Synthesis, Characterization and Biological Activity of Some 1,2,4-Triazine Derivatives

A. A. El-Barbary*, M. A. Sakran, A. M. El-Madani

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

Claus Nielsen

Retrovirus Laboratory, Department of Virology, State Serum Institute, DK-2300 Copenhagen, Denmark

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4-Amino-6-methyl-3-(2*H*)-thioxo-5-(4*H*)-oxo-1,2,4-triazine (**1**) was condensed with 2-methyl (or phenyl)-4*H*-3,1-benzoxazin-4-one (**5a,b**) in boiling acetic acid to give compounds **8-11**. Reacting 1 with chloroacetyl chloride afforded the corresponding chloroacetamido and triazinothiadiazine derivatives **12** and **13**. Condensing **2** with succinic anhydride and/or phthalic anhydride yielded compounds **14** and **15**. Benzoylation of 4-amino-6-methyl-3-(2*H*)-thioxo-5-(4*H*)-oxo-2-(2,3,4,5-tetra-*O*-acetyl-α-D-glucopyranosyl)-1,2,4-triazine (**19**) afforded the corresponding 4-*N,N*-dibenzoyl derivative **20**. Deblocking of the *N*-2 glycoside **21** and the *S*-glycoside **22** by methanolic ammonia gave compounds **23** and **24**. Acetylation of 4-amino glycoside **25a** afforded the corresponding 4-mono- and 4-diacetyl derivatives **26** and **27**. Deamination of **25a,b** yielded compounds **28a,b**. Methylation of compound **28b** afforded the corresponding *N*4- and *S*-methyl derivatives **29** and **30**.

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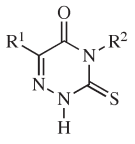
1,2,4-Triazines are important classes of compounds that act as antimicrobial [1], antiviral [2], anti-inflammatory [3-5] and antimalarial [6] agents. Some of them are used as antibacterial [7-9] and antidiabetics [10]. 3-Sulfanilamido-5-dimethylethyl-1,2,4-triazine is manufactured and used as a sulfa drug [11]. 6-Azacytidine derivatives show antiviral effects on the adenovirus genome [12], whereas some triazinone derivatives are used as antiulcer agents [13]. Fluorene containing substituted-3-thioxo-1,2,4-triazine-5-ones exhibit antihuman immune virus activity [14]. Moreover, some substituted 1,2,4-triazino[5,6-*b*]indole derivatives act as antiviral and anticancer agents [15]. This prompted us to make further investigation in this area. Some of 1,2,4-triazine derivatives **1-4** were prepared according to the reported methods [16].



1-4

	R^1	R^2
1	Me	NH_2
2	4-$MeOC_6H_4$-CH=CH-	NH_2
3	4-ClC_6H_4-CH=CH-	NH_2
4	Me	N=CHPh

4-Amino-6-methyl-3-(2*H*)-thioxo-5-(4*H*)-oxo-1,2,4-triazine (**1**) was condensed with 2-methyl-4*H*-3,1-benzoxazin-4-ones (**5a,b**) in boiling acetic acid to give 6-methyl-4-(2-methyl-4-(3*H*)-oxo-*N*3-quinazolinyl)-3-(2*H*)-thioxo-5-(4*H*)-oxo-1,2,4-triazine (**8**) and 6-methyl-4-(2-diacetylaminobenzoyl)amino-3-(2*H*)-thioxo-5-(4*H*)-oxo-1,2,4-triazine (**9**). Condensing **1** with 2-phenyl-4*H*-3,1-benzoxazin-4-one (**5b**) in the same above reaction conditions afforded 6-methyl-4-(2-phenyl-4-(3*H*)-oxo-*N*3-quinazolinyl)-3-(2*H*)-thioxo-5-(4*H*)-oxo-1,2,4-triazine (10) and 6-methyl-4-acetylamino-3-(2*H*)-thioxo-5-(4*H*)-oxo-1,2,4-triazine (**11**) (Figure 1).

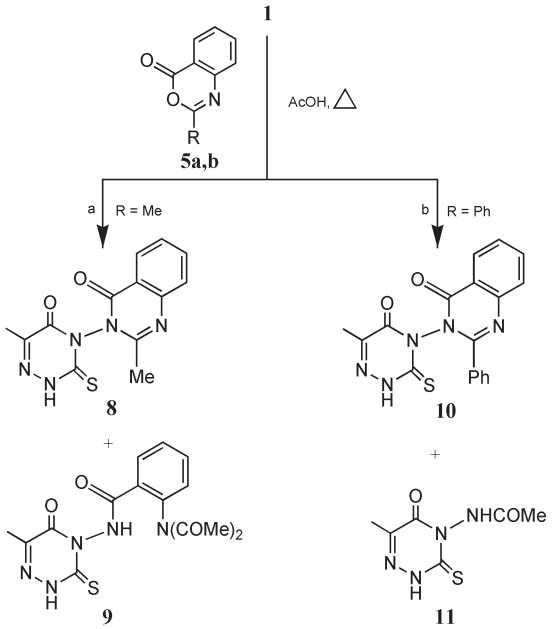


Figure 1

The formation of compound **8** was explained according to the following postulated mechanism: the reaction pro-

ceeds by nucleophilic attack of 4-aminotriazine **1** on C-4 of compound **5a** leading to the intermediate 6 which rearranged to the open ring structure **7** which then, cyclized with elimination of water to give compound **8**. Compound **7** undergoes acetylation by acetic acid to afford compound **9**. Compound **11** was formed due to acetylation of **1** by acetic acid (Figure 2).

