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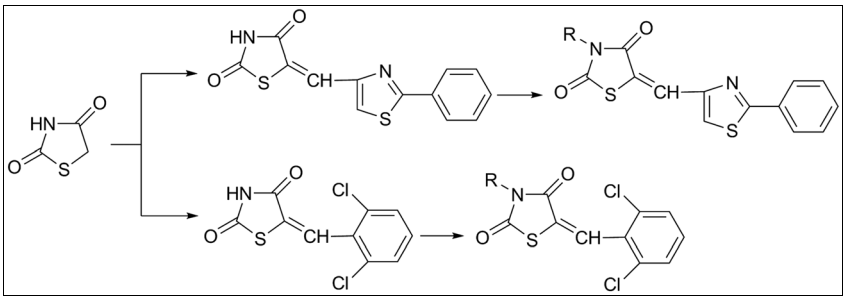

A total of 17 new N-substituted derivatives (**2b–k** and **3b–h**) of 5-((2-phenylthiazol-4-yl)methylene) thiazolidine-2,4-dione (**2a**) and 5-(2,6-dichloro- benzylidene)thiazolidine-2,4-dione (**3a**) were synthesized. The structural elucidation of the newly synthesized compounds was based on elemental analysis and spectroscopic data (MS, ^{1}H NMR, ^{13}C NMR), and their antimicrobial activities were assessed *in vitro* against several strains of Gram-positive and Gram-negative bacteria and one fungal strain (*Candida albicans*) as growth inhibition diameter. Some of them showed modest to good antibacterial activity against Gram-negative *Escherichia coli* and *Salmonella typhimurium* and Gram-positive *Staphylococcus aureus*, *Bacillus cereus*, and *Enterococcus fecalis* bacterial strains, whereas almost all the compounds were inactive against *Listeria monocytogenes*. All of the synthesized compounds showed moderate to very good activity against *C. albicans*.

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INTRODUCTION

Since their discovery, antibiotics have dramatically improved public health by enabling millions of people to live longer, more productive lives. The very success of these drugs has often resulted in an inappropriate and irrational use of antimicrobial drugs that has led to the development of antimicrobial resistance, a worldwide public health problem that continues to grow. In spite of the large number of antibacterial agents available for medical use, the dramatically increasing number of pathogens resistant to different classes of antibiotics and chemotherapeutics, and emerging infectious diseases over the past decades, lead to the necessity for developing new approaches to antimicrobial therapy, especially for seeking, testing, and validating novel therapeutics with little or no cross-resistance [1].

Thiazoles and their derivatives (thiazolines, thiazolidines, thiazolidinones, and thiazolidinediones) have attracted continuous interest over the years because of their broad spectrum of biological activities [2]. Recently, were found applications of thiazoles in drug development for the treatment of inflammation [3], bacterial [4], fungal [5], HIV infections [6], pain [7], allergies, hypertension, schizophrenia, as hypnotics, and as fibrinogen receptor antagonists with antithrombotic activity [8,9].

Thiazolidine-2,4-dione derivatives have been studied extensively and found to serve as basic pharmacophore for various biological profiles: antidiabetic, anticancer, antimicrobial, analgesic, cardiotonic, aldose reductase inhibitors, and anti-inflammatory [10]. Some thiazolidine-2,4-dione compounds are used in the treatment of type II diabetes by increasing the sensitivity towards insulin and give potential anti-inflammatory activity by inhibiting monocyte/macrophage activation and expression of inflammatory mediators [11]. In addition, thiazolidine-2,4-dione-based molecules have remarkable antiproliferative effect on vascular smooth muscle, cause G0/G1 cell cycle arrest in cancer [12] and show significant antibacterial and antifungal activities [13]. It has been reported that the insertion of arylidene moieties at the fifth position of the thiazolidine-2,4-dione ring enhanced the antimicrobial activity [14,15].

Prompted by these findings and as part of our efforts to discover potentially active new antimicrobial agents, we report in the present work, the synthesis of two series of

5-arylidene-thiazolidine-2,4-diones, various substitution in the third position, at the nitrogen atom and evaluation of their antibacterial and antifungal activities.

RESULTS AND DISCUSSION

Chemistry. The target compounds, N-substituted 5-((2-phenylthiazol-4-yl)methylene)thiazolidine-2,4-diones (**2b–k**) and N-substituted 5-(2,6-dichloro benzylidene) thiazolidine-2,4-diones (**3b–h**) were prepared via the route depicted in Schemes 1 and 2.

