Synthesis and Biological Evaluation of Various 2-substituted 1,3,4-oxadiazoles Carrying Diphenylsulfone Moiety

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*To discover new derivatives which may possess biological activities, we synthesized a novel 5-[4-(4-X-phenylsulfonyl)phenyl]-1,3,4-oxadiazoles various substituted in 2-position from 4-(4-X-benzensulfonyl) benzoic acid hydrazides **1(a-c)**, X=H, Cl, Br. All the novel compounds were characterized by elemental analysis, IR, ^{1}H- and ^{13}C-NMR and were screened for their in vitro growth inhibiting activity against different strains of bacteria and withal the plant-growth regulating effects were examined. From the biological activity results, we found that the most compounds showed low activities.*

Keywords: 2-substituted-5-[4-(4-X-phenylsulfonyl)phenyl]-1,3,4-oxadiazoles, plant-growth regulating effect, antibacterial activity

Among different heterocyclic systems five-member heterocycles represent a class of compounds of biological significance. In fact, azoles occupy a unique place in the realm of natural and synthetic organic chemistry. These compounds have intrinsic biological activities and constitute the structural feature of many bioactive compounds. 1,3,4-Oxadiazoles exhibit a broad spectrum of biological activities such as antimicrobial, antiviral, anti-inflammatory [1-6] and their synthesis and transformations have been received particular interest for a long time. The 1,3,4-oxadiazoles are also known to have plant growth regulating effects, without citotoxicity [7-9].

To discover new 1,3,4-oxadiazole derivatives which may possess antimicrobial and plant growth regulating effects, we report here the synthesis of some derivatives of the title structures for evaluation of their biological activity.

In the present work, 4-(4-X-benzensulfonyl) benzoic acid hydrazides **1(a-c)**, X=H, Cl, Br [10] were used as the key intermediate for further synthesis. Nucleophilic adition of hydrazides **1(a-c)** to different isothiocyanate led to N^{1}-[4-(4-X-phenylsulfonyl)benzoyl]-N^{4}-R-thiosemi-carbazide **2(a-c)** [11-14]. The reaction of acylthiosemicarbazides with mercury acetate in dimethylsulfoxide and with ethylchloroacetate in presence of anhydrous sodium acetate and ethanol at reflux, afforded 2-R-amino-5-[4-(4-X-phenylsulfonyl)phenyl]-1,3,4-oxadiazoles **3**, **4, 5, 6** [15, 16], by ciclodehydrosulphuration reaction.

When hydrazide **1b** was treated with carbon disulfide and potassium hydroxide in ethanolic medium, 5-[4-(4-chlorophenylsulfonyl)phenyl]-1,3,4-oxadiazole-2-thiol **7** was obtained [17]. Conversion of **7** into **8** or **9** derivatives was achieved by reaction with secondary cyclic amines (named piperidine or morpholine) in presence of H_2O_2 (aminolysis reaction) and when **7** was treated with dimethylsulfate in alkaline medium, the S-methyl derivative **10** was obtained.

Reaction of hydrazide **1a** with chloroacetic acid under reflux in presence of $POCl_3$ gave derivative **11** by dehydrating ring closure (scheme 1)

Experimental part

The melting points were determined with Boetius apparatus and are uncorrected. The IR spectra were recorded on a FTS-135 BIO-RAD or Vertex 70 Brucker apparatus in KBr pellets (4000-400 cm^{-1} range). The NMR spectra were registered on a VARIAN GEMINI 300 BB apparatus working at 300 MHz for ^{1}H and at 75 MHz for ^{13}C and using TMS as internal standard.

Chemistry

The detailed chemistry and the synthetic parts of the 2,5-disubstituted 1,3,4-oxadiazoles **3, 4, 5(a-c), 6(a-c)** have been reported recently and discussed elsewhere [15, 16].

Preparation of 1-(5-[4-(4-chlorophenylsulfonyl)phenyl]-1,3,4-oxadiazol-2-yl)piperidine **(8)**

To a solution of 5-[4-(4-chlorophenylsulfonyl)phenyl]-1,3,4-oxadiazole-2-thiol **(7)** (0.001 mol) in 10 mL piperidine, 3 mL of hydrogen peroxide 30% were added drop wise during stirring. The reaction mixture was further stirred for 3h at room temperature, to give a yellowish precipitate **(8)**, which was filtered, washed with water and recrystallized from chloroform : petroleum ether 1:1 (v:v)

73,2% yield; m.p.: 114-116°C; Anal. Calc. (%) for $C_{19}H_{18}ClN_3O_3S$ (403.88 g/mol): C-56.50; H-4.49; N-10.40; Found: C-56.58; H-4.43; N-10.47

