Synthesis and Structure of 3,4-Dihydropyrido[2′,3′:3,4]pyrazolo[1,5-*a*][1,3,5]triazin-2-amines [1]

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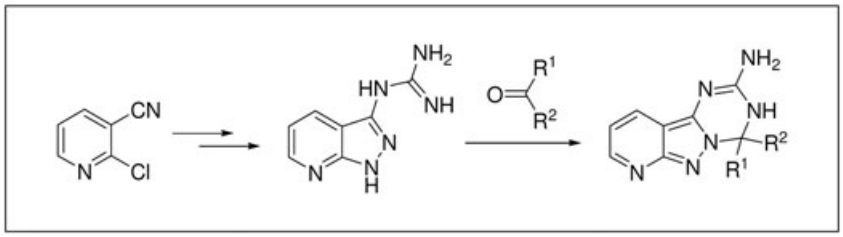
This article is dedicated to Professor Boris Ya. Syropyatov with our best wishes on the occasion of his 70th birthday.



A new convenient synthon for heterocyclic chemistry, namely 1*H*-pyrazolo[3,4-*b*]pyridin-3-ylguanidine was successfully prepared by selective guanylation of 1*H*-pyrazolo[3,4-*b*]pyridin-3-amine. A series of 3,4-dihydropyrido[2′,3′:3,4]pyrazolo[1,5-*a*][1,3,5]triazin-2-amines was synthesized from 1*H*-pyrazolo[3,4-*b*] pyridin-3-ylguanidine using aldehydes or ketones as one-carbon inserting reagents. The tautomeric preferences of the products were determined using spectroscopic (*e.g.*, 2D NOESY NMR) and single crystal X-ray diffraction data.

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INTRODUCTION

Pyrazolo[1,5-*a*][1,3,5]triazine ring system has been known since the first report by Checchi and Ridi in 1957 [2] on the synthesis of the compounds with this heterocyclic core. Now, the pyrazolo[1,5-*a*][1,3,5]triazine nucleus is well recognized as a template for the development of new heterocyclic molecules with potential therapeutic properties [3]. However, information on pyrazolo[1,5-*a*][1,3,5]triazines fused with other rings, particularly pyridine ring, is limited. The available data concerning synthesis of pyrido[2′,3′:3,4] pyrazolo[1,5-*a*][1,3,5]triazines are fragmentary and the products lack appropriate structural characterization [4–7].

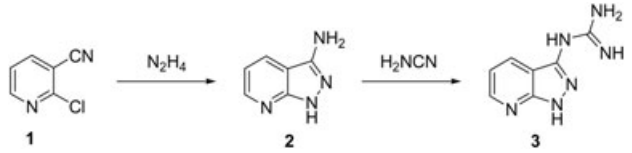
N-Heterocyles bearing guanidine moiety in the position vicinal to the endocyclic nitrogen atom are useful building blocks for the construction of the fused amino-1,3,5-triazines. The annelation of the triazine ring can be achieved *via* a cyclocondensation of the heterylguanidines with a variety of one-carbon inserting reagents. In our program on the synthesis of fused 1,3,5-triazines, this strategy has been successfully applied for various 1,2,4-triazol-5-yl- [8–12], benzimidazol-2-yl- [13–18], benzoxazol-2-yl- [18], benzothiazol-2-yl- [18], pyrimidin-2-yl- [19,20], and quinazolin-2-yl- [17,21] substituted guanidines. Among fused 1,3,5-triazines obtained by this approach, dihydro-1,3,5-triazines appeared to be the more interesting group in terms of their biological activity (*viz.*, antifolate [14,16], antibacterial [13], and anticancer [12,17] properties).

This study is designed with the objective to synthesize a series of 3,4-dihydropyrido[2′,3′:3,4]pyrazolo[1,5-*a*][1,3,5] triazines *via* the cyclocondensation of 1*H*-pyrazolo[3,4-*b*] pyridin-3-guanidine (**3**) with carbonyl compounds (*i.e.*, aldehydes and ketones). The structural features of the products, particularly tautomeric preferences are also discussed herein.

