

## Synthesis and study of biological activity of some new 1,4-benzothiazines

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*N*-(4-methylpyrimidin-2-one-4-yl)-1,4-benzothiazine-2,3-dione **5**, 2-thio-2,6-dimethyl[1,3,5]triazino[3,4-*c*]-1,4-benzothiazine **9**, [1,2,4]-triazino-2-oxo-[3,4-*c*][1,4]-benzothiazine **13**, 5-arylidene-1*H*-1,4-benzothiazine[1,3,4]triazole **16a-b**, 2-thio-6-methyl[1,3,5]triazino[3,4-*c*]benzothiazine **19**, *N*-(2-propanoyl)-1,4-benzothiazne-3(1*H*)-one **20**, tricyclic compound cyclopenteno-1,4-benzothiazine **21** have been synthesized and characterized by spectral data.

**Keywords:** 2-methyl-1,4-benzothiazine, synthesis, applications

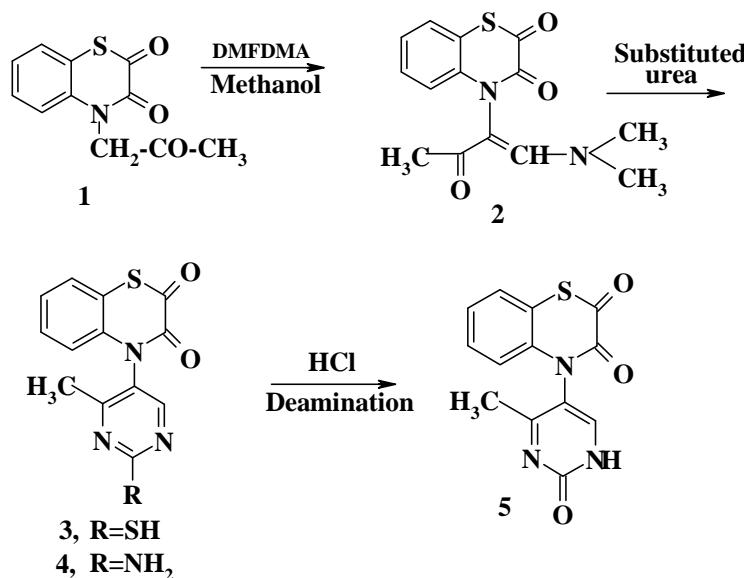
**IPC: Int.Cl.<sup>8</sup> C07D**

The various 1,4-benzothiazinones have been reported to possess wide range of pharmaceutical and biological activities<sup>1-30</sup> similar to that of phenothiazines because 1,4-benzothiazine resemble structurally to phenothiazines in having a fold along nitrogen-sulfur axis. The benzothiazines containing four membered azetidinone and five membered thiazolidinone rings at 4-position show better antibacterial and antifungal activity<sup>6</sup>. Prompted by these observations here, we report the synthesis and biological activities of some new 1,4-benzothiazines.

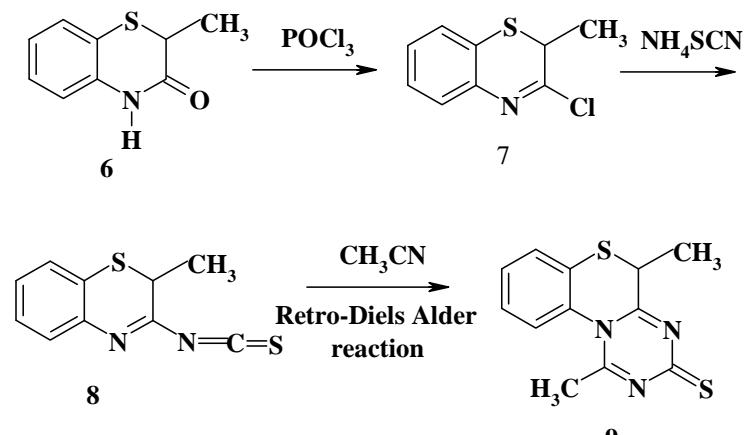
### Results and Discussion

The compound **1** was reacted with DMF-DMA in methanol to form an intermediate compound **2** which when reacted with substituted urea gave compounds **3** and **4** (**Scheme I**). The formation of **3** and **4** was explained on the basis of a <sup>1</sup>H NMR signal at  $\delta$  4.78 due to NH<sub>2</sub> in **4** and the signal at  $\delta$  10.2 due to -SH in **3**. The compound **4** when treated with HCl deamination to get **5**, the formation of which was ensured on the basis of <sup>1</sup>H NMR signal due to NH. The compound **6** was refluxed with POCl<sub>3</sub> to get **7**, the formation of which was confirmed by the appearance of an IR band at 760 cm<sup>-1</sup> due to C-Cl stretching. The compound **7** when refluxed with ammonium sulfocyanide furnished **8**. The formation of **8** was explained on the basis of an IR band encountered at 2050 cm<sup>-1</sup> due to N=C=S. (**Scheme II**)

