

## THIAZOLIDINONE BASED 2,5-DISUBSTITUTED-1,3,4-THIADIAZOLE: SYNTHESIS AND ANTIMICROBIAL EVALUATION

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### ABSTRACT

Substituted salicylic acid and thiosemicarbazide were refluxed in acidic medium to obtain 2-amino-5-(o-hydroxysubstituted phenyl)-1,3,4-thiadiazol (1) which on treatment with various aryl aldehydes and then with thioylglycolic acid gives 2-(substitutedphenyl)-3-(2-hydroxysubstitutedphenyl-1,3,4-thiadiazol-2-yl) thiazolidin-4-ones (3). Structure of the compounds (3<sub>a-1</sub>) were confirmed on the basis of IR and <sup>1</sup>H NMR data. All the compounds were tested against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans* and *Aspergillus niger*.

**Keywords:** Thiadiazole, Thiazolidinone, Antibacterial, Antifungal.

### INTRODUCTION

1,3,4-Thiadiazoles represents one of the most active class of compounds possessing variety of biological and pharmacological activities, viz., anticancer[1], antiviral[2], anti-inflammatory[3], analgesic[4], carbonic anhydrase inhibitors[5], anticonvulsant[6], H<sub>2</sub>-antagonists[7], antibacterial[8] and antifungal activities[9]. Further thiazolidinone are well known for their antimicrobial activity[10]. In this paper, we have synthesized some new thiazolidinone derivatives containing thiadiazole moiety. All the synthesized compounds were screened for antimicrobial activity against some selected microbes.

### MATERIAL AND METHOD

The chemicals and solvents used for the experimental work were commercially procured from E. Merck, CDH, S. D. Fine Chem. and Qualigens, all from India. Melting points were determined in an open capillary tube and are uncorrected. IR spectra (cm<sup>-1</sup>) were recorded on a FTIR-8400s Shimadzu system. The proton magnetic resonance spectra (H NMR) were recorded on a Bruker 300 MHz instrument (Bruker, Germany) in DMSO-*d*<sub>6</sub> using tetramethylsilane as internal standard. Chemical shifts (δ) are expressed in ppm. Progress of each step was observed by TLC.

#### Step-I: Synthesis of 2-amino-5-(o-hydroxy substituted phenyl)-1,3,4-thiadiazol (1<sub>a,b</sub>)

An ethanolic solution of substituted salicylic acid was mixed with aqueous solution of thiosemicarbazide with continuous stirring. Few

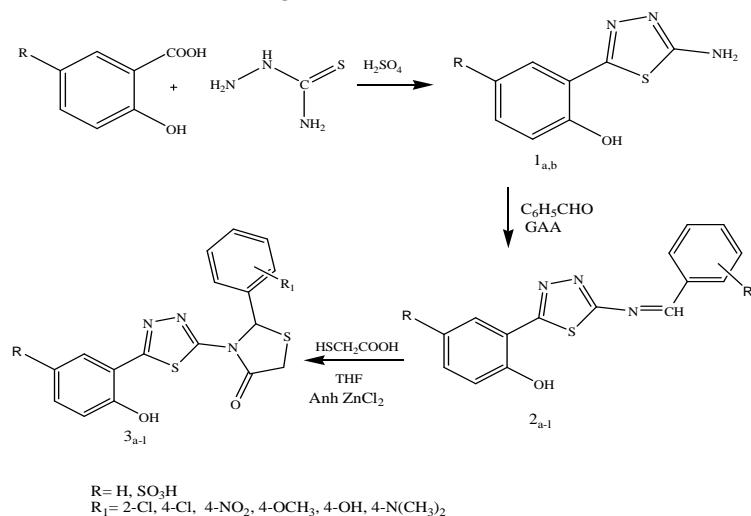
drops of concentrated sulphuric acid were added and the solution was refluxed for 3 hours. The crude product is obtained on cooling, washed with cold water and recrystallized with ethanol to obtain the product (1<sub>a,b</sub>). Yield 93%; m.p. 159°C. IR (KBr, cm<sup>-1</sup>) 1620 (C=N Str), 1050 (N-N), 675 (C-S-C), 3290 (N-H), 3045 (Ar-CH), 1230 (C-O Str). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): 7.43-7.77 (m, 4H, ArH), 8.2(s, 1H, OH) and 6.12(s, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable).

#### STEP-II: Synthesis of 2-(5-(substitutedbenzylideneamino)-1,3,4-thiadiazole-2-yl)substituted phenol (2<sub>a-1</sub>)

Equimolar quantities of (1) and different aryl aldehydes in methanol (50 ml) with 2 ml of glacial acetic acid were refluxed for 4-6 hours. The crude product obtained on cooling was recrystallized with ethanol. Yield 68%; m.p.144 °C. IR (KBr, cm<sup>-1</sup>) 1545 (C=N Str), 1047 (N-N), 695 (C-S-C), 3218 (N-H), 2937 (Ar-CH), 1678 (C-O Str), 824 (C-Cl). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): 7.89-8.16 (m, 7H, ArH), 7.78 (s, 1H, OH), and 9.49(s, 1H, NH, D<sub>2</sub>O exchangeable).

