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Nucleophilic ring opening of 1,4-disubstituted 2-pyrrolidones with hydrazine. Synthesis of azoles with a high antibacterial activity

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3-(1*H*-Benzimidazol-2-yl)-4-[(phenyl and 4-substituted phenyl)amino]butanohydrazides were synthesized in good yields by treating the corresponding 4-(1*H*-benzimidazol-2-yl)-1-phenyl(substituted phenyl)-2-pyrrolidinones with the excess of hydrazine monohydrate. The utility of the newly synthesized hydrazides in the preparation of pyrroles, pyrazoles, oxadiazoles and triazoles has been demonstrated. All compounds were screened for their antibacterial activity. A significant antibacterial activity was found.

Keywords: pyrrolidin-2-ones, ring-opening, hydrazides, azoles, antibacterial activity

INTRODUCTION

The synthesis of substituted benzimidazole derivatives is of considerable importance, because most of these compounds have a promising biological activity [1–10]. Also, the compounds whose molecules possess an azole ring, such as pyrrole [11–13], 1,3,4-oxadiazole [14–19] and 1,2,4-triazole [19–23], are often characterized as good antimicrobial agents. In our previous works [24–27], we have reported that the heating under reflux of 4-(1*H*-benzimidazol-2-yl)-1-(substituted phenyl)pyrrolidin-2-ones in a 20% aqueous sodium hydroxide solution leads to the opening of the 2-pyrrolidinone cycle, followed by the formation of sodium salts of the corresponding *N*-substituted γ-amino acids. These acids are obtained by acidifying the corresponding salt solutions with acetic acid and can be easily cyclized to the initial pyrrolidin-2-ones under the influence of heat or mineral acids. Therefore, the hydrazides of γ-amino acids, which are used for the synthesis of heterocyclic compounds, were obtained by heating them for a long time under reflux with hydrazine monohydrate in toluene, using the azeotropic water separation.

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EXPERIMENTAL

Chemistry

General methods. TLC was performed on Merck silica gel 60 F254 (Kieselgel 60 F254) plates. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ascend 400 (^{1}H 400 MHz, ^{13}C 101 MHz) spectrometer. Chemical shifts were expressed as δ, ppm relative to TMS. The IR spectra (ν, cm^{-1}) were recorded on a PerkinElmer 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. Mass spectra were measured with Xevo TQ-S and Bruker maXis 4G mass spectrometers.

General procedure for the preparation of 3-(1*H*-benzimidazol-2-yl)-4-[(4-substituted phenyl)amino]butanohydrazides (2a–e)

A mixture of **1a–e** (1 mmol) and 4 mL of hydrazine monohydrate (30 mmol) was heated at reflux for 1 h. Then the reaction mixture was cooled to room temperature and diluted with 40 mL of H_2O. The precipitate was filtered off, washed with water, and dried. All products were purified by recrystallization from water.

3-(1*H*-Benzimidazol-2-yl)-4-(phenylamino)butanohydrazide (2a). White solid, yield 0.25 g (80%), mp 212–213°C; IR (KBr): 3319, 3174, 3116, 2960, 2896, 1678 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.37 (br. s, 1H, CNH), 9.10 (s, 1H, CONH), 7.48 (br. s, 2H, ArH), 7.15–7.04 (m, 5H, ArH), 6.66–6.58 (m, 2H, ArH), 6.53 (t, *J* = 7.2 Hz, 1H, $NHCH_2$), 4.13 (br. s, 2H, NH_2), 3.73–3.68 (m, 1H, CH), 3.52–3.23 (m, 2H, $NHCH_2$), 2.71–2.58 (m, 2H, $COCH_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6); δ = 170.0 (C=O), 156.3 (C=N), 156.1, 153.0, 148.5, 148.4, 128.9, 121.2, 119.5, 115.8, 112.1 (ArC), 46.8 (CH_2NH), 35.7 ($COCH_2$), 35.6 (CH) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{20}N_5O$: 310.1662; found: 310.1668.

3-(1*H*-Benzimidazol-2-yl)-4-[(4-methylphenyl)-amino]butanohydrazide (2b). White solid, yield 0.24 g (74%), mp 218–219°C; IR (KBr): 3315, 3176, 3116, 2863, 2818, 1681 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.25 (br. s, 1H, CNH), 9.08 (s, 1H, CONH), 7.48 (br. s, 2H, ArH), 7.14–7.10 (m, 2H, ArH), 6.88 (d, *J* = 8.1 Hz, 2H, ArH), 6.54 (d, *J* = 8.4 Hz, 2H, ArH), 5.49 (br. s, 1H, $NHCH_2$), 4.15 (br. s, 2H, NH_2), 3.72–3.42 (m, 1H, CH), 3.45–3.25 (m, 2H, $NHCH_2$), 2.70–2.57 (m, 2H, $COCH_2$), 2.14 (s, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 170.0 (C=O), 156.4, 155.1, 146.2, 136.8, 133.2, 129.4, 129.1, 124.1, 119.5, 112.2 (ArC), 47.1 (CH_2NH), 35.7 ($COCH_2$), 35.6 (CH), 20.1 (CH_3) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{22}N_5O$: 324.1819; found: 324.1818.

3-(1*H*-Benzimidazol-2-yl)-4-[(4-fluorophenyl) amino]butanohydrazide (2c). White solid, yield 0.31 g (95%), mp 235–236°C; IR (KBr): 3420, 3321, 3168, 2907, 2884, 1661, 1630 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.25 (br. s, 1H, CNH), 9.09 (s, 1H, CONH), 7.51, 7.43 (2br. s, 2H, ArH), 7.15–7.08 (m, 2H, ArH), 6.90 (t, *J* = 8.9 Hz, 2H, ArH), 6.67–6.56 (m, 2H, ArH), 5.69 (t, *J* = 6.2 Hz, 1H, N*H*CH_2), 4.14 (s, 2H, NH_2), 3.73–3.40 (m, 1H, CH), 3.32–3.27 (m, 2H, $NHCH_2$), 2.69–2.58 (m, 2H, $COCH_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 169.9 (C=O), 156.3 (C=N), 155.0,155.4, 153.1, 145.2, 135.7, 134.1, 121.5, 121.4, 118.2, 115.4, 115.3, 115.2, 115.1, 112.8, 112.7, 111.0 (ArC), 47.3 (CH_2NH), 35.7 ($COCH_2$), 35.5 (CH) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{19}FN_5O$: 456.2401; found: 456.2405.

3-(1*H*-Benzimidazol-2-yl)-4-[(4-bromophenyl) amino]butanohydrazide (2d). White solid, yield 0.31 g (80%), mp 229–230°C; IR (KBr): 3321, 3174, 3118, 2901, 2840, 1679 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.25 (s, 1H, CNH), 9.09 (s, 1H, CONH), 7.57–7.38 (m, 2H, ArH), 7.19 (d, *J* = 8.8 Hz, 2H, ArH), 7.16–7.07 (m, 2H, ArH), 6.06 (d, *J* = 8.8 Hz, 2H, ArH), 6.01 (t, *J* = 6.1 Hz, 1H, $NHCH_2$), 4.17 (s, 2H, NH_2), 3.72–3.64 (m, 1H, CH), 3.49–3.27 (m, 2H, $NHCH_2$), 2.70–2.53 (m, 2H, $COCH_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 169.9 (C=O), 156.1 (C=N), 147.7, 143.2, 134.1, 131.4, 121.5, 120.9, 118.3, 114.0, 111.0, 106.3 (ArC), 46.6 (CH_2NH), 35.7 ($COCH_2$), 35.3 (CH) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{19}BrN_5O$: 388.0773; found: 388.0767.