The compound **8** when subsequently subjected to Retro-Diels-Alder reaction with methyl cyanide to get the desired tricyclic compound **9**, the formation of which was ascertained on the basis of an IR band observed at 1190 cm<sup>-1</sup> due to C=S. When 2-aminothiophenol was refluxed with ethyl chloroacetate in 33% NaOH formed 1,4-benzothiazine-3(2*H*)-one **10**. The formation of **10** (**Table I**) was ascertained on the basis of IR bands encountered at 3300-2900 and 1660 cm<sup>-1</sup> due to NH and cyclic >C=O respectively. This was also confirmed from <sup>1</sup>H NMR signals observed at  $\delta$  3.37 and 10.07 due to S-CH<sub>2</sub> and NH respectively. Compound **10** when refluxed with ethyl chloroacetate in presence of K<sub>2</sub>CO<sub>3</sub> in acetone afforded **11**, the structure of which ensured on the basis of IR bands appeared at 1740 and 1690-1680 cm<sup>-1</sup> due to ester >C=O and cyclic >C=O respectively. The compound **11** was subsequently reacted with hydrazine hydrate in methanol to form **12**. The formation of **12** was explained on the basis of IR bands observed at 3350-3100, 1690 and 1630 cm<sup>-1</sup> due to NHNH<sub>2</sub>, acyclic amido >C=O and cyclic >C=O as well as the <sup>1</sup>H NMR signals observed at  $\delta$  3.89, 4.56 and 7.58 due to N-CH<sub>2</sub>, NH<sub>2</sub> and CONH<sub>2</sub> respectively. The compound **12** was refluxed in acetic acid in presence of ammonium acetate to get the desired tricyclic compound, **13**. The formation of **13** was confirmed from the IR bands observed at 3680-3200, 1760 and 1590 cm<sup>-1</sup> due to NH or enolic OH,



Scheme I



Scheme II

cyclic amido C=O and C=N respectively. The compound **10** was refluxed with hydrazine hydrate in methanol to yield **14**, the formation of which was ensured from the IR bands observed at 3312-2912 and 1665  $\text{cm}^{-1}$  due to  $\text{NH}_2$  and C=N respectively. It was also supported by  $\text{M}^+$  peak at 179 (100%) in its mass spectrum. The compound **14** when reacted with substituted aldehydes and ketones in presence of acetic acid formed **15** (Scheme III). Its formation was ensured on the basis of IR bands encountered at 1620  $\text{cm}^{-1}$  due to C=N and disappearance of IR band due to  $\text{NH}_2$ . The compound **15** was subsequently cyclized by refluxing in presence of the catalyst thallium acetate to get the desired tricyclic product **16**, the formation of which was explained on the basis of disappearance

of IR band due to  $\text{NH}_2$ . The compound **10** when heated in refluxing  $\text{POCl}_3$  gave **17**, the formation of which was ascertained on the basis of IR band observed at 760  $\text{cm}^{-1}$  due to C-Cl. The compound **17** was refluxed with ammonium sulfocyanide to form **18** (Scheme IV). The formation of **18** was ensured from an IR band observed at 2050  $\text{cm}^{-1}$  due to  $-\text{N}=\text{C}=\text{S}$ . The compound **18** was subsequently subjected to Retro-Diels-Alder reaction with methyl cyanide to get the desired tricyclic compound **19**, the formation of which was confirmed on the basis of an IR band encountered at 1190  $\text{cm}^{-1}$  due to C=S. Further, the compound **10** was refluxed with chloroacetone in presence of  $\text{K}_2\text{CO}_3$  to form **20**, the formation of which was confirmed on the basis of IR bands appearing at

**Table I**—Physical data for compound **15a-I**

Compd	R <sup>1</sup>	R <sup>2</sup>	Mol. Formula	m.p. °C	Found % (Required)		
					C	H	N
<b>15a</b>	H	3-(OCH <sub>3</sub> ),2(OH),C <sub>6</sub> H <sub>3</sub>	C <sub>16</sub> H <sub>15</sub> O <sub>2</sub> N <sub>3</sub> S	165	62.15 (61.34)	3.98 (4.79)	12.9 (13.4)
<b>15b</b>	CH <sub>3</sub>	4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	C <sub>17</sub> H <sub>17</sub> ON <sub>3</sub> S	180	64.68 (65.59)	6.27 (5.46)	14.31 (13.5)
<b>15c</b>	H	4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	C <sub>16</sub> H <sub>15</sub> ON <sub>3</sub> S	158	63.83 (64.64)	4.84 (5.05)	13.8 (14.14)
<b>15d</b>	H	-CH=CHC <sub>6</sub> H <sub>5</sub>	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> S	170	70.34 (69.62)	4.72 (5.11)	13.82 (14.33)
<b>15e</b>	H	-C <sub>6</sub> H <sub>5</sub>	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> S	158	66.73 (67.41)	5.15 (4.86)	14.82 (15.73)
<b>15f</b>	H	4-OH-C <sub>6</sub> H <sub>4</sub>	C <sub>15</sub> H <sub>13</sub> ON <sub>3</sub> S	188	64.21 (63.60)	5.18 (4.59)	13.75 (14.84)
<b>15g</b>	H	4-Cl-C <sub>6</sub> H <sub>4</sub>	C <sub>15</sub> H <sub>12</sub> N <sub>3</sub> SCl	174	58.71 (59.70)	4.59 (3.98)	12.84 (13.93)
<b>15h</b>	H	3-OCH <sub>3</sub> ,4-OH,C <sub>6</sub> H <sub>3</sub>	C <sub>16</sub> H <sub>15</sub> O <sub>2</sub> N <sub>3</sub> S	178	62.15 (61.34)	3.88 (4.79)	12.71 (13.42)
<b>15i</b>	H	2-OH-C <sub>6</sub> H <sub>4</sub>	C <sub>15</sub> H <sub>13</sub> ON <sub>3</sub> S	175	64.23 (63.60)	3.78 (4.59)	13.89 (14.84)

