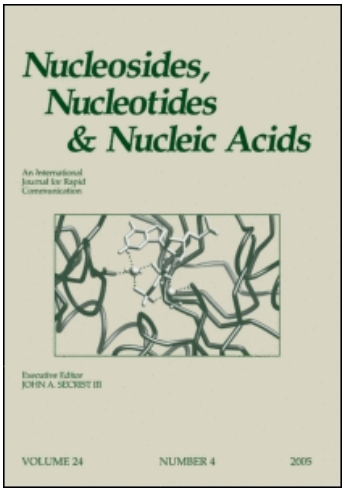

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Acyclo *C*-Nucleoside Analogs. Regioselective Annellation of a Triazole Ring to 5-Methyl-1,2,4-Triazino[5,6-*b*]Indole and Formation of Certain 3-Poly Hydroxyalkyl Derivatives

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ACYCLO *C*-NUCLEOSIDE ANALOGS. REGIOSELECTIVE ANNELLATION OF A TRIAZOLE RING TO 5-METHYL-1,2,4-TRIAZINO[5,6-*b*]INDOLE AND FORMATION OF CERTAIN 3-POLY HYDROXYALKYL DERIVATIVES

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ABSTRACT

Cyclodehydrogenation of the ethylidene derivative of (5-methyl-1,2,4-triazino[5,6-*b*]indol-3-yl)hydrazine (1) gave the angular isomer, 1,10-dimethyl-1,2,4-triazolo[3',4':3,4][1,2,4]triazino[5,6-*b*]indole (4). The linear isomer, 3,10-dimethyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-*b*]indole (7) could be prepared regioselectively by the cyclodehydration of the acetyl derivative of 1. The cyclodehydrogenation was extended to the monosaccharide derivatives of 1. The role of the N-methyl group on the site of annellation has been discussed.

INTRODUCTION

A number of 1,2,4-triazines and fused-ring analogs have various biological activities[1-4]. The 1,2,4-triazino[5,6-*b*]indole ring has been found to be a useful carrier for various functional groups for developing antiviral and antibacterial activities[3-10]. (5-Methyl-1,2,4-triazino[5,6-*b*]indol-3-yl)hydrazine (1) shows antihypertensive activity[11]

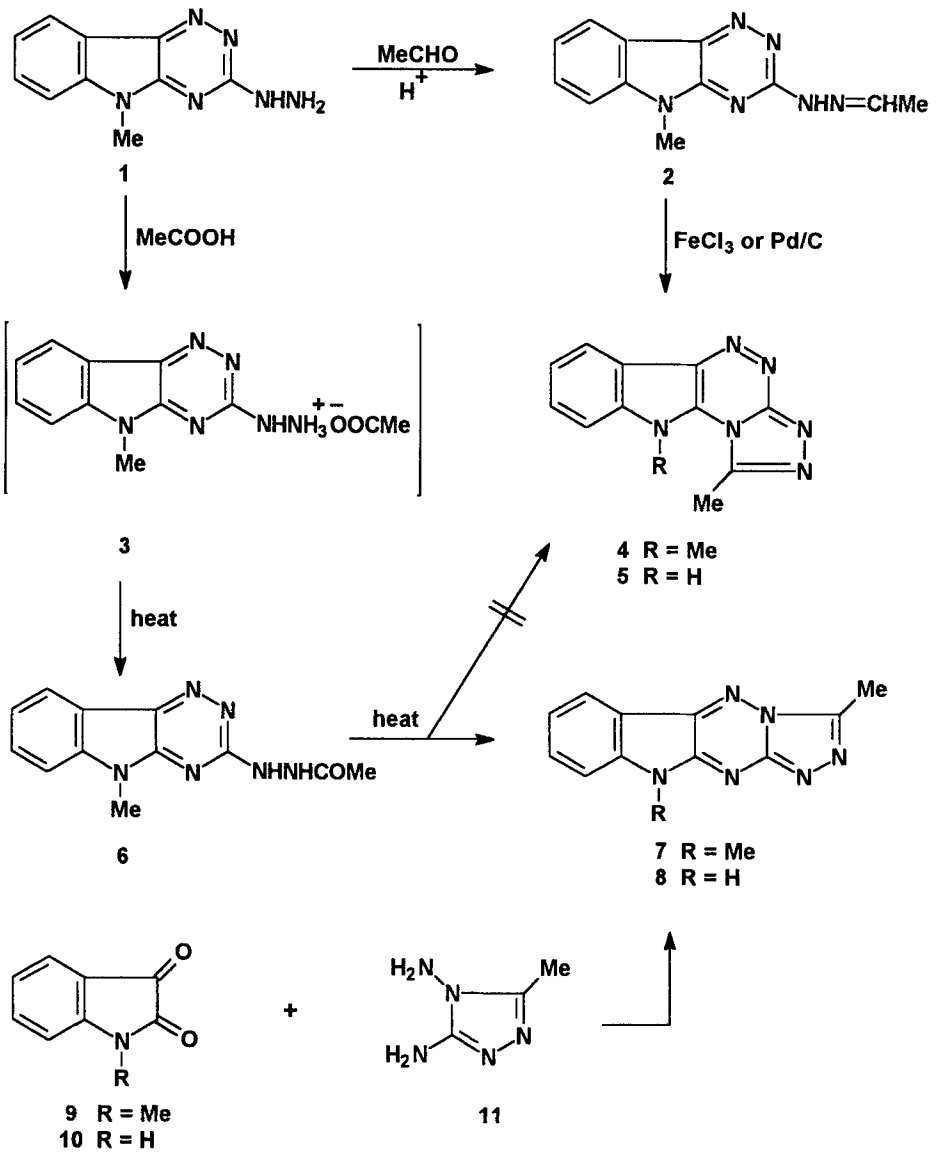
in addition to the antiviral activity. The imidazo, pyrimidino or triazolo-1,2,4-triazino-[5,6-*b*]indoles show antiviral and antibacterial properties[12]. The arylidene moiety of 3-arylidene- and heterocyclic formylidenehydrazono-1,2,4-triazino[5,6-*b*]indole derivatives has been found to play a role in their activity against *Staphylococcus aureus* and *Bacillus cereus* as well as P388 lymphocytic leukemia[10].

