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## Nucleosides, Nucleotides and Nucleic Acids

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### Double-headed Acyclo C-Nucleoside Analogues. Functionalized 1,2-bis-(1,2,4-Triazol-3-yl)ethane-1,2-diol

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## DOUBLE-HEADED ACYCLO C-NUCLEOSIDE ANALOGUES. Functionalized 1,2-bis-(1,2,4-Triazol-3-yl)ethane-1,2-diol

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□ Reaction of L-tartaric acid with thiocarbonylhydrazide afforded (1R, 2S)-1,2-bis(4-amino-5-mercapto-1,2,4-triazol-3-yl)-ethane-1,2-diol (**3**). The functional groups in **3** allowed the construction of fused heterocycles on the 1,2,4-triazole rings, mainly of the 1,2,4-triazolo[3,4-b][1,3,4]thiadiazine type as in **4**, **5**, **7**, **10**, **13** and 1,2,4-triazolo[3,4-b][1,3,4]thiadiazole type as in **14**.

**Keywords** L-Tartaric acid; Ethane-1,2-diol; 1,2,4-Triazolo-[3,4-b][1,3,4]-thiadiazine; 1,2,4-Triazolo[3,4-b][1,3,4]thiadiazole; Acyclonucleoside

### INTRODUCTION

Considerable attention has been drawn to the synthesis of several triazole ring systems owing to their valuable properties.<sup>[1–3]</sup> The incorporation of various substituents on the 1,2,4-triazole ring and its fusion with various heterocyclic systems led to compounds with enhanced biological activities.<sup>[1,2,4–7]</sup> Moreover, the functionality in 4-amino-5-mercapto-3-substituted-1,2,4-triazoles makes them key precursors for the formation of fused heterocyclic compounds containing s-triazolo[3,4-b][1,3,4]thiadiazole and s-triazolo[3,4-b][1,3,4]thiadiazine ring systems.<sup>[7]</sup> We have been interested in the acyclic nucleosides and their C-nucleoside analogues.<sup>[8–12]</sup> Recently, the syntheses of the *seco* C-nucleosides 4-amino-3-(D-gluco- or D-galacto-pentitol-1-yl)-5-mercapto-1,2,4-triazoles and 4-amino-3-(D-glycero-D-gluco-hexitol-1-yl)-5-mercapto-1,2,4-triazole<sup>[13–15]</sup> were undertaken with the expectation that they would have improved biological activity over those without the

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alditolyl residue. However, the activity of the *gluco* analogue in this series as an inhibitor for glycosidase enzymes<sup>[16]</sup> was found to be less than the simple analogue, 4-amino-5-mercapto-1,2,4-triazole, without the alditolyl moiety.<sup>[17]</sup> These results led us to synthesize varied analogues the 4-amino-5-mercapto-1,2,4-triazole ring, particularly significant will be the double headed *seco* C-nucleoside type where two identical rings are linked to both ends of an ethanediol moiety.

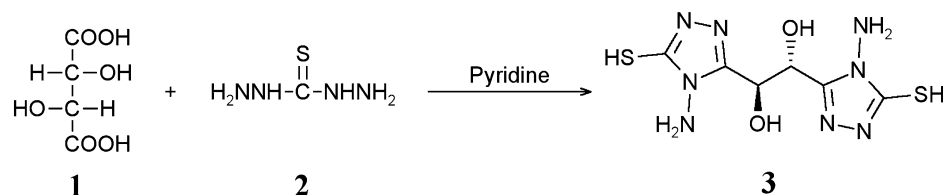
## RESULTS AND DISCUSSION

The synthesis of (1*R*,2*S*)-1,2-*bis*-(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)ethane-1,2-diol (**3**) has been achieved by the dehydrative cyclisation of L-tartaric acid **1** with thiocarbohydrazide **2** in dry pyridine (Scheme 1).

