Monatsh Chem (2014) 145:319–327
DOI 10.1007/s00706-013-1096-2

ORIGINAL PAPER

The synthesis of *S*-substituted derivatives of 3-[2-[(4-methylphenyl)amino]ethyl]-4-phenyl-4,5-dihydro-1*H*-1,2,4-triazole-5-thiones and their antioxidative activity

Ingrida Tumosienė · Ilona Jonuškienė · Kristina Kantminienė · Zigmuntas Jonas Beresnevičius

Received: 14 June 2013 / Accepted: 29 September 2013 / Published online: 25 October 2013

Abstract A series of novel *S*-substituted derivatives of 3-[2-[(4-methylphenyl)amino]ethyl]-4-phenyl-4,5-dihydro-1*H*-1,2,4-triazole-5-thiones was synthesized by the reaction of 1,2,4-triazole-5-thiones with alkyl, benzyl, and phenacyl halides as well as halogen-containing esters or amides. The reactions were carried out in DMF in the presence of KOH, K_2CO_3, or triethylamine, or in dioxane in the presence of NaH. The synthesized compounds were screened for their free radical scavenging activity. *N*-[2-[5-(Butylsulfanyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]ethyl]-4-methylaniline showed excellent antioxidant activity, 2.5 times higher than that of the antibiotic control (cefazolin).

Keywords Alkylations · Heterocycles · Antioxidant activity

Introduction

Heterocyclic compounds form a significant group of biologically active compounds. Among them, compounds containing the triazolethione moiety deserve special attention owing to their wide array of biological activities. The biological activity of 1,2,4-triazolethiones depends on the nature of the substituents; therefore, the chemical functionalization of the triazole ring is a promising and facile approach to the synthesis of novel compounds possessing useful properties. For example, triazolethiones containing 3-benzofuranyl [1], 3-benzoimidazolylethyl [2], and 3-indolyl [3] moieties show antimicrobial activity. 1,4-Dimethyl-3-(dichlorophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-5-thiones exhibit strong antidepressant activity and low toxicity [4]. 1,2,4-Triazole-3-thiones containing methylphenyl and chlorophenyl or nitrophenyl groups showed antioxidative and urease inhibitory activities [5]. Triazolethiones containing substituents at two or three nitrogens in the heterocycle have been identified as antibacterial and antifungal agents [6]. 4-Amino-(substituted benzamidoalkyl)-1,2,4-triazole-5(1*H*)-thiones showed anticancer activity against a human tumor cell line, leukemia (K-562) [7]. Plant growth regulation [8] activity was exhibited by 3-(3-hydroxybutyl)-4-substituted benzylidene)amino-1*H*-1,2,4-triazole-5-thiones, the strength of which depends on the substituents in the phenyl group.

Thione–thiol tautomerism is characteristic of triazolethiones; therefore, they easily form *S*-alkyl (or *S*-substituted) derivatives which elicit a broad spectrum of biological activities as well. 3-Bromophenylsulfonylphenyl 5-ethyl (or phenacyl, or ethoxycarbonylmethyl) thio-1,2,4-triazoles possess antibacterial properties [9], whereas 3-phenyl-5-pyridazinylthio-1,2,4-triazole derivatives exhibit insecticidal activity [10]. 3-Naphthoxymethyl-5-ethylthio-1,2,4-triazole derivatives have shown good hypolipidemic activity [11]. 4-Amino-3-furyl-5-phenyl (or ethoxycarbonylmethyl) thio-1,2,4-triazoles possess anti-HIV activity [12]. *S*-Alkyl-1,2,4-thiazole derivatives containing the tetrahydrobenzothiophenyl moiety as well as bis-compounds obtained by alkylation of these compounds with diiodomethane have displayed anti-Alzheimer activity [13].

As a continuation of our search for biologically active compounds [14], we report herein the synthesis of

I. Tumosienė · I. Jonuškienė · Z. J. Beresnevičius (✉)
Department of Organic Chemistry, Kaunas University of Technology, Radvilėnų pl. 19, 50254 Kaunas, Lithuania
e-mail: zigmuntas.beresnevicius@ktu.lt

K. Kantminienė
Department of General Chemistry, Kaunas University of Technology, Radvilėnų pl. 19, 50254 Kaunas, Lithuania

S-substituted derivatives of 3-[2-[(4-methylphenyl)amino]-ethyl]-4-phenyl-4,5-dihydro-1*H*-1,2,4-triazole-5-thiones, and the investigation of the structure–activity relationship and influence of *S*-substituents on the biological activity of the synthesized compounds. Depending on the pH of the medium, triazolethiones can exist in the thione or thiole form. In alkylation reactions, their oxo analogues, triazolones, form *N*-substituted derivatives under acidic conditions and *S*-substituted derivatives in basic medium. To the best of our knowledge, the products of triazolethione alkylation and acylation reactions have been isolated from the reaction mixtures only under basic conditions when the thione–thiol equilibrium of 1,2,4-triazole-5-thiones is shifted towards the formation of thioles.

1,2,4-Triazole-5-thiones were alkylated with alkyl, benzyl, and phenacyl halides as well as halo-carboxylic acids, their amides, and esters. The synthesized compounds were tested for antioxidative activity; their activity was compared to that of non-alkylated compounds.

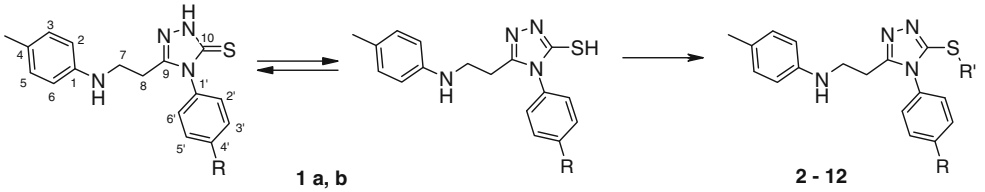
Results and discussion

3-[2-[(4-Methylphenyl)amino]ethyl]-4-phenyl-4,5-dihydro-1*H*-1,2,4-triazole-5-thione (**1a**) and its 4-(4-methylphenyl) homologue **1b** were synthesized from *N*-(4-methylphenyl)-β-alanines via semicarbazides by heating the latter at reflux in aqueous potassium hydroxide solution and subsequently acidifying the reaction mixture [15] (Scheme 1).

Alkylation reactions of **1** were performed using three methods (A, B, C). Alkylation employing haloalkanes and chloroacetamide was carried out in the presence of KOH and K_2CO_3 (method A). Method B was used for alkylation with chloroacetate and phenacyl bromides in the presence of triethylamine. The reaction products were isolated in 63–85 % yield after diluting the reaction mixture with water. Alkylation reaction of **1a** with (chloromethyl)benzene according to method A provided the target product **7a** in only 41 % yield, therefore the other methods were tested. The yield of the *S*-benzyl derivative according to the conditions of method B was 59 %, whereas alkylation reaction in the presence of NaH (method C) gave **7a** in 78 % yield. The starting compounds **1a** and **1b** are only slightly soluble, whereas *S*-alkyl derivatives dissolve well in common organic solvents.

In the ^{1}H NMR spectra of the *S*-substituted derivatives, the singlet of the NH group proton in the heterocyclic moiety is absent in comparison with the spectra of the starting triazolethiones **1** (approx. 13.7 ppm), whereas signals of the protons at the α-position of the *S*-substituent are observed in the range of 2.95–4.90 ppm. In the spectra of *S*-alkyl derivatives **2–6**, these resonances are shifted upfield and are found at approx. 3.00 ppm, and in the spectra of the derivatives

Scheme 1



	R	R'
1a	H	-
1b	CH_3	-
2a	H	CH_3CH_2-
2b	CH_3	CH_3CH_2-
3a	H	$(CH_3)_2CH$
4a	H	$CH_3CH_2CH_2CH_2$-
4b	CH_3	$CH_3CH_2CH_2CH_2$-
5a	H	$(CH_3)_2CHCH_2$-
6a	H	$(CH_3)_2CHCH_2CH_2$-
7a	H	$C_6H_5CH_2$-
8a	H	$C_2H_5OCOCH_2$-
8b	CH_3	$C_2H_5OCOCH_2$-
9a	H	NH_2COCH_2-
10a	H	$C_6H_5COCH_2$-
10b	CH_3	$C_6H_5COCH_2$-
11a	H	4-$ClC_6H_4COCH_2$-
12a	H	4-$NO_2C_6H_4COCH_2$-

containing a benzyl group (**7a**) or carbonylmethyl group (**8–12**) the respective proton resonances are in the range of 4.01–4.90 ppm.

