Journal of the Serbian Chemical Society

JSCS@tmf.bg.ac.rs • www.shd.org.rs/JSCS

J. Serb. Chem. Soc. 74 (10) 1041–1049 (2009)
JSCS–3898

UDC 547.79+66.095.253:615.281–188
Original scientific paper

New S-alkylated 1,2,4-triazoles incorporating diphenyl sulfone moieties with potential antibacterial activity

STEFANIA F. BARBUCEANU[1]*, GABRIELA L. ALMAJAN[1], IOANA SARAMET[1], CONSTANTIN DRAGHICI[2], RADU SOCOTEANU[3] and FLORICA BARBUCEANU[4]

[1]*Carol Davila University of Medicine and Pharmacy, Faculty of Pharmacy, Organic Chemistry Department, Traian Vuia Street 6, 020956, Bucharest,* [2]*C. D. Neniţescu Institute of Organic Chemistry, Romanian Academy, Splaiul Independenţei 202B, 060023, Bucharest,* [3]*I. G. Murgulescu Institute of Physical Chemistry, Romanian Academy, Splaiul Independentei 202, 77208, Bucharest and* [4]*Institute forDiagnosis and Animal Health, Dr. Staicovici Street 63, 050557, Bucharest, Romania*

(Received 29 January, revised 22 April 2009)

Abstract: Alkylation of the 5-{4-[(4-bromophenyl)sulfonyl]phenyl}-4-(3/4-methylphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones **3a**,**b** with various alkylation agents, *i.e.*, ethyl bromide, phenacyl bromide and ethyl chloroacetate, afforded the S-substituted 1,2,4-triazoles **4-6a**,**b**. The structures of these new compounds were elucidated by elemental analysis and IR, UV, ^{1}H-NMR, ^{13}C--NMR and MS spectroscopy. The newly synthesized products were tested for their antibacterial effects.

Keywords: alkylation; 1,2,4-triazole-3-thione; antibacterial activity.

INTRODUCTION

A large number of bioactive molecules contain a functionalized 1,2,4-triazole nucleus. Various compounds containing the 1,2,4-triazole ring are well known as drugs. For example, fluconazole, itraconazole and voriconazole are used as antimicrobial drugs;[1] ribavirin has antiviral action,[2] while vorozole, letrozole and anastrozole are non-steroidal drugs used for the treatment of cancer.[3,4]

In addition, various 1,2,4-triazoles are associated with different biological activities. Among 1,2,4-triazole derivatives, mercapto- and thione-substituted 1,2,4--triazole ring systems have been studied and, to date, a variety of antibacterial, antifungal,[5–7] antitubercular,[8,9] anti-inflammatory, analgesic,[10,11] antitumoral,[12,13] antiviral[14] and anticonvulsant[15] properties have been reported for a large number of these compounds.

* Corresponding author. E-mail: stefaniafelicia_barbuceanu@yahoo.com
doi: 10.2298/JSC0910041B

Furthermore, diphenyl sulfone derivatives were also found to possess antibacterial activity.[16,17]

The incorporation of these two moieties into a single molecule and alkylation of the –SH group can change the activity of the obtained novel compounds.

Prompted by the observed biological activities of the above-mentioned compounds and in continuation of ongoing research on the synthesis of heterocyclic compounds containing nitrogen and sulfur with expected biological activity,[18–21] the synthesis and characterization of several *S*-alkylated 1,2,4-triazoles are described in this report. All the newly synthesized compounds were characterized by IR, UV-Vis, ^{1}H- and ^{13}C-NMR spectroscopy. In addition, the structure of compounds **4a**,**b**, **5b** and **6b** were confirmed by mass spectrometry. These new compounds were investigated for their antimicrobial activity.

