Aromatization and Ring Cyclization: A Reasonable Understanding on the Ring Cyclization Mechanism of 3-Amino-6-hydrazino-1,2,4-triazin-5(2*H*)-one Reacted with One-carbon Fragment Reagents or Nitrous Acid

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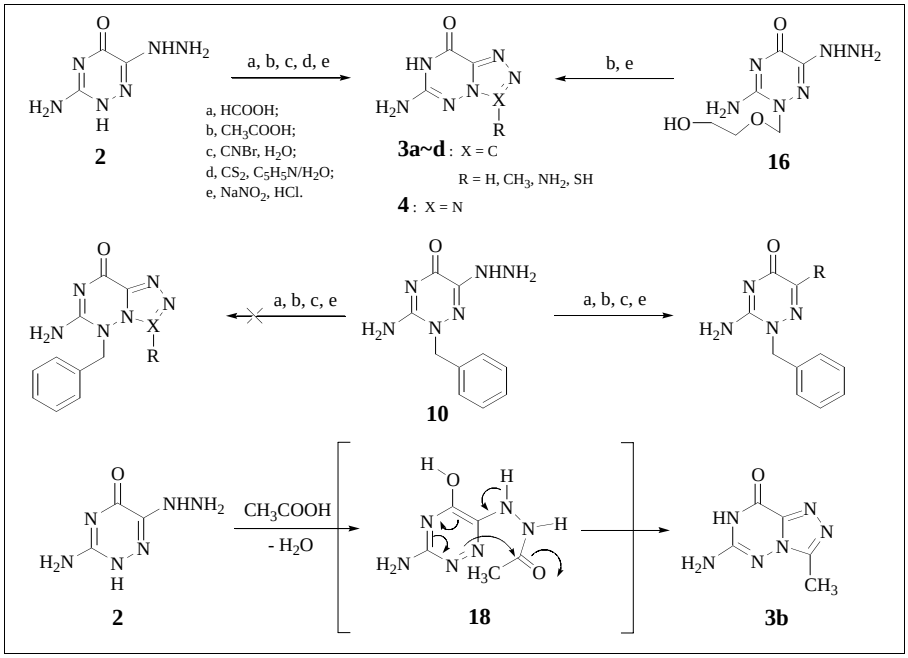

The cyclization mechanism for the title compound (**2**) reacting with one-carbon fragment reagents or nitrous acid to afford heterobicyclic compounds 6-amino-3-substituted-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-ones (**3a~d**) or 6-amino-1,2,3,4-tetrazolo[5,1-*f*][1,2,4]triazin-8(7*H*)-one (**4**), respectively, is explored in this paper. When 3-amino-2-benzyl-6-hydrazino-1,2,4-triazin-5(2*H*)-one (**10**), the N-2 benzylated derivative of **2**, is treated under the same conditions, ring cyclization does not occur; instead, 3-amino-2-benzyl-6-substituted-1,2,4-triazin-5(2*H*)-ones (**11,12,14**) and 2-*N*-(2-amino-1-benzyl-4-oxo-1,2,4-triazin-5-yl)semicarbazide (**13**) are formed. Alternatively, when 3-amino-6-hydrazino-2-[(2-hydroxyethoxy)methyl]-1,2,4-triazin-5(2*H*)-one (**16**), a compound bearing the 2-[(2-hydroxyethoxy)methyl] side-chain at N-2 of **2** by an N-C-O bond, reacts with glacial acetic acid or nitrous acid, the side-chain is cleaved through acidolysis to affford the ring-closed compound 6-amino-3-methyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (**3b**) or compound **4**, respectively. From these results, we suggest a cyclization mechanism that the ring cyclization is dependent on the aromatization of the 1,2,4-triazine ring, which influence the reactivity and reaction behavior of the π-deficient 1,2,4-triazine.

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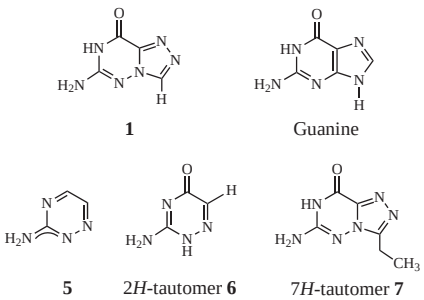
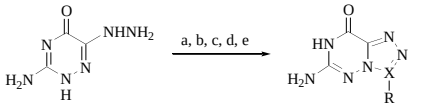
Introduction.

The 1,2,4-triazines and their condensed derivatives form an important class of heteroaromatic compounds with various biochemically interesting properties and pharmacologically significant activities [1-5]. The structure moiety of 6-amino-1,2,4-triazolo[3,4-*f*][1,2,4]-triazin-8(7*H*)-one (**1**), the isosteric isomer of guanine, is a tautomeric heterobicycle which may retain the Watson-Crick type hydrogen bonding sites of the aglycon moiety.



