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# Synthesis and antibacterial screening of some 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] acetic acids

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**ABSTRACT**

*A series of 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] acetic acids were prepared and evaluated for their antibacterial activity. Title compounds were synthesized from aryloxyacetic acid hydrazides. Aryloxyacetic acid hydrazides **1** on refluxing with carbon disulfidein presence ofmethanolic potassium hydroxide and then on acidification with hydrochloric acid yielded 5-aryloxymethyl-1, 3, 4-oxadiazole-2-thiones **2**. 2-Chloro acetic acid on reaction with **2** in basic media and then on acidification with dilute hydrochloric acid furnished the title compounds **3**. Structures of these compounds were characterized by modern spectroscopic techniques. All the compounds were studied for their in vitro antibacterial activity against two Gram positive strains (Bacillus subtilis and Staphylococcus aureus) and two Gram negative strains (Escherichia coli and Pseudomonas aeruginosa) and their minimum inhibitory concentration (MIC) were determined.*

**Keywords:** 1, 3, 4-Oxadiazoles, antibacterial activity, minimum inhibitory concentration (MIC).

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## INTRODUCTION

The significant consumption of chemotherapeutic agents as the medicine for infectious diseases leads to the growth of microbial resistance to existing drugs. The development of resistance to the main classes of antibacterial drugs is accepted as a major health concern of global population. This turn out to be the challenge for the researchers working in the field of medicinal chemistry for the development of new antimicrobial drugs having a different mechanism of action to fight against the problem of multi-drug resistance [1]. Heterocyclic compounds continue to fascinate great interest due to their diverse biological activities. Amongst them five membered heterocyclic compounds occupy a unique place in the field of natural and synthetic organic chemistry. In recent years, attention has progressively been given to the synthesis of the compounds containing 1, 3, 4-oxadiazole nucleusas a lead of developing new antibacterial agents. 1, 3, 4-Oxadiazole derivatives constitute an important class of heterocycles displayingvarious biological activities like antibacterial [2-6], antifungal [7, 8], insecticidal [9], herbicidal [10], anticancer [11], anti-inflammatory [12]*etc.* Further, [5-(aryl)-1, 3, 4-thiadiazole-2-ylthio] acetates and propionateshave been found to possess antimycobacterialactivity [13]. These reports including our continuing research work in the field of synthesis and antimicrobial activity of medicinally important compounds [14, 15] encouraged us to undertake the synthesis of some 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] acetic acids. The synthesized compounds were characterized on the basis of modern analytical techniques. These compounds were studied for their *in vitro* antibacterial activity.

## MATERIALS AND METHODS

The purity of the synthesized compounds were checked by thin layer chromatography on silica gel G in different solvent systems using iodine vapors as detecting agent. Melting points were determined by Toshniwal Melting Point Boiling Point Determination Apparatus in open capillary tubes and are uncorrected. Infra-red spectra were recorded on Shimadzu 8000-FTIRSpectrophotometer in KBr Phase. Proton NMR spectra were recorded in $CDCl_3$on Bruker Avance DRX-300 FT-NMR Spectrometer using tetramethylsilane as internal standard.Aryloxyacetic acid hydrazides **1a-g**weresynthesized by the reaction of hydrazine hydrate with the corresponding methyl esters of aryloxy acetic acids as given in the literature [16]. Similarly, 5-aryloxymethyl-1, 3, 4-oxadiazole-2-thiones **2a-g** were prepared according to the method reported earlier [17].

**General Procedure for the Synthesis of 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] acetic acids:** 5-Aryloxymethyl-1, 3, 4-oxadiazole-2-thione (**2a-g**, 0.01 M) was dissolved in sodium hydroxide solution (10%, 10 ml). This solution was added drop-wise into a solution of 2-chloro acetic acid (0.011 M) which was previously neutralized with saturated solution of sodium carbonate, and mixture was stirred for 6 to 8 h. After completion of reaction the product was obtained by precipitation with dilute hydrochloric acid. The title compound was filtered, washed, dried and re-crystallized from the rectified spirit. The physical and analytical data of the synthesized title compounds are given as follows.

