Indian Journal of Heterocyclic Chemistry Vol. 24, Jan.-March, 2015, pp. 329-332

# SYNTHESIS AND ANTIMICROBIAL SCREENING OF NOVEL 3-ARYL-2(4-(PYRROLIDIN-1-YL) PHENYL) THIAZOLIDIN-4-ONES

Sandeep D. Pardeshi, Jayant P. Sonar, S.A. Dokhe, A.M. Zine and Shivaji N. Thore\* Department of Chemistry, Vinayakrao Patil Mahavidyalaya, Vaijapur, Dist. Aurangabad-423701 E-mail : snthore@rediffmail.com

### Received 15 Oct. 2014; Accepted 31 Jan. 2015

A series of novel 3-aryl-2(4-(pyrrolidin-1-yl) phenyl) thiazolidin-4-ones has been synthesized and screened for antibacterial activity. From the synthesized compounds 4a, 4d and 4f show moderate antibacterial activity.

4-Thiazolidinones, one of the members of sulfur and nitrogen containing heterocycles are the core structure of a number of biologically important compounds<sup>1</sup>. These are reported to exhibit bioactivities like anticonvulsant<sup>2</sup>, antimicrobial<sup>3</sup>, antidiarrheal<sup>4</sup>, antidiabetic<sup>5</sup>, anti HIV<sup>6</sup>, anticancer<sup>7</sup>, antihistamine<sup>8</sup>, antifungal<sup>9</sup>, antioxidant<sup>10</sup>, anti YFV (Yellow Fever Virus)<sup>11</sup>, antitubercular<sup>12</sup>, analgesic, antiinflammatory<sup>13</sup> activities.

Five member heterocyclic compounds and their derivatives have been reported to show important biological properties<sup>14</sup>. One of the member from this i.e. Pyrrolidine ring act as an intermediate for many pharmaceuticals<sup>15</sup>, food, pesticide<sup>16</sup>, paints, textile and polymer materials<sup>17</sup>. Pyrrolidine derivatives have been reported to show different important biological activities like anticancer<sup>18</sup>. So present study was undertaken to synthesise 4-thiazolidinone containing pyrrolidine moiety by reacting Schiff base with mercapto acetic acid.

In the present work Schiff bases (imines) 3a-3j were prepared by reacting aldehyde and various aromatic amines. The 4-thiazolidinones 4a-4j were prepared by reacting imines with mercapto acetic acid using toluene or dioxan as solvent, in both solvent system the yield is nearly same only the time consumption is different.

#### Antimicrobial activity

Compounds **3a-3j** and **4a-4j** were screened for in vitro antimicrobial activity against *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 25923), *E. Coli* (ATCC25922) and *Candida sp.*, using disc diffusion method. Each compound was dissolved in DMSO to get concentration of 50µg/mL. Discs of Whatmann filter paper no. 41 (6 mm) were



Compd	R	R,	R <sub>2</sub>	Yield	M.P.
				(%)	(°C)
	Н	H	noponik pił tra mie s	63	150-151
3b	н	Н	Н	58	140-141
3c	OCH.	on i - H indiana from	nga giri - Hayayay - P	61	117-118
3d	CH	besize Hings erill mon	CH	60	125-127
3e	CH	Н	Hard Hard Hard Hard Hard Hard Hard Hard	59	98-100
3f	Н	H	Br	64	125-128
3a	н	H	OCH,	61	120-121
3h	Н	OCH	H	60	114-116
3i	H	Н	CH	58	119-120
3i	Н	CH,	H	59	118-121
4a	H	H H	F	55	108-110
4b	H	nitres Hid believed	etem H	48	115-119
4c	OCH.	drak in Hannahan Sila	Starni H Linnin	51	121-123
4d	CH,	H H	CH	40	105-107
4e	CH.	Honore Honore Honore	Н	55	106-108
4f	H	min entre on m	Br	59	131-132
4a	н	instellib al roligio	OCH	45	126-128
4h	H	OCH.	which H thistogra	40	111-117
4	Н	H	CH	45	115-117
4j	H	CH3	H Manada	44	105-106

Table-1 Physical data of compounds **3**a-**3**j and **4**a-4j

prepared, discs were placed on the surface of inoculated agar plate and 10µL of each dissolved compound was loaded on disc. The compound was allowed to diffuse for 10 min. DMSO was used as control. The Petri dishes were incubated at 37° for 24 hr for bacteria and at 29° for fungi. Bioactivity was determined by measuring diameter of inhibition zone in mm and is presented in Table-2.

## Experimental

Melting points were recorded by open capillary method and are uncorrected. IR spectra were recorded in KBr disc on Shimadzu IR Affinity 1 spectrophotometer. <sup>1</sup>H NMR were recorded on a Varian As 400 MHz spectrophotometer in CDCl<sub>3</sub>/DMSO- $d_{s}$ , chemical shift are in  $\delta$  ppm relative to TMS. Mass spectra were taken on a Macro mass spectrometer (Waters) by electrospray method (Es.).