The fusion of a heterocyclic ring *via* the cyclization of a functional group at the 3-position of 1,2,4-triazino[5,6-*b*]indole may proceed in two directions, at N-2 or N-4 to give linear[13-17] or angular[18-21] structures, respectively. The angular structure has been found to be the favored one for products from the oxidative cyclization of the aldehyde derivatives of **1**. This finding is contrary to previous studies[22,23] on the derivatives of **1**, whereby the isolated products had the linear isomeric structures. In this report on our continuing studies[23,26,27] the mode of cyclization of **1** has been investigated and the corresponding acyclo-*C*-nucleoside analogues have been constructed based upon the importance of *C*-nucleosides[24,25] and acyclonucleosides[26].

RESULTS AND DISCUSSION

The starting hydrazine **1** was prepared as previously reported[3] by the cyclocondensation of *N*-methylisatin 3-thiosemicarbazone to give the corresponding triazine, whose reaction with hydrazine gave **1**. Reaction of **1** with acetaldehyde gave **2** and similarly the reaction with various monosaccharides including **D**-galactose, **D**-glucose, **D**-mannose, **D**-arabinose, **L**-arabinose, **D**-ribose and **D**-xylose gave the hydrazones **12a-g**. The annellation of the triazole ring to the triazine ring was achieved by oxidation of the hydrazones with $FeCl_3$/EtOH or with Pd/C to give the corresponding triazolo derivatives **4** and **15**. The selection of the angular isomer **4** was based on a model experiment by which the synthesis[12] of **7** was achieved by the condensation of *N*-methylisatin (**9**) with 3,4-diamino-5-methyl-4*H*-1,2,4-triazole (**11**). This reaction had been anticipated to proceed *via* the condensation of the more reactive amino group of **11** with the more reactive C-3 carbonyl group of **9** followed by condensative cyclization to give the linear isomer **7** in a similar manner[23] to the reaction of **11** with **10** to give **8**. The latter, however, was found to be different from **4** as obtained by the oxidative cyclization of **2**.

