

HETEROCYCLES, Vol. 92, No. 7, 2016, pp. 1224 - 1243. © 2016 The Japan Institute of Heterocyclic Chemistry  
Received, 7th April, 2016, Accepted, 25th April, 2016, Published online, 16th May, 2016  
DOI: 10.3987/COM-16-13479

## PROSPECTIVE STUDY DIRECTED TO THE SYNTHESIS OF SYMMETRICAL LINKED BIS-RHODANINE DERIVATIVES WITH THEIR ANTIMICROBIAL ACTIVITY

Wael A. A. Arafa,<sup>1,2\*</sup> Raafat M. Shaker,<sup>3</sup> and Saleh A. Rabeh<sup>4,5</sup>

<sup>1</sup>Chemistry Department, College of Science, Aljouf University, P.O. Box 2014, Sakaka, Aljouf, Kingdom of Saudi Arabia. <sup>2</sup>Chemistry Department, Faculty of Science, Fayoum University, P.O. Box 63514, Fayoum, Egypt. <sup>3</sup>Chemistry Department, Faculty of Science, Minia University, 61519 Minia, Egypt. <sup>4</sup>Department of Biology, College of Science, Aljouf University, Sakaka, P.O. Box 2014, Aljouf, Kingdom of Saudi Arabia. <sup>5</sup>National Institute of Oceanography and Fisheries (NIOF), Inland Waters and Aquaculture Branch, Greater Cairo, Egypt. E-mail: waarafa@ju.edu.sa, waa00@fayoum.edu.eg

**Abstract** – One-pot three-component reactions of diamines, carbon disulfide and dialkyl acetylenedicarboxylates under conventional or ultrasound methods furnishing bis-rhodanines in good yields are described. Knoevenagel condensation reaction between 5,5-methylene-bis-salicylaldehyde, pyrazole-3,5-dicarbaldehyde or terephthalaldehyde and *N*-alkylrhodanines afforded bis-arylidenerhodanines. While, the condensation between 2,6-diformylphenols and *N*-alkylrhodanines furnished only the mono-arylidenerhodanines. The newly synthesized compounds were characterized by HRMS and NMR spectral data. The compounds were screened for their *in vitro* antimicrobial activities. All the tested compounds showed pronounced activities, suggesting that the rhodanine moiety plays an important role in enhancing the antimicrobial properties of this class of compounds.

## INTRODUCTION

Rhodanine-based compounds have attracted interest in medicinal chemistry, exhibiting pharmacological and therapeutic properties,<sup>1,2</sup> ever since the introduction of Epalrestat and Ciglitazone into clinical use for the treatment of diabetic complications and type 2 diabetes mellitus, respectively.<sup>3</sup> The chemical derivatization of this class of compounds give rise to derivatives with a broad spectrum of biological

activities. For example, some rhodanine derivatives possess antibacterial,<sup>4</sup> antifungal,<sup>5</sup> antiviral,<sup>6</sup> antimalarial,<sup>7</sup> aldose reductase inhibitors,<sup>8</sup> antitumor,<sup>9</sup> and anti-inflammatory<sup>1</sup> activities. Simultaneously, rhodanines have been reported as hepatitis C virus (HCV) protease inhibitors<sup>10</sup> and used as inhibitors of uridine diphospho-*N*-acetylmuramate/*L*-alanine ligase.<sup>11</sup> Additionally, some rhodanine derivatives have been reported to inhibit cancer cell migration.<sup>12</sup> Rhodanines were found to have noteworthy mildew-proofing activity that make them used as plant fungicides.<sup>13</sup> Chemically, rhodanine and its derivatives are of interest due to coordination capacity and their use as metal extracting agents.<sup>14</sup> Also, some of them have higher sensitivity and selectivity for the analysis of many noble metal ions.<sup>15</sup> They were also reported to be effective as corrosion inhibitors.<sup>16</sup> The application of ultrasound irradiation in organic synthesis has been used in recent years.<sup>17</sup> A large number of organic reactions can be carried out in a shorter time, higher reaction yield, and milder conditions under sonication. These unique effects of ultrasound waves in organic synthesis are due to the phenomenon of cavitations, which is a physical process that creates, enlarges, and collapses vaporous cavities in an irradiated liquid, thus, enhancing their transfer and allowing chemical reactions to take place.<sup>18</sup> In recent years, attention has been increasingly paid to the synthesis of bis-heterocyclic compounds, which exhibit various biological activities.<sup>19-21</sup> As part of our growing interest in synthesizing bis-heterocyclic compounds of interesting biological activities<sup>22-26</sup> and in connection with the increasing importance of the preparation of small libraries of compounds with variations of substituents,<sup>27</sup> we describe herein an easy and inexpensive synthetic route for the synthesis of a set of mono and bis-rhodanines under conventional and ultrasound irradiation with an aim to find novel and more potent antibacterial and antifungal agents.

## RESULTS AND DISCUSSION

### Chemistry

A careful literature survey reveals that there have been no reports on the synthesis of bis-rhodanines via reaction of diamines, CS<sub>2</sub> and dialkyl acetylenedicarboxylates. In order to determine the optimal reaction conditions for the synthesis of bis-rhodanines, we decided to launch our studies toward conventional method. To accomplish this conversion, we carried out the reaction utilizing two moles of dimethyl acetylenedicarboxylate **1a**, two moles of carbon disulfide and one mole of *p*-xylyldiamine **2a** as a model reaction. In this set of experiments, a variety of different solvents such as water, ethanol, ethanol/water, and PEG-400 were tested with the target to determine the optimum reaction conditions. The results are summarized in Table 1.

As can be seen, the best solvent for this reaction was EtOH/H<sub>2</sub>O (20/80%), affording compound **3a** in 57% of yield in 10 h (Table 1, Entry 5). Searching for an alternative method for the preparation of bis-rhodanines, we decided to carry out the synthesis of this compound, **3a**, under ultrasound irradiation.

**Table 1.** Optimization of the reaction conditions for the synthesis of bis-rhodanine **3a** at room temperature under conventional (Conv.) and ultrasound (US) methods<sup>a</sup>

Entry	Solvent	Method	Time (h)	Yield (%) <sup>c</sup>
1	H <sub>2</sub> O	Conv.	5	45
2	EtOH	Conv.	5	40
3	EtOH / H <sub>2</sub> O (80/20%)	Conv.	10	43
4	EtOH / H <sub>2</sub> O (50/50%)	Conv.	10	50
5	EtOH / H <sub>2</sub> O (20/80%)	Conv.	10	57
6	EtOH / H <sub>2</sub> O (20/80%)	Conv.	24	59
7	PEG-400	Conv.	12	35
8	EtOH / H <sub>2</sub> O (20/80%)	US	5 <sup>b</sup>	82
9	EtOH / H <sub>2</sub> O (20/80%)	US	10 <sup>b</sup>	82

<sup>a</sup>Reaction conditions: **1a** (2 mmol), CS<sub>2</sub> (2 mmol) and **2a** (1 mmol) in solvent (5 mL) at room temperature; <sup>b</sup>Time in minutes; <sup>c</sup>Yields of isolated products.

To achieve this, we used the same molar ratio employed in the conventional method. From Table 1 (Entry 8), we can observe that ultrasound irradiation method afforded the respective compound **3a** in a much better yield compared with the conventional method and in a short reaction time. In order to further improve the yield and decrease the reaction time, we tried to increase the reaction temperature under ultrasound irradiation. The effect, however, was not remarkable and the reaction yield decreased. Consequently, it was indicated that there was no remarkable temperature effect on this reaction. We also observed the effect of frequency of ultrasound irradiation on the model reaction. When the frequency of the ultrasound was 25 kHz, the model reaction afforded the required product **3a** in 82% yield at 25 °C. Utilizing 40 kHz did not change reaction yield a significant amount (80% in the same time). It is clear that there is an optimum frequency for effective synthesis of bis-rhodanines in the frequency of 25 kHz. This is due to the fact that lower ultrasonic frequencies produce larger cavitation bubbles than higher frequencies. Therefore, larger cavitation bubbles require more energy to produce and, in turn, release a larger amount of energy when they implode. With this optimum condition, a series of bis-rhodanines was synthesized in EtOH/H<sub>2</sub>O (20/80%) as a solvent using the ultrasound irradiation method (Table 2). From Table 2, it is indicated that the clear difference in the reaction efficiencies with or without sonication

suggests that the reaction with ultrasound conditions proceeded in a more efficient way than the reaction under conventional conditions.