EXPERIMENTAL

Materials, methods and instruments

Commercially available chemicals and solvents were used as received from Sigma-Aldrich and Merck. The melting points of the new compounds were determined with a Boetius apparatus and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Vertex 70 Bruker spectrometer and the wave numbers are given in cm^{-1}. The NMR spectra were registered on a Varian Gemini 300 BB spectrometer working at 300 MHz for a ^{1}H and 75 MHz for ^{13}C in DMSO-d_6 or $CDCl_3$ (10/1, v/v). All chemical shifts are reported in δ (ppm) using TMS as the internal standard. The mass spectrum of compound **4a** was acquired with a hybrid quadrupole – time of flight (QqTOF) high resolution mass spectrometer model API QStar Pulsar produced by Applied Biosystems/SCIEX. The instrument was operated in the positive ions mode, using an atmospheric pressure pneumatically-assisted electrospray ionization interface (ESI, AB model Turboionspray). The voltage of the mass spectrometer (MS) source was set at 5000 V. Molecular ions were detected in full scan over an adequate mass range. Stock solutions were prepared at 1 mg/ml in DMSO. The sample solution (2 μg/ml in water/methanol 1/1, v/v) was introduced by direct infusion at a flow rate of 20 μl/min into the MS interface by means of a built-in Harvard syringe pump. The mass spectra of the compounds **4b**, **5b** and **6b** were registered using a Varian 1200 L/MS/MS triple quadrupole mass spectrometer coupled with a high performance liquid chromatograph operating with a Varian ProStar 240 pump and a Varian ProStar 410 automatic injector. An atmospheric pressure chemical ionization interface (APCI) was used in order to obtain the ions. The liquid chromatography was performed on a Hypersil Gold (Thermo) column with a pre-column; the mobile phase was 30 % water and 70 % methanol. The UV-Vis spectra were measurement on a SPECORD 40 Analytik, Jena, in methanolic solution (2.5×10^{-5} mol/l). The elemental analyses were performed with ECS 40-10, COSTEH instrument.

General procedure for the preparation of new S-alkylated 1,2,4-triazoles

To a stirred solution of 1,2,4-triazole-3-thione **3a**,**b** (1.0 mmol) and sodium ethoxide (1.0 mmol of sodium dissolved in 10 mL ethanol) was added the alkylation agent (1.0 mmol). The reaction mixture was stirred at room temperature for 12 h, and then poured into ice water. The crude product was filtered off, washed with water and recrystallized from ethanol.

Biological activity

The compounds were tested for their *in vitro* growth inhibitory activity against the following Gram-negative bacteria: *Acinetobacter baumannii* (Ab) ATCC 19606; *Citrobacter freundii* (Cf) ATCC 8090, *Escherichia coli* (Ec) ATCC 11775 and *Pseudomonas aeruginosa* (Pa) ATCC 9027, and the following Gram-positive bacteria: *Enterococcus faecalis* (Ef) ATCC 19433, *Staphylococcus aureus* (Sa) ATCC 12600, *Staphylococcus epidermidis* (Se) ATCC 14990 and *Bacillus cereus* (Bc) ATCC 14579, using the paper disk diffusion method.[22] Suspensions in sterile peptone water from 24 h cultures of micro-organisms were adjusted to 0.5 McFarland. Mueller-Hinton Petri dishes of 90 mm diameter were inoculated using these suspensions. Paper disks (5 mm in diameter) containing 10 μL of the to be tested substance (at a concentration of 2048 μg/mL in DMSO) were placed in a circular pattern in each inoculated plate. The plates were incubated at 37 °C for 18–24 h. The inhibitory activity was measured (in mm) as the diameter of the observed inhibition zones. The tests were repeated to confirm the findings and the average of the readings was taken into consideration. Discs with only DMSO were used as the control and ampicillin (10 μg/50μL) served as the control drug.

