Synthesis and Antibacterial Activity of Some Triazole, Thiadiazole and Oxadiazole Derivatives

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*This study presents synthesis of new heterocyclic compounds from 1,2,4-triazole, 1,3,4-thiadiazole and 1,3,4-oxadiazole class obtained by cyclization of corresponding acylthiosemicarbazide, in different media. The new intermediate acylthiosemicarbazide was obtained by treatment of 4-(4-chlorophenylsulfonyl)-benzoic acid hydrazide **1** with 4-fluorophenyl isothiocyanate. Structures of the new compounds were identified by spectroscopic technique (IR, UV-VIS, ^{1}H-NMR, ^{13}C-NMR, MS) and also confirmed by elemental analysis. The new compounds have been screened for their in vitro antibacterial activities against several type strains of oral streptococci.*

Keywords: 1,2,4-triazole, 1,3,4-thia(oxa)diazole, acylthiosemicarbazide, 4-(4-chlorophenyl-sulfonyl)phenyl moiety, 4-fluorophenyl moiety, antibacterial activity

The resistance of bacteria against antimicrobial agents has become a widespread medical problem. Because of this development of resistance, many drugs which were very effective long ago before became now useless. Moreover, the toxic effects produced by many antibiotics must not be forgotten. So, the need for new antimicrobial is a priority in the medical world.

Several five-membered aromatic systems having three heteroatoms at symmetrical position have been studied because of their interesting biological properties. It is well established that various derivatives of 1,2,4-triazole, 1,3,4-thiadiazole and 1,3,4-oxadiazole exhibit broad spectrum of biological properties including antibacterial [1-11].

Because diarylsulfones are known in the literature for their antibacterial activity [12,13], the goal of the present study was to synthesize new derivatives from triazole, thiadiazole and oxadiazole class containing a diarylsulfone fragment in order to discover new antibacterial agents.

In previous studies [14,15] we reported the synthesis of some new heterocyclic compounds from these classes that contain both 4-(4-X-phenylsulfonyl)phenyl (X = H, Br) and 4-fluorophenyl radical moieties.

It is well known that the presence of halogenated groups in organic molecules often confers significant and useful changes in their chemical, physical and biological properties due to the elevated electronegativity and lipophilic character of halogen atoms [16].

Knowing this data from the literature, the aim of this study was to synthesize new derivatives of these classes that contain on the 4-(4-X-phenylsulfonyl)phenyl fragment, instead of bromine, the chlorine atom, more electronegative, because the presence of this atom could increase the biological activity of these compounds.

For this purpose, new derivatives from triazole, thiadiazole and oxadiazole class, containing in their molecule both 4-(4-chlorophenylsulfonyl)phenyl and 4-fluorophenyl fragments, were synthesized by cyclization of corresponding acylthiosemicarbazide, in different media, and were tested for their antibacterial activity against some oral streptococcal type strains. The oral streptococci belong to the normal flora of the oral cavity, but sometimes they can produce infective endocarditis and other kind of infections.

Experimental part

Melting points were determined on a Böetius apparatus and were not corrected. The IR spectra were recorded with a Vertex 70 Bruker spectrophotometer (in KBr pellet). The IR bands are given as w – weak, m – medium, s – intense, vs – very intense. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded, in DMSO-d_6, on a Varian Gemini 300BB instrument, at room temperature, operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C-NMR. Chemical shifts were given as δ values in parts per million (ppm) relative to tetramethylsilane as internal standard and coupling constants *J* in Hz. Spin multiplets are given as: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet) and w (wide). The mass spectra ESI-MS were recorded with a triple quadrupole mass spectrometer Varian 1200 L/MS/MS, coupled with a high performance liquid chromatograph with Varian ProStar 240 SDM ternar pump. The sample solution (2 μg/mL in chloroform/methanol 2/1, v/v) was introduced in the ESI interface by direct infusion, after a tenth dilution with methanol, at a flow rate of 20μL/min. The UV spectra were recorded, in methanolic solutions, on a SPECORD 40 Analytik Jena spectrophotometer.

Synthesis of new compounds

The title compounds were synthesized according to the sequence shown in the Scheme 1.

