Synthesis and Antitumor Activity of New Substituted Mercapto-1,2,4-Triazine Derivatives, Their Thioglycosides, and Acyclic Thioglycoside Analogs

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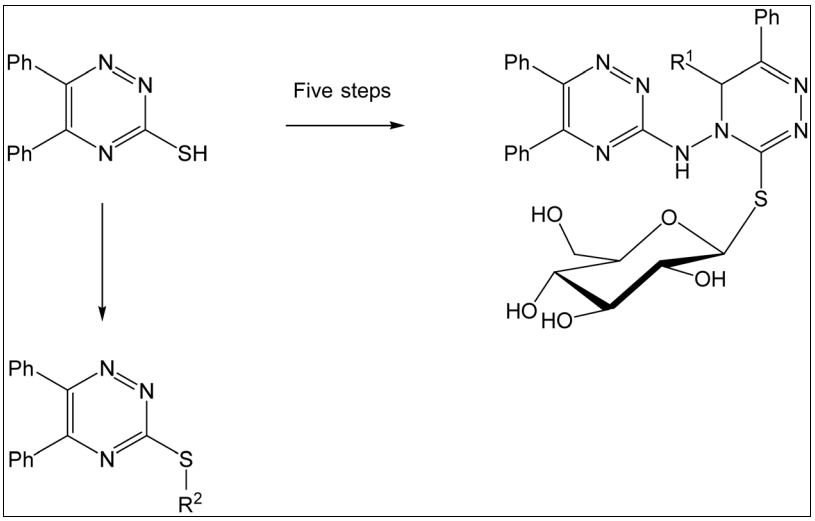

New 1,2,4-triazine and their derived thioglycoside derivatives were synthesized from 5,6-diphenyl-1,2,4-triazine-3-thiol. Furthermore, the corresponding acyclic thioglycoside analogs were synthesized from the corresponding mercapto derivatives and acyclic oxygenated alkyl halides. The newly synthesized compounds were evaluated for their antitumor activity and some of them showed high inhibition activities.

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INTRODUCTION

The structural diversity and biological importance of nitrogen containing heterocycles have made them attractive synthetic targets. Substituted 1,2,4-triazines represent an important class of nitrogen containing heterocycles. 1,2,4-Triazines and their derivatives occupy a pivotal position in modern medicinal chemistry because of their high-potential for biological activity [1]. 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], 2]. They have been reported to possess a broad spectrum of biological activities, including antifungal [3], [4], anti-HIV [5], anticancer [6], antiinflammatory [7], analgesic [8], and antihypertensive activities [9]. Besides this, triazines were used as herbicides, pesticides, and dyes [10,11]. Certain azanucleosides(6-azacytosine, 6-azauracil), structurally based on the 1,2,4-triazine nucleus, have displayed an impressive array of biological activities, among which antitumor [12,13], antiviral [14,15], antimicrobial [16], antiinflammatory [17], antimalarial [18], and antifungal [19] properties have been cited in the scientific literature. In addition, 6-azaisocytosine (e.g., 3-amino-1,2,4-triazin-5(2H)-one), an isosteric isomer of 6-azacytosine and 6-azauracil, is of great biological interest because of its resistance to deaminase, while azaribine the well-known antiviral drug is structurally associated with the 1,2,4-triazine moiety [20]. Various condensed 1,2,4-triazines found applications as pharmaceuticals, herbicides, pesticides, and dyes [21–26]. The 1,2,4-triazine core is a versatile synthetic platform to access a wide range of condensed heterocyclic ring systems *via* intramolecular Diels-Alder reactions with a vast array of dienophiles. In addition, the triazine ring system is a key component of commercial dyes, herbicides, insecticides, and more recently, pharmaceutical compositions [27]. Many 1,2,4-triazines have been screened *in vitro* supporting their anticancer activities [28]. Owing to the above facts and my interest in the attachment of carbohydrate moieties to newly synthesized heterocycles [29,30], the aim of the present article is the synthesis of new 1,2,4-triazine derivatives, and their thioglycoside and acyclic *S*-thioglycoside analogs in an ongoing search for new biologically active leads with potential antitumor activity.

