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Synthesis and Characterization of New Triheterocyclic Compounds Consisting of 1,2,4-Triazol-3-one, 1,3,4-Thiadiazole and 1,3,4-Oxadiazole Rings

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A series of acetic acid derivatives (**2a-c)** was synthesized by the condensation of compounds **1a-c** with chloroacetic acid. The treatment of carboxylic acid derivatives with thiosemicarbazide in phosphorus oxychloride and subsequent diazotation of the products (**3a-c**) afforded 5-alkyl-2-[(5-chloro-1,3,4-thiadiazol-2-yl)methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one derivatives (**4a-c**). The treatment of compounds **4a-c** with thiourea produced 5-alkyl-2-[(5-mercapto-1,3,4-thiadiazol-2-yl)methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one derivatives (**5a-c**). Subsequently, compounds **5a-c** were converted to acid hydrazides by treatment with hydrazine hydrate after esterification (**7a-e**). Moreover, the reaction of compounds **7a-c** with carbon disulfite in the presence of KOH afforded 5-alkyl-2-[(5-{[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]thio}-1,3,4-thiadiazol-2-yl)methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (**8a-c)**.

Key Words: 1,2,4-triazol-3-one 1,3,4-thiadiazole, 1,3,4-oxadiazole, thiosemicarbazide, diazotation, deamination.

Introduction

The synthesis of compounds incorporating both 1,2,4-triazole and 1,3,4-thiadiazole rings has been attracting widespread attention due to their diverse pharmacological properties such as antimicrobial, anti-inflammatory, analgesic and antitumoral activities[1−7]. In addition, several 1,3,4-oxadiazole derivatives have been reported to possess diverse biological activities[8−13]. Although there are a number of antibiotics which are commercially used in medicine, the synthesis of new compounds is of vital importance due to increasing drug resistance. Moreover, it is important to obtain therapeutical compounds having less toxic effects.

4-Amino-1,3,4-thiadiazoles, which can be prepared via the cyclization of the compounds involving a thiosemicarbazone structure in the presence of ammonium ferric sulfate or from the reaction of carboxylic acids with thiosemicarbazide in the presence of phosphorus oxychloride, are useful intermediates for further reactions, and some piperazinyl quinolone derivatives have been obtained as antimicrobial agents by using some 4-amino-1,3,4-thiadiazoles[14−16]. Moreover, 4-amino-5-alkyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones

(**1**) behave as good nucleophiles in most reactions, and some *N*-substituted derivatives have been prepared in our laboratories as biologically active compounds[17−19].

It has been reported that compounds containing an –SH group can be easily converted to their S-substituted derivatives [5,20−24].

Prompted by these observations, we aimed to obtain 1,2,4-triazol-3-one derivatives also incorporating 1,3,4-thiadiazole and 1,3,4-oxadiazole rings as possible biological active compounds. The alkyl groups at position 5 of the 1,2,4-triazol-3-one ring were selected as an aliphatic (methyl), an aromatic-aliphatic (benzyl) and an aromatic (phenyl) group (Figure).

Results and Discussion

Compounds **2a-c** were obtained from the reaction of compounds **1a-c** with chloroacetic acid in basic media and their structures were confirmed using IR, ^{1}H NMR and ^{13}C NMR spectral data and elemental analysis (for compound **2a** only). The IR spectrum of compounds **2a-c** displayed no absorption derived from NH stretching; instead, a new signal representing the carboxyl group was observed. In the NMR spectra of compounds **2a-c** 2 new signals originating from the CH_2COOH group were recorded.

Compounds **3a-c** were prepared by the reaction of carboxylic acid derivatives (**2a-c**) with thiosemicarbazide in phosphorus oxychloride. The ^{1}H NMR spectra of compounds **3a-c** showed 2 different $–NH_2$ signals (exch. with D_2O).

