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# Synthesis, characterization and study of antibacterial and antifungal activities of some 1,3,4-oxadiazole compounds

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**ABSTRACT**

*Two new series of 2-alkylthio-5-aryl-1,3,4-oxadiazole (aryl = 2-hydroxyphenyl, 5-bromofuryl and alkyl = H, $CH_2CH_3$, $CH_2(CH_2)_2CH_3$, $CH_2Ph$, $CH_2CO_2CH_2CH_3$, $CH_2CO_2H$) were synthesized and characterized by elemental analysis, UV-visible spectrophotometer, FT-IR spectrophotometer and $^1$H-NMR spectrophotometer. The prepared compounds were examined against two bacterial strains, Gram negative (E. coli) and Gram positive (S. aureus), and against pathogenic fungi Aspergillus niger. MIC was determined for all compounds against two bacterial strains. $LD_{50}$ values were determined for some selected compounds which have showed a good antimicrobial activity. These results showed that the selected compounds exhibited moderate toxic values and the $LD_{50}$ were in the range 1.85-2.9g/kg.*

**Keywords:** 1,3,4-oxadiazole, antibacterial activity, antifungal activity, $LD_{50}$.

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## INTRODUCTION

1,3,4-Oxadiazole derivatives are well known to have a wide range of biological activities. Examples of such activities are anti-inflammatory[1], antifungal, antiparasitic and antimicrobial[2] effects. Furthermore, bis-mercapto-1,3,4-oxadiazoles were used as active substances to control Meloidogyne incognita in tomato[3]. 1, 3, 4 oxadiazole derivatives of acridone showed the significant antimicrobial activity against the microorganisms[4].

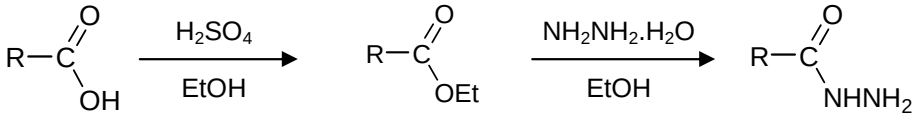
Several methods have been used for the synthesis of these kinds of compounds from acylic precursors. Some of them are the oxidative cyclizations of acyl hydrazones, acyl thioureas, and acyl thiosemicarbazides.[5] 2,5-Disubstituted 1,3,4-oxadiazoles of various structures can be prepared by several procedures. The starting compounds can be carboxylic acids and hydrazine; they are converted into diacylhydrazides via several intermediates. The cyclodehydration of diacylhydrazides under the action of $POCl_3$ yields 1,3,4-oxadiazoles; these compounds can also be prepared by cyclodehydration of diaroylhydrazines and diacylhydrazines under the action of various dehydrating agents (organic acid anhydrides, $PCl_5$, $H_2SO_4$).[6] Vereshchagin and his cowork[7] synthesized 1,3,4-oxadiazole by reaction of C-substituted tetrazoles with carboxylic acid chlorides. Thiol groups in some 1,3,4-oxadiazole-2-thiol may be used as linkages to prepare some S-linked heterocyclic compounds. Some of these compounds were prepared by S. S. Patil and his coworker[8].

Antibacterial activity of some compounds as quinolones derivatives[9] and quinoxaline derivatives[10], may be enhanced by modification of these compounds by the addition of 1,3,4-oxadiazole ring, such as norfloxacin, ciprofloxacin, ofloxacin and sparfloxacin have been modified to give corresponding 1,3,4-oxadiazole compounds.

## EXPERIMENTAL SECTION

The uncorrected melting points of the compounds were recorded on a Gallenkamp Thermal Point Apparatus. UV-Visible spectra were measured as solution ($10^{-4}$ M) in analar ethanol with quartz 1cm$^2$ length cells using Pheonix Range of Spectrophotometer and FT.IR spectra were recorded as KBr disks using FT.IR 8400S SHIMADZU (Japan), in the technique Laboratory of Chemistry Department, College of Science, Basra University, Iraq. H-NMR spectra were measured using Bruker model ultra shield 300MHz (Switzerland), and CHNS analysis were performed using EuroVector model EA3000A (Italy) in the analytical Laboratory of AL-ALBAYET University, Jordan. Thin layer chromatography of the products was performed using suitable eluents, and the spots were visualized using UVS-11 MINERALIGHT LAMP at 254 nm instrument.