Compounds **8a** and **8b** were characterized by the presence of additional signals derived from the ester group, which are observed in the ^{1}H NMR spectrum at 1.17 and 1.15 ppm (–OCH_2CH_3), and 4.09 and 4.10 (–OCH_2CH_3) ppm, respectively. The resonance of the NH group proton is shifted downfield in comparison with the spectrum of the starting compound **1**. The carbons of the ester groups resonated at 14.0 and 13.9, and 61.3 and 61.1 ppm, respectively, in the ^{13}C NMR spectrum. The signal of the CO carbon is observed at 154 ppm.

Introduction of the acetyl group usually increases or enhances the biological activity of the compound. Therefore, **1a** was heated at reflux with acetic anhydride to provide *N*-(4-methylphenyl)-*N*-[2-(4-phenyl-5-sulfanylidene-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)ethyl]acetamide (**13**), which on treatment with iodoethane or (chloromethyl)benzene gave *S*-alkyl derivatives **14** and **15**. In comparison with the spectra of non-acylated compounds, the protons of the benzene ring resonated at lower field in the ^{1}H NMR spectra of **14** and **15** because of the deshielding effect of the acyl group. In the same manner, the NCH_2 group is strongly deshielded by the acyl group and its proton resonances are shifted downfield. The resonances of Ar′ protons are shifted upfield. The NH group proton singlet is absent, whereas there is a singlet ascribed to the CH_3 group protons.

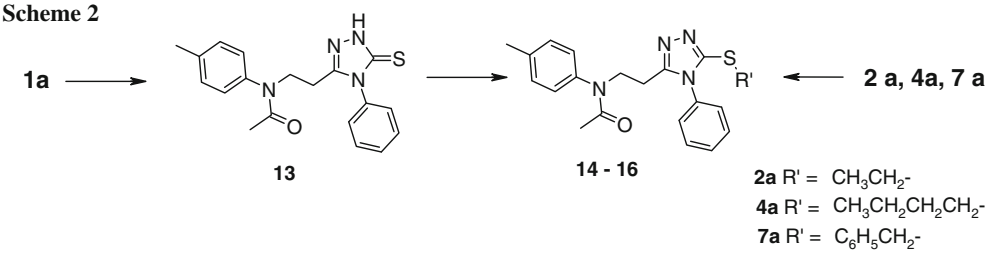
Compounds **14** and **15** as well as *N*-[2-[5-(butylsulfanyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]ethyl]-*N*-(4-methylphenyl)-acetamide (**16**) were also synthesized from *S*-alkyl compounds **2a**, **4a**, and **7a** (Scheme 2). Under the influence of the electron-withdrawing ethanoyl group, the proton signals of the *p*-tolyl and NCH_2 groups are shifted downfield by 0.27–0.54 ppm in the ^{1}H NMR spectrum for **16** in comparison with the corresponding proton signals in the spectrum for the non-acylated compound **4a**.

Ester **8a** on treatment with hydrazine hydrate was converted to the corresponding hydrazide **17** [16, 17] (Scheme 3). The signals that originated from the ester functionality in **8a** disappeared; instead, new signals due to the hydrazide structure were recorded at 5.41 and 9.37 ppm, respectively. Further support for the formation of the hydrazide structure is the appearance of strong absorption vibrations indicating the presence of $NHNH_2$ at 3,397–2,860 cm^{-1} in the FTIR spectrum.

The antioxidative activity of the synthesized compounds was evaluated by 2,2-diphenyl-1-(2,4,6-trinitrophenyl)hydrazyl (DPPH) radical scavenging method. Cefazolin, a widely used first-generation cephalosporin antibiotic, with high antioxidative action, was used as a control. As seen from the results presented in Table 1, 3-[2-[(4-methylphenyl)amino]ethyl]-4-phenyl-4,5-dihydro-1*H*-1,2,4-triazole-5-thione (**1a**) showed a very high scavenging ability which surpassed that of cefazolin. Among the *S*-substituted triazole derivatives, butyl derivative **4a** showed approx. 80 % scavenging action, whereas when an isopentyl group was introduced, the scavenging property disappeared (**6a**).

The presence of the methyl group in the phenyl ring of the heterocyclic moiety diminished the scavenging activity (**2a**, **2b**, **4a**, and **4b**) or had no influence on it (**8a** and **8b**).

Scheme 2



Scheme 3

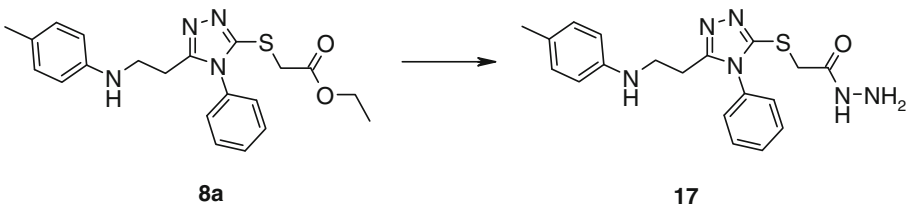


Table 1 Antioxidant activity of compounds **1–17**

Compound	R	R′	DPPH scavenging/%
Cefazolin			32.06
1a	H	–	67.10
1b	CH_3	–	49.08
2a	H	CH_3CH_2–	44.13
2b	CH_3	CH_3CH_2–	39.27
3a	H	$(CH_3)_2CH$–	40.28
4a	H	$CH_3CH_2CH_2CH_2$–	80.73
4b	CH_3	$CH_3CH_2CH_2CH_2$–	53.88
5a	H	$(CH_3)_2CHCH_2$–	35.25
6a	H	$(CH_3)_2CHCH_2CH_2$–	0.0
7a	H	$C_6H_5CH_2$–	39.27
8a	H	$C_2H_5OCOCH_2$–	33.38
8b	CH_3	$C_2H_5OCOCH_2$–	34.56
9a	H	NH_2COCH_2–	30.46
10a	H	$C_6H_5COCH_2$–	0.0
10b	CH_3	$C_6H_5COCH_2$–	33.50
11a	H	4-$ClC_6H_4COCH_2$–	32.86
12a	H	4-$NO_2C_6H_4COCH_2$–	52.93
13	H	–	54.10
17	H	$NH_2NHCOCH_2$–	42.66

The presence of the methyl group in the compounds containing a phenacyl fragment had a positive influence on the activity (**10a** and **10b**). A similar effect was observed for the chloro and nitro substituents—compound **10a** had no scavenging ability, whereas the activity of the chloro (**11a**) and nitro (**12a**) derivatives was close to that of cefazolin or even surpassed it.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Avance III 400 spectrometer (400 and 100 MHz, respectively) using TMS as an internal standard and DMSO-d_6 as a solvent. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quin = quintuplet, sext = sextet, sep = septet, b = broad. 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, Exeter Analytical) and their results were found to be in good agreement (±0.2 %) with the calculated values. Melting points were determined on a Mel-Temp melting point apparatus (Electrothermal, A Bibby Scientific Company, USA). 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-[2-[(4-Methylphenyl)amino]ethyl]-4-phenyl-4,5-dihydro-1*H*-1,2,4-triazole-5-thione (**1a**) and 3-[2-[(4-methyl phenyl)amino]ethyl]-4-(4-methylphenyl)-4,5-dihydro-1*H*-1,2,4-triazole-5-thione (**1b**) were prepared as described earlier [15]; their ^{1}H NMR spectra were identical to those described in Ref. [15].

