Synthesis of Bis Azole, Diazole, and Triazole Derivatives from *N*-(4-Chloro/Iodophenyl)-*N*-carboxyethyl-β-alanine Dihydrazides

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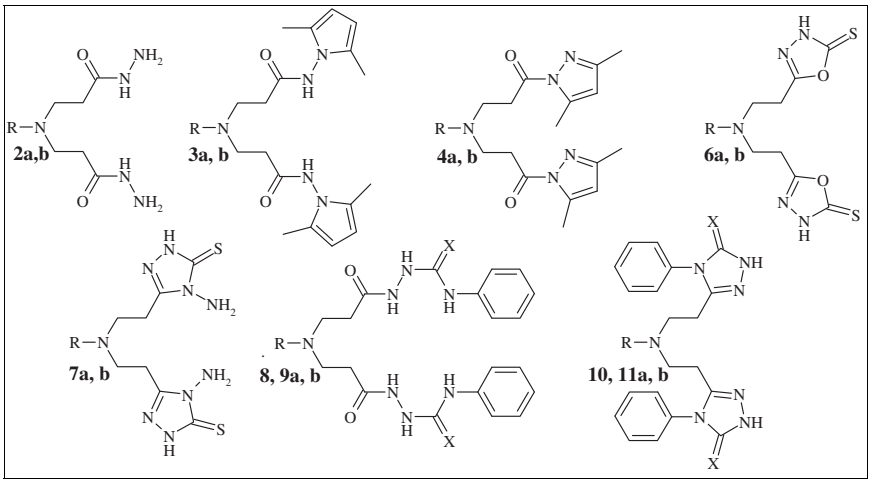

A new potentially biologically active *N*-(4-chloro/iodophenyl)-*N*-carboxyethyl-β-alanine derivatives **(2–4, 8, 9a,b)** and products of their cyclization **(6, 7, 10, 11a,b)** were obtained and characterized by the methods of ^{1}H-NMR, ^{13}C-NMR, IR, mass spectroscopy, and elemental analysis.

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INTRODUCTION

Modification of β-amino acids as potential substances for organic synthesis is presently a prevailing method. Their fragments are structural parts of peptides, coenzymes, alkaloids, and antibiotics. Substituted β-amino acids are excellent synthons for the synthesis of azetidine [1–4], pyridine [5–8], pyrimidine [9–11], quinoline [12,13], and other heterocyclic systems [14,15] possessing valuable practical properties. Carbohydrazides of N-substituted β-amino acids can be used in the synthesis of important heterocyclic compounds. Recently, the heterocyclicstructures such as azole [16], oxadiazoles, and triazole derivatives have appeared to be fast track because of their diverse fungicidal [11,14,17], antiinflammatory [15] antibacterial [11,17], antiviral [18], anticancer [19], antihelminthic [20], crop-protective (herbicidal, fungicidal, and insecticidal) [20] biological activities. Considering the aforementioned facts, this work relates to the synthesis and structural studies of some heterocyclic structures derived from *N*-(4-chloro/iodophenyl)-*N*-carboxyethyl-β-alanines.

