



## Original article

## Synthesis and antibacterial activity of some new thiazole and thiophene derivatives

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## ABSTRACT

Dibenzobarrelene **1** was reacted with cyanoacetic acid hydrazide and thiosemicarbazide to give the corresponding 3-oxo-propionitrile and thioamide derivatives **2** and **16**, respectively. The base-catalyzed reaction 3-oxo-propionitrile derivative **2** with phenyl isothiocyanate yielded the non-isolable intermediate **3**. Treatment of **3** with dilute HCl afforded the corresponding thiocarbamoyl derivative **4**. The intermediate **3**, thiocarbamoyl **4** and thioamide derivatives **16** were utilized as key intermediates for the synthesis of some new thiazole **5**, **6a**, **6b**, **7**, **8**, **10a**, **10b**, **12**, **14a**, **15**, **17a**, **17b**, and **18**; and thiophene **13a–d** derivatives, respectively. The newly synthesized compounds were characterized by IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and mass spectral studies. Representative compounds of the synthesized product were tested and evaluated as antibacterial agent.

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## 1. Introduction

Thiazoles and their derivatives have attracted continuing interest over the years because of their varied biological activities [1,2], recently found application in drug development for the treatment of allergies [3], hypertension [4], inflammation [5], schizophrenia [6], bacterial [7], HIV infections [8], hypnotics [9] and more recently for the treatment of pain [10], as fibrinogen receptor antagonists with antithrombotic activity [11] and as new inhibitors of bacterial DNA gyrase B [12]. Thiophene, in particular, has been investigated by Royer et al. [13]; they reported the effectiveness of some mono and poly halogenated thiophene carboxanilides against *Biomphalaria glabrata*. Other thiophene containing compounds have been also evaluated [14, 15].

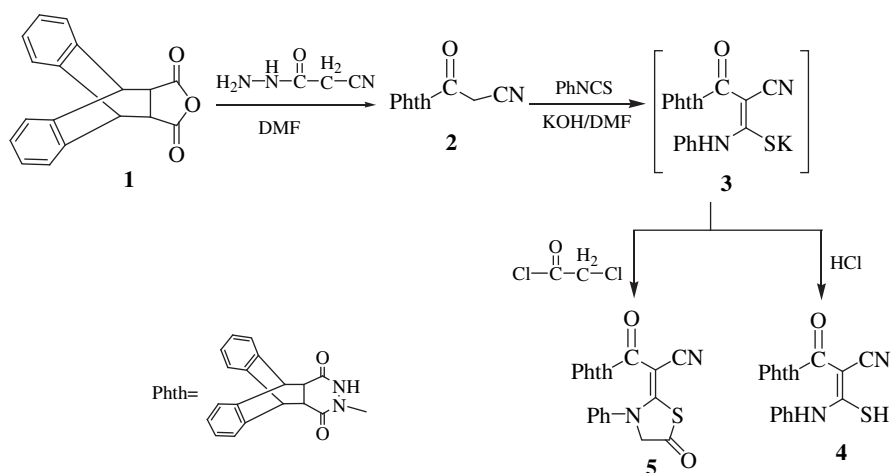
In view of the above mentioned findings and as continuation of our effort [16–19], to identify new candidates that may be value designing new, potent, selective and less toxic antibacterial agents, we report in the present work the synthesis of some new thiazole, thiazolidinone, thiazoline and thiophene derivatives starting from Dibenzobarrelene **1**.

## 2. Chemistry

The synthetic procedures adopted to obtain the target compounds are depicted in Schemes 1–5. Dibenzobarrelene [20] **1** was reacted with cyanoacetic acid hydrazide reported previously [16], to give 3-oxo-propionitrile derivative **2**. It is known that, a great variety of reactants bearing the  $\text{N}=\text{C}=\text{S}$  fragment undergo cyclization on reaction with  $\alpha$ -halocarbonyl compounds to afford thiazoles, 2,3-dihydrothiazoles and thiazolidines [21], which have been shown to exhibit antiprotozoal [22] and fungicidal properties [23]. Thus, the base-catalyzed reaction of acidic methylene compound **2** with phenyl isothiocyanate in dry DMF at room temperature yields the non-isolable potassium salt **3**. Treatment of **3** with dilute HCl gave the thiocarbamoyl derivative **4**. The thiocarbamoyl derivative **4** was confirmed based on analytical and spectral data. The mass spectrum exhibited peaks at  $m/z$  433, 290, 202, 178 and **77** corresponding to  $(\text{M}^+-\text{HSCN}, \text{S})$   $(\text{M}^+-\text{C}_{10}\text{H}_6\text{N}_2\text{OS})$  ethenoanthracene, anthracene and phenyl, respectively. Cyclization of the potassium salt of thiocarbamoyl derivative **3** with chloroacetyl chloride afforded thiazolidin-5-one derivative **5**. The IR spectrum of compound **5** revealed the presence of strong absorption band at  $1750\text{ cm}^{-1}$  due to  $(\text{CO})$  group. This considered being a strong conformation for the thiazolidinone nucleus formation, another piece of evidence for cyclization, the appearance of a singlet signal, equivalent to two protons in  $^1\text{H}$  NMR spectrum at

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Scheme 1.

$\delta$  3.90 ppm which represent the  $C_4$  protons of thiazolidinone nucleus. In addition the  $^{13}\text{C}$  NMR spectrum displayed the characteristics signals at  $\delta$  173.4, 112.1 and 75.0 due to  $C_5$  (thiazolidin-5-one), CN and  $\text{CH}_2$  carbons, respectively beside all other carbons at the expected regions.

2-Arylideno-1,3-thiazolidinone derivatives **6a, b** were synthesized by refluxing of compound **5** with the appropriate aromatic aldehydes in a mixture of dimethylformamide and glacial acetic acid and in the presence of catalytic amount of fused sodium acetate. Compounds **6a, b** were confirmed on the basis of analytical and spectral data. Also, the  $^1\text{H}$  NMR spectrum of compound **6b** revealed the presence of characteristic singlet signals due to methoxy and NH protons at  $\delta$  3.8 and 10.3, respectively. Moreover, the  $^{13}\text{C}$  NMR spectrum of **6b** revealed the presence of signals due to  $C_5$ ,  $C_4$  (thiazolidin-5-one), CN and  $\text{OCH}_3$  carbons at  $\delta$  164.0, 142.0, 111.9 and 55.5, respectively.

