Synthesis and Antitumor Activity of New 1,2,4-Triazine and [1,2,4]Triazolo[4,3-*b*][1,2,4]triazine Derivatives and Their Thioglycoside and Acyclic *C*-Nucleoside Analogs

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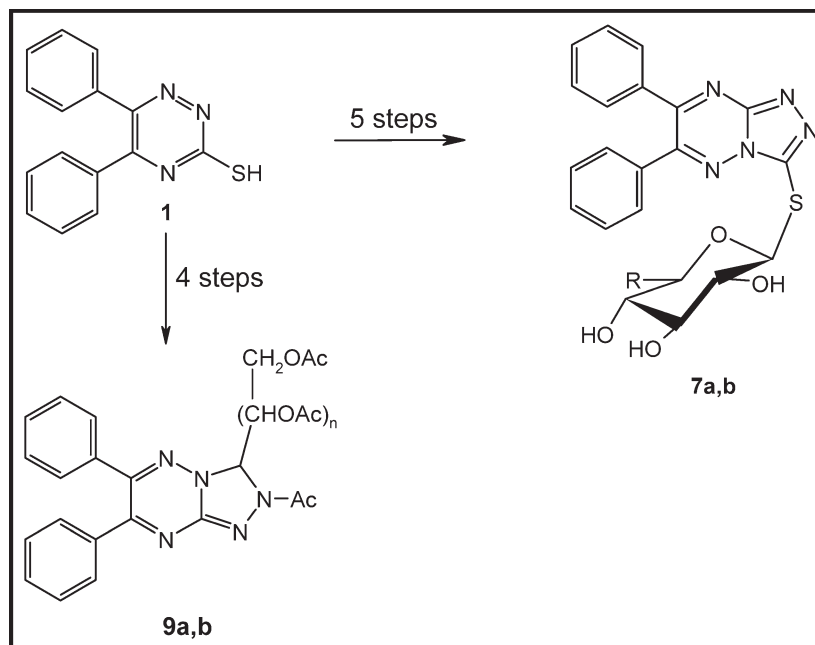[a]Department of Photochemistry, National Research Centre, Cairo, Egypt
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New 1,2,4-triazine and their derived 1,2,4-triazolo[3,4-*b*][1,2,4]triazine derivatives were synthesized starting from 5,6-diphenyl-1,2,4-triazine-3-thiol. Furthermore, the corresponding 1,2,4-triazolo[3,4-*b*] [1,2,4]-triazine thioglycosides and acyclic *C*-nucleoside analogs were synthesized. The newly synthesized compounds were evaluated for their antitumor activity and some of them showed high inhibition activities.

INTRODUCTION

1,2,4-Triazines and their condensed derivatives occupy a pivotal position in modern medicinal chemistry, because of their high potential biological activities. The 1,2,4-triazine ring is a prominent structural motif found in numerous natural and synthetic biologically active compounds. For example, the well-known antiviral drug azaribine is structurally based on the 1,2,4-triazine scaffold [1]. In addition, certain azanucleosides, for example, 6-azacytosine and 6-azauracil, bearing the 1,2,4-triazine heterocycle, have displayed an impressive array of biological activities, among which antiviral [2,3] and antitumor [4,5] activities. Condensed 1,2,4-triazines found various applications as pharmaceuticals, herbicides, pesticides, and dyes [6,7]. They showed an interesting broad spectrum of antiproliferative activity and a pronounced growth inhibitory activity against leukemic cell lines and a wide range of cancer cells [8,9] revealing *in vitro* antitumor and antifungal activities [10,11]. It is noteworthy that many potential antiviral and anticancer drugs have been modeled on them [12,13]. 1,2,4-Triazine derivatives are known to possess antitubercular, antibacterial, fungicidal, insecticidal, herbicides hypotensive, and hypothermic activities [6,14–17]. Many 1,2,4-triazines have been screened *in vitro* supporting their anti-HIV and anti-cancer activities [18,19]. On the other hand, the glycosylthio heterocycles [20–23] and the acyclic nucleoside analogs with modification of both the glycon part and the heterocyclic base have stimulated extensive research as biological

inhibitors [24–27]. Owing to the above facts and our interest in the attachment of carbohydrate moieties to newly synthesized heterocycles [28–32], our aim is the synthesis of new 1,2,4-triazine and [1,2,4]triazolo[4,3-b][1,2,4]triazine derivatives and their thioglycoside and acyclic C-nucleoside analogs in an ongoing search for new biologically active leads with potential antitumor activity.

RESULTS AND DISCUSSION

The starting compound 5,6-diphenyl-1,2,4-triazine-3-thiol (**1**) was synthesized according to a reported procedure [33] by Saxena *et al.* Methylation of **1** with methyl iodide in acetone in the presence of K_2CO_3 at room temperature afforded 3-(methylthio)-5,6-diphenyl-1,2,4-triazine (**2**) in 80% yield. Reaction of **2** with hydrazine hydrate in ethanol gave 3-hydrazinyl-5,6-diphenyl-1,2,4-triazine (**3**). The ^1H NMR spectrum of **2** revealed the presence of the S-CH_3 signal at δ 2.44 ppm, which disappeared in the ^1H NMR spectrum of the hydrazine derivative **3** and instead two signals appeared at δ 5.52 and 9.94 ppm corresponding to the NH_2 and NH groups, respectively.

