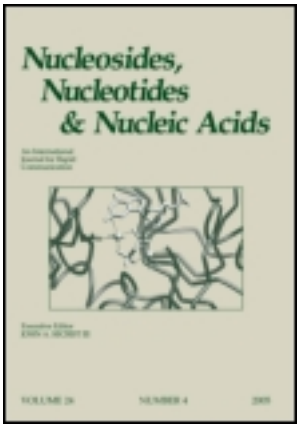

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Glycosylation, Sugar Hydrazones, and Antimicrobial Evaluation of Some 6-Substituted-1,2,4-Triazines

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GLYCOSYLATION, SUGAR HYDRAZONES, AND ANTIMICROBIAL EVALUATION OF SOME 6-SUBSTITUTED-1,2,4-TRIAZINES

A. A. El-Barbary, Y. A. Hafiz, and M. S. Abdel-Wahed

Chemistry Department, Faculty of Science, Tanta University, Tanta, Egypt

□ *Hydrazinolysis of 4-amino-6-[2-(4-methoxyphenyl)vinyl]-3-thioxo-3,4-dihydro-2H-[1,2,4] triazin-5-one* ***(1)*** *gave the corresponding hydrazino derivatives* ***(2)*** *Cyclocondensation of* ***(2)*** *with carbon disulfide furnished 8-amino-6-[2-(4-methoxyphenyl)vinyl]-3-thioxo-2,8-dihydro-3H-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7-one* ***(3)*** *which was treated with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide* ***(4)*** *in pyridine to give the corresponding N-glucosyl derivative* ***5****, which deblocked to give* ***8****. Compound* ***2*** *was reacted with isatin* ***9*** *and/or isatoic anhydride* ***10*** *to afford* ***11*** *and* ***12****. Treatment of* ***11*** *and* ***12*** *with* ***(4)*** *in pyridine gave the corresponding mono glucosyl derivatives* ***13*** *and* ***14****, which were deblocked by ammonia and afforded* ***15*** *and* ***16****. Condensation of* ***2*** *with aldoses afforded the corresponding cyclic products* ***17a-f*** *and with D-fructose furnished* ***18****. Acetylation of* ***17b, d*** *afforded the corresponding polyacetyl derivatives* ***19b,d****. Compound* ***2*** *condensed with some aromatic aldehydes in boiling methanol and gave* ***20a–f****. The newly synthesized compounds were tested as antimicrobial agents.*

Keywords Hydrazinolysis; glycosides; sugar hydrazones; antibacterial activity

INTRODUCTION

1,2,4-Triazine ring systems have been reported as potential biologically active agents.[1] As a kind of widely used biologically active compound, derivatives of triazinone compounds exhibit anticancer, antiulcer, and anti-inflammatory effects. In the agricultural field, this class of compounds shows activities, such as insecticides, herbicides, plant growth regulators, and increasing crop yields.[2,3] Moreover, 1,2,4-triazine derivatives have been investigated for some time for their effects on the central nervous system.[4–6] In the last decade, numerous fused 1,2,4-triazines have been synthesized and

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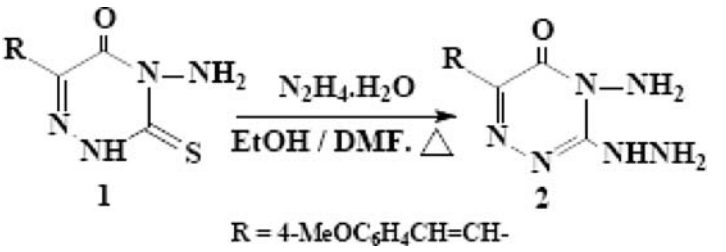


SCHEME 1 Synthesis of 3-hydrazino-1,2,4-triazine derivative.

screened in vitro, revealing their anti-HIV and anti-cancer activities[7–11] as well as selective weed control in wheat, antibacterial, antiviral, antifungal, anti-inflammatory, anticonvulsant activities, and carrageen induced edema inhibitor.[12–14]

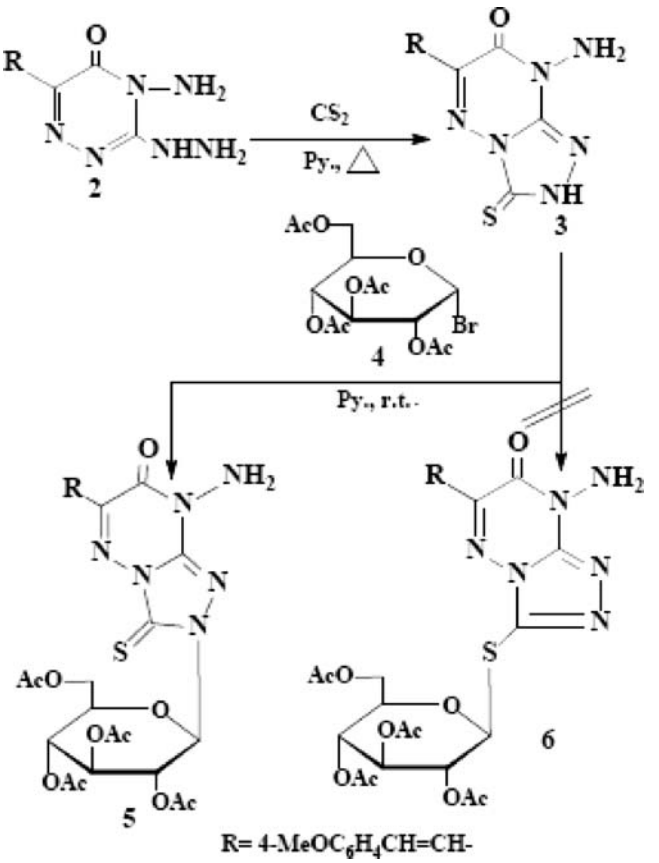
RESULTS AND DISCUSSION

Different carbohydrazides were found to be useful as medicaments especially in the treatment of inflammatory and autoimmune diseases, osteoarthritis, respiratory diseases, tumors, cachexia, cardiovascular diseases, fever, hemorrhage, and sepsis. Carbohydrazides and related compounds exhibited antifungal, antiviral, and bacteriostatic.[15] Accordingly, hydrazinolysis of compound **1** could be achieved by its treatment with a boiling mixture of hydrazine, MeOH/DMF to afford 4-amino-3-hydrazino-6-[2-(4-methoxyphenyl)vinyl]-4*H*-[1,2,4]triazin-5-one **(2)** (Scheme 1).

Cyclocondensation of **2** with carbon disulfide in pyridine at 80°C was achieved to afford 8-amino-6-[2-(4-methoxyphenyl)vinyl]-3-thioxo-2,8-dihydro-3*H*-[1,2,4] triazolo[4,3-b][1,2,4]triazin-7-one **(3)**. The structure of **3** was established with spectroscopic data. Its ^{1}H NMR spectrum showed a singlet at δ 8.35 assigned to NH proton, which appear at 3455 cm^{-1} in its IR spectrum (Scheme 2).

Direct glycosidation of compound **3** was reported to offer a convenient selective synthesis of the 2-glycosyl derivative.[16,17] So, coupling of **3** with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide **(4)** in pyridine afforded 8-amino-6-[2-(4-methoxyphenyl) vinyl]-3-thioxo-7,8-dihydro-2-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1,2,4-triazolo[4,3-b][1,2,4]triazine-7-one **(5)** as the sole product (TLC; Scheme 2).

