# New 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles bearing Substituted (phenylsulfonyl)phenyl Moiety as Possible Antimicrobial Agents

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*A facile synthesis of 3,6-disubstituted-1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazoles **(2)**, **(3)** has been achieved by reaction of 4-amino-5-[4-(4-chloro-phenylsulfonyl)phenyl]-4H-1,2,4-triazole-3-thiol **(1)** with aromatic isothiocyanate in DMF and with various aromatic acids in $POCl_3$. The structures of the synthesized compounds were supported by IR, $^1$H-NMR, $^{13}$C-NMR and elemental analysis. The obtained compounds were evaluated for in vitro antimicrobial activity against Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853, Staphilococcus aureus ATCC 25923, Candida scotti and Candida albicans ATCC 90028. The preliminary results of antimicrobial activities indicated that the tested compounds exhibited a moderate to low activity against tested strains.*

*Keywords: triazolothiadiazoles; antimicrobial activity*

In recent years, the chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives have received considerable attention owing to their synthetic and effective biological importance. Heterocycles bearing a symmetrical triazoles or 1,3,4-thiadiazole moiety are reported to show a broad spectrum of pharmacological properties such as antimicrobial, anticancer, antitubercular, antiinflammatory, analgesic and anticonvulsant activities [1-4]. Derivatives of 1,2,4-triazole and 1,3,4-thiadiazole condensed nucleus system (triazolothiadiazoles) were found to have diverse pharmacological activities such as fungicidal, bactericidal, insecticidal, herbicidal, anticancer, antiinflammatory.

For this reason and as a continuation of our efforts directed toward the synthesis of new heterocyclic compounds with anticipated biological activities [5,6], in this paper we proposed to synthesize a new series of this condensed system, which combine these two biolabile components (1,2,4-triazole and 1,3,4-thiadiazole) in a ring together to give a compact and planar structure and evaluated them for their antimicrobial profile after subtle structural modification.

## Experimental part

The melting points were determined with Boetius apparatus and are uncorrected. The IR spectra were recorded on a Vertex 70 Brucker apparatus in KBr pellets (4000-400 $cm^{-1}$ range). The NMR spectra (in DMSO-$d_6$, at room temperature) were registered on a Varian Gemini 300 BB apparatus working at 300 MHz for $^1$H and 75 MHz for $^{13}$C, using TMS as internal standard. The content of C, H, and N were done with ECS-40-10-Costeh micro-dosimeter, after drying the compounds at 105°C.

### *Chemistry*

The starting material, 4-amino-5-[4-(4-chloro-phenylsulfonyl)phenyl]-4*H*-1,2,4-triazole-3-thiol **1** was prepared in good yield earlier, by the reaction of the corresponding oxadiazole with hydrazine hydrate [7].

*General procedure for synthesis of 3-[4-(4-chloro-phenylsulfonyl)phenyl]-6-N-(substituted-phenyl)amino-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles **(2)***

An equimolar mixture (1 mmol) of 4-amino-5-[4-(4-chloro-phenylsulfonyl)phenyl]-4*H*-1,2,4-triazole-3-thiol **(1)** and aryl isothiocyanate in dimethylformamide (10 mL) was refluxed for 20-22 h. The reaction mixture was cooled to room temperature and then gradually poured on to crushed ice with stirring. The mixture was allowed to stand overnight and the solid separated out was filtered, and washed thoroughly with cold water. The compound so obtained was dried and recrystallized from ethanol.

*3-[4-(4-chloro-phenylsulfonyl)phenyl]-6-N-(4-bromophenyl)amino-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole **2a***:

