2,); 2.57 (dd, 1H, *J* = 6.0 Hz, *J* = 15.3 Hz, CH_2,); 3.86–4.00 (m, 1H, CH); 6.35 (s, 0.5H, NH); 6.37 (s, 0.5H, NH); 6.69 (d, 0.5H, *J* = 8.7 Hz, H-3',5' Ar); 6.71 (d, 1.5H, *J* = 8.7 Hz, H-3',5' Ar); 7.35 (t, 1H, *J* = 7.5 Hz, H-6 Ar); 7.46 (t, 1H, *J* = 7.5 Hz, H-5 Ar); 7.78 (d, 0.5H, *J* = 8.7 Hz, H-2',6' Ar); 7.90 (dd, 1.5H, *J* = 8.7 Hz, H-2', 6' Ar); 7.92 (dd, 1H, *J* = 0.6 Hz, *J* = 8.1 Hz, H-4 Ar); 8.03 (dd, 1H, *J* = 0.6 Hz, *J* = 8.1 Hz, H-7 Ar); 12.31 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 20.10 (C-12); 40.83 (C-10); 44.75 (C-9); 112.10 (C-3',5'); 120.05 (C-1'); 121.67 (C-6); 121.77 (C-5); 124.22 (C-4); 126.11 (C-7); 128.68 (C-2',6'); 133.65 (C-7a); 150.42 (C-4'); 153.82 (C-4a); 167.87 (C-2); 172.56 (C-11). MS (CI, 20 V), *m/z* (%): 313 $[M+H]^+$ (100). Anal. calcd. for $C_{17}H_{16}N_2O_2S$, %: C, 65.36; H, 5.16; N, 8.97. Found, %: C, 65.21; H, 5.21; N, 9.14.

***N*-[4-(1,3-Benzothiazol-2-yl)phenyl-*N*-(2-carboxyethyl)-β-alanine (3)**. A mixture of amine **1** (1.13 g, 5 mmol) and acrylic acid (1.36 ml, 20 mmol) was heated at reflux temperature for 20 h. The crystals formed were isolated according to the same procedure as **2a**. Yield 1.34 g (72%). M. p. 196–197 °C (isopropyl alcohol). ^{1}H NMR (DMSO-d_6) δ: 2.47 (t, 4H, *J* = 6.9 Hz, CH_2CO); 3.66 (t, 4H, *J* = 6.9 Hz, CH_2N); 6.71 (d, 0.5H, *J* = 8.7 Hz, H-3',5' Ar); 6.8 (d, 1.5H, *J* = 8.7 Hz, H-3',5' Ar); 7.35 (t, 1H, *J* = 7.95 Hz, H-6 Ar); 7.47 (t, 1H, *J* = 7.95 Hz, H-5 Ar); 7.82 (d, 0.5H, *J* = 8.7 Hz, H-2',6' Ar); 7.87 (d, 1.5H, *J* = 8.7 Hz, H-2',6' Ar); 7.93 (d, 1H, *J* = 7.95 Hz, H-4 Ar); 8.00 (d, 1H, *J* = 7.95 Hz, H-7 Ar); 12.31 (s, 2H, OH). ^{13}C NMR (DMSO-d_6) δ: 33.29 (C-10); 46.8 (C-9); 111.38, 111.76 (C-3',5'); 119.73 (C-1'); 121.71 (C-6); 121.80 (C-5); 124.27 (C-4); 126.20 (C-7); 128.70 (C-2',6'); 133.76 (C-7a); 149.48 (C-4'); 153.90 (C-4a); 167.74 (C-2); 174.06 (C-11). MS (CI, 20 V), *m/z* (%): 371 $[M+H]^+$ (70). Anal. calcd. for $C_{19}H_{18}N_2O_4S$, %: C, 61.61; H, 4.90; N, 7.56. Found, %: C, 61.42; H, 4.79; N, 7.48.

***N*-[4-(1,3-Benzothiazol-2-yl)-2-bromophenyl]-β-alanine (4a)**. To a solution of alanine **2a** (0.59 g, 2 mmol) in acetic acid (15 ml), Br_2 (0.32 g, 2 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 3 h. Afterwards, the reaction mixture was poured into water (100 ml) and the precipitate formed was filtered off, washed with water, and crystallized from isopropyl alcohol. Yield 0.5 g (66%). M. p. 160–161 °C. ^{1}H NMR (DMSO-d_6) δ: 2.61 (t, 2H, *J* = 6.6 Hz, CH_2CO); 3.49 (q, 2H, *J* = 6.6 Hz, *J* = 11.4 Hz, $\underline{CH_2}NH$); 5.93 (t, 1H, *J* = 4.8 Hz, NH); 6.89 (d, 1H, *J* = 8.7 Hz, H-5' Ar); 7.40 (dt, 1H, *J* = 1.2 Hz, *J* = 7.2 Hz, H-6 Ar); 7.51 (dt, 1H, *J* = 1.2 Hz, *J* = 7.2 Hz, H-5 Ar); 7.88 (dd, 1H, *J* = 2.1 Hz, *J* = 8.7 Hz, H-6' Ar); 7.97 (dd, 1H, *J* = 1.2 Hz, *J* = 7.2 Hz, H-4 Ar); 8.08 (dd, 1H, *J* = 1.2 Hz, *J* = 7.2 Hz, H-7 Ar); 8.14 (d, 1H, *J* = 2.1 Hz, H-2' Ar); 12.50 (s, 2H, OH). ^{13}C NMR (DMSO-d_6) δ: 33.14 (C-10); 38.67 (C-9); 108.61 (C-3'); 111.01 (C-5'); 121.71 (C-1'); 122.04 (C-6); 122.08 (C-5) 124.76 (C-4); 126.41 (C-7); 128.56 (C-6'); 130.73 (C-2'); 133.87 (C-7a); 147.11 (C-4'); 153.57 (C-4a); 166.17 (C-2); 173.10 (C-11). MS (CI, 20 V), *m/z* (%): 379 $[M+2H]^+$ (100). Anal. calcd. for $C_{16}H_{13}BrN_2O_2S$, %: C, 50.94; H, 3.47; N, 7.43. Found, %: C, 50.89; H, 3.59; N, 7.52.

