

## Studies on Some Bioactive 1,1-Bis(2-benzylidene-5-arylidene-1,3-thiadiazolidin-4-one)cyclopropane

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**ABSTRACT.** Some novel heterocyclic derivatives of 1,1-bis(2-phenyl-5-arylidene-1,3-thiadiazolidin-4-one)cyclopropane **4(a-i)** have been synthesized from cyclopropane dicarboxylic acid and substituted thiadiazole moieties. All the synthesized compounds have been characterized by elemental and spectral (I.R., <sup>1</sup>H-NMR, Mass) analysis. Furthermore, above said compounds were screened for their antifungal and antibacterial activities. Compound **4c** was found the most potent one which further evaluated for lesser toxicity test.

**Key words:** Bis-phenylarylidinylthiadiazolidinone cyclopropane, Antifungal, Antibacterial, Acute toxicity

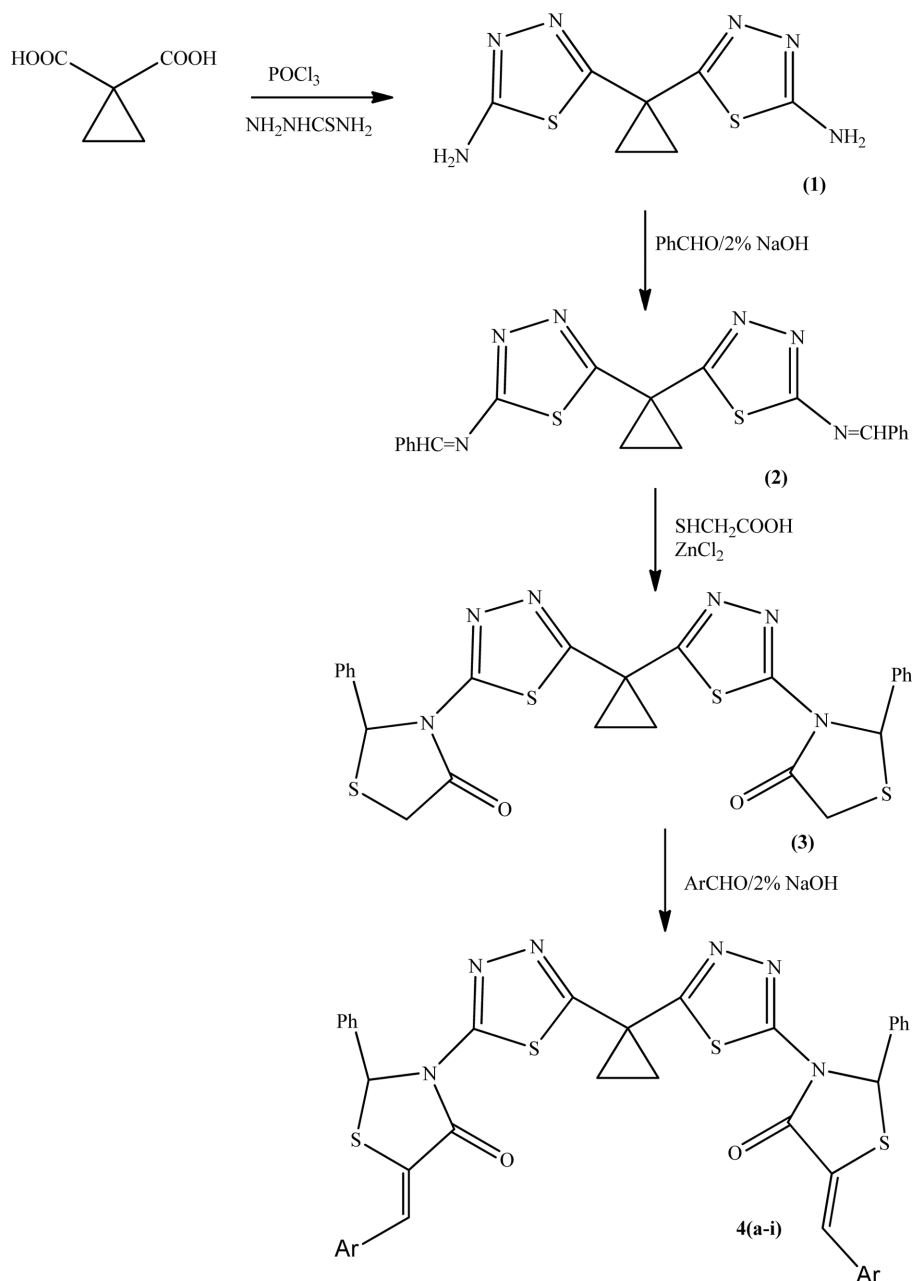
### INTRODUCTION

Widespread antibiotic resistance, the emergence of new pathogens in addition to the resurgence of old ones, and the lack of effective new therapeutics exacerbate the problems of antimicrobial resistance.<sup>1</sup> The recent literature is enriched with progressive findings about the synthesis of 1,3,4-thiadiazole moiety and their broad spectrum of pharmacological actions such as anti-bacterial,<sup>2</sup> anti-fungal,<sup>2</sup> anti-tubercular,<sup>3</sup> anti-convulsant,<sup>4</sup> anti-inflammatory,<sup>5</sup> analgesic,<sup>5</sup> anti-depressant,<sup>6</sup> anti-viral,<sup>7</sup> and anti-helicobacter.<sup>8</sup> Similarly, thiazolidine-4-one ring system is also found to possess diverse biological activities such as antimicrobial,<sup>9</sup> anti-convulsant,<sup>10</sup> antidiarrheal,<sup>11</sup> anti-cancer,<sup>12</sup> K<sup>+</sup> channel inhibitory<sup>13</sup> and anti-histaminic.<sup>14</sup> These two heterocyclic moieties individually as well as in bis<sup>15-16</sup> form showed potent pharmacological activity especially antimicrobial and thus aroused our interest in synthesizing the combination of the two moieties. On the other hand, esters of 1,1-cyclopropane dicarboxylic acid were found to possess important insecticidal activity.<sup>17</sup> Based on the wide spectrum of biological profile of 1,1-cyclopropane dicarboxylic acid, thiadiazole and thiazolidin-4-one and their importance in pharmaceutical, and biological field, and in continuation of our ongoing research on biologically active heterocycles,<sup>18,19</sup> it was thought of interest to accommodate 1,1-cyclopropane dicarboxylic acid, thiadiazole, thiazolidin-4-one and aryl aldehyde moieties