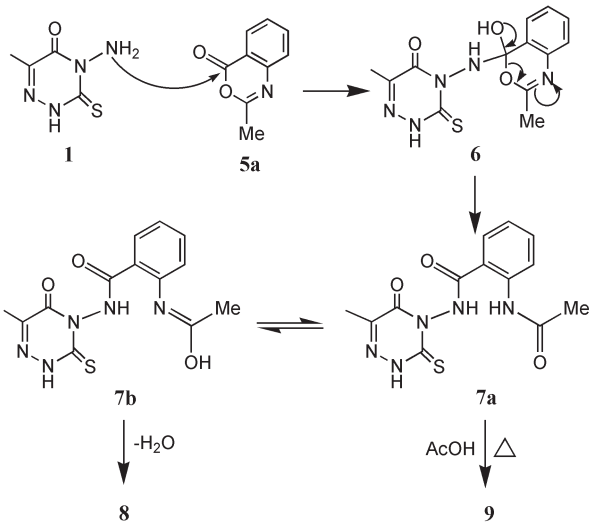


Figure 2

Treatment of **1** with chloroacetylchloride in dioxane in the presence of triethylamine at 10 °C gave 6-methyl-4-(*N*-chloroacetamido)-3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine (**11**) and 3-methyl-4,7-dioxo-4,6,7,8-tetrahydro-1,2,4-triazino[3,4-*b*][1,3,4]thiadiazine (**12**) (Figure 3).

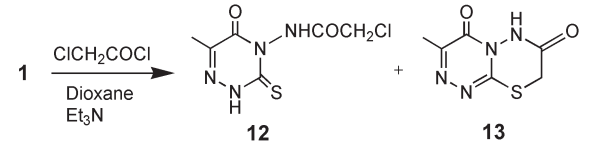


Figure 3

Fusion of 4-amino-6-(4-methoxystyryl)-3-(2*H*)-thioxo-5-(4*H*)-oxo-1,2,4-triazine (**2**) with succinic anhydride at 155 ° afforded 6-(4-methoxystyryl)-4-(*N*-succinimido)-3-(2*H*)-thioxo-5-(4*H*)-oxo-1,2,4-triazine (**14**). Similarly, with phthalic anhydride it afforded 6-(4-methoxystyryl)-4-(*N*-phthalimido)-3-(2*H*)-thioxo-5-(4*H*)-oxo-1,2,4-triazine (**15**) (Figure 4).

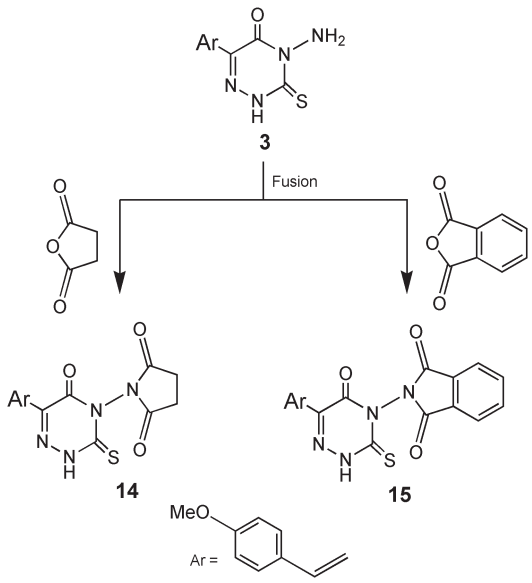


Figure 4

Some glycosides of 1,2,4-triazine have been reported to have biological and medicinal activities [17-20].

Mansour *et al* [21-23] have reported that stirring 4,6-diaryl-3-thioxo-5-oxo-2,3,4,5-tertrahydro-1,2,4-triazines (**16**) at room temperature with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**17**) in aqueous acetone containing one equivalent of KOH afforded only the corresponding *N*-2 glucosyl derivative (**18**) (Figure 5).

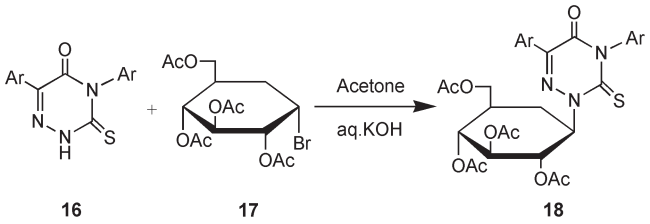


Figure 5

We've reported recently [24] that when **1** was treated with **17** under the same reaction condition it afforded the corresponding *N*-2 glucosyl derivative **19** which on benzoylation yielded the corresponding 4-*N*,*N*-dibenzoylamino derivative **20** (Figure 6).

Coupling 4-benzylideneamino-6-methyl-3-(2*H*)-thioxo-5-(4*H*)-oxo-1,2,4-triazine (**4**) with **17** under the same reaction conditions described above afforded 4-benzylideneamino-6-methyl-3-(2*H*)-thioxo-5-(4*H*)-oxo-2-(2,3,4,5-tetra-*O*-acetyl-α-D-glucopyranosyl)-1,2,4-triazine (**21**) and 4-benzylideneamino-6-methyl-5-(4*H*)-

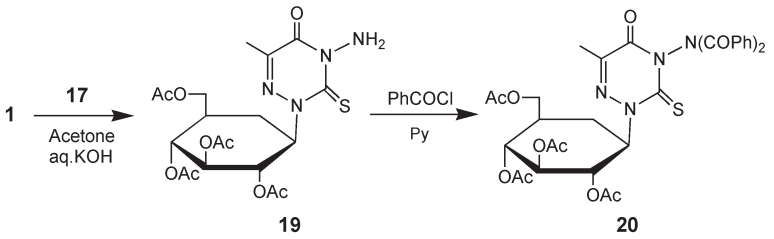


Figure 6

oxo-3-(2,3,4,5-tetra-*O*-acetyl-α-D-glucopyranosyl)thio-1,2,4-triazine (**22**). Treatment of the *N*-2 glycoside (**21**) with methanolic ammonia at 0° gave the corresponding 4-benzylideneamino-6-methyl-3-(2*H*)-thioxo-5-(4*H*)-oxo-2-(2,3,4,5-tetrahydro-α-*D*-glucopyranosyl)-1,2,4-triazine (**23**). While, the *S*-glycoside **22** in the same reaction conditions undergoes cleavage and desulfurization to give 3,5-dioxo-1,2,4-triazine derivative **24** (Figure 7).

The mass spectrum of compound **23** showed the molecular ion peak M^+ at 230.00, which corresponds to the expected molecular formula.