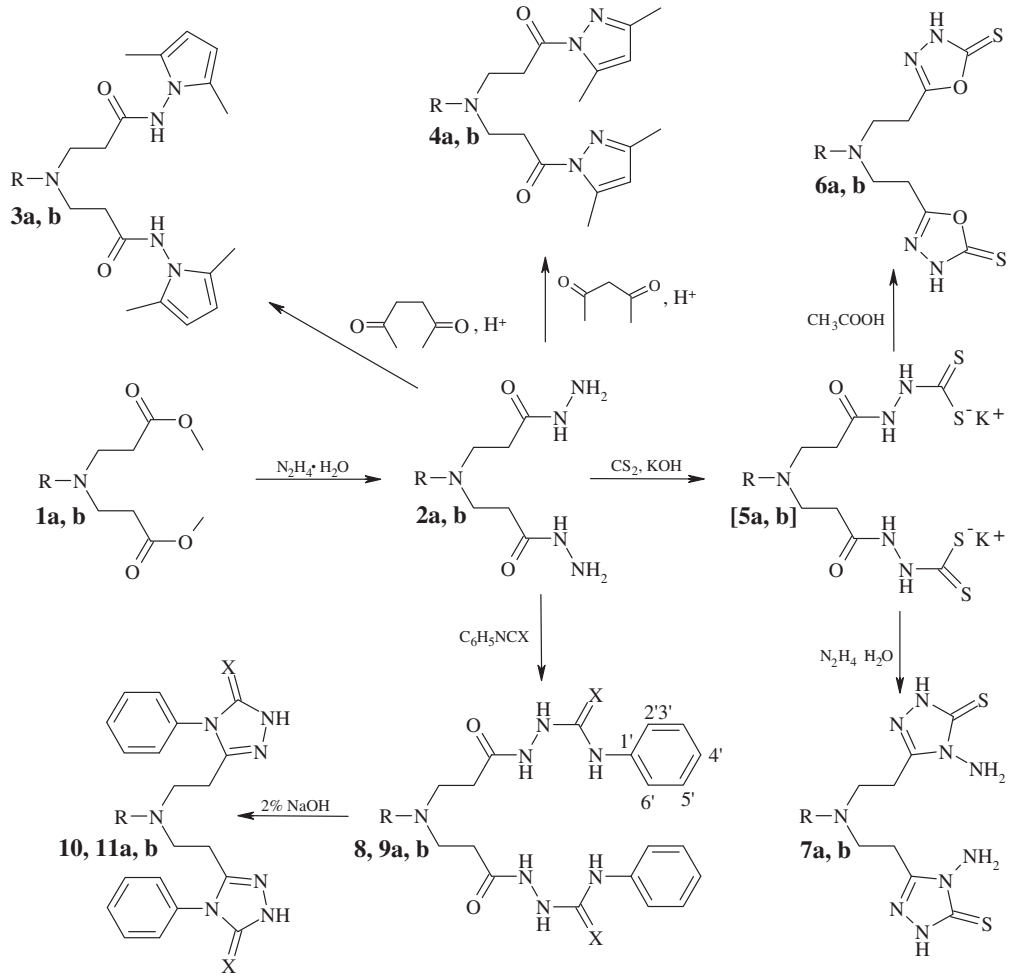
RESULTS AND DISCUSSION

Azoles and their separate structural fragments are among the most extensively studied compounds [22–28]. In continuation of our interest in the chemistry of N-substituted β-amino acids, *N*-(4-chloro/iodophenyl)-*N*-carboxyethyl-β-alanine dihydrazides were selected for the synthesis of bis azole, diazole, and triazole derivatives (Scheme 1).

The structure of all the newly synthesized compounds has been confirmed by elemental analysis, IR, mass, and ^{1}H-NMR and ^{13}C-NMR spectral data. The assignment of resonances in the NMR spectra was based on the chemical shift theory, multiplicities, intensity, and a comparison with similar spectral characteristics of structurally related compounds [29–41].

The starting compounds—carbohydrazides **2a,b**—were synthesized by the reaction of dicarboxylic acid esters and hydrazine hydrate in boiling 2-propanol with 78–80% yields as illustrated in Scheme 1. Azole derivatives can be obtained by the interaction of carbohydrazides and diketones. Functionalized pyrrole derivatives **3a,b** were prepared by refluxing a mixture of the corresponding

Scheme 1. Synthesis of compounds **2–11a,b**.



R = **a)** 4-Cl-C_6H_4; **b)** 4-I-C_6H_4; **8, 10** X = O; **9, 11** X = S

carbohydrazide **2**, 2,5-hexanedione, 2-propanol, and the catalytic amount of glacial acetic acid. The obtained products were identified from the characteristic resonances of the four CH_3 groups of the pyrrole ring varying in the range 1.92–1.98 ppm with the intensity ratio of 0.1:0.8:0.1 and signals at 5.62 and 5.69 ppm, attributed to the CH groups. Such dissolution of signals may be conditioned by constrained rotation of pyrrole fragments of symmetric molecules around the amide bond. The peaks of the above-mentioned appropriate groups in the usual region of the ^{13}C-NMR spectra confirmed the formation of the pyrrole heterocycle.

In this work, bis 3,5-dimethylpyrazole derivatives **4a,b** in a good yield were prepared by refluxing a mixture of the corresponding carbohydrazide **2**, 2,4-pentanedione, 2-propanol, and a catalytic amount of hydrochloric acid. The resonances at 2.15 and 2.45 ppm (CH_3 groups), and 6.17 ppm (C═CH─C group) in the ^{1}H-NMR spectra confirmed formation of pyrazole rings. The resonances at ~ 13.38 ppm and ~ 14.00 ppm of CH_3 groups in the ^{13}C-NMR spectra of the **4a,b** molecules and the signals at ~ 111.00 ppm, which were attributed to the CH, prove the presence of the five-membered heterocycle. The resonances observed at about 143.00 ppm and at about 151.40 ppm were ascribed to the carbons of the N-C and N═C groups of heterocycles, respectively.

One of the ways to obtain oxadiazole heterosystems is their synthesis from dithiocarbazates. In this work, bis 1,3,4-oxadiazoles **6a,b** were prepared by refluxing respective dihydrazides **2a,b**, carbon disulfide, and potassium hydroxide in 2-propanol, followed by the dissolution of the resulting potassium dithiocarbazates **5a,b** in water and treatment of the obtained solution with acetic acid to pH 6. The presence of broad singlets at ~ 14.35 ppm of NH protons in ^{1}H-NMR

spectra and two resonances at ~ 162.30 ppm and ~ 177.62 ppm, attributed to the N=C and C=S groups, respectively, in ^{13}C-NMR spectra confirmed the formation of five-membered oxadiazole rings in compound **6a,b**.

Dithiocarbazates **5a,b** were also used for the synthesis of triazoles. The bis 4-amino-1,2,4-triazole derivatives **7a,b** were prepared by refluxing the aqueous solution of dithiocarbazates **5a,b** with hydrazine hydrate. The ^{1}H-NMR and ^{13}C-NMR spectra showed the new signals differing from the ones of **6a,b**. The most important evidence for the structure of **7a,b** was the appearance of resonances at ~ 150.05 ppm (C=N) and ~ 165.91 ppm (C=S) in ^{13}C-NMR spectra. The NH group signals integrated for one proton and the NH_2 ones integrated for two protons, which resonated at ~ 13.50 ppm and at 5.60 ppm, respectively, in ^{1}H-NMR spectra also confirmed the products of this cyclization.