Condensation of thiazolidin-5-one derivative **5** with isatin or ninhydrine in dimethylformamide in the presence of a catalytic amount of triethylamine gave the corresponding arylidine derivatives

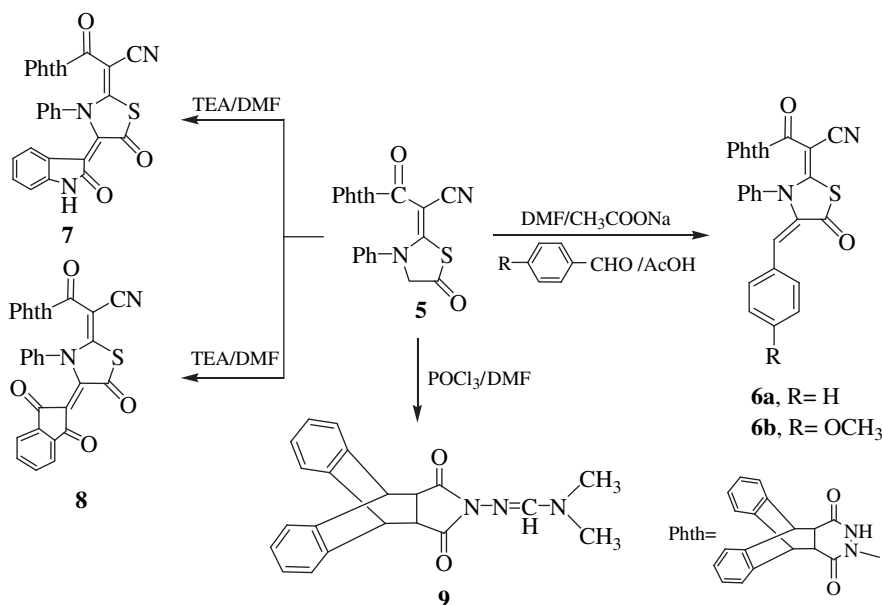
**7, 8**, respectively. Elemental analysis, IR,  $^1\text{H}$  NMR, Mass spectrum are in agreement with the proposed structure (c.f. Section 4)

The thiazolidin-5-one derivative **5** gave unexpected *N*-substituted isindole derivative **9** upon treatment with excess of Vilsmeier reagent at  $80^\circ\text{C}$ . Formation of the compound **9** is explained by the following plausible mechanism (Scheme 3).

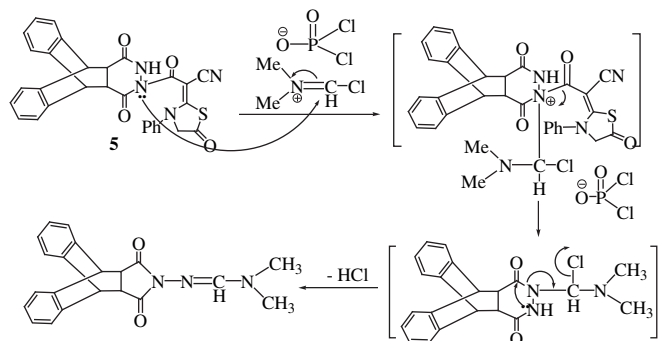
Assignment of the product **9** was based on the analytical and spectral data. (c.f. Section 4) Moreover, the  $^1\text{H}$  NMR spectrum showed characteristic singlet signals at  $\delta$  3.1 and 3.2 due to six protons of two methyl group and multiplet at  $\delta$  7.0–7.5 due to eight aromatic and  $\text{N}=\text{CH}$  protons.

*In situ* cyclization of the intermediate **3** with chloroacetone, phenacyl bromide or ethyl chloroacetate following the reported reaction conditions [24,25] afforded the thiazole derivatives **10a, b** and thiazolidin-4-one derivative **12**, respectively.

Compounds **10a, b** and **12** were obtained in high yield by refluxing of compound **4** with the previous  $\alpha$ -halo-compounds in ethanol/DMF. Also, treatment of thiocarbonyl derivative **3** or **4** with chloroacetonitrile gave **12** this reaction may be explained by



Scheme 2.



Scheme 3.

the intermediacy of the 4-iminothiazolidine derivative **11**. Similar behavior was reported in literature [25–27]. The structures **10a**, **b** and **12** were supported by IR,  $^1\text{H}$  NMR, and mass spectra. The  $^1\text{H}$  NMR of **10a** revealed in addition to the expected signals, signals at  $\delta$  1.8 (s, 3H,  $\text{CH}_3$ ) and 6.9 (s, 1H,  $\text{C}_5\text{-H}$  of thiazolidine). Moreover, the  $^1\text{H}$  NMR spectrum of **12** exhibited a characteristic signal at  $\delta$  3.95 (s, 2H,  $\text{CH}_2$ ).

On the other hand, the base catalytic reactions of thiocarbamoyl derivative **4** with the previous  $\alpha$ -halo-compounds gave the corresponding thiophene derivatives **13a–d**, as previously described method.[28] The IR spectrum of compounds **13a–c** were characterized by the disappearance of cyano group and appearance of NH and CO bands. The  $^1\text{H}$  NMR spectrum of **13a** displayed beside the expected signals, a characteristic signal at  $\delta$  2.1 (s, 3H,  $\text{CH}_3$ ). Also, the  $^1\text{H}$  NMR of **13b** showed signals at  $\delta$  7.1–7.6 (m, 20H, ArH,  $\text{NH}_2$ ).

Reaction of the thiocarbamoyl derivative **4** with dibromoalkane, namely, 1,2-dibromoethane and 1,3-dibromopropane in ethanol

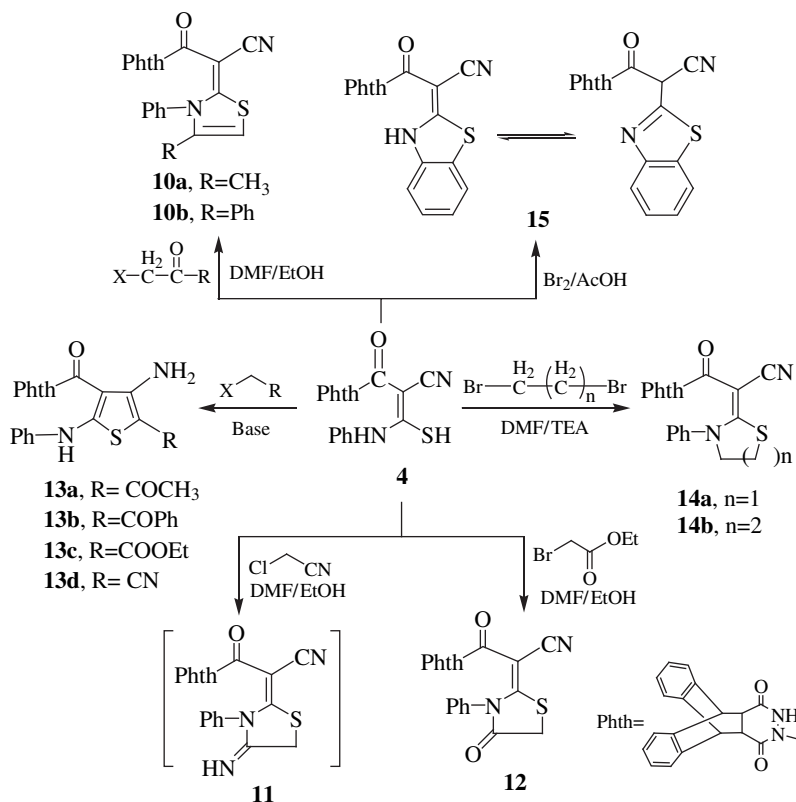
and in the presence of triethylamine gave the corresponding cyclic ketene *S,N*-acetal **14a,b**. Similar reaction was reported in the literature [29]. The structure of **14a,b** were based on their analytical and spectral data. The  $^1\text{H}$  NMR spectrum of **14a** displayed characteristic signals at  $\delta$  3.2 (t, 2H,  $\text{N-CH}_2$ ), 4.1 (t, 2H,  $\text{CH}_2\text{-S}$ ) and 9.4 (s, 1H, NH), beside the expected signals for other protons.