The new compounds **(2-6)** (X= Cl) were obtained by the same procedures as derivatives ($X\text{-}C_6H_4\text{-}SO_2\text{-}C_6H_4\text{-}$; X= H, Br) described previously [14,15]. The 4-(4-chloro-

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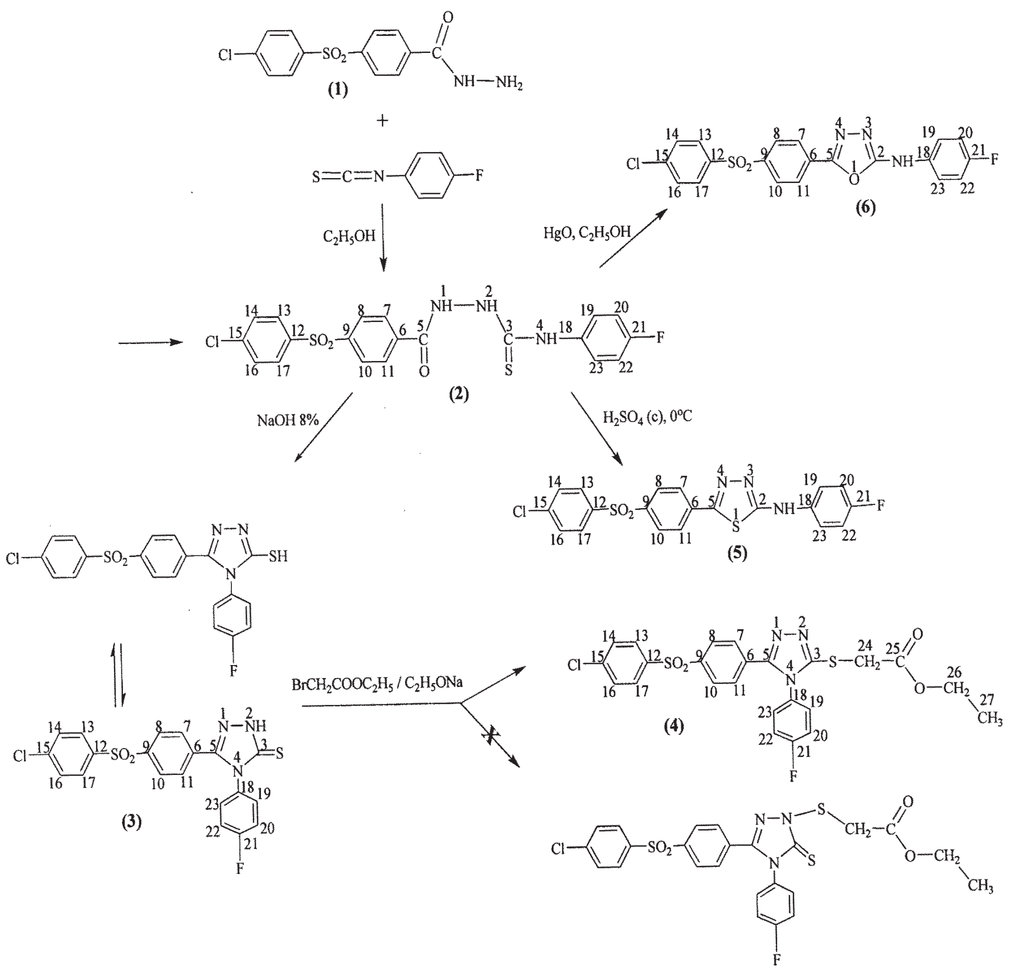

Scheme 1

phenylsulfonyl)benzoic acid hydrazide **(1)** was synthesized following the method described in literature [17].

The new intermediate from acylthiosemicarbazide class **(2)** was obtained by reaction of hydrazide **(1)** with 4-fluorophenyl isothiocyanate.

Cyclodehydration of this compound **(2)**, in presence of sodium hydroxide, occurred with obtaining of 5-(4-(4-chlorophenylsulfonyl)phenyl)-4-(4-fluorophenyl)-2*H*-1,2,4-triazole-3(4*H*)-thione **(3)**, while in presence of sulfuric acid led to 5-(4-(4-chlorophenylsulfonyl)phenyl)-N-(4-fluorophenyl)-1,3,4-thiadiazol-2-amine **(5)**. Alkylation of 1,2,4-triazole **(3)** with ethyl bromoacetate, in presence of sodium ethoxide, afforded ethyl 2-(5-(4-(4-chlorophenylsulfonyl)phenyl)-4-(4-fluorophenyl)-4*H*-1,2,4-triazol-3ylthio)acetate **(4)**.