The starting compounds for the synthesis of phenyl-substituted triazoles—*N*-phenylhydrazinecarboxamides **8a,b** and *N*-phenylhydrazinecarbothioamides **9a,b**— were synthesized by refluxing the respective dihydrazides **2a,b** with phenyliso- and phenylisothiocyonates in methanol. Characteristic resonances observed at 170.48 ppm (-CH_2CONH-) and at ~ 155.30 ppm (-NHCONH-) in ^{13}C-NMR spectra and resonances at 8.05 ppm (-CONHNHCO-), ~ 8.73 ppm (-CONHPh), 9.77 ppm (-CONHNHCO-) in ^{1}H-NMR spectra confirmed the formation of compounds **8a,b**. The intensity ratio of NH signals was found to be ~ 1:1:1. Resonances at 8.05 ppm and 9.77 ppm were observed as doublets with a spin–spin coupling constant (*J*) of 1.5 Hz.

The ^{13}C-NMR spectra of the molecules **9a,b** possessing a -CONHNHCSNHPh fragment showed resonances at ~ 170.50 ppm and ~ 181.00 ppm, which were attributed to C=O and C=S groups, respectively. In the ^{1}H-NMR spectra of compounds **9a,b**, the broad singlets at ~ 9.60 ppm and 10.00 ppm were ascribed to the six NH groups. Their intensity ratio was found to be 0.6:0.4. The low intensity (0.08) traces of resonances observed in the spectral region of NH protons should be a result of a competition between the intermolecular and intramolecular hydrogen bonding.

The conversion of semicarbazides **8, 9a,b** to bis triazoles **10, 11a,b** was carried out by refluxing them in 2% aqueous NaOH solution with the subsequent acidification of the reaction mixture with acetic acid. The sharp singlets at ~ 11.80 ppm were assigned to the NH group in ^{1}H-NMR spectra and confirmed the formation of compounds **10a, b**. The extremely broad singlets at 13.77 (**11a**) and 13.26 (**11b**) ppm in the ^{1}H-NMR spectra of compounds **11a,b** may be ascribed to protons of the NH group. The resonances at ~ 150.10 ppm and ~ 167.60 ppm were assigned to C=N and C=S atoms, respectively, of the five-membered heterocycle moiety of compounds **11a,b** in ^{13}C-NMR spectra. The chemical shifts of C=N and C=S atoms of the **11a,b** and **7a,b** triazole heterocycles were found to differ by a negligible margin. This implies additionally that the five-membered heterocycle was formed properly because the value of the β-influence of the NH_2 substituent (**7a,b**) is similar to the Ph (**11a,b**) one [29].

EXPERIMENTAL

The ^{1}H and ^{13}C-NMR spectra were recorded with a Varian Unity Inova (300 MHz, 75 MHz) spectrometer operating in the Fourier transform mode, using DMSO-d_6 and $CDCl_3$ as solvents and TMS as an internal reference (chemical shifts in δ, ppm). IR spectra (v, cm^{-1}) were recorded on a Perkin-Elmer Spectrum BX FTIR spectrometer using KBr tablets. Mass spectra were obtained with a Waters ZQ 2000 spectrometer using the atmospheric pressure chemical ionization mode and operating at 25 V. Elemental analyses were performed with a CE-440 elemental analyzer. Melting points were determined with an automatic APA1 melting point apparatus and are uncorrected. TLC was performed with Merck, Silica gel 60 F_{254} (Kieselgel 60 F_{254}) silica gel plates.

General procedure for the synthesis of dihydrazides of *N*-(4-halophenyl)-*N*-carboxyethyl-β-alanine 2a,b. To a solution of the corresponding amino acid dimethyl ester **1** (13.74 g, 40 mmol) in 2-propanol (50 mL) hydrazine hydrate (12 g, 240 mmol) was added, and the mixture was refluxed for 1 h. On completing the reaction, the mixture was cooled to room temperature, the precipitate was filtered off, washed with 2-propanol, and dried to give **2a** and **2b** in 9.57 g (80%) and 12.25 g (78%) yields, respectively.

3-[4-Chloro(3-hydrazino-3-oxopropyl)anilino]propanohydrazide (2a). This compound was obtained as a white powder (a mixture of 2-propanol and water), mp 148–149°C; IR: NH_2 3273, NH 3229, C=O 1645, 1632 cm^{-1}; ^{1}H-NMR: δ 2.24 (t, 4H, CH_2CO, *J* = 7.2 Hz), 3.48 (t, 4H, CH_2N, *J* = 7.2 Hz), 4.20 (s, 4H, CONHNH_2), 6.68 (d, 2H, 2,6-H_{ar}, *J* = 9.1 Hz), 7.17 (d, 2H, 3,5-H_{ar}, *J* = 9.1 Hz), 9.04 ppm (s, 2H, CONHNH_2); ^{13}C-NMR: δ 31.25 (CH_2CO), 46.83 (CH_2N), 113.18 (C-2,6), 119.15 (C-4), 128.69 (C-3,5), 145.78 (C-1), 169.74 ppm (CONHNH_2). Anal. Calcd. for $C_{12}H_{18}IN_5O_2$: C, 48.08; H, 6.05; N 23.36. Found: C, 48.26; H, 6.06; N 23.29.

3-[(3-Hydrazino-3-oxopropyl)-4-iodoanilino]propanohydrazide (2b). This compound was obtained as a white powder (a mixture of 2-propanol and water), mp 144–145°C; IR: NH_2 3278, NH 3228, C=O 1646, 1636 cm^{-1}; ^{1}H-NMR: δ 2.24 (t, 4H, CH_2CO, *J* = 7.0 Hz), 3.47 (t, 4H, CH_2N, *J* = 7.0 Hz); 4.20 (s, 4H, CONHNH_2), 6.53 (d, 2H, 2,6-H_{ar}, *J* = 8.9 Hz), 7.41 (d, 2H, 3,5-H_{ar}, *J* = 8.9 Hz); 9.04 ppm (s, 2H, CONHNH_2); ^{13}C-NMR: δ 31.99 (CH_2CO), 47.46 (CH_2N), 76.47 (C-4), 114.43 (C-2,6), 129.88 (C-3,5), 147.31 (C-1), 170.51 ppm (CONHNH_2); MS: *m/z* 391 (M^+). Anal. Calcd. for $C_{12}H_{18}IN_5O_2$: C, 36.84; H, 4.64; N, 17.90. Found: C 36.81; H 4.54; N 17.85.