The thiocarbamoyl derivative **4** undergo oxidative cyclization on treating with bromine in acetic acid, to give benzothiazole derivative **15**, similar behavior was recorded [30]. The structure of compound **15** was established on the basis of elemental analysis and spectral data. (c.f. Section 4)

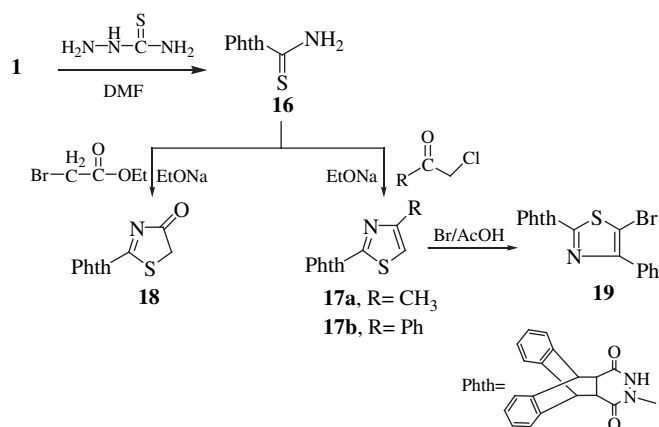
Dibenzobarralene (**1**) was reacted with thiosemicarbazide as reported, [31] to give thioamide derivative **16**. Compound **16** was reacted with an equimolar amount of  $\alpha$ -halo-compounds namely, chloroacetone, phenacyl bromide and ethyl chloroacetate in ethanol and in the presence of sodium ethoxide to afford thiazole and thiazolidinone derivatives **17a, b** and **18**, respectively. The structure of **17a, b** was deduced from IR,  $^1\text{H}$  NMR and mass spectra. IR spectra of **17a, b** showed bands at 3300–3290 (NH) and 1790–1706  $\text{cm}^{-1}$  (CO).  $^1\text{H}$  NMR spectrum of **17a** showed signals at  $\delta$  2.1 (s, 3H,  $\text{CH}_3$ ) and 7.1–7.4 (m, 9H, Ar H).

Also, the  $^1\text{H}$  NMR spectrum of **17b** exhibited signals at  $\delta$  7.1–7.7 (m, 14H, Ar H), beside the expected signals for other protons at their chemical shift. The structure of **18** was established by IR and  $^1\text{H}$  NMR spectra. The  $^1\text{H}$  NMR spectrum showed signal at  $\delta$  3.9(s, 2H,  $\text{CH}_2$ ).

5-Bromothiazole derivative **19** was obtained by bromination of **17b** in glacial acetic acid at 90 °C. The structure of **19** was established on the basis of its spectral data. The mass spectrum of **19** exhibited the molecular ion peak at  $m/z$  527, which is in agreement with the molecular formula  $\text{C}_{27}\text{H}_{18}\text{BrN}_3\text{O}_2\text{S}$ , in addition, to revealing  $[\text{M}^+ + 2]$  peak at  $m/z$  529. Also, fragment ion peaks were exhibited  $m/z$  at 449 and 178 due to  $[\text{M}^+ - \text{Br}]$  and anthracene.



Scheme 4.



Scheme 5.

### 3. Pharmacology

The antibacterial activity of the tested compounds in comparison with that of some control drugs is shown in Table 1. The results revealed that compounds **8**, **9**, **13b** and **14b** showed activity against *Bacillus thuringiensis* as Gram-positive bacteria lower than the compared control, ampicillin and chloramphenicol minimal inhibitory concentration (MIC) values  $< 50 \mu\text{g ml}^{-1}$ . Compounds **10a**, **12**, **14a**, **17b** and **18** were exhibited activities equal to the compared control drugs against the Gram-positive bacteria *B. thuringiensis* ( $\text{MIC} < 12.5 \mu\text{g ml}^{-1}$ ), while, the compounds **10b**, **15**, **17a** and **17b** were two times as of control drugs ( $\text{MIC} < 6 \mu\text{g ml}^{-1}$ ). Furthermore, determination of antibacterial activity against the Gram-negative *Escherichia coli*, indicated that compound **10b** was two times as active as ampicillin and chloramphenicol ( $\text{MIC} < 6 \mu\text{g ml}^{-1}$ ), while compounds **14a**, **17a** and **17b** displayed half the activity of both control drugs ( $\text{MIC} < 50 \mu\text{g ml}^{-1}$ ). On the

**Table 1**  
Inhibition zone (IZ) in mm diameter and (MIC) in  $\mu\text{g ml}^{-1}$  of antibacterial activities of the newly synthesized compounds.

Compound no.	Gram-positive bacteria <i>Bacillus thuringiensis</i>		Gram-negative bacteria <i>Escherichia coli</i>	
	IZ	MIC	IZ	MIC
<b>4</b>	22	12.5	22	12.5
<b>5</b>	17	–	18	–
<b>6a</b>	–	–	14	–
<b>6b</b>	11	–	13	–
<b>7</b>	15	–	15	–
<b>8</b>	19	50	25	12.5
<b>9</b>	20	50	21	12.5
<b>10a</b>	28	12.5	30	12.5
<b>10b</b>	39	6	40	6
<b>12</b>	24	12.5	26	12.5
<b>13a</b>	15	–	13	–
<b>13b</b>	17	50	20	12.5
<b>13d</b>	–	–	20	12.5
<b>14a</b>	22	12.5	15	50
<b>14b</b>	19	50	25	12.5
<b>15</b>	30	6	26	12.5
<b>17a</b>	40	6	16	50
<b>17b</b>	23	12.5	15	50
<b>18</b>	24	12.5	26	12.5
<b>19</b>	–	–	12	–
Reference drugs				
Ampicillin	18	12.5	19	12.5
Chloroamphenicol	23	12.5	19	12.5

other hand, compounds **4**, **8**, **9**, **10a**, **12**, **13b**, **13d**, **14b**, **15** and **18** exhibited the activities equal to both control drugs ( $\text{MIC} < 12.5 \mu\text{g ml}^{-1}$ ).