**2-(5-(phenoxymethyl)-1,3,4-oxadiazol-2-ylsulfanyl) acetic acid (3a):**Yield: 89%; m.p.: 150-152 ºC; IR (KBr, $cm^{-1}$): 3200-2400 broad band (O-H), 1736 (C=O), 1607 (C=N–N=C), 1265, 1069 (C-O-C), 783, 706 (monosubstituted benzene).$^1$H NMR ($CDCl_3$): δ (ppm) 11.72 (s, 1H, COOH), 7.27-7.37 (m, 5H, ArH), 4.12 (s, 2H, $CH_2$).

**2-(5-((4-methylphenoxy) methyl)-1, 3, 4-oxadiazol-2-ylsulfanyl) acetic acid (3b):**Yield: 86%; m.p.: 155-156 ºC; IR (KBr, $cm^{-1}$): 3200-2400 broad band (O-H), 1735 (C=O), 1608 (C=N–N=C), 1263, 1068 (C-O-C),826 (*p*-disubstituted benzene).$^1$H NMR ($CDCl_3$): δ (ppm) 11.70 (s, 1H, COOH), 7.26-7.36 (m, 4H, ArH), 4.12 (s, 2H, $CH_2$), 2.41-2.43 (3H, s, aromatic methyl protons).

**2-(5-((4-methoxyphenoxy) methyl)-1, 3, 4-oxadiazol-2-ylsulfanyl) acetic acid (3c):**Yield: 80%; m.p.:121-122 ºC; IR (KBr, $cm^{-1}$): 3300-2400 broad band (O-H), 1732 (C=O), 1613(C=N–N=C), 1224, 1071 (C-O-C), 832 (*p*-disubstituted benzene).$^1$H NMR ($CDCl_3$): δ (ppm) 11.71 (s, 1H, COOH), 7.28-7.38 (m, 4H, ArH), 4.11 (s, 2H, $CH_2$), 3.86 (3H, s, aromatic methoxy protons).

**2-(5-((4-chlorophenoxy)methyl)-1,3,4-oxadiazol-2-ylsulfanyl) acetic acid (3d):** Yield: 88%; m.p.: 144-146 ºC; IR (KBr, $cm^{-1}$): 3200-2400 broad band (O-H), 1736 (C=O), 1616 (C=N–N=C), 1252, 1065 (C-O-C), 797, 833 (*p*-disubstitutedbenzene).$^1$H NMR ($CDCl_3$): δ (ppm) 11.72 (s, 1H, COOH), 7.27-7.34 (m, 4H, ArH), 4.12 (s, 2H, $CH_2$).

**2-(5-((4-bromophenoxy)methyl)-1,3,4-oxadiazol-2-ylsulfanyl) acetic acid (3e):** Yield: 86%; m.p.: 160-162 ºC; IR (KBr, $cm^{-1}$): 3200-2400 broad band (O-H), 1732 (C=O), 1601 (C=N–N=C), 1256, 1036 (C-O-C), 833 (*p-di*substituted benzene).$^1$H NMR ($CDCl_3$): δ (ppm) 11.72 (s, 1H, COOH), 7.27-7.37 (m, 4H, ArH), 4.12 (s, 2H, $CH_2$).

**2-(5-((4-fluorophenoxy)methyl)-1,3,4-oxadiazol-2-ylsulfanyl) acetic acid (3f):** Yield: 82%; m.p.: 148-149 ºC; IR (KBr, $cm^{-1}$): 3200-2400 broad band (O-H), 1735 (C=O), 1609 (C=N–N=C), 1251, 1032 (C-O-C), 838 (*p-di*substituted benzene).$^1$H NMR ($CDCl_3$): δ (ppm) 11.73 (s, 1H, COOH), 7.29-7.39 (m, 4H, ArH), 4.13 (s, 2H, $CH_2$).

