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Nasser R. El-Brollosy<sup>a</sup>

<sup>a</sup> Chemistry Department, Faculty of Science, Tanta University, Tanta, Egypt Published online: 04 Oct 2006.

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### SYNTHESIS AND REACTIONS OF SOME NEW 1,2,4-TRIAZINE DERIVATIVES OF BIOLOGICAL INTEREST

#### NASSER R. EL-BROLLOSY\*

Chemistry Department, Faculty of Science, Tanta University, Tanta, Egypt

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4-Amino-3-mercapto-6-methyl-1,2,4-triazin-5(4H)-one (1) and its 5-thioxo derivative 4 were reacted with phenacyl halides at different reaction conditions to yield the S-phenacyl derivatives **2a,b**, **5** as well as the corresponding triazino[3,4-b][1,3,4]thiadiazines **3a,b**, **6**. Treatment of 1 with acrylonitrile gave 4-amino-3-(2-cyanoethyl)thio-6-methyl-1,2,4-triazin-5(4H)-one (7), which was condensed with various aldehydes to afford the corresponding anils **10a-c**. Acid hydrolysis of **10b** gave the corresponding acid **11**, whereas **7** yielded 4-amino-3-hydroxy-6-methyl-5(4H)-oxo-1,2,4-triazine hydrochloride (**12**) under the same condition. Some new compounds exhibited antibacterial and antifungal activities.

*Keywords: as*-triazines; thiation; hydrolysis; triazino[3,4-b][1,3,4]thiadiazines; antibacterial activity; antifungal activity

#### INTRODUCTION

In recent years, there has been increasing interest in the synthesis of heterocyclic compounds containing a 1,2,4-triazine ring because of their biological significance. Several 1,2,4-triazines have been demonstrated to be of herbicidal, antihypertensive, and antiviral activity<sup>1-12</sup> as well as activity against *Staphylococcus aureus, Bacillus cereus* and P388 Lymphocytic leukemia<sup>6,8</sup>. Moreover, 1,2,4-triazines are regarded as 6-aza analogues of pyrimidine bases, needless to say that pyrimidines, in general, have a great biological importance<sup>9</sup>. Encouraged by the above-mentioned findings, we found it is interesting to investigate the synthesis and the antibacterial as well as antifungal activities of some new 1,2,4-triazine derivatives.

<sup>\*</sup> Corresponding Author.

#### **RESULTS AND DISCUSSION**

4-Amino-3-mercapto-6-methyl-1,2,4-triazin-5(4H)-one (1) was prepared by the reaction of thiocarbohydrazide with pyruvic acid according to the method of Dornow et al.<sup>13</sup>. Treatment of 1 with 4-fluolophenacyl chloride and/or 4-bromophenacyl bromide in methanol at room temperature in the presence of N,N-dimethylethylamine (DMEA) afforded high yields of the corresponding phenacylthic derivatives 2a,b which were cyclized to 8H-7-aryl-3-methyl-as-triazino[3,4-b][1,3,4]thiadiazin-4-ones (3a,b) by heating in methanol for one hour. Compounds 3a,b were also obtained via the reaction of **1** with phenacyl halides in boiling methanol<sup>14</sup>. Thiation of compound 1 with phosphorus pentasulfide in boiling anhydrous pyridine afforded 4-amino- 3-mercapto-6-methyl-1,2,4-triazine-5(4H)-thione (4), in 63 % yield. Treatment of compound 4 with 4-bromophenacyl bromide in boiling methanol vielded a separable mixture of 4-amino-3-(4-bromophenacyl)thio-6-methyl-1,2,4-triazine-5(4H)-thione (5) and 8H-7-(4-bromophenyl)-3-methyl-as-triazino[3,4-b][1,3,4]thiadiazine-4-thione (6) in 65 % total yield, which on further heating for 2 hrs., gave 6 as a sole product in 60 % yield. Compounds 5 and 6 were separated from the mixture by treatment with boiling dilute acetic acid that dissolved 5. Compound 6 was obtained by another pathway when 3b was treated with phosphorus pentasufide in boiling anhydrous pyridine (Scheme 1).

