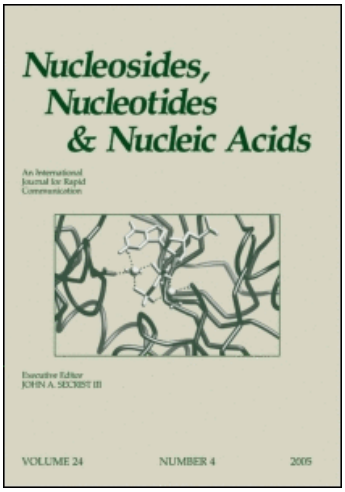

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of Some Novel *N*-Ribosyl-1,2,4-Triazin-6(1*H*)-/Ones or Thiones as Potential Antibacterial and Antifungal Chemotherapeutics

Nasser S. A. M. Khalil[a]
[a] Central Laboratory for Food and Feed, Agricultural Research Center, Giza, Egypt

To cite this Article Khalil, Nasser S. A. M.(2005) 'Synthesis of Some Novel *N*-Ribosyl-1,2,4-Triazin-6(1*H*)-/Ones or Thiones as Potential Antibacterial and Antifungal Chemotherapeutics', Nucleosides, Nucleotides and Nucleic Acids, 24: 2, 111 — 120
To link to this Article: DOI: 10.1081/NCN-200051902
URL: http://dx.doi.org/10.1081/NCN-200051902

Nucleosides, Nucleotides, and Nucleic Acids, 24 (2):111–120, (2005)

ISSN: 1525-7770 print/ 1532-2335 online
DOI: 10.1081/NCN-200051902

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SYNTHESIS OF SOME NOVEL *N*-RIBOSYL-1,2,4-TRIAZIN-6(1*H*)-/ONES OR THIONES AS POTENTIAL ANTIBACTERIAL AND ANTIFUNGAL CHEMOTHERAPEUTICS

Nasser S. A. M. Khalil ▫ *Central Laboratory for Food and Feed, Agricultural Research Center, Giza, Egypt*

▫ *Ribosylation of 3-aryl-5-benzyl(or substituted benzyl)-1,2,4-triazin-6(1H)-/ones or thiones with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose gave the corresponding 3-aryl-5-benzyl(or substituted benzyl)-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazin-6(1H)-/ones or thiones. The structure of the new ribosides was confirmed chemically and spectroscopically.*