General procedure for the synthesis of 3-[(4-halophenyl)({2-[(2,5-dimethyl-1H-pyrrol-1-yl)carbamoyl]ethyl})amino]-*N*-(2,5-dimethyl-1H-pyrrol-1-yl)propanamides 3a,b. A mixture of the corresponding carbohydrazide **2** (3 mmol), 2,5-hexanedione (1.14 g, 10 mmol), 2-propanol (20 mL), and a catalytic amount (1.0 mL) of glacial acetic acid was refluxed for 6 h, cooled to room temperature, and diluted with water (20 mL). The formed organic residue was filtered off, washed with 2-propanol, and dried to give **3a** and **3b** in 1.18 g (86%) and 1.32 g (80%) yields, respectively.

3-[(4-Chlorophenyl)({2-[(2,5-dimethyl-1H-pyrrol-1-yl)carbamoyl]ethyl})amino]-N-(2,5-dimethyl-1H-pyrrol-1-yl)propanamide (3a).

This compound was obtained as a white powder (2-propanol), mp 232–234°C; IR: NH 3260, C=O 1724, 1668 cm^{-1}; NMR, a mixture of isomers: ^{1}H-NMR: δ 1.92, 1.94, 1.98 (3s, 0.1:0.8:0.1 (12H), CH_3), 2.56 (t, 4H, CH_2CO, *J* = 6.8 Hz), 3.67 (t, 4H, NCH_2, *J* = 6.8 Hz), 5.62, 5.69 (s, 0.8:0.2 (4H), CH), 6.60, 6.81 (d, 0.2:0.8 (2H), 2,6-H_{ar}, *J* = 9.2 Hz), 7.14, 7.23 (d, 0.2:0.8 (2H), 3,5-H_{ar}, *J* = 9.1 Hz), 10.63, 10.66 ppm (3s, 0.2:0.8 (2H), NH); ^{13}C-NMR: δ 10.84, 10.91 (CH_3), 31.01 ($\underline{C}H_2CO$), 46.40 (CH_2N), 102.85, 103.88 (CH), 113.34, 113.83 (C-2,6), 119.76 (C-4), 126.57 ($\underline{C}$-CH_3), 128.82 (C-3,5), 145.66 (C-1), 170.04, ppm (C=O); MS: *m/z* 456 (M^+), 458 (M^++2). Anal. Calcd. for $C_{24}H_{30}ClN_5O_2$: C, 63.22; H, 6.63; N, 15.36. Found: 62.98; H 6.44; N 15.21.

3-[(4-Iodophenyl)({2-[(2,5-dimethyl-1H-pyrrol-1-yl)carbamoyl]ethyl})amino]-N-(2,5-dimethyl-1H-pyrrol-1-yl)propanamide (3b). This compound was obtained as a white powder (2-propanol), mp 199–201°C; IR: NH 3299, C=O 1682 cm^{-1}; NMR, a mixture of isomers: ^{1}H-NMR: δ 1.92, 1.93, 1.95, 1.98 (4s, 0.1:0.7:0.1:0.1 (12H), CH_3), 2.54 (t, 4H, CH_2CO, *J* = 6.6 Hz), 3.65 (t, 4H, NCH_2, *J* = 6.6 Hz), 5.62, 5.69 (s, 0.8:0.2 (4H), CH), 6.44, 6.66 (d, 0.2:0.8 (2H), 2,6-H_{ar}, *J* = 9.0 Hz), 7.39, 7.48 (d, 0.2:0.8 (2H), 3,5-H_{ar}, *J* = 8.9 Hz), 10.63, 10.67, 10.68 ppm (3s, 0.1:0.1:0.8 (2H), NH); ^{13}C-NMR: δ 10.88, 10.96 (CH_3), 30.97, 31.19 ($\underline{C}H_2CO$), 46.26, 46.36 (CH_2N), 77.28 (C-4), 102.88, 103.91 (CH), 115.01, 115.07 (C-2,6), 126.59, 127.06 ($\underline{C}$-CH_3), 137.45 (C-3,5), 146.38 (C-1), 170.06, 170.20 ppm (C=O); MS: *m/z* 548 (M^++1), 549 (M^++2). Anal. Calcd. for $C_{24}H_{30}IN_5O_2$: C, 52.66; H, 5.52; N, 12.79. Found C 52.49; H 5.43; N 12.93.

General procedure for the synthesis of 3-[(4-halophenyl)[3-(3,5-dimethyl-1H-pyrazol-1-yl)-3-oxopropyl]amino]-1-(3,5-dimethyl-1H-pyrazol-1-yl)propan-1-ones 4a,b. A mixture of the corresponding carbohydrazide **2** (3 mmol), 2,4-pentanedione (1 g, 10 mmol), 2-propanol (15 mL), and a catalytic amount (0.5 mL) of hydrochloric acid was refluxed for 5 h, cooled to room temperature, and diluted with water (20 mL). The formed organic residue was filtered off, washed with 2-propanol, and dried to give **4a** and 4**b** in 1.07 g (83%) and 1.16 g (74%) yields, respectively.