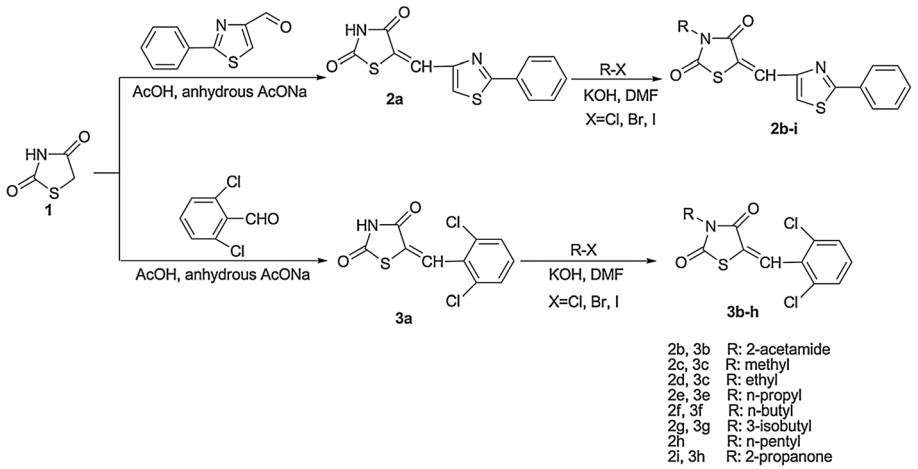
The general method known as Knoevenagel condensation was used to synthesize the 5-arylidene-thiazolidine-2,4-diones (**2a** and **3a**) in good yields (85–95%). 5-((2-phenylthiazol-4-yl)methylene)thiazolidine-2,4-dione (**2a**) was prepared by Knoevenagel condensation of thiazolidine-2,4-dione with 2-phenylthiazole-4-carbaldehyde in refluxing glacial acetic acid in the presence of anhydrous sodium accetate. 5-(2, 6-dichlorobenzylidene)thiazolidine-2,4-dione (**3a**) was prepared according to the procedures described in the literature [16,17].

The 5-arylidene-2,4-thiazolidinediones (**2a** and **3a**) were considered for N-alkylation so they were converted into potassium salts at the N3 position using anhydrous potassium hydroxide in dimethylformamide (DMF) under continuous stirring at room temperature. The potassium salts obtained were then treated with various halogenated derivatives in DMF under continuous stirring at room temperature to give the target compounds, N-substituted-5-arylidene-thiazolidine-2,4-diones (**2b–k** and **3b–h**, respectively) in 47–89% yields. The synthesis of the alkylating agents **4** and **5** was reported in a previous article [18].

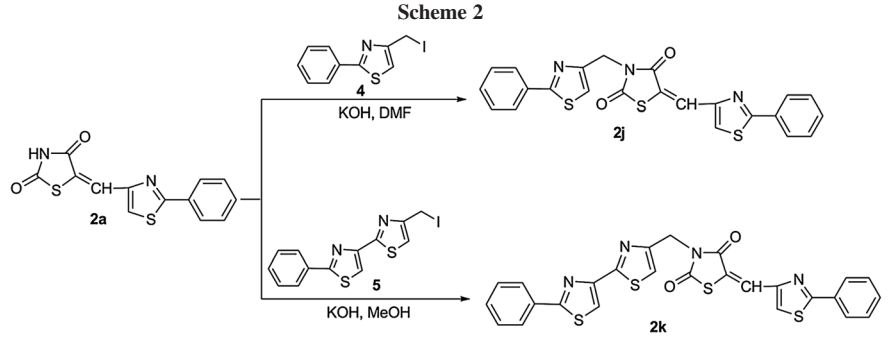
All newly synthesized compounds (**2a–k** and **3a–h)** were characterized by melting point, elemental analysis, and spectroscopic data (^{1}H NMR, ^{13}C NMR, and MS). All compounds gave very good CHNS quantitative elemental analysis results. All spectral data were in accordance with the assumed structures. The physical data, the yields, and the spectral characterizations of the synthesized compounds are presented in Experimental section, along with the details of the synthetic procedures.

^{1}H NMR spectra of synthesized compounds **2a–k** and **3a–h** showed one signal for the methylidene proton, as a singlet at 7.7–7.95 ppm, that supported the formation of 5-arylidene-thiazolidine-2,4-diones. The NH proton appeared as a singlet in the 12.5–12.8 ppm region in the ^{1}H NMR spectra of compounds **2a** and **3a** and was absent in the ^{1}H NMR spectra of **2b–k** and **3b–h**, thus substantiating the formation of N-substituted derivatives. ^{13}C NMR spectra of

Scheme 1



Scheme 2



the synthesized compounds were in accordance with the assumed structures.

The mass spectra of the synthesized compounds gave idea about the fragmentation of the final compounds with their corresponding mass and showed the correct molecular ions (M^+ or $M+1$), as suggested by their molecular formulas.

Antibacterial/antifungal activity. *In vitro* antimicrobial activity was evaluated by agar disc diffusion method according to the National Committee for Clinical Laboratory Standards guidelines. Antibacterial activity of newly synthesized compounds **2a–k** and **3`a–h** was evaluated against various pathogenic Gram-negative (*Salmonella typhimurium* ATCC 13311 and *Escherichia coli* ATCC 25922) and Gram-positive (*Listeria monocytogenes* ATCC 35152, *Staphylococcus aureus* ATCC 25923, *Bacillus cereus* ATCC 13061, and *Enterococcus fecalis* ATCC 29212) bacterial strains. Antifungal activity of the aforementioned compounds was evaluated against a strain of *Candida albicans* ATCC 90028.