Keywords Synthesis, β-D-Ribosyls, 1,2,4-Triazines, Antibacterial, Antifungal

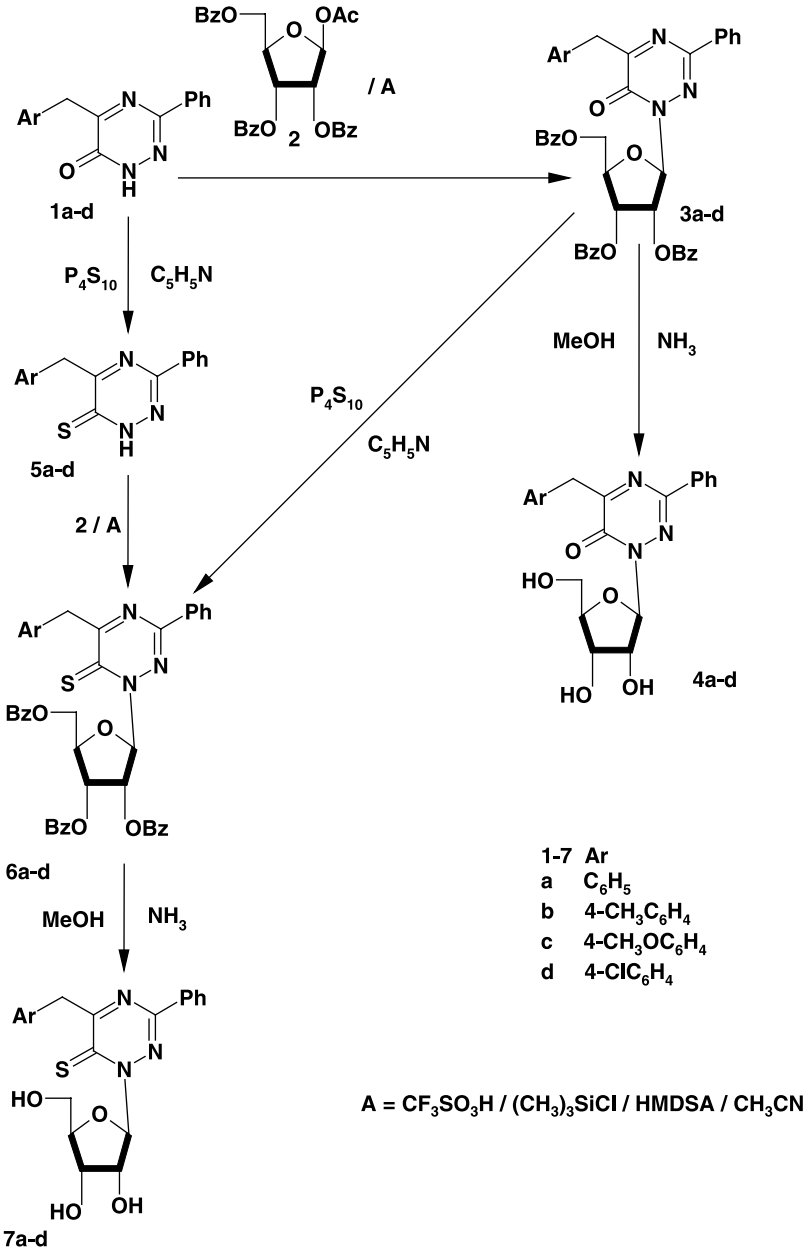
INTRODUCTION

N-Glycosides of 1,2,4-triazines are considered to be one of the most biologically active classes of compounds, possessing a wide spectrum of activities such as cytotoxics, antivirals, enzyme inhibitors, immunosuppressives, antipsoriatics, bacteriostatics, antitumors, as well as floor and wall disinfectants.[1–10] Therefore, it would be of interest to synthesize some novel *N*-ribosides of 3-aryl-5-benzyl(or substituted benzyl)-1,2,4-triazin-6(1*H*)-/ones or thiones of expected interesting biological activities and report the antimicrobial screening of three selected compounds. The glucosyl and galactosyl analogues are reported.[11,12]

RESULTS AND DISCUSSION

In the present investigation, the starting 3-aryl-5-benzyl(or substituted benzyl)-1,2,4-triazin-6(1*H*)-/ones **1a–d** or thiones **5a–d** were allowed to react with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **2** to give the corresponing 3-aryl-5-benzyl (or substituted benzyl)-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazin-6(1*H*)-/ones **3a–d** or thiones **6a–d** following a simplified one-step/one-pot nucleoside

Received 2 September 2004, accepted 17 December 2004.
Address correspondence to Nasser S. A. M. Khalil, Central Laboratory for Food and Feed, Agricultural Research Center, Giza, Egypt; E-mail: nasserkhalil_23@hotmail.com



SCHEME 1 Synthesis of *N*-ribosyl-1,2,4-triazin-6(1*H*)ones or thiones.

synthesis as shown in Scheme 1. The structures of compounds **3a–d**, **6a–d** were assigned based on the following evidences:

1. The β-configuration of compounds **3a–d**, **6a–d** is confirmed from their ^{1}H NMR spectral data, which revealed the anomeric proton at δ 6.82–6.62 with a coupling constant consistent with similar reported data.[13–16]
2. The IR spectra of compounds **3a–d** showed the amide carbonyl function at 1674–1666 cm^{-1}.
3. Thiation of compounds **3a–d** gave the corresponding thiones **6a–d**, which their IR spectra showed the absence of the amide carbonyl function at 1674–1666 cm^{-1}.

Debenzoylation of compounds **3a–d**, **6a–d** was achieved via their treatment with methanolic ammonia to give the free ribosides **4a–d**, **7a–d**, respectively. The structure of compounds **4a–d**, **7a–d** was confirmed based on their analytical and spectral data. Thus, the IR spectra of these compounds not only showed the absence of the ester carbonyl function at 1728 cm^{-1}, but also showed the appearance of the hydroxyl function at 3669–3400 cm^{-1}. Moreover, the ^{1}H NMR data of these compounds revealed the absence of the aromatic protons of the benzoate groups at δ 8.30–7.02 (via calculation of proton integration ratios) and the appearance of the exchangeable OH protons' signals at δ 5.18–4.59.

Biological Evaluation

As a part of our program directed toward the synthesis of new 1,2,4-triazine nucleosides with possible potential biological activity,[9,10,12,17,18] compounds **7b d** were tested for antimicrobial activity (in vitro) against against *Aspergillus fumigatus*, *Penicillium italicum*, *Syncephalastrum racemosum*, *Candida albicans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Escherichia coli*. Table 1 shows the inhibitory effects of compounds **7b d** against these organisms. The screening results of these compounds showed that compound **7d** having a Cl atom has the greatest inhibitory effect against one or more types of microorganisms followed by compound **7c** having a methoxy group then compound **7b** having a methyl group. Thus, compound **7b** showed moderate activity against *Aspergillus fumigatus* (at all tested concentrations; 5, 2.5, 1 mg/mL), *Penicillium italicum* (at concentration 5 mg/mL), *Syncephalastrum racemosum* (at concentration 5 mg/mL), and *Escherichia coli* (at concentration 5 mg/mL). Compound **7c** showed activity against *Aspergillus fumigatus* (promising activity at concentration 5 mg/mL; moderate activity at concentration 2.5 mg/mL), *Penicillium italicum* (moderate activity at concentration 5 mg/mL), *Candida albicans* (moderate activity at all tested concentrations; 5, 2.5, 1 mg/mL), and *Escherichia coli* (promising activity at concentration 5 mg/mL; moderate activity at concentration 2.5 mg/mL). Compound **7d** showed activity against *Aspergillus fumigatus* (promising activity at concentrations 5, 2.5 mg/mL; moderate activity at concentration 1 mg/mL), *Penicillium italicum*

TABLE 1 Antimicrobial Activity of Compounds 7b = d Compared to Standard Antimicrobial Agents