3-[(4-Chlorophenyl)[3-(3,5-dimethyl-1H-pyrazol-1-yl)-3-oxopropyl]amino]-1-(3,5-dimethyl-1H-pyrazol-1-yl)propan-1-one (4a). This compound was obtained as a white powder (2-propanol), mp 109–110°C; IR: C=O 1724, C=N 1600, 1580 cm^{-1}; ^{1}H-NMR: δ 2.15 (s, 6H, 5′-CH_3), 2.45 (s, 6H, 3′-CH_3), 3.26 (t, 4H, CH_2 CO, *J* = 6.9 Hz), 3.72 (t, 4H, NCH_2, *J* = 7.1 Hz), 6.17 (s, 2H, CH), 6.83 (d, 2H, 2,6-H_{ar}, *J* = 9.2 Hz), 7.18 ppm (d, 2H, 3,5-H_{ar}, *J* = 9.1 Hz); ^{13}C-NMR: δ 13.36 (5′-CH_3), 13.98 (3′-CH_3), 32.96 ($\underline{C}H_2CO$), 46.10 (CH_2N), 111.11 (CH), 113.55 (C-2,6), 119.57 (C-4), 128.73 (C-3,5), 143.07 (N-$\underline{C}$-CH_3), 151.40 (N=$\underline{C}$-CH_3), 154.66 (C-1), 171.84 ppm (C=O). Anal. Calcd. for $C_{22}H_{26}ClN_5O_2$: C, 61.75; H, 6.12; N, 16.37. Found: 61.57; H 6.13; N 16.32.

3-[(4-Iodophenyl)[3-(3,5-dimethyl-1H-pyrazol-1-yl)-3-oxopropyl]amino]-1-(3,5-dimethyl-1H-pyrazol-1-yl)propan-1-one (4b). This compound was obtained as a white powder (2-propanol), mp 128–129°C; IR: C=O 1723, C=N 1590 cm^{-1}; ^{1}H-NMR: δ 2.15 (s, 6H, 5′-CH_3), 2.45 (s, 6H, 3′-CH_3), 3.26 (t, 4H, CH_2CO, *J* = 7.0 Hz), 3.70 (t, 4H, NCH_2, *J* = 7.1 Hz), 6.17 (s, 2H, CH), 6.68 (d, 2H, 2,6-H_{ar}, *J* = 9.1 Hz), 7.44 ppm (d, 2H, 3,5-H_{ar}, *J* = 8.9 Hz); ^{13}C-NMR: δ 13.39 (5′-CH_3), 14.02 (3′-CH_3), 32.92 ($\underline{C}H_2CO$), 45.94 (CH_2N), 77.06 (C-4), 111.14 (CH), 114.76 (C-2,6), 137.34 (C-3,5), 143.10 (N-$\underline{C}$-CH_3), 151.44 (N=$\underline{C}$-CH_3), 146.43 (C-1), 171.84 ppm (C=O). Anal. Calcd. for $C_{22}H_{26}IN_5O_2$: C, 50.88; H, 5.05; N, 13.48. Found: C 50.98; H 5.18; N 13.55.

General procedure for the synthesis of 1,3,4-oxadiazole-2(3H)-thiones 6a,b. A mixture of the corresponding dihydrazide **2** (5 mmol), potassium hydroxide (1.35 g, 20 mmol), carbon disulfide (1.52 g, 20 mmol), and 2-propanol (50 mL) was refluxed for 24 h, and then the volatile fractions were separated under reduced pressure. The obtained residue was dissolved in water (30 mL), and the solution was acidified with acetic acid to pH 6. The formed product was filtered off, washed with water, and dried to give **6a** and **6b** in 1.42 g (74%) and 1.81 g (76%) yields, respectively.

5-(2-{4-Chloro[2-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)ethyl]anilino}ethyl)-1,3,4-oxadiazole-2(3H)-thione (6a). This compound was obtained as a yellow powder (2-propanol), mp 159–160°C; IR: NH 3133, C=N 1617, 1597, C=S 1256, C-O-C 1156 cm^{-1}; ^{1}H-NMR: δ 2.99 (t, 4H, CH_2C=N, *J* = 7.0 Hz), 3.68 (t, 4H, CH_2N, *J* = 7.0 Hz), 6.74 (d, 2H, 2,6-H_{ar}, *J* = 9.1 Hz), 7.19 (d, 2H, 3,5-H_{ar}, *J* = 9.1 Hz), 14.38 ppm (br. s, 2H, NH); ^{13}C-NMR: δ 23.17 ($\underline{C}H_2C$=N), 46.34 (CH_2N), 113.74 (C-2,6), 120.35 (C-4), 128.99 (C-3,5), 145.17 (C-1), 162.31 (C=N), 177.65 ppm (C=S). Anal. Calcd. for $C_{14}H_{14}ClN_5O_2S_2$: C, 43.80; H, 3.68; N, 18.24. Found: C, 43.75; H, 3.57; N, 18.20.

