Monatshefte für Chemie 138, 777–785 (2007)
DOI 10.1007/s00706-007-0649-7
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

Synthesis of 1,2,4-Triazol-3-ylmethyl-, 1,3,4-Oxa-, and -Thiadiazol-2-ylmethyl-1*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidinediones

Farag A. El-Essawy, Ahmed F. Khattab, and **Adel A.-H. Abdel-Rahman***

Faculty of Science, Department of Chemistry, Menoufia University, Shebin El-Koam, Egypt

Received December 15, 2006; accepted (revised) January 3, 2007; published online May 31, 2007

Summary. 1-Carbethoxymethyl-4,6-dimethyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione was synthesized and treated with hydrazine hydrate to give the corresponding hydrazide. The latter hydrazide was treated either with phenylisothiocyanate or with carbon disulfide/alc. KOH to afford the corresponding thiosemicarbazide and oxadiazole derivatives. Alkylation of 2-mercapto-1,3,4-oxadiazole with dimethyl sulfate or ethyl chloroacetate gave the corresponding 2-methylthio-, and 2-ethylthioglycolate derivatives. Formation of 1,3,4-thiadiazole, 5-mercapto-1,2,4-triazole, and 1,3,4-oxadiazole were carried out by treating of the latter thiosemicarbazide with conc. H_2SO_4, NaOH/HCl, and HgO. Treating of 5-mercapto-1,2,4-triazole with ethyl chloroacetate afforded the thioglycolate ester. Hydrolysis of the latter with hydrazine hydrate afforded the hydrazide derivatives. Condensation of these hydrazides with monosaccharide aldoses gave the corresponding sugar hydrazones. The novel compounds were tested for antiviral activity against hepatitis B virus and showed moderate activities.

Keywords. 1,2,4-Triazole; 1,3,4-Oxadiazole; 1,3,4-Thiadiazole; 6-Azido-1,3-dimethyuracil; Triazolopyrimidines.

Introduction

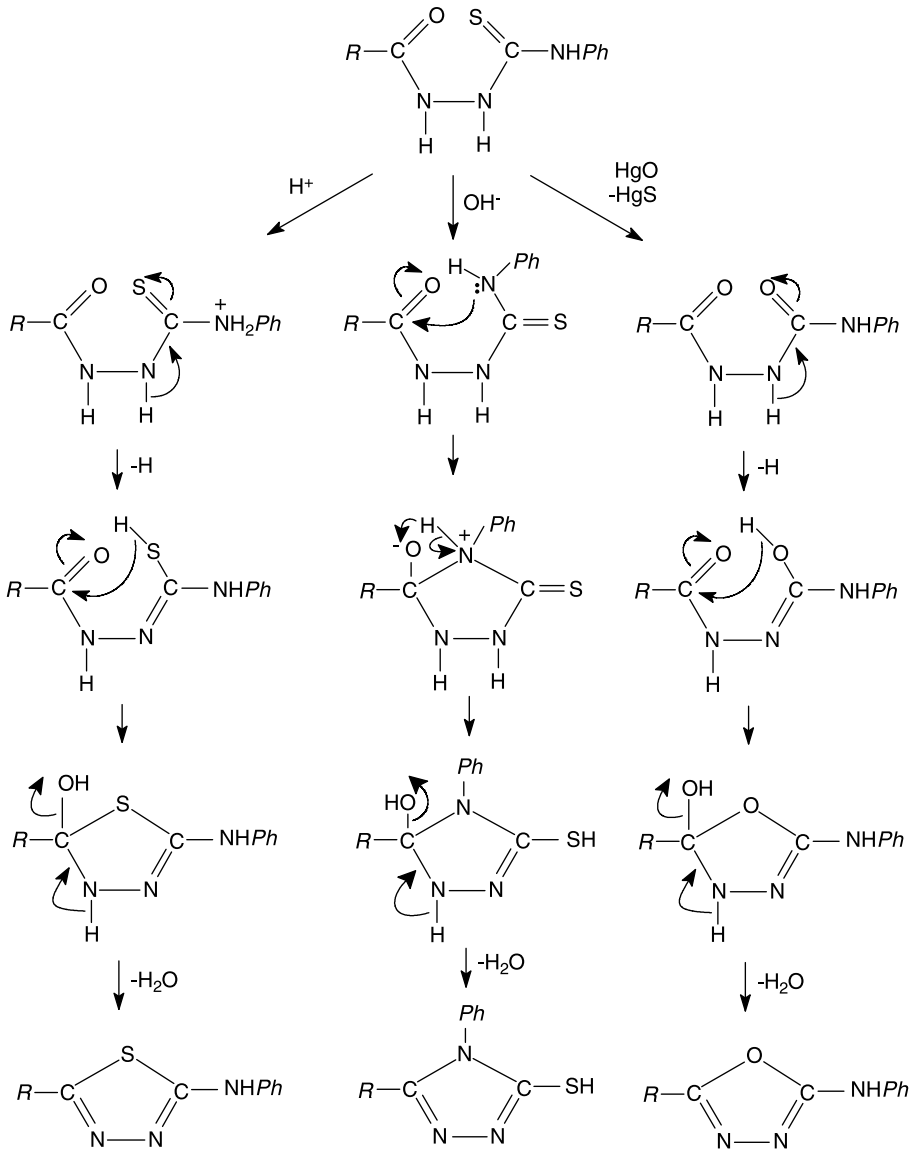
Triazoles, oxa-, and thiadiazoles have been the subject of chemical and biological studies on account of their interesting pharmacological properties, such as antimicrobial, antiinflammatory, analgesic, and antitumoral activities [1–7]. In addition, several 1,3,4-oxadiazole derivatives have been reported to possess biological activities [8–14]. 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. A number of syntheses for substituted derivatives of these heterocyclic systems have been developed. Arylthiosemicarbazides are versatile intermediates for the synthesis of substituted triazoles, oxa-, and thiadiazoles [15–18]. The retrosynthetic analysis leads to the conclusion that arylthiosemicarbazides can have ambident sites for cyclization, which readily afford these heterocycles carrying various substituents as shown in Scheme 1. In addition, several compounds containing the 1,2,3-triazolo[4,5-*d*]pyrimidine residue are considered as potential purine antagonists [19]. Therefore, we wanted to develop an efficient procedure for the synthesis of new heterocyclic systems containing 1,2,4-triazoles, 1,3,4-oxa-, and -thiadiazoles linked with 1,2,3-triazolo[4,5-*d*]pyrimidines. Our interest in the synthesis of such compounds was to shed some light on their biological study as antiviral agents as a part of our program aimed at the development of new heterocyclic compounds as antiviral agents [20–23].