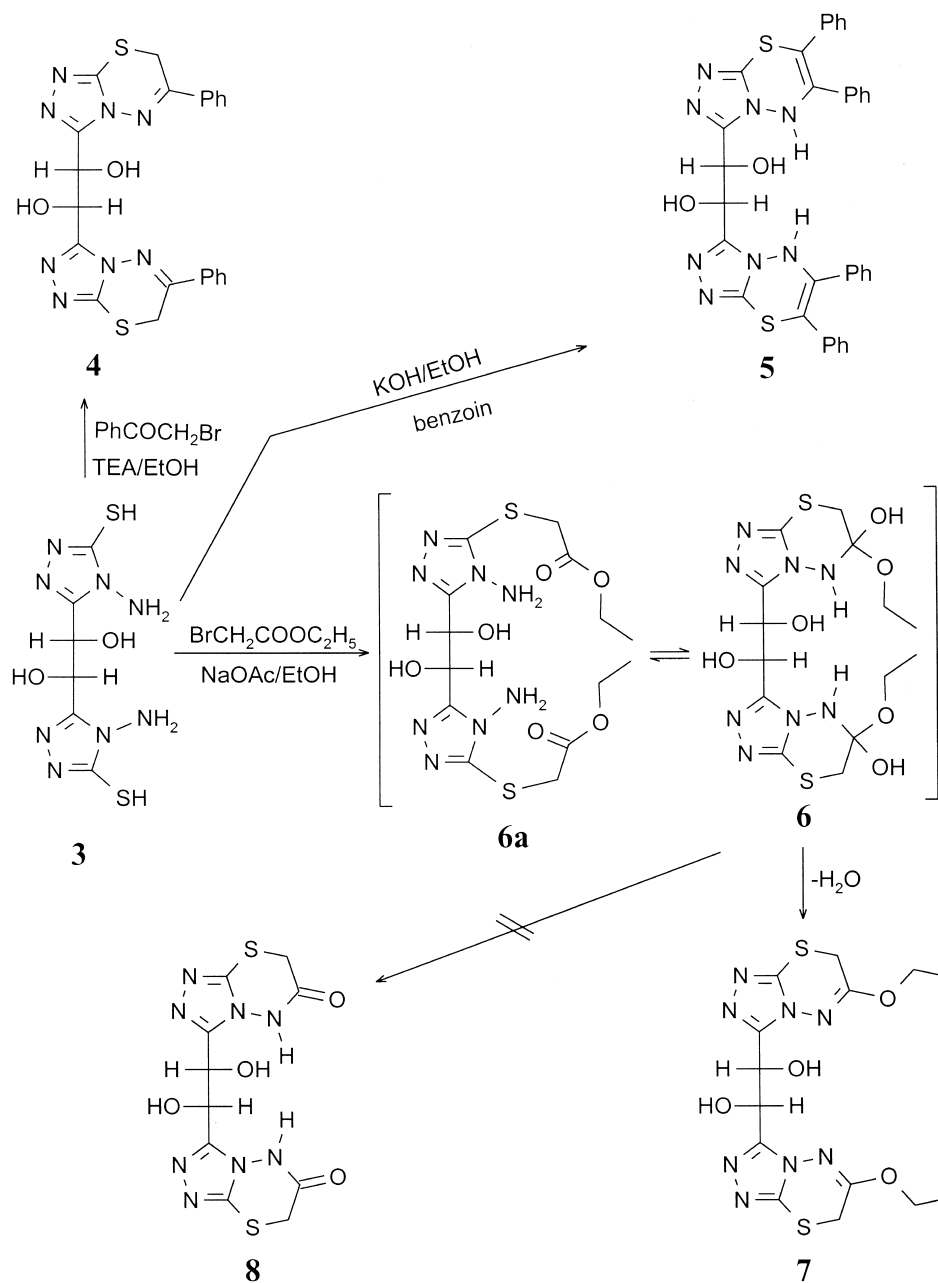
The <sup>1</sup>H NMR spectrum of **3** exhibited a doublet at  $\delta$  5.24 for the two CH groups in addition to the signals of the amino and thiol groups at  $\delta$  5.52 and 13.54, respectively. The appearance of one signal at  $\delta$  67.3 for the CH group in the <sup>13</sup>C NMR spectrum confirmed that the product was a result from similar reactions on both of the carboxyl groups. The aminomercaptotriazole **3** reacted with phenacyl bromide under basic conditions to afford the triazolothiadiazine derivative **4** in good yield. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of **4** showed characteristic singlet for the SCH<sub>2</sub> group at  $\delta$  4.27 and  $\delta$  22.85, respectively.

Cycloaddition of compound **3** with benzoin afforded the triazolothiadiazine derivative **5**. Its IR spectrum showed a broad band at 3380 and 3416 cm<sup>-1</sup> for NH and OH stretching frequencies, and its <sup>1</sup>H NMR spectrum indicated the presence of aromatic protons at  $\delta$  7.22–7.58 and the NH proton at  $\delta$  8.01, 8.03, respectively.

Heating compound **3** with ethyl bromoacetate under basic conditions in dry ethanol gave product **7**. Its elemental analysis indicated the loss of a molecule of water from the possible alkylated product **6**. On the other hand, the infrared spectrum of **7** showed the absence of absorptions, which could be correlated to the ester or amide groups existing in **6** and **8**, respectively. Consequently, structures **6** or **8** were ruled out from consideration, leaving structure **7** as the most probable one. Structure **7** was confirmed from the analysis of its <sup>1</sup>H NMR spectrum, which showed the presence of the ethyl