5-(2-{4-Iodo[2-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)ethyl]anilino}ethyl)-1,3,4-oxadiazole-2(3H)-thione (6b). This compound was obtained as a yellow powder (2-propanol), mp 152–153°C; IR: NH 3131, C=N 1616, 1587, C=S 1257, C-O-C 1157 cm^{-1}; ^{1}H-NMR: δ 2.94 (t, 4H, CH_2C=N, *J* = 6.9 Hz), 3.67 (t, 4H, CH_2N, *J* = 6.9 Hz), 6.59 (d, 2H, 2,6-H_{ar}, *J* = 9.0 Hz), 7.43 (d, 2H, 3,5-H_{ar}, *J* = 8.8 Hz), 14.36 ppm (br. s, 2H, NH); ^{13}C-NMR: δ 23.12 ($\underline{C}H_2C$=N), 46.18 (CH_2N), 78.04 (C-4), 114.81 (C-2,6), 137.57 (C-3,5), 145.93 (C-1), 162.26 (C=N), 177.63 ppm (C=S). Anal. Calcd. for $C_{14}H_{14}IN_5O_2S_2$: C, 35.38; H, 2.97; N, 14.73. Found: C, 35.47; H, 2.83; N, 14.64.

General procedure for the synthesis of 1,2,4-triazole-3-thiones 7a,b. A mixture of the corresponding dihydrazide **2** (5 mmol), potassium hydroxide (1.35 g, 20 mmol), carbon disulfide (1.52 g, 20 mmol), and 2-propanol (50 mL) was refluxed for 24 h, and then the volatile fractions were separated under reduced pressure. The obtained residue was dissolved in water (5 mL), and hydrazine hydrate (1.5 g, 30 mmol) was added. The mixture was refluxed for 20 h, diluted with water (10 mL), cooled down, and acidified with acetic acid to pH 6. The formed product was filtered off, washed with water, 2-propanol, and dried to give **7a** and **7b** in 1.48 g (72%) and 1.81 g (72%) yields, respectively.

4-Amino-5-(2-{[2-(4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)ethyl]-4-chloroanilino}ethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (7a). This compound was obtained as a white powder (methanol), mp 269–270°C; IR: NH_2 3258, NH 3118, C=N 1630, 1596, C=S 1297, 1284 cm^{-1}; ^{1}H-NMR: δ 2.88 (t, 4H, CH_2C=N, *J* = 7.0 Hz), 3.68 (t, 4H, CH_2N, *J* = 7.0 Hz), 5.60 (s, 4H, NH_2), 6.82 (d, 2H, 2,6-H_{ar}, *J* = 9.0 Hz), 7.18 (d, 2H, 3,5-H_{ar}, *J* = 9.0 Hz), 13.50 ppm (s, 2H, NH); ^{13}C-NMR: δ 22.39 ($\underline{C}H_2C$=N), 46.89 (CH_2N), 113.33 (C-2,6), 119.63 (C-4), 128.80 (C-3,5), 145.40 (C-1), 150.07 (C=N), 165.92 ppm (C=S); MS: *m/z* 412 (M^+), 414 (M^++2). Anal. Calcd. for $C_{14}H_{18}ClN_9S_2$: C, 40.82; H, 4.40; N, 30.60. Found: C, 40.96; H, 4.25; N, 30.51.

4-Amino-5-(2-{[2-(4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-ethyl]-4-iodoanilino}ethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (7b). This compound was obtained as a yellow

powder (methanol), mp 194–196°C; IR: NH_2 3256, NH 3120, C=N 1626, 1588, C=S 1296, 1284 cm^{-1}; ^{1}H-NMR: δ 2.86 (t, 4H, CH_2C=N, *J* = 6.4 Hz,), 3.61 (m, 4H, CH_2N, *J* = 6.4 Hz), 5.60 (s, 4H, NH_2), 6.68 (d, 2H, 2,6-H_{ar}, *J* = 8.5 Hz), 7.42 (d, 2H, 3,5-H_{ar}, *J* = 8.5 Hz), 13.49 ppm (s, 2H, NH); ^{13}C-NMR: δ 22.35 (CH_2C=N), 46.73 (CH_2N), 77.14 (C-4), 114.53 (C-2,6), 137.37 (C-3,5), 146.16 (C-1), 150.04 (C=N), 165.90 ppm (C=S). Anal. Calcd. for $C_{14}H_{18}IN_9S_2$: C, 33.40; H, 3.60; N, 25.04. Found: C, 33.51; H, 3.61; N, 25.12.

General procedure for the synthesis of semicarbazides 8a, b. A mixture of the corresponding dihydrazide **2** (10 mmol), phenyl isocyanate (3.57 g, 30 mmol), and methanol (50 mL) was refluxed for 2 h, then cooled to room temperature, the formed precipitate was filtered off, washed with methanol, and dried to give **8a** and **8b** in 4.95 g (92%) and 5.67 g (90%) yields, respectively.

3,3′-[(4-Chlorophenyl)imino]bis[N′-(phenylcarbamoyl) propanohydrazide] (8a). This compound was obtained as a white powder (methanol), mp 209–210°C; IR: NH 3304, C=O 1656, 1604 cm^{-1}; ^{1}H-NMR: δ 2.42 (t, 4H, CH_2CO, *J* = 6.9 Hz), 3.50 (t, 4H, CH_2N, *J* = 6.9 Hz) 6.7–7.5 (m, 14H, H_{ar}), 8.05 (s, 2H, CONHNHCO, *J* = 1.5 Hz), 8.73 (s, 2H, CONHPh), 9.77 ppm (s, 2H, CONHNHCO, *J* = 1.5 Hz); ^{13}C-NMR: δ 31.16 (CH_2CO), 46.56 (CH_2N), 113.39 (C-2,6), 118.50 (C-2',6′), 119.41 (C-4), 121.92 (C-4′), 128.68 (C-3′,5′), 128.88 (C-3,5), 139.59 (C-1′), 145.80 (C-1), 155.29 (NHCONH), 170.48 ppm (CH_2CONH). Anal. Calcd. for $C_{26}H_{28}ClN_7O_4$: C, 58.04; H, 5.25; N, 18.22. Found: C, 58.20; H, 5.15; N, 18.12.

