Chemistry of Heterocyclic Compounds, Vol. 43, No. 3, 2007

DERIVATIVES OF 4-AMINO-4H-1,2,4-TRIAZOLE-3-THIOLS LINKED TO THE PYRROLE CYCLE AND SOME PRODUCTS OF THEIR S-ALKYLATION

A. T. Bijev and P. Prodanova

This study offers an access to 21 new heterocyclic compounds representing pyrrole derivatives of 4-amino-4H-1,2,4-triazole-3-thiols or 1,3,4-oxadiazole-2-thiols. The principal synthetic approach is based on the cyclization of substituted potassium 2-(pyrrolecarbonyl)hydrazine-1-carbodithionate with hydrazine hydrate to 5-(substituted pyrrolyl)-4-amino-4H-1,2,4-triazole-3-thiols, followed by S-alkylation with methyl iodide or benzyl chloride. Among the resulted thirteen S-alkyl derivatives, five 1,3,4-oxadiazole derivatives have been isolated as secondary products and their formation is explained as being the result of S-alkylation of intermediate 1,3,4-oxa- diazole-2-thiols, generated in the alkaline medium.

Keywords: pyrroles, 4H-1,2,4-triazole, alkylation, cyclization.

Due to their diverse biological activity, bis-heterocyclic systems containing the 1,2,4-triazole ring linked to another aromatic or heteroaromatic ring are of interest in synthetic and pharmaceutical chemistry. Some related structures published recently include 5-HT(1A) serotonin receptor ligands [1, 2], 1,2,4-triazole derivatives for anti-HIV and antifungal evaluation [3, 4], anti-inflammatory [5] and antibacterial agents [6], as well as benzodiazepine receptor agonists [7].

Despite the diverse pharmacological activities related to pyrrole compounds (such as anti-inflammatory [8, 9], antitumor [10, 11], cytotoxic [12], anti-HIV-1 [13], sedative [14], etc.), no structural combinations between heterocycles of 4H-1,2,4-triazole and 1H-pyrrole have been reported as yet. This fact motivated us to synthesize 5-(substituted pyrrolyl)-4-amino-4H-1,2,4-triazole-3-thiols and their S-alkyl derivatives as perspective candidates for pharmacological evaluations.

The synthetic approach was based on the cyclization of available substituted hydrazinecarbodithionic acids of pyrrole [15] to 4-amino-4H-1,2,4-triazole-3-thiols followed by selective S-alkylation. The analogous preparation of 5-(pyrazole-4-yl)-1,2,4-triazole-3-thiols was already reported [16].

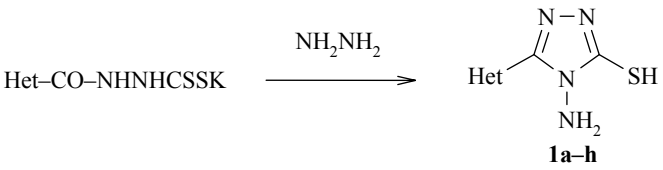
4-Amino-5-(substituted pyrrolyl)-4H-1,2,4-triazole-3-thiols **1a–h** were prepared by cyclization of hydrazinecarbodithionic acids HetCONHNHCSSK (where Het is a pyrrole residue) after heating with hydrazine hydrate.

The starting hydrazinecarbodithionic acids HetCONHNHCSSK (in the form of K-salts, known also as dithiocarbazates) were synthesized earlier [15] from the relevant carboxylic acids of pyrrole *via* hydrazinolysis of their esters and treatment of the resulted hydrazides with carbon disulfide in alkali media.

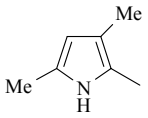
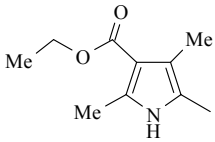
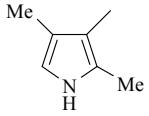
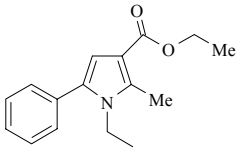
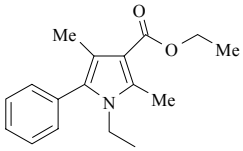
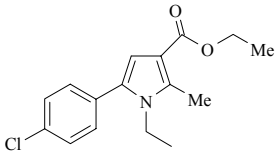
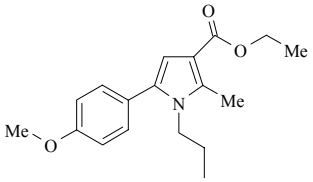
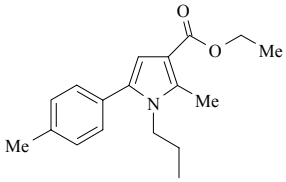
University of Chemical Technology and Metallurgy Department of Organic Synthesis and Fuels, 1756 Sofia, Bulgaria; e-mail: a.bijev@uctm.edu, e-mail: pprodanova@abv.bg. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 383-391, March, 2007. Original article submitted April 12, 2006.

 0009-3122/07/4303-0306

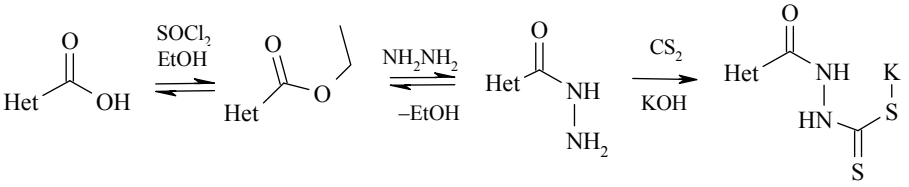
Scheme 1



1a–h

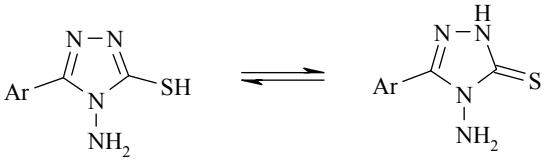
Het		
a 	**b** 	**c** 
d 	**e** 	**f** 
g 	**h** 	

Scheme 2



Such types of aminosulfanyltriazoles as products **1a–h** are recognized to exist both in thione and thiol tautomeric forms [16-19]. Nevertheless, these structures have usually been presented as thiol compounds for simplicity, including the cases where SH proton could not be located in the ^{1}H NMR spectrum [19].