RESULTS AND DISCUSSION

1*H*-Pyrazolo[3,4-*b*]pyridin-3-amine (**2**), required for the synthesis of guanidine **3**, was prepared using previously reported [22] reaction of 2-chloro-3-cyanopyridine (**1**) with hydrazine (Scheme 1). The guanylation of **3** with cyanamide in the presence of acid proceeded at the exocyclic nitrogen affording 1*H*-pyrazolo[3,4-*b*]pyridin-3-ylguanidine (**3**) as a salt. The ^{1}H NMR spectrum of the hydrochloride of compound **3** contained a broad signal of four protons at 8.05 ppm corresponding to the guanidine group and two deuterium oxide exchangeable singlets at 12.05 and 13.56 ppm,

Scheme 1. Synthesis of 1*H*-pyrazolo[3,4-*b*]pyridin-3-ylguanidine (**3**).



therefore, suggesting protonation of the endocyclic pyridine nitrogen rather than the guanidine group of **3**. The base **3** is freely soluble in aqueous solutions of strong alkali (*e.g.*, sodium hydroxide) but can be conveniently isolated by treatment of salt **3**·HCl with aqueous sodium carbonate.

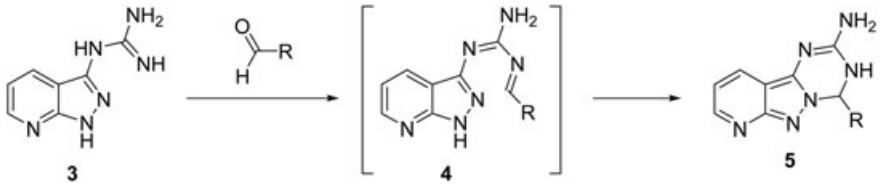
In the piperidine-catalyzed reaction with pyrazolo[3,4-*b*] pyridin-3-ylguanidine (**3**), aldehydes acted as electrophilic one-carbon inserting reagents providing hitherto unknown 4-het(aryl)-3,4- dihydropyrido[2′,3′:3,4]pyrazolo[1,5-*a*][1,3,5] triazin-2-amines (**5**) (Scheme 2 and Table 1). The signals of the sp^3-hybridized carbon atom of **5** in ^{13}C-NMR spectra at 63–70 ppm (Table 2) confirmed that the triazine ring closure had occurred and ruled out structure **4** (probable intermediate in the reaction).

The amino group, methine proton at the sp^3-hybridized carbon, and endocyclic NH signals at 6.43–6.61, 6.81–7.15, and 7.87–8.11 ppm, respectively (Table 2), appeared in the regions characteristic for the similar fused aryl-substituted dihydro-1,3,5-triazines with the primary amino group [8,12–17,21].

The reaction of guanidine **3** with acetone under catalysis of piperidine led to the formation of 3,4-dihydropyrido [2′,3′:3,4]pyrazolo[1,5-*a*][1,3,5]triazin-2-amine (**6**) with two geminal methyl groups (Scheme 3). Spiro fused analog **7** was prepared similarly by heating **3** with cyclopentanone in ethanol. The signals in ^{13}C-NMR spectra at 70.6 and 80.0 ppm (for **6** and **7**, respectively) indicated the creation of quaternary sp^3-hybridized carbon atoms formed due to the triazine ring annelation.

3,4-Dihydropyrido[2′,3′:3,4]pyrazolo[1,5-*a*][1,3,5]triazines **5**, **6**, and **7** might be involved in the prototropic annular tautomerism. Possible migration of the proton from one to another endocyclic nitrogen atom might result in the existence of four tautomers: 3,4-dihydro- (**A**), 1,4-dihydro- (**B**), 4,6-dihydro- (**C**), and 4,7-dihydro- (**D**) forms (Scheme 4).