Treating the same acylthiosemicarbazide **(2)** with yellow mercury oxide, 5-(4-(4-chlorophenylsulfonyl)phenyl)-N-(4-fluorophenyl)-1,3,4-oxadiazol-2-amine **(6)** was obtained due to the cyclodesulfurization.

Preparation of 1-(4-(4-chlorophenylsulfonyl) benzoyl)-4-(4-fluorophenyl)-thiosemicarbazide (2)

A mixture of **(1)** (1 mmol) and 4-fluorophenyl isothiocyanate (1 mmol) in absolute ethanol (3 mL) was refluxed for 10 h. After cooling, the formed solid was filtered off and crystallized from ethanol to give white crystals of acylthiosemicarbazide **(2)**.

m.p.: 175-176°C; yield 92.0%; Elemental analysis (%) - Found C:51.86; H:3.33; N:8.98; Calcd. for $C_{20}H_{15}ClFN_3O_3S_2$ (463.93g/mol): C:51.78; H:3.26; N:9.06

IR (KBr; cm^{-1}): 3316s, 3170s, 3088w, 3045w, 1681s, 1530s, 1509s, 1478m, 1319s, 1297s, 1260m, 1220s, 1158vs, 836m, 756m; UV-Vis (CH_3OH) (λ_{max}/nm, (log ε)): 203.5 (4.58); 225 (4.34); 252 (4.48); 359.5 (2.71); ESI-MS, *m/z* (%): $[M+H]^+$ 464 (^{35}Cl); $[M+H]^+$ 466 (^{37}Cl)

The spectral data ^{1}H-NMR and ^{13}C-NMR are presented in tables 1 and 2.

Preparation of 5-(4-(4-chlorophenylsulfonyl)phenyl)-4-(4-fluorophenyl)-2H-1,2,4-triazole-3(4H)-thione (3)

A mixture of **(2)** (1 mmol) and NaOH 8% solution (8 mL) was heated under reflux for 4. The obtained solution was cooled, acidified with a diluted solution of HCl 1% (pH = ~ 5,5). The obtained precipitated was separated by filtration, washed with water, dried and recrystallized from $CHCl_3$/petroleum ether (1:1, v/v).

m.p.: 284-285°C; yield 97.2%; Elemental analysis (%) - Found C:53.98; H:2.88; N:9.33; Calcd. for $C_{20}H_{13}ClFN_3O_2S_2$ (445.92g/mol): C:53.87; H:2.94; N:9.42

IR (KBr; cm^{-1}): 3418w, 3086m, 3022w, 1601s, 1580m, 1536m, 1512s, 1475m, 1327vs, 1283m, 1250m, 1224m, 1160vs, 840m, 768s; UV-Vis (CH_3OH) (λ_{max}/nm, (log ε)): 205 (4.63); 255.5 (4.47); 322.5 (3.92); ESI-MS, *m/z* (%): $[M+H]^+$ 446 (^{35}Cl); $[M+H]^+$ 448 (^{37}Cl)

The spectral data ^{1}H-NMR and ^{13}C-NMR are presented in tables 1 and 2.

Preparation of ethyl 2-(5-(4-(4-chlorophenylsulfonyl) phenyl)-4-(4-fluorophenyl)-4H-1,2,4-triazol-3-ylthio)acetate (4)

To a solution of compound **(3)** (1 mmol) in sodium ethoxide (prepared from 23 mg metallic sodium in 10 mL ethanol), ethyl bromoacetate (1 mmol) was added with stirring at room temperature. The reaction mixture was stirred at room temperature for 12 h, and then was poured into ice water. The obtained precipitate was filtered off, washed with water, dried and recrystallized from ethanol.

m.p.: 174-175°C; yield 72.0%; Elemental analysis (%) - Found C:54.27; H:3.54; N:7.81; Calcd. for $C_{24}H_{19}ClFN_3O_4S_2$ (532.01g/mol): C:54.18; H:3.60; N:7.90

IR (KBr; cm^{-1}): 3090m, 3074m, 2982m, 2936w, 2902w, 2840w, 1724s, 1601m, 1582m, 1511s, 1473m, 1439m, 1322s, 1286s, 1229m, 1160vs, 845m, 768s; UV-Vis (CH_3OH) (λ_{max}/nm, (log ε)): 204 (4.63); 244 (4.21); 281 (4.23); ESI-MS, *m/z* (%): $[M+H]^+$ 532 (^{35}Cl), $[M+H]^+$ 534 (^{37}Cl)

The spectral data ^{1}H-NMR and ^{13}C-NMR are presented in tables 1 and 2.