3-(1*H*-Benzimidazol-2-yl)-4-[(4-methoxyphenyl) amino]butanohydrazide (2e). White solid, yield 0.25 g (74%), mp 210–211°C; IR (KBr): 3319, 3178, 3116, 2884, 1679 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.24 (br. s, 1H, CNH), 9.08 (s, 1H, CONH), 7.53, 7.42 (2 br. s, 2H, ArH), 7.13–7.11 (m, 2H, ArH), 6.71 (d, *J* = 8.9 Hz, 2H, ArH), 6.58 (d, *J* = 8.9 Hz, 2H, ArH), 5.30 (br. s, 1H, $NHCH_2$), 4.18 (br. s, 2H, NH_2), 3.75–3.65 (m, 1H, CH), 3.63 (s, 3H, CH_3), 3.44–3.20 (m, 2H, NHC*H*$_2$), 2.70–2.57 (m, 2H, $COCH_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 170.0 (C=O), 156.4 (C=N), 155.9, 150.8, 143.2, 142.7, 132.5, 121.3, 120.8, 118.3, 114.7, 113.9, 113.1, 111.0 (ArC), 55.3 (CH_3), 47.6 (CH_2NH), 37.4 ($COCH_2$), 35.4 (CH) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{22}N_5O_2$: 340.1773; found: 340.1768.

Ethyl [2-(5-oxo-1-phenylpyrrolidin-3-yl)-1*H*-benzimidazol-1-yl]acetate (3). A mixture of **1a** (0.28 g, 1 mmol), K_2CO_3 (0.83 g, 6 mmol), KOH (0.34 g, 6 mmol), tetrabutylammonium iodide (2.21, 6 mmol) and 50 mL of toluene was heated to the boiling point. Afterwards, 0.64 mL ethyl 2-chloroacetate (0.73 g, 6 mmol) was added over 10 min and the reaction mixture was heated at reflux for 3 h. It was filtered while still hot, the filtrate was cooled, the precipitate was isolated by filtration and washed with propan-2-ol to afford a white solid, yield 0.33 g (91%), mp 156–157°C (CAS Reg. No. 912903-48-1); IR (KBr): 1732, 1696 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.69–7.62 (m, 3H, ArH), 7.53–7.50 (m, 1H, ArH), 7.39 (t, *J* = 8.0 Hz, 2H, ArH), 7.25–7.14 (m, 3H, ArH), 5.32 (s, 2H, NCH_2CO), 4.29–4.11 (m, 5H, CH_2O, CH, $NHCH_2$), 3.05–2.89 (m, 2H, $COCH_2$), 1.24 (t, *J* = 7.1 Hz, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 171.7, 168.3 (C=O), 155.5 (C=N), 139.2, 135.7, 128.7, 124.1, 122.3, 121.9, 119.5, 118.7, 110.1 (ArC), 52.0 (NCH_2), 44.4 ($COCH_2N$), 37.6 (CH_2CO), 23.1 (CH), 19.2 (CH_2O), 13.5 (CH_3) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{22}N_3O_3$: 364.1661; found: 364.1671.

2-[2-(5-Oxo-1-phenylpyrrolidin-3-yl)-1*H*-benzimidazol-1-yl]acetohydrazide (4). A mixture of **3** (0.36 g, 1 mmol), hydrazine monohydrate (0.16 g, 3 mmol) and 20 mL of propan-2-ol was heated at reflux for 1 h. The reaction mixture was cooled down, the precipitate was isolated by filtration, washed with propan-2-ol, dried and recrystallized from water to afford a white solid, yield 0.33 g (95%), mp 249–250°C; IR (KBr): 3284, 3046, 1683, 1663 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.64 (br. s, 1H, NH), 7.68 (d, *J* = 8.0 Hz, 2H, ArH), 7.62 (d, *J* = 7.9 Hz, 1H, ArH), 7.46 (d, *J* = 7.5 Hz, 1H, ArH), 7.39 (t, *J* = 7.9 Hz, 2H, ArH), 7.27–7.09 (m, 3H, ArH), 4.94 (br. s, 2H, NCH_2CO), 4.56 (s, 2H, NH_2), 4.31–4.22 (m, 2H, $NHCH_2$), 4.18–4.10 (m, 1H, CH), 3.04–3.00 (m, 2H, $COCH_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 171.99, 165.99 (C=O), 155.78 (C=N), 141.77, 139.26, 135.77, 128.71, 124.06, 122.13,

121.72, 119.49, 118.78, 110.00 (ArC), 52.19 (NCH_2), 44.44 ($COCH_2N$), 37.70 (CH_2CO), 28.60 (CH) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{20}N_5O_2$: 350.1617; found: 350.1616.

3-[1-(2-Hydrazinyl-2-oxoethyl)-1*H*-benzimidazol-2-yl]-4-(phenylamino)butanohydrazide (5). A mixture of **3** (0.36 g, 1 mmol) or **4** (0.35 g, 1 mmol) and hydrazine monohydrate (1.62 g, 30 mmol) was heated at reflux for 2 or 1 h, respectively. The reaction mixture was cooled down, the liquid fractions were removed under reduced pressure, and the residue was diluted with 40 mL of propan-2-ol, the precipitate was isolated by filtration, washed with propan-2-ol, dried, and recrystallized from propan-2-ol to afford a white solid, yield respectively: 0.29 g (76%), 0.31 g (81%), mp 204–205°C; IR (KBr): 3306, 1683, 1600 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.69, 9.66 (2s, 1H, NH), 9.07 (d, 1H, NH), 7.58–7.40 (m, 2H, ArH), 7.21–7.06 (m, 5H, ArH), 6.60–6.58 (m, 2H, ArH), 6.11 (br. s, 1H, N*H*CH_2), 5.05–4.79 (m, 2H, NCH_2CO), 4.29 (br. s, 4H, $2NH_2$), 3.74 (br. s, 1H, CH), 3.76–3.36 (m, 2H, NHC*H*$_2$), 2.69, 2.67 (2s, 2H, $COCH_2$), 2.52 (s, 6H, $2CH_3$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 172.3, 170.3 (C=O), 155.9 (C=N), 142.1, 139.7, 136.3, 129.2, 124.6, 122.7, 122.3, 120.0, 119.2, 110.6 (ArC), 52.4 (NCH_2), 44.9 ($COCH_2N$), 38.0 (CH_2CO), 28.96 (CH) ppm; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{23}N_7O_2Na$: 404.2089; found: 404.2093.

1-Phenyl-4-{1-[(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}pyrrolidin-2-one (6). A mixture of KOH (0.17 g, 3 mmol), 10 mL of methanol and CS_2 (0.18 mL, 3 mmol) was stirred at room temperature for 20 min. Afterwards, compound **4** (0.35 g, 1 mmol), dissolved in 20 mL methanol, was added into the mixture, and the obtained reaction mixture was heated at reflux for 8 h. The cooled reaction mixture was diluted with diethyl ether 60 mL, the precipitate was filtered off, washed with diethyl ether and dissolved in 10 mL H_2O. The solution was acidified with HCl to pH 2. The precipitate was filtered off, washed with water and recrystallized from methanol to afford a white solid, yield 0.27 g (69%), mp 164–165°C; IR (KBr): 3071, 1703 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.49 (br. s, 2H, ArH), 7.15–7.05 (m, 4H, ArH), 6.62 (d, *J* = 7.4 Hz, 2H, ArH), 6.54 (t, *J* = 7.2 Hz, 1H, ArH), 5.84 (br. s, 1H, NH), 5.59 (s, 2H, NCH_2CO), 3.84–3.74 (m, 2H, NCH_2), 3.57–3.52 (m, 1H, CH), 3.35–2.21 (m, 2H, $COCH_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 178.2 (C=S), 171.8 (C=O), 159.2, 155.8 (C=N), 141.8, 139.2, 135.3, 128.7, 124.1, 122.7, 122.3, 119.5, 119.0, 110.4 (ArC), 52.1 (NCH_2), 38.1 ($COCH_2N$), 37.7 (CH_2CO), 28.5 (CH) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{18}N_5O_2S$: 392.1181; found: 392.1192.

