

## Synthesis and biological activity of 4-(N-arylidene acetylhydrazido)-1,4-benzothiazin-2,3-diones, azetidinones and thiazolidinones

M HOGALE\* and A UTHALE

Department of Chemistry, Shivaji University, Kolhapur 416 004, India

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**Abstract.** 1,4-Benzothiazin-2,3-dione (I) on N-methyl ethoxylation with ethyl chloracetate gives (II) which on reaction with hydrazine hydrate yields 4-(acetylhydrazido)-1,4-benzothiazin-2,3-dione (III). This was further condensed with different aldehydes to form the 4-(N-arylidene acetylhydrazido)-1,4-benzothiazin-2,3-dione (IV). These compounds are converted into a series of  $\beta$ -lactams (V) and 4-thiazolidinones (IV). The antibacterial and antifungal activities of the compounds have been determined.

**Keywords.** Synthesis; biological activity; benzothiazinones; azetidinones; thiazolidinones.

### 1. Introduction

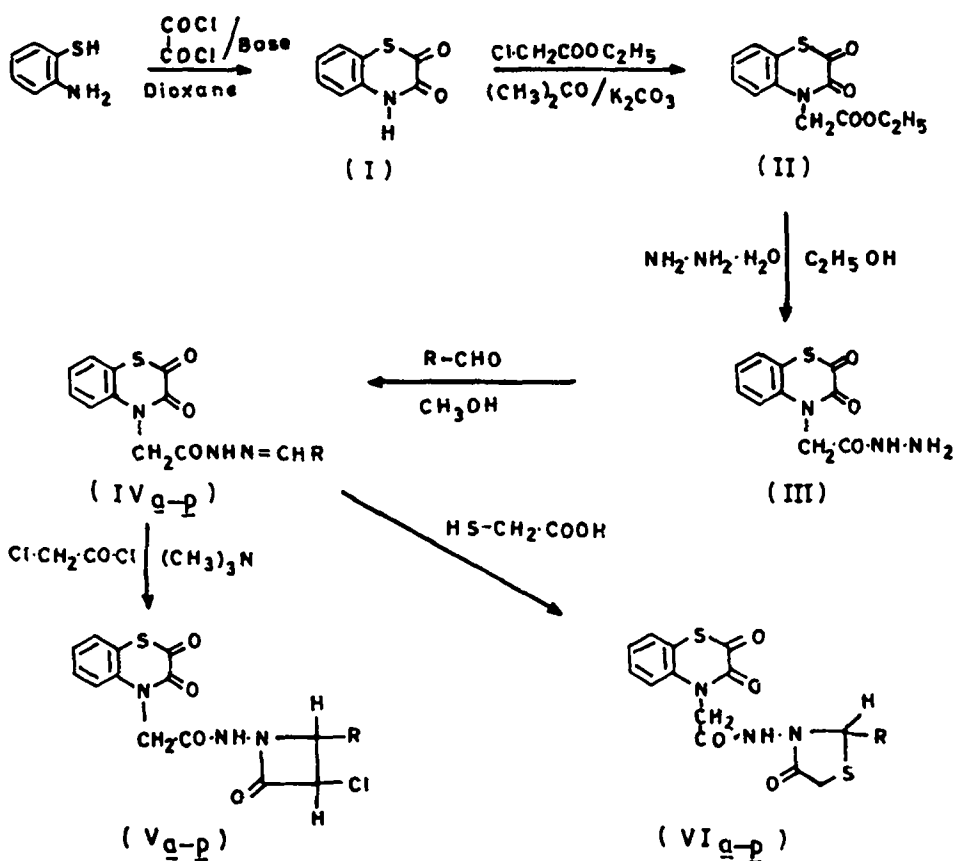
In an earlier work (Hogale and Nikam 1988) we have reported the synthesis of several 1,4-benzoxazin-3(2H)-one derivatives of biological importance. In continuation of this programme we thought it would be interesting to substitute the 1-position with a sulphur and the 4-position with an acetylhydrazido group. Gujral *et al* (1957) have deduced that incorporation of an aryl group with an -NHNH- bridge imparts better activity. A number of investigations (Troutman and Long 1948; Surrey 1947, 1949; Zoha 1971; Parmar *et al* 1972; El-Shafei *et al* 1977; Lipkir *et al* 1977; Kumar *et al* 1982) have reported that incorporation of an azetidinone or a thiazolidinone moiety enhances the biological activity. Therefore in the present study, we have introduced four-membered azetidinone and five-membered thiazolidinone rings in the side chain at the 4-position of the 1,4-benzothiazin-2,3-dione.