Scheme 2. Synthesis of 4-(het)aryl-3,4-dihydropyrido[2′,3′:3,4]pyrazolo[1,5-a][1,3,5]triazin-2-amines (**5**).



5: R = Ph (**a**), 4-MeC$_6$H$_4$ (**b**), 4-MeOC$_6$H$_4$ (**c**), 4-ClC$_6$H$_4$ (**d**), 2-Furyl (**e**), 2-Thienyl (**f**), 2-Pyridyl (**g**), 4-Pyridyl (**h**)

Table 1

4-(Het)aryl-3,4-dihydropyrido[2′,3′:3,4]pyrazolo[1,5-*a*][1,3,5]triazin-2-amines (**5**).

					Analysis %, Calcd./Found		
Compound	R	mp (ºC)	Yield (%)	Molecular Formula	C	H	N
5a	Ph	259–260	95	$C_{14}H_{12}N_6$	63.62	4.58	31.80
					63.65	4.60	31.67
5b	4-MeC$_6$H$_4$	239–240	90	$C_{15}H_{14}N_6$	64.73	5.07	30.20
					64.81	5.10	30.03
5c	4-MeOC$_6$H$_4$	234–235	88	$C_{15}H_{14}N_6O$	61.21	4.79	28.55
					61.04	4.83	28.32
5d	4-ClC$_6$H$_4$	240–241	89	$C_{14}H_{11}ClN_6$	56.29	3.71	28.13
					56.22	3.80	28.01
5e	2-Furyl	243–244	63	$C_{12}H_{10}N_6O$	56.69	3.96	33.05
					56.48	4.03	32.98
5f	2-Thienyl	251–252	79	$C_{12}H_{10}N_6S$	53.32	3.73	31.09
					53.20	3.77	31.00
5g	2-Pyridyl	255–256	86	$C_{13}H_{11}N_7$	58.86	4.18	36.96
					58.83	4.23	36.88
5h	4-Pyridyl	217–218	88	$C_{13}H_{11}N_7$	58.86	4.18	36.96
					58.78	4.28	36.72

Table 2

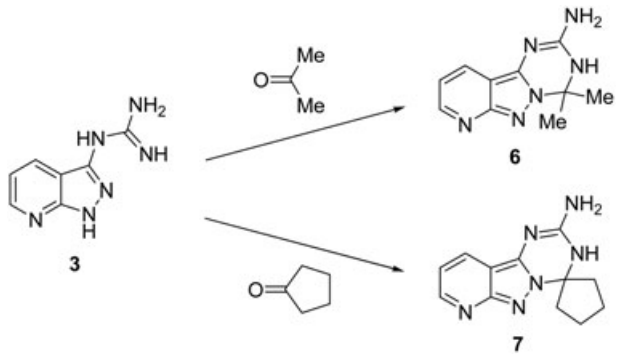
Spectral data of 4-(het)aryl-3,4-dihydropyrido[2′,3′:3,4]pyrazolo[1,5-*a*][1,3,5]triazin-2-amines (**5**).