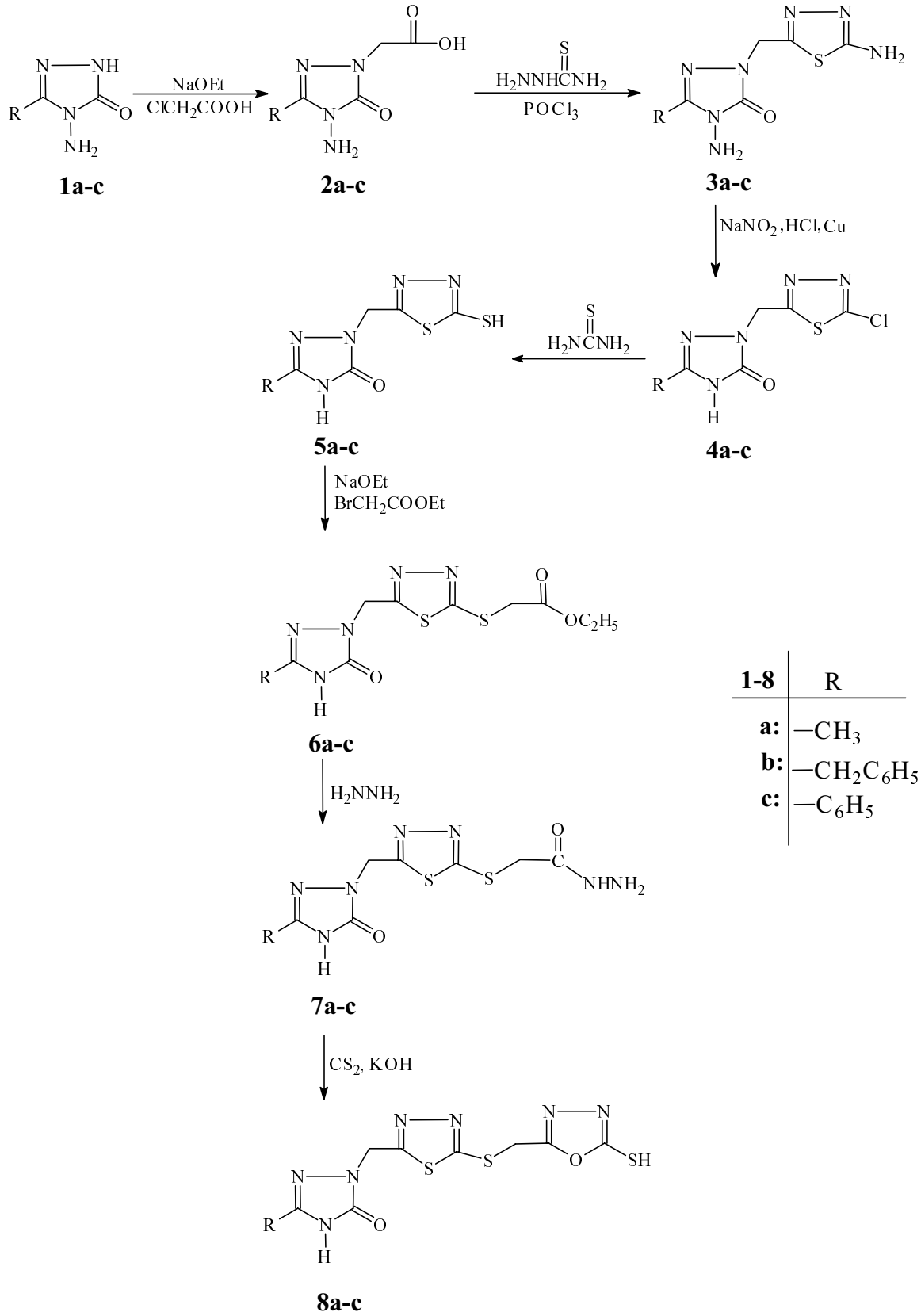
It has been reported that the diazotation of amino thiadiazoles in hydrochloric acid in the presence of copper powder results in the substitution of the amino group with chlorine[14]. On the other hand, deamination can be achieved when 4-amino-5-alkyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones are treated with nitrous acid[25]. In the ^{1}H NMR spectrum, the $–NH_2$ signals disappeared when compounds **3a-c** were converted to compounds **4a-c**; instead a new signal originating from triazole-NH was observed.

The reaction of compounds **4a-c** with thiourea in ethanol produced 5-alkyl-[(5-mercapto-1,3,4-thiadiazol-2-yl)methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (**5a-c**). The signal appeared at 12.04-12.53 ppm in the ^{1}H NMR spectra of compounds **5a-c** was attributed to the –SH group.

Ethyl ({5-[(3-methyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl]-1,3,4-thiadiazol-2-yl}thio)acetates (**6a-c**) were obtained from the reaction of compounds **5a-c** with ethyl bromoacetate in the presence of sodium ethoxide. The NMR spectra of compounds **6a-c** displayed additional 3 signals due to the esteric group.