### 2. Results and discussion

1,4-Benzothiazin-2,3-dione (I) on N-methyl ethoxylation with ethyl chloroacetate yielded 4-(carbethoxymethyl)-1,4-benzothiazin-2,3-dione (II) which when condensed with hydrazine hydrate formed 4-(acetylhydrazido)-1,4-benzothiazin-2,3-dione (III). The compound (III) on refluxing with different aldehydes yielded Schiff's bases (IV<sub>a</sub>-p). The four-membered  $\beta$ -lactam ring was introduced by the cycloaddition of monochloro ketene in the presence of triethylamine at the azomethine group of the

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\* For correspondence



Scheme 1. (Refer to table 1 for substituents  $a-p$  at R.)

Schiff's base (IV $a-p$ ) to yield 4-(aryl)-1-(1',4'-(benzothiazin-2',3'-dioxoacetamidyl)-3-chloro-2-azetidino)-3-chloro-2-azetidino-1-one (V $a-p$ ). The five-membered thiazolidinone ring was introduced by the reaction of (IV $a-p$ ) with thioglycolic acid in THF containing anhydrous ZnCl<sub>2</sub> to yield (VI $a-p$ ) (scheme 1). The structures of all the compounds have been supported by elemental analyses and spectral data (table 1).

### 3. Biological activity

The compounds (IV $a-p$ ) and (VI $a-p$ ) were tested *in vitro* for their antibacterial activity against gram-positive and gram-negative bacteria (*Bacillus subtilis*, *Salmonella typhimurium*, *Escherichia coli*, and *Klebsiella pneumonia*). The test organisms were grown overnight at 37°C in buffered glucose broth. A loopful (5 mm dia) of the test organism was added to the buffered glucose broth containing two-fold serially diluted test compounds and incubated at 37°C for 24 h. The control experiments were run in a similar manner and contained equal amounts of buffer in which the test compounds were dissolved. The last dilution inhibiting growth was taken as minimum inhibitory concentration (MIC) in  $\mu\text{g/ml}$ . The MIC values of the

Table 1. Physical data of Schiff's bases, azetidinones and thiazolidinones.