Compound	Dimethyl sulfoxide-d_6/TMS, δ (ppm)	
	^{1}H-NMR (300 MHz)	^{13}C-NMR (75 MHz)
5a	6.52 (2H, s, NH_2), 6.79 (1H, dd, ^3J = 8.1, ^3J = 4.3 Hz, H-9), 6.89 (1H, s, H-4), 7.27–7.44 (5H, m, Ph), 7.96 (1H, dd, ^3J = 8.1, ^4J = 1.8 Hz, H-10), 8.01 (1H, s, NH), 8.41 (1H, dd, ^3J = 4.3, ^4J = 1.8 Hz, H-8)	69.0 (C-4), 103.4 (C-10a), 113.7 (C-9), 126.1 (C-2′ and C-6′), 128.6 (C-3′ and C-5′), 128.8 (C-4′), 130.1 (C-10), 140.6, 140.7 (C-10b and C-1′), 151.3 (C-8), 153.1 (C-6a), 157.4 (C-2)
5b	2.28 (3H, s, Me), 6.44 (2H, s, NH_2), 6.78 (1H, dd, ^3J = 8.3, ^3J = 4.1 Hz, H-9), 6.82 (1H, d, ^3J = 1.9 Hz, H-4), 7.15–7.23 (4H, m, C_6H_4), 7.90 (1H, d, ^3J = 1.8 Hz, NH), 7.94 (1H, dd, ^3J = 8.3, ^4J = 1.5 Hz, H-10), 8.40 (1H, dd, ^3J = 4.1, ^4J = 1.5 Hz, H-8)	20.6 (Me), 68.8 (C-4), 103.4 (C-10a), 113.6 (C-9), 126.0 (C-2′ and C-6′), 129.0 (C-3′ and C-5′), 130.0 (C-10), 137.9 (C-4′), 138.2 (C-1′), 140.5 (C-10b), 151.2 (C-8), 153.1 (C-6a), 157.3 (C-2)
5c	3.73 (3H, s, OMe), 6.43 (2H, s, NH_2), 6.77 (1H, dd, ^3J = 8.3, ^3J = 4.1 Hz, H-9), 6.81 (1H, d, ^3J = 1.5 Hz, H-4), 6.94 (2H, d, ^3J = 8.7 Hz, H-3′ and H-5′), 7.23 (2H, d, ^3J = 8.7 Hz, H-2′ and H-6′), 7.87 (1H, d, ^3J = 1.5 Hz, NH), 7.93 (1H, dd, ^3J = 8.3, ^4J = 1.8 Hz, H-10), 8.39 (1H, dd, ^3J = 4.1, ^4J = 1.8 Hz, H-8)	55.1 (OMe), 68.7 (C-4), 103.4 (C-10a), 113.6 (C-9), 113.9 (C-3′ and C-5′), 127.5 (C-2′ and C-6′), 130.0 (C-10), 132.9 (C-1′), 140.5 (C-10b), 151.2 (C-8), 153.1 (C-6a), 157.3 (C-2), 159.6 (C-4′)
5d	6.50 (2H, s, NH_2), 6.79 (1H, dd, ^3J = 8.3, ^3J = 4.1 Hz, H-9), 6.91 (1H, d, ^3J = 1.9 Hz, H-4), 7.31 (2H, d, ^3J = 8.5 Hz, H-2′ and H-6′), 7.48 (2H, d, ^3J = 8.5 Hz, H-3′ and H-5′), 7.94 (1H, dd, ^3J = 8.3, ^4J = 1.5 Hz, H-10), 7.97 (1H, d, ^3J = 1.8 Hz, NH), 8.41 (1H, dd, ^3J = 4.1, ^4J = 1.8 Hz, H-8)	68.2 (C-4), 103.4 (C-10a), 113.8 (C-9), 128.0, 128.6 (C-2′ and C-6′ and C-3′ and C-5′), 130.0 (C-10), 133.3 (C-4′), 139.6 (C-1′), 140.6 (C-10b), 151.4 (C-8), 153.0 (C-6a), 157.4 (C-2)
5e	δ 6.39–6.56 (4H, m, NH_2, H-3′, and H-4′), 6.78 (1H, dd, ^3J = 8.3, ^3J = 4.1 Hz, H-9), 6.95 (1H, s, H-4), 7.64 (1H, s, H-5′), 7.87–7.99 (2H, m, H-10 and NH), 8.41 (1H, dd, ^3J = 4.1, ^4J = 1.9 Hz, H-8)	63.0 (C-4), 103.4 (C-10a), 108.4, 110.4 (C-3′ and C-4′), 113.7 (C-9), 130.0 (C-10), 140.6 (C-10b), 143.6 (C-5′), 151.4 (C-8), 151.9 (C-2′), 153.1 (C-6a), 157.4 (C-2)
5f	6.54 (2H, s, NH_2), 6.79 (1H, dd, ^3J = 7.9, ^3J = 4.1 Hz, H-9), 7.01 (1H, dd, ^3J = 4.9, ^3J = 3.8 Hz, H-4′), 7.14–7.22 (2H, m, H-4 and H-3′), 7.53 (1H, dd, ^3J = 5.3, ^4J = 0.8 Hz, H-5′), 7.93 (1H, dd, ^3J = 8.3, ^4J = 1.9 Hz, H-10), 8.08 (1H, s, NH), 8.42 (1H, dd, ^3J = 4.1, ^4J = 1.9 Hz, H-8)	65.1 (C-4), 103.5 (C-10a), 113.8 (C-9), 125.9, 126.6, 127.2 (C-3′, C-4′, and C-5′), 130.0 (C-10), 140.1 (C-10b), 143.9 (C-2′), 151.4 (C-8), 152.9 (C-6a), 157.4 (C-2)
5g	6.45 (2H, s, NH_2), 6.79 (1H, d, ^3J = 8.3, ^3J = 4.1 Hz, H-9), 6.88 (1H, d, ^3J = 1.9 Hz, H-4), 7.18 (1H, d, ^3J = 7.9 Hz, H-3′), 7.39 (1H, dd, ^3J = 7.5, ^3J = 4.9 Hz, H-5′), 7.82 (1H, td, ^3J = 7.6, ^4J = 1.6 Hz, H-4′), 7.96 (1H, dd, ^3J = 8.3, ^4J = 1.5 Hz, H-10), 8.03 (1H, d, ^3J = 1.9 Hz, NH), 8.41 (1H, dd, ^3J = 4.1, ^4J = 1.9 Hz, H-8), 8.57 (1H, d, ^3J = 4.5 Hz, H-6′)	69.9 (C-4), 103.5 (C-10a), 113.6 (C-9), 120.9 (C-3′), 124.1 (C-5′), 130.1 (C-10), 137.3 (C-4′), 141.1 (C-10b), 149.4 (C-6′), 151.4 (C-8), 153.1 (C-6a), 157.3 (C-2), 158.3 (C-2′)
5h	6.61 (2H, s, NH_2), 6.81 (1H, dd, ^3J = 8.1, ^3J = 4.1 Hz, H-9), 6.96 (1H, s, H-4), 7.27 (2H, dd, ^3J = 4.3, ^4J = 1.5 Hz, H-3′ and H-5′), 7.96 (1H, dd, ^3J = 8.1, ^4J = 1.7 Hz, H-10), 8.11 (1H, s, NH), 8.44 (1H, dd, ^3J = 4.1, ^4J = 1.7 Hz, H-8), 8.61 (2H, dd, ^3J = 4.3, ^4J = 1.5 Hz, H-2′ and H-6′)	67.7 (C-4), 103.4 (C-10a), 113.9 (C-9), 120.8 (C-3′ and C-5′), 130.1 (C-10), 140.8 (C-10b), 148.4 (C-4′), 150.1 (C-2′ and C-6′), 151.6 (C-8), 153.0 (C-6a), 157.5 (C-2)