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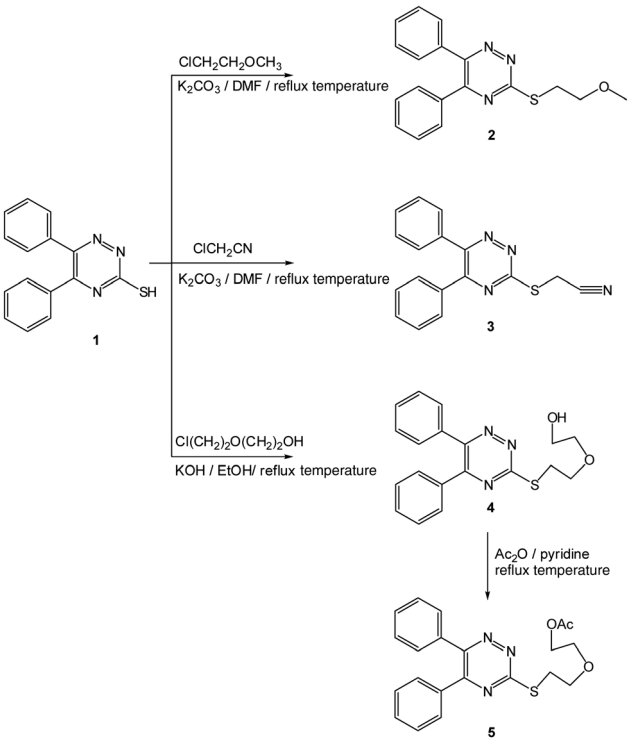
RESULTS AND DISCUSSION

The starting compound 5,6-diphenyl-1,2,4-triazine-3-thiol (**1**) was synthesized according to a previously reported procedure [31]. When compound **1** was alkylated with chloroethylmethylether in DMF and in presence of potassium carbonate at room temperature, 3-(2-methoxyethyl)thio derivative **2** was formed in 80% yield. Its ^{1}H NMR spectrum showed the signal of the OCH_3 group at δ 3.82 ppm in addition to the CH_2 signals each as triplet at δ 4.22 and 4.86 ppm. When the thiol derivative **1** was allowed to react with chloroacetonitrile under the same reaction conditions 2-(5,6-diphenyl-1,2,4-triazin-3-ylthio)acetonitrile (**3**) was formed. Its IR spectrum revealed the presence of a characteristic absorption band at 2204 cm^{-1} for the CN group and its ^{1}H NMR spectrum agreed with the assigned structure. Reaction of the thiol **1** with 2-(2-chloroethoxy)ethanol under reflux in ethanol in presence of potassium hydroxide afforded 2-(2-(5,6-diphenyl-1,2,4-triazin-3-ylthio)ethoxy) ethanol (**4**), which was acylated by means of acetic anhydride to produce the corresponding *O*-acetyl derivative **5**. The IR spectrum of **4** showed the absorption band for the hydroxyl group at 3359 cm^{-1}, which disappeared in the corresponding spectrum of **5** and instead an absorption band for the carbonyl group appeared. In addition, the ^{1}H NMR spectrum of the acetyl derivative **5** revealed the presence of the acetyl methyl signal at δ 2.11 ppm (see Experimental section) (Scheme 1).