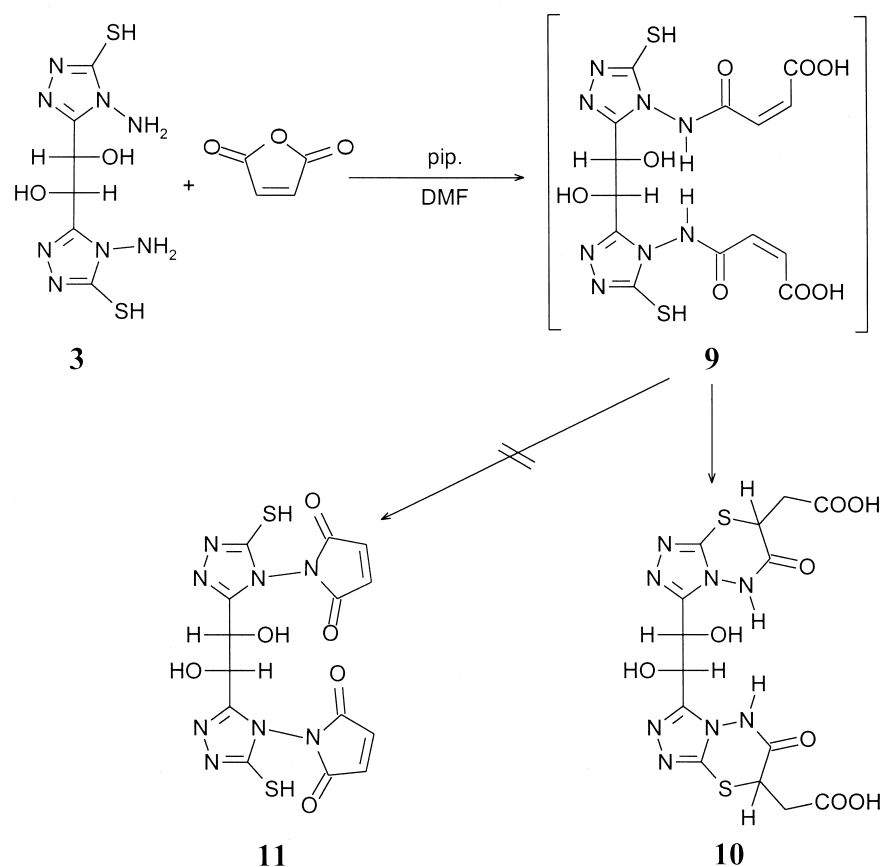
SCHEME 1



SCHEME 2

group at  $\delta$  1.62 and 4.09 as triplet and quartet characteristic for  $\text{CH}_3$  and  $\text{CH}_2$  groups, and its  $^{13}\text{C}$  NMR spectrum showed their carbons at  $\delta$  13.91 and 61.03. Moreover, no signals corresponding to the NH groups were found in the spectrum. The formation of **7** can be rationalized by the formation of the hemiketal intermediate **6**, from the expected alkylation product **6a**, which preferentially loses water rather than ethanol to give **7** instead of **8**.

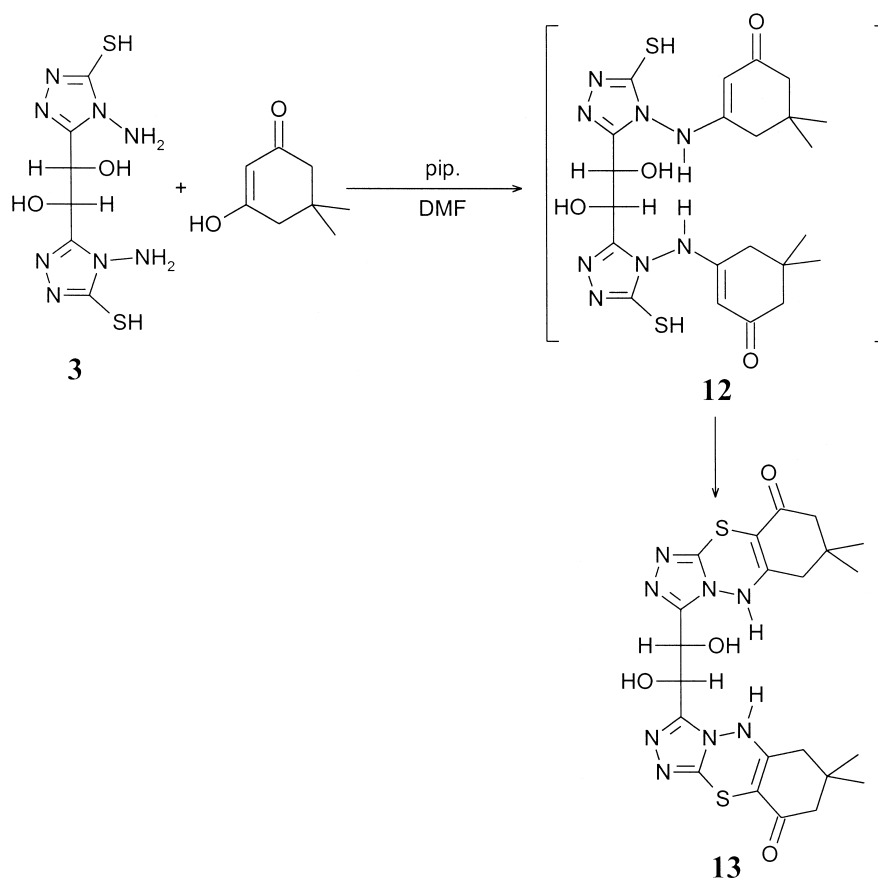
The reaction of **3** with maleic anhydride in DMF and a few drops of piperidine afforded a compound, which did not have the structure of the amide **9** or the imide **11**. Its  $^1\text{H}$  NMR spectrum showed a signal at  $\delta$  13.54 that is compatible to the COOH group, and a singlet in a down-field region at  $\delta$  7.56 instead of the amino group in their precursors and could be attributed to an NH group. The protons on the maleic anhydride double-bond carbons did not appear as olefinic protons but appeared as a doublet at  $\delta$  2.97 that was integrated for four protons of two  $\text{CH}_2\text{CO}$  that is linked to a CH group, which appeared as a triplet at  $\delta$  5.55, indicating the presence of a  $\text{CHCH}_2$



SCHEME 3

group. Consequently, the structure of the products could be **10**. This can be explained by starting the attack of the amino group on one of the carbonyl in maleic anhydride leading to opening of the anhydride ring to give the amide, which can undergo intramolecular Michael addition of the thiol to the olefinic double-bond to afford the triazolothiadiazine derivative **10**.