In an attempt to find alternative routes to **4**, the reaction of **1** with acetic acid was carried out, during which a precipitation took place after heating caused by the probable formation of the amide **6** *via* the salt **3**. Further heating led to the formation of the fused



Scheme 1

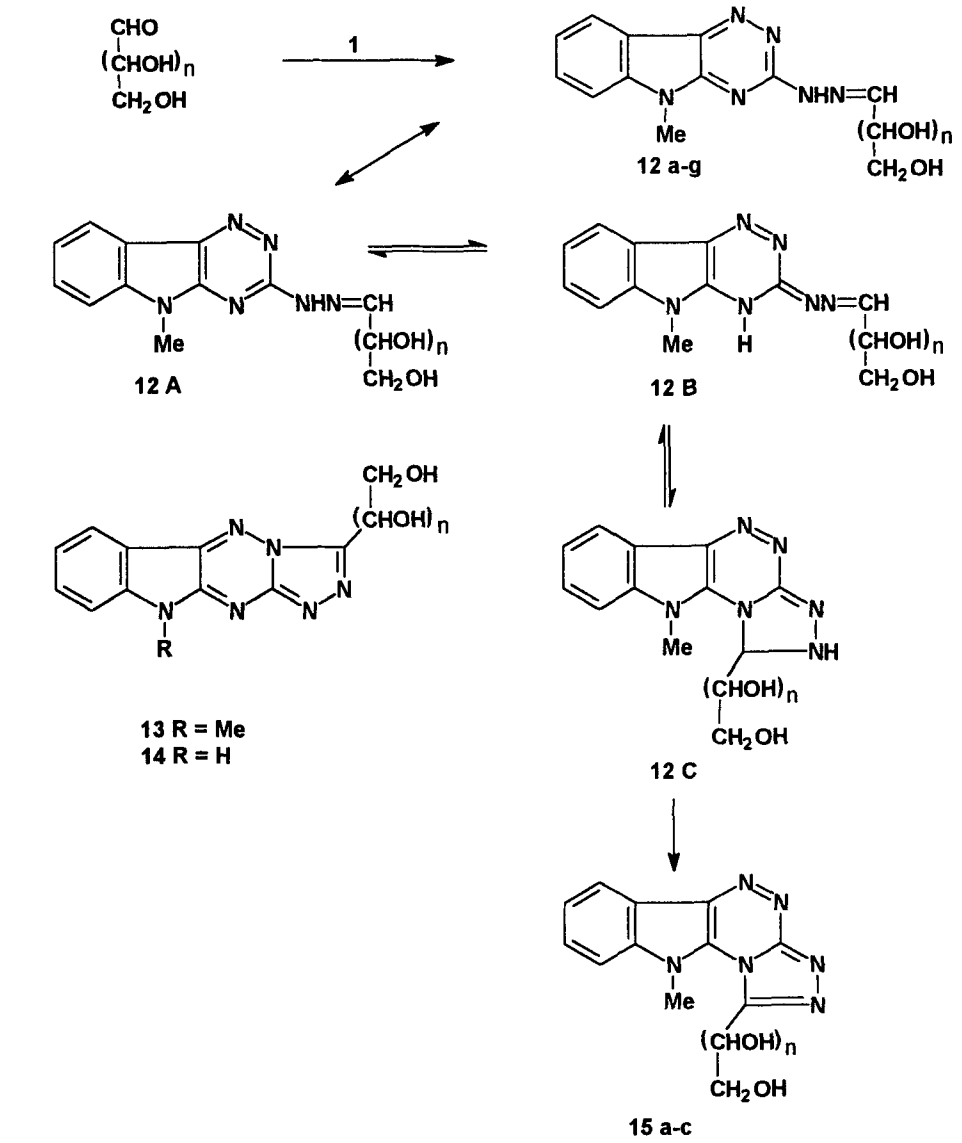
triazolo ring with a linear arrangement as in **7**. This behaviour was similar to that of the corresponding unmethylated derivative, where **8** was the product of dehydrative cyclization and not the angular isomer **5**. This alternative formation of **7** provided additional confirmatory evidence for the assignment of the structure of the isomeric products.