On the other hand, when 4-amino-6-substituted 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazines **2** and **3** were treated with **17** in DMF containing one equivalent of aqueous K_2CO_3 they gave the corresponding *N*-glycosides **25a,b**. The ^{1}H-nmr spectrum of **25a** showed a doublet at δ 6.89 ppm assigned to the anomeric proton of the glucose moiety with J = 9.90 Hz corresponding to a diaxial orientation of H-1' and H-2' protons, which indicates the β-configuration of the glycoside. Its ^{13}C-nmr

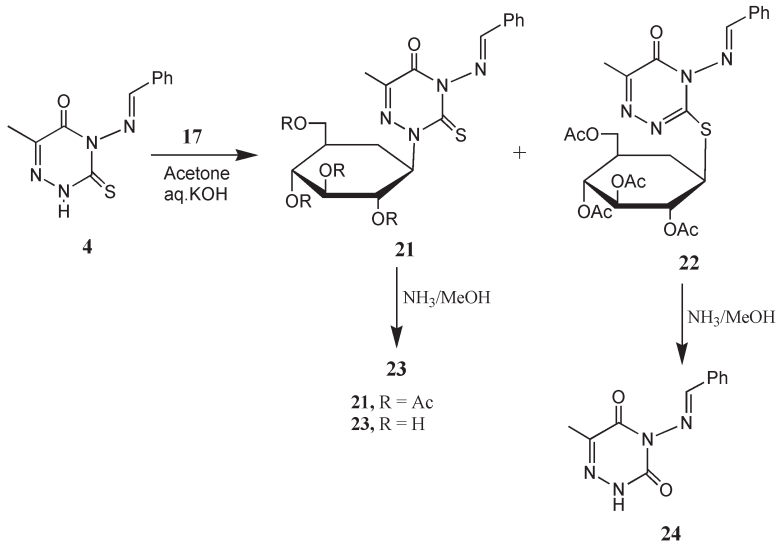
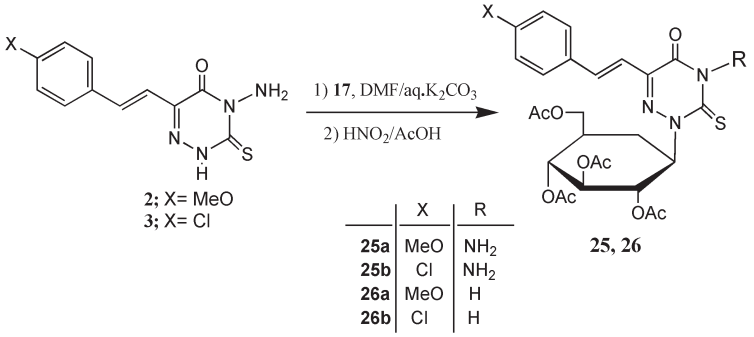


Figure 7



	X	R
25a	MeO	NH_2
25b	Cl	NH_2
26a	MeO	H
26b	Cl	H

Figure 8

spectrum showed a signal at δ 86.78 ppm corresponding to the C-1' atom of the β-configuration. Similarly, compound **25b** was established to have the *N*-glycosidic linkage with β-configuration. Compounds **25a,b** were readily deaminated by nitrous acid in acetic acid to give compounds **26a,b** (Figure 8).

Acetylation of compound **25a** by acetic anhydride in pyridine at r.t. afforded the corresponding mono- and di-acetyl derivatives **27** and **28** (Figure 9).

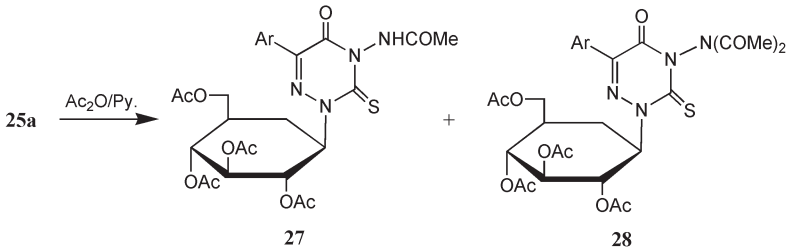


Figure 9

Stirring compound **26b** with MeI in a mixture of DMF and K_2CO_3 gave the corresponding *N*-4 and *S*-methyl derivatives **29** and **30** (Figure 10).

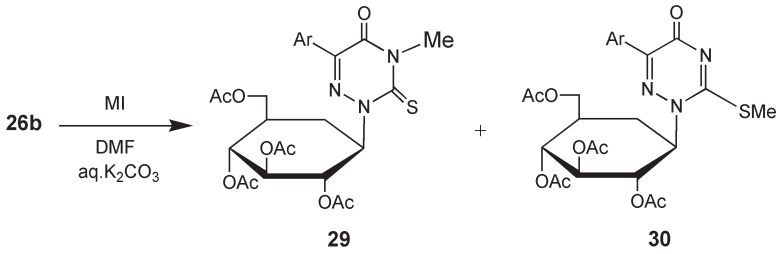


Figure 10

The test for activity against HIV-1 was performed in MT4 cell cultures infected with either wild type HIV-1 (strain IIIB) or non nucleoside reverse transcriptase inhibitors (NNRTIs) resistant HIV-1 (strain N119) that harbored a substitution of cysteine for the tyrosine at position 181 in the reverse transcriptase enzyme (Cys181Tyr mutant strain). Compounds **8**, **11**, **12**, **19**, **22**, **25a**, **25b**, **26b** and **28** have been tested against HIV-1. None of them have showed any activity against HIV-1 at 100 μM. The HIV-1 strains HTLV-IIIB [25] and the NNRTI resistant strain N119 [26] were propagated in H9 cells [27] at 37°, 5% CO_2 using RPMI 1640 with 10% heat-inactivated fetal calf serum (FCS) and antibiotics (growth medium). Culture supernatant was filtered (0.45 nm), aliquotted and stored at –80 °C until use. Both HIV-1 strains were obtained from NIH AIDS.

EXPERIMENTAL

All melting points are uncorrected and performed by the open capillary melting point apparatus Microanalyses were performed by Microanalysis Unit, Faculty of Science, Cairo University, Egypt. IR spectra were recorded with a Perkin-Elmer spectrometer. The nmr spectra were recorded on a Bruker AC 250 FT nmr spectrometer using TMS as an internal standard DMSO as a solvent. Mass spectra (MS) were recorded using electron ionization (E.I.) on a Varian Mat 311A spectrometer.

