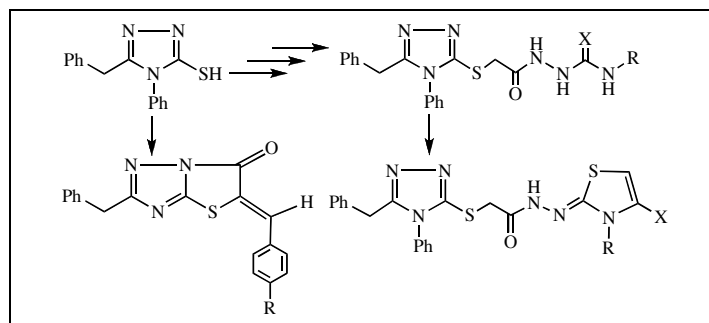


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3-Benzyl-4-phenyl-1,2,4-triazole-5-thiol (**1**) was synthesized and used as starting material for preparation of 1,2,4-triazole bearing substituted thiosemicarbazides moiety (**4a-d**) in high yields. The thiosemicarbazides **4a-d** were cyclized in basic medium to give two triazole rings linked by thiomethylene group (**5a-d**), while cyclization of thiosemicarbazides **4a-d** with chloroacetyl chloride in the presence of  $\text{CHCl}_3$  and  $\text{K}_2\text{CO}_3$  afforded the thiazolidinone derivatives **6a-d**. The reaction of thiosemicarbazides **4a-c** with phenacyl bromide in the presence of EtOH and fused  $\text{CH}_3\text{COONa}$  gave the corresponding thiazoline ring systems **7a-c**. Condensation of the 3-benzyl-1,2,4-triazole-5(1*H*)-thiol (**1**) with chloroacetic acid and aromatic aldehydes (**8a-g**) in boiling acetic acid/acetic anhydride mixture in the presence of fused sodium acetate gave one single isomer only, which might be **9a-g** or **10a-g**. Upon application of Micheal addition reaction on compounds **9a-e** with cyclic secondary amines such as piperidine or morpholine the 2-benzyl-6-( $\alpha$ -amino-aryl/methyl)-1,3-thiazolo[3,2-*b*][1,2,4]triazol-5-ols (**11a-j**) were obtained in good yields. The structure of all new compounds were determined using both spectral and elemental analyses.

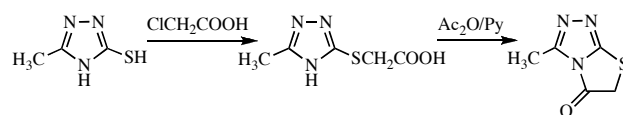
*J. Heterocyclic Chem.*, **45**, 897 (2008).

## INTRODUCTION

Thiosemicarbazides are convenient intermediates for synthesis of several heterocycles such as triazoles, thiazolines and thiazolidinones. It has been reported that thiosemicarbazide derivatives have antitubercular [1,2], antifungal [2-4] and hypoglycemic [5] activities. These findings encouraged us to synthesize new *s*-triazole derivatives incorporated thiosemicarbazide moiety, thiazoline, thiazolidinone or triazole ring systems. Several thiazolo[3,2-*b*]-[1,2,4]triazol-5(6*H*)-ones [6-12] have been prepared directly in one step reaction using the mercaptotriazole, chloroacetic acid and aromatic aldehydes.

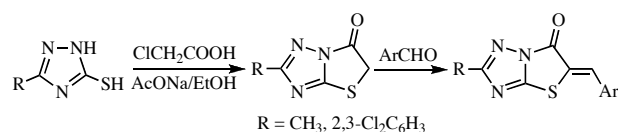
Kendall *et al.* [13] have reported that the synthesis of 1,3-thiazolo-1,2,4-triazoles occurred by the reaction of 3-mercapto-5-methyl-1,2,4-triazole with chloroacetic acid to give the 1,2,4-triazolylthioglycolic acid derivative, which on ring closure in the presence of acetic anhydride/pyridine mixture afforded the thiazolo[2,3-*c*]-1,2,4-triazol-5(6*H*)-one. No rigorous proof was given to exclude the possible alternative structure 1,3-thiazolo[2,3-*b*]-1,2,4-triazole, Scheme 1.

Scheme 1



Gogoi [14] and Tozkoparan [15] and coworkers, have studied also the cyclization of this type of reaction for the preparation of the 2-substituted-6-arylidene[thiazolo[3,2-*b*]-1,2,4-triazol-5-(6*H*)-one, either in two steps or in one step reaction. Direct condensation of 1,2,4-triazole-3-thiol with chloroacetic acid and aromatic aldehydes under the same reaction conditions gave the same result [10,16], Scheme 2.

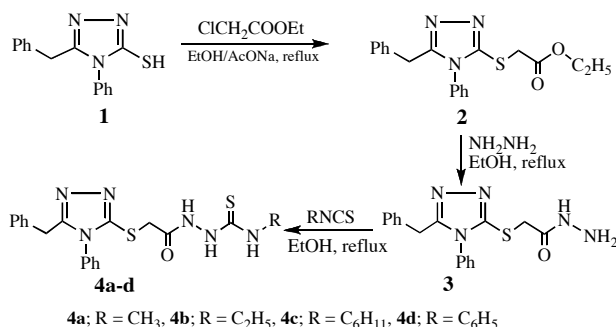
Scheme 2



## RESULTS AND DISCUSSION

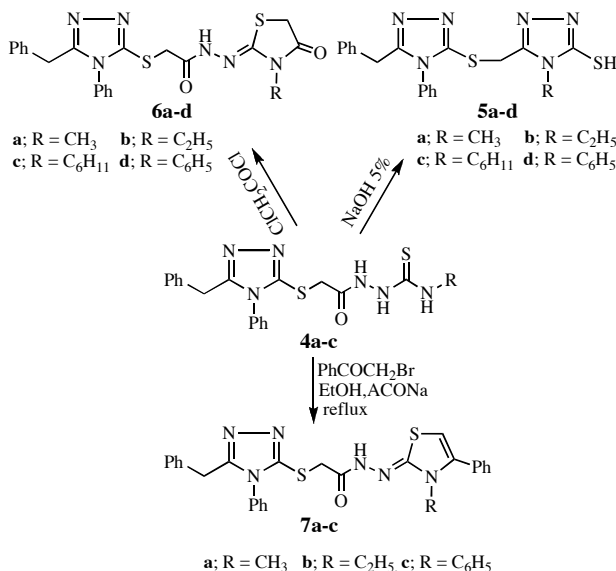
The 3-benzyl-4-phenyl-1,2,4-triazole-5-thiol (**1**) was prepared according to the reported method in good yield [17]. Treatment of **1** with ethyl chloroacetate in boiling ethanol containing fused sodium acetate gave the corresponding ester **2** in 85% yields. The latter was reacted with hydrazine hydrate in refluxing ethanol to give the corresponding crystalline hydrazide **3** as colorless needles in 90% yield. The hydrazide derivative **3** was treated with the appropriate isothiocyanate derivatives in boiling ethanol to afford the corresponding 1-[(5'-benzyl-4'-phenyl-1,2,4-triazol-3'-yl)thioacetyl]-4-substituted-thiosemicarbazides (**4a-d**) in high yields as shown in Scheme 3.

Scheme 3



On cyclization of the thiosemicarbazides **4a-d** in basic medium the 5-benzyl-4-phenyl-3-[(5'-mercapto-4'-substituted-s-triazol-3'-yl)methylthio]-s-triazoles **5a-d** were obtained in good yield. Further, the thiosemicarbazides **4a-d** were reacted with chloroacetyl chloride in boiling CHCl<sub>3</sub> in the presence of anhydrous K<sub>2</sub>CO<sub>3</sub> afforded the

Scheme 4

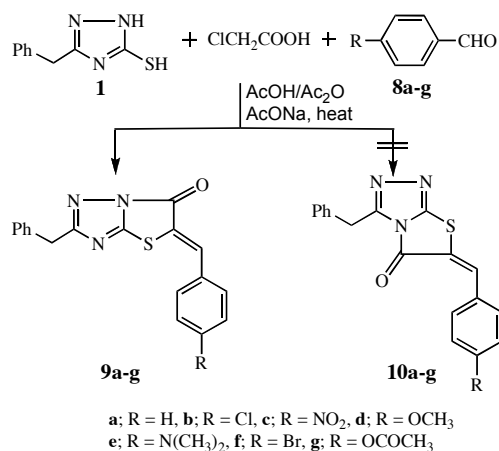


*N*-(3-substituted-4-oxothiazolidine-2-ylidene)-*N'*-[(5'-benzyl-4-phenyl-s-triazol-3'-yl)thioacetyl]hydrazines (**6a-d**) [18,19]. While, reaction of the thiosemicarbazides **4a-c** with phenacyl bromide in boiling ethanol in the presence of fused sodium acetate gave the *N*-(4-phenyl-3-substituted-2,3-dihydrothiazol-2-ylidene)-*N'*-[(5'-benzyl-4'-phenyl-s-triazol-3'-yl)thioacetyl]hydrazines (**7a-c**) respectively, Scheme 4.

The structures of the compounds **2**, **3**, **4a-d**, **6a-d** and **7a-c** were confirmed on the basis of their spectral and elemental analysis and are in satisfactory agreement with the suggested structure. The IR spectra of compounds **4a-d** showed the appearance of three NH groups at  $\nu$  3300, 3200 and 3150 cm<sup>-1</sup> respectively. Compounds **5a-d** revealed an absorption band at  $\nu$  3070 ~ 3090 cm<sup>-1</sup> characterized to the NH besides the absorption band at  $\nu$  1070 cm<sup>-1</sup> due to the presence of the (C=S) group. The lowering of the NH absorption bands in compounds **5a-d** might be attributed to the tautomeric nature of the HN=C=S  $\leftrightarrow$  N=C-SH group. While the IR spectra of compounds **6a-d** and **7a-c** exhibited only one sharp absorption band at  $\nu$  3150 ~ 3200 cm<sup>-1</sup>, characteristic of the presence of the NH group, appeared in all compounds.

On the other hand, condensation of the 3-benzyl-1,2,4-triazole-5-(1*H*)-thiol (**1**) with chloroacetic acid [9] and appropriate aromatic aldehydes **8a-g** in boiling glacial acetic acid/acetic anhydride mixture in the presence of fused sodium acetate gave only one pure product, which may be **9** or **10**, Scheme 5.