**Table 2.** Comparison between conventional and ultrasound methods for synthesis of **3-5** in terms of time and yield<sup>a</sup>

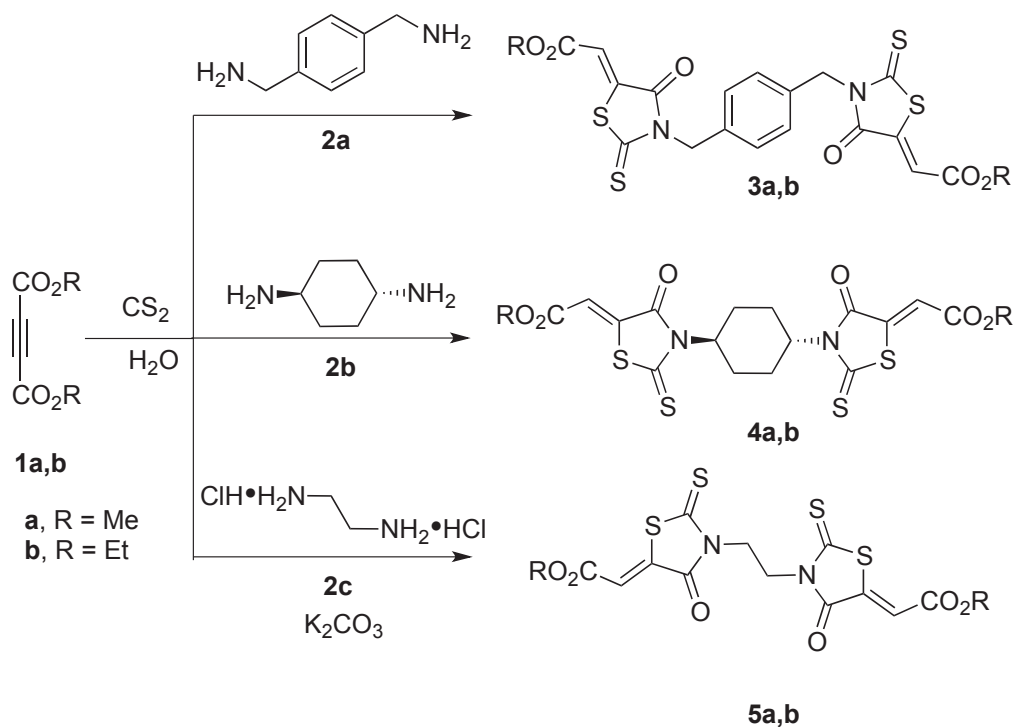
Entry	Compound	Conventional <sup>b</sup>		Ultrasound <sup>c</sup>	
		Time (h)	Yield (%) <sup>d</sup>	Time (min)	Yield (%) <sup>d</sup>
1	<b>3a</b>	10	57	5	82
2	<b>3b</b>	12	60	5	75
3	<b>4a</b>	10	58	10	77
4	<b>4b</b>	10	60	10	72
5	<b>5a</b>	12	62	5	80
6	<b>5b</b>	10	65	5	81

<sup>a</sup>Reaction conditions: **1a, b** (2 mmol), CS<sub>2</sub> (2 mmol) and **2a-c** (1 mmol) in EtOH/H<sub>2</sub>O (5 mL) at rt;

<sup>b</sup>Reaction under stirring condition; <sup>c</sup>Reaction under ultrasound irradiation; <sup>d</sup>Yields of isolated products.

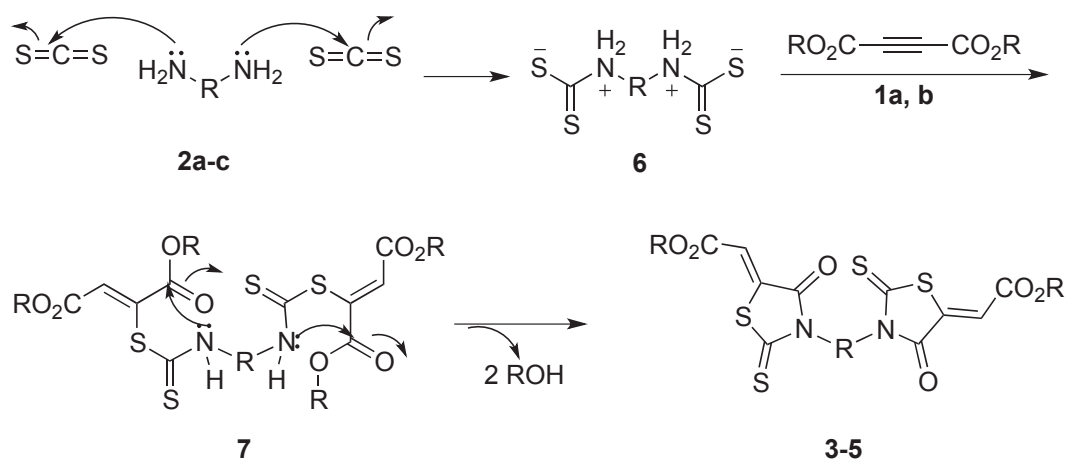
This study obviously showed that the required compounds **3-5** (Scheme 1) were obtained in much longer reaction time (10-12 h) and comparatively lower yield (57-65%) under conventional method, whereas under ultrasound irradiation the products were obtained in 5-10 min with the yields of 72-82% (Table 2). Thus, ultrasound irradiation was found to have advantageous effects on the synthesis of bis-rhodanine derivatives. This result is due to the phenomenon of cavitations, which is grown by reducing the ambient pressure under ultrasound irradiation. The collapse of cavities established an uncommon environment for reactions. The gases inside the cavity are compressed, generating intense heat that increases the temperature of the liquid immediately surrounding the cavity and creates a local hot spot to accelerate the reaction.<sup>28</sup>

The structures of the bis-rhodanines **3-5** were deduced from their IR, HRMS, NMR spectra and elemental analysis. The HRMS spectra of the compounds **3-5** revealed that they contain two moles of rhodanine units per one mole of diamines **2a-c**. For example, the mass spectrum of **3a** displayed the molecular ion (M + Na) at *m/z* 530.9789. The <sup>1</sup>H NMR spectrum of **3a** exhibited four sharp singlets readily recognized as arising from the aromatic moiety ( $\delta = 7.25$ ), the vinylic CH ( $\delta = 6.76$ ), methylene ( $\delta = 5.22$ ) protons and methyl group ( $\delta = 3.85$ ). The <sup>13</sup>C NMR spectrum of **3a** showed 9 distinct resonances in agreement with the proposed structure. The IR spectrum of **3a** exhibited absorption bands due to the two carbonyl groups at 1722, 1715 cm<sup>-1</sup> and the C=S group at 1266 cm<sup>-1</sup>.



**Scheme 1.** Synthesis of bis-rhodanine derivatives **3-5**

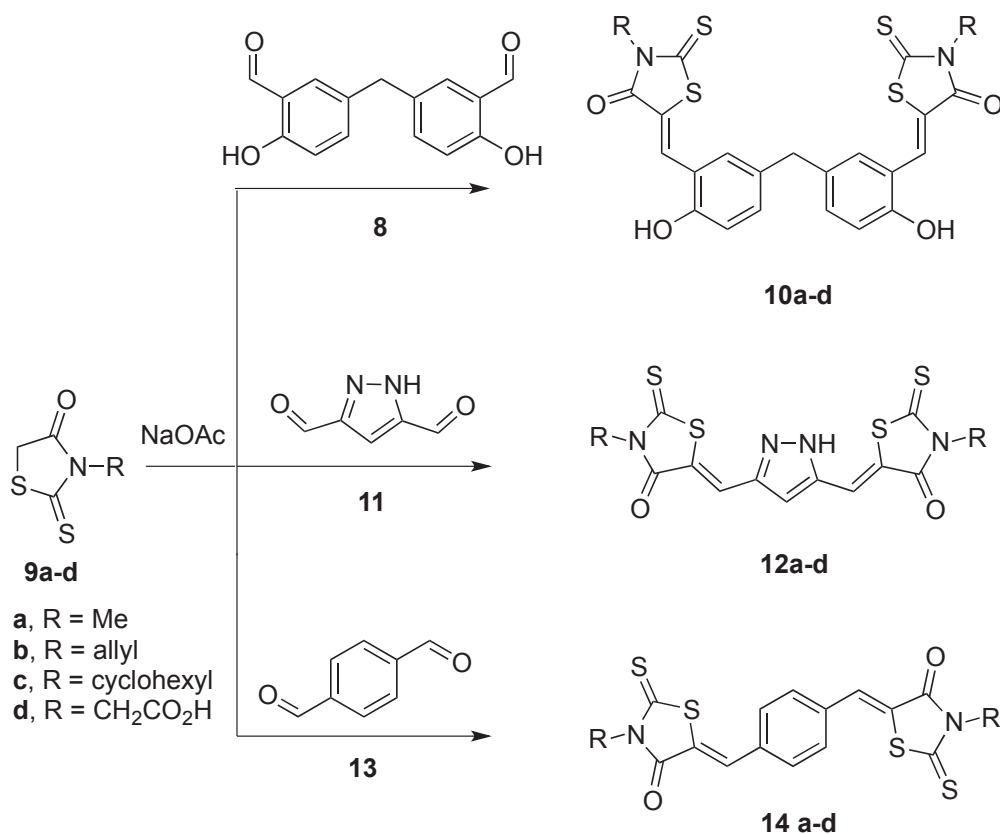
On the basis of the experimental results, a plausible mechanism for the formation of bis-rhodanines **3-5** is presented in Scheme 2. The initial step in this reaction is the nucleophilic attack of diamines **2a-c** to carbon disulfide to afford the di-carbodithioate intermediate **6**, which subsequently reacts with **1a,b** to form the second intermediate **7**. Intramolecular ring cyclization of **7** gave the isolable bis-rhodanine derivatives **3-5** (Scheme 2).