Scheme 3

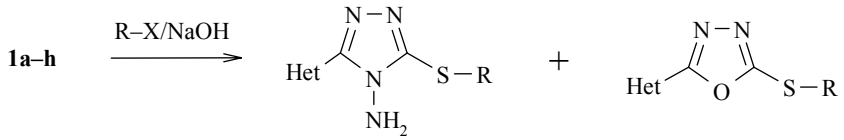


Ar = pyrazolyl, benzothiazolyl, 4-pyridyl, 2-thienyl

The synthesis of the targeted S-substituted derivatives was *via* S-alkylation of the thiol forms of **1a**–**h** with methyl iodide or benzyl chloride. In order to assure selectivity in the presence of the 4-NH_2 group, the alkylation was carried out in alkaline medium, affording the S–Na salts of 4-amino-5-sulfanyl-1,2,4-triazoles

1a–**h**. However, during the S-alkylation performed according to scheme 4 under thin layer chromatography (TLC) control, we observed the formation of the secondary products and succeeded in separating and purifying some of them by preparative TLC. Eventually, the S-methylation of **1a** and the S-benzylation of **1d** and **1f** yielded, parallel to the expected products **2** (**2a**$_1$, **2d**$_2$, and **2f**$_2$, respectively), also the alternative products **3** (**3a**$_1$, **3d**$_2$, and **3f**$_2$). These by-products whose ^{1}H NMR spectra did not show signals for NH_2 protons were identified as derivatives of S-alkyl 1,3,4-oxadiazole-5-thiols. The new oxadiazoles **3c**$_2$ and **3h**$_1$, proved to be the only pure products isolated from alkylation of **1c** and **1h**, respectively.

Scheme 4



2a,b,d–g **3a,c,d,f,h**

2 a$_1$**,b**$_1$**,e**$_1$**, 3a**$_1$**,h**$_1$ R = Me; **2 b**$_2$**,d**$_2$**,e**$_2$**,f**$_2$**,g**$_2$**, 3 c**$_2$**,d**$_2$**,f**$_2$ R = $PhCH_2$

Het are the same as in Scheme 1 (S-methyl products are denoted with subscript 1)
(S-benzyl derivatives have subscript 2)

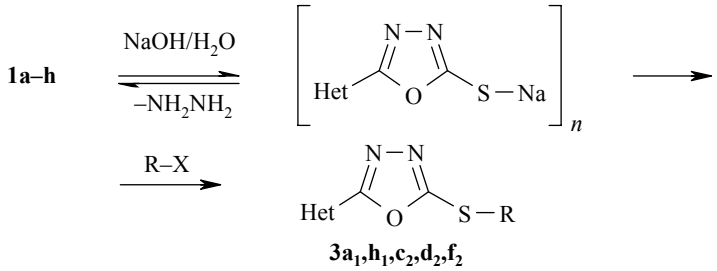
The purity of the new compounds was proved in acceptable error range (within ±0.4%) by elemental analyses, and their identities were confirmed by ^{1}H NMR and IR spectra, interpreted in the Experimental section. Adequate molecule ions for 1,3,4-oxadiazole derivatives **3** were registered by MS analysis.

The formation of the accompanying 1,3,4-oxadiazole derivatives was unexpected because no secondary products were found in the synthesis (75% yield) of analogous pyrazole derivative 4-amino-5-{[3,5-dimethyl-1-(4-nitrophenyl)pyrazol-4-yl]methyl}-4H-1,2,4-triazole-3-thiol [16].

A similar conversion of hydrazides to 1,3,4-oxadiazoles by treatment with carbon disulfide in alkaline medium has been reported earlier [17, 20, 21].

Unlike the cases cited above, no oxadiazoles (as possible prerequisites for secondary reactions) were found as by-products in the synthesis of **1a–h**. Therefore the oxadiazole derivatives **3a**$_1$, **3c**$_2$, **3d**$_2$, **3h**$_1$, and **3f**$_2$ should appear in the next step during the S-alkylation of **1a–h**, where in the alkaline solution 5-(substituted pyrrolyl)-4-amino-4H-1,2,4-triazole-3-thiols **1a–h** generate some amounts of intermediate 2-oxadiazolethiolates capable of being S-alkylated.

Scheme 5



3a$_1$**,h**$_1$**,c**$_2$**,d**$_2$**,f**$_2$

This explanation complies with the reversibility of the opposite conversion of substituted 1,3,4-oxadiazole-2-thiols to 4-amino-4H-1,2,4-triazole-3-thiols by refluxing with hydrazine [22].

1,3,4-Oxadiazole derivatives are also well known for a wide range of biological activities, including anti-inflammatory [23, 24], antimicrobial [25], and antitumor effects [26], and the development of a parallel access to such type of compounds may be a favorable supplement to the synthesis of the principal 1H-1,2,4-triazoles. The pharmacological activity of the newly synthesized compounds is under evaluation.