Scheme 5



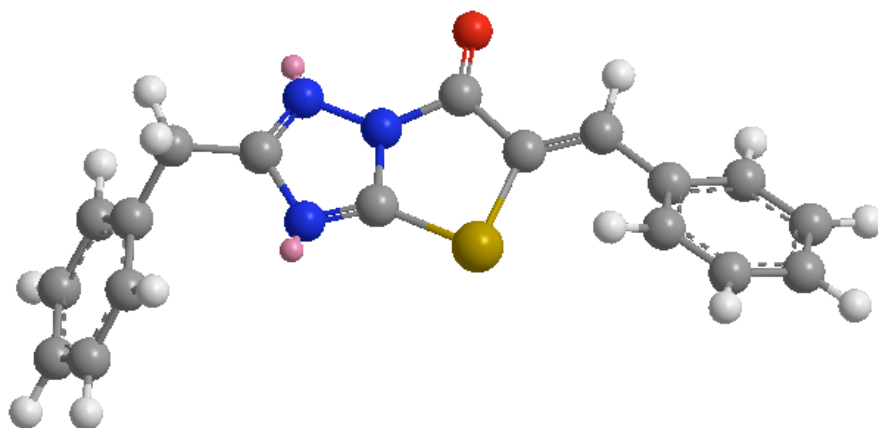
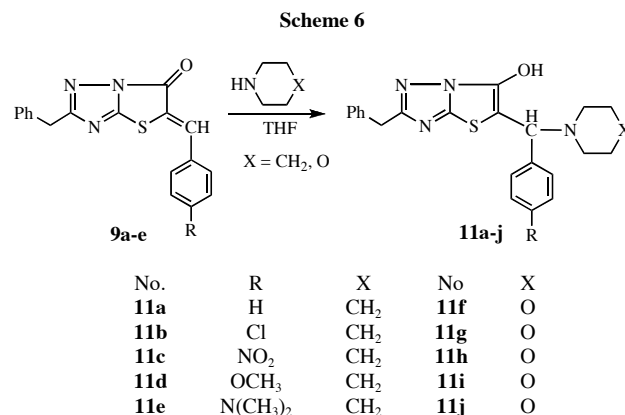
The experimental <sup>1</sup>H-NMR spectral analysis and molecular modeling calculations of compounds **9** and **10** were found in satisfactory agreement with similar results reported in literature [6]. The data obtained herein support that formation of the derivatives **9a-g** are favored over compounds **10a-g**. The <sup>1</sup>H-NMR spectral data of the products showed a singlet at  $\delta$  4.2-4.1 ppm which

attributed to the methylene protons (CH<sub>2</sub>) in addition to the other expected protons, detailed of NMR spectra are summarized in the experimental section. The IR spectra of **9a-g** showed bands at 3030 (C-H aromatic), 2920 (C-H aliphatic), 1730-1710 (C=O) and 1610-1580 (C=N), in addition compound **9g** exhibited an additional band at 1750 cm<sup>-1</sup> for the second (C=O) due to the acetylation of the hydroxyl group (OH). The mass spectra of compounds **9e** and **9g** showed the molecular ion peaks M<sup>+</sup> at m/z 377 (75%) and 362 (100%) respectively.

On the other hand the molecular modeling study revealed that the formation of compounds **9a-g** is more favorable than **10a-g**, Table 1. Our studies based on the MMX-M calculation, MOPAC force field calculation of MM2+ type [20]. Further the stereochemistry of compounds **9a-g** has been achieved also by molecular modeling calculations, which indicate that the (*E*) configuration is more stable than the (*Z*) isomer, Table 1.

Moreover, when compounds **9a-e** were reacted with

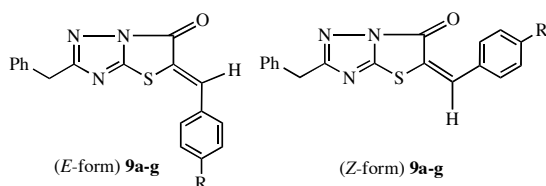
cyclic secondary amines such as piperidine or morpholine, in tetrahydrofuran under the conditions of Michael addition reaction gave the expected 2-benzyl-6-( $\alpha$ -amino-aryl-methyl)-1,3-thiazolo[3,2-*b*]-1,2,4-triazole-5-ols (**11a-j**) in relatively high yields, Scheme 6.



**Figure 1.** Ball and stick model of the isomer **9a** drawn from Chem3D 9.0.1.

**Table 1**

The molecular mechanical calculations of compounds **9a-g** (*E*-form and *Z*-form) and **10a-g**.



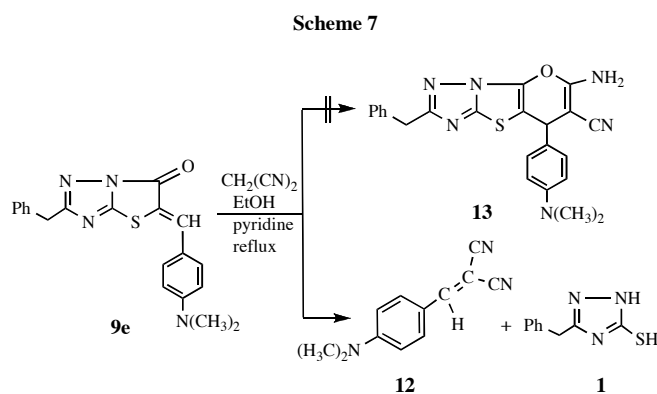
Compd. No. <b>9 and 10</b>	R	<i>E</i> (k.cal./mol.)	<i>E</i> (k.cal./mol.)	<i>E</i> (k.cal./mol.)
		Comp. <b>9a-g</b> ( <i>E</i> -form)	Comp. <b>9a-g</b> ( <i>Z</i> -form)	Comp. <b>10a-g</b>
<b>a</b>	H	46.247	51.138	52.974
<b>b</b>	Cl	46.197	51.329	52.803
<b>c</b>	NO <sub>2</sub>	48.484	49.637	54.224
<b>d</b>	OCH <sub>3</sub>	53.419	53.899	54.848
<b>e</b>	N(CH <sub>3</sub> ) <sub>2</sub>	50.544	56.129	57.668
<b>f</b>	Br	45.679	50.905	52.339
<b>g</b>	OCOCH <sub>3</sub>	49.447	56.507	56.585

The structure of the addition products **11a-j** was confirmed by their elemental and spectral analysis. The IR spectra of **11a-j** showed an absorption band at 3200-3100 cm<sup>-1</sup> (OH group) due to the enolic form instead of the band at 1730-1710 cm<sup>-1</sup> (C=O) of the ketonic form. The <sup>1</sup>H-NMR spectral data of **11a-j** in CDCl<sub>3</sub> showed a set of signals at  $\delta$  8.3-6.6 (m, aromatic protons) of the starting **9a-e**,  $\delta$  7.0-6.8 (s, 1H, ArCHN),  $\delta$  4.2-4.1 (s, 2H, PhCH<sub>2</sub>) and at  $\delta$  3.7-1.3 (m, 10H, 5 CH<sub>2</sub> of piperidine) or at  $\delta$  3.8-3.3 ppm (m, 8H, 4CH<sub>2</sub> of morpholine). The mass spectra of **11a,b** and **11g** showed molecular ion peaks M<sup>+</sup> with weak intensity at m/z 404 (3%) (**11a**), 438 (1%), 440 (2%) (**11b**) and 442 (1%) (**11g**) respectively, the base peak is (M<sup>+</sup> - 85) or (M<sup>+</sup> - 87) due to loss of a piperidine or morpholine molecule respectively.

The UV spectra of compounds **9a-f** showed a bathochromic shift (red shift) of about 204-103 nm as a

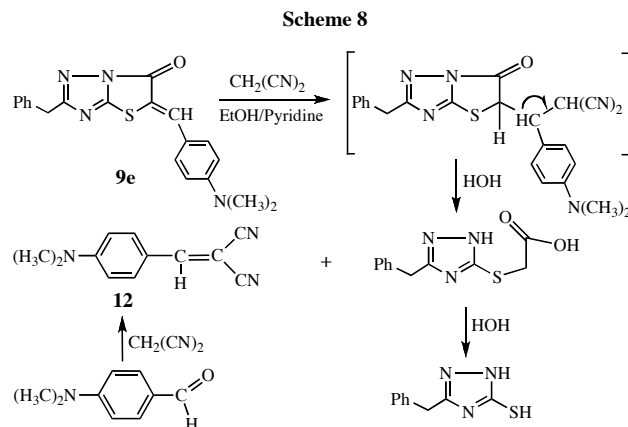
result of cyclization and the extended conjugation occurring in the parent 1,2,4-triazole **1**, which has  $\lambda_{\max}$  at 254, 210 nm. The effect of substituent on the absorption wave length ( $\lambda_{\max}$ ) was shown in the following order  $N(\text{CH}_3)_2 > \text{OCH}_3 > \text{NO}_2 > \text{Br} > \text{Cl} > \text{H}$ . However, the Micheal addition reaction products **11a-j** showed a hypsochromic shift (blue shift) of 38-99 nm due to the shortening of conjugation.

Finally, the reaction of **9e** with malononitrile in ethanol in the presence of pyridine as basic catalyst gave the 4-*N,N*-dimethylaminobenzylidene malononitrile (**12**) in 82% yield instead of the targeted compound **13** besides the formation of the starting 3-benzyl-4-phenyl-1,2,4-triazole-5-thiol (**1**) in low yield [21]. The IR spectrum of compound **12** showed a strong band at  $2200\text{ cm}^{-1}$  due to the presence of two identical  $\text{C}\equiv\text{N}$  groups, while its  $^1\text{H-NMR}$  spectrum in  $\text{CDCl}_3$  showed signals at  $\delta$  7.8 and 6.7 (d, 4H, aromatic-H), 7.4 (s, 1H,  $\text{CH}=\text{C}$ ) and 3.15 ppm (s, 6H, 2  $\text{N}(\text{CH}_3)_2$ ). On the other hand, an authentic sample of compound **12** was also prepared by the reaction of 4-*N,N*-dimethylaminobenzaldehyde and malononitrile, Scheme 7. The product **12** was found to be identical with that obtained by the reaction explained in Scheme 7, in terms of melting temperature and mixed melting temperature [22]. Also the IR,  $^1\text{H-NMR}$ , mass spectral data and elemental analysis of both compounds were found similar.

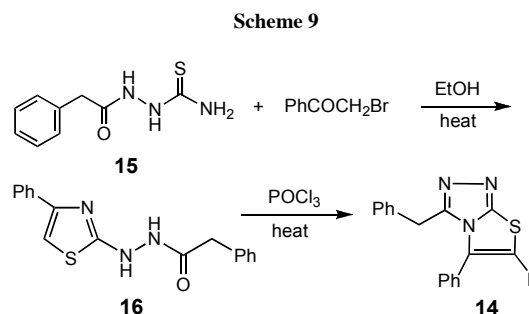


The mechanism of the formation of both compounds **12** and the starting material **1** is formulated to be as in Scheme 8.