Ethyl salicylate, ethyl 5-bromofuroate, salicylic hydrazide and 5-bromofuroic hydrazide were prepared according to the literatures[11,12], as shown in scheme 1.

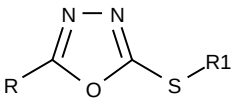


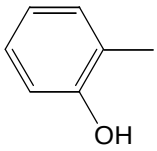
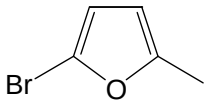

**Scheme 1**

**Preparation of Compounds**

The parent 1,3,4-Oxadiazoles and their derivatives are shown in Table 1.

**Table 1 Name and symbol of the prepared 1,3,4-Oxadiazole compounds**




| R | $R_1$ | Symbol | Name |
|---|---|---|---|
|  | -H | SO | 5-(2-hydroxyphenyl)-1,3,4-oxadiazole-2-thiol |
| | $-CH_2-CH_3$ | SO1 | 2-ethylthio-5-(2-hydroxyphenyl)-1,3,4-oxadiazole |
| | $-CH_2-(CH_2)_2-CH_3$ | SO2 | 2-butylthio-5-(2-hydroxyphenyl)-1,3,4-oxadiazole |
| | $-CH_2-Ph$ | SO3 | 2-benzylthio-5-(2-hydroxyphenyl)-1,3,4-oxadiazole |
| | $-CH_2CO_2C_2H_5$ | SO4 | 2-ethoxycarbonylmethylthio-5-(2-hydroxyphenyl)-1,3,4-oxadiazole |
| | $-CH_2CO_2H$ | SO5 | 2-carboxymethylthio-5-(2-hydroxyphenyl)-1,3,4-oxadiazole |
|  | -H | BO | 5-(5-bromofuryl)-1,3,4-oxadiazole-2-thiol |
| | $-CH_2-CH_3$ | BO1 | 2-ethylthio-5-(5-bromofuryl)-1,3,4-oxadiazole |
| | $-CH_2-(CH_2)_2-CH_3$ | BO2 | 2-butylthio-5-(5-bromofuryl)-1,3,4-oxadiazole |
| | $-CH_2-Ph$ | BO3 | 2-benzylthio-5-(5-bromofuryl)-1,3,4-oxadiazole |
| | $-CH_2CO_2C_2H_5$ | BO4 | 2-ethoxycarbonylmethylthio-5-(5-bromofuryl)-1,3,4-oxadiazole |
| | $-CH_2CO_2H$ | BO5 | 2-carboxymethylthio-5-(5-bromofuryl)-1,3,4-oxadiazole |

**General procedure for the preparation of 1,3,4-oxadiazole-2-thiol**

The compounds SO and BO were prepared by the same method.[13] To a solution containing 95% ethanol and 0.1 mole of sodium hydroxide (dissolved in the least amount of water), 0.1 mole of hydrazides was added, followed by 0.15 mole of carbon disulfide. The reaction mixture was heated under reflux for 3hrs till all the evolution of hydrogen sulfide ceased. The resulting mixture was diluted with water and acidified with diluted hydrochloric acid containing ice. The reaction mixture was allowed to stand at the ice bath for 30 minutes, filtered, washed with water and recrystallized from methanol. The characterizations of products are listed in Table 2.

**General procedure for the preparation of mercaptoalkyl derivatives**

The compounds SO1, SO2, BO1 and BO2 were prepared by the same procedure[14]. A mixture of 0.015 mole of SO or BO, 0.018 mole of alkyl bromides and 0.02 mole of sodium acetate in 50 ml of ethanol was heated under reflux for 3 hrs, then allowed to cool, and poured into 100 ml of cold water containing ice. The solid product was collected and recrystallized from ethanol. The characterizations of the products are listed in Table 2.