The treatment of acetic acid ethyl ester derivatives (**6a-c**) with hydrazine hydrate afforded 2-({[(3-alkyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl]-1,3,4-thiaidazol-2-yl}thio)aceto-hydrazide derivatives (**7a-c**). In the ^{1}H NMR spectra of compounds **7a-c** new signals belonging to the $–NHNH_2$ group were observed, while the signals originating from the ester group disappeared.

The reaction of compounds **7a-c** with carbon disulfite in the presence of KOH caused the conversion of the hydrazide group to the 1,3,4-oxadiazole ring, and hence 5-alkyl-2-[(5-{[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]thio}-1,3,4-thiadiazol-2-yl)methyl]- 2,4-dihydro-3*H*-1,2,4-triazol-3-ones (**8a-c)** were obtained after acidic treatment. In the ^{1}H NMR spectra of 1,3,4-oxadiazole derivatives (**8a-c**) no signal belonging to the $–NHNH_2$ group was observed, which appeared at 4.71-4.75 ppm ($-NH\underline{NH_2}$) and 9.19-9.25 ppm ($-\underline{NH}NH_2$) (exch. with D_2O) in the ^{1}H NMR spectra of the parent compounds (**7a-c**).


NaOEt
ClCH2COOH
H2NNHCNH2
POCl3
NaNO2, HCl, Cu
H2NCNH2
NaOEt
BrCH2COOEt
H2NNH2
CS2, KOH
1a-c
2a-c
3a-c
4a-c
5a-c
6a-c
7a-c
8a-c
1-8 | R
a: —CH3
b: —CH2C6H5
c: —C6H5

Figure

Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian-Mercury 200 MHz spectrometer. The IR spectra were measured as potassium bromide pellets using a Perkin-Elmer 1600 series FTIR spectrometer. Combustion analysis (for the selected compounds, **2a**, **3b, 4c, 5a, 6b, 7a** and **8c**) was performed on a Carlo Erba 1106 elemental analyzer. All the chemicals were obtained from Fluka Chemie AG Buchs (Switzerland). Compounds **1a-c** were synthesized using a published method [26].

General method for the synthesis of compounds 2

The corresponding compound 5-alkyl-4-amino-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**1**) (10 mmol) was refluxed with an equivalent amount of sodium in absolute ethanol for 1 h. Then chloroacetic acid (10 mmol) was added and refluxed for an additional 5 h. After evaporating the reaction content at 35-40 °C under reduced pressure, a solid appeared. This crude product was recrystallized from ethanol/water (1:1) to afford the desired compound.

(4-Amino-3-methyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl) acetic acid (2a): Yield: 78%; mp. 161 °C; Analysis (% calc/found): for $C_5H_8N_4O_3$ C: 34.89/35.13, H: 4.68/4.69, N: 32.55/32.24; IR (KBr) (ν, cm^{-1}), 3415, 3218 (NH_2+OH), 1751 (carboxyl-C=O), 1711 (triazole-C=O), 1587 (-C=N); ^{1}H NMR (DMSO-d$_6$) δ 2.09 (s, CH_3), 5.30 (s, NCH_2), 5.38 (s, NH_2), 12.27 (bs, OH); ^{13}C NMR (DMSO-d$_6$) δ 10.41 (CH_3), 48.51 (NCH_2), 148.85 (triazole C-3), 153.37 (triazole C-5), 176.15 (carboxyl C=O).

(4-Amino-3-benzyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl) acetic acid (2b): Yield: 68%; mp. 124 °C; IR (KBr) (ν, cm^{-1}), 3415, 3223 (NH_2+OH), 1749 (carboxyl-C=O), 1710 (triazole-C=O), 1580 (-C=N); ^{1}H NMR (DMSO-d$_6$) δ 3.69 (s, benzylic CH_2), 5.30 (s, NCH_2), 5.37 (s, NH_2), 7.03-7.14 (m, 3H, arH), 7.21-7.30 (m, 2H, arH), 12.86 (bs, OH); ^{13}C NMR (DMSO-d$_6$) δ 34.41 (benzylic CH_2), 48.50 (NCH_2), arC [118.62 (CH), 120.47 (CH), 122.38 (2CH), 122.83 (CH), 124.19 (C)], 147.68 (triazole C-3), 153.34 (triazole C-5), 177.73 (carboxyl C=O).