1730-1715 and 1689 cm<sup>-1</sup> due to cyclic amido >C=O and acyclic >C=O respectively. The compound **20** when cyclized with sodium methoxide in methanol afforded the desired tricyclic compound **21** (**Scheme V**). Its formation was ensured from IR bands observed at 3500 and 1640 cm<sup>-1</sup> due to enolic OH and conjugated >C=O.

### Biological activity of selected compounds

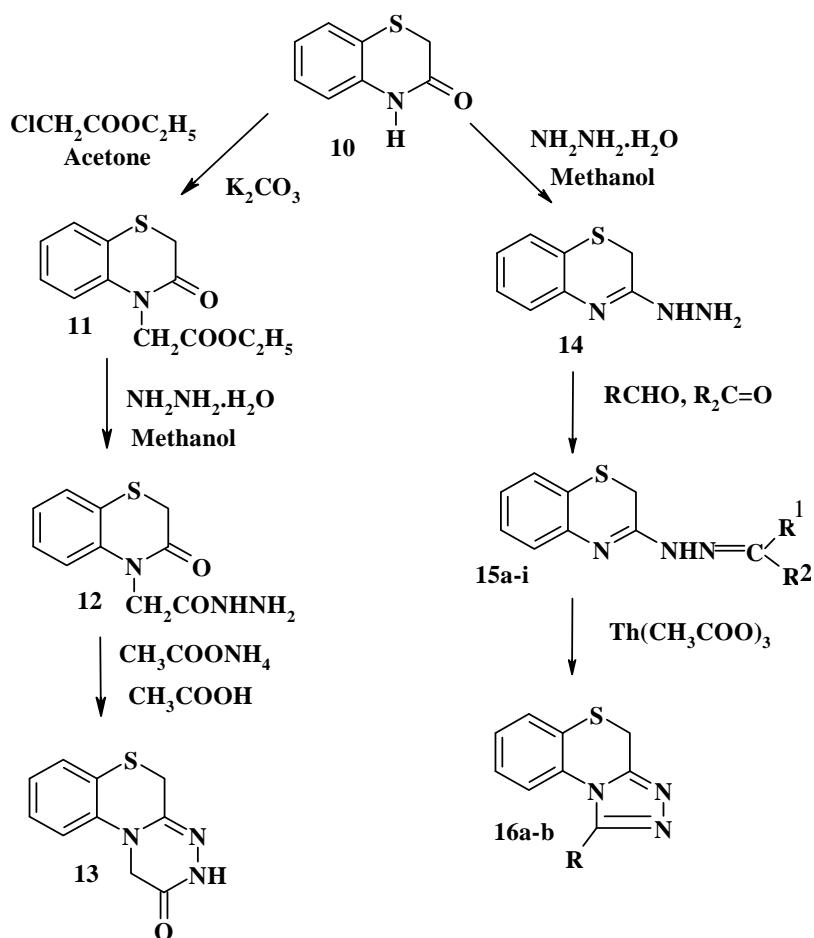
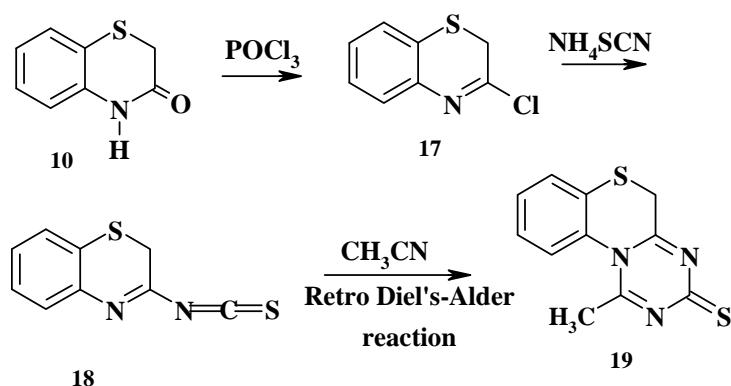
Some of the synthesized compounds were screened for their antibacterial activity against gram-positive (*Bacillus subtilis* and *S. aureus*), gram-negative (*Salmonella paratyphi* and *Pseudomonas* spp.) and antifungal activity against *Aspergillus niger* and *Rhizopus*. The test microorganisms were grown for 24 hr at 37°C in a buffered nutrient agar. A 24 hr old culture of test microorganism was added to the medium, a sterile paper disc (6 mm) prepared in a solution of test compound with concentration 100 mg/mL of DMF was placed over it and incubated at 37°C for 24 hr. A control experiment was also run in a similar manner using the solvent. The antibacterial activity exhibited by the test compounds is depicted in terms of diameter of zone of inhibition: Inactive (less than 13 mm), less active (13-16 mm), moderately active (17-20 mm) and highly active (21-27 mm) respectively. The antifungal activity of test compounds was determined by nutrient medium

