Journal of Pharmaceutical, Chemical and Biological Sciences
ISSN: 2348-7658
CODEN: JPCBBG
Impact Factor (GIF): 0.701
Impact Factor (SJIF): 3.905
March- May 2017; 5(1):17-22
Published on: 19 April 2017

Research Article

Synthesis, chemical transformation and antimicrobial activity of the products of 5-(4-aminophenyl)-1,3,4-oxadiazolin-2-thiones interaction to alkyl esters of haloacetic acids

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Received: 01 March 2017 **Revised:** 25 March 2017 **Accepted:** 02 April 2017

ABSTRACT

The reactions of 5-(4-aminophenyl)-1,3,4-oxadiazolin-2-thione with homologous series (C_1-C_4,$CH_2C_6H_5$) alkyl esters of chloroacetic acid were investigated, and only S-products (**2-7**) have been synthesised. By condensation of α-[5-(4-aminophenyl) -1,3,4-oxadiazolin-2-ylthio] acetate butyl ester with aromatic aldehydes new compounds **(6a-d)** (Schiff bases) were obtained and identified. The antimicrobial activity of the Compounds **1-7** and **6a-d** was assessed against different microorganisms using the agar-disc diffusion. Results revealed that *E. coli* are susceptible to the effect of Compounds **3** and **4**, displaying inhibition zone diameters between 10- 12 mm.

Keyword: 5-(4-aminophenyl)-1,3,4-oxadiazolin-2-thione; alkylation, aromatic aldehyde; alkyl esters of mono chloroacetic acid; antimicrobial activity

INTRODUCTION

A wide variety of biological activity of 1,3,4-oxadiazol-2-thiones, the five-membered heterocycles having two nitrogen, an oxygen and sulfur atoms in the molecule attracted much attention from researchers who is looking for a new therapeutic molecules. Numerous types of biological activity of this class of compounds, such as antibacterial, antifungal, antiviral, anticonvulsant, anti-inflammatory, antitumor, etc. were reported previously [1-4]. Continuing the study of 5-substituted-1,3,4-oxadiazolin-2-thiones chemical transformations [5-10], we made a reaction of 5-(4-aminophenyl) -1,3,4-oxadiazolin-2-thione with alkyl esters of chloroacetic acid and studied antibacterial activity of synthesized compounds on Gram-positive bacteria *Staphylococcus aureus* (ATCC 25923) and *Bacillus subtilis* (RKMUz -5); Gram-negative bacteria *Pseudomonas aeruginosa* (ATCC 27879) and *Escherichia coli* (RKMUz - 221); and the fungus *Candida albicans* (RKMUz - 247). The literature contains several reports of oxadiazoltiones reactions with chloroacetic acid and certain alkyl esters. Thus, the work [11, 12] describes the reaction of 5-aryl-1,3,4-oxadiazolin-2-thiones of haloid alkyl acids, including chloroacetic acid, to produce S-products. The same result was obtained by reacting of chloroacetic acid ethyl ether with some oxadiazoltiones [13-15].

MATERIALS AND METHODS

^{1}H NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ on a Varian 400-MR spectrometer operating accordingly at 400 MHz. Hexamethyldisiloxane (HMDSO) used as an internal standard, and chemical shift of ^{1}H was recorded in ppm. MPs were measured on a Boetius and were uncorrected. IR spectra were recorded on an IR Fury System 2000 (PerkinElmer) as KBr pellets, UV spectra were recorded on a Lambda-16 spectrometer PerkinElmer in ethanol. The reactionary process was monitored by TLC on Whatman UV-254 precoated aluminium plates and Merck silica gel $60F_{254}$ using $CHCl_3$ - EtOH, 24: 1 system and developed plates were visualised under UV lamp and iodine tank, where necessary. Solvents were purified by standard procedures. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated with an RVO-64 ROT VAC Evaporator at reduced pressure.