(4-Amino-5-oxo-3-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl) acetic acid (2c): Yield: 81%; mp. 175 °C; IR (KBr) (ν, cm^{-1}), 3409, 3211 (NH_2+OH), 1752 (carboxyl-C=O), 1718 (triazole-C=O), 1593 (-C=N); ^{1}H NMR (DMSO-d$_6$) δ 5.32 (s, NCH_2), 5.33 (s, NH_2), 7.11-7.24 (m, 3H, arH), 7.26-7.35 (m, 2H, arH), 12.74 (bs, OH); ^{13}C NMR (DMSO-d$_6$) δ 47.45 (NCH_2), arC [120.23 (CH), 120.62 (CH), 121.65 (2CH), 123.13 (CH), 124.75 (C)], 147.24 (triazole C-3), 153.26 (triazole C-5), 177.59 (carboxyl C=O).

General method for the synthesis of compounds 3

A mixture of corresponding compound **2** (10 mmol) and an equivalent amount of thiosemicarbazide in phosphorus oxychloride (20 mL) was refluxed in a water bath for 2 h. After evaporating the reaction content under reduced pressure, an oily product was obtained. This was recrystallized from ethanol to afford the desired product.

4-Amino-2-[(5-amino-1,3,4-thiadiazol-2-yl)methyl]-5-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (3a): Yield: 52%; mp. 238 °C; IR (KBr) (ν, cm^{-1}), 3352, 3224 and 3191 ($2NH_2$), 1717 (triazole-C=O), 1603 and 1587 (-C=N); ^{1}H NMR (DMSO-d$_6$) δ 1.98 (s, CH_3), 4.67 (s, thiadiazole-NH_2), 5.16 (s,

NCH_2), 5.32 (s, triazole-NH_2); ^{13}C NMR (DMSO-d_6) δ 10.77 (CH_3), 48.51 (NCH_2), 141.64 (thiadiazole-C-2), 143.67 (triazole C-3), 148.45 (thiadiazole C-5), 152.81 (triazole C-5).

4-Amino-2-[(5-amino-1,3,4-thiadiazol-2-yl)methyl]-5-benzyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (3b): Yield: 55%; mp. 213 °C; Analysis (calc/found %): for $C_{12}H_{13}N_7OS$ C: 47.51/48.13, H: 4.32/4.49, N: 32.32/32.54; IR (KBr) (ν, cm^{-1}), 3353, 3221 and 3091 ($2NH_2$), 1717 (triazole-C=O), 1601 and 1594 (-C=N); ^{1}H NMR (DMSO-d_6) δ 3.62 (s, benzylic CH_2), 4.72 (s, NCH_2), 4.83 (s, thiadiazole-NH_2), 5.27 (s, triazole-NH_2), 6.93-7.12 (m, 3H, arH), 7.18-7.25 (m, 2H, arH); ^{13}C NMR (DMSO-d_6) δ 30.09 (benzylic CH_2), 51.78 (NCH_2), arC:[123.18 (CH), 124.57 (CH), 125.71 (2CH), 126.83 (CH), 129.54 (C)], 142.48 (thiadiazole-C-2), 143.11 (triazole C-3), 149.52 (thiadizole C-5), 153.25 (triazole C-5).

4-Amino-2-[(5-amino-1,3,4-thiadiazol-2-yl)methyl]-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (3c): Yield: 61%; mp. 258 °C; IR (KBr) (ν, cm^{-1}), 3352, 3224 and 3184 ($2NH_2$), 1717 (triazole-C=O), 1611 and 1582 (-C=N); ^{1}H NMR (DMSO-d_6) δ 4.82 (bs, NCH_2+ thiadiazole-NH_2), 5.32 (s, triazole-NH_2), 6.98-7.16 (m, 3H, arH), 7.21-7.28 (m, 2H, arH); ^{13}C NMR (DMSO-d_6) δ 51.37 (NCH_2), arC:[119.64 (CH), 121.93 (CH), 122.37 (2CH), 123.34 (CH), 124.16 (C)], 142.88 (thiadiazole-C-2), 143.31 (triazole C-3), 149.56 (thiadizole C-5), 154.15 (triazole C-5).

General method for the synthesis of compounds 4

A mixture of corresponding compound **3** (10 mmol) and an excess amount of $NaNO_2$ (30 mmol) was added in the form of small amounts into a solution of conc. HCl (30 mL) and ice-water containing Cu powder (0.5 g) while stirring. After stirring the reaction content at 0 °C for 1 h the mixture was allowed to reach room temperature and was stirred for an additional 2 h. Then it was heated in a water bath for 2 h. The reaction mixture was cooled to room temperature and extracted 3 times with $CHCl_3$. The combined extracts were washed with $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. After evaporating the solution under reduced pressure, an oily product was obtained. This was recrystallized from ethanol to afford compounds **4**.