EXPERIMENTAL

All commercial chemicals used in this study as starting materials and reagents were purchased from "Merck" (Darmstadt, Germany). The melting points were determined with a capillary digital melting point apparatus IA 9200 Electrothermal, Southend-on-Sea, UK. The IR spectra were registered on a Specord IR-71 instrument, Carl Zeiss, Jena, Germany (KBr). The ^{1}H NMR spectra (250 MHz, 20°C) were registered on a Bruker Spectrospin WM250 spectrometer (Faenlanden, Switzerland), using TMS as internal standard. All NH and SH protons were D_2O exchangeable. Molecular ions of oxadiazole derivatives were registered on HP 6890 GC-HP 5973 MSD, Palo Alto, CA, USA, EI, 70 eV.

TLC characteristics of the products were measured on aluminum sheets of silica gel 60 F_{254}, Merck 1.05554 at ambient temperature using a benzene–methanol mobile phase (the R_f value and the relevant C_6H_6–MeOH ratio are given for each of the new compounds).

4-Amino-5-hetaryl-4H-1,2,4-triazole-3-thiols 1a-h (General procedure). To a solution of 20 mmol of the relevant hydrazinecarbodithionic acid (K-salt) dissolved in 5 cm^3 of H_2O 40 mmol of hydrazine hydrate was added. The mixture was refluxed for 1 h, cooled, diluted with water, and acidified with acetic acid. The residue was filtered off, washed with cold water, and dried. Recrystallization from benzene/CCl_4 afforded **1a-h** in 80-85% yields.

4-Amino-5-(3,5-dimethylpyrrol-2-yl)-4H-1,2,4-triazole-3-thiol (**1a**). Mp 213-214°C, R_f 0.63 (5:1). IR spectrum, ν, cm^{-1}: 1370 (CH_3), 2980 (CH_3), 3280, 3100 (NH + NH_2), 3420 (SH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.22, 2.40 (6H, 2s, 2CH_3); 3.50 (2H, br. s, NH_2); 5.5 (1H, s, SH); 5.75 (1H, s, H-4); 10.95 (1H, s, NH). Found, %: C 45.58; H 5.05. $C_8H_{11}N_5S$. Calculated, %: C 45.92; H 5.30.

Ethyl 5-(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)-2,4-dimethylpyrrole-3-carboxylate (**1b**). Mp 223-225°C, R_f 0.41 (5:1). IR spectrum, ν, cm^{-1}: 1430 (CH_3 + CH_2), 1700 ($COOC_2H_5$), 2980 (CH_3 + CH_2), 3150, 3330 (NH + NH_2), 3420 (SH). ^{1}H NMR (DMSO-d_6), δ, ppm (*J*, Hz): 1.20 (3H, t, *J* = 7.0, C<u>H</u>$_3$CH$_2$); 2.22, 2.40 (6H, 2s, 2CH_3); 3.50 (2H, br. s, NH_2); 4.05 (2H, q, *J* = 7.0, OCH_2); 5.5 (1H, s, SH); 10.95 (1H, s, NH). Found, %: C 46.62; H 5.07. $C_{11}H_{15}N_5O_2S$. Calculated, %: C 46.96; H 5.37.

4-Amino-5-(2,4-dimethylpyrrol-3-yl)-4H-1,2,4-triazole-3-thiol (**1c**). Mp 211–213°C, R_f 0.74 (10:3). IR spectrum, ν, cm^{-1}: 1370 (CH_3), 2980 (CH_3), 3100, 3270 (NH + NH_2), 3410 (SH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.20, 2.35 (6H, 2s, 2CH_3); 3.65 (2H, br. s, NH_2); 5.60 (1H, s, SH); 5.80 (1H, s, H-5); 10.95 (1H, s, NH). Found, %: C 46.15; H 5.12. $C_8H_{11}N_5S$. Calculated, %: C 45.92; H 5.30.

Ethyl 1-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)methyl]-2-methyl-5-phenylpyrrole-3-carboxylate (**1d**). Mp 234-236°C, R_f 0.41 (5:1). IR spectrum, ν, cm^{-1}: 700, 745 (C_6H_5), 1480 (CH_3 + CH_2), 1680 ($COOC_2H_5$), 2940, 2955 (CH_3 + CH_2), 3100, 3180 (NH_2), 3280 (SH). ^{1}H NMR (acetone-d_6), δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 7.1, C<u>H</u>$_3$CH$_2$); 2.45 (3H, s, CH_3); 3.70 (1H, br. s, SH); 4.20 (4H, q, *J* = 7.1, OCH_2); 4.80 (2H, s, NH_2); 5.00 (2H, s, NCH_2); 6.60 (1H, s, H-4); 6.95-7.50 (5H, m, C_6H_5). Found, %: C 56.84; H 5.26. $C_{17}H_{19}N_5O_2S$. Calculated, %: C 57.13; H 5.36.

Ethyl 1-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)methyl]-2,4-dimethyl-5-phenylpyrrole-3-carboxylate (**1e**). Mp 246-248°C, R_f 0.54 (10:3). IR spectrum, ν, cm^{-1}: 700, 755 (C_6H_5), 1495 (CH_3 + CH_2), 1680 ($COOC_2H_5$), 2960, 2995 (CH_3 + CH_2), 3200, 3400 (NH + NH_2), 3460 (SH). ^{1}H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 1.35 (3H, t, *J* = 7.1, C<u>H</u>$_3$CH$_2$); 2.05, 2.45 (6H, 2s, 2CH_3); 3.00 (1H, br. s, SH); 4.15 (2H, q, *J* = 7.1, OCH_2); 4.85 (2H, br. s, NH_2); 4.95 (2H, s, NCH_2); 6.95–7.50 (5H, m, C_6H_5). Found, %: C 58.54; H 5.78. $C_{18}H_{21}N_5O_2S$. Calculated, %: C 58.20; H 5.70.