71% yield; m.p.: 210-212°C; Anal. Calc. (%) for $C_{21}H_{13}BrClN_5O_2S_2$ (546.85 g/mol): C-46.12; H-2.40; N-12.81; Found: C-46.07; H-2.36; N-12.74; IR (KBr, $cm^{-1}$): 3125 (NH); 3065 (aromatic CH); 1588, 1543, 1495 (C=N + $C=C_{aryl}$); 1321, 1294, 1156 ($SO_2$); 1259 (N-N=C); 1010 (N-N); 694 (C-S-C); 767 (C-Cl); 573 (C-Br); $^1$H-NMR (DMSO-$d_6$, δ, ppm): 11.09 (s, 1H, NH); 7.96 (d, 2H, *J* = 8.7 Hz, aromatic protons); 7.90 (d, 2H, *J* = 8.7 Hz, aromatic protons); 7.89 (d, 2H, *J* = 8.7 Hz, aromatic protons); 7.51 (d, 2H, *J* = 8.7 Hz, aromatic protons); 7.35 (d, 2H, *J* = 8.6 Hz; aromatic protons); 7.12 (d, 2H, *J* = 8.6 Hz, aromatic protons); $^{13}$C-NMR (DMSO-$d_6$, δ, ppm): 163.61 (C3-triazole ring); 159.58 (C5-triazole ring); 154.29 (C=N-thiadiazole ring); 141.40, 139.62, 139.50, 139.41, 134.64, 116.70 (quaternary aromatic ring carbons); 132.40, 129.80, 129.74, 128.50, 127.83, 122.35 (CH-aromatic ring carbons)

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*3-[4-(4-chloro-phenylsulfonyl)phenyl]-6-N-(4-methoxylphenyl)amino-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole* ***2b:***

68% yield; m.p.: 200-202°C; Anal. Calc. (%) for $C_{22}H_{16}ClN_5O_3S_2$ (497.98 g/mol): C-53.06; H-3.24; N-14.06; Found: C-53.01; H-3.20; N-14.02; IR (KBr, $cm^{-1}$): 3165 (NH); 3074 (aromatic CH); 2925, 2861 ($CH_3$); 1612, 1583, 1510 (C=N + $C=C_{aryl}$); 1322, 1292, 1157 ($SO_2$); 1260 (N-N=C); 1011 (N-N); 692 (C-S-C); 764 (C-Cl); $^1$H-NMR (DMSO-$d_6$, δ, ppm): 11.01 (s, 1H, NH); 8.02 (d, 2H, *J* = 8.7 Hz, aromatic protons); 7.98 (d, 2H, *J* = 8.7 Hz, aromatic protons); 7.93 (d, 2H, *J* = 8.7 Hz, aromatic protons); 7.85 (d, 2H, *J* = 8.7 Hz, aromatic proton); 7.80 (d, 2H, *J* = 8.8 Hz; aromatic protons); 7.62 (d, 2H, *J* = 8.8 Hz aromatic protons); 3.83 (s, 3H, $OCH_3$); $^{13}$C-NMR (DMSO-$d_6$, δ, ppm): 163.72 (C3-triazole ring); 158.85 (C5-triazole ring); 152.74 (C=N-thiadiazole ring); 153.30, 141.42, 139.62, 139.38, 135.60, 132.80 (quaternary aromatic ring carbons); 130.21, 128.80, 128.53, 128.92, 121.70, 115.10 (CH-aromatic ring carbons); 55.74 ($OCH_3$).

*3-[4-(4-chloro-phenylsulfonyl)phenyl]-6-N-(4-methylphenyl)amino-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole* ***2c***:

69% yield; m.p.: 190-192°C; Anal. Calc. (%) for $C_{22}H_{16}ClN_5O_2S_2$ (481.98 g/mol): C-54.82; H-3.35; N-14.53; Found: C-54.78; H-3.33; N-14.49; IR (KBr, $cm^{-1}$): 3238 (NH); 3081 (aromatic CH); 2920, 2851 ($CH_3$); 1612, 1583, 1510 (C=N + $C=C_{aryl}$); 1325, 1290, 1160 ($SO_2$); 1261 (N-N=C); 1008 (N-N); 690 (C-S-C); 766(C-Cl); $^1$H-NMR (DMSO-$d_6$, δ, ppm): 10.98 (s, 1H, NH); 7.96 (d, 2H, *J* = 8.0 Hz, aromatic protons); 7.90 (d, 2H, *J* = 8.0 Hz, aromatic protons); 7.89 (d, 4H, *J* = 8.0 Hz, aromatic protons); 7.51 (d, 2H, *J* = 8.0 Hz, aromatic protons);7.33 (d, 2H, *J* = 8.3 Hz, aromatic protons); 7.24 (d, 2H, *J* = 8.3 Hz; aromatic protons); 2.54 (s, 3H, $CH_3$); $^{13}$C-NMR (DMSO-$d_6$, δ, ppm): 164.12 (C3-triazole ring); 159.64 (C5-triazole ring); 152.72 (C=N-thiadiazole ring); 141.40, 139.48, 139.27, 137.50, 135.85, 131.20 (quaternary aromatic ring carbons); 131.12, 129.87, 129.14, 128.56, 127.80, 120.30 (CH-aromatic ring carbons); 21.36 ($CH_3$).