in a single molecular frame work of designing to synthesize some novel bis heterocycles for enhancing biological activity with lesser toxicity.

### RESULTS AND DISCUSSION

1,1-Cyclopropane dicarboxylic acid prepared according to the method in the literature.<sup>20</sup> 1,1-Cyclopropane dicarboxylic acid was treated with thiosemicarbazide and phosphorous oxychloride to furnish 1,1-bis(2-amino-1,3,4-thiadiazol-5-yl)cyclopropane (**1**) in good yield. Reaction of compound (**1**) with benzaldehyde in presence of 2% sodium hydroxide solution afforded 1,1-bis(2-benzylidene-1,3,4-thiadiazol-5-yl)cyclopropane (**2**). On heterocyclization of compound (**2**) with thioglycolic acid in presence of anhydrous zinc chloride yielded 1,1-bis[2-(2-phenyl-1,3-thiazolidin-4-one)-1,3,4-thiadiazol-5-yl]cyclopropane (**3**). The synthesis of target derivatives i.e. 1,1-bis[2-(2-benzylidene-5-arylidene-1,3-thiazolidin-4-one)-1,3,4-thiadiazol-5-yl]cyclopropane **4(a-i)** were afforded by the reaction of different arylaldehyde with compound (**3**) in presence of 2% sodium hydroxide solution (*Scheme 1*). Synthetically derived molecules were assayed using the cup plate method for antimicrobial activity against selected pathogenic clinical strains. The screening results were compared with standard ampicillin trihydrate and fluconazole respectively for antibacterial and antifungal testing. Furthermore the most potent congener was also tested for



Ar = C<sub>6</sub>H<sub>5</sub>, 2-ClC<sub>6</sub>H<sub>4</sub>, 3-ClC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 2-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 4-OHC<sub>6</sub>H<sub>4</sub>, 3-OCH<sub>3</sub>(4-OH)C<sub>6</sub>H<sub>3</sub>, 4-N(CH<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>4</sub>

### Scheme 1.

lethal dose. From the antimicrobial screening data of compounds **3** and **4a-i**, it was found that conversion of thiazolidinone derivative i.e. **3** into arylidenes of thiazolidinone i.e. **4a-i**, brought enhancing antibacterial and antifungal activity. Among the derivatives **4a-i**, derivative **4c**, **4d** and **4e** showed remarkable potency against the used pathogenic strains. On the other hand, remaining compounds exhibited mild to moderate activity. In compounds **4c**, **4d**

and **4e**; compound **4c** was found the most potent one, showing broad spectrum inhibitory profile having lesser toxicity.