	Compounds											
	7b[a]			**7c**[a]			**7d**[a]			St.[b]		
Test organisms	5	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1
Aspergillus fumigatus	+	+	+	++	+	0	++	++	+	+++	+++	++
Penicillium italicum	+	0	0	+	0	0	++	++	+	+++	+++	++
Syncephalastrum racemosum	+	0	0	0	0	0	0	0	0	+++	+++	+++
Candida albicans	0	0	0	+	+	+	+	+	+	++	++	++
Staphylococcus aureus	0	0	0	0	0	0	0	0	0	++	++	++
Pseudomonas aeruginosa	0	0	0	+	+	+	0	0	0	+++	++	++
Bacillus subtilis	0	0	0	+	0	0	0	0	0	++	++	++
Escherichia coli	+	0	0	++	+	0	+++	++	++	+++	++	++

Note: The test was done using the diffusion agar technique. Inhibition values = 0.1–0.5 cm beyond control = +; Inhibition values = 0.6–1.0 cm beyond control = ++; Inhibition values = 1.1–1.5 cm beyond control = +++; 0 = not detected.

[a]100 µl of each conc. (5, 2.5, 1 mg/mL) was tested.

[b]St. = Reference standard; Chloramphenicol was used as a standard antibacterial agent and Terbinafin was used as a standard antifungal agent.

(promising activity at concentrations 5, 2.5 mg/mL; moderate activity at concentration 1 mg/mL), *Candida albicans* (moderate activity at all tested concentrations; 5, 2.5, 1 mg/mL), and *Escherichia coli* (as potent as standard chloramphenicol at all tested concentrations).

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 1430 spectrometer. ^{1}H NMR spectra were recorded at 200 MHz with a Varian GEMINI 200 spectrometer. The abbreviations pt and pq denote pseudotriplet and pseudoquartet signals, respectively. The starting compounds **1a–d**,[19,20] **5a–d**[11] were prepared as reported. TLC was performed on Fluka silica gel 60 F_{254} aluminum sheets, and products were detected using 254 nm light. Fluka silica gel 60 (70–230 mesh) was used for column chromatography. Elemental analyses were carried out at the Micro Analytical Center, Cairo University, Giza, Egypt. Antimicrobial screening of compounds **7b d** was carried out at the Medical Mycology Lab, the Regional Center for Mycology and Biotechnology, Al Azhar University, Cairo, Egypt.

5-Benzyl (or substituted benzyl)-3-phenyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazin-6(1*H*)-ones (3a-d).

General Procedure. To a mixture of each of compounds **1a–d** (2 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**) (2 mmol) in acetonitrile (20 mL) were added consecutively hexamethyldisilazane (2.2 mmol),

trimethylchlorosilane (2.2 mmol), and trifluoromethanesulfonic acid (2.4 mmol). The reaction mixture was heated at reflux temperature with exclusion of humidity (using $CaCl_2$ guard tube fitted over the refluxing condenser) until the reaction was judged complete by TLC (18–24 h), using petroleum ether (bp 40–60°C)/EtOAc (60:40, v/v) as a developing system. The excess acetonitrile was evaporated on a rotavap and the formed residue was dissolved in dichloromethane (30 mL), washed ($NaHCO_3$, brine), dried (Na_2SO_4), evaporated, column chromatographed (petroleum ether [bp 40–60°C] → 60% EtOAc/petroleum ether [bp 40–60°C]), and recrystallized from dichloromethane/petroleum ether (bp 40–60°C) to give pale yellow crystals of compounds **3a–d**.

5-Benzyl-3-phenyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazin-6(1*H*)-one (3a). Using the general procedure, **1a** gave **3a** (75%); R_f = 0.87; mp 114°C; IR (KBr) 1728 (C = O benzoate), 1674 (C = O amide) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.14–7.17 (m, 25H, ArH), 6.74 (d, 1H, *J* = 4.8 Hz, H-1′), 6.32 (pt, 1H, *J* = 5.5 Hz, H-2′), 6.24 (pt, 1H, *J* = 5.3 Hz, H-3′), 4.76 (m, 1H, H-4′), 4.68 (dd, 1H, *J* = 4.0 Hz, 11.5 Hz, H-5′), 4.48 (dd, 1H, *J* = 4.5 Hz, 11.7 Hz, H-5″), 4.23 (s, 2H, $C_6H_5CH_2$). Anal. Calcd. for $C_{42}H_{33}N_3O_8$: C, 71.28; H, 4.70; N, 5.94. Found: C, 71.44; H, 4.63; N, 5.68.

5-(4-Methylbenzyl)-3-phenyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazin-6(1*H*)-one (3b). Using the general procedure, **1b** gave **3b** (72%); R_f = 0.85; mp 130°C; IR (KBr) 1728 (C = O benzoate), 1666 (C = O amide) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.3–7.02 (m, 24H, ArH), 6.62 (d, 1H, *J* = 5.0 Hz, H-1′), 6.29 (pt, 1H, *J* = 5.2 Hz, H-2′), 6.16 (pt, 1H, *J* = 5.3 Hz, H-3′), 4.82 (m, 1H, H-4′), 4.66 (dd, 1H, *J* = 4.1 Hz, 11.3 Hz, H-5′), 4.44 (dd, 1H, *J* = 4.3 Hz, 11.5 Hz, H-5″), 4.12 (s, 2H, 4-$CH_3C_6H_4CH_2$), 2.28 (s, 3H, 4-$CH_3C_6H_4CH_2$). Anal. Calcd. for $C_{43}H_{35}N_3O_8$: C, 71.56; H, 4.89; N, 5.82. Found: C, 71.71; H, 4.83; N, 5.77.