Preparation of 5-(4-(4-chlorophenylsulfonyl)phenyl)-N-(4-fluorophenyl)-1,3,4-thiadiazol-2-amine (5)

A solution of **(2)** (1 mmol) in conc. sulfuric acid (40 mL) was stirred at 0°C for 3 h and then at room temperature for 3 h. The reaction mixture was neutralized with a diluted solution of ammonium hydroxide and then, the obtained solid was collected by filtration, washed with water, dried and recrystallized from $CHCl_3$/petroleum ether (1:1, v/v).

m.p.: 245-247°C; yield 89.2%; Elemental analysis (%) - Found C:53.94; H:2.83; N:9.50; Calcd. for $C_{20}H_{13}ClFN_3O_2S_2$ (445.92 g/mol): C:53.87; H:2.94; N:9.42

IR (KBr; cm^{-1}): 3307m, 3089m, 3060m, 1617m, 1558s, 1510s, 1494s, 1327s, 1280m, 1230m, 1157s, 834m, 765s; UV-Vis (CH_3OH) (λ_{max}/nm, (log ε)): 205 (4.40); 262 (4.25); 346 (4.18); ESI-MS, *m/z* (%): $[M+H]^+$ 446 (^{35}Cl); $[M+H]^+$ 448 (^{37}Cl)

The spectral data ^{1}H-NMR and ^{13}C-NMR are presented in tables 1 and 2.

Preparation of 5-(4-(4-chlorophenylsulfonyl)phenyl)-N-(4-fluorophenyl)-1,3,4-oxadiazol-2-amine (6)

To a solution of thiosemicarbazide **(2)** (5 mmol) in ethanol, the yellow mercuric oxide (10 mmol) was added and the reaction mixture was refluxed for 8 h. The residue obtained after removal of solvent by distillation under reduced pressure was dissolved in DMF. At this solution was added ethanol (ethanol:DMF 1:1,v/v) and allowed to stand overnight. The obtained precipitated was filtered off, dried and recrystallized from ethanol.

m.p.: 293-295°C; yield 56%; Elemental analysis (%) - Found C:55.77; H:2.94; N:9.69; Calcd. for $C_{20}H_{13}ClFN_3O_3S$ (429.85 g/mol): C:55.88; H:3.05; N:9.78

IR (KBr; cm^{-1}): 3304m, 3073w, 3015w, 1622s, 1590s, 1582s, 1516s, 1324m, 1293s, 1236m, 1157vs, 840m, 772s; UV-Vis (CH_3OH) (λ_{max}/nm, (log ε)): 203 (4.38); 251 (4.29); 327 (4.21); ESI-MS, *m/z* (%): $[M+H]^+$ 430 (^{35}Cl); $[M+H]^+$ 432 (^{37}Cl)

The spectral data ^{1}H-NMR and ^{13}C-NMR are presented in tables 1 and 2.

Antibacterial activity testing

The *in vitro* testing of the antibacterial activity of compounds was performed using the broth microdilution method, in order to detect the minimum inhibitory concentrations (MIC). The compounds were dissolved in dimethyl sulfoxide (2048 μg/mL). This solvent showed no antibacterial activity against the tested bacterial strains.

Series of binary dilutions of the new compounds (from 1:2 to 1:256) were performed in Mueller-Hinton cation-adjusted broth supplied with 3% lysed horse blood, in 96-well plates, in a broth volume of 50μL/well.

The antibacterial activity of the compounds was tested against the following strains of oral streptococci: *S. anginosus* NCTC 10713, *S. mitis* ATCC 6249, *S. mutans* ATCC 25175, *S. parasanguinis* ATCC 15909, *S. salivarius* ATCC 13419, *S. sanguinis* ATCC 10556 and *S. vestibularis* ATCC 49124. An inoculum adjusted at 0.5 Mc.Farland turbidity was made from each type strain and was afterwards diluted in Mueller-Hinton broth to 1/100, in order to obtain a bacterial density of 1 x 10^6 CFU/mL. From the diluted inoculum, 50 μL were added in all the wells containing the tested compounds and in the wells with the positive growth control (which already contained 50 μL of compound-free broth). The wells with the negative growth (the sterility control) were filled in only with 100 μL compound-free broth.