*General procedure for synthesis of 3-[4-(4-chloro-phenylsulfonyl)phenyl]-6-(substituted-phenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles* ***(3)***

A mixture of 4-amino-5-[4-(4-chloro-phenylsulfonyl) phenyl]-4*H*-1,2,4-triazole-3-thiol **(1)** (5 mmol) and aromatic acid (5 mmol) in phosphoryl chloride (10 mL) was heated under reflux until hydrogen chloride no longer evolved. The obtained mixture was cooled to room temperature and the viscous material thus formed was added in small portions to a mixture of 20 g of sodium hydroxide, 50 ml of water, and 50 g of ice using a cooling bath. The mixture was kept for 0.5 h at room temperature and adjusted to pH 8 by adding a 2M solution of sodium hydroxide. The obtained precipitate was filtered off, washed on a filter with warm water, dried in air and recrystallized from ethanol.

*6-(4-bromophenyl)-3-[4-(4-chloro-phenylsulfonyl)phenyl]-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole* ***3a***:

70% yield; m.p.: 204-205°C; Anal. Calc. (%) for $C_{21}H_{12}BrClN_4O_2S_2$ (531.83 g/mol): C-47.43; H-2.27; N-10.53; Found: C-47.39; H-2.23; N-10.48; IR (KBr, $cm^{-1}$): 3084 (aromatic CH); 1619, 1599, 1573, 1548 (C=N + $C=C_{aryl}$); 1326, 1290, 1158 ($SO_2$); 1258 (N-N=C); 1010 (N-N); 765 (C-Cl); 698 (C-S-C); 575 (C-Br); $^1$H-NMR (DMSO-$d_6$, δ, ppm): 7.96 (s, 4H, aromatic protons);.7.90 (dd, 2H, *J* = 8.6 Hz, aromatic protons); 7.66 (d, 2H, *J* = 8.8 Hz, aromatic protons); 7.64 (d, 2H, *J* = 8.6 Hz; aromatic protons); 7.50 (d, 2H, *J* = 8.8 Hz, aromatic protons); $^{13}$C-NMR (DMSO-$d_6$, δ, ppm): 167.63 (C3-triazole ring); 159.16 (C5-triazole ring); 154.31 (C=N-thiadiazole ring); 141.38, 141.28, 138.71, 135.61, 132.51, 123.17 (quaternary aromatic ring carbons); 132.15, 129.82, 129.75, 129.54, 128.74, 128.52 (CH-aromatic ring carbons).

*6-(4-chlorophenyl)-3-[4-(4-chloro-phenylsulfonyl)phenyl]-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole* ***3b***:

72% yield; m.p.: 173-174°C; Anal. Calc. (%) for $C_{21}H_{12}Cl_2N_4O_2S_2$ (487.38 g/mol): C-51.75; H-2.48; N-11.50; Found: C-51.70; H-2.44; N-11.46; IR (KBr, $cm^{-1}$): 3081 (aromatic CH); 1610, 1589, 1574 (C=N + $C=C_{aryl}$); 1318, 1289, 1160 ($SO_2$); 1261 (N-N=C); 1007 (N-N); 768 (C-Cl); 683 (C-S-C); $^1$H-NMR (DMSO-$d_6$, δ, ppm): 7.98 (d, 2H, *J* = 8.7 Hz, aromatic protons); 7.95 (d, 2H, *J* = 8.7 Hz, aromatic protons); 7.89 (d, 2H, *J* = 8.5 Hz, aromatic protons); 7.78 (d, 2H, *J* = 8.5 Hz; aromatic protons); 7.54 (d, 2H, *J* = 8.4 Hz; aromatic protons); 7.41 (d, 2H, *J* = 8.4 Hz; aromatic protons); $^{13}$C-NMR (DMSO-$d_6$, δ, ppm): 165.32 (C3-triazole ring); 157.96 (C5-triazole ring); 151.16 (C=N-thiadiazole ring); 140.30, 139.96, 139.12, 137.16, 134.31, 131.62 (quaternary aromatic ring carbons); 130.41, 129.71, 129.34, 128.90, 128.81, 127.92 (CH-aromatic ring carbons).