4-{1-[(4-Amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methyl]-1*H*-benzimidazol-2-yl}-1-phenylpyrrolidin-2-one (7). A mixture of KOH (0.17 g, 3 mmol), 10 mL methanol and CS_2 (0.18 mL, 3 mmol) was stirred at room temperature for 20 min. Afterwards, compound **4** (0.35 g, 1 mmol), dissolved in 10 mL of methanol, was added into the mixture, and the obtained reaction mixture was heated at reflux for 8 h. The cooled reaction mixture was diluted with diethyl ether 60 mL, the precipitate was filtered off, washed with diethyl ether and dissolved in 10 mL of hydrazine monohydrate. The solution was heated at reflux for 20 h. The reaction mixture was cooled down, diluted with 20 mL of water and acidified with acetic acid to pH 6. The precipitate was filtered off and recrystallized from water to afford a white solid, yield 0.25 g (62%), mp 162–163°C; IR (KBr): 3169, 3054, 2971, 1652 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.64 (br. s, 1H, NH), 7.69–7.13 (m, 9H, ArH), 5.30 (br. s, 2H, NH_2), 4.94 (s, 1H, CH_2N), 4.27, 4.21 (2br. s, 2H, NCH_2), 4.18–4.10 (m, 1H, CH), 3.03 (br. s, 2H, $COCH_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 172.0 (C=S), 168.8 (C=O), 155.1 (C=N), 147.7, 141.7, 135.2, 132.9, 129.8, 128.6, 128.0, 120.9, 118.9, 117.8, 110.2 (ArC), 51.9 (NCH_2), 45.1 ($COCH_2N$), 37.5 (CH_2CO), 28.2 (CH) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{20}N_7OS$: 406.1450; found: 406.1452.

***N*-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-2-[2-(1-phenyl-5-oxopyrrolidin-3-yl)-1*H*-benzimidazol-1-yl]acetamide (8).** A mixture of **4** (0.35 g, 1 mmol), hexane-2,5-dione (0.29 g, 2.5 mmol), 30 mL of propan-2-ol and 1 mL acetic acid was heated at reflux for 4 h. Afterwards, 100 mL of cold water was added to the reaction mixture. The precipitate was filtered off and recrystallized from propan-2-ol to afford a white solid, yield 0.34 g (80%), mp 219–220°C; IR (KBr): 3199, 1679 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 11.19 (s, 1H, NH), 7.68–7.15 (m, 9H, ArH), 5.65 (s, 2H, CHCH), 5.28 (s, 2H, NCH_2CO), 4.30–4.21 (m, 3H, $NHCH_2$, CH), 3.05–2.97 (m, 2H, $COCH_2$), 2.01 (s, 6H, $2CH_3$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 171.9, 166.6 (2C=O), 155.7 (C=N), 141.9, 135.7, 128.7, 126.8, 124.1, 122.3, 122.0, 119.5, 119.0, 109.7 (ArC), 103.3 (CHCH), 52.1 (CH_2CO), 44.3 ($COCH_2N$), 37.6 (NCH_2), 28.6 (CH), 11.0 ($2CH_3$) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{26}N_5O_2$: 428.2086; found: 428.2084.

2-(2-[2-{5-Oxo-1-phenylpyrrolidin-3-yl}-1*H*-benzimidazol-1-yl]acetyl)-*N*-phenylhydrazine-1-carbothioamide (9). Phenyl isothiocyanate (0.18 mL 1.5 mmol) was added dropwise to the solution of **4** (0.35 g, 1 mmol) in 30 mL of 1,4-dioxane, and the reaction mixture was heated at reflux for 4 h. Then it was cooled down and diluted with 50 mL of H_2O. The precipitate was filtered off, washed with water and recrystallized from methanol to afford a white solid, yield 0.36 g (74%), mp 191–192°C; IR (KBr): 3628, 3278, 3057, 1717, 1675 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.56 (s, 1H, CSNH), 9.76 (s, 1H, CONH), 7.69–7.14 (m, 14H, ArH), 5.12 (s, 2H, $COCH_2N$), 4.29–4.23 (m, 2H, $NHCH_2$), 4.20–4.13 (m, 1H, CH), 3.04–3.02 (m, 2H, $COCH_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 179.9 (C=S), 171.9, 170.0 (C=O), 155.6 (C=N), 141.8, 139.2, 138.9, 135.9, 128.7, 128.2, 124.1, 122.2, 121.8, 119.5, 118.8, 110.1 (ArC), 46.8 (CH_2NH), 35.7 ($COCH_2$), 35.6 (NCH_2), 28.8 (CH) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{25}N_6O_2S$: 485.1763; found: 485.1771.

4-{1-[(4-Phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methyl]-1*H*-benzimidazol-2-yl}-1-phenylpyrrolidin-2-one (10). A mixture of **9** (0.48 g, 1 mmol)

in 20 mL of a 5% aqueous NaOH solution was heated at reflux for 1 h. Then the reaction mixture was cooled to room temperature and acidified with HCl to pH 2. The precipitate was filtered off, washed with water and recrystallized from methanol to afford a white solid, yield 0.45 g (97%), mp 189–190°C; IR (KBr): 3321, 1723, 1679 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.92 (s, 1H, NH), 7.66–7.05 (m, 14H, ArH), 5.43–5.27 (m, 2H, CCH_2N), 3.57–3.35 (m, 2H, NCH_2), 3.33–3.30 (m, 1H, CH), 2.90–2.71 (m, 2H, $COCH_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 173.3 (C=S), 168.8 (C=O), 156.3 (C=N), 148.0, 134.9, 132.9, 129.8, 129.5, 129.1, 128.0, 121.9, 121.7, 119.4, 118.4, 116.0, 111.7, 110.3 (ArC), 46.8 (CH_2NH), 36.8 ($COCH_2$), 32.3 (CH) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{23}N_6OS$: 467.1656; found: 467.1664.

5-[2-(1*H*-Benzimidazol-2-yl)-3-(phenylamino) propyl]-1,3,4-oxadiazole-2(3*H*)-thione (11). A mixture of KOH (0.17 g, 3 mmol), 10 mL of methanol and CS_2 (0.18 mL, 3 mmol) was stirred at room temperature for 20 min. Afterwards, compound **2a** (0.30 g, 1 mmol), dissolved in 20 mL of methanol, was added into the mixture, and the obtained reaction mixture was heated at reflux for 8 h. The cooled reaction mixture was diluted with diethyl ether (60 mL), the precipitate was filtered off, washed with diethyl ether and dissolved in 10 mL of H_2O. The solution was acidified with HCl to pH 2. The precipitate was filtered off and recrystallized from methanol to afford a white solid, yield 0.25 g (71%), mp 172–173°C; IR (KBr): 3051, 2920, 1602 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.41 (s, 1H, CNH), 12.37 (br. s, 1H, NNHCS), 7.51 (br. s, 2H, ArH), 7.16–7.07 (m, 5H, ArH), 6.65 (d, *J* = 7.4 Hz, 2H, ArH), 6.56 (t, *J* = 7.2 Hz, 1H $NHCH_2$), 3.86–3.81 (m, 1H, CH), 3.60–3.41 (m, 2H, $NHCH_2$), 3.35–3.25 (m, 2H, $COCH_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 177.6 (C=S), 162.1, 153.9 (C=N), 146.9, 135.4, 128.7, 123.3, 122.7, 121.1, 119.6, 115.6, 114.5, 113.6 (ArC), 46.3 (CH_2NH), 35.7 ($COCH_2$), 26.9 (CH) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{18}N_5OS$: 352.1242; found: 352.1277.

4-Amino-5-[2-(1*H*-benzimidazol-2-yl)-3-(phenylamino)propyl]-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (12). A mixture of KOH (0.17 g, 3 mmol), 10 mL of methanol and CS_2 (0.18 mL, 3 mmol) was stirred at room temperature for 20 min. Afterwards, compound **2a** (0.30 g, 1 mmol), dissolved in 10 mL of methanol, was added into the mixture, and the obtained reaction mixture was heated at reflux for 8 h. The cooled reaction mixture was diluted with diethyl ether 60 mL, the precipitate was filtered off, washed with diethyl ether and dissolved in 10 mL of hydrazine monohydrate. The solution was heated at reflux for 20 h. The reaction mixture was cooled to room temperature, diluted with 20 mL of water, and acidified with acetic acid to pH 6. The precipitate was filtered off and recrystallized from water to afford a white solid, yield 0.26 g (71%), mp 157–158°C; IR (KBr): 3421, 3321, 3240, 3138, 2994 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.39 (s, 1H, CNH), 12.35 (br. s, 1H, NNHCS), 7.49 (br. s, 2H, ArH), 7.15–7.05 (m, 4H, ArH), 6.63 (d, *J* = 7.4 Hz, 2H, ArH), 6.63 (t, *J* = 7.4 Hz, 1H, ArH), 5.84 (br. s, 2H, $NHCH_2$), 5.59 (s, 2H, NH_2), 3.84–3.79 (m, 1H, CH), 3.56–3.39 (m, 2H, $NHCH_2$), 3.35–3.21 (m, 2H, $COCH_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 173.2 (C=S), 165.6, 155.4 (C=N), 150.6, 148.3, 129.0, 121.3, 115.9, 112.1 (ArC), 47.1 (CH_2NH), 36.1 ($COCH_2$), 26.7 (CH) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{20}N_7S$: 366.1501; found: 366.1506.