*General procedure for synthesis of N-[2-(5-substituted sulfanyl)-4-phenyl-4H-1,2,4-triazol-3-yl]ethyl]-4-methylanilines **2–12***

Method A. To 1.24 g **1a** (4 mmol) or 1.3 g **1b** (4 mmol) dissolved in 5 cm^3 DMF, 0.15 g KOH powder (4 mmol), 0.5 g K_2CO_3, and 5 mmol alkyl halide were added. The reaction mixture was stirred at 35–40 °C for 3–8 h. Afterwards 30 cm^3 cold water was added; the precipitate formed was isolated by filtration and recrystallized from propan-2-ol (unless indicated otherwise).

Method B. To 1.24 g **1a** (4 mmol) or 1.3 g **1b** (4 mmol) dissolved in 5 cm^3 DMF, 0.51 g triethylamine (0.70 cm^3, 5 mmol) and alkyl halide (5 mmol) were added. The reaction mixture was stirred at room temperature for 2–6 h. Afterwards 30 cm^3 cold water was added; the precipitate formed was isolated by filtration and recrystallized from propan-2-ol.

N-[2-[5-(Ethylsulfanyl)-4-phenyl-4H-1,2,4-triazol-3-yl]-ethyl]-4-methylaniline (**2a**, $C_{19}H_{22}N_4S$)
Prepared according to method A from **1a** and 0.78 g (0.4 cm^3) iodoethane by stirring for 3 h. Yield 0.93 g (69 %); m.p.: 85–86 °C; TLC: $R_f = 0.28$ (acetone/hexane = 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.27$ (t, $J = 7.2$ Hz, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.76 (t, $J = 7.2$ Hz, 2H, CH_2-C), 3.05 (q, $J = 7.2$ Hz, 2H, CH_3CH_2), 3.26 (t, $J = 7.2$ Hz, 2H, $NHCH_2$), 5.47 (s, 1H, NH), 6.28 (d, $J = 8.4$ Hz, 2H, $H_{(2,6)}$Ar), 6.81 (d, $J = 8.4$ Hz, 2H, $H_{(3,5)}$Ar), 7.41–7.47 (m, 2H, $H_{(3,5)}$Ar′), 7.54–7.62 (m, 3H, $H_{(2,4,6)}$Ar′) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 14.8$ (CH_3CH_2), 20.0 (Ar–CH_3), 24.7 (C-8), 26.5 (CH_3CH_2), 40.7 (C-7), 112.0 (C-2,6), 124.1 (C-4), 127.4 (C-3′,5′), 129.3 (C-4′), 129.7 (C-2′,6′), 129.8 (C-3,5), 133.0 (C-1′), 145.6 (C-1), 149.7 (C-9), 153.9 (C-10) ppm; IR (KBr): $\overline{\nu} = 3{,}305$ (NH), 1,513, 1,498 (C=N), 1,267 (C–S–C) cm^{-1}; MS (ESI, 25 eV): m/z (%) = 339 ([M+H]$^+$, 100).

N-[2-[5-(Ethylsulfanyl)-4-(4-methylphenyl)-4H-1,2,4-triazol-3-yl]ethyl]-4-methylaniline (**2b**, $C_{20}H_{24}N_4S$)
Prepared according to method A from **1b** and 0.78 g (0.4 cm^3) iodoethane. Yield 1.41 g (62 %); m.p.: 96–97 °C; TLC: $R_f = 0.26$ (acetone/hexane = 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.27$ (t, $J = 7.2$ Hz, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.73 (t,

$J = 7.2$ Hz, 2H, CH_2-C), 3.04 (q, $J = 7.2$ Hz, 2H, CH_3CH_2), 3.23 (t, $J = 7.2$ Hz, 2H, $NHCH_2$), 5.45 (s, 1H, NH), 6.27 (d, $J = 8.1$ Hz, 2H, $H_{(2,6)}$Ar), 6.80 (d, $J = 8.1$ Hz, 2H, $H_{(3,5)}$Ar), 7.29 (d, $J = 8.1$ Hz, 2H, $H_{(3,5)}$Ar′), 7.37 (d, $J = 8.1$ Hz, 3H, $H_{(2,6)}$Ar′) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 14.7$ (CH_3), 20.0 (Ar-CH_3), 20.7 (Ar′-CH_3), 24.7 (C-8), 26.4 (CH_3CH_2), 40.7 (C-7), 112.0 (C-2,6), 124.1 (C-4), 127.1 (C-3′,5′), 129.2 (C-4′), 130.2 (C-2′,6′), 130.4 (C-3,5), 139.6 (C-1′), 145.6 (C-1), 149.8 (C-9), 153.9 (C-10) ppm; IR (KBr): $\overline{\nu} = 3{,}304$ (NH), 1,514, 1,499 (C=N), 1,268 (C–S–C) cm^{-1}; MS (ESI, 25 eV): *m/z* (%) = 353 ([M+H]$^+$, 100).

4-Methyl-N-[2-[4-phenyl-5-(propan-2-ylsulfanyl)-4H-1,2,4-triazol-3-yl]ethyl]aniline (**3a**, $C_{20}H_{24}N_4S$)

Prepared according to method A from **1a** and 0.85 g (0.50 cm^3) 2-iodopropane. Yield 1.05 g (75 %); m.p.: 103–104 °C; TLC: $R_f = 0.32$ (acetone/hexane = 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.27$ (d, $J = 6.9$ Hz, 6H, $2CH_3$), 2.11 (s, 3H, CH_3), 2.75 (t, $J = 7.2$ Hz, 2H, CH_2-C), 3.24 (t, $J = 7.2$ Hz, 2H, $NHCH_2$), 3.59 (sep, $J = 6.9$ Hz, 1H, CH), 5.45 (s, 1H, NH), 6.26 (d, $J = 8.4$ Hz, 2H, $H_{(2,6)}$Ar), 6.80 (d, $J = 8.4$ Hz, 2H, $H_{(3,5)}$Ar), 7.39–7.44 (m, 2H, $H_{(3,5)}$Ar′), 7.53–7.60 (m, 3H, $H_{(2,4,6)}$Ar′) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 20.0$ (Ar-CH_3), 23.0 (CH_3), 24.8 (C-8), 38.3 (CH), 40.6 (C-7), 112.0 (C-2,6), 124.1 (C-4), 127.5 (C-3′,5′), 129.2 (C-4′), 129.7 (C-2′,5′), 129.7 (C-3,5), 133.2 (C-1′), 145.6 (C-1), 149.07 (C-9), 153.8 (C-10) ppm; IR (KBr): $\overline{\nu} = 3{,}290$ (NH), 1,514, 1,497 (C=N), 1,262 (C–S–C) cm^{-1}; MS (ESI, 25 eV): *m/z* (%) = 353 ([M+H]$^+$, 90).

N-[2-[5-(Butylsulfanyl)-4-phenyl-4H-1,2,4-triazol-3-yl]-ethyl]-4-methylaniline (**4a**, $C_{21}H_{26}N_4S$)

Prepared according to method A from **1a** and 0.92 g (0.57 cm^3) 1-iodobutane. Isolation by column chromatography (acetone/hexane 1:1, $R_f = 0.37$) afforded 1.01 g (69 %) **4a**. M.p.: 113–114 °C; ^{1}H NMR (DMSO-d_6): $\delta = 0.84$ (t, $J = 7.5$ Hz, 3H, CH_3), 1.32 (sext, $J = 7.5$ Hz, 3H, CH_2), 1.59 (quin, $J = 7.5$ Hz, 2H, CH_2), 2.12 (s, 3H, CH_3), 2.78 (t, $J = 7.2$ Hz, 2H, CH_2-C), 3.05 (t, $J = 7.2$ Hz, 2H, CH_2), 3.33 (t, $J = 7.2$ Hz, 2H, $NHCH_2$), 4.91 (s, 1H, NH), 6.51 (d, $J = 8.1$ Hz, 2H, $H_{(2,6)}$Ar), 6.93 (d, $J = 8.1$ Hz, 2H, $H_{(3,5)}$Ar), 7.42–7.47 (m, 2H, $H_{(3,5)}$Ar′), 7.56–7.62 (m, 3H, $H_{(2,4,6)}$Ar′) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 13.3$ (CH_3), 20.1 (Ar-CH_3), 21.0 ($CH_3CH_2CH_2CH_2$), 23.9 (C-8), 30.9 ($CH_3CH_2CH_2CH_2$), 31.7 ($CH_3CH_2CH_2CH_2$), 42.3 (C-7), 114.6 (C-2,6), 127.4 (C-4), 127.8 (C-3′,5′), 129.5 (C-4′), 129.9 (C-2′,6′), 130.0 (C-3,5), 132.8 (C-1′), 142.5 (C-1), 150.2 (C-9), 153.4 (C-10) ppm; IR (KBr): $\overline{\nu} = 3{,}283$ (NH), 1,514, 1,496 (C=N), 1,260 (C–S–C) cm^{-1}; MS (ESI, 25 eV): *m/z* (%) = 367 ([M+H]$^+$, 80).