The products from the oxidation of sugar derivatives were assigned as the angular structure **15** rather than **13** based on the above model study. The formation of **15** may be caused by the propensity of the N-4 rather than N-2 of the triazine ring to be involved in a ring chain tautomerism to form **12C**. Subsequent dehydrogenation of **12C** would readily give **15**. This result may be attributed to the more nucleophilic character of N-4 compared to N-2 as a consequence of the contribution of the resonating structures **12A**, which tautomerises to **12B**. The involvement of N-4 in the ring chain tautomerism as well as in the cyclization step would lead to a contribution of chain or cyclic tautomers and subsequently to products possessing the azo group such as in **15**. Although these are the structures that are assigned for the products, they may not be the strictly favored ones from a theoretical point of view. A higher contribution to the ground state of one of the two Kekule' structures of the simple triazine ring which does not possess an azo group has been proposed from theoretical calculation[1-4]. Although, this has been supported by X-ray crystallographic structure determination of the simple 1,2,4-triazine ring, its fusion to a heterocyclic ring may change the situation. The stabilization factor that played a major role in the annellation process seems to be the higher resonance energy resulting from the preservation of the 10 π-electron system of the indole ring in **15** and in the tautomeric intermediate **12C**. This represents the opposite situation to that described with the unsubstituted analogs[25,26] to give **14**. The methyl group may induce the pair of electrons of N-5 to be more available for contribution in preserving the aromatic ring character of the indole ring by an inductive effect.

Conventional acetylation of **12** and **15** gave the peracetyl derivatives **16** and **18**, respectively. The structure **17** was ruled out based on the spectral data[28].

Periodate oxidation of **12a** and **15a** gave the aldehydes **19** and **20**, respectively. This indicated that the periodate could not achieve an oxidative cyclization of the hydrazone. Condensation of **20** with the hydrazine **1** afforded the corresponding hydrazone **21**.

The functional groups in the products were confirmed by bands in their IR spectra indicating the presence of OCN group (1707 cm^{-1}) in **6** and the absence of this band in the spectrum of **7**. Double bond vibrations for C=N appear in the region 1604-1574 cm^{-1}. The spectra of the acetates **16** and **18** showed the presence of OAc groups (1742-1754



Scheme 2

cm^{-1}) instead of the hydroxyl groups (3391-3458 cm^{-1}) of their precursors. Compounds **16** showed an additional band at 1695-1698 cm^{-1} due to the NAc group. The IR spectrum of **21** showed the absence of the aldehydic group (1700 cm^{-1}) that was present in its precursor.

EXPERIMENTAL

General methods. -- Melting points were determined on a Meltemp apparatus and are uncorrected. IR spectra were recorded with a Unicam SP1025 spectrometer. ^1H NMR spectra were determined with a Varian EM-390 spectrometer. The chemical shifts are expressed in the δ scale using tetramethylsilane as a reference. TLC was performed on Bakerflex silica gel 1B-F (2.5-7.5 cm) plates. Microanalyses were performed in the unit of Microanalysis at the Universities of Cairo, El-Mansoura and Assuit.

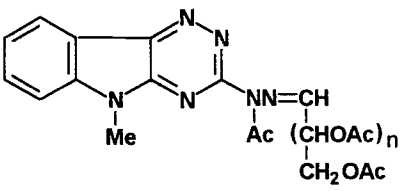
Acetaldehyde (5-methyl-1,2,4-triazino[5,6-*b*]indol-3-yl)hydrazone (2): To a solution of **1** (2.14 g, 10 mmol) in EtOH (50 ml), MeCHO (0.4 ml, 10 mmol) and two drops of AcOH were added and the reaction mixture was heated under reflux for 2 h. The product that separated out on cooling, was filtered, washed with EtOH and dried. It was recrystallized from EtOH as yellow crystals (1.4 g, 65%), m.p. 304-305°C; ν_{max}(KBr): 3211 (NH) and 1607 cm^{-1} (C=N).

Anal. Calcd. for $C_{12}H_{12}N_6$ (240.27): C 60.0; H 5.0; N 35.0. Found: C 60.3; H 5.2; N 35.4.

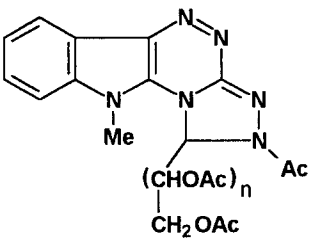
1,10-Dimethyl-1,2,4-triazolo[3',4':3,4][1,2,4]triazino[5,6-*b*]indole (4): (a) A 2M solution of $FeCl_3$ in EtOH (1.0 ml) was added dropwise to a boiling solution of **2** (2.4 g, 10 mmol) in EtOH (150 ml). Heating was continued for 15 min. and the mixture was kept overnight at RT and then concentrated under reduced pressure to about 10 ml. The product that separated out was filtered, washed repeatedly with H_2O and recrystallized from EtOH-DMF as yellow crystals (1.5 g, 62%), m.p. 234-235°C; ν_{max}(KBr): 1604 cm^{-1} (C=N); ^1H NMR (DMSO-d_6) δ : 2.63 (s, 3 H, C-Me), 3.58 (s, 3 H, N-Me), 7.12 (t, 1 H, *J* 7.0 Hz, H-7), 7.53 (d, 1 H, *J* 7.0 Hz, H-9), 7.50 (t, 1 H, *J* 7.0 Hz, H-8) and 7.90 (d, 1 H, *J* 7.0 Hz, H-6).