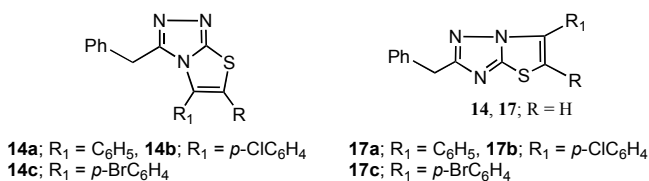
Unfortunately we tried to grow such crystal of any compound of **9a-g** enough for X-Ray analysis but we could not succeed. This forced us to search how compounds **9a-g** are formed and how the reaction proceeds. We concluded that in three ways: theoretically how the cyclization took place, chemically and finally using the  $^1\text{HNMR}$  spectral data obtained experimentally and compare it with the estimated one. To proof chemically how the reaction and the cyclization occurs another chemical reactions should be used in this



comparison to find out why the isomers **9a-g** is formed rather than **10a-g**. We applied an unequivocal synthesis of 5-phenyl-3-benzyl-1,3-thiazolo[2,3-*c*][1,2,4]triazole (**14**). A mixture of 1-phenylacetyl-3-thiosemicarbazide (**15**) and phenyl bromomethyl ketone was refluxed in ethanol to give 2-(phenylacetyl-hydrazino)-4-phenylthiazole (**16**). Refluxing of **16** in  $\text{POCl}_3$  afforded the isomeric 3-benzyl-5-phenyl-1,3-thiazolo[2,3-*c*]-[1,2,4]triazole (**14**) as previously reported for similar compounds, Scheme 9 [23].



The synthesized compound **14** were found to be different on comparison with the isomeric compounds **17a-c**, which synthesized using the procedures reported in literature [24]. The direct reaction of **1** with acetophenone derivatives in acetic acid catalyzed by concentrated sulfuric acid lead to the formation of **17a-c** rather than the formation of **14**. We found also the synthesized compounds **17a-c** using the literature method were identical with those obtained by our method [24].



Another proof we used the estimation  $^1\text{HNMR}$  (ACD/HNMR 1.0) for comparison purposes with the

experimental  $^1\text{H}$ NMR data summarized in the experimental section to proof which of the structures **9a-g** or **10a-g** were obtained. We found that our suggested structures **9a-g** was in satisfactory agreement with the estimated **9a-g**. The experimental  $^1\text{H}$  NMR spectra of compounds **9a-g** showed a sharp singlet at  $\delta$  8.00 – 8.3 ppm typical for the CH=C proton linked to the aryl group, which is in agreement with the estimated one appearing at  $\delta$  8.14 for all derivatives indicating that the

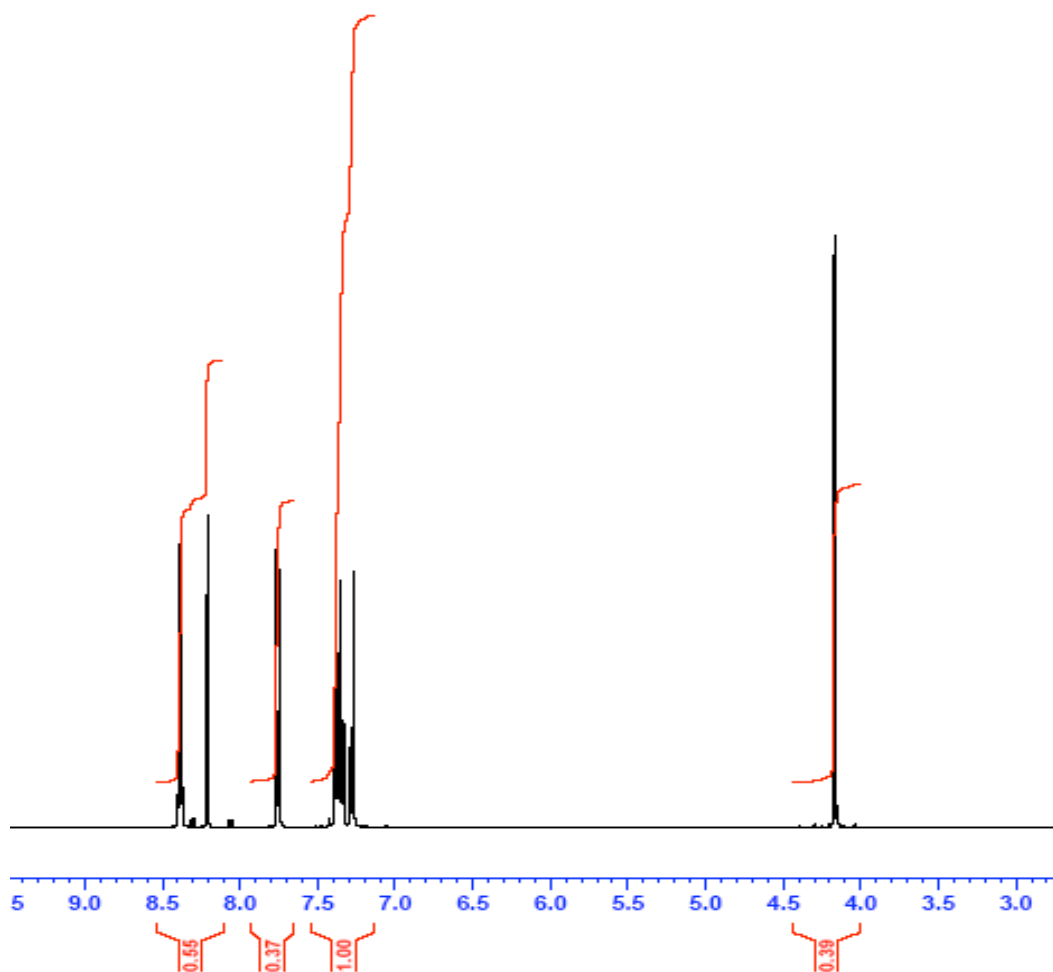
isomers **9a-g** were obtained rather than **10a-g** (CH=C appeared at  $\delta$  6.76 ppm). The comparison of these spectra with theoretical predictions for both isomers is given in Table 2.

## EXPERIMENTAL

Melting points were recorded on a Gallencamp melting point apparatus. Infrared spectra (IR) were measured on a Shimadzu

**Table 2**  
Chemical shifts of the CH and CH<sub>2</sub> in the Experimental and Estimated  $^1\text{H}$ NMR Data of Compounds **9a-j** (ppm).

Compd. No.	R	$^1\text{H}$ NMR				Compd. No.	$^1\text{H}$ NMR	
		Experimental		Estimated			Estimated	
		CH <sub>2</sub>	CH	CH <sub>2</sub>	CH	CH <sub>2</sub>	CH	
<b>9a</b>	H	4.20	8.20	4.78	8.14	<b>10a</b>	4.50	6.76
<b>9b</b>	Cl	4.20	8.10	4.79	8.14	<b>10b</b>	4.50	6.76
<b>9c</b>	NO <sub>2</sub>	4.15	8.30	4.79	8.14	<b>10c</b>	4.50	6.76
<b>9d</b>	OCH <sub>3</sub>	4.20	8.20	4.79	8.14	<b>10d</b>	4.50	6.76
<b>9e</b>	N(CH <sub>3</sub> ) <sub>2</sub>	4.20	8.05	4.79	8.14	<b>10e</b>	4.50	6.76
<b>9f</b>	Br	4.10	8.00	4.79	8.14	<b>10f</b>	4.50	6.76
<b>9j</b>	OCOCH <sub>3</sub>	4.15	8.20	4.79	8.14	<b>10j</b>	4.50	6.76



**Figure 2.** The experimental  $^1\text{H}$ NMR spectrum of **9b** (R = Cl) in  $\text{CDCl}_3$ , 500 MHz.

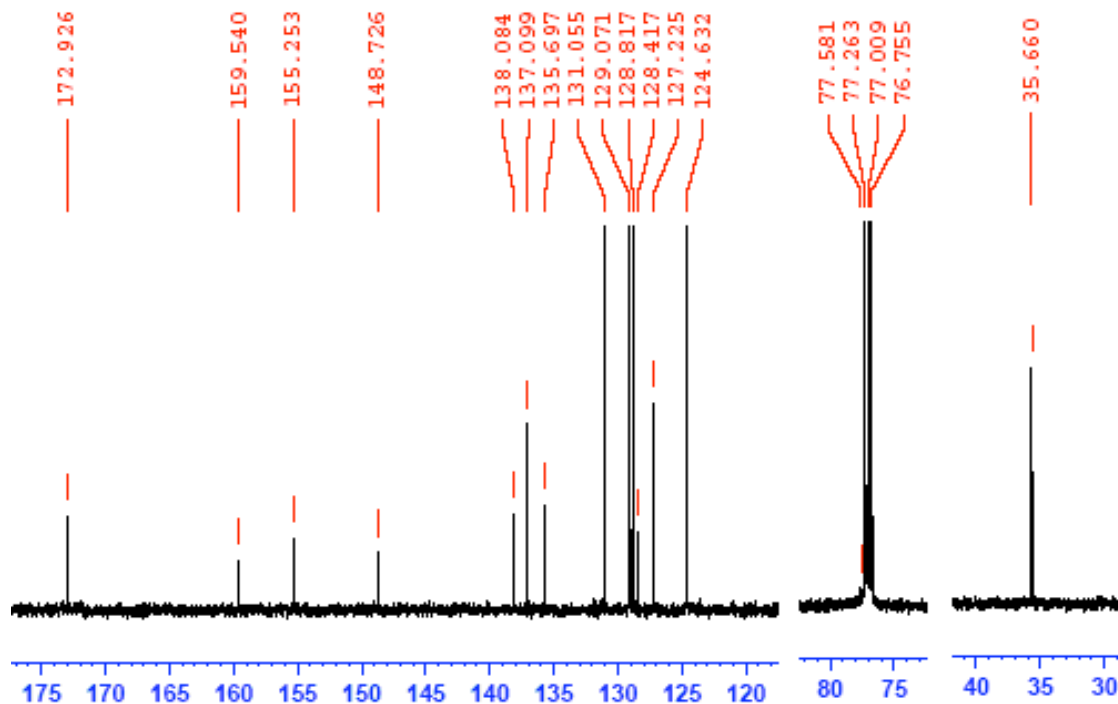


Figure 3. The experimental  $^{13}\text{C}$ NMR spectrum of **9b** (R = Cl) in  $\text{CDCl}_3$ , 125 MHz.