**Scheme 2.** Plausible reaction mechanism for synthesis of bis-rhodanine derivatives **3-5**

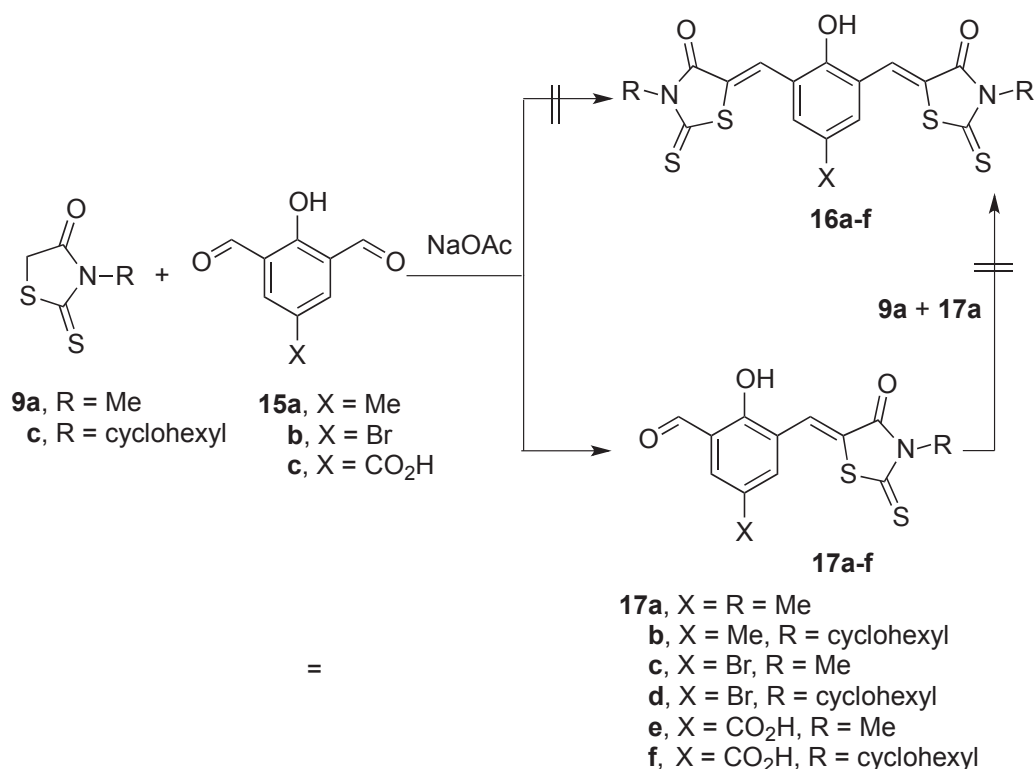
*N*-Alkylrhodanines are inexpensive commercially available reagents which make their use attractive as the starting material for the synthesis of many biologically active derivatives. With the aim to extend the

scope of our investigation and to obtain other series of bis-rhodanine derivatives, we chose an alternative protocol incorporating di-aldehydes and *N*-alkylrhodanines. A series of new bis-rhodanine analogues were synthesized as outlined in Scheme 3. Salicylaldehyde was reacted with formaldehyde in the presence of catalytic amount of sulfuric acid leading to the formation of 5,5-methylene-bis-salicylaldehyde **8**,<sup>29</sup> which upon treatment with *N*-alkylrhodanine derivatives **9a-d** under Knoevenagel condensation conditions afforded the final compounds **10a-d** with control of the double bond stereochemistry (Scheme 3). Compounds **10a-d** were obtained in 89-95% yields. The structures of the synthesized compounds **10a-d** were substantiated by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and HRMS. The IR (KBr) spectra of compounds **10a-d** exhibited absorption bands of the stretching vibrations of the OH group of the phenol moiety (~3300 cm<sup>-1</sup>). In addition, the IR spectra display characteristic bands of C=O groups (intense bands around 1690 cm<sup>-1</sup>) and C=S stretching vibrations in the 1274-1249 cm<sup>-1</sup> range. <sup>1</sup>H NMR spectrum which showed two singlets around 7.8 and 4.0 ppm assigned to the two vinylic protons and methylene protons, respectively. As expected, the condensation reaction could give rise to two possible stereoisomers (*E* and *Z*); it was found that the thermodynamically stable *Z*-isomer was formed selectively over the *E*-isomer as characterized by the down-field shift of their methine-group protons when compared to that of the *E*-isomer.



**Scheme 3.** Synthesis of bis-rhodanine derivatives **10**, **12** and **14**

Further, pyrazole-3,5-dicarbaldehyde **11**<sup>30</sup> or terephthalaldehyde **13** was condensed with rhodanines **9a-d** in the presence of sodium acetate under refluxing in acetic acid to provide Knoevenagel products **12a-d** and **14a-d**, respectively in excellent yields (Scheme 3). The structures of compounds **12a-d** and **14a-d** were assigned by <sup>1</sup>H and <sup>13</sup>C NMR spectra and mass spectrometric data which are consistent with the proposed bis-rhodanine structures. For example, the <sup>1</sup>H NMR of compound **12a** shows two singlets at 14.51, 7.68 ppm, with integrals in the ratio 1:2, which were readily assigned to the N-H proton of the pyrazole ring and to the =C-H proton, respectively. The existence of two C=S groups at  $\delta$  196.1, and two C=O at  $\delta$  166.7 is confirmed by <sup>13</sup>C NMR spectroscopy. It is obvious that, the molecular ion peaks are in good agreement with their suggested empirical formula as indicated from HRMS and elemental analyses. This finding attracted our intention to study the reaction of rhodanines **9a,c** with 2,6-diformylphenols **15a-c**. Thus, heating a 1:2 molar mixture of 2,6-diformylphenols **15a-c** with rhodanines **9a,c**, respectively under Knoevenagel conditions furnished, in each case, a single product (TLC) (Scheme 4). Based on their spectral data (HRMS, IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR), the 2-hydroxy-5-substituted-3-((Z)-3-alkyl-4-oxo-2-thioxothiazolidin-5-ylidene)methyl)benzaldehyde structures **17a-f** were assigned to the reaction products.



**Scheme 4.** Synthesis of mono-rhodanine derivatives **17a-f**

The HRMS analyses of derivatives **17a-f** revealed that they contained one mole of 2,6-diformylphenols **15a-c** per one mole of rhodanines **9a,c**. For example, the mass spectrum of derivative **17f**, revealed ion

peaks at  $m/z$  390.0462 corresponding to (M - H). Its  $^1\text{H}$  NMR revealed five characteristic singlet signals at  $\delta$  12.18 (OH,  $\text{CO}_2\text{H}$ ), 10.04 (CHO), 7.99 (=CH), 8.45 and 8.36 (ArH) ppm. Also, the proton signals of the cyclohexane moiety were clearly observed.

In the  $^{13}\text{C}$  NMR spectrum of compound **17f**, a thiocarbonyl carbon and an aldehydic carbonyl-carbon resonate at  $\delta$  195.6 and 194.2 ppm, respectively. Also,  $^{13}\text{C}$  NMR spectrum showed signal for (=CH) in the Knoevenagel condensed product, **17f** at about  $\delta$  136.3 ppm. The reason for this deshielding is attributed to the cis position of the carbonyl function of the rhodanine ring to the (=CH) and hence the *Z*-configuration. Many efforts were made to prepare the bis-rhodanines **16a-f**. The reaction between *N*-methylrhodanine **9a** and 2-hydroxy-5-methylbenzene-1,3-dialdehyde **15a** was chosen for this study. When the Knoevenagel condensation of these compounds was attempted using ammonium acetate, piperidinium acetate (PA), or sodium methoxide as the catalyst and under refluxing conditions, only the mono condensation product was obtained in 65-80% yield (Table 3). Also, the same reaction using MW irradiation gave the mono-rhodanines with an improvement in the reaction yields (70-90%, Table 3). Furthermore, by the re-reaction of the mono-rhodanine **17a** with excess *N*-methylrhodanine **9a** under the above conditions, the starting materials, again, were likewise recovered (Scheme 3). The formation of mono-rhodanines rather than bis-rhodanines might be attributed to the deactivation of the aldehydic carbonyl group after the condensation of the first one.

**Table 3.** Screening of catalysts, temperature and reaction time for the synthesis of **17a**

Base	Method	Temp. ( $^{\circ}\text{C}$ )	Time (min)	Yield (%)
NaOAc	Conv.	120	5 <sup>a</sup>	70
NaOAc	Conv.	120	48 <sup>a</sup>	77
NaOAc	MW	90	10	75
NaOAc	MW	90	20	82
NH <sub>4</sub> OAc	Conv.	120	5 <sup>a</sup>	65
NH <sub>4</sub> OAc	MW	90	20	74
PA	Conv.	120	5 <sup>a</sup>	65
PA	MW	90	20	70
NaOMe	Conv.	120	5 <sup>a</sup>	80
NaOMe	MW	90	20	90

<sup>a</sup>Time in hours.