Derivatives of **1** may be prepared from suitably substituted 1,2,4-triazoles as reported by Becker *et al.* [6]. Lovelette, however, described a more convenient synthesis and facile ring closure reaction by reacting the compound 3-amino-6-hydrazino-1,2,4-triazin-5(2*H*)-one (**2**) with one-carbon fragment reagents (*e.g.* aliphatic acids, orthoesters, cyanogen bromide or carbon disulfide) or nitrous acid to afford 6-amino-3-substituted-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-ones (**3a~d**), 3-substituted derivatives **1**, or 6-amino-1,2,3,4-tetrazolo[1,5-*f*]-[1,2,4]triazin-8(5*H*)-one (**4**), respectively (Scheme 1) [7].

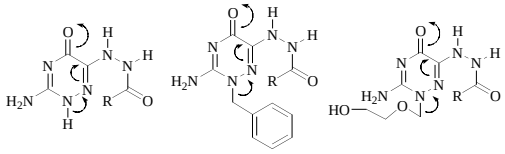
Scheme 1



2 **3a~d** : X = C, R = H, CH_3, NH_2, SH; **4** : X = N

a, HCOOH; b, CH_3COOH; c, CNBr, H_2O; d, CS_2, C_5H_5N/H_2O; e, $NaNO_2$, HCl.

Since the correct dominant tautomeric structure makes it possible to properly interpret the detailed mechanisms of reactions, the biological activities and the functions of tautomeric heterocycles [8], we investigated on the Kekulé structure which gave higher contribution to the ground state of the basic structure 3-amino-1,2,4-triazine (**5**) [9]. Additionally, we studied the prototropic tautomerism of 3-amino-1,2,4-triazin-5(2*H*)-one (**6**) and 6-amino-3-ethyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (**7**) by X-ray crystallographic analysis [10,11], which revealed the predominant tautomeric structure of compound **6** as the 2*H*-tautomer and that of compound **7** as the 7*H*-tautomer (not the 5*H*-tautomer as speculated by Lovelette [7]). These results inspired us to understand more about the actual mechanism for this ring cyclization of the compound **2** reacting with one-carbon fragment reagents to afford tautomeric heterobicycles (**3**). One of our previous study [12] has proved the hypothesis that the ring cyclization is dependent on the resonance of the 2*H*-5-one to the 5-ol on the 1,2,4-triazine ring (Figure 1. type I structure). This is based on the fact that when 3-amino-2-benzyl-6-hydrazino-1,2,4-triazin-5(2*H*)-one (**10**), an N-2 benzylated derivative of **2**, is treated with *N*,*N*-dimethylformamide (DMF) and acetic acid to afford 3-amino-2-benzyl-6-(2-formylhydrazino)-1,2,4-triazin-5(2*H*)-one (**11**), no ring cyclization is observed since the N-2 benzyl group prevents the prototropic tautomerism required in the formation of the aromatic intermediate (Figure 1. type II structure). Similar to the above way to clarify the cyclization mechanism, in this paper we treated compound **10** with one-carbon fragment reagents (formic acid, glacial acetic acid or cyanogen bromide) or nitrous acid, expecting no observed ring cyclization.



Type I Type II Type III

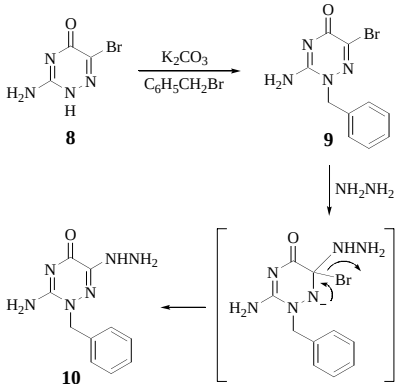
Figure 1. Illustration on the electron resonance of three different structure types.

On the contrary, a side-chain on N-2 may undergo bond-breaking and then the 1,2,4-triazine ring may be aromatized by the electron pair resonating from N-2 to 5-oxo (Figure 1. type III structure). In such a case, ring cyclization will be observed. As we know, the chemical character of methylene carbon in N-C-O bond is similar to that in O-C-O bond, which could be acidolyzed in acidic conditions. Accordingly, we synthesized the compound 3-amino-6-hydrazino-2-[(2-hydroxyethoxy)methyl]-1,2,4-triazin-5(2*H*)-one (**16**) which contains a 2-[(2-hydroxyethoxy)methyl] side-chain attached by an N-C-O bond on N-2 of compound **2**, then treated **16** with glacial acetic acid or nitrous acid, trying to validate the cyclization mechanism.

Results and Discussion.

We improved the product yield (>50%) of the requisite compound 3-amino-2-benzyl-6-bromo-1,2,4-triazin-5(2*H*)-one (**9**), which was prepared by a new method from 3-amino-6-bromo-1,2,4-triazin-5(2*H*)-one (**8**) refluxed with potassium carbonate and benzyl bromide in dry acetone catalyzed by 18-crown-6-ether (Scheme 2). Compound **9** is identical in every respect with the corresponding compound in our previous report [12]. Hydrazination of **9** gave compound **10** successfully by nucleophilic hetero-aromatic substitution (the hydrazination mechanism as illustrated in Scheme 2).