*6-(4-methoxyphenyl)-3-[4-(4-chloro-phenylsulfonyl)phenyl]-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole* ***3c***:

69% yield; m.p.: 200-202°C; Anal. Calc. (%) for $C_{22}H_{15}ClN_4O_3S_2$ (482.96 g/mol): C-54.71; H-3.13; N-11.60; Found: C-54.69; H-3.10; N-11.57; IR (KBr, $cm^{-1}$): 3081 (aromatic CH);

IR (KBr, $cm^{-1}$): 3088 (aromatic CH); 2943, 2879 ($CH_3$); 1608, 1592, 1534 (C=N + $C=C_{aryl}$); 1316, 1288, 1159 ($SO_2$); 1268 (N-N=C); 1009 (N-N); 769 (C-Cl); 687 (C-S-C); $^1$H-NMR (DMSO-$d_6$, δ, ppm): 7.96 (d, 2H, *J* = 8.5 Hz, aromatic protons); 7.90 (d, 2H, *J* = 8.5 Hz, aromatic protons); 7.85 (dd, 2H, *J* = 8.0, aromatic protons); 7.76 (d, 2H, *J* = 8.0 Hz, aromatic protons); 7.12-7.68 (m, 4H, aromatic protons); 3.83 (s, 3H, $OCH_3$); $^{13}$C-NMR (DMSO-$d_6$, δ, ppm): 163.54 (C3-triazole ring); 160.62 (C5-triazole ring); 154.94 (C=N-thiadiazole ring); 152.64, 142.13, 140.54, 139.02, 134.21, 125.81 (quaternary aromatic ring carbons); 129.28, 128.54, 128.04, 127.92, 126.84, 114.82 (CH-aromatic ring carbons); 55.80 ($OCH_3$).

*6-(4-aminophenyl)-3-[4-(4-chlorophenylsulfonyl)phenyl]-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole* ***3d***:

71% yield; m.p.: 194-196°C; Anal. Calc. (%) for $C_{21}H_{14}ClN_5O_2S_2$ (467.95 g/mol): C-53.90; H-3.02; N-14.97; Found: C-53.86; H-2.98; N-14.93; IR (KBr, $cm^{-1}$): 3081 (aromatic CH);

IR (KBr, $cm^{-1}$): 3365, 3224 ($NH_2$); 3068 (aromatic CH); 1610, 1581, 1544 (C=N + $C=C_{aryl}$); 1321, 1292, 1160 ($SO_2$); 1255 (N-N=C); 1011 (N-N); 764 (C-Cl); 705 (C-S-C); $^1$H-NMR (DMSO-$d_6$, δ, ppm): 8.01 (d, 2H, *J* = 8.5 Hz, aromatic protons); 7.98 (d, 2H, *J* = 8.5 Hz, aromatic protons); 7.82 (d, 2H, *J* = 8.2 Hz, aromatic protons); 7.76 (d, 2H, *J* = 8.4 Hz; aromatic protons); 7.51 (d, 2H, *J* = 8.2 Hz, aromatic protons); 6.70 (d, 1H, *J* = 8.4 Hz; aromatic proton); 6.58 (d, 1H, *J* = 8.4 Hz; aromatic proton); 5.82 (s, 2H, $NH_2$); $^{13}$C-NMR (DMSO-$d_6$, δ, ppm): 164.78 (C3-triazole ring); 156.31 (C5-triazole ring); 152.65 (C=N-thiadiazole ring); 145.64, 140.75, 139.24, 138.87, 135.48, 133.80 (quaternary aromatic ring carbons); 13.76, 130.06,129.65, 129.16,128.51, 118.18 (CH-aromatic ring carbons).