IR (KBr, cm^{-1}): 3087m, 2936m , 2852m, 1581i, 1572s, 1325i, 1287i, 1159fi, 1012i, 1070i, 766fi

^{1}H-NMR ($CDCl_3$, δ, ppm, *J*, Hz): 8.06 (d; 8.9; 2H; H-7,11); 8.11 (d; 8.9; 2H; H-8,10); 7.91 (d; 8.7; 2H; H-13,17); 7.52 (d, 8.7; 2H; H-14,16); 2.77 (t; 5.5; 4H; H-18,22); 1.58 (qv; 5.5; 2H; H-19,21); 1.39 (m; 1H; H-20)

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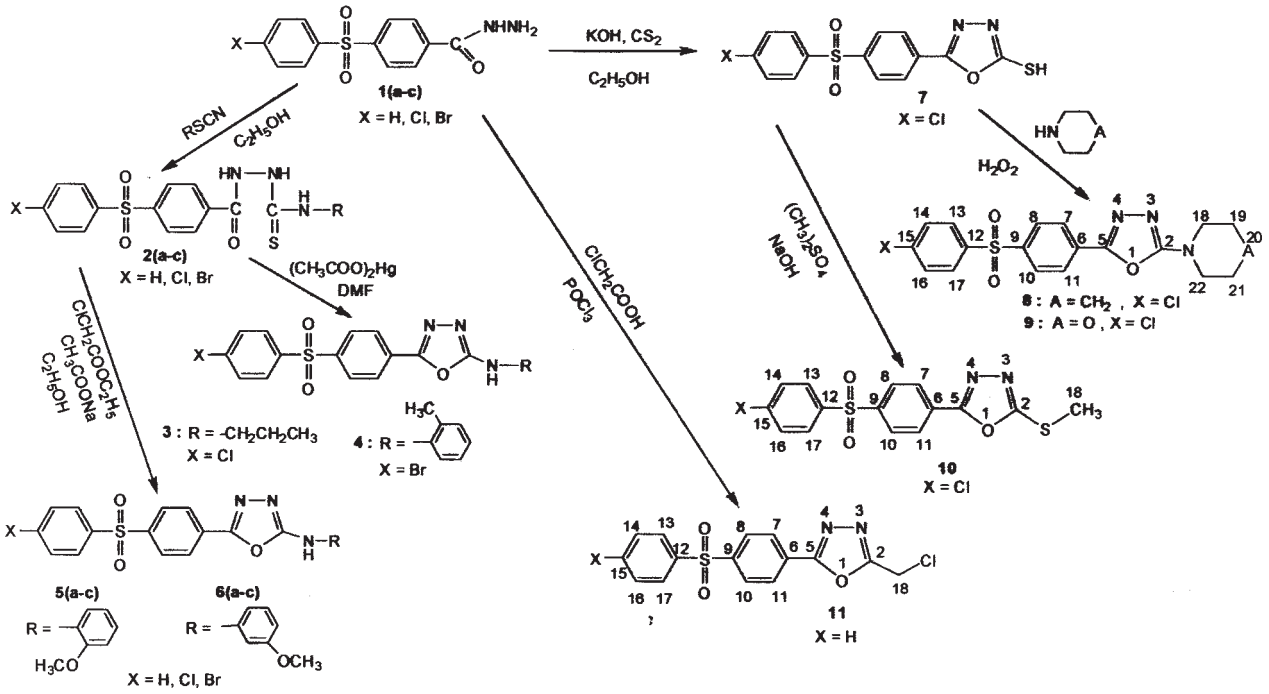


Scheme 1

^{13}C-NMR ($CDCl_3$, δ, ppm): 166.20 (C-2); 164.35 (C-5); 127.85 (C-6); 128.45 (C-7,11); 127.31 (C-8,10); 144.12 (C-9); 140.37 (C-12); 129.43 (C-13,17); 130.02 (C-14,16); 138.95 (C-15); 46.94 (C-18,22); 25.63 (C-19,21); 24.76 (C-20)

Preparation of 4-(5-[4-(4-chlorophenylsulfonyl)phenyl]-1,3,4-oxadiazol-2-yl)morpholine **(9)**

To a solution of 5-[4-(4-chlorophenylsulfonyl)phenyl]-1,3,4-oxadiazole-2-thiol **(7)** (0.001 mol) in 10 mL morpholine, 3 mL of hydrogen peroxide were added drop wise during stirring. The reaction mixture was further stirred for 6h at room temperature, to give a yellowish precipitate **(9)**, which was filtered, washed with water and recrystallized from chloroform:petroleum ether 1:1 (v:v)