Scheme 2

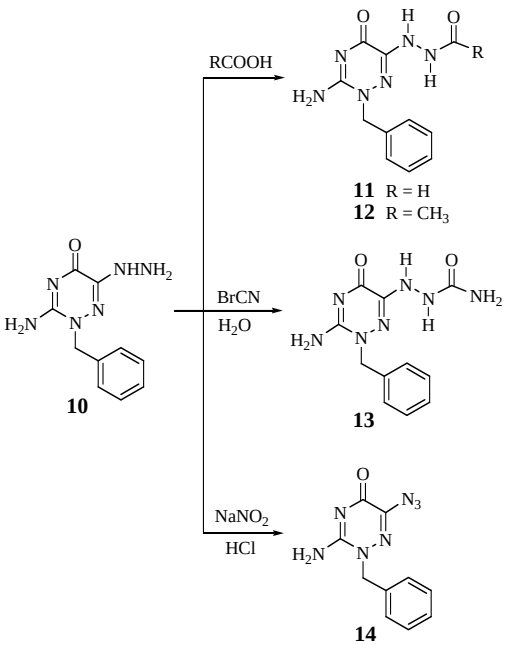


8 **9** **10**

Scheme 3 shows that compound **10** reacts with one-carbon fragment reagents or nitrous acid to afford compounds **11**-**14**, respectively. Compound **10** was treated with hot formic acid to give 3-amino-2-benzyl-6-(2-formylhydrazino)-1,2,4-triazin-5(2*H*)-one (**11**). The ^{1}H nmr spectrum revealed a conformer mixture of **11** in a ratio of about 2:1, and the same chemical shift was observed between the major conformer and the product from **10** reacted with DMF and acetic acid [12].

When compound **10** was treated with hot glacial acetic acid, 3-amino-2-benzyl-6-(2-acetylhydrazino)-1,2,4-triazin-5(2*H*)-one (**12**) was isolated. The ^{1}H nmr spectrum found a conformer mixture of **12** in a ratio of about 10:1, and revealed δ 1.81 ($COCH_3$), 8.04 (N*H*NHCO) and 9.60 (NHN*H*CO) ppm for the acetylhydrazino group. The structures of the major conformers of **11** and **12** were derived from the MM2 and *ab initio* HF/6-31G minimization calculations carried out by the CSGAMESS suite of computer programs. Figure 2 shows the most stable conformations and major/minor conformers of **11** and **12**.

Scheme 3



Treatment of compound **10** with cyanogen bromide refluxed in water led to 2-*N*-(2-amino-1-benzyl-4-oxo-1,2,4-triazin-5-yl)semicarbazide (**13**). The ^{1}H nmr spectrum showed δ 5.98 ppm corresponding to $CONH_2$ and two singlets at δ 7.41 and 7.71 ppm corresponding to the N*H*NHCO and NHN*H*CO protons, respectively.

Reaction of compound **10** with nitrous acid at 0 °C gave 3-amino-6-azido-2-benzyl-1,2,4-triazin-5(2*H*)-one (**14**). The ir spectrum exhibiting an intense absorption at 2122 cm^{-1}, which was diagnostic for the existence of the 6-azido functional group.

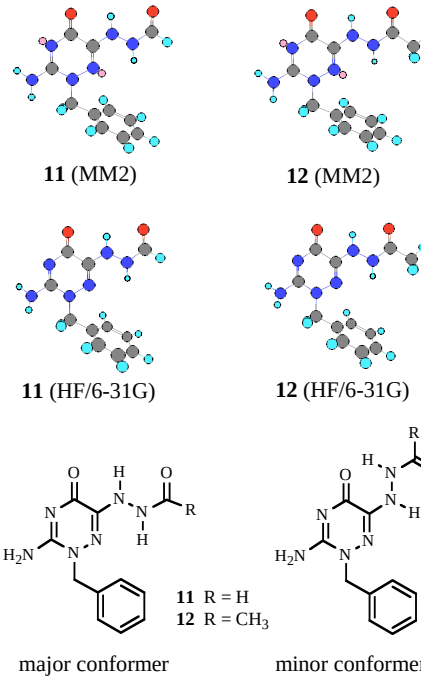
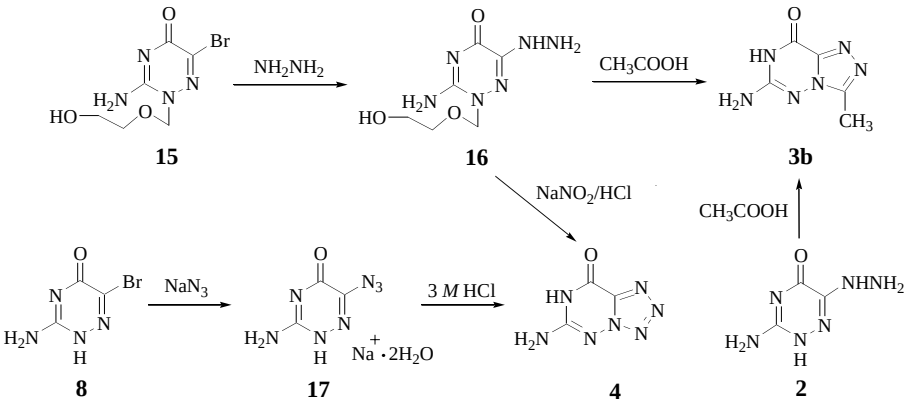


Figure 2

The existence of benzyl groups of these compounds **11**-**14** was shown by its ^{1}H nmr spectrum. The ir spectra of the carbonyl groups on **11**-**14** (*i.e.*, 1666, 1639, 1679 and 1642 cm^{-1}, respectively) suggested that these four compounds did not undergo acidolysis and the ring closure didn't occur, because the intense ir absorption at 1719-1725 cm^{-1} (the carbonyl absorption for fused triazines) indicated the occurrence of ring closure [6,7,12]. This result proved that if tautermerism of the 2*H*-5-one to the 5-ol on the hydrazino-1,2,4-triazine did not occur, no cyclization would be observed (Figure 1. type II structure).