It is worth mentioning that incorporation of phthalazine moiety to thiophene and thiazole caused significant activity against both *B. thuringiensis* and *E. coli*.

In conclusion, we reported herein a simple and convenient route for the synthesis of some new heterocyclic based on phthalazine for antibacterial evaluation.

## 4. Experimental

### 4.1. General

All melting points are in degree centigrade and are uncorrected. TLC analysis was carried out on silica gel 60 F<sub>254</sub> precoated aluminum sheets. Infrared spectra were recorded on FTIR 5300 spectrometer and Perkin Elmer spectrum RXIFT-IR system ( $\lambda$ ,  $\text{cm}^{-1}$ ) using potassium bromide wafer technique, faculty of science El Azhar University.  $^1\text{H}$  NMR spectra were determined on a Varian XL 200 MHz, Faculty of Science, Cairo University, a Bruker WP 300 Georg-August University Goettingen, Germany and a Bruker AC 300 Eberhard-Karls University, Tuebingen, Germany, in  $\text{CDCl}_3$  or DMSO solvent using TMS as internal standard.  $^{13}\text{C}$  NMR spectra were determined on Bruker AC 300 Eberhard-Karls University, Tuebingen, Germany, in  $\text{CDCl}_3$  or DMSO solvent using TMS as internal standard. Mass spectra were recorded on GC–MS QP-1000 EX. Shimadzu (Japan), Faculty of Science, Cairo University, ESI MS with Quattro Triple Quadrupole Mass Finigan MAT–Incos 50 ESILCQ (Finigan), Georg-August University Goettingen, Germany and FAB + Q<sub>3</sub>MS LMR UP LR, Eberhard-Karls University, Tuebingen, Germany, Elemental analyses (C, H, and N) were carried out at the micro analytical center of Cairo Univ., Giza, Egypt, the results were found to be in good agreement ( $\pm 0.30\%$ ) with the calculated values. Microbiology screening was carried out on Botany Department, faculty of Science Mansoura University under supervision of Dr. A.A. El-Morsi, Lecturer and A. Shawky, Assistant Lecturer.

#### 4.1.1. Synthesis of 3-(1,4-dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzono-benzo[g]-phthalazin-2-yl)-2-phenylthiocarbonyl-3-oxo-propiononitrile (**4**)

To a cold suspension of finally divided KOH (0.28 g; 0.005 mole) in dry dimethylformamide (25 ml) were added the nitrile derivative **2** (1.78 g; 0.005 mole) followed by phenyl isothiocyanate (0.67 g; 0.005 mole). The mixture was stirred at room temperature for 12 h, then poured into ice-cold water and acidified with 0.1 N HCl to a pH 3–4. The resulting precipitate was filtered off, dried and crystallized from aqueous ethanol to give **4**.

Yield 80%, 2.0 g; mp 204–205 °C; IR (KBr):  $\nu/\text{cm}^{-1}$  = 3364, 3300 (2NH), 2188 (CN), 1728 and 1652 (CO) 1580, 1560  $\text{cm}^{-1}$  (CSNH).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{ppm}}$  = 3.3 (s, 2H, C<sub>11</sub>–H, C<sub>12</sub>–H), 4.3 (br, 1H, SH), 4.8 (s, 2H, C<sub>9</sub>–H, C<sub>10</sub>–H), 6.9–7.6 (m, 14H, Ar H, NH) and 12.5 (br, 1H, NH). EIMS ( $m/z$ ) (%) = 433 (1.4,  $\text{M}^+$ –HCN, S) 290 (5.1), 204 (5.1), 202 (7.8), 178 (100) and 77 (5.5). (+)-ESI mass spectrum showed one quasi-molecular ion peak at 537.3 ( $[\text{M}+\text{H}+2\text{Na}]^+$ ), the (–)-ESI mass spectrum showed one quasi-molecular ion peak at 491.6 ( $[\text{M}+\text{H}]^-$ ) pointing 492 as the molecular mass of the compound. Anal. for  $\text{C}_{28}\text{H}_{20}\text{N}_4\text{O}_3\text{S}$  (492.55): calcd.: C 68.28, H 4.09, N 11.37%, found: C, 68.43; H, 4.15; N, 11.50%.

#### 4.1.2. Synthesis of 3-(1,4-dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzono-benzo[g]-phthalazin-2-yl)-3-oxo-2-(5-oxo-3-phenylthiazolidin-2-ylidene) propiononitrile (**5**)

To a cold suspension of finally divided KOH (0.28 g; 0.005 mole) in dry dimethylformamide (25 ml) were added the nitrile derivative

**2** (1.78 g; 0.005 mole) followed by phenyl isothiocyanate. The mixture was stirred at room temperature for 12 h, then cooled again to 0 °C, treated with the chloroacetyl chloride (0.56 g; 0.005 mole) and left to stand at room temperature for 24 h. The mixture was poured into ice-cold water. The resulting precipitate was filtered off, dried and crystallized from DMF-ethanol to give **5**.

Yield 72%, 1.9 g; mp > 320 °C; IR (KBr):  $\nu/\text{cm}^{-1}$  = 3390 (NH), 2190 (CN) and 1790, 1750, 1716, 1692  $\text{cm}^{-1}$  (CO).  $^1\text{H}$  NMR (DMSO):  $\delta_{\text{ppm}}$  = 3.32 (s, 2H, C<sub>11</sub>-H, C<sub>12</sub>-H), 3.9 (s, 2H, CH<sub>2</sub>), 4.7 (s, 2H, C<sub>9</sub>-H, C<sub>10</sub>-H), and 7.0–7.4 (m, 13H, Ar H) and 10.3 (s, 1H, NH).  $^{13}\text{C}$  NMR (DMSO):  $\delta_{\text{ppm}}$  = 173.4, 173.2 m 171.6, 142.0, 138.8, 134.9, 130.4, 129.3, 129.2, 128.3, 126.7, 126.2, 124.7, 124.2, 112.14, 95.2, 75.0, 44.18 and 40.11; EIMS ( $m/z$ ) (%) = 532 (0.87, M<sup>+</sup>) 487 (0.37), 400 (0.5), 366 (13.7), 243 (6.9), 242 (38.6), 214 (2.02), 178 (100) and 77 (4.9). Anal. for C<sub>30</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub>S (532.57): calcd.: C 67.66, H 3.79, N 10.52%, found: C 67.71, H 3.94, N 10.27%.