RESULTS AND DISCUSSIONS

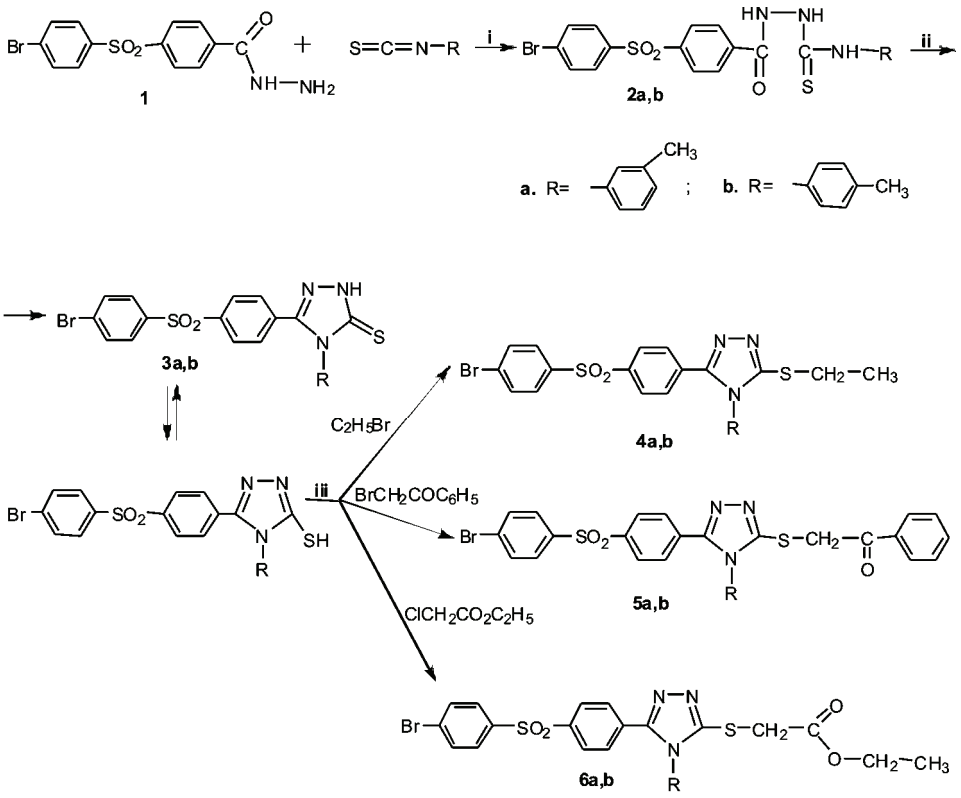
Chemistry

The key intermediates used in the synthesis of the S-alkylated 1,2,4-triazoles, the 5-{4-[(4-bromophenyl)sulfonyl]phenyl}-4-(3/4-methylphenyl)-2,4-dihydro-3*H*--1,2,4-triazole-3-thiones **3a** and **3b**,[23–25] were prepared starting from 4-[(4-bromophenyl)sulfonyl]benzoic acid hydrazide **1**.[26] The reaction of **1** with 3- or 4-methylphenyl isothiocyanates in refluxing ethanol gave the N^1-{4-[(4-bromophenyl)sulfonyl]benzoyl}-N^4-(3/4-methylphenyl)thiosemicarbazides (**2a**,**b**). 5-{4--[(4-Bromophenyl)sulfonyl]phenyl}-4-(3/4-methylphenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones (**3a**,**b**) were synthesized by treating the corresponding thiosemicarbazides **2a**,**b** with 8 % NaOH.[23,24,27] In the present study, the reaction of the 1,2,4-triazoles **3a**,**b** with ethyl bromide, phenacyl bromide or ethyl chloroacetate in presence of absolute ethanol gave the new S-alkylated triazoles **4**–**6a**,**b**.

The synthetic route of the compounds is outlined in Scheme 1.

Analytical and spectral data of the newly prepared compounds

*3-{4-[(4-Bromophenyl)sulfonyl]phenyl}-5-(ethylthio)-4-(3-methylphenyl)-4*H--*1,2,4-triazole (**4a**)*. Yield: 59 %; m.p. 168–170 °C. Anal. Calcd. for $C_{23}H_{20}BrN_3O_2S_2$ (514.46 g/mol): C, 53.70; H, 3.92; S, 12.47. Found: C, 53.79; H, 3.88; S, 12.41. IR (KBr, cm^{-1}): 3084, 3061 (C–H stretching of aromatic ring), 2972, 2929, 2868 (CH_3, CH_2 stretching), 1601 (C=N stretching of triazole ring), 1572, 1460 (C=C-stretching of aromatic ring), 1326, 1160 (SO_2 stretching), 576 (C–Br). ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 7.98 (1H, *br d*, aromatic, J = 7.2 Hz), 7.79 (2H, *d*, aromatic, J = 8.5 Hz), 7.75 (2H, *d*, aromatic, J = 8.5 Hz), 7.62 (4H, *d*, aromatic, J = 8.5 Hz), 7.30–7.40 (2H, *m*, aromatic), 7.00 (1H, *br s*, aromatic), 3.29 (2H, *q*, –SC**H**$_2$CH$_3$, J = 7.3 Hz), 2.40 (3H, *s*, –CH$_3$); 1.41 (3H, *t*, –SCH$_2$C**H**$_3$, J = 7.3 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$, δ / ppm): 154.35 (C_3),



Scheme 1. The synthetic route of the title compounds.

152.87 (C_5), 141.95, 140.69, 140.51, 134.05, 132.66, 131.93, 131.09, 129.97, 129.25, 128.47, 128.31, 127.79, 127.70, 124.34 (aromatic ring), 26.95 (–S**C**H_2CH_3), 21.17 (–CH_3), 14.69 (–SCH_2**C**H_3). MS (ESI/QTOF, *m*/*z*): 514.0223 $[M+H]^+$, 516.0165 $[M+H]^+$. UV–Vis (CH_3OH) (λ_{max} / nm (log ε)): 207 (4.69), 249 (4.36), 288 (4.29).