76.5% yield; m.p.:157-158°C; Anal. Calc. (%) for $C_{18}H_{16}ClN_3O_4S$ (405.85 g/mol): C-53.27; H-3.97; N-10.35; Found: C-53.33; H-3.93; N-10.29

IR (KBr, cm^{-1}): 3091m, 2960m , 2861m, 1580i, 1550s, 1325fi, 1287i, 1159fi, 1012i, 1070i, 766fi

^{1}H-NMR ($CDCl_3$, δ, ppm, *J*, Hz): 8.05 (d; 8.7; 2H; H-7,11); 8.16 (d; 2H; 8.7; H-8,10); 7.89 (d; 8.7; 2H; H-13.17); 7.50 (d; 8.7; 2H; H-14.16); 3.73 (t; 5.0; 4H; H-19,21); 3.29 (t; 5.0; 4H; H-18,22)

^{13}C-NMR ($CDCl_3$, δ, ppm): 165.12 (C-2); 164.39 (C-5); 127.87 (C-6); 128.40 (C-7,11); 127.65 (C-8,10); 144.02 (C-9); 140.47 (C-12); 129.24 (C-13,17); 129.81 (C-14.16); 139.20 (C-15); 55.92 (C-18.22); 67.44 (C-19.21)

Preparation of 5-[4-(4-chlorophenylsulfonyl)phenyl]-2-(methylthio)-1,3,4-oxadiazole **(10)**

Dimethyl sulfate (0.0011 mol) was added drop wise to a solution of 5-[4-(4-chloro-phenylsulfonyl)phenyl]-1,3,4-oxadiazole-2-thiol **(7b)** (0.0011 mol) in aqueous NaOH (1M, 2.4 mL) with stirring, at room temperature for 6h. The obtained yellow precipitate was filtered, washed with water and recrystallized from ethanol to give compound **(10)**.

50.58% yield; m.p.: 181-182°C; Anal. Calc. (%) for: $C_{15}H_{11}ClN_2O_3S_2$ (366.84 g/mol) C-49.11; H-3.02; N-7.64; Found: C-49.19; H-2.97; N-7.71

IR (KBr, cm^{-1}): 3095m, 2975s, 2933m, 2875s, 1572i, 1467fi, 1325fi, 1285i, 1157fi, 1069i, 1009i, 763fi

^{1}H-NMR ($CDCl_3$, δ, ppm, *J*, Hz): 8.11 (d; 8.6; 2H; H-7,11); 8.22 (d; 8.6; 2H; H-8,10); 7.98 (d; 8.7; 2H; H-13,17); 7.56 (d; 8.7; 2H; H-14,16); 2.86 (s; 3H; H-18)

^{13}C-NMR ($CDCl_3$, δ, ppm): 166.42 (C-2); 164.17 (C-5); 129.81 (C-6); 127.87 (C-7,11); 127.40 (C-8,10); 143.69 (C-9); 140.44 (C-12); 128.36 (C-13,17); 129.25 (C-14.16); 139.24 (C-15); 14.60 (C-18)

Preparation of (2-chloromethyl)-5-[(4-phenylsulfonyl) phenyl]-1,3,4-oxadiazole **(11)**

To a solution of 4-(phenylsulfonyl)benzohydrazide **(1a)** (0.001 mol) in 2 mL $POCl_3$, 0.001 mol chloroacetic acid was added and the reaction mixture was refluxed for 7h. The excess $POCl_3$ was evaporated under vacuum; the residue was treated with water-ice and neutralized with diluted NaOH. The resulting solid was filtered and washed with water.

66,5% yield; m.p.:107-109°C; Anal. Calc. (%) for $C_{15}H_{11}ClN_2O_3S$ (334.77 g/mol): C-53.82; H-3.31; N-8.37; Found: C-53.87; H-3.26; N-8.46

IR (KBr, cm^{-1}): 3087m, 3060m, 2930m , 2875m, 1570i, 1545m, 1478m, 1320fi, 1285i, 1160fi, 1089i, 1013m,765fi

^{1}H-NMR (DMSO-d_6, δ, ppm, *J*, Hz): 8.09 (d; 8.5; 2H; H-7,11); 8.14 (d; 2H; 8.5; H-8,10); 7.95 (dd; 7.5; 1.5; 2H; H-13,17); 7.54-7.65 (m; 3H; H-14,15,16); 4.75 (s; 2H; H-18)