5-(4-Methoxybenzyl)-3-phenyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazin-6(1*H*)-one (3c). Using the general procedure, **1c** gave **3c** (83%); R_f = 0.84; mp 116°C; IR (KBr) 1728 (C = O benzoate), 1674 (C = O amide) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.11–7.36 (m, 24H, ArH), 6.75 (d, 1H, *J* = 4.9 Hz, H-1′), 6.35 (pt, 1H, *J* = 5.6 Hz, H-2′), 6.19 (pt, 1H, *J* = 5.4 Hz, H-3′), 4.89 (m, 1H, H-4′), 4.61 (dd, 1H, *J* = 4.2 Hz, 11.4 Hz, H-5′), 4.52 (dd, 1H, *J* = 4.4 Hz, 11.9 Hz, H-5″), 3.90 (s, 2H, 4-$CH_3OC_6H_4CH_2$), 3.76 (s, 3H, 4-$CH_3OC_6H_4CH_2$). Anal. Calcd. for $C_{43}H_{35}N_3O_9$: C, 70.01; H, 4.78; N, 5.70. Found: C, 70.20; H, 4.69; N, 5.74.

5-(4-Chlorobenzyl)-3-phenyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazin-6(1*H*)-one (3d). Using the general procedure, **1d** gave **3d** (85%); R_f = 0.79; mp 117°C; IR (KBr) 1728 (C = O benzoate), 1674 (C = O amide) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.14–7.14 (m, 24H, ArH), 6.74 (d, 1H,

J = 4.8 Hz, H-1′), 6.34 (pt, 1H, *J* = 5.3 Hz, H-2′), 6.16 (pt, 1H, *J* = 5.5 Hz, H-3′), 4.85 (m, 1H, H-4′), 4.64 (dd, 1H, *J* = 4.2 Hz, 11.4 Hz, H-5′), 4.56 (dd, 1H, *J* = 4.4 Hz, 11.7 Hz, H-5″), 4.23 (s, 2H, 4-$ClC_6H_4CH_2$). Anal. Calcd. for $C_{42}H_{32}ClN_3O_8$: C, 67.97; H, 4.35; N, 5.66. Found: C, 68.02; H, 4.44; N, 5.75.

5-Benzyl (or substituted benzyl)-3-phenyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)1,2,4-triazin-6(1*H*)-thiones (6a–d).

General Procedure (A). To a mixture of each of compounds **5a–d** (2 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**) (2 mmol) in acetonitrile (20 mL) were added consecutively hexamethyldisilazane (2.2 mmol), trimethylchlorosilane (2.4 mmol), and trifluoromethanesulfonic acid (2.4 mmol). The reaction mixture was heated at reflux temperature with exclusion of humidity (using $CaCl_2$ guard tube fitted over the refluxing condenser) until the reaction was judged complete by TLC (18–24 h), using petroleum ether (bp 40–60°C)/EtOAc (60:40, v/v) as a developing system. The excess acetonitrile was evaporated on a rotavap and the formed residue was dissolved in dichloromethane (30 mL), washed ($NaHCO_3$, brine), dried (Na_2SO_4), evaporated, column chromatographed (petroleum ether [bp 40–60°C] → 60% EtOAc/petroleum ether [bp 40–60°C]) and recrystallized from dichloromethane/petroleum ether (bp 40–60°C) to give yellow crystals of compounds **6a–d**.

General Procedure (B). To a solution of each of compounds **3a–d** (1 mmol) in dry pyridine (5 mL) was added phosphorous pentasulfide (2 mmol). The reaction mixture was heated at reflux temperature for 6 h. After cooling, the products were extracted from the oily materials with ethanol (10 mL). The supernatant solutions were decanted, acidified with acetic acid (0.5 mL), concentrated, and diluted with water. The precipitates were collected by filtration, dried at room temperature, dissolved in diethyl ether, and treated with charcoal (0.5 g), filtered, and the filtrates evaporated at room temperature. The resulting solids were recrystallized from diethyl ether/petroleum ether (bp 40–60°C) to give yellow crystals of compounds **6a–d**.

5-Benzyl-3-phenyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazin-6(1*H*)-thione (6a). Using the general procedure (A) or (B) with **5a** or **3a**, respectively, gave **6a** (77% or 55%); R_f = 0.89; mp 122°C; IR (KBr) 1728 (C = O benzoate) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.12–7.13 (m, 25H, ArH), 6.77 (d, 1H, *J* = 4.9 Hz, H-1′), 6.37 (pt, 1H, *J* = 5.1 Hz, H-2′), 6.19 (pt, 1H, *J* = 5.4 Hz, H-3′), 4.82 (m, 1H, H-4′), 4.69 (dd, 1H, *J* = 4.2 Hz, 11.4 Hz, H-5′), 4.48 (dd, 1H, *J* = 4.4 Hz, 11.5 Hz, H-5″), 4.22 (s, 2H, $C_6H_5CH_2$). Anal. Calcd. for $C_{42}H_{33}N_3O_7S$: C, 69.70; H, 4.60; N, 5.81; S, 4.43. Found: C, 69.84; H, 4.72; N, 5.92; S; 4.52.