On the other hand, we prepared compound **16** by refluxing 3-amino-6-bromo-2-[(2-hydroxyethoxy)methyl]-1,2,4-triazin-5(2*H*)-one (**15**) [13] with hydrazine monohydrate in ethanol (Scheme 4). The 6-hydrazino group of **16** was characterized by the ^{1}H nmr spectrum at δ 3.92 (NHNH_2) and 7.30 (N*H*NH_2) ppm. When **16** was treated with hot glacial acetic acid, product **3b** was isolated. The ^{1}H and ^{13}C nmr spectra confirmed that the 2-[(2-hydroxyethoxy)methyl] side-chain was lost. The intense ir absorption of **3b** at 1729 cm^{-1} suggested the occurrence of ring closure [6,7,12]. Furthermore, the mass spectrum and the elemental analyses confirmed the formula as $C_5H_6N_6O$. Further confirmation of the structure of **3b** *via* alternative approach was to synthesize **3b** by reacting **2** with hot glacial acetic acid, as described by Lovelette

Scheme 4



(Scheme 4) [7]. The most contributing prototropic tautomerism of **3b** was conjectured by the X-ray analysis of **7** as the 7*H*-tautomer. Taking these evidences together, the structure of **3b** was assigned as 6-amino-3-methyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one.

When compound **16** was treated with sodium nitrite in hydrochloride solution, compound **4** was isolated (Scheme 4). The ^{1}H and ^{13}C nmr spectra revealed the 2-[(2-hydroxyethoxy)methyl] side-chain was lost. The mass spectrum and the elemental analyses confirmed the formula of **4** as $C_3H_3N_7O$. The ir spectrum exhibited the intense absorption of carbonyl group for similar fused triazines but not of azido group. We checked the structure of **4** by an alternative approach as described below. Compound **8** refluxed with sodium azide in ethanol to afford compound **17**, which had an intense ir absorption for 6-azido group at 2206 cm^{-1}. The formula of **17**, a sodium bihydrate salt, was confirmed by elemental analyses as $C_3H_3N_7O{\bullet}Na^{+}{\bullet}2H_2O$. Compound **17** was then stirred with 3 *M* hydrochloric acid at room temperature overnight to give **4** (Scheme 4). From these results we proved that the 2-[(2-hydroxyethoxy)methyl] side-chain on N-2 underwent bond-breaking and then the ring cyclization occurred (Figure 1. type III structure).

The product from fragment $HOCH_2CH_2OCH_2$- of compound **16** after reaction with hot glacial acetic acid (Scheme 4) was isolated and characterized by the ^{1}H nmr (200 MHz) spectrum [δ_H 2.08 (6H), 3.86 (2H), 4.24 (2H), 5.34 (2H)] and the ^{13}C nmr (200 MHz) spectrum [δ_C 20.63, 62.15, 70.29, 79.96, 174.73]. Additional supporting evidence was the GC/MS spectrum [m/z 177 (M^{+}+1), 133 (M^{+}–CH_3CO), 117, 101, 89, 87, 73, 59, 45, 43]. Taken together, we assigned the product's molecular formula as $CH_3COOCH_2OCH_2CH_2OCOCH_3$, acetic acid 2-acetoxy-

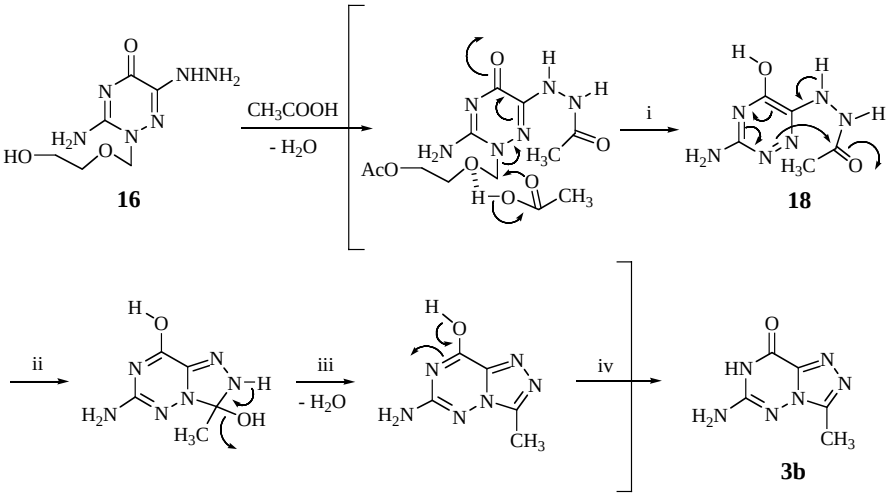


Figure 3. The proposed mechanism for the acidolysis and ring cyclization of compound **16** refluxed with glacial acetic acid to form compound **3b**. i, electron resonance and aromatization; ii, deprotonation, £k-electron resonance and ring cyclization; iii, dehydration; iv, the most contributed protropic tautomerism.