^{13}C-NMR (DMSO-d_6, δ, ppm): 163.75 (C-2); 159.86 (C-5); 124.75 (C-6); 128.26 (C-7,11); 127.55 (C-8, 10); 141.92 (C-9); 139.95 (C-12); 129.50 (C-13,17); 128.90 (C-14,16); 131.61 (C-15); 33.15 (C-18)

Biology

The effects of some of the 1,3,4-oxadiazole compounds on root growth of wheat were determined according to Constantinescu bioassay–*Triticum* test [18, 19]. The method consists in the study of the influence of substances at various dilutions on the root elongation and mitotic film. The solutions to be tested were placed in Petri dishes having a diameter of 10 cm and then the wheat caryopses with the main root of 1 cm were introduced. The dishes

were covered with their lids and then the caryopses were left in contact with the solutions for 5 days. In parallel, a control sample was prepared, in which the test solutions were replaced by distilled water. Root elongation was evaluated at the same time for 5 days. Observations were made as to the morphological changes as well as to the aspect and length of main radicles. All the compounds were tested at 1; 0.5; 0.066 mM concentrations. The data represent the average values from **2** independent experiments and results were processed statistically with t-Student test.

For the microscopic study, after 24 h, the embryonic roots of two caryopses from each Petri dish were sectioned at a distance of 5 mm from the tip and were stained (with slight heating) with diluted acetic orceine, a dye with great affinity for chromatin in an acid medium (the acid *p*H is necessary for the hydrolysis of the chromatin which will be stained in red). The stained sections were microscopically examined by LaboPhot II Nikon microscope (ocular 10x, object-glass 100x) by immersion in cedar oil.

The various 1,3,4-oxadiazole compounds were tested for their in vitro antibacterial activity against the Gram-positive: *Enterococcus faecalis* ATCC 19433; *Staphylococcus aureus* ATCC 12600; *Staphylococcus epidermidis* ATCC 14990; *Bacillus subtilis* ATCC 6633 and the Gram-negative bacteria: *Acinetobacter baumannii* ATCC 19606; *Citrobacter freundii* ATCC 8090; *Pseudomonas aeruginosa* ATCC 9027 using the paper disc diffusion method [20] (for the qualitative determination) and the serial dilutions in liquid broth method [21] for determination of MIC. Chloramphenicol was used as control drug.

For the qualitative determination, suspensions in sterile peptone water from 24 h cultures of microorganisms were adjusted to 0.5 McFarland. Muller-Hinton Petri dishes of 90 mm were inoculated using these suspensions. Paper disks (6 mm in diameter) containing 10 μL of the substance to be tested (at a concentration of 2048 μg/mL in DMSO) were placed in a circular pattern in each inoculated plate. Incubation of the plates was done at 37°C for 18-24 h. Reading of the results was done by measuring the diameters of the inhibition zones generated by the tested substances using a ruler.

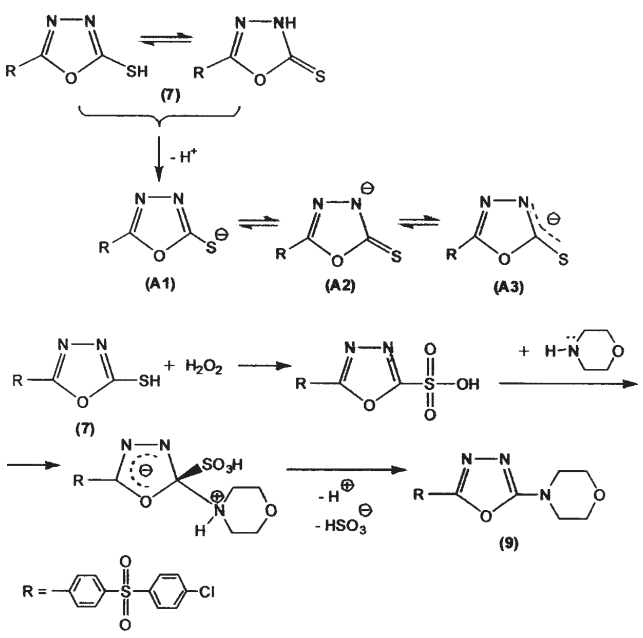
For the determination of MIC the materials used were 96-well plates, suspensions of microorganism (0.5 McFarland), Muller-Hinton broth (Merck), and solutions of the substances to be tested (2048 μg/mL in DMSO). The following concentrations of the substances to be tested were obtained in the 96-well plates: 1024; 512; 256; 128; 64; 32; 16; 8; 4; 2 μg/mL. After incubation at 37°C for 18-24 h , the MIC for each tested substance was determined by macroscopic observation of bacterial growth. It corresponds to the well with the lowest concentration of the tested substance where bacterial growth was clearly inhibited.