2-[(5-Chloro-1,3,4-thiadiazol-2-yl)methyl]-5-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (4a): Yield: 65%; mp. 287 °C; IR (KBr) (ν, cm^{-1}), 3162 (NH), 1746 (triazole-C=O), 1603 and 1572 (-C=N); ^{1}H NMR (DMSO-d_6) δ 2.11 (s, CH_3), 5.17 (s, NCH_2), 11.39 (s, NH); ^{13}C NMR (DMSO-d_6) δ 11.29 (CH_3), 50.51 (NCH_2), 143.24 (thiadiazole C-2), 144.56 (triazole C-3), 153.88 (triazole C-5), 159.23 (thiadiazole C-5).

2-[(5-Chloro-1,3,4-thiadiazol-2-yl)methyl]-5-benzyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (4b): Yield: 55%; mp. 294 °C; IR (KBr) (ν, cm^{-1}), 3165 (NH), 1746 (triazole-C=O), 1618 and 1576 (-C=N); ^{1}H NMR (DMSO-d_6) δ 3.62 (s, benzylic CH_2), 5.18 (s, NCH_2), 7.11-7.28 (m, 5H, arH), 11.47 (s, NH); ^{13}C NMR (DMSO-d_6) δ 31.16 (benzylic CH_2), 49.97 (NCH_2), arC [119.97 (CH), 123.65 (2CH), 127.12 (CH), 128.05 (CH), 129.14 (C)], 142.24 (thiadiazole C-2), 144.83 (triazole C-3), 154.62 (triazole C-5), 159.23 (thiadiazole C-5).

2-[(5-Chloro-1,3,4-thiadiazol-2-yl)methyl]-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (4c): Yield: 59%; mp. 278 °C; Analysis (% calc/found): for $C_{11}H_8ClN_5OS$ C: 44.98/45.63, H: 2.74/2.73, N: 23.84/23.76; IR (KBr) (ν, cm^{-1}), 3035 (NH), 1754 (triazole-C=O), 1601 and 1593 (-C=N); ^{1}H NMR (DMSO-d_6) δ 5.41 (s, NCH_2), 7.04-7.21 (m, 3H, arH), 7.23-7.36 (m, 2H, arH), 12.08 (s, NH); ^{13}C NMR (DMSO-d_6) δ 51.48 (NCH_2), arC [126.93 (CH), 127.11 (2CH), 129.62 (2CH), 129.89 (C)], 142.85 (thiadiazole C-2), 143.63

(triazole C-3), 153.35 (triazole C-5), 159.41 (thiadiazole C-5).

General method for the synthesis of compounds 5

The solution of corresponding compound **4** (10 mmol) in ethanol was refluxed with an excess amount of thiourea (30 mmol) for 5 h. After cooling the reaction mixture to room temperature, a mixture consisting of conc. HCl (3 mL) and water was added. The formed solid was filtered, washed with water and recrystallized from ethanol.

2-[(5-Mercapto-1,3,4-thiadiazol-2-yl)methyl]-5-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (5a): Yield: 72%; mp. 321 °C; Analysis (% calc/found): for $C_6H_7N_5OS_2$ C: 31.43/31.68, H: 3.08/3.12, N: 30.55/30.42; IR (KBr) (ν, cm^{-1}), 3118 (NH), 2552 (SH), 1729 (triazole-C=O), 1612 and 1543 (-C=N), 1163 (C=S); ^{1}H NMR (DMSO-d_6) δ 2.05 (s, CH_3), 4.88 (s, NCH_2), 11.36 (s, NH), 12.47 (s, SH); ^{13}C NMR (DMSO-d_6) δ 10.92 (CH_3), 51.48 (NCH_2), 141.95 (thiadiazole C-2), 142.63 (triazole C-3), 152.47 (thiadiazole C-5), 153.12 (triazole C-5).

5-Benzyl-2-[(5-mercapto-1,3,4-thiadiazol-2-yl)methyl]- 2,4-dihydro-3*H*-1,2,4-triazol-3-one (5b): Yield: 69%; mp. >350 °C; IR (KBr) (ν, cm^{-1}), 3089 (NH), 2552 (SH), 1736 (triazole-C=O), 1609 and 1558 (-C=N), 1162 (C=S); ^{1}H NMR (DMSO-d_6) δ 3.68 (s, benzylic CH_2), 5.11 (s, NCH_2), 7.19-7.21 (m, 3H, arH), 7.25-7.32 (m, 2H, arH), 11.67 (s, NH), 12.04 (s, SH); ^{13}C NMR (DMSO-d_6) δ 34.05 (benzylic CH_2), 51.48 (NCH_2), arC [121.65 (CH), 122.18 (2CH), 123.57 (2CH), 128.16 (C)], 141.95 (thiadiazole C-2), 142.63 (triazole C-3), 152.47 (thiadiazole C-5), 153.12 (triazole C-5).