## Antimicrobial Activity

### Antibacterial activity

The results of antibacterial screening of the newly synthesized compounds are presented in (Table 4). From these results, it has been revealed that most of the tested compounds possess good antibacterial activity in the range of 1.56-50  $\mu\text{g/mL}$ . Among the first series of the synthesized **3-5**, compound **5b** exhibited the maximum activity among this series with a MIC value of 3.12  $\mu\text{g/mL}$  against *S. aureus*, *M. luteus* and *P. vulgaris* but 6.25  $\mu\text{g/mL}$  against *K. pneumonia*. Compounds **3b** and **4b** which contains ethyl groups exhibited very best activity against *M. luteus* (MIC 3.12  $\mu\text{g/mL}$ ) and good inhibition against *S. aureus* (MIC 6.25  $\mu\text{g/mL}$ ), but against *P. vulgaris* and *K. pneumonia*, they exhibited moderate activities. Other derivatives, **3a**, **4a** and **5a** exhibited moderate to poor activity. Of the compounds tested, compound **10c** (possessing both hydroxyl group and acetic acid moiety) showed the highest level of inhibitory activity against *S. aureus* with a MIC value of 1.56  $\mu\text{g/mL}$ , which was comparable to that of the positive control, ciprofloxacin. Among the bis-arylidenerhodanines **10**, **12** and **14**, derivatives **12c** and **14c** having an acetic acid moiety exhibited excellent activity against both Gram positive and Gram negative strains with MIC value of 3.12  $\mu\text{g/mL}$ . From the results of the other *N*-alkyl substituted compounds, it was observed that compounds **10a**, **10b** and **10d** (with two hydroxyl groups) exhibited good activity against all the bacteria strains. Whereas, compounds **12a**, **12b**, **12d**, **14a**, **14b** and **14d** exhibited good to moderate activities (6.25-12.5  $\mu\text{g/mL}$ ) against *M. luteus* and *S. aureus* but poor activity against the rest of the bacterial strains. Among the mono-arylidenerhodanines **17a-f**, compounds **17c** and **17d**, having both bromo and hydroxyl exhibited excellent activity against all bacterial strain with MIC value of 3.12  $\mu\text{g/mL}$ . Compounds **17a,b** having methyl group exhibited pronounced activity against Gram positive bacterial strains with MIC value of 6.25  $\mu\text{g/mL}$  and good activity against Gram negative bacterial strains with MIC value of 12.5  $\mu\text{g/mL}$ . Compounds **17e,f** having carboxylic acid groups exhibited good activities against *K. pneumonia* with MIC value of 6.25  $\mu\text{g/mL}$  and moderate activities with MIC of 12.5  $\mu\text{g/mL}$  against *M. luteus* but low activities against the rest of the bacterial strains. Herein, we can conclude that the substituents are essential for the pronounced activity.

### Antifungal activity

The antifungal screening revealed that most of the tested compounds showed excellent to moderate fungal inhibition. Some of the synthesized compounds, **3-5**, showed good antifungal activity against *C. albicans* at 6.24-12.5  $\mu\text{g/mL}$  and poor activity against *B. cinerea*. From the antifungal results of the bis-arylidene derivatives, **10**, **12**, **14**, it was clear that only compounds with *N*-methyl group, **10a**, **12a** and **14a**, were found to be more active with MIC values of 12.5-25  $\mu\text{g/mL}$  and the other derivatives exhibited poor activity. Moreover, the *p*-bromophenyl derivatives, **17c** and **17d**, are highly active against *C. albicans* (MIC 3.12  $\mu\text{g/mL}$ ) and good against *B. cinerea* (MIC 6.25  $\mu\text{g/mL}$ ). While the other

mono-arylidenerhodanine derivatives exhibited good to moderate activity against the fungal strains. Preliminary structure–activity relationships (SARs) analysis indicated that, bromo, hydroxyl and carboxyl groups might play an important role in determining their inhibitory activities. The substituents introduced in the nitrogen atom of the rhodanine rings may have hindered docking of the inhibitor to microorganisms. Rhodanine derivatives bearing an alkyl ester group at position-5 might be beneficial to increase the inhibitory activities.

**Table 4.** *In vitro* antimicrobial activity of synthesized compounds

Compounds	MIC in $\mu\text{g/mL}$ (zone of inhibition in mm)					
	Gram positive bacteria		Gram negative bacteria		Fungi	
	<i>S. aureus</i>	<i>M. luteus</i>	<i>P. vulgaris</i>	<i>K. pneumonia</i>	<i>C. albicans</i>	<i>B. cinerea</i>
<b>3a</b>	25 (16-17)	25 (16-18)	12.5 (18-21)	25 (16-18)	6.25 (22-24)	50 (12-14)
<b>3b</b>	6.25 (22-24)	3.12 (26-28)	12.5 (18-22)	12.5 (18-21)	12.5 (18-21)	50 (12-14)
<b>4a</b>	50 (11-14)	50 (10-14)	25 (15-18)	50 (11-14)	12.5 (18-21)	25 (15-16)
<b>4b</b>	6.25 (21-24)	3.12 (25-28)	12.5 (18-22)	12.5 (18-22)	12.5 (19-22)	50 (11-13)
<b>5a</b>	25 (16-18)	50 (10-12)	25 (17-18)	25 (15-18)	6.25 (21-24)	25 (15-18)
<b>5b</b>	3.12 (26-28)	3.12 (25-27)	3.12 (27-28)	6.25 (21-24)	6.25 (21-24)	25 (16-18)
<b>10a</b>	6.25 (22-25)	12.5 (18-21)	6.25 (22-24)	6.25 (22-24)	12.5 (18-21)	25 (17-19)
<b>10b</b>	12.5 (17-20)	6.25 (21-24)	12.5 (18-20)	6.25 (21-24)	50 (11-13)	50 (11-12)
<b>10c</b>	1.56 (33-35)	3.12 (26-27)	3.12 (25-29)	3.12 (25-28)	50 (11-13)	50 (11-13)
<b>10d</b>	6.25 (21-24)	12.5 (17-21)	6.25 (21-24)	6.25 (21-24)	50 (11-13)	50 (11-12)
<b>12a</b>	6.25 (23-24)	12.5 (19-22)	25 (15-18)	25 (15-18)	12.5 (18-21)	12.5 (19-22)
<b>12b</b>	12.5 (19-21)	12.5 (16-21)	25 (15-17)	25 (15-18)	50 (10-11)	25 (15-16)
<b>12c</b>	3.12 (26-28)	3.12 (25-28)	3.12 (26-27)	3.12 (26-27)	50 (11-12)	50 (11-13)

<b>12d</b>	12.5 (18-22)	6.25 (22-24)	25 (15-17)	50 (10-11)	25 (15-18)	25 (15-17)
<b>14a</b>	12.5 (19-22)	12.5 (18-20)	25 (15-18)	25 (15-18)	25 (14-16)	25 (15-17)
<b>14b</b>	6.25 (22-24)	12.5 (19-22)	25 (15-18)	25 (15-19)	25 (15-19)	25 (15-19)
<b>14c</b>	3.12 (26-28)	3.12 (28-29)	3.12 (27-28)	3.12 (26-28)	50 (10-12)	25 (15-17)
<b>14d</b>	12.5 (19-21)	12.5 (19-20)	25 (15-16)	25 (15-18)	25 (15-19)	25 (15-19)
<b>17a</b>	6.25 (21-24)	6.25 (21-24)	12.5 (18-21)	12.5 (19-21)	12.5 (19-21)	25 (15-17)
<b>17b</b>	6.25 (21-24)	6.25 (21-24)	12.5 (18-21)	12.5 (18-21)	12.5 (18-21)	25 (15-19)
<b>17c</b>	3.12 (25-27)	3.12 (25-27)	3.12 (26-28)	3.12 (26-28)	3.12 (26-28)	6.25 (21-24)
<b>17d</b>	3.12 (25-27)	3.12 (25-27)	3.12 (25-27)	3.12 (27-28)	3.12 (25-27)	6.25 (21-24)
<b>17e</b>	25 (15-17)	12.5 (18-21)	25 (15-17)	6.25 (22-24)	12.5 (19-22)	12.5 (19-21)
<b>17f</b>	50 (10-11)	12.5 (19-21)	25 (15-18)	6.25 (21-24)	12.5 (16-21)	25 (15-19)
Ciprofloxacin	1.56 (30-33)	1.56 (30-35)	1.56 (29-31)	1.56 (33-35)	NA	NA
Fluconazole	NA	NA	NA	NA	1.56 (35-36)	1.56 (34-34)
DMSO	NI	NI	NI	NI	NI	NI

NA = not applicable, NI = no inhibition.

In summary, we have successfully combined the advantages of ultrasound technology with multicomponent reactions to facilitate the rapid construction of symmetrically linked bis-rhodanines **3-5**. Furthermore, a series of mono- and bis-arylidenerhodanines was also synthesized. Structures of newly synthesized compounds were evaluated by NMR, HRMS and elemental analyses. The synthesized compounds were evaluated for their antibacterial and antifungal activities. The results showed that most of the compounds have good levels of antimicrobial activity.

## EXPERIMENTAL

**Materials.** The organic reagents and solvents were purchased from Sigma–Aldrich and used without

further purification. The purity of all the compounds was routinely checked by TLC on Silica gel-GF 254 (Merck) coated plates. 5,5-Methylene-bis-salicylaldehyde **8**,<sup>29</sup> *N*-cyclohexylrhodanine **9d**,<sup>31</sup> 2,6-diformylphenols **15**,<sup>27</sup> and 1*H*-pyrazole-3,5-dicarbaldehyde **11**<sup>30</sup> were synthesized according to procedures described in the literature.