*3-{4-[(4-Bromophenyl)sulfonyl]phenyl}-5-(ethylthio)-4-(4-methylphenyl)-4*H*-1,2,4-triazole (**4b**)*. Yield: 62 %; m.p. 171–173 °C. Anal. Calcd. for $C_{23}H_{20}BrN_3O_2S_2$ (514.46 g/mol): C, 53.70; H, 3.92; S, 12.47. Found: C, 53.62; H, 3.85; S, 12.42. IR (KBr, cm^{-1}): 3084, 3057 (C–H stretching of aromatic ring); 2972, 2929, 2868 (CH_3, CH_2 stretching), 1599 (C=N stretching of triazole ring), 1572, 1514 (C=C-stretching of aromatic ring), 1326, 1160 (SO_2 stretching), 574 (C–Br). ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 7.81 (2H, *d*, aromatic, *J* = 8.4 Hz), 7.76 (2H, *d*, aromatic, *J* = 8.4 Hz), 7.63 (2H, *d*, aromatic, *J* = 8.4 Hz), 7.58 (2H, *d*, aromatic, *J* = 8.4 Hz), 7.33 (2H, *d*, aromatic, *J* = 8.2 Hz), 7.08 (2H, *d*, aromatic, *J* = 8.2 Hz), 3.29 (2H, *q*, –S**H**$_2CH_3$, *J* = 7.3 Hz), 2.45 (3H, *s*, –CH_3),

1.42 (3H, *t*, –$SCH_2C\mathbf{H}_3$, *J* = 7.3 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$, δ / ppm): 154.54 (C_3), 152.88 (C_5), 141.65, 140.81, 140.74, 140.08, 132.66, 131.10, 130.87, 129.22, 128.49, 128.03, 127.78, 126.87 (aromatic ring), 26.78 (–$S\mathbf{C}H_2CH_3$), 21.32 (–CH_3), 14.66 (–$SCH_2\mathbf{C}H_3$). MS (APCI, *m*/*z*): 514 $[M+H]^+$, 516 $[M+H]^+$. UV–Vis (CH_3OH) (λ_{max} / nm (log ε)): 206 (4.66), 249 (4.35), 287 (4.25).

*2-{[5-(4-((4-Bromophenyl)sulfonyl)phenyl)-4-(3-methylphenyl)-4*H*-1,2,4-triazol-3-yl]-thio}-1-phenylethanone (**5a**)*. Yield: 81 %; m.p. 189–191 °C. Anal. Calcd. for $C_{29}H_{22}BrN_3O_3S_2$ (604.54 g/mol): C, 57.62; H, 3.67; S, 10.61. Found: C, 57.70; H, 3.59; S, 10.56; IR (KBr, cm^{-1}): 3084, 3062 (C–H stretching of aromatic ring), 2953, 2922, 2852 (CH_3, CH_2 stretching), 1681 (C=O stretching), 1598 (C=N stretching of triazole ring), 1573, 1490 (C=C-stretching of aromatic ring), 1324, 1160 (SO_2 stretching), 577 (C–Br). ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 8.07 (2H, *dd*, aromatic, *J* = 7.9 Hz; 1.5 Hz), 7.82 (2H, *d*, aromatic, *J* = = 8.5 Hz), 7.76 (2H, *d*, aromatic, *J* = 8.6 Hz), 7.64 (2H, *d*, aromatic, *J* = 8.6 Hz), 7.62 (2H, *d*, aromatic, *J* = 8.5 Hz), 7.61 (1H, *br t*, aromatic, *J* = 7.9 Hz), 7.50 (2H, *t*, aromatic, *J* = 7.9 Hz), 7.41 (1H, *t*, aromatic, *J* = 7.9 Hz), 7.36 (1H, *br d*, aromatic, *J* = 7.9 Hz), 7.05 (2H, *m*, aromatic), 4.99 (2H, *s*; –SCH_2CO–), 2.41 (3H, *s*, –CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$, δ / ppm): 192.87 (C=O), 153.72 (C_3), 153.15 (C_5), 142.14, 140.94, 135.20, 133.88, 133.50, 132.71, 131.60, 131.40, 130.18, 129.28, 129.08, 129.18, 128.85, 128.72, 128.55, 127.85, 127.60, 124.28 (aromatic ring), 41.02 (–$S\mathbf{C}H_2CO$–), 21.24 (–CH_3). UV–Vis (CH_3OH) (λ_{max} / nm (log ε)): 206 (4.61), 248 (4.40), 285 (4.21).