The anomeric proton of similar β-N- glucosides having an adjacent C=S was reported to appear more down field than that for the β-S-glucosides due to the anisotropic deshielding effect of the C=S.[18–23] So the position of the anomeric proton at δ 5.25 with $J_{1'} = 8.93$ Hz confirmed the β-N- structure of compound **5** and excluded the possible isomeric β-S- structure of compound **6**. The mass spectrum of **5** showed the parent ion peak at m/z = 646 (M^+, 6.30%; Scheme 2).

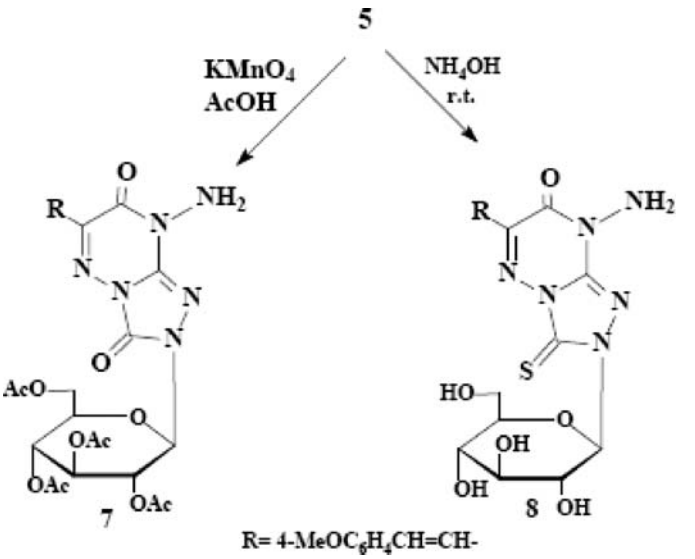


SCHEME 2 Coupling of **3** with acetyl-D-glucopyranosyl bromide derivative.

Oxidation of **5** with potassium permanganate at 25°C furnished 8-amino-6-[2-(4-methoxyphenyl)vinyl]-7,8-dihydro-2-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1,2,4-triazolo[4,3-b][1,2,4]triazine-3,7-dione **(7)**, whose IR spectrum showed (2 C=O) at 1600 and 1680 cm^{-1} (Scheme 3).

Deblocking of **5** was achieved by its treatment with ammonia solution at r.t to afford 8-Amino-6-[2-(4-methoxyphenyl)vinyl]-3-thioxo-2-(β-D- glucopyranosyl)-2,8-dihydro-3*H*-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7-one **(8)**. Its ^{1}H NMR spectrum showed a doublet at δ 5.19 ppm assigned to the anomeric proton of the glucose moiety with $J_{1'} = 9.13$ Hz according to a diaxial orientation of $H_{1'}$ and $H_{2'}$ protons, which confirmed its β-configuration[24] (Scheme 3).

The Schiff bases of isatin were investigated for their pharmaceutical properties[25] and Isatoic anhydride possesses some synthetic potential in this respect due to its ability to undergo various cyclization reactions.[26] Thus, condensation of **2** with isatin **9** and/or isatoic anhydride **10** in anhydrous boiling dioxane furnished 3-({4-amino-6-[2-(4-



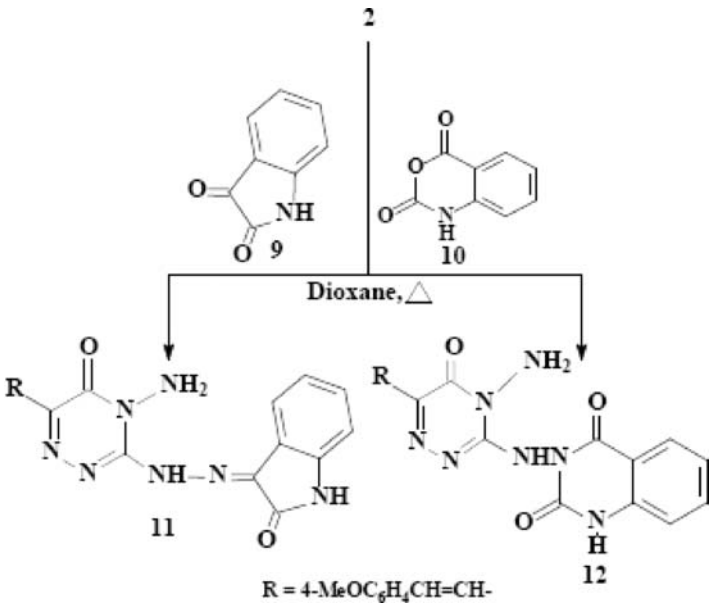
SCHEME 3 Oxidation of compound **5**.

methoxyphenyl)vinyl]-5-oxo-4,5-dihydro[1,2,4]triazin-3-yl} hydrazono)-1,3-dihydro-indol-2-one **(11)** and 3-{4-amino-6-[2-(4-methoxyphenyl)vinyl]-5-oxo-4,5-dihydro[1,2,4]triazin-3-ylamino}-1*H*-quinazoline-2,4-dione **(12)**, respectively (Scheme 4). Compounds **11** and **12** were elucidated by spectroscopic data. Thus, infrared (IR) spectrum of **11** showed, (2 CO) bands at 1613 and 1716 cm^{-1} and ^1H NMR spectrum showed a doublet (2H, 2 NH) at 8.45 ppm. The mass spectrum of **11** showed the parent ion peak at m/z = 403 (M^+, 100%).

Similarly, IR spectrum of **12** showed, (3 CO) bands at 1500, 1595, and 1640 cm^{-1} and its ^1H NMR spectrum showed a singlet (2H, 2 NH) at 6.18 ppm. In addition, its mass spectrum showed the parent ion peak at m/z = 419 (M^+, 17.20%; Scheme 4).

Coupling compounds **11** and/or **12** with **(4)** in pyridine at room temperature gave 6-[3-({4-amino-6-[2-(4-methoxyphenyl)vinyl]-5-oxo-4,5- dihydro[1,2,4]triazin-3-yl} hydrazono)-1-(2,3,4,6-tetra-O-acetyl-β-D- glucopyranosyl)-2,3-dihydroindole-2-one **(13)** and 6-(3-{4-amino-6-[2-(4-methoxyphenyl)vinyl]-5-oxo-4,5-dihydro[1,2,4] triazin-3-ylamino}-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1*H*-quinazoline-2,4-dione **(14)**, respectively. The ^1H NMR spectra of **13** and **14** showed the position of the anomeric protons at δ 4.25 and 4.67 with $J_{1'} = 9.35$ and 9.59 Hz confirmed the β-N- structure of **13** and **14** in addition to the presence of OAc groups at the range 2.09–2.58 ppm. Their IR spectra showed bands at the range 1748–1750 cm^{-1} (OAc; Scheme 5).