N-[2-[5-(Butylsulfanyl)-4-(4-methylphenyl)-4H-1,2,4-triazol-3-yl]ethyl]-4-methylaniline (**4b**, $C_{22}H_{28}N_4S$)

Prepared according to method A from **1b** and 0.92 g (0.57 cm^3) 1-iodobutane. Isolation by column chromatography (acetone/hexane 1:1, $R_f = 0.44$) afforded 0.98 g (64 %) **4b**. M.p.: 124–125 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 0.84$ (t, $J = 7.2$ Hz, 3H, CH_3), 1.32 (sext, $J = 7.2$ Hz, 3H, CH_2), 1.59 (quin, $J = 7.2$ Hz, 2H, CH_2), 2.11 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.72 (t, $J = 7.2$ Hz, 2H, CH_2-C), 3.03 (t, $J = 7.2$ Hz, 2H, CH_2), 3.21 (t, $J = 7.2$ Hz, 2H, $NHCH_2$), 5.44 (s, 1H, NH), 6.25 (d, $J = 8.0$ Hz, 2H, $H_{(2,6)}$Ar), 6.80 (d, $J = 8.0$ Hz, 2H, $H_{(3,5)}$Ar), 7.30 (d, $J = 8.0$ Hz, 2H, $H_{(3,5)}$Ar′), 7.37 (d, $J = 8.0$ Hz, 2H, $H_{(2,6)}$Ar′) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 13.3$ (CH_3), 20.0 (Ar-CH_3), 20.7 (Ar′-CH_3), 21.0 ($CH_3CH_2CH_2CH_2$), 24.7 (C-8), 30.9 ($CH_3CH_2CH_2CH_2$), 31.7 ($CH_3CH_2CH_2CH_2$), 40.7 (C-7), 112.0 (C-2,6), 124.1 (C-4), 127.1 (C-3′,5′), 129.3 (C-4′), 130.3 (C-2′,6′), 130.5 (C-3,5), 139.6 (C-1′), 145.7 (C-1), 149.9 (C-9), 154.0 (C-10) ppm; IR (KBr): $\overline{\nu} = 3{,}284$ (NH), 1,515, 1,497 (C=N), 1,261 (C–S–C) cm^{-1}; MS (ESI, 25 eV): *m/z* (%) = 381 ([M+H]$^+$, 100).

4-Methyl-N-(2-[5-[(2-methylpropyl)sulfanyl]-4-phenyl-4H-1,2,4-triazol-3-yl]ethyl)aniline (**5a**, $C_{21}H_{26}N_4S$)

Prepared according to method A from **1a** and 0.69 g (0.54 cm^3) 1-bromo-2-methylpropane. Yield 1.02 g (70 %); m.p.: 139–140 °C; TLC: $R_f = 0.67$ (acetone/hexane = 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 0.90$ (d, $J = 6.6$ Hz, 6H, 2 CH_3), 1.86 (sep, $J = 6.6$ Hz, 1H, CH), 2.11 (s, 3H, CH_3), 2.73 (t, $J = 6.9$ Hz, 2H, CH_2-C), 2.95 (d, $J = 6.9$ Hz, 2H, CH_2), 3.21 (q, $J = 6.9$ Hz, $J = 13.8$ Hz, 2H, $NHCH_2$), 5.44 (t, $J = 6.3$ Hz, 1H, NH), 6.24 (d, $J = 8.4$ Hz, 2H, $H_{(2,6)}$Ar), 6.80 (d, $J = 8.4$ Hz, 2H, $H_{(3,5)}$Ar), 7.40–7.46 (m, 2H, $H_{(3,5)}$Ar′), 7.55–7.61 (m, 3H, $H_{(2,4,6)}$Ar′) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 20.0$ (Ar-CH_3), 21.3 (CH_3), 24.7 (C-8), 27.8 (CH), 40.5 (CH_2), 40.6 (C-7), 112.0 (C-2,6), 124.1 (C-4), 127.5 (C-3′,5′), 129.3 (C-4′), 129.8 (C-2′,6′), 129.9 (C-3,5), 133.1 (C-1′), 145.7 (C-1), 149.9 (C-9), 153.9 (C-10) ppm; IR (KBr): $\overline{\nu} = 3{,}289$ (NH), 1,515, 1,496 (C=N), 1,262 (C–S–C) cm^{-1}; MS (ESI, 25 eV): *m/z* (%) = 367 ([M+H]$^+$, 70).

4-Methyl-N-(2-[5-[(3-methylbutyl)sulfanyl]-4-phenyl-4H-1,2,4-triazol-3-yl]ethyl)aniline (**6a**, $C_{22}H_{28}N_4S$)

Prepared according to method A from **1a** and 0.99 g (0.65 cm^3) 1-iodo-3-methylbutane. Yield 1.17 g (77 %); m.p.: 109–110 °C; TLC: $R_f = 0.64$ (acetone/hexane = 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 0.84$ (d, $J = 6.3$ Hz, 6H, 2 CH_3), 1.51 (q, $J = 7.2$ Hz, 2H, CH_2), 1.59 (sep, $J = 6.6$ Hz, 1H, CH), 2.11 (s, 3H, CH_3), 2.74 (t, $J = 7.2$ Hz, 2H, CH_2-C), 3.04 (t, $J = 7.2$ Hz, 2H, CH_2), 3.23 (q, $J = 7.2$ Hz, 2H, $NHCH_2$), 5.45 (t,

$J = 6.3$ Hz, 1H, NH), 6.25 (d, $J = 8.4$ Hz, 2H, $H_{(2,6)}Ar$), 6.80 (d, $J = 8.4$ Hz, 2H, $H_{(3,5)}Ar$), 7.40–7.46 (m, 2H, $H_{(3,5)}Ar'$), 7.54–7.61 (m, 3H, $H_{(2,4,6)}Ar'$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 20.0$ (Ar-CH_3), 21.9 (CH_3), 24.7 (C-8), 26.6 (CH), 30.2 (CH_2CH_2), 37.8 (CH_2CH_2), 40.6 (C-7), 112.0 (C-2,6), 124.1 (C-4), 127.4 (C-3′,5′), 129.3 (C-4′), 129.8 (C-2′,6′), 129.3 (C-3,5), 133.1 (C-1′), 145.7 (C-1), 149.8 (C-9), 153.9 (C-10) ppm; IR (KBr): $\overline{\nu} = 3{,}292$ (NH), 1,513, 1,498 (C=N), 1,264 (C–S–C) cm^{-1}; MS (ESI, 25 eV): m/z (%) = 381 ([M+H]$^+$, 100).

N-[2-[5-(Benzylsulfanyl)-4-phenyl-4H-1,2,4-triazol-3-yl]-ethyl]-4-methylaniline (**7a**, $C_{24}H_{24}N_4S$)

Method A. Prepared from **1a** and 0.63 g (0.58 cm^3) (chloromethyl)benzene. Yield 0.66 g (41 %).