Scheme 1

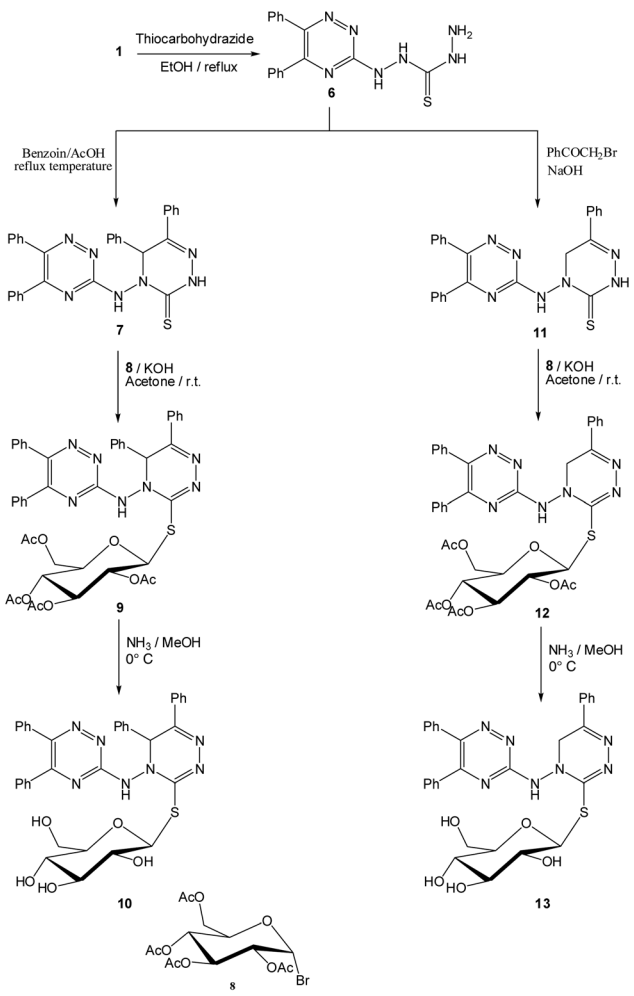


Refluxing compound **1** with thiocarbohydrazide in absolute ethanol afforded thiocarbohydrazide derivative **6**, which was reacted with benzoin in glacial acetic acid to afford 4-(5,6-diphenyl-1,2,4-triazin-3-ylamino)-5,6-diphenyl-4,5-dihydro-1,2,4-triazine-3(2H)-thione (**7**) [32]. Its ^{1}H NMR spectrum showed the signals of the aromatic protons corresponding to four phenyl groups in the range δ 7.21–7.85 ppm. Reaction of the latter thione **7** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**8**) gave the corresponding acetylated thioglycoside derivative **9**. The IR spectrum of the produced acetylated glucoside showed the C=O absorption bands at 1737 cm^{-1}. The ^{1}H NMR spectrum of the glucoside **9** showed signals corresponding to the acetyl–methyl signals and the sugar protons in addition to the aromatic protons. The anomeric proton appeared at δ 5.75 ppm with coupling constants J = 10.2 indicating the β-orientation of the thioglycosidic bond. The anomeric proton of β-*N*-glucosides having an adjacent C=S, was reported [33–37] to appear at higher chemical shift because of the anisotropic deshielding effect of the CS. The ^{13}C NMR spectra of **9** showed a signal at δ 88.95 ppm corresponding to the anomeric C-1 that 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 compound **9** was treated with methanolic ammonia at 0°C, the corresponding deacetylated thioglycoside derivative **10** was obtained in 73.9% yield. Its structure was confirmed by IR, NMR, and elemental analysis which agreed with the assigned structure (see Experimental section).

On the other hand, reaction of thiocarbohydrazide derivative **6** with phenacyl bromide in NaOH solution at reflux temperature afforded the corresponding derivative **11** with two 1,2,4-triazine rings in its structure. Its ^{1}H NMR spectrum showed signals corresponding to the CH_2 group in the dihydro 1,2,4-triazine ring at δ 5.25 ppm in addition to the aromatic protons signals for three phenyl groups. When compound **11** was reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**8**) it gave the corresponding acetylated thioglycoside derivative **12**. The ^{1}H NMR spectrum showed the acetyl methyl signals at δ 1.87–2.11 ppm in addition to the signals corresponding to the sugar protons signals at δ 4.04–5.74 ppm. The chemical shift value as well as the coupling constant of the anomeric proton indicated the thioglucosidic β-configuration. Treatment of the thioglucoside **12** with methanolic ammonia at 0°C produced the deacetylated thioglycoside derivative **13**. Its IR spectrum showed the hydroxyl absorption bands at 3466–3447 cm^{-1} and its ^{1}H NMR spectrum showed signals for the hydroxyl groups and the aromatic protons which agreed with the assigned structure, see Experimental section (Scheme 2).