*6-[(3-bromo-4-chloro)phenyl)]-3-[4-(4-chlorophenylsulfonyl)phenyl]-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole* ***3e***:

68% yield; m.p.: 156-158°C; Anal. Calc. (%) for $C_{21}H_{11}BrCl_2N_4O_2S_2$ (566.28 g/mol): C-44.54; H-1.96; N-9.89; Found: C-44.51; H-1.93; N-9.86; IR (KBr, $cm^{-1}$): 3075 (aromatic CH); 1612, 1584, 1574 (C=N + $C=C_{aryl}$); 1324, 1290, 1159 ($SO_2$); 1261 (N-N=C); 1008 (N-N); 768 (C-Cl); 695 (C-S-C); 576 (C-Br); $^1$H-NMR (DMSO-$d_6$, δ, ppm): 8.04 (d, 2H, *J* = 8.3 Hz, aromatic protons); 8.00 (d, 2H, *J* = 8.3 Hz, aromatic protons); 7.92 (d, 2H, *J* = 8.3 Hz, aromatic protons); 7.78 (d, 2H, *J* = 8.3 Hz, aromatic protons); 7.68 (d, 1H, *J* = 8.6 Hz; aromatic proton); 7.58 (d, 1H, *J* = 8.6 Hz, aromatic proton); 7.54 (d, 1H, *J* = 8.6 Hz, aromatic proton); $^{13}$C-NMR (DMSO-$d_6$, δ, ppm): 161.92 (C3-triazole ring); 156.66 (C5-triazole ring); 154.12 (C=N-thiadiazole ring); 143.47 140.12, 139.25, 134.98, 131.98, 123.54, 115.18 (quaternary aromatic ring carbons); 134.53, 131.54, 130.41, 129.94, 128.74, 128.72 (CH-aromatic ring carbons).

*Antibacterial activity*

The newly prepared compounds were screened for their antibacterial activity against two Gram-negative bacteria: *Escherichia coli (Ec)* ATCC 25922, *Pseudomonas aeruginosa (Pa)* ATCC 27853, one Gram-positive bacteria: *Staphylococcus aureus (Sa)* ATCC 25923 and two yeasts: *Candida scotti (Cs)* and *Candida albicans (Ca)* ATCC 90028, by using the serial dilutions in liquid broth method [8,9] for determination of MIC. The materials used were 96-well plates, suspensions of microorganism (0.5 McFarland), Muller–Hinton broth (for bacteria), and Sabouraud dextrose agar (for yeasts), solutions of the substances to be tested (2048 mg/mL in DMSO). The following concentrations of the substances to be tested were obtained in the 96-well plates: 1024; 512; 256; 128; 64;32; 16; 8; 4; 2 mg/mL. After incubation at 37°C for 18–20 h for bacterial strains and for 48 h for *C.albicans* and *C. scotti*, the MIC for each tested substance was determined by macroscopic observation of microbial growth. It corresponds to the well with the lowest concentration of the tested substance where microbial growth was clearly inhibited. Ampicillin and Aztreonam for bacteria and Amphotericine for the yeasts were used as standard drugs.

