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ORIGINAL PAPER

The synthesis of azole derivatives from 3-[(4-methylphenyl)amino]-propanehydrazide and its *N*′-phenylcarbamoyl derivatives, and their antibacterial activity

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Abstract 5-[2-[(4-Methylphenyl)amino]ethyl]-1,3,4-oxadiazol-2(3*H*)-thione, 5-[2-[(4-methylphenyl)amino]ethyl]-1,3,4-oxadiazol-2(3*H*)-one, *N*-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-[(4-methylphenyl)amino]propanamide, and a series of *N*-[(phenylcarbamoyl)amino]-3-[(4-methylphenyl)amino]-propanamides and 3-[(4-methylphenyl)(phenylcarbamoyl)-amino]-*N*-[(phenylcarbamoyl)amino]propanamides, and their thio analogues were synthesized from 3-[(4-methylphenyl)-amino]propanehydrazide. 1,3,4-Oxadiazole-2(3*H*)-thione was converted to 4-amino-2,4-dihydro-5-[2-[(4-methylphenyl)-amino]ethyl]-3*H*-1,2,4-triazole-3-thione, whereas cyclization of *N*′-phenylcarbamoyl derivatives provided thiazole, oxadiazoles, and thiadiazole, as well as triazole derivatives. Two of the synthesized compounds exhibited good antibacterial activity against *Rhizobium radiobacter*.

Keywords Amino acids · Biological activity · Cyclization · Heterocycles · 1,3,4-Oxa(thia)diazoles · 1,2,4-Triazoles

Introduction

N-Substituted amino acids as well as their hydrazides, amides, and hydrazones have continuously attracted attention of researchers owing to their properties that are useful in technological applications as well as biological activity. They are also suitable compounds as synthons in the synthesis of various heterocyclic compounds. Cyclization of hydrazine derivatives is a well-known method for azole synthesis [1]. The five-membered heterocyclic nucleus plays a vital role in many biological activities; thus, azole derivatives have been demonstrated to possess antibacterial [2, 3], anti-inflammatory [4], antitumor [5], antifungal [3], and antimicrobial [6–9] activities. 5-Mercapto-1,2,4-triazoles containing the furyl radical are potential anti-HIV-1 agents [10], whereas substituted triazole-3-thiones have demonstrated antidepressant activity [11].

Previously, we described the cyclization of *N*-phenyl-*β*-alanine hydrazide, *N*-phenyl- and *N*-(*p*-tolyl)-*N*-carboxyphenyl-*β*-alanine dihydrazides, *N*,*N*′-bis(hydrazinocarbonylethyl)-1,4-phenylenediamine, and their semicarbazides and thiosemicarbazides into compounds containing one or several azole fragments [2, 12–14]. As a continuation of our search for compounds possessing antibacterial and antifungal activities, we report herein the synthesis of heterocyclic compounds from 3-(4-methylphenylamino)propanehydrazide (**1**) and its carbamoyl derivatives. Cyclization of *N*′-phenylcarbamoyl derivatives to oxazole and thiazole, oxadiazole and thiadiazole, as well as triazole derivatives was carried out. Some of the synthesized compounds were tested for antibacterial activity.

Results and discussion

N-(4-Methylphenyl)-*β*-alanine hydrazide (**1**) was obtained from *N*-phenyl-*β*-alanine by heating at reflux with hydrazine in toluene as described elsewhere [15]. Reaction of **1** in a solution of ethyl xanthogenate in ethanol, without isolation of the intermediate potassium salt of

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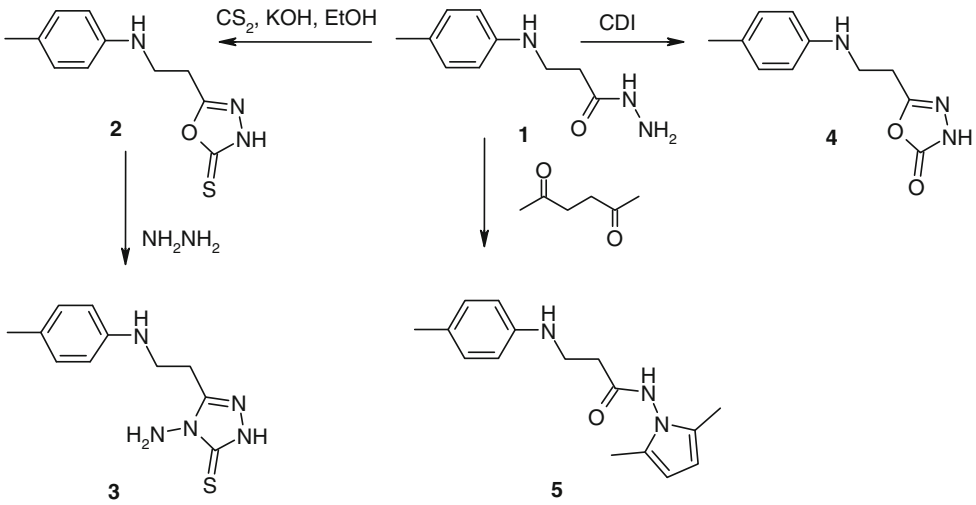
Scheme 1



propanedithionate, and subsequent acidification of the reaction mixture with hydrochloric acid provided 5-[2-[(4-methylphenyl)amino]ethyl]-1,3,4-oxadiazol-2(3*H*)-thione (**2**) (Scheme 1). Heating of oxadiazole-2-thione **2** at reflux with hydrazine and subsequent acidification of the reaction mixture with acetic acid resulted in formation of 4-amino-2,4-dihydro-5-[2-[(4-methylphenyl)amino]ethyl]-3*H*-1,2,4-triazole-3-thione (**3**). In our previous work [16], **3** was obtained by melting *N*-(2-carboxyethyl)-*N*-(4-methylphenyl)-*β*-alanine with thiocarbohydrazide.

Oxadiazol-2-one **4** was synthesized by the reaction of **1** with 1,1′-carbonyldiimidazole (CDI) in dioxane. In the ^{1}H NMR spectrum of **4**, a singlet attributed to the NH proton in the 1,3,4-oxadiazole moiety is observed at 10.30 ppm, whereas the proton of the same group in its thio analogue **2** resonated at 13.99 ppm owing to the stronger deshielding effect of the thioxo group.

Reaction of **1** with 2,5-hexanedione in propan-2-ol in the presence of a catalytic amount of acetic acid provided *N*-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-[(4-methylphenyl)amino]propanamide (**5**). Carbon resonances ascribed to the CH_3 groups in the pyrrole moiety are observed at 10.86 ppm in the ^{13}C NMR spectrum of **5**, whereas resonances at 102.77 ppm and 126.65 ppm confirm the existence of a pyrrole ring in this compound.