Ethyl 1-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)methyl]-5-(4-chlorophenyl)-2-methylpyrrole-3-carboxylate (**1f**). Mp 218-220°C, R_f 0.62 (10:3). IR spectrum, ν, cm^{-1}: 820 (*p*-C_6H_4), 1470 (CH_3 + CH_2), 1690 ($COOC_2H_5$), 2900, 2955 (CH_3 + CH_2), 3190, 3240 (NH_2), 3400 (SH). ^{1}H NMR (acetone-d_6), δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 7.1, C<u>H</u>$_3$CH$_2$); 2.45 (3H, s, CH_3); 3.70 (2H, br. s, NH_2); 4.20 (2H, q, *J* = 7.1, OCH_2); 4.85 (1H, br. s, SH); 5.10 (2H, s, NCH_2); 6.60 (1H, s, H-4); 7.35 (4H, m, C_6H_4). Found, %: C 51.78; H 4.37. $C_{17}H_{18}ClN_5O_2S$. Calculated, %: C 52.10; H 4.63.

Ethyl 1-[2-(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)ethyl]-5-(4-methoxyphenyl)-2-methyl-1H-3-pyrrole-carboxylate (**1g**). Mp 185-187°C, R_f 0.44 (10:3). IR spectrum, ν, cm^{-1}: 775 (C_6H_4), 1495 (CH_3 + CH_2), 1700 ($COOC_2H_5$), 2050 (SH), 2960, 2995 (CH_3 + CH_2), 3200, 3400 (NH + NH_2), 3480 (SH). ^{1}H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 1.40 (3H, t, *J* = 7.0, $C\underline{H}_3CH_2$); 1.60 (2H, br. s, NH_2); 2.50 (3H, s, 2-CH_3); 2.86 (2H, t, *J* = 6.8, $C\underline{H}_2CH_2N$); 3.80 (3H, s, CH_3O); 4.20-4.30 (4H, m, OCH_2 + NCH_2); 6.50 (1H, s, H-4); 6.90, 7.20 (4H, 2d, *J* = 8.5, C_6H_4). Found, %: C 57.05; H 5.85. $C_{19}H_{23}N_5O_3S$. Calculated, %: C 56.84; H 5.77.

Ethyl 1-[2-(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)ethyl]-2-methyl-5-(4-methylphenyl)pyrrole-3-carboxylate (**1h**). Mp 147–148°C, R_f 0.55 (5:1). IR spectrum, ν, cm^{-1}: 820 (*p*-C_6H_4), 1490 (CH_3 + CH_2), 1690 ($COOC_2H_5$), 2960 (CH_3 + CH_2), 3190, 3240 (NH_2), 3400 (SH). ^{1}H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 7.2, $C\underline{H}_3CH_2$); 2.40, 2.55 (6H, 2s, $2CH_3$); 2.95 (2H, t, *J* = 7.5, $C\underline{H}_2CH_2N$); 4.27 (2H, q, *J* = 7.2, OCH_2); 4.35 (2H, q, *J* = 7.5, NCH_2); 5.75 (2H, br. s, NH_2); 6.50 (1H, s, H-4); 7.18 (4H, br. s, C_6H_4); 12.50 (1H, s, SH). Found, %: C 59.35; H 6.12. $C_{19}H_{23}N_5O_2S$. Calculated, %: C 59.20; H 6.01.

Ethyl 5-[4-amino-5-(methylsulfanyl)-4H-1,2,4-triazol-3-yl]-2,4-dimethylpyrrole-3-carboxylate (**$2b_1$**) **and ethyl 1-{[4-amino-5-(methylsulfanyl)-4H-1,2,4-triazol-3-yl]methyl}-2,4-dimethyl-5-phenyl-pyrrole-3-carboxy-late** (**$2e_1$**) **(**General procedure). To a stirred solution containing 3 mmol of **1b** or **1e** in 6 cm^3 1M NaOH 1.11 g of MeI (7.8 mmol) was added dropwise at 10°C. The mixture was stirred at ambient temperature for 1.0-1.5 h (TLC control), cooled, and filtered off. The precipitated product was washed with water and recrystallized from ethanol/water to afford **$2b_1$** or **$2e_1$**, respectively. Yields: 0.655 g, 74 % of **$2b_1$** and 0.935 g, 81 % of **$2e_1$**.

Ethyl 5-[4-amino-5-(methylsulfanyl)-4H-1,2,4-triazol-3-yl]-2,4-dimethylpyrrole-3-carboxylate (**$2b_1$**). Mp 221-222°C, R_f 0.50 (5:1). IR spectrum, ν, cm^{-1}: 1450, 1485 (CH_3+CH_2), 1695 ($COOC_2H_5$), 2850 (SCH_3), 2960, 2995 (CH_3 + CH_2), 3150, 3330 (NH + NH_2). ^{1}H NMR (DMSO-d_6), δ, ppm (*J*, Hz): 1.25 (3H, t, *J* = 7.0, $C\underline{H}_3CH_2$); 2.25, 2.45 (6H, 2s, $2CH_3$); 2.55 (3H, s, CH_3S); 4.10 (2H, q, *J* = 7.0, OCH_2); 4.40 (2H, br. s, NH_2); 11.00 (1H, s, NH). Found, %: C 48.98; H 5.57. $C_{12}H_{17}N_5O_2S$. Calculated, %: C 48.80; H 5.80.