Isolation of the phenacylthio derivatives 2a,b and 5, at different reaction conditions, suggests a mechanism for formation of the triazino[3,4-*b*][1,3,4]thiadiazines **3a,b** and **6**. In such mechanism, a nucleophilic attack of the phenacyl halides occurs by the mercapto group to give the *S*-alkylated products **2a,b** and **5**; and then an internal nucleophilic attack by the NH<sub>2</sub> group on the CO takes place with a loss of a H<sub>2</sub>O molecule to afford the final products **3** and **6** (Scheme 2).

Compound 1 was treated with acrylonitrile in boiling methanol in the presence of *DMEA* to give 4-amino-3-(2-cyanoe-thyl)thio-6-methyl-1,2,4-triazin-5(4*H*)-one (7), in 96 % yield, rather than the expected *N*-derivative 8 (as reported for similar triazines)<sup>15</sup>. Addition reaction of 1 on acrylonitrile through the mercapto group forming the cyanoethylthio derivative 7 was clearly confirmed by "Distortionless Enhancement by Polarization Transfer" (DEPT) spectrum which shows two negative-signed signals at 15.60 and 52.76 ppm corresponding to SCH<sub>2</sub> and <u>C</u>H<sub>2</sub>CN, respectively (Figure 1). Also, the structure of 7 was



SCHEME 1



**SCHEME 2** 

confirmed by its mass spectrum which shows a fragment at m/e = 86 (21) %) corresponding to NCCH<sub>2</sub>CH<sub>2</sub>S<sup>+</sup>. Compound 7 was condensed with benzaldehyde, 2,6-dichlorobenzaldehyde and cinnamaldehyde in methanol to afford the corresponding arylideneamino derivatives 10a-c in 72 -84 % yields. Condensation of compound 1 with vanillin, crotonaldehyde and 4-aminoacetophenone gave the corresponding anils **9a-c** in 60 - 82 %yields. In case of the condensation reaction with crotonaldehyde or cinnamaldehyde, an unseparable mixture of Z/E isomers was obtained in 1:4  $^{13}C$ (according NMR). 4-(2,6-Dichlorobenzyliratio to dene)amino-3-(2-cyanoethyl)thio-6-methyl-1,2,4-triazin-5(4H)-one (10b) was, also, obtained in 73 % yield when 9 (Ar =  $2,6-Cl_2C_6H_4$ -)<sup>16</sup> was treated with acrylonitrile in boiling methanol in the presence of DMEA. Acid hydrolysis of 10b afforded the corresponding acid 11 in 51 % yield, while compound 7, under the same reaction conditions, gave 4-amino-3-hydroxy-1,2,4-triazin-5(4H)-one as a hydrochloride salt (12) in 38 % yield (Scheme 3).



The structures of the newly synthesized compounds were confirmed by analytical data, IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and mass spectra. Assignments of

signals are based on DEPT and expected chemical shifts values. IR spectra of **4** and **6** showed the absence of CO band (1730 cm<sup>-1</sup>), while spectra of **7** and **10a-c** showed CN band at 2249 – 2243 cm<sup>-1</sup>, which was not observed in the spectrum of **11**. <sup>1</sup>H NMR spectra of **3a,b, 6, 9a-c** and **10a-c** showed the absence of NH<sub>2</sub> ( $\delta$  6.03 – 6.88), whereas the spectrum of **11** showed the carboxylic proton at  $\delta$  10.36. <sup>13</sup>C NMR spectra of **7** and **10a-c** showed the signal corresponding to CH<sub>2</sub>adjacent to S-atom in the high field region (15.50 – 15.60 ppm), while <u>CH<sub>2</sub>CN</u> and CN appeared at 52.22 – 52.76 and 117.98 – 118.29 ppm, respectively.



FIGURE 1 DEPT spectrum of compound 7

#### **BIOLOGICAL RESULTS**

The standardized disc method<sup>17</sup> was adopted for testing the antimicrobial activity of the compounds **2a**, **3a**, **4**, **5**, **7**, **9a**, **10b**, and **11**. Filter paper discs were moistened with the tested compound solution in dimethylsulphoxide of specific concentration 1 mg/disc and carefully placed on an agar culture plates that have been previously inoculated separately with the microorganisms; Aspergillus niger, Aspergillus flavus, Aspergillus fumigatus, Penicillium notatum, Candida albicans and Staphyllococuss aureus. After incubation, the diameter of the growth inhibition around the disc was measured. Compounds **2a**, **4**, **5** and **11** were found to be active

against A. fumigatus, C. albicans and S. aureus; compounds 2a, 4 and 11 showed activity against P. notatum; compounds 4 and 5 showed activity against A. niger while no compounds was found to be possess marked activity against A. flavus (table I).