470 IR spectrometer (KBr, max in  $\text{cm}^{-1}$ ).  $^1\text{H}$ NMR Spectra were recorded at room temperature on a Varian EM-390, 90 MHz Spectrometer or on a JEOL LA 400 MHz FT-NMR spectrometer. Chemical shifts are denoted in  $\delta$  ppm values, relative to tetramethylsilane (TMS) as internal standard,  $J$  values are given in Hz.  $\text{CDCl}_3$  is used as a deuterated solvent unless otherwise stated. MS Spectra was obtained using a JEOL JMS-600 mass spectrometer. Elemental analyses were recorded on a Perkins Elmer 240C elemental analyzer (Assiut University unit). The solvents were distilled before use. Compounds **1**, **14** and **17a-c** were prepared according to the method previously described in literature [24].

**Synthesis of ethyl (5-benzyl-4-phenyl-1,2,4-triazol-3-yl)mercaptoacetate (2).** To a solution of 3-benzyl-4-phenyl-1,2,4-triazol-5-thiol (**1**) [6] (0.01 mol) in ethanol (50 mL) and anhydrous sodium acetate (1.0 g) ethyl chloroacetate (0.015 mole) was added, then the mixture was refluxed for 2 hours. The reaction mixture was cooled, filtered and the crude product was washed with water and crystallized from ethanol/benzene mixture to give the corresponding ester derivative **2** as colorless needles crystals in 85% yield, Mp. 75-76°C. IR (KBr)  $\nu = 3050\text{w}$  (C-H aromatic), 2990m, 2910m (C-H aliphatic), 1700s (C=O), 1590s (C=N), 1400s, 1530s, 1450s, 1500s (C-H aromatic), 1280s, 1130s, 1010s (C-O, C-H, C-N), 700s, 730s, 750s  $\text{cm}^{-1}$  (aromatic).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta = 7.6-6.9$  (m, 10H, aromatic-H), 4.0 (s, 2H,  $\text{Ph-CH}_2$ -), 4.1 (s, 2H,  $\text{SCH}_2\text{CO}$ ), 4.2 (t, 3H,  $\text{CH}_3$ ), 1.2 ppm (t, 3H,  $\text{CH}_3$ ). Elemental analysis for  $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$  (353.45); Calcd: C, 64.57; H, 5.42; N, 11.89; S, 9.07%. Found: C, 64.66; H, 5.30; N, 11.80; S, 8.71%.

**Synthesis of (5-benzyl-4-phenyl-1,2,4-triazol-3-yl)mercaptoacetic hydrazide (3).** A mixture of the ester **2** (0.01 mole) and hydrazine hydrate (0.015 mole) was refluxed in ethanol (50 mL)

for 3 hours, then cooled at room temperature, filtered and crystallized from ethanol to give white needles crystals of the hydrazide derivative **3** in 90% yield, Mp. 151-152°C. IR (KBr)  $\nu = 3300\text{s}$ , 3200s, 3150m (NH-NH<sub>2</sub>), 3030w (C-H aromatic), 2960w (C-H aliphatic), 1580s (C=O), 3050w (C-H aromatic), 1590s (C=N), 1400s, 1450s, 1500s  $\text{cm}^{-1}$  (C-H aromatic),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta = 9.3$  (s, 1H, NH), 7.6-6.8 (m, 10H, aromatic-H), 3.8 (s, 2H,  $\text{Ph-CH}_2$ -), 3.9 (s, 2H,  $\text{SCH}_2\text{CO}$ ), 4.0 ppm (s, 2H,  $\text{NH}_2$ ), and the (NH-NH<sub>2</sub>) protons are exchangeable with  $\text{D}_2\text{O}$ . Elemental analysis for  $\text{C}_{17}\text{H}_{17}\text{N}_5\text{OS}$  (339.42). Calcd: C, 60.16; H, 5.05; N, 20.63; S, 9.45%. Found: C, 59.78; H, 4.82; N, 20.59; S, 9.10%.

**Synthesis of 1-(2-(5-benzyl-4-phenyl-4H-1,2,4-triazol-3-ylthio)acetyl)-4-substituted-thiosemicarbazides (4a-d).** General procedure: A mixture of hydrazide **3** (0.01 mole) and appropriate isothiocyanate derivatives (0.015 mole) in ethanol (50 mL) was refluxed for 2 hours. The reaction mixture was then cooled and the precipitate thus formed was collected by filtration and crystallized from ethanol to give the thiosemi-carbazide derivatives **4a-d** as colorless needles in high yields.

**1-(2-(5-Benzyl-4-phenyl-4H-1,2,4-triazol-3-ylthio)acetyl)-4-methylthiosemicarbazide (4a).** R =  $\text{CH}_3$ . This compound was obtained as needles crystals in 82% yield, Mp. 171-173 °C. IR (KBr)  $\nu = 3300\text{s}$ , 3200s, 3150m (three N-H), 3040w (C-H aromatic) 2960w (C-H aliphatic), 1700s (C=O) and at 1140s (C=S) 1250s, 1140s, 1000s (C-O, C-H, C-N), 700s, 760s, 800s  $\text{cm}^{-1}$  (aromatic).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 90 MHz)  $\delta$  ppm = 10.6, 9.3, 8.4 (s, 3H, 3 NH), 7.6-6.7 (m, 10H, aromatic-H), 3.8 (s, 2H,  $\text{Ph-CH}_2$ -), 4.0 (s, 2H,  $\text{SCH}_2\text{CO}$ ), 2.9 (d, 3H,  $\text{CH}_3$ ). Elemental analysis for  $\text{C}_{19}\text{H}_{20}\text{N}_6\text{OS}_2$  (412.54). Calcd: C, 55.32; H, 4.88; N, 20.37; S, 15.54%. Found: C, 54.91; H, 5.05; N, 20.22; S, 15.14%.

**1-(2-(5-Benzyl-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)acetyl)-4-ethylthiosemicarbazide (4b).** R = C<sub>2</sub>H<sub>5</sub>. This compound was obtained as needles crystals in 89% yield, Mp. 159-161 °C. IR (KBr)  $\nu$  = 3300s, 3200s, 3150m (three N-H), 3040w (C-H aromatic) 2960w, 2920w (C-H aliphatic), 1700s (C=O) and at 1140s (C=S) 1250s, 1140s, 1000s (C-O, C-H, C-N), 700s, 760s, 800s cm<sup>-1</sup> (aromatic). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  ppm = 10.1, 8.6, 8.4 (s, 3H, 3 NH), 7.5-6.8 (m, 10H, aromatic-H), 3.8 (s, 2H, Ph-CH<sub>2</sub>-), 4.0 (s, 2H, SCH<sub>2</sub>CO), 3.6 (m, 2H, CH<sub>2</sub>), 1.2 (t, 3H, CH<sub>3</sub>). Elemental analysis for C<sub>20</sub>H<sub>22</sub>N<sub>6</sub>OS<sub>2</sub> (426.57). Calcd: C, 56.32; H, 5.20; N, 19.70; S, 15.03%. Found: C, 56.37; H, 5.06; N, 19.61; S, 14.70%.

**1-(2-(5-Benzyl-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)acetyl)-4-cyclohexylthiosemicarbazide (4c).** R = C<sub>6</sub>H<sub>11</sub>. This compound was obtained as crystals in 86% yield, Mp. 173-174 °C. IR (KBr)  $\nu$  = 3300s, 3210s, 3160m (three N-H), 3050w (C-H aromatic) 2970s, 2960m, 2920w (C-H aliphatic), 1710s (C=O), 1140s (C=S), 1250s, 1140s, 1000s (C-O, C-H, C-N), 710s, 760s, 800s cm<sup>-1</sup> (aromatic). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  ppm = 9.8, 8.4, 7.4 (s, 3H, 3 NH), 7.4-6.8 (m, 10H, aromatic-H), 3.8 (s, 2H, Ph-CH<sub>2</sub>-), 3.9 (s, 2H, SCH<sub>2</sub>CO), 1.9-1.0 (m, 11H, C<sub>6</sub>H<sub>11</sub>). Elemental analysis for C<sub>24</sub>H<sub>28</sub>N<sub>6</sub>OS<sub>2</sub> (480.64). Calcd: C, 59.97; H, 5.87; N, 17.48; S, 13.34%. Found: C, 59.57; H, 5.66; N, 17.30; S, 13.20%.

**1-(2-(5-Benzyl-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)acetyl)-4-phenylthiosemicarbazide (4d).** R = C<sub>6</sub>H<sub>5</sub>. This compound was obtained as needles crystals in 82% yield, Mp. 184-185 °C. IR (KBr)  $\nu$  = 3300s, 3200s, 3150m (three N-H), 3050w (C-H aromatic) 2960w (C-H aliphatic), 1720s (C=O), 1140s (C=S) 1260s, 1140s, 1020s (C-O, C-H, C-N), 700s, 760s, 800s cm<sup>-1</sup> (aromatic). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 90 MHz)  $\delta$  ppm = 10.7, 9.8, 9.8 (s, 3H, 3 NH), 7.7-6.8 (m, 15H, aromatic-H), 3.8 (s, 2H, Ph-CH<sub>2</sub>-), 3.9 (s, 2H, SCH<sub>2</sub>CO). Elemental analysis for C<sub>24</sub>H<sub>22</sub>N<sub>6</sub>OS<sub>2</sub> (474.61). Calcd: C, 60.74; H, 4.67; N, 17.70; S, 13.51%. Found: C, 60.78; H, 4.81; N, 17.66; S, 13.22%.

**Synthesis of 5-[(5-benzyl-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)methyl]-4-substituted-4*H*-1,2,4-triazole-3-thioles (5a-d).** General procedure: A solution of thiosemicarbazides **4a-d** (2 mmol) in sodium hydroxide (50 mL 5%) was refluxed gently for 3 hours. The reaction mixture was then cooled and acidified with dilute HCl, the crude product thus obtained was crystallized from ethanol to give **5a-d** as white needles crystals in 70 ~ 87% yield.

**5-[(5-Benzyl-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)methyl]-4-methyl-4*H*-1,2,4-triazole-3-thiol (5a).** R = CH<sub>3</sub>. This compound was obtained as white needles crystals in 81% yield, Mp. 164-165 °C. IR (KBr)  $\nu$  = 3090m (N-H), 3030m (C-H aromatic) 2900m (C-H aliphatic), 1570s (C=N), 1070s (C=S), 1130m (C-H), 1000s (C-N), 690s, 730s, 750s cm<sup>-1</sup> (aromatic). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  ppm = 12.8 (s, 1H, NH), 7.6-6.9 (m, 10H, aromatic-H), 4.2 (s, 2H, Ph-CH<sub>2</sub>), 4.5 (s, 2H, SCH<sub>2</sub>-), 3.5 (s, 3H, CH<sub>3</sub>). Elemental analysis for C<sub>19</sub>H<sub>18</sub>N<sub>6</sub>S<sub>2</sub> (394.52). Calcd: C, 57.84; H, 4.60; N, 21.30; S, 16.25%. Found: C, 58.17; H, 4.42; N, 21.34; S, 15.90%.