Method B. Prepared from **1a** and 0.63 g (0.58 cm^3) (chloromethyl)benzene. Yield 0.94 g (59 %).

Method C. To 1.24 g **1a** (4 mmol) dissolved in 5 cm^3 DMF, 0.12 g NaH (5 mmol) was added. The reaction mixture was stirred at room temperature until evolution of hydrogen stopped (approx. 10 min), and 0.63 g (chloromethyl)benzene (0.58 cm^3, 5 mmol) dissolved in 5 cm^3 dioxane was then added dropwise. The reaction mixture was stirred at 50 °C for 2 h. Afterwards 30 cm^3 cold water was added and the precipitate formed was isolated by filtration. Recrystallization from propan-2-ol afforded 1.25 g (78 %) **7a**; m.p.: 134–135 °C; TLC: $R_f = 0.44$ (acetone/hexane = 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.11$ (s, 3H, CH_3), 2.74 (t, $J = 7.2$ Hz, 2H, CH_2-C), 3.23 (t, $J = 7.2$ Hz, 2H, NHCH_2), 4.32 (s, 2H, CH_2), 5.45 (s, 1H, NH), 6.26 (d, $J = 8.4$ Hz, 2H, $H_{(2,6)}Ar$), 6.82 (d, $J = 8.4$ Hz, 2H, $H_{(3,5)}Ar$), 7.17–7.44 (m, 7H, HAr′ + HAr″), 7.46–7.67 (m, 3H, HAr′) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 20.0$ (Ar-CH_3), 24.7 (C-8), 36.3 (CH_2), 40.7 (C-7), 112.0 (C-2,6), 124.1 (C-4), 127.3 (C-3′,5′), 128.3 (C-3″,5″), 128.8 (C-4″), 129.3 (C-4′), 129.7 (C-2′,6′), 129.8 (C-3,5), 132.9 (C-1′), 134.4 (C-1″), 137.0 (C-2″,6″), 145.6 (C-1), 149.4 (C-9), 154.0 (C-10) ppm; IR (KBr): $\overline{\nu} = 3{,}318$ (NH), 1,520, 1,497 (C=N), 1,288 (C–S–C) cm^{-1}; MS (ESI, 25 eV): m/z (%) = 401 ([M+H]$^+$, 100).

Ethyl 2-[(5-[2-[(4-methylphenyl)amino]ethyl]-4-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]acetate (**8a**, $C_{21}H_{24}N_4O_2S$)

Prepared according to method B from **1a** and 0.61 g (0.54 cm^3) ethyl chloroacetate except that the reaction mixture was stirred for 20 min at 35 °C. Yield 2.38 g (86 %); m.p.: 84–85 °C; TLC: $R_f = 0.33$ (acetone/hexane = 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.17$ (t, $J = 7.2$ Hz, 3H, CH_3CH_2), 2.11 (s, 3H, CH_3), 2.74 (t, $J = 7.2$ Hz, 2H, CH_2-C), 3.21 (t, $J = 7.2$ Hz, 2H, NHCH_2), 4.01 (s, 2H, CH_2), 4.09 (q, $J = 7.2$ Hz, 2H, CH_3CH_2), 5.43 (s, 1H, NH), 6.25 (d, $J = 8.1$ Hz, 2H, $H_{(2,6)}Ar$), 6.80 (d, $J = 8.1$ Hz, 2H, $H_{(3,5)}Ar$), 7.42–7.48 (m, 2H, $H_{(3,5)}Ar'$), 7.57–7.65 (m, 3H, $H_{(2,4,6)}Ar'$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 14.0$ (CH_3CH_2), 20.0 (Ar-CH_3), 24.6 (C-8), 33.9 (CH_2), 40.7 (C-7), 61.3 (CH_3CH_2), 112.1 (C-2,6), 124.3 (C-4), 127.3 (C-3′,5′), 129.3 (C-4′), 130.0 (C-2′), 130.1 (C-3), 132.8 (C-1′), 145.7 (C-1), 149.1 (C-9), 154.2 (C=O), 168.1 (C-10 C–S–) ppm; IR (KBr): $\overline{\nu} = 3{,}301$ (NH), 1,744 (C=O), 1,521, 1,448 (C=N), 1,309 (C–S–C), 1,165 (C–O–C) cm^{-1}; MS (ESI, 25 eV): m/z (%) = 397 ([M+H]$^+$, 90).

Ethyl 2-[[4-(4-methylphenyl)-5-[2-[(4-methylphenyl)-amino]ethyl]-4H-1,2,4-triazol-3-yl]sulfanyl]acetate (**8b**, $C_{22}H_{26}N_4O_2S$)

Prepared according to method B from **1b** and 0.61 g (0.54 cm^3) ethyl chloroacetate except that the reaction mixture was stirred for 30 min at 35 °C. Yield 1.39 g (85 %); m.p.: 134–135 °C; TLC: $R_f = 0.44$ (acetone/hexane = 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.15$ (t, $J = 7.2$ Hz, 3H, CH_3CH_2), 2.12 (s, 3H, CH_3), 2.73 (t, $J = 7.2$ Hz, 2H, CH_2-C), 2.41 (s, 3H, CH_3), 3.21 (t, $J = 7.2$ Hz, 2H, NHCH_2), 4.01 (s, 2H, CH_2), 4.10 (q, $J = 7.2$ Hz, 2H, CH_3CH_2), 5.45 (s, 1H, NH), 6.26 (d, $J = 8.1$ Hz, 2H, $H_{(2,6)}$ Ar), 6.81 (d, $J = 8.1$ Hz, 2H, $H_{(3,5)}Ar$), 7.33 (d, $J = 8.1$ Hz, 2H, $H_{(3,5)}Ar'$), 7.40 (d, $J = 8.1$ Hz, 3H, $H_{(2,6)}Ar'$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 13.9$ (CH_3CH_2), 20.0 (Ar-CH_3), 20.7 (Ar′-CH_3), 24.5 (C-8), 33.8 (CH_2), 40.7 (C-7), 61.1 (CH_3CH_2), 112.1 (C-2,6), 124.2 (C-4), 127.0 (C-3′), 129.2 (C-4′), 130.1 (C-2′), 130.4 (C-3), 139.8 (C-1′), 145.6 (C-1), 149.1 (C-9), 154.2 (C=O), 168.0 (C-10) ppm; IR (KBr): $\overline{\nu} = 3{,}300$ (NH), 1,746 (C=O), 1,522, 1,449 (C=N), 1,309 (C–S–C), 1,164 (C–O–C) cm^{-1}; MS (ESI, 25 eV): m/z (%) = 411 ([M+H]$^+$, 90).

2-[[5-[2-[(4-Methylphenyl)amino]ethyl]-4-phenyl-4H-1,2,4-triazol-3-yl]sulfanyl]acetamide (**9a**, $C_{19}H_{21}N_5OS$)

Prepared according to method A from **1a** and 0.47 g 2-chloroacetamide. Yield 1.14 g (78 %); m.p.: 147–148 °C; TLC: $R_f = 0.54$ (acetone/hexane/CH_3OH = 1:1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.11$ (s, 3H, CH_3), 2.74 (t, $J = 7.2$ Hz, 2H, CH_2-C), 3.22 (q, $J = 7.2$ Hz, 2H, NHCH_2), 3.37 (s, 2H, CH_2), 5.44 (t, $J = 6.3$ Hz, 1H, NH), 6.25 (d, $J = 8.1$ Hz, 2H, $H_{(2,6)}Ar$), 6.81 (d, $J = 8.1$ Hz, 2H, $H_{(3,5)}Ar$), 7.25 (s, 1H, NH_2), 7.44–7.51 (m, 2H, $H_{(3,5)}Ar'$), 7.56–7.63 (m, 3H, $H_{(2,4,6)}Ar'$), 7.68 (s, 1H, NH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 20.0$ (Ar-CH_3), 24.6 (C-8), 35.9 (CH_2), 40.7 (C-7), 112.0 (C-2,6), 124.2 (C-4), 127.4 (C-3′,5′), 129.3 (C-4′), 129.9 (C-2′,6′), 130.0 (C-3,5), 132.9 (C-1′), 145.7 (C-1), 149.8 (C-9), 153.9 (C=O), 168.6 (C-10) ppm; IR (KBr): $\overline{\nu} = 3{,}366$–$2{,}860$ (NH, NH_2), 1,693 (C=O),

1,523, 1,498 (C=N), 1,268 (C–S–C) cm^{-1}; MS (ESI, 25 eV): *m/z* (%) = 368 ($[M+H]^+$, 100).