5-(4-Methylbenzyl)-3-phenyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazin-6(1*H*)-thione (6b). Using the general procedure (A) or (B) with **5b** or **3b**, respectively, gave **6b** (75% or 54%); R_f = 0.83; mp 146°C; IR (KBr) 1728 (C = O benzoate) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.29–7.13 (m, 24H, ArH), 6.74 (d, 1H, *J* = 5.3 Hz, H-1′), 6.25 (pt, 1H, *J* = 5.2 Hz, H-2′), 6.19 (pt, 1H, *J* = 5.4 Hz, H-3′), 4.88 (m, 1H, H-4′), 4.66 (dd, 1H, *J* = 4.1 Hz, 11.0 Hz, H-5′), 4.44 (dd, 1H, *J* = 4.3 Hz, 11.2 Hz, H-5″), 4.19 (s, 2H, 4-$CH_3C_6H_4CH_2$), 2.25 (s, 3H, 4-$CH_3C_6H_4CH_2$). Anal. Calcd. for $C_{43}H_{35}N_3O_7S$: C, 70.00; H, 4.78; N, 5.70; S, 4.35. Found: C, 69.92; H, 4.89; N, 5.61; S, 4.44.

5-(4-Methoxybenzyl)-3-phenyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazin-6(1*H*)-thione (6c). Using the general procedure (A) or (B) with **5c** or **3c**, respectively, gave **6c** (85% or 57%); R_f = 0.79; mp 122°C; IR (KBr) 1728 (C = O benzoate) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.14–7.30 (m, 24H, ArH), 6.82 (d, 1H, *J* = 5.0 Hz, H-1′), 6.32 (pt, 1H, *J* = 5.1 Hz, H-2′), 6.22 (pt, 1H, *J* = 5.5 Hz, H-3′), 4.84 (m, 1H, H-4′), 4.63 (dd, 1H, *J* = 4.1 Hz, 11.2 Hz, H-5′), 4.55 (dd, 1H, *J* = 4.3 Hz, 11.6 Hz, H-5″), 3.96 (s, 2H, 4-$CH_3OC_6H_4CH_2$), 3.78 (s, 3H, 4-$CH_3OC_6H_4CH_2$). Anal. Calcd. for $C_{43}H_{35}N_3O_8S$: C, 68.51; H, 4.68; N, 5.57; S, 4.25. Found: C, 68.54; H, 4.79; N, 5.48; S, 4.18.

5-(4-Chlorobenzyl)-3-phenyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazin-6(1*H*)-thione (6d). Using the general procedure (A) or (B) with **5d** or **3d**, respectively, gave **6d** (86% or 60%); R_f = 0.79; mp 128–130°C; IR (KBr) 1728 (C = O benzoate) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.12–7.15 (m, 24H, ArH), 6.72 (d, 1H, *J* = 4.9 HzH-1′), 6.31 (pt, 1H *J* = 5.6 Hz, H-2′), 6.14 (pt, 1H, *J* = 5.7 Hz, H-3′), 4.80 (m, 1H, H-4′), 4.62 (dd, 1H, *J* = 4.2 Hz, 11.1 Hz, H-5′), 4.56 (dd, 1H, *J* = 4.3 Hz, 11.6 Hz, H-5″), 4.25 (s, 2H, 4-$ClC_6H_4CH_2$). Anal. Calcd. for $C_{42}H_{32}ClN_3O_7S$: C, 66.53; H, 4.25; N, 5.54; S, 4.23. Found: C, 66.48; H, 4.39; N, 5.66; S, 4.34.

5-Benzyl-3-phenyl-1-β-D-ribofuranosyl-1,2,4-triazin-6(1*H*)-ones (4a–d)/or thiones (7a–d).

General Procedure. Dry gaseous ammonia was passed through a solution of each of compounds **3a–d** or **6a–d** (1 mmol) in dry methanol (10 mL) for about 1 h while cooling and stirring. The reaction mixture was kept stirring at room temperature until complete as shown by TLC (10 to 24 h), using chloroform/methanol (80:20, v/v) as a developing system. The resulting mixture was then concentrated at reduced pressure to afford a semisolid residue, which was boiled in chloroform (100 mL), collected by discarding chloroform via decantation, washed several times with boiled chloroform, collected again by discarding chloroform via decantation, dried at room temperature, column chromatographed

(chloroform → 20% methanol/chloroform), and recrystallized from methanol to give pale crystals of compounds **4a–d** and pale yellow crystals of compounds **7a–d**.