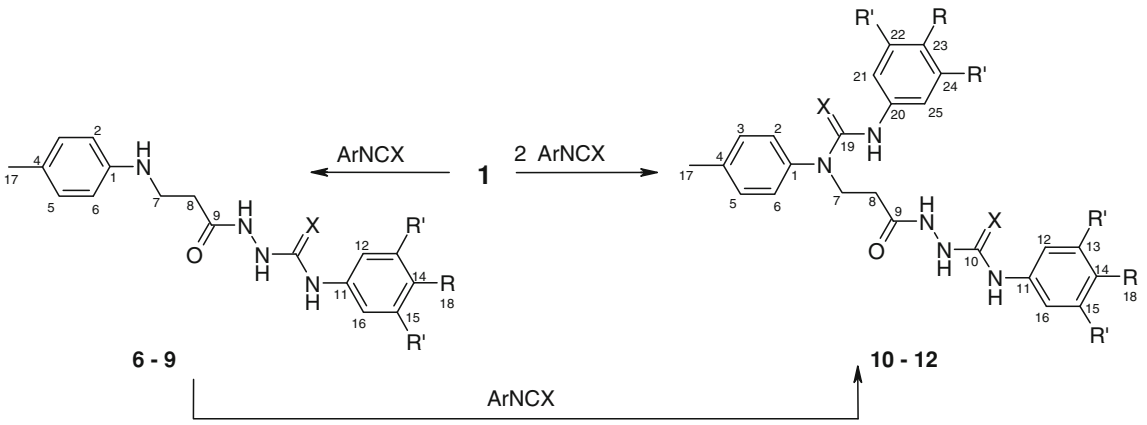
Acid semicarbazides and thiosemicarbazides are easily synthesized from the respective hydrazides and organic isocyanates. On cyclization, they produce oxadiazoles and triazolones and their thio analogues [2, 13]. Depending on the ratio of the reacting substances, reaction of **1** with phenyl isocyanates resulted in formation of propanehydrazide phenylcarbamoyl derivatives **6** and **9** and di(phenylcarbamoyl) derivative **10** (Scheme 2). In a similar way, phenylthiocarbamoyl propanamides **7** and **8** and di(phenylthiocarbamoyl) propanamides **11** and **12** were synthesized when phenyl isothiocyanates were used.

The rates of reaction of propanehydrazide **1** with phenyl isocyanates may be different. Its reaction with *p*-tolyl isothiocyanate was very facile, e.g., after 15 min the crystals of **9** started precipitating from the reaction mixture. In the ^{1}H NMR spectra of semicarbazides **6–9**, additional aromatic proton resonances are present in comparison with the spectrum of **1**, and two triplets attributed to two methylene CH_2 group protons are shifted downfield by 0.13–0.41 and 0.05–0.67 ppm. The introduction of the second phenylcarbamoyl group into molecules of semicarbazides **6–9** markedly increased the solubility of the compounds obtained. Semicarbazides **6–9** are soluble in DMSO and DMF only, whereas their phenylcarbamoyl derivatives **10–12** are soluble in such organic solvents as aromatic hydrocarbons, alcohols, dioxane, and tetrahydrofuran.

The direction of semicarbazide cyclization depends on the reaction conditions. At room temperature on treatment with phosphorus oxychloride or concentrated sulfuric acid, semicarbazides undergo dehydration and cyclize to oxadiazole or thiadiazole derivatives [2], whereas triazolones or triazolethiones are obtained under the action of alkali [2, 6].

Reaction of **6–9** in aqueous solutions of KOH or NH_2NH_2 at reflux temperature and subsequent acidification of the reaction mixtures provided 2,4-dihydro-5-[2-[(4-methylphenyl)amino]ethyl]-4-phenyl-3*H*-1,2,4-triazol-3-one (**13**), dihydrotriazolone **14**, 2,4-dihydro-5-[2-[(4-methylphenyl)amino]ethyl]-4-phenyl-3*H*-1,2,4-triazole-3-thione (**15**), and dihydrotriazolethione **16**, accordingly (Scheme 3). Carbamoyl groups attached to the secondary nitrogen atom in dicarbamoyl derivatives **10–12** underwent hydrolysis on treatment with alkali or hydrazine and, thus, triazole derivatives **13–16** were obtained.

In the ^{1}H NMR spectra of **13–16**, a deshielding effect of the triazole ring on the adjacent methylene group is observed. Its triplets are shifted downfield to the region of

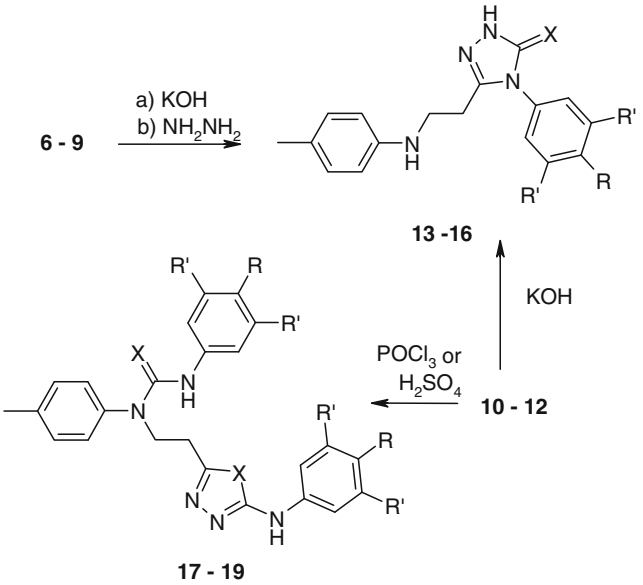


6 X = O, R = R' = H
7 X = O, R = H, R = CH_3,
8 X = S, R = R' = H
9 X = S, R = CH_3, R' = H
Ar = C_6H_5; 4-$CH_3C_6H_4$; 3,5-$(CH_3)_2C_6H_3$

10 X = O, R = R' = H
11 X = S, R = R' = H
12 X = S, R = CH_3, R' = H

Scheme 2

Scheme 3



13 X = O, R = R' = H
14 X = O, R = H, R'= CH_3
15 X = S, R = R' = H
16 X = S, R= CH_3, R' = H

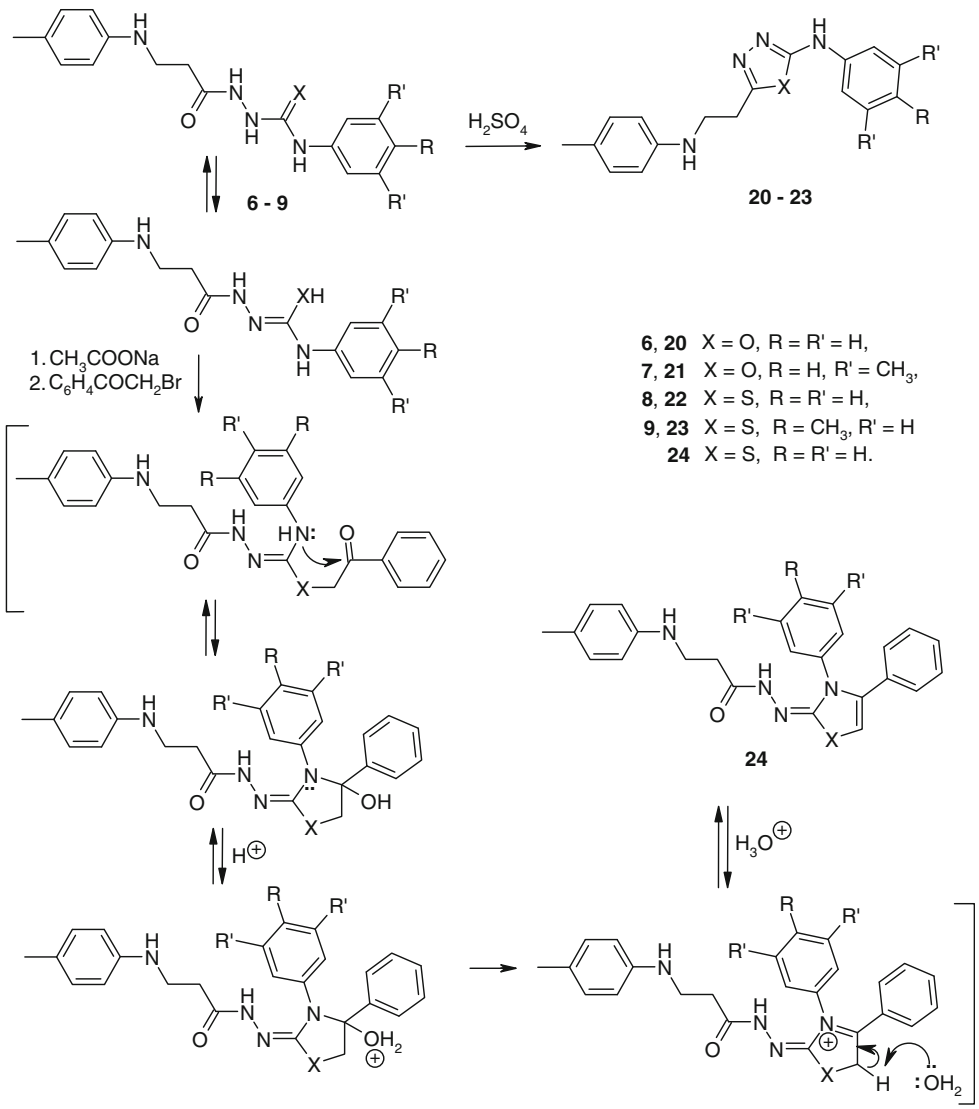
17 X = O, R = R' = H
18 X = S, R = R' = H
19 X = S, R = CH_3, R' = H