When **3** was reacted with carbon disulphide in ethanol in the presence of potassium hydroxide, 6,7-diphenyl-[1,2,4]triazolo[4,3-b][1,2,4]triazine-3(2H)-thione (**4**) was obtained in 78% yield. The ^1H NMR spectrum of **4** showed the signals of the aromatic protons and the NH group and the ^{13}C NMR spectrum reveled the presence of the C=S signal at δ 172.35 ppm. The signals at δ 156.48, 157.94, 158.12 ppm corresponding to three C=N groups in the ^{13}C NMR spectrum of **4** indicate that the cyclization has taken place to afford the triazolo[4,3-b][1,2,4]triazin-3(2H)-thione structure and not 1,2,4-triazolo[3,4-c][1,2,4]triazin-3(2H)-thione structure. In the later structure two of these signals will correspond to C—N and not to C=N and would appear at lower chemical shifts.
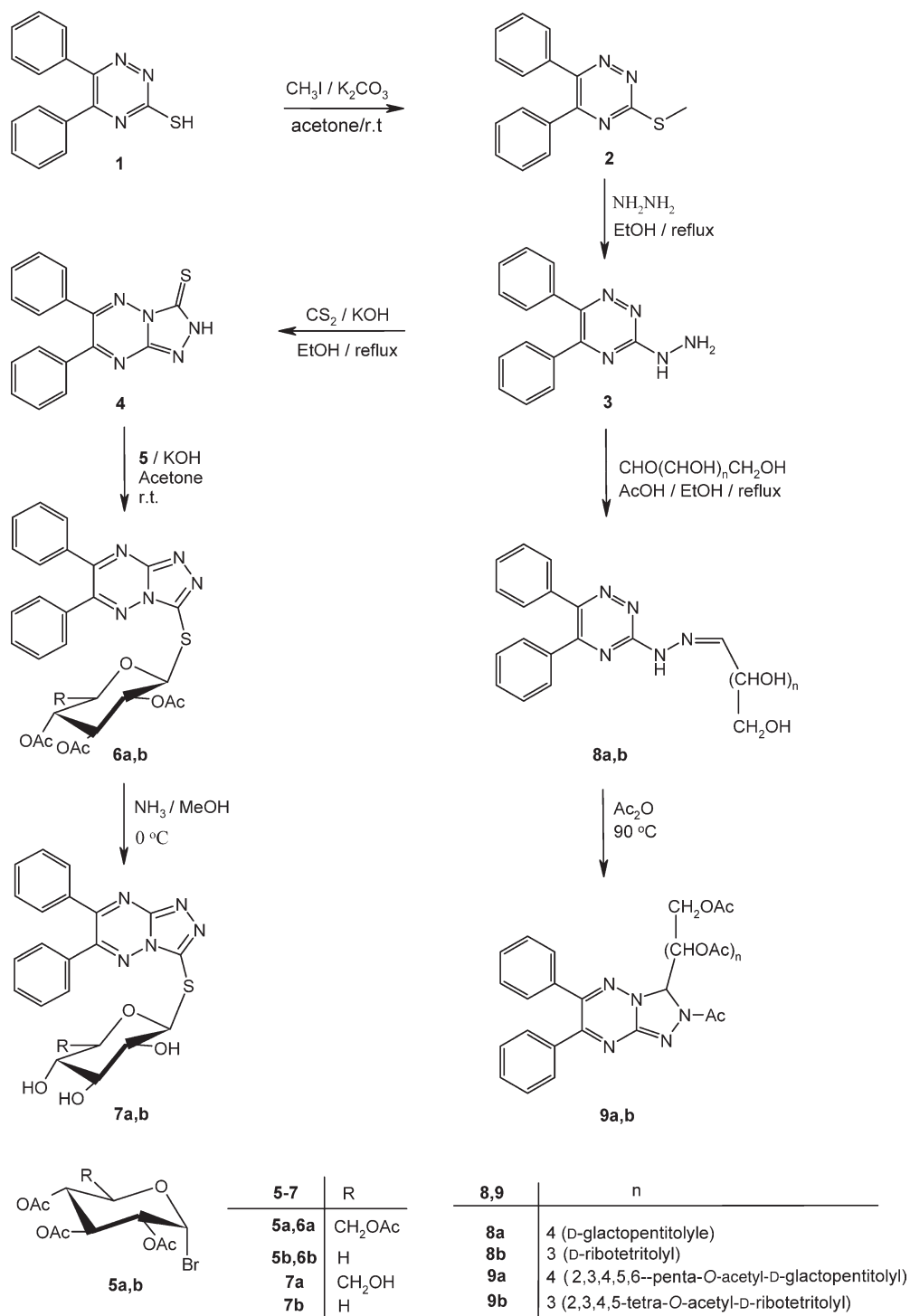
Reaction of **4** with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (**5a**) or 2,3,4-tri-O-acetyl-α-D-xylopyranosyl bromide (**5b**) gave the corresponding acetylated thioglycoside derivatives **6a,b**, respectively. The assignments of sugar protons were based on the chemical shift equivalences to the assigned structures of related sugar thioglycosides [29,32]. Thus, the ^1H NMR spectra of the glycosides **6a,b** showed signals corresponding to the acetyl-methyl signals and the sugar protons in addition to the aromatic protons. The anomeric protons appeared at δ 5.70 and 5.72 ppm with coupling constants J = 10.2 and 9.8 Hz for **6a** and **6b**, respectively, indicating the β-orientation of the thioglycosidic bond. The anomeric proton of β-N-glucosides having an

adjacent C=S, was reported [29,34–37] to appear at higher chemical shift because of the anisotropic deshielding effect of the C=S. The ^{13}C NMR spectra of **6a,b** showed a signal at δ 88.98 and 88.56 ppm corresponding to the anomeric C-1, which also confirmed the β-configuration. The absence of a peak corresponding to the C=S group indicates that the attachment of the sugar has taken place at the sulfur atom and not on the nitrogen atom.

When compounds **6a,b** were treated with methanolic ammonia at 0°C, the deacetylated thioglycoside derivatives **7a,b** were obtained in moderate yields. The structures of the deprotected glycosides **7a,b** were conformed by IR, ^1H- and ^{13}C NMR, and elemental analysis (see experimental part). When 3-hydrazinyl-5,6-diphenyl-1,2,4-triazine (**3**) was allowed to react with D-galactose, or D-ribose in an aqueous ethanolic solution and a catalytic amount of acetic acid, the corresponding sugar hydrazones **8a,b** were obtained, respectively. The IR spectra of **8a,b** showed the presence of characteristic absorption bands corresponding to the hydroxy groups in the region 3478–3448 cm^{-1}. The ^1H NMR spectra showed the signals of the sugar chain protons at δ 3.30–5.79 ppm and the C-1 methine proton as doublet in the range δ 7.48–7.52 ppm in addition to the aromatic protons in the region δ 7.27–7.73 ppm.

It is well known that the reaction of sugar hydrazinyl derivatives with acetic anhydride give the respective per-O-acetyl derivatives. However, it has been reported [38–42] that when the reaction was carried out at high temperature in boiling acetic anhydride, cyclization usually takes place in addition to per-O-acetylation to afford C-nucleoside analogs. We reported previously [38] the synthesis of 1,2,4-triazolo[1,3,4]oxadiazole acyclic nucleoside analogous by the reaction of hydrazinyl sugars with boiling acetic anhydride. Thus, when the hydrazinyl sugars **8a,b** were heated in acetic anhydride at 100°C they gave the triazolotriazine acyclic nucleosides **9a,b**, respectively. The structures of compounds **9a,b** were confirmed by their IR, ^1H NMR, and ^{13}C NMR spectra. The IR spectra of **9a,b** showed characteristic absorption bands in the carbonyl frequency region at 1668–1662 cm^{-1} and 1742–1738 cm^{-1} corresponding to the carbonyl amide and the carbonyl ester groups, respectively indicating the presence of N-acetyl group in addition to the O-acetyl groups. The ^1H NMR spectra of **9a,b** showed the signals of the O-acetyl-methyl protons each as singlet in the range δ 1.85–2.18 ppm and the N-acetyl-methyl protons in the range δ 2.23–2.28 ppm. The rest of the alditolyl chain protons appeared in the range δ 4.16–5.77 ppm. The ^{13}C NMR spectrum of **9a,b** showed the resonances of the acetyl-methyl carbons at δ 20.32–29.70 ppm. The value of the chemical shift of the C—N-Ac (C-1 in the original sugar chain moiety)

Scheme 1. Synthesis of [1,2,4]triazolo[4,3-b][1,2,4]triazine thioglycosides and acyclic *C*-nucleosides.