## Results and discussions

*Chemistry*

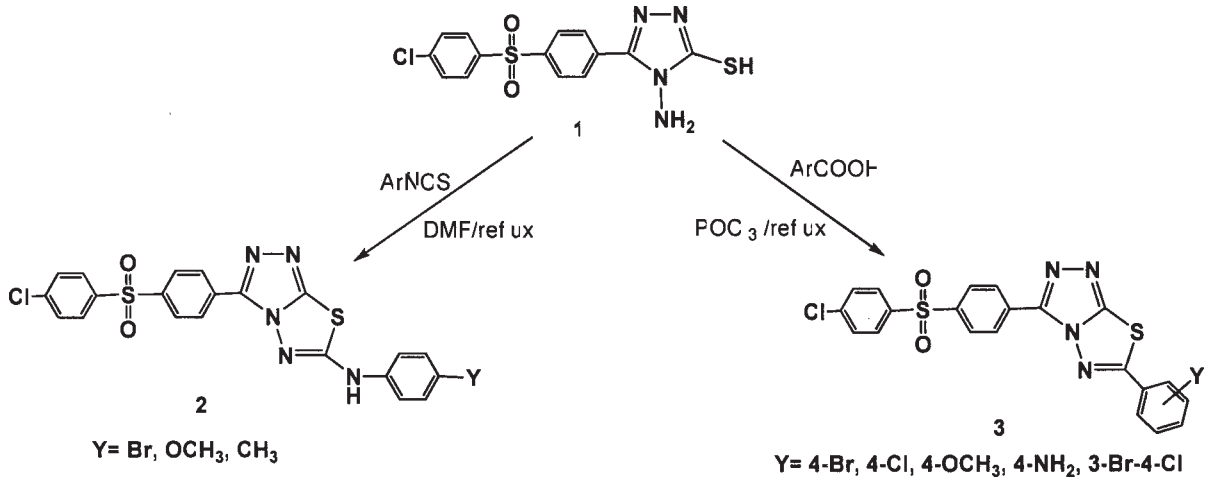
The preparation of 3,6-disubstituted-[1,2,4]-triazolo-[3,4-*b*]-1,3,4-thiadiazole derivatives (**2,3**) are depicted in scheme 1.

The triazole **1** was converted to 3-[4-(4-chlorophenylsulfonyl)phenyl]-6-N-(substituted-phenyl)amino-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles **2** by reacting with different aryl isothiocyanates in the presence of DMF. Cyclocondensation of the SH and $NH_2$ functions of **1** with various substituted aromatic acids in the presence of phosphorus oxychloride afforded a series of 3-[4-(4-chlorophenylsulfonyl)phenyl]-6-(substituted-phenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles **3.**

The build up of N-bridged condensed heterocycle, **2a-c** from **1** is evidenced by its IR, $^1$H-NMR, $^{13}$C-NMR. Infrared spectra of these compounds were in accordance with our structural proposal: there is a broad band in 3125-3238 $cm^{-1}$ region, assigned to NH group, new band appears in 1588-1618 $cm^{-1}$ region, which is attributed to stretching frequency of N=C group formed by ring closure for all compounds and additional, for **2b, c**, asymmetric and symmetric stretching frequencies of $CH_3$ group appeared 2851-2920 $cm^{-1}$. In addition, the $^1$H-NMR spectra contain a characteristic singlet signal around 11 ppm due to the N*H* proton and the new positive signal in 152-154 ppm region in $^{13}$C-NMR spectra corresponding to quaternary carbon of N=*C* group.

In the IR spectra of compounds **3a-e,** the absence of absorption bands due to -SH (-C=S) and -$NH_2$ stretching frequencies of parent compounds **1** clearly indicated the fusing between compounds **1** and aromatic acid in the presence of phosphorus oxychloride. All the compounds show absorption peaks for N-N=C in the region of 1255-1268 $cm^{-1}$ and for C-S-C, in the region of 683-705 $cm^{-1}$. The new band which appears in 1608-1619 $cm^{-1}$ region is attributed to stretching frequency of N=C group of the thiadiazole ring. These data were very similar to previous reports [10-14].

The $^1$H-NMR spectra of compound **3c** showed a singlet at 3.83 ppm integrating for three protons of the methyl group. The singlet signal observed at 5.82 ppm integrating for two protons was assigned to –$NH_2$ group in **3d**. As previous reports [15,16], the $^{13}$C signals of triazole-C-3 and triazole-C-5 in newly synthesized compounds were observed around 160.48-166.17 ppm and 150.32-154.31 ppm, respectively, while $^{13}$C signals derived from C-6 of triazolothiadiazole ring of compounds **4,5** were recorded at 154.76-159.16 ppm. The other signals present in $^{13}$C-NMR spectra of compounds **2,3** were recorded at the expected chemical shifts. Moreover, elemental analyses are consistent with the structures proposed for compounds **2,3**.