**2-(5-((4-nitrophenoxy)methyl)-1,3,4-oxadiazol-2-ylsulfanyl) acetic acid (3g):** Yield: 85%; m.p.: 155-157 ºC; IR (KBr, $cm^{-1}$): 3200-2400 broad band (O-H), 1730 (C=O), 1606 (C=N–N=C), 1265, 1068 (C-O-C), 833 (*p*-disubstituted benzene).$^1$H NMR ($CDCl_3$): δ (ppm) 11.72 (s, 1H, COOH), 7.27-7.35 (m, 3H, ArH), 4.11 (s, 2H, $CH_2$).

**Antibacterial Activity:** All the titled compounds were studied for their *in vitro* antibacterial activity against two Gram positive strains, *i.e., Bacillus subtilis* (MTCC 121) and *Staphylococcus aureus* (MTCC 96) and two Gram negative strains, *i.e., Escherichia coli* (MTCC 40) and *Pseudomonas aeruginosa* (MTCC 2453).Antibacterial activity was checked by serial two fold dilutiontechnique [18]. Ciprofloxacin was used as a standard drug. Stock solutions of the compounds wereprepared in dimethyl sulfoxide having aconcentration of 10 μg $ml^{-1}$. Double strength nutrient brothwas used as a growth media. The stock solution was seriallydiluted to give concentrations of 5.0 -0.01 μg $ml^{-1}$ in nutrientbroth. The inoculum size was approximately $10^6$ colonyforming units (CFU/ml). The inoculated tubes were incubatedfor 24 h at 37(±1) °C. After 24 h, the inoculated culture tubeswere macroscopically examined for turbidity. The culture tubeshowing turbidity (lower concentration) and the culture tubeshowing no turbidity (higher concentration) gave theminimum inhibitory concentration (MIC) for the compound.The MIC for the title compounds and the standard drug, *i.e.*,ciprofloxacin are given in Table 1.

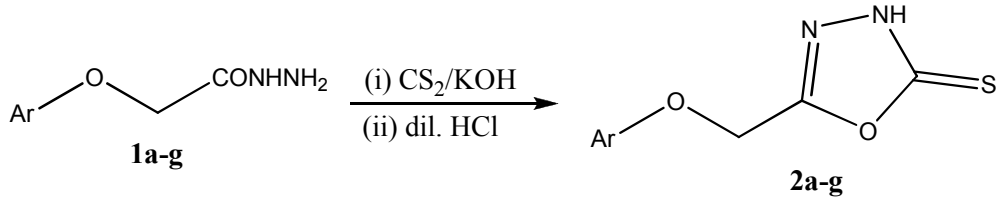
**Table 1: *In Vitro* Antibacterial Activity of the Title Compounds (3a-g)**

| Compound | Minimum Inhibitory Concentration µg ml$^{-1}$ | | | |
|---|---|---|---|---|
| | ***S. aureus*** **(MTCC 121)** | ***B. subtilis*** **(MTCC 96)** | ***E. coli*** **(MTCC 40)** | ***P. aeruginosa*** **(MTCC 2453)** |
| **3a** | 0.65 | 0.60 | 0.55 | 0.60 |
| **3b** | 0.60 | 0.55 | 0.50 | 0.60 |
| **3c** | 0.60 | 0.55 | 0.50 | 0.60 |
| **3d** | 0.55 | 0.50 | 0.40 | 0.50 |
| **3e** | 0.55 | 0.50 | 0.40 | 0.50 |
| **3f** | 0.45 | 0.45 | 0.35 | 0.45 |
| **3g** | 0.40 | 0.40 | 0.30 | 0.40 |
| **Standard Drug** | 0.15 | 0.12 | 0.01 | 0.25 |