5-7	R
5a,6a	CH$_2$OAc
5b,6b	H
7a	CH$_2$OH
7b	H

8,9	n
8a	4 (D-glactopentitolyle)
8b	3 (D-ribotetritolyl)
9a	4 (2,3,4,5,6--penta-*O*-acetyl-D-glactopentitolyl)
9b	3 (2,3,4,5-tetra-*O*-acetyl-D-ribotetritolyl)

appeared at δ 92.12 and 92.24 ppm whose value indicated its *N,N*-acetal nature rather than being a C=N. The signals at δ 152.46–153.58 ppm in **9a** and **9b** indicated the presence of C-6 and C-7 as C=N and not C—N confirming the triazolino[4,3-b][1,2,4]triazine and not triazolino[4,3-cb][1,2,4]triazine; the later will

contain C-6 and C-7 as C—N, which would appear at lower chemical shift. The signals at δ 169.12–171.10 ppm correspond to the carbonyl groups (Scheme 1).

Reaction of **1** with ethyl chloroacetate in acetone afforded the corresponding *S*-substituted ethyl ester derivative **10** in 82% yield. Hydrazinolysis of the ester

10 in ethanol gave the corresponding hydrazide derivative **11**. The IR spectrum of the ester **10** showed an absorption band at 1738 cm^{-1}, which disappeared in the corresponding spectrum of acid hydrazide **11** and instead showed characteristic absorption bands at 3476 and 1678 cm^{-1} for the NH_2 and C=O, respectively. The ^1H NMR spectrum of the hydrazide **11** showed signals corresponding to the NH_2, the two CH_2 in addition to the aromatic protons and the NH signal. The ^{13}C NMR of compound **10** revealed the presence of the CH_2 signals at δ 41.14 and 48.14 ppm in addition to the C=O group at δ 169.45 ppm.

When the hydrazide **11** was allowed to react with carbon disulphide in ethanol in the presence of potassium hydroxide the corresponding 1,3,4-oxadiazole-2-thione derivative **12** was afforded in 80% yield. Reaction of thione derivative **12** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**5**), the corresponding acetylated thioglycoside **13** was obtained. The ^1H NMR spectrum of the latter compound showed signals corresponding to the acetyl-methyl signals and the sugar protons in addition to the aromatic protons. The anomeric proton signal appeared at δ 5.72 ppm with a coupling constant 9.8 indicating the β-orientation of the thioglycosidic bond. The ^{13}C NMR spectrum of **13** showed a signal at δ 89.12 ppm corresponding to the anomeric C-1, which also confirmed the β-configuration. The absence of a peak corresponding to the C=S group indicates that the attachment of the sugar has taken place at the sulfur atom and not on the nitrogen atom. Treatment of the acetylated thioglycoside **13** with methanolic ammonia gave the deacetylated thioglycoside derivative **14** (Scheme 2). Its structure was conformed by IR, ^1H- and ^{13}C NMR, and elemental analysis, which agreed with the assigned structure (see experimental part).

Antitumor activity. The antitumor activity of the newly synthesized compounds was investigated against Ehrlich Ascites Carcinoma cells (EAC). These cells were maintained by weekly intraperitoneal transplantation of 2.5×10^6 cells in female Swiss albino mice. The tumor is characterized by a moderately rapid growth, which leads to the death of the mice in about 20 days due to the distal metastasis. EAC is of mammary origin; as spontaneous breast cancer served as the original tumor from which an ascites variant was obtained [43].

Cytotoxicity assay. Ascites fluid was withdrawn under aseptic conditions (ultraviolet laminar flow system) from the peritoneal cavity of tumor bearing mice by needle aspiration after 7 days of EAC cells inoculation. To adjust the number of EAC cells/mL, tumor cells obtained were diluted several times with normal saline. EAC viable cells were counted by trypan blue exclusion method where, 10 μL trypan blue (0.05%) was mixed

with 10 μL of the cell suspension. Within 5 min, the mixture was spread onto haemocytometer, covered with a cover slip and then the cells were examined under microscope. Dead cells are blue stained but viable cells are not [44]. Cell suspension was adjusted to contain 2.5×10^6 viable cells/mL.

EAC cells, RPMI medium, drugs, and DMSO were added in sterile test tubes according to trypan blue exclusion method [44]. The cells were incubated for 1 and 24 h at 37°C under a constant over lay of 5% CO_2. EAC viable cells were counted by trypan blue exclusion using haemocytometer as mentioned above. The cell surviving fraction was calculated from the relation *T/C*; where, *T* and *C* represent the number of viable cells in a unit volume and the number of total (viable + dead) cells in the same unit volume, respectively.

The *in vitro* studies. The effects of the newly synthesized compounds were assessed on the viability of EAC cells using trypan blue exclusion test. The anti-tumor efficacy of the compounds against ESC cell lines was demonstrated compared with doxorubicin. The obtained results revealed that compounds **3, 4, 7b, 9b, 10,** and **11** were the most active derivatives among the series of tested compounds and affected the EAC cell viability on a dose dependent manner whereas other compounds exhibited little or no activity. The effective dose calculated as IC_{50}, which correspond to the compound concentration resulted in 50% mortality in the total cells count and presented in (Table 1). The 1,2,4-triazine derivatives **4, 9b,** and **10** displayed the highest activity with IC_{50} values 40, 44, and 45 μg/mL, respectively, followed by compounds **3** and **11**.