Deblocking of **13** and/or **14** was achieved by their treatment with ammonia solution at room temperature to afford 3-({4-Amino- 6-[2-(4-



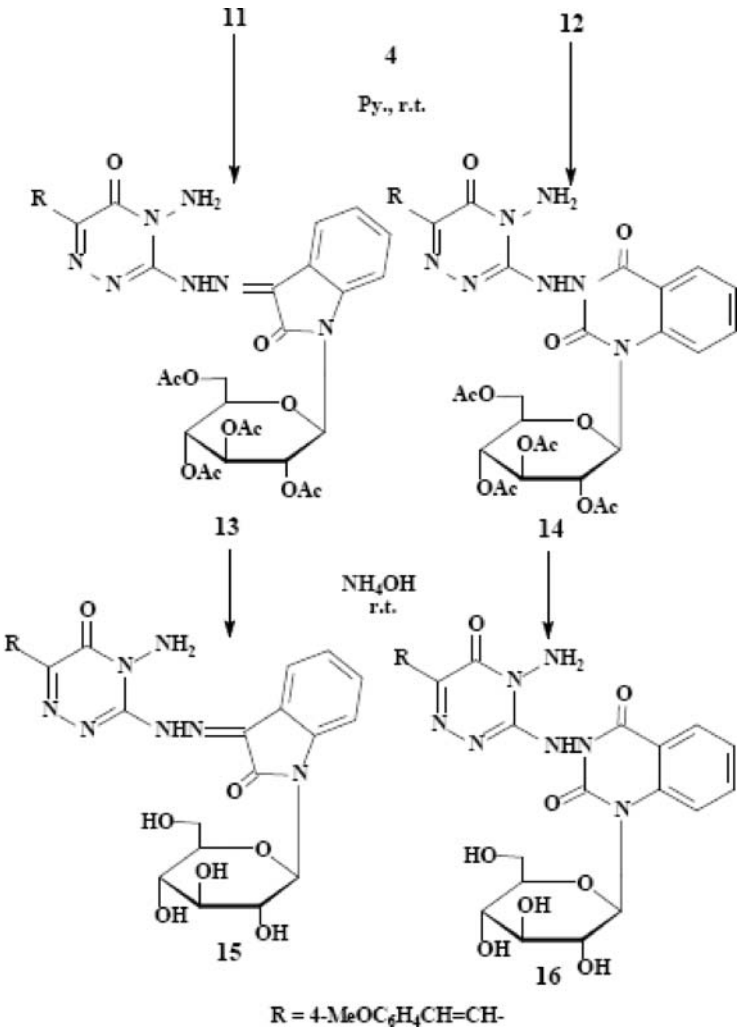
SCHEME 4 Condensation of **2** with isatin and/or isatoic anhydride.

methoxyphenyl)vinyl]-5-oxo-4,5-dihydro[1,2,4] triazin -3-yl}hydrazono) - 1 - (β-D-glucopyranosyl)-1,3-dihydroindol-2-one **(15)** and 3-4- Amino-6-[2-(4-methoxyphenyl)vinyl]-5-oxo-4,5-dihydro[1,2,4] triazin-3-ylamino}-1-(β-D-glucopyranosyl)-1*H*-quinazoline-2,4-dione **(16)**, respectively (Scheme 5). The ^{1}H NMR spectra of **15** and **16** showed the position of the anomeric protons at δ 4.82 and 4.80 ppm with $J_{1'} = 9.18$ and 9.23 Hz confirmed the β-N-structure of **15** and **16** in addition to the presence of (OH) groups at the range 3.38–3.97 ppm. Their IR spectra showed bands at the range 3396–3746 cm^{-1} (OH) (Scheme 5).

Compound **2** was reacted with some aldoses namely, D-glucose, D-galactose, D-mannose, D-ribose, L-arabinose and/or D-xylose in anhydrous boiling dioxane to yield the corresponding sugar hydrazones 4-amino-6-[2-(4-methoxyphenyl)vinyl]-3-[N′-(polyhydroxyhexylidene)hydrazinyl]-4H-[1,2,4]triazin-5-one **17a–f** (Scheme 6).

The structure of compounds **17a–f** was confirmed by spectral evidences. The ^{1}H NMR spectra showed structure **17a–f** fitted with the recorded data. For example, the ^{1}H NMR spectrum of **17a** showed a signal at 5.72 ppm (1H) corresponded to (NH) proton and a signal at 7.69 ppm (1H) corresponded to CH=N. The ^{1}H NMR spectra of **17b–f** showed similar patterns to that discussed above (Scheme 6).

Similarly, compound **2** reacted with D-fructose under the same reaction conditions to give 4-amino-6-[2-(4-methoxyphenyl)vinyl]-3-[N′-(2,3,4,5-

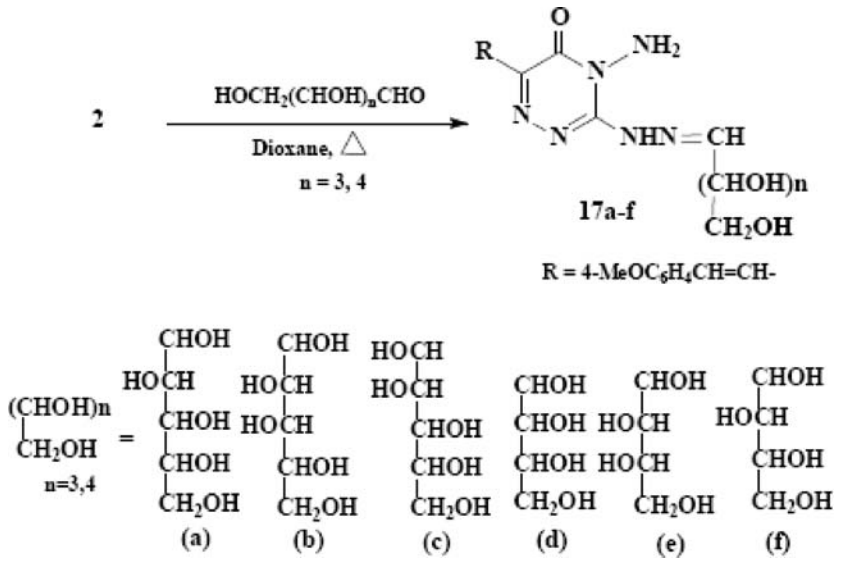


SCHEME 5 Coupling of **11** and/or **12** with acetyl-D-glucopyranosyl bromide derivative.

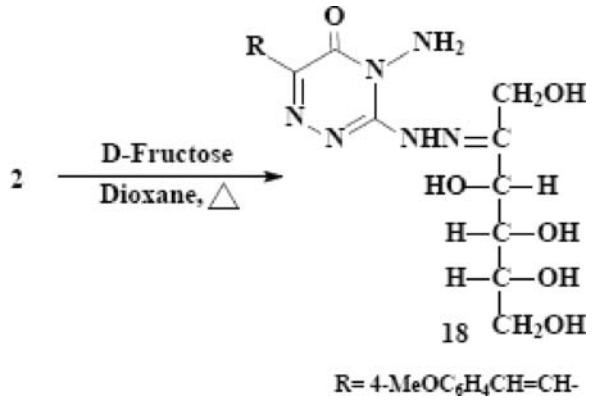
tetrahydroxy-1-hydroxymethylpentylidene)hydrazine]-4H-[1,2,4]triazin-5-one **(18)** (Scheme 7).

Acetylation of the sugar hydrazones **17b**,**d** with acetic anhydride in anhydrous pyridine at room temperature afforded the polyacetyl derivatives **19b**,**d** (Scheme 8). The ^{1}H NMR spectra of the products **19b**,**d** confirmed the presence of OAc groups in addition to the NAc group. Their IR spectra showed bands at 1630–1670 (NAc) and 1684–1746 cm^{-1} (OAc).