2.57–2.64 ppm when compared with the chemical shifts of methylene group protons in the spectra of **6**–**9**.

At room temperature when dissolved in concentrated sulfuric acid, semicarbazides **6**, **7** and thiosemicarbazides **8**, **9** underwent cyclization to 5-[2-[(4-methylphenyl)-amino]ethyl]-*N*-phenyl-1,3,4-oxadiazol-2-amine (**20**), its dimethyl homologue **21**, and their thio analogues 5-[2-[(4-methylphenyl)amino]ethyl]-*N*-phenyl-1,3,4-thiadiazol-2-amine (**22**) and dihydrothiadiazol-2-amine **23** (Scheme 4).

In the ^{1}H NMR spectrum of **17**, proton resonances of NHAr and NHAr′ are shifted downfield in comparison with the spectrum of **10** owing to the influence of the oxadiazole moiety and are observed at 8.68 and 9.75 ppm. Singlets of the NHNH group protons, which are present in the spectrum of phenylcarbamoyl semicarbazide **10** at 7.89 and 8.03 ppm, are absent. In a similar manner, in the ^{1}H NMR spectrum of **18**, proton resonances of NHAr and NHAr′ are shifted downfield in comparison with the spectrum of **11** owing to the influence of the thiadiazole moiety and are observed at 8.71 and 10.29 ppm. Singlets of the NHNH group protons, characteristic of phenylcarbamoyl semicarbazide **11** and observed at 9.56 and 9.59 ppm, are absent in the spectrum of **18**. The proton in the NH group adjacent to Ar′

Scheme 4



resonates in the region of 9.79–10.35 ppm in the ^{1}H NMR spectra of **20**–**23**.

N-(3,4-Diphenyl-2(3*H*)-thiazolylidene)-3-[(4-methylphenyl)amino]propanehydrazide (**24**) was synthesized by heating **8** at reflux with phenacyl bromide. The formation of **24** was supported by the presence of one resonance of an NH group at 10.90 ppm, absence of two NH group spectral signals, a new singlet at 7.99 ppm ascribed to the SCH group, and new proton resonances attributed to the aromatic moiety in the ^{1}H NMR spectrum.

Some of the synthesized compounds were evaluated for their antibacterial activity against a strain of *Rhizobium radiobacter* (*Agrobacterium tumefaciens*) by the diffusion technique [16, 17]. *R. radiobacter* is a soil-borne, Gram-negative bacterium, which is a causative agent of "crown gall" disease, an economically important disease of many plants [18]. Activities of the tested compounds were compared with the known antibacterial agent ampicillin.

As seen from the data presented in Table 1, *R. radiobacter* is sensitive to compounds **5**, **18**, **22**, and **23**; furthermore, 1,3,4-thiadiazol-2-amines **22** and **23** are active in a broader range of concentrations, whereas **2**, **3**, and **21** did not exhibit antibacterial activity against the tested microorganism strain.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Inova 300 spectrometer (300 and 75 MHz, respectively) using TMS as an internal standard and DMSO-d_6 as a solvent. IR spectra were taken on a Perkin-Elmer Spectrum Bx FT-IR spectrometer. Mass spectra were recorded on a Waters Micromass ZQ 2000 instrument. Elemental analyses (C, H, N) were performed on an Elemental Analyzer CE-440, and their results were found to be in good agreement (±0.2 %) with the calculated values. Melting

Table 1 Antibacterial activity of **2**, **3**, **5**, **18**, and **21–23** against *Rhizobium radiobacter* determined by the diffusion method

Compound	Concentration/μg cm^{-3}				
	50	150	250	450	550
2	–[a]	–	–	–	–
3	–	–	–	–	–
5	–	–	–	–	+[b]
18	–	–	–	–	+
21	–	–	–	–	–
22	–	–	+	+	+
23	–	–	+	+	+

[a] The compound did not exhibit antibacterial activity

[b] The compound exhibited antibacterial activity

points were determined on an Auto probe analyzer APA 1. Monitoring of the reaction course and purity of the compounds prepared was carried out using TLC on silica gel plates (Merck, F_{254}). Silica gel (Acros Organics, New Jersey, USA, 0.035–0.070 mm) was used for column chromatography.

3-[(4-Methylphenyl)amino]propanehydrazide (**1**, $C_{10}H_{15}N_3O$)

A mixture of 35.84 g *N*-(4-methylphenyl)-*β*-alanine (0.2 mol) and 10 g hydrazine (0.2 mol) in 100 cm^3 toluene was heated at reflux with complete azeotropic separation of the formed water. The liquid fractions were concentrated in vacuo. Recrystallization of the residue from propan-2-ol afforded 26.63 g (69 %) **1**. m.p.: 135–136 °C (Ref. [15] m.p. 135–136 °C).

5-[2-[(4-Methylphenyl)amino]ethyl]-1,3,4-oxadiazol-2(3H)-thione (**2**, $C_{11}H_{13}N_3OS$)

To 1.68 g KOH (30 mmol) dissolved in 50 cm^3 ethanol, 3 cm^3 CS_2 (3.8 g, 50 mmol) was added dropwise and the mixture was stirred at room temperature for 15 min. Afterwards 5.79 g **1** (30 mmol) dissolved in 50 cm^3 ethanol was added and the reaction mixture was heated at reflux for 24 h. The liquid fractions were concentrated in vacuo and the residue was dissolved in 150 cm^3 H_2O and acidified with HCl to pH 3–4. The precipitate was isolated by filtration and washed with methanol. Recrystallization from methanol afforded 5.01 g (71 %) **2**. m.p.: 66–67 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.14 (s, 3H, CH_3), 2.93 (t, J = 6.60 Hz, 2H, CH_2CN), 3.37 (t, J = 6.60 Hz, 2H, CH_2N), 5.48 (br s, 1H, *NH*CH_2), 6.49 (d, J = 8.40 Hz, 2H, $H_{(2,6)}$Ar), 6.90 (d, J = 8.40 Hz, 2H, $H_{(3,5)}$Ar), 13.99 (s, 1H, NNH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.99 (CH_3), 25.25 (C-8), 40.21 (C-7), 112.35 (C-2, 6), 124.58 (C-4), 129.36 (C-3, 5), 145.61 (C-1), 162.64 (C-9), 177.68 (C-10) ppm; IR (KBr): $\bar{\nu}$ = 3,364, 3,276 (NH), 1,618 (C=N), 1,318 (C=S) cm^{-1}; MS (ESI, 20 eV): *m*/*z* (%) = 236 ($[M+1]^+$, 100).