***N*-[4-(1,3-Benzothiazol-2-yl)-2-bromophenyl]-α-methyl-β-alanine (4b)** was prepared from alanine **2b** (0.312 g, 1 mmol) and Br_2 (0.28 g, 1.75 mmol) according to the synthesis procedure of **4a**. Yield 0.3 g (79%). M. p. 103–104 °C (isopropyl alcohol / water). ^{1}H NMR (DMSO-d_6) δ: 1.04 (d, 3H, *J* = 6.9 Hz, CH_3); 2.63–2.75 (m, 1H, CH); 3.50 (dd, 1H, *J* = 7.5 Hz, *J* = 12.9 Hz, CH_2); 3.67 (dd, 1H, *J* = 7.5 Hz, *J* = 12.9 Hz, CH_2); 6.89 (s, 0.5H, NH); 6.91 (s, 0.5H, NH); 7.38–7.59 (m, 3H, H-5',6,5 Ar); 7.80 (dd, 1H, *J* = 2.1 Hz, *J* = 8.1 Hz, H-6' Ar); 8.05 (d, 1H, *J* = 7.8 Hz, H-4 Ar); 8.13 (d, 1H, *J* = 7.8 Hz, H-7 Ar); 8.17 (d, 1H, *J* = 2.1 Hz, H-2' Ar); 10.29 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 14.73 (C-12); 39.87 (C-10); 49.30 (C-9); 113.92 (C-3'); 119.01 (C-5'); 122.23 (C-6); 122.45 (C-5); 125.10 (C-6'); 126.45 (C-4); 127.26 (C-7); 127.90 (C-2'); 131.19 (C-4'); 134.16 (C-7a); 146.34 (C-4'); 153.54 (C-4a); 166.90 (C-2); 176.00 (C-11). MS (CI, 20 V), *m/z* (%): 393 $[M+2H]^+$ (100). Anal. calcd. for $C_{17}H_{15}BrN_2O_2S$, %: C, 52.18; H, 3.86; N, 7.16. Found, %: C, 52.38; H, 3.64; N, 7.05.

***N*-[4-(1,3-Benzothiazol-2-yl)-2-bromophenyl]-β-methyl-β-alanine (4c)** was prepared from alanine **2c** (0.312 g, 1 mmol) and Br_2 (0.28 g, 1.75 mmol) according to the synthesis procedure of **4a** except that the reaction duration was 16 h. Yield 0.32 g (82%). M. p. 121–122 °C (isopropyl alcohol). ^{1}H NMR (DMSO-d_6) δ: 1.26 (d, 3H, *J* = 6.3 Hz, CH_3); 2.58 (dd, 1H, *J* = 6.3 Hz, *J* = 15.6 Hz, CH_2); 2.68 (dd, 1H, *J* = 6.3 Hz, *J* = 15.6 Hz, CH_2); 3.87–4.06 (m, 1H, CH); 5.65 (br. s, 1H, NH); 6.92 (d, 1H, *J* = 8.7 Hz, H-5' Ar); 7.40 (dt, 1H, *J* = 0.9 Hz, *J* = 8.7 Hz, H-6 Ar); 7.51 (dt, 1H, *J* = 0.9 Hz, *J* = 8.7 Hz, H-5 Ar); 7.88 (dd, 1H, *J* = 2.1 Hz, *J* = 8.7 Hz, H-6' Ar); 8.03 (d, 1H, *J* = 7.8 Hz, H-4 Ar); 8.11 (d, 1H, *J* = 7.8 Hz, H-7 Ar); 8.15 (d, 1H, *J* = 2.1 Hz, H-2' Ar); 10.32 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 19.68 (C-12); 40.07 (C-10); 45.32 (C-9); 108.80 (C-3'); 111.44 (C-5'); 121.67 (C-1'); 122.05 (C-6); 122.08 (C-5); 124.77 (C-4); 126.43 (C-7); 128.32 (C-6'); 130.8 (C-2'); 133.88 (C-7a); 146.37 (C-4'); 153.55 (C-4a); 166.15 (C-2); 172.80 (C-11). MS (CI, 20 V), *m/z* (%): 393 $[M+2H]^+$ (100). Anal. calcd. for $C_{17}H_{15}BrN_2O_2S$, %: C, 52.18; H, 3.86; N, 7.16. Found, %: C, 52.34; H, 3.72; N, 7.19.

***N*-[4-(1,3-Benzothiazol-2-yl)-2-iodophenyl]-β-alanine (5a)**. To a solution of alanine **2a** (0.298 g, 1 mmol) in acetic acid (10 ml), a solution of ICl (0.21 g, 1.3 mmol) in acetic acid (10 ml) was added dropwise at 30 °C and the reaction mixture was heated at reflux temperature for 3 h. Afterwards, it was cooled to room temperature, the crystals formed were filtered off, washed with water and crystallized from isopropyl alcohol. Yield 0.29 g (68%). M. p. 145–146 °C. ^{1}H NMR (DMSO-d_6) δ: 2.54 (t, 0.5H, *J* = 6.9 Hz, CH_2CO); 2.61 (t, 1.5H, *J* = 6.9 Hz, CH_2CO); 3.36 (t, 0.5H, *J* = 6.9 Hz, $\underline{CH_2}NH$); 3.48 (t, 1.5H, *J* = 6.9 Hz, $\underline{CH_2}NH$); 5.55 (br. s, 1H, NH); 6.72 (d, 0.3H, *J* = 8.7 Hz, H-5' Ar); 6.78 (d, 0.7H, *J* = 8.7 Hz, H-5' Ar); 7.40 (t, 1H, *J* = 7.7 Hz, H-6 Ar); 7.51 (t, 1H, *J* = 7.7 Hz, H-5 Ar); 7.82 (d, 0.3H, *J* = 8.7 Hz, H-6' Ar); 7.88 (dd, 0.7H, *J* = 2.1 Hz, *J* = 8.7 Hz, H-6' Ar); 7.97 (d, 1H, *J* = 7.8 Hz, H-4 Ar); 8.07 (d, 1H, *J* = 7.8 Hz, H-7 Ar); 8.36 (d, 1H, *J* = 2.1 Hz, H-2' Ar); 10.31 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 33.10 (C-10); 39.03 (C-9); 84.93 (C-3'); 110.00 (C-5'); 122.01 (C-6); 122.41 (C-5); 122.54 (C-1'); 124.72 (C-4); 126.39 (C-7); 128.94 (C-6'); 133.83 (C-7a); 137.24 (C-2'); 149.54 (C-4'); 153.56 (C-4a); 166.02 (C-2); 173.15 (C-11). MS (CI, 20 V), *m/z* (%): 425 $[M+H]^+$ (100). Anal. calcd. for $C_{16}H_{13}IN_2O_2S$, %: C, 45.30; H, 3.09; N, 6.60. Found, %: C, 45.58; H, 3.20; N, 6.65.

***N*-[4-(1,3-Benzothiazol-2-yl)-2-iodophenyl]-α-methyl-β-alanine (5b)**. To a solution of alanine **2b** (0.312 g, 1 mmol) in acetic acid (10 ml), a solution of ICl (0.21 g, 1.3 mmol) in acetic acid (10 ml) was added dropwise at 30 °C and the reaction mixture was heated at reflux temperature for 6 h. Liquid fraction was removed with a rotary evaporator, water (50 ml) was poured onto the residue, 10% aqueous Na_2CO_3 solution was added to pH 5. The crystals formed were filtered off, dried, and crystallized from isopropyl alcohol / water mixture. Yield 0.25 g (57%). M. p. 61–62 °C. ^{1}H NMR (DMSO-d_6) δ: 1.22 (d, 3H, *J* = 7.2 Hz, CH_3); 2.50–2.60 (m, 1H, CH); 3.25 (s, 1H, CH_2); 3.27 (s, 1H, CH_2); 6.02 (s, 1H, NH); 6.71 (d, 1H, *J* = 8.7 Hz, H-5' Ar); 7.39 (dt, 1H, *J* = 0.9 Hz, *J* = 7.2 Hz, H-6 Ar); 7.49 (dt, 1H, *J* = 0.9 Hz, *J* = 7.2 Hz, H-5 Ar); 7.84 (dd, 1H, *J* = 2.1 Hz, *J* = 8.7 Hz, H-6' Ar); 7.95 (d, 1H, *J* = 7.8 Hz, H-4 Ar); 8.04 (d, 1H, *J* = 7.8 Hz, H-7 Ar); 8.29 (d, 0.3H, *J* = 2.1 Hz, H-2' Ar); 8.34 (d, 0.7H, *J* = 2.1 Hz, H-2' Ar); 10.48 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 15.71 (C-12); 38.74 (C-10): 47.21 (C-9); 109.06 (C-3); 119.04 (CH); 121.96 (C-6); 122.00 (C-5); 124.58 (C-4); 127.90 (C-1'); 128.88 (C-7); 133.78 (C-7a); 137.10 (C-2'); 150.01 (C-4'); 153.60 (C-4a); 166.09 (C-2); 177.48 (C-11).