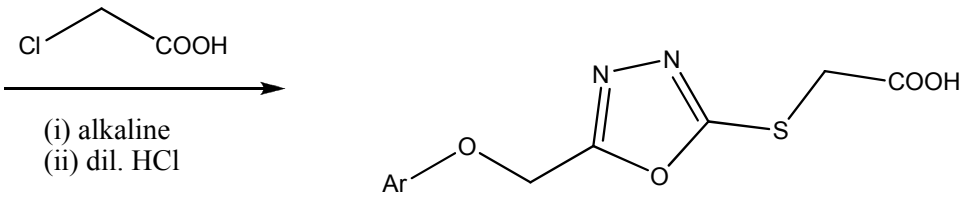
## RESULTS AND DISCUSSION

### Chemistry

The syntheses of 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] acetic acids **3** were accomplished following the steps outlined in Scheme 1. Reaction of aromatic carboxylic acid hydrazides **1** with carbon disulfide and methanolic potassium hydroxide and then acidification with dilute hydrochloric acid yielded the corresponding 5-aryloxymethyl-1, 3, 4-oxadizole-2-thiones **2.** The intermediates **2** on reaction with 2-chloro acetic acid in basic medium and then subsequent acidification with dilute hydrochloric acid afforded the title compounds **3** in good yield.




**1a-g** **2a-g**




**3a-g**

| **Ar** | |
|---|---|
| 3a | $C_6H_5$ |
| 3b | $CH_3$-C6$H_4$ |
| 3c | $CH_3O$-$C_6H_4$ |
| 3d | Cl-$C_6H_4$ |
| 3e | Br-$C_6H_4$ |
| 3f | F-$C_6H_4$ |
| 3g | $NO_2$-$C_6H_4$ |

**Scheme 1: Synthesis of 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] acetic acids**

Infrared spectra of each compound showed a broad band for O-H *stretching* vibrations in the range of 3200-2400 $cm^{-1}$. The C=O *stretching* vibrations for the carboxyl group were absorbed in the range of 1736-1730 $cm^{-1}$. The absorption for aromatic C-H *bending* vibrations was observed below 900 $cm^{-1}$. IR absorption bands due to C-O-C grouping of 1, 3, 4-oxadiazole nucleus were observed in the range of 1275-1200 $cm^{-1}$ and 1077-1020 $cm^{-1}$. Similarly, the grouping C=N-N=C of 1, 3, 4-oxadiazole nucleus also showed the IR absorption in the assigned range of 1670-1600 $cm^{-1}$. In case of $^1$H NMR, the chemical shiftvalue for carboxyl group was observed in the range of 12.41-11.72 δ (ppm) and appeared as singlet (s).Aromatic protons appeared as multiplet (m) in the assigned value of 6.99-7.67 δ (ppm). Methylene protons appeared as singlet at δ (ppm) 4.13-4.11.

**Minimum Inhibitory Concentration (MIC)**

The reference standard ciprofloxacin inhibited Gram positive bacteria *S. aureus* and *Bacillus subtilis* at MIC of 0.15 μg $ml^{-1}$ and 0.12 μg $ml^{-1}$respectivelywhereas MIC against Gram negative bacteria *E. coli* and *P. aeruginosa* were found to be in the range of 0.01 μg $ml^{-1}$ and 0.25 μg $ml^{-1}$ respectively. All the synthesized compounds **3a-g**showed significant antibacterial activity against *P. aeruginosa* (MIC 0.40-0.60μg $ml^{-1}$), *S. aureus* (MIC 0.40-0.65μg $ml^{-1}$) and *B. subtilis* (MIC 0.40-0.60μg $ml^{-1}$) whereas moderate antibacterial activity was found against *E. coli* (MIC 0.30-0.55μg $ml^{-1}$) as compared to the standard drug ciprofloxacin (Table 1). Compounds containing 4-nitro moiety (**3g**) was found to be most active. The results of the MIC for the standard drug, ciprofloxacin, against the bacterial strains used were found to be within the range as reported in literature [19-21].

## CONCLUSION

Present work describes a straightforward synthesis of new 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl]acetic acids. The structures of the synthesized title compounds were ascertained by the modern analytical techniques. The title compounds were screenedfor*in vitro* antibacterial activityagainst two Gram positive strains, *i.e., Bacillus subtilis* (MTCC 121) and *Staphylococcus aureus* (MTCC 96) and two Gram negative strains, *i.e., Escherichia coli* (MTCC 40) and *Pseudomonas aeruginosa* (MTCC 2453).Compounds **3g** exhibited significant activity against all the bacterial strains used in this study. These results suggest that some more compounds should be synthesized and checked for antibacterial activity to explore the possibility of 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl]acetic acids as a novel series of antibacterial drugs.

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