4-Amino-2,4-dihydro-5-[2-[(4-methylphenyl)amino]ethyl]-3H-1,2,4-triazole-3-thione (**3**, $C_{11}H_{15}N_5S$)

A mixture of 2.35 g **2** (10 mmol), 0.32 g NH_2NH_2 (10 mmol), and 30 cm^3 dioxane was heated at reflux for 8 h, and then acidified with acetic acid to pH 3. The precipitate was isolated by filtration and washed with H_2O until pH 7. Recrystallization from propan-2-ol afforded 1.39 g (56 %) **3**. m.p.: 105–106 °C (Ref. [19], oily residue); ^{1}H NMR, IR, and MS spectra were found to be identical with the literature ones [19].

5-[2-[(4-Methylphenyl)amino]ethyl]-1,3,4-oxadiazol-2(3H)-one (**4**, $C_{11}H_{13}N_3O_2$)

A mixture of 1.93 g **1** (10 mmol) and 1.94 g 1,1′-carbonyldiimidazole (12 mmol) in 40 cm^3 dry dioxane was heated at reflux for 12 h. H_2O (30 cm^3) was added and the crystalline precipitate was isolated by filtration. Purification by column chromatography (acetone/hexane 1:1, R_f = 0.8) afforded 1.34 g (61 %) **4**. m.p.: 144–145 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.14 (s, 3H, CH_3), 2.93–2.99 (m, 2H, CH_2CN), 3.18–3.27 (m, 2H, *CH*$_2$NH), 5.25 (t, J = 6.10 Hz, 1H, *NH*CH_2), 6.49 (d, J = 8.10 Hz, 2H, $H_{(2,6)}$Ar), 6.90 (d, J = 8.10 Hz, 2H, $H_{(3,5)}$Ar), 10.29 (s, 1H, NNH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.99 (CH_3), 32.97 (C-8), 43.53 (C-7), 112.33 (C-2, 6), 124.36 (C-4), 129.32 (C-3, 5), 146.07 (C-1), 150.98 (C-9), 169.63 (C-10) ppm; IR (KBr): $\bar{\nu}$ = 3,361, 2,975 (NH), 1,691 (C=O), 1,522 (C=N) cm^{-1}; MS (ESI, 25 eV): *m*/*z* (%) = 220 ($[M+1]^+$, 50).

N-(2,5-Dimethyl-1H-pyrrol-1-yl)-3-[(4-methylphenyl)amino]propanamide (**5**, $C_{16}H_{21}N_3O$)

A mixture of 0.97 g **1** (5 mmol), 40 cm^3 propan-2-ol, 0.46 g 2,5-hexanedione (10 mmol), and 1 cm^3 acetic acid was heated at reflux for 12 h. Afterwards 20 cm^3 cold H_2O was added. Recrystallization of the precipitate from ethanol afforded 0.85 g (63 %) **5**. m.p.: 131–132 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.97 (s, 6H, 2 CH_3), 2.14 (s, 3H, CH_3), 2.54 (t, J = 6.90 Hz, 2H, $COCH_2$), 3.32 (q, J = 6.6 Hz, J = 12.90 Hz, 2H, NH*CH*$_2$), 5.38 (t, J = 8.40 Hz, 1H, NH), 5.62 (s, 2H, 2 CH), 6.53 (d, J = 8.40 Hz, 2H, $H_{(2,6)}$Ar), 6.91 (d, J = 8.40 Hz, 2H, $H_{(3,5)}$Ar), 10.59 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 10.86 (2 CH_3), 19.99 (CH_3), 33.18 (C-8), 39.70 (C-7), 102.77 (C-11, 12), 112.23 (C-2, 6), 124.18 (C-4), 126.65 (C-10, 13), 129.31 (C-3, 5), 146.06 (C-1), 170.30 (C=O) ppm; IR (KBr): $\bar{\nu}$ = 3,360, 3,277 (NH), 1,663 (C=O), 1,524 (CN) cm^{-1}; MS (ESI, 25 eV): *m*/*z* (%) = 272 ($[M+1]^+$, 70).

3-[(4-Methylphenyl)amino]-N-[(phenylcarbamoyl)amino]propanamide (**6**, $C_{17}H_{20}N_4O_2$)
To 1.93 g **1** (10 mmol) dissolved in 20 cm^3 methanol, 1.09 cm^3 phenyl isocyanate (1.19 g, 10 mmol) was added dropwise and heated at reflux for 1 h. The crystalline precipitate was isolated by filtration and washed with methanol. Recrystallization from DMF/H_2O afforded 2.54 g (81 %) **6**. m.p.: 132–133 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.14 (s, 3H, CH_3), 2.27 (t, J = 7.20 Hz, 2H, CH_2CO), 3.18 (q, J = 6.90 Hz, J = 13.20 Hz, 2H, CH_2NH), 4.18 (s, 2H, NHAr′), 5.28 (t, J = 5.55 Hz, 1H, *NH*CH_2), 6.47 (d, J = 8.40 Hz, 2H, $H_{(2,6)}$Ar), 6.88 (d, J = 8.40 Hz, 2H, $H_{(3,5)}$Ar), 6.95 (t, J = 8.10 Hz, 1H, $H_{(4)}$Ar′), 7.25 (t, J = 8.10 Hz, 2H, $H_{(3,5)}$Ar′), 7.49 (d, J = 8.10 Hz, 2H, H $_{(2,6)}$ Ar′), 8.78, 9.02 (2 s, 2H, *NHNH*CO) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.99 (C-17), 33.38 (C-8), 39.71 (C-7), 112.16 (C-2, 6), 118.37 (C-12, 16), 121.74 (C-14), 124.03 (C-4), 128.53 (C-13, 15), 129.27 (C-3, 5), 139.61 (C-11), 146.23 (C-1), 155.95 (C-10), 170.13 (C-9) ppm; IR (KBr): $\bar{\nu}$ = 2,829–3,311 (NH), 1,669, 1,643 (CO), 1,525 (O=C–N) cm^{-1}; MS (APCI+, 25 eV): *m*/*z* (%) = 335 ([M+Na]$^+$, 100).

N-[[(3,5-Dimethylphenyl)carbamoyl]amino]-3-[(4-methylphenyl)amino]propanamide (**7**, $C_{19}H_{24}N_4O_2$)
Prepared from 1.93 g **1** (10 mmol) and 1.045 cm^3 3,5-dimethylphenyl isocyanate (1.41 g, 10 mmol) by following the same procedure as for the synthesis of **6** except that the duration of heating at reflux was 3 h. Yield 1.33 g (39 %); m.p.: 145–146 °C (from DMF/H_2O); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.13 (s, 3H, CH_3), 2.18 (s, 6H, 2 CH_3), 2.40 (t, J = 7.05 Hz, 2H, CH_2CO), 3.84 (t, J = 7.05 Hz, 2H, *CH*$_2$NH), 6.57 (d, J = 9.30 Hz, 2H, $H_{(2,6)}$Ar), 6.91–7.10 (m, 5H, $H_{(3,5)}$Ar + HAr′), 7.63 (s, 1H, NH), 7.95 (s, 1H, NH), 8.55 (s, 1H, NH), 9.72 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.04 (CH_3Ar), 21.05 (2 CH_3), 32.24 (C-8), 46.08 (C-7), 112.36 (C-2, 6), 124.33 (C-4), 127.95 (C-12, 16), 129.34 (C-3, 5), 137.25 (C-14), 137.57 (C-11), 139.40 (C-13, 15), 146.31 (C-1), 155.38 (C-9), 170.72 (C-10) ppm; IR (KBr): $\bar{\nu}$ = 2,861–3,275 (NH), 1,668, 1,616 (CO), 1,527 (O=C–N) cm^{-1}; MS (APCI+, 25 eV): *m*/*z* (%) = 341 ([M+1]$^+$, 100).