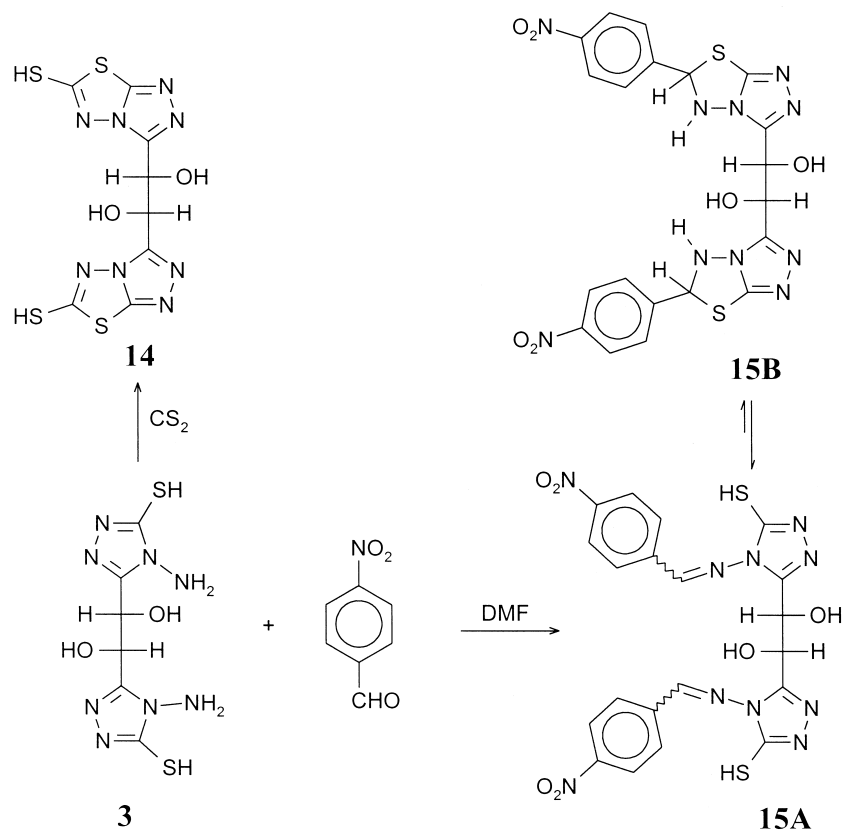
Treatment of **3** with dimedone in dry DMF and few drops of piperidine gave a product tentatively assigned the structure 6,7,8,9-tetrahydro-7,7-dimethyl-9-oxo-5*H*-1,2,4-triazolo[3,4-*b*]benzo[*e*][1,3,4]thiadiazin-3-yl]ethane-1,2-diol **13**, rather than the enamine **12**. This cyclization has been proved by the absence of the SH group and the dimedone olefinic protons in the  $^1\text{H}$  NMR spectrum of **13**, which in the meantime exhibited singlets at  $\delta$  1.04, 2.60, 3.38 for the protons of the dimedone-methyl and methylene groups. The NH signal appeared at  $\delta$  7.57. Moreover, the structure has been based also on similar structures given for products resulting from reactions of the same functionality, on other triazole derivatives, with dimedone.<sup>[18]</sup>



SCHEME 4

The reaction of **3** with carbon disulfide in presence of alcoholic KOH gave the expected triazolothiadiazole **14**. The structure was elucidated by IR,  $^1\text{H}$ , and  $^{13}\text{C}$  NMR spectra. The SH appeared as singlet at  $\delta$  13.46, in addition to the expected signals of the ethanediol and the absence of the  $\text{NH}_2$  signal. Its  $^{13}\text{C}$  NMR spectrum showed these signals characteristic for the  $\text{C}=\text{N}$  at  $\delta$  150.8, 150.9, 165.9.

Treatment of triazole **3** with *p*-nitrobenzaldehyde in acetic acid or DMF furnished a product whose  $^1\text{H}$  NMR spectrum indicated that its solution in  $\text{DMSO}-d_6$  showed the existence of Schiff base **15A** as the major form in addition to the cyclic structure **15B** as a minor one in a ratio 1:0.25. Moreover, the spectrum showed two signals at  $\delta$  10.17 and 10.25, indicating the presence of two geometric isomer, *syn* and *anti* of the  $\text{CH}=\text{N}$  group. The irradiation of the CH group doublet at  $\delta$  5.36 caused the OH group doublet at  $\delta$  6.52 to collapse, confirming the assignment for both signals.



SCHEME 5

## EXPERIMENTAL

Melting points were determined with a Melt-Temp apparatus and are uncorrected. IR spectra were recorded for the compounds in a matrix of a KBr with Perkin Elmer FTIR 1600 Spectrometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were determined with a JEOL-JNM-LA400 spectrometer. The chemical shifts are expressed on the  $\delta$  (ppm) scale using TMS as the standard.