(Sabouraud's broth) method and the results recorded in terms of percentage inhibition of growth of test fungi *Aspergillus niger* and *Rhizopus* using specol-21 Digital (Toshniwal) at 530 nm. According to the analytical results obtained, it is evident that the test compounds (**1**, **14**, **6**, **15c** and **15f**) have been found to be active against the test microorganisms. Out of these compound **1** and **14** showed highly promising antifungal activity against *Aspergillus niger* but other test compounds exhibited weak antifungal activity. The antifungal activity of **14** is co-related with the -NHNH<sub>2</sub> group at position-3. The analytical data of antibacterial and antifungal activity of selected compounds have been given in **Table II**.

### Experimental Section

Melting points were taken in an open capillary tube and were uncorrected. IR spectra (KBr/Nujol) were recorded on a Perkin-Elmer 783 spectrophotometer and <sup>1</sup>H NMR spectra (DMSO-*d*<sub>6</sub>/CDCl<sub>3</sub>) on a Bruker Ac 300F spectrometer (300 MHz) using TMS as an internal standard. The mass spectra were recorded by EIMS technique on an Autospec mass spectrometer. The progress of reaction and purity of samples were checked by TLC using silica gel.

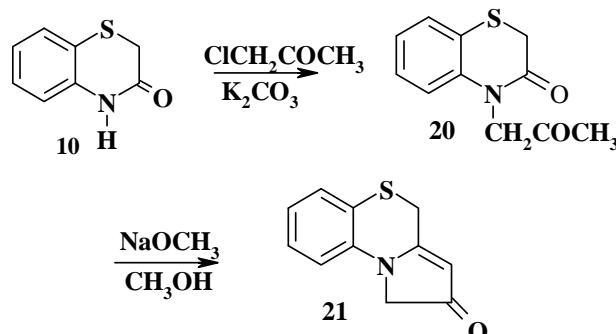
**Synthesis of *N*-(2-dimethylamino-1-acetylacryl)-1,4-benzothiazine-2,3-dione **2**.** The mixture of **1** (0.45 g, 0.0019 mole) and dimethylformamide-

**Scheme III****Scheme IV**

dimethylacetal (0.238 g; 0.0019 mole) in methanol (10 mL) was stirred for 30 min and heated on a steam-bath at 70°C for 2 hr. The reaction mixture cooled and the excess of solvent removed under vacuum to get a yellowish-red product, which was crystallized from ethylacetate. Yield 0.16 g, (30%), m.p. 220°C, Found:

C, 58.25; H, 5.12; N, 9.18.  $\text{C}_{14}\text{H}_{14}\text{O}_3\text{N}_2\text{S}$  required C, 57.93; H, 4.83; N, 9.65%.

**Synthesis of *N*-2-substituted-(4-methyl diazine)-1,4-benzothiazine-2,3-dione 3 and 4.** The mixture of **2** (0.06 g, 0.002 mole) and substituted urea (0.015 g, 0.002 mole) was dissolved in methanol (5 mL). To



Scheme V

this mixture 2*N* NaOH (2 mL) was added drop-wise with constant stirring during the period of one hr and the reaction mixture heated on a steam-bath for 2 hr. The reaction mixture was then cooled and the excess of solvent removed under vacuum. The residue dissolved in water and precipitated by 30% acetic acid crystallized from ethanol.

**Compound 3:** R=SH, Yield 0.040 g, (66%), m.p. >320°C, Found: C, 52.38; H, 3.29; N, 12.86. C<sub>13</sub>H<sub>9</sub>O<sub>2</sub>N<sub>3</sub>S<sub>2</sub> required C, 51.49; H, 2.97; N, 13.87%. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.8 (3H, s, Ar-CH<sub>3</sub>), 4.78 (2H, s, Ar-NH<sub>2</sub>, exchangeable with D<sub>2</sub>O), 6.6-7.5 (4H, m, Ar H), 8.2 (1H, s, =CH).