2-[(5-Mercapto-1,3,4-thiadiazol-2-yl)methyl]-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (5c): Yield: 62%; mp. >350 °C; IR (KBr) (ν, cm^{-1}), 3021 (NH), 2558 (SH), 1741 (triazole-C=O), 1612 and 1593 (-C=N), 1219 (C=S); ^{1}H NMR (DMSO-d_6) δ 5.23 (s, NCH_2), 7.04-7.12 (m, 3H, arH), 7.17-7.22 (m, 2H, arH), 12.53 (bs, NH+SH); ^{13}C NMR (DMSO-d_6) δ 51.17 (NCH_2), arC [121.16 (2CH), 12.53 (3CH), 129.26 (C)], 142.91 (thiadiazole C-2), 143.67 (triazole C-3), 152.47 (thiadiazole C-5), 153.84 (triazole C-5).

General method for the synthesis of compounds 6

The corresponding compound **5** (10 mmol) was refluxed with an equivalent amount of sodium in absolute ethanol for 1 h. Then ethyl bromoacetate (10 mmol) was added and refluxed for an additional 5 h. After evaporation at 35-40 °C under reduced pressure, a solid appeared. This was recrystallized from ethanol-water (1:1) to afford the desired compound.

Ethyl ({5-[(3-methyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl]-1,3,4-thiadiazol-2-yl}thio)acetate (6a): Yield: 83%; mp. 157 °C; IR (KBr) (ν, cm^{-1}), 3098 (NH), 1728 (triazole-C=O), 1687 (exocyclic-C=O), 1601 and 1584 (-C=N); ^{1}H NMR (DMSO-d_6) δ 1.18 (t, -$OCH_2\underline{CH_3}$, J= 5.8 Hz), 1.98 (s, CH_3), 3.92 (s, SCH_2), 4.10 (q, -$O\underline{CH_2}CH_3$, J= 5.8 Hz), 5.43 (s, NCH_2), 11.34 (s, NH); ^{13}C NMR (DMSO-d_6) δ 10.27 (CH_3), 14.74 (-$OCH_2\underline{CH_3}$), 47.05 (SCH_2), 51.18 (NCH_2), 61.17 (-$O\underline{CH_2}CH_3$), 144.27 (thiadiazole C-2), 146.54 (triazole C-3), 152.25 (thiadiazole C-5), 154.47 (thiadiazole C-5), 167.25 (exocyclic C=O).

Ethyl ({5-[(3-benzyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl]-1,3,4-thiadiazol-2-yl}thio)acetate (6b): Yield: 76%; mp. 147 °C; Analysis (calc/found %): for $C_{16}H_{17}N_5O_3S_2$ C:

49.09/48.85, H: 4.38/ 4.38, N: 17.89/17.21; IR (KBr) (ν, cm^{-1}), 3098 (NH), 1732 (triazole-C=O), 1684 (exocyclic-C=O), 1596 and 1568 (-C=N); ^{1}H NMR (DMSO-d_6) δ 1.57 (t, -$OCH_2\underline{CH_3}$, J= 6.0 Hz), 3.22 (benzylic CH_2), 3.97 (s, SCH_2), 4.15 (q, -$O\underline{CH_2}CH_3$, J= 6.0 Hz), 5.43 (s, NCH_2), 7.05-7.16 (m, 3H, arH), 7.21-7.28 (m, 2H, arH), 12.05 (s, NH); ^{13}C NMR (DMSO-d_6) δ 14.82 (-$OCH_2\underline{CH_3}$), 32.27 (benzylic CH_2), 46.60 (SCH_2), 51.17 (NCH_2), 61.09 (-$O\underline{CH_2}CH_3$), arC [122.32 (CH), 123.16 (2CH), 123.21 (CH), 124.36 (CH), 124.85 (C)], 144.28 (thiadiazole C-2), 145.75 (triazole C-3), 152.53 (thiadiazole C-5), 154.53 (thiadiazole C-5), 167.64 (exocyclic C=O).