**(1*R*,2*S*)-1,2-bis(4-Amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)ethane-1,2-diol (3).** A mixture of **1** (10 mmol) and **2** (20 mmol) in pyridine (10 mL) was heated under reflux for 6 h. The reaction mixture was cooled and poured into cold water. The product was filtered, washed with water and crystallized from hot water to give white crystals (60% yield); mp 225–226°C. IR (KBr): 3299 (NH), 3350 (OH)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 5.24 (d,  $J$  = 1.7 Hz, 2 H, 2 CH), 5.52 (s, 4 H, 2  $\text{NH}_2$ ), 6.15, 6.16 (2 d, 2 H,  $J$  = 2.8 Hz, 2 OH), 13.54 (s, 2 H, 2 SH).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  = 67.3 (2 CH), 151.8 (2 NCS), 166.2 (2 NCN). Anal. Calcd for  $\text{C}_6\text{H}_{10}\text{N}_8\text{O}_2\text{S}_2$  (290.3): C, 24.82; H, 3.47; N, 38.60. Found: C, 24.53; H, 3.72; N, 38.45.

**(1*R*,2*S*)-1,2-bis[6-Phenyl-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl]ethane-1,2-diol (4).** A solution of phenacyl bromide (20 mmol) in anhydrous ethanol (10 mL) was added dropwise to a solution of **3** (10 mmol) and 3 drops of triethylamine in ethanol (10 mL). The mixture was heated under reflux for 6 h and then cooled. The precipitate was crystallized from DMF to afford the pure product (87% yield); mp 259–260°C. IR (KBr): 1625 (C=N), 3375 (OH)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 4.27 (s, 4 H, 2  $\text{CH}_2\text{S}$ ), 4.29 (br s, 2 H, 2 OH), 5.61 (s, 2 H, 2 CH), 7.46–7.99 (m, 8 H, 8 Ar-H), 8.01 (d,  $J$  = 7.2 Hz, 2 H, 2 Ar-H).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  = 22.9 (2  $\text{CH}_2\text{S}$ ), 65.6 (2 CH), 127.4, 128.8, 131.7, 133.3, 140.4, 152.8, 154.4 (Ar-C and C=N). Anal. Calcd for  $\text{C}_{22}\text{H}_{18}\text{N}_8\text{O}_2\text{S}_2$  (490.6): C, 53.86; H, 3.70; N, 22.84. Found: C, 53.75; H, 3.53; N, 22.76.

**(1*R*,2*S*)-1,2-bis[6,7-Diphenyl-5*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl]ethane-1,2-diol (5).** A mixture of **3** (10 mmol), benzoin (20 mmol) and 1 N aqueous KOH (5 mL) in dry ethanol (10 mL) was boiled under reflux for 4 h. The reaction mixture was cooled and poured into ice-cold water. The precipitate was filtered, washed with water and crystallized from ethanol (67% yield); mp 263–264°C. IR (KBr): 3380 (NH), 3416 (OH)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 4.56 (d,  $J$  = 1.8 Hz, 2 H, 2 CH); 5.95 (d,  $J$  = 1.8 Hz, 2 H, 2 OH), 7.22–7.58 (m, 20 H, Ar-H), 8.03 (s, 2 H, 2 NH).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  = 75.7 (2 CH), 127.2, 127.3, 127.6, 127.7, 128.3, 128.4, 128.5, 128.6, 133.1, 134.6, 139.7, 199.1 (Ar-C, C=N and CS). Anal. Calcd for  $\text{C}_{34}\text{H}_{26}\text{N}_8\text{O}_2\text{S}_2$  (642.8): C, 63.53; H, 4.08; N, 17.43. Found: C, 63.25; H, 3.85; N, 17.28.



**(1*R*,2*S*)-1,2-bis[6-Ethoxy-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl]ethane-1,2-diol (7).** To a solution of **3** (10 mmol) and anhydrous sodium acetate (2 mmol) in anhydrous ethanol (10 mL), ethyl bromoacetate (40 mmol) was added. The reaction mixture was heated under reflux for 8 h and then cooled. The product was filtered, washed with H<sub>2</sub>O and ethanol, and crystallized from ethanol to give colorless crystals (90% yield); mp 180–181°C. IR (KBr): 1616 (C=N), 3421 (OH) cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ = 1.16 (t, *J* = 2.1 Hz, 6 H, 2 CH<sub>3</sub>); 3.99 (s, 4 H, 2 CH<sub>2</sub>S), 4.09 (q, *J* = 2.1 Hz, 4 H, 2 CH<sub>2</sub>), 5.17 (s, 2 H, 2 CH), 6.01 (br s, 2 H, 2 OH). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ = 13.91 (CH<sub>3</sub>), 32.62 (CH<sub>2</sub>S), 61.01 (CH<sub>2</sub>O), 65.30 (2 CH), 151.0, 155.6, 168.3 (3 C=N). Anal. Calcd for C<sub>14</sub>H<sub>18</sub>N<sub>8</sub>O<sub>4</sub>S<sub>2</sub> (426.5): C, 39.43; H, 4.25; N, 26.27. Found: C, 39.32; H, 4.05; N, 26.07.