MS (CI, 20 V), *m/z* (%): 439 $[M+H]^+$ (100). Anal. calcd. for $C_{17}H_{15}IN_2O_2S$, %: C, 46.59; H, 3.45; N, 6.39. Found, %: C, 46.41; H, 3.46; N, 6.58.

***N*-[4-(1,3-Benzothiazol-2-yl)-2-iodophenyl]-β-methyl-β-alanine (5c)** was prepared from **2c** (0.312 g, 1 mmol) according to the synthesis procedure of **5a**. Yield 0.32 g (73%). M. p. 78–79 °C (acetic acid / water). ^{1}H NMR (DMSO-d_6) δ: 1.25 (d, 3H, *J* = 6.0 Hz, CH_3); 2.44–2.58 (m, 2H, CH_2); 3.86–4.00 (m, 1H, CH); 5.91 (s, 1H, NH); 6.74 (d, 1H, *J* = 6.0 Hz, H-5' Ar); 7.39 (dt, 1H, *J* = 0.9 Hz, *J* = 6.9 Hz, H-6 Ar); 7.50 (dt, 1H, *J* = 0.9 Hz, *J* = 6.9 Hz, H-5 Ar); 7.86 (dd, 1H, *J* = 2.1 Hz, *J* = 8.7 Hz, H-6' Ar); 7.96 (d, 1H, *J* = 7.8 Hz, H-4 Ar); 8.06 (d, 1H, *J* = 7.8 Hz, H-7 Ar); 8.36 (d, 1H, *J* = 2.1 Hz, H-2' Ar). ^{13}C NMR (DMSO-d_6) δ: 19.46 (C-12); 41.00 (C-10); 45.78 (C-9); 85.08 (C-2'); 110.20 (C-5'); 121.96 (C-6); 122.07 (C-5); 122.85 (C-1'); 124.62 (C-4); 126.33 (C-7); 128.93 (C-6'); 133.80 (C-7a); 137.33 (C-1'); 148.97 (C-4'); 153.60 (C-4a); 166.03 (C-2); 173.54 (C-11). MS (CI, 20 V), *m/z* (%): 439 $[M+H]^+$ (100). Anal. calcd. for $C_{17}H_{15}IN_2O_2S$, %: C, 46.59; H, 3.45; N, 6.39. Found, %: C, 46.58; H, 3.35; N, 6.35.

***N*-[4-(1,3-Benzothiazol-2-yl)-2,6-dibromophenyl]-β-alanine (6a)**. To a solution of alanine **2a** (0.596 g, 2 mmol) in acetic acid (15 ml), a solution of Br_2 (0.8 g, 5 mmol) in acetic acid (15 ml) was added dropwise at 30 °C and the reaction mixture was heated at 80 °C for 3 h. Afterwards, it was cooled to room temperature, precipitate formed was filtered off, washed with water, and crystallized from isopropyl alcohol. Yield 0.62 g (68%). M. p. 183–184 °C. ^{1}H NMR (DMSO-d_6) δ: 2.57 (t, 2H, *J* = 6.6 Hz, CH_2CO); 3.62 (t, 2H, *J* = 6.6 Hz, $\underline{CH_2}NH$); 6.35 (br. s, 1H, NH); 7.45 (dt, 1H, *J* = 1.2 Hz, *J* = 7.8 Hz, H-6 Ar); 7.54 (dt, 1H, *J* = 1.2 Hz, *J* = 7.8 Hz, H-5 Ar); 8.02 (dd, 1H, *J* = 0.6 Hz, *J* = 7.8 Hz, H-4 Ar); 8.15 (d, 1H, *J* = 7.0 Hz, H-7 Ar); 8.17 (s, 2H, H-2',6' Ar). ^{13}C NMR (DMSO-d_6) δ: 34.87 (C-10); 42.85 (C-9); 114.61 (C-3',5'); 122.27 (C-6); 122.65 (C-5); 125.46 (C-1'); 126.68 (C-4); 126.88 (C-7); 131.11 (C-2',6'); 134.36 (C-7a); 146.62 (C-4'); 153.23 (C-4a); 164.04 (C-2); 173.07 (C-11). MS (CI, 20 V), *m/z* (%): 460 $[M+4H]^+$ (40), 458 $[M+2H]^+$ (80). Anal. calcd. for $C_{16}H_{12}Br_2N_2O_2S$, %: C, 42.13; H, 2.65; N, 6.14. Found, %: C, 42.38; H, 2.54; N, 6.26.

***N*-[4-(1,3-Benzothiazol-2-yl)-2,6-dibromophenyl]-α-methyl-β-alanine (6b)** was prepared from **2b** (0.312 g, 1 mmol) and Br_2 (0.48 g, 3 mmol) according to the synthesis procedure of **6a** except that smaller volume of acetic acid (10 ml) was used to prepare the solutions. Yield 0.32 g (68%). M. p. 151–152 °C (isopropyl alcohol). ^{1}H NMR (DMSO-d_6) δ: 1.16 (d, 2H, *J* = 6.9 Hz, CH_3); 2.65 (sxt, 1H, *J* = 6.9 Hz, CH); 2.99–3.35 (m, 2H, CH_2); 5.27 (br. s, 1H, NH); 7.46 (t, 1H, *J* = 8.1 Hz, H-6 Ar); 7.55 (t, 1H, *J* = 8.1 Hz, H-5 Ar); 8.03 (d, 1H, *J* = 8.1 Hz, H-4 Ar); 8.13 (d, 1H, *J* = 8.1 Hz, H-7 Ar); 8.16 (s, 2H, H-2',6' Ar). ^{13}C NMR (DMSO-d_6) δ: 14.90 (C-12); 38.70 (C-10); 49.54 (C-9); 113.81 (C-3',5'); 122.74 (C-6); 122.62 (C-5); 125.41 (C-1'); 126.44 (C-4); 126.65 (C-7); 131.2 (C-2',6'); 134.33 (C-7a); 146.46 (C-4'); 153.26 (C-4a); 164.06 (C-2); 176.25 (C-11). MS (CI, 20 V), *m/z* (%): 474 $[M+4H]^+$ (40), 472 $[M+2H]^+$ (80). Anal. calcd. for $C_{17}H_{14}Br_2N_2O_2S$, %: C, 43.43; H, 3.00; N, 5.96. Found, %: C, 43.12; H, 2.84; N, 5.84.

