Synthesis and Biological Evaluation of Various New Substituted 1,3,4-oxadiazole-2-thiols

GABRIELA LAURA ALMAJAN[1]*, STEFANIA FELICIA BARBUCEANU[1], IOANA SARAMET[1], MIHAELA DINU[2], CRISTIAN VASILE DOICIN[3],CONSTANTIN DRAGHICI[4]

[1] Organic Chemistry Department, Faculty of Pharmacy, Traian Vuia Street 6, 020956, Bucharest, Romania

[2] Pharmaceutical Botany Department, Faculty of Pharmacy, Traian Vuia Street 6, 020956, Bucharest, Romania

[3] Manufacturing Engineering Department, Faculty of Engineering and Management of Technological Systems, Splaiul Independentei 313, Bucharest, Romania

[4] C.D.Nenitescu Institute of Organic Chemistry, Romanian Academy, 202B Splaiul Independentei, 060023, Bucharest, Romania

5-[4-(4X-phenylsulfonyl)phenyl]-1,3,4-oxadiazole-2-thiols, X=H, Cl, Br, reacted with ethyl chloroacetate to give S-alkylated compounds. Aminomethylation of the thione form of oxadiazoles yielded N(3)-derivatives. All the products have been characterized by elemental analysis, IR, ^{1}H-NMR and ^{13}C-NMR. The plant-growth regulating effects of the title compounds were examined. From the biological activity results, we found that most compounds showed weak stimulatory activities at low concentrations.

Keywords: 1,3,4-oxadiazole-2-thiol, S-alkylated derivatives, Mannich bases, plant-growth regulating effect

A diversity of biological effects is associated with 1,3,4-oxadiazole-2-thiols and their derivatives. These include significant antimicrobial, anti-inflammatory and antiviral activities [1-8]. At the same time, they are important intermediates in organic synthesis, because the N(3) and exocyclic sulphur are nucleophilic and are readily attacked by electrophilic agents [9].

The 1,3,4-oxadiazole-2-thiols are also known to have plant growth regulating activity [10,11]. Some of these are found to be useful as herbicides such as phenoxyalkyl [11] and aryloxymethyl [12] analogues of 1,3,4-oxadiazole-2-thiols.

In continuation of our studies of diphenylsulfones chemistry, we report herein on the reactions of 5-[4-(4X-phenylsulfonyl)phenyl]-1,3,4-oxadiazole-2-thiols **1(a-c)** with some S or N-electrophiles and how the new derivatives can eventually modify the biological activity of the parent compounds.

Upon treatment of 1,3,4-oxadiazole-2-thiols **1(a-c)** with ethyl chloroacetate at room temperature in sodium ethoxide as base, S-alkyl derivatives **2(a-c)** were obtained. Compounds **1(a-c)** were allowed to undergo the Mannich reaction with dipropylamine and formaldehyde 37% in absolute ethanol to achieve the formation of compounds **3(a-c)** (scheme 1).

The title compounds have been investigated for their biological activities in regulating the growth of wheat using the phytobiological method [13,14], known as the *Triticum* test.

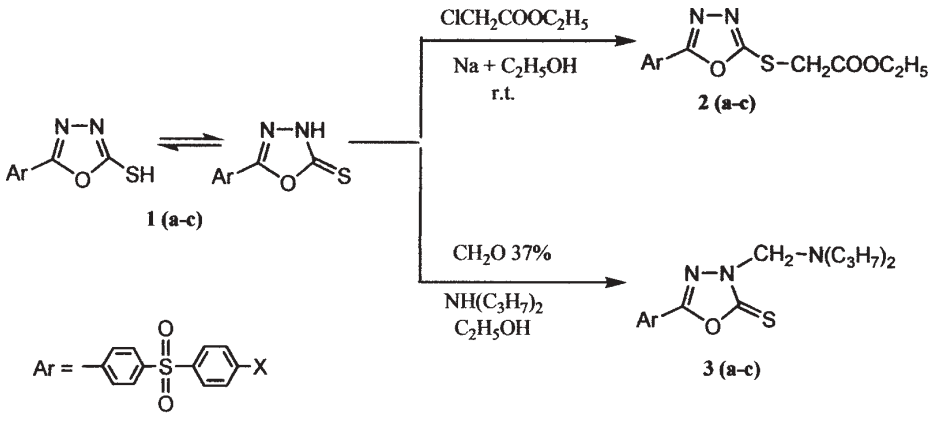
Experimental part

The melting points were determined with Boetius apparatus and are uncorrected. The IR spectra were recorded on a FTS-135 BIO-RAD apparatus in KBr pellets. 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.

