

Article

## Molecular and Crystal Structure of 7,7-Dimethyl-2-pyridin-4-yl-6,7-dihydro-1,2,4-triazolo[1,5-*a*][1,3,5]triazin-5-amine [1]

Anton V. Dolzhenko <sup>1,\*</sup>, Geok Kheng Tan <sup>2</sup>, Lip Lin Koh <sup>2</sup>, Anna V. Dolzhenko <sup>3</sup> and Wai Keung Chui <sup>4</sup>

<sup>1</sup> School of Pharmacy, Faculty of Health Sciences, Curtin University of Technology, GPO Box U1987, Perth 6845, Western Australia, Australia

<sup>2</sup> Department of Chemistry, Faculty of Science, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore

<sup>3</sup> Perm State Pharmaceutical Academy, 2 Plevaya Street, Perm 614990, Russia

<sup>4</sup> Department of Pharmacy, Faculty of Science, National University of Singapore, 18 Science Drive 4, Singapore 117543, Singapore

\* Author to whom correspondence should be addressed; E-Mails: Anton.Dolzhenko@curtin.edu.au or DolzhenkoAV@gmail.com; Tel.: +61-8-9266-3747; Fax: +61-8-9266-2769.

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**Abstract:** When crystallized from ethanol, 7,7-dimethyl-2-pyridin-4-yl-6,7-dihydro-1,2,4-triazolo[1,5-*a*][1,3,5]triazin-5-amine forms crystals which have monoclinic ( $P2_1/n$ ) symmetry with unit cell dimensions  $a = 7.3326(5) \text{ \AA}$ ,  $b = 19.4897(14) \text{ \AA}$ ,  $c = 8.6586(6) \text{ \AA}$ ,  $\alpha = 90^\circ$ ,  $\beta = 106.069(2)^\circ$ ,  $\gamma = 90^\circ$ ,  $V = 1189.06(14) \text{ \AA}^3$ ,  $Z = 4$ . The triazine ring in the molecule has a flattened boat conformation with *gem*-dimethyl groups as flagpole and bowsprit at the bow. The puckering parameters for the ring are:  $Q = 0.2996(14) \text{ \AA}$ ,  $\theta = 111.7(3)^\circ$  and  $\varphi = 124.1(3)^\circ$ . In the crystal, molecules are arranged in the three types of chains generated by the intermolecular  $\text{NH}\cdots\text{N}$  hydrogen bonds. The extended chains with the  $C(11)$  graph-set motif running along a  $[010]$  axis are formed by the amino group hydrogen atom and the pyridine nitrogen atom of another molecule. The  $C(4)C(6)$  chains with the  $R^2_2(8)$  binary graph-set motif running along a  $[101]$  direction are formed by linking the amino group hydrogen atom and the hydrogen atom at the triazine nitrogen atom with the triazole and triazine nitrogen atoms of another molecule, respectively. The centrosymmetric inverted dimers are formed via the  $\text{C-H}\cdots\pi$  interactions between the methyl group hydrogen and the pyridine ring of the pair molecule.