Anal. Calcd. for $C_{12}H_{10}N_6$ (238.25): C60.5; H 4.2; N 35.3. Found: C 60.6; H 4.0; N 35.6.

(b) A solution of **2** (0.6 g, 2.5 mmol) in EtOH (40 ml) was treated with Pd/C (0.6 g). The reaction mixture was boiled under reflux for 2 h. and then filtered off. The product



16 a,d,e



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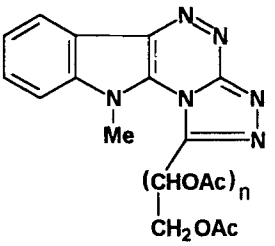
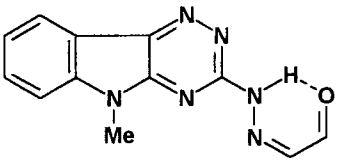


18 a-c



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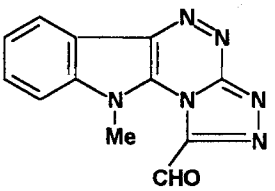

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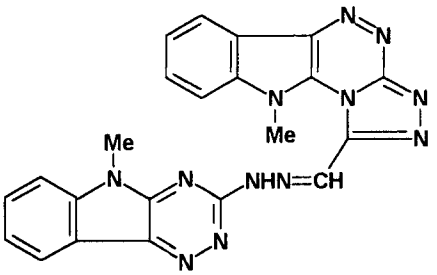

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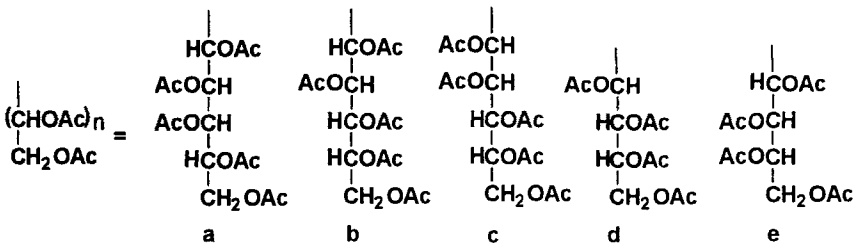

Scheme 3

that separated out on cooling was recrystallized from EtOH as yellow crystals (0.5 g, 89%), m.p. 234-235°C, identical with the product from (a).

3-Acetylhydrazino-5-methyl-1,2,4-triazino[5,6-*b*]indole (6): A solution of **1** (2.14 g, 10 mmol) in AcOH (20 ml) was boiled for 1 h. The orange product that separated out on cooling, was filtered off and recrystallized from EtOH-DMF to give orange crystals (1.7 g, 80%), m.p. > 300°C; ν_{max}(KBr): 3261 (NH), 1707 (OCN) and 1605 cm^{-1} (C=N and C=C). ^{1}H NMR (DMSO-d6) δ: 2.77 (s, 3 H, COMe), 3.75 (s, 3 H, N-Me), 7.42 (t, 1 H, H-8), 7.68 (d, 1 H, $J_{6,7}$ 5.8 Hz H-6), 7.82 (t, 1 H, H-7) and 8.22 (d, 1 H, $J_{8,9}$ 3.9 Hz, H-9).

Anal. Calcd. for $C_{12}H_{12}N_6O$ (256.27): C 56.2; H 4.1; N 32.8. Found: C 56.0: H 4.0; N 32.7.