The starting compound **1(a-c)** was synthesized by the reaction of 4-(4-X-benzenesulfonyl)-benzoic acid hydrazides (X=H,Cl,Br) with carbon disulphide and potassium hydroxide in ethanolic medium [15].

*a) General procedure for preparation of S-alkylated derivatives **2(a-c)***

Reaction of **1(a-c)** with ethylchloroacetate was performed after the general method of Ashani [16]: to a solution of 0.11g (5 mili-gram atoms) metallic sodium in 10 mL anhydrous ethanol the solid oxadiazoles **1(a-c)** (5 mmoles) were added while stirring. The reaction mixtures were stirred at room temperature for 2h. Ethyl



Scheme 1

* email: laura.almajan@gmail.com; Tel.: 021-3180744/234

chloroacetate (5 mmoles) was added and the reaction mixtures were stirred at room temperature for 4 h. The formed solids were filtered, washed with water and recrystallized from ethanol.

ethyl 2-(5-(4-(phenylsulfonyl)phenyl)-1,3,4-oxadiazol-2-ylthio)acetate (2a)

77% yield; m.p.:124-126°C; Anal. Calc. (%) for $C_{18}H_{16}N_2O_5S_2$ (404.46 g/mol): C-53.45; H-3.99; N-6.93; S-15.86. Found: C-53.51; H-3.93; N-7.01; S-15.78

IR (KBr, cm^{-1}): 3099, 2983, 2933, 2875, 1738, 1552, 1472, 1445, 1314, 1156, 1069, 1000

^{1}H-RMN and ^{13}C-RMN (table 1)

ethyl 2-(5-(4-(4-chlorophenylsulfonyl)phenyl)-1,3,4-oxadiazol-2-ylthio)acetate (2b)

74% yield; m.p.:166-167°C; Anal. Calc. (%) for $C_{18}H_{15}ClN_2O_5S_2$ (438.91 g/mol): C-49.26; H-3.44; N-6.38; S-14.61. Found: C-49.32; H-3.38; N-6.47; S-14.55

IR (KBr, cm^{-1}): 3091, 2985, 2933, 2875, 1739, 1580, 1554, 1472, 1317, 1288, 1159, 1069, 1010, 769

^{1}H-RMN and ^{13}C-RMN (table 1)

ethyl 2-(5-(4-(4-bromophenylsulfonyl)phenyl)-1,3,4-oxadiazol-2-ylthio)acetate (2c)

86% yield; m.p.:163-164°C; Anal. Calc. (%) for $C_{18}H_{15}BrN_2O_5S_2$ (483.36 g/mol): C-44.73; H-3.13; N-5.80; S-13.27. Found: C-44.79; H-3.07; N-5.88; S-13.18

IR (KBr, cm^{-1}): 3089, 2985, 2935, 2875, 1739, 1572, 1554, 1471, 1317, 1288, 1156, 1067, 1007, 571

^{1}H-RMN and ^{13}C-RMN see Table 1

b) General procedure for preparation of Mannich bases ***3(a-c)*** [17]

A mixture of 1,3,4-oxadiazole **1(a-c)** (0.01 mole) and dipropylamine (0.01 mole) was refluxed in ethanol (50 mL) with 37% formaldehyde (0.02 mole) for 3 h. The resulting solid was filtered, dried and recrystalised from absolute ethanol.

3-((dipropylamino)methyl)-5-(4-(phenylsulfonyl)phenyl)-1,3,4-oxadiazole-2(3H)-thione (3a)

58% yield; m.p.: 145-147°C; Anal. Calc. (%) for $C_{21}H_{25}N_3O_3S_2$ (431.57 g/mol): C-58.44, H-5.84, N-9.74; S-14.86. Found: C-58.52, H-4.76, N-9.82; S-14.78

IR (KBr, cm^{-1}): 3089, 2935, 2853, 1592, 1480, 1438, 1321, 1291, 1157, 1248, 1223, 1009, 1086