Ethyl ({5-[(3-phenyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl]-1,3,4-thiadiazol-2-yl}thio)acetate (6c): Yield: 68%; mp. 153 °C; IR (KBr) (ν, cm^{-1}), 3063 (NH), 1725 (triazole-C=O), 1686 (exocyclic-C=O), 1604 and 1551 (-C=N); ^{1}H NMR (DMSO-d_6) δ 1.37 (t, -$OCH_2\underline{CH_3}$, J= 5.7 Hz), 3.98 (s, SCH_2), 4.15 (q, -$O\underline{CH_2}CH_3$, J= 6.0 Hz), 5.43 (s, NCH_2), 7.05-7.26 (m, 5H, arH), 12.05 (s, NH); ^{13}C NMR (DMSO-d_6) δ 14.82 (-$OCH_2\underline{CH_3}$), 46.60 (SCH_2), 51.17 (NCH_2), 61.09 (-$O\underline{CH_2}CH_3$), arC [121.92 (2CH), 122.16 (2CH), 123.18 (CH), 124.73 (C)], 144.28 (thiadiazole C-2), 146.25 (triazole C-3), 152.63 (thiadiazole C-5), 154.82 (thiadiazole C-5), 167.79 (exocyclic C=O).

General method for the synthesis of compounds 7

A solution of the corresponding compound **6** (10 mmol) in *n*-butanol was refluxed with hydrazine hydrate (25 mmol) for 4 h. After cooling it to room temperature, a white solid appeared. This was recrystalized from ethanol to afford the desired product.

2-({5-[(3-Methyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl]-1,3,4-thiadiazol-2-yl}thio)acetohydrazide (7a): Yield: 85%; mp. 317 °C; Analysis (% Calc/found): for $C_8H_{11}N_7O_2S_2$ C: 31.89/32.43, H: 3.68/3.79, N: 32.54/32.27; IR (KBr) (ν, cm^{-1}), 3358, 3218 and 3056 (NH+NH_2), 1717 (triazole-C=O), 1696 (exocyclic-C=O), 1627 and 1564 (-C=N); ^{1}H NMR (DMSO-d_6) δ 2.12 (s, CH_3), 4.64 (s, SCH_2), 4.73 (-NH$\underline{NH_2}$), 5.42 (s, NCH_2), 9.25 (-$\underline{NH}NH_2$), 11.23 (s, NH); ^{13}C NMR (DMSO-d_6) δ 11.76 (CH_3), 47.05 (SCH_2), 50.88 (NCH_2), 144.95 (thiadiazole C-2), 146.53 (triazole C-3), 152.56 (thiadiazole C-5), 154.68 (thiadiazole C-5), 168.52 (exocyclic-C=O).

2-({5-[(3-Benzyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl]-1,3,4-thiadiazol-2-yl}thio)acetohydrazide (7b): Yield: 85%; mp. 329 °C; IR (KBr) (ν, cm^{-1}), 3357, 3218 and 3098 (NH+NH_2), 1726 (triazole-C=O), 1684 (exocyclic C=O), 1603 and 1548 (-C=N); ^{1}H NMR (DMSO-d_6) δ 3.62 (benzylic CH_2), 4.68 (s, SCH_2), 4.71 (-NH$\underline{NH_2}$), 5.37 (s, NCH_2), 7.05-7.13 (m, 3H, arH), 7.18-7.26 (m, 2H, arH), 9.19 (bs, -$\underline{NH}NH_2$), 12.05 (s, -NH); ^{13}C NMR (DMSO-d_6) δ 32.27 (benzylic CH_2), 46.60 (SCH_2), 51.17 (NCH_2), arC [122.32 (2CH), 123.16 (2CH), 123.21 (CH), 124.36 (C)], 144.28 (thiadiazole C-2), 145.75 (triazole C-3), 152.53 (thiadiazole C-5), 154.53 (thiadiazole C-5), 168.24 (exocyclic C=O).

2-({5-[(3-Phenyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl]-1,3,4-thiadiazol-2-yl}thio)acetohydrazide (7c): Yield: 71%; mp. 341°C; IR (KBr) (ν, cm^{-1}), 3362, 3224 and 3067 (NH+NH_2), 1725 (triazole-C=O), 1694 (exocyclic-C=O), 1594 and 1549 (-C=N); ^{1}H NMR (DMSO-d_6) δ 4.67 (s, SCH_2), 4.75 (-NH$\underline{NH_2}$), 5.43 (s, NCH_2), 7.05-7.16 (m, 3H, arH), 7.21-7.28 (m, 2H, arH), 9.19 (bs, -$\underline{NH}NH_2$); 12.05 (s, NH); ^{13}C NMR (DMSO-d_6) δ 46.63 (SCH_2), 51.28 (NCH_2), arC [122.14 (CH), 122.19 (2CH), 123.82 (CH), 124.15 (CH), 124.91 (C)], 144.28 (thiadiazole C-2), 146.25 (triazole C-3), 152.63 (thiadiazole C-5),

153.572 (triazole C-5), 168.39 (exocyclic C=O).