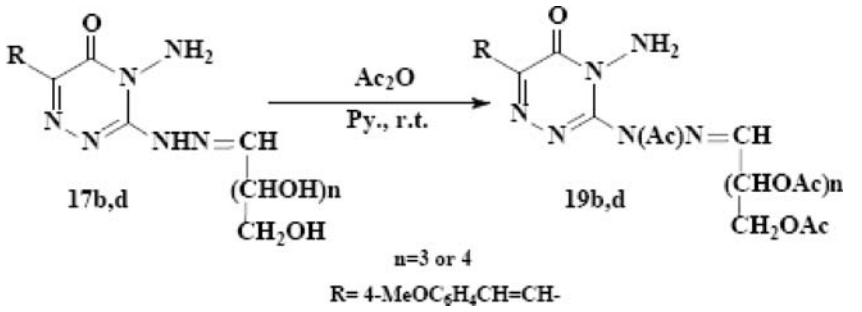
Compound **2** condensed with some aromatic aldehydes in boiling methanol and gave the corresponding hydrazones **20a–f**. Their structures could be assigned as two tautomeric forms **i** and **ii**. Both tautomers were observed in the ^{1}H NMR spectra where the signals correspond to the



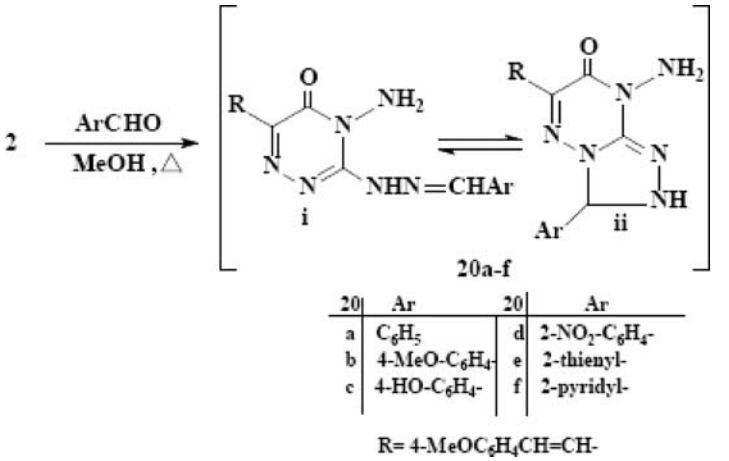
SCHEME 6 Condensation of **2** with some aldoses.



SCHEME 7 Reaction of **2** with D-fructose.



SCHEME 8 Acetylation of **17b,d**.



SCHEME 9 Condensation of **2** with some aldehydes.

CH—NH and CH=N groups are all present. This indicates the presence of a ring-chain tautomerism and the two tautomers coexist in a dynamic equilibrium (Scheme 9).

As an example, the ^{1}H NMR spectrum of compound **20a** showed a signal at 5.42 ppm corresponds to NH_2 protons and a signal at 10.41 ppm corresponds to CH=N proton. Its IR spectrum showed a sharp band at 3238 cm^{-1} attributed to the presence of NH_2 group.

BIOLOGICAL ACTIVITY

The newly synthesized compounds were screened for their in *vitro* antibacterial activities using the cut plug method[27] against the gram positive bacteria (*Bacillus subtilius* and *Staphylococcus aureus*) and the gram negative bacteria (*Escherichia coli, Salmonella typhae,* and *Klebsilla sp.*) and antifungal activity against yeast (*Candida albicans*) using Chloramophenicol and Streptomycin as standard drugs. The results are summarized and illustrated in Table 1.

The results revealed that most of the tested compounds showed antibacterial or/and antifungal (anticandidal) activity with varying magnitudes. The zone of inhibition above 7 mm in diameters was taken as a positive result.

Compounds **17a–f** and **18** showed low antimicrobial activities, except **17c**. The effect differed according to the presence of polyhydroxy side chain.

Compound **20e** showed only antibacterial but not antifungal activity. On the other hand, compound **20f** showed the highest antibacterial and antifungal effect may be due to the presence of a pyridyl ring.

TABLE 1 Diameters of inhibition zones (mm) of newly synthesized triazines against different test bacteria on nutrient agar and yeast after 24 hours by the cut-plug method on nutrient agar at 35–37°C

	Tasted organisms					
Cpd.	*Escherichia coli*	*Bacillus subtilus*	*Staphylococcus aurus*	*Salmonella typhae*	*Klebsilla sp.*	*Candida albicans*
Chloramophenicol (30 μgm)	20	20	38	—	23	—
Streptomycin (10 μgm)	14	23	12	—	11	—
(1)	12	—	—	10	12	10
(2)	10	20	15	10	20	25
(3)	17	20	25	17	17	25
(5)	17	17	—	13	15	20
(8)	17	10	—	17	17	15
(11)	—	—	—	—	—	—
(12)	9	7	—	—	—	10
(13)	10	—	10	—	—	—
(14)	—	—	—	—	—	—
(15)	—	9	—	—	15	10
(16)	10	9	—	—	10	15
(17a)	15	13	11	13	12	13
(17b)	13	12	12	11	—	12
(17c)	—	—	—	—	—	—
(17d)	15	20	15	15	15	15
(17e)	—	—	10	—	—	11
(17f)	—	—	—	13	—	12
(18)	17	8	20	10	13	20
(19b)	15	17	18	13	15	10
(19d)	—	—	—	15	—	15
(20a)	—	—	—	—	—	—
(20b)	—	—	—	—	—	—
(20c)	—	—	—	—	—	—
(20d)	8	—	—	—	—	8
(20e)	10	12	11	10	—	—
(20f)	40	35	25	45	35	40

EXPERIMENTAL

All melting points are uncorrected and performed by the open capillary melting point apparatus. Microanalyses were performed by Microanalysis Unit, Faculty of Science, Tanta University, Egypt. IR spectra were recorded with a Perkin-Elmer spectrometer (Perkin-Elmer, Waltham, MA, USA). The NMR spectra were recorded on a Bruker 300 MHz and Bruker 200 MHz spectrometer (Bruker, Bellerica, MA, USA) using TMS as an internal standard, DMSO and $CHCl_3$ as solvents. Mass spectra (MS) were recorded using electron ionization (E.I.) on a Varian Mat 311A spectrometer.

Compound 1 was prepared according to literature method.[28]
Compound 2 was prepared according to literature method.[29]

8-Amino-6-[2-(4-methoxyphenyl)vinyl]-3-thioxo-2,8-dihydro-3*H* [1,2,4]triazolo [4,3-b][1,2,4]triazin-7-one (3)

Compound **2** (2.74 g, 0.01 mol) and carbon disulfide (10 ml) in anhydrous pyridine (25 ml) was refluxed for 5 hours (TLC). The solvent was removed under vacuo and the residue was refluxed for 1 hour in acetic acid and cooled, the solid product formed was filtered off, and recrystallized from DMF/EtOH to give compound **3**. (72.8%); m.p. 151–152°C; **IR (KBr)**, 1601 (CN), 2933 (CH), 3455(NH) cm^{-1}; **^{1}H NMR** (DMSO-d_6): δ 3.75 (s, 3H, CH_3O-4), 3.82 (s, 2H, NH_2), 7.11–7.93 (m, 6H, H_{arom}), 8.35 (s, 1H, NH).

Anal. For $C_{13}H_{12}N_6O_2S$ Calcd.: C, 49.36; H, 3.82; N, 26.57. Found: C, 49.33; H, 3.79; N, 26.48.