***N*-[4-(1,3-Benzothiazol-2-yl)-2,6-dibromophenyl]-β-methyl-β-alanine (6c)** was prepared from **2c** (0.312 g, 1 mmol) according to the synthesis procedure of **6b**. Yield 0.35 g (74%). M. p. 55–56 °C (isopropyl alcohol). ^{1}H NMR (DMSO-d_6) δ: 1.27 (d, 3H, *J* = 6.3 Hz, CH_3); 2.53–2.59 (m, 2H, CH_2); 3.91–4.18 (m, 1H, CH); 4.87 (br. s, 1H, NH); 7.46 (t, 1H, *J* = 7.5 Hz, H-6 Ar); 7.55 (t, 1H, *J* = 7.5 Hz, H-5 Ar); 8.03 (d, 1H, *J* = 7.5 Hz, H-4 Ar); 8.12 (d, 1H, *J* = 7.5 Hz, H-7 Ar); 8.17 (s, 2H, H-2',6' Ar). ^{13}C NMR (DMSO-d_6) δ: 20.80 (C-12); 41.33 (C-10); 49.96 (C-9); 115.88 (C-3',5'); 122.24 (C-6); 122.69 (C-5); 125.46 (C-1'); 126.64 (C-4); 127.03 (C-7); 131.04 (C-2',6'); 134.40 (C-7a); 146.31 (C-4'); 153.24 (C-4a); 163.97 (C-2); 172.64 (C-11). MS (CI, 20 V), *m/z* (%): 474 $[M+4H]^+$ (35), 472 $[M+2H]^+$ (70). Anal. calcd. for $C_{17}H_{14}Br_2N_2O_2S$, %: C, 43.43; H, 3.00; N, 5.96. Found, %: C, 43.36; H, 3.05; N, 6.11.

***N*-[4-(1,3-Benzothiazol-2-yl)-2-bromophenyl]-*N*-(2-carboxyethyl)-β-alanine (7)** was prepared from diacid **3** (0.37 g, 1 mmol) in acetic acid (10 ml), a solution of Br_2 (0.28 g, 1.75 mmol) in acetic acid (10 ml) was added dropwise at 30 °C and the reaction mixture was stirred at 30 °C for 16 h. Afterwards, saturated aqueous $Na_2S_2O_4$ solution was added. Precipitate formed was filtered off, washed with water, and crystallized from isopropyl alcohol. Yield 0.28 g (62%). M. p. 174–175 °C. ^{1}H NMR (DMSO-d_6) δ: 2.42 (t, 4H, *J* = 6.9 Hz, CH_2CO); 3.43 (t, 4H, *J* = 6.9 Hz, CH_2N); 7.40 (d, 1H, *J* = 8.4 Hz, H-5' Ar); 7.56 (dt, 1H, *J* = 1.2 Hz, *J* = 7.8 Hz, H-6 Ar); 7.70 (dt, 1H, *J* = 1.2 Hz, *J* = 7.8 Hz, H-5 Ar); 8.01 (dd, 1H, *J* = 2.1 Hz, *J* = 8.4 Hz, H-6' Ar); 8.14 (d, 1H, *J* = 1.2 Hz, H-4 Ar); 8.17 (d, 1H, *J* = 1.2 Hz, H-7 Ar); 8.28 (d, 1H, *J* = 1.2 Hz, H-2' Ar); 12.19 (br. s, 2H, OH). ^{13}C NMR (DMSO-d_6) δ: 31.94 (C-10); 47.76 (C-9); 119.93. 120.53 (C-2'); 122.32 (C-6); 122.75 (C-5); 124.47 (C-5'); 125.49 (C-4'); 126.69 (C-4); 127.12 (C-7); 128.82 (C-6'); 131.75 (C-3'); 134.42 (C-7a); 150.66 (C-1'); 153.44 (C-4a); 165.37 (C-2); 172.99 (C-13). MS (CI, 20 V), *m/z* (%): 451 $[M+2H]^+$ (90). Anal. calcd. for $C_{19}H_{17}BrN_2O_4S$, %: C, 50.79; H, 3.81; N, 6.23. Found, %: C, 50.53; H, 4.02; N, 6.33.

***N*-[4-(1,3-Benzothiazol-2-yl)-2,6-dibromophenyl]-*N*-(2-carboxyethyl)-β-alanine (8)**. To a solution of diacid **3** (0.37 g, 1 mmol) in acetic acid (10 ml), a solution of Br_2 (0.48 g, 3 mmol) in acetic acid (10 ml) was added dropwise at 30 °C and the reaction mixture was heated at 80 °C for 6 h. Afterwards, the liquid fraction was removed with a rotary evaporator, water (25 ml) was poured onto the residue, 10% aqueous Na_2CO_3 solution was added to pH 5. The precipitate formed was filtered off, washed with water, and crystallized from acetic acid. Yield 0.42 g (80%). M. p. 83–84 °C. ^{1}H NMR (DMSO-d_6) δ: 2.45 (t, 4H, *J* = 6.6 Hz, CH_2CO); 3.38

(t, 4H, *J* = 6.6 Hz, CH_2N); 7.43 (dt, 1H, *J* = 1.2 Hz, *J* = 7.8 Hz, H-6 Ar); 7.58 (dt, 1H, *J* = 1.2 Hz, *J* = 7.8 Hz, H-5 Ar); 8.03 (dd, 1H, *J* = 0.6 Hz, *J* = 7.8 Hz, H-4 Ar); 8.14 (dd, 1H, *J* = 0.6 Hz, *J* = 7.8 Hz, H-7 Ar); 8.22 (s, 2H, H-2',6' Ar); 12.33 (br. s, 2H, OH). ^{13}C NMR (DMSO-d_6) δ: 38.47 (C-12); 40.26 (C-11); 115.42 (C-3',5'); 122.29 (C-6); 122.71 (C-5); 126.73 (C-1'); 126.89 (C-4); 127.01 (C-7); 130.00 (C-2',6'); 135.36 (C-7a); 146.64 (C-4'); 153.42 (C-4a); 164.12 (C-2); 176.05 (C-13). MS (CI, 20 V), *m/z* (%): 532 $[M+4H]^+$ (30), 530 $[M+2H]^+$ (60). Anal. calcd. for $C_{19}H_{16}Br_2N_2O_4S$, %: C, 43.20; H, 3.05; N, 5.30. Found, %: C, 43.42; H, 3.08; N, 5.28.