**Compound 4:** R=NH<sub>2</sub>, R<sub>f</sub>: 0.83 in benzene + acetone (1:1); Yield 10%, m.p.>300°C, Found: C, 53.66; H, 4.38; N, 18.77. C<sub>13</sub>H<sub>10</sub>O<sub>2</sub>N<sub>4</sub>S required C, 54.54; H, 3.49; N, 19.58%.

**Synthesis of *N*-(4-methylpyrimidin-2-one-4-yl)-1,4-benzothiazine-2,3-dione 5.** In a round bottom flask (50 mL) fitted with a reflux condenser, compound 4 (0.02 g, 0.000069 mole) and 0.2 mL of 1*N* HCl in ethanol (5 mL) was refluxed on a steam-bath for 0.5 hr. The reaction mixture was then cooled, concentrated and the residue triturated with ice-cold water to get a crystalline product. R<sub>f</sub>: 0.5 in benzene + acetone (1:1); Yield 0.01 g, (50%), m.p. >300°C, Found: C, 57.78; H, 2.97; N, 15.57. C<sub>13</sub>H<sub>8</sub>O<sub>2</sub>N<sub>3</sub>S required C, 57.77; H, 2.96; N, 15.55%. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.80 (3H, s, N=C-CH<sub>3</sub>), 6.5-7.5 (4H,

m, Ar-H), 10.5 (1H, s, exchangeable with D<sub>2</sub>O, CONH).

**Synthesis of 3-chloro-2-methyl-1,4-benzothiazine 7.** In a round bottom flask (100 mL) fitted with a reflux condenser and a guard tube, a mixture of 6 (0.16 g, 0.0007 mole) and phosphorus oxychloride (4 mL) refluxed on an oil-bath at 130-40°C for 5 hr. The reaction mixture was then cooled and poured onto crushed ice with stirring. The separated solid was filtered, washed with water and crystallized from benzene. R<sub>f</sub>: 0.9 in benzene + acetone (1:3); Yield 0.12 g, (70%), m.p. >270°C, Found: C, 55.79; H, 4.76; N, 6.28. C<sub>9</sub>H<sub>8</sub>NSCl required C, 54.68; H, 4.05; N, 7.09%. IR (KBr): 1600 (C=N), 760 cm<sup>-1</sup> (C-Cl); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.32 (3H, d, CH<sub>3</sub>), 3.4-3.5 (1H, q, CH-CH<sub>3</sub>), 6.95-7.35 (4H, m, Ar-H).

**Synthesis of 2-methyl-1,4-benzothiazine-(1*H*)-3-yl-isocyanate 8.** In a round bottom flask (50 mL) fitted with a reflux condenser, a mixture of 7 (0.045 g, 0.00022 mole) and ammonium sulphocyanide (0.017 g, 0.00022 mole) in acetone (3 mL) was stirred under reflux for 2 hr. The reaction mixture was then cooled, and concentrated under vacuum. The solid obtained was washed with water and crystallized out from ethanol. R<sub>f</sub>: 0.06 in benzene + acetone (1:3); Yield 0.023 g, (48%), m.p. 178°C, Found: C, 53.73; H, 4.35; N, 13.63. C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>S<sub>2</sub> required C, 54.54; H, 3.64; N, 12.72%. IR (KBr): 2050 (-N=C=S), 1600 cm<sup>-1</sup> (C=N); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.3 (3H, d, CH<sub>3</sub>), 3.4 (1H, q, CH-CH<sub>3</sub>), 6.95-7.35 (4H, m, Ar-H).

**Synthesis of 2,6-dimethyl-2-thio-[1,3,5]triazino-[3,4-*c*]1,4-benzothiazine 9.** In a round bottom flask (50 mL) fitted with a reflux condenser and a guard tube, a mixture of 8 (0.066 g, 0.0003 mole) and methyl cyanide (0.02 g, 0.0005 mole) was refluxed on a steam-bath for 5 hr, cooled and concentrated under vacuum to get the reddish-brown product. R<sub>f</sub>: 0.41 in benzene + acetone (1:3); Yield 0.052 g, (66%); m.p. 133°C; Found: C, 54.76; H, 4.68; N, 15.98. C<sub>12</sub>H<sub>11</sub>N<sub>3</sub>S<sub>2</sub> required C, 55.17; H, 4.21; N, 16.09%. IR

Table II—Analytical data showing antibacterial activity and antifungal activity of selected test compounds in mm

Compd	Antibacterial activity				Antifungal Activity	
	<i>Salmonella paratyphi</i>	<i>Bacillus subtilis</i>	<i>Pseudomonas spp.</i>	S. Aureus	<i>Aspergillus Niger</i>	<i>Rhizopus</i>
<b>1</b>	14	19.00	15.00	14.20	12.20	8.60
<b>6</b>	13.00	14.00	13.00	13.00	0.00	2.00
<b>14</b>	13.80	14.30	13.08	14.00	10.00	2.00
<b>15c</b>	13.00	13.00	13.00	13.00	0.00	1.00
<b>15f</b>	13.10	13.00	13.00	13.00	0.00	0.00

(KBr): 1600 (C=N), 1190  $\text{cm}^{-1}$  (C=S);  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.2 (3H, d,  $\text{CH}_3$ ), 2.1 (3H, s, N=C- $\text{CH}_3$ ), 3.2 (1H, q,  $\text{CH-CH}_3$ ), 7-7.5 (4H, m, Ar-H).