ethoxymethyl ester (MW 176.17). A reasonable mechanism explaining the reaction mechanism for the acidolysis and cyclization of **16** to form **3b** is shown in Figure 3. Initially the hydrazino group and the 2-[(2-hydroxyethoxy)methyl] side-chain of **16** were acetylated. The acetylated 2-[(2-acetoxyethoxy)methyl] side-chain was then acidolyzed by glacial acetic acid. The N-2 electron pair then resonated to the 5-oxo to aromatize the 1,2,4-triazine ring, forming the important intermediate 3-amino-6-(2-acetyldrazino)-1,2,4-triazin-5-ol (**18**). Sequentially, deprotonation of the *N*-1 hydrogen of the 6-acetylhydrazino group gave the electron pair into 1,2,4-triazine ring *via* π-electron resonance. The 1,2,4-triazine ring then served as a nucleophile, allowing for the intramolecular cyclization at N-1 of the intermediate **18**, followed by dehydration and tautomerization to the predominant form 7*H*-tautomer **3b**.

Figure 4 shows the proposed cyclization mechanism for **2** refluxed with glacial acetic acid to form the 7*H*-tautomer **3b**. This may serve as a typical cyclization mechanism of **2** reacted with one-carbon fragment reagents.

Conclusions.

In this research we suggest that the mechanism for the cyclization of **2** reacted with one-carbon fragment reagents incorporates three important points: (1) the tautomerism of the N-2 hydrogen with the C-5 oxo group aromatizes the 1,2,4-triazine ring, (2) the aromatized 1,2,4-triazine ring supplies a π-electron resonance pathway, and (3) deprotonation of the *N*-1 hydrogen the 6-hydrozino group gives the electron pair into the aromatic π-deficient 1,2,4-triazine ring, thus increases its nucleophilicity which leads to the ring cyclization. Briefly, the ring cyclization is dependent on the aromatization of the 1,2,4-triazine ring, which influence the reactivity and reaction behavior of the π-deficient 1,2,4-triazine. This reasonable understanding on the cyclization mechanism will benefit us when synthesizing new heterobicycles of 6-amino-3-substituted-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-ones from such as 3-amino-6-[2-alkylidenehydrazinyl]-1,2,4-triazin-5(2*H*)-ones or 3-amino-6-[2-arylidenehydrazinyl]-1,2,4-triazin-5(2*H*)-ones.

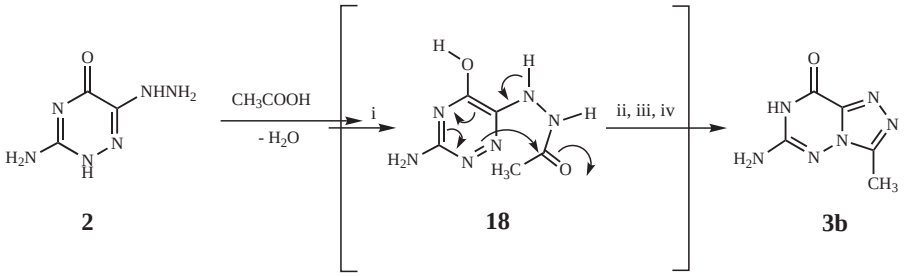


Figure 4. The proposed mechanism for the ring cyclization of compound **2** refluxed with glacial acetic acid to form compound **3b**. The processes of i, ii, iii and iv are the same as Figure 3.

EXPERIMENTAL

Melting points were measured on a YANACO micromelting point apparatus and were uncorrected. The ir spectra were taken with potassium bromide (KBr) discs on a Perkin-Elmer FTIR 1650 spectrophotometer and the uv absorption spectra were recorded on a Shimadzu UV-Visible spectrophotometer. The ^{1}H and ^{13}C nmr spectra were obtained in dimethylsulfoxide-d_6 (DMSO-d_6) on a Varian Gemini 200 (200 MHz) or a Varian Unity 400 (400 MHz) spectrometer. Chemical shifts are expressed in ppm (δ) with tetramethylsilane (Me_4Si) as an internal standard. Coupling constants J are given in Hertz (Hz); multiplicities were recorded as broad peaks (br), singlet (s), doublets (d), triplets (t), quartets (q), and multiplets (m). Thin layer chromatography (tlc) analyses were performed on silica gel plates (Merck 60 F_{254}, 0.2 mm thickness), and the components were detected by uv light (254 nm). The ms and hrms spectra were obtained on a Quattro VG-5022 spectrometer and VG 70-250S GC/MS, respectively, with an ionization potential of 70 eV. Elemental analyses were performed on a Heraeus CHN-O-Rapid elemental analyzer. All the solvents used were dried and distilled under argon prior to use.