### Antimicrobial test

All the newly synthesized compounds were screened for their antibacterial and antifungal activity. All the bacterial and fungal strains were clinical isolates, identified

with conventional morphological and biochemical methods. Microorganisms employed antibacterial studies were *Staphylococcus aureus*, *Escherichia coli*, *Klasiella pneumoniae* and *Proteus vulgaris*. Disk diffusion method<sup>21,22</sup> was used for determination of the preliminary antibacterial activity. Disks measuring 6.25 mm in diameter were punched from Whatman no. 1 filter paper. Batches of 100 disks were dispensed to each screw-capped bottle and sterilized by dry heat at 140 °C for an h. The test compounds were prepared with different concentrations using DMF. One milliliter containing 100 times the amount of chemical in each disk was added to each bottle, which contained 100 disks. Disks of each concentration were for placed in triplicate in nutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at 37 °C for 24 h. Ampicillin trihydrate was used as a standard drug. Solvent and growth controls were kept and zones of inhibition were noted. The inhibition zone values of the tested compounds against the tested bacteria strains summarized in *Table 1*. On the other hand, the newly prepared compounds were screened for their in vitro antifungal activity against *Aspergillus fumigatus* (plant isolate), *Candida glabrata*, *Candida albicans* and *Candida krusei* in DMSO by the serial plate dilution method.<sup>23,24</sup> Fluconazole (antifungal) was used as reference drug. Sabouraud's agar media were prepared by dissolving peptone (1 g), D-glucose (4 g), and agar (2 g) in distilled water (100 ml) and adjusting the pH to 5.7. Normal saline was used to make a suspension of the spore of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 ml saline to get a suspension of the corresponding species. Agar media (20 ml) was poured

into each petri dish. Excess suspension was decanted and the plates were dried by placing in an incubator at 37 °C for 1 h. Using an agar punch wells were made into each well labeled. A control was also prepared in triplicate and maintained at 37 °C for 3-4 days. Antifungal activity was determined by measuring the diameter of the inhibition zone. The inhibitory data of the tested compounds against the tested fungal strains were recorded in *Table 1*.

#### Acute toxicity test

Lethal dose<sup>25</sup> (LD<sub>50</sub>) of test compounds were determined in albino mice. After 24 h of drug administration, percent mortality in each group was observed from the data obtained LD<sub>50</sub>. Data revealed that compound **4c** does not show any toxicity up to dose of 12.20 mg/ml body weight in mice.

## EXPERIMENTAL

#### Material

All the chemicals used for the preparation of desired derivatives, were obtained from Sisco Research Laboratories (SRL), Mumbai, India; Qualigen Fine Chemicals, Mumbai, India; E. Merck Ltd., New Delhi, India. Reference drugs ampicillin trihydrate and fluconazole were procured from Ind-Swift Pharmaceutical, Panjab, India and Macleods Pharmaceutical, Mumbai, India respectively.

#### Measurement

The melting points of the compounds were determined in open glass capillaries with the help of thermonic melting points apparatus (Campbell Electronics, Mumbai, India)

**Table 1.** Antibacterial and antifungal data for the synthesized compounds (**4a-i**)

Comp. no.	Antibacterial inhibition (mm)				Antifungal inhibition (mm)			
	<i>S. aureus</i>	<i>E. Coli</i>	<i>K. pneumoniae</i>	<i>P. vulgaris</i>	<i>A. fumigatus</i>	<i>C. glabrata</i>	<i>C. albicans</i>	<i>C. krusei</i>
4a	-	10	4	10	5	8	10	-
4b	12	-	4	12	10	8	12	15
4c	15	20	26	25	14	16	15	13
4d	14	15	20	18	-	10	7	7
4e	16	-	15	17	16	-	12	10
4f	-	7	-	15	14	4	5	-
4g	12	10	14	8	-	9	7	9
4h	15	12	8	6	14	12	-	-
4i	10	12	10	16	12	-	-	-
Ampicillin trihydrate (std.)	16	20	20	20	-	-	-	-
Fluconazole (std.)	-	-	-	-	20	15	16	15
DMF (control)	-	-	-	-	-	-	-	-

-: showing no activity

and are uncorrected. The homogeneity of all the newly synthesized compounds were routinely checked by TLC on silica gel G plates and spots were located by using iodine chamber. Elemental analysis was performed in Heraeus CHN rapid analyser. The results were found within the  $\pm 0.4\%$  of theoretical values. Infrared spectra were recorded on KBr pellets on a Perkin Elmer system 2000 FTIR spectrometer and  $^1\text{H-NMR}$  spectra on Bruker DPX 200 using TMS as internal standard.