3-(1*H*-Benzimidazol-2-yl)-*N*-(2,5-dimethyl-1*H*-pyrrol-1-yl)-4-(phenylamino)butanamide (13). A mixture of 0.30 g **2a** (1 mmol), hexane-2,5-dione (0.25 mL, 2 mmol), 0.5 mL glacial acetic acid and 15 mL of propan-2-ol was heated at reflux for 2 h, the liquid fractions were removed under reduced pressure, the residue was diluted with 20 mL of water, and the solution was heated to a gentle boil. The precipitate was filtered off, washed with water, dried and recrystallized from propan-2-ol to afford a white solid, yield 0.35 g (90%), mp 232–233°C; IR (KBr): 3410, 3202, 1681 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.35 (s, 1H, CNH), 10.74 (s, 1H, CONH), 7.55, 7.45 (2br. s, 2H, ArH), 7.19–7.05 (m, 4H, ArH), 6.68 (d, *J* = 8.1 Hz, 2H, ArH), 6.56 (t, *J* = 7.2 Hz, 1H, ArH), 5.87 (s, 1H, $NHCH_2$), 5.60–5.49 (m, 2H, 2CH), 3.82–3.74 (m, 1H, CH), 3.59–3.37 (m, 2H, $NHCH_2$), 3.01–2.85 (m, 2H, $COCH_2$), 2.09, 1.95, 1.61 (3s, 6H, $2CH_3$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 170.3 (C=O), 155.6 (C=N), 148.4, 129.0, 126.9, 126.6, 120.9, 119.5, 115.9, 112.1, 110.9 (ArC), 102.8, 102.7 (CHCH), 46.9 (CH_2NH), 35.7 ($COCH_2$), 35.4 (CH), 11.0, 10.5 (CH_3) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{26}N_5O$: 388.2137; found: 388.2152.

2-[3-(1*H*-Benzimidazol-2-yl)-4-(phenylamino)-butanoyl]-*N*-phenylhydrazine-1-carbothioamide (14). Phenyl isothiocyanate (0.18 mL 1.5 mmol) was added dropwise to the solution of **2a** (0.30 g, 1 mmol) in 30 mL of 1,4-dioxane, and the reaction mixture was heated at reflux for 4 h. Then it was cooled to room temperature and diluted with 50 mL of H_2O. The precipitate was filtered off, washed with water and recrystallized from methanol to afford a white solid, yield 0.35 g (79%), mp 204–205°C; IR (KBr): 3216, 3029, 1600 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.48 (br. s, 1H, CNH), 10.12, 10.06 (2s, 1H, NH), 9.79, 9.76 (2s, 1H, NH), 9.61, 9.54 (2s,1H, NH), 7.56–7.08 (m, 14H, ArH), 6.94 (t, *J* = 7.3 Hz, 0.35H, $NHCH_2$), 6.67 (d, *J* = 7.9 Hz, 1H ArH), 6.54 (t, *J* = 7.3 Hz, 0.65H, $NHCH_2$), 4.38–4.27 (m, 1H, CH), 3.59–3.41 (m, 2H, $NHCH_2$), 2.84–2.77 (m, 2H, $COCH_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 182.9 (C=S), 172.0 (C=O), 156.1 (C=N), 155.1, 148.4, 143.0, 140.5, 139.0, 129.9, 129.5, 128.9, 128.4, 128.0, 125.9, 125.6, 123.6, 116.8, 112.1 (ArC), 46.5 (CH_2NH), 35.6 ($COCH_2$), 35.0 (CH) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{25}N_6OS$: 445.1798; found: 445.1777.

5-[2-(1*H*-Benzimidazol-2-yl)-3-(phenylamino) propyl]-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (15). A mixture of **9** (0.43 g, 1 mmol) in 20 mL of the 5% aqueous NaOH solution was heated at reflux for 1 h. Then the reaction mixture was cooled to room temperature and acidified with HCl to pH 2. The precipitate was filtered off, washed with water and recrystallized from methanol

to afford a white solid, yield 0.37 g (87%), mp 149–150°C; IR (KBr): 3051, 2920, cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 13.64 (s, 1H, CNH), 12.33 (br. s, 1H, CSNH), 7.56–6.50 (m, 9H, ArH), 5.77 (br. s, 1H, $NHCH_2$), 3.71–3.64 (m, 1H, CH), 3.48–3.26 (m, 2H, $NHCH_2$), 3.09–2.98 (m, 2H, $COCH_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 167.5 (C=S), 155.1 150.8 (C=N), 148.1, 133.5, 129.5, 129.4, 128.9, 128.8, 128.6, 128.3, 118.2, 117.8, 115.9, 112.0 (ArC), 46.8 (CH_2NH), 36.4 ($COCH_2$), 27.5 (CH) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{23}N_6S$: 427.1704; found: 427.1715.

5-[3-(Phenylamino)-2-{1-[(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}propyl]-1,3,4-oxadiazole-2(3*H*)-thione (16). A mixture of KOH (0.17 g, 3 mmol), 10 mL of methanol and CS_2 (0.18 mL, 3 mmol) was stirred at room temperature for 20 min. Afterwards, compound **5** (0.38 g, 1 mmol), dissolved in 20 mL of methanol, was added into the mixture, and the obtained reaction mixture was heated at reflux for 8 h. The cooled reaction mixture was diluted with diethyl ether 60 mL, the precipitate was filtered off, washed with diethyl ether and dissolved in 10 mL of H_2O. The solution was acidified with HCl to pH 2. The precipitate was filtered off, washed with water and recrystallized from methanol to afford a white solid, yield 0.32 g (69%), mp 183–184°C; IR (KBr): 3398, 3261, 2967, 2853 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 14.25 (br. s, 1H, NH), 7.69–7.55 (m, 4H, ArH), 7.29–7.23 (m, 3H, ArH), 7.07 (t, *J* = 7.8 Hz, 2H, ArH), 6.58–6.51 (m, 1H $NHCH_2$), 5.23 (s, 1H, NH), 5.16 (d, *J* = 5.7 Hz, 2H, NCH_2), 3.84–3.77 (m, 1H, CH), 3.52–3.43 (m, 2H, $NHCH_2$), 3.36 (d, *J* = 6.9 Hz, 2H, $COCH_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 178.0, 177.6 (C=S), 162.4, 154.9 (C=N), 148.0, 139.2, 129.1, 128.7, 124.1, 122.4, 119.5, 116.3, 112.1, 110.5, 110.2 (ArC), 46.8 (CH_2CO), 44.4 (CH_2N), 33.4 (NCH_2), 27.8 (CH) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{20}N_7O_2S_2$: 466.1101; found: 466.1102.