The coupling of the H-4 and NH signals (^3J = 0–1.9 Hz) in ^{1}H NMR spectra of **5** suggested the equilibrium to be shifted toward 3,4-dihydro-tautomeric form **A**. In a 2D NOESY experiment conducted on **6**, a strong pair of cross-peaks was observed for the *gem*-dimethyl signal at 1.72 ppm and the N H signal at 7.62 ppm. The close spatial relationship of the methyl groups and the proton at annular nitrogen atom might correspond to the 3,4-dihydro- (**A**) or 4,6-dihydro- (**C**) tautomeric forms. X-ray crystallographic study [23] on **6** was performed to differentiate between these two tautomers. The crystals suitable for X-ray diffraction analysis were obtained by recrystallization of **6** from ethanol. The molecule of **6** crystallized together with one ethanol molecule, therefore providing the ethanol monosolvate of **6**. Similarly to the previously reported [10,24] fused *gem*-dimethyl substituted amino-1,3,5-triazines, **6** existed in the crystal as a tautomer with the labile hydrogen atom located at the triazine nitrogen atom adjacent to the quaternary sp^3-hybridized carbon atom (Fig. 1). Considering the similarity of the spectral data for **5**–**7**, we concluded that 3,4-dihydro-tautomeric form **A** was generally preferred in solution and solid states for all series of the compounds.