3-[(4-Methylphenyl)amino]-N-[(phenylcarbamothioyl)-amino]propanamide (**8**, $C_{17}H_{20}N_4OS$)
Prepared from 1.93 g **1** (10 mmol) and 1.90 cm^3 phenyl isothiocyanate (1.35 g, 10 mmol) by following the same procedure as for the synthesis of **6** except that the duration of heating at reflux was 1.5 h. Yield 2.20 g (67 %); m.p.: 162–163 °C (from DMF/H_2O); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.33 (s, 3H, CH_3), 2.63 (t, J = 7.80 Hz, 2H, CH_2CO), 4.35 (t, J = 7.80 Hz, 2H, *CH*$_2$NH), 7.21–7.32 (m, 9H, HAr + HAr′), 8.73 (s, 1H, NH), 9.52 (s, 1H, NH), 9.58 (s, 1H, NH), 9.96 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.65 (CH_3), 30.85 (C-8), 50.45 (C-7), 112.22 (C-2, 6), 124.65 (C-4), 125.78 (C-14), 127.57 (C-12, 16), 127.79 (C-13, 15), 129.41 (C-3, 5), 139.70 (C-11), 140.47 (C-1), 170.10 (C-9), 181.56 (C-10) ppm; IR (KBr): $\bar{\nu}$ = 2,966–3,363 (NH), 1,702 (CO), 1,504 (O=C–N), 1,330 (C=S) cm^{-1}; MS (ESI, 20 eV): *m*/*z* (%) = 351 ([M+Na]$^+$, 60).

3-[(4-Methylphenyl)amino]-N-[[(4-methylphenyl)carbamothioyl]amino]propanamide (**9**, $C_{18}H_{22}N_4OS$)
Prepared from 1.93 g **1** (10 mmol) and 2.99 cm^3 *p*-tolyl isothiocyanate (1.49 g, 25 mmol) by following the same procedure as for the synthesis of **6** except that the duration of heating at reflux was 20 min. Yield 2.02 g (59 %); m.p.: 184–185 °C (from DMF/H_2O); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.15 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.46 (t, J = 6.90 Hz, 2H, CH_2CO), 3.26 (t, J = 6.90 Hz, 2H, *CH*$_2$NH), 5.34 (s, 1H, NH), 6.50 (d, J = 8.40 Hz, 2H, $H_{(2,6)}$Ar), 6.90 (d, J = 8.40 Hz, 2H, $H_{(3,5)}$Ar), 7.09–7.17 (m, 2H, $H_{(3,5)}$ Ar′), 7.25–7.33 (m, 2H, $H_{(2,6)}$ Ar′), 9.51 (s, 2H, 2 NH), 9.96 (s, 1H, NHAr′) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.05 (CH_3-Ar′), 20.52 (CH_3-Ar), 33.29 (C-8), 39.28 (C-7), 112.29 (C-2, 6), 124.25 (C-4), 125.80 (C-11), 128.50 (C-12, 16), 129.34 (C-3, 5), 134.22 (C-13, 15), 136.42 (C-14), 146.27 (C-1), 170.74 (C-9), 180.95 (C-10) ppm; IR (KBr): $\bar{\nu}$ = 3,360, 3,270, 3,138, 2,969 (NH), 1,684 (CO), 1,512 (O=C–N), 1,378 (C=S) cm^{-1}; MS (ESI, 25 eV): *m*/*z* (%) = 365 ([M+Na]$^+$, 100).

3-[(4-Methylphenyl)(phenylcarbamoyl)amino]-N-[(phenylcarbamoyl)amino]propanamide (**10**, $C_{24}H_{25}N_5O_3$)
Method A. Prepared from 1.93 g **1** (10 mmol) and 2.7 cm^3 phenyl isocyanate (2.97 g, 25 mmol) by following the same procedure as for the synthesis of **6** except that the duration of heating at reflux was 4 h. Yield 3.23 g (75 %) (from propan-2-ol).

Method B. A mixture of 0.78 g **6** (2.5 mmol), 10 cm^3 DMF, and 0.27 cm^3 phenyl isocyanate (0.30 g, 2.6 mmol) was heated at reflux for 6 h. Afterwards 30 cm^3 H_2O was added. The resin-like product formed was washed with 3 × 10 cm^3 H_2O. Twice repeated recrystallization from propan-2-ol afforded 0.79 g (73 %) **10**. m.p.: 145–146 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.34 (s, 3H, CH_3), 2.44 (t, J = 7.20 Hz, 2H, CH_2CO), 3.88 (t, J = 7.20 Hz, 2H, CH_2N), 6.89–7.01 (m, 4H, HAr), 7.16–7.29 (m, 5H, HAr′), 7.37–7.51 (m, 5H, HAr″), 7.89 (s, 1H, NH), 8.03 (s, 1H, NH), 8.72 (s, 1H, NH), 9.78 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.63 (CH_3), 32.19 (C-8), 46.04 (C-7), 112.25, 118.54, 119.72, 121.84, 121.92, 127.81, 128.17, 128.54, 128.69, 139.05, 139.52, 139.88 (CAr), 154.47 (CO), 155.28 (CO), 170.51 (CS) ppm; IR (KBr): $\bar{\nu}$ = 2,924–3,422 (NH), 1,705, 1,656 (CO), 1,529

(OCN) cm^{-1}; MS (ESI, 25 eV): *m/z* (%) = 431 ($[M+1]^+$, 100).

3-[(4-Methylphenyl)(phenylcarbamothioyl)amino]-N-[(phenylcarbamothioyl)amino]propanamide (**11**, $C_{24}H_{25}N_5OS_2$)

Method A. Prepared from 1.93 g **1** (10 mmol) and 4.52 cm^3 phenyl isothiocyanate (3.38 g, 25 mmol) by following the same procedure as for the synthesis of **6**. Yield 3.24 g (70 %).

Method B. Prepared from 1.93 g **1** (10 mmol) and 0.47 cm^3 phenyl isothiocyanate (0.34 g, 2.6 mmol) by following the same procedure as for the synthesis of **10** (method B). Yield 0.79 g (68 %); m.p.: 157–158 °C (from propan-2-ol); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.33 (s, 3H, CH_3), 2.64 (t, J = 7.80 Hz, 2H, CH_2CO), 4.35 (t, J = 7.80 Hz, 2H, CH_2N), 7.06–7.48 (m, 14H, HAr, HAr′, HAr″), 8.73 (s, 1H, NH), 9.56 (s, 1H, NH), 9.59 (s, 1H, NH), 9.96 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.63 (CH_3), 30.85 (C-8), 50.42 (C-7), 112.81, 119.78, 124.63, 125.75, 127.55, 127.76, 127.96, 130.46, 137.00, 139.03, 139.69, 140.44 (CAr), 170.15 (CO), 180.79 (CS), 181.55 (CS) ppm; IR (KBr): $\bar{\nu}$ = 2,960–3,360 (NH), 1,709 (CO), 1,369 (CS) cm^{-1}; MS (ESI, 25 eV): *m/z* (%) = 464 ($[M+1]^+$, 40).