**(1*R*,2*S*)-1,2-bis[7-Carboxymethyl-6,7-dihydro-6-oxo-5*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl]ethane-1,2-diol (10).** A mixture of **3** (10 mmol) maleic anhydride (20 mmol) and 3 drops of piperidine in DMF (20 mL) was heated under reflux for 24 h, cooled, and poured into ice-water. The product was crystallized from DMF/ethanol (84% yield), mp 295–296°C. IR (KBr): 1680 (C=O), 1714 (C=O), 3152 (NH), 3384 br (OH) cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ = 2.97 (d, *J* = 2.4 Hz, 4 H, 2 CH<sub>2</sub>CO), 5.28 (d, *J* = 1.8 Hz, 2 H, 2 OH), 5.55 (t, *J* = 2.4 Hz, 2 H, 2 HCS), 5.76 (s, 2 H, 2 CH), 7.56 (s, 2 H, 2 NH), 13.54 (s, 2 H, 2 COOH). Anal. Calcd for C<sub>14</sub>H<sub>14</sub>N<sub>8</sub>O<sub>8</sub>S<sub>2</sub> (486.4): C, 34.57; H, 2.90; N, 23.04. Found: C, 34.32; H, 2.60; N, 22.80.

**(1*R*,2*S*)-1,2-bis-[6,7,8,9-Tetrahydro-7,7-dimethyl-9-oxo-5*H*-1,2,4-tri-azolo[3,4-*b*]benzo[*e*][1,3,4]thiadiazin-3-yl]ethane-1,2-diol (13).** A solution of **3** (10 mmol) and dimedone (20 mmol) in dry DMF (20 mL) and a few drops of piperidine was heated under reflux for 24 h. The reaction mixture was cooled and poured into ice-cold water and then crystallized from DMF/ethanol to give brown crystals (77% yield); mp 320–321°C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ = 1.04 (s, 12 H, 4 CH<sub>3</sub>); 2.60 (s, 4 H, 2 × 6-CH<sub>2</sub>); 3.38 (s, 4 H, 2 × 8-CH<sub>2</sub>); 5.78 (br s, 2 H, 2 CH), 6.06 (br s, 2 H, 2 OH), 7.57 (s, 2 H, 2 NH). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ = 27.6, 27.7, 32.4, 40.5, 50.9, 117.7, 125.2, 147.4, 167.1, 196.8. Anal. Calcd for C<sub>22</sub>H<sub>26</sub>N<sub>8</sub>O<sub>4</sub>S<sub>2</sub> (530.6): C, 49.80; H, 4.94; N, 21.12. Found: C, 49.98; H, 4.58; N, 21.02.

**(1*R*,2*S*)-1,2-bis[6-Mercapto-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]ethane-1,2-diol (14).** To a solution of KOH (15 mmol) in dry ethanol (20 mL) was added **3** (10 mmol) followed by CS<sub>2</sub> (50 mL) with stirring. The reaction mixture was heated under reflux for 24 h, cooled, and poured into ice-cold water and then acidified with glacial acetic acid. The precipitate was collected and crystallized from aqueous ethanol (50% yield); mp 250–251°C. IR (KBr): 1620 (C=N), 3480 (OH) cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ =

4.15 (br s, 2 H, 2 OH), 5.24 (s, 2 H, 2 CH), 13.46 (s, 2 H, 2 SH).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  65.2 (2 CH), 150.8, 150.9, 165.9 (3 C=N). Anal. Calcd for  $\text{C}_8\text{H}_6\text{N}_8\text{O}_2\text{S}_4$  (374.5): C, 25.66; H, 1.61; N, 29.92. Found: C, 25.53; H, 1.60; N, 29.54.

**(1*R*,2*S*)-1,2-bis-[4-*p*-Nitrobenzylideneamino-5-mercapto-1,2,4-triazolo-3-yl]ethane-1,2-diol (15).** A mixture of **3** (10 mmol) and *p*-nitrobenzaldehyde (20 mmol) in DMF (20 mL) was refluxed for 8 h, cooled, and then poured into ice-cold water. The yellow precipitate was crystallized from DMF/ethanol (80% yield in ratio 1:0.25%); mp 267–268°C. IR (KBr): 1601 (C=N), 3185 (NH), 3425 (OH)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  = 5.36 (d,  $J$  = 1.8 Hz, 2 H, 2 CH), 6.52 (d,  $J$  = 1.7 Hz, 2 H, 2 OH), 7.50–8.46 (m, 8 H, Ar-H), 10.17, 10.23 (2s, 2 H, 2 CH=N), 11.27 (s, 0.5 H, 2 NH), 14.03 (s, 2 H, 2 SH).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  = 54.6, 65.5 (2 CH); 123.8, 123.9, 124.2, 129.6, 129.8, 130.5, 137.8, 139.9, 149.2, 150.5, 160.1 and 161.5 (Ar-C, C=N) and 192.2 (CS). Anal. Calcd for  $\text{C}_{20}\text{H}_{16}\text{N}_{10}\text{O}_6\text{S}_2$  (556.5): C, 43.17, H, 2.90; N, 25.17. Found: C, 43.08; H, 2.58; N, 25.12.