3-Amino-6-hydrazino-1,2,4-triazin-5(2*H*)-one (**2**) and 3-amino-6-bromo-1,2,4-triazin-5(2*H*)-one (**8**)

Both compounds were prepared as described by Lovelette [7].

3-Amino-2-benzyl-6-hydrazino-1,2,4-triazin-5(2*H*)-one (**10**) and 3-amino-6-bromo-2-[(2-hydroxyethoxy)methyl]-1,2,4-triazin-5(2*H*)-one (**15**)

Both compounds were prepared as described by us [12,13].

3-Amino-2-benzyl-6-bromo-1,2,4-triazin-5(2*H*)-one (**9**)

A solution of **8** (0.57 g, 3 mmoles) in dry acetone (30 mL) was mixed with anhydrous potassium carbonate (0.41 g, 3

mmoles) and a catalytic amount of 18-crown-6-ether (0.08 g, 0.3 mmoles). Then benzyl bromide (0.51 g, 3 mmoles) was added and refluxed for 24 hours. The solvent was evaporated to afford a crude product which was then applied to a silica gel (230-400 mesh) column. The column was eluted with a mixed solvent of chloroform and methanol (60:1) and the proper fractions were combined and evaporated. The residue thus obtained was recrystallized from dichloromethane and ethanol (5:1) to give a white crystal compound 0.46 g (55%) of **9**, which was a material identical in every respect with the corresponding compound in our previous research [12].

3-Amino-2-benzyl-6-(2-formylhydrazino)-1,2,4-triazin-5(2*H*)-one (**11**).

A solution of compound **10** (0.70 g, 3 mmoles) in 99% formic acid (15 mL) was refluxed for 12 hours. Cooling separated white crystal 0.42 g. The filtrate was evaporated to 3 mL to give 0.13 g. The total crude compound was recrystallized from ethanol to afford **11** (0.41 g, 53%). The product was a white crystal with a conformer mixture in a ratio of about 2:1. The major conformer was a material identical in every respect with the corresponding compound in our previous research [12]; and the minor conformer showed the following spectral data: ^{1}H nmr (400 MHz): δ 5.00 (s, 2H, CH_2), 7.02 (s, 2H, NH_2), 7.22-7.37 (m, 5H, C_6H_5), 7.92 (d, 1H, J = 10.8, N*H*NHCO), 8.75 (s, 1H, CHO), 9.27 (d, 1H, J = 10.8, NHN*H*CO); ^{13}C nmr (200 MHz): δ 54.95 (CH_2), 146.58 (C-6), 154.58 (C-3), 158.28 (C-5), 167.55 (CO).

3-Amino-2-benzyl-6-(2-acetylhydrazino)-1,2,4-triazin-5(2*H*)-one (**12**).

A solution of compound **10** (0.70 g, 3 mmoles) in glacial acetic acid (15 mL) was refluxed for 12 hours. Cooling separated white crystal 0.61 g. The filtrate was evaporated to 3 mL to give 0.11 g. The total crude compound was recrystallized from ethanol to afford **12** (0.61 g, 74%). The product was a white crystal with a conformer mixture in a ratio of about 10:1; mp > 300 °C (from EtOH); ir: (ν, cm^{-1}) 3366, 3190, 1639 (C=O), 1508, 1267, 1077; uv: (0.1 *N* HCl): λ_{max} nm (log ε) 207 (4.01), 240 (3.80), 294 (3.55); (H_2O): λ_{max} nm (log ε) 222 (3.88), 285 (3.35); (0.1 *N* NaOH): λ_{max} nm (log ε) 229 (4.41), 268 (4.11), 332 (3.98); the major conformer ^{1}H nmr (400 MHz): δ 1.81 (s, 3H, CH_3), 4.96 (s, 2H, CH_2), 6.96 (s, 2H, NH_2), 7.23-7.37 (m , 5H, C_6H_5), 8.04 (d, 1H, J = 2.2, N*H*NHCO), 9.60 (d, 1H, J = 2.2, NHN*H*CO); ^{13}C nmr (400 MHz): δ 20.51 (CH_3), 54.88 (CH_2), 145.16 (C-6), 154.11 (C-3), 158.04 (C-5), 168.02 (CO), 127.13, 127.50, 128.44, 135.85 (C_6H_5); the minor conformer ^{1}H nmr (400 MHz): δ 1.73 (s, 3H, CH_3), 5.00 (s, 2H, CH_2), 7.01 (s, 2H, NH_2), 7.23-7.37 (m, 5H, C_6H_5), 7.35 (d, 1H, J = 15.6, N*H*NHCO), 8.73 (d, 1H, J = 15.6, NHN*H*CO); ms: m/z (EI) 274 (M^+, 14), 232 (13), 141 (35), 91 (100), 69 (8), 65 (19); hrms: m/z Calcd. for $C_{12}H_{14}N_6O_2$: 274.1178. Found: 274.1180.

Anal. Calcd. for $C_{12}H_{14}N_6O_2$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.53; H, 5.17; N, 30.40.

2-*N*-(2-Amino-1-benzyl-4-oxo-1,2,4-triazin-5-yl)semicarbazide (**13**).