Results and Discussion

Synthesis

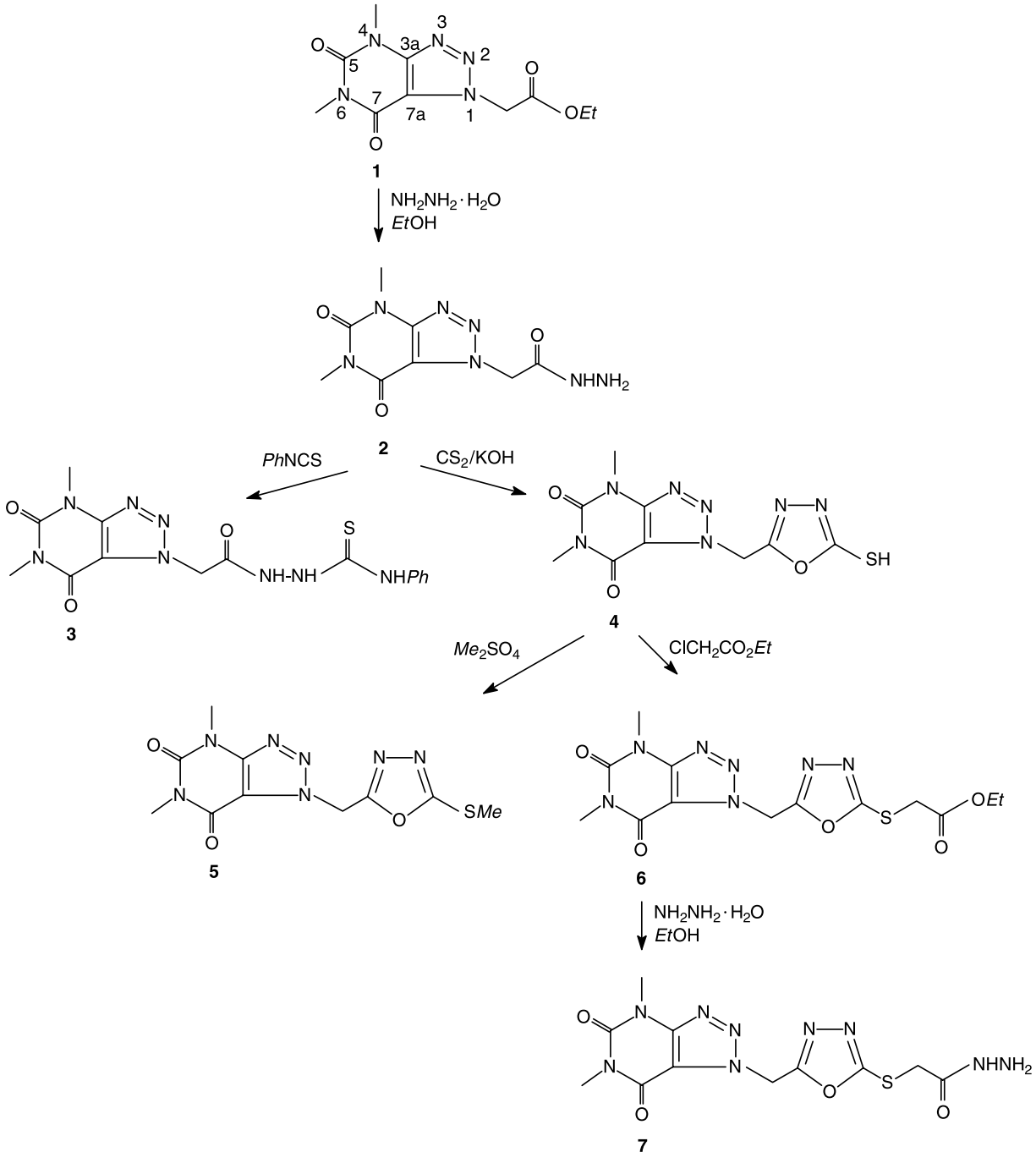
The starting material 1-carbethoxymethyl-4,6-dimethyl-1*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**1**) [24] was synthesized by refluxing 6-azido-1,3-

* Corresponding author. E-mail: adelnassar63@hotmail.com



Scheme 1

dimethyluracil [25] with ethyl chloroacetate in dry *DMF* containing anhydrous potassium carbonate. Treatment of **1** with hydrazine hydrate in ethanol gave the corresponding hydrazide derivative **2** in 89% yield. The IR spectrum shows the characteristic band for N–CO at 1660–1685 cm^{-1}. The hydrazide **2** was treated with phenylisothiocyanate in absolute ethanol under reflux to afford 1-{4,6-dimethyl-1*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione}-acetyl-4-phenyl thiosemicarbazide (**3**) in 92% yield. Compound **3** shows a characteristic carbonyl frequency at 1680–1695 cm^{-1}. Treatment of the hydrazide **2** with carbon disulfide in alcoholic potassium hydroxide at reflux temperature afforded the corresponding mercaptooxadiazole derivative **4** in 83% yield. Compound **4** shows a characteristic SH frequency at 2570 cm^{-1}. Methylation of **4** with dimethyl sulfate afforded the corresponding methylthio derivative **5** in 88% yield. The ^{1}H NMR spectrum showed a singlet at $\delta = 2.52$ ppm for the S*Me* which indicated that S-alkylation had taken place. Reaction of **4** with ethyl chloroacetate/OH^- gave the corresponding ethyl thioglycolate **6** in 78% yield. Its IR spectrum shows a characteristic C=O absorption at 1690–1700 cm^{-1} and its ^{1}H NMR spectrum agrees with the structure. Treatment of **6** with hydrazine hydrate in ethanol gave the corresponding hydrazide derivative **7** in 81% yield (Scheme 2).



