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

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### ABSTRACT

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

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

### INTRODUCTION

The considerable use of chemotherapeutic agents as the medication for infectious diseases leads to the development of microbial resistance to current drugs. The advent of resistance to the foremost classes of antibacterial drugs is accepted as a major health concern of worldwide population. This turn out to be the challenge for the medicinal chemists for the development of novel antimicrobial drugs having a different mechanism of action to battle the problem of multi-drug resistance [1]. Heterocyclic compounds continue to fascinate considerable 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 increasingly been given to the synthesis of 1, 3, 4-oxadiazole derivatives as a source of developing new antibacterial agents. 1, 3, 4-Oxadiazole derivatives constitute an important class of heterocycles possessing diverse 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] propionates have been found to possess antimycobacterial activity [13]. These reports including our ongoing research program in the field of synthesis and antimicrobial activity of medicinally important compounds [14, 15] inspired us to undertake the synthesis of some 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] propanoic acids. The synthesized compounds were characterized on the basis of modern analytical techniques. These compounds were evaluated for their *in vitro* antibacterial activity.

### MATERIALS AND METHODS

The purity of the synthesized compounds were ascertained by thin layer chromatography on silica gel G in various 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-FTIR Spectrophotometer in KBr Phase. Proton NMR spectra were recorded in CDCl<sub>3</sub> on Bruker Avance DRX-300 FT-NMR Spectrometer using tetramethyl silane as internal standard. Aryloxyacetic acid hydrazides **1a-g** were prepared by the reaction of hydrazine hydrate with the corresponding methyl esters of aryloxy acetic acids as described in the literature [16]. Similarly, 5-aryloxymethyl-1, 3, 4-oxadiazole-2-thiones **2a-g** were synthesized according to the method reported earlier [17].

**General Procedure for the Synthesis of 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] propanoic 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 propanoic 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) propanoic acid (3a):** Yield: 86%; m.p.:120-122 °C; IR (KBr, cm<sup>-1</sup>): 3300-2400 broad band (O-H), 1732 (C=O), 1609 (C=N-N=C), 1225, 1070 (C-O-C), 781, 708 (monosubstituted benzene). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ (ppm) 11.72 (s, 1H, COOH), 7.27-7.37 (m, 4H, ArH), 4.46-4.53 (q, 1H, CH), 1.75-1.78 (d, 3H, CH<sub>3</sub>).

**2-(5-((4-methylphenoxy) methyl)-1, 3, 4-oxadiazol-2-ylsulfanyl) propanoic acid (3b):** Yield: 81%; m.p.:123-124 °C; IR (KBr, cm<sup>-1</sup>): 3300-2400 broad band (O-H), 1731 (C=O), 1611 (C=N-N=C), 1227, 1072 (C-O-C), 824 (*p*-disubstituted benzene). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ (ppm) 11.72 (s, 1H, COOH), 7.28-7.38 (m, 4H, ArH), 4.46-4.53 (q, 1H, CH), 2.41-2.43 (3H, s, aromatic methyl protons), 1.75-1.78 (d, 3H, CH<sub>3</sub>).

**2-(5-((4-methoxyphenoxy) methyl)-1, 3, 4-oxadiazol-2-ylsulfanyl) propanoic acid (3c):** Yield: 81%; m.p.:123-124 °C; IR (KBr, cm<sup>-1</sup>): 3300-2400 broad band (O-H), 1731 (C=O), 1611 (C=N-N=C), 1227, 1072 (C-O-C), 835 (*p*-disubstituted benzene). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ (ppm) 11.72 (s, 1H, COOH), 7.28-7.38 (m, 4H, ArH), 4.46-4.53 (q, 1H, CH), 3.88 (3H, s, aromatic methoxy protons), 1.74-1.77 (d, 3H, CH<sub>3</sub>).

**2-(5-((4-chlorophenoxy) methyl)-1,3,4-oxadiazol-2-ylsulfanyl)propanoic acid (3d):**Yield: 85%; m.p.: 126-128 °C; IR (KBr, cm<sup>-1</sup>): 3200-2400 broad band (O-H), 1734 (C=O), 1620 (C=N-N=C), 1256, 1072 (C-O-C), 831 (*p*-disubstituted benzene). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ (ppm) 11.72 (s, 1H, COOH), 7.27-7.34 (m, 4H, ArH), 4.47-4.54 (q, 1H, CH), 1.76-1.78 (d, 3H, CH<sub>3</sub>).

**2-(5-((4-bromophenoxy) methyl)-1, 3, 4-oxadiazol-2-ylsulfanyl) propanoic acid (3e):** Yield: 83%; m.p.: 1146-1147 °C; IR (KBr, cm<sup>-1</sup>): 3200-2400 broad band (O-H), 1732 (C=O), 1601 (C=N-N=C), 1256, 1036 (C-O-C), 832 (*p*-disubstituted benzene). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ (ppm) 11.75 (s, 1H, COOH), 7.27-7.37 (m, 4H, ArH), 4.47-4.54 (q, 1H, CH), 1.76-1.78 (d, 3H, CH<sub>3</sub>).