A solution of compound **10** (0.70 g, 3 mmoles) with cyanogen bromide (0.64 g, 6 mmoles) in water (20 mL) was refluxed for 24 hours. Cooling separated a white crystal compound, which was washed with ice water and then recrystallized from ethanol to give product **13** (0.48 g, 58%), mp 263-265 °C (from EtOH); ir: (ν, cm^{-1}) 3330, 3215, 1679 (C=O), 1589, 1451, 1089; uv: (0.1 *N* HCl): λ_{max} nm (log ε) 205 (3.86); (H_2O): λ_{max} nm (log ε) 266 (3.73); (0.1 *N* NaOH): λ_{max} nm (log ε) 218 (3.37), 266 (3.54) ; ^{1}H nmr (200 MHz): δ 4.43 (d, 1H, J = 13.1, C*H*H-C_6H_5), 5.03 (d, 1H, J = 13.1, CH*H*-C_6H_5), 5.98 (s, 2H, $CONH_2$), 6.49 (s, 2H, 2-NH_2). 7.22 (s, 5H, C_6H_5), 7.41 (s, 1H, N*H*NHCO), 7.71 (s, 1H, NHN*H*CO); ^{13}C nmr (200 MHz): δ 53.22 (CH_2), 141.02 (C-6), 156.56 (C-3), 157.39 (C-5), 158.56 (CO), 128.00, 128.36, 130.12, 135.02 (C_6H_5); ms: m/z (EI) 275 (M^+, 1), 149 (30), 127 (24), 106 (98), 91 (100), 77 (20), 71 (4), 65 (21); hrms: m/z Calcd. for $C_{11}H_{13}N_7O_2$: 275.1131. Found: 275.1131.

Anal. Calcd. for $C_{11}H_{13}N_7O_2$: C, 48.00; H, 4.76; N, 35.62. Found: C, 47.73; H, 4.78; N, 35.41.

3-Amino-6-azido-2-benzyl-1,2,4-triazin-5(2*H*)-one (**14**).

To a solution of compound **10** (0.70 g, 3 mmoles) in 6 *M* hydrochloric acid (6 mL) under stirring at 0 °C, a solution of sodium nitrite (0.24 g, 3.5 mmoles) in water (6 mL) was added drop by drop. After the addition was complete, stirring was continued for an additional 10 minutes and the precipitate was collected. The solid precipitate was suspended in 15 mL of water and was stirred at room temperature overnight. Collection of the precipitate and recrystallization from ethanol produced **14** (0.45 g, 62%), mp 170-171 °C (from EtOH); ir: (ν, cm^{-1}) 3380, 3113, 2122 (N_3), 1642 (C=O), 1535, 1374, 1271, 1152, 1081; uv: (0.1 *N* HCl): λ_{max} nm (log ε) 206 (3.68), 238 (3.31), 296 (3.02), 298 (3.15); (H_2O): λ_{max} nm (log ε) 206 (3.95), 234 (3.94), 236 (3.52), 294 (3.34); (0.1 *N* NaOH): λ_{max} nm (log ε) 239 (3.49); ^{1}H nmr (200 MHz): δ 5.08 (s, 2H, CH_2), 7.27-7.39 (m, 5H, C_6H_5), 7.46 (s, 2H, NH_2); ^{13}C nmr (400 MHz): δ 55.34 (CH_2), 142.73 (C-6), 154.96 (C-3), 158.70 (C-5), 127.24, 127.78, 128.61, 135.21 (C_6H_5); ms: m/z 243 (M^+, 1), 217 (4), 129 (2), 106 (9), 91 (100), 77 (12), 69 (16), 65 (49); hrms: m/z Calcd. for $C_{10}H_9N_7O$: 243.0869. Found: 243.0872.

Anal. Calcd. for $C_{10}H_9N_7O$: C, 49.38; H, 3.73; N, 40.31. Found: C, 49.65; H, 3.66; N, 40.38.

3-Amino-6-hydrazino-2-[(2-hydroxyethoxy)methyl]-1,2,4-triazin-5(2*H*)-one (**16**).

A solution of compound **15** (0.53 g, 2 mmoles) and hydrazine monohydrate (0.4 g, 8 mmoles) in ethanol (30 mL) was refluxed for 16 hours. Evaporating the solvent to 5 mL *in vacuo* afforded a crude solid which was recrystallised from methanol to give white crystal compound **16** (0.32g, 74%), mp 214-215 °C (from MeOH); ir: (ν, cm^{-1}) 3397, 3362, 1677 (C=O), 1618, 1561, 1511, 1109, 1054; uv: (0.1 *N* HCl): λ_{max} nm (log ε) 221 (4.25), 272 (3.73); (H_2O): λ_{max} nm (log ε) 224 (4.19), 288 (3.51); (0.1 *N* NaOH): λ_{max} nm (log ε) 225 (4.31); ^{1}H nmr (200 MHz): δ 3.52-3.58 (m, 4H, OCH_2CH_2O), 3.92 (s, 2H, NHN*H*$_2$), 4.72 (t, 1H, 4'-OH), 5.17 (s, 2H, NCH_2O), 6.90 (s, 2H, NH_2), 7.30 (s, 1H, N*H*NH$_2$); ^{13}C nmr (200 MHz): δ 60.31 (C-4'), 70.52 (C-3'), 81.88 (C-1'), 146.96 (C-6),154.69 (C-3), 158.87 (C-5); ms: m/z 216 (M^+, 31), 153 (32), 142 (100), 113 (7), 91 (30), 85 (27), 69 (69).