**Keywords:** triazoles; triazines; 5-azapurines; hydrogen bonds; CH $\cdots$  $\pi$  interactions

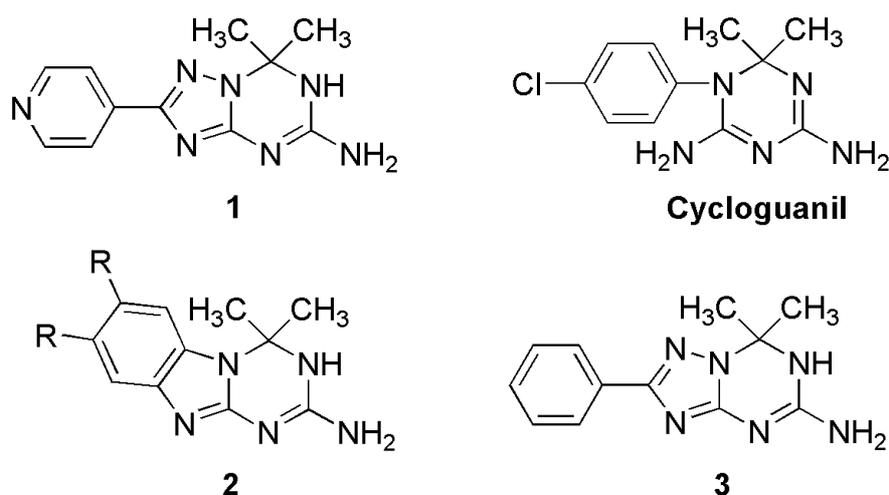
## 1. Introduction

Compounds with 1,2,4-triazolo[1,5-*a*]triazine ring system have not been found in nature. However, this heterocyclic system resembles purine which is one of the most important heterocycles in nature. The additional bridge nitrogen atom of 1,2,4-triazolo[1,5-*a*]triazines makes them 5-azaisosters of purines. The chemistry and biological activity of 1,2,4-triazolo[1,5-*a*]triazines have been extensively explored and this heterocyclic system has been well recognized as a promising scaffold for the construction of molecules with diverse biological effects [2].

In our search for potential therapeutic agents in this class of compounds we developed a number of effective synthetic procedures for 1,2,4-triazolo[1,5-*a*]triazines [3-7] with particular interest to the heterocyclizations of 1,2,4-triazol-3(5)-yl guanidines [4-7]. Consequently, a series of structural investigations of 1,2,4-triazolo[1,5-*a*]triazines using X-ray diffraction analysis [8-12] appeared complementing an earlier work by Gilardi [13].

In continuation of our research program on the synthesis and structural analysis of potentially bioactive 1,2,4-triazolo[1,5-*a*]triazines, we synthesized 7,7-dimethyl-2-pyridin-4-yl-6,7-dihydro-1,2,4-triazolo[1,5-*a*][1,3,5]triazin-5-amine (**1**) according to the previously reported general procedure [6,7] and report herein its molecular and crystal structure. The molecule **1** shares *gem*-dimethyl substituted dihydro-1,3,5-triazin-5-amine structure moiety with the antifolate drug cycloguanil and its fused analogues **2** (Figure 1) also inhibiting dihydrofolate reductase [14-16].

**Figure 1.** The title molecule **1**, cycloguanil, and structurally related *gem*-dimethyl substituted fused dihydro-1,3,5-triazines.



## 2. Results and Discussion

Crystals suitable for the X-ray diffraction analysis were obtained by recrystallization from ethanol (colorless blocks, m.p. 302 °C). The crystal and instrumental parameters used in the unit cell determination and data collection are summarized in Table 1.

**Table 1.** Crystal data and structure refinement for 7,7-dimethyl-2-pyridin-4-yl-6,7-dihydro-1,2,4-triazolo[1,5-*a*][1,3,5]triazin-5-amine (**1**).