The 96-microwell plates sealed with sterile adhesive sheet and covered by their lid were incubated aerobically at 37°C for 24 h. In addition, an inoculum control for each bacterial strain was prepared by removing an aliquot of 10 μL just after inoculating the positive growth control wells, diluting it with 10 mL of Mueller-Hinton broth by vortexing, and afterwards, by spreading of 100 μL of the diluted

Table 1

SPECTRAL DATA OF ^{1}H-NMR OF NEW COMPOUNDS (2-6) (DMSO-d_6; δ, ppm, *J*, Hz)

No comp.	H-7, H-11	H-8, H-10	H-13, H-17	H-14, H-16	H-19 H-23	H-20 H-22	H-24	H-26	H-27	NH
(2)	8.07s	8.07s	7.93d (8.8)	7.64d (8.8)	7.30sl	7.08t (7.7)	-	-	-	9.86ws 9.96ws 10.82ws
(3)	7.68d (8.5)	7.96d (8.5)	7.92d (8.5)	7.54d (8.5)	7.43dd (8.8;5.2)	7.33t (8.8)	-	-	-	14.10s
(4)	7,69d (8.5)	7.96d (8.5)	7.47d (8.5)	7.59d (8,5)	7.56dd (8.6;6.9)	7.43t (8.8)	4.11s	4.10q (7.1)	1.18t (7.1)	-
(5)	8.07s	8.07s	8.00d (8.8)	7.70d (8.8)	7.68dd (8.8;5.5)	7.21t (8.8)	-	-	-	10.72ws
(6)	8.16d (8.5)	8.04d (8.5)	8.00d (8.5)	7.70d (8.5)	7.61dd (9.0;5.0)	7.20t (9.0)	-	-	-	10.85s

Table 2

SPECTRAL DATA OF ^{13}C-NMR OF NEW COMPOUNDS (2-6) (DMSO-d_6; δ, ppm *J*, Hz)

No comp.	C-2	C-3	C-5	C-6	C-7, C-11	C-8, C-10	C-9	C-12	C-13, C-17	C-14, C-16	C-15	C-18	C-19 C-23	C-20 C-22	C-21	C-24	C-25	C-26	C-27
(2)	-	181.80	164.58	137.22	129.33	127.53	143.39	139.43	129.54	130.05	139.20	135.30	129.30d (16.0)	114.72d (22.1)	158.90d (246.3)	-	-	-	-
(3)	-	169.18	149.05	130.66	130.07	127.76	141.98	139.28	129.60	129.49	139.60	134.52	131.20d (8.9)	116.40d (22.9)	162.30d (247.4)	-	-	-	-
(4)	-	153.03	152.46	131.33	130.07	129.59	141.48	139.29	127.88	128.93	139.22	131.34	130.10d (6.8)	117.32d (23.4)	162.58d (248.5)	33.98	168.01	61.39	14.01
(5)	165.31	-	155.62	135.01	129.40	128.41	139.56	136.74	127.80	130.00	139.06	141.27	119.55d (7.7)	115.71d (22.3)	157.55d (239.3)	-	-	-	-
(6)	160.42	-	156.57	128.52	128.40	126.62	142.02	139.30	129.47	130.04	139.32	156.58	118.86d (7.7)	115.68d (22.6)	157.46d (239.0)	-	-	-	-

inoculum on a Columbia blood agar plate with further aerobic incubation 5% CO_2 atmosphere, at 37°C for 24 h.

The MIC were determined the next day, after checking the macroscopic aspect of the positive and negative growth controls. The MIC values were considered the lowest concentrations of the tested compounds that inhibited the microbial growth, indicated by the last well without any turbidity or growth button.

For detecting the minimum bactericidal concentrations (MBC), aliquots of 10 μL were removed from all the wells without visible bacterial growth and from the positive and negative growth controls too, and inoculated in spots on Columbia blood agar plates by an electronic pipette. After a 48h period of incubation in 5% CO_2 atmosphere, at 37°C, the MBC values were considered to be the lowest concentrations of the compounds able to kill ≥ 99.9% of the final bacterial inoculum.