### Synthesis

#### Preparation of 1,1-bis(2-amino-1,3,4-thiadiazol-5-yl)cyclopropane (1)

A mixture of 1,1-cyclopropane dicarboxylic acid<sup>15</sup> (0.01 mol), thiosemicarbazide (0.02 mol) and phosphorous oxychloride (5 ml) was gently refluxed for 30 minutes. After cooling, water (10 ml) was added and the reaction mixture was refluxed for four hours. The reaction mixture was cooled, poured into ice-water slowly with continuous stirring, neutralized with aqueous 3% KOH solution, filtered and recrystallized by methanol: Yield: 67%; m.p.: 235 °C;  $R_f$ : 0.50. Anal. Calcd. for  $\text{C}_7\text{H}_8\text{N}_6\text{S}_2$ : C, 34.99; H, 3.36; N, 34.97%. Found: C, 35.00; H, 3.35; N, 34.98%. IR (KBr,  $\text{cm}^{-1}$ ): 3280 ( $\text{NH}_2$ ), 1605 ( $\text{C}=\text{N}$ ), 665 ( $\text{C-S-C}$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ,  $\delta/\text{ppm}$ ): 6.40 (s, 4 H, 2 X 2H,  $\text{NH}_2$ ), 1.18-1.00 (m, 4H, 2 X 2H,  $\text{CH}_2$ ). MS ( $m/z$ , %): 240.31.

#### Preparation of 1,1-bis(2-benzylidene-1,3,4-thiadiazol-5-yl)cyclopropane (2)

The stirred ethanolic solution of compound 1 (0.1 mol) with benzaldehyde (0.1 mol) in presence of a few drops of 2% sodium hydroxide solution was refluxed for 2-5 h. The completion of reaction was checked by TLC and excess of solvent was distilled out. The cooled residue was poured into ice-water, filtered, dried and the solid recrystallized by ethanol: Yield: 54%; m.p.: 211 °C;  $R_f$ : 0.58. Anal. Calcd. for  $\text{C}_{21}\text{H}_{16}\text{N}_6\text{S}_2$ : C, 60.55; H, 3.87; N, 20.18%. Found: C, 60.56; H, 3.90; N, 20.20%. IR (KBr,  $\text{cm}^{-1}$ ): 3282 ( $\text{NH}_2$ ), 3025 ( $\text{C-H-Ar}$ ), 2938 ( $\text{C-H}$ ), 1622 ( $\text{C-C}$  of aromatic ring), 1603 ( $\text{C}=\text{N}$ ), 670 ( $\text{C-S-C}$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ,  $\delta/\text{ppm}$ ): 8.60 (s, 2H, 2 X H,  $\text{N}=\text{CH.C}_6\text{H}_5$ ), 6.65-7.40 (m, 10 H, 2 X 5 H,  $\text{C}_6\text{H}_5$ ), 1.10-0.94 (m, 4H, 2 X 2H,  $\text{CH}_2$ ). MS ( $m/z$ , %): 416.52.

#### Preparation of 1,1-bis[2-(2-benzylidene-1,3-thiazolidin-4-one)-1,3,4-thiadiazol-5-yl]cyclopropane (3)

A mixture of compound 2 (0.1 mol) in  $N,N'$ -dimethyl formamide and thioglycolic acid (0.01 mol) in presence of anhydrous zinc chloride was refluxed for 2-4 h. After

