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NOTE

Synthesis of Some Novel Substituted Arylidene and Substituted Benzylthiazolidine-2,4-dione Analouges as Chemotherapeutic Agents

SACHIN MALIK[1,*], ASHISH CHOUDHARY[1] and RADHE SHYAM BAHARE[2]

[1]Faculty of Pharmacy, Babu Banarasi Das National Institute of Technology and Management, Lucknow-227 105, India
[2]Poona College of Pharmacy, Bharati Vidyapeeth University, Pune-411 038, India

*Corresponding author: E-mail: pr.sachinmalik@gmail.com

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A series of 5-substituted arylidene and 3-substituted benzylthiazolidine-2,4-dione derivatives were synthesized from thiazolidinedione and substituted benzyl chloride followed by the addition of substituted aromatic aldehydes. All the compounds **1a-e** and **2a-c** were screened for their *in vitro* antimicrobial activity using cup plate method.

Key Words: Thiazolidine-2,4-dione, Heterocyclic compounds, PPARγ, Antimicrobial activity.

Thiazolidinedione derivatives have been the subject of extensive research because of their involvement in the regulation of different physiological processes. Thiazolidi-nediones such as troglitazone, pioglitazone, rosiglitazone and various substituted thiazolidinediones are potent reducer of plasma glucose level *in vivo* and *in vitro*[1,2]. Besides their anti-diabetic potency, these thiazolidinedione derivatives have been shown to exert antiinflammatory effects on vascular cells[3-5]. Thiazolidinediones were also found to inhibit the production of inflammatory cytokines and the expression of inducible nitric oxide synthesis in monocytes/macrophages[6]. It has been shown that thiazolidinediones suppress the growth of several cancer cell lines including colon, breast and prostate *in vivo* and *in vitro*[7]. Differently substituted thiazolidinedione moiety has been found to have other interesting activities such as aldose reductase inhibition[8] and antimicrobial activity[9]. So in present work, an attempt has been made to synthesize analogues of 5-substituted arylidene and 3-substituted benzyl-thiazolidine-2,4-dione expecting their enhanced antimicrobial activity.

5-Substituted arylidene and 3-substituted benzyl-thiazolidine-2,4-dione (**3**) was prepared by a nucleophilic addition of 3-substituted benzylthiazolidine-2,4-dione (**2**) with selected substituted aromatic aldehydes[10]. Synthetic pathway is shown in Fig. 1. Thiazolidinedione (**1**) was refluxed with substituted benzyl chloride as 4-nitrobenzyl chloride or 4-chloro benzyl chloride for *ca.* 18 h[11]. The substituted 3-benzylthiazolidine-2,4-dione (**2**) was obtained in this way.

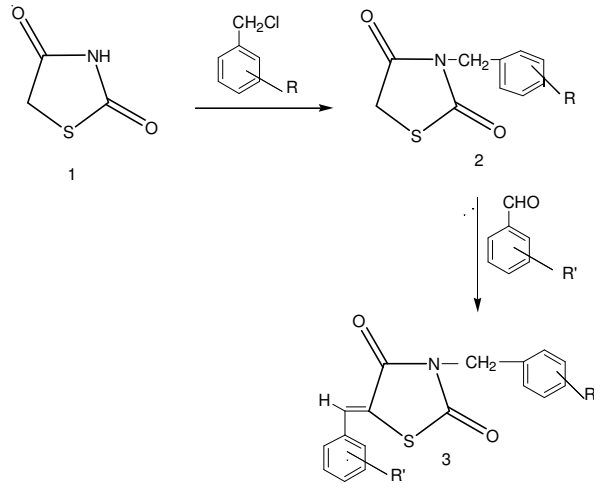

Fig. 1. Synthetic pathway of 5-arylidene-3-benzylthiazolidine-2,4-dione

5-Substituted arylidene and 3-substituted benzylthia-zolidine-2,4-diones (1a-e and 2a-c): To a solution containing 0.01 mol (0.143 g) of benzaldehyde and 0.01 mol (0.25 g) of 3-substituted benzylthiazolidine-2,4-dione in 1 mL of hot acetic acid, 0.01 mol (0.338 g) of fused sodium acetate was added and the mixture was refluxed for 1.5 h. The product was obtained by pouring the mixture into water and recrystallizing the resulting solid from ethanol.

5-(4-Methoxy benzylidene)-3-(4-nitro benzyl)-thiazolidine-2,4-dione (1a): $C_{18}H_{14}N_2O_5S$, yield: 83.2 %, m.p. 180-183 °C. TLC ethanol:chloroform (9:1) R_f: 0.62. IR (KBr,

ν_{max}, cm^{-1}): 1595, 1670, 1650, 3050, 1550, 1020. MS (FAB) m/z: 370 (M^+), 371 (M^++1, 100 %).

5-(4-Hydroxy-3-methoxy benzylidene)-3-(4-nitro benzyl)thiazolidine-2,4-dione (1b): $C_{18}H_{14}N_2O_6S$, yield: 78.5 %, m.p. 195-200 °C. TLC ethanol:chloroform (9:1) R_f: 0.55. IR (KBr, ν_{max}, cm^{-1}): 1540, 1520, 3045, 1675, 1720, 3000, 1100, 3320. MS (FAB) m/z: 386 (M^+), 386 (M^+, 100 %).