**5-[(5-Benzyl-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)methyl]-4-ethyl-4*H*-1,2,4-triazole-3-thiol (5b).** R = C<sub>2</sub>H<sub>5</sub>. This compound was obtained as white needles crystals in 86% yield, Mp. 194-195 °C. IR (KBr)  $\nu$  = 3100m (N-H), 3030m (C-H aromatic) 2900m (C-H aliphatic), 1590s (C=N), 1080s (C=S), 1130m (C-H), 1000s (C-N), 690s, 730s, 750s cm<sup>-1</sup> (aromatic). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  ppm = 13.8 (s, 1H, NH), 7.7-6.9 (m,

10H, aromatic protons), 4.0 (s, 2H, PhCH<sub>2</sub>), 4.4 (s, 2H, SCH<sub>2</sub>), 4.1 (q, 2H, CH<sub>2</sub>), 1.3 (t, 3H, CH<sub>3</sub>). MS m/z (%) = 408 (15), 368 (5), 294 (2), 267 (100), 266 (50), 252 (7), 234 (18), 190 (2), 166 (2), 149 (20), 116 (16), 91 (70), 77 (25), 65 (21), 51 (17). Elemental analysis for C<sub>20</sub>H<sub>20</sub>N<sub>6</sub>S<sub>2</sub> (408.55). Calcd: C, 58.80; H, 4.93; N, 20.57; S, 15.70%. Found: C, 58.51; H, 5.15; N, 20.35; S, 15.91%.

**[(5-Benzyl-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)methyl]-4-cyclohexyl-4*H*-1,2,4-triazole-3-thiol (5c).** R = C<sub>6</sub>H<sub>11</sub>. This compound was obtained as needles crystals in 70% yield, Mp. 105-106 °C. IR (KBr)  $\nu$  = 3070m (N-H), 3030m (C-H aromatic) 2960m, 2900m (C-H aliphatic), 1590s (C=N), 1070s (C=S), 1130m (C-H), 1020s (C-N), 690s, 730s, 760s cm<sup>-1</sup> (aromatic). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  ppm = 12.9 (s, 1H, NH), 7.5-6.8 (m, 10H, aromatic protons), 4.0 (s, 2H, PhCH<sub>2</sub>), 4.5 (s, 2H, SCH<sub>2</sub>-), 1.9-1.1 (m, 11H, C<sub>6</sub>H<sub>11</sub>). Elemental analysis for C<sub>24</sub>H<sub>26</sub>N<sub>6</sub>S<sub>2</sub> (462.64). Calcd: C, 62.31; H, 5.66; N, 18.17; S, 13.86%. Found: C, 62.26; H, 5.56; N, 17.82; S, 13.71%.

**[(5-Benzyl-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)methyl]-4-phenyl-4*H*-1,2,4-triazole-3-thiol (5d).** R = C<sub>6</sub>H<sub>5</sub>. This compound was obtained as white needles crystals in 87% yield, Mp. 190-191 °C. IR (KBr)  $\nu$  = 3070m (N-H), 3010m (C-H aromatic) 2890m (C-H aliphatic), 1580s (C=N), 1070s (C=S), 1150m (C-H), 1000s (C-N), 680s, 730s, 750s cm<sup>-1</sup> (aromatic). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  ppm = 13.2 (s, 1H, NH), 7.5-6.9 (m, 15H, aromatic-H), 4.0 (s, 2H, PhCH<sub>2</sub>), 4.2 (s, 2H, SCH<sub>2</sub>-). Elemental analysis for C<sub>24</sub>H<sub>20</sub>N<sub>6</sub>S<sub>2</sub> (456.60). Calcd: C, 63.13; H, 4.42; N, 18.41; S, 14.04%. Found: C, 63.20; H, 4.47; N, 18.27; S, 14.16%.

**Synthesis of 2-(5-benzyl-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)-N'-(3-substituted-4-oxothiazolidin-2-ylidene)acetohydrazide (6a-d).** General procedure: A mixture of thiosemicarbazides **4a-d** (2 mmol), chloroacetyl chloride (2 mmol) and potassium carbonate (1 gm) in chloroform (30 mL) was refluxed on water-bath for 3 hours. The excess chloroform was removed evaporated and the resulting solid products was washed with cold water to remove the excess K<sub>2</sub>CO<sub>3</sub> and dried followed by crystallization from ethanol to give the corresponding compounds **6a-d** as needles crystals in 64 ~ 86% yields.

**2-(5-Benzyl-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)-N'-(3-methyl-4-oxothiazolidin-2-ylidene)acetohydrazide (6a).** R = CH<sub>3</sub>. This compound was obtained as white crystals in 82% yield, Mp. 204-205 °C. IR (KBr)  $\nu$  = 3180m (N-H), 3030w (C-H aromatic) 2960m, 2930m (C-H aliphatic), 1750s, 1700s (2 C=O), 1650s (C=N), 1130m (C-H), 1030m (C-N), 690s, 730s, 750s cm<sup>-1</sup> (aromatic). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)  $\delta$  ppm = 10.9 (s, 1H, NH), 7.5-6.9 (m, 10H, aromatic-H), 4.11, 4.09, 3.91 (s, 6H, 3 CH<sub>2</sub>), 3.02 (s, 3H, CH<sub>3</sub>). MS m/z (%) = 452 (9), 324 (5), 308 (18), 281 (63), 267 (100), 266 (65), 234 (85), 186 (1), 172 (32), 145 (25), 129 (19), 115 (2), 91 (88), 77 (23), 65 (16), 51 (10). Elemental analysis for C<sub>21</sub>H<sub>20</sub>N<sub>6</sub>O<sub>2</sub>S<sub>2</sub> (452.56). Calcd: C, 55.73; H, 4.45; N, 18.56; S, 14.17%. Found: C, 55.79; H, 4.40; N, 18.50; S, 13.86%.

**2-(5-Benzyl-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)-N'-(3-ethyl-4-oxothiazolidin-2-ylidene)acetohydrazide (6b).** R = C<sub>2</sub>H<sub>5</sub>. This compound was obtained as white crystals in 79% yield, Mp. 174-175 °C. IR (KBr)  $\nu$  = 3150m (N-H), 3050w (C-H aromatic) 2980m, 2950m (C-H aliphatic), 1750s, 1700s two (C=O), 1640s (C=N), 1130m (C-H), 1040m (C-N), 690s, 730s, 760s cm<sup>-1</sup> (aromatic). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  ppm = 10.9 (s, 1H, NH), 7.5-6.9 (m, 10H, aromatic-H), 3.95, 3.90, 3.70 (s, 6H, 3 CH<sub>2</sub>), 3.20 (t, 2H, CH<sub>2</sub>), 1.05 (q, 3H, CH<sub>3</sub>). MS m/z (%) =

466 (5), 324 (6), 308 (12), 281 (86), 267 (77), 266 (50), 234 (38), 200 (10), 186 (16), 159 (6), 143 (9), 129 (5), 91 (100), 77 (23), 65 (17), 51 (11). Elemental analysis for  $C_{22}H_{22}N_6O_2S_2$  (466.59). Calcd: C, 56.63; H, 4.75; N, 18.01; S, 13.74%. Found: C, 56.50; H, 4.88; N, 18.08; S, 13.39%.

**2-(5-Benzyl-4-phenyl-4H-1,2,4-triazol-3-ylthio)-N'-(3-cyclohexyl-4-oxothiazolidin-2-ylidene)acetohydrazide (6c).** R =  $C_6H_{11}$ . This compound was obtained as white crystals in 64% yield, M.p. 170-171 °C. IR (KBr)  $\nu$  = 3150m (N-H), 3050w (C-H aromatic) 2980m, 2950m (C-H aliphatic), 1750s, 1700s two (C=O), 1640s (C=N), 1130m (C-H), 1040m (C-N), 690s, 730s, 760s  $cm^{-1}$  (aromatic).  $^1H$ NMR ( $CDCl_3$ , 400 MHz)  $\delta$  ppm = 7.5-6.9 (m, 10H, aromatic-H and NH proton), 4.00, 3.95, 3.80 (s, 6H, 3  $CH_2$ -), 1.80-1.12 (m, 11H,  $C_6H_{11}$ ). MS m/z (%) = 520 (1), 324 (3), 308 (3), 281 (18), 267 (100), 266 (57), 254 (1), 240 (4), 234 (46), 213 (3), 197 (4), 183 (1), 91 (46), 77 (16), 65 (11), 51 (8). Elemental analysis for  $C_{26}H_{28}N_6O_2S_2$  (520.68). Calcd: C, 59.98; H, 5.42; N, 16.14; S, 12.32%. Found: C, 59.72; H, 5.36; N, 16.00; S, 12.02%.

**2-(5-Benzyl-4-phenyl-4H-1,2,4-triazol-3-ylthio)-N'-(3-phenyl-4-oxothiazolidin-2-ylidene)acetohydrazide (6d).** R =  $C_6H_5$ . This compound was obtained as pale yellow crystals in 86% yield, M.p. 166-167 °C. IR (KBr)  $\nu$  = 3200m (N-H), 3050m (C-H aromatic) 2980m (C-H aliphatic), 1740s, 1700s two (C=O), 1640s (C=N), 1130m (C-H), 1040m (C-N), 690s, 730s, 760s  $cm^{-1}$  (aromatic).  $^1H$ NMR ( $CDCl_3$ , 400 MHz)  $\delta$  ppm = 7.60-6.85 (m, 15H, aromatic-H and NH proton), 4.00, 3.95, 3.85 (s, 6H, 3  $CH_2$ ). MS m/z (%) = 514 (11), 324 (10), 308 (20), 281 (50), 267 (15), 266 (31), 248 (35), 234 (47), 207 (18), 191 (24), 177 (7), 91 (72), 77 (100), 65 (47), 51 (70). Elemental analysis for  $C_{26}H_{22}N_6O_2S_2$  (514.63). Calcd: C, 60.68; H, 4.31; N, 16.33; S, 12.46%. Found: C, 59.92; H, 4.61; N, 16.40; S, 11.61%.

**2-(5-Benzyl-4-phenyl-4H-1,2,4-triazol-3-ylthio)-N'-(3-substituted-4-phenylthiazol-2(3H)-ylidene)acetohydrazides (7a-c).** General procedure: A mixture of thiosemicarbazides **4a,b** and **4d** (0.002 mole), phenacyl bromide (0.002 mole) and anhydrous sodium acetate in ethanol (30 mL) was refluxed for 6 hours, then, ethanol was evaporated and the product washed with water several times, then crystallized from ethanol to give **7a-c**, respectively, as white needles in 62-74% yield.

