Asian Journal of Chemistry Vol. 21, No. 1 (2009), 617-626

Synthesis of Tautomeric Forms of 5-(2-Hydroxyphenyl)-4-substituted-3*H*-1,2,4-triazole-3-thione

AHMET CANSIZ, AHMET ÇETIN, PELIN KUTULAY and METIN KOPARIR*
Chemistry Department, Faculty of Arts and Sciences
Firat University, 23119 Elazig, Turkey
Fax: (90)(424)2370011; Tel: (90)(424)2370000
E-mail: mkoparir@hotmail.com

In this study, salicylic acid hydrazide **1** was converted into 1,4-substituted thiosemicarbazides (**2a-f**). The 1,4-substituted thiosemicarbazides were then converted into 5-(2-hydroxy phenyl)-4-substituted-3*H*-1,2,4-triazole-3-thione (**3a-f**). In addition, the aminomethylation compounds of 5-(2-hydroxy phenyl)-4-substituted-3*H*-1,2,4-triazole-3-thione (**4a-f**) were synthesized by the Mannich reaction of **3a-f** and then {[5-(2-hydroxy phenyl)-4-methyl-4*H*-1,2,4-triazol-3-yl]thio}acetic acid (**5a-f**) were prepared by **3a-f**. The structures of all the synthesized compounds were confirmed by elemental analyses, X-ray, FT-IR, ^{1}H NMR and ^{13}C NMR spectra. Their thiol-thione tautomeric equilibrium is described.

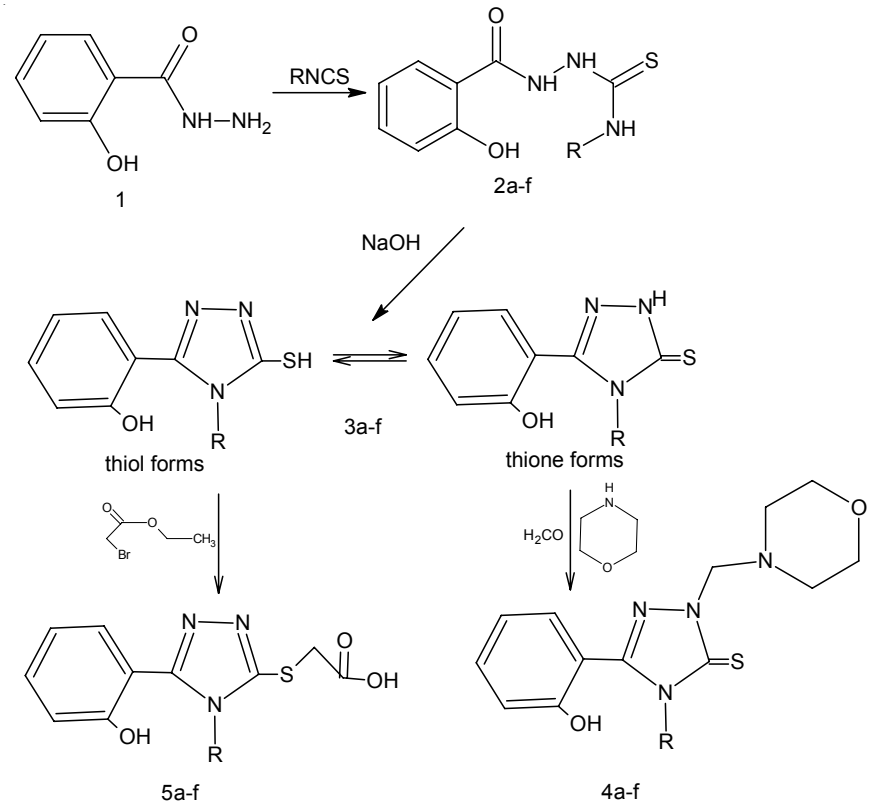
Key Words: 1,2,4-Triazole, Thiol/thione tautomeric forms.

INTRODUCTION

The ring-closure reactions of carbohydrazides are well-known and have been extensively studied. In these types reactions, five-membered heterocycles with three heteroatoms are formed, such as 1,2,4-triazolees.Triazoles and their derivatives have been proven to be effective bactericides, pesticides and fungicides[1-3]. Further, some findings that the 1,2,4-triazole nucleus is associated with diverse pharmacological activities such as analgesic, anti-asthematic, diuretic, antihypertensive and antiinflammatory properties have made them important chemotherapeutic agents[4-7]. Acyl hydrazides have been in general use as the starting materials in some 1,2,4-triazole syntheses[8,9]. In addition there are some studies on electronic structures and thiol-thione tautomeric equilibrium of heterocyclic thione derivatives[10-15].

The new derivatives were prepared following the reaction sequences depicted in **Scheme-I**. Initial compounds were prepared from salicylic acid hydrazide (**1**). 1-(2-Hydroxybenzoyl)-4-substituted thiosemicarbazides (**2a-f)** were prepared in yields ranging from 88 to 95 % by the condensation of compound **1** with aryl-alkyl isothiocyanates. Ring closure of arylthiosemicarbazides in an alkaline medium is a well known method for the synthesis

of 5-(2-hydroxyphenyl)-4-substituted-3*H*-1,2,4-triazole-3-thione (**3a-f**) were obtained in 62-79 % yields from the respective **2a-f** by this method. A series of Mannich bases of 5-(2-hydroxyphenyl)-4-substituted-3*H*-1,2,4-triazole-3-thione (**4a-f**) were then synthesized by the reaction of **3a-f** with morpholine and formaldehyde in ethanol. **5a-f** were obtained from reaction of **3a-f** with ethyl bromoacetate in an alkaline medium. Finally, we have also partly contributed to this progress by obtaining new 18 derivatives of 1,2,4-triazole nucleus.