1-[4-(1,3-Benzothiazol-2-yl)phenyl]dihydro-2,4(1*H*,3*H*)-pyrimidinedione (9a). A mixture of acid **2a** (1.49 g, 5 mmol), carbamide (1.5 g, 25 mmol), and acetic acid (20 ml) was heated at reflux temperature for 5 h. Afterwards, conc. HCl was added to pH 2 and the reaction mixture was heated at reflux temperature for 2 h. The reaction mixture was cooled to room temperature, water (100 ml) was added, the precipitate formed was filtered off, washed with water, and crystallized from acetic acid. Yield 2.39 g (74%). M. p. 255–256 °C. ^{1}H NMR (DMSO-d_6) δ: 2.76 (t, 2H, *J* = 6.6 Hz, CH_2CO); 3.91 (t, 2H, *J* = 6.6 Hz, CH_2N); 7.48 (dt, 1H, *J* = 0.9 Hz, *J* = 7.8 Hz, H-6 Ar); 7.52–7.61 (m, 3H, H-3',5',5 Ar); 8.08 (d, 1H, *J* = 7.8 Hz, H-4 Ar); 8.12 (d, 2H, *J* = 8.7 Hz, H-2',6' Ar); 8.16 (d, 1H, *J* = 7.8 Hz, H-7 Ar); 10.56 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 30.92 (C-12); 44.07 (C-13); 122.30 (C-6); 122.74 (C-5); 125.21 (C-3',5'); 125.44 (C-4); 126.62 (C-7); 127.35 (C-2',6'); 129.50 (C-1'); 134.41 (C-7a); 144.52 (C-4'); 151.94 (C-9); 153.52 (C-4a); 166.59 (C-2); 170.55 (C-11). MS (CI, 20 V), *m/z* (%): 346 $[M+Na]^+$ (100), 324 $[M+H]^+$ (40). Anal. calcd. for $C_{17}H_{13}N_3O_2S$, %: C, 63.14; H, 4.05; N, 12.99. Found, %: C, 63.00; H, 3.95; N, 13.08.

1-[4-(1,3-Benzothiazol-2-yl)phenyl]-5-methyldihydro-2,4(1*H*,3*H*)-pyrimidinedione (9b) was prepared from **2b** (1.53 g, 4.9 mmol) and carbamide (0.90 g, 15 mmol) in acetic acid (15 ml) according to the synthesis procedure of **9a**. Yield 1.43 g (86%). M. p. 197–199 °C (acetic acid). ^{1}H NMR (DMSO-d_6) δ: 1.17 (d, 3H, *J* = 6.6 Hz, CH_3); 2.86–2.99 (m, 1H, CH); 3.70–3.92 (m, 2H, CH_2); 7.27–8.21 (m, 8H, H Ar); 10.53 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 12.08 (C-14); 34.80 (C-12); 50.24 (C-13); 122.27 (C-6); 122.77 (C-5); 125.15 (C-3',5'); 125.46 (C-4); 126.60 (C-7); 127.75 (C-2', 6'); 129.58 (C-1'); 134.41 (C-7a); 144.42 (C-4'); 151.92 (C-9); 153.52 (C-4a); 166.56 (C-2); 173.08 (C-11). MS (CI, 20 V), *m/z* (%): 338 $[M+H]^+$ (100). Anal. calcd. for $C_{18}H_{15}N_3O_2S$, %: C, 64.08; H, 4.48; N, 12.45. Found, %: C, 64.36; H, 4.48; N, 12.35.

1-[4-(1,3-Benzothiazol-2-yl)phenyl]-6-methyldihydro-2,4(1*H*,3*H*)-pyrimidinedione (9c) was prepared from **2c** (1.15 g, 3.7 mmol) and carbamide (1.2 g, 20 mmol) in acetic acid (15 ml) according to the synthesis procedure of **9a**. Yield 0.46 g (37%). M. p. 218–219.5 °C (acetic acid). ^{1}H NMR (DMSO-d_6) δ: 1.23 (d, 3H, *J* = 6.6 Hz, CH_3); 2.46 (dd, 1H, *J* = 6.6 Hz, *J* = 16.5 Hz, CH_2); 3.16 (dd, 1H, *J* = 6.6 Hz, *J* = 16.5 Hz, CH_2); 4.15–4.24 (m, 1H, CH); 7.44–8.31 (m, 8H, H Ar); 10.56 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 18.58 (C-14); 37.67 (C-12); 51.15 (C-13); 122.29 (C-6); 122.74 (C-5); 125.48 (C-4); 126.62 (C-7); 127.38 (C-3', 5'); 127.60 (C-2', 6'); 130.51 (C-1'); 134.47 (C-7a); 143.31 (C-4'); 151.23 (C-9); 153.51 (C-4a); 166.48 (C-2); 169.91 (C-11). MS (CI, 20 V), *m/z* (%): 338 $[M+H]^+$ (100). Anal. calcd. for $C_{18}H_{15}N_3O_2S$, %: C, 64.08; H, 4.48; N, 12.45. Found, %: C, 64.30; H, 4.66; N, 12.35.

1-[4-(1,3-Benzothiazol-2-yl)phenyl]dihydro-4(1*H*,3*H*)-pyrimidinone-2-thione (10a). A mixture of acid **2a** (1.49 g, 5 mmol), KSCN (2.4 g, 25 mmol), and acetic acid (20 ml) was heated at reflux temperature for 20 h, then conc. HCl was added to pH 2, and the mixture was heated at reflux temperature for additional 1.5 h. Afterwards, the mixture was cooled to room temperature, water (50 ml) was added, the precipitate formed was filtered off, washed with water, and crystallized from acetic acid. Yield 1.02 g (60%). M. p. 214–215 °C. ^{1}H NMR (DMSO-d_6) δ: 2.87 (t, 2H, *J* = 6.9 Hz, CH_2CO); 4.01 (t, 2H, *J* = 6.9 Hz, CH_2N); 7.5 (dt, 1H, *J* = 1.2 Hz, *J* = 8.7 Hz, H-6 Ar); 7.56 (dt, 1H, *J* = 1.2 Hz, *J* = 8.7 Hz, H-5 Ar); 7.6 (d, 2H, *J* = 8.7 Hz, H-3',5' Ar); 8.10 (d, 1H, *J* = 8.7 Hz, H-4 Ar); 8.17–8.21 (m, 3H, H-2',6',7 Ar); 11.41 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 30.30 (C-12); 48.48 (C-13); 122.35 (C-6); 122.87 (C-5); 125.58 (C-4); 126.66 (C-7); 127.83 (C-3',5'); 128.14 (C–2',6'); 131.64 (C-1'); 134.54 (C-7a); 147.34 (C-4'); 153.49 (C-4a); 166.39 (C-2); 166.9 (C-11); 179.39 (C-9). MS (CI, 20 V), *m/z* (%): 340 $[M+H]^+$ (100). Anal. calcd. for $C_{17}H_{13}N_3OS_2$, %: C, 60.15; H, 3.86; N, 12.38. Found, %: C, 60.26; H, 3.86; N, 12.05.

1-[4-(1,3-Benzothiazol-2-yl)]-5-methylphenyl]dihydro-4(1*H*,3*H*)-pyrimidinone-2-thione (10b) was prepared from **2b** (1.56 g, 5 mmol) and KSCN (1 g, 10 mmol) in acetic acid (10 ml) according to the synthesis procedure of **10a**. Yield 1.37 g (77%). M. p. 164–165 °C (acetic acid). ^{1}H NMR (DMSO-d_6) δ: 1.24 (d, 3H, *J* = 6.6 Hz, CH_3); 2.60 (dd, 1H, *J* = 3.6 Hz, *J* = 16.5 Hz, CH_2,); 3.30 (dd, 1H, *J* = 3.6 Hz, *J* = 16.5 Hz, CH_2); 3.84–3.90 (m, 1H, CH); 7.41–8.20 (m, 8H, H Ar); 11.47 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.95 (C-14); 37.87 (C-12); 55.12 (C-13); 119.04 (C-3',5'); 122.34 (C-6); 122.48 (C-5); 126.48 (C-4); 126.67 (C-7); 127.93 (C-2',6'); 128.84 (C-1'); 134.42 (C-7a'); 142.08 (C-4'); 153.49 (C-4a); 166.26 (C-2); 166.71 (C-11); 176.03 (C-9). MS (CI, 20 V), *m/z* (%): 354 $[M+H]^+$ (100). Anal. calcd. for $C_{18}H_{15}N_3OS_2$, %: C, 61.16; H, 4.28; N, 11.89. Found, %: C, 60.94; H, 4.50; N, 11.64.