#### Synthesis of imines 3a-3j : General procedure

To a solution of 4-(pyrrolidin-1-yl) benzaldehyd (1) (0.010 mol) in 50 mL ethanol, various aromatic amines (2) (0.015 mol) were added. The reaction mixture was made acidic by adding 1-2 drops of gl acetic acid and refluxed for 4 hr. After completion of reaction as indicated by TLC, hexane: ethyl acetate (8:2), the solvent was removed by rotary evaporator, the residue was recrystallised from ethanol to give compounds **3a-3**j.

**3**c: IR : cm<sup>-1</sup> 1590 (C=N), 1610 (C=C), <sup>1</sup>H NMR (400 MHz, DMSO):  $\delta$  1.99 (t, 4H, CH<sub>2</sub>), 3.33 (t, 4H, N-CH<sub>2</sub>), 3.85 (s, 3H, OCH<sub>3</sub>), 6.55 (d, 2H, J=8.8 Hz, ArH); 6.89-7.13 (m, 4H, ArH), 7.75-7.77 (m, 2H, ArH), 8.19 (s, 1H, imine proton); Mass : m/z 281 (M+1).

# Synthesis of thiazolidinones 4a-4j : General procedure

#### Method A

To a solution of **3**a (0.005 mol) in 30 mL toluene, mercapto acetic acid (0.0055 mol) was added. The reaction mixture was refluxed for 8 hr. After completion of reaction as indicated by TLC, hexane: ethyl acetate (8:2), the solvent was removed by rotary evaporator, the residue was treated with saturated solution of NaHCO<sub>3</sub>, extracted with ethyl acetate, dried over

Compd	Pseudomonas aeruginosa (ATCC27853)	Staphylococcus aureus (ATCC 25923)	<i>E. coli</i> (ATCC25922)	Candida sp	
4a	12mm	12mm	18mm		
4b	DEGIUMI CISCHLA DOLLO	Ineid of the second	Lenge ( Leolar )		
4c	-	10131	B bits detailer and B.	avenation issued ave	
4d	10mm	10mm	(nation) end thanks in	Langer, Langer, Langer,	
4e		(2010S)		- 128	
4f	12mm	10mm	16mm	o) C.K. Erwaster	
4g	(Med. Chips. H. (2001)	- Curren	2011), ta-	6704-, 865, 24	
4h	Constant The Research	17. 8. 10.	d S. Krithen A.B.	M. Putnishweiml die	
4i	Tor Store of	mail:0 -	-	Pharms 50 #200gt, 15t	
4j	A CONTRACTOR OF THE OWNER	N 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Annual Those service	D. Simon P. Veneral	
Gentamycin	24mm	21mm	27mm	Rhanne Circle Inc.	
Nystatin	a mar t <u>e</u> r oor sam taad	·	and a start being	23 mm	

Table-2 Antimicrobial activity data of 4a-4i

anhyd.  $Na_2SO_4$  and solvent was distilled off. The residue was recrystallised from ethanol to give compound 4a. Similarly 4b-4j were prepared.

#### Method B

To a solution of **3**a (0.005 mol) in 30 mL dioxan, mercapto acetic acid (0.0055 mol) was added. To the resulting solution pinch of  $ZnCl_2$  was added. The reaction mixture was refluxed for 16 hr. After completion of reaction as indicated by TLC, hexane: ethyl acetate (8:2), the solvent was removed by rotary evaporator, the residue was treated with saturated solution of NaHCO<sub>3</sub>, extracted with ethyl acetate, dried with Na<sub>2</sub>SO<sub>4</sub> and solvent was distilled off. The residue was recrystallised from ethanol to give compound **4**a. Similarly **4**b-**4**j were prepared.

4d : IR : 1680 (CO), 1532 (aromatic): <sup>1</sup>H NMR (400 MHz, DMSO): 2.02 (t, 8.60 Hz, 4H, CH<sub>2</sub>), 2.31 (s, 6H, Ar-CH<sub>3</sub>), 3.35 (t, 8.6 Hz, 4H, CH<sub>2</sub>), 4.12-4.19 (m, 2H, CH<sub>2</sub>), 5.92 (s, 1H, CH), 6.51-7.76 (m, 7H, ArH). Mass : m/z 353 (M+1).

#### Acknowledgement

The authors are thankful to the Head, Department of Chemistry, Vinayakrao Patil Mahavidyalaya, Vaijapur for providing laboratory facilities, Mr. Uday Khedkar, Director, BAC-TEST Laboratory, Nashik, for antimicrobial analysis. The authors are thankful to the Director, SAIF, Punjab University, Chandigarh for spectral analysis.

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