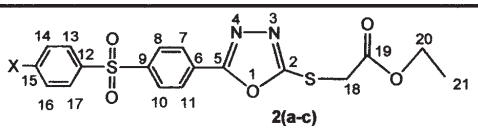
^{1}H-RMN and ^{13}C-RMN (table 1)

·5-(4-(4-chlorophenylsulfonyl)phenyl)-3-((dipropylamino)methyl)-1,3,4-oxadiazole-2(3H)-thione (3b)

53% yield; m.p.: 217-219°C; Anal. Calc (%) for $C_{21}H_{24}ClN_3O_3S_2$ (466.02 g/mol): C-54.12, H-5.19, N-9.02; S-13.76. Found: C-54.20, H-5.12, N-9.11; S-13.66

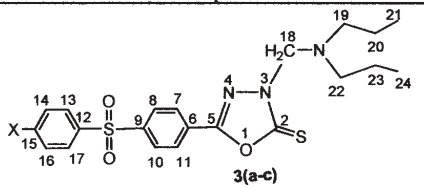
Table 1

NMR DATA OF COMPOUNDS **2(a-c), 3(a-c)**



2(a-c)

	^{1}H-NMR ($CDCl_3$, δ, ppm, *J*, Hz):	^{13}C-NMR ($CDCl_3$, δ, ppm)
2a	8.02 (d; 8.9; 2H; H-7,11); 8.13 (d; 8.9; 2H; H-8,10); 7.97 (dd; 7.1; 2.0; 2H; H-13,17); 7.61 (t; 7.1; 2H; H-14,16); 7.54 (tt; 7.1; 2.0; 1H; H-15); 4.12 (s; 2H; H-18); 4.25 (q; 7.1; 2H; H-20); 1.30 (t; 7.1; 3H; H-21)	167.86 (C-2); 164.5 (C-5) 7; 127.60 (C-6); 128.42 (C-7,11); 127.84 (C-8,10); 144.43 (C-9); 140.80 (C-12); 127.40 (C-13,17); 129.4 (C-14,16); 133.65 (C-15); 34.38 (C-18); 164.62 (C-19); 62.50 (C-20); 14.05 (C-21)
2b	8.05 (d; 8.2; 2H; H-7,11); 8.14 (d; 8.2; 2H; H-8,10); 7.91 (d; 8.2; 2H; H-13,17); 7.52 (d; 8.2; 2H; H-14,16); 4.13 (s; 2H; H-18); 4.25 (q; 7.0; 2H; H-20); 1.30 (t; 7.0; 3H; H-21)	167.15 (C-2); 164.36 (C-5); 127.85 (C-6); 128.41 (C-7,11); 127.49 (C-8,10); 143.9 (C-9); 140.50 (C-12); 129.28 (C-13,17); 129.83 (C-14,16); 139.31 (C-15); 34.38 (C-18); 164.47 (C-19); 62.50 (C-20); 14.05 (C-21)
2c	8.05 (d; 8.8; 2H; H-7,11); 8.14 (d; 8.8; 2H; H-8,10); 7.83 (d; 8.2; 2H; H-13,17); 7.68 (d; 8.2; 2H; H-14,16); 4.13 (s; 2H; H-18); 4.25 (q; 7.1; 2H; H-20); 1.30 (t; 7.1; 3H; H-21)	167.28 (C-2); 164.03 (C-5); 128.15 (C-6); 128.45 (C-7,11); 127.53 (C-8,10);) 142.80 (C-9); 139.67 (C-12); 129.36 (C-13,17); 132.86 (C-14,16); 128.50 (C-15); 34.40 (C-18); 164.25 (C-19); 62.53 (C-20); 14.08 (C-21)



3(a-c)