Results and discussions

Chemistry

1,3,4-Oxadiazole **(7)** can exist in the negative polarization state as three equilibrium forms with a negative charge localized on the thione sulfur (A1), or on the internal nitrogen N-3 (A2), or delocalized on the thioamido group (A3) (scheme 2).

Aminolysis reaction of **(7)** is a nucleophilic substitution which is taking place first by oxidation of thiol group at the appropriate sulfonic acid derivative, which is attacked by the secondary amine. In the second step, the formed



Scheme 2

intermediate is stabilized by the diarylsulfonyl group from the 5-position of 1,3,4-oxadiazole ring.

The IR spectra of the products **(8), (9)** contains absorption bands at 2960-2852 cm^{-1} which are attributed to symmetric and asymmetric stretching bands of $-CH_2-$ group from the piperidinyl/morpholinyl moiety. The absence of the absorption bands at 2600-2500 cm^{-1} (μ_{SH}) [17] in the spectra of **(8), (9)** provides evidence for the elimination of thiol group during the reaction with secondary amines and H_2O_2.

In the ^{1}H-NMR spectra of these compounds the signals belonging to methylenic protons of the amino moiety were recorded at 3.77-3.29 ppm as triplets and 2.77-1.39 ppm, respectively as multiplet. In the ^{13}C-NMR spectra, new signals at 67.44-24.76 ppm which are attributed to methylenic carbons from the amino group were seen and these confirm the bonding of 1,3,4-oxadiazole with amino nitrogen [22].

The characteristic C=N stretching band (1581-1570 cm^{-1}), a medium band at 1089-1069 cm^{-1} (C-O-C absorption band) and N-N stretching band around 1010 cm^{-1}were identified in each IR spectra of newly synthesized compounds and indicates the presence of 1,3,4-oxadiazole ring. All the compounds have strong absorption bands at 1325 and 1160 cm^{-1} respectively, which are attributed to asymmetric and symmetric vibrations of SO_2 group and medium band in range 3095-3087 cm^{-1} which is evidence of the presence of aromatic C-H bonds.

The presence of the alkyl group ($-CH_3$ and $-CH_2-$) in **(10)** and **(11)** respectively can be confirmed by observing absorption bands at 2936-2930 cm^{-1} and 2875-2852 cm^{-1}.

All the NMR spectra of newly compounds exhibit two characteristic sub-spectra, one for diarylsulfone moiety and another for the remaining functional side-chain. In the ^{13}C-NMR spectra, the presence of the 2,5-disubstituted 1,3,4-oxadiazole unit was supported by the appearance of two quaternary signals (C-2; C-5) in range 163.75-166.20 ppm and 159.86-164.39 ppm respectively, low values in comparison with **(7)** [17], probably because of absence of influence of –SH/=S group. The chemical shifts of the $-\underline{C}H_3$ in **(10)** and $-\underline{C}H_2-$ in **(11)** appear at δ = 14.60 ppm and 33.15 ppm respectively, which are approximately similar with the value reported in the literature [23, 24].

Table 1
PLANT GROWTH REGULATING ACTIVITIES OF TESTED COMPOUNDS (THE LENGTH OF ROOT IS MEAN VALUE OF MEASUREMENTS MADE IN DAY 5 OF TREATMENT)