4-Amino-5-({2-[1-(4-amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-3-(phenylamino)propan-2-yl]-1*H*-benzimidazol-1-yl}methyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (17). A mixture of KOH (0.17 g, 3 mmol), 10 mL of methanol and CS_2 (0.18 mL, 3 mmol) was stirred at room temperature for 20 min. Afterwards, compound **5** (0.38 g, 1 mmol), dissolved in 10 mL of methanol, was added into the mixture, and the obtained reaction mixture was heated at reflux for 8 h. The cooled reaction mixture was diluted with 60 mL of diethyl ether, the precipitate was filtered off, washed with diethyl ether and dissolved in 10 mL hydrazine monohydrate. The solution was heated at reflux for 20 h. The reaction mixture was cooled to room temperature, diluted with 20 mL of water and acidified with acetic acid to pH 6. The precipitate was filtered off and recrystallized from water to afford a white solid, yield 0.41 g (83%), mp 167–168°C; IR (KBr): 3339, 3303, 3250, 3167, 3133, 3100, 3035 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 11.19 (s, 1H, NH), 10.77 (2s, 1H, NH), 7.66–7.15 (m, 9H, ArH), 6.56 (d, *J* = 8.8 Hz, 2H, NH_2), 6.08 (t, *J* = 5.9 Hz, 1H, $NHCH_2$), 5.65 (s, 2H, NH_2), 5.31–5.11 (m, 2H, NCH_2), 3.85–3.78 (m, 1H, CH), 3.56–3.42 (m, 2H, $NHCH_2$), 3.00–2.91 (m, 2H, $COCH_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 170.4, 170.1 (C=S), 156.1 (C=N), 148.2, 142.2, 135.2, 129.1, 126.5, 121.6, 119.5, 118.4, 116.1, 112.0, 110.1, 102.8 (ArC), 46.7 (CH_2CO), 44.3 (CH_2N), 36.4 (CH_2NH), 32.6 (CH) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{24}N_{11}S_2$: 494.1657; found: 494.1659.

***N*-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-3-(1-{2-[(2,5-dimethyl-1*H*-pyrrol-1-yl)amino]-2-oxoethyl}-1*H*-benzimidazol-2-yl)-4-(phenylamino)butanamide (18).** A mixture of **5** (0.38 g, 1 mmol), hexane-2,5-dione (0.48 g, 5 mmol), 30 mL of propan-2-ol and 1 mL of acetic acid was heated at reflux for 4 h. Afterwards, 50 mL of cold water were added. The precipitate was isolated by filtration and recrystallization from propan-2-ol to afford a white solid, yield 0.48 g (89%), mp 147–148°C; IR (KBr): 3268, 2921, 1681 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 11.19 (s, 1H, NH), 10.77 (s, 1H, NH), 7.64–6.57 (m, 9H, ArH), 6.05 (t, *J* = 5.9 Hz, 1H, NH), 5.64 (s, 2H, 2CH), 5.57 (s, 1H, CH), 5.50 (s, 1H, CH), 5.31–5.11 (m, 2H, NCH_2CO), 4.56 (s, 2H, NH_2), 3.83–3.78 (CH), 3.58–3.44 (m, 2H, $NHCH_2$), 2.98–2.91 (m, 2H, $COCH_2$), 1.98, 1.94 (2s, 9H, $3CH_3$), 1.42 (s, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 170.4, 166.9 (C=O), 156.3 (C=N), 147.2, 142.3, 135.0, 128.7, 126.5, 122.1, 121.9, 119.2, 118.6, 113.3, 109.7 (ArC), 103.3, 102.9 (CH), 46.7 (NCH_2), 43.9 ($COCH_2N$), 36.3 (CH_2CO), 32.6 (CH), 10.9, 10.2 (CH_3) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{31}H_{36}N_7O_2$: 538.2930; found: 538.2924.

2-[2-{2-(4-Oxo-1-(phenylamino)-4-[2-(phenylcarbamothioyl)hydrazinyl]butan-2-yl)-1*H*-benzimidazol-1-yl}acetyl]-*N*-phenylhydrazine-1-carbothioamide (19). Phenyl isothiocyanate (0.36 mL 3 mmol) was added dropwise to the solution of **5** (0.38 g, 1 mmol) in 30 mL of 1,4-dioxane, and the reaction mixture was heated at reflux for 6 h. Then it was cooled to room temperature and diluted with 60 mL of water. The precipitate was filtered off, washed with water and recrystallized from methanol to afford a white solid, yield 0.56 g (86%), mp 169–170°C; IR (KBr): 3213, 3112, 2939, 1598 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.57 (br. s, 1H, NH), 9.77 (s, 2H, 2NH), 7.68–7.14 (m, 20H, ArH, N*H*CH_2), 5.18–5.12 (m, 2H, $COCH_2N$), 4.30–4.11 (m, 4H, NH, CH, NHC*H*$_2$), 3.03 (d, *J* = 8.1 Hz, 2H, $COCH_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 181.4, 181.1 (C=S), 171.9 (C=O), 155.6 (C=N), 141.8, 139.2, 138.9, 135.9, 128.7, 128.2, 124.1, 122.2, 121.8, 119.5, 118.8, 110.1 (ArC), 52.2 (NCH_2), 44.3 ($COCH_2N$), 37.7 (CH_2CO), 28.8 (CH) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{33}H_{34}N_9O_2S_2$: 652.2277; found: 652.2264.

4-Phenyl-5-{[2-(1-[4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-3-(phenylamino)-propan-2-yl)-1*H*-benzimidazol-1-yl]methyl}-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (20). A mixture of **19** (0.65 g, 1 mmol) in 20 mL of the 5% aqueous NaOH solution was heated at reflux for 1 h. Then the reaction mixture was cooled down and acidified with HCl to pH 2. The precipitate was filtered off, washed with water and recrystallized from

methanol to afford a white solid, yield 0.56 g (91%), mp 199–200°C; IR (KBr): 3415, 3197, 2694, 1683 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 13.93 (s, 1H, NH), 12.33 (br. s, 1H, NH), 7.71–6.99 (m, 19H, ArH), 6.61–6.48 (m, 1H, N*H*CH_2), 5.48–5.26 (m, 2H, $COCH_2N$), 3.88 (br. s, 1H, CH), 3.05 (t, *J* = 8.3 Hz, 2H, $NHCH_2$), 2.87–2.73 (m, 2H, $COCH_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 173.2 (C=S), 173.0 (C=O), 156.5 (C=N), 147.9, 141.7, 138.6, 134.8, 132.9, 129.5, 129.1, 128.7, 128.0, 126.1, 123.6, 122.4, 122.0, 121.0, 119.5, 116.9, 116.0, 112.0, 111.7 (ArC), 74.0 (NCH_2), 46.7 ($COCH_2N$), 36.7 (CH_2CO), 32.3 (CH) ppm; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{33}H_{30}N_9S_2$: 616.2067; found: 616.2051.