Scheme-I

EXPERIMENTAL

Melting points were determined in an open capillary tube on a digital Gallenkamp melting point apparatus and are uncorrected. Elemental analyses (C, H, N) were caried out using LECO-932 CHNSO by Technical and Scientific Research Council of Turkey, TUBITAK. The IR spectra were recorded

for KBr disks with a Mattson 1000 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varian-Mercury-Plus 400 MHz ^{1}H NMR, 100 MHz ^{13}C NMR spectrometer in DMSO-d_6 and D_2O with TMS as an internal standard. Starting materials was obtained from Fluka or Aldrich.

General procedure for the synthesis of 2-(2-hydroxybenzoyl)-N-substituted hydrazine-carbothioamide (2a-f): 1.52 g (0.01 mol) salicylic acid hydrazide (**1**) in 50 mL of absolute ethanol was heated until it dissolved. 0.01 mol appropriate substituted isothiocyanate derivatives was added and the reaction mixture were refluxed for 5 h. After the completion of the reaction, the crude product which precipitated on cooling was filtered, washed with diethyl ether, dried and crystallized from suitable solvents.

2-(2-Hydroxybenzoyl)hydrazinecarbothioamide (2a): 1.47 g (70 %), m.p. 157-158 °C; IR (KBr, ν_{max}, cm^{-1}): 3323-3111 (NH and OH), 3073-3010 (Ar.CH), 1666 (C=O), 1615 (NH), 1590-1460 (C=C), 1262 (C=S); ^{1}H NMR (ppm): δ 4.70 (s, 2H, S=C-NH_2), 6.86 (t, *J* = 8.25, 1H, H3), 6.97 (d, *J* = 8.85, 1H, H1), 7.35 (t, *J* = 7.03, 1H, H2), 7.77 (dd, *J* = 7.96, 1.43, 1H, H4), 10.03 (br, 1H, NH-CO), 12.6 (br, 2H, OH, N-NH-C=S); Anal. calcd. (%) for $C_8H_9N_3O_2S$: C 46.49, H 4.29, N 19.89; Found: C 48.60, H 4.29, N 20.87.

N-Ethyl-2-(2-hydroxybenzoyl)hydrazinecarbothioamide (2b): 1.86 g (78 %), m.p. 216-218 ºC; IR (KBr, ν_{max}, cm^{-1}): 3317-3110 (NH and OH), 3073-3010 (Ar. CH), 2996-2938 (Aliph. CH), 1673 (C=O), 1622 (NH), 1608-1468 (C=C), 1263 (C=S); ^{1}H NMR (ppm): δ 1.04 (t, *J* = 6.97, 3H, CH_3), 3.47 (q, *J* = 6.68, 2H, CH_2), 6.87-6.93 (m, 2H, H1, H3), 7.42 (t, *J* = 8.43, 1H, H2), 7.83 (dd, *J* = 7.70, 1.10, 1H, H4), 8.13 (s, 1H, S=C-NH-C), 9.37 (br, 1H, NH-CO), 10.52 (br, 1H, NH-C=S), 11.90 (br, 1H, OH); Anal. calcd. (%) for $C_{10}H_{13}N_3O_2S$: C 50.19, H 5.48, N 17.56; found: C 50.16, H 5.46, N 17.57.

2-(2-Hydroxybenzoyl)-N-phenylhydrazinecarbothioamide (2c): 2.44 g (85 %), m.p. 200-202 ºC; IR (KBr, ν_{max}, cm^{-1}): 3420-3118 (NH and OH), 3080-3010 (Ar.CH), 1666 (C=O), 1624 (NH), 1610-1464 (C=C), 1265 (C=S); ^{1}H NMR (ppm): δ 6.90-6.95 (m, 2H, H1, H3), 7.12-7.15 (t, *J* = 7.33, 1H, H7), 7.32 (t, *J* = 8.40, 2H,, H6a, H6b), 7.40-7.45 (m, 3H, H2, H5a, H5b), 7.87 (d, *J* = 7.32, 1H, H4) 9.86 (br, 2H, NH-CO, S=C-NH-C), 10.71 (br, 1H, NH-CS), 11.87 (br, 1H, OH); Anal. calcd. (%) for $C_{14}H_{13}N_3O_2S$: C 58.52, H 4.56, N 14.62; found: C 58.54, H 4.59, N 14.58.