Scheme 2

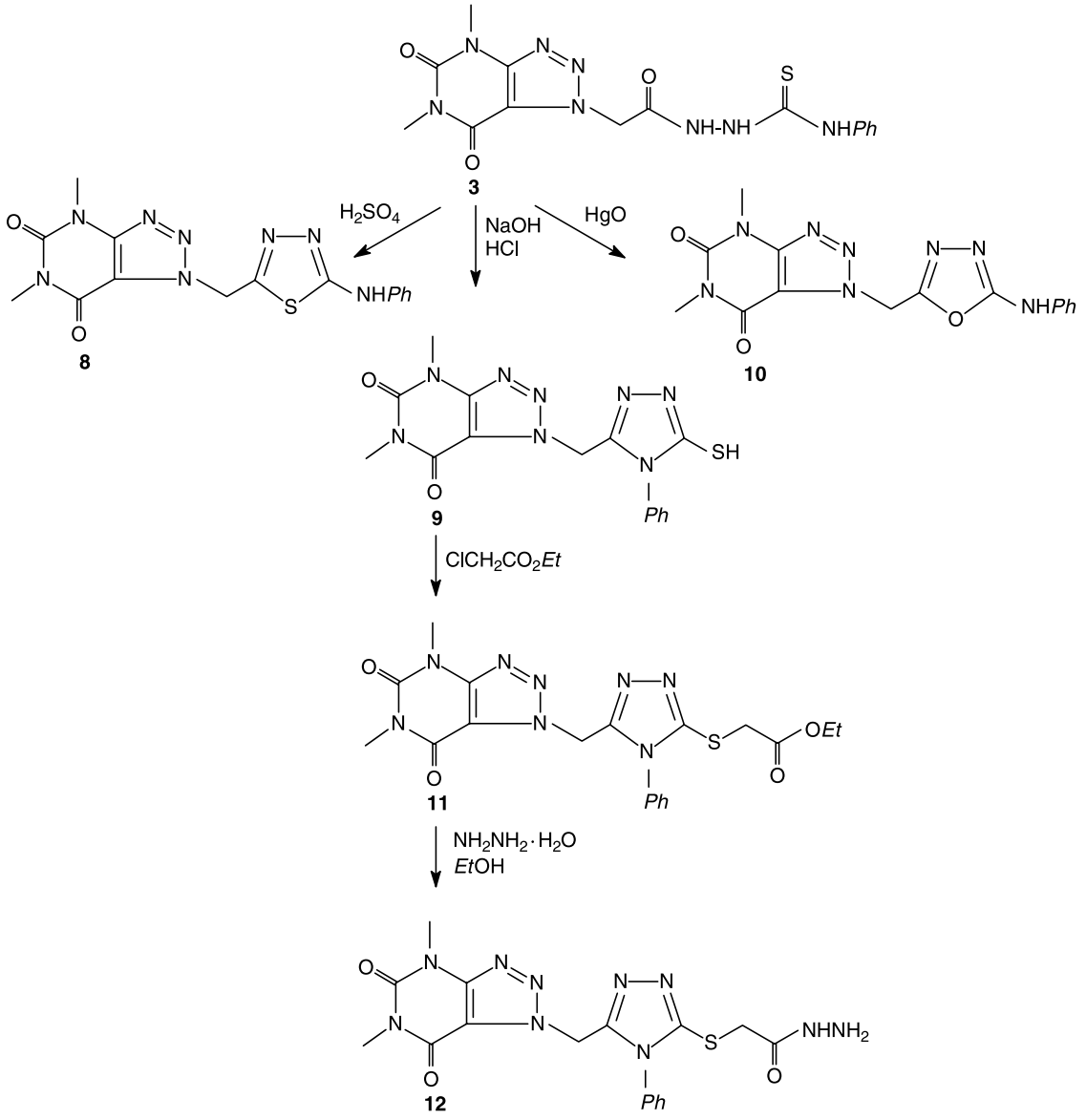
When the thiosemicarbazide **3** was treated with sulfuric acid, 1,3,4-thiadiazole derivative **8** was formed in 80% yield. The preferred formation of the thiadiazole ring under such acidic conditions can be due to the loss of nucleophilicity of N-4 as a result of its protonation leading to an increase in the nucleophilicity of the sulfur atom towards the attack of the carbonyl carbon. On the other hand, when the cyclization of **3** was carried out under alkaline conditions, the nucleophilicity of N-4 is enhanced and leads to cyclization with the carbonyl carbon atom to give the 1,2,4-triazole derivative **9** in 85% yield. When the cyclization was performed by mercuric oxide, the 1,3,4-oxadiazole derivative **10** was formed in 71% yield. The mode of cyclization includes desulfurization by mercuric oxide, which introduces

the oxygen atom in the cyclization process. Reaction of **9** with ethyl chloroacetate/OH^- gave the corresponding ethyl thioglycolate **11** in 80% yield. Treatment of **11** with hydrazine hydrate in ethanol gave the corresponding hydrazide derivative **12** in 79% yield (Scheme 3).

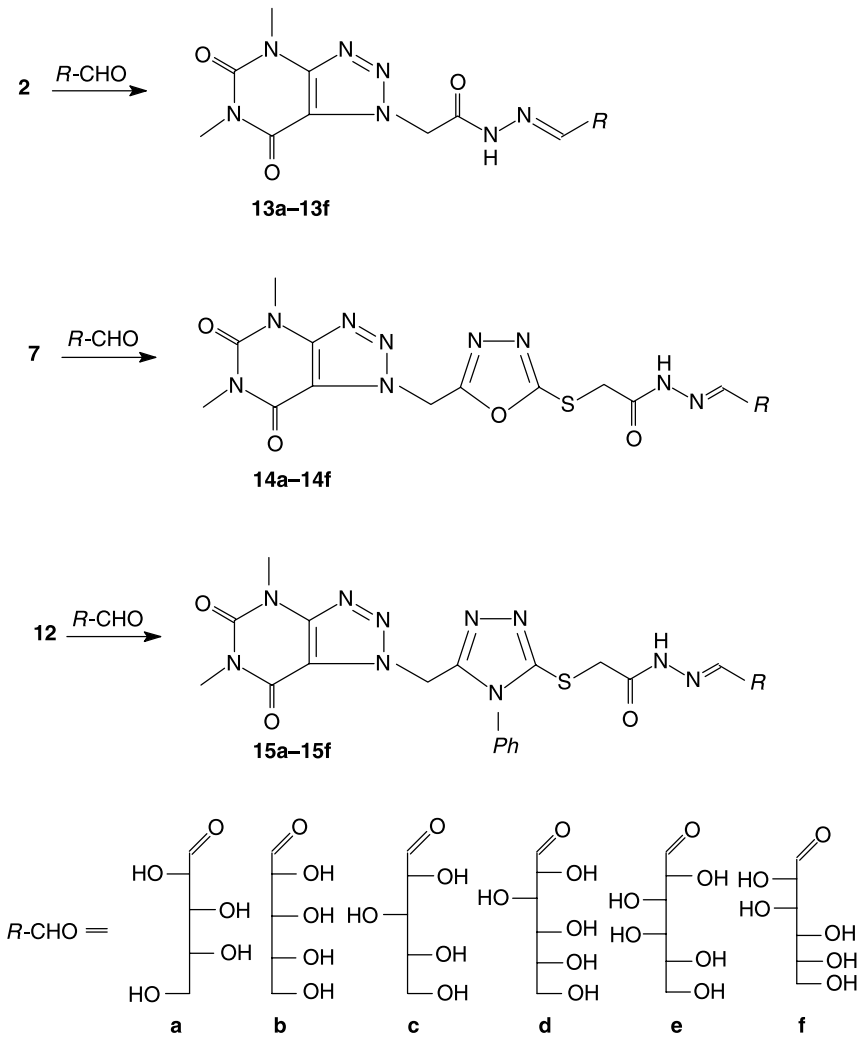
Condensation of the hydrazides **2**, **7**, and **12** with L-arabinose, D-ribose, D-xylose, D-glucose, D-galactose, and D-mannose gave the corresponding sugar hydrazones **13a**–**13f** (70–85%), **14a**–**14f** (68–80%), and **15a**–**15f** (66–77%) – Scheme 4. The ^{1}H NMR spectra of the hydrazones **13**–**15** confirmed the presence of sugar protons in the range 3.14–4.23 ppm and a doublet at $\delta = 7.20$–7.50 ppm corresponding to the proton at C-1 of the sugar. The assignments of NH and OH groups in these compounds were achieved by D_2O exchange.