**2-(5-Benzyl-4-phenyl-4H-1,2,4-triazol-3-ylthio)-N'-(3-methyl-4-phenylthiazol-2(3H)-ylidene)acetohydrazide (7a).** R =  $CH_3$ . This compound was obtained as white crystals in 66% yield, M.p. 224-225 °C. IR (KBr)  $\nu$  = 3150m (N-H), 3050w (C-H aromatic) 2960m, 2910w (C-H aliphatic), 1660s (C=O), 1580s (C=N), 1160m (C-H), 1070m (C-N), 690s, 730s, 750s  $cm^{-1}$  (aromatic).  $^1H$ NMR ( $CDCl_3$ , 400 MHz)  $\delta$  ppm = 10.2 (s, 1H, NH), 7.4-6.8 (m, 15H, aromatic-H), 5.8 (s, 1H, CH=), 3.8, 3.9 (s, 4H, 2  $CH_2$ ), 3.2 (s, 3H,  $CH_3$ ). MS m/z (%) = 512 (7), 438 (8), 378 (20), 363 (1), 335 (2), 322 (15), 308 (11), 281 (20), 279 (37), 239 (36), 265 (95), 252 (20, 248 (11), 236 (38, 233 (96), 220 (85), 205 (60), 190 (45), 176 (10), 165 (10), 149 (35), 134 (30), 118 (47), 102 (45), 91 (100), 77 (67), 65 (40), 51 (35), 39 (30). Elemental analysis for  $C_{27}H_{24}N_6OS_2$  (512.66). Calcd: C, 63.26; H, 4.72; N, 16.39; S, 12.51%. Found: C, 63.10; H, 4.99; N, 16.48; S, 11.95%.

**2-(5-Benzyl-4-phenyl-4H-1,2,4-triazol-3-ylthio)-N'-(3-ethyl-4-phenylthiazol-2(3H)-ylidene)acetohydrazide (7b).** R =  $C_2H_5$ . This compound was obtained as white crystals in 62% yield, M.p. 136-137 °C. IR (KBr)  $\nu$  = 3200m (N-H), 3030w (C-H aromatic) 2960m, 2910w (C-H aliphatic), 1650s (C=O), 1580s

(C=N), 1160m (C-H), 1060m (C-N), 690s, 730s, 750s  $cm^{-1}$  (aromatic).  $^1H$ NMR ( $CDCl_3$ , 400 MHz)  $\delta$  ppm = 10.5 (s, 1H, NH), 7.5-6.9 (m, 15H, aromatic-H), 5.8 (s, 1H, CH=), 4.0, 3.9 (s, 4H, 2  $CH_2$ ), 3.8 (q, 2H,  $CH_2$ ), 1.2 (t, 3H,  $CH_3$ ). Elemental analysis for  $C_{28}H_{26}N_6OS_2$  (526.69). Calcd: C, 63.85; H, 4.98; N, 15.96; S, 12.18%. Found: C, 63.61; H, 5.17; N, 15.66; S, 11.98%.

**2-(5-Benzyl-4-phenyl-4H-1,2,4-triazol-3-ylthio)-N'-(3-phenyl-4-phenylthiazol-2(3H)-ylidene)acetohydrazide (7c).** R =  $C_6H_5$ . This compound was obtained as white crystals in 74% yield, M.p. 213-214 °C. IR (KBr)  $\nu$  = 3250m (N-H), 3030m (C-H aromatic) 2960m, (C-H aliphatic), 1560s (C=O), 1580s (C=N), 1160m (C-H), 1030m (C-N), 690s, 730s, 750s  $cm^{-1}$  (aromatic).  $^1H$ NMR ( $DMSO-d_6$ , 400 MHz)  $\delta$  ppm = 10.8 (s, 1H, NH), 7.7-6.9 (m, 20H, aromatic-H), 5.9 (s, 1H, CH=), 4.5, 3.9 (s, 4H, two- $CH_2$ -), 3.2 (s, 3H,  $CH_3$ ). Elemental analysis for  $C_{32}H_{26}N_6OS_2$  (574.73). Calcd: C, 66.88; H, 4.56; N, 14.62; S, 11.16%. Found: C, 66.48; H, 4.91; N, 14.44; S, 11.02%.

**Synthesis of (E)-2-benzyl-6-arylidenethiazolo[3,2-b][1,2,4]-triazol-5(6H)-ones (9a-g).** General procedure: A mixture of 3-benzyl-1,2,4-triazole-5(1H)-thiol (**1**) (5 mmol), aromatic aldehydes (**8**; 5 mmol), chloroacetic acid (5 mmol) and fused sodium acetate (10 mmol) was refluxed in acetic acid/acetic anhydride (25:5 mL) mixture for 3 hours. The reaction mixture was then cooled, filtered and crystallized from acetic acid to give the thiazolo[3,2-b][1,2,4]triazol-5(6H)-ones **9a-g** in 66 ~ 87% yields. The  $R_f$  values were measured using benzene/ethyl acetate mixture as an eluent in ratio (9:1) and the UV absorption data of compounds **9a-f** were measured in  $CHCl_3$  in concentration ( $2 \times 10^{-5}$  mol/Liter).

**(E)-2-Benzyl-6-benzylidenethiazolo[3,2-b][1,2,4]triazol-5(6H)-one (9a).** R = H. This compound was obtained as colorless crystals in 74% yield, M.p. 142-143 °C.  $R_f$  = 0.63. IR (KBr)  $\nu$  = 3030m (C-H aromatic) 2960m, (C-H aliphatic), 1730s (C=O), 1590s (C=N), 1500s, 1460s, 1440s (aromatic skeleton), 690s, 730s, 750s  $cm^{-1}$  (C-H aromatic).  $^1H$ NMR ( $CDCl_3$ , 90 MHz)  $\delta$  = 7.70-7.30 (m, 10H, aromatic-H), 8.20 (s, 1H, CH), 4.20 (s, 2H,  $CH_2$ ). UV at  $\lambda_{max}$  ( $\epsilon$ ) = 357.5 (21500), 302.5 (16950), 242.5 (9800) nm ( $L \text{ mol}^{-1} \text{ cm}^{-1}$ ), Abs. = 0.430, 0.339, 0.196 respectively. Elemental analysis for  $C_{18}H_{13}N_3OS$  (319.39). Calcd: C, 67.69; H, 4.10; N, 13.15; S, 10.03%. Found: C, 67.48; H, 3.82; N, 13.20; S, 9.78%.

**(E)-6-(4-Chlorobenzylidene)-2-benzylthiazolo[3,2-b][1,2,4]-triazol-5(6H)-one (9b).** R = Cl. This compound was obtained as yellow crystals in 85% yield, M.p. 187-188 °C.  $R_f$  = 0.65. IR (KBr)  $\nu$  = 3030m (C-H aromatic) 2960m, (C-H aliphatic), 1730s (C=O), 1590s (C=N), 1500s, 1480s, 1400s (aromatic skeleton), 690s, 730s, 760s  $cm^{-1}$  (C-H aromatic).  $^1H$ NMR ( $DMSO-d_6$ , 90 MHz)  $\delta$  ppm = 7.80-7.20 (m, 9H, aromatic-H), 8.15 (s, 1H, CH), 4.20 (s, 2H,  $CH_2$ ).  $^1H$ NMR ( $CDCl_3$ , 500 MHz)  $\delta$  ppm = 8.40-8.37 (m, 2H, aromatic-H), 8.21 (s, 1H, arylidene-CH), 7.77-7.74 (m, 2H, aromatic-H), 7.40-7.33 (m, 3H, aromatic-H), 7.3-7.28 (m, 2H, aromatic-H), 4.17 (s, 2H,  $CH_2Ph$ ).  $^{13}C$ NMR ( $CDCl_3$ , 135 MHz)  $\delta$  ppm = 172.92 (C-2), 159.54 (C=O), 155.25 (C-8), 148.72 (CH=), 138.08, 137.09, 135.69 (aromatic-C), 131.05, 129.07, 128.81, 128.41, 127.22, 124.63 (aromatic-CH), 35.66 ( $CH_2$ ). UV at  $\lambda_{max}$  ( $\epsilon$ ) = 362.0 (21500), 310.0 (16950), 246.5 (9800) nm ( $L \text{ mol}^{-1} \text{ cm}^{-1}$ ), Abs. = 0.439, 0.319, 0.228 respectively. Elemental analysis for  $C_{18}H_{12}ClN_3OS$  (353.83). Calcd: C, 61.10; H, 3.41; N, 11.87; S, 9.06%. Found: C, 61.31; H, 3.45; N, 11.64; S, 8.88%.



**(E)-6-(4-Nitrobenzylidene)-2-benzylthiazolo[3,2-*b*][1,2,4]-triazol-5(6*H*)-one (9c).** R = NO<sub>2</sub>. This compound was obtained as yellow crystals in 79% yield, Mp. 201-202 °C, R<sub>f</sub> = 0.53. IR (KBr)  $\nu$  = 3050m (C-H aromatic) 2960m, (C-H aliphatic), 1730s (C=O), 1600s (C=N), 1500s, 1470s, 1410s (aromatic skeleton), 690s, 720s, 760s cm<sup>-1</sup> (C-H aromatic). <sup>1</sup>HNMR (DMSO-d<sub>6</sub>, 90 MHz)  $\delta$  ppm = 8.20-7.30 (m, 9H, aromatic-H), 8.3 (s, 1H, CH), 4.15 (s, 2H, CH<sub>2</sub>). UV at  $\lambda_{\max}$  ( $\epsilon$ ) = 370.0 (21200), 302.5 (23800), 247.5 (10600) nm (L mol<sup>-1</sup> cm<sup>-1</sup>), Abs. = 0.424, 0.476, 0.212 respectively. Elemental analysis for C<sub>18</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub>S (364.37). Calcd: C, 59.33; H, 3.31; N, 15.36; S, 8.79%. Found: C, 59.29; H, 3.42; N, 15.56; S, 8.61%.