3-[(4-Methylphenyl)[(4-methylphenyl)carbamothioyl]amino]-N-[[(4-methylphenyl)carbamothioyl]amino]propanamide (**12**, $C_{26}H_{29}N_5OS_2$)

Method A. A mixture of 1.93 g **1** (10 mmol) and 2.29 cm^3 *p*-tolyl isothiocyanate (3.73 g, 25 mmol) was heated at reflux for 1 h. The crystalline precipitate was isolated by filtration. Recrystallization from propan-2-ol afforded 3.83 g (78 %) **12**.

Method B. Prepared from 0.86 g **9** (2.5 mmol) and 0.24 cm^3 *p*-tolyl isothiocyanate (0.39 g, 2.6 mmol) by following the same procedure as for the synthesis of **10** (method B). Yield 0.81 g (66 %); m.p.: 172–173 °C (propan-2-ol); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.16 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.46 (t, J = 6.90 Hz, 2H, CH_2CO), 3.25 (t, J = 6.90 Hz, 2H, CH_2N), 6.49 (d, J = 8.40 Hz, 2H, $H_{(2,6)}$Ar), 6.90 (d, J = 8.40 Hz, 2H, $H_{(3,5)}$Ar), 7.02–7.08 (m, 4H, HAr′), 7.19–7.25 (m, 4H, HAr″), 9.50 (s, 2H, NH), 9.95 (s, 2H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.03, 20.47, 20.63 (CH_3), 33.31 (C-8), 50.42 (C-7), 112.25 (C-2, 6), 123.82 (C-4), 125.87 (C-14, 21), 128.25, 128.80 (C-13, 15, 20, 22), 129.31 (C-3, 5), 133.53, 130.48 (C-12, 16, 19, 23), 136.42 (C-11), 136.78 (C-18), 146.26 (C-1), 169.43 (CO), 171.23 (CS), 179.52 (CS) ppm; IR (KBr): $\bar{\nu}$ = 3,360, 3,271, 3,138, 2,969 (NH), 1,684 (CO), 1,513 (O=C–N), 1,378, 1,356 (C=S) cm^{-1}; MS (ESI, 25 eV): *m/z* (%) = 492 ($[M+1]^+$, 90).

2,4-Dihydro-5-[2-[(4-methylphenyl)amino]ethyl]-4-phenyl-3H-1,2,4-triazol-3-one (**13**, $C_{17}H_{18}N_4O$)

A mixture of 0.78 g **6** (2.5 mmol) and 25 cm^3 20 % aqueous KOH solution was heated at reflux for 4 h and then cooled to room temperature. Afterwards conc. HCl was added to pH 4. The crystalline precipitate was isolated by filtration and washed with H_2O. Recrystallization from DMF/H_2O afforded 0.35 g (48 %) **13**. m.p.: 153–154 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.12 (s, 3H, CH_3-Ar), 2.61 (t, J = 7.20 Hz, 2H, CH_2C), 3.09–3.19 (m, 2H, NHCH_2), 5.37 (s, 1H, NHAr), 6.27 (d, J = 8.25 Hz, 2H, $H_{(2,6)}$Ar), 6.82 (d, J = 8.25 Hz, 2H, $H_{(3,5)}$Ar), 7.38–7.45 (m, 2H, HAr′), 7.48–7.55 (m, 3H, HAr′), 11.70 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.96 (CH_3), 25.75 (C-8), 39.60 (C-7), 111.98 (C-2, 6), 124.14 (C-4), 127.54 (C-12, 16), 128.60 (C-14), 129.28 (C-13, 15), 129.38 (C-3, 5), 132.87 (C-11), 145.21 (C-1), 145.71 (C-9), 154.33 (C-10) ppm; IR (KBr): $\bar{\nu}$ = 3,326, 2,890 (NH), 1,670 (CO), 1,528 (C=N), 1,499 (C–N) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 295 ($[M+1]^+$, 20), 317 ($[M+Na]^+$, 70).

4-(3,5-Dimethylphenyl)-2,4-dihydro-5-[2-[(4-methylphenyl)amino]ethyl]-3H-1,2,4-triazol-3-one (**14**, $C_{19}H_{22}N_4O$)

Prepared from 0.68 g **7** (2 mmol) by following the same procedure as for the synthesis of **13** to afford 0.42 g (65 %) **14**. m.p.: 202–203 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.11 (s, 3H, CH_3), 2.28 (s, 6H, 2 CH_3), 2.57 (t, J = 7.20 Hz, 2H, CH_2C), 3.15 (t, J = 7.20 Hz, 2H, NHCH_2), 5.41 (s, 1H, NHAr), 6.26 (d, J = 8.40 Hz, 2H, $H_{(2,6)}$Ar), 6.81 (d, J = 8.40 Hz, 2H, $H_{(3,5)}$Ar), 6.96 (d, J = 0.60 Hz, 2H, $H_{(2,6)}$Ar′), 7.10 (d, J = 0.60 Hz, 1H, $H_{(4)}$Ar′), 11.75 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.09 (CH_3), 20.71 (2 CH_3), 25.77 (C-8), 39.90 (C-7), 112.11 (C-2, 6), 124.33 (C-4), 125.17 (C-12, 16), 129.43 (C-3, 5), 130.14 (C-14), 132.76 (C-11), 138.93 (C-13, 15), 145.46 (C-1), 145.81 (C-9), 154.58 (C-10) ppm; IR (KBr): $\bar{\nu}$ = 3,355, 2,917 (NH), 1,698 (CO), 1,527 (C=N), 1,455 (C–N) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 323 ($[M+1]^+$, 90).

2,4-Dihydro-5-[2-[(4-methylphenyl)amino]ethyl]-4-phenyl-3H-1,2,4-triazole-3-thione (**15**, $C_{17}H_{18}N_4S$)

Method A. A mixture of 1.57 g **8** (5 mmol) and 50 cm^3 20 % aqueous KOH solution was heated at reflux for 3 h and then cooled to room temperature. Afterwards conc. HCl was added to pH 4. The crystals formed were isolated by filtration and washed with H_2O. Recrystallization from DMF/H_2O afforded 0.64 g (83 %) **15**.

Method B. A mixture of 0.66 g **7** (2 mmol), 0.064 g NH_2NH_2 (2 mmol), and 10 cm^3 methanol was heated at 50–60 °C for 4 h. Afterwards 40 cm^3 cold H_2O was added

to the reaction mixture. The precipitate was isolated by filtration and purified by column chromatography (acetone/hexane 1:1, $R_f = 0.87$). Recrystallization from DMF/H_2O afforded 0.31 g (50 %) **15**.

Method C. A mixture of 0.93 g **11** (2 mmol) and 20 cm^3 10 % aqueous KOH solution was heated at reflux for 4 h. The crystalline precipitate was isolated by filtration. Recrystallization from DMF/H_2O afforded 0.61 g (98 %) **15**. m.p.: 173–174 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.11$ (s, 3H, CH_3), 2.63 (t, $J = 7.20$ Hz, 2H, CH_2C), 3.16 (q, $J = 7.20$ Hz, $J = 13.80$ Hz, 2H, NH*CH*$_2$), 5.43 (t, $J = 6.60$ Hz, 1H, NHAr), 6.24 (d, $J = 8.25$ Hz, 2H, $H_{(2,6)}$Ar), 6.79 (d, $J = 8.25$ Hz, 2H, $H_{(3,5)}$Ar), 7.34–7.49 (m, 5H, HAr′), 13.76 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 19.99$ (CH_3), 25.30 (C-8), 39.71 (C-7), 111.98 (C-2, 6), 124.22 (C-4), 127.24 (C-12, 16), 128.38 (C-14), 128.55 (C-13, 15), 129.42 (C-3, 5), 133.66 (C-11), 145.58 (C-1), 150.52 (C-9), 167.54 (C-10) ppm; IR (KBr): $\bar{\nu} = 3{,}310$, 2,920 (NH), 1,525 (C=N), 1,497 (C–N), 1,298 (C=S) cm^{-1}; MS (ESI, 20 eV): *m/z* (%) = 331 ($[M+Na]^+$, 100).