#### 4.1.3. Synthesis of 3-(1,4-dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzo-benzo[g]-phthalazin-2-yl)-3-oxo-2-(4-arylidene-5-oxo-3-phenyl-thiazolidin-2-ylidene) propionitrile (**6a, b**)

**4.1.3.1. General procedure.** To a mixture of **5** (2.66 g; 0.005 mole) and benzaldehyde or anisaldehyde (0.005 mole) in DMF (15 ml), fused sodium acetate (0.5 g) was added followed by glacial acetic acid (0.5 ml). The reaction mixture was heated on water bath for 2 h, and then poured into ice-cold water. The resulting precipitate was filtered off, dried and recrystallized from EtOH-DMF to give **6a, b**.

**6a**, yield 65%, 2.00 g; mp > 320 °C; IR (KBr):  $\nu/\text{cm}^{-1}$  = 3378 (NH), 2201(CN) and 1731, 1671,  $\text{cm}^{-1}$  (CO). (+)-ESI mass spectrum showed three quasi-molecular ion peaks at 643.2, ([M + Na]<sup>+</sup>) 665.2 ([M-H + 2Na]<sup>+</sup>) and 1263.0 ([2M + Na]<sup>+</sup>), the (–)-ESI mass spectrum showed two quasi-molecular ion peaks at 619.2 ([M-H]<sup>–</sup>) and 1238.7 ([2M-2H]<sup>–</sup>) pointing 620 as the molecular mass of the compound. Anal. for C<sub>37</sub>H<sub>24</sub>N<sub>4</sub>O<sub>4</sub>S (620.68): calcd.: C 71.60, H 3.90, N 9.03%; found: C 71.95, H 4.12, N 9.39%.

**6b**, yield 70%, 2.27 g; mp > 320 °C; IR (KBr):  $\nu/\text{cm}^{-1}$  = 3339 (NH), 2190 (CN) and 1752, 1722, 1691  $\text{cm}^{-1}$  (CO);  $^1\text{H}$  NMR (DMSO):  $\delta_{\text{ppm}}$  = 3.35 (s, 2H, C<sub>11</sub>-H, C<sub>12</sub>-H), 3.8 (s, 3H, OCH<sub>3</sub>), 4.7 (s, 2H, C<sub>9</sub>-H, C<sub>10</sub>-H), 7.0–7.7 (m, 17H, Ar H) and 10.3 (br, 1H, NH).  $^{13}\text{C}$  NMR (DMSO):  $\delta_{\text{ppm}}$  = 173.1, 166.1, 164.0, 161.3, 142.0, 138.9, 134.9, 134.1, 132.6, 130.6, 129.4, 129.2, 128.2, 126.6, 126.2, 125.8, 124.7, 124.2, 115.0, 111.9, 74.7, 55.5, 44.2 and 40.1. Anal. for C<sub>38</sub>H<sub>26</sub>N<sub>4</sub>O<sub>5</sub>S (650.70): calcd.: C 70.14, H 4.03, N 8.61%; found: C 70.44, H 3.97, N 8.46%.

#### 4.1.4. Reaction of **5** with isatin and ninhydrine

**4.1.4.1. General procedure.** A mixture of **5** (2.66 g; 0.005 mole) and isatin or ninhydrine (0.005 mole) in DMF (15 ml) was added TEA (0.5 ml). The reaction mixture was heated on water bath for 3 h, and then poured into ice-cold water. The resulting precipitate was filtered off, dried and recrystallized from benzene–EtOH to give **7, 8**.

#### 4.1.5. 2-[4-(2-Oxo-1,2-dihydro-3H-indol-3-ylidene)-5-oxo-3-phenyl-1,3-thiazolidin-2-ylidene]-3-oxo-3-(1,4-dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzo-benzo[g]-phthalazin-2-yl)propionitrile (**7**)

Yield 80%, 2.60 g; mp > 320 °C; IR (KBr):  $\nu/\text{cm}^{-1}$  = 3238, 3222 (2NH), 2201(CN) and 1731, 1701  $\text{cm}^{-1}$  (CO).  $^1\text{H}$  NMR (DMSO):  $\delta_{\text{ppm}}$  = 3.4 (s, 2H, C<sub>11</sub>-H, C<sub>12</sub>-H), 4.8 (s, 2H, C<sub>9</sub>-H, C<sub>10</sub>-H), 7.0–7.6 (m, 17H, Ar H), 10.4 (s, 1H, NH isatine) and 11.1 (s, 1H, NH). (+)-ESI mass spectrum showed two quasi-molecular ion peaks at 684.2, ([M + Na]<sup>+</sup>) and 1345.1 ([2M + Na]<sup>+</sup>), the (–)-ESI mass spectrum showed two quasi-molecular ion peaks at 660.2 ([M-H]<sup>–</sup>) and 1320.8 ([2M-2H]<sup>–</sup>) pointing 661 as the molecular mass of the compound. Anal. for C<sub>38</sub>H<sub>23</sub>N<sub>5</sub>O<sub>5</sub>S (661.68): calcd.: C 68.98, H 3.50, N 10.58%, found: C 68.93, H 3.54, N 10.59%.

#### 4.1.6. 2-[4(1,3-Dioxo-1,3-dihydro-2H-indene-2-ylidene)5-oxo-3-phenyl-1,3-thiazolidin-2-ylidene]3-oxo-3-(1,4-dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzo-benzo[g]-phthalazin-2-yl)propionitrile (**8**)

Yield 63%, 2.10 g; mp > 320 °C; IR (KBr):  $\nu/\text{cm}^{-1}$  = 3342 (NH), 2192(CN) and 1732, 1707, 1671  $\text{cm}^{-1}$  (CO). Anal. for C<sub>39</sub>H<sub>22</sub>N<sub>4</sub>O<sub>6</sub>S (674.68): calcd.: C 69.43, H 3.29, N 8.30%; found: C 69.44, H 3.07, N 8.25%.

#### 4.1.7. Synthesis of N,N-dimethyl-N-(1,3-dioxo-1,3,3a,4,9,9a-hexahydro-4,9-benzo-benzo[F]isoindol-2-yl)formamidine (**9**)

A solution of **5** (2.66 g, 0.005 mole) in DMF (20 ml) was added drop wise to a well stirred cold solution of POCl<sub>3</sub> (2.3 g, 0.015 mole) in DMF (10 ml). The reaction mixture was stirred for other 3 h, at room temperature, and then heated on water both at 90 °C for 3 h. The reaction mixture was poured into ice-cold water, basified with NaHCO<sub>3</sub>. The separated product was filtered off and crystallized from ethanol followed by further purification using column chromatography to give **9**.