3,10-Dimethyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-*b*]indole (7): (a) A solution of **9** (0.16 g, 1.0 mmol), **11** (0.15 g, 1.0 mmol) and $MeCO_2Na$ (0.08 g, 1.0 mmol) in a mixture of EtOH (20 ml) and H_2O (5 ml) was heated under reflux for 1 h. AcOH (0.2 ml) was added, and heating was continued for 2 h. The product that separated out on cooling was filtered off, washed with EtOH and recrystallized from EtOH-DMF as orange crystals (0.14 g, 82%), m.p. 330°C (lit.[12] m.p. 331-332°C), ν_{max} (KBr): 1604 cm^{-1} (C=N). ^{1}H NMR (DMSO-d6) δ: 2.74 (s, 3 H, C-Me), 3.72 (s, 3 H, N-Me), 7.39 (dd, 1 H, H-7), 7.65 (d, 1 H, $J_{8,9}$ 8.3 Hz, H-9), 7.80 (dd, 1 H, $J_{7,8}$ 7.3 Hz, H-8) and 8.19 (d, 1 H, $J_{6,7}$ 7.7 Hz, H-6).

(b) A solution of **1** (0.21 g, 1 mmol) in AcOH (20 ml) was boiled for 8 h. The orange product that separated out on cooling was filtered off and recrystallized from EtOH-DMF (0.17 g, 80%), m.p. 330°C. It is identical with the product from method (a).

Sugar (5-methyl-1,2,4-triazino[5,6-*b*]indol-3-yl)hydrazone (12a-g): A solution of the respective sugar (10 mmol) in H_2O (5 ml), was treated with a solution of **1** (2.14 g, 10 mmol) in EtOH (50 ml) and few drops of AcOH. The mixture was boiled under reflux for 2 h. The product that separated out on cooling, was filtered, washed with EtOH and dried. The yellow product was recrystallized from EtOH-DMF (Table 1).

1-(Alditol-1-yl)-10-methyl-1,2,4-triazolo[3',4':3,4][1,2,4]triazino[5,6-*b*]indole (15a-c): A 2M solution of $FeCl_3$ in EtOH (0.5 ml) was added dropwise to a boiling solution of **12** (1.0 g, 3.62 mmol) in EtOH (150 ml). Heating was continued for 15 min. and the mixture was kept overnight at RT and then concentrated under reduced pressure to about 20 ml and the residue was recrystallized from EtOH-DMF as yellow crystals (Table 1).

Table 1. Elemental Analysis

Compd. No.	Yield %	Mp °C	Molecular formula (M.wt)	Calcd. Found	Analysis % C	H	N
12a	70	184-185	$C_{16}H_{20}N_6O_5$		51.1	5.3	22.3
			(376.37)		50.9	5.0	22.2
12b	64	179-198	$C_{16}H_{20}N_6O_5$		51.1	5.3	22.3
			(376.37)		51.3	5.2	22.0
12c	60	179-182	$C_{16}H_{20}N_6O_5$		51.1	5.3	22.3
			(376.37)		51.3	4.9	22.5
12d	72	165-167	$C_{15}H_{18}N_6O_4$		52.0	5.2	24.3
			(346.34)		52.4	5.5	24.2
12e	70	194-196	$C_{15}H_{18}N_6O_4$		52.0	5.2	24.3
			(346.34)		52.4	5.1	24.0
12f	60	162-164	$C_{15}H_{18}N_6O_4$		52.0	5.2	24.3
			(346.34)		51.7	5.3	24.2
12g	60	182-184	$C_{15}H_{18}N_6O_4$		52.0	5.2	24.3
			(346.34)		52.2	5.2	24.5
15a	55	238-240	$C_{16}H_{18}N_6O_5$		51.3	4.8	22.5
			(374.35)		51.5	4.6	22.3
15b	60	260-263	$C_{16}H_{18}N_6O_5$		51.3	4.8	22.5
			(374.35)		51.6	4.7	22.5
15c	56	245-248	$C_{16}H_{18}N_6O_5$		51.3	4.8	22.5
			(374.35)		51.2	4.6	22.1
16a	75	190-191	$C_{28}H_{32}N_6O_{11}$		53.5	5.1	13.4
			(628.59)		53.3	5.3	13.5
16d	75	170-173	$C_{25}H_{28}N_6O_9$		54.0	5.0	15.1
			(556.52)		53.7	5.3	15.1
16e	70	168-171	$C_{25}H_{28}N_6O_9$		54.0	5.0	15.1
			(556.52)		53.7	5.3	15.0
18a	65	198-200	$C_{26}H_{28}N_6O_{10}$		53.4	4.8	14.4
			(584.53)		53.1	4.7	14.6
18b	60	226-228	$C_{26}H_{28}N_6O_{10}$		53.4	4.8	14.4
			(584.53)		53.1	4.8	14.2
18c	60	214-216	$C_{26}H_{28}N_6O_{10}$		53.4	4.8	14.4
			(584.53)		53.3	4.5	14.6