3,3′-[(4-Iodophenyl)imino]bis[N′-(phenylcarbamoyl) propanohydrazide] (8b). This compound was obtained as a white powder (methanol), mp 191–193°C; IR: NH 3287, C=O 1656, 1621, 1601 cm^{-1}; ^{1}H-NMR: δ 2.42 (t, 4H, CH_2CO, *J* = 7.0 Hz), 3.56 (t, 4H, CH_2N, *J* = 7.0 Hz), 6.5–7.5 (m, 14H, H_{ar}), 8.05 (s, 2H, CONHNHCO, *J* = 1.5 Hz), 8.74 (s, 2H, CONHPh), 9.77 ppm (s, 2H, CONHNHCO, *J* = 1.5 Hz); ^{13}C-NMR: δ 31.31 (CH_2CO), 46.41 (CH_2N), 76.78 (C-4), 114.60 (C-2,5), 118.51 (C-2′,6′), 121.94 (C-4′), 128.69 (C-3′,5′), 137.47 (C-3,5), 139.59 (C-1′), 146.55 (C-1), 155.31 (NHCONH), 170.48 ppm (CH_2CONH). Anal. Calcd. for $C_{26}H_{28}IN_7O_4$: C, 49.61; H, 4.48; N, 15.58. Found: C, 49.86; H, 4.32; N, 15.43.

General procedure for the synthesis of thiosemicarbazides 9a,b. A mixture of the corresponding dihydrazide **2** (10 mmol), phenyl isothiocyanate (4.05 g, 30 mmol), and methanol (50 mL) was refluxed for 2 h, and then cooled to room temperature; the formed precipitate was filtered off, washed with methanol, and dried to give **9a** and **9b** in 5.47 g (96%) and 6,29 g (95%) yields, respectively.

3,3′-[(4-Chlorophenyl)imino]bis[N′-(phenylthiocarbamoyl) propanehydrazide] (9a). This compound was obtained as a white powder (methanol), mp 152–154°C; IR: NH 3212, 3192, C=O 1681, C=S 1184, 1163 cm^{-1}; ^{1}H-NMR: δ 2.46 (t, 4H, CH_2CO, *J* = 7.0 Hz), 3.56 (t, 4H, CH_2N, *J* = 7.0 Hz), 6.7–7.4 (m, 14H, H_{ar}), 9.60, 10.00 ppm (2s, 6H, all NH); ^{13}C-NMR: δ 31.15 (CH_2CO), 46.27 (CH_2N), 113.39 (C-2,6), 119.44 (C-4), 125.28 (C-4′), 126.26 (C-2′,6′), 128.13 (C-3′,5′), 128.88 (C-3,5), 139.09 (C-1′), 145.85 (C-1), 170.42 (C=O), 180.94 ppm (C=S). Anal. Calcd. for $C_{26}H_{28}ClN_7O_2S_2$: C, 54.77; H, 4.95; N, 17.20. Found: C, 54.60; H, 4.78; N, 17.04.

3,3′-[(4-Iodophenyl)imino]bis[N′-(phenylthiocarbamoyl) propanohydrazide] (9b). This compound was obtained as a white powder (methanol), mp 162–164°C; IR: NH 3211, 3182, C=O 1681, C=S 1182, 1161 cm^{-1}; ^{1}H-NMR: δ 2.46 (t, 4H, CH_2CO, *J* = 7.0 Hz), 3.5–3.6 (m, 4H, CH_2N), 6.6–7.5 (m, 14H, H_{ar}), 9.59, 10.00 ppm (2s, 6H, all NH); ^{13}C-NMR: δ 31.11 (CH_2CO), 46.07 (CH_2N), 76.78 (C-4), 114.64 (C-2,6), 125.24 (C-4′), 126.23 (C-2′,6′), 128.13 (C-3′,5′), 137.45 (C-3,5), 139.09 (C-1′), 146.59 (C-1), 170.61 (C=O), 181.02 ppm (C=S). Anal. Calcd. for $C_{26}H_{28}IN_7O_2S_2$: C, 47.20; H, 4.27; N, 14.82. Found: C, 47.05; H, 4.16; N, 14.65.

General procedure for the synthesis of 1,2,4-triazol-3-ones 10a,b. A mixture of the corresponding semicarbazide **6** (1 mmol) and 2% aqueous sodium hydroxide solution (20 mL) was refluxed for 3 h, cooled to room temperature, and acidified with acetic acid to pH 6. The formed organic residue was filtered off, washed with water, and dried to give **10a** and **10b** in 0.33 g (65%) and 0.39 g (65%) yields, respectively.