No.	A. niger	A. flavus	A. fumigatus	P. notatum	C. albicans	S. aureus
2a	-	-	11	б	17	5
<b>3a</b>	-	-	-		-	-
4	12	-	17	13	15	26
5	19	-	12	-	21	7
7	-	-	-	-	-	-
9a	-	-	-	-	-	-
10b	-	-	-	-	-	-
11	-	-	9	5	12	4

TABLE I Diameters of the inhibition zones (mm) exhibited by the tested compounds

#### **EXPERIMENTAL**

Melting points (uncorrected) were determined using a Gallenkamp apparatus. IR spectra were recorded on a Unicam SP 1200 spectrophotometer using KBr discs ( $\nu$  in cm<sup>-1</sup>). NMR spectra were recorded on a Brucker AC spectrometer – operating at 400 MHz for <sup>1</sup>H and 100 MHz for <sup>13</sup>C measurements – using *DMSO-d*<sub>6</sub>as a solvent and *TMS* as an internal standard (Chemical shifts in  $\delta$ , ppm). Mass spectra were recorded on Quattro II Triple quadrupole mass spectrometer, electron impact (EI) at 70 eV and chemical ionization (CI) using ammonia as ionization gas. Analytical data (C, H, N) were within ± 0.4% of the theoritical values.

#### 4-Amino-3-aroylmethylthio-6-methyl -1,2,4-triazin-5(4H)-ones (2a,b)

A solution of compound 1 (1.58 g, 0.01 mol) in methanol (20 ml) and *DMEA* (5 ml) was treated with 4-Fluorophenacyl chloride and/or 4-bromophenacyl bromide (0.01 mol). The reaction mixture was stirred at

room temperature for 45 min. The precipitated solids were filtered, washed with  $H_2O$  and crystallized from methanol.

#### Compound 2a

Yield, 2.3 g (78 %); m.p., 191 – 192°C. <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 2.25 (s, 3H, CH<sub>3</sub>), 4.72 (s, 2H, CH<sub>2</sub>), 6.04 (s, 2H, NH<sub>2</sub>), 7.36 (m, 2H, 2'-H, 6'-H), 8.12 (2 × d, 2H, J = 5.7 Hz, J<sub>EH</sub> = 8.2 Hz, 3'-H, 5'-H).

<sup>13</sup>C NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 17.06 (CH<sub>3</sub>), 38.44 (CH<sub>2</sub>), 115.36 (d, *J* = 21.7 Hz, C-3', C-5'), 131.32 (d, *J* = 9.5 Hz, C-2', C-6'), 132.76 (C-1'), 152.65 (C-6), 153.98 (C-3), 160.56 (CO), 163.97 (d, *J* = 172 Hz, C-4'), 191.87 (CO).

EI MS, m/z (%) = 294 (M<sup>+</sup>, 18), 276 (98), 261 (100) and 248 (30).

#### Compound 2b

Yield, 2.87 g (81 %); m.p., > 300 (dec.) <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 2.25 (s, 3H, CH<sub>3</sub>), 4.70 (s, 2H, CH<sub>2</sub>), 6.03 (s, 2H, NH<sub>2</sub>), 7.75, 7.97 (2 × d, *J* = 7.5 Hz, H<sub>arom</sub>.)

<sup>13</sup>C NMR ([D<sub>6</sub>]DMSO):  $\delta = 17.06$  (CH<sub>3</sub>), 38.40 (CH<sub>2</sub>), 127.65, 130.32, 131.85, 135.07 (C<sub>arom</sub>.), 152.64 (C-6), 153.99 (C-3), 160.51 (CO), 192.61 (CO). CI MS, m/z (%) = 355 (MH<sup>+</sup>, 91) and 357 (MH<sup>+</sup> + 2, 89), for <sup>79</sup>Br and <sup>81</sup>Br, respectively.