**Apparatus.** The melting points of the synthesized compounds were determined on Electrothermal IA9100 melting point apparatus (UK). High resolution mass spectra (HRMS) measurements were recorded on a Bruker Daltonics microTOF spectrometer with an electrospray ionizer. IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer, using samples prepared as KBr discs. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts ( $\delta$ ) are reported in ppm, using the residual solvent CDCl<sub>3</sub>  $\delta_{\text{H}} = 7.26$  and  $\delta_{\text{C}} = 77.16$ ; DMSO-*d*<sub>6</sub>  $\delta_{\text{H}} = 2.50$  and  $\delta_{\text{C}} = 39.52$ ) as internal standard. Splitting patterns are designated as singlet (s), doublet (d), triplet (t), doublet of doublet (dd) and broad (br). Splitting patterns that could not be interpreted are designated as multiplet (m). Microwave irradiation was carried out using Lavis-1000 multi Quant microwave oven using sealed vessels. Ultrasonication was performed in a SY5200DH-T ultrasound cleaner with a frequency of 25 and 40 kHz and an output power of 250 W. The reaction vessel was placed in the maximum energy area in the cleaner. Water was added or removed in order to control the water bath temperature.

### General procedure for the synthesis of compounds 3-5:

#### Conventional method

To a mixture of dialkyl acetylenedicarboxylates **1a,b** (2 mmol) and carbon disulfide (2 mmol) in EtOH/H<sub>2</sub>O (5 mL, 20/80%) was added of diamines **2a-c** (1 mmol) portionwise over a period of 5 min. The reaction mixture was stirred at room temperature for 10-12 h (the reaction was monitored by TLC). After that time, the precipitate was filtered off, washed with water (3x10 mL), dried and recrystallized from EtOH to produce **3-5**.

#### Ultrasonication method

To a mixture of dialkyl acetylenedicarboxylates **1a,b** (2 mmol) and carbon disulfide (2 mmol) in EtOH/H<sub>2</sub>O (5 mL, 20/80%) was added of diamines **2a-c** (1 mmol) portionwise over a period of 5 min. The mixture was sonicated in the water bath of an ultrasonic cleaner under atmospheric conditions (Table 2). After the completion of the reaction (monitored by TLC), the resulting precipitate was filtered off, washed with water (3x10 mL) and recrystallized from EtOH to produce **3-5**.

**Dimethyl (2*Z*,2'*Z*)-2,2'-{benzene-1,4-diylbis[methanediyl(4-oxo-2-thioxo-1,3-thiazolidin-3-yl-5-ylidene)]}diethanoate (3a).** Yellow crystals, yield 82%, mp 251-252 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  7.25 (s, 4H, Ar), 6.76 (s, 2H, =CH), 5.22 (s, 4H, CH<sub>2</sub>), 3.85 (s, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  195.8, 166.3, 165.2, 141.2, 133.8, 130.3, 117.4, 52.3, 46.6. IR (KBr,  $\nu_{\text{max}}$ , cm<sup>-1</sup>): 1722, 1715 (C=O), 1266 (C=S). HRMS (EI) for (M + Na)<sup>+</sup>: calcd. 530.9790; found 530.9789. Anal.

Calcd for C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>O<sub>6</sub>S<sub>4</sub>: C, 47.23; H, 3.17; N, 5.51%. Found: C, 47.20; H, 3.21; N, 5.54%.

**Diethyl (2Z,2'Z)-2,2'-{benzene-1,4-diylbis[methanediyl(4-oxo-2-thioxo-1,3-thiazolidin-3-yl-5-ylidene)]}diethanoate (3b).** Yellow crystals, yield 75%, mp 276-278 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 7.32 (s, 4H, Ar), 6.77 (s, 2H, =CH), 5.19 (s, 4H, CH<sub>2</sub>), 4.26 (q, *J* 7.1 Hz, 4H, CH<sub>2</sub>CH<sub>3</sub>), 1.30 (t, *J* 7.3 Hz, 6H, CH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 195.6, 166.5, 165.0, 141.5, 134.5, 129.3, 117.6, 62.2, 46.8, 14.1. IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 1720, 1710 (C=O), 1259 (C=S). HRMS (EI) for (M + Na)<sup>+</sup>: calcd. 559.0096; found 559.0094. Anal. Calcd for C<sub>22</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>S<sub>4</sub>: C, 49.24; H, 3.76; N, 5.22%. Found: C, 49.29; H, 3.70; N, 5.18%.

**Dimethyl (2Z,2'Z)-2,2'-[trans-cyclohexane-1,4-diylbis(4-oxo-2-thioxo-1,3-thiazolidin-3-yl-5-ylidene)]diethanoate (4a).** Yellow crystals, yield 77%, mp 227-229 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 6.80 (s, 2H, =CH), 3.88 (s, 6H, CH<sub>3</sub>), 3.26 (dd, *J* 6.6, 3.6 Hz, 2H, cyclohexane), 1.99-1.97 (m, 4H, cyclohexane), 1.70-1.68 (m, 4H, cyclohexane). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 194.8, 166.2, 165.2, 140.2, 130.7, 66.7, 52.5, 33.2. IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 1724, 1712 (C=O), 1264 (C=S). HRMS (EI) for (M + Na)<sup>+</sup>: calcd. 508.9944; found 508.9947. Anal. Calcd for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub>S<sub>4</sub>: C, 44.43; H, 3.73; N, 5.76%. Found: C, 44.40; H, 3.77; N, 5.70%.

**Diethyl (2Z,2'Z)-2,2'-[trans-cyclohexane-1,4-diylbis(4-oxo-2-thioxo-1,3-thiazolidin-3-yl-5-ylidene)]diethanoate (4b).** Yellow crystals, yield 72%, mp 243-245 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 6.77 (s, 2H, =CH), 4.25 (q, *J* 7.2 Hz, 4H, CH<sub>2</sub>CH<sub>3</sub>), 3.24 (m, 2H, cyclohexane), 2.01-1.99 (m, 4H, cyclohexane), 1.71-1.68 (m, 4H, cyclohexane), 1.30 (q, *J* 7.2 Hz, 6H, CH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 195.0, 166.5, 165.0, 139.9, 129.8, 66.9, 62.4, 33.2, 14.2. IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 1719, 1702 (C=O), 1281 (C=S). HRMS (EI) for (M + Na)<sup>+</sup>: calcd. 537.0260; found 537.0257. Anal. Calcd for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub>S<sub>4</sub>: C, 46.67; H, 4.31; N, 5.44%. Found: C, 46.64; H, 4.28; N, 5.40%.

**Dimethyl (2Z,2'Z)-2,2'-[ethane-1,2-diylbis(4-oxo-2-thioxo-1,3-thiazolidin-3-yl-5-ylidene)]diethanoate (5a).** Yellow crystals, yield 80%, mp 114-116 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 6.79 (s, 2H, =CH), 3.82 (s, 4H), 3.77 (s, 6H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 195.2, 166.3, 165.8, 140.2, 129.9, 58.7, 53.3. IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 1729, 1708 (C=O), 1248 (C=S). HRMS (EI) for (M + Na)<sup>+</sup>: calcd. 454.9475; found 454.9477. Anal. Calcd for C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>O<sub>6</sub>S<sub>4</sub>: C, 38.88; H, 2.80; N, 6.48%. Found: C, 38.90; H, 2.76; N, 6.46%.

**Diethyl (2Z,2'Z)-2,2'-[ethane-1,2-diylbis(4-oxo-2-thioxo-1,3-thiazolidin-3-yl-5-ylidene)]diethanoate (5b).** Yellow crystals, yield 81%, mp 127-129 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 6.82 (s, 2H, =CH), 4.21 (q, *J* 7.2 Hz, 4H, CH<sub>2</sub>CH<sub>3</sub>), 3.80 (s, 4H), 1.33 (q, *J* 7.2 Hz, 6H, CH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 194.6, 166.3, 165.4, 138.7, 131.4, 63.0, 58.3, 14.3. IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 1724, 1710 (C=O), 1290 (C=S). HRMS (EI) for (M + Na)<sup>+</sup>: calcd. 482.9790; found 482.9787. Anal. Calcd for C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>O<sub>6</sub>S<sub>4</sub>: C, 41.72; H, 3.50; N, 6.08%. Found: C, 41.78; H, 3.45; N, 6.12%.

**General procedure for the synthesis of compounds 10, 12 and 14:**

To a stirred solution of bis-aldehydes **8**, **11** or **13** (1 mmol) in acetic acid (20 mL) were added 3-alkylrhodanines **9a-d** (2.1 mmol) and sodium acetate (0.169 g, 2.2 mmol). The mixture was heated to 120 °C and the reaction was continued for 4 h at that temperature. Then the reaction mixture was allowed to cool to room temperature. The solid was collected by filtration and washed with water (3x10 mL). After drying in air, the crude product was purified by crystallization from dioxane.