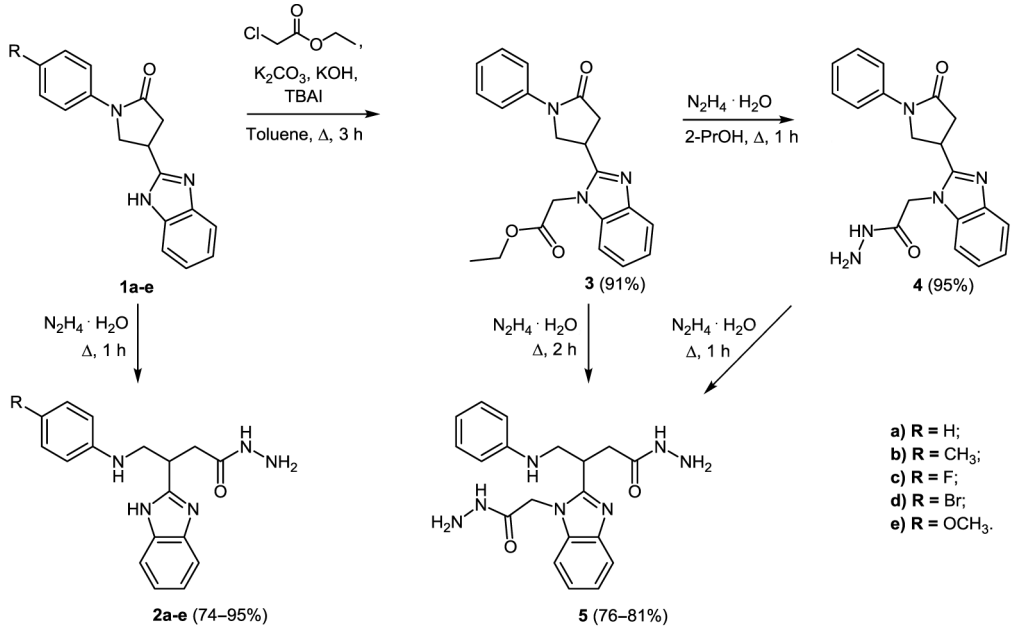
MICROBIOLOGY

The following bacteria strains were used: gram-positive cocci *Staphylococcus aureus* (ATCC 9144), gram-negative rods *Escherichia coli* (ATCC 8739), *Pseudomonas aeruginosa* (NCTC 6750) and *Bacillus cereus* (ATCC). The tryptic soy agar (TSA) and the tryptic soy broth (TSB) were used for bacteria cultivation and antibacterial activity tests. The antimicrobial activity of the compounds was determined by testing their different concentrations against *B. cereus*, *S. aureus*, *E. coli*, *P. aeruginosa* and *B. cereus* strains by the broth-dilution and spread plate methods [28, 29]. The test bacteria *S. aureus*, *E. coli*, *P. aeruginosa* and *B. cereus* were streaked out on TSA plates and incubated at 37°C for 24 h. A representative colony was placed in 5 cm^3 of TSB and incubated at 37°C for 24 h. *S. aureus*, *E. coli*, *P. aeruginosa* and *B. cereus* cultures containing 10^7 CFU/cm^3 (colony-forming units corresponding to MC Farland's) were prepared by dilution with TSB and used for antimicrobial tests. Solutions of the tested compounds in the range of concentrations 1000, 500, 250, 125, 62.5, 31.25, 15.6, 7.8, 3.9, 1.95 and 0.98 μg/cm^3 were prepared for each sample. The test organisms (100 μL) were added to each tube and incubated at 37°C for 24 h. At the end of this period, a small amount of the diluted mixture from each tube was pulled out and spread on the TSA. The plates were incubated at 37°C for 48 h. The growth of bacterial cells was observed on agar plates. The lowest concentration of the bacterial material, at which no growth was observed, was considered as the minimum bactericidal concentration (MBC) value [30]. The minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial that inhibits the visible growth of a microorganism after overnight incubation. Oxytetracycline inoculated with the test bacteria *S. aureus*, *E. coli*, *P. aeruginosa* and *B. cereus* in the tubes and plates was used as a control for antibacterial activity screening. The growth of the test microorganism cells was observed on agar plates.

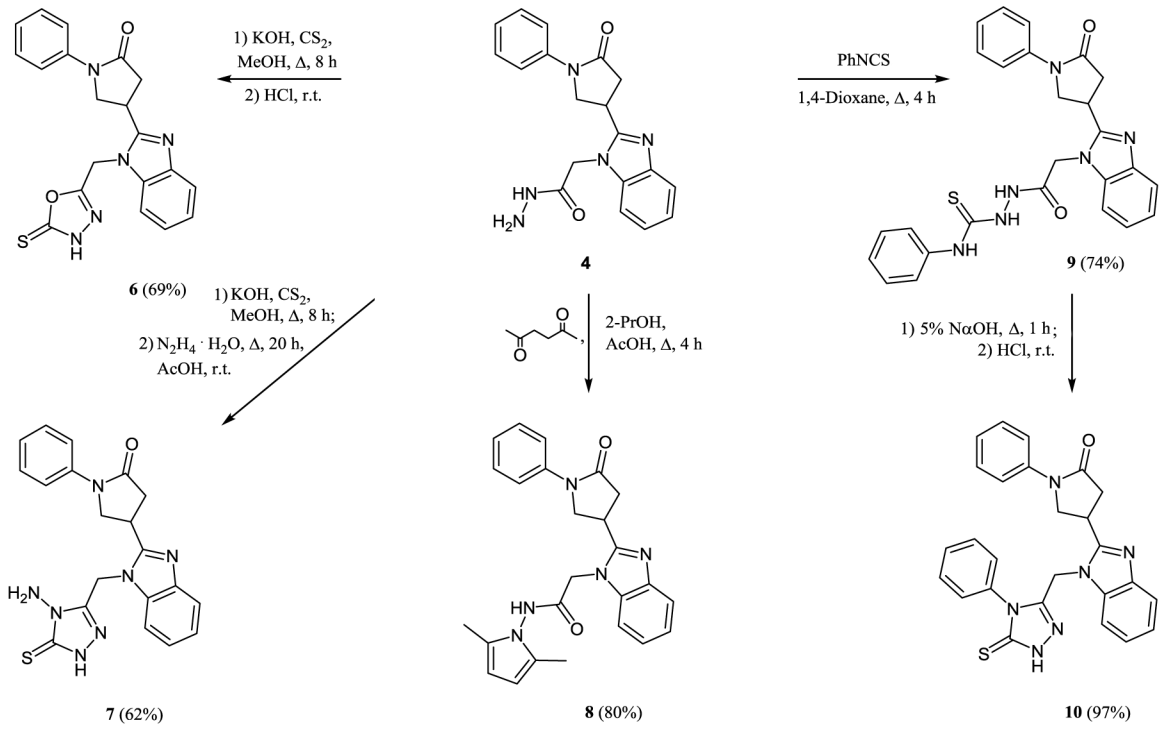
RESULTS AND DISCUSSION

Chemistry

In this work, we have determined that 3-(1*H*-benzimidazol-2-yl)-4-[(phenyl and 4-substituted phenyl)amino] butanohydrazides (**2a–f**) can be obtained in good yields directly from the corresponding 4-(1*H*-benzimidazol-2-yl)-1-phenyl(substituted phenyl)-2-pyrrolidinones **1a–e** (Scheme 1) by heating them under reflux in an excess of hydrazine monohydrate. The synthesized hydrazides **2a–e** were isolated from the reaction mixtures by diluting them with water.