Condensation of **1** with 2-methyl-4*H*-3,1-benzoxazin-4-one: Formation of **8** and **9**.

A mixture of **1** (1.60 g., 0.01 mole) and **5a** (0.01 mole) was refluxed in glacial acetic acid (30 ml) for 24 hr (tlc). The reaction mixture was cooled and poured on ice. The solid obtained was collected by filtration and chromatographed on a column of silica gel with chloroform:methanol (10:1, v/v) to give **8** and **9**.

6-Methyl-4-(2-methyl-4-(3*H*)-oxo-*N*3-quinazolinyl)-3-(2*H*)-thioxo-5-(4*H*)-oxo-1,2,4-triazine (**8**).

This compound was obtained in 40 % yield (1.21 g); mp 217-218°; ^{1}H-nmr (DMSO-d_6): δ 2.39 (s, 3H, CH_3), 2.5 (s,

3H, CH_3), 7.60 (t), 7.70 (d), 7.90 (t), 8.10 (d) (m, 4H, H_{arom}); ^{13}C-nmr (DMSO-d_6): δ 16.29 (CH_3), 19.88 (CH_3) 127.82, 128.86, 129.48, 131.97, 133.87, 135.95, 147.9, 150.4, 153.4, 156.2, 172.8 (quinazolinone C's, triazine C's and O=C's); EI MS: *m/z* 301.00 (M^+); ir (KBr): ν (cm^{-1}) 1606 (C=N), 1683 (CO), 3367 (NH).

Anal. Calcd. for $C_{13}H_{11}N_5O_2S$: C, 51.82; H, 3.68; N, 23.24. Found: C, 51.62; H, 3.45; N, 23.33.

6-Methyl-4-(2-diacetylaminobenzoyl)amino-3-(2*H*)-thioxo-5-(4*H*)-oxo-1,2,4-triazine (**9**).

This compound was obtained in 25 % yield (0.90 g); mp 207-209°; ^{1}H-nmr (DMSO-d_6): δ 2.01, 2.30, 2.39 (9H, $3CH_3$) 7.54 (d), 7.70 (t), 7.86 (t), 8.13 (d) (m, 4H, H_{arom}); ^{13}C-nmr (DMSO-d_6): ν 10.16, 14.37 ($2CH_3CO$), 16.61 (CH_3), 127.82, 128.86, 129.48, 131.97, 133.87, 135.57, 141.53, 147.56 (quinazolinone C's), 152.69, 157.83 (C-3 and C-6), 161.09, 165.26 (2CO); EI MS: *m/z* 361.30 (M^+); ir (KBr): ν (cm^{-1}) 1610 (C=N), 1996 (CO), 3213 (NH).

Anal. Calcd. for $C_{15}H_{15}N_5O_4S$: C, 49.85; H, 4.18; N, 19.38; Found: C, 49.92; H, 3.98; N, 19.36.

Condensation of **1** with 2-Phenyl-4*H*-3,1-benzoxazin-4-one: Formation of **10** and **11**.

A mixture of 1 (1.60 g., 0.01 mole) and **5b** (2.07 g., 0.015 mole) was refluxed in glacial acetic acid (30 ml) for 24 hr (tlc). The reaction mixture was cooled and poured on ice. The solid obtained was collected by filtration and chromatographed on a column of silica gel with chloroform:methanol (10:1, v/v) to give **10** and **11**.

6-Methyl-4-(2-phenyl-4-(3*H*)-oxo-*N*3-quinazolinyl)-3-(2*H*)-thioxo-5-(4*H*)-oxo-1,2,4-triazine (**10**).

This compound was obtained in 50% yield (1.82 g); mp 172-174°; ^{1}H-nmr (DMSO-d_6): δ 3.44 (s, 1H, CH_3), 7.24-8.29 (m, 9H, H_{arom}); ^{13}C-nmr (DMSO-d_6): δ 16.00 (CH_3), 117.60, 119.76, 122.85, 127.21, 129.63, 131.44, 132.15, 133.92, 134.75 (C_{arom}), 141.26, 164.79 (C-3 and C-6), 170.51 (2C=O); ir (KBr): ν (cm^{-1}) 1638 (C=N), 1679 (CO), 3040 (NH).

Anal. Calcd. for $C_{18}H_{13}N_5O_2S$: C, 59.49; H, 3.61; N, 19.27. Found: C, 59.54; H, 3.57; N, 19.23.

6-Methyl-4-acetylamino-3-(2*H*)-thioxo-5-(4*H*)-oxo-1,2,4-triazine (**11**).

This compound was obtained in 30 % yield (0.6 g); mp 222-224°; ^{1}H-nmr (DMSO-d_6): δ 1.90 (s, 3H,CH_3CO), 2.10 (s, 3H, triazine CH_3), 10.90 (s, 1H, NHCO), 13.70 (s, 1H, triazine NH); ^{13}C-nmr (DMSO-d_6): δ 16.60 (CH_3), 20.20 (CH_3CO), 147.60, 151.50, 167.40, (C-3, C-6, C-5), 175.20 ($COCH_3$); EI MS: *m/z* 200.00 (M^+); ir (KBr): ν (cm^{-1}) 1609 (C=N), 1680 (CO), 3228 (NH).

Anal. Calcd. for $C_6H_8N_4O_2S$: C, 35.99; H, 4.03; N, 27.98. Found: C, 35.46; H, 4.00; N, 27.79.

Reaction of 1 with Chloroacetylchloride: Formation of **12** and **13**.

Compound **1** (0.01 mole) was dissolved in dioxane (15 ml), then chloroacetyl chloride (1.20 g, 0.01 mole) was added with cooling to 10 °C. Triethylamine (1.0 g., 0.01 mole) dissolved in dioxane (5 ml) was added dropwise with stirring at 10 °C. The mixture was stirred for 6 hr at r.t. (tlc). The solvent was evaporated till dryness under reduced pressure and the residual solid was chromatographed on a column of silica gel with petroleum ether:ethyl acetate (5:1, v/v) to give **12** and **13**.