From the antitumor activity results and structure activity relationship, it could be concluded that the attachment of acyclic ribotetritolyl sugar moiety to the [1,2,4]triazolo[4,3-*b*][1,2,4]triazine ring system displayed higher activity than the corresponding analogous with galactopentitolyl moiety. Furthermore, the [1,2,4]triazolo[4,3-*b*][1,2,4]triazine thioglycoside with the free hydroxyl xylopyranosyl sugar moiety revealed higher activity than the corresponding acetylated analog or the thioglycoside with the glucopyranosyl sugar moiety. Moreover, the [1,2,4]triazolo[4,3-*b*][1,2,4]triazine thioglycosides displayed higher inhibition activity the 1,3,4-oxadiazole thioglycoside derivatives. The substituted hydrazine derivative of the 1,2,4-triazine ring system **3** displayed relatively higher activity than the corresponding acid hydrazide **11**, which revealed lower activity.

EXPERIMENTAL

Melting points were determined with a kofler block apparatus and are uncorrected. The IR spectra were recorded on a perkin-Elmer model 1720 FTIR spectrometer for KBr disc.

Scheme 2. Synthesis of (1,2,4-triazin-3-yl)methylthio-1,3,4-oxadiazole thioglycosides.
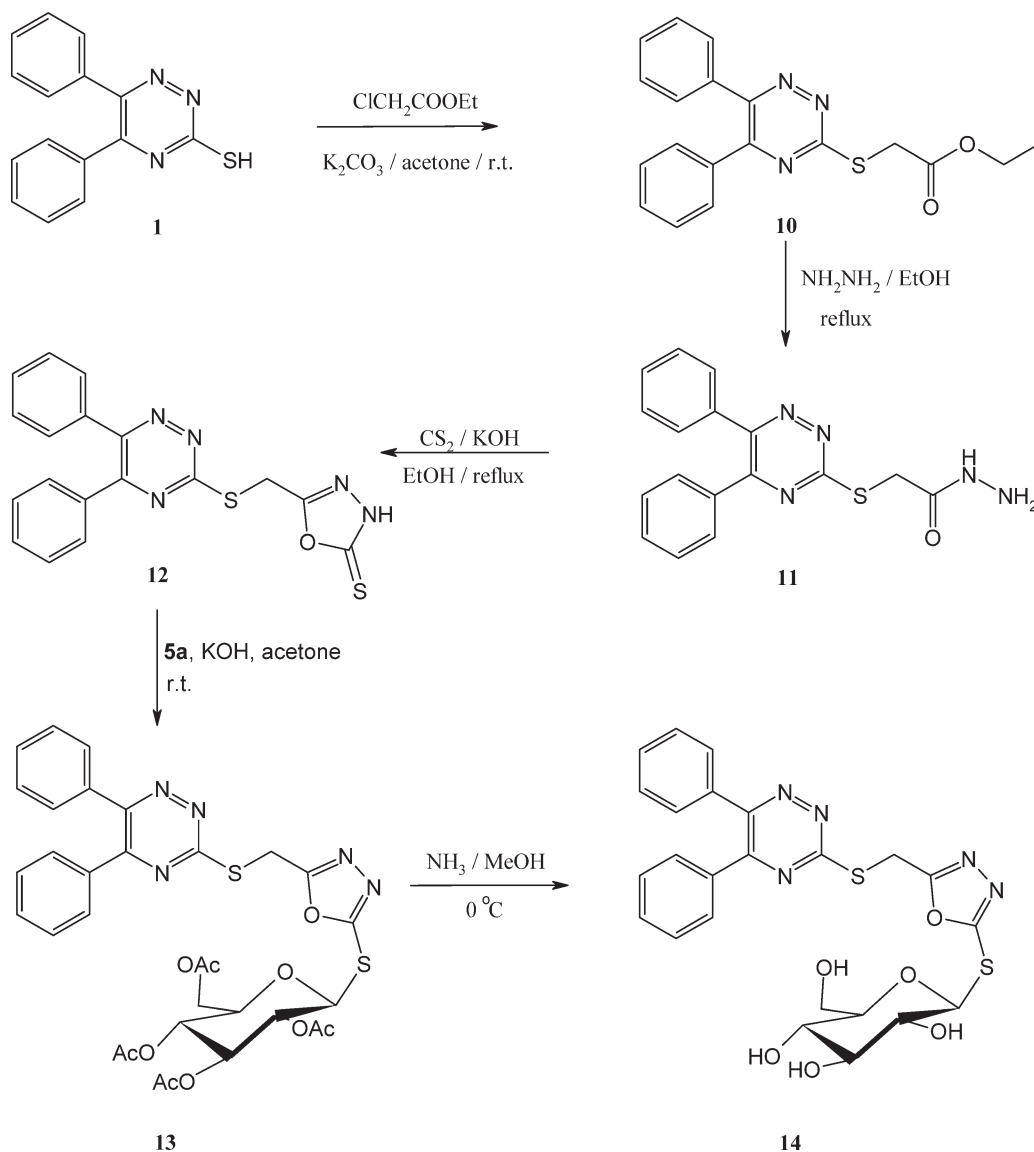
NMR spectra were recorded on a varian Gemini 200 NMR Spectrometer at 300 MHz for ¹H and 75 MHz for ¹³C or on a brucker Ac-250 FT spectrometer at 250 MHz for ¹H and at 62.9 MHz for ¹³C. Chemical shifts were reported in δ scale (ppm) relative to TMS as a standard and the coupling constants J values are given in Hz. The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F₂₄₅. Elemental analyses were determined on a Perkin Elmer 240 (microanalysis) at the Microanalytical data centre at Faculty of science, Cairo University, Egypt.

3-Methylsulfanyl-5,6-diphenyl-1,2,4-triazine (2). To a solution of 5,6-diphenyl-1,2,4-triazine-3-thiol (**1**) (2.65 g, 10 mmol) and potassium carbonate (1.38 g, 10 mmol) in acetone (25 mL), was added methyl iodide (1.42 g, 10 mmol). The solution was stirred at room temperature for 2 h and the solvent was evaporated under reduced pressure. The resulting solid product was recrystallized from ethanol as yellow solid,

2.34 g (80%), mp 130–131°C; IR (KBr) ν: 1608 (C=N) cm⁻¹; ¹H NMR (DMSO-d_6, 300 MHz): δ 2.44 (s, 3H, SCH₃), 7.26 (m, 3H, Ar-H), 7.31 (m, 3H, Ar-H), 7.37 (m, 2H, Ar-H), 7.71 (m, 2H, Ar-H); ¹³C NMR (DMSO-d_6, 75 MHz): δ 22.14

Table 1

The IC₅₀ (µg/mL) of compounds **3** and **9–11**.

Compound	IC₅₀ (µg/mL)
3	51
4	40
7b	68.5
9b	44
10	45
11	62.5
Doxorubicin	38

(CH$_3$), 127.73–141.05 (Ar-C), 152.60 (C-5), 153.44 (C-6), 156.87 (C-3). *Anal*. Calcd for C$_{16}$H$_{13}$N$_3$S: C, 68.79; H, 4.69; N, 15.04. Found: C, 68.60; H, 4.52; N, 14.78.