2-(2-Hydroxybenzoyl)-N-(4-methylphenyl)hydrazinecarbothioamide (2d): 2.25 g (75 %), m.p. 215-216 ºC; IR (KBr, ν_{max}, cm^{-1}): 3390-3118 (N-H and O-H), 3080-3000 (Ar. C-H), 2990-2880 (Al. C-H), 1660 C=O), 1634 (N-H), 1609-1458 (C=C), 1262 (C=S); ^{1}H NMR (ppm): δ 2.26 (s, 3H, CH_3), 6.93 (q, *J* = 8.43, 2H, H1, H3), 7.12 (d, *J* = 8.43, 2H, H6a, H6b), 7.30 (d, *J* = 7.86, 2H, H5a, H5b), 7.43 (t, *J* = 8.43, 1H, H2),

7.87 (d, *J* = 7.33, 1H, H4), 9.78 (br, 2H, NH-CO, SC-NH-C), 10.70 (br, 1H, NH-CS), 11.88 (br, 1H, OH) Anal. calcd. (%) for $C_{15}H_{15}N_3O_2S$: C 59.78, H 5.02, N 13.94; Found: C 59.79, H 5.08, N 13.90.

N-Benzyl-2-(2-hydroxybenzoyl)hydrazinecarbothioamide (2e): 2.25 (75 %), m.p. 214 ºC; IR (KBr, ν_{max}, cm^{-1}): 3285-3168 (NH and OH), 3100-3000 (Ar. CH), 2983-2938 (Al. CH), 1666 (C=O), 1641 (NH), 1602-1460 (C=C), 1255 (C=S); ^{1}H NMR (ppm): δ 4.71 (d, *J* = 6.23, 2H, NH-CH_2), 6.88-6.93 (m, 2H, H1, H3), 7.18-7.22 (m, 1H, H7), 7.28 (s, 2H, H5a, H5b), 7.29 (s, 4H, H6a, H6b), 7.42 (t, *J* = 8.43, 1H, H2), 7.85 (d, *J* = 8.06, 1H, H4), 8.70 (br, 1H, S=C-NH-C), 9.54 (br, 1H, NH-CO), 10.60 (br, 1H, NH-CS), 11.94 (br, 1H, OH); Anal. calcd. (%) for $C_{15}H_{15}N_3O_2S$: C 59.78, H 5.02, N 13.94; found: C 59.77, H 5.04, N 13.93.

N-Allyl-2-(2-hydroxybenzoyl)hydrazinecarbothioamide (2f): 1.76 g (70 %), m.p. 210-211 ºC; IR (KBr, ν_{max}, cm^{-1}): 3281-3131 (NH and OH), 3100-3000 (Ar.CH), 3041-2955 (C=CH), 1667 (C=O), 1641 (NH), 1250 (C=S), 975-910 (-CH=CH_2); ^{1}H NMR (ppm): δ 4.08 (t, *J* = 5.50, 2H, NH-CH_2-CH), 5.04 (dd, 1H, *Jcis* = 7.80, 1.47, NH-CH_2-CH=CH_2), 5.12 (dd, 1H, *Jt* = 15.40, 1.83, NH-CH_2-CH=CH_2), 5.80 (dq, *J* = 11.13, 5.13, 1H, NH-CH_2-CH=CH_2), 6.90 (q, *J* = 7.82, 2H, H1, H3), 7.42 (t, *J* = 8.05, 1H, H2,), 7.83 (d, *J* = 7.80, 1H, H4), 8.32 (br, 1H, S=C-NH-C), 9.48 (br, 1H, NH-CO), 10.55 (br, 1H, NH-CS), 11.90 (br, 1H, OH). ^{13}C NMR (ppm): δ 182.33, 168.10, 160.13, 135.51, 134.77, 129,29, 119.47, 117.88, 116.01, 115.47, 46.64); Anal. calcd. (%) for $C_{12}H_{15}N_3O_2S$: C 54.32, H 5.70, N 15.84; found: C 54.34, H 5.71, N 15.84.

General procedure for the synthesis of 5-(2-hydroxyphenyl)-4-substituted-3*H*-1,2,4-triazole-3-thione (3a-f): A solution of 0.01 mole **2a-f** in 50 mL 1 N NaOH solution was heated under reflux for 5 h. The mixture was cooled and acidified to pH 3 with concentrated hydrochloric acid was added. The precipitate was filtered and washed several times with distilled water. The pure compounds were obtained following crystallization from suitable solvent.

5-(2-Hydroxyphenyl)-3*H*-1,2,4-triazole-3-thione (3a): 1.55 g (80 %), m.p. 240-242 ºC; IR (KBr, ν_{max}, cm^{-1}): 3560-3180 (OH and NH), 3110-3060 (Ar.CH), 1621 (C=N), 1254 (C=S); ^{1}H NMR (ppm): δ 6.81-7.87 (m, 6H, Ar.CH, NH, OH), 13.95 (br, 1H, SH); Anal. calcd. (%) for $C_8H_7N_3OS$: C 49.73, H 3.65, N 21.75; found: C 49.71, H 3.67, N 21.76.

5-(2-Hydroxyphenyl)-4-ethyl-3*H*-1,2,4-triazole-3-thione (3b): 1.88 g (85 %), m.p. 254-258 ºC; IR (KBr, ν_{max}, cm^{-1}): 3540-3120 (OH), 3118-3040 (Ar.CH), 2983 (Al. CH), 2938, 2762, 2565 (SH), 1628 (C=N); ^{1}H NMR (ppm): δ 1.03 (t, *J* = 7.32, 3H, CH_3), 3.47 (q, *J* = 7.32, 2H, CH_2), 6.93 (t, *J* = 7.30, 1H, H1), 6.99 (d, *J* = 8.05, 1H, H3), 7.29 (dd, *J* = 8.05, 1.47, 1H, H4), 4.39 (t, 7.40, 1H, H2), 10.30 (br, 1H, OH). 13.77 (br, 1H, SH);

Anal. calcd. (%) for $C_{10}H_{11}N_3OS$: C 54.28, H 5.01, N 18.99; found: C 54.27, H 5.02, N 18.93.