The antimicrobial activity

Microbial strains

The antimicrobial activity was evaluated using standard microbial strains: Gram-positive bacteria *Staphylococcus aureus* (ATCC 25923) and *Bacillus subtilis* (RKMUz - 5); Gram-negative bacteria *Pseudomonas aeruginosa* (ATCC 27879) and *Escherichia coli* (RKMUz - 221); and the fungus *Candida albicans* (RKMUz - 247). The RKMUz microorganism cultures were obtained from the strain collection of the Institute of Microbiology, Academy of Sciences of the Republic of Uzbekistan.

Evaluation of the antimicrobial activity using the disc diffusion method

The antibacterial activity of the compounds **1-7** and **6a-d** was determined by using the modified agar-disc diffusion method [16,17]. Sterile nutrient agar (25g agar/l distilled water) was inoculated with bacterial cells (200 µl of the bacterial cell in 2 ml 0.9% NaCl suspension and 20 ml medium) and poured into Petri dishes to give a solid medium. *Candida albicans* (1×10^6 colony forming units per ml) was inoculated into sterile Mueller-Hinton-agar. Forty microliters of test material (0.2 mg/per disc of the compounds) were applied on sterile paper discs (Whatman No.1, 6 mm diameter). Ampicillin, ceftriaxone and nystatin (20 µg/disc) were used as positive controls and the solvents as negative controls. The solvents were allowed to evaporate in a stream of air. The discs were deposited on the surface of inoculated agar plates. Plates were kept for three h in the refrigerator to enable the diffusion of the substances into the agar. Plates with bacteria were incubated for 24 h at 37°C and plates with yeasts for 48 h at 26°C. The inhibition zone (including the disc diameter) was measured and recorded after the incubation time. An average zone of inhibition was calculated for the three replicates in independent assays.

Synthesis method

5-(4-aminophenyl)-1,3,4-oxadiazolin-2-thione (**1**) was synthesised according to the method described in [10].

α-[5-(4-aminophenyl)-1,3,4-oxadiazolin-2-ylthio]acetate alkyl esters (**2-7**) **synthesis. (General procedure).**

An equimolar amount of 5-(4-aminophenyl) - 1,3,4-oxadiazol-2-thione, chloroacetic acid alkyl ester and K_2CO_3 was boiled in 20 ml of dry acetone for 7h. After removing the solvent, the residue was washed with water, alkali solution to remove thione residues, and with cold water until neutral reaction appearance. The purity of the substances obtained as the white or milk-white powder does not require further purification by recrystallization.

α-[5-(4-aminophenyl)-1,3,4-oxadiazolin-2-ylthio]acetate methyl ester (2). Yield 98%, white powder, mp 157-158°C. Rf=0.30, UV, λ max, nm, 310.6;

NMR^{1}H, δ, (J, Hz): 3.77 (3H, s, OC<u>H</u>$_3$), 4.10 (2H, s, S-C<u>H</u>$_2$), 5.10 (2H, brs, N<u>H</u>$_2$), 6.71 (2H, d, J=8.8, H-3,5), 7.67 (2H, d, J=8.8, H-2,6).

IR,ν, cm^{-1}: 1714 ($COOCH_3$), 1168 (C-O-C, oxadiazol).

α-[5-(4-aminophenyl)-1,3,4-oxadiazolin-2-ylthio]acetate ethyl ester (3). Yield 87%, white powder, mp115-116°C. Rf= 0.74, UV, λ max, nm, 311.4;

NMR^{1}H, δ, (J,Hz): 1.29 (3H, t, *J*=6.9, C<u>H</u>$_3$), 4.07 (2H, s, S-C<u>H</u>$_2$), 4.11 (2H, brs, N<u>H</u>$_2$), 4.25 (2H, t, *J*=6.9, OC<u>H</u>$_2$CH$_3$), 6.71 (2H, d, *J*=8.0, H-3,5), 7.76 (2H, d, *J*=8.0, H-2,6).

IR,ν, cm^{-1}: 1717 ($COOC_2H_5$), 1179 (C-O-C, oxadiazol).