Antitumor activity. The Antitumor activity of the newly synthesized compounds was investigated against Ehrlich

Scheme 2



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 kills the mice in about 20 days due to the distal metastasis. EAC is of mammary origin; since spontaneous breast cancer served as the original tumor from which an ascites variant was obtained [38].

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. 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 [39]. 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 earlier. 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 antitumor efficacy of the compounds against ESC cell lines was demonstrated compared to doxorubicin. The obtained results revealed that compounds **2, 4, 6, 10, 12,** and **13**

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 **13** and **4** displayed the highest activity with IC_{50} values 40, and 42 μg/mL, respectively followed by compound **12**.

From the antitumor activity results and structure activity relationship, it could be concluded that the attachment of glucopyranosyl sugar moiety to the substituted 1,2,4-triazine-3-thiol ring system resulted in higher activities. Furthermore, the 1,2,4-triazinyl thioglycoside with the free hydroxyl glucopyranosyl sugar moiety revealed higher activity than the corresponding acetylated analogs. Moreover, the [(glucopyranosyl)thio]-6-phenyl-1,2,4-triazine derivative displayed higher inhibition activity than the corresponding [(glucopyranosyl)thio]-5,6-diphenyl-1,2,4-triazine derivatives. The attachment of acyclic oxygenated hydroxyalkyl group to the 1,2,4-triazinyl thiol moiety revealed higher inhibition activity.

Table 1

The IC_{50} (μg/mL) of synthesized compounds.

Compound	IC_{50} (μg/mL)
2	57
4	42
6	54
10	56
12	49
13	40
Doxorubicin	38

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. NMR spectra were recorded on a varian Gemini 200 NMR Spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C or on a brucker Ac-250 FT spectrometer at 250 MHz for ^{1}H and at 62.9 MHz for ^{13}C. 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 F_{245}. Elemental analyses were performed at the Microanalytical data centre at Faculty of science, Cairo University, Egypt. The antitumor activity investigation of the synthesized compounds was carried out at the laboratory of biochemistry, radiation research and technology center, Cairo, Egypt.

3-(2-Methoxyethylthio)-5,6-diphenyl-1,2,4-triazine (2). To a solution of 5,6-diphenyl-1,2,4-triazin-3-thiol **1** (2.65 g, 10 mmol) and potassium carbonate (1.38 g, 10 mmol) in DMF (20 mL), was added chloroethylmethylether (20 mmol). The solution was stirred at room temperature for 5 h, the solvent was removed under reduced pressure and water (100 mL) was added, and the solid that formed was filtered off, and recrystallized from ethanol as yellow crystals, 2.6 g (80.4%), mp 120–122°C; IR (KBr) v: 3055 (CH), 1611 (C=N) cm^1; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.82 (s, 3H, OCH_3), 4.22 (t, 2H, *J* = 5.4 Hz, CH_2), 4.86 (t, 2H, *J* = 5.4 Hz, CH_2), 7.29 (m, 3H, Ar—H), 7.38 (m, 2H, Ar—H), 7.44 (m, 2H, Ar—H), 7.60 (d, 1H, *J* = 7.4 Hz, Ar—H), 7.75 (m, 2H, Ar—H). Anal. Calcd. for $C_{18}H_{17}N_3OS$: C, 66.85; H, 5.3; N, 12.99. Found: C, 66.57; H, 5.35; N, 12.77.