Pyrido[2′,3′:3,4]pyrazolo[1,5-*a*][1,3,5]triazines **5**–**7** underwent a series of biological screening assays. They showed

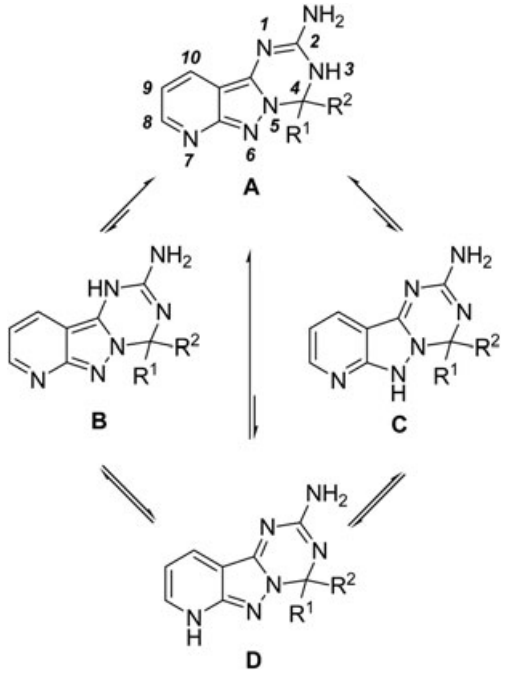
Scheme 3. Reaction of 1*H*-pyrazolo[3,4-*b*]pyridin-3-ylguanidine (**3**) with ketones.



neither appreciable antiproliferative activity against MDA-MB-231 breast cancer cell line nor dihydrofolate reductase inhibitory activity. They were also found to be inactive in the ApoE secretion, cell cycle, anti-angiogenesis, insulin secretion, and Wnt pathway Eli Lilly's phenotypic bioassay modules.

In conclusion, a series of new 3,4-dihydropyrido[2′,3′:3,4] pyrazolo[1,5-*a*][1,3,5]triazines **5-7** was successfully synthesized using cyclocondensation of 1*H*-pyrazolo[3,4-*b*]pyridin-3-ylguanidine (**3**) with carbonyl compounds. The developed method is general, and a variety of aldehydes and ketones can be applied as one-carbon inserting reagents for the triazine ring annelation. The products **5**–**7** appear to exist as the 3,4-dihydro-tautomers in the solution and solid state.

Scheme 4. Possible tautomeric forms of 3,4-dihydropyrido [2′,3′:3,4] pyrazolo[1,5-a][1,3,5]triazin-2-amines (annular tautomerism).



EXPERIMENTAL

Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. Analytical thin layer chromatography (TLC) was carried out on aluminum plates coated with silica gel 60 F254 (Merck) with detection by UV light. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker DPX-300 spectrometer in the dimethyl sulfoxide-d_6 (DMSO-d_6) solution using tetramethylsilane (TMS) as an internal reference. Assignments were done on the basis of 2D ^{1}H–^{1}H COSY, ^{1}H–^{13}C HMQC, and NOESY experiments.