## REFERENCES

1. Temple, C. *1,2,4-Triazoles in The Chemistry of Heterocyclic Compounds*, Montgomery, J.A., Ed.; John Wiley and Sons: New York, 1981.
2. El Ashry, E.S.H.; Awad, L.F.; Winkler, M. A new approach to the synthesis of nucleosides of 1,2,4-triazole. *J. Chem. Soc. Perkin 1* **2000**, 829–834.
3. (a) Holla, B.S.; Poojary, K.N.; Kalluraya, B.; Gowda, P.V. Synthesis, characterization and antifungal activity of some N-bridged heterocycles derived from 3-(3-bromo-4-methoxyphenyl)-4-amino-5-mercapto-1,2,4-triazole. *Farmaco* **1996**, 51, 793–799. (b) Ergenc, N.; Ulusoy, N.; Capan, G.; Sanis, G.O.; Kiraz, M. Synthesis and antimicrobial properties of new 4-(alkylidene/arylidene)-amino-5-(2-furanyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones and 6-aryl-3-(2-furanyl)-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines. *Arch. Pharm.* **1996**, 329, 427–430. (c) Lee, A.R.T. Antiinflammatory triazoles. U.S. Patent **1996**, 720, 5498; Chem. Abstr. **1996**, 125, 10824K. (d) Udupi, R.H.; Bhat, A.R. Synthesis of 4-(*N*-pyridylcarboxamido)-5-mercapto-3-substituted 1,2,4-triazoles for possible antitubercular activity. *Indian J. Heterocycl. Chem.* **1996**, 6, 41–45.
4. (a) El Ashry, E.S.H.; Rashed, N.; Taha, M.; Ramadan, E. Condensed 1,2,4-triazine: I. Fused to heterocycles with three-, four- and five-membered rings. *Adv. Heterocycl. Chem.* **1994**, 59, 39–177. (b) El Ashry, E.S.H.; Rashed, N.; Mousaad, A.; Ramadan, E. Condensed 1,2,4-triazine: II. Fused to heterocycles with six and seven-membered rings and fused to two heterocyclic rings. *Adv. Heterocycl. Chem.* **1994**, 61, 207–328.
5. (a) El-Saadani, M.A.; El-Gamal, B.A.B.; El Kholy, G.I.; El Sayed, M.M.; El Ashry, E.S.H. Effect of triazine derivatives on carbohydrate metabolism in rats. *J. Med. Res. Inst.* **1993**, 14, 293–305. (b) El-Gamal, B.A.B.; El-Saadani, M.A.; El Sayed, E.K.A.; El Sayed, M.M.; El Ashry, E.S.H. Effect of triazine derivatives on lipid components of rat tissues and serum. *J. Med. Res. Inst.* **1994**, 15, 119–128.
6. (a) Mousaad, A.; Abdel Hamid, H.; El Nemer, A.; El Ashry, E.S.H. Synthesis of 3-(alditol-1-yl)triazolo[4',3':2,3]-1,2,4-triazino[5,6-*b*]indoles. *Bull. Chem. Soc. Jap.* **1992**, 65, 546–552. (b) Rashed, N.; El Nemer, A.; El Ashry, E.S.H. 10-Carboethoxymethyl-3-phenyl-1,2,4-triazolo[4',3':2,3]-1,2,4-triazino[5,6-*b*]indole and derivatives at its 10-position. *Arch. Pharm.* **1992**, 326, 153–156.
7. (a) Paolo, F.; Daniele, S.; France, S.; Noemi, P. 3,6-Disubstituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles: Synthesis, antimicrobial and antiviral activity. II. *Farmaco* **1996**, 51, 659–663. (b) Gupta, R.;