Yield 50%, 0.86 g; mp 320, R<sub>F</sub> = 0.55 (ethylacetate: petr.ether 1:1). IR (KBr):  $\nu/\text{cm}^{-1}$  = 2926 (C–H aliphatic), 1692 (CO) and 1622  $\text{cm}^{-1}$  (C=N);  $^1\text{H}$  NMR (CDCl<sub>3</sub>):  $\delta_{\text{ppm}}$  = 3.1 (s, 3H, CH<sub>3</sub>), 3.2 (s, 3H, CH<sub>3</sub>), 3.4 (s, 2H, C<sub>11</sub>-H, C<sub>12</sub>-H), 4.8 (s, 2H, C<sub>9</sub>-H, C<sub>10</sub>-H) and 7.0–7.5 (m, 9H, Ar H, CH=N). (+)-ESI mass spectrum showed three quasi-molecular ion peaks at 346 ([M + H]<sup>+</sup>), 368 and 713 ([2M + Na]<sup>+</sup>) pointing 345 as the molecular mass of the compound. Anal. for C<sub>21</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub> (345.39): calcd.: C 73.03, H 5.54, N 12.17%; found: C 73.35, H 5.47, N 12.25%.

#### 4.1.8. Synthesis of compounds **10a, b** and **12**

##### 4.1.8.1. General procedure

**4.1.8.1.1. Method (A).** To a cold suspension of finally divided KOH (0.28 g; 0.005 mole) in dry dimethylformamide (25 ml), **2** was added (1.78 g; 0.005 mole) followed by phenyl isothiocyanate (0.67 g; 0.005 mole). The mixture was stirred at room temperature for 12 h, and then treated with appropriate halogenated compound (0.005 mole) and stirred at room temperature for additional 12 h. The reaction mixture was poured into ice-cold water. The resulting precipitate was filtered off, dried and crystallized from the proper solvent to give **10a, b** and **12**.

**4.1.8.1.2. Method (B).** To a suspension of **4** (1 g, 0.002 mole) in ethanol (10 ml) appropriate  $\alpha$ -halogenated compounds (0.002 mole) and DMF (3 ml) were added. The reaction mixture was heated under reflux for 3 h, then cooled and neutralized with saturated sodium acetate solution. The resulting precipitate was filtered off, dried and crystallized from EtOH/benzene for compounds (**10a, b**) and DMF/MeOH for compound (**12**).

#### 4.1.9. 3-(1,4-Dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzo-benzo[g]-phthalazin-2-yl)-2-(4-methyl-3-phenyl-1,3-thiazol-2-(3H)ylidene)-3-oxo-propionitrile (**10a**)

Yield 74% (Method A), 92% (Method B); mp 320 °C; IR (KBr):  $\nu/\text{cm}^{-1}$  = 3390 (NH), 2180 (CN) and 1728, 1638 (CO).  $^1\text{H}$  NMR (DMSO):  $\delta_{\text{ppm}}$  = 1.8 (s, 3H, CH<sub>3</sub>), 3.3 (s, 2H, C<sub>11</sub>-H, C<sub>12</sub>-H), 4.7 (s, 2H, C<sub>9</sub>-H, C<sub>10</sub>-H), 6.9 (s, 1H, C<sub>5</sub>-H thiazole), 7.0–7.8 (m, 13H, Ar H) and 9.5 (br, 1H, NH). Anal. for C<sub>31</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub>S (530.60): calcd.: C 70.17, H 4.18, N 10.56%; found: C 70.20, H 4.23, N 10.62%.

#### 4.1.10. 3-(1,4-Dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzo-benzo[g]-phthalazin-2-yl)-2-(3,4-diphenyl-1,3-thiazol-2-(3H)ylidene)-3-oxo-propionitrile (**10b**)

Yield 75% (Method A), 86% (Method B); mp 310 °C; IR (KBr):  $\nu/\text{cm}^{-1}$  = 3368 (NH), 2186 (CN) and 1728, 1700, 1630 (CO). (+)-ESI mass spectrum showed one quasi-molecular ion peak at 615.6

( $[M + Na]^+$ ), the (–)-ESI mass spectrum showed two quasi-molecular ion peaks at 591.2 ( $[M-H]^-$ ) and 1183.0 ( $[2M-H]^-$ ) pointing 592 as the molecular mass of the compound. Anal. for  $C_{36}H_{24}N_4O_3S$  (592.67): calcd.: C 72.96, H 4.08, N 9.45%; found: C 72.66, H 4.28, N 9.40%.

#### 4.1.11. 3-(1,4-Dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzobenzog[*g*]-phthalazin-2-yl)-2-(4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)-3-oxo-propiononitrile (**12**)

Yield 63% (Method A), 75% (Method B); mp > 320 °C; IR (KBr):  $\nu/cm^{-1}$  = 3388 (NH), 2190 (CN) and 1734, 1700 (CO).  $^1H$  NMR (DMSO):  $\delta_{ppm}$  = 3.4 (s, 2H,  $C_{11}-H$ ,  $C_{12}-H$ ), 3.9 (s, 2H,  $CH_2$ ), 4.8 (s, 2H,  $C_9-H$ ,  $C_{10}-H$ ), 7.1–7.6 (m, 13H, Ar H) and 10.1 (br, 1H, NH). (+)-ESI mass spectrum showed two quasi-molecular ion peak at 555 ( $[M + Na]^+$ ) and 1086.7 ( $[2M + Na]^+$ ), the (–)-ESI mass spectrum showed one quasi-molecular ion peak at 531 ( $[M-H]^-$ ), pointing 532 as the molecular mass of the compound. Anal. for  $C_{30}H_{20}N_4O_4S$  (532.57): calcd.: C 67.66, H 3.79, N 10.52%; found: C 67.51, H 3.82, N 10.56%.

#### 4.1.12. Synthesis of thiophene derivatives **13a–d**

4.1.12.1. General procedure. To a solution of **4** (1 g; 0.002 mole) and sodium metal (0.05 g, 0.0021 mole) in absolute EtOH (10 ml), the selected  $\alpha$ -halo compound (0.002 mole) was added, triethylamine (0.2 ml) instead of Na metal in case of chloroacetone. The reaction mixture was heated under reflux for 3 h. The product obtained after addition of water was filtered, dried and crystallized from EtOH/benzene (**13a**, **13c** and **13d**), MeOH/DMF (**13b**).