8-amino-6-[2-(4-methoxyphenyl)vinyl]-3-thioxo-7,8-dihydro-2-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1,2,4-triazolo[4,3-b][1,2,4]triazine-7-one (5)

To a suspension of compound **3** (3.16g, 0.01 mol) in anhydrous pyridine (15 ml), 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide **(4)** (4.1g, 0.01 mol) was added with stirring and cooling to 10°C over a period of 10 minutes. The stirring was continued at room temperature overnight (TLC). The reaction mixture was poured onto ice water. The solid obtained was filtered off, dried and recrystallized from DMF to afford **5**. (61%); m.p. 219–220°C; **MS:** m/z 646 (M^+, 6.30); **IR (KBr)**, 1603 (CN), 1640 (C = ON), 1783 (C = OO) cm^{-1}; **^{1}H NMR** (DMSO-d_6) δ 2.15, 2.27, 2.29, 2.37 (4s, 12H, 4Ac), 3.53 (s, 3H, OCH_3), 3.95 (dd, 1H, $J_{H\text{-}5'\text{-}H\text{-}4'} = 2.13$ Hz, $J_{H\text{-}5'\text{-}H\text{-}5''} = 11.23$ Hz, H-5′), 4.11 (t, 1H, $J = 2.33$ Hz, H-4′), 4.53 (dd, 1H, $J_{H\text{-}3'\text{-}H\text{-}4'} = 3.19$ Hz, $J_{H\text{-}3'\text{-}H\text{-}2'} = 10.00$ Hz, H-3′), 4.99 (dd, 1H, $(J_{H\text{-}2'\text{-}H\text{-}1'} + J_{H\text{-}2'\text{-}H\text{-}3'})/2 = 7.14$ Hz, H-2′), 5.25 (d, 1H, $J' = 8.93$, H-1′), 5.61 (s, 2H, NH_2),7.44–7.89 (m, 6H, H_{arm}).

Anal. For $C_{27}H_{30}N_6O_{11}S$ Calcd.: C, 50.15; H, 4.68; N, 12.75. Found: C, 50.07; H, 4.63; N, 13.00.

8-amino-6-[2-(4-methoxyphenyl)vinyl]-7,8-dihydro-2-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1,2,4-triazolo[4,3-b][1,2,4]triazine-3,7-dione (7)

To a solution of **5** (6.46 g, 0.01 mol) in glacial acetic acid (25 ml), a solution of potassium permanganate (0.3 g, 0.02 mol) in water (10 ml) was added gradually with stirring for 30 minutes. Stirring was continued for 5 hours at room temperature, and the mixture was then poured onto crushed ice. The resulting solid was collected and recrystallized from DMF to afford **7**. (65%); m.p. 232–235°C; **IR (KBr)**, 1600 and 1680 (2 CO), 2987 (CH), 3183 (NH_2) cm^{-1}.

Anal. For $C_{27}H_{30}N_6O_{12}$ Calcd.: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.22; H, 4.73; N, 13.09.

8-Amino-6-[2-(4-methoxyphenyl)vinyl]-3-thioxo-2-(β-D-glucopyranosyl)-2,8-dihydro-3*H*-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7-one (8)

Stirring of compound **5** (6.46 g, 0.01 mol) in ammonia solution (20 ml) overnight until the starting material was consumed (TLC). The solid obtained was filtered, dried and recrystallized from ethanol to afford **8.** (78%); m.p. 195–196°C; **IR (KBr)**, 1614 (CN), 3353 (NH_2), 3499 (OH) cm^{-1}; **^{1}H NMR** (DMSO-d_6) δ 3.71(s, 3H, OCH_3), 4.08–4.47 (m, 4H, 4OH), 4.55 (dd, 1H, J = 7.08 Hz, H-5′), 4.91 (d, 1H, J = 2.37 Hz, H-4′), 5.09 (d, 1H, J = 2.98 Hz H-3′), 5.19 (d, 1H, J = 9.13 Hz H-1′,2′), 5.28 (s, 2H, NH_2), 5.38 and 5.54 (s, 2H, H-1′, 2′), 7.68–8.23 (m,6H,H_{arm}).

Anal. For $C_{19}H_{22}N_6O_7S$ Calcd.: C, 47.69; H, 4.63; N, 17.44. Found: C, 47.55; H, 4.57; N, 17.44.

Reaction of 2 with Isatin and Isatoic Anhydride: Formation of 11 and 12

A mixture of **2** (2.74 g, 0.01 mol) and isatin or isatoic anhydride (0.01 mol) was refluxed in dioxane (25 ml) for 3–5 hours (TLC). The solvent was removed under vaccuo and the residue was recrystallized from DMF/water to give **11** and **12**, respectively.

3-({4-Amino-6-[2-(4-methoxyphenyl)vinyl]-5-oxo-4,5-dihydro[1,2,4] triazin-3-yl} hydrazono)-1,3-dihydro-indol-2-one (11). (96%); m.p. > 300°C; **MS**: m/z 403 (M^+, 100); **IR** (KBr), 1613 and 1716 (2CO), 3212 (NH_2), 3303 (NH) cm^{-1}; **^{1}H NMR** (DMSO-d_6) δ 3.42 (s, 3H, CH_3O-4), 5.67 (s, 2H, NH_2), 6.81 (t, 2H, J = 4.4 Hz, H_{arom}), 7.18 (t, 2H, J = 7.7 Hz, H_{arom}), 7.54 (d, 2H, J = 3.6 Hz, H_{arom}), 7.61 (q, 2H, J = 4.3 Hz, H_{arom}), 7.76 (d, 2H, J = 8.3 Hz, H_{arom}), 8.45 (d, 2H, 2NH), 10.59 (s, 1H, OH). Anal. For $C_{20}H_{17}N_7O_3$ Calcd.: C, 59.55; H, 4.25; N, 24.31. Found: C, 59.47; H, 4.17; N, 24.22.

3-{4-Amino-6-[2-(4-methoxyphenyl)vinyl]-5-oxo-4,5-dihydro[1,2,4] triazin-3-ylamino}-1H-quinazoline-2,4-dione (12). (80%); m.p. 284–286°C; **MS**: m/z 419 (M^+, 17.20); **IR (KBr)**, 1500, 1595 and 1640 (3CO), 3263 (NH_2), 3437 (NH) cm^{-1}; **^{1}H NMR** (DMSO-d_6) δ 3.45 (s, 3H, CH_3O-4), 5.23 (s, 2H, NH_2), 6.18 (s, 2H, 2NH), 7.25–7.78 (m, 10H, H_{arom}). Anal. For $C_{20}H_{17}N_7O_4$ Calcd.: C, 57.28; H, 4.09; N, 23.38. Found: C, 57.12; H, 4.19; N, 22.86.

Reaction of Compound 11 and/or 12 with (4): Formation of 13 and 14

To a suspension of compounds **11** and/or **12** (0.01 mol) in anhydrous pyridine (15 ml), **(4)** (4.1g, 0.01 mol) was added with stirring and cooling to 10°C over a period of 10 minutes. The stirring was continued at room temperature overnight (TLC). The reaction mixture was poured onto ice, and the solid obtained was filtered off, dried, and recrystallized from DMF to afford **13** and **14**.

6-[3-({4-amino-6-[2-(4-methoxyphenyl)vinyl]-5-oxo-4,5-dihydro[1,2,4] triazin-3-yl}hydrazono)-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-2,3-dihydroindole-2-one (13). (63%); m.p. 260–262°C; **IR (KBr)**, 1605 (CN), 1750 (C=OO), 3424 (NH) cm^{-1}; ^{1}**H NMR** (DMSO-d_6) δ 2.38, 2.43, 2.49, 2.58 (4s, 12H, 4Ac), 3.22 (s, 3H, CH_3O-4), 3.82 (s, 2H, NH_2), 4.11–4.25 (m, 7H, H_{pyran}, $J_{1'} = 9.35$ Hz), 6.99–7.23 (m, 4H, H_{arm}), 7.25–7.48 (m, 6H, H_{arm}), 8.23 (s, 1H, NH). Anal. For $C_{34}H_{35}N_7O_{12}$ Calcd.: C, 55.66; H, 4.81; N, 13.36. Found: C, 55.23; H, 4.79; N, 13.27.