Compound	R	M.P. (°C)	Yield (%)	Molecular formula*
IV <sub>a</sub>	-CH <sub>2</sub> -CH <sub>2</sub> ·CH <sub>3</sub>	97	70	C <sub>14</sub> H <sub>15</sub> O <sub>3</sub> N <sub>3</sub> S
b	-C <sub>6</sub> H <sub>5</sub>	191	65	C <sub>17</sub> H <sub>13</sub> O <sub>3</sub> N <sub>3</sub> S
c	- <i>o</i> -C <sub>6</sub> H <sub>4</sub> ·OH	197	69	C <sub>17</sub> H <sub>13</sub> O <sub>4</sub> N <sub>3</sub> S
d	- <i>m</i> -C <sub>6</sub> H <sub>4</sub> ·OH	201	70	C <sub>17</sub> H <sub>13</sub> O <sub>4</sub> N <sub>3</sub> S
e	- <i>p</i> -C <sub>6</sub> H <sub>4</sub> ·OH	181	60	C <sub>17</sub> H <sub>13</sub> O <sub>4</sub> N <sub>3</sub> S
f	- <i>p</i> -C <sub>6</sub> H <sub>4</sub> -OCH <sub>3</sub>	169	59	C <sub>18</sub> H <sub>15</sub> O <sub>4</sub> N <sub>3</sub> S
g	- <i>o</i> -C <sub>6</sub> H <sub>4</sub> -Cl	155	65	C <sub>17</sub> H <sub>12</sub> O <sub>3</sub> N <sub>3</sub> S
h	- <i>p</i> -C <sub>6</sub> H <sub>4</sub> -Cl	190	75	C <sub>17</sub> H <sub>12</sub> O <sub>3</sub> N <sub>3</sub> SCl
i	-2,4-C <sub>6</sub> H <sub>3</sub> Cl <sub>2</sub>	149	80	C <sub>17</sub> H <sub>11</sub> O <sub>3</sub> N <sub>3</sub> SCl
j	- <i>m</i> -C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub>	113	73	C <sub>17</sub> H <sub>12</sub> O <sub>3</sub> N <sub>4</sub> S
k	- <i>p</i> -C <sub>6</sub> H <sub>4</sub> ·NO <sub>2</sub>	117	70	C <sub>17</sub> H <sub>12</sub> O <sub>3</sub> N <sub>4</sub> S
l	- <i>p</i> -C <sub>6</sub> H <sub>4</sub> -N(CH <sub>3</sub> ) <sub>2</sub>	133	85	C <sub>19</sub> H <sub>18</sub> O <sub>3</sub> N <sub>4</sub> S
m	-CH=CH-C <sub>6</sub> H <sub>5</sub>	179	60	C <sub>19</sub> H <sub>15</sub> O <sub>3</sub> N <sub>3</sub> S
n	-C <sub>4</sub> H <sub>3</sub> O	129	65	C <sub>15</sub> H <sub>11</sub> O <sub>4</sub> N <sub>3</sub> S
o	-CH=CH·CH <sub>3</sub>	107	63	C <sub>14</sub> H <sub>13</sub> O <sub>3</sub> N <sub>3</sub> S
p	-C <sub>5</sub> H <sub>4</sub> N	127	70	C <sub>16</sub> H <sub>12</sub> O <sub>3</sub> N <sub>4</sub> S
V <sub>a</sub>	-CH <sub>2</sub> -CH <sub>2</sub> ·CH <sub>3</sub>	167	71	C <sub>16</sub> H <sub>16</sub> O <sub>4</sub> N <sub>3</sub> SCl
b	-C <sub>6</sub> H <sub>5</sub>	142	69	C <sub>19</sub> H <sub>14</sub> O <sub>4</sub> N <sub>3</sub> SCl
c	- <i>o</i> -C <sub>6</sub> H <sub>4</sub> ·OH	177	67	C <sub>19</sub> H <sub>14</sub> O <sub>5</sub> N <sub>3</sub> SCl
d	- <i>m</i> -C <sub>6</sub> H <sub>4</sub> ·OH	197	80	C <sub>19</sub> H <sub>14</sub> O <sub>5</sub> N <sub>3</sub> SCl
e	- <i>p</i> -C <sub>6</sub> H <sub>4</sub> ·OH	130	70	C <sub>19</sub> H <sub>14</sub> O <sub>5</sub> N <sub>3</sub> SCl
f	- <i>p</i> -C <sub>6</sub> H <sub>4</sub> -OCH <sub>3</sub>	167	81	C <sub>20</sub> H <sub>16</sub> O <sub>5</sub> N <sub>3</sub> SCl
g	- <i>o</i> -C <sub>6</sub> H <sub>4</sub> -Cl	213	60	C <sub>19</sub> H <sub>13</sub> O <sub>4</sub> N <sub>3</sub> SCl <sub>2</sub>
h	- <i>p</i> -C <sub>6</sub> H <sub>4</sub> -Cl	197	67	C <sub>19</sub> H <sub>13</sub> O <sub>4</sub> N <sub>3</sub> SCl <sub>2</sub>
i	-2,4-C <sub>6</sub> H <sub>3</sub> Cl <sub>2</sub>	211	80	C <sub>19</sub> H <sub>12</sub> O <sub>4</sub> N <sub>3</sub> SCl <sub>3</sub>