Ethyl 1-{[4-amino-5-(methylsulfanyl)-4H-1,2,4-triazol-3-yl]methyl}-2,4-dimethyl-5-phenylpyrrole-3-carboxylate (**$2e_1$**). Mp 126-128°C, R_f 0.69 (5:1). IR spectrum, ν, cm^{-1}: 700, 760 (C_6H_5), 1465 (CH_3 + CH_2), 1690 ($COOC_2H_5$), 2900 (SCH_3), 2940, 2965 (CH_3 + CH_2), 3050, 3285 (NH_2). ^{1}H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 1.35 (3H, t, *J* = 7.1, $C\underline{H}_3CH_2$); 2.05, 2.50 (6H, 2s, $2CH_3$); 2.60 (3H, s, CH_3S); 4.15 (2H, q, *J* = 7.1, OCH_2); 4.90 (2H, s, NCH_2); 5.10 (2H, s, NH_2); 7.00–7.30 (5H, m, C_6H_5). Found, %: C 58.93; H 6.26. $C_{19}H_{23}N_5O_2S$. Calculated, %: C 59.20; H 6.01.

Ethyl 5-[4-amino-5-(benzylsulfanyl)-4H-1,2,4-triazol-3-yl]-2,4-dimethylpyrrole-3-carboxylate (**$2b_2$**), **ethyl 1-{[4-amino-5-(benzylsulfanyl)-4H-1,2,4-triazol-3-yl]methyl}-2,4-dimethyl-5-phenylpyrrole-3-carboxy-late** (**$2e_2$**) **and ethyl 1-{2-[4-amino-5-(benzylsulfanyl)-4H-1,2,4-triazol-3-yl]ethyl}-5-(4-methoxy-phenyl)-2-methylpyrrole-3-carboxylate** (**$2g_2$**) (General procedure). To a stirred solution containing 1 mmol of **1b, 1e,** or **1g** in 2 cm^3 1M NaOH 0.126 g $PhCH_2Cl$ (1 mmol) dissolved in 1 ml ethanol was slowly added dropwise at 10°C. The mixture was stirred at ambient temperature for 0.5-1.0 h (TLC control), cooled, and filtered off. The precipitated product was washed with water and recrystallized from ethanol/water to afford 0.278 g, 75% of **$2b_2$**, 0.387 g, 84% of **$2e_2$**, and 0.378 g, 77% of **$2g_2$**, respectively.

Ethyl 5-[4-amino-5-(benzylsulfanyl)-4H-1,2,4-triazol-3-yl]-2,4-dimethylpyrrole-3-carboxylate (**$2b_2$**). Mp 240-242°C, R_f 0.33 (5:1). IR spectrum, ν, cm^{-1}: 710, 780 (C_6H_5), 1450, 1495 (CH_3 + CH_2), 1700 ($COOC_2H_5$), 2890 (SCH_2), 2960, 2995 (CH_3 + CH_2), 3150, 3320 (NH + NH_2). ^{1}H NMR (DMSO-d_6), δ, ppm (*J*, Hz): 1.25 (3H, t, *J* = 7.1, $C\underline{H}_3CH_2$); 2.25, 2.45 (6H, 2s, $2CH_3$); 4.10 (2H, q, *J* = 7.1, OCH_2); 4.30 (2H, s, SCH_2); 5.70 (2H, s, NH_2); 6.95-7.40 (5H, m, C_6H_5). Found, %: C 57.86; H 5.95. $C_{18}H_{21}N_5O_2S$. Calculated, %: C 58.20; H 5.70.

Ethyl 1-{[4-amino-5-(benzylsulfanyl)-4H-1,2,4-triazol-3-yl]methyl}-2,4-dimethyl-5-phenylpyrrole-3-carboxylate (**$2e_2$**). Mp 155-157°C, R_f 0.71 (5:1). IR spectrum (KBr), ν, cm^{-1}: 700 + 760 (C_6H_5), 1485 (CH_3 + CH_2), 1685 ($COOC_2H_5$), 2900 + 2960 (SCH_2 + CH_3 + CH_2), 3300 (NH_2). ^{1}H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 7.1, $C\underline{H}_3CH_2$); 2.05 + 2.50 (6H, 2s, $2CH_3$); 3.50 (2H, s, NH_2); 4.05 (2H, s, CH_2S); 4.15 (2H, q, *J* = 7.1, OCH_2); 4.90 (2H, s, NCH_2); 6.90-7.30 (10H, m, $2C_6\underline{H}_5$). Found, %: C 64.75; H 5.97. $C_{25}H_{27}N_5O_2S$. Calculated, %: C 65.05; H 5.90.

Ethyl 1-{2-[4-amino-5-(benzylsulfanyl)-4H-1,2,4-triazol-3-yl]ethyl}-5-(4-methoxyphenyl)-2-methylpyrrole-3-carboxylate (2g$_2$). Mp 117-119°C, R_f 0.56 (5:1). IR spectrum, ν, cm^{-1}: 700, 770 (C_6H_5), 1490 (CH_2), 1680 ($COOC_2H_5$), 2900 (SCH_2 + CH_3), 3050, 3100 (NH_2). ^{1}H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 1.40 (3H, t, *J* = 7.0, C<u>H</u>$_3$CH$_2$); 2.50 (3H, s, 2-CH_3); 2.85 (2H, t, *J* = 6.8, C<u>H</u>$_2$CH$_2$N); 3.50 (2H, s, CH_2S); 3.80 (3H, s, CH_3O); 4.20-4.40 (4H, m, OCH_2 + NCH_2); 4.73 (2H, br. s, NH_2); 6.45 (1H, s, H-4); 6.86, 7.10 (4H, 2d, *J* = 8.5, C_6H_4); 7.15-7.40 (5H, m, C_6H_4 + C_6H_5). Found, %: C 63.76; H 6.05. $C_{26}H_{29}N_5O_3S$. Calculated, %: C 63.52; H 5.95.