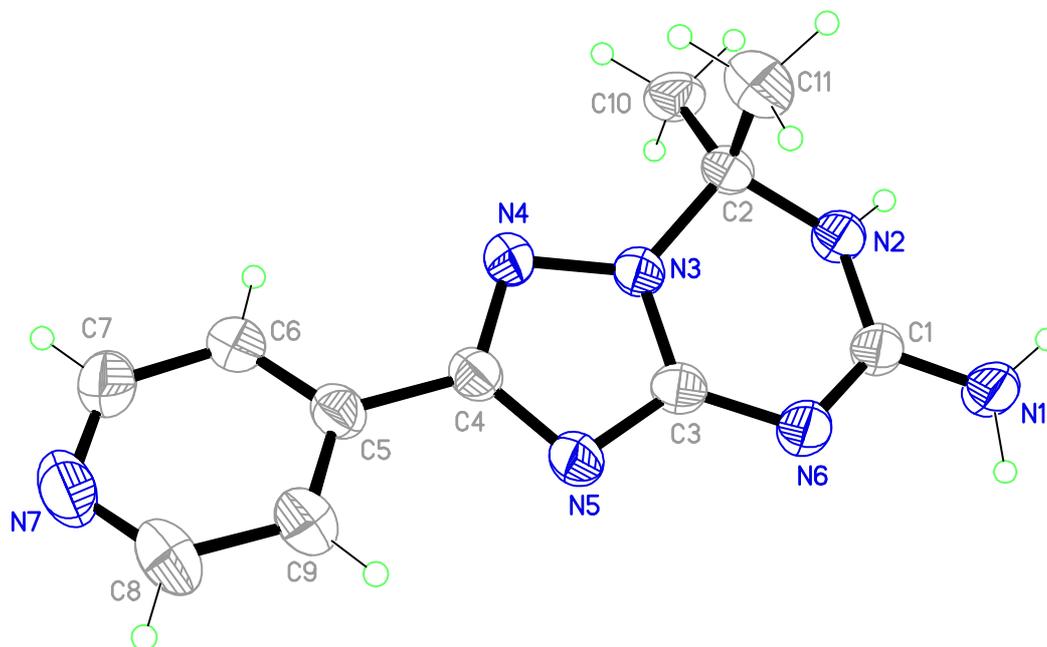
Crystal data		Refinement	
Empirical formula	C <sub>11</sub> H <sub>13</sub> N <sub>7</sub>	Refinement method	Full-matrix least-squares on $F^2$
Formula weight	243.28	Data/restraints/parameters	2736/0/177
Temperature	295(2) K	Goodness-of-fit on $F^2$	1.057
Wavelength, $\lambda$	0.71073 Å	Final $R$ indices	$R_1 = 0.0476$ ,
Crystal system	monoclinic	$[I > 2\sigma(I)]$	$wR_2 = 0.1188$
Space group	P2 <sub>1</sub> /n	$R$ indices (all data)	$R_1 = 0.0582$ ,
Unit cell dimensions	$a = 7.3326(5)$ Å $b = 19.4897(14)$ Å $c = 8.6586(6)$ Å $\alpha = 90^\circ$ $\beta = 106.069(2)^\circ$ $\gamma = 90^\circ$	Largest diff. peak and hole	0.268 and $-0.213$ eÅ <sup>-3</sup>
Volume	1189.06(14) Å <sup>3</sup>		
$Z$	4		
Density (calculated)	1.359 mg/m <sup>3</sup>		
Absorption coefficient	0.091 mm <sup>-1</sup>		
F(000)	512		
Crystal size	0.70 × 0.40 × 0.20 mm		

### 2.1. Molecular Structure

The drawing of the molecule with the atom-labeling scheme (displacement thermal ellipsoids are drawn at the 50% probability level) is shown in Figure 2. The bond lengths and angles comprising the key features of the 6,7-dihydro-1,2,4-triazolo[1,5-*a*][1,3,5]triazine core are given in Table 2. Bond distances indicate extensive delocalization within the heterocyclic ring system and the amino group. In general, the geometry of the 7,7-dimethyl-6,7-dihydro-1,2,4-triazolo[1,5-*a*][1,3,5]triazin-5-amine skeleton is similar to that of the earlier reported [11] structure with the 2-phenyl substitution (compound **3**, Figure 1).

The 1,2,4-triazolo[1,5-*a*][1,3,5]triazine core of the molecule is nearly planar with C2 atom deviated to higher extent (*viz.* 0.2455(14) Å) from the mean plane of the system due to sp<sup>3</sup> hybridized nature of the carbon C2 atom. The mean planes of the 1,2,4-triazolo[1,5-*a*][1,3,5]triazine (C1/N2/C2/N3/N4/C4/N5/C3/N6) and pyridine (C5/C6/C7/N7/C8/C9) rings make a dihedral angle of 21.49(7)°. This is more than twice higher than the corresponding value for **3**.