For antibacterial testing, Mueller-Hinton agar medium was used. For antifungal testing, Mueller-Hinton medium supplemented with 2% glucose (providing adequate growth of yeasts) and 0.5 mg/mL methylene blue (providing a better definition of the inhibition zone diameter) was used. The inoculum was prepared by suspending five representative colonies, obtained from an 18–24 h culture on nonselective nutritive agar medium, in sterile distilled water. The cell density was adjusted to the density of a 0.5 McFarland standard by measuring the absorbance in a spectrophotometer at a wavelength of 530 nm and adding sterile distilled water as required (corresponding to a population of $1–5 \times 10^6$ CFU/mL). Six-millimeter diameter wells were cut from the agar using a sterile cork borer, and a predetermined volume of each compound solution was delivered into the wells. A sterile swab was soaked in suspension, and then, the Mueller-Hinton agar plates were inoculated by streaking the entire surface. After drying for 10–15 min, the 6-mm diameter wells were inoculated with 50 µL from 10 mg/mL solution in dimethyl sulfoxide (DMSO) (Merck, Germany) of each compound (50 µg/well). Ciprofloxacin (50 µg/well) and fluconazole (50 µg/well) were used as standard drugs. The plates were incubated at 35°C. Zone diameters were measured to the nearest whole millimeter at a point in which there will be no visible growth after 24–48 h. The solvent used for the preparation of the newly synthesized compound solutions, DMSO, did not show inhibition against the tested bacterial and fungal strains. Results were obtained in duplicate.

The results of antifungal and antibacterial activity of 5-arylidene-thiazolidine-2,4-diones (**2a** and **3a**) and their N-substituted derivatives (**2b–k** and **3b–h**, respectively) are reported in Table 1, in comparison with those of the reference drugs, ciprofloxacin and fluconazole.

The tested compounds presented a modest inhibitory activity against the Gram-positive and the Gram-negative bacteria, except compound **3a** that showed a good inhibitory activity against the tested Gram-negative bacterial strains, similar to that of ciprofloxacin (50 µg/well), used as standard drug. **3a** was the only compound that presented antibacterial activity against *L. monocytogenes*. All of the synthesized compounds are active and showed moderate activity against *E. fecalis*, *E. coli*, and *S. typhimurium* (8–14 mm inhibition zone). The 5-((2-phenylthiazol-4-yl)methylene) thiazolidine-2,4-diones **2a–k** were more active than the 5-(2,6-dichlorobenzylidene) thiazolidine-2,4-diones **3b–h**, suggesting that the presence of thiazole moiety increases the antibacterial activity of the compounds. Compounds **2e–g** were more active than compounds **2a–d**,**i** against *S. typhimurium*, suggesting that the substitution of N3 with lipophilic alkyl groups enhances the antibacterial properties. Regarding the antifungal activity, most of the synthesized compounds showed good inhibition against *C. albicans*, at test concentrations. The most active compounds were **2k**, with three thiazole rings in the structure, and the unsubstituted 5-(2,6-dichlorobenzylidene)thiazolidine-2,4-dione **3a**, which presented very good antifungal activity; the inhibitory activity being significantly more powerful than that of fluconazole (50 µg/well), used as standard drug. Concerning the antibacterial and antifungal activities, the most active compound was **3a**, suggesting that the presence of chlorine atoms on the aromatic ring, which increases the lipophilicity of the compound, and also the unsubstituted nitrogen atom of the 5-arylidene-thiazolidine-2,4-dione plays an important role in enhancing the antimicrobial properties of this class of compounds.

CONCLUSIONS

In conclusion, a series of new 5-((2-phenylthiazol-4-yl) methylene)thiazolidine-2,4-dione and 5-(2,6-dichlorobenzylidene)thiazolidine-2,4-dione derivatives have been synthesized by the Knoevenagel condensation method starting from thiazolidine-2,4-dione and the corresponding aromatic aldehydes. All compounds were characterized with the help of analytical techniques: ^{1}H NMR, ^{13}C NMR, mass, and elemental analysis and were evaluated for their antibacterial and antifungal activities against several Gram-positive, Gram-negative bacteria, and *C. albicans*. The antimicrobial activity results indicated that some of the tested compounds showed promising antibacterial and antifungal activities.

EXPERIMENTAL

Chemistry. Solvents and some alkylating agents were obtained from commercial sources. Compound **3a** and the noncommercially available variants of the alkylating agents 4-(iodomethyl)-2-phenylthiazole (**4**) and 4-(iodomethyl)-2′-phenyl-2,

Table 1

Antimicrobial activity of the synthesized compounds **2a–k** and **3a–h**.