5-Benzyl-3-phenyl-1-β-D-ribofuranosyl-1,2,4-triazin-6(1*H*)-one (4a). Using the general procedure, **3a** gave **4a** (80%);R_f = 0.92; mp 175°C; IR (KBr) 3663–3429 (OH), 1673 (C = O amide) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.09–7.11 (m, 10H, ArH), 6.56 (d, 1H, *J* = 4.0 Hz, H-1′), 5.11 (d, 1H, *J* = 5.6 Hz, 2′-OH-exchangeable), 4.92 (d, 1H, *J* = 6.5 Hz, 3′-OH-exchangeable), 4.62 (t, 1H, *J* = 5.3 Hz, 5′-OH-exchangeable), 4.56 (pt, 1H, *J* = 5.2 Hz, H-2′), 4.19 (pq, 1H, H-3′), 3.78 (m, 1H, H-4′), 3.66 (dd, 1H, *J* = 4.5 Hz, 11.6 Hz, H-5′), 3.53 (dd, 1H, *J* = 4.7 Hz, 11.6 Hz, H-5″), 4.21 (s, 2H, $C_6H_5CH_2$). Anal. Calcd. for $C_{21}H_{21}N_3O_5$: C, 63.79; H, 5.35; N, 10.63. Found: C, 63.66; H, 5.24; N, 10.74.

5-(4-Methylbenzyl)-3-phenyl-1-β-D-ribofuranosyl-1,2,4-triazin-6(1*H*)-one (4b). Using the general procedure, **3b** gave **4b** (78%);R_f = 0.88; mp 197°C; IR (KBr) 3661–3422 (OH), 1673 (C = O amide) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.12–7.14 (m, 9H, ArH), 6.59 (d, 1H, *J* = 4.1 Hz, H-1′), 5.14 (d, 1H, *J* = 5.2 Hz, 2′-OH-exchangeable), 4.99 (d, 1H, *J* = 6.2 Hz, 3′-OH-exchangeable), 4.61 (t, 1H, *J* = 5.2 Hz, 5′-OH-exchangeable), 4.55 (pt, 1H, *J* = 5.4 Hz, H-2′), 4.29 (pq, 1H, H-3′), 3.79 (m, 1H, H-4′), 4.18 (s, 2H, 4-$CH_3C_6H_4CH_2$), 3.61 (dd, 1H, *J* = 4.4 Hz, 11.4 Hz, H-5′), 3.52 (dd, 1H, *J* = 4.4 Hz, 11.7 Hz, H-5″), 2.25 (s, 3H, 4-$CH_3C_6H_4CH_2$). Anal. Calcd. for $C_{22}H_{23}N_3O_5$: C, 64.54; H, 5.66; N, 10.26. Found: C, 64.44; H, 5.49; N, 10.37.

5-(4-Methoxybenzyl)-3-phenyl-1-β-D-ribofuranosyl-1,2,4-triazin-6(1*H*)-one (4c). Using the general procedure, **3c** gave **4c** (78%); R_f = 0.87; mp. 201–202°C; IR (KBr) 3661–3400 (OH), 1673 (C = O amide) cm^{-1}; 1H NMR (DMSO-d_6) δ 8.07–7.16 (m, 9H, ArH), 6.61 (d, 1H, *J* = 4.7 Hz, H-1′), 5.17 (d, 1H, *J* = 5.5 Hz, 2′-OH-exchangeable), 4.91 (d, 1H, *J* = 6.7 Hz, 3′-OH-exchangeable), 4.59 (t,1H, *J* = 5.0 Hz, 5′-OH-exchangeable), 4.62 (pt, 1H, *J* = 5.4 Hz, H-2′), 4.26 (pq, 1H, H-3′), 3.92 (s, 3H, 4-$CH_3OC_6H_4CH_2$), 3.78 (s, 2H, 4-$CH_3OC_6H_4CH_2$), 3.71 (m, 1H, H-4′), 3.66 (dd, 1H, *J* = 4.4 Hz, 11.3 Hz, H-5′), 3.53 (dd, 1H, *J* = 4.2 Hz, 11.3 Hz, H-5″). Anal. Calcd. for $C_{22}H_{23}N_3O_6$: C, 62.11; H, 5.45; N, 9.88. Found: C, 62.01; H, 5.64; N, 10.02.

5-(4-Chlorobenzyl)-3-phenyl-1-β-D-ribofuranosyl-1,2,4-triazin-6(1*H*)-thione (4d). Using the general procedure, **3d** gave **4d** (78%); R_f = 0.90; mp 194–196°C; 3670–3421 (OH), 1673 (C = O amide) cm^{-1}; 1H NMR (DMSO-d_6) δ 8.11–7.06 (m, 9H, ArH), 6.57 (d, 1H, *J* = 4.5 Hz, H-1′), 5.18 (d, 1H, *J* = 5.6 Hz, 2′-OH-exchangeable), 4.97 (d, 1H, *J* = 6.4 Hz, 3′-OH-exchangeable), 4.62 (t, 1H, *J* = 5.1 Hz, 5′-OH-exchangeable), 4.55 (pt, 1H, *J* = 5.2 Hz, H-2′), 4.24 (pq, 1H, H-3′), 3.76 (m, 1H, H-4′), 3.62 (dd, 1H, *J* = 4.6 Hz, 11.3

Hz, H-5′), 3.53 (dd, 1H, *J* = 4.7 Hz, 11.4 Hz, H-5″), 4.17 (s, 2H, 4-$ClC_6H_4CH_2$). Anal. Calcd. for $C_{21}H_{20}ClN_3O_5$: C, 58.68; H, 4.69; N, 9.78. Found: C, 58.84; H, 4.51; N, 9.66.