6-Methyl-4-(*N*-chloroacetamido)-3-(2*H*)-thioxo-5-(4*H*)-oxo-1,2,4-triazine (**12**).

This compound was obtained in 45 % yield (1.05 g); mp 150-151°; ^{1}H-nmr (DMSO-d_6): δ 2.15 (s, 3H, triazine CH_3), 4.30 (d, 2H, CH_2), 13.74 (s, 1H, triazine NH), 11.43 (s, 1H, NHCO); ^{13}C-nmr (DMSO-d_6): δ 16.65 (CH_3), 40.55 (CH_2), 147.67 (C-3), 151.21 (C-6), 164.30 (C-5), 174.74 (NHCO); EI MS: *m/z* 234.00 (M^+); ir (KBr): ν (cm^{-1}) 1609 (C=N), 1694 (CO, amide), 1726 (CO, acetyl), 3219 (NH).

Anal. Calcd. for $C_6H_7ClN_4O_2S$: C, 30.71; H, 3.01; N, 23.88; Cl, 15.11. Found: C, 30.60; H, 2.97; N, 23.84; Cl, 14.94.

3-Methyl-4,7-dioxo-4,6,7,8-tetrahydro-1,2,4-triazino[3,4-*b*]-[1,3,4]thiadiazine (**13**).

This compound was obtained in 25 % yield 0.49 g (25%); mp 187-189°; ^{1}H-nmr (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 3.86 (s, 2H, CH_2), 12.50 (broad s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 17.31 (CH_3), 45.24 (C-8), 147.30 (C-10), 151.19 (C-3), 155.46 (C-7) and 164.96 (C-4) ; EI MS: *m/z* 197.90 (M^+); ir (KBr): ν (cm^{-1}) 1528 (C=N), 1675 (CO), 3219 (NH).

Anal. Calcd. for $C_6H_6N_4O_2S$: C, 36.36; H, 3.05; N, 28.27. Found: C, 36.47; H, 2.96; N, 28.17.

Synthesis of 6-(4-Methoxystyryl)-4-(*N*-succinimido)-3-(2*H*)-thioxo-5-(4*H*)-oxo-1,2,4-triazine (**14**).

A mixture of **2** (0.01 mole) and succinic anhydride (0.01 mole) was fused at 155 °C in an oil bath for 3 hr (tlc). The reaction mixture was cooled and poured on ice-cold water. The solid obtained was collected by filtration and chromatographed on a column of silica gel with petroleum ether:ethyl acetate (3:1, v/v) to give **14**. Yield 1.43 g (40%); mp 236-238°; ^{1}H-nmr (DMSO-d_6): δ 2.90 (m, 4H, $2CH_2$), 3.60 (s, 3H, MeO), 6.71-7.70 (m, 6H, H_{arom}), 13.90 (s, broad, 1H, NH); %); ir (KBr): ν (cm^{-1}) 1599 (C=N), 1738 (CO), 3298 (NH).

Anal. Calcd. for $C_{16}H_{14}N_4O_4S$: C, 53.62; H, 3.94; N, 15.63. Found: C, 53.60; H, 3.86; N, 15.49.

Synthesis of 6-(4-Methoxystyryl)-4-(*N*-phthalimido)-3-(2*H*)-thioxo-5-(4*H*)-oxo-1,2,4-triazine (**15**).

A mixture of **2** (0.01 mole) and phthalic anhydride (0.01 mole) was fused at 198 °C in an oil bath for 3 hr (tlc). The reaction mixture was cooled to r.t. and treated with cold water. The solid obtained was collected by filtration and chromatographed on a column of silica gel with petroleum ether:ethyl acetate (3:1, v/v) to give (**15**). Yield 3.08 g (48 %); mp 292-293°; ^{1}H-nmr (DMSO-d_6): δ 3.80 (s, 3H, OCH_3), 6.80-8.10 (m, 10H, H_{arom} and CH=CH), 14.40 (broad s, 1H, NH); %); ir (KBr): ν (cm^{-1}) 1599 (C=N), 1750 (CO), 3288 (NH).

Anal. Calcd. for $C_{20}H_{14}N_4O_4S$: C, 59.11; H, 3.47; N, 13.79. Found: C, 59.18; H, 3.37; N, 13.71.

Action of Methanolic Ammonia on Compounds 21 and 22: Formation of **23** and **24**.

To a suspension of each of compounds **21** and/or **22** (0.005 mole) in anhydrous methanol (15 ml), a saturated solution of ammonia in anhydrous methanol (20 ml) was added. The reaction mixture was stirred at r.t. for 1 hr and left overnight in the refrigerator. The solvent was evaporated under reduced pressure and the residue was purified over a column of silica gel with chloroform:methanol (5:1, v/v) to afford **23** and **24**, respectively.

4-Benzylideneamino-6-methyl-3-(2*H*)-thioxo-5-(4*H*)-oxo-2-(2,3,4,5-tetrahydro-α-D-glucopyranosyl)-1,2,4-triazine (**23**).

This compound was obtained ain 67 % yield (1.36 g); mp 168-169 °C; ^{1}H-nmr (DMSO-d_6): δ 2.10 (s, 3H, CH_3), 3.20-3.70 (m, 2H, H-6', H-5'), 3.44 (m, 1H, H-4'), 3.66 (m, 2H, H-3', H-2'), 4.51 (s,1H, HO-6') 4.97 (s, 1H, HO-4'), 5.16 (s, 1H, HO-3'),5.27 (d, 1H, H-1'), 5.34 (s, 1H, HO-2'), 7.44-7.65 (m, 5H, H_{arom}), 8.34 (s, 1H, CH=N); ^{13}C-nmr (DMSO-d_6): δ 11.28 (CH_3), 82.81, 81.64, 78.80, 71.76, 69.70, 60.58 (C-1', C-2', C-3', C-4', C-5'and C-6'), 126.68, 129.01, 130.00, 134.34 (C_{arom}), 142.96 151.53, 160.74, 167.11 (C-3, C-6, CH=N, C-5); EI MS: *m/z* 408.00 (M^+); ir (KBr): ν (cm^{-1}) 1611 (C=N), 1673 (CO), 3409 (OH).