*2-{[5-(4-((4-Bromophenyl)sulfonyl)phenyl)-4-(4-methylphenyl-4*H*-1,2,4-triazol-3-yl]-thio}-1-phenylethanone (**5b**)*. Yield: 72 %; m.p. 224–226 °C. Anal. Calcd. for $C_{29}H_{22}BrN_3O_3S_2$ (604.54 g/mol): C, 57.62; H, 3.67; S, 10.61. Found: C, 57.72; H, 3.62; S, 10.58. IR (KBr, cm^{-1}): 3063 (C–H stretching of aromatic ring), 2960, 2922, 8264 (CH_3, CH_2 stretching), 1681 (C=O stretching), 1597 (C=N stretching of triazole ring), 1573, 1513 (C=C-stretching of aromatic ring); 1323, 1160 (SO_2 stretching), 576 (C–Br). ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 8.04 (2H, *br d*, aromatic, *J* = 7.9 Hz), 7.82 (2H, *d*, aromatic, *J* = 8.5 Hz), 7.76 (2H, *d*, aromatic, *J* = 8.5 Hz), 7.63 (2H, *d*, aromatic, *J* = 8.5 Hz), 7.60 (1H, *br t*, aromatic, *J* = 7.9 Hz), 7.58 (2H, *d*, aromatic, *J* = 8.5 Hz), 7.49 (2H, *br t*, aromatic, *J* = 7.9 Hz), 7.32 (2H, *d*, aromatic, *J* = 8.2 Hz), 7.13 (2H, *d*, aromatic, *J* = = 8.2 Hz), 4.98 (2H, *s*, –SCH_2CO–), 2.46 (3H, *s*, –CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$, δ / ppm): 192. 96 (C=O), 153.92 (C_3), 153.24 (C_5), 141.94, 141.15, 141.10, 140.15, 135.40, 134.07, 132.78, 131.54, 131.14, 129.34, 129.24, 129.20, 128.93, 128.61, 127.92, 126.92 (aromatic ring), 41.29 (–$S\mathbf{C}H_2CO$–), 21.42 (–CH_3). MS (APCI, *m*/*z*): 604 $[M+H]^+$, 606 $[M+H]^+$. UV–Vis (CH_3OH) (λ_{max} / nm (log ε)): 205 (4.68), 248 (4.42), 286 (4.21).

*Ethyl 2-{[5-(4-((4-bromophenyl)sulfonyl)phenyl)-4-(3-methylphenyl)-4*H*-1,2,4--triazol-3yl]thio}acetate (**6a**)*. Yield: 87 %; m.p. 169–170 °C. Anal. Calcd. for

$C_{25}H_{22}BrN_3O_4S_2$ (572.50 g/mol): C, 52.45; H, 3.87; S, 11.20; Found: C, 52.50; H, 3.82; S, 11.17. IR (KBr, cm^{-1}): 3080 (C–H stretching of aromatic ring), 2981, 2929, 2868 (CH_3, CH_2 stretching), 1728 (–C=O stretching of –COOH group), 1599 (C=N stretching of triazole ring), 1572, 1490 (C=C stretching of aromatic ring); 1322, 1160 (SO_2 stretching), 578 (C–Br). ^{1}H-NMR ($CDCl_3$, δ / ppm): 7.82 (2H, *d*, aromatic, *J* = 8.6 Hz), 7.76 (2H, *d*, aromatic, *J* = 8.6 Hz), 7.63 (2H, *d*, aromatic, *J* = 8.6 Hz), 7.58 (2H, *d*, aromatic, *J* = 8.6 Hz), 7.06 (2H, *m*, aromatic), 7.38 (2H, *m*, aromatic), 4.12 (2H, *s*, $–SCH_2COO–$), 4.22 (2H, *q*, $–COOC\mathbf{H}_2CH_3$, *J* = 7.1 Hz), 2.40 (3H, *s*, $–CH_3$), 1.28 (3H, *t*, $–COOCH_2C\mathbf{H}_3$, *J* = 7.1 Hz). ^{13}C-NMR ($CDCl_3$, δ / ppm): 167.99 (–COO), 153.20 (C_3), 153.00 (C_5), 142.13, 140.88, 140.43, 133.69, 132.70, 131.68, 131.34, 130.13, 129.28, 128.74, 128.53, 127.83, 127.62, 124.29 (aromatic ring), 62.01 ($–COO\mathbf{C}H_2CH_3$), 34.57 ($–S\mathbf{C}H_2COO–$), 21.21 ($–CH_3$), 14.06 ($–COOCH_2\mathbf{C}H_3$). UV–Vis (CH_3OH) (λ_{max} / nm (log ε)): 206 (4.68), 249 (4.33), 285 (4.32).