	Inhibition zone in millimeters						
	Gram-positive bacteria				Gram-negative bacteria		Fungi
Compound	*Staphylococus aureus*	*Listeria monocytogenes*	*Bacillus cereus*	*Enterococcus fecalis*	*Escherichia coli*	*Salmonella typhimurium*	*Candida albicans*
2a	10	-	14	8	8	12	20
2b	11	-	14	8	10	12	22
2c	8	-	11	10	8	11	16
2d	8	-	8	8	8	13	12
2e	8	-	7	10	6	15	17
2f	8	-	8	10	6	15	10
2g	10	-	10	10	8	15	16
2h	8	-	11	8	6	12	11
2i	8	-	8	8	6	10	10
2j	7	-	-	8	8	11	12
2k	14	-	12	10	8	10	35
3a	20	20	20	16	6	11	35
3b	-	-	8	10	8	11	10
3c	7	-	7	10	10	9	16
3d	10	-	7	8	8	9	18
3e	8	-	8	8	8	10	16
3f	-	-	11	11	6	12	18
3g	-	-	9	10	8	10	16
3h	-	-	10	10	8	8	15
Ciprofloxacin	20	22	22	20	24	22	-
Fluconazole	-	-	-	-	-	-	25

Ciprofloxacine (50 μg/well) and fluconazole (50 μg/well) were used as standard drugs.
Hyphen (-) indicates the compound has no activity.

4′-bisthiazole (**5**) were prepared according to methodologies described in the literature [16–18].

The melting points were taken with an electrothermal melting point meter and are uncorrected. Analytical thin layer chromatography (TLC) was used to monitor the reaction progress and was carried out on precoated silica gel $60F_{254}$ sheets using heptane–ethyl–acetate 1:1 system and UV absorption for visualization. Yields were not optimized. The ^{1}H NMR spectra were recorded at room temperature on a Bruker Avance NMR (Karlsruhe, Germany) spectrometer operating at 400 and 500 MHz and were in accordance with the assigned structures. Chemical shift values were reported relative to tetramethylsilane (TMS) as internal standard. The samples were prepared by dissolving the compounds in DMSO-d_6 ($\delta_H = 2.51$ ppm) as solvent, and the spectra were recorded using a single excitation pulse of 12 μs (^{1}H NMR). ^{13}C NMR spectra were recorded on Bruker spectrometer (125 MHz) in DMSO-d_6. GC–MS analyses were performed with an Agilent (Darmstadt, Germany) gas chromatograph 6890 equipped with an apolar Macherey Nagel Permabond (Dueren, Germany) SE 52 capillary column. Elemental analysis was registered with a Vario El CHNS (Hanau, Germany) instrument.

5-((2-Phenylthiazol-4-yl)methylene)thiazolidine-2,4-dione (2a). To a solution of 2-phenylthiazole-4-carbaldehyde (945 mg, 5 mmol) in glacial acetic acid (2 mL) were added anhydrous sodium acetate (820 mg, 10 mmol) and thiazolidine-2,4-dione (585 mg, 5 mmol). The mixture was refluxed for 5 h. After cooling, the reaction mass was poured into ice-cold water. The precipitated solid was filtered, washed with water to remove the remaining traces of acetic acid, and then dried. The product was recrystallized from ethanol. Yield (85%), light brown solid, mp 275°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 12.5 (s, 1H, NH), 8.29 (s, 1H, C_5–thiazole–H), 8.08–8.013 (m, 2H, Ar-H), 7.77 (s, 1H, –CH═), 7.54–7.59 (m, 3H, Ar-H) ppm; ^{13}C NMR (DMSO-d_6) δ: 123.84 (CH), 124.28 (CH), 126.80 (2CH), 127.36 (C), 129.95 (2CH), 131.48 (C), 132.49 (CH), 150.61 (C), 166.20 (C═O), 168.36 (C), 170.19 (C═O) ppm; MS (EI, 70 eV) *m/z* (%): 289 (M + 1). *Anal.* Calcd for $C_{13}H_8N_2O_2S_2$: C, 54.15; H, 2.80; N, 9.72; S, 22.24. Found: C, 53.96; H, 2.62; N, 9.50 (9.72); S, 22.41 (22.24).

2-(2,4-Dioxo-5-((2-phenylthiazol-4-yl)methylene)thiazolidin-3-yl)acetamide (2b). A 1 mmol (288 mg) of **2a** was dissolved in DMF (3.5 mL), and fine dispersed anhydrous potassium hydroxide (84 mg, 1.5 mmol) was added. The mixture was stirred for 30 min at room temperature to give the potassium salt of 5-((2-phenylthiazol-4-yl)methylene)thiazolidine-2,4-dione. To the resulting suspension was added 2-iodoacetamide as alkylating agent (202 mg, 1.1 mmol). The mixture was stirred at room temperature for 8 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mass was poured into ice-cold water. The resulted precipitate was filtered, washed with water, dried, and then recrystallized from absolute methanol. Yield (82%), gray solid, mp 283°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.395 (s, 1H, C_5–thiazole–H), 8.038–8.058 (m, 2H, Ar-H), 7.81 (s, 1H, –CH═), 7.72 (s, 2H, NH_2), 7.569–7.615 (m, 3H, Ar-H), 4.241 (s, 2H, CH_2) ppm; ^{13}C NMR (DMSO-d_6) δ: 43.82 (CH_2), 123.75 (CH), 124.19 (CH), 126.75 (2CH), 127.26 (C), 129.82 (2CH), 131.53 (C), 132.41 (CH), 150.71 (C), 166.28 (C═O), 166.87 (C═O), 168.43 (C), 170.29 (C═O) ppm; MS (EI, 70 eV) *m/z* (%):

346 (M + 1). *Anal*. Calcd for $C_{15}H_{11}N_3O_3S_2$: C, 52.16; H, 3.21; N, 12.17; S, 18.57. Found: C, 51.96; H, 3.16; N, 12.00; S, 18.87.