#### 8H-7-aryl-3-methyl-as-triazino[3,4-b][1,3,4]thiadiazin-4-ones (3a,b)

#### Method A

Compound 2 (0.005 mol) was heated under reflux in methanol (15 ml) for 1 h. On cooling, the precipitate was filtered, dried and crystallized from ethanol.

#### Compound 3a

Yield, 1.3 g (94 %); m.p., > 300 (dec.) <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 2.36 (s, 3H, CH<sub>3</sub>), 4.34 (s, 2H, CH<sub>2</sub>), 7.43 (m, 2H, 2'-H, 6'-H), 8.08 (2 × d, 2H, J = 5.4 Hz,  $J_{EH}$  = 9.0 Hz, 3'-H, 5'-H).

<sup>13</sup>C NMR ([D<sub>6</sub>]DMSO):  $\delta = 17.71$  (CH<sub>2</sub>), 21.89 (CH<sub>3</sub>), 116.20 (d, J = 21.7 Hz, C-3', C-5'), 129.59 (C-1'), 130.48 (d, J = 9.2 Hz, C-2', C-6'), 149.37 (C-3), 150.74 (C-10), 157.19 (C-7), 158.19 (CO), 164.20 (d,

J = 161.4 Hz, C-4'). EI MS, m/z (%) = 276 (M<sup>+</sup>, 96), 248(40), 121(100) and 101(61).

#### Compound 3b

Yield, 1.55 g (92 %); m.p., 217–218°C, lit.<sup>14</sup>, m.p., 217°C.

#### Method B

A mixture of compound 1 (1.58 g, 0.01 mol) and 4-fluorophenacyl chloride (1.73 g, 0.01 mol) was heated under reflux in methanol (20 ml) for 1 h. After cooling to room temperature, the precipitate was filtered, dried and crystallized from ethanol to afford **3a** in 76 % yield ((2.1 g).

#### 4-Amino-3-mercapto-6-methyl-1,2,4-triazine-5(4H)-thione (4)

A mixture of 1 (1.58 g, 0.01 mol) and  $P_4S_{10}(2.22 \text{ g}, 0.005 \text{ mol})$  was heated under reflux in anhydrous pyridine (20 ml) for 1.5 h. The reaction mixture was cooled to room temperature and poured onto crushed ice. The precipitate thus formed was filtered, washed with cold water, dried and crystallized from methanol to afford 4 in 63 % yield (1.1 g); m.p., 143–144°C.

<sup>1</sup>H NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 2.37 (s, 3H, CH<sub>3</sub>), 7.55(s, 2H, NH<sub>2</sub>), 14.42 (s, 1H, SH).

<sup>13</sup>C NMR ([D<sub>6</sub>]DMSO): δ = 21.54 (CH<sub>3</sub>), 150.44(C-6), 163.00 (C-3), 167.11 (C-5).

EI MS, m/z (%) = 174 (M<sup>+</sup>, 98), 158 (11), 144(6), 101(12) and 74(66).

#### 4-Amino-3-(4-bromophenacyl)thio-6-methyl-1,2,4-triazine-5(4*H*)thione (5) and 8*H*-7-(4-bromophenacyl)-3-methyl-*as*-triazino[3,4-*b*] [1,3,4]thiadiazine-4-thione (6)

A mixture of compound 4 (1.74 g, 0.01 mol) and 4-bromophenacyl bromide (2.77 g, 0.01 mol) was heated under reflux in methanol (25 ml) for 1 h. The reaction mixture was cooled to room temperature and the precipitated solid was filtered. The solid was treated with boiling dilute acetic acid (30 ml) and filtered hot. The filtrate was evaporated till dryness *in vacuo* and the product was crystallized from methanol to afford 5 in 44 % (1.63 g) yield, while the residue was crystallized from methanol to give 6 in 21 % (0.74 g) yield,. On further heating of the reaction mixture for 2 h, compound **6** was precipitated as a sole product in 60 % yield (2.12 g).

#### **Compound 5**

m.p., 191 - 192°C.