3-(3,5-Dimethylpyrrol-2-yl)-5-(methylsulfanyl)-4H-1,2,4-triazol-4-amine (2a$_1$) and 2-(3,5-dimethylpyrrol-2-yl)-5-(methylsulfanyl)-1,3,4-oxadiazole (3a$_1$). Triazole **1a** (0.627 g, 3 mmol) was treated as described in the procedure used for the preparation of **2b$_1$** and **2e$_1$**. The TLC check proved that the resulting residue consisted of two products with R_f values 0.60 and 0.77 (in benzene–ethanol, 5:1). They were separated on TLC plates with silica gel 60 F_{254} for preparative layer chromatography (layer thickness 2 mm) using the same mobile phases to yield: 0.207 g, 31 % of **2a$_1$** as 4H-1,2,4-triazole derivative with R_f 0.60 and 0.150 g, 24 % of **3a$_1$** as 1,3,4-oxadiazole derivative with R_f 0.77.

3-(3,5-Dimethylpyrrol-2-yl)-5-(methylsulfanyl)-4H-1,2,4-triazol-4-amine (2a$_1$). Mp 192–194°C, R_f 0.60 (5:1). IR spectrum, ν, cm^{-1}: 1450, 1485 (CH_3), 2850 (SCH_3), 2960, 2995 (CH_3), 3150, 3330 (NH + NH_2). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.30 (6H, s, 2CH_3); 2.65 (3H, s, SCH_3); 4.25 (2H, s, NH_2); 5.65 (1H, s, H-4). Found, %: C 48.75; H 6.03. $C_9H_{13}N_5S$. Calculated, %: C 48.41; H 5.87.

2-(3,5-Dimethylpyrrol-2-yl)-5-(methylsulfanyl)-1,3,4-oxadiazole (3a$_1$). Mp 162–164°C, R_f 0.77 (5:1). IR spectrum, ν, cm^{-1}: 1375, 1490 (CH_3), 2900 (SCH_3), 2960, 2995 (CH_3). ^{1}H NMR ($CDCl_3$), δ, ppm: 2.35 (6H, s, 2CH_3); 2.70 (3H, s, SCH_3); 5.70 (1H, s, H-4); 9.90 (1H, s, NH). Mass spectrum, *m*/*z*: 209 [M]$^+$. Found, %: C 51.26; H 5.37. $C_9H_{11}N_3OS$. Calculated, %: C 51.66; H 5.30.

Ethyl 2-methyl-5-(4-methylphenyl)-1-{2-[5-(methylsulfanyl)-1,3,4-oxadiazol-2-yl]ethyl}pyrrole-3-carboxylate (3h$_1$). Triazole **1h** (1.155, 3 mmol) was treated as described in the procedure used for the preparation of **2b$_1$** and **2e$_1$.** The product obtained was recrystallized from ethanol/water to yield 0.750 g (65%) of **3h$_1$**.

Ethyl 2-methyl-5-(4-methylphenyl)-1-{2-[5-(methylsulfanyl)-1,3,4-oxadiazol-2-yl]ethyl}pyrrole-3-carboxylate (3h$_1$). Mp 96-97°C, R_f 0.79 (5:1). IR spectrum, ν, cm^{-1}: 780 (C_6H_4), 1480 (CH_3 + CH_2), 1685 ($COOC_2H_5$), 2900 (SCH_3), 2960 (CH_3 + CH_2). ^{1}H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 1.34 (3H, t, *J* = 7.2, C<u>H</u>$_3$CH$_2$); 2.39, 2.60, 2.65 (9H, 3s, 3CH_3); 2.95 (2H, t, *J* = 7.5, C<u>H</u>$_2$CH$_2$N); 4.20-4.40 (4H, m, OCH_2 + NCH_2); 6.52 1(H, s, H-4); 7.20 (4H, br. s, C_6H_4). Mass spectrum, *m*/*z*: 385 [M]$^+$. Found, %: C 61.95; H 6.21. $C_{20}H_{23}N_3O_3S$. Calculated, %: C 62.32; H 6.01.

Ethyl 1-{[4-amino-5-(benzylsulfanyl)-4H-1,2,4-triazol-3-yl]methyl}-2-methyl-5-phenylpyrrole-3-carboxylate (2d$_2$) and ethyl 1-{[5-(benzylsulfanyl)-1,3,4-oxadiazol-2-yl]methyl}-2-methyl-5-phenylpyrrole-3-carboxylate (3d$_2$) (General procedure). Triazole **1d** (0.357 g, 1 mmol) was treated as described in the procedure for the preparation of **2b$_2$**, **2e$_2$**, and **2g$_2$**. The resulting precipitate was filtered off after 2 h-stirring, and the TLC check indicated a mixture of two products with R_f values 0.45 and 0.88 (in benzene–methanol, 5:1). They were separated on TLC plates with silica gel 60 F_{254} for preparative layer chromatography (layer thickness 2 mm) using the same mobile phase as follows: 0.160 g, 36 % of **2d$_2$** as 4H-1,2,4-triazole derivative with R_f 0.45 and 0.120 g, 28 % of **3d$_2$** as 1,3,4-oxadiazole derivative with R_f 0.88.