3-Methyl-5-((2-phenylthiazol-4-yl)methylene)thiazolidine-2,4-dione (2c). Using the procedure described earlier for **2b** using iodomethane (212 mg, 1.5 mmol), we recrystallized the title compound from absolute ethanol. Yield (59%), white solid, mp 228–230°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.366 (s, 1H, C_5–thiazole–H), 8.030–8.048 (m, 2H, Ar-H), 7.78 (s, 1H, –CH═), 7.579–7.595 (m, 3H, Ar-H), 3.106 (s, 3H, N–CH_3) ppm; ^{13}C NMR (DMSO-d_6) δ: 28.72 (CH_3), 123.86 (CH), 124.35 (CH), 126.95 (2CH), 127.30 (C), 129.86 (2CH), 131.55 (C), 132.45 (CH), 150.69 (C), 166.19 (C═O), 168.38 (C), 170.23 (C═O) ppm; MS (EI, 70 eV) *m/z* (%): 303 (M + 1). *Anal*. Calcd for $C_{14}H_{10}N_2O_2S_2$: C, 55.61; H, 3.33; N, 9.26; S, 21.21. Found: C, 55.30; H, 3.02; N, 8.98; S, 21.16.

3-Ethyl-5-((2-phenylthiazol-4-yl)methylene)thiazolidine-2,4-dione (2d). The compound was prepared according to the procedure for **2b** using iodoethane (234 mg, 1.5 mmol), and absolute ethanol was used for recrystallization. Yield (53%), white solid, mp 165–168°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.371 (s, 1H, C_5–thiazole–H), 8.035–8.051 (m, 2H, Ar-H), 7.76 (s, 1H, –CH═), 7.496–7.598 (m, 3H, Ar-H), 3.21 (m, 2H, CH_2), 1.25 (t, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6) δ: 13.31 (CH_3), 36.55 (CH_2), 123.81 (CH), 124.29 (CH), 126.82 (2CH), 127.34 (C), 129.92 (2CH), 131.49 (C), 132.47 (CH), 150.64 (C), 166.17 (C═O), 168.34 (C), 170.17 (C═O) ppm; MS (EI, 70 eV) *m/z* (%): 317 (M + 1). *Anal*. Calcd for $C_{15}H_{12}N_2O_2S_2$: C, 56.94; H, 3.82; N, 8.85; S, 20.27. Found: C, 56.72; H, 3.65; N, 8.53; S, 20.57.

5-((2-Phenylthiazol-4-yl)methylene)-3-propylthiazolidine-2,4-dione (2e). The compound was prepared according to the procedure for **2b** using 1-bromopropane (184 mg, 1.5 mmol). Absolute ethanol was used for recrystallization. Yield (78%), brown solid, mp 130°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.368 (s, 1H, C_5–thiazole–H), 8.028–8.044 (m, 2H, Ar-H), 7.75 (s, 1H, –CH═), 7.492–7.596 (m, 3H, Ar-H), 3.3 (m, 2H, N–CH_2), 1.62 (m, 2H, CH_2), 0.94 (t, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6) δ: 13.61 (CH_3), 26.76 (CH_2), 38.52 (CH_2), 123.89 (CH), 124.32 (CH), 126.88 (2CH), 127.39 (C), 129.97 (2CH), 131.46 (C), 132.41 (CH), 150.61 (C), 166.13 (C═O), 168.38 (C), 170.11 (C═O) ppm; MS (EI, 70 eV) *m/z* (%): 331 (M + 1). *Anal*. Calcd for $C_{16}H_{14}N_2O_2S_2$: C, 58.16; H, 4.27; N, 8.48; S, 19.41. Found: C, 58.12; H, 4.18; N, 8.19; S, 19.71.

3-Butyl-5-((2-phenylthiazol-4-yl)methylene)thiazolidine-2,4-dione (2f). The compound was prepared according to the procedure for **2b** using 1-bromobutane (205 mg, 1.5 mmol) and was recrystallized from absolute ethanol. Yield (81%), light brown solid, mp 139°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.365 (s, 1H, C_5–thiazole–H), 8.031–8.045 (m, 2H, Ar-H), 7.73 (s, 1H, –CH═), 7.483–7.591 (m, 3H, Ar-H), 3.28 (m, 2H, N–CH_2), 1.28–1.51 (m, 4H, $2CH_2$), 0.96 (t, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6) δ: 13.95 (CH_3), 19.90 (CH_2), 29.69 (CH_2), 41.20 (CH_2), 123.72 (CH), 124.40 (CH), 126.85 (2CH), 127.44 (C), 129.97 (2CH), 131.54 (C), 132.49 (CH), 150.65 (C), 166.40 (C═O), 168.40 (C), 170.36 (C═O) ppm; MS (EI, 70 eV) *m/z* (%): 345 (M + 1). *Anal*. Calcd for $C_{17}H_{16}N_2O_2S_2$: C, 59.28; H, 4.68; N, 8.13; S, 18.62. Found: C, 59.18; H, 4.45, N, 8.06; S, 18.89.