**(E)-6-(4-Methoxybenzylidene)-2-benzylthiazolo[3,2-*b*][1,2,4]-triazol-5(6*H*)-one (9d).** R = OCH<sub>3</sub>. This compound was obtained as greenish yellow crystals in 81% yield, Mp. 183-184 °C, R<sub>f</sub> = 0.48. IR (KBr)  $\nu$  = 3030m (C-H aromatic) 2960m, (C-H aliphatic), 1710s (C=O), 1590s (C=N), 1500s, 1460s, 1440s (aromatic skeleton), 690s, 750s cm<sup>-1</sup> (C-H aromatic). <sup>1</sup>HNMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  = 7.70-7.20 (m, 9H, aromatic-H), 8.20 (s, 1H, CH), 4.20 (s, 2H, CH<sub>2</sub>), 3.9 (s, 3H, OCH<sub>3</sub>). UV at  $\lambda_{\max}$  ( $\epsilon$ ) = 380.5 (30100), 314.5 (8000), 247.0 (12700) nm (L mol<sup>-1</sup> cm<sup>-1</sup>), Abs. = 0.602, 0.160, 0.255 respectively. Elemental analysis for C<sub>19</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S (349.41). Calcd: C, 65.31; H, 4.32; N, 12.02; S, 9.17%. Found: C, 65.15; H, 4.16; N, 11.94; S, 8.84%.

**(E)-6-(4-*N,N*-Dimethylaminobenzylidene)-2-benzylthiazolo[3,2-*b*][1,2,4]triazol-5(6*H*)-one (9e).** R = N(CH<sub>3</sub>)<sub>2</sub>. This compound was obtained as red crystals in 87% yield, Mp. 203-204 °C. R<sub>f</sub> = 0.37, IR (KBr)  $\nu$  = 3030m (C-H aromatic) 2960m, (C-H aliphatic), 1710s (C=O), 1580s (C=N), 1500s, 1460s, 1440s (aromatic skeleton), 690s, 720s, 760s cm<sup>-1</sup> (C-H aromatic). <sup>1</sup>HNMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  = 7.70-6.60 (m, 9H, aromatic-H), 8.05 (s, 1H, CH), 4.20 (s, 2H, CH<sub>2</sub>), 3.1 (s, 6H, N(CH<sub>3</sub>)<sub>2</sub>). UV at  $\lambda_{\max}$  ( $\epsilon$ ) = 458.5 (54150), 316.5 (5050), 268.5 (9350) nm (L mol<sup>-1</sup> cm<sup>-1</sup>), Abs. = 1.083, 0.101, 0.187 respectively. Elemental analysis for C<sub>20</sub>H<sub>18</sub>N<sub>4</sub>OS (362.46). Calcd: C, 66.28; H, 5.01; N, 15.46; S, 8.84%. Found: C, 66.40; H, 5.00; N, 15.49; S, 8.05%.

**(E)-6-(4-Bromobenzylidene)-2-benzylthiazolo[3,2-*b*][1,2,4]-triazol-5(6*H*)-one (9f).** R = Br. This compound was obtained as yellow crystals in 91% yield, Mp. 194-195 °C, R<sub>f</sub> = 0.66. IR (KBr)  $\nu$  = 3030m (C-H aromatic) 2960m, (C-H aliphatic), 1710s (C=O), 1580s (C=N), 1500s, 1460s, 1440s (aromatic skeleton), 690s, 720s, 760s cm<sup>-1</sup> (C-H aromatic). <sup>1</sup>HNMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  = 7.60-7.20 (m, 9H, aromatic-H), 8.00 (s, 1H, CH), 4.10 (s, 2H, CH<sub>2</sub>). UV at  $\lambda_{\max}$  ( $\epsilon$ ) = 363.5 (26100), 312.0 (18000), 246.5 (11550) nm (L mol<sup>-1</sup> cm<sup>-1</sup>), Abs. = 0.522, 0.360, 0.231 respectively. Elemental analysis for C<sub>18</sub>H<sub>12</sub> BrN<sub>3</sub>OS (398.28). Calcd: C, 54.28; H, 3.03; N, 10.55; S, 8.05%. Found: C, 54.64; H, 2.83; N, 10.60; S, 7.90%.

**(E)-6-(4-Acetyloxybenzylidene)-2-benzylthiazolo[3,2-*b*][1,2,4]triazol-5(6*H*)-one (9g).** R = OCOCH<sub>3</sub>. This compound was obtained as colorless crystals in 66% yield, Mp. 123-124 °C, R<sub>f</sub> = 0.39. IR (KBr)  $\nu$  = 3030m (C-H aromatic) 2960m, (C-H aliphatic), 1760s (OCO), 1730s (C=O), 1580s (C=N), 1500s, 1460s, 1440s (aromatic skeleton), 690s, 720s, 760s cm<sup>-1</sup> (C-H aromatic). <sup>1</sup>HNMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  = 7.60-7.20 (m, 9H, aromatic-H), 8.00 (s, 1H, CH), 4.10 (s, 2H, CH<sub>2</sub>), 2.35 (s, 3H, COCH<sub>3</sub>). Elemental analysis for C<sub>20</sub>H<sub>15</sub> N<sub>3</sub>O<sub>3</sub>S (377.42). Calcd: C, 63.64; H, 4.00; N, 11.13; S, 8.49%. Found: C, 63.58; H, 4.21; N, 11.01; S, 8.37%.

**Synthesis of 2-Benzyl-6-[phenyl(piperidin-1-yl)morpholin-1-yl)methyl]thiazolo[3,2-*b*][1,2,4]triazol-5-**

**ols (11a-j).** General procedure: To a solution of **9a-e** (2 mmol) in tetrahydrofuran (20 mL) a solution of piperidine or morpholine (3 mmol) was added and the mixture was stirred for 6 hours at room temperature. The crude product thus formed was crystallized from benzene/cyclohexane mixture to give the addition products **11a-j** in 65 ~ 75% yield. The UV absorption spectra of compounds **11a-j** were measured in CHCl<sub>3</sub> in concentration of 4x10<sup>-5</sup> mol/liter.

**2-Benzyl-6-[phenyl(piperidin-1-yl)methyl]thiazolo[3,2-*b*][1,2,4]triazol-5-ol (11a).** R = H, X = CH<sub>2</sub>. This compound was obtained as colorless crystals in 67% yield, Mp. 130-131 °C. IR (KBr)  $\nu$  = 3100m (O-H), 3030m (C-H aromatic) 2960m, (C-H aliphatic), 1590s (C=N), 1520s, 1480s, 1440s (aromatic skeleton), 680s, 750s, 700s cm<sup>-1</sup> (C-H aromatic). <sup>1</sup>HNMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  = 7.70-7.30 (m, 10H, aromatic-H), 6.90 (s, 1H, CH), 4.20 (s, 2H, CH<sub>2</sub>), 3.7-3.2 (m, 4H, N(CH<sub>2</sub>)<sub>2</sub>), 1.7-1.4 (m, 6H, (CH<sub>2</sub>)<sub>3</sub>). UV at  $\lambda_{\max}$  ( $\epsilon$ ) = 274 (13800), 234 (9375) nm (L mol<sup>-1</sup> cm<sup>-1</sup>), Abs. = 0.552, 0.375 respectively. Elemental analysis for C<sub>23</sub>H<sub>24</sub> N<sub>3</sub>OS (404.54). Calcd: C, 68.29; H, 5.98; N, 13.85; S, 7.93%. Found: C, 68.40; H, 6.31; N, 13.88; S, 7.58%.

**2-Benzyl-6-[(4-chlorophenyl)(piperidin-1-yl)methyl]thiazolo[3,2-*b*][1,2,4]triazol-5-ol (11b).** R = Cl, X = CH<sub>2</sub>. This compound was obtained as colorless crystals in 70% yield, Mp. 171-172 °C. IR (KBr)  $\nu$  cm<sup>-1</sup> = 3180m (O-H), 3050m (C-H aromatic) 2940m, (C-H aliphatic), 1600s (C=N), 1520s, 1480s, 1440s (aromatic skeleton), 680s, 750s, 700s (C-H aromatic). <sup>1</sup>HNMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  = 7.80-7.20 (m, 9H, aromatic-H), 6.80 (s, 1H, CH), 4.10 (s, 2H, CH<sub>2</sub>), 3.5-3.2 (m, 4H, N(CH<sub>2</sub>)<sub>2</sub>), 1.6-1.4 (m, 6H, (CH<sub>2</sub>)<sub>3</sub>), UV at  $\lambda_{\max}$  ( $\epsilon$ ) = 283 (18225), 236 (11575) nm (L mol<sup>-1</sup> cm<sup>-1</sup>), Abs. = 0.729, 0.463 respectively. Elemental analysis for C<sub>23</sub>H<sub>23</sub> Cl N<sub>4</sub>OS (438.98). Calcd: C, 62.93; H, 5.28; N, 12.76; S, 7.30%. Found: C, 62.82; H, 5.63; N, 12.76; S, 6.86%.

**2-Benzyl-6-[(4-nitrophenyl)(piperidin-1-yl)methyl]thiazolo[3,2-*b*][1,2,4]triazol-5-ol (11c).** R = NO<sub>2</sub>, X = CH<sub>2</sub>. This compound was obtained as yellow crystals in 69% yield, Mp. 175-176 °C. IR (KBr)  $\nu$  = 3120m (O-H), 3030m (C-H aromatic) 2900m, (C-H aliphatic), 1600s (C=N), 1500s, 1440s (aromatic skeleton), 750s, 730s, 690s cm<sup>-1</sup> (C-H aromatic). <sup>1</sup>HNMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  = 7.80-7.20 (m, 9H, aromatic-H), 6.80 (s, 1H, CH), 4.10 (s, 2H, CH<sub>2</sub>), 3.45, 3.13 (m, 4H, N(CH<sub>2</sub>)<sub>2</sub>), 1.50 (m, 4H, (CH<sub>2</sub>)<sub>2</sub>), 1.33 (m, 2H, CH<sub>2</sub>), UV at  $\lambda_{\max}$  ( $\epsilon$ ) = 332 (1575), 243 (14650) nm (L mol<sup>-1</sup> cm<sup>-1</sup>), Abs. = 0.623, 0.586 respectively. Elemental analysis for C<sub>23</sub>H<sub>23</sub> N<sub>3</sub>O<sub>3</sub>S (449.54). Calcd: C, 61.45; H, 5.16; N, 15.68; S, 7.13%. Found: C, 61.31; H, 4.89; N, 15.57; S, 7.00%.