- Sudan, S.; Kachroo, P.L. Reaction of 3-substituted-4-amino-5-mercapto-1,2,4-triazoles with substituted cinnamic acids. *Indian J. Chem. Sect. B* **1996**, 35, 718–720. (c) Gupta, R.; Sudan, S.; Kachroo, P.L. Bridgehead nitrogen heterocycles: Synthesis and biological activities of s-triazolo[3,4-*b*][1,2,4]thiadiazole system. *J. Ind. Chem. Soc.* **1996**, 73, 625–626. (d) Kalluraya, B.; Chimbalkar, R.; Gunaga, P. Synthesis and biological activities of some 1,2,4-triazole and 1,3,4-oxadiazoles. *Indian J. Heterocycl. Chem.* **1996**, 6, 103–106. (e) Holla, B.S.; Shivanada, M.K.; Akberali, P.M.; Baliga, S.S. Studies on arylfuran derivatives. Part VI. Synthesis, characterization, and antibacterial activities of some 6-(5-aryl-2-furyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles and 6-(5-nitro-2-furyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles. *Farmaco* **1996**, 51, 785–792. (f) Bala, S.; Gupta, R.P.; Sachdeva, M.L.; Singh, A.; Puraji, H.K. Heterocyclic systems containing bridgehead nitrogen atom: Part XXXIII—Synthesis of s-triazolo[3,4-*b*][1,3,4]thiadiazine, s-triazolo[3,4-*b*][1,3,4]thiadiazino[6,7-*b*]quinoxaline and as triazino[3,4-*b*][1,3,4]thiadiazines. *Indian J. Chem.* **1978**, 16B, 481–483. (g) Xiao, S.W.; Hui, X.-P.; Chu, Ch.-H.; Zhang, Z.Y. Reactions of 4-amino-3-(1-*p*-chlorophenyl-5-methyl-1,2,3-triazol-4-yl)-5-mercapto-s-triazole. *Indian J. Chem.* **2000**, 39B, 779–782.
8. (a) El Ashry, E.S.H.; El Kilany, Y. Acyclonucleosides: Part 1. *seco*-Nucleosides. *Adv. Heterocycl. Chem.* **1995**, 67, 391–432. (b) El Ashry, E.S.H.; El Kilany, Y. Acyclonucleosides: Part 2. *diseco*-Nucleosides. *Adv. Heterocycl. Chem.* **1997**, 68, 1–88. (c) El Ashry, E.S.H.; El Kilany, Y. Acyclonucleosides: Part 3. tri, tetra, and penta *seco*-Nucleosides. *Adv. Heterocycl. Chem.* **1998**, 69, 129–215.
  9. (a) Knutsen, L.J.S. The chemistry of 2'-deoxyribo-*C*-nucleosides. *Nucleosides & Nucleotides* **1992**, 11, 961–983. (b) Hacksell, U.; Daves, G.D. The chemistry and biochemistry *C*-nucleosides and *C*-arylglycosides. *Progr. Med. Chem.* **1985**, 22, 1–65. (c) Chu, C.K.; El-Kabbani, P.M.; Thompson, B.B. Determination of the anomeric configuration of *C*-nucleosides by proton and carbon-13 NMR spectroscopy. *Nucleosides & Nucleotides* **1984**, 3, 1–31.
  10. James, S.R. Synthesis methods in *C*-nucleoside chemistry. *J. Carbohydr. Nucleosides Nucleotides* **1979**, 6, 417–465.
  11. Hanessian, S.; Pernet, A.G. Synthesis of naturally occurring *C*-nucleosides, their analogues, and functionalized *C*-glycosyl precursors. *Adv. Carbohydr. Chem. Biochem.* **1976**, 33, 111–188.
  12. (a) Tsuchiya, K.; Kobayashi, S.; Kurokawa, T.; Nakagawa, T.; Shimada, T.; Nakamura, H.; Litaka, Y.; Kitagawa, T.; Tatsuta, K. A novel acricide produced by *Streptomyces*, sp. NK11687. II. Structure elucidation. *J. Antibiot.* **1995**, 48, 630–643. (b) Tatsuta, K.; Kitagawa, M.; Horiuchi, T.; Tsuchiya, K.; Shimada, N. Syntheses and absolute structures of the disaccharide and aglycon of Acaricidal gualamycin. *J. Antibiot.* **1995**, 48, 741–744. (c) Shaban, M.A.E.; Nasr, A.Z. Nucleosides and their analogs I: *C*-Nucleosides of hetero monocyclic bases. *Adv. Heterocycl. Chem.* **1997**, 68, 223–256.
  13. Awad, L.F.; El Ashry, E.S.H. Synthesis and conformational analysis of *seco* *C*-nucleosides and their *diseco* double-headed analogues of the 1,2,4-triazole, 1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazoles. *Carbohydr. Res.* **1998**, 312, 9–22.
  14. El Ashry, E.S.H.; Awad, L.F. *Seco* *C*-nucleoside analogs of the 1,2,4-triazole. *Nucleosides, Nucleotides & Nucleic Acids* **2001**, 20, 901–902.
  15. El Ashry, E.S.H.; Awad, L.F. Novel synthesis of *seco* type of acyclo *C*-nucleosides of 1,2,4-triazole and 1,2,4-triazolo[3,4-*b*][1,3,4]-thiadiazine. *Nucleosides Nucleotides Nucleic Acids* **2001**, 20, 103–109.
  16. (a) El Ashry, E.S.H.; Rashed, N.; Shobier, A.H. Glycoside inhibitors and their chemotherapeutic value, part 1. *Pharmazie* **2000**, 55, 251–262. (b) El Ashry, E.S.H.; Rashed, N.; Shobier, A.H. Glycoside inhibitors and their chemotherapeutic value, part 2. *Pharmazie* **2000**, 55, 331–348. (c) El Ashry, E.S.H.; Rashed, N.; Shobier, A.H. Glycoside inhibitors and their chemotherapeutic value, part 3. *Pharmazie* **2000**, 56, 403–415.
  17. Balbaa, M.; Mansour, H.; El-Sawy, H.; El Ashry, E.S.H. Inhibition of some hepatic glycosides by the *diseco* nucleoside, 4-amino-3-(D-glucopentitol-1-yl)-5-mercapto-1,2,4-triazole and its 3-methyl analog. *Nucleosides, Nucleotides & Nucleic Acids* **2002**, 21, 695–708.
  18. Kidwai, M.; Goel, Y.; Kumar, P.; Kumar, K. Microwave induced synthesis and antimicrobial activity of bridgehead nitrogen heterocycles: Reactions of 4-amino-5-mercapto-3-(4'-methyl-quinolinyl-2'-oxymethyl)/(tetrazolyl-1'-methyl)-1,2,4-s-triazoles. *Indian J. Chem.* **1997**, 36B, 782–786.