



## Synthesis and Antimicrobial Activity of Some New Substituted Aryloxy-4-Thiazolidinones

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**Abstract:** Nine new substituted aryloxy-4-thiazolidinones have been prepared from corresponding schiff bases and thioglycolic acid in benzene using Stark and Dien apparatus. The synthesized compounds were identified by spectral studies and screened for antimicrobial activity.

**Key words:** Schiff base, Synthesis, 4-thiazolidinone, Anti-microbial activity

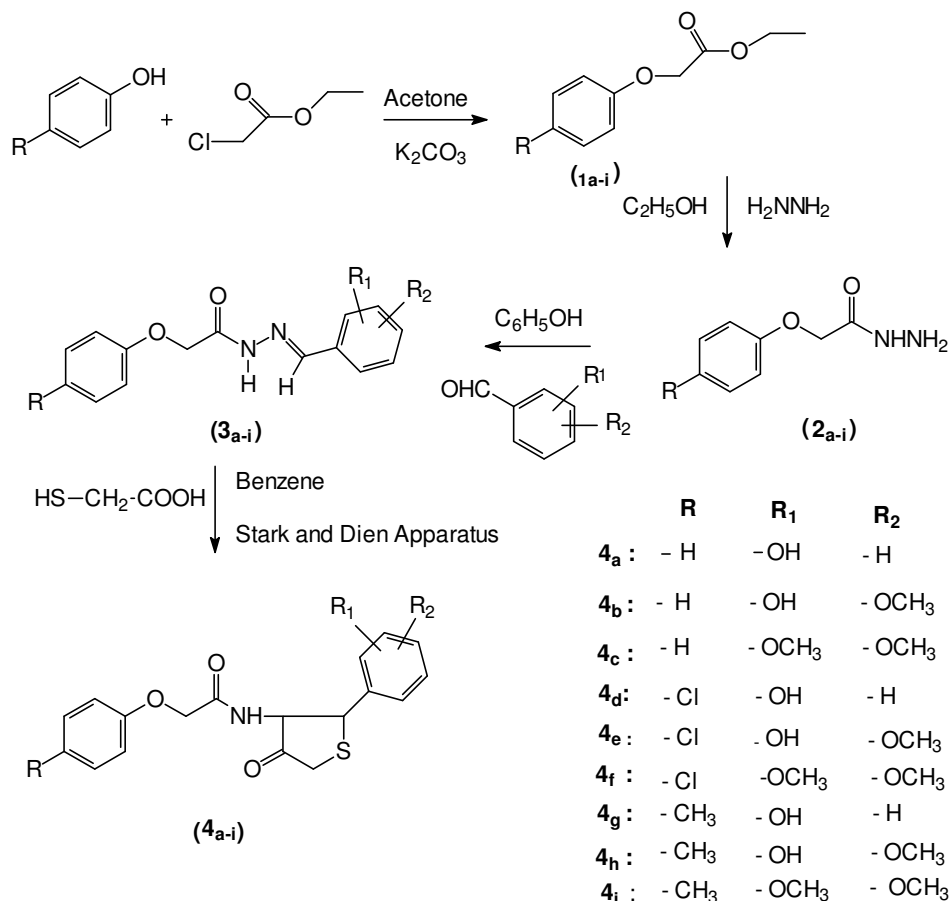
### Introduction

4-thiazolidinones are well known heterocyclic compounds for their spectrum of biological activities such as antibacterial<sup>1</sup>, antifungal<sup>2</sup>, antitubercular<sup>3</sup>, anthelmintic<sup>4</sup>, anti-inflammatory<sup>5</sup>, antithyroid<sup>6</sup>, local anaesthetic<sup>7</sup>, monoamine oxidase inhibition<sup>8</sup> etc. In the present study we synthesized nine aryloxy-4-thiazolidinone derivatives (4a-i) by condensing proper substituted Schiff bases and thioglycolic acid in benzene using Stark and Dien apparatus (**Scheme- 1**). The structures of these derivatives were assigned on the basis of elemental analysis, IR and <sup>1</sup>H NMR spectral data. The compounds were screened for antimicrobial activity.

### Experimental

The IR spectra were recorded on Perkin -Elmer FTIR 881 spectrophotometer. Melting points were determined on Boitus melting point apparatus and were uncorrected. <sup>1</sup>H NMR spectra were recorded on Jeol JNM 90 MHz NMR spectrometer using TMS as internal standard.