Compd.	First assay				Second assay			
	Conc. (mM)	Root(±SD*) (mm)	p-value	Effect (%)	Conc. (mM)	Root(±SD*) (mm)	p-value	Effect (%)
Control		87.5±4.28				96.3±5.14		
3	1	38.0±4.66	<0.001	+63.87	1	40.5±1.58	<0.001	+64.65
	0.5	87.1±9.14	NS	+3.51	0.5	92.4±2.06	NS	+4.51
	0.066	90.0±4.36	NS	-3.22	0.066	99.7±1.70	NS	-3.94
4	1	44.0±2.66	<0.001	+56.12	1	47.3±1.66	<0.001	+56.76
	0.5	70.4±2.52	<0.01	+22.06	0.5	73.9±1.93	<0.001	+25.95
	0.066	80.5±3.30	<0.01	+9.03	0.066	88.6±0.94	<0.001	+8.92
5a	1	56.8±2.14	0.005	+39.61	1	65.3±3.04	<0.001	+35.92
	0.5	57.6±1.92	0.005	+38.58	0.5	67.5±1.92	<0.001	+33.37
	0.066	59.5±1.73	0.005	+36.13	0.066	69.2±2.50	<0.001	+31.40
5b	1	54.8±3.02	0.005	+42.19	1	57.6±1.75	<0.0001	+44.84
	0.5	70.8±6.23	<0.01	+21.54	0.5	78.3±2.48	<0.0001	+20.85
	0.066	89.2±1.43	NS	-21.9	0.066	111.6±2.83	0.01	-17.72
5c	1	48.0±3.62	<0.001	+50.96	1	57.0±2.06	<0.0001	+45.53
	0.5	59.1±1.12	0.005	+36.45	0.5	68.3±1.04	<0.001	+32.44
	0.066	67.0±1.36	0.01	+26.45	0.066	75.6±1.16	<0.0001	+23.98
6a	1	86.0±0.62	NS	+1.93	1	94.2±2.07	NS	+2.43
	0.5	89.4±2.50	NS	-2.45	0.5	98.1±3.20	NS	-2.08
	0.066	93.3±2.20	NS	-7.48	0.066	101.0±0.20	0.01	-5.44
6b	1	63.6±6.09	0.02	+30.83	1	67.4±3.27	0.02	+33.48
	0.5	92.2±4.30	NS	-6.06	0.5	97.2±2.72	NS	-1.04
	0.066	100.4±5.28	<0.02	-16.64	0.066	105.4±3.56	0.01	-10.54
6c	1	53.1±2.01	0.005	+44.38	1	62.1±1.11	0.005	+39.62
	0.5	80.4±0.34	NS	+9.16	0.5	89.7±1.32	NS	+7.65
	0.066	96.2±1.24	NS	-11.22	0.066	104.3±0.35	0.01	-9.26
8	1	11.8±1.76	<0.0001	+97.67	1	10.5±0.71	<0.0001	+99.42
	0.5	53.5±2.39	0.005	+43.87	0.5	52.9±3.51	<0.0001	+50.28
	0.066	97.9±2.24	<0.01	-13.42	0.066	106.7±2.23	<0.001	-12.05
9	1	10.4±0.84	<0.0001	+99.48	1	10.3±0.48	<0.0001	+99.65
	0.5	23.8±3.15	<0.0001	+82.19	0.5	30.0±0.94	<0.0001	+76.82
	0.066	70.1±9.52	<0.01	+22.45	0.066	75.8±1.62	<0.001	+23.75
10	1	43.0±3.97	<0.001	+57.42	1	44.1±1.66	<0.0001	+60.48
	0.5	85.6±1.17	NS	-2.45	0.5	93.1±1.85	<0.01	-3.70
	0.066	98.1±2.98	<0.01	-13.67	0.066	105.9±1.37	<0.01	-11.12
11	1	11.8±1.75	<0.0001	+97.67	1	10.5±0.52	<0.0001	+99.42
	0.5	53.9±4.02	0.005	+43.35	0.5	55.3±1.88	<0.0001	+47.50
	0.066	107.9±9.65	0.003	-26.32	0.066	114.9±2.99	<0.0001	-21.55

* SD = standard deviation
NS = the two means are not significantly different
p-value = significance level (statistical significance in two-population (independent) t-Test)
positive value = inhibiting effect on wheat root growth
negative value = stimulating effect on wheat root growth

Biological activity

The influence of the compounds **(3)-(6)** and **(8)-(11)** on the growth of wheat is presented in Table 1. After treating with solutions of 1; 0.5; 0.066 mM concentrations of tested compounds for 5 days , from the difference in length between the main root of caryopses treated with the title compounds and those treated with distilled water (latest day), the plant growth regulating activities have been determined with the following formula:

$$effect\ (\%) = 100 - \frac{the\ length\ of\ sample's\ radicle\ (mm) - 10\ mm}{the\ length\ of\ reference's\ radicle\ (mm) - 10\ mm} x\ 100,$$

where *10 mm* represents initial length of main root. A positive result implies an inhibition, whereas a negative result represents a growth increase [25].

All derivatives at 1mM inhibited wheat root growth (for **8,9,11**–with more than 90%). Inhibitory activity declined with the decrease of the concentration applied, at 0.066 mM, its action were found to be easily stimulative.

In general, 2-R-amino-1,3,4-oxadiazoles were less active than remainder tested compounds. The better effect have **5b** and **11** (stimulating effect ~ 20%), probably because of the presence of the chlorine containing moieties in their structure (fig. 1).

The microscopic studies showed mitodepressive and mitostatic effects for 1mM and 0.5 mM concentrations: the cellular size is changed, shape of the cell is irregular, the cytoplasm is separated from the cell membrane and nuclei with hypertrophied nucleolus were observated.

The investigation of antibacterial screening data revealed that all the tested compounds showed low bacterial inhibition (table 2).