1-[4-(1,3-Benzothiazol-2-yl)phenyl]-6-methyldihydro-4(1*H*,3*H*)-pyrimidinone-2-thione (10c) was prepared from **2c** (1.56 g, 5 mmol) and KSCN (1 g, 10 mmol) in acetic acid (10 ml) according to the synthesis procedure of **10a**. Yield 1.21 g (69%). M. p. 199–200 °C (acetic acid). ^{1}H NMR (DMSO-d_6) δ: 1.25 (d, 3H, *J* = 6.6 Hz, CH_3); 2.60 (dd, 1H,

J = 3.6 Hz, *J* = 16.5 Hz, CH_2); 3.31 (dd, 1H, *J* = 3.6 Hz, *J* = 16.5 Hz, CH_2); 4.14–4.27 (m, 1H, CH); 7.45–8.23 (m, 8H, H Ar); 11.47 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 17.86 (C-14); 36.93 (C-12); 55.05 (C-13); 122.40 (C-6); 122.95 (C-5); 125.67 (C-4); 126.74 (C-7); 127.98 (C-3',5'); 129.38 (C-2',6'); 132.04 (C-1'); 134.61 (C-7a); 146.07 (C-4'); 153.53 (C-4a); 166.38 (C-2); 166.58 (C-11); 178.39 (C-9). MS (CI, 20 V), *m/z* (%): 354 $[M+H]^+$ (100). Anal. calcd. for $C_{18}H_{15}N_3OS_2$, %: C, 61.16; H, 4.28; N, 11.89. Found, %: C, 61.45; H, 4.19; N, 11.87

***N*-[4-(1,3-Benzothiazol-2-yl)phenyl]-*N*-carbamoyl-β-alanine (11a)**. Dihydropyrimidinedione **9a** (3.23 g, 10 mmol) was dissolved in 10% aqueous NaOH solution (15 ml) with heating, the formed solution was filtered and acidified with 15% acetic acid solution to pH 5. The precipitate formed was filtered off and washed with water. Yield 1.28 g (38%). M. p. 121–122.5 °C. ^{1}H NMR (DMSO-d_6) δ: 2.74 (t, 2H, *J* = 6.6 Hz, CH_2CO); 3.34 (t, 2H, *J* = 6.6 Hz, CH_2N); 6.41 (br. s, 2H, NH_2); 6.75 (d, 2H, *J* = 9.0 Hz, H-3',5' Ar); 7.34 (dt, 1H, *J* = 1.5 Hz, *J* = 6.9 Hz, H-6 Ar); 7.46 (dt, 1H, *J* = 1.5 Hz, *J* = 6.9 Hz, H-5 Ar); 7.89 (d, 2H, *J* = 8.9 Hz, H-2',6' Ar); 7.89 (dd, 1H, *J* = 1.1 Hz, *J* = 8.5 Hz, H-4 Ar); 7.98 (dd, 1H, *J* = 1.1 Hz, *J* = 8.5 Hz, H-7 Ar); 10.34 (s, 1H, OH). MS (CI, 20 V), *m/z* (%): 364 $[M+Na]^+$ (90), 342 $[M+H]^+$ (25). Anal. calcd. for $C_{17}H_{15}N_3O_3S$, %: C, 59.81; H, 4.43; N, 12.31. Found, %: C, 59.94; H, 4.52; N, 12.24.

***N*-[4-(1,3-Benzothiazol-2-yl)phenyl]-*N*-carbamoyl-α-methyl-β-alanine (11b)** was prepared from **9b** (1.18 g, 3.5 mmol) according to the synthesis procedure of **11a**. Yield 0.86 g (70%). M. p. 143–144 °C (1,4-dioxane / water). ^{1}H NMR (DMSO-d_6) δ: 1.07 (d, 2H, *J* = 6.9 Hz, CH_3); 1.16 (d, 1H, *J* = 6.9 Hz, CH_3); 2.57 (sxt, 1H, *J* = 6.9 Hz, CH); 3.58 (d, 0.5H, *J* = 6.9 Hz, CH_2); 3.83 (d, 1.5H, *J* = 6.9 Hz, CH_2); 5.96 (br. s, 2H, NH_2); 7.33–7.56 (m, 8H, H Ar). ^{13}C NMR (DMSO-d_6) δ: 14.66 (C-14); 38.47 (C-10); 51.15 (C-9); 122.30 (C-6); 122.79 (C-5); 125.45 (C-4); 126.62 (C-7); 128.10 (C-3',5'); 128.19 (C-2',6'); 130.27 (C-1'); 134.43 (C-7a); 145.38 (C-4'); 153.56 (C-4a); 157.02 (C-12); 166.69 (C-2); 175.92 (C-11). MS (CI, 20 V), *m/z* (%): 356 $[M+H]^+$ (90). Anal. calcd. for $C_{18}H_{17}N_3O_3S$, %: C, 60.83; H, 4.82; N, 11.82. Found, %: C, 60.44; H, 4.81; N, 11.79.

***N*-[4-(1,3-Benzothiazol-2-yl)phenyl-*N*-carbamothioyl-β-alanine (12a)**. Dihydropyrimidinonethione **10a** (0.847 g, 2.5 mmol) was dissolved in 10% aqueous NaOH solution (10 ml), the formed solution was filtered and acidified with 15% acetic acid solution to pH 3–4. The precipitate formed was filtered off, washed with water, and crystallized from acetic acid / water mixture. Yield 0.63 g (71%). M. p. 115–116.5 °C. ^{1}H NMR (DMSO-d_6) δ: 2.56 (t, 2H, *J* = 6.9 Hz, CH_2CO); 3.36 (t, 2H, *J* = 6.9 Hz, CH_2N); 6.21 (br. s, 2H, NH_2); 6.75 (d, 2H, *J* = 8.7 Hz, H-3',5' Ar); 7.28–7.36 (m, 2H, H-5,6 Ar); 7.65–7.73 (m, 2H, H-2',6' Ar); 7.88 (d, 2H, *J* = 8.7 Hz, H-4,7 Ar); 12.36 (br. s, 1H, OH). MS (CI, 20 V), *m/z* (%): 358 $[M+H]^+$ (60). Anal. calcd. for $C_{17}H_{15}N_3O_2S_2$, %: C, 57.12; H, 4.23; N, 11.76. Found, %: C, 57.31; H, 4.36; N, 11.61.