2-(5,6-Diphenyl-1,2,4-triazin-3-ylthio)acetonitrile (3). To a solution of **1** (2.65 g, 10 mmol) and potassium carbonate (1.38 g, 10 mmol) in DMF (20 mL), was added chloroacetonitrile (20 mmol). The solution was stirred at room temperature for 8 h, the solvent was removed under reduced pressure and water (100 mL) was added. The solid that formed was filtered off, and recrystallized from ethanol as yellow crystals, 2.2 g (72.3%), mp 125–127°C; IR (KBr) v: 3050 (CH), 2204 (CN), 1612 (C=N) cm^1; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.54 (s, 2H, CH_2), 7.26 (m, 3H, Ar—H), 7.34 (m, 2H, Ar—H), 7.44 (m, 2H, Ar—H), 7.59 (d, 1H, *J* = 7.4 Hz, Ar—H), 7.72 (m, 2H, Ar—H). Anal. Calcd. for $C_{17}H_{12}N_4S$: C, 67.08; H, 3.97; N, 18.41. Found: C, 67.0; H, 4.0; N, 18.44.

2-(2-(5,6-Diphenyl-1,2,4-triazin-3-ylthio)ethoxy)ethanol (4). To a solution of **1** (2.65 g, 10 mmol) and potassium hydroxide (0.0112 g, 20 mmol) in EtOH (20 mL), was added 2-(2-(chloroethoxy)ethanol (10 mmol). The solution was heated at reflux temperature for 3 h, the solvent was removed under reduced pressure and the solid that formed was filtered off, and recrystallized from ethylacetate as white crystals, 2.0 g (56.58%), mp 130–132°C. IR (KBr) v: 3359 (OH), 1614 (C=N) cm^1; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.79 (t, 2H, *J* = 6.2 Hz, CH_2), 4.24 (t, 2H, *J* = 5.6 Hz, CH_2), 4.57 (m, 2H, CH_2), 4.79 (t, 1H, *J* = 6.8 Hz, OH), 5.14 (t, 2H, *J* = 6.2 Hz, CH_2), 7.29 (m, 3H, Ar—H), 7.41 (m, 2H, Ar—H), 7.46 (m, 2H, Ar—H), 7.61 (d, 1H, *J* = 7.4 Hz, Ar—H), 7.82 (m, 2H, Ar—H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 41.25, 48.15, 52.82, 54.29 (4CH_2), 128.63–158.29 (15Ar—C). Anal. Calcd. for $C_{19}H_{19}N_3O_2S$: C, 64.57; H, 5.42; N, 11.89.Found: C, 65.0; H, 5.52; N, 12.0.

2-(2-(5,6-Diphenyl-1,2,4-triazin-3-ylthio)ethoxy)ethyl acetate (5). Compound **4** (0.01 mmol) in acetic anhydride (10 mL), was refluxed for 2 h, and the solvent was removed under reduced pressure. The solid that formed was filtered off, and recrystallized from ethanol as white crystals, 2.8 g (70.8%); mp 145–147°C; IR (KBr) v: 1735 (C=O), 1614 (C=N) cm^1; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.11 (s, 3H, CH_3), 3.82 (t, 2H, *J* = 6.2 Hz, CH_2), 4.25 (t, 2H, *J* = 5.6 Hz, CH_2), 4.57 (t, 2H, *J* = 6.2 Hz, CH_2), 5.16 (t, 2H, *J* = 5.6 Hz, CH_2), 7.25 (m, 3H, Ar—H), 7.40 (m, 2H, Ar—H), 7.52 (m, 2H, Ar—H), 7.69 (d, 1H, *J* = 7.4 Hz, Ar—H), 7.85 (m, 2H, Ar—H). Anal. Calcd. for $C_{21}H_{21}N_3O_3S$: C, 63.78; H, 5.35; N, 10.63. Found: C, 63.55; H, 5.65; N, 10.39.