#### 4.1.13. 2-[(5-Acetyl-4-amino-2-anilino-3-thienyl)carbonyl]-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzobenzog[*g*]-phthalazine-1,4-dione (**13a**)

Yield 70%; mp 268 °C; IR (KBr):  $\nu/cm^{-1}$  = 3436, 3350, 3196 (NH), and 1734, 1636 (CO).  $^1H$  NMR (DMSO):  $\delta_{ppm}$  = 2.1 (s, 3H,  $CH_3$ ), 3.4 (s, 2H,  $C_{11}-H$ ,  $C_{12}-H$ ), 4.9 (s, 2H,  $C_9-H$ ,  $C_{10}-H$ ), 7.2–7.6 (m, 15H, Ar H,  $NH_2$ ), 9.8 (br, 1H,  $NHPh$ ) and 10.7 (br, 1H, NH). Anal. for  $C_{31}H_{24}N_4O_4S$  (548.61): calcd.: C 67.87, H 4.41, N 10.21; found: C 67.91, H 4.48, N 10.31%.

#### 4.1.14. 2-[(4-Amino-2-anilino-5-benzoyl-3-thienyl)carbonyl]-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzobenzog[*g*]-phthalazine-1,4-dione (**13b**)

Yield 63%; mp 276 °C; IR (KBr):  $\nu/cm^{-1}$  = 3452, 3318, 3218 (NH), and 1792, 1718, 1630 (CO).  $^1H$  NMR (DMSO):  $\delta_{ppm}$  = 3.45 (s, 2H,  $C_{11}-H$ ,  $C_{12}-H$ ), 4.9 (s, 2H,  $C_9-H$ ,  $C_{10}-H$ ), 7.1–7.6 (m, 20H, Ar H,  $NH_2$ ), 9.5 (br, 1H,  $NHPh$ ) and 10.5 (br, 1H, NH). (+)-ESI mass spectrum showed three quasi-molecular ion peak at 611 ( $[M + H]^+$ ) and 1242 ( $[2M + Na]^+$ ), the (–)-ESI mass spectrum showed one quasi-molecular ion peak at 609 ( $[M-H]^-$ ) pointing 610 as the molecular mass of the compound. Anal. for  $C_{36}H_{26}N_4O_4S$  (610.68): calcd.: C 70.80, H 4.29, N 9.17%; found: C 70.73, H 4.14, N 9.26%.

#### 4.1.15. Ethyl-[3-amino-5-anilino-4-[(1,4-dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzobenzog[*g*]-phthalazin-2-yl)carbonyl]thiophene-2-carboxylate (**13c**)

Yield 65%; mp 243 °C; IR (KBr):  $\nu/cm^{-1}$  = 3426 (br, NH) and 1725, 1688 (CO). (+)-ESI mass spectrum showed two quasi-molecular ion peaks at 601.2 ( $[M + Na]^+$ ) and 1179 ( $[2M + Na]^+$ ), the (–)-ESI mass spectrum showed two quasi-molecular ion peaks at 577.3 ( $[M-H]^-$ ) and 1154.5 ( $[2M-H]^-$ ) pointing 578 as the molecular mass of the compound. Anal. for  $C_{32}H_{26}N_4O_5S$  (578.64): calcd.: C 66.42, H 4.53, N 9.68%; found: C 66.31, H 4.73, N 9.84%.

#### 4.1.16. 3-Amino-5-anilino-4-[(1,4-dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzobenzog[*g*]-phthalazin-2-yl)carbonyl]thiophene-2-carbonitrile (**13d**)

Yield 78%; mp > 315 °C; IR (KBr):  $\nu/cm^{-1}$  = 3428, 3352, 3271 (NH,  $NH_2$ ), 2192 (CN) and 1725, 1659 (CO). Anal. for  $C_{30}H_{21}N_5O_3S$

(531.58): calcd.: C 67.78, H 3.98, N 13.17%; found: C 67.81, H 3.86, N 13.42%.

#### 4.1.17. Reaction of compound **4** with dibromoalkane

4.1.17.1. General procedure. To suspension of **4** (1 g; 0.002 mole) in absolute ethanol (10 ml), dibromoalkane (0.002 mole) and TEA (0.2 ml) were added. The reaction mixture was heated under reflux for 10 h. The product obtained after addition of water was filtered, dried and crystallized from the dilute EtOH to give **14a, b**.

#### 4.1.18. (1,4-Dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzobenzog[*g*]-phthalazin-2-yl)-3-oxo-2-(3-phenyl-1,3-thiazolidin-2-ylidene)-propiononitrile (**14a**)

Yield 76%, 0.7 g; mp 293 °C; IR (KBr):  $\nu/cm^{-1}$  = 3194 (NH), 2190 (CN), and 1792, 1730, 1662  $cm^{-1}$  (CO).  $^1H$  NMR (DMSO):  $\delta_{ppm}$  = 3.2 (t, 2H,  $CH_2-N$ ), 3.3 (s, 2H,  $C_{11}-H$ ,  $C_{12}-H$ ), 4.1 (t, 2H,  $S-CH_2$ ), 4.7 (s, 2H,  $C_9-H$ ,  $C_{10}-H$ ), 7.1–7.4 (m, 13H, Ar H) and 9.4 (s, 1H, NH). Anal. for  $C_{30}H_{22}N_4O_3S$  (518.59): calcd.: C 69.48, H 4.28, N 10.80%; found: C 69.32, H 4.35, N 10.77%.

#### 4.1.19. 3-(1,4-Dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzobenzog[*g*]-phthalazin-2-yl)-3-oxo-2-(3-phenyl-1,3-thiazinan-2-ylidene)-propiononitrile (**14b**)

Yield 70%, 0.7 g; mp 223 °C; IR (KBr):  $\nu/cm^{-1}$  = 3252 (NH), 2188 (CN), and 1797, 1730  $cm^{-1}$  (CO). (+)-ESI mass spectrum showed two quasi-molecular ion peaks at 555.2 ( $[M + Na]^+$ ) and 1087.1 ( $[2M + Na]^+$ ), the (–)-ESI mass spectrum showed two quasi-molecular ion peaks at 531.2 ( $[M-H]^-$ ) and 1063.1 ( $[2M-H]^-$ ) pointing 532 as the molecular mass of the compound.

Anal. for  $C_{31}H_{24}N_4O_3S$  (532.61): calcd.: C 69.91, H 4.54, N 10.52%; found: C 69.85, H 4.62, N 10.43%.