3-Hydrazino-5,6-diphenyl-1,2,4-triazine (3). A solution of **2** (2.79 g, 10 mmol) and hydrazine hydrate (0.5 g, 10 mmol) in ethanol (20 mL) was heated under reflux for 6 h. The solution was cooled and the resulting precipitate was filtered and recrystallized from ethanol as yellow crystals, mp 188–189°C; 2.15 g (82%), IR (KBr) ν: 3363 (NH$_2$), 3310 (NH), 1610 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.52 (s, 2H, NH$_2$), 7.24 (m, 3H, Ar-H), 7.33 (m, 3H, Ar-H), 7.41 (m, 2H, Ar-H), 7.72 (m, 2H, Ar-H), 9.94 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 126.88–141.12 (Ar-C), 152.65 (C-5), 153.76 (C-6), 156.89 (C-3). *Anal*. Calcd for C$_{15}$H$_{13}$N$_5$: C, 68.42; H, 4.98; N, 26.60. Found: C, 68.22; H, 4.82; N, 26.42.

6,7-Diphenyl-1,2,4-triazolo[4,3-b][1,2,4]triazin-3(2H)-thione (4). To a solution of **3** (2.63 g, 10 mmol) in ethanol (20 mL) was added a solution of potassium hydroxide (0.56 g, 10 mmol) dissolved in water (2 mL) and carbon disulphide (3 mL). The solution was heated under reflux for 15 h. The solvent was evaporated and the residue was dissolved in water, filtered off, and acidified with dilute hydrochloric acid. The formed precipitate was filtered off, washed with water and recrystallized from ethanol as yellow solid, mp 152–153°C; 2.37 g (78%), IR (KBr) ν: 3305 (NH), 1610 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.27 (m, 3H, Ar-H), 7.33 (m, 3H, Ar-H), 7.39 (m, 2H, Ar-H), 7.75 (m, 2H, Ar-H), 12.14 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 128.26–142.14 (Ar-C), 156.48, 157.94, 158.12 (3C=N), 172.35 (C=S). *Anal*. Calcd for C$_{16}$H$_{11}$N$_5$S: C, 62.93; H, 3.63; N, 22.93. Found: C, 62.65; H, 3.54; N, 22.77.

3-(2,3,4,6-Tetra-O-acetyl-β-D-glycopyranosyl)-6,7-diphenyl-3,5-dihydro-1,2,4-triazolo[4,3-b][1,2,4]triazine (6a,b). General procedure: To a solution of **4** (1.52 g, 5 mmol) in aqueous potassium hydroxide [(0.28 g, 5 mmol) in distilled water (16 mL)] was added a solution of 2,3,4,6-tetra-O-acetyl-α-D-gluco (**5a**) or 2,3,4-tri-O-acetyl-α-D-Xylopyranosyl bromide (**5b**) (5 mmol) in acetone (20 mL). The reaction mixture was stirred at room temperature until reaction was judged complete by TLC using chloroform/methanol 99.5:0.5. The solvent was evaporated under reduced pressure at 40°C and the residue was washed with distilled water to remove potassium bromide formed. The product was dried, and recrystallized from ethanol.

3-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-6,7-diphenyl-3,5-dihydro-1,2,4-triazolo[4,3-b][1,2,4]triazine (6a). This compound was obtained as yellow solid, 2.58 g (81%), mp 139–140°C; IR (KBr) ν: 1742 (C=O), 1612 (C=N) cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.87, 1.89, 2.05, 2.10 (4s, 12H, 4CH$_3$), 4.02 (m, 1H, H-5′), 4.10 (dd, J = 11.4 Hz, J = 2.8 Hz, 1H, H-6′), 4.14 (dd, J = 11.4, 3.2 Hz, 1H, H-6″), 4.90 (t, J = 9.3 Hz, 1H, H-4′), 5.18 (dd, J = 9.6 Hz, J = 9.3 Hz, 1H, H-3′), 5.34 (t, J = 9.6 Hz, 1H, H-2′), 5.70 (d, J$_{1′,2′}$ = 10.2 Hz, 1H, H-1′), 7.28 (m, 3H, Ar-H), 7.36 (m, 3H, Ar-H), 7.39 (m, 2H, Ar-H), 7.76 (m, 2H, Ar-H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 19.31, 19.52, 20.16, 20.26 (4CH$_3$), 62.87 (C-6′), 64.21 (C-4′), 68.62 (C-3′), 70.34 (C-2′), 71.82 (C-5′), 88.98 (C-1′), 127.26–143.14 (Ar-C), 154.78, 156.52, 157.92, 158.18 (4C=N), 169.78, 170.14, 170.56, 170.84 (4C=O). *Anal*. Calcd for C$_{30}$H$_{29}$N$_5$O$_9$S: C, 56.69; H, 4.60; N, 11.02. Found: C, 56.37; H, 4.49; N, 10.89.

3-(2,3,4-Tri-O-acetyl-β-D-xylopyranosyl)-6,7-diphenyl-3,5-dihydro-1,2,4-triazolo[4,3-b][1,2,4]triazine (6b). This compound was obtained as yellow solid, 2.23 g (79%), 143–144°C, IR (KBr) ν: 1740 (C=O), 1610 (C=N) cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.88, 2.05, 2.10 (3s, 9H, 3CH$_3$), 4.10 (dd, J = 11.4 Hz, J = 2.8 Hz, 1H, H-5′), 4.14 (m, 1H, H-5″), 4.90 (t, J = 9.4 Hz, 1H, H-4′), 5.18 (dd, J = 9.4 Hz, J = 9.2 Hz, 1H, H-3′), 5.34 (t, J = 9.2 Hz, 1H, H-2′), 5.72 (d, J$_{1′,2′}$ = 9.8 Hz, 1H, H-1′), 7.31 (m, 3H, Ar-H), 7.35 (m, 3H, Ar-H), 7.38 (m, 2H, Ar-H), 7.74 (m, 2H, Ar-H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 20.16, 20.26, 20.31 (3CH$_3$), 65.87 (C-5′), 67.21 (C-3′), 68.62 (C-4′), 70.34 (C-2′), 88.56 (C-1′), 128.26–143.25 (Ar-C), 154.88, 156.59, 157.94, 158.22 (4C=N), 169.78, 170.14, 170.80 (3C=O). *Anal*. Calcd for C$_{27}$H$_{25}$N$_5$O$_7$S: C, 57.54; H, 4.47; N, 12.43. Found: C, 57.28; H, 4.31; N, 12.55.