	^{1}H-NMR ($CDCl_3$, δ, ppm, *J*, Hz):	^{13}C-NMR ($CDCl_3$, δ, ppm)
3a	8.07 (s; 2H; H-7,11); 8.07 (s; 2H; H-8,10); 7.93 (dd; 7.5; 1.4; 2H; H-13,17); 7.56 (t, 7.5; 2H; H-14,16); 7.43 (tt; 7.5; 1.4; 1H; H-15); 5.15 (s, 2H; H-18); 2.72 (t; 7.3; 4H; H-19,22); 1.59 (sx; 7.3; 2H; H-20,23); 0.90 (t; 7.3; 2H; H-21,24)	178.53 (C-2); 157.35 (C-5); 127.38 (C-6); 128.48 (C-7,11); 127.18 (C-8,10); 144.81 (C-9); 140.65 (C-12); 127.18 (C-13,17); 129.64 (C-14,16); 133.72 (C-15); 68.65 (C-18); 54.15 (C-19,22); 21.24 (C-20,23); 11.56 (C-21,24)
3b	8.06 (s; 2H; H-7,11); 8.06 (s; 2H; H-8,10); 7.91 (d; 8.5; 2H; H-13,17); 7.51 (d, 8.5; 2H; H-14,16); 5.14 (s, 2H; H-18); 2.70 (t; 7.3; 4H; H-19,22); 1.57 (sx; 7.3; 2H; H-20,23); 0.91 (t; 7.3; 2H; H-21,24)	178.42 (C-2); 157.86 (C-5); 127.42 (C-6); 128.49 (C-7, 11); 127.22 (C-8,10); 144.52 (C-9); 140.62 (C-12); 129.37 (C-13,17); 129.88 (C-14,16); 139.62 (C-15); 68.92 (C-18); 54.27 (C-19,22); 21.20 (C-20,23); 11.52 (C-21,24)
3c	8.07 (s; 2H; H-7,11); 8.07 (s; 2H; H-8,10); 7.83 (d; 8.7; 2H; H-13,17); 7.68 (d, 8.7; 2H; H-14,16); 5.15 (s, 2H; H-18); 2.71 (t; 7.4; 4H; H-19,22); 1.58 (sx; 7.4; 2H; H-20,23); 0.91 (t; 7.4; 2H; H-21,24)	178.07 (C-2); 157.21 (C-5); 127.10 (C-6); 128.42 (C-7,11); 127.20 (C-8,10); 144.21 (C-9); 139.72 (C-12); 129.33 (C-13,17); 132.84 (C-14,16); 133.04 (C-15); 68.50 (C-18); 53.93 (C-19,22); 21.00 (C-21,23); 11.57 (C-21,24)

s-singlet; d-doublet; t-triplet; q-quartet; sx-sextet; m-multiplet

IR (KBr, cm^{-1}): 3087, 2964, 2933, 2867, 1579, 1472, 1325, 1288, 1158, 1253, 1225, 1011, 1086, 767

^{1}H-RMN and ^{13}C-RMN (table 1)

5-(4-(4-bromophenylsulfonyl)phenyl)-3-((dipropylamino)methyl)-1,3,4-oxadiazole-2(3H)-thione (3c)

69% yield; m.p.: 230-231°C; Anal. Calc. (%) for $C_{21}H_{24}BrN_3O_3S_2$ (510.47 g/mol): C-49.41, H-4.74, N-8.23; S-12.56. Found: C-49.48, H-4.68, N-8.31; S-12.45

IR (KBr, cm^{-1}): 3087, 2962, 2933, 2867, 1611, 1572, 1468, 1325, 1291, 1158, 1245, 1221, 1009, 1070, 581

^{1}H-RMN and ^{13}C-RMN (table 1)

c) Biological activity

The effects of the title compounds on root growth of wheat were determined according to the bioassay – *Triticum* test. 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 karyopses with the main root of 1 cm were introduced. The dishes were covered with their lids and then the karyopses 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 on the morphological changes as well as on the aspect and length of main radicles.

For the microscopic study, after 24 h, the embryonic roots of two karyopses from each Petri dish were sectioned at a distance of 5 mm from the tip and were stained (with slight heating) with diluted acetic orcein, a dye with great affinity for chromatin in an acid medium (the acid pH is necessary for the hydrolysis of the chromatin which will stained in red). The stained sections were microscopically examined by immersion in cedar oil.

All the compounds were tested at 1; 0.5; 0.066 mM concentrations. The data represents the average values from 2 independent experiments and results were processed statistically with t-Student test.

Results and discussions

Chemistry

According to the data from literature, the products of alkylation and aminomethylation of 1,3,4-oxadiazole-2-thiols 5-arylsubstituted were identified as S-derivatives and N-substituted derivatives, respectively [18-20].