3-Isopentyl-5-((2-phenylthiazol-4-yl)methylene)thiazolidine-2,4-dione (2g). Using the procedure described for **2b** using 1-bromo-3-methylbutane (226 mg, 1.5 mmol), the title compound was synthesized and recrystallized from absolute ethanol. Yield (89%), light brown solid, mp 137–138°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.362 (s, 1H, C_5–thiazole–H), 8.03–8.04 (m, 2H, Ar-H), 7.71 (s, 1H, –CH═), 7.48–7.59 (m, 3H, Ar-H), 3.26 (m, 2H, N–CH_2), 1.64 (m, 1H, CH), 1.56 (m, 2H, CH_2), 0.94 (d, 6H, $2CH_3$) ppm; ^{13}C NMR (DMSO-*d6*) δ: 22.66 ($2CH_3$), 25.82 (CH), 36.39 (CH_2), 39.96 (CH_2), 123.70 (CH), 124.37 (CH), 126.83 (2CH), 127.42 (C), 129.93 (2CH), 131.51 (C), 132.47 (CH), 150.61 (C), 166.31 (C═O), 168.35 (C), 170.30 (C═O) ppm; MS (EI, 70 eV) *m/z* (%): 359 (M + 1). *Anal*. Calcd for $C_{18}H_{18}N_2O_2S_2$: C, 60.31; H, 5.06; N, 7.81; S, 17.89. Found: C, 60.12; H, 5.01; N, 7.68; S, 18.11.

3-Pentyl-5-((2-phenylthiazol-4-yl)methylene)thiazolidine-2,4-dione (2h). The title compound was prepared using the procedure described for **2b** using 1-iodopentane (297 mg, 1.5 mmol) and was recrystallized from absolute ethanol. Yield (84%), light brown solid, mp 110°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.361 (s, 1H, C_5–thiazole–H), 8.03–8.04 (m, 2H, Ar-H), 7.71 (s, 1H, –CH═), 7.48–7.59 (m, 3H, Ar-H), 3.24 (m, 2H, N–CH_2), 1.29–1.64 (m, 6H, $3CH_2$), 0.91 (t, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6) δ: 14.27 (CH_3), 22.12 (CH_2), 27.26 (CH_2), 28.76 (CH_2), 41.41 (CH_2), 123.70 (CH), 124.39 (CH), 126.84 (2CH), 127.41 (C), 129.94 (2CH), 131.52 (C), 132.48 (CH), 150.64 (C), 166.38 (C═O), 168.37 (C), 170.34 (C═O) ppm; MS (EI, 70 eV) *m/z* (%): 359 (M + 1). *Anal*. Calcd for $C_{18}H_{18}N_2O_2S_2$: C, 60.31; H, 5.06; N, 7.81; S, 17.89. Found: C, 59.97; H, 4.84; N, 7.49; S, 18.17 (17.89).

3-(2-Oxopropyl)-5-((2-phenylthiazol-4-yl)methylene)thiazolidine-2,4-dione (2i). The title compound was synthesized according to the procedure described for **2b** using 1-chloropropan-2-one (185 mg, 2 mmol) and was recrystallized from absolute methanol. Yield (80%), white solid, mp 215°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.407 (s, 1H, C_5–thiazole–H), 8.042–8.061 (m, 2H, Ar-H), 7.81 (s, 1H, –CH═), 7.585–7.601 (m, 3H, Ar-H), 4.663 (s, 2H, CH_2), 2.258 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6) δ: 27.60 (CH_3), 50.94 (CH_2), 123.75 (CH), 124.42 (CH), 126.86 (2CH), 127.44 (C), 129.92 (2CH), 131.56 (C), 132.49 (CH), 150.68 (C), 166.39 (C═O), 168.39 (C), 170.31 (C═O), 200.71 (C═O) ppm; MS (EI, 70 eV) *m/z* (%): 345 (M + 1). *Anal*. Calcd for $C_{16}H_{12}N_2O_3S_2$: C, 55.80; H, 3.51; N, 8.13; S, 18.62. Found: C, 55.49; H, 3.31; N, 8.03; S, 18.94.

3-((2-Phenylthiazol-4-yl)methyl)-5-((2-phenylthiazol-4-yl) methylene) thiazolidine-2,4-dione (2j). The title compound was synthesized according to the procedure described for **2b** using 4-(iodomethyl)-2-phenylthiazole [18] (301 mg, 1 mmol) and was recrystallized from absolute methanol. Yield (67%), white solid, mp 229–230°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.391 (s, 1H, C_5–thiazole–H), 7.88 (s, 1H, –CH═), 7.57–8.04 (m, 10H, Ar-H), 7.53 (s, 1H, C_5–thiazole–H), 3.43 (s, 2H, CH_2) ppm; ^{13}C NMR (DMSO-d_6) δ: 42.37 (CH_2), 116.92 (CH), 122.61 (2CH), 126.97 (5CH), 128.17 (4CH), 130.06 (2C), 133.15 (C), 134.00 (C), 151.42 (C), 152.90 (C), 165.48 (C, C═O), 167.44 (C), 171.17 (C═O) ppm; MS (EI, 70 eV) *m/z* (%): 462 (M + 1). *Anal*. Calcd for $C_{23}H_{15}N_3O_2S_3$: C, 59.85; H, 3.28; N, 9.10; S, 20.84. Found: C, 59.65; H, 3.17; N, 9.02; S, 21.12.