3-(β-D-Glycopyranosyl)-6,7-diphenyl-3,5-dihydro-1,2,4-triazolo-[4,3-b][1,2,4]triazine (7a,b). General Procedure: Dry gaseous ammonia was passed through a solution of a protected nucleoside **6a,b** (5 mmol) in dry methanol (15 mL) at 0°C for 1 h, and then the mixture was stirred at 0°C for about 5 h. The solvent was evaporated under reduced pressure at 40°C to give a solid residue, which was recrystallized from ethanol.

3-(β-D-Glucopyranosyl)-6,7-diphenyl-3,5-dihydro-1,2,4-triazolo[4,3-b][1,2,4]triazine (7a). This compound was obtained as yellow solid, 2.08 g (82%), mp 192–193°C; IR (KBr) ν: 3475–3451 (OH), 1614 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.41 (m, 2H, H-6′,6″), 3.45 (m, 1H, H-5′), 3.90 (m, 2H, H-3′,4′), 4.27 (t, J = 9.4 Hz, 1H, H-2′), 4.70 (t, J = 6.2, 1H, OH), 4.83 (d, J = 6.4 Hz, 1H, OH), 5.15 (m, 1H, OH), 5.24 (m, 1H, OH), 5.72 (d, J$_{1′,2′}$ = 10.2 Hz, 1H, H-1′), 7.28 (m, 3H, Ar-H), 7.36 (m, 3H, Ar-H), 7.37 (m, 2H, Ar-H), 7.75 (m, 2H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 61.46 (C-6′), 64.14 (C-4′), 68.83 (C-3′), 71.33 (C-2′), 72.18 (C-5′), 88.70 (C-1′), 128.25–143.68 (Ar-C), 154.85, 156.56, 157.84, 158.24 (4C=N). *Anal*. Calcd for C$_{22}$H$_{21}$N$_5$O$_5$S: C, 56.52; H, 4.53; N, 14.98. Found: C, 56.41; H, 4.48; N, 14.72.

3-(β-D-Xylopyranosyl)-6,7-diphenyl-3,5-dihydro-1,2,4-triazolo[4,3-b][1,2,4]triazine (7b). This compound was obtained as yellow solid, 1.91 g (80%), mp 195–196°C; IR (KBr) ν: 3470–34481 (OH), 1610 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.44 (m, 2H, H-5′,5″), 3.97 (m, 2H, H-3′,4′), 4.29 (t, J = 9.4 Hz, 1H, H-2′), 4.61 (t, J = 6.2, 1H, OH), 5.16 (m, 1H, OH), 5.25 (m, 1H, OH), 5.74 (d, J$_{1′,2′}$ = 9.8 Hz, 1H, H-1′), 7.32 (m, 3H, Ar-H), 7.37 (m, 3H, Ar-H), 7.40 (m, 2H, Ar-H), 7.77 (m, 2H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 62.41 (C-5), 64.66 (C-4), 68.98 (C-3), 71.30 (C-2), 88.75 (C-1), 129.12-143.87 (Ar-C), 154.78, 156.52, 157.89, 158.34 (4C=N). *Anal*. Calcd for C$_{21}$H$_{19}$N$_5$O$_4$S: C, 57.66; H, 4.38; N, 16.01. Found: C, 57.48; H, 4.29; N, 15.77.

General procedure for the synthesis of compounds 8a,b. To a well stirred solution of the respective monosaccharide (5 mmol) in water (1 mL), and glacial acetic acid (1 mL) was added 3-hydrazinyl-5,6-diphenyl-1,2,4-triazine (**3**) (1.32 g, 5 mmol) in ethanol (15 mL). The mixture was heated under reflux for 3 h and the resulting solution was concentrated and left to cool. The formed precipitate was filtered off, washed with water and ethanol, then dried and recrystallized from ethanol.

3-(2-D-Galactopentitolylidenehydrazinyl)-5,6-diphenyl-1,2,4-triazine (8a). This compound was obtained as white solid 1.81 g (85%), mp 197–198°C; IR (KBr) ν: 3478–3466 (OH),

3310 (NH), 1610 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.30–3.39 (m, 2H, H-6′,6″), 3.73 (m, 1H, H-5′), 4.12 (m, 1H, H-4′), 4.25 (t, J = 7.4 Hz, 1H, H-3′), 4.36 (dd, J = 7.4 Hz, J = 7.8 Hz, 1H, H-2′), 4.45 (m, 1H, OH), 4.48 (d, J = 6.4 Hz, 1H, OH), 5.19 (m, 1H, OH), 5.63 (t, J = 4.6 Hz, 1H, OH), 5.79 (t, J = 4.6 Hz, 1H, OH), 7.27 (m, 3H, Ar-H), 7.34 (m, 3H, Ar-H), 7.42 (m, 2H, Ar-H), 7.48 (d, 1H, $J_{1′,2′}$ = 7.8 Hz, H-1′), 7.73 (m, 2H, Ar-H), 9.94 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 62.10 (C-6′), 63.05 (C-5′), 69.21 (C-4′), 74.44 (C-2′), 75.71 (C-3′), 127.88–142.22 (Ar-C), 150.89 (C-1′), 152.608 (C-5), 153.57 (C-6), 156.92 (C-3). *Anal*. Calcd for C$_{21}$H$_{23}$N$_5$O$_5$: C, 59.29; H, 5.45; N, 16.46. Found: C, 59.11; H, 5.30; N, 16.39.

5,6-Dipheny-3-(2-D-ribotetritolylidenehydrazinyl)-1,2,4-triazine (8b). This compound was obtained as white solid, 1.64 g (83%), mp 195–196°C; IR (KBr) ν: 3475–3448 (OH), 3325 (NH), 1612 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.49–3.53 (m, 2H, H-5′,5″), 3.73 (m, 1H, H-4′), 4.12 (m, 1H, H-3′), 4.36 (dd, J = 7.4 Hz, J = 7.8 Hz, 1H, H-2′), 4.45 (m, 1H, OH), 4.88 (d, J = 6.4 Hz, 1H, OH), 5.60 (t, J = 4.6 Hz, 1H, OH), 5.72 (t, J = 4.6 Hz, 1H, OH), 7.28 (m, 3H, Ar-H), 7.36 (m, 3H, Ar-H), 7.42 (m, 2H, Ar-H), 7.52 (d, 1H, $J_{1′,2′}$ = 7.8 Hz, H-1′), 7.73 (m, 2H, Ar-H), 9.98 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 62.22 (C-5′), 63.15 (C-4′), 69.32 (C-3′), 74.56 (C-2′), 127.882–142.28 (Ar-C), 150.44 (C-1′), 152.49 (C-5), 153.50 (C-6), 156.38 (C-3). *Anal*. Calcd for C$_{20}$H$_{21}$N$_5$O$_4$: C, 60.75; H, 5.35; N, 17.71. Found: C, 60.65; H, 5.29; N, 17.58.