Scheme 1. Synthesis of hydrazides **2a–e** and dihydrazide **5**

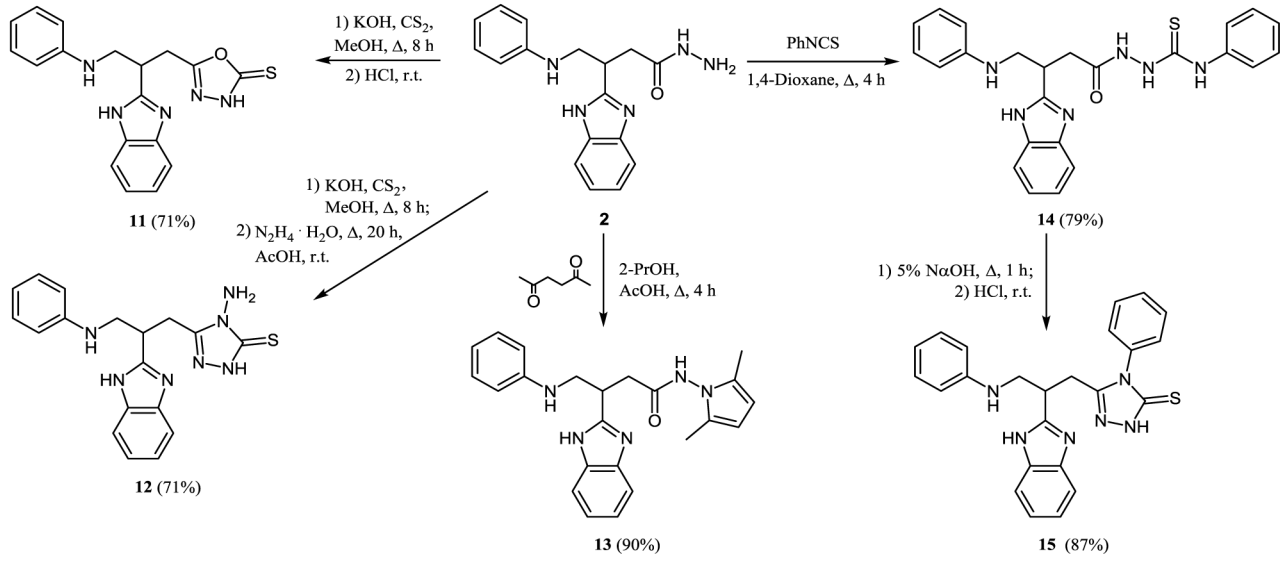


Scheme 2. Synthesis of azoles **6–10**

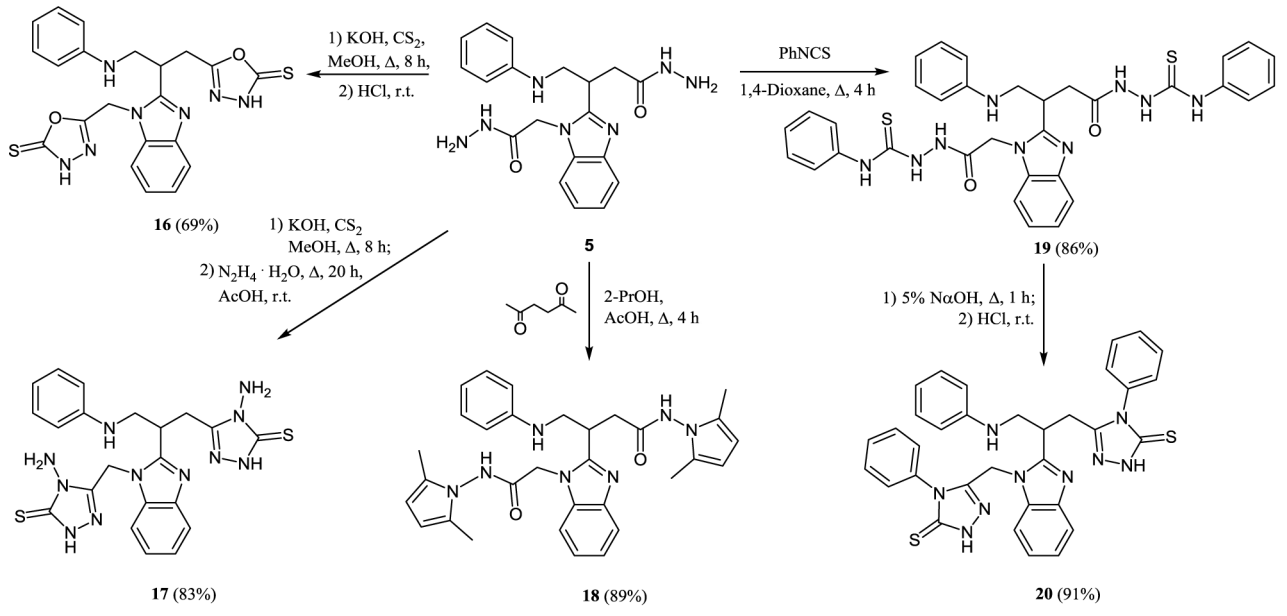
Also similarly reacting pyrrolidinone **3** containing an *N*-substituted benzimidazole ring, and dihydrazide **5** was formed. The broad singlet of PhNH and 4-R-PhNH at 5.30–6.53 ppm in the ^{1}H NMR spectra of compounds **2a–e** and **5** confirmed the existence of an open chain.

Hence, a simple method is proposed for the preparation of 3-(1*H*-benzimidazol-2-yl)-4-[(4-substituted phenyl) amino]butanohydrazides in a high yield, which are versatile precursors in the synthesis of a series of heterocyclic systems. One of the practical goals of this work was the synthesis of antibacterial compounds; a hydrazide fragment was used for the synthesis of functionalized azoles to evaluate their influence on antibacterial properties. Therefore, 2-[2-(5-oxo-1-phenylpyrrolidin-3-yl)-1*H*-benzimidazol-1-yl]acetohydrazide **(4)** was synthesized (Scheme 2). This compound was obtained from ester **3** which was synthesized by alkylating **1a** with ethyl 2-chloroacetate. The hydrazinolysis of the ester was carried out under mild conditions in the boiling propan-2-ol.

The synthesis route of functionalized azoles is presented in Schemes 2–4. All oxadiazoles, **6, 11** and **16**, were synthesized from hydrazides **2a, 4** and **5** and carbon disulphide



Scheme 3. Synthesis of azoles **11–15**



Scheme 4. Synthesis of azoles **16–20**

in methanol, in the presence of potassium hydroxide, and the corresponding potassium dithiocarbazates were formed. The latter were converted to the respective oxadiazoles **6, 11** and **16** while acidifying them with hydrochloric acid.

The corresponding aminotriazoles **7, 12** and **17** were obtained by heating potassium dithiocarbazates with hydrazine monohydrate. The proton resonances at 5.30, 5.59 and 5.65 ppm, attributed to the NH_2 group of compounds **7**, **12** and **17**, confirmed the substitution at the 4th position of the triazole ring.

The reactions of hydrazides **2a, 4** and **5** with pentane-2,4-dione and hexane-2,5-dione were investigated. It was found that hydrazides **2a, 4** and **5** with hexane-2,5-dione gave compounds **8, 13** and **18** with a dimethylpyrrole ring. Hydrazides **2a** and **5** with pentane-2,4-dione were cyclized into 2-pyrrolidinone derivatives during the reaction, probably due to the diketone acidity.

The starting compounds for the synthesis of phenylsubstituted triazoles – thiosemicarbazides **9, 14** and **19** were synthesized by refluxing the respective dihydrazides **2a, 4** and **5** with phenylisothiocyanate in 1,4-dioxane. The conversion of thiosemicarbazides **9, 14** and **19** to triazoles **10, 15** and **20** was carried out by refluxing them in the aqueous 5% NaOH solution with the subsequent acidification of the reaction mixture with hydrochloric acid.

The analysis of the aromatic region of the ^{1}H and ^{13}C NMR spectra compounds **10, 15** and **20** showed the additional spectral peaks characteristic of a phenyl ring.

Biology

The antimicrobial activity of compounds **2–20** was screened by testing their different concentrations against the gram-positive cocci *Staphylococcus aureus* (ATCC 9144) and gram-negative rods *Escherichia coli* (ATCC 8739), *Pseudomonas aeruginosa* (NCTC 6750) and *Bacillus cereus* (ATCC 11778) by the broth and spread-plate methods. The minimum inhibition concentration (MIC, μg/cm^3) and the minimum bactericidal concentration (MBC, μg/cm^3) values are presented in the Table. A broad-spectrum antibiotic oxytetracycline was used as a positive control for *S. aureus*, *E. coli*, *P. aeruginosa* and *B. cereus*. The antibiotic was effective at the 62.5 μg/cm^3 concentration of MIC and MBC against the test strains *S. aureus* and *B. cereus*, and at 250 μg/cm^3 of MIC and MBC against *E. coli* and *P. aeruginosa in vitro.* The screening data for antibacterial activity have revealed that the majority of the synthesized compounds possess the antibacterial activity higher than that of oxytetracycline. Among hydrazydes **2 a–e, 4** and **5**, an exceptional antibacterial activity was demonstrated by compound **2d** containing a bromo substituent in the benzene ring with the MIC values of 0.98 μg/cm^3 and the MBC values of 1.95 μg/cm^3 against *E. coli* and *S. aereus* strains, which are almost 60 and 130 times, respectively, higher than those for the control. Hydrazide **4** demonstrated an exceptional antibacterial activity on all tested bacteria. Oxadiazole-5-thione derivatives **6, 11** and **16** containing an acyclic aliphatic chain or a pyrrolidinone moiety almost did not inhibit bacterial growth at all. The presence of an acyclic fragment -NH-NH-SC-NH- in semicarbazides **9, 14** and **19** containing an acyclic aliphatic chain did not inhibit bacterial growth at all, whereas **9**, containing a pyrrolidinone moiety, exhibited an average antibacterial activity in comparison with the other screened compounds. Among the latter, an exceptional antibacterial activity has been demonstrated by 1,2,4-triazole-3-thiones **10, 15** and **20** with a phenyl substituent in the triazole ring, and the highest antibacterial

Table. **Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values for the tested compounds 2–20**