Table 2

PLANT GROWTH REGULATION ACTIVITIES OF COMPOUNDS **1-3(a-c)** (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		
1a	1	13.5±3.53	<0.0001	-84.57	1	14.5±0.52	<0.0001	-84.94
	0.5	27.7±3.19	<0.0001	-68.34	0.5	28.5±2.36	<0.0001	-70.40
	0.066	89.2±4.43	<0.001	+1.94	0.066	101.6±3.83	<0.0001	+5.50
1b	1	10.0±0.00	<0.0001	-88.57	1	10.0±0.00	<0.0001	-89.61
	0.5	46.0±3.80	<0.001	-47.42	0.5	43.6±1.07	<0.0001	-54.72
	0.066	100.7±2.77	<0.05	+15.08	0.066	110.6±1.43	<0.0001	+14.84
1c	1	11.8±1.75	<0.0001	-87.51	1	10.5±0.52	<0.0001	-89.09
	0.5	53.9±2.32	<0.005	-38.40	0.5	55.3±1.88	<0.0001	-42.57
	0.066	107.9±4.65	<0.003	+23.31	0.066	114.9±2.99	<0.0001	+19.31
2a	1	43.0±3.79	<0.0001	-50.85	1	44.1±1.66	<0.0001	-54.20
	0.5	74.5±2.27	<0.03	-14.85	0.5	83.1±1.85	<0.01	-13.70
	0.066	96.1±3.45	<0.05	+9.82	0.066	105.9±1.37	<0.01	+9.96
2b	1	26.6±1.89	<0.0001	-69.6	1	29.3±1.49	<0.0001	-69.57
	0.5	42.1±3.17	<0.001	-51.88	0.5	46.9±2.18	<0.0001	-51.29
	0.066	97.4±2.95	<0.05	+11.31	0.066	107.7±2.60	<0.03	+11.83
2c	1	27.9±2.58	<0.001	-68.11	1	30.9±1.52	<0.0001	-67.91
	0.5	74.2±3.04	<0.03	-15.20	0.5	81.5±1.26	<0.001	-15.36
	0.066	102.2±2.05	<0.05	+16.80	0.066	111.7±1.88	<0.001	+15.99
3a	1	10.4±0.84	<0.0001	-88.11	1	10.3±0.48	<0.0001	-89.30
	0.5	23.8±1.15	<0.0001	-72.80	0.5	28.8±0.94	<0.0001	-70.09
	0.066	70.1±2.52	<0.01	-19.88	0.066	63.3±1.62	<0.0001	-34.26
3b	1	10.0±0.00	<0.0001	-88.57	1	10.0±0.00	<0.0001	-89.61
	0.5	11.0±0.66	<0.0001	-87.42	0.5	10.9±0.31	<0.0001	-88.68
	0.066	79.5±1.66	<0.01	-9.14	0.066	83.9±1.35	<0.01	-12.87
3c	1	38.3±2.12	<0.001	-55.22	1	41.7±1.56	<0.0001	-56.69
	0.5	72.9±3.77	<0.01	-16.68	0.5	79.2±1.93	<0.0001	-17.75
	0.066	81.9±5.94	<0.01	-6.40	0.066	89.2±3.30	<0.002	-7.37

* SD = standard deviation

p-value = significance level (statistical significance in two-population (independent) t-Test)