**Synthesis of 1,4-benzothiazine-3(2H)-one 10.** In a round bottom flask (250 mL) fitted with a reflux condenser and a guard tube, a mixture of 2-aminothiophenol (3.51 g, 0.028 mole) and ethyl chloroacetate (3.43 g, 0.028 mole) in 33% NaOH (17.5 mL) was refluxed on a steam-bath for 5 hr. The reaction mixture was then cooled, filtered, the filtrate was neutralized with dilute HCl, and the precipitate separated out was washed with water and crystallized from 60% ethanol.  $R_f$ : 0.25 in pure benzene; Yield 2.49 g, (54%), m.p.175°C, Found: C, 57.83; H, 3.89; N, 9.27.  $\text{C}_8\text{H}_7\text{ONS}$  required C, 58.18; H, 4.28; N, 8.48%. IR (KBr): 3300-2900 (NH), 1660  $\text{cm}^{-1}$  (cyclic >C=O);  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  3.37 (2H, s, S- $\text{CH}_2$ ), 6.93-7.43 (4H, m, Ar-H), 10.07 (1H, s, NH exchangeable with  $\text{D}_2\text{O}$ ).

**Synthesis of *N*-ethoxycarbonylmethyl-1,4-benzothiazine-3(1H)-one 11.** In a round bottom flask (250 mL) fitted with a reflux condenser and a guard tube, the mixture of **10** (1.81 g, 0.011 mole) and ethyl chloroacetate (1.35 g, 0.011 mole) in acetone containing  $\text{K}_2\text{CO}_3$  (2.0 g) was refluxed on an oil-bath for 20 hr. The reaction mixture was cooled, filtered, the solvent removed at vacuum and the crude product extracted in chloroform, washed with water and was concentrated under vacuum to get reddish-yellow oil.  $R_f$ : 0.58 in pure benzene; Yield 1.187 g, (43%), Found: C, 56.78; H, 6.18; N, 6.38.  $\text{C}_{12}\text{H}_{13}\text{O}_3\text{NS}$  required: C, 57.37; H, 5.79; N, 5.57%. IR (KBr): 1740 (ester >C=O), 1690-1600  $\text{cm}^{-1}$  (cyclic amido >C=O).

**Synthesis of *N*-hydrazidomethyl-1,4-benzothiazine-3(1H)-one 12.** In a round bottom flask (100 mL) fitted with a reflux condenser and a guard tube, the mixture of **11** (1.0 g, 0.0039 mole) and hydrazine hydrate (80%) (0.2 g, 0.0039 mole) in methanol (5 mL) was heated on a steam-bath at 80°C for 4 hr. The reaction mixture was then cooled, poured onto a crushed ice, stirred, the precipitate filtered and the solid crystallized from ethanol.  $R_f$ : 0.57 in pure benzene; Yield 0.231 g, (25%), Found: C, 51.24; H, 3.85; N, 18.37.  $\text{C}_{10}\text{H}_{11}\text{O}_2\text{N}_3\text{S}$  required: C, 50.63; H, 4.64; N, 17.72 %. IR (KBr): 3350-3100 (-NHNH<sub>2</sub>), 1690 (acyclic amido >C=O), 1630  $\text{cm}^{-1}$  (cyclic >C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ , 3.46 (2H, s, S- $\text{CH}_2$ ), 3.89 (2H, brs, NH<sub>2</sub> exchangeable with  $\text{D}_2\text{O}$ ), 4.56 (2H, s, N- $\text{CH}_2$ ), 7.0-7.39 (4H, m, Ar-H), 7.58 (1H, s, NH exchangeable with  $\text{D}_2\text{O}$ ).

**Synthesis of [1,2,4]-triazino-2-oxo[3,4-*c*]-1,4-benzothiazine 13.** In a round bottom flask (50 mL) fitted with a reflux condenser, a mixture of **12** (0.06 g, 0.00025 mole) and ammonium acetate (0.02 g, 0.00025 mole) in acetic acid (5 mL) was heated on an oil-bath till yellow colour of the reaction mixture changes to dark brown. The reaction mixture was then cooled, poured onto crushed ice, neutralized with 25% ammonia, the precipitate was filtered and the solid was crystallized from ethanol. Yield: 0.04 g, (54%), m.p.163°C, Found: C, 55.28; H, 3.02; N, 18.68.  $\text{C}_{10}\text{H}_9\text{ON}_3\text{S}$  required: C, 54.79; H, 4.11; N, 19.17%. IR (KBr): 3350-3100 (-NHNH<sub>2</sub>), 1690 (acyclic amido >C=O), 1630  $\text{cm}^{-1}$  (cyclic >C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  3.46 (2H, s, S- $\text{CH}_2$ ), 3.89 (2H, brs, NH<sub>2</sub> exchangeable with  $\text{D}_2\text{O}$ ), 4.56 (2H, s, N- $\text{CH}_2$ ), 7.0-7.39 (4H, m, Ar-H), 7.58 (1H, s, NH exchangeable with  $\text{D}_2\text{O}$ ).