General method for the synthesis of compounds 8

Corresponding compound **7** (10 mol) and CS_2 (0.60 mL, 10 mol) were added to a solution of KOH (0.56 g, 10 mol) in 50 mL of H_2O and 50 mL of ethanol. The reaction mixture was refluxed for 3 h. After evaporating it to dryness under reduced pressure, a solid was obtained. This was dissolved in 300 mL of H_2O and acidified with conc. HCl. The precipitate was filtered, washed with H_2O and recrystallized from an appropriate solvent to afford the desired compound.

2-[(5-{[(5-Mercapto-1,3,4-oxadiazol-2-yl)methyl]thio}-1,3,4-thiadiazol-2-yl)methyl]-5-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (8a): Yield: 77%; mp. >350 °C; IR (KBr) (ν, cm^{-1}), 3096 (NH), 2567 (SH), 1705 (triazole-C=O), 1594 and 1549 (-C=N), 1168 (-C=S); ^{1}H NMR (DMSO-d_6) δ 2.09 (s, CH_3), 4.05 (SCH_2), 4.83 (s, NCH_2), 12.05 (s, NH), 14.21 (s, SH); ^{13}C NMR (DMSO-d_6) δ 11.03 (CH_3), 43.54 (SCH_2), 45.28 (NCH_2), 144.28 (thiadiazole C-2), 145.79 (triazole C-3), 152.59 (thiadiazole C-5), 153.51 (triazole C-5), 158.11 (oxadiazole C-2), 175.65 (oxadiazole C-5).

5-Benzyl-2-[(5-{[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]thio}-1,3,4-thiadiazol-2-yl) methyl]- 2,4-dihydro-3*H*-1,2,4-triazol-3-one (8b): Yield: 75%; mp. 343 °C; IR (KBr) (ν, cm^{-1}), 3026 (NH), 2601 (SH), 1705 (triazole-C=O), 1612 and 1589 (-C=N), 1163 (-C=S); ^{1}H NMR (DMSO-d_6) δ 3.13 (s, benzylic CH_2), 4.05 (SCH_2), 4.92 (s, NCH_2), 6.97-7.18 (m, 3H, arH), 7.24-7.32 (m, 2H, arH), 11.49 (s, NH), 13.79 (s, SH); ^{13}C NMR (DMSO-d_6) δ 33.12 (benzylic CH_2), 44.63 (SCH_2), 45.28 (NCH_2), arC [119.83 (2CH), 121.65 (CH); 122.33 (CH), 123.66 (CH), 124.32 (C)], 144.36 (thiadiazole C-2), 144.92 (triazole C-3), 152.62 (thiadiazole C-5), 153.17 (triazole C-5), 158.12 (oxadiazole C-2), 175.70 (oxadiazole C-5).

2-[(5-{[(5-Mercapto-1,3,4-oxadiazol-2-yl)methyl]thio}-1,3,4-thiadiazol-2-yl)methyl]-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (8c): Yield: 75%; mp. >350 °C; Analysis (calc/found %): for $C_{14}H_{11}N_7O_2S_3$ C: 41.47/41.89, H: 2.73/ 2.78, N: 24.18/24.03; IR (KBr) (ν, cm^{-1}), 3027 (NH), 1724 (triazole-C=O), 1606 and 1595 (-C=N), 1203 (-C=S); ^{1}H NMR (DMSO-d_6) δ 4.05 (SCH_2), 5.12 (s, NCH_2), 6.98-7.23 (m, 3H, arH), 7.26-7.38 (m, 2H, arH), 12.25 (s, NH), 14.26 (s, SH); ^{13}C NMR (DMSO-d_6) δ 44.16 (SCH_2), 46.98 (NCH_2), arC [118.37 (CH), 119.83 (CH), 122.15 (CH); 122.34 (CH), 123.53 (CH), 124.64 (C)], 144.36 (thiadiazole C-2), 143.62 (triazole C-3), 152.60 (thiadiazole C-5), 153.31 (triazole C-5), 158.46 (oxadiazole C-2), 175.69 (oxadiazole C-5).

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