**2-Benzyl-6-[(4-methoxyphenyl)(piperidin-1-yl)methyl]thiazolo[3,2-*b*][1,2,4]triazol-5-ol (11d).** R = OCH<sub>3</sub>, X = CH<sub>2</sub>. This compound was obtained as pale yellow crystals in 71% yield, Mp. 128-129 °C. IR (KBr)  $\nu$  = 3150m (O-H), 3030m (C-H aromatic) 2920m, (C-H aliphatic), 1590s (C=N), 1500s, 1440s (aromatic skeleton), 680s, 750s, 700s cm<sup>-1</sup> (C-H aromatic). <sup>1</sup>HNMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  = 7.60-7.30 (m, 9H, aromatic-H), 6.90 (s, 1H, CH), 4.20 (s, 2H, CH<sub>2</sub>), 3.65 (s, 3H, OCH<sub>3</sub>) 3.6-3.2 (m, 4H, N(CH<sub>2</sub>)<sub>2</sub>), 1.6-1.4 (m, 6H, (CH<sub>2</sub>)<sub>3</sub>), UV at  $\lambda_{\max}$  ( $\epsilon$ ) = 313 (15800), nm (L mol<sup>-1</sup> cm<sup>-1</sup>), Abs. = 0.632. Elemental analysis for C<sub>24</sub>H<sub>26</sub> N<sub>4</sub>O<sub>2</sub>S (434.56). Calcd: C, 66.33; H, 6.03; N, 12.88; S, 7.38%. Found: C, 66.41; H, 5.82; N, 12.80; S, 7.12%.

**2-Benzyl-6-[(4-*N,N*-dimethylaminophenyl)(piperidin-1-yl)methyl]thiazolo[3,2-*b*][1,2,4]triazol-5-ol (11e).** R = N(CH<sub>3</sub>)<sub>2</sub>,

X = CH<sub>3</sub>. This compound was obtained as orange crystals in 75% yield, Mp. 182-183 °C. IR (KBr)  $\nu$  = 3150m (O-H), 3030m (C-H aromatic) 2920m, (C-H aliphatic), 1590s (C=N), 1500s, 1440s (aromatic skeleton), 680s, 720s, 780s cm<sup>-1</sup> (C-H aromatic). <sup>1</sup>HNMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  = 7.70-6.60 (m, 9H, aromatic-H), 6.90 (s, 1H, CH), 4.10 (s, 2H, CH<sub>2</sub>), 3.65 (s, 3H, OCH<sub>3</sub>), 3.5-3.3 (m, 4H, N (CH<sub>2</sub>)<sub>2</sub>), 1.6-1.3 (m, 6H, (CH<sub>2</sub>)<sub>3</sub>), 2.90 (s, 6H, N(CH<sub>3</sub>)<sub>2</sub>). UV at  $\lambda_{\max}$  ( $\epsilon$ ) = 359 (26150), 324 (12000) nm (L mol<sup>-1</sup> cm<sup>-1</sup>), Abs. = 1.046, 0.480 respectively. Elemental analysis for C<sub>25</sub>H<sub>29</sub>N<sub>5</sub>O<sub>5</sub>S (447.61). Calcd: C, 67.08; H, 6.53; N, 15.64; S, 7.16%. Found: C, 67.21; H, 6.71; N, 15.74; S, 6.99%.

**2-Benzyl-6-[morpholino(phenyl)methyl]thiazolo[3,2-b][1,2,4]triazol-5-ol (11f).** R = H, X = O. This compound was obtained as colorless crystals in 65% yield, Mp. 174-175 °C. IR (KBr)  $\nu$  = 3150m (O-H), 3030m (C-H aromatic) 2920m, (C-H aliphatic), 1590s (C=N), 1500s, 1440s (aromatic skeleton), 680s, 720s, 780s cm<sup>-1</sup> (C-H aromatic). <sup>1</sup>HNMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  = 7.80-7.30 (m, 10H, aromatic-H), 6.90 (s, 1H, CH), 4.20 (s, 2H, CH<sub>2</sub>), 3.80-3.40 (m, 8H, 4CH<sub>2</sub>). UV at  $\lambda_{\max}$  ( $\epsilon$ ) = 281 (14375), 236 (11025) nm (L mol<sup>-1</sup> cm<sup>-1</sup>), Abs. = 0.575, 0.441 respectively. Elemental analysis for C<sub>22</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub>S (406.51). Calcd: C, 65.00; H, 5.46; N, 13.78; S, 7.88%. Found: C, 64.77; H, 5.90; N, 13.79; S, 7.59%.

**2-Benzyl-6-[morpholino(4-chlorophenyl)methyl]thiazolo[3,2-b][1,2,4]triazol-5-ol (11g).** R = Cl, X = O. This compound was obtained as colorless crystals in 72% yield, Mp. 141-142 °C. IR (KBr)  $\nu$  = 3160m (O-H), 3050m (C-H aromatic) 2920m, (C-H aliphatic), 1590s (C=N), 1420s, 1450s, 1480s (aromatic skeleton), 680s, 710s, 750s cm<sup>-1</sup> (C-H aromatic). <sup>1</sup>HNMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  = 7.48-7.17 (m, 9H, aromatic-H), 6.77 (s, 1H, CH), 4.10 (s, 2H, CH<sub>2</sub>), 3.26 (m, 4H, O(CH<sub>2</sub>)<sub>2</sub>), 3.41 (m, 2H, NCH<sub>2</sub>), 3.28 (m, 2H, NCH<sub>2</sub>). UV at  $\lambda_{\max}$  ( $\epsilon$ ) = 288 (14500), 233 (10400) nm (L mol<sup>-1</sup> cm<sup>-1</sup>), Abs. = 0.580, 0.416 respectively. MS m/z (%) = 442 (7) [M<sup>+</sup>], 440 (7) [M<sup>+</sup>], 354 (98), 352 (98), 325 (16), 323 (27), 289 (4), 243 (3), 220 (1), 208 (9), 190 (20), 169 (41), 167 (100), 135 (28), 117 (21), 116 (31), 103 (34), 91 (43), 87 (38), 77 (18), 57 (35). Elemental analysis for C<sub>22</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>2</sub>S (440.96). Calcd: C, 59.93; H, 4.79; N, 12.71; S, 7.26%. Found: C, 60.11; H, 4.48; N, 12.60; S, 7.24%.

**2-Benzyl-6-[morpholino(4-nitrophenyl)methyl]thiazolo[3,2-b][1,2,4]triazol-5-ol (11h).** R = NO<sub>2</sub>, X = O. This compound was obtained as yellow crystals in 74% yield, Mp. 179-180 °C. IR (KBr)  $\nu$  = 3120m (O-H), 3030m (C-H aromatic) 2920m, (C-H aliphatic), 1590s (C=N), 1500s, 1440s (aromatic skeleton), 690s, 730s, 750s cm<sup>-1</sup> (C-H aromatic). <sup>1</sup>HNMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  = 8.30-7.30 (m, 9H, aromatic-H), 6.80 (s, 1H, CH), 4.20 (s, 2H, CH<sub>2</sub>), 3.70-3.30 (m, 8H, 4CH<sub>2</sub>). UV at  $\lambda_{\max}$  ( $\epsilon$ ) = 239 (12800), 246 (11800) nm (L mol<sup>-1</sup> cm<sup>-1</sup>), Abs. = 0.512, 0.472 respectively. Elemental analysis for C<sub>22</sub>H<sub>21</sub>N<sub>5</sub>O<sub>4</sub>S (451.51). Calcd: C, 58.53; H, 4.69; N, 15.50; S, 7.10%. Found: C, 58.54; H, 4.41; N, 15.56; S, 7.31%.

**2-Benzyl-6-[morpholino(4-methoxyphenyl)methyl]thiazolo[3,2-b][1,2,4]triazol-5-ol (11i).** R = OCH<sub>3</sub>, X = O. This compound was obtained as pale yellow crystals in 68% yield, Mp. 137-138 °C. IR (KBr)  $\nu$  = 3150m (O-H), 3030m (C-H aromatic) 2920m, (C-H aliphatic), 1590s (C=N), 1430, 1500s, 1520s (aromatic skeleton), 690s, 710s, 740s cm<sup>-1</sup> (C-H aromatic). <sup>1</sup>HNMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  = 7.70-7.20 (m, 9H, aromatic-H), 6.80 (s, 1H, CH), 4.10 (s, 2H, CH<sub>2</sub>), 3.60-3.40 (m, 8H, 4CH<sub>2</sub>), 3.8 (s, 3H, OCH<sub>3</sub>). UV at  $\lambda_{\max}$  ( $\epsilon$ ) = 311 (20025) nm (L mol<sup>-1</sup> cm<sup>-1</sup>), Abs. = 0.801. Elemental analysis for

C<sub>23</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>S (436.54). Calcd: C, 63.28; H, 5.54; N, 12.83; S, 7.34%. Found: C, 62.50; H, 6.01; N, 12.84; S, 7.39%.

**2-Benzyl-6-[morpholino(4-N,N-dimethylaminophenyl)methyl]thiazolo[3,2-b][1,2,4]triazol-5-ol (11j).** R = N(CH<sub>3</sub>)<sub>2</sub>, X = O. This compound was obtained as orange crystals in 71% yield, Mp. 165-166 °C. IR (KBr)  $\nu$  = 3200m (O-H), 3050m (C-H aromatic) 2960m, (C-H aliphatic), 1590s (C=N), 1430, 1480s, 1510s (aromatic skeleton), 690s, 700s, 750s cm<sup>-1</sup> (C-H aromatic). <sup>1</sup>HNMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  = 7.70-6.60 (m, 9H, aromatic-H), 6.80 (s, 1H, CH), 4.10 (s, 2H, CH<sub>2</sub>), 3.60-3.40 (m, 8H, 4CH<sub>2</sub>), 3 (s, 6H, N (CH<sub>3</sub>)<sub>2</sub>). UV at  $\lambda_{\max}$  ( $\epsilon$ ) = 366 (21200), 326 (11200) nm (L mol<sup>-1</sup> cm<sup>-1</sup>), Abs. = 0.848, 0.448 respectively. Elemental analysis for C<sub>24</sub>H<sub>27</sub>N<sub>5</sub>O<sub>2</sub>S (449.58). Calcd: C, 64.12; H, 6.04; N, 15.58; S, 7.12%. Found: C, 64.17; H, 5.81; N, 15.49; S, 7.27%.

**Synthesis of 4-(N,N-dimethylaminobenzylidene)malononitrile (12).** A mixture of **9e** (3 mmol) with malononitrile and few drops of pyridine in ethanol (30 mL) was refluxed on a water bath for 3 hours. The reaction mixture was cooled and the precipitate thus obtained was collected by filtration, dried and crystallized from ethanol to give the unexpected benzylidene-malononitrile **12** as orange needles in 82% yield, Mp. 180-181°C (Lit. [21] 179-180°). In addition a minor amount of the starting compound was isolated as colorless crystals and identified by analysis as 3-benzyl-4-phenyl-1,2,4-triazol-5-thiol (**1**) [6]. An authentic sample of **12** was prepared by the reaction of *p*-N,N-dimethylaminobenzaldehyde (10 mmol) and malononitrile (12 mmol) in ethanol in the presence of piperidine for comparison purpose.

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