**Synthesis of 3-hydrazino-1H-1,4-benzothiazine 14.** In a round bottom flask (100 mL) fitted with a reflux condenser, a mixture of **10** (0.683 g, 0.0041 mole) and hydrazine hydrate (80%) (0.207 g, 0.0041 mole) in methanol (20 mL) was heated on a steam-bath for 2 hr. The reaction mixture was then concentrated and cooled to get the crystalline product.  $R_f$ : 0.36 in pure benzene; Yield 0.32 g, (84%), m.p.180°C, Found: C, 61.24; H, 4.93; N, 22.67.  $\text{C}_9\text{H}_9\text{N}_3\text{S}$  required: C, 60.33; H, 5.02; N, 23.46%. IR (KBr): 3311-2912 (-NHNH<sub>2</sub>), 1665  $\text{cm}^{-1}$  (C=N); MS (EIMS): m/z 179, 164, 150, 136, 120, 109 and 96.

**Synthesis of 3-[2-Hydryxy-3-methoxybenzilidene-hydrazino]-1H-1,4-benzothiazazine 15a-i.** In a round bottom flask (50 mL) fitted with a reflux condenser, a mixture of **14** (0.1 g, 0.00055 mole) and substituted aldehyde or ketone (0.00055 mole) in the presence of acetic acid (2-3 mL) was dissolved in ethanol (3 mL) and refluxed on a steam-bath for 4 hr. The reaction mixture was then concentrated and cooled to get the crystalline product. **15a**:  $R_f$ : 0.19 in benzene; Yield 0.117 g, (68%), m.p.165°C, IR (KBr): 3320-3000 (NH and -OH), 1675 (HC=N), 1600  $\text{cm}^{-1}$ ; **15b**:  $R_f$ : 0.21 in benzene; Yield 0.9 g, (66%), m.p.180°C, IR (KBr): 3350-3100 (NH), 1740-1640 (HC=N), 1570  $\text{cm}^{-1}$  (C=N). **15c**:  $R_f$ : 0.18 in benzene, yield 0.055 g, (56%), m.p.158°C, IR (KBr): 3350-3150 (NH), 1730-1610 (HC=N), 1590  $\text{cm}^{-1}$  (C=N). **15d**:  $R_f$ : 0.29 in benzene; Yield 0.025 g, (51%), m.p.170°C, IR (KBr): 3300-3100 (NH), 1740-1640 (HC=N), 1570  $\text{cm}^{-1}$  (C=N). **15e**:  $R_f$ : 0.12 in benzene; Yield 0.08 g, (54%), m.p.158°C, IR (KBr): 3250-3150 (NH), 1680 (HC=N), 1600  $\text{cm}^{-1}$  (C=N). **15f**:  $R_f$ : 0.18 in benzene;

Yield 0.065 g, (81%), m.p.188°C, IR (KBr): 3250-3150 (NH), 1680 (HC=N), 1600 cm<sup>-1</sup> (C=N). **15g**: R<sub>f</sub>: 0.2 in benzene; Yield 0.04 g, (46%), m.p.174°C, IR (KBr): 3340-3150 (NH), 1670 (HC=N), 1580 cm<sup>-1</sup> (C=N). **15h**: R<sub>f</sub>: 0.19 in benzene; Yield 0.045 g, (27%), m.p.178°C, IR (KBr): 3300-3140 (NH), 1675 (HC=N), 1590 cm<sup>-1</sup> (C=N). **15i**: R<sub>f</sub>: 0.15 in benzene; Yield 0.098 g, (62%), m.p.175°C, IR(KBr): 3350-3140 (NH), 1670 (HC=N), 1600 cm<sup>-1</sup> (C=N) (**Table I**).

**Synthesis of 5-arylidene-(1*H*)-1,2,4-triazolo[3,4-c]benzothiazine 16a-b.** In a round bottom flask (50 mL) fitted with a reflux condenser and a guard tube, a mixture of **15** (0.00055 mole) and thallium acetate (0.00055 mole) were dissolved in acetic acid and refluxed on an oil-bath for about 8 hr. The reaction mixture was then cooled, neutralized by 25% ammonia and filtered to get the product. **16a**: R= 3-(OCH<sub>3</sub>)-C<sub>6</sub>H<sub>4</sub>; R<sub>f</sub>: 0.08 in pure benzene; Yield (35-52%), m.p.208°C, Found: C, 67.24; H, 3.96; N, 12.87. C<sub>17</sub>H<sub>15</sub>ON<sub>3</sub>S required: C, 66.45; H, 4.88; N, 13.68%. IR (KBr): 1725-1650 (C=N), 1590 cm<sup>-1</sup> (C=C); <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.2 (2H, s, S-CH<sub>2</sub>), 3.77 (3H, s, OCH<sub>3</sub>), 7-7.8 (8H, m, Ar-H).