2,4-Dihydro-4-(4-methylphenyl)-5-[2-[(4-methylphenyl)-amino]ethyl]-3H-1,2,4-triazole-3-thione
(**16**, $C_{18}H_{20}N_4S$)
Method A. Prepared from 0.51 g **9** (45 mmol) by following the same procedure as for the synthesis of **15** (method A) to afford 0.64 g (83 %) **16**.

Method B. Prepared from 0.34 g **9** (1 mmol) and 0.064 g NH_2NH_2 (2 mmol) by following the same procedure as for the synthesis of **15** (method B) to afford 0.15 g (50 %) **16**. m.p.: 192–193 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.12$ (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.62 (t, $J = 7.20$ Hz, 2H, CH_2C), 3.16 (q, $J = 7.05$ Hz, $J = 14.10$ Hz, 2H, *CH*$_2$NH), 5.42 (t, $J = 6.00$ Hz, 1H, NHAr), 6.25 (d, $J = 8.10$ Hz, 2H, $H_{(2,6)}$Ar), 6.81 (d, $J = 8.10$ Hz, 2H, $H_{(3,5)}$Ar), 7.26–7.38 (m, 4H, HAr′), 13.72 (s, 1H, NHAr′) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 19.99$ (CH_3-Ar), 20.73 (CH_3-Ar′), 25.26 (C-8), 39.71 (C-7), 112.00 (C-2, 6), 124.19 (C-4), 128.09 (C-14), 129.27 (C-12, 16), 129.87 (C-13, 15), 131.05 (C-3, 5), 139.11 (C-11), 145.58 (C-1), 150.61 (C-9), 167.59 (C-10) ppm; IR (KBr): $\bar{\nu} = 3{,}392$, 2,935 (NH), 1,524 (C = N), 1,494 (C–N), 1,338 (C=S) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 348 ($[M+Na+1]^+$, 50).

3-(4-Methylphenyl)-1-phenyl-3-[2-[5-(phenylamino)-1,3,4-oxadiazol-2-yl]ethyl]urea (**17**, $C_{24}H_{23}N_5O_2$)
To 5 cm^3 conc. H_2SO_4 was added 0.52 g **10** (1.2 mmol) in portions and the reaction mixture was stirred at room temperature for 30 min. Afterwards, it was added dropwise into ice-water mixture. The crystalline precipitate was isolated by filtration. Recrystallization from ethanol afforded 0.43 g (87 %) **17**. m.p.: 98–99 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.34$ (s, 3H, CH_3), 2.43 (t, $J = 7.20$ Hz, 2H, CH_2CO), 3.87 (t, $J = 7.20$ Hz, 2H, CH_2N), 8.68, 9.75 (2 s, 2H, Ar*NH*, Ar′NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 20.58$ (CH_3), 32.18 (C-8), 39.71 (C-7), 110.22, 118.50, 119.68, 121.78, 121.88, 127.76, 128.12, 128.49, 130.08, 136.07, 139.47, 139.83 (CAr), 154.42 (C-9), 155.21 (C-10), 170.44 (CS) ppm; IR (KBr): $\bar{\nu} = 3{,}360$, 2,929 (NH), 1,512 (CN) cm^{-1}; MS (ESI, 25 eV): *m/z* (%) = 414 ($[M+1]^+$, 100).

3-(4-Methylphenyl)-1-phenyl-3-[2-[5-(phenylamino)-1,3,4-thiadiazol-2-yl]ethyl]thiourea (**18**, $C_{24}H_{23}N_5S_2$)
Prepared from 0.56 g **11** (1.2 mmol) by following the same procedure as for the synthesis of **17** except that $POCl_3$ was used instead of conc. H_2SO_4 to afford 0.45 g (84 %) **18**. m.p.: 93–94 °C (ethanol); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.32$ (s, 3H, CH_3), 3.28 (t, $J = 7.35$ Hz, 2H, CH_2CN), 4.47 (t, $J = 7.35$ Hz, 2H, CH_2NH), 6.96–7.58 (m, 14H, HAr, HAr′, HAr″), 8.71 (s, 1H, NHAr′), 10.29 (s, 1H, NHAr″) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 20.60$ (CH_3), 27.66 (C-8), 53.57 (C-7), 117.22, 121.70, 124.76, 125.97, 127.43, 127.74, 128.98, 130.44, 137.07, 139.55, 140.39, 140.60 (CAr), 156.28 (C-9), 164.35 (C-10), 181.75 (C=S) ppm; IR (KBr): $\bar{\nu} = 3{,}367$, 2,924 (NH), 1,510 (CN) cm^{-1}; MS (ESI, 25 eV): *m/z* (%) = 446 ($[M+1]^+$, 100).

1,3-Bis(4-methylphenyl)-3-(2-[5-[(4-methylphenyl)amino]-1,3,4-thiadiazol-2-yl]ethyl)thiourea (**19**, $C_{26}H_{27}N_5S_2$)
Prepared from 0.49 g **12** (1 mmol) by following the same procedure as for the synthesis of **17** to afford 0.21 g (44 %) **19**. m.p.: 97–98 °C (propan-2-ol); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.16$ (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.13 (t, $J = 6.60$ Hz, 2H, CH_2CN), 3.36 (t, $J = 6.60$ Hz, 2H, CH_2N), 6.57 (d, $J = 8.40$ Hz, 2H, $H_{(2,6)}$Ar), 6.93 (d, $J = 8.40$ Hz, 2H, $H_{(3,5)}$Ar), 7.08–7.17 (m, 4H, HAr′), 7.42–7.54 (m, 4H, HAr″), 10.19 (s, 2H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 20.03$, 20.26, 20.46 (CH_3), 29.21 (C-8), 42.72 (C-7), 112.84, 117.20, 124.99, 126.07, 127.50, 128.24, 129.31, 129.39, 130.34, 130.48, 138.39, 145.33 (CAr), 157.02 (C-9), 164.42 (C-10), 181.75 (CS) ppm; IR (KBr): $\bar{\nu} = 3{,}358$, 2,910 (NH), 1,515 (CN) cm^{-1}; MS (ESI, 25 eV): *m/z* (%) = 474 ($[M+1]^+$, 70).

5-[2-[(4-Methylphenyl)amino]ethyl]-N-phenyl-1,3,4-oxadiazol-2-amine (**20**, $C_{17}H_{18}N_4O$)
A mixture of 0.62 g **6** (2 mmol) and 5 cm^3 conc. H_2SO_4 was stirred at room temperature until fully dissolved (approx. 20 min). The reaction mixture was added dropwise to an ice/water mixture. The crystalline precipitate was isolated by filtration and washed with H_2O. Recrystallization from methanol afforded 0.57 g (98 %) **20**. m.p.: 114–115 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.23$ (s,

3H, CH_3), 2.29 (t, $J = 7.20$ Hz, 2H, CH_2CO), 3.47 (t, $J = 7.20$ Hz, 2H, CH_2NH), 6.89–6.99 (m, 2H, HAr), 7.15–7.21 (m, 2H, HAr), 7.36–7.48 (m, 5H, HAr′), 8.76 (s, 1H, NHAr), 9.78 (s, 1H, NHAr′) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 20.70$ (CH_3), 32.32 (C-8), 46.12 (C-7), 112.63 (C-2, 6), 119.85 (C-12, 16), 124.27 (C-4), 128.29 (C-14), 128.69 (C-13, 15), 130.24 (C-3, 5), 136.29 (C-11), 139.90 (C-1), 155.39 (C-9), 169.61 (C-10) ppm; IR (KBr): $\bar{\nu} = 3{,}310$, 2,919 (NH), 1,520 (CN) cm^{-1}; MS (APCI+, 25 eV): m/z (%) = 295 ([M+1]$^+$, 90).