5-Benzyl-3-phenyl-1-β-D-ribofuranosyl-1,2,4-triazin-6(1*H*)-thione (7a). Using the general procedure, **6a** gave **7a** (79%); R_f = 0.96; mp 152–154°C; IR (KBr) 3660–3425 (OH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.14–7.17 (m, 10H, ArH), 6.54 (d, 1H, *J* = 4.3 Hz, H-1′), 5.14 (d, 1H, *J* = 5.9 Hz, 2′-OH-exchangeable), 4.96 (d, 1H, *J* = 6.7 Hz, 3′-OH-exchangeable), 4.66 (t, 1H, *J* = 5.0 Hz, 5′-OH-exchangeable), 4.58 (pt, 1H, *J* = 5.5 Hz, H-2′), 4.25 (pq, 1H, H-3′), 3.76 (m, 1H, H-4′), 3.68 (dd, 1H, *J* = 4.7 Hz, 11.7 Hz, H-5′), 3.51 (dd, 1H, *J* = 4.8 Hz, 11.9 Hz, H-5″), 4.23 (s, 2H, $C_6H_5CH_2$). Anal. Calcd. for $C_{21}H_{21}N_3O_4S$: C, 61.30; H, 5.14; N, 10.21; S, 7.79. Found: C, 61.24; H, 5.02; N, 10.34; S, 7.95.

5-(4-Methylbenzyl)-3-phenyl-1-β-D-ribofuranosyl-1,2,4-triazin-6(1*H*)-thione (7b). Using the general procedure, **6b** gave **7b** (75%); R_f = 0.95; mp 169°C IR (KBr) 3667–3425 (OH) cm^{-1}; 1H NMR (DMSO-d_6) δ 8.19–7.11 (m, 9H, ArH), 6.64 (d, 1H, *J* = 4.5 Hz, H-1′), 5.16 (d, 1H, *J* = 5.7 Hz, 2′-OH-exchangeable), 4.98 (d, 1H, *J* = 6.5 Hz, 3′-OH-exchangeable), 4.63 (t, 1H, *J* = 5 Hz, 5′-OH-exchangeable), 4.58 (pt, 1H, *J* = 5.3 Hz, H-2′), 4.27 (pq, 1H, H-3′), 3.78 (m, 1H, H-4′), 4.23 (s, 2H, 4-$CH_3C_6H_4CH_2$), 3.67 (dd, 1H, *J* = 4.5 Hz, 11.6 Hz, H-5′), 3.52 (dd, 1H, *J* = 4.7 Hz, 11.8 Hz, H-5″), 2.27 (s, 3H, 4-$CH_3C_6H_4CH_2$). Anal. Calcd. for $C_{22}H_{23}N_3O_4S$: C, 62.10; H, 5.45; N, 9.88; S, 7.54. Found: C, 62.23; H, 5.56; N, 9.62; S, 7.68.

5-(4-Methoxybenzyl)-3-phenyl-1-β-D-ribofuranosyl-1,2,4-triazin-6(1*H*)-thione (7c). Using the general procedure, **6c** gave **7c** (87%); R_f = 0.89; mp 201–203°C; IR (KBr) 3669–3438 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.11–7.23 (m, 9H, ArH), 6.54 (d, 1H, *J* = 4.5 Hz, H-1′), 5.12 (d, 1H, *J* = 5.6 Hz, 2′-OH-exchangeable), 4.94 (d, 1H, *J* = 6.6 Hz, 3′-OH-exchangeable), 4.62 (t, 1H, *J* = 5.3 Hz, 5′-OH-exchangeable), 4.60 (pt, 1H, *J* = 5.4 Hz, H-2′), 4.26 (pq, 1H, H-3′), 3.97 (s, 2H, 4-$CH_3OC_6H_4CH_2$), 3.77 (s, 3H, 4-$CH_3OC_6H_4CH_2$), 3.74 (m, 1H, H-4′), 3.65 (dd, 1H, *J* = 4.5 Hz, 11.7 Hz, H-5′), 3.51 (dd, 1H, *J* = 4.8 Hz, 11.6 Hz, H-5″). Anal. Calcd. for $C_{22}H_{23}N_3O_5S$: C, 59.85; H, 5.25; N, 9.52; S, 7.26. Found: C, 60.03; H, 5.22; N, 9.74; S, 7.19.

5-(4-Chlorobenzyl)-3-phenyl-1-β-D-ribofuranosyl-1,2,4-triazin-6(1*H*)-thione (7d). Using the general procedure, **6d** gave **7d** (81%); R_f = 0.93; mp 222°C; 3660–3425 (OH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.17–7.12 (m, 9H, ArH), 6.62 (d, 1H, *J* = 4.3 Hz, H-1′), 5.16 (d, 1H, *J* = 5.8 Hz, 2′-OH-exchangeable), 4.96 (d, 1H, *J* = 6.8 Hz, 3′-OH-exchangeable), 4.67 (t, 1H, *J* = 5.0Hz, 5′-OH-exchangeable), 4.58 (pt, 1H, *J* = 5.3 Hz, H-2′), 4.24 (pq, 1H, H-

3′), 3.76 (m, 1H, H-4′), 3.67 (dd, 1H, J = 4.7 Hz, 11.6 Hz, H-5′), 3.53 (dd, 1H, J = 4.7 Hz, 11.9 Hz, H-5″), 4.21 (s, 2H, 4-$ClC_6H_4CH_2$). Anal. Calcd. for $C_{21}H_{20}ClN_3O_4S$: C, 56.56; H, 4.52; N, 9.42; S, 7.19. Found: C, 56.61; H, 4.42; N, 9.63, S, 7.34.