Results and discussions

Chemistry

The structures of compounds **(2-6)** were established by their IR, ^{1}H-NMR, ^{13}C-NMR and MS spectra.

The IR absorptions due to the C=O and C=S functions from new acylthiosemicarbazide **(2)** appeared at 1681 and 1260 cm^{-1}, respectively. In the ^{1}H-NMR spectrum of this acyclic compound **(2)**, three singlets were observed at the 9.86, 9.96 and 10.86 ppm region representing the protons of the NH group. Also, the ^{13}C-NMR spectrum exhibited two important signals characteristic to C=S and C=O carbons which appear at 181.80 ppm and 164.58 ppm, respectively [18].

Absence of carbonyl absorption band in IR spectrum of new heterocyclic compounds **(3)**, **(5)** and **(6)** confirmed that cyclization, of acylthiosemicarbazide **(2)** took place, in different media.

Since 1,2,4-triazol-3-thione may exist in thiole-thione tautomeric forms, our investigation showed that in this case thione structure dominates both in solid state and in solution. Thus, the IR spectrum of **(3)** showed two characteristic absorption bands at 1250 cm^{-1} and 3418 cm^{-1} attributed to νC=S and νNH group respectively. The νSH band which appears in region 2500-2650 cm^{-1} [19-21] is not presented in IR spectra of this compound. Also, the presence in ^{1}H-NMR spectrum of the signal due to the NH proton, at 14.10 ppm [22,23] and in ^{13}C-NMR spectrum of C=S carbon, at 169.18 ppm [18,21], supported that the thione form of the triazoline ring of compound **(3)** is predominantly in the solution.

In case of alkylate 1,2,4-triazole **(4)**, the carbonyl group of ester which appears in IR at 1724 cm^{-1} and in ^{13}C-NMR spectrum at 168.01 ppm is very important. The absence in its IR spectrum of νNH and νC=S absorption bands demonstrated that alkylation of triazole **(3)** took place at sulfur and not at nitrogen atom. Moreover, this finding is supported by ^{13}C-NMR spectrum, because the C-3 carbon atom signal is more shielded than that of triazole **(3)** (169.18 ppm) and occurs at 153.03 ppm [24]. Other important signals present in the ^{1}H-NMR spectrum of **(4)** are those characteristic of protons and carbons from S-CH_2 and OCH_2-CH_3 groups which resonates at 4.11 ppm (singlet; SCH_2), 4.10 ppm (quartet; $OC\underline{H}_2$-CH_3) and 1.18 ppm (triplet; OCH_2-$\underline{C}H_3$). Also, in ^{13}C-NMR spectra these carbons appear at 33.98 ppm for SCH_2, 61.39 ppm for $O\underline{C}H_2$-CH_3 and 14.01 ppm for OCH_2-$\underline{C}H_3$.

In the IR spectra of heterocyclic compounds **(5)** and **(6)** is present one single absorption band characteristic to amino group which appears in thiadiazole at 3307 cm^{-1} and in oxadiazole at 3304 cm^{-1}. Also, in ^{1}H-NMR spectra of these compounds, the singlet signal of proton from amino group appears at 10.72 ppm (in thiadiazole) [1,20,22,25] and at 10.85 ppm (in oxadiazole) [26,27].

The presence of C-2 and C-5 heterocyclic carbons signals in ^{13}C-NMR spectra at 165.31 ppm (thiadiazole)/ 160.42 ppm (oxadiazole) and 155.62 ppm (thiadiazole)/ 156.57 ppm (oxadiazole) respectively is another proof that these compounds were obtained [18, 27,28].

The νC=N absorption band characteristic to triazole/ (oxa)thiadiazole ring is present in 1601-1622 cm^{-1} range [23,25,27,29,30].

The synthesized compounds **(2-4)** were further confirmed by the mass spectral analysis. The appearance of molecular ions confirmed the presence of these derivatives.

Antibacterial activity

The values of the MIC and MBC (μg/mL) of the new compounds against the 7 oral streptococcal type strains are presented in table 3.