Anal. Calcd. for $C_{17}H_{20}N_4O_6S$: C, 49.99; H, 4.94; N, 13.72; S, 7.84. Found: C, 49.83; H, 4.98; N, 13.68; S, 7.81.

4-Benzylideneamino-6-methyl-3,5-(2*H*,4*H*)-dioxo-1,2,4-triazine (**24**).

This compound was obtained in 58 % yield (0.66 g); mp 198-199°; ^{1}H-nmr (DMSO-d_6): δ 2.18 (s, 3H, CH_3), 7.58-7.95 (m, 5H, H_{arom}), 8.78 (s, 1H, CH=N), 12.52 (bs, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 16.62 (CH_3), 129.23, 129.78, 132.10, 133.01 (C_{arom}), 142.69, 147.46, 153.46, 171.65 (C-3, C-6, CH=N, C-5); EI MS: *m/z* 231.00 (M^+, 100 %), 203.70 ($C_{10}H_{11}N_4O$, 1.70 %), 126.90 ($C_4H_4N_3O_2$, 23.60 %), 103.90 ($C_7H_6N^+$, 16.90 %). ir (KBr): ν (cm^{-1}) 1602 (C=N), 1721 (CO), 2934 (NH).

Anal. Calcd. for $C_{11}H_{10}N_4O_2$: C, 57.39; H, 4.38; N, 24.34. Found: C, 57.26; H, 4.39; N, 24.37.

Synthesis of 4-*N,N*-Dibenzoylamino-6-methyl-3-(2*H*)-thioxo-5-(4*H*)-oxo-2-(2,3,4,5-tetra-*O*-acetyl-α-D-glucopyranosyl)-1,2,4-triazine (**20**).

To a solution of compound **19** (0.01 mole) in anhydrous pyridine (25 ml), benzoyl chloride (5 ml) was added dropwise with stirring and cooling to 0°. The stirring was then continued at r.t. overnight (tlc). The reaction mixture was poured onto ice. The solid obtained was collected by filtration and chromatographed on a column of silica gel with petroleum ether:ethyl acetate (3:1, v/v) to give (**20**). Yield 5.29 (76 %); mp 170-171 ºC; ^{1}H-nmr (DMSO-d_6): δ 1.89-2.00 (4s, 12H, 4CH_3CO), 2.28 (s, 1H, CH_3), 4.05 (d, 1H, H-6'), 4.19-4.39 (m, 1H, H-5'), 5.00 (t, 1H, H-4'), 5.43 (t, 1H, H-3'), 5.65 (t, 1H, H-2'), 6.94 (d, 1H, H-1'), 7.34-7.73 (m, 5H, H_{arom}); ^{13}C-nmr (DMSO-d_6): δ 16.69 (CH_3), 20.06, 20.19, 20.32, 20.48 (4*C*H_3CO), 86.75, 73.06, 72.13, 69.06, 67.50, 61.38 (C-1', C-2', C-3', C-4', C-5', C-6'), 128.71, 129.07, 132.93, 133.36 (C_{arom}), 147.21, 149.86, 168.25 (C-3, C-6, C-5), 168.88, 169.50, 169.68, 170.17 (4*C*OCH_3), 175.15 (2*C*OPh); ir (KBr): ν (cm^{-1}) 1743 (CO, acetyl), 1696 (CO, amide), 1631 (C=N); EI Hrms *m/z* 696.4450 (M^+, $C_{32}H_{32}N_4O_{12}S$) requires 696.1729.

Deamination of Compounds **25a,b**: Formation of **26a,b**.

To a solution of each of compounds **25a,b** (0.01 mole) in acetic acid (15 ml) was added dropwise a solution of sodium nitrite (1.4 g, 0.02 mole in 1 ml water) with stirring and cooling to 5 °C. The reaction mixture was then stirred at r.t. overnight (tlc). After dilution with cold water, the solid obtained was collected by filtration and chromatographed on a column of silica gel with petroleum ether:ethyl acetate (3:1, v/v) to give **26a,b**, respectively.

6-(4-Methoxystyryl)-3-(2*H*)-thioxo-5-(4*H*)-oxo-2-(2,3,4,5-tetra-*O*-acetyl-α-D-glucpyranosyl)-1,2,4-triazine (**26a**).

This compound was obtained ain 60 % yield (3.54 g); mp 241-242°; ^{1}H-nmr (DMSO-d_6): δ 1.90-2.03 (4s, 12H, 4CH_3CO), 3.81 (s, 3H, CH_3O), 4.02 (d, 1H, H-6'), 4.22 (m, 1H, H-5'), 5.02 (t, 1H, H-4'), 5.54 (t, 1H, H-3'), 5.63 (t, 1H, H-2'), 6.88-7.79 (m, H-1', CH=CH, H_{arom}); ^{13}C-nmr (DMSO-d_6): δ 20.30 (4*C*H_3CO), 55.45 (CH_3O), 85.90, 73.63, 72.72 69.09, 68.18, 61.81 (C-1', C-2', C-3', C-4', C-5', C-6'), 114.55, 128.64, 129.55, 141.37 (C_{arom} and CH=CH), 147.73, 160.91, 169.55 (C-3, C-6, C-5), 170.16, 170.46, 170.91 (4*C*OCH_3); g. 42); ir (KBr): ν (cm^{-1}) 1603 (C=N), 1747 (CO), 3427 (NH); EI Hrms *m/z* 591.2200 (M^+, $C_{26}H_{29}N_3O_{11}S$) requires 591.1590.

6-(4-Chlorostyryl)-3-(2*H*)-thioxo-5-(4*H*)-oxo-2-(2,3,4,5-tetrahydro-*O*-acetyl-α-D-glucpyranosyl)-1,2,4-triazine (**26b**).