5-(2-{4-Chloro[2-(5-oxo-4-phenyl-4,5-dihydro-1H-1,2,4-triazol-3-yl)ethyl]anilino}-ethyl)-4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-one (10a). This compound was obtained as a white powder (2-propanol), mp 218–220°C; IR: NH 3190, C=O 1707, C=N 1594, 1579 cm^{-1}; ^{1}H-NMR: δ 2.53 (t, 4H, CH_2C=N, *J* = 7.8 Hz), 3.24 (t, 4H, CH_2N, *J* = 7.8 Hz), 6.00 (d, 2H, 2,6-H_{ar}, *J* = 9.0 Hz), 6.91 (d, 2H, 3,5-H_{ar}, *J* = 9.0 Hz), 7.3–7.6 (m, 10H, H_{ar}), 11.82 ppm (s, 2H, NH); ^{13}C-NMR: δ 23.43 (CH_2C=N), 48.72 (CH_2N), 112.48 (C-2,6), 119.39 (C-4), 127.51 (C-3′,5′), 128.71 (C-3,5 + C-4′), 129.50 (C-2′,6′), 132.74 (C-1′), 144.86 (C=N), 144.90 (C-1), 154.28 ppm (C=O). MS: *m/z* 502 (M^+), 504 (M^++2). Anal. Calcd. for $C_{26}H_{24}ClN_7O_2$: C, 62.21; H, 4.82; N, 19.53. Found: C, 62.03; H, 4.74; N, 19.44.

5-(2-{4-Iodo[2-(5-oxo-4-phenyl-4,5-dihydro-1H-1,2,4-triazol-3-yl)ethyl]anilino}ethyl)-4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-one (10b). This compound was obtained as a yellow powder (2-propanol), mp 157–159°C; IR: NH 3188, C=O 1706, C=N 1582 cm^{-1}; ^{1}H-NMR: δ 2.53 (t, 4H, CH_2C=N, *J* = 7.6 Hz), 3.25 (t, 4H, CH_2N, *J* = 7.6 Hz), 5.88 (d, 2H, 2,6-H_{ar}, *J* = 9.0 Hz), 7.17 (d, 2H, 3,5-H_{ar}, *J* = 9.0 Hz), 7.3–7.5 (m, 10H, H_{ar}), 11.77 ppm (s, 2H, NH); ^{13}C-NMR: δ 23.39 (CH_2C=N), 46.52 (CH_2N), 76.82 (C-4), 113.69 (C-2,6), 127.50 (C-3′,5′), 128.71 (C-4′), 129.51 (C-2′,6′), 132.72 (C-1′), 137.25 (C-3,5), 144.85 (C=N), 145.79 (C-1), 154.27 ppm (C=O). MS: *m/z* 594 (M^++1), 595 (M^++2). Anal. Calcd. for $C_{26}H_{24}IN_7O_2$: C, 52.62; H, 4.08; N, 16.52. Found: C, 52.72; H, 4.18; N, 16.44.

General procedure for the synthesis of 1,2,4-triazole-3-thiones 11a,b. A mixture of the corresponding thiosemicarbazide **7** (1 mmol) and 2% aqueous sodium hydroxide solution (20 mL) was refluxed for 3 h, cooled to room temperature, and acidified with acetic acid to pH 6. The formed organic residue was filtered off, washed with water, and dried to give **11a** and **11b** in 0.40 g (74%) and 0.46 g (73%) yields, respectively.

5-(2-{4-Chloro[2-(4-phenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)ethyl]anilino}-ethyl)-4-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (11a). This compound was obtained as a white powder (2-propanol), mp 261–263°C; IR: NH 3402, C=N 1598, 1571, C=S 1280 cm^{-1}; ^{1}H-NMR: δ 2.56 (t, 4H, CH_2C=N, *J* = 7.2 Hz), 3.33 (t, 4H, CH_2N, *J* = 7.0 Hz), 5.98 (d, 2H, 2,6-H_{ar}, *J* = 9.0 Hz), 6.90 (d, 2H, 3,5-H_{ar}, *J* = 9.0 Hz), 7.4–7.6 (m, 10H, H_{ar}), 13.77 ppm (s, 2H NH); ^{13}C-NMR: δ 23.03 (CH_2C=N), 46.92 (CH_2N), 112.55 (C-2,6), 119.60 (C-4), 128.38 (C-3′,5′), 128.70 (C-3,5), 129.54 (C-2′,6′ + C-4′), 133.54 (C-1′), 144.78 (C-1), 150.10 (C=N), 167.62 ppm (C=S); MS: *m/z* 534 (M^+), 536 (M^++2). Anal. Calcd. for $C_{26}H_{24}ClN_7S_2$: C, 58.47; H, 4.53; N, 18.36. Found: C, 58.32; H, 4.37; N, 18.45.

5-(2-{4-Iodo[2-(4-phenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)ethyl]anilino}-ethyl)-4-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (11b). This compound was obtained as a white powder (2-propanol), mp 149–151°C; IR: NH 3340, C═N 1588, 1572, C═S 1285 cm^{-1}; ^{1}H-NMR: δ 2.55 (t, 4H, CH_2C═N, J = 7.3 Hz), 3.31 (t, 4H, CH_2N, J = 7.3 Hz), 5.85 (d, 2H, 2,6-H_{ar}, J = 9.0 Hz), 7.15 (d, 2H, 3,5-H_{ar}, J = 9.0 Hz), 7.4–7.6 (m, 10H, H_{ar}), 13.26 ppm (br. s, 2H, NH); ^{13}C-NMR: δ 23.01 ($\underline{CH_2}$C═N), 46.76 (CH_2N), 77.10 (C-4), 113.75 (C-2,6), 128.39 (C-3′,5′), 129.54 (C-2′,6′ + C-4′), 133.57 (C-1′), 137.30 (C-3,5), 145.59 (C-1), 150.08 (C═N), 167.61 ppm (C═S); MS: *m/z* 626 (M^+). Anal. Calcd. for $C_{26}H_{24}IN_7S_2$: C, 49.92; H, 3.87; N, 15.67. Found: C, 49.78; H, 3.69; N, 15.77.

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