**(5Z,5'Z)-5,5'-{Methanediylbis[(6-hydroxybenzene-3,1-diyl)-(Z)-methylidene]}bis(3-methyl-2-thioxo-1,3-thiazolidin-4-one) (10a).** Yellow crystals, yield 95%, mp 212-213 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> 11.65 (s, 2H, OH), 7.66 (s, 2H, =CH), 7.38 (d, *J* 7.4 Hz, 2H, Ar), 7.33 (s, 2H, Ar), 6.99 (d, *J* 7.4 Hz, 2H, Ar), 4.01 (s, 2H, CH<sub>2</sub>), 3.22 (s, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ<sub>C</sub> 197.2, 166.7, 156.0, 138.3, 133.9, 132.4, 127.9, 120.7, 118.5, 115.6, 39.8, 32.7. IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3104 (OH), 1663 (C=O), 1263 (C=S). HRMS (EI) for (M - H)<sup>+</sup>: calcd. 513.0070; found 513.0069. Anal. Calcd for C<sub>23</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>S<sub>4</sub>: C, 53.68; H, 3.53; N, 5.44%. Found: C, 53.61; H, 3.59; N, 5.40%.

**(5Z,5'Z)-5,5'-{Methanediylbis[(6-hydroxybenzene-3,1-diyl)-(Z)-methylidene]}bis(3-(prop-2-en-1-yl)-2-thioxo-1,3-thiazolidin-4-one) (10b).** Yellow crystals, yield 89%, mp 229-230 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> 11.68 (s, 2H, OH), 7.92 (s, 2H, =CH), 7.37 (d, *J* 7.4 Hz, 2H, Ar), 7.35 (s, 2H, Ar), 6.97 (d, *J* 7.4 Hz, 2H, Ar), 5.97-5.89 (m, 2H, CH<sub>2</sub>=CH-CH<sub>2</sub>), 5.31-5.26 (m, 4H, CH<sub>2</sub>=CH-CH<sub>2</sub>), 4.75-4.72 (d, *J* 9.12 Hz, 4H, CH<sub>2</sub>=CH-CH<sub>2</sub>), 3.98 (s, 2H, CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ<sub>C</sub> 197.7, 166.2, 156.2, 137.9, 133.4, 132.7, 131.9, 127.9, 121.0, 119.1, 118.8, 115.8, 47.2, 39.9 ppm. IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3380 (OH), 1677 (C=O), 1266 (C=S). HRMS (EI) for (M)<sup>+</sup>: calcd. 566.0461; found 566.0463. Anal. Calcd for C<sub>27</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>S<sub>4</sub>: C, 57.22; H, 3.91; N, 4.94%. Found: C, 57.41; H, 3.87; N, 4.99%.

**(5Z,5'Z)-5,5'-{Methanediylbis[(6-hydroxybenzene-3,1-diyl)-(Z)-methylidene]}bis(3-cyclohexyl-2-thioxo-1,3-thiazolidin-4-one) (10c).** Yellow crystals, yield 90%, mp 196-198 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> 11.77 (s, 2H, OH), 7.89 (s, 2H, =CH), 7.40 (d, *J* 7.5 Hz, 2H, Ar), 7.36 (s, 2H, Ar), 6.99 (d, *J* 7.5 Hz, 2H, Ar), 4.89 (br, 2H, cyclohexane), 4.01 (s, 2H, CH<sub>2</sub>), 1.86-1.83 (m, 8H, cyclohexane), 1.71-1.64 (m, 8H, cyclohexane), 1.33-1.19 (m, 4H, cyclohexane). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ<sub>C</sub> 196.4, 165.8, 155.6, 138.2, 133.2, 131.5, 121.0, 119.1, 118.1, 115.8, 58.0, 39.7, 27.8, 26.0, 25.2. IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3265 (OH), 1694 (C=O), 1274 (C=S). HRMS (EI) for (M - H)<sup>+</sup>: calcd. 649.1322; found 649.1320. Anal. Calcd for C<sub>33</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub>S<sub>4</sub>: C, 60.89; H, 5.27; N, 4.30%. Found: C, 60.85; H, 5.31; N, 4.35%.

**(5Z,5'Z)-5,5'-{Methanediylbis[(6-hydroxybenzene-3,1-diyl)-(Z)-methylidene]}bis(4-oxo-2-thioxo-1,3-thiazolidin-3-ylacetic acid) (10d).** Yellow crystals, yield 90%, mp 268 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> 13.30 (br, 2H, COOH), 12.11 (s, 2H, OH), 7.91 (s, 2H, =CH), 7.34 (d, *J* 7.5 Hz, 2H, Ar), 7.38 (s, 2H, Ar), 7.13 (d, *J* 7.5 Hz, 2H, Ar), 4.79 (s, 4H, CH<sub>2</sub>COOH), 3.96 (s, 2H, CH<sub>2</sub>). <sup>13</sup>C NMR (100



MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  193.8, 173.2, 166.4, 156.1, 138.5, 134.0, 132.1, 120.3, 119.7, 118.4, 114.6, 45.8, 39.7. IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3285 (OH), 1695, 1669 (C=O), 1249 (C=S). HRMS (EI) for (M - H)<sup>+</sup>: calcd. 600.9870; found 600.9869. Anal. Calcd for C<sub>25</sub>H<sub>18</sub>N<sub>2</sub>O<sub>8</sub>S<sub>4</sub>: C, 49.82; H, 3.01; N, 4.65%. Found: C, 49.70; H, 3.08; N, 4.71%.

**(5Z,5'Z)-5,5'-[1H-Pyrazole-3,5-diyl-di-(Z)-methylidene]bis(3-methyl-2-thioxo-1,3-thiazolidin-4-one) (12a).** Brown crystals, yield 83%, mp 312-314 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  14.51 (s, 1H, NH), 7.68 (s, 2H, =CH), 7.18 (s, 1H, pyrazole-C4), 3.70 (s, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  196.1, 166.7, 153.9, 134.2, 122.7, 110.6, 32.6. IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3326 (NH), 1701 (C=O), 1273 (C=S). HRMS (EI) for (M - H)<sup>+</sup>: calcd. 380.9607; found 380.9609. Anal. Calcd for C<sub>13</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub>S<sub>4</sub>: C, 40.82; H, 2.64; N, 14.65%. Found: C, 40.88; H, 2.60; N, 14.71%.

**(5Z,5'Z)-5,5'-[1H-Pyrazole-3,5-diyl-di-(Z)-methylidene]bis[3-(prop-2-en-1-yl)-2-thioxo-1,3-thiazolidin-4-one] (12b).** Brown crystals, yield 85%, mp 342-343 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  14.53 (s, 1H, NH), 7.64 (s, 2H, =CH), 7.20 (s, 1H, pyrazole-C4), 5.77-5.73 (m, 2H, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.27-5.23 (m, 4H, CH<sub>2</sub>CH=CH<sub>2</sub>), 4.67-4.60 (m, 4H, CH<sub>2</sub>CH=CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  195.8, 166.9, 152.5, 135.3, 131.0, 121.9, 118.8, 111.4, 46.9. IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3310 (NH), 1695 (C=O), 1274 (C=S). HRMS (EI) for (M + Na)<sup>+</sup>: 456.9898; found 456.9896. Anal. Calcd for C<sub>17</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>S<sub>4</sub>: C, 46.98; H, 3.25; N, 12.89%. Found: C, 46.90; H, 3.31; N, 12.83%.

**(5Z,5'Z)-5,5'-[1H-Pyrazole-3,5-diyl-di-(Z)-methylidene]bis(3-cyclohexyl-2-thioxo-1,3-thiazolidin-4-one) (12c).** Brown crystals, yield 78%, mp 289-290 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  14.61 (s, 1H, NH), 7.68 (s, 2H, =CH), 7.12 (s, 1H, pyrazole-C4), 4.87 (br, 2H, cyclohexane), 2.32-2.28 (m, 8H, cyclohexane), 1.85-1.82 (m, 8H, cyclohexane), 1.69-1.67 (m, 4H, cyclohexane). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  192.2, 164.4, 141.2, 139.4, 129.7, 128.5, 57.4, 27.6, 23.9, 19.9. IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3264 (NH), 1687 (C=O), 1284 (C=S). HRMS (EI) for (M - H)<sup>+</sup>: 517.0855; found 517.0859. Anal. Calcd for C<sub>23</sub>H<sub>26</sub>N<sub>4</sub>O<sub>2</sub>S<sub>4</sub>: C, 53.25; H, 5.05; N, 10.80%. Found: C, 53.18; H, 5.16; N, 10.89%.

**2,2'-(1H-Pyrazole-3,5-diylbis{(Z)-methylidene[(5Z)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl-5-ylidene]})-diacetic acid (12d).** Brown crystals, yield 80%, mp 374-376 °C, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  14.67 (s, 1H, NH), 12.62 (br, 2H, COOH), 7.91 (s, 2H, =CH), 7.14 (s, 1H, pyrazole-C4), 4.72 (s, 4H, CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  193.0, 172.5, 165.6, 142.0, 138.5, 130.3, 128.2, 46.2. IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3264 (OH, NH), 1704, 1687 (C=O), 1290 (C=S). HRMS (EI) for (M - H)<sup>+</sup>: 468.9405; found 468.9402. Anal. Calcd for C<sub>15</sub>H<sub>10</sub>N<sub>4</sub>O<sub>6</sub>S<sub>4</sub>: C, 38.29; H, 2.14; N, 11.91%. Found: C, 38.16; H, 2.20; N, 11.88%.