2-[[5-[2-[(4-Methylphenyl)amino]ethyl]-4-phenyl-4H-1,2,4-triazol-3-yl]sulfanyl]-1-phenylethan-1-one (**10a**, $C_{25}H_{24}N_4OS$)

Prepared according to method B from 0.93 g **1a** (3 mmol) and 0.594 g 2-bromo-1-phenylethanone (3 mmol). Yield 0.81 g (63 %); m.p.: 138–139 °C; TLC: $R_f = 0.38$ (acetone/hexane = 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.11$ (s, 3H, CH_3), 2.75 (t, $J = 7.2$ Hz, 2H, CH_2-C), 3.22 (t, $J = 7.2$ Hz, 2H, NH*CH*$_2$), 4.87 (s, 2H, CH_2), 5.45 (s, 1H, NH), 6.26 (d, $J = 8.1$ Hz, 2H, $H_{(2,6)}$Ar), 6.81 (d, $J = 8.1$ Hz, 2H, $H_{(3,5)}$Ar), 7.45–7.51 (m, 2H, $H_{(3,5)}$Ar′), 7.52–7.63 (m, 5H, $H_{(2,4,6)}$Ar′ + $H_{(3,5)}$Ar″), 7.68 (t, $J = 7.2$ Hz, 1H, $H_{(4)}$Ar″), 8.01 (d, $J = 6.9$ Hz, 2H, $H_{(2,6)}$Ar″) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 20.0$ (Ar-CH_3), 24.6 (C-8), 40.0 (CH_2), 40.6 (C-7), 112.0 (C-2,6), 124.2 (C-4), 127.3 (C-3′,5′), 128.3 (C-3″,5″), 128.7 (C-4″), 129.3 (C-4′), 129.9 (C-2′,6′), 130.0 (C-3,5), 132.9 (C-1′), 133.6 (C-1″), 135.2 (C-2″,6″), 145.6 (C-1), 149.3 (C-9), 154.0 (C-10), 193.0 (C=O) ppm; IR (KBr): $\overline{\nu} = 3{,}289$ (NH), 1,692 (C=O), 1,514, 1,447 (C=N), 1,326 (C–S–C) cm^{-1}; MS (ESI, 25 eV): *m/z* (%) = 429 ($[M+H]^+$, 100).

2-[[4-(4-Methylphenyl)-5-[2-[(4-methylphenyl)-amino]ethyl]-4H-1,2,4-triazol-3-yl]sulfanyl]-1-phenylethan-1-one (**10b**, $C_{26}H_{26}N_4OS$)

Prepared according to method B from **1b** and 1.0 g 2-bromo-1-phenylethanone. Yield 0.72 g (81 %); m.p.: 141–142 °C; TLC: $R_f = 0.76$ (acetone/hexane = 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.12$ (s, 3H, CH_3), 2.41 (s, 3H, Ar′-CH_3), 2.72 (t, $J = 7.2$ Hz, 2H, CH_2-C), 3.20 (t, $J = 7.2$ Hz, 2H, NH*CH*$_2$), 4.85 (s, 2H, CH_2), 5.42 (s, 1H, NH), 6.25 (d, $J = 8.1$ Hz, 2H, $H_{(2,6)}$Ar), 6.80 (d, $J = 8.1$ Hz, 2H, $H_{(3,5)}$Ar), 7.31–7.42 (m, 4H, HAr′), 7.55 (t, $J = 7.5$ Hz, 2H, $H_{(3,5)}$Ar″), 7.68 (t, $J = 7.5$ Hz, 2H, $H_{(4)}$Ar″), 8.00 (d, $J = 7.5$ Hz, 2H, $H_{(2,6)}$Ar″) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 20.0$ (Ar-CH_3), 20.7 (Ar′-CH_3), 24.6 (C-8), 40.0 (CH_2), 40.7 (C-7), 112.0 (C-2,6), 124.2 (C-4), 127.1 (C-3′,5′), 128.3 (C-3″,5″), 128.7 (C-4″), 129.2 (C-4′), 130.2 (C-2′,6′), 130.4 (C-3,5), 133.6 (C-1″), 135.2 (C-2″,6″), 139.8 (C-1′), 145.6 (C-1), 149.4 (C-9), 154.1 (C-10), 193.1 (C=O) ppm; IR (KBr): $\overline{\nu} = 3{,}290$ (NH), 1,694 (C=O), 1,513, 1,446 (C=N), 1,327 (C–S–C) cm^{-1}; MS (ESI, 25 eV): *m/z* (%) = 443 ($[M+H]^+$, 70).

1-(4-Chlorophenyl)-2-[[5-[2-[(4-methylphenyl)-amino]ethyl]-4-phenyl-4H-1,2,4-triazol-3-yl]sulfanyl]-ethan-1-one (**11a**, $C_{25}H_{23}ClN_4OS$)

Prepared according to method B from 0.93 g **1a** and 1.17 g 2-bromo-1-(4-chlorophenyl)ethanone. Yield 0.96 g (52 %); m.p.: 149–150 °C; TLC: $R_f = 0.76$ (acetone/hexane = 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.11$ (s, 3H, CH_3), 2.73 (t, $J = 7.2$ Hz, 2H, CH_2-C), 3.20 (t, $J = 7.2$ Hz, 2H, NH*CH*$_2$), 4.83 (s, 2H, CH_2), 5.44 (s, 1H, NH), 6.24 (d, $J = 8.1$ Hz, 2H, $H_{(2,6)}$Ar), 6.80 (d, $J = 8.1$ Hz, 2H, $H_{(3,5)}$Ar), 7.44–7.51 (m, 2H, $H_{(3,5)}$Ar′), 7.57–7.66 (m, 5H, $H_{(2,4,6)}$Ar′ + HAr″), 7.44–7.51 (d, $J = 8.7$ Hz, 2H, HAr″) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 19.9$ (Ar-CH_3), 24.6 (C-8), 39.9 (CH_2), 40.6 (C-7), 112.0 (C-2,6), 124.2 (C-4), 127.3 (C-3′,5′), 128.8 (C-4″), 129.3 (C-4′), 129.9 (C-3″,5″), 130.0 (C-3,5), 130.2 (C-2′,6′), 132.8 (C-1′), 133.9 (C-1″), 138.5 (C-2″,6″), 145.6 (C-1), 149.2 (C-9), 154.0 (C-10), 192.2 (C=O) ppm; IR (KBr): $\overline{\nu} = 3{,}290$ (NH), 1,695 (C=O), 1,517, 1,450 (C=N), 1,326 (C–S–C) cm^{-1}; MS (ESI, 25 eV): *m/z* (%) = 464 ($[M+H]^+$, 100).