<sup>1</sup>H NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 2.57 (s, 3H, CH<sub>3</sub>), 4.83 (s, 2H, CH<sub>2</sub>), 6.88 (s, 2H, NH<sub>2</sub>), 7.73, 7.88 (2 × d, 4H, *J* = 8.6 Hz, H<sub>arom</sub>.). CI MS, m/z (%) = 371 (MH<sup>+</sup>, 18).

#### Compound 6

m.p., 213 – 214°C.

<sup>1</sup>H NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 2.47 (s, 3H, CH<sub>3</sub>), 4.38 (s, 2H, CH<sub>2</sub>), 7.78, 7.99 (2 × d, 4H, *J* = 8.6 Hz, H<sub>arom</sub>.).

# Thiation of 8*H*-7-(4-bromophenyl)-3-methyl-*as*-triazino[3,4-*b*][1,3,4] thiadiazin-4-one (3b)

A mixture of compound **3b** (1.68 g, 0.005 mol) and  $P_4S_{10}$  (1.11 g, 0.0025 mol) was heated under reflux in anhydrous pyridine (15 ml) for 1.5 h. The reaction mixture was cooled to room temperature and poured onto crushed ice. The precipitate was filtered, washed with cold water, dried and crystallized from methanol to give **6** in 54 % (0.95 g) yield.

#### 4-Amino-3-(2-cyanoethyl)thio-6-methyl-1,2,4-triazin-5(4H)-one (7)

Acrylonitrile (0.72 ml, 0.011 mol) was added to a solution of compound 1 (1.58 g, 0.01 mol) in methanol (20 ml) and *N*,*N*-dimethylethylamine (*DMEA*) (5 ml). The reaction mixture was heated under reflux for 3 h. and then cooled to room temperature. The product was filtered and crystallized from methanol. Yield, 2.02 g (96 %); m.p., 150°C.

IR (KBr):  $v = 2243 \text{ cm}^{-1}$  (CN)

<sup>1</sup>H NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 2.24 (s, 3H, CH<sub>3</sub>), 3.05 (t, 2H, *J* = 6.5 Hz, CH<sub>2</sub>), 4.61 (t, 2H, *J* = 6.5 Hz, CH<sub>2</sub>), 6.62 (s, 2H, NH<sub>2</sub>).

<sup>13</sup>C NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 15.60 (CH<sub>2</sub>), 15.78 (CH<sub>3</sub>), 52,76 (CH<sub>2</sub>), 118.17 (CN), 144.96 (C-6), 147.77 (C-3), 168.00 (CO).

EI MS, m/z (%) = 211 (M<sup>+</sup>, 36), 195 (100), 130 (28), 108 (14) and 102 (38).

#### 4-Arylideneamino-3-mercapto-6-methyl-1,2,4-triazin-5(4*H*)ones (9a,b)

Vanillin and/or crotonaldehyde (0.01 mol) was added to a suspension of compound 1 (1.58 g, 0.01 mol) in methanol (20 ml). The reaction mixture was heated under reflux for 1 h. On cooling to room temperature, the precipitated solid was filtered, dried and crystallized from the appropriate solvent.

#### Compound 9a

Yield, 2.4 g (82 %); m.p., 201°C (MeOH).

<sup>1</sup>H NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 2.18 (s, 3H, CH<sub>3</sub>), 3.84 (s, 3H, OCH<sub>3</sub>), 6.93 – 7.48 (m, 3H, H<sub>arom</sub>.), 8.41 (s, 1H, OH), 10.10 (s, 1H, CH), 13.65 (s, 1H, SH).

<sup>13</sup>C NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 16.88 (CH<sub>3</sub>), 55.65 (OCH<sub>3</sub>), 110.49, 115.62, 123.13, 124.92, 150.08, 151.76 (C<sub>arom</sub>.), 147.14 (C-6), 148.12 (C-3), 170.84 (CO), 172.48 (CH).

EI MS, m/z (%) = 292 (M<sup>+</sup>, 100), 150 (52), 149 (98), 143 (79), 134 (91), and 106 (87).