Elemental analysis was carried out on Carlo Erba 1108 instrument. Column chromatography was carried out using silica gel (finer than 200#, ACME) and Flash Chromatography (FC) was performed on BUCHI Sepacore Advanced Flash Chromatography system.



Scheme-1

### General procedure for the preparation of 4-thiazolidinones

#### Preparation of aryloxy ethyl acetates (1 a-c)

Mixture of Phenol (0.2 mol), ethyl chloro acetate (0.2 mol) and anhydrous potassium carbonate (0.2 mol) was taken in a round bottom flask containing 300ml of acetone and refluxed on a water bath for 16hrs. Excess of acetone was removed from the reaction mixture and the contents were cooled to room temperature and poured into ice-cold water with constant stirring. The oily layer was extracted with ether in a separating funnel. Ether layer was collected and the excess of ether was removed. The ester so obtained was purified by distillation under reduced pressure.

**Preparation of aryloxy acethydrazides (2a-c)**

Aryloxy ethyl acetate (0.2 mol) and Hydrazine hydrate (0.2 mol) were taken in a round bottom flask containing 250 ml of ethanol. This mixture was refluxed on a water bath for 4 h, after excess of ethanol was removed from the reaction mixture by distillation and cooled to room temperature and poured into ice-cold water. The solid separated was collected by filtration and dried. Further purification was done by recrystallizing from ethanol.

**Preparation of Schiff bases (3a-c)**

Aryloxy acet hydrazide (0.2 mol) and appropriately substituted aldehyde (0.2 mol) were dissolved in minimum quantity of ethanol and the mixture was taken in a round bottom flask. To this mixture 2 or 3 drops of conc. sulphuric acid was added and this mixture is refluxed on a water bath for 10 hrs. After refluxing the excess of ethanol was removed from the reaction mixture and cooled it to room temperature. Then it was poured into ice-cold water and filtered. The solid obtained was collected and recrystallized from ethanol.

**Preparation of 2-(substituted phenyl)-3-substituted phenoxy-acetamido-4-thiazolidinones**

Schiff base (0.2 mol) and thioglycolic acid (0.22 mol) and benzene (200 ml) were taken in a Stark and Dien apparatus. This mixture was refluxed on a water bath for 12 hrs and the excess of benzene was removed by evaporation. The contents were cooled to room temperature, poured into ice-cold water and filtered. The solid so obtained was collected and purified by recrystallization from ethanol.

Table 1. Characterisation data of compounds (4<sub>a-i</sub>)

Compd.	m.f.	m.p. (°C)	Yield (%)	Elemental analysis (%)					
				N		O		S	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
4 <sub>a</sub>	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> SO <sub>4</sub>	196	56	8.1	7.9	18.6	18.4	9.3	9.1
4 <sub>b</sub>	C <sub>18</sub> H <sub>19</sub> N <sub>2</sub> SO <sub>5</sub>	212	64	7.5	7.8	21.4	21.6	8.6	8.5
4 <sub>c</sub>	C <sub>19</sub> H <sub>22</sub> N <sub>2</sub> SO <sub>5</sub>	220	67	7.2	6.9	20.6	20.5	8.3	8.4
4 <sub>d</sub>	C <sub>17</sub> H <sub>15</sub> ClNSO <sub>3</sub>	210	65	7.4	7.6	16.9	17.1	8.5	8.6
4 <sub>e</sub>	C <sub>18</sub> H <sub>17</sub> ClN <sub>2</sub> SO <sub>5</sub>	217	68	6.9	6.6	19.6	19.4	7.8	7.6
4 <sub>f</sub>	C <sub>19</sub> H <sub>19</sub> ClN <sub>2</sub> SO <sub>5</sub>	226	72	6.6	6.5	18.9	18.8	7.6	7.5
4 <sub>g</sub>	C <sub>18</sub> H <sub>18</sub> N <sub>2</sub> SO <sub>4</sub>	205	61	7.8	7.9	17.9	17.6	8.9	9.0
4 <sub>h</sub>	C <sub>19</sub> H <sub>20</sub> N <sub>2</sub> SO <sub>5</sub>	234	63	7.2	7.4	20.6	20.4	8.3	8.2
4 <sub>i</sub>	C <sub>20</sub> H <sub>22</sub> N <sub>2</sub> SO <sub>5</sub>	227	64	7.0	6.8	19.9	19.8	8.0	7.8