**General procedure for the preparation of mercaptobenzyl derivatives**

The compounds SO3 and BO3 were prepared by the same procedure[15]. To a solution of 0.01 mole of SO or BO and 0.05 mole of sodium acetate in 30-50 ml of absolute ethanol, 0.01 mole of benzyl chloride was added. The reaction mixture was refluxed for 4 hrs. The content was then poured into crushed ice and a solid mass which separated out was filtered and recrystallized from ethanol. The characterizations of the product are listed in Table 2.

**General procedure for the preparation of mercaptoethoxycarbonylmethyl derivatives**

The compounds SO5and BO5 were prepared by the same method[16]. A solution of 0.01 mole of SO or BO and 0.01 mole of sodium hydroxide in (30-50 ml) of absolute ethanol was heated under reflux for 30 minutes. A 0.01 mole ethyl bromoacetate was added and the resulting mixture was refluxed for 4 hrs. After cooling, the solution was poured on ice and the solid mass which separated out was recrystallized from ethanol and dried at room temperature. The characterizations of the products are listed in Table 2.

**Table 2 Characterizations of the prepared compounds**

| Compd. | M. Wt. (g/mole) | m. p. ($^oC$) | Crystals shape | Yield (%) | $R_f$ | Eluent |
|---|---|---|---|---|---|---|
| SO | 194.21 | 177-180 | white crystals | 72.8 | 0.78 | Ethyl acetate: ethanol(7:3) |
| BO | 247.07 | 174-176 | white crystals | 69.28 | 0.70 | |
| SO1 | 222.26 | 37-38 | white long needle crystals | 73.17 | 0.72 | ethyl acetate: ethanol (8:2) |
| SO2 | 250.32 | 40-43 | white needle crystals | 68.8 | 0.72 | |
| BO1 | 275.12 | 46-48 | white crystals | 74.85 | 0.68 | |
| BO2 | 303.18 | 53-56 | white plated crystals | 73.36 | 0.63 | |
| SO3 | 284.33 | 107-109 | white needle crystals | 89.51 | 0.62 | ethyl acetate:ethanol: hexane (7:2:1) |
| BO3 | 337.19 | 78-80 | yellowish white crystals | 81.68 | 0.53 | |
| SO4 | 280.30 | 69-71 | white cotton crystals | 85.47 | 0.67 | ethyl acetate:ethanol: hexane (6:3:1) |
| BO4 | 333.16 | 54-56 | white cotton crystals | 89.98 | 0.66 | |
| SO5 | 252.25 | 147-150 | white fine powder | 70.00 | 0.71 | ethyl acetate:ethanol: hexane (6:2:2) |
| BO5 | 305.11 | 148-150 | yellowish white powder | 70.07 | 0.70 | |