#### 4.1.20. Synthesis of 3-(1,4-dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzobenzog[*g*]-phthalazin-2-yl)-3-oxo-2-(benzo[d]thiazol-2-(3H)-ylidene)-propiononitrile (**15**)

To a solution of compound **4** (1 g; 0.002 mole) in glacial acetic acid (10 ml) was cooled at 0 °C, A solution of bromine (0.32 g; 0.004 mole) in glacial acetic acid (5 ml) was added drop wise during 10 min. with stirring. Stirring was continued for 6 h. The obtained product after adding ice-cold water, filtered, dried and crystallized from a mixture of EtOH and  $CHCl_3$  to give **15**.

Yield 70%, 0.686 g; mp 217 °C; IR (KBr):  $\nu/cm^{-1}$  = 3300, 3220 (2NH), 2194 (CN), 1732, 1665 (CO) and 1613  $cm^{-1}$  (C=N). (+)-ESI mass spectrum of **15** showed two quasi-molecular ion peak at 513 ( $[M + Na]^+$ ) and 1002.8 ( $[2M + Na]^+$ ), the (–)-ESI mass spectrum showed one quasi-molecular ion peak at 489 ( $[M-H]^-$ ), pointing 490 as the molecular mass of the compound. Anal. for  $C_{28}H_{18}N_4O_3S$  (490.53): calcd.: C 68.56, H 3.70, N 11.42%; found: C 68.44, H 3.51, N 11.60%.

#### 4.1.21. Synthesis of 2-(4-substituted-1,3-thiazol-2-yl)-1,4-dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzobenzog[*g*]-phthalazine (**17a, b**)

To a suspension of **16** (3.5 g; 0.01 mole) in absolute EtOH (30 ml) containing Na metal (0.27 g; 0.012 mole), the selected  $\alpha$ -halo ketone, namely chloroacetone or phenacyl bromide (0.01 mole) was added. The reaction mixture was heated under reflux for 3 h, and then cooled. The obtained product was filtered, dried and crystallized from MeOH-DMF to give **17a, b**.

**17a**; yield 65%, 2.5 g; mp 273 °C; IR (KBr):  $\nu/cm^{-1}$  = 3300 (NH), and 1706  $cm^{-1}$  (br, CO);  $^1H$  NMR ( $CDCl_3$ ):  $\delta_{ppm}$  = 2.1 (s, 3H,  $CH_3$ ), 3.3 (s, 2H,  $C_{11}-H$ ,  $C_{12}-H$ ), 4.85 (s, 2H,  $C_9-H$ ,  $C_{10}-H$ ), 7.1–7.4 (m, 9H, Ar H), and 10.2 (s, 1H, NH). (+)-ESI mass spectrum showed three quasi-molecular ion peaks at 388 ( $[M + H]^+$ ), 410 ( $[M + Na]^+$ ) and 796.8 ( $[2M + Na]^+$ ), the (–)-ESI mass spectrum showed one



quasi-molecular ion peak at 386 ( $[M-H]^-$ ), pointing 387 as the molecular mass of the compound. Anal. for  $C_{22}H_{17}N_3O_2S$  (387.45): calcd.: C 68.20, H 4.42, N 10.85%; found: C 68.15, H 4.38, N 10.76%.

**17b**; 83% yield, 3.7 g; mp 278 °C; IR (KBr):  $\nu/cm^{-1}$  = 3290 (NH), and 1790, 1726  $cm^{-1}$  (CO).  $^1H$  NMR (DMSO):  $\delta_{ppm}$  = 3.4 (s, 2H,  $C_{11}-H$ ,  $C_{12}-H$ ), 4.8 (s, 2H,  $C_9-H$ ,  $C_{10}-H$ ), 7.1–7.7 (m, 14H, Ar H), and 10.0 (s, 1H, NH). Anal. for  $C_{27}H_{19}N_3O_2S$  (449.52): calcd.: C 72.14, H 4.26, N 9.35; found: C 72.09, H 4.16, N 9.06%.

#### 4.1.22. Synthesis of 2-(4-oxo-1,3-thiazolidin-2-yl)-1,4-dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzobenzothiazine (**18**)

To a suspension of **16** (3.5 g; 0.01 mole) in absolute EtOH (30 ml) containing Na metal (0.27 g; 0.012 mole), ethyl bromoacetate (1.67 g; 0.01 mole) was added. The reaction mixture was heated under reflux for 4hrs, and then cooled. The obtained product was filtered, dried and crystallized from MeOH-DMF to give **18**.

Yield 78%, **3g**; mp 295 °C; IR (KBr):  $\nu/cm^{-1}$  = 3270 (NH), and 1722  $cm^{-1}$ (CO).  $^1H$  NMR (DMSO):  $\delta_{ppm}$  = 3.3 (d, 2H,  $C_{11}-H$ ,  $C_{12}-H$ ), 3.9 (s, 2H,  $CH_2$ ), 4.8 (d, 2H,  $C_9-H$ ,  $C_{10}-H$ ), 7.1–7.6 (m, 8H, Ar H), and 12.2 (s, 1H, NH). Anal. for  $C_{21}H_{15}N_3O_3S$  (389.43): calcd.: C 64.77, H 3.88, N 10.79%, found: C 64.84, H 3.65, N 10.97%.

#### 4.1.23. Synthesis of 2-(5-bromo-4-phenyl-1,3-thiazol-2-yl)-1,4-dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzobenzothiazine (**19**)

A mixture of bromine (0.4 g; 0.025 mole) in glacial acetic acid (4 ml) was added drop wise over a period of 10 min. to a hot solution of **17a** (1.1 g; 0.025 mole) in acetic acid (20 ml). The reaction was heated on water bath for 2 h; the separated product after adding ice water was filtered, washed with water and crystallized from DMF/MeOH to give **19**.

Yield 66%, 0.8 g; mp 242 °C; IR (KBr):  $\nu/cm^{-1}$  = 3440(NH) and 1733, 1681(CO)  $cm^{-1}$ ; EIMS ( $m/z$ ) (%) = 529 (2.3,  $M^+ + 2$ ), 527 (2.29,  $M^+$ ), 449 (3.3), 351 (5.69), 271 (10.67), 204 (0.97), 203 (4.27), 202 (6.76), 178 (100) and 82 (6.72). Anal. for  $C_{27}H_{18}BrN_3O_2S$  (528.42): calcd.: C 61.37, H 3.43, N 7.95%, found: C 61.30, H 3.52, N 7.89%.

#### 4.2. In vitro antimicrobial activity

The tested compounds were evaluated by the agar diffusion technique [32] using a 2 mg  $ml^{-1}$  solution in DMSO. The test organisms were *B. theringiensis* as Gram-positive bacteria and *E. coli* as Gram-negative bacteria. A control using DMSO without the test compound was included for each organism. The MIC of the most active compounds was measured using the twofold serial broth dilution method [33]. Ampicillin and chloamphenicol in DMSO were used as reference drugs.

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