5-(2-Hydroxyphenyl)-4-phenyl-3*H*-1,2,4-triazole-3-thione (3c): 2.42 g (90 %), m.p. 300-301 ºC; IR (KBr, ν_{max}, cm^{-1}): 3382-3240 (OH), 3118-3065 (Ar.CH), 2932, 2760, 2565 (SH), 1628 (C=N); ^{1}H NMR (ppm): δ 6.71 (d, *J* = 8.05, 1H, H1), 6.78 (t, *J* = 7.32, 1H, H3), 7.19-7.37 (m, 7H, Ar.CH), 9.87 (br, 1H, OH), 13.99 (br, 1H, SH); Anal. calcd. (%) for $C_{14}H_{11}N_3OS$: C 62.43, H 4.12, N 15.60; Found: C 62.45, H 4.14, N 15.70.

5-(2-Hydroxyphenyl)-4-(4-tolyl)-3*H*-1,2,4-triazole-3-thione (3d): 2.41 (85 %), m.p. 293-295 ºC; IR (KBr, ν_{max}, cm^{-1}): 3320-3180 (OH), 3080-3035 (Ar.CH), 2930-3000 (Aliph. CH), 2932, 2758, 2560 (SH), 1628 (C=N); ^{1}H NMR (ppm): δ 2.25 (s, 3H, CH_3), 6.72 (d, *J* = 8.05, 1H, H1), 6.77 (t, *J* = 8.05, 1H, H3), 7.17-7.18 (m, 4H, H5a, H5b, H6a, H6b), 7.23 (t, *J* = 8.05, 1H, H2), 7.27 (dd, *J* = 8.05, 2.30, 1H, H4), 9.87 (br, 1H, OH). 13.95 (br, 1H, SH). ^{13}C NMR (ppm): δ 168.36, 156.54, 150.51, 138.89, 132.50, C5: 129.73, 128.28, 119.45, 116.34, 114.08, 21.35); Anal. calcd. (%) for $C_{15}H_{13}N_3OS$: C 63.58, H 4.62, N 14.83; found: C 63.62, H 4.64, N 14.84.

5-(2-Hydroxyphenyl)-4-benzyl-3*H*-1,2,4-triazole-3-thione (3e): 2.41 g (85 %), m.p. 198-200 ºC; IR (KBr, ν_{max}, cm^{-1}): 3298 (OH), 3080-3035 (Ar. CH), 3000-2930 (Aliph. CH), 2925, 2752, 2562 (SH), 1628 (C=N); ^{1}H NMR (ppm): δ 5.16 (s, 2H, N-CH_2), 6.79 (t, *J* = 7.32, 1H, H3), 6.88-6.70 (m, 3H, H1, H5a, H5b), 7.02-7.04 (m, 2H, H2, H4), 7.22-7.24 (m, 2H, H6a, H6b), 7.34 (m, 1H, H7), 10.40 (br, 1H, OH), 13.94 (br, 1H, SH); Anal. calcd. (%) for $C_{15}H_{13}N_3OS$: C 63.58, H 4.62, N 14.83; found: C 63.60, H 4.61, N 14.81.

5-(2-Hydroxyphenyl)-4-allyl-3*H*-1,2,4-triazole-3-thione (3f): 1.96 (80 %), m.p. 298-300 ºC; IR (KBr, ν_{max}, cm^{-1}): 3281-3100 (OH), 3090-3025 (Ar. CH), 3000-2930 (C=CH), 1628 (C=N), 1260 (C=S), 975-910 (CH=CH_2); ^{1}H NMR (ppm): δ 4.80 (d, *J* = 7.32, 2H, CH_2-CH=CH_2), 5.20-5.22 (m, 2H, CH_2-CH=CH_2), 5.82 (dq, *J* = 7.33, 1.10, 1H, Ar-CH_2-CH=CH_2), 6.78-6.80 (m, 2H, H1, H3), 7.21-7.23, 2H, H2, H4), 10.45 (br, 1H, OH); Anal. calcd. (%) for $C_{11}H_{11}N_3OS$: C 56.63, H 4.75, N 18.01; found: C 56.64, H 4.78, N 18.00.

General procedure for the synthesis of 4-substituted-5-(2-hydroxyphenyl)-2-(morpholin-4-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (4a-f): A slurry consisting 0.002 mol of **3a-f**, ethanol (10 mL) and (0.289 mL, 0.003 mol, 37 %) formalin was made. To this slurry, morpholine (0.002 mole, 0.174 mL) was added dropwise, with cooling and shaking. The reaction mixture was allowed to stand at room temprature for 1 h with occasional shaking after which it was warmed on a steam bath for 0.5 h. At the end of period the contents were cooled and the product obtained was recrystallized from suitable solvent.