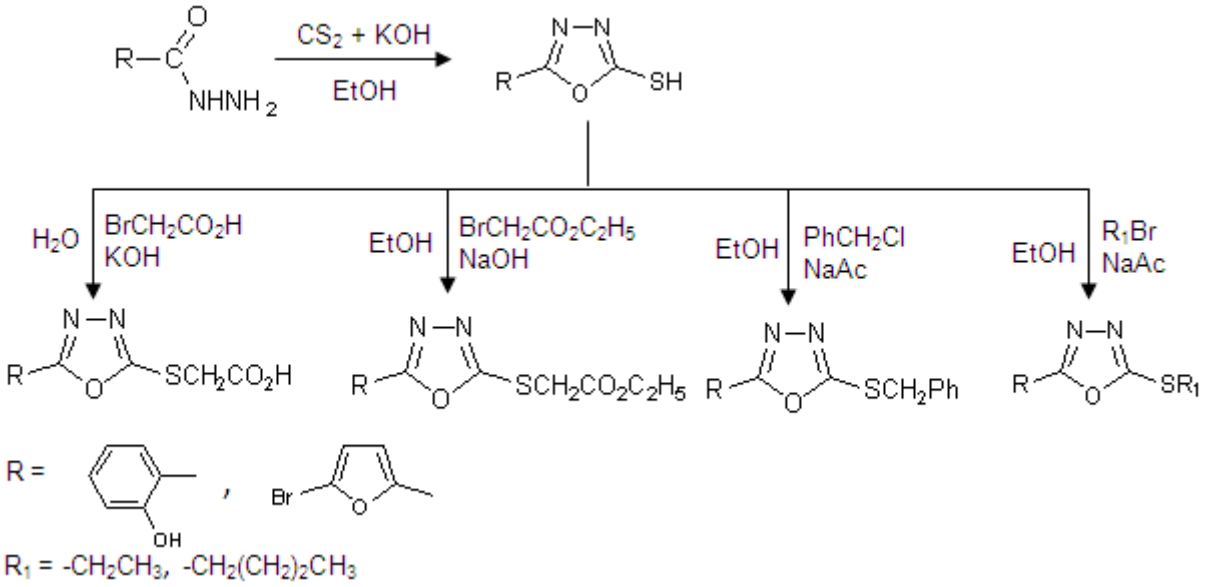



Table 3 shows the CHNS of some of the prepared compounds

**General procedure for the preparation of mercaptocarboxymethyl derivatives**

The compounds SO6 and BO6 were prepared by the same method[17]. A mixture of 0.1 mole of SO or BO, 0.1 mole of monobromoacetic acid and 20-40 ml of aqueous potassium hydroxide solution (0.1 mole) was refluxed for 3 hrs. The hot solution was filtered and the filtrate was acidified with 2 M hydrochloric acid to pH (3-4). The product was precipitated out, filtered, washed with water and recrystallized from a mixture of ethanol:water (5:1). The product was dried at room temperature. The characterizations of the products are listed in Table 2.

**Antimicrobial activity:**

The in vitro antimicrobial activity was carried out against two bacteria by paper disc diffusion method[18, 19] and one fungi by wells method[20]. All the synthesized compounds were tested for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and antifungal activity against *Aspergillus niger*. Fluconazole was used as standard for antifungal activity, whereas amoxicillin and streptomycin were used as standard antibacterial activity. The compounds were tested at a concentration of 1000 µg/ml. Solvent dimethyl sulfoxide was used as control. The zone of inhibition was compared with the standard drug. The results are tabulated in Table 3.

Filter paper disc diffusion method was used in the determination of MIC for preliminary active compounds against these two bacterial strains. Diverse concentrations of each compound were prepared (500, 400, 300, 200 and 100 μg/ml) in dimethyl sulfoxide by dilution from stock solutions. The visible zone of microbial growth inhibition around the discs was measured. The results are listed in Table 4.

**Table 3-2 CHNS analysis of oxadiazole compounds**

| Sample Name | Mol. Formula | C% | H% | N% | S% |
|---|---|---|---|---|---|
| SO1 | $C_{10}H_{10}N_2O_2S$ | 54.18 | 4.48 | 12.49 | 14.46 |
| Calculated value | | 54.04 | 4.53 | 12.60 | 14.43 |
| SO2 | $C_{12}H_{14}N_2O_2S$ | 57.82 | 5.71 | 11.44 | 12.38 |
| Calculated value | | 57.61 | 5.64 | 11.19 | 12.81 |
| SO3 | $C_{15}H_{12}N_2O_2S$ | 63.79 | 4.12 | 9.84 | 11.59 |
| Calculated value | | 63.39 | 4.25 | 9.85 | 11.28 |
| SO5 | $C_{11}H_8N_2O_5S$ | 47.91 | 3.25 | 11.54 | 12.42 |
| Calculated value | | 47.61 | 3.20 | 11.11 | 12.71 |
| BO1 | $C_8H_7BrN_2O_2S$ | 34.51 | 2.56 | 10.15 | 11.64 |
| Calculated value | | 34.92 | 2.56 | 10.18 | 11.66 |
| BO2 | $C_{10}H_{11}BrN_2O_2S$ | 39.91 | 3.56 | 9.12 | 10.68 |
| Calculated value | | 39.61 | 3.65 | 9.24 | 10.57 |
| BO3 | $C_{13}H_9BrN_2O_2S$ | 47.54 | 2.71 | 8.52 | 9.88 |
| Calculated value | | 46.30 | 2.69 | 8.30 | 9.50 |
| BO5 | $C_9H_5BrN_2O_5S$ | 31.78 | 1.62 | 9.09 | 11.07 |
| Calculated value | | 31.49 | 1.65 | 9.18 | 10.51 |

**Short-term toxicity ($LD_{50}$)**[20]
The short-term toxicity, study in term of $LD_{50}$ of some active compounds, was determined in Swiss albino mice BALB/c, weighting about 25 gm, one month old and were housed under controlled conditions.