Per-O-acetyl aldehydo sugar-1-acetyl-1-(5-methyl-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazone (16a,d,e): A cold solution of **12** (1.5 mmol) in dry pyridine (5.0 ml) was treated with Ac_2O (5.0 ml). The mixture was kept overnight at RT with occasional shaking. It was poured onto crushed ice and the product, that separated out, was filtered off, washed repeatedly with H_2O, dried and recrystallized from EtOH as yellow crystals (Table 1).

1-(Penta-*O*-acetyl-pentitol-1-yl)-10-methyl-1,2,4-triazolo[3',4':3,4][1,2,4]triazino-[5,6-*b*]indole (18a-c): A cold solution of **15** (0.5 g, 1.3 mmol) in dry pyridine (5.0 ml) was treated with Ac_2O (5.0 ml). The reaction mixture was kept for 3 days at RT with occasional shaking, then poured onto crushed ice and the product was filtered off, washed with H_2O and dried. It was recrystallized from EtOH as yellow needles (Table 1).

Glyoxal mono(5-methyl-1,2,4-triazino[5,6-*b*]indol-3-yl)hydrazone (19): A suspension of **12a** (1.8 g, 5.0 mmol) in distilled H_2O (100 ml) was treated with a solution of $NaIO_4$ (4.3 g, 20.0 mmol) in distilled H_2O (50 ml). The mixture was stirred for 5 h. and then kept overnight at RT The product was filtered, washed successively with H_2O, $Na_2S_2O_3$ and KI solutions and dried. It was recrystallized from EtOH-DMF as yellow crystals (0.7 g, 40%), m.p. 265-268°C; ν_{max}(KBr): 3218 (NH), 1712 (CHO) and 1609 cm^{-1} (C=N). ^1H NMR (DMSO-d_6) δ: 3.75 (s, 3 H, N-Me), 7.30-8.33 (m, 6 H, aromatic methine and aldehydic protons) and 10.13 (s, 1 H, NH).

Anal. Calcd. for $C_{12}H_{10}N_6O$ (254.25): C 56.7; H 3.9; N 33.1. Found: C 56.9; H 3.9; N 33.0.

1-Carbaldehydo-10-methyl-1,2,4-triazolo[3',4':3,4][1,2,4]triazino[5,6-*b*]indole (20): A suspension of **15a** (1.8 g, 5.0 mmol) in distilled H_2O (100 ml) was treated with a solution of $NaIO_4$ (4.3 g, 20.0 mmol) in distilled H_2O (50 ml). The mixture was then processed as above. The product was recrystallized from EtOH-DMF as yellow crystals (0.8 g, 45%), m.p. 298-299°C; ν_{max} (KBr): 1700 (CHO) and 1606 cm^{-1} (C=N).

Anal. Calcd. for $C_{12}H_8N_6O$ (252.23): C 57.1; H 3.2; N 33.3. Found C 57.1; H 3.1; N 33.0.

(10-Methyl-1,2,4-triazolo[3',4':3,4][1,2,4]triazino[5,6-*b*]indol-1-yl)carbaldehyde (5-methyl-1,2,4-triazino[5,6-*b*]indol-3-yl)hydrazone (21): To a solution of **20** (0.25 g, 1.0 mmol) in EtOH (15 ml), a solution of **1** (0.2 g, 1.0 mmol) in EtOH (10 ml) and few drops of AcOH were added. The mixture was heated under reflux for 1 h, and the product that separated out on cooling was filtered off, washed with EtOH and dried. It was recrystallized from EtOH-DMF as red crystals (0.2 g, 60%), m.p.> 300°C; ν_{max}(KBr): 3203 (NH) and 1605 cm^{-1} (C=N).

Anal. Calcd. for $C_{22}H_{16}N_{12}$ (448.45): C 58.9; H 3.6; N 37.5; Found: C 59.1; H 3.7; N 37.2.

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