**Figure 2.** A view of the 7,7-dimethyl-2-pyridin-4-yl-6,7-dihydro-1,2,4-triazolo[1,5-*a*][1,3,5]triazin-5-amine (**1**) molecule, showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.



**Table 2.** Selected geometric parameters for 7,7-dimethyl-2-pyridin-4-yl-6,7-dihydro-1,2,4-triazolo[1,5-*a*][1,3,5]triazin-5-amine (**1**).

Bond Lengths, Å			
N1-C1	1.3308(19)	N4-C4	1.3236(18)
N2-C1	1.3459(17)	N5-C3	1.3270(18)
N2-C2	1.4607(18)	N5-C4	1.3588(18)
N3-C3	1.3447(17)	N6-C1	1.3249(17)
N3-N4	1.3669(16)	N6-C3	1.3544(18)
N3-C2	1.4659(16)		
Bond Angles, °			
C1-N2-C2	123.57(12)	N6-C1-N2	123.45(13)
C3-N3-N4	110.73(11)	N1-C1-N2	118.64(13)
C3-N3-C2	122.48(12)	N2-C2-N3	103.42(11)
N4-N3-C2	125.76(11)	N5-C3-N3	109.47(12)
C4-N4-N3	101.20(11)	N5-C3-N6	126.38(13)
C3-N5-C4	102.89(11)	N3-C3-N6	124.13(12)
C1-N6-C3	113.86(12)	N4-C4-N5	115.70(12)
N6-C1-N1	117.87(13)		

The triazine ring C1/N2/C2/N3/C3/N6 in the molecule adopts a flattened boat conformation with atoms C2 and N6 at the bow and stern. The angle C10-C2-C11 between the flagpole and bowsprit geminal methyl groups is 111.88(13)°. This value is within the range (111.33–112.40) observed for the structurally related molecules [11,17].

The sum of the magnitudes of the six intraring torsion angles ( $P$ ) around the 1,3,5-triazine ring is  $19.51(8)^\circ$  that indicates a reasonable level of the ring planarity but allow the Cremer–Pople analysis of the ring puckering [18]. The Cremer–Pople system describes six-atom rings using puckering amplitude ( $Q$ ) and orientation angles ( $\theta$  and  $\varphi$ ). The puckering amplitude ( $Q$ ), which is a measure of the average displacement of the ring atoms away from a best-fit plane, is equal to  $0.2996(14)$  Å for the triazine ring C1/N2/C2/N3/C3/N6. The angle  $\theta$  describes where the puckering occurs around the ring and  $\varphi$  is an inversion angle that accounts for the possibility of inverted ring forms. Ideally, boat conformers should have  $\theta = 90^\circ$  and  $\varphi = 0, 60, 120, 180, 240$  or  $300^\circ$ . The orientation angles  $\theta$  and  $\varphi$  characterizing the triazine ring are  $111.7(3)^\circ$  and  $124.1(3)^\circ$ , respectively that confirms the flattened boat conformation of the ring. Similar conformation was observed for structurally related 7,7-dimethyl-2-phenyl-6,7-dihydro-1,2,4-triazolo[1,5-*a*][1,3,5]triazin-5-amine [11]. However, changing type of the ring fused to the *gem*-dimethyl substituted amino-1,3,5-triazine [11,17] or position of the fusion [10] appear to affect the triazine ring conformation.

## 2.2. Crystal Structure

In the crystal of 7,7-dimethyl-2-pyridin-4-yl-6,7-dihydro-1,2,4-triazolo[1,5-*a*][1,3,5]triazin-5-amine (1), molecules form a hydrogen bond connected network of three types of chains. A hydrogen atom of the primary amino group N1-H1A and the hydrogen atom at the endocyclic N2 atom act as hydrogen donors forming intermolecular N...HN hydrogen bonds with the triazole and triazine N5 and N6 atoms, respectively (Table 3). These contacts arrange molecules into the running along a  $[101]$  direction  $C(4)C(6)$  chains with the  $R^2_2(8)$  binary graph-set motif [19] (Figure 3). The  $C(11)$  extended chains parallel to a  $[010]$  axis consist of the molecules linked via the NH...N hydrogen bonds between the second hydrogen atom of the amino group N1-H1B and the N7 atom of the pyridine ring (Table 3, Figure 4).