2-[[5-[2-[(4-Methylphenyl)amino]ethyl]-4-phenyl-4H-1,2,4-triazol-3-yl]sulfanyl]-1-(4-nitrophenyl)ethan-1-one (**12a**, $C_{25}H_{23}N_5O_3S$)

Prepared according to method B from **1a** and 1.0 g 2-bromo-1-(4-nitrophenyl)ethanone. Yield 1.01 g (71 %); m.p.: 182–183 °C; TLC: $R_f = 0.68$ (acetone/hexane = 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.11$ (s, 3H, CH_3), 2.74 (t, $J = 7.2$ Hz, 2H, CH_2-C), 3.20 (t, $J = 7.2$ Hz, 2H, NH*CH*$_2$), 4.90 (s, 2H, CH_2), 5.43 (s, 1H, NH), 6.24 (d, $J = 8.4$ Hz, 2H, $H_{(2,6)}$Ar), 6.80 (d, $J = 8.4$ Hz, 2H, $H_{(3,5)}$Ar), 7.45–7.51 (m, 2H, $H_{(3,5)}$Ar′), 7.57–7.64 (m, 3H, $H_{(2,4,6)}$Ar′), 8.23 (d, $J = 8.4$ Hz, 2H, HAr″), 8.36 (d, $J = 8.4$ Hz, 2H, HAr″) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 20.0$ (Ar-CH_3), 24.6 (C-8), 40.1 (CH_2), 40.6 (C-7), 112.0 (C-2,6), 123.8 (C-4″), 124.2 (C-4), 127.3 (C-3′,5′), 129.3 (C-4′), 129.8 (C-3″,5″), 129.9 (C-3,5), 130.0 (C-2′), 132.8 (C-1′), 140.0 (C-2″,6″), 145.6 (C-1), 150.0 (C-9), 154.1 (C-10), 192.6 (C=O) ppm; IR (KBr): $\overline{\nu} = 3{,}288$ (NH), 1,690 (C=O), 1,515, 1,450 (C=N), 1,298 (C–S–C) cm^{-1}; MS (ESI, 25 eV): *m/z* (%) = 474 ($[M+H]^+$, 90).

N-(4-Methylphenyl)-N-[2-(4-phenyl-5-sulfanylidene-4,5-dihydro-1H-1,2,4-triazol-3-yl)ethyl]acetamide (**13**, $C_{19}H_{20}N_4OS$)

A mixture of 1.24 g **1** (4 mmol) in 10 cm^3 acetic anhydride was heated at reflux for 6 h. To the reaction mixture 30 cm^3 water was added and the mixture was kept at 4 °C for 24 h. The aqueous solution was decanted and the residue was crystallized from a propan-2-ol/water mixture to afford 0.98 g (70 %) **13**. M.p.: 191–192 °C; TLC: $R_f = 0.6$ (acetone/hexane = 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.63$ (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.61 (t, $J = 6.9$ Hz, 2H, CH_2C), 3.64 (t, $J = 6.9$ Hz, 2H,

NHCH_2), 7.04 (d, $J = 8.1$ Hz, 2H, $H_{(2,6)}$Ar), 7.21 (d, $J = 8.1$ Hz, 2H, $H_{(3,5)}$Ar), 7.32–7.37 (m, 2H, $H_{(3,5)}$Ar′), 7.47–7.53 (m, 3H, $H_{(2,4,6)}$Ar′), 13.72 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 20.5$ (Ar-CH_3), 22.2 (CH_3), 23.8 (C-8), 45.3 (C-7), 127.7 (C-2,6), 128.2 (C-4), 129.3 (C-3′,5′), 129.4 (C-4′), 130.0 (C-2′,6′), 133.5 (C-3,5), 137.2 (C-1′), 139.6 (C-1), 149.7 (C-9), 167.6 (C=O), 169.1 (C=S) ppm; IR (KBr): $\overline{\nu} = 2{,}920$ (NH), 1,660 (C=O), 1,509 (C=N), 1,497 (C–N), 1,340 (C=S) cm^{-1}; MS (ESI, 25 eV): m/z (%) = 353 ([M+H]$^+$, 80).

N-[2-[5-(Ethylsulfanyl)-4-phenyl-4H-1,2,4-triazol-3-yl]-ethyl]-N-(4-methylphenyl)acetamide (**14**, $C_{21}H_{24}N_4OS$)

Method A. To 0.35 g **13** (1 mmol) dissolved in 10 cm^3 methanol, 0.1 g triethylamine (0.14 cm^3, 1 mmol) was added and the reaction mixture was stirred at room temperature for 10 min. Afterwards 0.16 g iodoethane (0.08 cm^3, 1 mmol) was added dropwise and the reaction mixture was stirred at 35 °C for 4 h. The liquid fractions were concentrated in vacuo. Recrystallization of the residue from hexane afforded 0.19 g (51 %) **14**.

Method B. A mixture of 0.34 g **2a** (1 mmol) in 5 cm^3 acetic anhydride was heated at reflux for 2 h. Afterwards the liquid fractions were concentrated in vacuo and the residue was crystallized from hexane to afford 0.28 g (70 %) **14**. M.p.: 138–139 °C; TLC: $R_f = 0.23$ (acetone/hexane = 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.25$ (t, $J = 7.2$ Hz, $CH_3$$CH_2$), 1.62 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.73 (t, 2H, $J = 6.8$ Hz, 3H, CH_2-C), 3.02 (q, $J = 7.2$ Hz, 2H, $CH_3$$CH_2$), 3.67 (t, $J = 6.8$ Hz, 2H, NCH_2), 7.05 (d, $J = 7.6$ Hz, 2H, $H_{(2,6)}$Ar), 7.20 (d, $J = 7.6$ Hz, 2H, $H_{(3,5)}$Ar), 7.26–7.36 (m, 2H, $H_{(3,5)}$Ar'), 7.47–7.61 (m, 3H, $H_{(2,4,6)}$Ar′) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 14.7$ (CH_3), 20.5 (Ar-CH_3), 22.2 (CH_3), 23.2 (C-8), 26.4 ($CH_3$$CH_2$), 46.1 (C-7), 127.2 (C-2,6), 127.8 (C-3′,5′), 129.7 (C-4), 129.8 (C-4′), 130.0 (C-2′,6′), 132.9 (C-3,5), 137.1 (C-1′), 139.9 (C-1),149.8 (C-9), 153.0 (C-10), 169.0 (C=O) ppm; IR (KBr): $\overline{\nu} = 1{,}660$ (C=O), 1,509, 1,498 (C=N), 1,301 (C–S–C) cm^{-1}; MS (ESI, 25 eV): m/z (%) = 381 ([M+H]$^+$, 100).

N-[2-[5-(Butylsulfanyl)-4-phenyl-4H-1,2,4-triazol-3-yl]-ethyl]-N-(4-methylphenyl)acetamide (**15**, $C_{23}H_{28}N_4OS$)

A mixture of 0.73 g **4a** (2 mmol) and 5 cm^3 acetyl chloride was stirred at room temperature for 4 h. Afterwards 20 cm^3 distilled water was added to the reaction mixture. The precipitate formed was isolated by filtration and recrystallization from hexane afforded 0.68 g (84 %) **15**. M.p.: 122–123 °C; TLC: $R_f = 0.36$ (acetone/hexane = 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 0.84$ (t, $J = 7.2$ Hz, 3H, CH_3), 1.31 (sext, $J = 7.2$ Hz, 2H, CH_2), 1.57 (quin, $J = 7.2$ Hz, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.72 (t, $J = 7.2$ Hz, 2H, CH_2-C), 3.01 (t, $J = 7.2$ Hz, 2H, CH_2), 3.34 (s, 3H, CH_3), 3.67 (t, $J = 7.2$ Hz, 2H, NCH_2), 7.05 (d, $J = 8.0$ Hz, 2H, $H_{(2,6)}$Ar), 7.20 (d, $J = 8.0$ Hz, 2H, $H_{(3,5)}$Ar), 7.27–7.31 (m, 2H, $H_{(3,5)}$Ar′), 7.50–7.56 (m, 3H, $H_{(2,4,6)}$Ar′) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 13.3$ (CH_3), 20.5 (Ar-CH_3), 21.0 (CH_2), 22.2 (COCH_3), 23.2 (C-8), 30.9 ($CH_3CH_2CH_2CH_2$), 31.8 ($CH_3CH_2CH_2CH_2$), 46.1 (C-7), 127.2 (C-2,6), 127.8 (C-3′,5′), 129.7 (C-4), 129.8 (C-4′), 130.0 (C-2′,6′), 132.9 (C-3,5), 137.1 (C-1′), 139.9 (C-1), 149.9 (C-9), 152.9 (C-10), 169.0 (C=O) ppm; IR (KBr): $\overline{\nu} = 1{,}648$ (C=O), 1,516, 1,500 (C=N), 1,293 (C–S–C) cm^{-1}; MS (ESI, 25 eV): m/z (%) = 409 ([M+H]$^+$, 100).