2-Acetyl-3-(O-acetylsugar)-6,7-diphenyl-2H,3H-1,2,4-triazo-lino[4,3-b][1,2,4]triazine (9a,b). General procedure: A solution of **8a,b** (1 mmol) in acetic anhydride (5 mL) was boiled under reflux for 1 h. The resulting solution was poured onto crushed ice, and the product that separated out was filtered off, washed with sodium hydrogen carbonate and water and then dried well.

2-Acetyl-3-(2,3,4,5,6-penta-O-acetyl-D-galactopentitolyl)-6,7-diphenyl-2H,3H-1,2,4-triazolino[4,3-b][1,2,4]triazine (9a). This compound was obtained as white solid, 0.59 g (78%), mp 139–140°C; IR (KBr) ν: 1742 (C=O), 1668 (C=O), 1610 (C=N) cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.85, 1.98, 2.03, 2.10, 2.18, 2.23 (6s, 18H, 6CH$_3$), 4.16 (dd, J = 11.4 Hz, J = 2.8 Hz, 1H, H-5′), 4.21 (dd, J = 11.4 Hz, J = 3.2 Hz, 1H, H-5″), 5.14 (m, 1H, H-4′), 5.26 (dd, J = 6.5 Hz, J = 7.4 Hz, 1H, H-3′), 5.52 (dd, J = 7.4 Hz, J = 7.2 Hz, 1H, H-2′), 5.71 (t, J = 7.2 Hz, 1H, H-1′), 5.77 (d, J = 7.6 Hz, 1H, tria-zole-H), 7.29 (m, 3H, Ar-H), 7.34 (m, 3H, Ar-H), 7.42 (m, 2H, Ar-H), 7.74 (m, 2H, Ar-H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 20.34, 20.52, 20.58, 20.67, 20.75, 29.69 (6CH$_3$), 62.90 (C-5′), 65.38 (C-4′), 68.41 (C-3′), 69.7 (C-2′), 71.15 (C-1′), 92.12 (*C*—N-Ac), 127.82-142.44 (Ar-C), 152.47, 153.55, 156.27 (3C=N), 169.12, 169.77, 170.14, 170.48, 170.78, 171.05 (6CO). *Anal*. Calcd for C$_{33}$H$_{35}$N$_5$O$_{11}$: C, 58.49; H, 5.21; N, 10.33. Found: C, 58.31; H, 5.15; N, 10.29.

2-Acetyl-3-(2,3,4,5-tetra-O-acetyl-D-ribotetritolyl)-6,7-diphenyl-2H,3H-1,2,4-triazolino[4,3-b][1,2,4]triazine (9b). This compound was obtained as white solid, 0.48 g (75%) mp 141–142°C; IR (KBr) ν: 1738 (C=O), 1670 (C=O), 1605 (C=N) cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.86, 1.97, 2.03, 2.12, 2.28 (5s, 15H, 5CH$_3$), 4.18 (dd, J = 11.2 Hz, J = 2.8 Hz, 1H, H-4′), 4.24 (dd, J = 11.2 Hz, J = 3.4 Hz, 1H, H-4″), 5.15 (m, 1H, H-3′), 5.25 (dd, J = 6.8 Hz, J = 7.2 Hz, 1H, H-2′), 5.54

(t, J = 7.2 Hz, 1H, H-1′), 5.75 (d, J = 7.4 Hz, 1H, triazole-H), 7.30 (m, 3H, Ar-H), 7.33 (m, 3H, Ar-H), 7.44 (m, 2H, Ar-H), 7.78 (m, 2H, Ar-H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 20.32, 20.52, 20.64, 20.78, 29.70 (5CH$_3$), 62.90 (C-4′), 65.38 (C-3′), 68.41 (C-2′), 71.18 (C-1′), 92.24 (*C*—N-Ac), 128.12–143.45 (Ar-C), 152.46, 153.58, 156.25 (3C=N), 169.14, 169.79, 170.12, 170.75, 171.10 (5CO). *Anal*. Calcd for C$_{30}$H$_{31}$N$_5$O$_9$: C, 59.50; H, 5.16; N, 11.56. Found: C, 59.40; H, 5.11; N, 11.39.

Ethyl 2-(5,6-diphenyl-1,2,4-triazin-3-ylsulphanyl)acetate (10). To a well stirred solution of **1** (2.65 g, 10 mmol) and dry potassium carbonate (1.38 g, 10 mmol) in acetone (15 mL) was added ethyl chloroacetate (1.22 g, 10 mmol). The reaction mixture was stirred at room temperature for 6 h and then poured on ice-cold water. The precipitated solid was filtered, washed with water and recrystallized from ethanol to give compound **10** as white crystals, 2.73 g (78%), mp 141–142°C IR (KBr) ν: 1738 (C=O), 1605 (C=N) cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.84 (t, J = 5.2 Hz, 1H, CH$_3$), 3.92 (q, J = 5.2 Hz, 2H, CH$_2$), 4.88 (s, 2H, CH$_2$), 7.30 (m, 3H, Ar-H), 7.36 (m, 3H, Ar-H), 7.51 (m, 2H, Ar-H), 7.77 (m, 2H, Ar-H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 16.44 (CH$_3$), 41.24, 48.14 (2CH$_2$), 127.75–141.18 (Ar-C), 152.14 (C-5), 153.24 (C-6), 156.28 (C-3), 169.14 (C=O). *Anal*. Calcd for C$_{19}$H$_{17}$N$_3$O$_2$S: C, 64.94; H, 4.88; N, 11.96. Found: C, 64.72; H, 4.69; N, 11.78.