**(5Z,5'Z)-5,5'-[Benzene-1,4-diyl-di-(Z)-methylidene]bis(3-methyl-2-thioxo-1,3-thiazolidin-4-one) (14a).** Yellow crystals, yield 95%, mp 180-182 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  8.00 (s, 2H, =CH), 7.64 (s, 4H, Ar), 3.11 (s, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  193.3, 167.6, 140.2, 135.7, 124.8,

117.2, 32.4. IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 1684 (C=O), 1269 (C=S). HRMS (EI) for (M + H)<sup>+</sup>: 392.9859; found 392.9857. Anal. Calcd for C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>S<sub>4</sub>: C, 48.96; H, 3.08; N, 7.14%. Found: C, 48.90; H, 3.15; N, 7.21%.

**(5Z,5'Z)-5,5'-[Benzene-1,4-diyl-di-(Z)-methylidene]bis[3-(prop-2-en-1-yl)-2-thioxo-1,3-thiazolidin-4-one] (14b)**. Yellow crystals, yield 92%, mp 120-122 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  7.96 (s, 2H, =CH), 7.65 (s, 4H, Ar), 5.87-5.84 (m, 2H, CH<sub>2</sub>=CH-CH<sub>2</sub>), 5.18-5.14 (m, 4H, CH<sub>2</sub>=CH-CH<sub>2</sub>), 4.75-4.70 (m, 4H, CH<sub>2</sub>=CH-CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  191.2, 166.1, 139.9, 135.0, 133.7, 132.8, 125.9, 114.1, 46.5. IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 1698 (C=O), 1287 (C=S). HRMS (EI) for (M)<sup>+</sup>: 444.0095; found 444.0098. Anal. Calcd for C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S<sub>4</sub>: C, 54.03; H, 3.63; N, 6.30%. Found: C, 54.11; H, 3.58; N, 6.36%.

**(5Z,5'Z)-5,5'-[Benzene-1,4-diyl-di-(Z)-methylidene]bis(3-cyclohexyl-2-thioxo-1,3-thiazolidin-4-one) (14c)**. Golden yellow crystals, yield 95%, mp 155-157 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  8.01 (s, 2H, =CH), 7.66 (s, 4H, Ar), 5.06-5.00 (m, 2H, cyclohexane), 2.45-2.42 (m, 4H, cyclohexane), 1.94-1.91 (m, 4H, cyclohexane), 1.75-1.72 (m, 5H, cyclohexane), 1.47-1.40 (m, 7H, cyclohexane). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  193.3, 167.4, 139.0, 136.6, 130.6, 126.0, 58.3, 27.9, 26.0, 24.9. IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 1703 (C=O), 1285 (C=S). HRMS (EI) for (M + H)<sup>+</sup>: 529.1106; found 529.1106. Anal. Calcd for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S<sub>4</sub>: C, 59.06; H, 5.34; N, 5.30%. Found: C, 59.11; H, 5.30; N, 5.27%.

**2,2'-(Benzene-1,4-diylbis{(Z)-methylidene[(5Z)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl-5-ylidene]})diacetic acid (14d)**. Yellow crystals, yield 93%, mp 330-332 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  12.83 (br, 2H, COOH), 8.04 (s, 2H, =CH), 7.71 (s, 4H, Ar), 4.74 (s, 4H, CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  192.5, 170.2, 166.7, 140.3, 135.4, 131.0, 126.5, 46.9. IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3361 (OH), 1690, 1672 (C=O), 1270 (C=S). HRMS (EI) for (M - H)<sup>+</sup>: 478.9503; found 529.478.9505. Anal. Calcd for C<sub>18</sub>H<sub>12</sub>N<sub>2</sub>O<sub>6</sub>S<sub>4</sub>: C, 44.99; H, 2.52; N, 5.83%. Found: C, 44.83; H, 2.58; N, 5.87%.

### Synthesis of 17a-f:

#### Conventional method

Follow the same conventional procedure of the synthesis of compounds **10**, **12** and **14**.

#### Microwave method

To a 5 mL glass tube, sodium methoxide (1 mmol) was added to the mixture of 2,6-diformylphenols **15a-c** (0.5 mmol) and rhodanines **9a,c** (1.1 mmol) in acetic acid (2 mL). The reaction tube was placed inside the cavity of the microwave, operated at power 200-250 W. The tube was irradiated in the microwave oven for appropriate time and temperature (according to Table 3). The work-up and purification step was the same used for conventional thermal heating.

**2-Hydroxy-5-methyl-3-[(Z)-(3-methyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]benzaldehyde (17a)**. Yellow crystals, yield 90%, mp 214-216 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  11.90 (s, 1H, OH),



9.88 (s, 1H, CHO), 7.85 (s, 1H, =CH), 7.45 (s, 1H, Ar), 7.42 (s, 1H, Ar), 3.37 (s, 3H, NCH<sub>3</sub>), 2.40 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 196.3, 194.0, 167.3, 158.7, 136.4, 135.4, 129.4, 125.9, 123.7, 122.7, 120.8, 32.8, 20.5. IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3178 (OH), 1704, 1687 (C=O), 1269 (C=S). HRMS (EI) for (M - H)<sup>+</sup>: 292.0100; found 292.0103. Anal. Calcd for C<sub>13</sub>H<sub>11</sub>NO<sub>3</sub>S<sub>2</sub>: C, 53.22; H, 3.78; N, 4.77%. Found: C, 53.27; H, 3.64; N, 4.80%.

**3-[(Z)-(3-Cyclohexyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-hydroxy-5-methylbenzaldehyde (17b)**. Brown crystals, yield 90%, mp 241-243 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 11.56 (s, 1H, OH), 9.88 (s, 1H, CHO), 7.98 (s, 1H, =CH), 7.43 (s, 1H, Ar), 7.41 (s, 1H, Ar), 5.03-4.97 (m, 1H, cyclohexane), 2.39 (s, 3H, CH<sub>3</sub>), 1.90-87 (m, 2H, cyclohexane), 1.71-1.68 (m, 4H, cyclohexane), 1.44-1.22 (m, 4H, cyclohexane). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 196.4, 194.1, 167.6, 158.8, 136.8, 135.8, 129.6, 125.0, 123.5, 122.7, 120.6, 58.1, 27.8, 26.0, 25.0, 20.4. IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3211 (OH), 1694, 1679 (C=O), 1280 (C=S). HRMS (EI) for (M + Na)<sup>+</sup>: 384.0699; found 384.0698. Anal. Calcd for C<sub>18</sub>H<sub>19</sub>NO<sub>3</sub>S<sub>2</sub>: C, 59.81; H, 5.30; N, 3.87%. Found: C, 59.78; H, 5.39; N, 3.86%.

**5-Bromo-2-hydroxy-3-[(Z)-(3-methyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]benzaldehyde (17c)**. Brown crystals, yield 92%, mp 293-295 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 11.63 (s, 1H, OH), 9.89 (s, 1H, CHO), 7.86 (s, 1H, =CH), 7.75 (s, 1H, Ar), 7.66 (s, 1H, Ar), 3.39 (s, 3H, NCH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 195.5, 193.4, 166.5, 159.6, 137.6, 137.2, 125.2, 123.2, 121.7, 116.3, 111.6, 32.7. IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3217 (OH), 1703, 1684 (C=O), 1266 (C=S). HRMS (EI) for (M - H)<sup>+</sup>: 355.9049; found 355.9050. Anal. Calcd for C<sub>12</sub>H<sub>8</sub>BrNO<sub>3</sub>S<sub>2</sub>: C, 40.23; H, 2.25; N, 3.91%. Found: C, 40.30; H, 2.20; N, 3.88%.

**5-Bromo-3-[(Z)-(3-cyclohexyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-hydroxybenzaldehyde (17d)**. Brown crystals, yield 87%, mp 311-312 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 11.68 (s, 1H, OH), 9.87 (s, 1H, CHO), 7.88 (s, 1H, =CH), 7.73 (s, 1H, Ar), 7.67 (s, 1H, Ar), 5.02-4.96 (m, 1H, cyclohexane), 1.91-1.87 (m, 2H, cyclohexane), 1.71-1.69 (m, 4H, cyclohexane), 1.36-1.25 (m, 4H, cyclohexane). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 195.3, 193.3, 167.4, 159.4, 138.2, 137.2, 125.3, 123.0, 121.8, 116.3, 111.8, 58.2, 27.8, 26.0, 25.0 ppm. IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3243 (OH), 1711, 1682 (C=O), 1260 (C=S). HRMS (EI) for (M - H)<sup>+</sup>: 423.9677; found 423.9678. Anal. Calcd for C<sub>17</sub>H<sub>16</sub>NO<sub>3</sub>S<sub>2</sub>: C, 47.89; H, 3.78; N, 3.29%. Found: C, 47.83; H, 3.80; N, 3.32%.