**Anti-microbial activity**

The cup-plate method<sup>9, 10</sup> using Mueller – Hinton agar medium was employed to study the preliminary anti-bacterial activity of 4 (a-i) against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa*. Preparation of base layer medium, agar medium and peptone water was done as per the standard procedure. Each test compound (10 mg/ml) was prepared by dissolving 50mg in 5ml of dimethylformamide and used for testing. Same cup-plate method using PDA medium was employed to study the preliminary antifungal activity of 4 (a-i) against *Candida albicans* and *A. niger*. The PDA medium was purchased from HIMedia Laboratories Ltd, Mumbai, India. Preparation of nutrient broth, sub culture, base layer medium and PDA medium was done as per the standard procedure. Each test compound 50i g/cup was used for testing.

Table-2. IR, <sup>1</sup>H NMR Spectral data of the compounds (4<sub>a-i</sub>)

Compd code	IR (cm <sup>-1</sup> ) (KBr)	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) (δppm)
4a	848,1710,1497, 1215,1618,1677 3556	6.89 (3H, m, H-3', 6'', 2''), 7.51 – 7.86 (6H, m, H-4', 5', 6', 3'', 4'' and 5''), 5.11 (1H, s, H-2), 4.32 (2H, s, H <sub>2</sub> -Ċ) and 3.98 (2H, s, H <sub>2</sub> -5)
4b	689, 747, 1088, 1223,1681,1715, 3056,3225, 3468	7.51-7.72(m, 3H, H-3'',4'',5''), 7.11 (1H, br d, J=11.2Hz, H-6'), 6.92 (1H, br s, H-2'), 6.78 (2H, d, J=8Hz, H-2'', 6''), 6.48 (1H, d, J=11Hz, 5'), 5.12 (1H, s, H-2), 4.38 (2H, s, H <sub>2</sub> -Ċ), 3.95 (2H, s, H <sub>2</sub> -5), 3.82 (3H, s, -OCH <sub>3</sub> )
4c	739, 1088, 1223, 1685,1714,3055, 3065,3231, 3472	7.48-7.65 (3H, m, H-3'', 4'', 5''), 7.12 (br d, J = 11.1Hz, H-6'), 6.85 (1H, br s, H-2'), 6.75 (2H, d, J=8Hz, 2'', 6''), 6.46 (1H, d, J=11Hz, H-5'), 5.15 (1H, s, H-2), 4.31 (2H, s, H <sub>2</sub> -Ċ), 4.01 (2H, s, H <sub>2</sub> -5), 3.98 (3H, s, -OCH <sub>3</sub> ), 4.05 (3H, s, -OCH <sub>3</sub> )
4d	689, 747, 1088, 1223,1298, 417, 1497,1685,1705, 3066,3225, 3468	7.56 – 7.73 (3H, m, 4', 5', 6'), 7.11 (2H, d, J=9Hz, 2'', 6''), 6.92(2H, d, J=9Hz,3'', 5'' ), 6.85 (br d, J=9.2Hz, 3'), 5.15 91H, s, H-2), 4.31 (2H, s, H <sub>2</sub> -Ċ), 4.01 (2H, s, H <sub>2</sub> -5)
4e	689, 751, 1088, 1289,1668,1705, 3225,3468, 3510	7.18(2H, d, J=9Hz, H-2'', 6''), 7.09 (br d, J=11Hz, H-6'), 6.89 (2H, d, J=9Hz, H-3'', 5''), 6.81 (1H, br s, H-2'), 6.45 (1H, d, J=10Hz, H-5'), 5.12 (1H, s, H-2), 4.28(2H, s, H <sub>2</sub> -Ċ), 3.89 (2H, s, H <sub>2</sub> -5), 2.91 (3H, s, -OCH <sub>3</sub> )
4f	691, 751, 1088, 1292,1670,1705, 3223, 3472	7.16 (3H, m, 6', 2'', 6''), 6.90 (2H, d, J=8.5Hz, H-3'', 5''), 6.82 (1H, br s, H-2'), 6.51 (1H, d, J=10Hz, H-5'), 5.16 (1H, s, H-2), 4.32(2H, s, H <sub>2</sub> -Ċ), 4.02 (2H, s, H <sub>2</sub> -5), 3.91 (3H, s, -OCH <sub>3</sub> ), 4.03 (3H, s, -OCH <sub>3</sub> )
4g	689,742,1022,14 98,1608,1692, 1731,2918,2965, 3012	7.54 (-7.69 (3H, m, 4', 5', 6'), 7.31 (2H, d, J=8.8Hz), 7.18 (2H, d, J=8.8Hz), 6.89 (1H, br d, J=9Hz), 5.12 (1H, s, H-2), 4.28 (2H, s, H <sub>2</sub> -Ċ), 4.05 (2H, s, H <sub>2</sub> -5), 2.75 (3H, s, Ar-CH <sub>3</sub> )
4h	689,742,1022,14 89, 1608, 1692, 1731,2918,2965, 3012, 3468	7.35 (2H, d, J=8.5Hz, H-2'', 6''), 7.22 (2H, d, J=8.5Hz, H-3'', 5''), 7.10 (1H, dd, J=9, 2Hz), 6.85 (1H, d, d, J=2Hz, H-2'), 6.61 (1H, d, J=9Hz), 5.15 (1H, s, H-2), 4.25 (2H, s, H-Ċ), 4.11 (2H, s, H <sub>2</sub> -5), 4.01 (3H, s, -OCH <sub>3</sub> ), 2.69(3H, s, Ar-CH <sub>3</sub> )
4i	689,748,1022,14 89, 1608, 1692, 1731,2918,2966, 3018, 3476	7.33 (2H, d, J=9.1Hz, H-2'', 6''), 7.19 (2H, d, J=9.1Hz, H-3'', 5''), 7.16 (1H, d, J=1.8Hz, H-6'), 6.79 (1H, d, J=10Hz,H-2'), 6.52 (1H, d, J=10Hz, H-5'), 5.18 (1H, s, H-2), 4.25 (2H, s, H <sub>2</sub> -Ċ), 4.12 (2H, s, H <sub>2</sub> -5), 4.02 (3H, s, -OCH <sub>3</sub> ), 3.98 (3H, s, -OCH <sub>3</sub> ), 2.75 (3H, s, Ar-CH <sub>3</sub> )