Mice were divided into six groups, each group comprises of five mice. One of the six groups acted as control, while the other groups represented the tested groups. 0.5 ml of the olive oil was administrated orally by stomach tube to the control group, whereas the other groups were administrated, by the same method, the doses of the each compound in the range 1-5 mg/ml. All groups were observed for 72 hrs, and the mortality data were recorded.

## RESULTS AND DISCUSSION

The study includes the preparation of some of 1,3,4-oxadiazole-2-thiol derivatives from two types of carboxylic hydrazides, 5-bromofuroic hydrazide and salicylic hydrazide, followed by the preparation of S-substituted-OXD, as shown in Schemes 1 and 2. The synthesis of mercaptosubstituted-1,3,4-OXD involved sulfur nucleophilic substitution (an attack by SH) at the alkyl carbon of different R-X.

All prepared compounds were characterized by UV-Visible which showed three main absorption bands in the ranges 218-225nm, 253-281nm and 291-319 nm attributed to the electronic transition of $\pi \rightarrow \pi^*$ of the aromatic system of 2-hydroxyphenyl, 5-bromofuroic, benzyl and OXD rings[21, 22].

The IR data of the non substituted OXD compounds showed a band at 2767$cm^{-1}$ and 2773 $cm^{-1}$ which is characteristic of the S-H stretching[23] of SO and BO compounds, respectively, this band was lacked in the S-substituted derivatives S-R. All IR spectra of OXD compounds showed strong-medium bands at 1610-1647$cm^{-1}$ and 1517-1594 $cm^{-1}$ which are characteristic of the C=N and C=C ring stretching, respectively[24, 25]. Strong-medium bands at 1237-1267 $cm^{-1}$ and 1174-1200 $cm^{-1}$ which are characteristic for C-O-C asymmetric and symmetric stretching of OXD ring[26], respectively. Medium-weak absorption band at 3054-3137 $cm^{-1}$ and strong-medium band at 742-806 $cm^{-1}$ which are characteristic of aromatic C-H stretching and bending, respectively.

$^1$H-NMR spectra of the 1,3,4-oxadiazole derivatives show common peaks, singlet signal at high chemical shift about 10.2 ppm related to the proton of OH in the 2-hyroxyphenyl group because of the intramolecular hydrogen bonding[27], and multiplet signals at 6.7-7.7 ppm related to the protons of aromatic system of 2-hyroxyphenyl group. For the 5-bromofuroic derivatives, there are two doublet signals at 6.9 ppm and 7.3 ppm attributed to tow protons of 5-bromofuroic group.

$^1$H-NMR spectra of the mercaptobutyl-OXD exhibited a characteristic aliphatic system which gave signals between 0.912-3.292 ppm related to the protons of the butyl group. Whereas, the aliphatic system of mercaptoethoxycarbonylmethyl derivatives gave signals at 1.197-4.275 ppm referred to protons of ester group. For mercaptobenzyl derivatives, in the addition of protons of aliphatic system (-$CH_2$-) which appeared as singlet signal at 4.567 ppm, there are multiplet signals at 7.287-7.476 ppm attributed to the protons of aromatic system of benzyl group.

The antimicrobial activity of the compounds are evaluated as shown in Table 2. Among the series of compounds tested BO4 and BO5 showed better inhibition whereas SO1, SO4 and BO1 showed moderate inhibition with *E. coli*, *S. aureus* and *Aspergillus niger*. SO and BO exhibited a good inhibition against *E. coli* and *S. aureus*, respectively. The compounds BO4 and BO5 showed promising activity against *Aspergillus niger*. Therefore, we showed that azoles which contained the thioester end acted as antimicrobial agents. The thioester-linked product possessed catalytic activity similar to the native enzyme[28]. The antifungal activity of azoles was due to the blocking the ergosterol biosynthetic pathway, the main steroid found in fungal cell membranes[29-31].