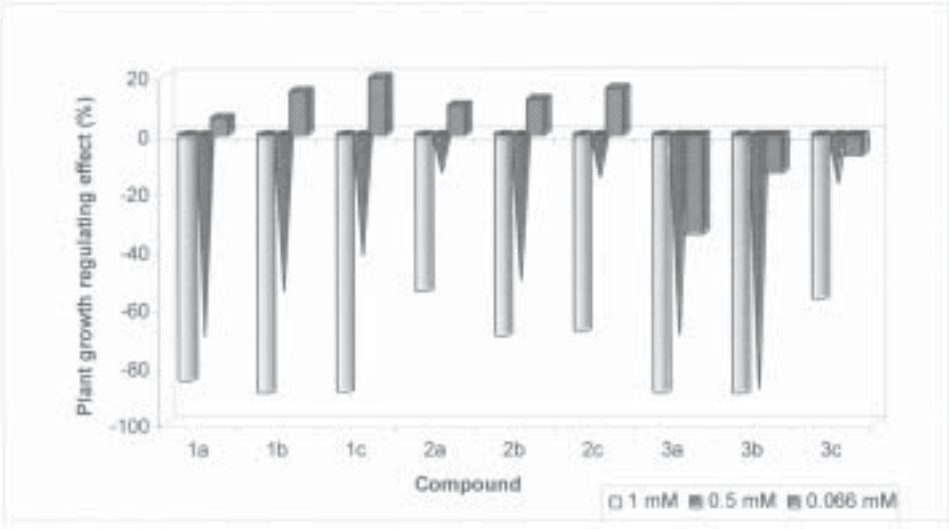


Fig. 1. Plant growth regulation activities of compunds **1-3(a-c)**

Comparison of the IR spectra of **2(a-c)** and **3(a-c)** shows a new medium band at 1245-1253 cm^{-1}, which was assigned to C=S stretching vibrations and is characteristic for N(3)-substituted derivatives **3(a-c)**.

The chemical shifts of the methylene group signals are most important in establishing the structure of **2(a-c)** and **3(a-c)** with ^{1}H-NMR spectroscopy.

The SCH_2 group signal for **2(a-c)** appears at 4.12-4.13 ppm, while the position of the NCH_2 group signal for **3(a-c)** is shifted somewhat downfield (table 1).

However, the major information permitting us unequivocally to established the structure of the S-derivatives **2(a-c)** and N-derivatives **3(a-c)** is provided by ^{13}C-NMR spectroscopy (table 1). The characteristic signals used for distinguishing between these compounds are the signals of the carbon atom of the C-S group (C-2), which are found in two narrow ranges: 167.15-167.86 and 178.07-178.53 ppm. The former group of signals corresponds to C-2 of S-derivatives **2(a-c)**, while the latter group corresponds to C-2 thione carbon of N-derivatives **3(a-c)**.

Furthermore, a significant difference in the chemical shifts of the methylene carbon in the side-chain is observed in the ^{13}C-NMR spectra of **2(a-c)** vs. **3(a-c)**. Thus, the SCH_2 signal for the compounds **2(a-c)** appears at ~ 34 ppm, while the NCH_2 signal in the spectra of **3(a-c)** is seen at ~ 68 ppm.

On the other hand, the NMR spectra of the new derivatives exhibits two characteristic subspectra, one for diarylsulfone moiety and another for the remaining functional side-chain and they present significant similarities with the other derivatives previously synthesized [21-24].

Biological activity

The effect of the title compounds **1(a-c)**, **2(a-c)** and **3(a-c)** on sprouting of wheat have been investigated. After treating with solutions of 1; 0.5; 0.066 mM concentrations of compounds **1-3** for 5 days, from the difference in length between the main root of karyopses treated with the title compounds and those treated with distilled water (latest day), the plant growth regulating activities have been determined (table 2). A positive result represents a growth increase, whereas a negative result implies an inhibition [25]:

$$\text{effect} = \frac{\textit{the length of sample's radicle} - \textit{the reference's length}}{\textit{the length of reference's radicle}} \; x\,100$$

All derivatives at 1mM and 0.5 mM concentrations inhibited wheat root growth with less than 90%. Inhibitory activity declined with the decrease of the concentration applied, except for compounds **3(a-c)** which inhibited the growth at all concentrations (fig. 1).

S-Alkylation of 1,3,4-oxadiazoles **1(a-c)** induced decrease of stimulatory effect of wheat root growth at 0.066 mM concentration, except **2a**, whose activity increase. In this case, diphenylsulfone moiety unsubstituted , as well as S-substitution were more effective than the compounds with incorporated halogen in the molecule.

Aminomethylation of 1,3,4-oxadiazoles **1(a-c)** inhibited root elongation, thereby inhibiting the cellular division: the cellular size is changed, shape of the cell is irregular, the cytoplasm is separated from the cell membrane and nuclei with hypertrophied nucleoles were observated.

Conclusions

In this paper we presented synthesis and characterization of six new derivatives with 1,3,4-oxadiazole nucleus obtained via S-alkylation and N(3)-aminomethylation of 5-[4-(4X-phenylsulfonyl)phenyl]-1,3,4-oxadiazole-2-thiols, X=H, Cl, Br.

All the compounds have been investigated for their biological activities concerning regulation of growth for wheat using the phytobiological method – the *Triticum* test.

The biological tests demonstrated a mitosys inhibition activity at high concentrations and a low stimulatory activity at 0.066 mM concentration, without citotoxicity.

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