Testing

Preliminary viral screening against HBV (Hep G2 2.2.15 cell method) [26–28] indicated that compounds **2**, **4**, **7**, **9**, **12**, **16**, **17**, **21**–**23**, and **26**–**29** are active against HBV replication with IC_{50} 83–99 μM and CC_{50} 88–95 μM, while compounds **3**, **5**, **6**, **8**, **10**, **11**, **13**–**15**, **18**–**20**, **24**, **25**, and **30** showed



Scheme 3



Scheme 4

moderate viral replication inhibition and moderate cytotoxicity.

Conclusions

1,2,4-Triazol-3-ylmethyl, 1,3,4-oxa-, and -thiadiazol-2-ylmethyl-1-[1,2,3]-triazolo[4,5-*d*]pyrimidindiones were synthesized in order to increase the number of tested compounds screened for anti-HBV activity.

Experimental

Melting points were determined using a *Kofler* block instrument. IR spectra were recorded with a Perkin-Elmer model 1720 FTIR (KBr), ^{1}H NMR spectra were recorded with Bruker AC 250 FT NMR spectrometer at 250 MHz with *TMS* as an internal standard. EIMS and FABMS spectra were recorded with a Finnigen MAT 312/AMD. The microanalyses were performed at the microanalytical unit, Cairo University, Egypt, and were found to agree favourably with the calculated values. Viral screening against HBV was conducted at the National Liver Institute, Menoufia University, Egypt.

1-Carbethoxymethyl-4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]-pyrimidine-5,7(4H,6H)-dione (**1**)

A mixture of 18.1 g 6-azido-1,3-dimethyluracil [25] (0.1 mol), 14.7 g ethyl chloroacetate (0.12 mol), and 13.8 g anhydrous K_2CO_3 (0.1 mol) in 30 cm^3 dry *DMF* was refluxed for 2 h (TLC). The solvent was removed *in vacuo* and the residue was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was recrystallized from ethanol to afford 12 g **1** (45%) (Ref. [24] 21%). Mp: 165–166°C; ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): $\delta = 1.22$ (t, $J = 6.1$ Hz, CH_3CH_2O), 3.41 (s, N^6–CH_3), 3.62 (s, N^4–CH_3), 4.25 (q, $J = 6.1$ Hz, CH_3CH_2O), 5.44 (s, N^1–CH_2) ppm; ^{13}C NMR (*DMSO*-d$_6$, 62.5 MHz): $\delta = 14.0$ (CH_3CH_2O), 27.8 (N^6–CH_3), 29.8 (N^4–CH_3), 48.3 (N^1–CH_2), 61.3 (CH_3CH_2O), 110.6 (C-7a), 150.2 (C-3a), 150.9 (C-5), 153.3 (C-7), 166.1 (C=O) ppm; MS: m/z (%) = 267 (M^+, 20).

1-Acetylhydrazine-4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]-pyrimidine-5,7(4H,6H)-dione (**2**, $C_8H_{11}N_7O_3$)
A mixture of 2.67 g **1** (10 mmol) and 1.25 g $N_2H_4 \cdot H_2O$ (25 mmol) in 30 cm^3 ethanol was heated under reflux for 3 h. The excess of ethanol was removed under reduced pressure and the resulting precipitate was filtered off, washed with ethanol, and recrystallized from ethanol to give 2.25 g **2** (89%). Mp: 145–146°C; IR (KBr): $\bar{\nu} = 3310$ and 3210 (NH), 2950 (C–H), 1660–1685 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.40$ (s, N^6–C*H*$_3$), 3.60 (s, N^4–C*H*$_3$), 4.82 (br, s, NHN*H*$_2$), 5.14 (s, N^1–C*H*$_2$), 9.45 (br, s, N*H*NH$_2$) ppm; ^{13}C NMR (*DMSO*-d_6, 62.5 MHz): $\delta = 27.7$ (N^6–*C*H$_3$), 29.9 (N^4–*C*H$_3$), 49.9 (N^1–*C*H$_2$), 111.7 (C-7a), 150.5 (C-5), 153.1 (C-3a), 154.9 (C-7), 168.0 (C=O) ppm; MS: m/z (%) = 254 ($M^+ + 1$, 14).

1-{4,6-Dimethyl-1H-[1,2,3]-triazolo[4,5-d]pyrimidine-5,7-(4H,6H)-dione}acetyl-4-phenyl thiosemicarbazide
(**3**, $C_{15}H_{16}N_8O_3S$)
To a solution of 2.53 g **2** (10 mmol) in 10 cm^3 ethanol, 1.35 g phenylisothiocyanate (10 mmol) were added. The reaction mixture was heated under reflux for 1 h. The product that separated on cooling was filtered off, washed with ethanol, and dried well to give 3.57 g **3** (92%). Mp: 170–171°C; IR (KBr): $\bar{\nu} = 1680$–1695 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.47$ (s, N^6–C*H*$_3$), 3.63 (s, N^4–C*H*$_3$), 5.20 (s, N^1–C*H*$_2$), 7.20–7.32 (m, *Ph*-H), 7.48–7.7.53 (m, *Ph*-H), 7.94 (br, s, NH) ppm; ^{13}C NMR (*DMSO*-d_6, 62.5 MHz): $\delta = 27.8$ (N^6–*C*H$_3$), 29.8 (N^4–*C*H$_3$), 50.6 (N^1–*C*H$_2$), 111.8 (C-7a), 125.9, 128.3, 139.0 (*Ph*-C), 150.5 (C-5), 153.1 (C-3a), 155.0 (C-7), 163.1 (C=O), 181.1 (C=S) ppm; MS: m/z (%) = 388 (M^+, 22).