1*H*-Pyrazolo[3,4-*b*]pyridin-3-amine (2). The mixture of 2-chloro-3-cyanopyridine (**1**, 6.93 g, 50 mmol) and hydrazine hydrate (80%, 6.2 mL, 100 mmol) in ethanol (60 mL) was heated under reflux with stirring for 6 h. After cooling at 4 °C, the precipitated product was filtered, washed with cold ethanol, dried and recrystallized from ethanol to give 5.76 g (86%) of **2**; mp: 183–184 °C [ref. 22; mp: 184–185 °C]; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.33 (2H, br s, NH_2), 6.96 (1H, dd, ^{3}J = 7.9, ^{3}J = 4.5 Hz, H-5), 8.15 (1H, dd, ^{3}J = 7.9, ^{4}J = 1.5 Hz, H-4), 8.35 (1H, dd, ^{3}J = 4.5, ^{4}J = 1.5 Hz, H-6), 11.88 (1H, br s, NH); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 106.1 (C-3a), 113.7 (C-5), 129.6 (C-4), 148.0 (C-3), 148.4 (C-6), 152.3 (C-7a).

1*H*-Pyrazolo[3,4-*b*]pyridin-3-ylguanidine (3). To the solution of 1*H*-pyrazolo[3,4-*b*]pyridin-3-amine (**2**, 4.20 g, 30 mmol) and cyanamide (1.39 g, 30 mmol) in ethanol (25 mL), concentrated hydrochloric acid (3 mL, 30 mmol) was added and the reaction mixture was heated under reflux with stirring for 6 h. After cooling, the precipitated 1*H*-pyrazolo[3,4-*b*]pyridin-3-ylguanidine hydrochloride was filtered, washed with cold ethanol, and dried. Free base **3** was obtained by treatment of aqueous solution of pyrazolo[3,4-*b*] pyridin-3-ylguanidine hydrochloride with 10% sodium carbonate solution (30 mL) with stirring and gentle heating at 40–50 °C for 10 min. After cooling, the precipitated product **3** (3.8 g, 72%) was filtered, washed with cold water, dried and used in the subsequent reactions without further purification. Analytical sample was

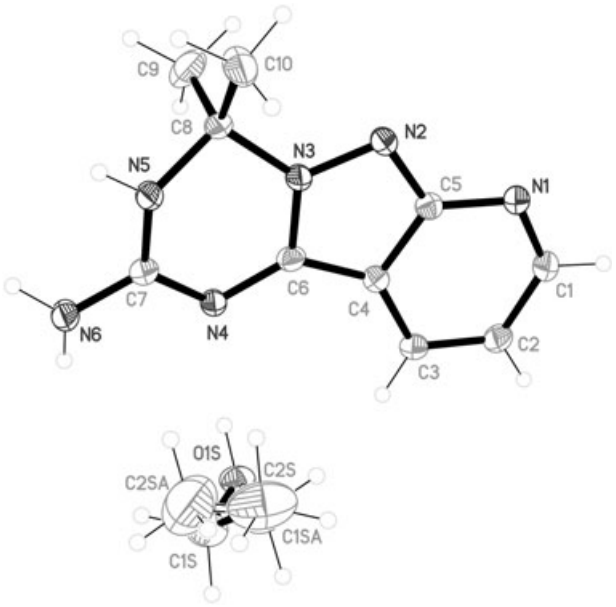


Figure 1. Molecular structure of 4,4-dimethyl-3,4-dihydropyrido [2′,3′:3,4]pyrazolo[1,5-*a*][1,3,5]triazin-2-amine (**6**) as an ethanol monosolvate. Displacement ellipsoids are drawn at the 50% probability level.

obtained by recrystallization from ethanol; mp: 256–257 °C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.55 (4H, br s, NHC(NH)NH_2), 7.00 (1H, dd, ^3J = 7.5, ^3J = 4.5 Hz, H-5), 8.05 (1H, dd, ^3J = 7.5, ^4J = 1.1 Hz, H-4), 8.39 (1H, dd, ^3J = 4.5, ^4J = 1.1 Hz, H-6), 12.38 (1H, br s, NH); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 110.7 (C-3a), 114.6 (C-5), 129.5 (C-4), 148.6 (C-6), 151.1 (C-3), 151.8 (C-7a), 156.0 (NHC(NH)NH_2); Anal. Calcd. for $C_7H_8N_6$: C, 47.72; H, 4.58; N, 47.70. Found: C, 47.64; H, 4.60; N, 47.72.