This compound was obtaineda in 70 % yield (4.16 g); mp 260-261°; ^{1}H-nmr (DMSO-d_6): δ 1.86, 1.89, 1.93, 1.95 (4s, 4CH_3CO), 4.01 (d, 2H, H-6'), 4.16-4.30 (m, 1H, H-5'), 5.01 (t, 1H, H-4'), 5.52 (t, 1H, H-3'), 5.61 (t, 1H, H-2'), 6.86 (d, 1H, H-1'), 7.06-7.77 (m, 6H, H_{arom} and CH=CH), 13.50 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 20.28 (4*C*H_3CO), 84.90, 72.91, 72.84, 68.58, 67.61, 61.50 (C-1', C-2', C-3', C-4', C-5'and C-6'), 118.99, 128.12, 129.66, 133.93, 134.59, 135.87 (C_{arom} and CH=CH), 144.52, 151.62, 174.67 (C-3, C-6, C-5), 168.94, 169.40, 169.70, 170.35 (4*C*OCH_3 acetyl); ir (KBr): ν (cm^{-1}) 1624 (C=N), 1747 (CO), 3215 (NH); EI Hrms *m/z* 595.1018 (M^+, $C_{25}H_{26}ClN_3O_{10}S$) requires 595.1027.

Acetylation of Compound **25a**: Formation of compounds **27** and **28**.

To a solution of **25a** (0.01 mole) in anhydrous pyridine (25 ml), acetic anhydride (5 ml) was added dropwise with stirring and cooling to 0 °C. The stirring was then continued at r.t. overnight (tlc). The reaction mixture was poured onto ice and the solid obtained was collected by filtration and chromatographed on a column of silica gel with petroleum ether:ethylacetate (3:1, v/v) to give **27** and **28**, respectively.

4-Acetylamino-6-(4-methoxystyryl)-3-(2*H*)-thioxo-5-(4*H*)-oxo-2-(2,3,4,5-tetra-O-acetyl-α-D-glucopyranosyl)-1,2,4-triazine (**27**).

This compound was obtaineda in 40 % yield (2.59 g); mp 198-199 °C; ^{1}H-nmr (DMSO-d_6): δ 1.88-2.10 (m, 15H, 5CH_3CO), 3.80 (s, 1H, CH_3O), 4.00-4.32 (m, 2H, H-6' and H-5'), 5.04 (t, 1H, H-4'), 5.62 (tt, 2H, H-3'and H-2'), 6.94 (d, 1H, H-1'), 6.98-7.82 (4H, H_{arom} and CH=CH), 11.10 (d, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 20.02, 20.14, 20.18, 20.23, 20.37 (5*C*H_3CO), 55.19 (CH_3O), 87.04, 73.15, 72.78, 69.07, 67.59, 61.48 (C-1', C-2', C-3', C-4', C-5', C-6'), 114.58, 115.35, 128.27, 129.52, 138.00 (C_{arom} and CH=CH), 149.52, 160.77, 167.15 (C-3, C-6, C-5), 168.96, 169.35, 169.54, 169.92, 175.44 (5*C*OCH_3); EI MS: *m/z* 648.00 (M^+); ir (KBr): ν (cm^{-1}) 1602 (CO, amide), 1746 (CO, acetyl).

Anal. Calcd. for $C_{28}H_{32}N_4O_{12}S$: C, 51.85; H, 4.97; N, 8.64. Found: C, 51.88; H, 5.11; N, 8.55.

4-*N,N*-Diacetylamino-6-(4-methoxystyryl)-3-(2*H*)-thioxo-5-(4*H*)-oxo-2-(2,3,4,5-tetra-*O*-acetyl-α-D-galucpyranosyl)-1,2,4-triazine (**28**).

This compound was obtained in 30 % yield (2.07 g); mp 184-186°; ^{1}H-nmr (DMSO-d_6): δ 1.92-2.05 (4s, 12H, 4CH_3CO), 2.39, 2.43 (2s, 6H, $(CH_3CO)_2N$), 3.83 (s, 3H, CH_3O), 4.08 (d, 1H, H-6'), 4.14-4.42 (m, 1H, H-5'), 5.11 (t, 1H, H-4'), 5.64 (tt, 2H, H-3'and H-2'), 7.04-7.92 (H-1', H_{arom} and CH=CH); ^{13}C-nmr

(DMSO-d_6): δ 20.11, 20.17, 20.28, 20.39 (4*C*H_3CO, sugar), 23.83, 24.33 (2*C*H_3CO amide) , 55.30 (CH_3O), 87.10, 73.20, 72.30, 69.20, 67.54, 61.40 (C-1', C-2', C-3', C-4', C-5', C-6'),114.57, 115.43, 128.06, 129.71, 138.57, 144.00 (C_{arom} and CH=CH), 149.71, 160.86, 168.57 (C-3, C-6, C-5), 169.00, 169.57, 169.71, 170.14, 174.57 (6*C*OCH_3); ir (KBr): ν (cm^{-1}) 1602 (CO, amide), 1746 (CO, acetyl).EI Hrms *m/z* 690.4010 (M^+, $C_{30}H_{34}N_4O_{13}S$) requires 690.1834.

Methylation of Compound **26b**: Formation of **29** and **30**.

Compound **26b** (0.01 mole) was dissolved in a mixture of DMF (20 ml) and aq. K_2CO_3 (1.38 g, 0.01mole in 10 ml water) and stirred for 10 min. Methyl iodide (1.42 g, 0.01 mole) was added and the mixture was stirred overnight at r.t. (tlc). The reaction mixture was poured onto ice and the solid obtained was collected by filtration and chromatographed on a column of silica gel with petroleum ether:ethyl acetate (3:1, v/v) to give **29** and **30**, respectively.

4-Methyl-6-(4-chlorostyryl)-5-(4*H*)-oxo-3-(2*H*)-thioxo-2-(2,3,4,5-tetra-*O*-acetyl-α-D-glucopyranosyl)-1,2,4-triazine (**29**).

This compound was obtained ain 35 % yield (2.13 g); mp 200 °C; ^{1}H-nmr (DMSO-d_6): δ 1.97-2.15 (4s, 12H, 4CH_3CO), 2.66 (s, 3H, CH_3-N), 4.13 (d, 1H, H-6'), 4.27-4.51 (m, 1H, H-5'), 5.13 (t, 1H, H-4'), 5.81 (tt, 1H, H-3' and H-2'), 6.26 (d, 1H, H-1'), 7.15-7.97 (m, 6H, H_{arom} and CH=CH); ^{13}C-nmr (DMSO-d_6): δ 20.11, 20.23, 20.38 (4*C*H_3CO), 30.61 (CH_3-N), 119.92, 129.17, 129.33, 134.0, 134.67, 136.5 (C_{arom} and CH=CH), 144.67, 157.96, 165.96 (C-3, C-6, C-5), 168.89, 169.45, 169.82, 170.22 (4*C*OCH_3); ir (KBr): ν (cm^{-1}) 1616 (C=N), 1660 (CO, amide), 1744 (CO, acetyl); EI Hrms *m/ z* 609.2820 (M^+, $C_{26}H_{28}ClN_3O_{10}S$) requires 609.1176.