***N′*-(5,6-Diphenyl-1,2,4-triazin-3-yl)thiocarbohydrazide (6).** A solution of 5,6-diphenyl-1,2,4-triazin-3-thiol **1** (2.65 g, 10 mmol) and thiocarbohydrazide (1.06 g, 0.01 mmol) in ethanol (20 mL) was refluxed for 4 h. The solution was allowed to cool at room temperature, the solid that formed was filtered off and recrystallized from benzene as white crystals, 2.6 g (77.06%); mp 130–132°C; IR (KBr) v: 3348–3217 (NH_2 and NH), 1610 (C=N) cm^1; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.71 (bs, 1H, NH), 5.91 (bs, 2H, NH_2), 6.07 (m, 1H, NH), 6.14 (m, 1H, NH), 7.20 (m, 3H, Ar—H), 7.33 (m, 2H, Ar—H), 7.40 (m, 2H, Ar—H), 7.52 (d, 1H, *J* = 7.4 Hz, Ar—H), 7.74 (m, 2H, Ar—H).

Anal. Calcd. for $C_{16}H_{15}N_7S$: C, 56.96; H, 4.48; N, 29.06. Found: C, 56.95; H, 4.50; N, 29.0.

4-(5,6-Diphenyl-1,2,4-triazin-3-ylamino)-5,6-diphenyl-4,5-dihydro-1,2,4-triazine-3(2H)-thione (7). A solution of thiocarbohydrazide derivative **6** (0.01 mmol) and benzoin (2.1 g 0.01 mmol) in glacial acetic acid (30 mL) was heated at reflux temperature for 3 h. The solution was allowed to cool and poured onto ice-cold water. The solid that formed was filtered off and recrystallized from ethylacetate as white crystals, 2.9 g (56.46%); mp 120–122°C; IR (KBr) v: 3072 (CH), 1610 (C=N) cm^1; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.29 (s, 1H, triazine H-5), 5.71 (bs, 1H, NH), 7.21 (m, 3H, Ar—H), 7.33–7.45 (m, 5H, Ar—H), 7.48–7.59 (m, 4H, Ar—H), 7.64–7.72 (m, 4H, Ar—H), 7.79 (m, 2H, Ar—H), 7.85 (m, 2H, Ar—H), 12.28 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 57.18 (triazine C-5), 128.23–158.11 (27Ar-C + triazine C-3,6), 172.81 (C=S). Anal. Calcd. for $C_{30}H_{23}N_7S$: C, 70.15; H, 4.51; N, 19.09. Found: C, 70.0; H, 4.50; N, 19.0.

***N*-{3-[(2,3,4,6-Tetra-*O*-acetyl-ß-D-glucopyranosyl)thio]-5,6-diphenyl-1,2,4-triazin-4(5*H*)-yl}-5,6-diphenyl-1,2,4-triazin-3-amine (9).** To a solution of the thione **7** (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 (**8**) (5 mmol) in acetone (20 mL). The reaction mixture was stirred at room temperature for 8 h. 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 solid, 3.0 g (71.1%); mp 98–100°C; IR (KBr) v: 1737 (C=O), 1610 (C=N) cm^1; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.86, 1.91, 2.04, 2.11 (4s, 12H, $4CH_3$), 4.05 (m, 1H, H-5′), 4.12 (dd, J = 11.4 Hz, J = 2.8 Hz, 1H, H-6′), 4.16 (dd, J = 11.4, 3.2 Hz, 1H, H-6′′), 4.91 (t, J = 9.3 Hz, 1H, H-4′), 5.18 (dd, J = 9.6 Hz, J = 9.3 Hz, 1H, H-3′), 5.29 (s, 1H, triazine H-5), 5.36 (t, J = 9.6 Hz, 1H, H-2′), 5.71 (bs, 1H, NH), 5.75 (d, $J_{1',2'}$ = 10.2 Hz, 1H, H-1′), 7.23 (m, 3H, Ar—H), 7.35–7.46 (m, 5H, Ar—H), 7.52–7.64 (m, 4H, Ar—H), 7.64–7.74 (m, 4H, Ar—H), 7.81 (m, 2H, Ar—H), 7.86 (m, 2H, Ar—H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.32, 19.50, 20.18, 20.27 ($4CH_3$), 57.24 (triazine C-5), 62.88 (C-6′), 64.37 (C-4′), 68.65 (C-3′), 70.39 (C-2′), 72.82 (C-5′), 88.95 (C-1′), 129.22–160.51 (27Ar-C + triazine C-3,6), 169.71, 170.15, 170.52, 170.80 (4C=O). Anal. Calcd. for $C_{44}H_{41}N_7O_9S$: C, 62.62; H, 4.90; N, 11.62. Found: C, 62.55; H, 4.90; N, 11.80.