6-(3-{4-amino-6-[2-(4-methoxyphenyl)vinyl]-5-oxo-4,5-dihydro[1,2,4] triazin-3-ylamino}-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1*H*-quinazoline-2,4-dione (14). (50%); m.p. 269–270°C; **IR (KBr)**, 1626 (CN), 1691 (C = O), 1748 (C = OO) cm^{-1}; ^{1}**H NMR** (DMSO-d_6) δ 2.09, 2.18, 2.23, 2.26 (4s, 12H, 4Ac), 3.14 (s, 3H,CH_3O-4), 3.92 (s, 2H, NH_2), 4.21, 4.36, 4.45, 4.59, 4.67 (5s, 7H, H_{pyran}, $J_{1'} = 9.59$ Hz), 6.60–6.88 (m, 10H, H_{arom}), 8.13 (s, 1H, NH). Anal. For $C_{35}H_{37}N_7O_{13}$ Calcd.: C, 55.04; H, 4.80; N, 12.84. Found: C, 55.11; H, 4.69; N, 12.77.

Deblocking of Compounds 13 and/or 14

Compounds **13** and/or **14** (0.01 mol) were stirred at room temperature with ammonia solution (20 ml) over night (TLC). The solid obtained was filtered off, dried and recrystalized from ethanol to afford **15** and **16**.

3-({4-Amino-6-[2-(4-methoxyphenyl)vinyl]-5-oxo-4,5-dihydro[1,2,4] triazin-3-yl}hydrazono)-1-(β-D-glucopyranosyl)-1,3-dihydroindol-2-one (15). (81%); m.p. 209–211°C; **IR (KBr)**, 1592 (CN), 3238 (NH_2), 3392 (OH) cm^{-1}; ^{1}**H NMR** (DMSO-d_6) δ 3.15 (s, 3H, CH_3O-4), 3.38–3.72 (m, 4H, OH), 4.08 (s, 2H, NH_2), 4.33, 4.42, 4.51, 4.69 and 4.82 (5s, 7H, H_{pyran}, $J_{1'} = 9.18$ Hz), 6.39–6.58 (m, 4H, H_{arom}), 6.61- 6.78 (m, 6H, H_{arm}),7.91 (s, 1H, NH). Anal. For $C_{26}H_{27}N_7O_8$ Cacld.: C, 55.22; H, 4.81; N, 17.34. Found: C, 54.98; H, 4.77; N, 17.14.

3-{4-Amino-6-[2-(4-methoxyphenyl)vinyl]-5-oxo-4,5-dihydro[1,2,4] triazin-3-ylamino}-1-(β-D-glucopyranosyl)-1*H*-quinazoline-2,4-dione (16). (89%); m.p. 225–226°C; **IR (KBr)**, 1595 (CN), 3398 (NH_2), 3746 (OH) cm^{-1}; ^{1}**H NMR** (DMSO-d_6) δ 3.24 (s, 3H, CH_3O-4), 3.57–3.97 (m, 4H, OH), 4.18 (s, 2H, NH_2), 4.41, 4.57, 4.61, 4.63 and 4.80 (5s, 7H, H_{pyran}, $J_{1'} = 9.23$

Hz), 6.71–6.89 (m, 4H, H_{arom}), 6.92–7.10 (m, 6H, H_{arom}),8.07 (s, 1H, NH). Anal. For $C_{27}H_{29}N_7O_9$ Calcd.: C, 54.45; H, 4.91; N, 16.46. Found: C, 54.33; H, 4.87; N, 16.18.

Condensation of 2 with Free Sugars: Formation of 17a–f and 18

General Procedure

A mixture of **2** (2.74 g, 0.01 mol) and aldohexoses, namely: D-glucose, D-galactose, D-mannose, aldopentoses, namely: D-ribose, L-arabinose, D-xylose, and/or fructose (0.01 mol) was refluxed in dioxane (20 ml) for 4 horus (TLC). After cooling, the precipitated solid was filtered off, washed with ethanol and recrystallized from DMF to afford **17a–f** and **18**.

4-Amino-6-[2-(4-methoxyphenyl)vinyl]-3-[N′-(2,3,4,5,6-pentahydroxyhexylidene)hydrazine]-4*H*-[1,2,4]triazin-5-one (17a). Using D-glucose in the general procedure gave **17a**. (82%); m.p. 195–196°C; **IR (KBr)**, 1600 (CN), 3208 (NH_2), 3425 (OH) cm^{-1}; ^{1}**H NMR** (DMSO-d_6) δ 2.51 (s, 3H, CH_3O-4), 3.67–3.75 (m, 4H, OH), 3.89 (s, 1H, OH), 4.35 (d, 2H, J = 5.36 Hz, H-5′), 4.49 (dd, 1H, J = 2.97 Hz, H-4′), 4.85 (dd, 1H, $J_{H\text{-}3'\text{-}H\text{-}4'}$ = 2.18 Hz, $J_{H\text{-}3'\text{-}H\text{-}2'}$ = 9.36 Hz, H-3′), 5.03 (t, 1H, J = 2.07, H-2′), 5.25 (s, 2H, NH_2), 5.68 (d, 1H, J = 2.78, H-1′), 5.72 (s, H, NH), 6.91–7.13 (m, 6H, H_{arom}), 7.69 (s, 1H, N = C<u>H</u>). Anal. For $C_{18}H_{24}N_6O_7$ Calcd.: C, 49.54; H, 5.54; N, 19.26. Found: C, 49.98; H, 5.72; N, 18.67.

4-Amino-6-[2-(4-methoxyphenyl)vinyl]-3-[N′-(2,3,4,5,6-pentahydroxyhexylidene)hydrazine]-4*H*-[1,2,4]triazin-5-one (17b). Using D-galactose in the general procedure gave 17b. (88%); m.p. 177–179°C; MS: m/z 436 (M^+, 16.30); **IR (KBr)**, 1590 (CN), 3248 (NH_2), 3368 (OH) cm^{-1}; ^{1}**H NMR** (DMSO-d_6) δ 2.95 (s, 3H, CH_3O-4), 4.11–4.58 (m, 5H, OH), 4.77 (m, 2H, H-5′), 5.38 (d, 1H, J = 2.76 Hz, H-4′), 5.61 (d, 1H, J = 2.99 Hz, H-3′), 5.91 (d, 1H, J = 2.33 Hz, H-2′), 6.11 (d, 1H, J = 2.93 Hz, H-1′), 6.35 (s, 2H, NH_2), 6.62 (s, H, NH), 7.38–7.63 (m, 6H, H_{arom}), 8.38 (s, 1H, N = C<u>H</u>). Anal. For $C_{18}H_{24}N_6O_7$ Calcd.: C, 49.54; H, 5.54; N, 19.26. Found: C, 49.38; H, 5.49; N, 19.16.

4-Amino-6-[2-(4-methoxyphenyl)vinyl]-3-[N′-(2,3,4,5,6-pentahydroxyhexylidene)hydrazine]-4*H*-[1,2,4]triazin-5-one (17c). Using D-mannose in the general procedure gave 17c. (76%); m.p. 183–185°C; MS: m/z 436 (M^+, 25.10); **IR (KBr)**, 1593 (CN), 3375(OH) cm^{-1}; ^{1}**H NMR** (DMSO-d_6) δ 2.74 (s, 3H, CH_3O-4), 3.67–4.22 (m, 5H, OH), 4.55 (d, 2H, J = 6.53 Hz, H-5′), 4.92 (d, 1H, J = 5.19 Hz, H-4′), 5.25 (dd, 1H, $J_{H\text{-}3'\text{-}H\text{-}4'}$ = 4.57 Hz, $J_{H\text{-}3'\text{-}H\text{-}2'}$ = 12.76 Hz, H-3′), 5.55 (t, 1H, J = 4.49, H-2′), 5.75 (d, 1H, J = 7.55, H-1′), 6.00 (s, 2H, NH_2), 6.42 (s, H, NH), 7.06–7.44 (m,6H,H_{arom}), 8.09 (s, 1H, N = C<u>H</u>). Anal. For $C_{18}H_{24}N_6O_7$ Calcd.: C, 49.54; H, 5.54; N, 19.26. Found: C, 49.43; H, 5.52; N, 19.20.