#### Compound 9b

Yield, 1.43 g (68 %); m.p.,  $170 - 172^{\circ}$ C (dioxane). <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO): (*predominant isomer*),  $\delta = 1.98$  (d, 3H, J = 5.5 Hz, CH<sub>3</sub>), 2.17 (s, 3H, CH<sub>3</sub>), 6.51 (m, 1H, CH), 6.63 (m, 1H, CH), 8.08 (d, 1H, J = 9.5 Hz, CH), 13.66 (s, 1H, SH).

<sup>13</sup>C NMR ([D<sub>6</sub>]DMSO): (predominant isomer),  $\delta$  = 16.82 (CH<sub>3</sub>), 18.83 (CH<sub>3</sub>), 127.26 (CH), 147.10 (C-6), 148.68 (CH), 149.78 (C-3), 170.60 (CO), 174.42 (CH).

EI MS, m/z (%) = 210 (M<sup>+</sup>, 34), 195 (2), 169 (4) and 143 (28).

#### 4-[1-(4-aminophenyl)ethylidene]amino-3-mercapto-6-methyl-1,2,4triazin-5(4*H*)-one (9c)

A mixture of compound 1 (1.58 g, 0.01 mol), 4-aminoacetophenone (1.35 g, 0.01 mol) and piperidine (3 ml) was heated under reflux in methanol (20 ml) for 3 h. The reaction mixture was cooled to room temperature and the precipitate was filtered. Crystallization from methanol afforded **9c** in 60 % (1.65 g) yield; m.p., > 300°C.

<sup>1</sup>H NMR ([D<sub>6</sub>]DMSO):  $\delta = 2.18$  (s, 3H, CH<sub>3</sub>), 3.22 (s, 3H, CH<sub>3</sub>), 6.53 (s, 2H, NH<sub>2</sub>), 8.26 (m, 4H, H<sub>arom</sub>.).

#### 4-Arylideneamino-3-(2-cyanoethyl)thio-6-methyl-1,2,4-triazin-5(4H)ones (10a-c)

#### Method A

A mixture of compound 7 (1.05 g, 0.005 mol) and the appropriate aldehyde (0.005 mol) in methanol (15 ml) was heated under reflux for 2 h. On cooling, the precipitated solid was filtered, washed with methanol, dried and crystallized.

#### Compound 10a

Yield, 74 % (1.11 g); m.p., 138 (MeOH).

IR (KBr):  $v = 2245 \text{ cm}^{-1}$  (CN).

<sup>1</sup>H NMR ([D<sub>6</sub>]DMSO):  $\delta$ ,= 2.26 (s, 3H, CH<sub>3</sub>), 3.08 (t, 2H, *J* = 6.5 Hz, CH<sub>2</sub>), 4.65 (t, 2H, *J* = 6.5 Hz, CH<sub>2</sub>), 7.66 – 7.94 (m, 5H, H<sub>arom</sub>.), 8.62 (s, 1H, CH). <sup>13</sup>C NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 15.54 (CH<sub>2</sub>), 17.03 (CH<sub>3</sub>), 52.26 (CH<sub>2</sub>), 118.29 (CN), 128.99, 129.27, 131.73, 133.30 (C<sub>arom</sub>.), 147.24 (C-6), 148.91 (C-3), 169.70 (CO), 173.06 (CH).

EI MS, m/z (%) = 299 (M<sup>+</sup>, 94), 222 (46), 217 (43), 195 (91) and 122 (100).

#### Compound 10b

Yield, 84 % (1.55 g); m.p. 181°C (AcOH).

IR, (KBr):  $v = 2249 \text{ cm}^{-1}$  (CN).

<sup>1</sup>H NMR ([D<sub>6</sub>]DMSO):  $\delta = 2.27$  (s, 3H, CH<sub>3</sub>), 3.07 (t, 2H, J = 6.5 Hz, CH<sub>2</sub>), 4.64 (t, 2H, J = 6.5 Hz, CH<sub>2</sub>), 7.59 – 7.66 (m, 3H, H<sub>arom</sub>.), 8.89 (s, 1H, CH).

<sup>13</sup>C NMR ([D<sub>6</sub>]DMSO): δ = 15.50 (CH<sub>2</sub>), 17.05 (CH<sub>3</sub>), 52.22 (CH<sub>2</sub>), 118.20 (CN), 127.98, 129.70, 133.47, 134.96 (C<sub>arom</sub>.), 147.42 (C-6), 148.52 (C-3), 169.55 (CO), 169.65 (CH).