**16b**: R=2-OH, 3-OCH<sub>3</sub> C<sub>6</sub>H<sub>3</sub>; R<sub>f</sub>: 0.08 in benzene, m.p. 217°C, IR (KBr): 1680-1640 (C=N), 1550 cm<sup>-1</sup> (C=C); <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.21 (2H, s, S-CH<sub>2</sub>), 3.8 (3H, s, OCH<sub>3</sub>), 7.1-7.8 (7H, m, Ar-H), 10.5 (1H, s, NH exchangeable with D<sub>2</sub>O).

**Synthesis of 3-chloro-(1*H*)-1,4-benzothiazine 17.** In a round bottom flask fitted with a reflux condenser, a mixture of **10** (0.25 g, 0.0014 mole) and POCl<sub>3</sub> (4 mL) was refluxed on oil-bath at 130-40°C for 5 hr, then cooled and poured on crushed ice. The separated solid was recrystallised from benzene. R<sub>f</sub>: 0.08 in benzene+acetone (1:3); Yield: 0.22 g (70%), m.p. >270°C, Found: C, 53.47; H, 4.01; N, 7.02. C<sub>8</sub>H<sub>6</sub>NSCl required: C, 52.31; H, 3.28; N, 7.26%. IR (KBr): 1600 (C=N), 760 cm<sup>-1</sup> (C-Cl); <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.37 (2H, s, S-CH<sub>2</sub>), 7.1-7.5 (4H, m, Ar H)s.

**Synthesis of 1,4-benzothiazine-(1*H*)-3-yl-isocyanate 18.** A mixture of **17** (0.145 g, 0.00079 mole) and ammonium sulphocyanide (0.06 g, 0.00079 mole) in acetone (3 mL) was refluxed with stirring for 2 hr, then cooled and filtered. The product was crystallized from ethanol. R<sub>f</sub>: 0.065 in benzene+ acetone (1:3); Yield 0.083 g (51%), m.p. 138°C, Found: C, 53.22; H, 2.91; N, 13.03. C<sub>9</sub>H<sub>6</sub>N<sub>2</sub>S<sub>2</sub> required: C, 52.42; H, 2.91; N, 13.59%. IR (KBr): 1620 (C=N), 1600 (C=C), 2050 cm<sup>-1</sup> (C=S); <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.1-7.55 (4 H, m, Ar H).

**Synthesis of 2-thio-6-methyl[1,3,5]triazino[3,4-c]benzothiazine 19.** To a solution of **18** (0.06 g, 0.00029 mole) in ethanol (5 mL) and methyl cyanide (0.012 g, 0.00029 mole) was added and mixture refluxed on steam-bath for 5 hr, then cooled, concentrated under vacuum to get reddish brown product. R<sub>f</sub>: 0.4 in benzene + acetone (1:3); Yield 0.05 g (70%), m.p. 117°C, Found: C, 52.13; H, 3.28; N, 15.03. C<sub>11</sub>H<sub>9</sub>N<sub>3</sub>S<sub>2</sub> required: C, 53.44; H, 3.64; N, 17.00%. IR (KBr): 1190 (C=S), 1600 cm<sup>-1</sup> (C=N); <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.18 (3H, s, =C-CH<sub>3</sub>), 7.0-7.6 (4H, m, ArH).

**Synthesis of N-(2-propanonyl)-1,4-benzothiazine-3(1*H*)-one, 20.** A mixture of compound **10** (0.05 mole), chloroacetone (0.13 mole) and K<sub>2</sub>CO<sub>3</sub> was refluxed on oil-bath for 24 hr, then cooled, filtered and crystallized from methanol. Yield (70%), m.p. 142°C, IR (KBr): 1680 (C=O), 1720 cm<sup>-1</sup> (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.12 (3H, s, CH<sub>3</sub>), 3.9 (2H, s, N-CH<sub>2</sub>), 7.2-8.25 (4H, m, Ar-H).

**Synthesis of cyclopenteno-1,4-benzothiazine, 21.** A mixture of **20** (0.08 g, 0.0004 mole) and sodium methoxide (0.008 g, 0.0004 mole) in methanol was refluxed on oil-bath for 4 hr. The separated solid was filtered and recrystallised from ethanol. Yield 0.02 g, (40%), m.p. 305°C, Found: C, 64.83; H, 4.37; N, 7.08. C<sub>11</sub>H<sub>9</sub>N<sub>3</sub>S<sub>2</sub> required: C, 65.02; H, 3.91; N, 6.89%. IR (KBr): 1640 cm<sup>-1</sup> (conjugated C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.37 (2H, s, S-CH<sub>2</sub>), 3.8 (2H, s, N-CH<sub>2</sub>), 6.7-8.25 (5H, m, Ar-H and CH)

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