α-[5-(4-aminophenyl)-1,3,4-oxadiazolin-2-ylthio]acetate propyl ester (4). Yield 89%, milk-white powder, mp 136-137°C. Rf =0.29, UV, λ max, nm, 313.0;
NMR¹H, δ, (J,Hz): 0.93 (3H, t, *J*=7.4, C<u>H</u>$_3$), 1.68 (2H, m, OCH$_2$C<u>H</u>$_2$CH$_3$), 4.08 (2H, s, S-C<u>H</u>$_2$), 4.13 (2H, brs, N<u>H</u>$_2$), 4.15 (2H, t, *J*=6.7, OC<u>H</u>$_2$CH$_2$CH$_3$), 6.70 (2H, d, *J*=8.4, H-3,5), 7.76 (2H, d, *J*=8.4, H-2,6).
IR,ν, cm^{-1}: 1718 (COOC$_3$H$_7$), 1175 (C-O-C, oxadiazol).

α-[5-(4-aminophenyl)-1,3,4-oxadiazolin-2-ylthio]acetate isopropyl ester (5). Yield 90%, milk-white powder, mp152-153°C. Rf=0.40, UV, λ max, nm, 312.1;
NMR¹H, δ, (J,Hz): 1.27 (6H, d, *J*=6.2, (C<u>H</u>$_3$)$_2$), 4.04 (2H, s, S-C<u>H</u>$_2$), 4.11 (2H, brs, N<u>H</u>$_2$), 5,08 (1H, septet, *J*=6.2, OC<u>H</u>(CH$_3$)$_2$), 6.71 (2H, d, *J*=8.2, H-3,5), 7.77 (2H, d, *J*=8.2, H-2,6).
IR,ν, cm^{-1}: 1721 (COOCH(CH$_3$)$_2$), 1174 (C-O-C, oxadiazol).

α-[5-(4-aminophenyl)-1,3,4-oxadiazolin-2-ylthio]acetate butyl ester (6). Yield 96%, white powder, mp, 84-85°C, Rf=0.34. UV, λ max, nm, 312.5;
NMR¹H, δ, (J,Hz): 0.91 (3H, t, J=7.4, C<u>H</u>$_3$), 1.37 (2H, m, CH$_2$CH$_2$C<u>H</u>$_2$CH$_3$), 1.63 (2H, m, CH$_2$C<u>H</u>$_2$CH$_2$CH$_3$), 4.08 (2H, c, S-C<u>H</u>$_2$), 4.11 (2H, brs, N<u>H</u>$_2$), 4.19 (2H, t, J=6.7, O-CH$_2$), 6.71 (2H, d, J=8.6, H-3,5), 7.77 (2H, d, J=8.6, H-2,6).
IR,ν, cm^{-1}: 1727 (COOC$_4$H$_9$), 1171 (C-O-C, oxadiazol).

α-[5-(4-aminophenyl)-1,3,4-oxadiazolin-2-ylthio]acetate benzoyl ester (7). Yield 94%, milk-white powder, mp, 124-125°C, Rf=0.23. UV, λ max, nm, 313.2;
NMR¹H, δ, (J,Hz): 4.09 (2H, brs, N<u>H</u>$_2$), 4.11 (2H, c, S-C<u>H</u>$_2$), 5.21 (2H, c, OC<u>H</u>$_2$), 6.69 (2H, d, *J*= 8.5, H-3,5), 7.26 (3H,м,H-3`,4`,5`), 7.37 (2H, d, *J*=7.1, H-2`,6`), 7.74 (2H, d, *J*=8.5, H-2,6).
IR,ν, cm^{-1}: 1736 (COOCH$_2$C$_6$H$_5$), 1158 (C-O-C, oxadiazol).

α-[5-(4-R/-benzylideneamino)phenyl)-1,3,4-oxadiazolin-2-thio]acetate butyl ester (6a-d). (General procedure).
4-5 drops of a glacial acetic acid were added to the mixture of 10 mmol α- [5- (4-aminophenyl)-1,3,4-oxadiazol-2-ylthio]butyl acetate and 10 mmol of aromatic aldehyde in ethanol. The reaction mixture was boiled for 10-15 hours, and the reaction was monitored by TLC. After removing the solvent, the residue was washed with water, alkali solution, and re-crystallized from the alcohol-heptane mixture.