5-(2-Hydroxyphenyl)-2-(morpholin-4-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (4a): 1.46 g (50 %), m.p. 257-259 ºC; IR (KBr, ν_{max}, cm^{-1}): 3480-3200 (OH, NH), 3120-3040 (Ar. CH), 2925-2860 (Al.CH), 1258 (C=S), 1623 (C=N); ^{1}H NMR (ppm): δ 2.70 (t, *J* = 4.40, 4H, CH_2-N-CH_2), 3.79 (t, *J* = 4.40, 4H, CH_2-O-CH_2), 5.09 (s, 2H, N-CH_2-N), 7.00 (d, *J* = 8.04, 1H, H1), 7.16 (t, *J* = 8.04, 1H, H3), 7.54 (t, *J* = 8.04, 1H, H2), 7.90 (dd, *J* = 8.04, 1.47, 1H, H4). 9.86 (br, 1H, OH); Anal. calcd. (%) for $C_{13}H_{16}N_4O_2S$: C 53.41, H 5.52, N 19.16; found: C 53.43, H 5.53, N 19.14.

4-Ethyl-5-(2-hydroxyphenyl)-2-(morpholin-4-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (4b): 1.76 g (55 %), m.p. 185-184 ºC; IR (KBr, ν_{max}, cm^{-1}): 3520-3240 (OH), 3198-3000 (Ar. CH), 2925-2854 (Al.CH), 1254 (C=S), 1618 (C=N); ^{1}H NMR (ppm): δ 1.04 (t, 3H, *J* = 7.32, CH_3), 3.88 (q, 2H, *J* = 6.97, CH_2-CH_3), 2.67 (t, *J* = 4.40, 4H, CH_2-N-CH_2), 3.78 (t, *J* = 4.40, 4H, CH_2-O-CH_2), 5.04 (s, 2H, N-CH_2-N), 6.89 (t, *J* = 8.43, 1H, H3). 7.16-7.26 (m, 3H, H1, H2, H4), 9.91 (br, 1H, OH); Anal. calcd. (%) for $C_{15}H_{20}N_4O_2S$: C 54.70, H 6.23, N 18.23; found: C 54.69, H 6.25, N 18.20.

5-(2-Hydroxyphenyl)-2-(morpholin-4-ylmethyl)-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (4c): 1.73 g (47 %), m.p. 203-204 ºC; IR (KBr, ν_{max}, cm^{-1}): 3488-3190 (OH), 3066-3000 (Ar. CH), 2970-2883 (Al. CH), 1252 (C=S), 1625 (C=N); ^{1}H NMR (ppm): δ 2.76 (t, *J* = 4.40, 4H, CH_2-N-CH_2), 3.57 (t, *J* = 4.40, 4H, CH_2-O-CH_2), 5.13 (s, 2H, N-CH_2-N), 6.72 (d, *J* = 7.34, 1H, H1), 6.81 (t, *J* = 7.70, 1H, H3), 7.20-7.40 (m, 7H, H2, H4, H5a, H5b, H6a, H6b, H7), 9.94 (br, 1H, OH); Anal. calcd. (%) for $C_{19}H_{20}N_4O_2S$: C 61.94, H 5.47, N 15.21; found: C 61.94, H 5.49, N 15.20.

5-(2-Hydroxyphenyl)-4-(4-tolyl)-2-(morpholin-4-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (4d): 1.92 g (44%), m.p. 130-132 ºC; IR (KBr, ν_{max}, cm^{-1}): 3340-3220 (OH), 3108-3000 (Ar. CH), 2960-2854 (Aliph. CH), 1621 (C=N); ^{1}H NMR (ppm): δ 2.23 (s, 3H, CH_3), 2.74-76 (m, 4H, CH_2-N-CH_2), 3.58 (t, *J* = 4.40, 4H, CH_2-O-CH_2), 5.13 (s, 2H, N-CH_2-N), 6.73-6.83 (m, 2H, H1, H3), 7.12 (d, *J* = 8.43, 2H, H6a, H6b), 7.14 (d, *J* = 8.43, 2H, H5a, H5b), 7.30-7.34 (m, 2H, H2, H4), 9.93 (br, 1H, OH); Anal. calcd. (%) for $C_{20}H_{22}N_4O_2S$: C 62.80, H 5.80, N 14.65; found: C 62.82, H 5.83, N 14.66.

4-Benzyl-5-(2-hydroxyphenyl)-2-(morpholin-4-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (4e): 1.98 g (50 %), m.p. 91-93 ºC; IR (KBr, ν_{max}, cm^{-1}): 3502-3245 (OH), 3140-2944 (Ar. and Al.CH), 1254 (C=S); ^{1}H NMR (ppm): δ 2.70 (t, *J* = 4.40, 4H, CH_2-N-CH_2), 3.55 (t, *J* = 4.40, 4H, CH_2-O-CH_2), 5.07 (s, 2H, N-CH_2-N), 5.38 (s, 2H, N-CH_2-ph), 6.44 (t, *J* = 7.33, 1H, H3), 6.55 (d, *J* = 8.03, 1H, H1), 6.82-7.20 (m, 7H, H5a, H5b, H7, H4, H2, H6a, H6b), 9.96 (br, 1H, OH); Anal. calcd. (%) for $C_{20}H_{22}N_4O_2S$: C 62.80, H 5.80, N 14.65; found: C 62.80, H 5.82, N 14.64.