Compound	*S. aureus*		*E. coli*		*P. aeruginosa*		*B. cereus*	
	MIC, μg/cm³	MBC, μg/cm³	MIC, μg/cm³	MBC, μg/cm³	MIC, μg/cm³	MBC, μg/cm³	MIC, μg/cm³	MBC, μg/cm³
2a	0.98	1.95	250	250	250	250	250	250
2b	250	250	250	250	500	500	250	250
2c	62.5	125	62.5	125	31.25	62.5	31.25	62.5
2d	0.98	1.95	0.98	1.95	250	250	500	500
2e	125	125	125	250	125	250	125	250
3	15.63	31.25	62.5	125	500	500	62.5	125
4	0.98	1.95	125	250	15.6	31.25	0.98	1.95
5	125	250	62.5	125	62.5	31.25	125	250
6	125	250	125	250	125	250	250	250
7	62.5	125	125	250	62.5	125	62.5	125
8	3.9	7.8	62.5	125	7.8	15.6	62.5	125
9	0.98	1.95	0.98	1.95	7.8	15.6	0.98	1.95
10	0.98	1.95	15.6	31.25	15.6	31.25	15.6	31.25
11	62.5	125	62.5	250	125	250	125	250
12	125	250	125	250	125	250	125	250
13	62.5	125	62.5	125	250	500	250	500
14	250	500	250	500	125	250	125	250
15	0.98	1.95	0.98	1.95	0.98	1.95	0.98	1.95
16	250	250	250	250	62.5	125	62.5	125
17	250	250	250	250	125	250	125	250
18	0.98	1.95	0.98	1.95	0.98	1.95	0.98	1.95
19	250	500	250	500	62.5	125	31.25	62.5
20	62.5	125	31.25	62.5	250	500	62.5	125
C*	62.5	62.5	250	250	250	250	62.5	62.5

* Oxytetracycline was used as a control for *S. aureus*, *E. coli*, *P. aeruginosa* and *B. cereus*.

activity was demonstrated among compounds with one 1,2,4-triazole fragment. The replacement of the benzene ring by NH_2 at the 4th position of the triazole ring in **7, 12** and **17** decreased the antibacterial activity against all tested bacteria strains. Pyrroles **8** and **18** showed a very good bactericidal activity against all tested bacteria.

CONCLUSIONS

In summary, a series of *N*-substituted γ-amino acid hydrazides bearing a benzimidazole moiety by the nucleophilic ring-opening reaction of pyrrolidin-2-one derivatives were obtained. On the basis of these compounds with a high antibacterial activity azoles were synthesized. *N*-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-3-(1-{2-[(2,5-dimethyl-1*H*-pyrrol-1-yl) amino]-2-oxoethyl}-1*H*-benzimidazol-2-yl)-4-(phenylamino)butanamide **(18)** and 5-[2-(1*H*-benzimidazol-2-yl)-3-(phenylamino)propyl]-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **(15)** with the MIC values of 0.98 μg/cm³ against *E. coli, S. aereus*, *P. aeruginosa and B. cereus* strains, which are almost 60 and 250 times higher, and with the MBC values of 1.95 μg/cm³, respectively, are almost 30 and 130 times higher as compared with the control.

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References

1. J. Wen, Y.-L. Luo, H.-Z. Zhang, H.-H. Zhao, C.-H. Zhou, G.-X. Cai, *Chin. Chem. Lett.*, **27**, 391 (2016).
2. M. Gaba, C. Mohan, *Med. Chem.*, **5**, 58 (2015).
3. U. A. Çevik, B. N. Sağlık, Y. Özkay, et al., *Curr. Pharm. Des.*, **23**, 2276 (2017).
4. M. P. Nitin, P. T. Gowda, *Int. Res. J. Pharm.*, **3**, 189 (2012).
5. R. S. Keri, C. K. Rajappa, S. A. Patil, B. M. Nagaraja, *Pharmacol. Rep.*, **68**, 1254 (2016).
6. E. Apohan, U. Yilmaz, O. Yilmaz, et al., *J. Organomet. Chem.*, **828**, 52 (2017).
7. R. Kenchappa, Y. D. Bodke, S. Telkar, M. A. Sindhe, *J. Chem. Biol.*, **10**, 11 (2017).

8. Y. Özkay, Y. Tunali, H. Karaca, İ. Işıkdağ, *Eur. J. Med. Chem*., **45**, 3293 (2010).
9. M. Bretner, A. Baier, K. Kopańska, et al., *Antivir. Chem. Chemother*., **16**, 315 (2005).
10. M. Alamgir, D. S. C. Black, N. Kumar, *Top. Heterocycl. Chem*., **9**, 87 (2007).
11. J. D. Bhosale, A. R. Shirolkar, U. D. Pete, et al., *J. Pharm. Res*., **7**, 582 (2013).
12. T. Tomašič, M. Mirt, M. Barančoková, et al., *Bioorganic Med. Chem*., **25**, 338 (2017).
13. V. A. Kokorekin, A. O. Terenťev, G. V. Ramenskaya, N. É. Grammatikova, G. M. Rodionova, A. I. Ilovaiskii, *Pharm. Chem. J.*, **47**, 422 (2013).
14. F. Macaev, Z. Ribkovskaia, S. Pogrebnoi, et al., *Bioorg. Med. Chem*., **19**, 6792 (2011).
15. J. Wu, S. Kang, L. Luo, et al., *Chem. Cent. J*., **7**, 64 (2013).
16. G. G. Ladani, M. P. Patel, *New J. Chem*., **39**, 9848 (2015).
17. Q.-R. Du, D.-D. Li, Y.-Z. Pi, et al., *Bioorg. Med. Chem*., **21**, 2286 (2013).
18. B. Kaya, W. Hussin, L. Yurttaş, et al., *Drug Res*., **67**, 275 (2017).
19. B. S. Patil, G. Krishnamurthy, M. R. Lokesh, N. D. Shashikumar, H. S. Bhojya Naik, P. R. Latthe, *Med. Chem. Res*., **22**, 3341 (2013).
20. J. Stefanska, D. Szulczyk, A. E. Koziol, et al., *Eur. J. Med. Chem*., **55**, 205 (2012).
21. T. C. Kühler, M. Swanson, B. Christenson, et al., *J. Med. Chem*., **45**, 4282 (2002).
22. T. Plech, B. Kaproń, A. Paneth, et al., *Eur. J. Med. Chem*., **97**, 94 (2015).
23. K. Gobis, H. Foks, K. Bojanowski, E. Augustynowicz-Kopeć, A. Napiórkowska, *Bioorg. Med. Chem*., **20**, 137 (2012).
24. M. Mickevicius, J. Z. Beresnevicius, V. Mickevicius, G. Mikulskiene, *Heteroatom Chem*., **17**, 47 (2006).
25. K. Mickevičienė, A. Voskienė, V. Mickevičius, *Res. Chem. Intermed*., **40**, 1619 (2014).
26. V. Strelciunaite, K. Anusevicius, I. Tumosiene, et al., *Heterocycles*, **2**, 235 (2016).
27. R. Vaickelioniene, V. Mickevicius, *Chem. Heterocycl. Compd.*, **42**, 753 (2006).
28. E. López-Oviedo, A. I. Aller, C. Martín, et al., *Antimicrob. Agents Chemother*., **50**, 1108 (2006).
29. B. Goodson, A. Ehrhardt, S. Ng, et al., *Antimicrob. Agents Chemother*., **43**, 1429 (1999).
30. M. Balouiri, M. Sadiki, S. K. Ibnsouda, *J. Pharm. Anal*., **6**, 71 (2016).

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NUKLEOFILINIS 1,4-DIPAKEISTŲ 2-PIROLIDINONŲ CIKLO ATIDARYMAS HIDRAZINU. AZOLŲ, PASIŽYMINČIŲ GEROMIS ANTIBAKTERINĖMIS SAVYBĖMIS, SINTEZĖ

S a n t r a u k a

Susintetinti nauji N-fenil pakeistų γ-aminorūgščių hidrazidai, turintys 1- ar 1,2-pakeisto benzimidazolo fragmentus tiesiogiai iš 1,4-dipakeistų-2-pirolidinonų virinant juos gryname hidrazino monohidrate. Gauti junginiai buvo panaudoti įvairių azolų – pirolo, oksadiazolo, triazolo – darinių sintezėje. Atlikti susintetintų junginių antibakteriniai tyrimai, naudojant *Staphylococcus aureus* (ATCC 9144), *Escherichia coli* (ATCC 8739), *Pseudomonas aeruginosa* (NCTC 6750) ir *Bacillus cereus* (ATCC) bakterijas. Nustatyta, kad dauguma tirtų junginių efektyviai slopina bakterijų dauginimąsi. Aktyviausi iš jų yra junginiai, savo struktūroje turintys pirolo ar fenilpakeistus triazolo ciklus.