α-[5-(4-benzylydeneaminophenyl)-1,3,4-oxadiazolin-2-ylthio] acetate butyl ester (6a). Yield 83%, yellow crystals, mp 116-117°C (EtOH/heptane), Rf=0.36. UV, λ max, nm,315.5;
NMR¹H,δ,(J,Hz): 0.78 (3H,t,J=7.2,C<u>H</u>$_3$), 1.23 (2H,m,CH$_2$CH$_2$C<u>H</u>$_2$CH$_3$), 1.49 (2H,m, CH$_2$C<u>H</u>$_2$CH$_2$CH$_3$), 4.06 (2H, t, J=6.5, O-C<u>H</u>$_2$CH$_2$CH$_2$CH$_3$), 4.25 (2H, s, S-C<u>H</u>$_2$), 7.39 (2H, d, J=8.5, H-3,5), 7.45-7.58 (3H, m, H-3`,4`,5`), 7.92 (2H, dd, J=7,9; 1.8, H-2`,6`), 7.95 (2H,d,J=8.5,H-2,6), 8.63 (1H,s,CH=N);
IR,ν,cm^{-1}: 1628 (C=N), 1164 (C-O-C, oxadiazol).

α-[5-(4-(p-chlorobenzilydeneamino)phenyl)-1,3,4-oxadiazolin-2-ylthio]acetate butyl ester (6b). Yield 80%, yellow crystals, mp 176-177°C (EtOH/heptane), Rf=0.32. UV, λmax,nm, 321.9;
NMR¹H,δ,(J,Hz): 0.86 (3H,t, *J*=7.4, C<u>H</u>$_3$), 1.32 (2H,m, CH$_2$CH$_2$C<u>H</u>$_2$CH$_3$), 1.58 (2H,m,CH$_2$C<u>H</u>$_2$CH$_2$CH$_3$), 4.06 (2H, s, S-CH$_2$), 4.14 (2H, t, *J*=6.7,O-C<u>H</u>$_2$CH$_2$CH$_2$CH$_3$), 7.22 (2H, d, *J*=8.6, H-2,6), 7.41 (2H, d, *J*=8.4, H-2`,6`), 7.80 (2H, d, *J*=8.4, H-3`,5`), 7.97 (2H, d, *J*=8.6, H-3,5), 8.37 (1H, s, CH=N);
IR,ν, cm^{-1}: 1625 (C=N), 1169 (C-O-C, oxadiazol).

α-[5-(4-(p-nitrobenzilydeneamino)phenyl)-1,3,4-oxadiazolin-2-ylthio]acetate butyl ester (6c). Yield 87%, dark yellow crystals, mp 197-198°C,(EtOH/heptane), Rf=0.35. UV, λ max,nm, 292.7;
NMR¹H,δ, (J,Hz): 0.86 (3H, t, *J*=7.4, C<u>H</u>$_3$), 1.32 (2H, m, CH$_2$CH$_2$C<u>H</u>$_2$CH$_3$), 1.58 (2H, m, CH$_2$C<u>H</u>$_2$CH$_2$CH$_3$), 4.08 (2H, s, S-CH$_2$), 4.13 (2H, t, *J*=6.6, O-C<u>H</u>$_2$CH$_2$CH$_2$CH$_3$), 7.32 (2H, d, *J*=8.5, H-2,6), 8,00 (2H, d, *J*=8.5, H-3,5), 8,09 (2H, d, *J*=8.8, H-2`,6`), 8,29 (2H, d, *J*=8.8, H-3`,5`), 8.59 (1H, s, CH=N);
IR,ν, cm^{-1}: 1627 (C=N), 1169 (C-O-C, oxadiazol).