5-(4-Chloro benzylidene)-3-(4-nitro benzyl)thiazolidine-2,4-dione (1c): $C_{17}H_{11}N_2O_4SCl$, yield: 85.7 %, m.p. 205-210 °C. TLC ethanol:chloroform (9:1) R_f: 0.72. IR (KBr, ν_{max}, cm^{-1}): 1522 and 1379, 1605, 976 and 886, 3416, 2946, 703 and 663. MS (FAB) m/z: 374 (M^+), 375 (M^++1, 100 %).

5-(3,4-Dimethoxy benzylidene)-3-(4-nitro benzyl)-thiazolidine-2,4-dione (1d): $C_{19}H_{16}N_2O_6S$, yield: 81.3 %, m.p. 172-179 °C. TLC ethanol:chloroform (9:1) R_f: 0.50. IR (KBr, ν_{max}, cm^{-1}): 1575, 1675 and 1480, 3060, 1575, 1740, 3010, 1150. MS (FAB) m/z: 400 (M^+), 401 (M^++1, 100 %).

5-(Furfural benzylidene)-3-(4-nitro benzyl)thiazolidine-2,4-dione (1e): $C_{15}H_{10}N_2O_5S$, yield: 74.4 %, m.p. 165-170 °C. TLC ethanol:chloroform (9:1) R_f: 0.45. IR (KBr, ν_{max}, cm^{-1}): 1390 and 1535, 1570, 3080, 1690, 1630, 700, 3110. MS (FAB) m/z: 330 (M^+), 331 (M^++1, 100 %).

5-(4-Methoxy benzylidene)-3-(4-chloro benzyl)-thiazolidine-2,4-dione (2a): $C_{18}H_{14}NO_3SCl$, yield: 80.3 %, m.p. 193-198 °C. TLC ethanol:chloroform (9:1) R_f: 0.52. IR (KBr, ν_{max}, cm^{-1}): 763, 1608, 1381, 1686, 1753, 669, 3022, 1150. MS (FAB) m/z: 359 (M^+), 360 (M^++1, 100 %).

5-(4-Chloro benzylidene)-3-(4-chloro benzyl)-thiazolidine-2, 4-dione (2b): $C_{17}H_{11}NO_2SCl_2$, yield: 82.1 %, m.p. 185-190 °C. TLC ethanol:chloroform (9:1) R_f: 0.48. IR (KBr, ν_{max}, cm^{-1}): 603 and 537, 3069, 667, 1676, 1751. MS (FAB) m/z: 363 (M^+), 364 (M^++1, 100 %).

5-(2-Chloro benzylidene)-3-(4-chloro benzyl)-thiazolidine-2, 4-dione (2c): $C_{17}H_{11}NO_2SCl_2$, yield: 75.9 %, m.p. 168-175 °C. TLC ethanol:chloroform (9:1) R_f: 0.66. IR (KBr, ν_{max}, cm^{-1}): 763, 1603 and 1381, 1686, 1753, 669, 3021. MS (FAB) m/z: 363 (M^+), 364 (M^++1).

TABLE-1
QUANTITATIVE SCREENING OF ANTIMICROBIAL ACTIVITY

Comp. code	Conc. (µg/mL)	Zone of inhibition				Fungus
		Gram+ve bacteria		Gram-ve bacteria		
		SA	BS	EC	PA	CA
Standard (ofloxacin)	100	+++	+++	+++	+++	
	200	+++	+++	+++	+++	
Standard (econazole)						
1a	50	-	-	-	+	
	100	-	-	-	+	
	150	-	-	++	++	
	200	++	+	+++	+++	
1b	50	-	-	-	-	
	100	-	-	++	-	
	150			++	++	
	200	+++	++	+++	++	
1c	50	-	-	-	-	
	100	-	-	-	-	
	150	-	-	-	-	
	200	-	-	-	-	
1d	50	-	-	-	-	
	100	-	++	-	+++	
	150	-	+++	-	+++	
	200	+++	+++	+++	+++	
1e	50	-	-	-	-	
	100	-	-	-	-	
	150	-	-	-	-	
	200	-	-	-	-	
2a	50	-	-	-	-	
	100	-	++	-	+++	
	150	-	+++	-	+++	
	200	+++	+++	+++	+++	
2b	50	-	-	-	-	
	100	-	-	+++	++	
	150	-	++	+++	++	
	200	+++	++	+++	+++	
2c	50	-	-	-	-	
	100	-	-	-	-	
	150	-	-	-	-	
	200	-	-	-	-	
Control (DMSO)	10 % v/v	-	-	-	-	-

SA = *Staphylococcus aureus*, BS = *Bacillus subtilis*, EC = *Escherichia coli*, PA = *Pseudomonas auruginosa*, CA = *Candida albicans*; Highly active = +++ (Inhibition zone greater than 12mm); Moderately active = ++ (Inhibition zone greater than 9-12 mm); Slightly active = + (Inhibition zone 6-9 mm); Inactive = - (< 6 mm).

The synthesized compounds (**1a-e** and **2a-c**) were screened for *in vitro* antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa* was assessed by cup plate method. The test solutions were prepared in 10 % DMSO which also works as control. Ofloxacin was used as standard at the concentration of 100 and 200 µg/mL. After 24 h of incubation at 37 ± 1 ºC zones of inhibition were measured in mm and activity was compared with standard as in Table-1. Among the compounds tested **1a**, **1b**, **1d**, **2a** and **2b** were found to be potent against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa*.

Conclusion

Compound **1a**, **1b**, **1d**, **2a** and **2b** were found to be potent due to the presence of electron donating group such as methoxy and hydroxy and results in good antimicrobial activity whereas compounds **1e** and **2c** have substitution with 2-chlorophenyl and furfural at 5th position of 2,4-thiazolidinedione and does not give any activity.

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