EI MS, m/z (%) = 372 (M<sup>+</sup> + 4, 8), 370 (M<sup>+</sup> + 2, 32), 368 (M<sup>+</sup>, 44), 197 (85), 191 (76) and 189 (100).

#### Compound 10c

Yield, 72 % (1.17 g); m.p., 111 – 113°C (MeOH).

IR (KBr):  $v = 2246 \text{ cm}^{-1}$  (CN).

<sup>1</sup>H NMR ([D<sub>6</sub>]DMSO): (predominant isomer),  $\delta = 2.26$  (s, 3H, CH<sub>3</sub>), 3.05 (t, 2H, J = 6.5 Hz, CH<sub>2</sub>), 4.63 (t, 2H, J = 6.5 Hz, CH<sub>2</sub>), 6.61 (m, 1H, CH), 7.31 (d, 1H, J = 8.9 Hz, CH), 7.38 – 7.73 (m, 5H, H<sub>arom</sub>.), 8.25 (d, 1H, J = 9.0 Hz, CH). <sup>13</sup>C NMR ([D<sub>6</sub>]DMSO): (predominant isomer),  $\delta = 15.56$  (CH<sub>2</sub>), 17.00 (CH<sub>3</sub>), 52.33 (CH<sub>2</sub>), 117.98 (CN), 123.14 (CH), 128.16, 128.93, 130.36, 134.79 (C<sub>arom</sub>.), 147.07 (C-6), 147.74 (CH), 148.86 (C-3), 169.96 (CO), 174.42 (CH).

CI MS, m/z (%) = 326 (MH<sup>+</sup>, 6), 229 (4), 214 (10) and 132 (100).

#### Method B

A mixture of compound 9 (R = H, Ar =  $2,6-Cl_2C_6H_3$ )<sup>16</sup> (1.57 g, 0.005 mol), acrylonitrile (0.4 ml, 0.006 mol) and *DMEA* (5 ml) was heated under reflux in methanol for 3 h. The reaction mixture was cooled to room temperature. The precipitate was filtered, dried and crystallized from methanol to give **10b** in 73 % (1.34 g) yield.

# 3-(2-Carboxyethyl)thio-4-(2,6-dichlorobenzylidene)amino-6-methyl-1, 2,4-triazin-5(4*H*)-one (11)

A mixture of compound **10b** (1.84 g, 0.005 mol) and 10 % HCl (10 ml) was heated under reflux for 5 h. HCl was removed under reduced pressure and the residue was crystallized from ethanol to afford **11** in 51 % (0.99 g) yield; m.p.,  $139^{\circ}$ C,

<sup>1</sup>H NMR ([D<sub>6</sub>]DMSO):  $\delta$  = 2.26 (s, 3H, CH<sub>3</sub>), 3.07 (t, 2H, *J* = 6.4 Hz, CH<sub>2</sub>), 4.64 (t, 2H, *J* = 6.4 Hz, CH<sub>2</sub>), 7.60 (m, 3H, H<sub>arom</sub>.), 8.90 (s, 1H, CH), 10.36 (s, 1H, COOH).

CI MS, m/z (%) = 388 (MH<sup>+</sup>, 8) and 390 (MH<sup>+</sup> + 2, 5), for  ${}^{35}$ Cl and  ${}^{37}$ Cl, respectively.

# 4-Amino-3-hydroxy-6-methyl-5(4H)-oxo-1,2,4-triazine hydrochloride (12)

A mixture of compound 7 (1.05 g, 0.005 mol) and 10 % HCl (10 ml) was heated under reflux for 5 h. HCl was removed *in vacuo* and the residue was treated with anhydrous acetone. The precipitated solid was filtered, washed with anhydrous acetone and dried to give 12in 38 % (0.34 g) yield; m.p., > 300°C. <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO):  $\delta = 2.14$  (s, 3H, CH<sub>3</sub>), 7.49 (s, NH<sub>3</sub><sup>+</sup>).

CI MS, m/z (%) = 179 (MH<sup>+</sup>, 5), 178 (M<sup>+</sup>, 24).

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