#### STEP-III: Synthesis of 2-(substitutedphenyl)-3-(2-hydroxy-substitutedphenyl-1,3,4-thiadiazol-2-yl) thiazolidin-4-one (3<sub>a-1</sub>)

Equimolar quantities of (2) and mercaptoacetic acid (10 ml) with small amount of anhydrous ZnCl<sub>2</sub> was added in 30 ml of THF and refluxed for 12-16 hours on water bath. The product separated was recrystallized with ethanol. yield 65%; m.p. 130°C. IR (KBr, cm<sup>-1</sup>) 1551 (C=N Str), 1056 (N-N), 634 (C-S-C), 3034 (Ar-CH), 904 (C-Cl) and 1678 (C=O Str).<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): 6.96-7.89 (m, 7H, ArH), 7.78 (s, 1H, OH) and 4.86-6.24 (m, 3H, thiazolidinone).



Scheme-I

### Antimicrobial activity

Cup plate method[11] using Muller-Hinton agar medium was employed to study the preliminary antibacterial activity of (3<sub>a-i</sub>) against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The agar medium was purchased from HI-media Laboratories Ltd, Mumbai, India.. Each compound was dissolved in DMSO. Ciprofloxacin was employed as standard (50µg /ml) to compare the results. The pH of all the test and control solution was maintained at 2-3 by using concentrated HCl, as the compounds were not diffused through agar medium at pH below 3. All the compounds were tested at concentration of 50 µg/ml.

Same cup plate method using PDA (potato dextrose agar) medium was employed to study the preliminary antifungal activity of (3<sub>a-i</sub>) against *Candida albicans* and *Aspergillus niger*. The agar medium was

purchased from HI-media Laboratories Ltd, Mumbai, India.. Each compound was dissolved in DMSO. Fluconazole was employed as standard (50µg/ml) to compare the results. The pH of all the test and control solution was maintained at 2-3 by using concentrated HCl, as the compounds were not diffused through agar medium at pH below 3. All the compounds were tested at concentration of 50µg/ml.

The cups each of 6mm diameter were made with a sterilized cork borer. The solutions of each test compound, control and reference standard were added to the cups. Plates were incubated for 24 hours for bactericidal and 48 hours for fungicidal activity and inhibition zone of test compounds were measured in mm (Table - I). Each experiment was repeated twice and the average of the two determinations was recorded.

Table I: Antimicrobial activity of synthesized compounds 3<sub>a-i</sub>

Compound No.	Inhibition zone (mm) <sup>a</sup>			
	<i>S. aureus</i>	<i>S. pyrogens</i>	<i>C. albicans</i>	<i>A. niger</i>
3 <sub>a</sub>	14	8	8	10
3 <sub>b</sub>	14	9	8	8
3 <sub>c</sub>	12	10	6	10
3 <sub>d</sub>	10	8	7	8
3 <sub>e</sub>	13	8	8	11
3 <sub>f</sub>	11	8	7	-
3 <sub>g</sub>	8	11	8	8
3 <sub>h</sub>	17	10	7	9
3 <sub>i</sub>	13	7	9	10
3 <sub>j</sub>	11	11	8	-
3 <sub>k</sub>	10	11	8	8
3 <sub>l</sub>	17	12	-	8
Ciprofloxacin	16	13	-	-
Fluconazole	-	-	10	12

<sup>a</sup>All the test and the standard drug were tested at the concentration of 50µg/ml

### RESULTS AND DISCUSSION

The title compounds 2-(substituted phenyl)-3-(2-hydroxy-substituted phenyl-1,3,4-thiadiazol-2-yl) thiazolidin-4-one (3<sub>a-i</sub>) were synthesized in good yields. The structures of the compounds were confirmed on the basis of spectral data. The antibacterial activity of the synthesized compounds were found to be better than antifungal activity. The antimicrobial activity of the compounds (Table I) indicated that most of the compounds have some degree of inhibitory activity. Among all the compounds tested, compounds (3<sub>h</sub>) and (3<sub>i</sub>) containing 4-chloro phenyl and 4-dimethyl amino phenyl group respectively showed maximum antibacterial activity while compounds (3<sub>e</sub>) and (3<sub>i</sub>) containing 4-hydroxy phenyl and 4-nitrophenyl showed maximum antifungal activity. Further research is required to modify the structure of the compounds in order to make them more potent antimicrobials.

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