Ethyl 1-{[4-amino-5-(benzylsulfanyl)-4H-1,2,4-triazol-3-yl]methyl}-2-methyl-5-phenylpyrrole-3-carboxylate (2d$_2$). Mp 128-133°C, R_f 0.45 (5:1). IR spectrum, ν, cm^{-1}: 700, 760 (C_6H_5), 1460 (CH_3 + CH_2), 1700 ($COOC_2H_5$), 2900, 2960 (SCH_2 + CH_3 + CH_2), 3300 (NH_2). ^{1}H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 1.35 (3H, t, *J* = 7.1, C<u>H</u>$_3$CH$_2$); 2.50 (3H, s, CH_3); 3.50 (2H, s, NH_2); 4.15 (2H, q, *J* = 7.1, OCH_2); 4.35 (2H, s, CH_2S); 5.15 (2H, s, NCH_2); 6.50 (1H, s, H-4); 6.90-7.30 (10H, m, 2C_6H_5). Found, %: C 64.06; H 5.73. $C_{24}H_{25}N_5O_2S$. Calculated, %: C 64.41; H 5.63.

Ethyl 1-{[5-(benzylsulfanyl)-1,3,4-oxadiazol-2-yl]methyl}-2-methyl-5-phenylpyrrole-3-carboxylate (3d$_2$). Mp 78-80°C, R_f 0.88 (5:1). IR spectrum, ν, cm^{-1}: 700, 760 (C_6H_5), 1460 ($CH_3 + CH_2$), 1700 ($COOC_2H_5$), 2900, 2960 ($SCH_2 + CH_3 + CH_2$). ^{1}H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 1.40 (3H, t, *J* = 7.1, C<u>H</u>$_3$CH$_2$); 2.60 (3H, s, CH_3); 4.00-4.40 (4H, m, $OCH_2 + SCH_2$); 5.15 (2H, s, NCH_2); 6.50 (1H, s, H-4); 7.10–7.40 (10H, m, $2C_6H_5$). Mass spectrum, *m*/*z*: 433 [M]$^+$. Found, %: C 66.15; H 5.12. $C_{24}H_{23}N_3O_3S$. Calculated, %: C 66.49; H 5.35.

2-(Benzylsulfanyl)-5-(2,4-dimethylpyrrol-3-yl)-1,3,4-oxadiazole (3c$_2$). Triazole **1c** (0.627 g, 3 mmol) was treated as described in the procedure for the preparation of **2b$_2$**, **2e$_2$**, and **2g$_2$**. After 2.5-h stirring, the product obtained was recrystallized from ethanol/water to yield 0.384 g, 45 % of compound **3c$_2$**. Mp 107-110°C, R_f 0.83 (10:3). IR spectrum, ν, cm^{-1}: 700, 745 (C_6H_5), 1485 ($CH_3 + CH_2$), 2900 ($SCH_2 + CH_3 + CH_2$), 3200 (NH). ^{1}H NMR (DMSO-d$_6$), δ, ppm: 2.25, 2.50 (6H, 2s, $2CH_3$); 4.50 (2H, s, SCH_2); 6.50 (1H, s, H-5); 7.20-7.45 (5H, m, C_6H_5); 10.90 (1H, s, NH). Mass spectrum, *m*/*z*: 285 [M]$^+$. Found, %: C 63.50; H 5.15. $C_{15}H_{15}N_3OS$. Calculated, %: C 63.13; H 5.30.

Ethyl 1-{[4-amino-5-(benzylsulfanyl)-4H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-2-methylpyrrole-3-carboxylate (2f$_2$) and ethyl 1-{[5-(benzylsulfanyl)-1,3,4-oxadiazol-2-yl]methyl}-5-(4-chlorophenyl)-2-methylpyrrole-3-carboxylate (3f$_2$) (General procedure). Triazole **1f** (0.391 g, 1 mmol) was treated as described in the procedure for the preparation of **2b$_2$**, **2e$_2$**, and **2g$_2$**. The resulting precipitate was filtered off after 2-h stirring, and the TLC check indicated a mixture of two products with R_f values of 0.45 and 0.60 (in benzene/ethanol 10:1). They were separated on TLC plates with silica gel 60 F_{254} for preparative thin layer chromatography (layer thickness 2 mm) using the same mobile phase as follows: 0.187 g, 39 % of **2f$_2$** as 4H-1,2,4-triazole derivative with R_f 0.45 and 0.135 g, 29 % of **3f$_2$** as 1,3,4-oxadiazole derivative with R_f 0.60.

Ethyl 1-{[4-amino-5-(benzylsulfanyl)-4H-1,2,4-triazol-3-yl]methyl}-5-(4-chlorophenyl)-2-methylpyrrole-3-carboxylate (2f$_2$). Mp 116-118°C, R_f 0.45 (10:1). IR spectrum, ν, cm^{-1}: 700, 775 (C_6H_5), 1480 (CH_2), 1695 ($COOC_2H_5$), 2900 ($SCH_2 + CH_2 + CH_3$), 3050-3100 (NH_2). ^{1}H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 1.35 (3H, t, *J* = 7.1, C<u>H</u>$_3$CH$_2$); 2.55 (3H, s, 2-CH_3); 4.30 (2H, q, *J* = 7.1, OCH_2); 4.40 (2H, s, SCH_2); 4.85 (2H, br. s, NH_2); 5.15 (2H, s, NCH_2); 6.45 (1H, s, H-4); 7.10-7.50 (9H, m, $C_6H_4 + C_6H_5$). Found, %: C 59.46; H 5.05. $C_{24}H_{24}ClN_5O_2S$. Calculated, %: C 59.81; H 5.02.