3-((2′-Phenyl-2,4′-bisthiazol-4-yl)methyl)-5-((2-phenylthiazol-4-yl)methylene) thiazolidine-2,4-dione (2k). A 1.7 mmol of **2a** (489 mg) was suspended in absolute methanol (2 mL), and a suspension of anhydrous potassium hydroxide (96 mg, 1.7 mmol) in absolute methanol (2 mL) was added. The resulting suspension was stirred for 10 min. A suspension of 4-(iodomethyl)-2′-phenyl-2,4′-bisthiazole [18] (646 mg, 1.7 mmol) in absolute methanol (10 mL) was added slowly, under continuous stirring to the reaction mixture. The resultant was stirred for 10 min at room temperature and then refluxed for 12 h. After cooling, the reaction

mass was poured into ice-cold water. The precipitated solid was filtered, washed with water, and dried. The product was recrystallized from absolute methanol. Yield (48%), white solid, mp 243°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.389 (s, 1H, C_5–thiazole–H), 8.22 (s, 1H, C_5–thiazole–H), 7.85 (s, 1H, –CH═), 7.58–8.03 (m, 10H, Ar-H), 7.57 (s, 1H, C_5–thiazole–H), 3.48 (s, 2H, CH_2) ppm; ^{13}C NMR (DMSO-d_6) δ: 39.97 (CH_2), 114.12 (CH), 122.04 (2CH), 122.90 (CH), 123.77 (2CH), 124.26 (2CH), 127.35 (4CH), 130.14 (2C), 131.40 (C, CH), 133.33 (C, CH), 149.84 (2C), 151.19 (C), 162.20 (C═O), 167.03 (2C), 170.79 (C═O) ppm; MS (EI, 70 eV) *m/z* (%): 545 (M + 1). *Anal*. Calcd for $C_{26}H_{16}N_4O_2S_4$: C, 57.33; H, 2.96; N, 10.29; S, 23.55. Found: C, 56.99; H, 2.61; N, 10.09; S, 23.42.

2-(5-(2,6-Dichlorobenzylidene)-2,4-dioxothiazolidin-3-yl) acetamide (3b). To a solution of **3a** (273 mg, 1 mmol) in DMF (3.5 mL) was added fine dispersed anhydrous potassium hydroxide (84 mg, 1.5 mmol). The mixture was stirred for 30 min at room temperature to give the potassium salt. To the resulting suspension was added 2-iodoacetamide (202 mg, 1.1 mmol), and the mixture was stirred at room temperature for 8 h. The reaction was monitored by TLC. After completion of the reaction, the mass was poured into ice-cold water under continuous stirring. The resulted compound was washed with water, dried, and then recrystallized from absolute ethanol. Yield (85%), white solid, mp 222–223°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 7.95 (s, 1H, –CH═), 7.76 (s, 2H, NH_2), 7.481–7.603 (m, 3H, Ar-H), 4.26 (s, 2H, CH_2) ppm; ^{13}C NMR (DMSO-d_6) δ: 44.00 (CH_2), 129.31 (2CH), 129.59 (CH), 130.54 (C), 131.62 (CH), 132.48 (C), 133.51 (2C), 164.35 (C═O), 166.71 (C═O), 167.19 (C═O) ppm; MS (EI, 70 eV) *m/z* (%): 332 (M + 1). *Anal*. Calcd for $C_{12}H_8Cl_2N_2O_3S$: C, 43.52; H, 2.43; N, 8.46; S, 9.68. Found: C, 43.33; H, 2.32; N, 8.36; S, 9.49.

5-(2,6-Dichlorobenzylidene)-3-methylthiazolidine-2,4-dione (3c). The compound was prepared according to the procedure described for **3b** using iodomethane (212 mg, 1.5 mmol) for alkylation of **3a** (273 mg, 1 mmol). Yield (69%), white solid, mp 94°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 7.88 (s, 1H, –CH═), 7.496–7.622 (m, 3H, Ar-H), 3.431 (s, 3H, N–CH_3) ppm; ^{13}C NMR (DMSO-d_6) δ: 28.51 (CH_3), 128.92 (2CH), 129.27 (CH), 130.93 (C), 131.75 (CH), 132.39 (C), 133.52 (2C), 164.85 (C═O), 166.99 (C═O) ppm; MS (EI, 70 eV) *m/z* (%): 289 (M + 1). *Anal*. Calcd for $C_{11}H_7Cl_2NO_2S$: C, 45.85; H, 2.45; N, 4.86; S, 11.13. Found: C, 45.54; H, 2.38; N, 4.65; S, 11.01.