1-(2-Mercapto-1,3,4-oxadiazol-5-ylmethyl)-4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione
(**4**, $C_9H_9N_7O_3S$)
A mixture of 2.53 g **2** (10 mmol) and 0.6 cm^3 CS_2 (10 mmol) was added to a solution of 0.56 g KOH (10 mmol) in 50 cm^3 H_2O and 50 cm^3 ethanol. The reaction mixture was refluxed for 4 h. After evaporating it to dryness under reduced pressure, a solid was obtained. This was dissolved in 50 cm^3 H_2O and acidified with conc. HCl. The precipitate was filtered off, washed with H_2O, and recrystallised from ethanol to afford 2.45 g **4** (83%). Mp: 283–285°C; IR (KBr): $\bar{\nu} = 2570$ (SH), 1670–1685 (C=O), 1590 and 1540 (–C=N), 1170 (–C=S) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.40$ (s, N^6–C*H*$_3$), 3.67 (s, N^4–C*H*$_3$), 5.66 (s, N^1–C*H*$_2$), 13.40 (br, s, SH) ppm; ^{13}C NMR (*DMSO*-d_6, 62.5 MHz): $\delta = 27.6$ (N^6–*C*H$_3$), 29.9 (N^4–*C*H$_3$), 43.6 (N^1–*C*H$_2$), 110.0 (C-7a), 147.0 (C-3a), 151.1 (C-5), 152.3 (C-7), 162.4, 171.2 (oxadiazole carbons) ppm; MS: m/z (%) = 295 (M^+, 15).

1-(2-Methythio-1,3,4-oxadiazol-5-ylmethyl)-4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione
(**5**, $C_{10}H_{11}N_7O_3S$)
A solution of 3.54 g **4** (12 mmol) in 10 cm^3 10% KOH solution was stirred for 1 h. The reaction mixture was treated dropwise with 1.76 g Me_2SO_4 (14 mmol). The precipitated solid was filtered off, washed with H_2O, and recrystallized from ethanol to afford 3.26 g **5** (88%). Mp: 174–175°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 2.52$ (s, S*Me*), 3.38 (s, N^6–C*H*$_3$), 3.55 (s, N^4–C*H*$_3$), 5.76 (s, N^1–C*H*$_2$) ppm; MS: m/z (%) = 309 (M^+, 33).

Ethyl {5-[4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]-pyrimidine-5,7(4H,6H)-dione]-(1,3,4-oxadiazol-2-yl)methyl}-thioglycolate (**6**, $C_{13}H_{15}N_7O_5S$)
A solution of 2.95 g **4** (10 mmol) was refluxed with 0.23 g Na (10 mmol) in 10 cm^3 absolute ethanol for 1 h. Then 1.22 g ethyl chloroacetate (10 mmol) were added and refluxed for an additional 6 h. After evaporation under reduced pressure, a solid appeared. This was recrystallized from *Et*OH:H_2O (1:1) to afford 2.97 g **6** (78%). Mp: 170–172°C; IR (KBr): $\bar{\nu} =$ 1690–1700 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 1.20$ (t, $J = 6.1$ Hz, C*H*$_3$CH$_2$O), 3.40 (s, N^6–C*H*$_3$), 3.63 (s, N^4–C*H*$_3$), 3.78 (s, SCH$_2$), 4.15 (q, $J = 6.1$ Hz, CH$_3$C*H*$_2$O), 5.74 (s, N^1–C*H*$_2$) ppm; ^{13}C NMR (*DMSO*-d_6, 62.5 MHz): $\delta = 14.0$ (*C*H$_3$CH$_2$O), 27.5 (N^6–*C*H$_3$), 29.9 (N^4–*C*H$_3$), 41.9 (SCH$_2$), 44.9 (N^1–*C*H$_2$), 61.9 (CH$_3$*C*H$_2$O), 110.2 (C-7a), 149.0 (C-3a), 150.5 (C-5), 152.1 (C-7), 168.7 (C=O), 169.2, 170.9 (oxadiazole carbons) ppm; MS: m/z (%) = 381 (M^+, 25).

{5-[4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione]-(1,3,4-oxadiazol-2-yl)methyl}-thioglycolylhydrazide (**7**, $C_{11}H_{13}N_9O_4S$)
A solution of 3.81 g **6** (10 mmol) in 30 cm^3 ethanol was refluxed with 1.25 g $N_2H_4 \cdot H_2O$ (25 mmol) for 4 h. After cooling it to room temperature, a white solid appeared. This was recrystallized from ethanol to afford 2.97 g **7** (81%). Mp: 295–296°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.41$ (s, N^6–C*H*$_3$), 3.64 (s, N^4–C*H*$_3$), 3.88 (s, SCH$_2$), 4.90 (br, s, NHN*H*$_2$), 5.74 (s, N^1–C*H*$_2$), 9.40 (br, s, N*H*NH$_2$) ppm; MS: m/z (%) = 368 ($M^+ + 1$, 11).

1-[(5-Phenylamino-1,3,4-thiadiazol-2-yl)methyl]-4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione (**8**, $C_{15}H_{14}N_8O_2S$)
A solution of 1.94 g **3** (5 mmol) in 10 cm^3 cold conc. H_2SO_4 was stirred until dissolution and then left at room temperature for 2 h. The reaction mixture was poured onto crushed ice and the precipitated product was filtered off, washed with H_2O, and recrystallized from ethanol to give 1.48 g **8** (80%). Mp: 205–207°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.40$ (s, N^6–C*H*$_3$), 3.59 (s, N^4–C*H*$_3$), 5.70 (s, N^1–C*H*$_2$), 6.99 (m, *Ph*-H), 7.33 (m, *Ph*-H), 7.52 (m, *Ph*-H), 11.99 (br, s, N*H*Ph) ppm; MS: m/z (%) = 370 (M^+, 34).