*Ethyl 2-{[5-(4-((4-bromophenyl)sulfonyl)phenyl)-4-(4-methylphenyl)-4*H*-1,2,4-triazol-3yl]thio}acetate (**6b**)*. Yield: 67 %; m.p. 209–211 °C. Anal. Calcd. for $C_{25}H_{22}BrN_3O_4S_2$ (572.50 g/mol): C, 52.45; H, 3.87; S, 11.20. Found: C, 52.55; H, 3.81; S, 11.25. IR (KBr, cm^{-1}): 3084 (C–H stretching of aromatic ring), 2987, 2929, 2868 (CH_3, CH_2 stretching), 1743 (–C=O stretching of –COOH group), 1599 (C=N stretching of triazole ring), 1572, 1513 (C=C– stretching of aromatic ring), 1323, 1161 (SO_2 stretching), 576 (C–Br). ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 (10/1, v/v), δ / ppm): 7.83 (2H, *d*, aromatic, *J* = 8.7 Hz), 7.77 (2H, *d*, aromatic, *J* = 8.6 Hz), 7.64 (2H, *d*, aromatic, *J* = 8.6 Hz), 7.60 (2H, *d*, aromatic, *J* = 8.7 Hz), 7.34 (2H, *d*, aromatic, *J* = 8.2 Hz), 7.14 (2H, *d*, aromatic, *J* = 8.2 Hz), 4.20 (2H, *q*, $–COOC\mathbf{H}_2CH_3$, *J* = 7.1 Hz), 4.08 (2H, *s*, $–SCH_2COO–$), 2.47 (3H, *s*, $–CH_3$) 1.28 (3H, *t*, $–COOCH_2C\mathbf{H}_3$, *J* = 7.1 Hz). ^{13}C-NMR ($CDCl_3$ + DMSO-d_6 (10/1, v/v, δ / ppm): 167.82 (–COO), 152.99 (C_3), 152.84 (C_5), 141.65, 141.25, 140.83, 140.73, 132.58, 131.33, 130.86, 129.10, 128.64, 128.35, 127.62, 126.67 (aromatic ring), 61.84 ($–COO\mathbf{C}H_2CH_3$), 34.21 ($–S\mathbf{C}H_2COO–$), 21.17 ($–CH_3$), 13.93 ($–COOCH_2\mathbf{C}H_3$). MS (APCI, *m*/*z*): 572 $[M+H]^+$, 574 $[M+H]^+$. UV–Vis (CH_3OH) (λ_{max} / nm (log ε)): 206 (4.61), 249 (4.28), 282 (4.23).

The spectral data of all the newly synthesized compounds are in full agreement with the proposed structures.

The infrared absorption spectra of the new S-alkylated 1,2,4-triazoles **4**–**6a**,**b** confirm the alkylation reaction by the disappearance of the stretching of the NH group, which appeared at ≈ 3400 cm^{-1} in the spectra of the triazoles **3a**,**b**.[23,24] In addition, the absence of the absorption band characteristic of the C=S group, which appeared in the spectra of the triazoles **3a**,**b**[23,24] at ≈ 1240 cm^{-1} proved that these compounds participated in the alkylation reaction in the thiolic tautomeric form and that substitution occurred at the sulfur atom.[28]

The C_3 and C_5 heterocyclic carbons from the new S-alkylated compounds **4**–**6a**,**b** resonated at 152.99–155.54 ppm and 152.88–153.24 ppm, respectively. The C_3 heterocyclic carbon of these new S-alkylated derivatives is more shielded than the C_3 heterocyclic carbon from 1,2,4-triazole intermediates **3a**,**b** ($\delta \approx 169$ ppm).[23,24] These results indicate that the alkylation occurred at the sulfur atom[29] and not at the N_2 nitrogen atom. Data from the literature indicated that if the alkylation had occurred at the N_2 heterocyclic nitrogen, the C_3 heterocyclic carbon would have resonated at 167–173 ppm.[30]

Antimicrobial activity

The potential antibacterial activity of compounds **2**–**6** towards eight standard strains was investigated. From the data presented in Table I, it may be seen that the thiosemicarbazides **2a** and **2b** showed the highest inhibition zone diameter against *E. coli*, *P. aeruginosa*, *S. aureus* and *S. epidermidis*, compared with the other tested compounds. Compounds **2a** and **2b** showed no inhibitory effects against *C. freundii* and *E. faecalis* and they were moderately active against *A. baumannii* and *B. cereus*. After cyclization of **2a** and **2b** forming the 1,2,4-triazoles **3a** and **3b**, it may be seen how these effects decreased and even completely disappeared in the case of some S-alkylation derivatives.