5-(2,6-Dichlorobenzylidene)-3-ethylthiazolidine-2,4-dione (3d). The compound was prepared according to the procedure described for **3b** using iodoethane (234 mg, 1.5 mmol). Yield (78%), white solid, mp 68–69°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 7.89 (s, 1H, –CH═), 7.482–7.654 (m, 3H, Ar-H), 3.384 (m, 2H, N–CH_2), 1.27 (t, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6) δ: 13.16 (CH_3), 37.48 (CH_2), 129.06 (2CH), 129.27 (CH), 130.77 (C), 131.70 (CH), 132.40 (C), 133.53 (2C), 164.52 (C═O), 166.77 (C═O) ppm; MS (EI, 70 eV) *m/z* (%): 303 (M + 1). *Anal*. Calcd for $C_{12}H_9Cl_2NO_2S$: C, 47.70; H, 3.00; N, 4.64; S, 10.61. Found: C, 47.74; H, 2.81; N, 4.30; S, 10.35.

5-(2,6-Dichlorobenzylidene)-3-propylthiazolidine-2,4-dione (3e). The compound was prepared according to the procedure described for **3b** using 1-bromopropane (184 mg, 1.5 mmol). Yield (73%), white solid, mp 58–59°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 7.91 (s, 1H, –CH═), 7.468–7.687 (m, 3H, Ar-H), 3.36 (m, 2H, N–CH_2), 1.68 (m, 2H, CH_2), 0.98 (t, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6) δ: 11.53 (CH_3), 20.96 (CH_2), 43.88 (CH_2), 129.12 (2CH), 129.27 (CH), 130.64 (C), 131.68 (CH), 132.40 (C), 133.53 (2C), 164.75 (C═O), 166.97 (C═O) ppm; MS (EI, 70 eV) *m/z* (%): 317 (M + 1). *Anal*. Calcd for $C_{13}H_{11}Cl_2NO_2S$: C, 49.38; H, 3.51; N, 4.43; S, 10.14. Found: C, 49.54; H, 3.41; N, 4.09; S, 9.84.

3-Butyl-5-(2,6-dichlorobenzylidene)thiazolidine-2,4-dione (3f). The compound was prepared according to the procedure described for **3b** using 1-bromobutane (205 mg, 1.5 mmol). Yield (47%), white solid, mp 31–32°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 7.92 (s, 1H, –CH═), 7.468–7.687 (m, 3H, Ar-H), 3.29 (m, 2H, N–CH_2), 1.25–1.52 (m, 4H, $2CH_2$), 0.97 (t, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6) δ: 13.91 (CH_3), 19.91 (CH_2), 29.58 (CH_2), 42.05 (CH_2), 129.12 (2CH), 129.27 (CH), 130.64 (C), 131.68 (CH), 132.41 (C), 133.52 (2C), 164.72 (C═O), 166.94 (C═O) ppm; MS (EI, 70 eV) *m/z* (%): 331 (M + 1). *Anal*. Calcd for $C_{14}H_{13}Cl_2NO_2S$: C, 50.92; H, 3.97; N, 4.24; S, 9.71. Found: C, 51.19; H, 3.72; N, 4.06; S, 9.64.

5-(2,6-Dichlorobenzylidene)-3-isopentylthiazolidine-2,4-dione (3g). The compound was prepared according to the procedure described for **3b** using 1-bromo-3-methylbutane (226 mg, 1.5 mmol). Yield (60%), white solid, mp 65°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 7.90 (s, 1H, –CH═), 7.508–7.692 (m, 3H, Ar-H), 3.25 (m, 2H, N–CH_2), 1.66 (m, 1H, CH), 1.57 (m, 2H, CH_2), 0.93 (d, 6H, $2CH_3$) ppm; ^{13}C NMR (DMSO-d_6) δ: 22.61 ($2CH_3$), 25.85 (CH), 36.32 (CH_2), 39.99 (CH_2), 129.15 (2CH), 129.34 (CH), 130.63 (C), 131.66 (CH), 132.45 (C), 133.56 (2C), 164.76 (C═O), 166.98 (C═O) ppm; MS (EI, 70 eV) *m/z* (%): 345 (M + 1). *Anal*. Calcd for $C_{15}H_{15}Cl_2NO_2S$: C, 52.33; H, 4.39; N, 4.07; S, 9.31. Found: C, 52.43; H, 4.53; N, 3.87; S, 8.98.

5-(2,6-Dichlorobenzylidene)-3-(2-oxopropyl)thiazolidine-2,4-dione (3h). The title compound was prepared according to the procedure described for **3b** using 1-chloropropan-2-one (185 mg, 2 mmol). Yield (81%), white solid, mp 140–141°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 7.94 (s, 1H, –CH═), 7.464–7.529 (m, 3H, Ar-H), 4.693 (s, 2H, CH_2), 2.278 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6) δ: 27.54 (CH_3), 50.98 (CH_2), 129.32 (2CH), 130.06 (CH), 130.25 (C), 131.56 (CH), 132.54 (C), 133.50 (2C), 164.09 (C═O), 166.44 (C═O), 200.75 (C═O) ppm; MS (EI, 70 eV) *m/z* (%): 331 (M + 1). *Anal*. Calcd for $C_{13}H_9Cl_2NO_3S$: C, 47.29; H, 2.75; N, 4.24; S, 9.71. Found: C, 47.09; H, 2.45; N, 3.98; S, 9.35.

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