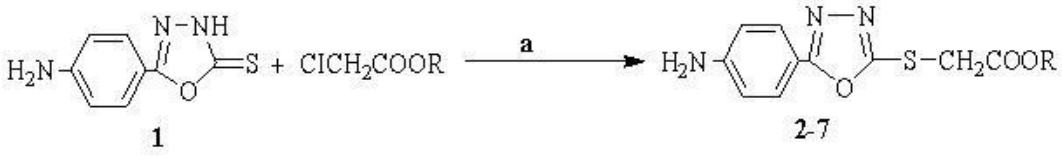
α-[5-(4-(p-dimethylaminobenzily - deneamino)phenyl)-1,3,4-oxadiazolin-2-ylthio]acetate butyl ester (6d). Yield 95%, yellow crystals, mp126-127°C,(EtOH/heptane), Rf=0,31. UV, λ max,nm, 379.3;

NMR^{1}H,δ, (J,Hz): 0.86 (3H, t, J=7.4, CH_3), 1.31 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$), 1.58 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$), 3.01 (6H, s, $N(CH_3)_2$), 4.05 (2H, s, S-CH_2), 4.14 (2H, t, J=6.6, O-$C\underline{H}_2CH_2CH_2CH_3$), 6.67 (2H, d, J=8.8, H-3`,5`), 7.20 (2H, d, J=8.5, H-2,6), 7.71 (2H, d, J=8.8, H-2`,6`), 7.92 (2H, t, J= 8.5, H-3,5), 8.26 (1H, s, CH=N);

IR,ν, cm^{-1}: 1628 (C=N), 1162 (C-O-C, oxadiazol).

RESULT AND DISCUSSION

We studied in detail the interaction of 5-(4-aminophenyl)-1,3,4-oxadiazolin-2-thione (**1**) with the homologous series of chloroacetic acid alkyl esters (C_1-C_4,$CH_2C_6H_5$). Reactions were carried out by boiling of equimolar amounts of thione, chloroacetic acid alkyl ester and K_2CO_3 in acetone, and interaction progress was monitored by TLC. The reaction conditions are given in Fig. 1.

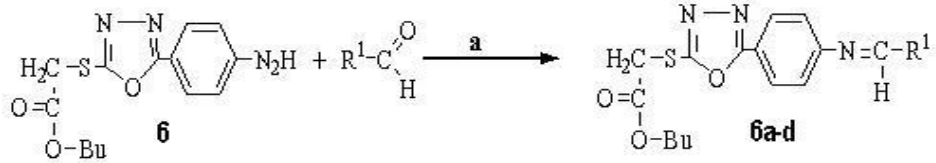


R= CH_3(**2**), C_2H_5(**3**), C_3H_7(**4**), i-C_3H_7(**5**), C_4H_9(**6**), CH_2-C_6H_5(**7**).

Fig.1. Reagent and conditions: a) $(CH_3)_2CO$, K_2CO_3, boiling for 7h.

Analysis of the products (IR, ^{1}H NMR spectra) showed that all the reactions produced S-derivatives: absence of C=S 1345-1380 cm^{-1} band, appearance of 1714-1774 cm^{-1} band in the respective CH_2SOO- in IR, as well as the presence of proton signals S-CH_2 and absence of N-CH_2 in the ^{1}H NMR spectrum of [5,6]. The experiments were carried out for 7h, and the results show a good flow of reactions with high (88-98%) yields of the products. When comparing the results of the reactions, it was found that the nature of the alkyl radical (length, branching of homologous series and the benzyl substituent) of chloroacetic acid esters have no noticeable effect on the yield of the desired products. A small decrease of compounds (**3-5**) yield is due to some losses during processing of reaction mixtures.

From the synthesised substances α-[5-(4-aminophenyl)-1,3,4-oxadiazolin-2-ylthio] acetate butyl ester (**6**) was subjected to further chemical transformation. Aromatic aldehydes reacting with the amino group of the ester in boiling ethanol and in the presence of a catalytic amount of glacial acetic acid afforded new compounds α-[5- (4- (R/-benzilydenamino) phenyl) -1,3,4 oxadiazolin-2-ylthio] acetate butyl ethers (**6a-d**) with 80-95% yield. The reaction conditions are given in Fig. 2.