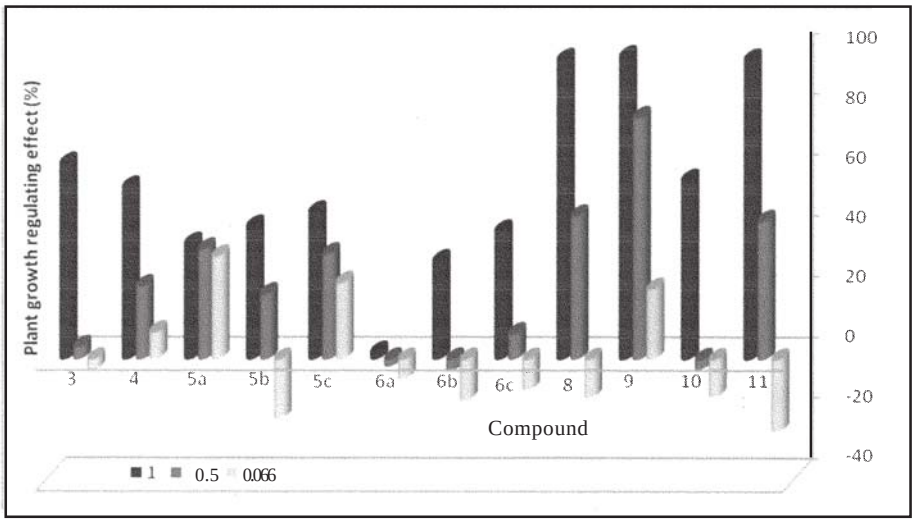


Fig. 1. Plant growth regulating effects of the tested compounds
(effect is the mean value of obtained dates in first and second assay)

Table 2
ANTIBACTERIAL ACTIVITIES OF TESTED COMPOUNDS AS MIC VALUES (μg/mL)

Compd.	X	Gram negative bacteria[a]			Gram positive bacteria[b]			
		Ab	*Cf*	*Pa*	*Ef*	*Sa*	*Se*	*Bs*
3	Cl	>1024	512	-	>1024	1024	-	-
4	Br	>1024	512	-	>1024	1024	-	-
5a	H	>1024	>1024	-	1024	>1024	-	-
5b	Cl	1024	256	512	1024	256	1024	>1024
5c	Br	NT	>1024	NT	NT	>1024	1024	>1024
6a	H	1024	512	>1024	512	1024	1024	>1024
6b	Cl	256	128	>1024	-	256	-	>1024
6c	Br	>1024	>1024	>1024	-	512	-	>1024
8	Cl	1024	512	512	512	512	-	512
9	Cl	512	256	1024	512	512	-	256
10	Cl	512	>1024	1024	256	256	-	512
11	H	128	256	-	256	128	-	>1024
Control	-	**128**	**128**	**64**	**64**	**64**	**64**	**64**

Note: [a]***Ab*** *(Acinetobacter baumannii* ATCC 19606*)*; ***Cf*** *(Citrobacter freundii* ATCC 8090*)*; ***Pa*** *(Pseudomona aeruginosa* ATCC 9027*)*;
[b]***Ef*** *(Enterococcus faecalis* ATCC 19433*)*; ***Sa*** *(Staphylococcus aureus* ATCC 12600*)*; ***Se*** *(Staphylococcu epidermidis* ATCC 14990*)*; ***Bs*** *(Bacillus subtilis* ATCC 6633)
Control = chloramphenicol
- = indicates bacteria are resistant to the compounds
NT = not tested

In all the derivatives the 4-(4-X-phenylsulfonyl)phenyl moiety was not very important factor for their antibacterial activity, since both compounds with X=H or X=halogen showed similar activity. *S. epidermidis* bacteria (ATCC 14990) are resistant to all the tested derivatives. Compounds **(5a), (6b), (9), (11)** showed good inhibitory action against *C. freundii* (ATCC 8090) and moderate against *S.aureus* (ATCC 12600) species, compared to that of standard, probably through their structure contains active groups attached in 2-position of the 1,3,4-oxadiazole ring (-NHR, morpholinyl, $-CH_2Cl$). The presence of $-SCH_3$ and $-SCH_2Cl$ groups in the 2 position of oxadiazole ring caused increase in activity against most of tested strains.

Conclusions

In this paper we have discussed the biological activities (plant growth regulating effects and antibacterial activity) of a library of twelve 5-[4-(4X-phenylsulfonyl)phenyl]-1,3,4-oxadiazole various substituted in 2-position. The structures of new compounds were determined by elemental analysis and spectral data.