4-Allyl-5-(2-hydroxyphenyl)-2-(morpholin-4-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (4f): 2.09 g (65 %), m.p. 171 ºC; IR (KBr, ν_{max}, cm^{-1}): 3320-3130 (OH), 3066-3000 (Ar. CH), 2990-2880 (Aliph. and olefenic C=CH), 1628 (C=N), 975-910 (-CH=CH_2); ^{1}H NMR (ppm): δ 2.70 (t, *J* = 4.40, 4H, CH_2-N-CH_2), 3.57 (t, *J* = 4.40, 4H, CH_2-O-CH_2), 4.62 (m, 2H, N-CH_2-CH=CH_2), 4.98-5.00 (m, 2H, N-CH_2-CH=CH_2), 5.62 (dq, *J* = 6.30, 5.17, 1H, N-CH_2-CH=CH_2), 5.02 (s, 2H, N-CH_2-N), 7.00-7.10 (m, 2H, H1, H3), 7.36-7.38-7.41 (m, 2H, H2, H4), 10.42 (br, 1H, OH); Anal. calcd. (%) for $C_{16}H_{20}N_4O_2S$: C 57.81, H 6.06, N 16.85; found: C 57.84, H 6.10, N 16.82.

General procedure for the synthesis of {[4-substituted-5-(2-hydroxy phenyl)-4*H*-1,2,4-triazole-3-yl]thio}acetic acid (5a-f): A solution of the 0.01 mol 3,5-disubstituted-1,2,4-triazolee **3a-f** and 0.01 mol sodium hyroxide in 30 mL ethanol was refluxed for 0.5 h. To this solution, 1.65 g of ethyl bromoacetate (0.01 mol) was added and the resulting mixture refluxed for 4 h. After cooling, the solution was poured on ice and the solid mass thus separated recrystallized from suitable solvent.

{[5-(2-Hydroxyphenyl)-4*H*-1,2,4-triazole-3-yl]thio}acetic acid (5a): 1.87 g (67 %), m.p. >350 ºC; IR (KBr, ν_{max}, cm^{-1}): 3518-3156 (NH and OH), 3120-2951 (Ar. and Aliph. CH), 1763 (C=O), 1624 (C=N); ^{1}H NMR (ppm): δ 3.78 (s, 2H, S-CH_2-COO), 6.7 (br, 1H, NH), 6.80-6.90 (m, 2H, H1, H3), 7.20-7.38 (m, 2H, H2, H4), 7.65 (br, 1H, OH)), 12.01 (br, 1H, COOH); Anal. calcd. (%) for $C_{10}H_9N_3O_3S$: C 47.80, H 3.61, N 16.72; found: C 47.77, H 3.62, N 16.75.

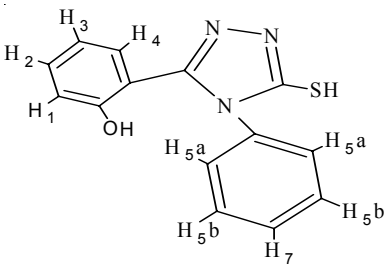
{[4-Ethyl-5-(2-hydroxyphenyl)-4*H*-1,2,4-triazole-3-yl]thio}acetic acid (5b): 1.66 g (54 %), m.p. > 350 ºC; IR (KBr, ν_{max}, cm^{-1}): 3548-3220 (OH), 3120-2950 (Ar. and Aliph. CH), 1775 (C=O), 1610 (C=N); ^{1}H NMR (ppm): δ 3.76 (s, 2H, S-CH_2-COO), 3.80 (m, 4H, N-CH_2-CH_3, OOC-CH_2-CH_3), 6.52 (t, *J* = 7.70, 1H, H3), 6.58 (d, *J* = 7.34, 1H, H1), 7.20 (dd, *J* = 7.70, 1.83, 1H, H4), 7.38 (t, *J* = 8.46, 1H, H2) 11.99 (br, 1H, COOH); Anal. calcd. (%) for $C_{12}H_{13}N_3O_3S$: C 51.60, H 4.69, N 15.04; found: C 51.63, H 4.73, N 15.01.

{[4-Phenyl-5-(2-hydroxyphenyl)-4*H*-1,2,4-triazole-3-yl]thio}acetic acid (5c): 2.13 g (65 %), m.p. > 350 ºC; IR (KBr, ν_{max}, cm^{-1}): 3598-3120 (OH), 3100-2920 (Ar. and Aliph. CH), 1720 (C=O), 1609 (C=N); ^{1}H NMR (ppm): δ 3.65 (s, 2H, S-CH_2-COO), 6.06 (t, *J* = 7.33, 1H, H3), 6.18 (d, *J* = 8.05, 1H, H1), 6.68-71 (m, 2H, H4, H2), 7.34 (s, 5H, ph.), 12.00 (br, 1H, COOH); Anal. calcd. (%) for $C_{16}H_{13}N_3O_3S$: C 58.70, H 4.00, N 12.84; found: C 58.76, H 4.10, N 12.85.