N-(3,5-Dimethylphenyl)-5-[2-[(4-methylphenyl)amino]ethyl]-1,3,4-oxadiazol-2-amine (**21**, $C_{19}H_{22}N_4O$)

Prepared from 0.68 g **7** (2 mmol) by following the same procedure as for the synthesis of **20** to afford 0.67 g (69 %) **21**. m.p.: 191–192 °C (methanol); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.19$ (s, 3H, CH_3), 2.29 (s, 6H, 2 CH_3), 2.59 (t, $J = 7.20$ Hz, 2H, CH_2CO), 3.51 (t, $J = 7.20$ Hz, 2H, CH_2NH), 7.05–7.39 (m, 7H, HAr + HAr′), 8.79 (s, 1H, NHAr), 9.87 (s, 1H, NHAr′) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 20.65$ (CH_3), 23.16 (2 CH_3), 29.37 (C-8), 46.54 (C-7), 111.70 (C-2, 6), 119.07 (C-12, 16), 122.25 (C-4), 130.54 (C-3, 5), 136.97 (C-14), 138.42 (C-11), 138.92 (C-13,15), 144.20 (C-1), 155.26 (C-9), 169.40 (C-10) ppm; IR (KBr): $\bar{\nu} = 3{,}309$, 2,920 (NH), 1,599 (CN) cm^{-1}; MS (APCI+, 25 eV): m/z (%) = 323 ([M+1]$^+$, 70).

5-[2-[(4-Methylphenyl)amino]ethyl]-N-phenyl-1,3,4-thiadiazol-2-amine (**22**, $C_{17}H_{18}N_4S$)

Prepared from 0.66 g **8** (2 mmol) by following the same procedure as for the synthesis of **20** to afford 0.58 g (94 %) **22**. m.p.: 152–153 °C (methanol); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.15$ (s, 3H, CH_3), 3.13 (t, $J = 7.50$ Hz, 2H, CH_2CO), 3.35 (t, $J = 7.50$ Hz, 2H, CH_2NH), 5.56 (s, 1H, NH), 6.53 (d, $J = 8.40$ Hz, 2H, $HAr_{(2,6)}$), 6.91 (d, $J = 8.40$ Hz, 2H, $HAr_{(3,5)}$), 6.96 (t, $J = 7.80$ Hz, 1H, $HAr'_{(4)}$), 7.32 (t, $J = 7.80$ Hz, 2H, $HAr'_{(3,5)}$), 7.59 (d, $J = 7.80$ Hz, 2H, $HAr'_{(2,6)}$), 10.21 (s, 1H, NHAr′) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 20.00$ (CH_3), 29.38 (C-8), 42.39 (C-7), 112.36 (C-2, 6), 117.07 (C-12, 16), 121.45 (C-14), 124.41 (C-4), 128.94 (C-13, 15), 129.35 (C-3, 5), 140.76 (C-11), 145.90 (C-1), 157.53 (C-9), 164.25 (C-10) ppm; IR (KBr): $\bar{\nu} = 3{,}360$, 2,923 (NH), 1,510 (CN) cm^{-1}; MS (APCI+, 25 eV): m/z (%) = 311 ([M+1]$^+$, 70).

5-[2-(4-Methylphenylamino)ethyl]-N-phenyl-1,3,4-thiadiazol-2-amine (**23**, $C_{18}H_{20}N_4S$)

Prepared from 0.86 g **9** (2.5 mmol) by following the same procedure as for the synthesis of **20** to afford 0.56 g (69 %) **23**. m.p.: 105–106 °C (ethanol); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.23$ (s, 3H, CH_3Ar'), 2.30 (s, 3H, CH_3Ar), 3.29 (t, $J = 6.60$ Hz, 2H, CH_2CN), 3.55 (t, $J = 6.60$ Hz, 2H, $NHCH_2$), 5.61 (s, 1H, $NHCH_2$), 7.05–7.18 (m, 4H, HAr), 7.44–7.56 (m, 4H, HAr′), 10.35 (s, 1H, NHAr′) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 20.34$ (CH_3Ar'), 20.51 (CH_3Ar), 27.30 (C-8), 46.51 (C-7), 112.29 (C-2, 6), 117.38 (C-12, 16), 121.96 (C-11), 123.09 (C-4), 129.38 (C-3, 5), 129.94 (C-13, 15), 138.37 (C-14), 155.56 (C-1), 157.42 (C-9), 164.67 (C-10) ppm; IR (KBr): $\bar{\nu} = 3{,}232$, 2,919 (NH), 1,514 (CN) cm^{-1}; MS (ESI, 25 eV): m/z (%) = 325 ([M+1]$^+$, 40).

N-(3,4-Diphenyl-2(3H)-thiazolylidene)-3-[(4-methylphenyl)amino]propanehydrazide (**24**, $C_{25}H_{24}N_4OS$)

To 3.28 g **8** (10 mmol) dissolved in 40 cm^3 ethanol, 1.98 g phenacyl bromide (10 mmol) and 16.4 g sodium acetate (200 mmol) were added and the reaction mixture was heated at reflux for 10 h. Afterwards it was cooled to room temperature, poured into ice-cold water while stirring and left overnight in the cold. The precipitate formed was isolated by filtration and washed with H_2O three times. Recrystallization from H_2O afforded 1.19 g (55 %) **24**. m.p.: 126–127 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.13$ (s, 3H, CH_3), 2.32–2.45 (m, 2H, CH_2CO), 3.14 (t, $J = 7.05$ Hz, 2H, CH_2NH), 5.23 (s, 1H, NHAr), 6.36–6.53 (m, 4H, HAr), 6.84–7.08 (m, 5H, HAr′), 7.31–7.48 (m, 5H, HAr″), 7.99 (s, 1H, SCH), 10.90 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 19.97$, 33.31, 47.69, 112.34, 120.87, 123.07, 124.39, 127.57, 128.33, 128.70, 128.88, 129.26, 129.43, 129.69, 139.09, 145.82, 150.22, 156.77, 170.55 ppm; IR (KBr): $\bar{\nu} = 3{,}354$, 2,916 (NH), 1,707 (CO), 1,580 (O=C–N) cm^{-1}; MS (ESI, 25 eV): m/z (%) = 468 ([M+K]$^+$, 40).

Biology

Antibacterial activity was tested using the disk diffusion technique. The microbial agent *R. radiobacter* was commercially available from the German Collection of Microorganisms and Cell Cultures (DSMZ). The zone of inhibition of bacterial growth was investigated. The main solution (1 mg/cm^3) of synthesized compounds was prepared in DMSO and was diluted at various concentrations (50, 150, 250, 450, 550 μg/cm^3) in DMSO. Cultures of *R. radiobacter* were cultivated in petri dishes for 24 h at 37 °C on Luria–Bertani (LB) agar medium. A bacterial suspension was prepared from cultivated bacterial cultures and 100 mm^3 inoculum containing bacterial cells (10^8 CFU/cm^3) was spread over LB agar medium. Filter paper disks were prepared by adding 25 mm^3 of each compound solution and then disks were put on LB agar medium. Ampicillin was used as the positive control, and DMSO was used as a negative control. The petri dishes were incubated for 24 h at 37 °C and zones of inhibition were then ascertained for each sample.

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