TABLE I. Antibacterial activity of the tested compounds (highly active: inhibition zone > 12 mm; moderately active: inhibition zone 9–12 mm; slightly active: inhibition zone 6–9 mm; inactive: inhibition zone < 6 mm)

Compd.	R	Inhibition zone diameter, mm							
		Gram-negative bacteria				Gram-positive bacteria			
		Ab	Cf	Ec	Pa	Ef	Sa	Se	Bc
2a	–C_6H_4–CH_3 (*m*)	10	–	14	15	–	17	13.5	12
3a	–C_6H_4–CH_3 (*m*)	10.5	10	11.5	13	11	12	8	16
4a	–C_6H_4–CH_3 (*m*)	9.5	11	–	9	–	–	12	14
5a	–C_6H_4–CH_3 (*m*)	–	15	–	10	–	–	–	13.5
6a	–C_6H_4–CH_3 (*m*)	–	10	–	11.5	–	–	–	15
2b	–C_6H_4–CH_3 (*p*)	8	–	16	14	–	18	11.5	10
3b	–C_6H_4–CH_3 (*p*)	8	12	12.5	11	11	11	–	15
4b	–C_6H_4–CH_3 (*p*)	–	12	–	–	–	–	9	12
5b	–C_6H_4–CH_3 (*p*)	–	16	–	–	–	–	–	12.5
6b	–C_6H_4–CH_3 (*p*)	–	–	–	–	–	–	–	13
Ampicillin	–	14	9	10	10	11	15	13	14
DMSO	–	5	5	5	5	5	5	5	5

All the tested compounds showed good inhibitory effects against *B. cereus*. Among the S-alkylated triazoles **4**–**6**, the most active compounds were **6a** against *B. cereus* (15 mm diameter inhibition zone) and **5b** against *C. freundii* (16 mm diameter inhibition zone). This could be explained by electropositive effect of the methyl group attached to the phenyl moiety on the heterocyclic ring, which is

overlapped the effect of the C=O group inlaid by the S–alkylation reaction and together favorably influenced the potency of the heterocyclic nuclei.

CONCLUSIONS

This study reports the synthesis of some new S-substituted 1,2,4-triazoles by alkylation, in alkaline media, of 5-{4-[(4-bromophenyl)sulfonyl]phenyl}-4-(3/4--methylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-thiones **3a**,**b** with various alkylation agents (ethyl bromide, phenacyl bromide and ethyl chloroacetate). The structures of new compounds were determined from spectral data and elemental analyses. The potential antibacterial effects of the synthesized compounds, compared with those of the parent triazoles and ampicillin, were investigated using different standard micro-organisms. The most active compounds were **5b** and **6a**, which exhibited promising activities against *C. freundii* and *B. cereus*. Further investigations are in progress.

ИЗВОД

НОВИ S-АЛКИЛОВАНИ 1,2,4-ТРИАЗОЛИ КОЈИ САДРЖЕ ДИФЕНИЛСУЛФОНСКЕ ГРУПЕ СА ПОТЕНЦИЈАЛНОМ АНТИБАКТЕРИЈСКОМ АКТИВНОШЋУ

STEFANIA F. BARBUCEANU[1], GABRIELA L. ALMAJAN[1], IOANA SARAMET[1], CONSTANTIN DRAGHICI[2], RADU SOCOTEANU[3] и FLORICA BARBUCEANU[4]

[1]*Carol Davila University of Medicine and Pharmacy, Faculty of Pharmacy, Organic Chemistry Department, Traian Vuia Street 6, 020956, Bucharest,* [2]*C. D. Nenițescu Institute of Organic Chemistry, Romanian Academy, Splaiul Independenței 202B, 060023, Bucharest,* [3]*I. G. Murgulescu Institute of Physical Chemistry, Romanian Academy, Splaiul Independentei 202, 77208, Bucharest и* [4]*Institute for Diagnosis and Animal Health, Dr. Staicovici Street 63, 050557, Bucharest, Romania*

Алкиловањем 5-{4-[(4-бромофенил)сулфонил]фенил}-4-(3/4-метилфенил)-2,4-дихидро--3*H*-1,2,4-триазол-3-тиона (**3a**,**b**) алкилујућим реагенсима као што су етил-бромид, фенацил--бромид и етил-хлорацетат добијени су S-супституисани 1,2,4-триазоли **4**–**6a**,**b**. Структура ових нових једињења потврђена је елементалном анализом као и IR, UV, ^{1}H-NMR, ^{13}C-NMR и MS спектрима. Испитивана је и антибактеријска активност ових једињења.