j	- <i>m</i> -C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub>	190	65	C <sub>19</sub> H <sub>13</sub> O <sub>6</sub> N <sub>4</sub> SCl
k	- <i>p</i> -C <sub>6</sub> H <sub>4</sub> ·NO <sub>2</sub>	221	60	C <sub>19</sub> H <sub>13</sub> O <sub>6</sub> N <sub>4</sub> SCl
l	- <i>p</i> -C <sub>6</sub> H <sub>4</sub> -N(CH <sub>3</sub> ) <sub>2</sub>	152	81	C <sub>21</sub> H <sub>19</sub> O <sub>4</sub> N <sub>3</sub> SCl
m	-CH=CH-C <sub>6</sub> H <sub>5</sub>	179	59	C <sub>21</sub> H <sub>16</sub> O <sub>4</sub> N <sub>3</sub> SCl
n	-C <sub>4</sub> H <sub>3</sub> O	207	58	C <sub>17</sub> H <sub>12</sub> O <sub>5</sub> N <sub>3</sub> SCl
o	-CH=CH·CH <sub>3</sub>	190	60	C <sub>16</sub> H <sub>14</sub> O <sub>4</sub> N <sub>3</sub> SCl
p	-C <sub>5</sub> H <sub>4</sub> N	203	57	C <sub>18</sub> H <sub>13</sub> O <sub>4</sub> N <sub>4</sub> SCl
VI <sub>a</sub>	-CH <sub>2</sub> -CH <sub>2</sub> ·CH <sub>3</sub>	167	60	C <sub>16</sub> H <sub>17</sub> O <sub>4</sub> N <sub>3</sub> S <sub>2</sub>
b	-C <sub>6</sub> H <sub>5</sub>	170	59	C <sub>19</sub> H <sub>15</sub> O <sub>4</sub> N <sub>3</sub> S <sub>2</sub>
c	- <i>o</i> -C <sub>6</sub> H <sub>4</sub> ·OH	201	60	C <sub>19</sub> H <sub>15</sub> O <sub>5</sub> N <sub>3</sub> S <sub>2</sub>
d	- <i>m</i> -C <sub>6</sub> H <sub>4</sub> ·OH	197	70	C <sub>19</sub> H <sub>15</sub> O <sub>5</sub> N <sub>3</sub> S <sub>2</sub>
e	- <i>p</i> -C <sub>6</sub> H <sub>4</sub> ·OH	209	65	C <sub>19</sub> H <sub>15</sub> O <sub>5</sub> N <sub>3</sub> S <sub>2</sub>
f	- <i>p</i> -C <sub>6</sub> H <sub>4</sub> -OCH <sub>3</sub>	167	80	C <sub>20</sub> H <sub>17</sub> O <sub>5</sub> N <sub>3</sub> S <sub>2</sub>
g	- <i>o</i> -C <sub>6</sub> H <sub>4</sub> -Cl	169	75	C <sub>19</sub> H <sub>14</sub> C <sub>4</sub> N <sub>3</sub> S <sub>2</sub> Cl
h	- <i>p</i> -C <sub>6</sub> H <sub>4</sub> -Cl	197	74	C <sub>19</sub> H <sub>14</sub> O <sub>4</sub> N <sub>3</sub> S <sub>2</sub> Cl
i	-2,4-C <sub>6</sub> H <sub>3</sub> Cl <sub>2</sub>	211	80	C <sub>19</sub> H <sub>13</sub> O <sub>4</sub> N <sub>3</sub> S <sub>2</sub> Cl
j	- <i>m</i> -C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub>	190	60	C <sub>19</sub> H <sub>14</sub> O <sub>6</sub> N <sub>4</sub> S <sub>2</sub>
k	- <i>p</i> -C <sub>6</sub> H <sub>4</sub> ·NO <sub>2</sub>	161	64	C <sub>19</sub> H <sub>14</sub> O <sub>6</sub> N <sub>4</sub> S <sub>2</sub>
l	- <i>p</i> -C <sub>6</sub> H <sub>4</sub> -N(CH <sub>3</sub> ) <sub>2</sub>	152	78	C <sub>21</sub> H <sub>20</sub> O <sub>4</sub> N <sub>4</sub> S <sub>2</sub>
m	-CH=CH-C <sub>6</sub> H <sub>5</sub>	179	63	C <sub>21</sub> H <sub>17</sub> O <sub>4</sub> N <sub>3</sub> S <sub>2</sub>
n	-C <sub>4</sub> H <sub>3</sub> O	207	65	C <sub>17</sub> H <sub>13</sub> O <sub>5</sub> N <sub>3</sub> S <sub>2</sub>
o	-CH=CH·CH <sub>3</sub>	190	59	C <sub>16</sub> H <sub>15</sub> O <sub>4</sub> N <sub>3</sub> S <sub>2</sub>
p	-C <sub>5</sub> H <sub>4</sub> ·N	159	66	C <sub>18</sub> H <sub>14</sub> O <sub>4</sub> N <sub>4</sub> S <sub>2</sub>