N-[2-[5-(Benzylsulfanyl)-4-phenyl-4H-1,2,4-triazol-3-yl]-ethyl]-N-(4-methylphenyl)acetamide (**16**, $C_{26}H_{26}N_4OS$)

Method A. To 0.35 g **13** (1 mmol) dissolved in 10 cm^3 methanol, 0.1 g triethylamine (0.14 cm^3, 1 mmol) was added and the mixture was stirred at room temperature for 10 min. Afterwards 0.13 g (chloromethyl)benzene (0.12 cm^3, 1 mmol) was added dropwise and the reaction mixture was stirred at 35 °C for 4 h. The liquid fractions were concentrated in vacuo and the residue was crystallized from hexane to afford 0.30 g (69 %) **16**.

Method B. A mixture of 0.4 g **7a** (1 mmol) and 5 cm^3 acetic anhydride was heated at reflux for 2 h. The liquid fractions were concentrated in vacuo and the residue was crystallized from hexane to afford 0.32 g (72 %) **16**. M.p.: 135–136 °C; TLC: $R_f = 0.41$ (acetone/hexane = 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.62$ (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.72 (t, $J = 7.2$ Hz, 2H, CH_2-C), 3.66 (t, $J = 7.2$ Hz, 2H, NCH_2), 4.29 (s, 2H, CH_2), 7.03 (d, $J = 8.4$ Hz, 2H, $H_{(2,6)}$Ar), 7.14-7.34 (m, 9H, HAr + HAr′ + HAr″), 7.44–7.56 (m, 3H, HAr′) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 20.6$ (Ar-CH_3), 22.2 (CH_3), 23.2 (C-8), 36.2 (CH_2), 46.1 (C-7), 127.1 (C-2,6), 127.4 (C-4), 127.8 (C-3′,5′), 128.4 (C-3″,5″), 128.9 (C-4″), 129.7 (C-4′), 129.8 (C-2′,6′), 130.0 (C-3,5), 132.8 (C-1″), 137.1 (C-1′), 137.1 (C-2″,6″), 139.9 (C-1), 149.5 (C-9), 153.1 (C-10), 168.9 (C=O) ppm; IR (KBr): $\overline{\nu} = 1{,}655$ (C=O), 1,495, 1,397 (C=N), 1,303 (C–S–C) cm^{-1}; MS (ESI, 25 eV): m/z (%) = 443 ([M+H]$^+$, 90).

2-[[3-[2-[(4-Methylphenyl)amino]ethyl]-4-phenyl-4,5-dihydro-1H-1,2,4-triazol-5-yl]sulfanyl]acetohydrazide (**17**, $C_{19}H_{24}N_6OS$)

To 1.98 g **8a** (5 mmol) dissolved in 40 cm^3 methanol, 0.48 g hydrazine hydrate (15 mmol) was added and the reaction mixture was stirred at room temperature for 6 h. Afterwards 40 cm^3 H_2O was added and the mixture was kept at 4 °C for 24 h. The precipitate was isolated by filtration and recrystallization from ethanol afforded 1.1 g (57 %) **17**. M.p.: 98–99 °C; TLC: $R_f = 0.74$ (acetone/hexane = 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.11$

(s, 3H, CH_3), 2.73 (t, $J = 7.2$ Hz, 2H, CH_2-C), 3.24 (t, $J = 7.2$ Hz, 2H, NHCH_2), 3.85 (s, 2H, CH_2), 4.43 (s, 1H, NH), 5.41 (s, 2H, NH_2), 6.27 (d, $J = 8.1$ Hz, 2H, $H_{(2,6)}$Ar), 6.81 (d, $J = 8.1$ Hz, 2H, $H_{(3,5)}$Ar), 7.42–7.51 (m, 2H, $H_{(3,5)}$Ar′), 7.53–7.64 (m, 3H, $H_{(2,4,6)}$Ar′), 9.37 (s, 1H, *NH*NH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 20.0$ (Ar-CH_3), 24.7 (C-8), 34.2 (CH_2), 40.7 (C-7), 112.0 (C-2,6), 124.2 (C-4), 127.4 (C-3′,5′), 129.3 (C-4′), 129.9 (C-2′,6′), 130.0 (C-3,5), 132.8 (C-1′), 145.7 (C-1), 149.6 (C-9), 154.0 (C=O), 166.1 (C-10) ppm; IR (KBr): $\bar{\nu} = 3{,}397$–$2{,}860$ (NH, NH_2), 1,670 (C=O), 1,519, 1,455 (C=N), 1,266 (C–S–C) cm^{-1}; MS (ESI, 25 eV): m/z (%) = 385 ($[M+H]^+$, 100).

Biology

The free radical scavenging activity of the compounds was measured by the widely used DPPH method [18]. Briefly, 1 cm^3 of a 1 mM solution of DPPH in ethanol was added to the solutions of tested compounds (1 mg cm^{-3} in DMSO). The mixture was shaken vigorously and allowed to stand at room temperature for 20 min. Afterwards the absorbance was measured at 517 nm in a spectrophotometer (UV-200-RS). Lower absorbance of the reaction mixture indicated higher free radical scavenging activity. The capability to scavenge the DPPH radical was calculated according to the following equation: DPPH scavenging effect/% = $(A_0 - A_1/A_0) \times 100$, where A_0 is the absorbance of the control reaction and A_1 is the absorbance in the presence of the samples.

References

1. Dawood KM, Farag AM, Abdel-Aziz HA (2005) Heteroat Chem 16:621
2. El-Masry AH, Fahmy HH, Abdelwahed SHA (2000) Molecules 5:1429
3. Farghaly AAH (2004) J Chin Chem Soc 51:147
4. Kane JM, Dudley MW, Sorensen SM, Miller FP (1988) J Med Chem 31:1253
5. Khan I, Ali S, Hameed S, Rama NH, Hussain MT, Wadood A, Uddin R, Ul-Haq Z, Khan A, Ali S, Choudhary MI (2010) Eur J Med Chem 45:5200
6. Wang QP, Zhang JQ, Damu GLV, Wan K, Zhang HZ, Zhou CH (2012) Sci China Chem 55:2134
7. Feng CT, Wang LD, Yau YG, Liu J, Li SH (2012) Med Chem Res 21:315
8. Zhang J, Zhang L, Lei X, Zhou C, Fu X, Zhang H (2009) J Chem Res 4:208
9. Barbuceanu SF, Almajan GA, Saramet I, Draghici C, Socoteanu R, Barbuceanu F (2009) J Serb Chem Soc 74:1041
10. Chai B, Qian X, Cao S, Liu H, Song G (2003) Arkivoc ii:141
11. Idrees GA, Aly OM, Abuo-Rahma GEAA, Radwan MF (2009) Eur J Med Chem 44:3973
12. Wu J, Liu X, Cheng X, Cao Y, Wang D, Li Z, Xu W, Panne-couque C, Witvrouw M, De Clerq E (2007) Molecules 12:2003
13. Dighe RD, Shiradkar MR, Rohom SS, Dighe PD (2011) Chem Sin 2:70
14. Tumosienė I, Kantminienė K, Pavilonis A, Maželienė Ž, Beresnevičius ZJ (2009) Heterocycles 78:59
15. Tumosienė I, Jonuškienė I, Kantminienė K, Beresnevičius ZJ (2012) Monatsh Chem 143:1441
16. Tumosiene I, Beresnevicius ZI (2007) Khim Geterotsikl Soedin 9:1353 [(2007) Chem Heterocycl Compd 43:1148]
17. Anusevičius K, Mickevičius V, Mikulskienė G (2010) Chemija 21:127
18. Madhu LN, Suchetha KN, Sarojini BK (2011) DIT 3:297