The cups of 9mm diameter were made by scooping out medium with a sterilized cork borer in a petri dish which was streaked with organisms. The solutions of each compound were added separately in the cups and petri dishes were subsequently inoculated. Ampicillin and Griesofulvin (6 ĩ g/cup and 25ĭ g/cup respectively) were used as standard reference drugs and dimethylformamide (DMF) used as control which did not show any inhibition. Zone of inhibition produced by each compound was measured in mm and the results are presented in Table 3.

Table 3. Zone of Inhibition of Compounds [4<sub>a-i</sub>]

Compound code	<i>S.aureus</i>	<i>B.subtilis</i>	<i>E.coli</i>	<i>P.aerugina</i>	<i>C. albicans</i>	<i>A. niger</i>
4a	6	8	7	10	9	7
4b	5	9	8	10	12	13
4c	6	8	5	7	9	17
4d	12	10	9	10	7	8
4e	7	8	9	6	8	6
4f	8	10	6	9	12	7
4g	8	9	7	6	7	9
4h	14	8	10	5	11	12
4i	7	8	9	6	10	13
Ampicillin	14	12	13	17	---	---
Griseofulvin	---	---	---	---	14	15
DMF	----	----	----	----	----	----

## Results and Discussion

All the tested compounds have shown antibacterial activity to some extent. Among the tested compounds 4<sub>b</sub>, 4<sub>d</sub>, 4<sub>f</sub> and 4<sub>h</sub> showed very good activity against the tested organisms. Compounds 4<sub>a</sub>, 4<sub>e</sub> and 4<sub>g</sub> are moderate antibacterial activity. The compounds 4<sub>a</sub>, 4<sub>b</sub> and 4<sub>i</sub> showed good antifungal activity and 4<sub>c</sub> and 4<sub>f</sub> showed moderate antibacterial activity. All the compounds synthesized possess electron releasing groups, on both the aromatic rings. There fore from the results it is evident that compounds having electron releasing groups like methyl, hydroxy and methoxy may be responsible for antibacterial and antifungal activities.

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