**3-Formyl-4-hydroxy-5-[(Z)-(3-methyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]benzoic acid (17e)**. Brown crystals, yield 88%, mp 302 °C, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> 13.30 (br, 2H, OH + COOH), 10.20 (s, 1H, CHO), 8.44 (d, *J* 1.9 Hz, 1H, Ar), 8.16 (d, *J* 1.8 Hz, 1H, Ar), 7.85 (s, 1H, =CH), 2.98 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ<sub>C</sub> 195.7, 194.3, 167.5, 166.4, 163.2, 136.5, 136.0, 125.3, 124.3, 123.6, 123.1, 122.8, 32.6. IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3219 (OH), 1701, 1670 (C=O), 1283 (C=S). HRMS (EI) for (M - H)<sup>+</sup>: 321.9842; found 321.9840. Anal. Calcd for C<sub>13</sub>H<sub>9</sub>NO<sub>5</sub>S<sub>2</sub>: C, 48.29; H, 2.81; N,

4.33%. Found: C, 48.36; H, 2.77; N, 4.30%.

**3-[(Z)-(3-Cyclohexyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-5-formyl-4-hydroxybenzoic acid (17f).** Brown crystals, yield 88%, mp 351-353 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> 12.18 (br, 2H, OH + COOH), 10.04 (s, 1H, CHO), 8.45 (d, *J* 1.9 Hz, 1H, Ar), 8.36 (d, *J* 1.9 Hz, 1H, Ar), 7.99 (s, 1H, =CH), 5.04 (br, 1H, cyclohexane), 1.75-1.72 (m, 2H, cyclohexane), 1.43-1.40 (m, 4H, cyclohexane), 1.36-1.29 (m, 4H, cyclohexane). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ<sub>C</sub> 195.6, 194.2, 167.4, 166.1, 163.1, 136.3, 136.2, 125.1, 124.0, 123.2, 123.0, 122.6, 115.7, 58.0, 27.8, 27.6, 26.0, 25.2. IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3310 (OH), 1698, 1684 (C=O), 1277 (C=S). HRMS (EI) for (M - H)<sup>+</sup>: 390.0464; found 390.0462. Anal. Calcd for C<sub>18</sub>H<sub>17</sub>NO<sub>5</sub>S<sub>2</sub>: C, 55.23; H, 4.38; N, 3.58%. Found: C, 55.17; H, 4.43; N, 3.50%.

### *In vitro* antimicrobial study<sup>32</sup>

The antimicrobial susceptibility testing was performed *in vitro* by the two fold broth dilution technique. All solutions were prepared under aseptic conditions. The Gram positive and negative bacteria utilized in this study included *S. aureus*, *M. luteus*, *P. vulgaris* and *K. pneumonia*. The antifungal activity was assayed against *C. albicans* and *B. cinerea*. The Minimum inhibitory concentration (MIC, µg/mL) were defined as the lowest concentrations of compound that completely inhibited the growth of each strain. Test compounds were dissolved in DMSO and then diluted in culture medium (Mueller–Hinton Broth for bacteria and Sabouraud Liquid Medium for fungi) to obtain final concentrations ranging from 1.56 to 50 µg/mL. The MICs were read after incubation at 37 °C for 24 h (bacteria) and at 30 °C for 48 h (fungi). In order to ensure that the solvent had no effect on the growth, a control test was performed containing inoculated broth suspended with 10% DMSO. Ciprofloxacin and Fluconazole were used as reference antibacterial and antifungal substances, respectively. All experiments were performed in duplicate.

### ACKNOWLEDGEMENTS

We would like to acknowledge the financial support from Aljouf University, research fund No. 35/342.

### REFERENCES

1. T. Tomasic and L. P. Masic, *Curr. Med. Chem.*, 2009, **16**, 1596.
2. T. Mendgen, C. Steuer, and C. D. Klein, *J. Med. Chem.*, 2012, **55**, 743.
3. N. Hotta, Y. Akanuma, R. Kawamori, K. Matsuoka, Y. Oka, M. Shichiri, T. Toyota, M. Nakashima, I. Yoshimura, N. Sakamoto, and Y. Shigeta, *Diabetes Care*, 2006, **29**, 1538.
4. L. Chao, L. Jia-Chun, L. Ya-Ru, G. Cheng, Z. Mei-Ling, L. Hong-Yan, L. Xiao-Zhen, Z. Chang-Ji, and P. Hu-Ri, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 3052.
5. M. Sortino, P. Delgado, S. Juarez, J. Quiroga, R. Abonia, B. Insuasty, M. Nogueras, L. Rodero, F. M. Garibotto, R. D. Enriz, and S. A. Zacchino, *Bioorg. Med. Chem.*, 2007, **15**, 484.

6. K. Nagahara, J. D. Anderson, G. D. Kini, N. K. Dalley, S. B. Larson, D. F. Smee, A. Jin, B. S. Sharma, and W. B. Jolley, *J. Med. Chem.*, 1990, **33**, 407.
7. K. Takasu, H. Inoue, H. S. Kim, M. Suzuki, T. Shishido, Y. Wataya, and M. Ihara, *J. Med. Chem.*, 2002, **45**, 995.
8. T. N. Reddy, M. Ravinder, P. Bagul, K. Ravikanti, C. Bagul, J. B. Nanubolu, K. Srinivas, S. K. Banerjee, and R. V. Jayathirtha, *Eur. J. Med. Chem.*, 2014, **71**, 53.
9. K. C. Wacothon, P. Ludovic, B. Anoubilé, B. Yves-Alain, L. G. Rémy, R. Myriam, C. Anne, and P. B. Jean, *Med. Chem. Res.*, 2015, **24**, 1653.
10. T. T. Talele, P. Arora, S. S. Kulkarni, M. R. Patel, S. Singh, M. Chudayeu, and N. Kaushik-Basu, *Bioorg. Med. Chem.*, 2010, **18**, 4630.
11. M. M. Sim, S. B. Ng, A. D. Buss, S. C. Crasta, K. L. Goh, and S. K. Lee, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 697.
12. J. H. Ahn, S. J. Kim, W. S. Park, S. Y. Cho, J. D. Ha, S. S. Kim, S. K. Kang, D. G. Jeong, S. K. Jung, S. H. Lee, H. M. Kim, S. K. Park, K. H. Lee, C. W. Lee, S. E. Ryu, and J. K. Choi, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2996.
13. P. S. Krishnan, *Nature*, 1951, **168**, 171.
14. A. A. El-Bindary, A. Z. El-Sonbati, M. A. Diab, and S. M. Morgan, *J. Mol. Liquids*, 2015, **201**, 36.
15. N. Pourreza and S. Rastegarzadeh, *Anal. Chim. Acta*, 2001, **437**, 273.
16. R. Solmaz, G. Kardas, B. Yazici, and M. Erbil, *Prot. Met.*, 2005, **41**, 581.
17. G. J. Safaei and R. Masoomi, *Scientia Iranica C.*, 2015, **22**, 894.
18. D. Nagargoje, P. Mandhane, S. Shingote, P. Badadhe, and C. Gill, *Ultrasound. Sonochem.*, 2012, **19**, 94.
19. S. S. Didwagh and P. B. Piste, *J. Chem. Pharm. Res.*, 2013, **5**, 271.
20. S. Kamila and E. R. Biehl, *Tetrahedron Lett.*, 2012, **53**, 3998.
21. D. C. Braddock, T. Cailleau, G. Cansell, S. A. Hermitage, R. H. Pouwer, J. M. Redmond, and A. J. P. White, *Tetrahedron: Asymmetry*, 2010, **21**, 2911.
22. R. M. Shaker, *ARKIVOC*, 2012, **i**, 1.
23. A. A. A. Wael and S. M. Asmaa, *Chinese J. Chem.*, 2011, **29**, 1661.
24. R. M. Shaker, Y. R. Ibrahim, F. F. Abdel-Latif, and A. Z. Hamoda, *Naturforsch.*, 2010, **65b**, 1148.
25. R. M. Shaker, *Heteroat. Chem.*, 2005, **16**, 507.
26. R. M. Shaker, A. F. Mahmoud, and F. F. Abdel-Latif, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 397.
27. A. A. A. Wael, D. K. Markus, L. Bao-Lin, Å. Torbjörn, L. Rong-Zhen, E. M. S. Per, and Å. Björn, *Phys. Chem. Chem. Phys.*, 2014, **16**, 11950.

28. W. Juxian, B. Xiaoguang, X. Changliang, W. Yucheng, L. Wei, S. Daqing, and Z. Yi, *Molecules*, 2012, **17**, 8674.
29. S. Guieu, J. Rocha, and A. M. S. Silva, *Tetrahedron*, 2014, **69**, 9329.
30. T. M. Laine, M. D. Kaerkaes, R. Liao, T. Aakermark, B. Lee, E. A. Karlsson, P. E. M. Siegbahn, and B. Aakermark, *Chem. Commun.*, 2015, **5**, 1862.
31. J. C. Liu, C. J. Zheng, M. X. Wang, and H. R. Piao, *Eur. J. Med. Chem.*, 2014, **74**, 405.
32. J. H. Jorgensen and F. C. Tonover, 'Antimicrobial Agents and Susceptibility Testing, Section X. in: *Clinical Microbiology*', ASM Press, Washington, DC, 1995, pp. 1275-1434.