4-Amino-6-[2-(4-methoxyphenyl)vinyl]-3-[N′-(2,3,4,5-tetrahydroxypentylidene) hydrazine]-4*H*-[1,2,4]triazin-5-one (17d). Using D-ribose in the

general procedure gave 17d. (85%); m.p. 170–171°C; **IR (KBr)**, 1595 (CN), 3210 (NH_2), 3266 (OH) cm^{-1}; ^{1}**H NMR** (DMSO-d_6) δ 2.51 (s, 3H, CH_3O-4), 3.69–3.75 (m, 4H, 4OH), 4.42 (d, 1H, $J = 5.83$ Hz, H-4′), 4.61 (s, 1H, H-3′), 4.75 (t, $J = 4.86$ Hz, H-2′), 4.91 (d, 1H, $J = 3.19$ Hz, H-1′), 5.03 (s, H, NH), 5.24 (s, 2H, NH_2), 6.89–7.55 (m,6H, H_{arom}), 7.74 (s, 1H, N = CH). Anal. For $C_{17}H_{22}N_6O_6$ Calcd.: C, 50.24; H, 5.46; N, 20.68. Found: C, 50.11; H, 5.42; N, 20.60.

4-Amino-6-[2-(4-methoxyphenyl)vinyl]-3-[N′-(2,3,4,5-tetrahydroxypentylidene) hydrazine]-4*H*-[1,2,4]triazin-5-one (17e). Using L-arabinose in the general procedure gave **17e**. (60%); m.p. 200–201°C; **IR (KBr)**, 1597 (CN), 3319 (OH) cm^{-1}; ^{1}**H NMR** (DMSO-d_6) δ 2.78 (s, 3H, CH_3O-4), 3.65–4.08 (m, 4H, OH), 4.35 (t, 1H, $J = 6.85$ Hz, H-4′), 4.62 (t, 1H, $J = 5.27$ Hz, H-3′), 4.82 (d, 1H, $J = 3.49$ Hz, H-2′), 4.96 (d, 1H, $J = 5.99$ Hz, H-1′), 5.19 (s, H, NH), 5.51 (s, 2H, NH_2), 6.74–7.45 (m, 6H, H_{arom}), 7.68 (s, 1H, N = CH). Anal. For $C_{17}H_{22}N_6O_6$ Calcd.: C, 50.24; H, 5.46; N, 20.68. Found: C, 50.23; H, 5.41; N, 20.44.

4-Amino-6-[2-(4-methoxyphenyl)vinyl]-3-[N′-(2,3,4,5-tetrahydroxypentylidene) hydrazine]-4*H*-[1,2,4]triazin-5-one (17f). Using D-xylose in the general procedure gave **17f**. (79%); m.p. 172–173°C; **IR (KBr)**, 1601 (CN), 3267 (NH_2), 3449 (OH) cm^{-1}; ^{1}**H NMR** (DMSO-d_6) δ 2.50 (s, 3H, CH_3O-4), 3.41–3.78 (m, 4H, 4OH), 4.11 (d, 1H, $J = 5.66$ Hz, H-4′), 4.38 (m, 1H, H-3′), 4.75 (d, 1H, $J = 6.43$ Hz, H-2′), 5.02 (d, 1H, $J = 2.83$ Hz, H-1′), 5.23 (s, H, NH), 5.53 (s, 2H, NH_2), 6.92–7.55 (m, 6H, H_{arom}), 7.73 (s, 1H, N = CH). Anal. For $C_{17}H_{22}N_6O_6$ Calcd.: C, 50.24; H, 5.46; N, 20.68. Found: C, 50.19; H, 5.39; N, 20.53.

4-Amino-6-[2-(4-methoxyphenyl)vinyl]-3-[N′-(1,2,3,4-tetrahydroxy-1-hydroxy- methylpentylidene)hydrazine]-3*H*-[1,2,4]triazin-5-one (18). Using D-fructose in the general procedure gave **18**. (76%); m.p. 192–194°C; **IR (KBr)**, 1599 (CN), 3251 (NH_2), 3423 (OH) cm^{-1}; ^{1}**H NMR** (DMSO-d_6) δ 2.49 (s, 3H, CH_3O-4), 3.59–4.12 (m, 5H, OH), 4.84 (d, 1H, $J = 6.09$ Hz, H-4′), 5.11 (m, 1H, H-3′), 5.45 (d, 1H, $J = 5.77$ Hz, H-2′), 5.61 (d, 1H, $J = 4.53$ Hz, H-1′), 5.85 (s, 2H, NH_2), 6.42 (s, H, NH), 6.82–7.21 (m, 6H, H_{arom}). Anal. For $C_{18}H_{24}N_6O_7$ Calcd.: C, 49.54; H, 5.54; N, 19.26. Found: C, 49.36; H, 5.51; N, 19.07.

Acetylation of 17b,d: Formation of 19b,d

To a suspension of each of **17b**,**d** (0.01 mol) in anhydrous pyridine (10 ml), acetic anhydride (7 ml) was added dropwise with stirring and cooling to 10°C over a period of 10 minutes. The stirring was continued at room temperature overnight (TLC). The reaction mixture was poured onto ice water. The solid obtained was filtered off, dried, and recrystallized from ethanol to afford compounds **19b**,**d**.

Acetic acid 2,3-diacetoxy-4-(acetyl-{4-amino-6-[2-(4-methoxyphenyl) vinyl]-5-oxo-4,5-dihydro-[1,2,4]triazin-3-yl}hydrazono)-1-(1,2-diacetoxy-ethyl) butyl ester (19b). (65%); m.p. 214–215°C; **IR (KBr)**, 1609 (CN), 1630 (C = ON), 1684 (C = OO) cm^{-1}; **^{1}H NMR** (DMSO-d_6) δ 2.43–2.98 (6s, 18H, 6Ac), 3.68 (s, 3H, CH_3O-4), 4.43 (dd, 2H, J = 7.38 Hz, H-5′), 4.78 (t, 1H, J = 2.38 Hz, H-4′), 4.81 (dd, 1H, $J_{H\text{-}3'\text{-}H\text{-}4'}$ = 1.88 Hz, $J_{H\text{-}3'\text{-}H\text{-}2'}$ = 10.57 Hz, H-3′), 5.23 (dd, 1H, $(J_{H\text{-}2'\text{-}H\text{-}1'} + J_{H\text{-}2'\text{-}H\text{-}3'})/2$ = 1.77 Hz, H-2′), 5.45 (d, 1H, J' = 2.29, H-1′),5.51 (d, 1H, J = 2.73, H-3), 5.82 (s, 2H, NH_2), 6.80–7.60 (m, 6H, H_{arom}). Anal. For $C_{30}H_{36}N_6O_{13}$ Calcd.: C, 52.32; H, 5.27; N, 12.20. Found: C, 52.06; H, 5.13; N, 11.87.