**2-(5-((4-fluorophenoxy) methyl)-1, 3, 4-oxadiazol-2-ylsulfanyl) propanoic acid (3f):** Yield: 81%; m.p.: 150-152 °C; IR (KBr, cm<sup>-1</sup>): 3200-2400 broad band (O-H), 1730 (C=O), 1602 (C=N-N=C), 1256, 1036 (C-O-C), 834 (*p*-disubstituted benzene). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ (ppm) 11.76 (s, 1H, COOH), 7.27-7.37 (m, 4H, ArH), 4.47-4.54 (q, 1H, CH), 1.76-1.78 (d, 3H, CH<sub>3</sub>).

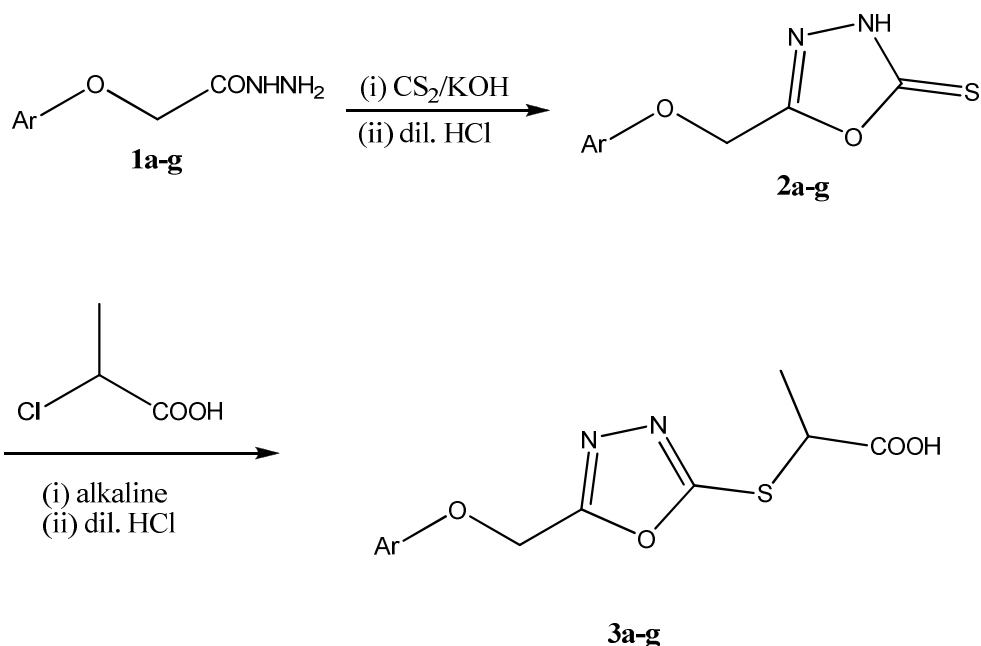
**2-(5-((4-nitrophenoxy) methyl)-1, 3, 4-oxadiazol-2-ylsulfanyl) propanoic acid (3g):** Yield: 86%; m.p.: 161-163°C; IR (KBr, cm<sup>-1</sup>): 3300-2400 broad band (O-H), 1732 (C=O), 1608 (C=N-N=C), 1224, 1070 (C-O-C), 834 (*p*-disubstituted benzene). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ (ppm) 11.72 (s, 1H, COOH), 7.27-7.35 (m, 3H, ArH), 4.46-4.53 (q, 1H, CH), 1.75-1.78 (d, 3H, CH<sub>3</sub>).

**Antibacterial Activity:** All the compounds were screened for their *in vitro* antibacterial activity against two Gram negative strains, *i.e.*, *Escherichia coli* (MTCC 40) and *Pseudomonas aeruginosa* (MTCC 2453), and two Gram positive strains, *i.e.*, *Bacillus subtilis* (MTCC 121) and *Staphylococcus aureus* (MTCC 96). Antibacterial activity was assessed by serial two fold dilution technique [18]. Ciprofloxacin was used as a standard drug. All the compounds were dissolved in dimethyl sulfoxide to give a concentration of 10 μg ml<sup>-1</sup>. Double strength nutrient broth was used as a growth media. The stock solution was serially diluted to give concentrations of 5.0 -0.01 μg ml<sup>-1</sup> in nutrient broth. The inoculum size was approximately 10<sup>6</sup> colony forming units (CFU/ml). The inoculated tubes were incubated for 24 h at 37(±1) °C. After 24 h, the inoculated culture tubes were macroscopically examined for turbidity. The culture tube showing turbidity (lower concentration) and the culture tube showing no turbidity (higher