General procedure for preparation of 4-(Het)aryl-3,4-dihydropyrido[2′,3′:3,4]pyrazolo[1,5-*a*][1,3,5]triazin-2-amines (5). To the solution of 1*H*-pyrazolo[3,4-*b*]pyridin-3-ylguanidine (**3**, 0.88 g, 5 mmol) and appropriate (het)arylaldehyde (5 mmol) in ethanol (15 mL), piperidine (0.30 mL, 3 mmol) was added and the mixture was heated under reflux with stirring for 3–16 h. After cooling, the precipitated product was filtered, washed with cold ethanol, dried and recrystallized from ethanol.

4,4-Dimethyl-3,4-dihydropyrido[2′,3′:3,4]pyrazolo[1,5-*a*][1,3,5]triazin-2-amine (6). To the solution of 1*H*-pyrazolo [3,4-*b*]pyridin-3-ylguanidine (**3**, 0.88 g, 5 mmol) in acetone (30 mL), piperidine (0.30 mL, 3 mmol) was added and the mixture was heated under reflux with stirring for 10 h. After cooling, the precipitated product was filtered, washed with cold acetone, dried and recrystallized from ethanol to give 0.84 g (78%) of **6**; mp: 285–286 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.72 (6H, s, Me_2), 6.28 (2H, s, NH_2), 6.77 (1H, dd, ^3J = 8.3, ^3J = 4.1 Hz, H-9), 7.62 (1H, s, NH), 7.89 (1H, dd, ^3J = 8.3, ^4J = 1.9 Hz, H-10), 8.42 (1H, dd, ^3J = 4.1, ^4J = 1.9 Hz, H-8); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 28.6 (Me_2), 70.6 (C-4), 103.5 (C-10a), 113.4 (C-9), 129.9 (C-10), 139.8 (C-10b), 150.9 (C-8), 153.4 (C-6a), 157.0 (C-2); Anal. Calcd. for $C_{10}H_{12}N_6$: C, 55.54; H, 5.59; N, 38.86. Found: C, 55.61; H, 5.60; N, 38.73.

4,4-Tetramethylene-3,4-dihydropyrido[2′,3′:3,4]pyrazolo[1,5-*a*][1,3,5]triazin-2-amine (7). To the solution of 1*H*-pyrazolo[3,4-*b*]pyridin-3-ylguanidine (**3**, 0.88 g, 5 mmol) and cyclopentanone (0.51 mL, 5.5 mmol) in ethanol (10 mL), piperidine (0.30 mL, 3 mmol) was added and the mixture was heated under reflux with stirring for 16 h. After cooling, the precipitated product was filtered, washed with cold ethanol, dried and recrystallized from ethanol to give 0.75 g (62%) of **7**; 248–249 °C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.73–2.01 (6H, m, $(CH_2)_2$, H-1′*ax*, and H-4′*ax*), 2.36–2.49 (2H, m, H-1′*eq* and H-4′*eq*), 6.24 (2H, s, NH_2), 6.76 (1H, dd, ^3J = 8.2, ^3J = 4.1 Hz, H-9), 7.72 (1H, s, NH), 7.89 (1H, dd, ^3J = 8.1, ^4J = 1.0 Hz, H-10), 8.41 (1H, dd, ^3J = 4.0, ^4J = 1.1 Hz, H-8); ^{13}C-NMR (75 MHz, DMSO-d_6): δ, 23.4 (C-1′ and C-4′), 39.8 (C-2′ and C-3′), 80.0 (C-4), 103.6 (C-10a), 113.5 (C-9), 129.8 (C-10), 140.5 (C-10b), 150.9 (C-8), 153.5 (C-6a), 157.0 (C-2); Anal. Calcd. for $C_{12}H_{14}N_6$: C, 59.49; H, 5.82; N, 34.69. Found: C, 59.35; H, 5.90; N, 34.64.

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