{[4-(4-Tolyl)-5-(2-hydroxyphenyl)-4*H*-1,2,4-triazole-3-yl]thio}acetic acid (5d): 2.05 g (60 %), m.p. 332-335 ºC; IR (KBr, ν_{max}, cm^{-1}): 3587-3131 (OH), 3100-2919 (Ar. and Aliph. CH), 1725 (C=O), 1621 (C=N); ^{1}H NMR

(ppm): δ 3.67 (s, 2H, S-CH_2-COO), 5.82 (t, *J* = 7.33, 1H, H3), 6.18 (d, *J* = 8.43, 1H, H1), 6.59 (dd, *J* = 8.36, 1.47, 1H, H4), 6.72 (dt, *J* = 8.43, 1.83, 1H, H2), 7.15 (d, *J* = 8.06, 2H, H6a, H6b), 7.20 (d, *J* = 8.43, 2H, H5a, H5b), 12.02 (br, 1H, COOH); ^{13}C NMR (ppm): δ 170.78, 170.38, 157.20, 151.44, 138.62, 133.24, 130.98, 130.91, 130.08, 127.68, 121.34, 115.13, 108.08, 40.00, 21.39; Anal. calcd. (%) for $C_{17}H_{15}N_3O_3S$: C 59.81, H 4.43, N 12.31; found: C 59.79, H 4.44, N 12.33.

{[4-Benzyl -5-(2-hydroxyphenyl)-4*H*-1,2,4-triazole-3-yl]thio}acetic acid (5e): 1.88 g (55 %), m.p. 321-324 ºC; IR (KBr, ν_{max}, cm^{-1}): 3552-3278 (OH), 3100-2944 (Ar. and Aliph. CH), 1722 (C=O), 1618 (C=N); ^{1}H NMR (ppm): δ 3.67 (s, 2H, S-CH_2-COO, 5.40 (s, 2H, N-CH_2-Ph), 6.04 (t, *J* = 7.33, 1H, H3), 6.35 (d, *J* = 8.03, 1H, H1), 6.82-6.86 (m, 3H, H5a, H5b, H7), 6.92-6.94 (m, 1H, H4), 8.10-7.20 (m, 3H, H2, H6a, H6b), 11.97(br, 1H, COOH); ^{13}C NMR (ppm): δ 171.25, 169.02, 158.75, 150.27, 138.37, 131.83, 131.46, 129.02, 127.69, 127.36, 121.38, 116.51, 108.99, 47.94, 41.06); Anal. calcd. (%) for $C_{17}H_{15}N_3O_3S$: C 59.81, H 4.43, N 12.31; found: C 59.78, H 4.45, N 12.30.



{[4-Allyl -5-(2-hydroxyphenyl)-4*H*-1,2,4-triazole-3-yl]thio}acetic acid (5f): 1.89 g (65 %), m.p. > 350 ºC; IR (KBr, ν_{max}, cm^{-1}): 3580-3188 (OH), 3120-2920 (Ar. and Aliph. (CH), 1776 (C=O), 1621 (C=N), 975-910 (-CH=CH_2); ^{1}H NMR (ppm): δ 3.65 (s, 2H, S-CH_2-COO), 4.45 (d, *J* = 4.87, 2H, N-CH_2-CH), 4.81 (dd, 1H, *Jcis* = 6.23, 1.10, NH-CH_2-CH=CH_2), 4.65-4.67 (m, 1H, N-CH_2-CH=CH_2), 4.97 (d, *J* = 11.00, 1H, N-CH_2-CH=CH_2), 5.62 (dq, 1H, *J* = 6.62, 5.13, NH-CH_2-CH=CH_2), 6.42 (t, *J* = 7.33, 1H, H3), 6.58 (d, *J* = 8.05, 1H, H1), 7.04 (d, *J* = 8.06, 1H, H4), 7.19 (t, *J* = 8.43, 1H, H2), 11.96(br, 1H, COOH); ^{13}C NMR (ppm): δ 175.40, 164.54, 132.90, 131.90, 131.69, 120.32, 117.25, 114.04, 69.39, 46.77, 38.62, 14.28); Anal. calcd. (%) for $C_{13}H_{13}N_3O_3S$: C 53.60, H 4.50, N 14.42; found: C 53.62, H 4.52, N 14.43.

RESULTS AND DISCUSSION

These synthetic reactions are summarized in **Scheme-I**. The characterization data of compounds **1** and **2a-f** and **3a-f** and **4a-f** and **5a-f** are given in the experimental section.

The IR spectra of the 1,4-substituted thiosemicarbazide derivatives **2a-f**, have C=O stretching bands at 1673-1660 cm^{-1} and C=S stretching bands at 1265-1250 cm^{-1}. The N-H protons of **2a-f**, were observed at 8.70-12.60 ppm, (O=C-NH-NH-C=S) and 6.86-8.32 ppm (S=C-NH-Ar/H/Ethyl/Allyl). Compounds **3a-f**, exist as thiol-thione tautomers as indicated by their IR spectra which showed a band due to SH and four bands due to N-C=S **I**, **II**, **III**, **IV**. The signal SH proton was too weak to be recorded presumably due to the extensive thiol-thione tautomerism and shows appear of 13.75-13.95 ppm (br, 1H). The ^{1}H NMR spectrum of **4a-f** shows appear of triplets δ = 2.60-2.80 (J = 4.46) and 3.70-3.90 (J = 4.42) for morpholine ring and a characteristic signal due to the -N-CH_2-N- protons appeared at 5.02-5.13 ppm. The ^{1}H NMR spectrum of **5a-f** shows singlet δ 3.60-2.80 ppm for the a S-CH_2-COOH methylene groups and δ 11.96-12.02 shows an broad carboxylic OH at room temperature in DMSO-d_6.