***N*-{3-[(β-D-Glucopyranosyl)thio]-5,6-diphenyl-1,2,4-triazin-4(5*H*)-yl}-5,6-diphenyl-1,2,4-triazin-3-amine (10).** Dry gaseous ammonia was passed through a solution of the acetylated thioglycoside **9** (5 mmol) in dry methanol (15 mL) at 0°C for 1 h, and 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 a yellow solid, 2.5 g (73.9%); m.p 95–97°C. IR (KBr) v: 3470–3450 (OH), 1610 (C=N) cm^1; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.43 (m, 2H, H-6′,6′′), 3.48 (m, 1H, H-5′), 3.92 (m, 2H, H-3′,4′), 4.31 (t, J = 9.4 Hz, 1H, H-2′), 4.75 (t, J = 6.2, 1H, OH), 4.85 (d, J = 6.4 Hz, 1H, OH), 5.21 (m, 1H, OH), 5.25 (m, 1H, OH), 5.33 (s, 1H, triazine H-5), 5.74 (bs, 1H, NH), 5.80 (d, $J_{1',2'}$ = 10.2 Hz, 1H, H-1′), 7.24 (m, 3H, Ar—H), 7.35–7.49 (m, 5H, Ar—H), 7.54–7.68 (m, 4H, Ar—H), 7.70–7.75 (m, 4H, Ar—H), 7.81 (m, 2H, Ar—H), 7.88 (m, 2H, Ar—H). Anal. Calcd. for $C_{36}H_{33}N_7O_5S$: C, 63.99; H, 4.92; N, 14.51. Found: C, 63.85; H, 4.90; N, 14.50.

4-(5,6-Diphenyl-1,2,4-triazin-3-ylamino)-6-phenyl-4,5-dihydro-1,2,4-triazine3(2H)-thione (11). A solution of thiocarbohydrazide derivative **6** (3.37g 0.01 mmol) and phenacyl bromide (1.99 g, 0.01 mmol) in (10%) NaOH solution (50 mL) was heated at reflux temperature for 6 h. The solution was allowed to cool and acidified with (10%) HCl solution, the solid that formed was filtered off and recrystallized from ethanol as white crystals, 2.7 g (61.71%); m.p 95–97°C. IR (KBr) v: 3072 (CH), 1610 (C=N) cm^1; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.21 (s, 1H, CH_2), 5.73 (bs, 1H, NH), 7.21 (m, 3H, Ar—H), 7.35 (m, 2H, Ar—H), 7.48–7.52 (m, 3H, Ar—H), 7.64–7.72 (m, 3H, Ar—H), 7.80 (m, 2H, Ar—H), 7.85 (m, 2H, Ar—H), 12.36 (s, 1H, NH). Anal. Calcd. for $C_{24}H_{19}N_7S$: C, 65.88; H, 4.38; N, 22.41. Found: C, 65.80; H, 4.60; N, 22.50.