1-[(5-Mercapto-4-phenyl-1,2,4-triazol-3-yl)methyl]-4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione (**9**, $C_{15}H_{14}N_8O_2S$)
A solution of 3.88 g **3** (10 mmol) in 50 cm^3 2 *N* NaOH was heated under reflux for 3 h. The reaction mixture was cooled and acidified with 2 *N* HCl. The resulting precipitate was filtered off, washed with ethanol and recrystallized from ethanol to give 3.14 g **9** (85%). Mp: 213–215°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.38$ (s, N^6–C*H*$_3$), 3.61 (s, N^4–C*H*$_3$), 5.81 (s, N^1–C*H*$_2$), 7.23–7.34 (m, *Ph*-H), 13.69 (br, s, SH) ppm; MS: m/z (%) = 370 (M^+, 22).

1-[(5-Phenylamino-1,3,4-oxadiazol-2-yl)methyl]-4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione (**10**, $C_{15}H_{14}N_8O_3$)
HgO (2.37 g, 11 mmol) was added to a solution of 3.88 g **3** (10 mmol) in 20 cm^3 methanol and the resulting mixture was refluxed for 3 h. The precipitated HgS was filtered off and washed with hot methanol. The filtrate on cooling gave a precipitate which was recrystallized from ethanol to give 2.51 g **10** (71%). Mp: 199–201°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.41$ (s, N^6–C*H*$_3$), 3.64 (s, N^4–C*H*$_3$), 5.73 (s, N^1–C*H*$_2$), 6.97 (m, *Ph*-H), 7.32 (m, *Ph*-H), 7.72 (m, *Ph*-H), 9.14 (br, s, N*H*Ph) ppm; MS: m/z (%) = 355 ($M^+ + 1$, 19).

Ethyl {5-[4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione]-4-phenyl-(1,2,4-triazol-3-yl)methyl} thioglycolate (**11**, $C_{19}H_{20}N_8O_4S$)
A solution of 3.70 g **9** (10 mmol) was refluxed with 0.23 g Na (10 mmol) in 10 cm^3 absolute ethanol for 1 h. Then 1.22 g ethyl chloroacetate (10 mmol) were added and refluxed for an additional 6 h. After evaporation under reduced pressure, a solid appeared. This was recrystallized from *Et*OH:H_2O (1:1) to afford 3.65 g **11** (80%). Mp: 183–185°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 1.25$ (t, $J = 6.1$ Hz, C*H*$_3$CH$_2$O), 3.41 (s, N^6–C*H*$_3$), 3.60 (s, N^4–C*H*$_3$), 3.89 (s, SCH$_2$), 4.17 (q, $J = 6.1$ Hz, CH$_3$C*H*$_2$O), 6.00 (s, N^1–C*H*$_2$), 7.25 (m, *Ph*-H), 7.49 (m, *Ph*-H) ppm; MS: m/z (%) = 456 (M^+, 10).

{5-[4,6-Dimethyl-1H-[1,2,3]-triazolo[4,5-d]pyrimidine-5,7-(4H,6H)-dione]-4-phenyl-(1,2,4-triazol-3-yl)methyl} thioglycolylhydrazide (**12**, $C_{17}H_{18}N_{10}O_3S$)
A solution of 4.56 g **11** (10 mmol) in 30 cm^3 ethanol was refluxed with 1.25 g $N_2H_4 \cdot H_2O$ (25 mmol) for 4 h. After cooling it to room temperature, a white solid appeared. This was recrystallized from ethanol to afford 3.49 g **12** (79%). Mp: 268–269°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.41$ (s, N^6–C*H*$_3$), 3.62 (s, N^4–C*H*$_3$), 3.84 (s, SCH$_2$), 4.95 (br, s, NHN*H*$_2$), 6.04 (s, N^1–C*H*$_2$), 7.28 (m, *Ph*-H), 7.39 (m, *Ph*-H), 9.34 (br, s, N*H*NH$_2$) ppm; MS: m/z (%) = 443 ($M^+ + 1$, 7).

Sugar {4,6-Dimethyl-1H-[1,2,3]-triazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione}acetylhydrazones ***13–15***
A solution of the sugar (10 mmol) in 3 cm^3 H_2O was treated with a solution of **2**, **7**, and **12** (10 mmol) in 100 cm^3 ethanol, and a few drops of glacial acetic acid. The mixture was boiled under reflux for 3–5 h (TLC). The excess of ethanol was removed under reduced pressure and the residue was triturated with 15 cm^3 diethyl ether. The product was filtered off, washed with ether, and recrystallized from ethanol.

L-(+)-Arabinose {4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]-pyrimidine-5,7(4H,6H)-dione}acetylhydrazone
(**13a**, $C_{13}H_{19}N_7O_7$)
Yield: 80%. Mp: 177–178°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.14$–3.40 (m, H-4′, H-5′, N^6–C*H*$_3$), 3.49 (s, H-3′), 3.60–3.65 (m, H-2′, N^4–C*H*$_3$), 4.39–4.51 (br, s, 4 × OH), 5.14 (s, N^1–C*H*$_2$), 7.50 (d, $J = 2.5$ Hz, H-1′), 8.90 (br, s, NH) ppm; MS: m/z (%) = 385 (M^+, 22).

D-(−)-Ribose {4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]-pyrimidine-5,7(4H,6H)-dione}acetylhydrazone
(**13b**, $C_{13}H_{19}N_7O_7$)
Yield: 81%. Mp: 150–152°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.14$–3.52 (m, H-2′, H-3′, H-4′, H-5′, N^6–C*H*$_3$), 3.65 (m, N^4–C*H*$_3$), 3.99–4.21 (br, s, 4 × OH), 5.43 (s, N^1–C*H*$_2$), 7.30 (d, $J = 2.5$ Hz, H-1′), 8.88 (br, s, NH) ppm; MS: m/z (%) = 385 (M^+, 18).

D-(+)-Xylose {4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]-pyrimidine-5,7(4H,6H)-dione}acetylhydrazone
(**13c**, $C_{13}H_{19}N_7O_7$)
Yield: 77%. Mp: 173–174°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.41$–3.69 (br, m, H-4′, H-5′, N^4–C*H*$_3$, N^6–C*H*$_3$), 3.59–3.61 (s, H-2′, H-3′), 4.42–4.92 (br, s, 4 × OH), 5.30 (s, N^1–C*H*$_2$), 7.20 (d, $J = 2.5$ Hz, H-1′), 8.98 (br, s, NH) ppm; MS: m/z (%) = 385 (M^+, 26).