completion of reaction (monitored by TLC), excess of solvent was distilled and cooled residual mass diluted with ice-water. The solid filtered, washed with water, dried and recrystallized by methanol: Yield: 56%; m.p.: 202 °C;  $R_f$ : 0.63. Anal. Calcd. for  $\text{C}_{25}\text{H}_{20}\text{N}_6\text{O}_2\text{S}_4$ : C, 53.17; H, 3.57; N, 14.88%. Found: C, 53.27; H, 3.55; N, 14.84%. IR (KBr,  $\text{cm}^{-1}$ ): 3284 ( $\text{NH}_2$ ), 2940 ( $\text{C-H}$ ), 3020 ( $\text{C-H Ar}$ ), 1702 ( $\text{C}=\text{O}$ ), 1620 ( $\text{C-C}$  of aromatic ring), 1610 ( $\text{C}=\text{N}$ ), 667 ( $\text{C-S-C}$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ,  $\delta/\text{ppm}$ ): 8.51 (s, 2H, 2X1H,  $\text{N}=\text{CH-Ar}$ ), 6.70-7.35 (m, 10H, 2X5H,  $\text{ArH}$ ), 3.70 (s, 4H, 2X 2H,  $\text{CH}_2$  of thiazolidinone ring), 1.08-0.96 (m, 4H, 2 X 2H,  $\text{CH}_2$ ). MS ( $m/z$ , %): 564.73.

#### General preparation of 1,1-bis[2-(5-phenyl-2-phenyl-1,3-thiazolidin-4-one)-1,3,4-thiadiazol-5-yl]cyclopropane (4a-i)

A well-stirred solution of compound 3 (0.01 mol) in glacial acetic acid was buffered with sodium acetate (0.02 mol) and added with the appropriate aryl aldehyde (0.015 mol). The solution was refluxed for 4-6 h and then poured into ice-cold water. The precipitate was filtered, washed with water and the resulting crude solid product. The crude products were recrystallized from appropriate solvents.

**1,1-Bis[2-(5-phenyl-2-phenyl-1,3-thiazolidin-4-one)-1,3,4-thiadiazol-5-yl]cyclopropane (4a):** Yield: 42%; m.p.: 234 °C;  $R_f$ : 0.67. Anal. Calcd. for  $\text{C}_{39}\text{H}_{28}\text{N}_6\text{O}_2\text{S}_4$ : C, 60.55; H, 3.87; N, 20.18%. Found: C, 60.56; H, 3.87; N, 20.20%. IR (KBr,  $\text{cm}^{-1}$ ): 3020 ( $\text{C-H-Ar}$ ), 2942 ( $\text{C-H}$ ), 1700 ( $\text{C}=\text{O}$ ), 1622 ( $\text{C-C}$  of aromatic ring), 1604 ( $\text{C}=\text{N}$ ), 673 ( $\text{C-S-C}$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ,  $\delta/\text{ppm}$ ): 8.59 (s, 2H, 2X H,  $\text{CH-Ph}$ ), 7.75 (s, 2H, 2 X 1H,  $\text{Ar-CH}=\text{C}$  of thiazolidinone ring), 6.61-7.60 (m, 20H, 2XAr and 2 X Ph), 1.01-0.90 (m, 4H, 2X 2H,  $\text{CH}_2$ ). MS ( $m/z$ , %): 740.94.

**1,1-Bis[2-(5-(2-chloro)phenyl-2-phenyl-1,3-thiazolidin-4-one)-1,3,4-thiadiazol-5-yl]cyclopropane (4b):** Yield: 49%; m.p.: 189 °C;  $R_f$ : 0.66. Anal. Calcd. for  $\text{C}_{39}\text{H}_{26}\text{N}_6\text{O}_2\text{S}_4\text{Cl}_2$ : C, 57.84; H, 3.24; N, 10.38%. Found: C, 57.80; H, 3.25; N, 10.40%. IR (KBr,  $\text{cm}^{-1}$ ): 3022 ( $\text{C-H-Ar}$ ), 2940 ( $\text{C-H}$ ), 1698 ( $\text{C}=\text{O}$ ), 1624 ( $\text{C-C}$  of aromatic ring), 1607 ( $\text{C}=\text{N}$ ), 668 ( $\text{C-S-C}$ ), 628 ( $\text{C-Cl}$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ,  $\delta/\text{ppm}$ ): 8.53 (s, 2H, 2X H,  $\text{CH-Ph}$ ), 7.89 (s, 2H, 2 X H,  $\text{Ar-CH}=\text{C}$  of thiazolidinone ring) 6.54-7.74 (m, 18H, 2XAr and 2 X Ph), 0.97-0.88 (m, 4H, 2X 2H,  $\text{CH}_2$ ). Found: C: 57.80, H, 3.25; N, 10.40%. MS ( $m/z$ , %): 809.83.