\* All the compounds were analysed satisfactorily for C, H and N.

**Table 2.** Antifungal screening data of compounds IV (a-p) and VI (a-p). (Average percent inhibition after 96 h.) Concentrations of the compounds used (10, 100 and 1000) are in ppm. The fungi tested were *Helminthosporium oryzae* and *Cerevisia sacchari*

Compound	<i>H. oryzae</i>			<i>C. sacchari</i>		
	1000	100	10	1000	100	10
IV <sub>a</sub>	40	20	15	42	20	14
b	38	20	10	38	15	11
c	35	23	13	44	18	12
d	51	28	14	55	24	10
e	44	21	13	52	22	13
f	68	35	18	71	31	28
g	47	31	11	58	33	14
h	53	30	13	61	29	10
i	76	38	21	83	39	23
j	40	21	10	43	20	—
k	43	18	—	41	21	10
l	53	26	11	50	22	11
m	46	22	14	38	21	10
n	61	33	18	73	30	21
o	33	21	10	43	21	12
p	60	39	19	71	29	10
V <sub>a</sub>	47	16	10	45	23	11
b	39	17	08	41	21	09
c	40	26	13	38	19	10
d	49	26	12	35	16	—
e	51	21	12	36	17	12
f	62	33	27	69	33	19
g	53	29	13	49	21	13
h	50	22	09	55	21	07
i	73	30	19	69	29	16
j	37	21	—	40	21	10
k	41	22	10	33	16	07
l	61	21	10	46	19	—
m	49	23	10	39	21	10
n	67	31	30	70	30	11
o	32	21	07	30	21	09
p	61	31	18	57	28	20
Dithane M-45	100	91	73	100	95	70

sample compounds were in the range 300 to 110 µg/ml. The results show that all the compounds possess moderate antibacterial activity.

The antifungal activity of the compounds (IV<sub>a-p</sub>) and (VI<sub>a-p</sub>) was evaluated against *H. oryzae* and *C. sacchari* by the agar plate technique at 1000, 100 and 10 ppm concentrations. A commercial fungicide Dithane M-45 was also tested under similar conditions for comparison. Antifungal testing results are presented in table 2.

Most of the tested compounds (IV<sub>a-p</sub>) and (VI<sub>a-p</sub>) were found toxic to test fungi at 1000 ppm but not so spectacularly at lower concentrations (100 ppm and 10 ppm). Compounds having halogen and methoxy groups on the phenyl ring attached to the five-membered thiazolidinone ring were found to show high antifungal activity.

#### 4. Experimental

All melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 237 spectrophotometer and PMR spectra in  $\text{CDCl}_3$  or TFA on a Perkin-Elmer R-32 spectrometer using TMS as an internal standard. Purity of the compounds was checked by TLC using plates coated with Silica-gel-G.