***N*-[4-(1,3-Benzothiazol-2-yl)phenyl]-*N*-carbamothioyl-β-methyl-β-alanine hydrate (12c)** was prepared from **10c** (0.354 g, 1 mmol) in 10% aqueous NaOH solution (10 ml) according to the synthesis procedure of **12a**. Yield 0.31 g (80%). M. p. 102 °C (decomp). ^{1}H NMR (DMSO-d_6) δ: 1.11 (d, 1H, *J* = 6.6 Hz, CH_3); 2.15 (dd, 1H, *J* = 6.0 Hz, *J* = 15.3 Hz, CH_2); 2.58 (dd, 1H, *J* = 6.0 Hz, *J* = 15.3 Hz, CH_2); 6.41 (br. s, 2H, NH_2); 5.76–5.92 (m, 1H, CH); 7.37 (d, 2H, *J* = 7.8 Hz, H-3',5' Ar); 7.50 (t, 1H, *J* = 7.5 Hz, H-6 Ar); 7.58 (t, 1H, *J* = 7.5 Hz, H-5 Ar); 8.11 (d, 1H, *J* = 7.8 Hz, H-4 Ar); 8.15–8.26 (m, 3H, H-2',6',7 Ar); 12.35 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 18.19 (C-13); 39.70 (C-10); 52.42 (C-9); 122.41 (C-6); 122.98 (C-5); 125.68 (C-4); 126.73 (C-7); 128.48 (C-3',5'); 130.95 (C-2',6'); 132.76 (C-1'); 134.58 (C-7a); 140.36 (C-4'); 153.52 (C-4a); 166.40 (C-2); 172.00 (C-11); 181.61 (C-12). MS (CI, 20 V), *m/z* (%): 390 $[M+H]^+$ (70), 372 $[M+H-H_2O]^+$ (60). Anal. calcd. for $C_{18}H_{17}N_3O_2S_2 \cdot H_2O$, %: C, 55.51; H, 4.92; N, 10.79. Found, %: C, 55.63; H, 4.90; N, 11.15.

***N*-[4-(1,3-Benzothiazol-2-yl)phenyl]-*N*-(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)-β-alanine (13a)**. A mixture of thioureido acid **12a** (1.14 g, 3.2 mmol), chloroacetic acid (0.41 g, 4 mmol), sodium acetate (0.38 g, 4 mmol), and acetic acid (15 ml) was heated at reflux temperature for 5 h, then water (50 ml) was added to the reaction mixture, the precipitate formed was filtered off, washed with water, and crystallized from acetic acid / ethanol mixture. Yield 0.27 g (21%). M. p. 158–159 °C. ^{1}H NMR (DMSO-d_6) δ: 2.12 (s, 2H, CH_2); 2.47 (t, 2H, *J* = 7.2 Hz, CH_2CO); 3.92 (t, 2H, *J* = 7.2 Hz, CH_2N); 7.38–8.21 (m, 8H, H Ar); 10.31 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 22.5 (C-10); 24.09 (C-9); 35.57 (C-14); 119.03 (C-3',5'); 122.90 (C-6); 125.60 (C-5); 126.68 (C-4); 127.93 (C-7); 128.23 (C-2',6'); 134.54 (C-7a); 142.10 (C-4'); 153.49 (C-4a); 153.57 (C-1'); 166.20 (C-2); 172.46 (C-11); 179.32 (C-15). MS (CI, 20 V), *m/z* (%): 398 $[M+H]^+$ (90). Anal. calcd. for $C_{19}H_{15}N_3O_3S_2$, %: C, 57.41; H, 3.80; N, 10.57. Found, %: C, 57.62 H, 3.64; N, 10.52.

***N*-[4-(1,3-Benzothiazol-2-yl)phenyl]-*N*-(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)-β-methyl-β-alanine (13c)** was prepared from thioureido acid **12c** (1.16 g, 3 mmol), chloroacetic acid (0.29 g, 3 mmol), and sodium acetate (0.26 g, 3 mmol) according to the synthesis procedure of **13a**. Yield 0.48 g (39%). M. p. 183–184 °C (isopropyl alcohol). ^{1}H NMR (DMSO-d_6) δ: 1.23 (d, 3H, *J* = 6.6 Hz, CH_3); 2.12 (s, 2H, CH_2); 3.10 (dd, 1H, *J* = 6.6 Hz, *J* = 17.4 Hz, CH_2CO); 3.23 (dd, 1H, *J* = 6.6 Hz, *J* = 17.4 Hz, CH_2CO); 4.15–4.23 (m, 1H, CH); 7.44 (dt, 1H, *J* = 1.2 Hz, *J* = 7.8 Hz, H-6 Ar); 7.54 (dt, 1H, *J* = 1.2 Hz, *J* = 17.8 Hz, H-5 Ar); 7.79 (d, 2H, *J* = 8.7 Hz, H-2',6' Ar); 8.02–8.20 (m, 4H, H-3',5',4,7 Ar); 10.30 (s, 1H, OH). ^{13}C NMR

(DMSO-d_6) δ: 18.59 (C-17); 24.10 (C-14); 37.69 (C-10); 51.17 (C-9); 119.05 (C-2',6'); 122.17 (C-5); 122.48 (C-6); 127.29 (C-1'); 127.40 (C-7); 127.23 (C-4); 127.94 (C-3',5'); 134.19 (C-7a); 143.31 (C-4'); 153.52 (C-12); 166.95 (C-2); 170.24 (C-11); 183.19 (C-15). MS (CI, 20 V), *m/z* (%): 412 $[M+H]^+$ (80). Anal. calcd. for $C_{20}H_{17}N_3O_3S_2$, %: C, 58.38; H, 4.16; N, 10.21. Found, %: C, 58.27; H, 4.36; N, 10.42.

1-[4-(1,3-Benzothiazol-2-yl)-2-bromophenyl]dihydro-2,4(1*H*,3*H*)-pyrimidinedione (14a) was prepared from **4a** (0.377 g, 1 mmol) and carbamide (0.2 g, 3.3 mmol) in acetic acid (10 ml) according to the synthesis procedure of **10a**. Yield 0.28 g (70%). M. p. 145–146 °C (acetic acid). ^{1}H NMR (DMSO-d_6) δ: 2.61 (t, 2H, *J* = 6.9 Hz, CH_2CO); 3.50 (t, 2H, *J* = 6.9 Hz, CH_2N); 6.88 (d, 0.7H, *J* = 8.7 Hz, H-5' Ar); 6.93 (d, 0.3H, *J* = 8.7 Hz, H-5' Ar); 7.40 (dt, 1H, *J* = 1.5 Hz, *J* = 8.5 Hz, H-6 Ar); 7.51 (dt, 1H, *J* = 1.5 Hz, *J* = 8.5 Hz, H-5 Ar); 7.87 (dd, 1H, *J* = 1.8 Hz, *J* = 8.7 Hz, H-6' Ar); 7.97 (d, 1H, *J* = 8.7 Hz, H-4 Ar); 8.07 (d, 1H, *J* = 8.7 Hz, H-7 Ar); 8.14 (d, 1H, *J* = 1.8 Hz, H-2' Ar); 10.61 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 33.15 (C-12); 38.68 (C-13); 108.61 (C-3'); 110.99 (C-5'); 121.72 (C-6); 122.02 (C-6'); 122.06 (C-5); 124.75 (C-1'); 126.39 (C-4); 128.24 (C-7); 130.68 (C-2'); 133.86 (C-7a); 147.10 (C-4'); 151.30 (C-9); 153.54 (C-4a); 166.16 (C-2); 173.07 (C-11). MS (CI, 20 V), *m/z* (%): 427 $[M+Na+2H]^+$ (80); 425 $[M+Na]^+$ (40). Anal. calcd. for $C_{17}H_{12}BrN_3O_2S$, %: C, 50.76; H, 3.01; N, 10.45. Found, %: C, 50.62; H, 2.92; N, 10.35.