Acetic acid 2,3-diacetoxy-1-acetoxymethyl-4-(acetyl-{4-amino-6-[2-(4-methoxyphenyl)vinyl]-5-oxo-4,5-dihydro-[1,2,4]triazin-3-yl}hydrazono)butyl ester (19d). (70%); m.p. 247–249°C; MS: m/z 616 (M^+, 2.30); **IR (KBr)**, 1614 (CN), 1670 (C = ON), 1746 (C = OO) cm^{-1}; **^{1}H NMR** (DMSO-d_6) δ 1.79–2.23 (m, 12H, 4C$\underline{H}_3$CO, 4Ac), 2.51 (s, 3H, NCOC$\underline{H}_3$), 3.68 (s, 3H, CH_3O-4), 3.45 (s, 2H, N$\underline{H}_2$), 4.91 (m, 1H, J = 5.73, H-5′), 5.22 (d, 1H, J = 3.18 Hz, H-4′), 5.81 (d, 1H, J = 4.54 Hz H-3′), 6.17 (s, 2H, H-1′, 2′), 6.22 (d, 1H, J = 3.33, H-3), 6.92–7.61 (m, 6H, H_{arom}). Anal. For $C_{27}H_{32}N_6O_{11}$ Calcd.: C, 52.60; H, 5.23; N, 13.63. Found: C, 52.49; H, 5.27; N, 13.61.

Condensation of Compound 2 with Aldehydes: Formation of 20a–f

A mixture of compound **2** (2.74 g, 0.01 mol) and some aromatic aldehydes, namely: benzaldehyde, 4-methoxybenzaldehyde, 4-hydroxybenzaldehyde, 2-nitrobenzaldehyde, thiophene-2-carboxaldehydem and/or pyridine-2-carboxaldehyde (0.01 mol) was refluxed in methanol (40 ml) for 2 hr (TLC) and cooled to room temperature the precipitated solid was filtered off, washed with ethanol and recrystallized from DMF/water mixture to afford compounds **20a–f**, respectively.

4-Amino-3-(N′-benzylidenehydrazino)-6-[2-(4-methoxyphenyl)vinyl]-4*H*-[1,2,4] triazin-5-one (20a taut i). (89%), m.p. 230–233°C, **IR (KBr)**, 1586 (CN), 2967 (CH), 3238 (NH_2), 3482 (NH) cm^{-1}; **^{1}H NMR** ($CDCl_3$): 3.81 (s, 3H, CH_3O-4), 5.42 (s, 2H, NH_2), 6.81 (d, 1H, J = 2.78 Hz, C$\underline{H}$-NH, *tautomer* ***ii***), 7.32 (s, 1H, NH), 7.40–7.82 (m, 9H, H_{arom}), 8.4 (s, 1H, H$\underline{N}$-N = C), 10.40 (s, 1H, C$\underline{H}$ = N). Anal. For $C_{19}H_{18}N_6O_2$ Calcd.: C, 62.97; H, 5.01; N, 23.19. Found: C, 62.83; H, 4.97; N, 23.27.

4-Amino-3-[N′-(4-methoxybenzylidene)hydrazino]-6-[2-(4-methoxyphenyl)vinyl]-4*H*-[1,2,4]triazin-5-one (20b taut i). (98%), m.p. 240–241°C, **IR (KBr)**, 1602 (CN), 2927 (CH), 3401 (NH) cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 3.81 (s, 6H, 2CH_3O-4), 5.40 (s, 2H, NH_2), 7.00 (m, 5H, H_{arom}), 7.12 (d, 1H, J = 2.59 Hz, C$\underline{H}$-NH, *tautomer ii*), 7.50–7.93 (m, 6H, H_{arom}), 8.43 (s, 1H, H$\underline{N}$-N = C), 10.22 (s, 1H, C$\underline{H}$ = N). Anal. For $C_{20}H_{20}N_6O_3$ Calcd.: C, 61.22; H, 5.14; N, 21.42. Found: C, 61.07; H, 5.11; N, 21.39.

4-Amino-3-[N′-(4-hydroxybenzylidene)hydrazino]-6-[2-(4-methoxyphenyl)vinyl]-4*H*-[1,2,4]triazin-5-one (20c taut i). (94%), m.p. 262–264°C, **IR (KBr)**, 1595 (CN), 2931 (CH), 3316 (NH) cm^{-1}; **^{1}H NMR** ($CDCl_3$): 3.82 (s, 6H, $2CH_3O$-4), 4.38 (s, 1H, OH), 5.73 (s, 2H, NH_2), 6.88–7.38 (m, 4H, H_{arom}), 7.50 (d, 1H, J = 2.49 Hz, CH-NH, *tautomer ii*), 7.18–7.99 (m, 6H, H_{arom}), 8.81 (s,1H,HN-N = C), 10.22 (s, 1H, CH = N). Anal. For $C_{19}H_{18}N_6O_3$ Calcd.: C, 60.31; H, 4.79; N, 22.21. Found: C, 60.19; H, 4.58; N, 22.18.

4-Amino-6-[2-(4-methoxyphenyl)vinyl]-3-[N′-(2-nitrobenzylidene) hydrazino]-4*H*-[1,2,4]triazin-5-one (20d taut i). (90%), m.p. 283–285°C, **IR (KBr)**, 1612 (CN), 1343 (NO_2), 3424 (NH) cm^{-1}; **^{1}H NMR** ($CDCl_3$): 3.84 (s, 3H, CH_3O-4), 5.51 (s, 2H, NH_2), 6.96 (m, 4H, H_{arom}), 7.13 (d, 1H, J = 2.33 Hz, CH-NH, *tautomer **ii***), 7.53–8.22 (m, 6H, H_{arom}), 8.83 (s, 1H, HN-N = C), 10.21 (s, 1H, CH = N). Anal. For $C_{19}H_{17}N_7O_4$ Calcd.: C, 56.02; H, 4.21; N, 24.07. Found: C, 55.58; H, 4.01; N, 24.64.

4-Amino-6-[2-(4-methoxyphenyl)vinyl]-3-(N′-thiophen-2-ylmethylene-hydrazino)-4*H*-[1,2,4]triazin-5-one (20e taut i). (93%), m.p. 255–256°C, **IR (KBr)**, 1601 (CN), 3085 (Ph), 3309 (NH_2), 3444 (NH) cm^{-1}; **^{1}H NMR** ($CDCl_3$): 3.22 (s, 3H, CH_3O-4), 5.71 (s, 2H, NH_2), 6.90 (d, 1H, J = 2.81 Hz, CH-NH, *tautomer ii*), 7.2 (m, 5H, H_{arom}), 7.51–7.80(m, 6H, H_{arom}), 8.8 (s, 1H, HN-N = C), 10.32 (s, 1H, CH = N). Anal. For $C_{17}H_{16}N_6O_2S$ Calcd.: C, 55.42; H, 4.38; N, 22.81. Found: C, 55.19; H, 4.27; N, 22.93.

4-Amino-6-[2-(4-methoxyphenyl)vinyl]-3-(N′-pyridin-2-ylmethylenehydrazino)-4H-[1,2,4]triazin-5-one (20f taut i). (93%), m.p. 242–243°C, **IR (KBr)**, 1606 (CN), 3055 (Ph), 3213 (NH_2), 3400 (NH) cm^{-1}; **^{1}H NMR** ($CDCl_3$): 3.73 (s, 3H, CH_3O-4), 5.59 (s, 2H, NH_2), 6.81–7.23 (m, 4H, H_{arom}), 7.44(d, 1H, J = 2.79 Hz, CH-NH, *tautomer ii*), 7.88 (m, 6H, H_{arom}), 8.43 (s, 1H, HN-N = C), 10.43 (s, 1H, CH = N). Anal. For $C_{18}H_{17}N_7O_2$ Calcd.: C, 59.50; H, 4.72; N, 26.98. Found: C, 59.35; H, 4.69; N, 26.87.

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