D-(+)-Glucose {4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]-pyrimidine-5,7(4H,6H)-dione}acetylhydrazone
(**13d**, $C_{14}H_{21}N_7O_8$)
Yield: 85%. Mp: 145–147°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.44$–3.89 (m, H-3′, H-4′, H-5′, H-6′, N^4–C*H*$_3$, N^6–C*H*$_3$), 4.27 (s, H-2′), 4.40–4.90 (br, s, 5 × OH), 5.34 (s, N^1–C*H*$_2$), 7.40 (d, $J = 2.5$ Hz, H-1′), 8.99 (br, s, NH) ppm; MS: m/z (%) = 415 (M^+, 23).

D-(+)-Galactose {4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]-pyrimidine-5,7(4H,6H)-dione}acetylhydrazone
(**13e**, $C_{14}H_{21}N_7O_8$)
Yield: 70%. Mp: 159–161°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.34$–3.93 (m, H-5′, H-6′, N^4–C*H*$_3$, N^6–C*H*$_3$), 4.12–4.23 (br, s, H-2′, H-3′, H-4′), 4.33–4.80 (br, s, 5 × OH), 5.39 (s, N^1–C*H*$_2$), 7.43 (d, $J = 2.5$ Hz, H-1′), 8.92 (br, s, NH) ppm; MS: m/z (%) = 415 (M^+, 10).

D-(+)-Mannose {4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]-pyrimidine-5,7(4H,6H)-dione}acetylhydrazone
(**13f**, $C_{14}H_{21}N_7O_8$)
Yield: 80%. Mp: 182–184°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.44$–3.78 (m, H-2′, H-3′, H-4′, H-5′, H-6′, N^4–C*H*$_3$, N^6–C*H*$_3$), 4.36–4.47 (br, s, 5 × OH), 5.43 (s, N^1–C*H*$_2$), 7.45 (d, $J = 2.5$ Hz, H-1′), 8.96 (br, s, NH) ppm; MS: m/z (%) = 415 (M^+, 6).

L-(+)-Arabinose {(1,3,4-oxadiazol-5-ylmethyl)-4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione} thioglycolylhydrazone (**14a**, $C_{16}H_{21}N_9O_8S$)
Yield: 79%. Mp: 155–157°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.14$–3.38–3.50 (m, H-3′, H-4′, H-5′, N^6–C*H*$_3$), 3.60–3.85 (m, H-2′, N^4–C*H*$_3$, SCH$_2$), 4.44–4.58 (br, s, 4 × OH), 5.66 (s, N^1–C*H*$_2$), 7.40 (d, $J = 2.5$ Hz, H-1′), 8.88 (br, s, NH) ppm.

D-(−)-Ribose {(1,3,4-oxadiazol-5-ylmethyl)-4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione} thioglycolylhydrazone (**14b**, $C_{16}H_{21}N_9O_8S$)
Yield: 80%. Mp: 190–192°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.30$–3.62 (m, H-2′, H-3′, H-4′, H-5′, N^4–CH_3, N^6–CH_3), 3.90–4.22 (br, s, 4 × OH, SCH_2), 5.63 (s, N^1–CH_2), 7.34 (d, $J = 2.5$ Hz, H-1′), 8.89 (br, s, NH) ppm.

D-(+)-Xylose {(1,3,4-oxadiazol-5-ylmethyl)-4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione} thioglycolylhydrazone (**14c**, $C_{16}H_{21}N_9O_8S$)
Yield: 77%. Mp: 203–204°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.40$–4.02 (br, m, H-2′, H-3′, H-4′, H-5′, N^4–CH_3, N^6–CH_3, SCH_2), 4.55–4.90 (br, s, 4 × OH), 5.70 (s, N^1–CH_2), 7.23 (d, $J = 2.5$ Hz, H-1′), 8.95 (br, s, NH) ppm.

D-(+)-Glucose {(1,3,4-oxadiazol-5-ylmethyl)-4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione} thioglycolylhydrazone (**14d**, $C_{17}H_{23}N_9O_9S$)
Yield: 80%. Mp: 195–197°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.44$–4.12 (br, m, H-2′, H-3′, H-4′, H-5′, H-6′, N^4–CH_3, N^6–CH_3, SCH_2), 4.40–4.70 (br, s, 5 × OH), 5.74 (s, N^1–CH_2), 7.40 (d, $J = 2.5$ Hz, H-1′), 8.90 (br, s, NH) ppm.

D-(+)-Galactose {(1,3,4-oxadiazol-5-ylmethyl)-4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione} thioglycolylhydrazone (**14e**, $C_{17}H_{23}N_9O_9S$)
Yield: 68%. Mp: 177–179°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.44$–4.23 (br, m, H-2′, H-3′, H-4′, H-5′, H-6′, N^4–CH_3, N^6–CH_3, SCH_2), 4.33–4.80 (br, s, 5 × OH), 5.66 (s, N^1–CH_2), 7.41 (d, $J = 2.5$ Hz, H-1′), 8.90 (br, s, NH) ppm.

D-(+)-Mannose {(1,3,4-oxadiazol-5-ylmethyl)-4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione} thioglycolylhydrazone (**14f**, $C_{17}H_{23}N_9O_9S$)
Yield: 73%. Mp: 162–163°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.40$–3.98 (br, m, H-2′, H-3′, H-4′, H-5′, H-6′, N^4–CH_3, N^6–CH_3, SCH_2), 4.40–4.52 (br, s, 5 × OH), 5.63 (s, N^1–CH_2), 7.42 (d, $J = 2.5$ Hz, H-1′), 8.97 (br, s, NH) ppm.

L-(+)-Arabinose {5-[4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]-pyrimidine-5,7(4H,6H)-dione]-4-phenyl-(1,2,4-triazol-3-yl)-methyl}thioglycolylhydrazone (**15a**, $C_{22}H_{26}N_{10}O_7S$)
Yield: 74%. Mp: 211–212°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.33$–3.54 (m, H-3′, H-4′, H-5′, N^6–CH_3), 3.60–3.85 (m, H-2′, N^4–CH_3, SCH_2), 4.44–4.58 (br, s, 4 × OH), 5.84 (s, N^1–CH_2), 7.30–7.44 (m, H-1′, *Ph*-H), 8.90 (br, s, NH) ppm.