R^1= C_6H_5(**6a**), 4-ClC_6H_4(**6b**), 4-$NO_2C_6H_4$(**6c**), 4-$(CH_3)_2NC_6H_4$(**6d**);

Fig.2. Reagent and conditions: a) EtOH, AcOH, boiling for 10-15h

On IR spectra the absorption bands corresponding to C=N bond in 1625-1628 cm^{-1} indicate the appearance of derivatives with altered functional amino group of the ester (6). The absence of NH_2-group signals at 4.09-4.13 ppm in the ^{1}H NMR spectra and the presence of a proton signal CH=N as a singlet in a weaker field of 8.26-8.63 ppm shows the condensation of the aromatic ring amino group in α-[5-(4-aminophenyl) -1,3,4-oxadiazolin-2-ylthio] acetate butyl ester. Complex proton signals with a chemical shift in the range of 6.67-8.00 ppm in the thione aromatic ring and aldehydes are present in all ^{1}H NMR spectra of the synthesised compounds.

This study presents the first comparative screening of the compounds **1-7** and **6a-d** to their antimicrobial activity**.** The antimicrobial activity of the compounds **1-7** and **6a-d** against *Bacillus subtilis, Staphylococcus aureus*,

Pseudomonas aeruginosa, Escherichia coli as well as fungi *Candida albicans* was assessed using the agar-disc diffusion method. The results of the current research were displayed in Table No.1 and revealed that *B. subtilis, S. aureus* and *E. coli* are susceptible to the antimicrobial activity of the compounds **1, 3** and **4**, displaying inhibition zone diameters between 7- 12 mm. The most active compound **4** exhibit an appreciable antibacterial effect against *E. coli* (Table 1).

Table 1. Antibacterial effect evaluated by diameter of inhibition zone (mm) for Compounds 1-7, and 6a-6d using agar disk diffusion assay

Samples	Gram-positive bacteria		Gram-negative bacteria		Fungi
	B. subtilis (RKMUz – 5)	*S. aureus* (ATCC 25923	*P. aeruginosa* (ATCC 27879)	*E. coli* (RKMUz - 221)	*C. albicans* (RKMUz - 247);
1	7	7	na	na	na
2	na	na	na	na	na
3	7	7	na	**10**	na
4	7	7	na	**12**	na
5	na	na	na	na	na
6	na	na	na	na	na
7	na	na	na	na	na
6a	na	na	na	na	na
6b	na	na	na	na	na
6c	na	na	na	na	na
6d	na	na	na	na	na
Ampicillin (20µg/disc)	24	27	nt	26	nt
Ceftriaxone (20 µg/disc)	nt	nt	25	nt	nt
Nystatin (20 µg /disc)	nt	nt	nt	nt	17

na- not active; nt – not tested

CONCLUSION

Thus, the reactions of 5-(4-aminophenyl)-1,3,4-oxadiazolin-2-thione with homologous series (C_1-C_4,$CH_2C_6H_5$) alkyl esters of chloroacetic acid were investigated, and only S-products have been synthesised with high yield. Possible N-alkyl derivatives were not detected by TLC or other spectroscopic methods. By condensation of α-[5-(4-aminophenyl)-1,3,4-oxadiazolin-2-ylthio] acetate butyl ester with aromatic aldehydes new Schiff bases were obtained and identified. The overall results of this study provide evidence that the compound 4 - α-[5-(4-aminophenyl)-1,3,4-oxadiazolin-2-ylthio]acetate propyl ester exhibit appreciable antibacterial activity against *E. coli*.

ACKNOWLEDGMENTS

Authors are thankful to the Academy of Sciences of the Republic of Uzbekistan for supporting this study (grant FA-F7-T207).

CONFLICT OF INTEREST STATEMENT

There is no conflict of interest associated with the authors of this paper.

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Cite this article as:
D.S.Ismailova, A.A.Ziyaev, S.A.Sasmakov, J.M. Abdurakhmanov, Sh.S. Azimova. Synthesis, chemical transformation and antimicrobial activity of the products of 5-(4-aminophenyl)-1,3,4-oxadiazolin-2-thiones interaction to alkyl esters of haloacetic acids. J Pharm Chem Biol Sci 2017; 5(1):17-22.