(Примљено 29. јануара, ревидирано 22. априла 2009)

REFERENCES

1. R. A. Fromtling, *Clin. Microbiol. Rev.* **1** (1988) 187
2. H. H. Balfour Jr., *N. Engl. J. Med.* **340** (1999) 1255
3. M. Clemons, R. E. Coleman, S. Verma, *Cancer Treat. Rev.* **30** (2004) 325
4. M. Serdar, N. Gümrükçüoğlu, Ş. Alpay Karaoğlu, N. Demirbaş, *Turk. J. Chem.* **31** (2007) 315
5. A. A. Siddiqui, A. Arora, N. Siddiqui, A. Misra, *Indian J. Chem. Sect. B* **44** (2005) 838
6. O. I. Abdel-Salam, S. F. Mohamed, *J. Chin. Chem. Soc.* **52** (2005) 1157
7. I. A. Shehata, *Saudi Pharm. J.* **11** (2003) 87
8. I. Mir, M. T. Siddiqui, *Tetrahedron* **26** (1970) 5235
9. I. Küçükgüzel, S. G. Küçükgüzel, S. Rollas, M. Kiraz, *Bioorg. Med. Chem. Lett.* **11** (2001) 1703

10. Y. Dündar, B. Çakir, E. Küpeli, M. F. Şahin, N. Noyanalpan, *Turk. J. Chem.* **31** (2007) 301
11. M. Amir, S. Kumar, *Acta Pharm.* **57** (2007) 31
12. H. N. Dogan, A. Duran, S. Rollas, *Indian J. Chem. Sect. B.* **44** (2005) 2301
13. A. Duran, H. N. Dogan, S. Rollas, *Il Farmaco* **57** (2002) 559
14. M. T. Abdel-Aal, W. A. El-Sayed, A. H. Abdel Aleem, E. S. H. El-Ashry, *Pharmazie* **58** (2003) 788
15. J. M. Kane, M. A. Staeger, C. R. Dalton, F. P. Miller, M. W. Dudley, A. M. L. Ogden, J. H. Kehne, H. J. Ketteler, T. C. McCloskey, Y. Senyah, P. A. Chmieleweski, J. A. Miller, *J. Med. Chem.* **37** (1994) 125
16. E. F. Elslager, Z. B. Gavrilis, A. A. Phillips, D. F. Worth, *J. Med. Chem.* **12** (1969) 357
17. R. Wolf, H. Matz, E. Orion, B. Tuzun, Y. Tuzun, *Dermatol. Online J.* **8** (2002) 2
18. Ş.-F. Bărbuceanu, G. L. Almăjan, I. Şaramet, B. Drăghici, *Rev. Chim.* **58** (2007) 945
19. Ş.-F. Bărbuceanu, G. L. Almăjan, I. Şaramet, B. Drăghici, *Rev. Chim.* **57** (2006) 1253
20. Ş. Bărbuceanu, L. Almăjan, I. Şaramet, B. Drăghici, *Rev. Chim.* **56** (2005) 1270
21. G. L. Almăjan, Ş. F. Bărbuceanu, I. Şaramet, C. Drăghici, *Rev. Chim.* **56** (2005) 1182
22. E. J. Stokes, P. M. Waterworth, in *Association of Clinical Pathologists Broadsheet*, BMJ Publishing Group, BMA House, London, 1972, p. 55
23. Ş.-F. Bărbuceanu, G. L. Almăjan, I. Şaramet, C. Drăghici, *Rev. Chim.* **57** (2006) 355
24. I. Şaramet, G.-L. Almăjan, Ş. Bărbuceanu, C. Drăghici, M. D. Banciu, *Rev. Roum. Chim.* **50** (2005) 19
25. G. L. Almăjan, A. Innocenti, L. Puccetti, G. Manole, Ş. Barbuceanu, I. Şaramet, A. Scozzafava, C. T. Supuran, *Bioorg. Med. Chem. Lett.* **15** (2005) 2347
26. A. Mavrodin, V. Zotta, M. Stoenescu, D. Oţeleanu, *Pharm. Zentralhalle Dtschl.* **95** (1956) 353
27. I. Şaramet, C. Drăghici, C. Bărcuţean, V. Rădulescu, T. Loloiu, M. D. Banciu, *Heterocyc. Commun.* **7** (2001) 369
28. H. H. Fahmy, A. El-Masry, S. H. Ali Abdelwahed, *Arch. Pharm. Res.* **24** (2001) 27
29. R. M. Shaker, A. F. Mahmoud, F. F. Abdel-Latif, *Phosphorus Sulfur Silicon Relat. Elem.* **180** (2005) 397
30. O. A. Al-Deeb, M. A. Al-Omar, N. R. El-Brollosy, E. E. Habib, T. M. Ibrahim, *Arzneim. Forsch./Drug Res.* **56** (2006) 40.