concentration) gave the minimum 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 $\mu\text{g ml}^{-1}$			
	<i>E. coli</i> (MTCC 40)	<i>P. aeruginosa</i> (MTCC 2453)	<i>S. aureus</i> (MTCC 121)	<i>B. subtilis</i> (MTCC 96)
3a	0.50	0.65	0.60	0.55
3b	0.45	0.60	0.55	0.50
3c	0.45	0.60	0.55	0.50
3d	0.40	0.55	0.50	0.45
3e	0.40	0.55	0.50	0.45
3f	0.35	0.45	0.40	0.40
3g	0.30	0.40	0.35	0.35
Standard Drug	0.01	0.25	0.15	0.12



Ar

- 3a C<sub>6</sub>H<sub>5</sub>
- 3b CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>
- 3c CH<sub>3</sub>O-C<sub>6</sub>H<sub>4</sub>
- 3d Cl-C<sub>6</sub>H<sub>4</sub>
- 3e Br-C<sub>6</sub>H<sub>4</sub>
- 3f F-C<sub>6</sub>H<sub>4</sub>
- 3g NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>

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

## RESULTS AND DISCUSSION

### Chemistry

The syntheses of 2-[5-(aryloxymethyl)-1,3,4-oxadiazol-2-ylsulfanyl] propanoic acids **3** were achieved following the steps outlined in Scheme 1. Reaction of aromatic carboxylic acid hydrazides **1** with methanolic potassium hydroxide and carbon disulfide and then acidification with dilute hydrochloric acid afforded the corresponding 5-aryloxymethyl-1,3,4-oxadiazole-2-thiones **2**. The intermediates **2** on reaction with 2-chloro propionic acid in

alkaline medium and then subsequent acidification with dilute hydrochloric acid furnished the title compounds **3** in good yield.

Infrared spectra of each compound showed a broad band for O-H *stretching* vibrations in the range of 3200-2400  $\text{cm}^{-1}$ . The C=O *stretching* vibrations for the carboxyl group were absorbed in the range of 1736-1730  $\text{cm}^{-1}$ . The absorption for aromatic C-H *bending* vibrations was observed below 900  $\text{cm}^{-1}$ . IR absorption bands due to C-O-C grouping of 1, 3, 4-oxadiazole nucleus were observed in the range of 1275-1200  $\text{cm}^{-1}$  and 1075-1020  $\text{cm}^{-1}$ . 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  $\text{cm}^{-1}$ . In case of  $^1\text{H}$  NMR, the chemical shift value for carboxyl group was observed in the range of 12.41-11.72  $\delta$  (ppm) and appeared as singlet (s). Aromatic protons appeared as multiplet (m) in the assigned value of 6.99-7.67  $\delta$  (ppm). Methylene protons appeared as singlet at  $\delta$  (ppm) 4.12 whereas methine and aliphatic methyl protons absorbed at  $\delta$  (ppm) 4.47-4.54 and  $\delta$  (ppm) 1.76-1.78, respectively. Both of them also showed splitting of signals and appeared as quartet (q) and doublet (d), respectively.

#### Minimum Inhibitory Concentration (MIC)

The reference standard ciprofloxacin inhibited Gram negative bacteria *E. coli* and *P. aeruginosa* at a MIC of 0.01  $\mu\text{g ml}^{-1}$  and 0.25  $\mu\text{g ml}^{-1}$ , respectively whereas against Gram positive bacteria *S. aureus* and *Bacillus subtilis* MIC was found to be 0.15  $\mu\text{g ml}^{-1}$  and 0.12  $\mu\text{g ml}^{-1}$ , respectively. All the synthesized compounds **3a-g** showed significant antibacterial activity against *P. aeruginosa* (MIC 0.40-0.65  $\mu\text{g ml}^{-1}$ ), *S. aureus* (MIC 0.35-0.60  $\mu\text{g ml}^{-1}$ ) and *B. subtilis* (MIC 0.35-0.55  $\mu\text{g ml}^{-1}$ ) whereas moderate antibacterial activity was found against *E. coli* (MIC 0.30-0.50  $\mu\text{g ml}^{-1}$ ) 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 study describes a straightforward synthesis of new 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] propanoic acids. The structures of the synthesized compounds were ascertained by the modern analytical techniques. The title compounds were evaluated for *in vitro* antibacterial activity against two Gram negative strains, *i.e.*, *Escherichia coli* (MTCC 40) and *Pseudomonas aeruginosa* (MTCC 2453), and two Gram positive strains, *i.e.*, *Bacillus subtilis* (MTCC 121) and *Staphylococcus aureus* (MTCC 96). 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 screened for antibacterial activity to explore the possibility of 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] propanoic acids as a novel series of antibacterial drugs.

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