Scheme 1. Synthesis of the title compounds

| Compd. | Gram-negative bacteria[a] | | Gram-positive bacteria[b] | Yeasts[c] | |
|---|---|---|---|---|---|
| | *Ec* | *Pa* | *Sa* | *Cs* | *Ca* |
| **2a** | 1024 | 1024 | 512 | 512 | 256 |
| **2b** | 1024 | 1024 | 1024 | 512 | 512 |
| **2c** | 1024 | 1024 | 1024 | 512 | 512 |
| **3a** | 1024 | 512 | 1024 | 512 | 256 |
| **3b** | 256 | 512 | 1024 | 512 | 1024 |
| **3c** | 512 | 512 | 512 | 512 | 512 |
| **3d** | 256 | 512 | 256 | 512 | 512 |
| **3e** | 128 | 512 | 128 | 256 | 128 |
| **Amp.** | - | - | <2 | - | - |
| **Azt.** | <2 | <2 | - | - | - |
| **Amph.** | - | - | - | <2 | 2 |

**Table1**
ANTIMICROBIAL ACTIVITY OF THE TITLE COMPOUNDS; MIC (μg/mL)

Note: [a] ***Ec*** (*Escherichia coli* ATCC 25922); ***Pa*** (*Pseudomonas aeruginosa* ATCC 27853)
[b] ***Sa*** (*Staphylococcus aureus* ATCC 25923);
[c] ***Cs*** (*Candida scotti*); Ca (*Candida albicans* ATCC 90028)
Amp: ampicillin; Azt: Aztreonam; Amph: Amphotericin
- no activity

*Antibacterial activity*

The preliminary results of antimicrobial activities indicated that the tested compounds exhibited a moderate activity against Gram-negative bacteria: *Escherichia coli (Ec)* ATCC 25922, *Pseudomonas aeruginosa (Pa)* ATCC 27853, one Gram-positive bacteria: *Staphylococcus aureus (Sa)* ATCC 25923 and two yeasts: *Candida scotti (Cs)* and *Candida albicans (Ca)* ATCC 90028 (table 1).

The data generated from this study (table 1) showed that compounds displayed low to moderate activity. The obtained results can be attributed to quite bulky structure of the tested compounds, to the nature of the fragments attached in different positions to these molecules, but they may be associated with the nature of tested bacterial species. Thus, we can see that none of the tested compounds has inhibitory action against *P. aeruginosa*. Note that if the tested molecule has more halogen atoms, antibacterial action is significantly better. Thus, in the studied serie the best antimicrobial effect has compound **3e** (MIC=128 μg/mL against *S. aureus*, *E. coli*, and *C. albicans)* probably due to the cumulative electron-withdrawing effect of the chlorine and bromine atoms which are directly attached to the phenyl ring of the thiadiazole, in addition to the chlorine atom attached to the diphenylsulfone moiety. In the serie of the 6-N-(substituted-phenyl)amino-triazolo-thiadiazoles **2**, the presence of Br, $CH_3$, $OCH_3$, to the phenyl ring of the thiadiazole was responsible for the decrease until disappearance of antibacterial activity. From these results it is clear that substituents affect the activity of compounds in different series. All the tested compounds, which are considered active, are less effective than drugs taken as a standard.

## Conclusions

Novel 3-[4-(4-chloro-phenylsulfonyl)phenyl]-6-(substituted-phenyl)/6-N-(substituted-phenyl)amino-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles were prepared and screened for their antimicrobial activities. The antibacterial data given for the compounds presented in this paper allowed us to state that the variation of antimicrobial activity may be associated with the nature of tested microorganisms and is due to the chemical structure of the tested compounds. From the obtained results it is clear that substituents affect the activity of compounds in different series. Also, the presence of more halogen atom in the structure has considerable increased the biological activity of the molecules. The best antibacterial effect has 6-[(3-bromo-4-chloro)phenyl)]-3-[4-(4-chloro-phenylsulfonyl)phenyl]-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole **3e** (MIC=128μg/mL against *S. aureus*, *E. coli*, and *C. albicans*).

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