X-ray study: In the these compounds **3b-e**, the planer triazole ring is effectively coplanar with the benzene ring, which facilitates the formation of three intramolecular interactions N–H···S (leading to athione tautomer in the solid state), O–H···N and C–H···N. Intermolecular N–H···S interactions lead to the formation of dimmers, which are, in turn, linked to each other by N–H···O hydrogen bonds. X-ray data of the Compounds**3b**, **3d**, **3e** has been described previously[11,13,14].

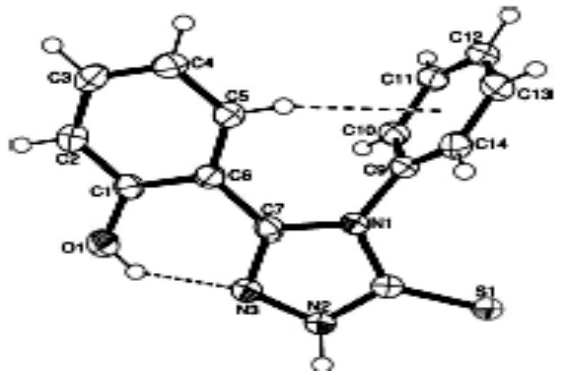


Fig. 1. An ORTEP-3 drawing of **3c**, showing the atom numbering scheme. Displacement ellipsoids are drawn at the 50 % probability level and H atoms are shown as spheres of arbitrary radii

We have carried out X-ray analysis for a few selected compounds that were prone to crystallization. All of these compounds are crystallized in the thione form. The crystallization of **3a-f** like compounds should be done in dark. Because these compounds can convert to the disulphides when they are exposed to the light for a long time. It has been reported that the

crystal structures of **3a-f** like compounds correspond to the thione form, but the reaction conditions for the synthesis of **5a-f** prove that can be in the thiol form too. Finally, the crystal structures of **3a-f** corresponded to the thione form, but they showed thiol-thione tautomerism in solution.

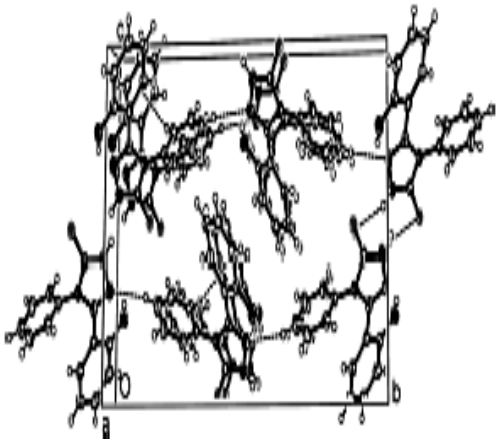


Fig. 2. A packing diagram for **3c**, with the intermolecular hydrogen bonds shown as dashed lines[12]. Crystallographic data (excluding structure fac.) for the structure in this paper have been publication in the free of charge, on application to ISSN 1600-5368

REFERENCES

1. A.K. Sengupta, O.P. Bajaj and U.J. Chandura, *J. Indian Chem. Soc.*, **55**, 962 (1978).
2. H. Singh, L.D.S. Yadav and B.K.J. Battacharya, *J. Indian Chem. Soc.*, **56**, 1013 (1979).
3. S. Giri, H. Singh, L.D.S. Yadav and R.K. Kahre, *J. Indian Chem. Soc.*, **55**, 168 (1978).
4. F.P. Kane, M.W. Dudley, S.M. Sorensen and F.P. Miller, *J. Med. Chem.*, **31**, 1253 (1986).
5. T. Hirota, K. Sasaki, H. Yamamoto and T. Nakayama, *J. Heterocycl. Chem.*, **28**, 257 (1991).
6. B.N. Goswami, J.C.S. Kataky and J.N. Baruah, *J. Heterocycl. Chem.*, **21**, 1225 (1984).
7. A.K. Sengupta and H.K. Misra, *J. Indian Chem. Soc.*, **58**, 508 (1981).
8. S. Bahadur and K.K. Pandey, *J. Indian Chem. Soc.*, **57**, 447 (1980).
9. A. Cansiz, M. Koparir and A. Demirdag, *Molecules*, **9**, 204 (2004).
10. M. Koparir, A. Çetin and A. Cansiz, *Molecules*, **10**, 475 (2005).
11. N. Dege, N. Özdemir, A. Çetin, A. Cansiz, M. Sekerci and M. Dinçer, *Acta Cryst.*, **E61**, 17 (2005).
12. S. Genç, N. Dege, A. Çetin, A. Cansiz, M. Sekerci and M. Dinçer, *Acta Cryst.*, **E60**, 1580 (2004).
13. S. Genç, N. Dege, A. Çetin, A. Cansiz, M. Sekerci and M. Dinçer, *Acta Cryst.*, **E60**, 1340 (2004).
14. N. Dege, A. Çetin, A. Cansiz, M. Sekerci, C. Kazaz, M. Dinçer and O. Güngör, *Acta Cryst.*, **E60**, 1883 (2004).
15. A. Cansiz, A. Çetin, M. Koparir and C. Kazaz, *Org. Chem. An Indian J.*, **2**, 140 (2006).

(*Received*: 24 January 2008; *Accepted*: 2 September 2008) AJC-6809