D-(−)-Ribose {5-[4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]-pyrimidine-5,7(4H,6H)-dione]-4-phenyl-(1,2,4-triazol-3-yl)-methyl}thioglycolylhydrazone (**15b**, $C_{22}H_{26}N_{10}O_7S$)
Yield: 71%. Mp: 139–141°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.33$–3.82 (br, m, H-2′, H-3′, H-4′, H-5′ N^4–CH_3, N^6–CH_3, SCH_2), 4.11–4.28 (br, s, 4 × OH), 5.83 (s, N^1–CH_2), 7.20 (d, $J = 2.5$ Hz, H-1′), 7.37–7.48 (m, *Ph*-H), 8.89 (br, s, NH) ppm.

D-(+)-Xylose {5-[4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]-pyrimidine-5,7(4H,6H)-dione]-4-phenyl-(1,2,4-triazol-3-yl)-methyl}thioglycolylhydrazone (**15c**, $C_{22}H_{26}N_{10}O_7S$)
Yield: 70%. Mp: 180–181°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.41$–3.99 (br, m, H-2′, H-3′, H-4′, H-5′, N^4–CH_3, N^6–CH_3, SCH_2), 4.49–4.90 (br, s, 4 × OH), 5.80 (s, N^1–CH_2), 7.20–7.40 (m, H-1′, *Ph*-H), 8.92 (br, s, NH) ppm.

D-(+)-Gluose {5-[4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]-pyrimidine-5,7(4H,6H)-dione]-4-phenyl-(1,2,4-triazol-3-yl)-methyl}thioglycolylhydrazone (**15d**, $C_{23}H_{28}N_{10}O_8S$)
Yield: 77%. Mp: 150–152°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.42$–3.97 (m, H-2′, H-3′, H-4′, H-5′, H-6′, N^4–CH_3, N^6–CH_3, SCH_2), 4.47–4.90 (br, s, 5 × OH), 5.74 (s, N^1–CH_2), 7.32–7.49 (m, H-1′, *Ph*-H), 8.94 (br, s, NH) ppm.

D-(+)-Galactose {5-[4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]-pyrimidine-5,7(4H,6H)-dione]-4-phenyl-(1,2,4-triazol-3-yl)-methyl}thioglycolylhydrazone (**15e**, $C_{23}H_{28}N_{10}O_8S$)
Yield: 66%. Mp: 169–171°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.44$–4.00 (m, H-5′, H-6′, N^4–CH_3, N^6–CH_3, SCH_2), 4.19–4.33 (m, H-2′, H-3′, H-4′), 4.50–4.87 (br, s, 5 × OH), 5.79 (s, N^1–CH_2), 7.32–7.49 (m, H-1′, *Ph*-H), 8.93 (br, s, NH) ppm.

D-(+)-Mannose {5-[4,6-dimethyl-1H-[1,2,3]-triazolo[4,5-d]-pyrimidine-5,7(4H,6H)-dione]-4-phenyl-(1,2,4-triazol-3-yl)-methyl}thioglycolylhydrazone (**15f**, $C_{23}H_{28}N_{10}O_8S$)
Yield: 75%. Mp: 144–145°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.44$–4.03 (br, m, H-2′, H-3′ H-4′, H-5′, H-6′, N^4–CH_3, N^6–CH_3, SCH_2), 4.44–4.67 (br, s, 5 × OH), 5.83 (s, N^1–CH_2), 7.33–7.50 (m, H-1′, *Ph*-H), 8.98 (br, s, NH) ppm.

References

[1] Henichart JP, Houssin R, Berier JL (1986) J Het Chem **23**: 1531
[2] Awad LF, El Ashry ESH (1998) Carbohydr Res **312**: 9
[3] Varvarasou A, Sistra-Papastaikoud T, Tsantili-Kakoulidou A, Vamvakides A (1998) Farmaco **53**: 320
[4] Palaska E, Sahin G, Kelicen P, Durlu NT, Altmok G (2002) Farmaco **57**: 101
[5] Holla BS, Poorjary KN, Rao BS, Shivananda MK (2002) Eur J Med Chem **37**: 511
[6] Amir M, Shikha K (2004) Eur J Med Chem **39**: 535
[7] Demirbas N, Alpay Karaoglu S, Demirbas A, Sancak K (2004) Eur J Med Chem **39**: 793
[8] Mishrah L, Said MK, Itokawa H, Takeya K (1995) Bioorg Med Chem **3**: 1241
[9] Ateş O, Kocabalkanli A, Cesur N, Otuk G (1998) Farmaco **53**: 541
[10] Kocabalkanli A, Ateş O, Otuk G (2001) Farmaco **56**: 975
[11] Sahin G, Palaska E, Ekizoglu M, Özalp M (2002) Farmaco **57**: 530
[12] Küçükgüzel ŞG, Oruç EE, Rollas S, Şahin F, Özbek A (2002) Eur J Med Chem **37**: 187

[13] Abdel-Aal MT, El-Sayed WA, El Ashry ESH (2006) Arch Pharm **339**: 656
[14] Demirbas N (2005) Turk J Chem **29**: 125
[15] Coburn RA, Bhooshan B, Glennon RA (1973) J Org Chem **38**: 3947
[16] Srivatsava U, Pather R, Bahel SC (1981) J Indian Chem Soc **58**: 822
[17] Katritzky AR, Rees CW (1984) Chem Heterocycl Comp **6**: 441
[18] Hiremath SP, Biradar JS, Kudari SM (1984) J Indian Chem Soc **61**: 74
[19] Robins RK (1964) J Med Chem **7**: 186
[20] Abdel-Aal MT, El-Sayed WA, Abdel-Aleem AH, El Ashry ESH (2003) Pharmazie **58**: 788
[21] El Ashry ESH, Abdel-Rahman A, Rashed N, Awad LF, Rasheed HA (2006) Nucleos Nucleot Nucl **25**: 299
[22] El-Essawy FA (2005) Nucleos Nucleot Nucl **24**: 1265
[23] Khallab AF, El-Essawy FA (2005) J Chem Res 736
[24] Senga K, Ichiba M, Nishigaki S (1977) Heterocycles **6**: 1915
[25] Pfleiderer W, Schündehütte KH (1958) Leibigs Ann Chem **612**: 158
[26] Sells MA, Zelent AZ, Shvartsman M, Acs G (1988) J Virol **62**: 2836
[27] Korba BE, Gerin JL (1992) Antiviral Res **19**: 55
[28] Fouad T, Nielsen C, Brunn L, Pederson EB (1998) J Az Med Fac (GIRLS) **19**: 1173