**1,1-Bis[2-(5-(3-chloro)phenyl-2-phenyl-1,3-thiazolidin-4-one)-1,3,4-thiadiazol-5-yl]cyclopropane (4c):** Yield: 51%; m.p.: 202 °C;  $R_f$ : 0.58. Anal. Calcd. for  $\text{C}_{39}\text{H}_{26}\text{N}_6\text{O}_2\text{S}_4\text{Cl}_2$ : C, 57.84; H, 3.24; N, 10.38%. Found: C: 57.83, H, 3.22; N, 10.47%. IR (KBr,  $\text{cm}^{-1}$ ): 3023 ( $\text{C-H-Ar}$ ), 2944 ( $\text{C-}$

H), 1691 (C=O), 1620 (C-C of aromatic ring), 1608 (C=N), 671 (C-S-C), 630 (C-Cl). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ/ppm): 8.54 (s, 2H, 2X H, CH-Ph), 7.95 (s, 2H, 2 X H, Ar-CH=C of thiazolidinone ring), 6.52-7.70 (m, 18H, 2XAr and 2 X Ph), 0.94-0.86 (m, 4H, 2X 2H, CH<sub>2</sub>). MS (*m/z*, %): 809.83.

**1,1-Bis[2-{5-(4-chloro)phenyl-2-phenyl-1,3-thiazolidin-4-one}-1,3,4-thiadiazol-5-yl]-cyclopropane (4d):** Yield: 56%; m.p.: 231 °C; R<sub>f</sub>: 0.62. Anal. Calcd. for C<sub>39</sub>H<sub>26</sub>N<sub>6</sub>O<sub>2</sub>S<sub>4</sub>Cl<sub>2</sub>: C, 57.84; H, 3.24; N, 10.38%. Found: C: 57.72, H, 3.30; N, 10.45%. IR (KBr, cm<sup>-1</sup>): 3020 (C-H-Ar), 2942 (C-H), 1692(C=O), 1622 (C-C of aromatic ring), 1604 (C=N), 672 (C-S-C), 627 (C-Cl). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ/ppm): 8.56 (s, 2H, 2X1H, CH-Ph), 7.88 (s, 2H, 2 X H, Ar-CH=C of thiazolidinone ring), 6.60-7.75 (m, 18H, 2XAr and 2 X Ph), 0.92-0.87 (m, 4H, 2X 2H, CH<sub>2</sub>). MS (*m/z*, %): 809.83.

**1,1-Bis[2-{5-(2-methyl)phenyl-2-phenyl-1,3-thiazolidin-4-one}-1,3,4-thiadiazol-5-yl]-cyclopropane (4e):** Yield: 46%; m.p.: 178 °C; R<sub>f</sub>: 0.66. Anal. Calcd. for C<sub>41</sub>H<sub>32</sub>N<sub>6</sub>O<sub>2</sub>S<sub>4</sub>: C, 60.04; H, 4.19; N, 10.93%. Found: C, 60.10; H, 4.05; N, 10.90%. IR (KBr, cm<sup>-1</sup>): 3021 (C-H-Ar), 2944 (C-H), 1702(C=O), 1623 (C-C of aromatic ring), 1605 (C=N). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ/ppm): 8.48 (s, 2H, 2X H, CH-Ph), 7.82 (s, 2H, 2 X H, Ar-CH=C of thiazolidinone ring), 6.53-7.69 (m, 18H, 2XAr and 2 X Ph), 1.23 (s, 6H, 2X 3H, Ar-CH<sub>3</sub>), 0.90-0.85 (m, 4H, 2X 2H, CH<sub>2</sub>). MS (*m/z*, %): 768.99.

**1,1-Bis[2-{5-(4-methyl)phenyl-2-phenyl-1,3-thiazolidin-4-one}-1,3,4-thiadiazol-5-yl]-cyclopropane (4f):** Yield: 55%; m.p.: 239 °C; R<sub>f</sub>: 0.70. Anal. Calcd. for C<sub>41</sub>H<sub>32</sub>N<sub>6</sub>O<sub>2</sub>S<sub>4</sub>: C, 60.04; H, 4.19; N, 10.93%. Found: C, 60.10; H, 4.05; N, 10.90%. IR (KBr, cm<sup>-1</sup>): 3023 (C-H-Ar), 2947 (C-H), 1699 (C=O), 1621 (C-C of aromatic ring), 1610 (C=N). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ/ppm): 8.65 (s, 2H, 2X H, CH-Ph), 7.87 (s, 2H, 2 X H, Ar-CH=C of thiazolidinone ring), 6.60-7.70 (m, 18H, 2XAr and 2 X Ph), 1.18 (s, 6H, 2X 3H, Ar-CH<sub>3</sub>), 0.90-0.80 (m, 4H, 2X 2H, CH<sub>2</sub>). MS (*m/z*, %): 768.99.