1-[4-(1,3-Benzothiazol-2-yl)-2-bromophenyl]-5-methyldihydro-2,4(1*H*,3*H*)-pyrimidinedione (14b) was prepared from **4b** (0.391 g, 1 mmol) and carbamide (0.5 g, 8.3 mmol) in acetic acid (10 ml) according to the synthesis procedure of **14a**. Yield 0.26 g (62%). M. p. 128–129 °C (isopropyl alcohol). ^{1}H NMR (DMSO-d_6) δ: 1.15 (d, 3H, *J* = 6.9 Hz, CH_3); 2.78 (sxt, 1H, *J* = 6.9 Hz, CH); 3.26–3.39 (m, 1H, CH_2); 3.44–3.57 (m, 1H, CH_2); 6.89 (d, 1H, *J* = 8.7 Hz, H-5' Ar); 7.37 (dt, 1H, *J* = 1.2 Hz, *J* = 8.7 Hz, H-6 Ar); 7.50 (dt, 1H, *J* = 1.2 Hz, *J* = 8.7 Hz, H-5 Ar); 7.86 (dd, 1H, *J* = 2.1 Hz, *J* = 8.4 Hz, H-6' Ar); 7.97 (d, 1H, *J* = 8.1 Hz, H-4 Ar); 8.06 (d, 1H, *J* = 8.1 Hz, H-7 Ar); 8.13 (d, 1H, *J* = 2.1 Hz, H-2' Ar); 10.29 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.71 (C-14); 38.12 (C-12); 45.45 (C-13); 108.55 (C-3'); 111.04 (C-5'); 121.72 (C-6); 121.98 (C-6'); 122.07 (C-5); 124.72 (C-4); 126.36 (C-7); 128.16 (C-2'); 130.66 (C-4'); 133.87 (C-7a); 147.06 (C-1'); 153.16 (C-9); 153.56 (C-4a); 166.14 (C-2); 168.07 (C-11). MS (CI, 20 V), *m/z* (%): 418 $[M+2H]^+$ (80). Anal. calcd. for $C_{18}H_{14}BrN_3O_2S$, %: C, 51.93; H, 3.39; N, 10.09. Found, %: C, 51.73; H, 3.68; N, 9.84.

1-[4-(1,3-Benzothiazol-2-yl)-2-bromophenyl]-6-methyldihydro-2,4(1*H*,3*H*)-pyrimidinedione (14c) was prepared from **4c** (0.391 g, 1 mmol) and carbamide (0.5 g, 8.3 mmol) in acetic acid (10 ml) according to the synthesis procedure of **14a**. Yield 0.16 g (38%). M. p. 95–96 °C (isopropyl alcohol). ^{1}H NMR (DMSO-d_6) δ: 1.26 (d, 3H, *J* = 6.6 Hz, CH_3); 2.57 (dd, 1H, *J* = 6.0 Hz, *J* = 15.6 Hz, CH_2); 2.70 (dd, 1H, *J* = 6.0 Hz, *J* = 15.6 Hz, CH_2); 4.0–4.09 (m, 1H, CH); 6.89 (d, 0.7H, *J* = 7.8 Hz, H-5' Ar); 6.93 (d, 0.3H, *J* = 7.8 Hz, H-5' Ar); 7.39 (t, 1H, *J* = 7.8 Hz, H-6 Ar); 7.50 (t, 1H, *J* = 7.8 Hz, H-5 Ar); 7.86 (d, 1H, *J* = 8.7 Hz, H-6' Ar); 7.97 (d, 1H, *J* = 8.7 Hz, H-4 Ar); 8.06 (d, 1H, *J* = 8.7 Hz, H-7 Ar); 8.14 (d, 1H, *J* = 1.8 Hz, H-2' Ar); 12.38 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 19.69 (C-14); 40.05 (C-12); 45.29 (C-13); 108.74 (C-3'); 111.38 (C-5'); 121.68 (C-6); 121.98 (C-6'); 122.07 (C-5); 124.72 (C-1'); 126.36 (C-4); 128.26 (C-7); 130.77 (C-2'); 133.88 (C-7a); 146.32 (C-4'); 153.51 (C-9); 153.56 (C-4a); 166.10 (C-2); 169.74 (C-11). MS (CI, 20 V), *m/z* (%): 418 $[M+2H]^+$ (100). Anal. calcd. for $C_{18}H_{14}BrN_3O_2S$, %: C, 51.93; H, 3.39; N, 10.09. Found, %: C, 52.20; H, 3.58; N, 9.89.

CONCLUSIONS

N-[4-(1,3-Benzothiazol-2-yl)phenyl]-β-alanine, its α- and β-methyl homologues, as well as *N*-[4-(1,3-benzothiazol-2-yl) phenyl-*N*-(2-carboxyethyl)-β-alanine were synthesized from 2-(4-aminophenyl)benzothiazole; their bromination and iodination reactions, as well as cyclization to 1-[4-(1,3-benzothiazol-2-yl)phenyl]dihydro-2,4(1*H*,3*H*)-pyrimidinediones and dihydropyrimidinone-2-thiones were carried out.

N-[4-(1,3-Benzothiazol-2-yl)phenyl]-*N*-(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)-β-alanines were obtained under treatment of *N*-[4-(1,3-benzothiazol-2-yl)phenyl-*N*-carbamothioyl-β-alanines with chloroacetic acid.

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N-[4-(1,3-BENZOTIAZOL-2-IL)FENIL]-B-ALANINŲ SINTEZĖ IR JŲ HETEROCIKLIZACIJA

S a n t r a u k a

2-(4-Aminofenil)benzotiazolui reaguojant su akrilo, metakrilo ir krotono rūgštimis, susintetinti *N*-[4-(1,3-benzotiazol-2-il)fenil]-β-alaninas, jo α- bei β-metilhomologai ir *N*-[4-(1,3-benzotiazol-2-il)fenil-*N*-(2-karboksietil)-β-alaninas. Juos brominant gauti monodariniai ir dibromfenilo dariniai, o veikiant β-alaninus jodo chloridu gauti tik monojodo dariniai. Virinant *N*-[4-(1,3-benzotiazol-2-il)fenil]-β-alaninus su karbamidu acto rūgštyje, išskirti pakeistieji dihidropirimidindionai, o su kalio tiocianatu – pakeistieji dihidropirimidinon-2-tionai. Šildant *N*-[4-(1,3-benzotiazol-2-il) fenil-*N*-tiokarbamoil-β-alaninus su chloracto rūgštimi, susintetinti *N*-[4-(1,3-benzotiazol-2-il)fenil]-*N*-(4-okso-4,5-dihidro-1,3-tiazol-2-il)-β-alaninai.