The values of MIC were ranging between: 32-64 μg/mL for triazole **(3)**, 32-128 μg/mL for S-alkylated 1,2,3-triazole **(4)**, 64-128 μg/mL for thiosemicarbazide **(2)** and thiadiazole **(5)**, and 64-256 μg/mL for oxadiazole. The values of MBC were ranging between: 64-256 μg/mL for **(3)**, 128-256 μg/mL for compounds **(2)**, **(4)** and **(5)**, and 128-512 μg/mL for **(6)**. In all cases, the MBC/MIC ratio was less or equal to 4, suggesting a bactericidal effect of the compounds against the tested oral streptococcal type strains.

For all compounds, the lowest MIC values were obtained when their action was investigated against *S. mutans*, while in case of *S. anginosus*, all MIC values were higher than 64 μg/mL, except for triazole **(3)**, when MIC was of 64 μg/L. The last one expressed the most important antibacterial activity among all compounds, but its alkylation, leading to derivative **(4)**, has not improved the antibacterial effect. In contrast, the derivative belonging to the 1,3,4-oxadiazole classes showed the weakest antimicrobial action.

Comparing the results of this study with those previously reported [14,15] in describing the synthesis of some

Table 3
THE MIC AND MBC (μg/mL) OF THE NEWLY SYNTHESIZED COMPOUNDS TESTED AGAINST SOME TYPE STRAINS OF ORAL STREPTOCOCCI

No. Comp.	*S. anginosus* NCTC 10713	*S. mutans* ATCC 25175	*S. mitis* ATCC 6249	*S. sanguinis* ATCC 10556	*S. parasanguinis* ATCC 15909	*S. salivarius* ATCC 13419	*S. vestibularis* ATCC 49124
	MIC/MBC	*MIC/MBC*	*MIC/MBC*	*MIC/MBC*	*MIC/MBC*	*MIC/MBC*	*MIC/MBC*
(2)	128/256	64/128	64/128	64/128	64/128	64/256	64/256
(3)	64/128	32/64	64/128	64/256	64/256	64/128	32/128
(4)	128/256	32/128	64/256	128/256	64/256	64/128	32/128
(5)	128/256	64/128	128/256	128/256	128/256	128/256	128/128
(6)	256/256	64/128	128/256	128/256	128/256	128/512	128/512

heterocyclic compounds belonging to the same classes containing both *4-fluoro-phenyl* and *4-(X phenylsulfonyl) phenyl* fragments, but X being H or Br, and their antimicrobial action against the same oral streptococcal strains, the following aspects were observed: a) the presence of chlorine atom in the molecule of the compounds has improved the antibacterial action of the respective: thiosemicarbazide against *S. sanguinis*, thiadiazole against *S. mutans*, and oxadiazole against *S. mitis* from *S. mutans*; b) the compounds with chlorine atom in their molecule and those without halogen atom exhibited a better antimicrobial activity than those containing the bromine atom, such as thiosemicarbazide and triazole-thione against *S. mutans*, thiadiazole against *S. anginosus*, and alkylate-triazole against: *S. mutans*, *S. mitis*, *S. salivarius*, *S. vestibularis* and *S. parasanguinis*; c) the compounds containing a chlorine or a bromine atom in the molecule proved to be more active on some oral streptococcal strains than those in which the halogen atom was missing, as in case of triazole-thione against *S. anginosus*, oxadiazole against *S. salivarius* and *S. vestibularis*, thiadiazole against *S. mitis* and *S salivarius*, and also in case of thiosemicarbazide against: *S. mitis*, *S. salivarius* and *S. parasanguinis*.

Conclusions

In this paper, we have prepared some new derivatives from 1,2,4-triazole, 1,3,4-thiadiazole, 1,3,4-oxadiazole class which have 4-(4-chlorophenylsulfonyl)phenyl and 4-fluorophenyl moieties. The structure of the obtained compounds was confirmed by different spectral methods and elemental analysis.

Testing *in vitro* these new compounds for their antimicrobial activity against several type strains of oral streptococci, it was noticed that *5-(4-(4-chlorophenyl-sulfonyl)phenyl)-4-(4-fluorophenyl)-2H-1,2,4-triazole-3(4H)-thione* **(3)** showed the best antibacterial action, suggesting the need of further investigation on more bacterial strains.

Based on the MIC values presented by the compounds containing the 4-(X-phenylsulfonyl)phenyl (X = H, Cl, Br) and 4-fluorophenyl fragments, it might be concluded that, in general, those derivatives containing a chlorine atom had a better antibacterial activity against some oral streptococcal strains than those containing one atom of bromine or those without halogen atom.

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