##### 4.1 1,4-Benzothiazin-2,3-dione (I)

A mixture of *o*-aminothiophenol (0.05 mol), oxalyl chloride (0.05 mol) and triethylamine (0.005 mol) in 1,4-dioxane (20 ml) was refluxed on a steam bath for 2 h, cooled and the separated solid treated with water, filtered and crystallised from ethanol to yield I: Yield 5.1 g (81.6%), m.p. 156° (Found: C, 53.59; H, 2.70; N, 7.75%;  $\text{C}_8\text{H}_5\text{O}_2\text{NS}$  requires C, 53.63; H, 2.79; N, 7.82%); IR (KBr): 3300–3250 ( $-\text{NH}$ ), 1690 ( $>\text{C}=\text{O}$ ), 1610  $\text{cm}^{-1}$  ( $>\text{C}=\text{C}<$ ); PMR (TFA): 6.8–7.3 (4H, *m*, Ar-H), 8.7 (1H, *brs*,  $-\text{NH}$ ).

##### 4.2 4-Carbethoxymethyl-1,4-benzothiazin-2,3-dione (II)

A mixture of I (0.025 mol), ethyl chloroacetate (0.025 mol) and anhydrous  $\text{K}_2\text{CO}_3$  (2 g) in acetone (40 ml) was refluxed for 11 h. The solvent was removed under vacuum and the separated solid was crystallised from ethanol to give II: Yield 3.7 g (80.97%), m.p. 143° (Found: C, 54.30; H, 4.10; N, 5.23%;  $\text{C}_{12}\text{H}_{11}\text{O}_4\text{NS}$  requires C, 54.33; H, 4.15; N, 5.28%); IR (KBr): 1720 ( $>\text{C}=\text{O}$ , ester), 1690 ( $>\text{C}=\text{O}$ ), 1600  $\text{cm}^{-1}$  ( $>\text{C}=\text{C}<$ ); PMR (TFA): 1.1 (3H, *t*,  $J = 8.5$  Hz,  $-\text{CH}_3$ ), 4.2 (2H, *q*,  $J = 8.5$  Hz,  $-\text{CH}_2$ ), 4.1 (2H, *s*,  $-\text{NCH}_2$ ), 6.8–7.5 (4H, *m*, Ar-H).

##### 4.3 4-(Acetylhydrazido)-1,4-benzothiazin-2,3-dione (III)

A mixture of hydrazine hydrate (0.024 ml) and compound (II) (0.012 ml) in ethanol (30 ml) was refluxed for 3 h on a water bath. On cooling the compound III separated out as white needles; Yield 3 g (90%), m.p. 152° (Found: C, 47.76; H, 3.54; N, 16.70%;  $\text{C}_{10}\text{H}_9\text{O}_3\text{S}$  requires C, 47.80; H, 3.59; N, 16.73%); IR (KBr): 3350–3200 ( $-\text{NH}\cdot\text{NH}_2$ ), 1690 ( $>\text{C}=\text{O}$ ,  $\delta$ -lactam), 1670 ( $>\text{C}=\text{O}$ , acyclic), 1600  $\text{cm}^{-1}$  ( $>\text{C}=\text{C}<$ ); PMR ( $\text{CDCl}_3$ ): 4.15 (2H, *s*,  $-\text{N}-\text{CH}_2$ ), 6.8–7.5 (4H, *m*, Ar-H), 8.0 (1H, *s*,  $-\text{CONH}$ ).