2-(5,6-Diphenyl-1,2,4-triazin-3-ylsulphanyl)acetohydrazide (11). Hydrazine hydrate (0.5 g, 10 mmol) was added to a solution of **10** (3.51 g, 10 mmol) in ethanol (25 mL) and the reaction mixture was heated under reflux for 3 h. After cooling, the precipitated solid was filtered, washed with ethanol and recrystallized from ethanol to afford compound **11** as white crystals, 2.99 g (89%), mp 203–204°C; IR (KBr) ν: 3476 (NH$_2$), 3325 (NH), 1678 (C=O), 1610 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.88 (s, 2H, CH$_2$), 5.48 (s, 2H, NH$_2$), 7.29 (m, 3H, Ar-H), 7.32 (m, 3H, Ar-H), 7.50 (m, 2H, Ar-H), 7.75 (m, 2H, Ar-H), 10.05 (s, IH, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): 48.31 (CH$_2$), 127.70–141.12 (Ar-C), 152.65 (C-5), 153.48 (C-6), 156.64 (C-3), 169.10 (C=O). *Anal*. Calcd for C$_{17}$H$_{15}$N$_5$OS: C, 60.52; H, 4.48; N, 20.76. Found: C, 60.38; H, 4.32; N, 20.59.

3-[(1,3,4-Oxadiazolo-2(3H)-thion-5-yl)methylsulfanyl]-5,6-di-phenyl-1,2,4-triazine (12). To a solution of **11** (3.37 g, 10 mmol) in ethanol (20 mL) was added a solution of potassium hydroxide (0.56 g, 10 mmol) in water (2 mL) and carbon disulphide (4 mL). The solution was heated under reflux for 12 h. The solvent was evaporated and the residue was dissolved in water, filtered, and acidified with dilute hydrochloric acid. The precipitate was filtered off, washed with water, and recrystallized from ethanol as yellow crystals, 3.03 g (80%), mp 190–191°C; IR (KBr) ν: 3352 (NH), 1610 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.95 (s, 2H, CH$_2$), 7.28 (m, 3H, Ar-H), 7.30 (m, 3H, Ar-H), 7.33 (m, 2H, Ar-H), 7.71 (m, 2H, Ar-H), 12.78 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ 47.14 (CH$_2$), 127.72–141.25 (Ar-C), 152.57 (C-5), 153.37 (C-6), 155.15 (oxadiazole C-5), 156.49 (C-3), 171.15 (C=S). *Anal*. Calcd for C$_{18}$H$_{13}$N$_5$OS$_2$: C, 56.97; H, 3.45; N, 18.46. Found: C, 56.78; H, 3.41; N, 18.32.

3-{[2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosylsulfanyl)-1,3,4-oxadiazolo-2(3H)-thion-5-yl]methylsulfanyl}-5,6-diphenyl-1,2,4-triazine (13). To a solution of the thiol **12** (1.89 g, 5

mmol) in aqueous potassium hydroxide [(0.28 g, 5 mmol) in distilled water (15 mL)] was added a solution of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (**5a**) (2.05 g, 5 mmol) in acetone (20 mL). The reaction mixture was stirred at room temperature until reaction was judged complete by TLC using chloroform/methanol 99.5:0.5. The solvent was evaporated under reduced pressure at 40°C and the residue was washed with distilled water to remove potassium bromide formed. The product was dried, and recrystallized from ethanol as yellow crystals 2.83 g (80%), mp 128–130°C; IR (KBr) ν: 1748 (C=O), 1608 (C=N) cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.86, 1.88, 2.05, 2.11 (4s, 12H, 4CH$_3$), 4.05 (m, 1H, H-5′), 4.14 (dd, J = 11.4 Hz, J = 3.2 Hz, 1H, H-6′), 4.14 (dd, J = 11.4 Hz, J = 3.4, 1H, H-6″), 4.91 (t, J = 9.2 Hz, 1H, H-4′), 4.97 (s, 2H, CH$_2$), 5.17 (dd, J = 9.4 Hz, J = 9.2 Hz, 1H, H-3′), 5.35 (t, $J_{2,3}$ = 9.4 Hz, 1H, H-2′), 5.72 (d, $J_{1,2}$ = 9.8 Hz, 1H, H-1′), 7.29 (m, 3H, Ar-H), 7.37 (m, 3H, Ar-H), 7.38 (m, 2H, Ar-H), 7.78 (m, 2H, Ar-H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 19.32, 19.54, 20.16, 20.25 (4CH$_3$), 48.56 (CH$_2$), 62.89 (C-6′), 64.22 (C-4′), 68.64 (C-3′), 70.35 (C-2′), 71.81 (C-5′), 89.12 (C-1′), 127.25–143.48 (Ar-C), 152.22 (C-5), 153.45 (C-6), 155.35 (oxadiazole C-2), 156.48 (C-3), 158.14 (oxadiazole C-5), 169.77, 170.18, 170.59, 170.87 (4C=O). *Anal.* Calcd for C$_{32}$H$_{31}$N$_5$O$_{10}$S$_2$: C, 54.15; H, 4.40; N, 9.87. Found: C, 53.89; H, 4.29; N, 9.72.

3-{[2-(β-D-Glucopyranosylsulfanyl)-1,3,4-oxadiazolo-2(3H)-thion-5-yl]methylsulfanyl}-5,6-diphenyl-1,2,4-triazine (14). Dry gaseous ammonia was passed through a solution of the acetylated thioglycosides **14** (3.55 g, 5 mmol) in dry methanol (15 mL) at 0°C for 1 h, and then the mixture was stirred at 0°C for about 6 h. The solvent was evaporated under reduced pressure at 40°C to give a solid residue, which was recrystallized from ethanol as yellow crystals 2.16 g (80%), mp 192–193°C; IR (KBr) ν: 3478–3450 (OH), 1608 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.39 (m, 2H, H-6′,6″), 3.44 (m, 1H, H-5′), 3.91 (m, 2H, H-3′,4′), 4.28 (t, J = 9.2 Hz, 1H, H-2′), 4.72 (t, J = 6.4, 1H, OH), 4.84 (d, J = 6.6 Hz 1H, OH), 5.05 (s, 2H, CH$_2$), 5.22 (m, 1H, OH), 5.25 (m, 1H, OH), 5.74 (d, $J_{1′,2′}$ = 9.8 Hz, 1H, H-1′), 7.29 (m, 3H, Ar-H), 7.37 (m, 3H, Ar-H), 7.41 (m, 2H, Ar-H), 7.80 (m, 2H, Ar-H); ^{13}C NMR (DMSO-d_6, 75 Hz): δ 49.28 (CH$_2$), 61.49 (C-6′), 64.18 (C-4′), 68.88 (C-3′), 71.37 (C-2′), 72.18 (C-5′), 89.18 (C-1′), 129.22–143.68 (Ar-C), 152.42 (C-5), 153.76 (C-6), 155.86 (oxadiazole C-2), 156.94 (C-3), 158.92 (oxadiazole C-5). *Anal.* Calcd for C$_{24}$H$_{23}$N$_5$O$_6$S$_2$: C, 53.22; H, 4.28; N, 12.93. Found: C, 53.40; H, 4.22; N, 12.75.

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