**1,1-Bis[2-{5-(2-hydroxy)phenyl-2-phenyl-1,3-thiazolidin-4-one}-1,3,4-thiadiazol-5-yl]cyclopropane (4g):** Yield: 49%; m.p.: 211 °C; R<sub>f</sub>: 0.66. Anal. Calcd. for C<sub>39</sub>H<sub>28</sub>N<sub>6</sub>O<sub>4</sub>S<sub>4</sub>: C, 60.60; H, 3.65; N, 10.87 %. Found: C, 60.58; H, 3.65; N, 10.90%. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ/ppm): 10.50 (s, 2H, 2 X H, HO-Ar), 8.52 (s, 2H, 2X H, CH-Ph), 7.85 (s, 2H, 2 X H, Ar-CH=C of thiazolidinone ring), 6.56-7.62 (m, 18H, 2XAr and 2 X Ph), 1.23 (s, 6H, 2X 3H, Ar-CH<sub>3</sub>), 0.93-0.81 (m, 4H, 2X 2H, CH<sub>2</sub>). MS (*m/z*, %): 772.94.

**1,1-Bis[2-{5-(4-hydroxy-3-methoxy)phenyl-2-phenyl-1,3-thiazolidin-4-one}-1,3,4-thiadiazol-5-yl]cyclopropane (4h):** Yield: 52%; m.p.: 256 °C; R<sub>f</sub>: 0.61. Anal. Calcd. for

C<sub>41</sub>H<sub>32</sub>N<sub>6</sub>O<sub>6</sub>S<sub>4</sub>: C, 59.12; H, 3.87; N, 10.09%. Found: C, 59.15; H, 4.00; N, 10.10%. IR (KBr, cm<sup>-1</sup>): 3022 (C-H-Ar), 2944 (C-H), 1692(C=O), 1620 (C-C of aromatic ring), 1607 (C=N), 668 (C-S-C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ/ppm): 9.65 (s, 2H, 2 X H, ArOH), 8.54 (s, 2H, 2X H, CH-Ph), 7.86 (s, 2H, 2 X H, Ar-CH=C of thiazolidinone ring), 6.50-7.57 (m, 16H, 2XAr and 2 X Ph), 3.25 (s, 6H, 2X 3H, CH<sub>3</sub>O-Ar), 1.07-0.96 (m, 4H, 2X 2H, CH<sub>2</sub>). MS (*m/z*, %): 832.99.

**1,1-Bis[2-{5-(4-N,N-dimethyl)phenyl-2-phenyl-1,3-thiazolidin-4-one}-1,3,4thiadiazol-5-yl]cyclopropane (4i):** Yield: 45%; m.p.: 190 °C; R<sub>f</sub>: 0.70. Anal. Calcd. for C<sub>43</sub>H<sub>38</sub>N<sub>8</sub>O<sub>2</sub>S<sub>4</sub>: C, 62.44; H, 4.63; N, 13.55%. Found: C, 60.50; H, 4.80; N, 13.50%. IR (KBr, cm<sup>-1</sup>): 3020 (C-H-Ar), 2942 (C-H), 1700 (C=O), 1622 (C-C of aromatic ring), 1604 (C=N), 671 (C-S-C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ/ppm): 8.51 (s, 2H, 2X1H, CH-Ph), 7.90 (s, 2H, 2 X H, Ar-CH=C of thiazolidinone ring), 6.56-7.71 (m, 18H, 2XAr and 2 X Ph), 1.56 (s, 12H, 2X (H<sub>3</sub>C)<sub>2</sub>-N, N,N-(H<sub>3</sub>C)<sub>2</sub>-Ar), 1.20-1.02 (m, 4H, 2X 2H, CH<sub>2</sub>). MS (*m/z*, %): 827.07.

## CONCLUSION

In the present study, our attention was focused on the synthesis an antimicrobial evaluation of a series of 1,1-bis(2-phenyl-5-arylidine-1,3-thiadiazolidin-4-one)cyclopropane. Based on the resulting biological evaluation data, compound **4c** possessing 3-chlorophenyl substitution; exhibited the most potent antimicrobial activity with lesser toxicity among all the synthesized cyclopropane derivatives of the series.