Methylthio-6-(4-chlorostyryl)-5-(2*H*)-oxo-2-(2,3,4,5-tetra-*O*-acetyl-α-D-glucopyranosyl)-1,2,4-triazine (**30**).

This compound was obtained in 25 % yield (1.52 g); mp 267-269 °C; ^{1}H-nmr (DMSO-d_6): δ 1.91-2.04 (4s, 12H, 4CH_3CO), 2.52 (s, 3H, CH_3-S), 4.05-4.4 (m, 2H, H-6' and H-5'), 5.08 (t, 1H, H-4'), 5.75 (tt, 2H, H-3' and H-2'), 6.22 (d, 1H, H-1'), 7.10-7.91 (m, 6H, H_{arom} and CH=CH); ir (KBr): δ (cm^{-1}) 1625 (C=N), 1665 (CO, amide), 1747 (CO, acetyl).

Anal. Calcd. for $C_{26}H_{28}ClN_3O_{10}S$: C, 51.26; H, 4.63; N, 6.90; Found: C, 51.29; H, 4.58; N, 6.80.

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REFERENCES AND NOTES

[*] Author to whom correspondence should be addressed: Fax +20 40 3350804; e-mail: aaelbarbary@hotmail.com.

[1] A. K. Mansour, S. B. Awad and S. Antown, *Z. Naturforsch.,* B29, 792 (1974).

[2] W. M. Davidson and W. D. Boykin, *J. Pharm. Sci.,* 65, 737 (1978).

[3] P. W. Hielman, R. D. Gielman, A. J. Scozzie, R. J. Wayner, M. J. Gollo and S. Z. Ariyan, *J. Pharm. Sci,* 69, 282 (1980).

[4] M. J. Gollo, P. W. Iteillman, R. J. Wayner and E. G. Robert, *German Offen,* 2, 84, 381*; Chem. Abstr*., 90, 121664m (1979).

[5] W. B. Lacefield, *French Demande,* 2, 243, 479; *Chem. Abstr.*, 89, 24372m (1979).

[6] L. C. March, G. S. Bajwa, J. Lee, K. Wasti and M. M. Joullie, *J. Med. Chem*., 19 (6), 845 (1976).

[7] I. Saikawa, Y. Suzaki and T. Osada, *Japanese Patent,* 7026, 294; *Chem. Abstr*., 73, 131036w (1970).

[8] I. Saikawa and T. Osada, *Japanese Patent,* 7026, 109; *Chem. Abstr*., 73, 131037x (1970).

[9] I. Saikawa, S. Kuroda and T. Osada, *Japanese Patent,* 7026, 108; *Chem. Abstr*., 73, 131038y (1970).

[10] I. Saikawa and T. Maeda, *Japanese Patent,* 7026, 106; *Chem. Abstr*., 73, 131039z (1970); *ibid*, 7026, 107; *Chem. Abstr.,* 73, 131040t (1970); *ibid*, 7026, 903; *Chem. Abstr*., 73, 131041z (1970).

[11] S. Kono, S. Zoga and T. Komaki, *Japanese Patent,* 6720, 313; *Chem. Abstr*., 69, 36183a (1968).

[12] L. N. Nosach, I. S. Dyachenko, S. I. Butenko, V. L. Zhovnovataya, M. Ya. Timofeeva, L. A. Tarasishin, I. V. Alekseeva and V. P. Chernetskii, *Nov. Podkhody Khimioter Virusn. Infekts.,* 87, 389 (1991); *Chem. Abstr*., 116, 227707y (1992).

[13] K. Hirai, H. Sugimoto and T. Mizushima, *Japanese Patent,* 61, 134; *Chem. Abstr*., 106, 67353j (1987).

[14] R. M. Abdel-Rahman, *Farmaco,* 46 (2), 379 (1991); *Chem. Abstr*., 120, 134427z (1994).

[15] N. H. Eshba, H. M. Salama, I. M. Labouta and A. Mohsen M. Omar, *Pharmazie*, 42, 664 (1987).

[16] A. Dornow, H. Menzel and P. Marx, *Chem. Ber*., 97, 2173 (1964).

[17] U. Niedballa and H. Vorbrüggen, *Angew. Chem. Internat. Ed.,* 9, 461 (1970); *Chem. Abstr*., 73, 66854v (1970).

[18] H. Vorbrüggen, K.H. Kolbe, U. Nieballa and P. Strehlke, *Ger. Patant 1,* 955, 695 (1971); *Chem. Abstr*., 75, 49513g (1971).

[19] U. Niedballa and H. Vorbrüggen, *Ger Patent 1*, 943, 428 (1971); *Chem. Abstr*., 74, 100361g (1971).

[20] U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, 39, 36654 (1974).

[21] A. K. Mansour, Y. A. Ibrahim and M. M. Eid, *Z. Naturforsch*., 316, 505 (1976).

[22] A. K. Mansour, Y. A. Ibrahim, M. M.Eid and S. A. L. Abdel-Hady, *J. Carbohydrate Nucleosides-Nucleotides*, 8, 81 (1981).

[23] M. M. Eid, S. A. L. Abdel-Hady and H. A. W. Ali, *Arch. Pharmazie*, 323, 243 (1990).

[24] M. A. Sakaran, A. A. El-Barbary, and A. M. El-Madani, *Delta J. Sci,* 22, 30 (1998).

[25] M. Popovic, M. G. Sarngadharan, E. Read and R. C. Gallo, *Science,* 224, 497 (1984).

[26] S. Harada, V. Kovanani and O. N. Vamamoto, *Science*, 229, 563 (1985).

[27] T. Mosmann, *J. Immunol. Methods*, 65, 55 (1983).