##### 4.4 4-(*N*-Arylidene acetylhydrazido)-1,4-benzothiazin-2,3-dione (IV<sub>a-p</sub>)

A mixture of III (0.002 mol) and the appropriate aldehyde (0.002 mol) in methanol (25 ml) was refluxed on a steam bath for 3 h. The solvent was removed under reduced pressure and the semi-solid obtained was treated with cold water. The solid formed was then filtered and recrystallised from ethanol to give IV<sub>a-p</sub>. IV<sub>f</sub>: Yield 0.3 g (59%), m.p. 169° (Found: C, 58.54; H, 4.06; N, 11.38%;  $\text{C}_{18}\text{H}_{15}\text{O}_4\text{N}_3\text{S}$  requires C, 58.50; H, 3.98; N, 11.25%); IR (KBr): 3300–3200 ( $-\text{NH}-$ ), 1690 ( $>\text{C}=\text{O}$ ,  $\delta$ -lactam), 1665 ( $>\text{C}=\text{O}$ , acyclic), 1620 ( $>\text{C}=\text{N}-$ ), 1600  $\text{cm}^{-1}$  ( $>\text{C}=\text{C}<$ ); PMR (TFA): 3.75 (3H, *s*,  $-\text{OCH}_3$ ), 4.45 (1H, *s*,  $-\text{N}=\text{CH}$ ), 4.1 (2H, *s*,  $-\text{NCH}_2$ ), 6.8–7.5 (4H, *m*, Ar-H).

4.5 4-(Aryl)-1-(1',4'-benzothiazin-2',3'-dioxoacetamidyl)-3-chloro-2-azetidiones ( $V_{a-p}$ )

To a stirred solution of the compound ( $IV_{a-p}$ ) (0.001 mol) and triethylamine (0.002 mol) in 1,4-dioxane (25 ml), monochloroacetyl chloride (0.001 mol) was added dropwise at room temperature. The reaction mixture was stirred for 30 min and then refluxed for 3 h. When the reaction was over the water-soluble salt formed was removed by filtration. The filtrate was collected and the excess solvent removed. The remaining semi-solid was treated with ice-cold water to get  $V_{a-p}$ . **Vf:** Yield 0.36 g (81%), m.p. 167°; (Found: C, 53.80; H, 3.50; N, 9.35%;  $C_{20}H_{16}O_5N_3SCl$  requires C, 53.87; H, 3.59; N, 9.42%); IR (KBr): 3300–3200 (–NH), 1740 ( $>C=O$ ,  $\beta$ -lactam), 1670 ( $>C=O$ , C=O acyclic),  $760\text{ cm}^{-1}$  (C–Cl); PMR (TFA): 3.85 (3H, s, –OCH<sub>3</sub>), 4.150 (2H, s, –NCH<sub>2</sub>), 4.5 (1H, d,  $J = 12\text{ Hz}$ , –C–H), 6.2 (1H, d,  $J = 12\text{ Hz}$ ,  $>CH-Cl$ ), 6.8–7.5 (9H, m, Ar–H).

4.6 3-(1',4'-Benzothiazin-2',3'-dioxoacetamidyl)-2-aryl,1,3-thiazolidin-4-one ( $VI_{a-p}$ )

Schiff's bases ( $IV_{a-p}$ ) (0.01 mol) in THF (30 ml) containing a pinch of anhydrous  $ZnCl_2$  and thioglycolic acid (0.01 mol) were refluxed for 8 h on a water bath. The reaction mixture was cooled and poured into ice-cold water to get  $VI_{a-p}$ . **VI:** Yield 3.3 g (80%), m.p. 167°; (Found: C, 54.10; H, 3.79; N, 9.40%)  $C_{20}H_{17}O_5N_3S_2$  requires C, 54.18; H, 3.84; N, 9.48%); IR (KBr): 3250–3200 (–NH–), 1690 ( $>C=O$ , cyclic),  $1665\text{ cm}^{-1}$  ( $>C=O$ , acyclic); PMR (TFA): 3.2 (1H, s, –C–H), 3.60 (2H, s, –CH<sub>2</sub>–S), 3.8 (3H, s, –OCH<sub>3</sub>), 4.1 (2H, s, –N–CH<sub>2</sub>), 6.9–7.7 (8H, m, Ar–H), 8.8 (1H, s, –CO–NH).

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