***N*-{3-[(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)thio]-6-phenyl-1,2,4-triazin-4(5*H*)-yl}-5,6-diphenyl-1,2,4-triazin-3-amine (12).** To a solution of the thione **11** (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 (**8**) (5 mmol) in acetone (20 mL). The reaction mixture was stirred at room temperature for 8 h. 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 a yellow solid, 2.0 g (52.13%); mp 103–105°C. IR (KBr) v: 1736 (C=O), 1612 (C=N) cm^1; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.87, 1.93, 2.05, 2.11 (4s, 12H, $4CH_3$), 4.04 (m, 1H, H-5′), 4.11 (dd, J = 11.4 Hz, J = 2.8 Hz, 1H, H-6′), 4.15 (dd, J = 11.4, 3.2 Hz, 1H, H-6′′), 4.90 (t, J = 9.3 Hz, 1H, H-4′), 5.16 (dd, J = 9.6 Hz, J = 9.3 Hz, 1H, H-3′), 5.25 (s, 2H, CH_2), 5.32 (t, J = 9.6 Hz, 1H, H-2′), 5.70 (bs, 1H, NH), 5.74 (d, $J_{1',2'}$ = 10.2 Hz, 1H, H-1′), 7.25 (m, 3H, Ar—H), 7.36 (m, 2H, Ar—H), 7.50–7.55 (m, 3H, Ar—H), 7.65–7.72 (m, 3H, Ar—H), 7.80 (m, 2H, Ar—H), 7.86 (m, 2H, Ar—H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.34, 19.51, 20.19, 20.27 ($4CH_3$), 56.94 (triazine C-5), 62.89 (C-6′), 64.37 (C-4′), 68.69 (C-3′), 70.44 (C-2′), 72.81 (C-5′), 89.16 (C-1′), 129.20–158.58 (21Ar-C + triazine C-3,6), 169.58, 170.02, 170.54, 170.60 (4C=O). Anal. Calcd. for $C_{38}H_{37}N_7O_9S$: C, 59.44; H, 4.86; N, 12.77. Found: C, 59.09; H, 4.90; N, 12.56.

***N*-{3-[(ß-D-Glucopyranosyl)thio]-6-phenyl-1,2,4-triazin-4(5H)-yl}-5,6-diphenyl-1,2,4-triazin-3-amine (13).** Dry gaseous ammonia was passed through a solution of the acetylated thioglycosides **12** (5 mmol) in dry methanol (15 mL) at 0°C for 1 h, and 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 a yellow solid, 2.5 g (83.4%); mp 100–102°C. IR (KBr) v: 3466–3447 (OH), 1615 (C=N) cm^1; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.45 (m, 2H, H-6′,6′′), 3.49 (m, 1H, H-5′), 3.94 (m, 2H, H-3′,4′), 4.31 (t, J = 9.4 Hz, 1H, H-2′), 4.74 (t, J = 6.2, 1H, OH), 4.84 (d, J = 6.4 Hz, 1H, OH), 5.23 (m, 1H, OH), 5.29 (m, 1H, OH), 5.22 (s, 2H, CH_2), 5.75 (bs, 1H, NH), 5.81 (d, $J_{1',2'}$ = 10.2 Hz, 1H, H-1′), 7.24 (m, 3H, Ar—H), 7.35–7.39 (m, 3H, Ar—H), 7.56 (m, 2H, Ar—H), 7.72–7.76 (m, 3H, Ar—H), 7.84 (m, 2H, Ar—H), 7.89 (m, 2H, Ar—H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ, 57.74 (triazine C-5), 61.25 (C-6′), 64.08 (C-4′), 68.730 (C-3′), 71.33 (C-2′), 73.14 (C-5′), 90.02 (C-1′), 130.11–159.88 (21Ar-C + triazine C-3,6). Anal. Calcd. for $C_{30}H_{29}N_7O_5S$: C, 60.09; H, 4.87; N, 16.35. Found: C, 60.01; H, 4.80; N, 16.28.

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