REFERENCES

1. Niedballa, U.; Vorbrüggen, H. Pyrimidine nucleosides. Chem. Abstr. **1971**, *74*, 88267d.
2. Vorbrüggen, H.; Niedballa, U. Pyrimidine nucleosides. Chem. Abstr. **1971**, *75*, 20912a.
3. Vorbrüggen, H.; Kolb, K.; Niedballa, U.; Strehlke, P. Therapeutical 2-thio-6-azauridines. Chem. Abstr. **1971**, *75*, 49513g.
4. Niedballa, U.; Vorbrüggen, H. Pyrimidine nucleosides. Chem. Abstr. **1971**, *74*, 100361q.
5. Roy-Durman, P. Analogues of Nucleic Acid Components. Springer Verlag: Berlin, 1970; 42–45.
6. Beranek, J.; Sorm, F. Acyl derivatives of 6-azacytidine. Chem. Abstr. **1964**, *61*, 13405f.
7. Zabolotnyi, D.K. Institute of Microbiology. 6-Azacytidine. Chem. Abstr. **1965**, *62*, 13222h.
8. Restivo, A.R. Azauridines. Chem. Abstr. **1969**, *70*, 47807d.
9. Mansour, A.K.; Eid, M.M.; Khalil, N.S.A.M. Selective synthesis and reactions of 6-substituted-2-β-galactosyl-1,2,4-triazines of potential anticancer activity. Nucleosides Nucleotides Nucleic Acids **2003**, *22* (1), 21–44.
10. Mansour, A.K.; Eid, M.M.; Khalil, N.S.A.M. Synthesis of some new 2-α-L-arabinopyranosyl-1,2,4-triazines of potential anticancer activity. Nucleosides Nucleotides Nucleic Acids **2003**, *22* (9), 1805–1823.
11. Eid, M.M.; Abdel Hady, S.A.; Ali, H.A.W. Reaction of some 1,2,4-triazines with acetobromoglucose. Arch. Pharm. **1990**, *323*, 243–245.
12. Mansour, A.K.; Eid, M.M.; Khalil, N.S.A.M. Synthesis of some *N*-galactosides of 3-aryl-5-benzyl(or substituted benzyl)-1,2,4-triazin-6(1*H*)-/ones or thiones of expected biological activity. Nucleosides Nucleotides Nucleic Acids **2003**, *22* (9), 1825–1833.
13. Vorbrüggen, H.; Krolikiewicz, K.L.; Bennua, B. Nucleoside synthesis, XXII. Nucleoside synthesis with trimethylsilyl triflate and perchlorate as catalysts. Chem. Ber. **1981**, *114*, 1234–1255.
14. Vorbrüggen, H.; Strehlke, P. Synthesis of Hall's methyl 2-thiouridine-5-acetate from yeast-t-RNA. Angew. Chem., Int. Ed. **1969**, *8* (12), 977–978.
15. Niedballa, U.; Vorbrüggen, H. A general synthesis of *N*-glycosides. I. Synthesis of pyrimidine nucleosides. J. Org. Chem. **1974**, *39* (25), 3654–3660.
16. Al-Masoudi, N.A.; Pfleiderer, W. Synthesis and reactions of 6- and 7-p-chlorophenyllumazine nucleosides. Nucleosides Nucleotides **1989**, *8* (8), 1485–1498.
17. Mansour, A.K.; Ibrahim, Y.A.; Khalil, N.S.A.M. Selective synthesis and structure of 6-arylvinyl-2- and 4-glucosyl-1,2,4-triazines of expected interesting biological activity. Nucleosides Nucleotides **1999**, *18* (10), 2265–2283.
18. Khalil, N.S.A.M.; Mansour, K.; Eid, M.M. Synthesis of some novel 6-benzyl(or substituted benzyl)-2-β-D-glucopyranosyl-1,2,4-triazolo[4,3-b][1,2,4]triazines as potential antimicrobial chemotherapeutics. Nucleosides Nucleotides Nucleic Acids **2004**, *23* (12), 1889–1910.
19. Nalepa, K.; Bekarek, V.; Slouka, J. Reaction of azlactones with amino compounds. V. Synthesis and structure of 3,5-disubstituted-6-hydroxy-1,2,4-triazines. J. Pract. Chem. **1972**, *314* (5–6), 851–856.
20. Nalepa, K.; Slouka, J. Reaction of azlactones with amino compounds. I. Hydrazinolysis of unsaturated azlactones and cyclization of the hydrazides formed to give 1,2,4-triazine derivatives. Monatsh. Chem. **1967**, *98* (2), 412–416.