Ethyl 1-{[5-(benzylsulfanyl)-1,3,4-oxadiazol-2-yl]methyl}-5-(4-chlorophenyl)-2-methylpyrrole-3-carboxylate (3f$_2$). Mp 107-109°C, R_f 0.60 (10:1). IR spectrum, ν, cm^{-1}: 700, 770 (C_6H_5), 1475 (CH_2), 1700 ($COOC_2H_5$), 2890 (SCH_2), 2950 ($CH_2 + CH_3$). ^{1}H NMR ($CDCl_3$), δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 7.1, C<u>H</u>$_3$CH$_2$); 2.55 (3H, s, 2-CH_3); 4.30 (2H, q, *J* = 7.1, OCH_2); 4.40 (2H, s, SCH_2); 5.15 (2H, s, NCH_2); 6.55 (1H, s, H-4); 7.10-7.40 (9H, m, $C_6H_4 + C_6H_5$). Mass spectrum, *m*/*z*: 467 [M]$^+$. Found, %: C 61.80; H 4.55. $C_{24}H_{22}ClN_3O_3S$. Calculated, %: C 61.60; H 4.74

This study was supported by Johnson & Johnson Pharmaceutical Research & Development, a division of Janssen Pharmaceutica N. V., Belgium, and is gratefully acknowledged.

REFERENCES

1. M. C. Sarvà, G. Romeo, F. Guerrera, M. Siracusa, L. Salerno, F. Russo, A. Cagnotto, and M. Goegan, T. Mennini, *Bioorg. Med. Chem.*, **10,** 313 (2002).
2. A. Kakefuda, T. Suzuki, T. Tobe, A. Tahara, S. Sakamoto, and S. Tsukamoto, *Bioorg. Med. Chem.*, **10**, 1905 (2002).
3. S. N. Pandeya, D. Sriram, G. Nath, and E. de Clerc, *Arzneimittelforsch.*, **50**, 55 (2000).
4. B. S. Holla, K. N. Poojary, B. Kalluraya, and P. V. Gowda, *Farmaco*, **51**, 793 (1996).
5 L. Labanauskas, V. Kalcas, E. Udrenaite, P. Gaidelis, A. Brukstus, and V. Dauksas, *Pharmazie*, **56**, 617 (2001).

6. N. G. Ulusoy, N. Ergenc, G. Otuk, and M. Kiraz, *Boll. Chim. Farm*., **146**, 417 (2001).
7. T. Akbarzadeh, S. A. Tabatabai, M. J. Khoshnoud, B. Shafaghi, and A. Shafiee, *Bioorg*. *Med*. *Chem*., **11**, 769 (2003).
8. K. Khanna, R. M. Weier, Y. Yu, P. Collins, J. Miyashiro, C. Koboldt, A. Veenhuizen, J. Currie, K. Seibert, and P. Isakson, *J. Med. Chem.*, **40**, 1619 (1997).
9. G. Danhardt, W. Kiefer, G. Kramer, S. Maehrlein, U. Nove, and B. Flebich, *Eur. J. Med. Chem*., **35**, 499 (2000).
10. N. Amishiro, A. Okamoto, C. Murakata, T. Tamaoki, M. Okabe, and J. Saito, *J. Med. Chem.*, **42**, 2946 (1999).
11. R. Perez-Tomas, B. Montaner, E. Llagostera, and V. Soto-Cerrato, *Biochem. Pharmacol*., **66**, 1447 (2003).
12. M. A. Evans, D. C. Smith, J. M. Holub, A. Argenti, M. Hoff, G. A. Dalglish, D. L. Wilson, B. M. Taylor, J. D. Berkowitz, B. S. Burnham, K. Krumpe, J. T. Gupton, T. C. Scarlett, R. Durham, and I. H. Hall, *Arch. Pharm*., **336**, 181 (2003).
13. G. A. Pinna, G. Loriga, G. Murineddu, G. Grella, M. Mura, L. Vargiu, C. Murgioni, and P. La Colla, *Chem. Pharm. Bull*., **49**, No 111406 (2001).
14. W. Malinka, M. Sieklucka-Dziuba, G. Rajtar, R. Rejdak, K. Rejdak, and Z. Kleinrok, *Pharmazie*, **55**, 9 (2000).
15. A. Bijev and P. Prodanova, *J. Univ. Chem. Technol. Met*. (Sofia), **39**, 141 (2004).
16. V. P. Himatkumar, P. S. Fernandes, and K. A. Vyas, *Indian J. Chem.*, **29B**, 135 (1990).
17. R. W. Young and K. H. Wood, *J. Am. Chem. Soc*., **77**, 400 (1955).
18. J. Sandstrom, *Adv. Heterocycl. Chem*., **9**, 165 (1968).
19. S. N. Sawhney, R. K. Tomer, O. Parkash, I. Prakash, and S. P. Singh, *Indian J. Chem.*, **19B**, 415 (1980).
20, E. Hoggarth, *J. Chem. Soc.*, 4811 (1952).
21. G. S. Gadaginamath, R. G. Joshi, and A. G. Kamat, *Rev. Roum. Chim*., **40**, 475 (1995).
22. J. R. Reid and N. D. Heindel, *J. Heterocycl. Chem*., **13**, 925 (1976).
23. V. Jakubkiene, M. M. Burbuliene, G. Mekuskiene, E. Udrenaite, P. Gaidelis, and P. Vainilavicius, *Farmaco*, **58**, 323 (2003).
24. G. Sahin, E. Palaska, P. Kelicen, R. Demirdamar, and G. Altinok, *Arzneimittelforsch*., **51**, 478 (2001).
25. G. Sahin, E. Palaska, M. Ekizoglu, and M. Ozalp, *Farmaco*, **57**, 539 (2002).
26. S. A. Rostom, M. A. Shalaby, and M. A. El-Demellawy, *Eur. J. Med. Chem.*, **38**, 959 (2003).