**Table 3 Antimicrobial activity of the synthesized compounds and standard drug at 1000 µg/ml**

| Compound | Inhibition zone (mm) | | |
|---|---|---|---|
| | *E. coli* | *S. aureus* | *Aspergillus niger* |
| SO | 19 | NI | NI |
| SO1 | 13 | 12 | 12 |
| SO2 | 15 | NI | 7 |
| SO3 | NI | 10 | NI |
| SO4 | 8 | 10 | 14 |
| SO5 | 16 | 15 | NI |
| BO | NI | 21 | 11 |
| BO1 | 10 | 8 | 7 |
| BO2 | NI | NI | 8 |
| BO3 | NI | NI | 6 |
| BO4 | 29 | 30 | 38 |
| BO5 | 11 | 21 | 34 |
| Amoxicillin | 39 | 40 | - |
| Streptomycin | 29 | 35 | - |
| Fluconazole | - | - | 23 |

*NI = No inhibition*

**Table 4 Minimum inhibition concentration (MIC) values of synthesized compounds against *E. coli* and *S. aureus***

| Compound | *E. coli* | | *S. aureus* | |
|---|---|---|---|---|
| | Inhibition zone (mm) | MIC (mg/ml) | Inhibition zone (mm) | MIC (mg/ml) |
| SO | 8 | 400 | NI | |
| SO1 | 9 | 500 | 8 | 500 |
| SO2 | 10 | 500 | - | |
| SO3 | - | | NI | |
| SO4 | NI | | 7 | 500 |
| SO5 | 9 | 400 | 9 | 500 |
| BO | - | | 7 | 300 |
| BO1 | NI | | NI | |
| BO2 | - | | - | |
| BO3 | - | | - | |
| BO4 | 8 | 300 | 8 | 200 |
| BO5 | 8 | 500 | 9 | 300 |

*NI = No inhibition*

*- = Not tested*

Table 4 showed that the compound BO4 gave the best activity at 200 µg/ml against *S. aureus*, whereas the compounds BO and BO5 gave an activity at 300 µg/ml. On the other hand, the compounds ST4 and BT5 gave an activity at 400 µg/ml.

While, for the activity against *E. coli*, we observed that the compound BO4 exhibited the an activity at low concentration 300 µg/ml, whereas the compound SO and SO5 exhibited an activity at 400 µg/ml.

$LD_{50}$ test in mice for the selected compounds BO4 and BO5 is shown in Table 5. The results of this test indicate that the values of the $LD_{50}$ for these two compounds were in the range 1.84-2.95 g/kg. According to the classification of Klassen and Doull, we can consider these compounds as moderate toxic materials.

**Table 5 The mortality percent of the compounds BO4 and BO5**

| Dose (g/kg) | Mortality | | | Total No. of mortality | Mortality% | $LD_{50}$ (g/kg) |
|---|---|---|---|---|---|---|
| | 1st day | 2nd day | 3rd day | | | |
| BO4 compound | | | | | | |
| 2 | 0 | 0 | 1 | 1 | 20 | 2.95 |
| 3 | 2 | 0 | 1 | 3 | 60 | |
| 3.5 | 2 | 1 | 0 | 3 | 60 | |
| 4 | 2 | 1 | 1 | 4 | 80 | |
| 4.5 | 3 | 1 | 1 | 5 | 100 | |
| BO5 compound | | | | | | |
| 1 | 1 | 0 | 0 | 1 | 20 | 1.84 |
| 1.5 | 1 | 1 | 0 | 2 | 40 | |
| 1.75 | 1 | 1 | 0 | 2 | 40 | |
| 2 | 1 | 1 | 1 | 3 | 60 | |
| 2.5 | 2 | 2 | 1 | 5 | 100 | |

## CONCLUSION

The present work describes a synthesis of 5-aryl-1,3,4-oxadiazole-2-thiole parent and its S-substituted derivatives. The antimicrobial profile of the synthesized compounds revealed that some compounds showed moderate to excellent antibacterial and antifungal activities compared with the standard drug. The mercaptoester-oxadiazoles have higher activity than other mercapto-derivatives and some oxadiazole parents. Some of mercaptoester- and mercaptoacid-oxadiazoles have greater activity than standard drug against the pathogenic fungus *Aspergillus niger*.

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