Investigations on the structure-activity relationships showed that the wheat growth regulating activity depends on 1,3,4-oxadiazole's substituent from 2-position, as well as on the presence of the halogen atom in the structure of the diarylsulfone moiety from 5-position. Microscopic study demonstrated a mitosis inhibition activity at high concentration and low stimulatory activity at 0.066 mM concentration, without citotoxicity.

The antibacterial study revealed that all the tested compounds showed low activity against various strains.

References

1. ŞAHIN G., PALASKA E., EKIZOĐLU M., ÖZALP M., Il Farmaco, **57**, 7, 2002, p.539
2. DE SONZA A.O., PRADO M.A.F., ALVES R.B., SILVA C.L., Pharmazie, **60**, 5, 2005, p. 396
3. FARGHALY A.R., EL-KASHEF H., Arkivoc, **xi**, 2006, p. 76
4. RAVINDRA K.C., VAGDEVI H.M., VAIDA V.P., PADMASHALI B., Indian J. Chem., **45B,** 11, 2006, p. 2506
5. HOLLA B.S., GONSALVES R., SHENOY S., Eur. J. Med. Chem., **35**, 2000, p.267

6. TIPERCIUC B., PARVU A., PALAGE M., ONIGA O., Farmacia, **47**, 1999, p.77
7. CHEN H.S., LI Z.M., WANG Z.W., Hecheng Huaxue, **7**, 1999, p.164 (Chem. Abstr. 2000, 132, 93247)
8. REDDY K.V., SABITHA G., RAO A.V.S., Indian J. Chem., **37B**, 1998, p. 697
9. ALMAJAN G.L., BARBUCEANU S.-F., SARAMET I., DINU M., DOICIN C.V., DRAGHICI C., Rev. Chim. (Bucuresti), **59**, nr. 4, 2008, p. 395
10. MAVRODIN A., ZOTTA V., STOENESCU V.M., OTELEANU D., Pharm. Zentr. Deutsch
95, 1956, p.353
11. SARAMET I., ALMAJAN G.L., BARBUCEANU S.-F., DRAGHICI C., BANCIU M.D., Rev. Roum. Chim., **50**, 1-2, 2005, p.19
12. SARAMET I., DRAGHICI C., BANCIU M.D., Rev. Roum. Chim., **41**, 5-6, 1995, p.465
13. BARBUCEANU S.-F., ALMAJAN G.L., SARAMET I., DRAGHICI B., Rev. Chim. (Bucuresti), **57**, nr. 12, 2006, p. 1253
14. BARBUCEANU S.-F., ALMAJAN G.L., SARAMET I., DRAGHICI B., Rev. Chim. (Bucuresti), **58**,no. 10, 2007, p. 945
15. ALMAJAN G.L., BARBUCEANU S.-F., SARAMET I., DRAGHICI B., Rev. Chim. (Bucuresti), **58**,nr. 2, 2007, p. 202
16. BARBUCEANU S.-F., ALMAJAN G.L., SARAMET I., DRAGHICI C., ENACHE C., Rev. Chim. (Bucuresti), **59**, nr. 3, 2008, p. 304
17. ALMAJAN G.L., BARBUCEANU S.-F., SARAMET I., DRAGHICI C., Rev. Chim. (Bucuresti), **56**, nr. 11, 2005, p. 1182
18. CONSTANTINESCU D.G., RETEZEANU M., OŢELEANU R., CONSTANTINESCU M., C.R. Acad. Sci. Paris, **265**, 1966, **p.** 2525
19. CONSTANTINESCU D.G., RETEZEANU M., OŢELEANU R., CONSTANTINESCU M., Die Pharmazie, **18**, 1963, p. 699
20. BARRY A., Procedures and theoretical considerations for testing antimicrobial agents in agar media, in: Lorian (Ed.), Antibiotics in Laboratory Medicine, fifth ed. Williams and Wilkins, Baltimore, 1991
21. NCCLS, National Committee for Clinical Laboratory Standard: Methods for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria; Approved guideline, Document M45-A, vol. 26 issue no. 19, Willanova, PA., USA, 1999
22. KATRITZKY A.R., AKHMEDOV Y.H., HALL D., Magn. Reson. Chem., **43,** 8, 2005, p.673
23. ALMASIRAD A., VOUSOOGHI N., TABATABAI S.A., KEBRIAEEZADEH A., SHAFIEE A., Acta Chim. Slov., **54,** 2007, p.317
24. KISS-SZIKSZAI A., PATONAY T., JEKÖ J., Arkivoc, **ii**, 2001, p.40
25. ANCUCEANU R., ISTUDOR I., DINU M., CODREANU M.V., Farmacia, **LIII**, nr. 4, 2005, p.28

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