Anal. Calcd. for $C_6H_{12}N_6O_3$: C, 33.33; H, 5.59; N, 38.87. Found: C, 33.43; H, 5.62; N, 38.91.

6-Amino-3-methyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (**3b**).

Method A. A solution of compound **16** (0.43 g, 2 mmoles) in glacial acetic acid (10 mL) was refluxed for 12 hours (monitored by tlc). Removal of excess acid *in vacuo* followed by recrystallization from water afforded a white crystal compound

3b (0.19 g, 57%), mp >300 °C (from water); ir: (ν, cm^{-1}) 3340, 3185, 1729 (C=O), 1625, 1517, 1408, 1283, 1131; uv: (0.1 *N* HCl): λ_{max} nm (log ε) 223 (4.24), 280 (3.41); (H_2O): λ_{max} nm (log ε) 218 (4.13); (0.1 *N* NaOH): λ_{max} nm (log ε) 228 (4.24); ^{1}H nmr (200 MHz): δ 2.45 (s, 3H, CH_3); 6.39 (s, 2H, NH_2); 11.47 (br s, 1H, NH); ^{13}C nmr (200 MHz): δ 9.26 (CH_3), 139.40 (C-8a), 146.74 (C-3), 150.31 (C-6), 151.80 (C-8); ms: m/z 166 (M^+, 35), 138 (3), 123 (5), 111 (8), 97 (6), 91 (4), 77 (5), 69 (24), 54 (32), 43 (100).

Anal. Calcd. for $C_5H_6N_6O$: C, 36.15; H, 3.64; N, 50.58. Found: C, 36.10; H, 3.70; N, 50.74.

Method B. Compound **2** (0.71 g, 5 mmoles) in glacial acetic acid (15 mL) was refluxed for 12 hours. Cooling separated a white crystal compound 0.56 g. The filtrate was evaporated to 3 mL to give 0.11 g. The total 0.67 g (81%) of the compound was a material identical in every respect with compound **3b**.

Sodium bihydrate 3-amino-6-azido-1,2,4-triazin-5(2*H*)-one (**17**).

A solution of compound **8** (0.95 g, 5 mmoles) and sodium azide (0.36 g, 5.5 mmoles) in water (25 mL) was refluxed for 16 hours. Evaporating the solvent to 5 mL *in vacuo* afforded a crude solid which was recrystallized from methanol to give white crystal compound **17** (0.57 g, 54%), mp >300 °C; ir: (ν, cm^{-1}) 3429, 2206 (N_3), 1642, 1561, 1498, 1388, 1274, 1102; ^{1}H nmr (200 MHz): δ 5.69 (s, 2H, NH_2); ^{13}C nmr (200 MHz): δ 137.62 (C-6), 160.06 (C-3), 162.39 (C-5).

Anal. Calcd. for $C_3H_3N_7O{\bullet}Na^+{\bullet}2H_2O$: C, 16.99; H, 3.33; N, 46.22. Found: C, 16.86; H, 3.23; N, 46.25.

6-Amino-1,2,3,4-tetrazolo[5,1-*f*][1,2,4]triazin-8(7*H*)-one (**4**).

Method A. To a solution of compound **16** (0.65 g, 3 mmoles) in 6 *M* hydrochloric acid (6 mL) under stirring at 0 °C, a solution of sodium nitrite (0.24 g, 3.5 mmoles) in water (6 mL) was added drop by drop. After the addition was complete, stirring was continued for an additional 10 minutes and was stirred at room temperature overnight. Collection of the precipitate and recrystallization from ethanol produced **4** (0.26 g, 57%), mp >300 °C (from EtOH); ir: (ν, cm^{-1}) 3392, 3313, 3210, 3175, 3086, 1742, 1716, 1641, 1474, 1390, 1300, 1085; uv: (0.1 *N* HCl): λ_{max} nm (log ε) 210 (4.17), 248 (3.71); (H_2O): λ_{max} nm (log ε) 208 (4.04), 252 (3.55); (0.1 *N* NaOH): λ_{max} nm (log ε) 223 (4.16), 252 (3.88); ^{1}H nmr (200 MHz): δ 6.89 (s, 2H, NH_2), 12.27 (br s, 1H, NH); ^{13}C nmr (200 MHz): δ 138.90 (C-8a), 151.85 (C-6), 152.56 (C-8); ms: m/z 154 (M^++1, 2), 127 (3), 125 (4), 97 (5), 85 (7), 82 (10), 69 (74), 54 (52), 43 (100).

Anal. Calcd. for $C_3H_3N_7O$: C, 23.53; H, 1.98; N, 64.02. Found: C, 23.37; H, 1.97; N, 64.05.

Method B. A solution of compound **17** (0.42 g, 2 mmoles) in 3 *M* hydrochloric acid (8 mL) was stirred at room temperature overnight. Collection of the precipitate and recrystallization from ethanol produced compound **4** (0.26 g, 85%).

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