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## REFERENCES

- (a) Bloom, B. R.; M. L. Cohen, M. L.; Donnenberg, M. S.; C. Walsh, Aderem, A.; Ulevitch, R. J.; Park, S. H.; Bendelac, A.; Seder, R. A.; Hill, A. V. S.; Fraser, C. M.; Eisen, J. A.; Salzman, S. L. *Nature* **2000**, *406*, 759. (b) Cohen, M. L. *Nature* **2000**, *406*, 762.
- Almasirad, A.; Tabatabai, S. A.; Faizi, M.; Kebriaeezadeh, A.; Mehrabi, N.; Dalvandi, A.; Shafiee, A. *Bioorg. Med. Chem. Lett.* **2002**, *10*, 2893.
- Foroumadi, A.; Kargar, Z.; Sakhteman, A.; Sharifzadeh, Z.; Feyzmohammadi, R.; Kazemi, M.; Shafiee, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1164.

4. Michael, R.; Stillings, M. R.; Welbourn, A. P.; Walter, D. S. *J. Med. Chem.* **1986**, *29*, 2280.
5. Schenone, S. S.; Brullo, C. C.; Bruno, O. O.; Bondavalli, F. F.; Ranise, A. A.; Filippelli, W. W.; Rinaldi, B. B.; Capuano, A. A.; Falcone, G. G. *Bioorg. Med. Chem.* **2006**, *14*, 1698.
6. Clerici, F.; Pocar, D.; Guido, M.; Loche, A.; Perlini, V.; Brufani, M. *J. Med. Chem.* **2001**, *44*, 931.
7. Kaya, A. B.; Chizhov, N. P.; Chigareva, N. G. *Pharm. Chem. J.* **1978**, *12*, 66.
8. Moshafi, M. H.; Meymandi, A. Y.; Esmacil, S.; Ebrahimi, S.; Emami, S.; Nakhjiri, M.; Siavoshi, F.; Omrani, M.; Vosoooghi, M.; Alipour, E.; Shafiee, A.; Foroumadi, A. *J. Serb. Chem. Soc.* **2011**, *76*, 201.
9. Tunçbilek, M.; Altanlar, N. *Il Farmaco* **1999**, *54*, 475.
10. Ergene, N.; Capan, G. *Il Farmaco* **1994**, *49*, 449.
11. Diurno, M. V.; Mazzoni, O.; Izzo, A. A.; Bolognese, A. *Il Farmaco* **1997**, *52*, 237.
12. Verma, A.; Saraf, S. K. *Eur. J. Med. Chem.* **2008**, *43*, 897.
13. Chavan, A. A.; Pai, N. R. *ARKIVOC* **2007**, 148.
14. Diurno, M. V.; Mazzoni, O.; Correale, G.; Monterry, I. G. *Il Farmaco* **1999**, *54*, 579.
15. Venkatapuram, P.; Konda, M.; Annaji, V. N. M.; Advireddy, P. *Chem. Pharm. Bull.* **2009**, *57*(6), 561.
16. Cherkupally, S. R.; Dasari, C. R.; Vookanti, Y.; Adki, N. *Org. Commun.* **2010**, *3:3*, 57.
17. Dekimpe, N.; De Buyck, L. *Bull. Soc. Chem. Belg.* **1977**, *86*, 55.
18. Panwar, H.; Verma, R. S.; Srivastava, V. K. *Indian J. Chem.* **2006**, *45B*, 2099.
19. Kumar, A.; Sharma, S.; Archana, Bajaj, K.; Sharma, S.; Panwar, H.; Singh, T.; Srivastava, V. K. *Bioorg. Med. Chem.* **2003**, *11*, 5293.
20. Czurny, M. R.; Semmel, M. F. *Org. Synth.* **1975**, *60*, 66.
21. Cruickshank, R.; Duguid, J. P.; Marion, B. P.; Swain, R. H. In *Medicinal Microbiology*, 12th ed; Churchill Livingstone: London, U.K., 1975.
22. Collins, A. H. *Microbiological Methods*, 2nd ed.; Butterworth: London, U.K., 1976.
23. Khan, Z. K. In vitro and vivo screening techniques for bioactivity screening and evaluation. In *Proceedings of the International Workshop on UNIDO-CDRI*, 1997.
24. Varma, R. S. *Antifungal Agents: Past, Present and Future Prospects*; National Academy of Chemistry and Biology: Lucknow, India, 1998.
25. Carrol, S. W. *Biometrics* **1952**, *9*, 249.