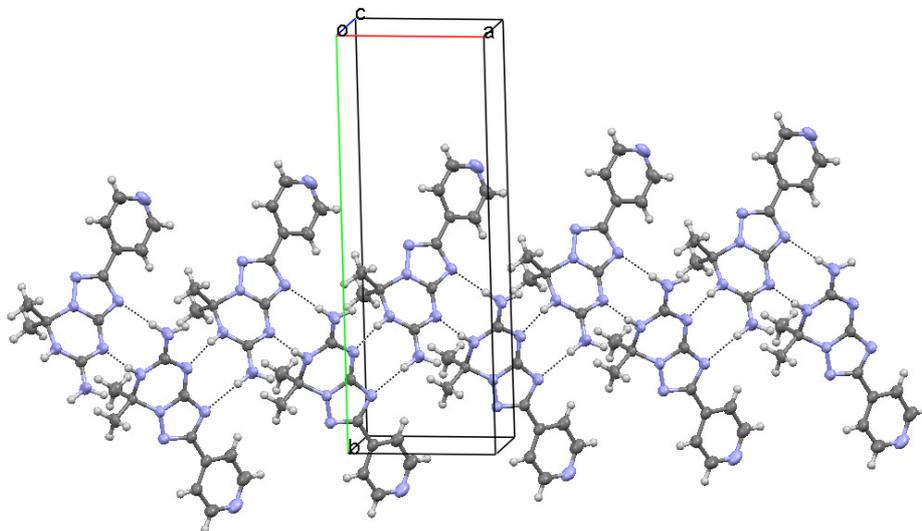
The C-H... $\pi$  contacts [20] with the classical T shape geometry between the methyl group hydrogen and the pyridine ring (C5/C6/C7/N7/C8/C9) at  $(-x, -y, 1-z)$  combine two molecules into a centrosymmetric inverted dimer (Table 2, Figure 5).

**Table 3.** Geometry of hydrogen bonds and CH... $\pi$  interactions in the crystal (Å, °).

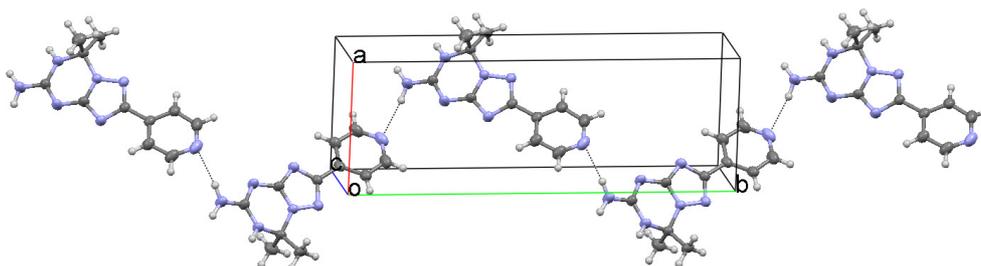
D-H...A	D-H	H...A	D...A	D-H...A
N1-H1A...N5 <sup>i</sup>	0.88(2)	2.06(2)	2.9444(18)	173.6(17)
N1-H1B...N7 <sup>ii</sup>	0.89(2)	2.21(2)	3.094(2)	170.3(16)
N2-H2...N6 <sup>i</sup>	0.841(18)	2.128(18)	2.9648(17)	172.9(16)
C10-H10C...Cg <sup>iii</sup>	0.96	2.60	3.5557(17)	173

Cg is the centroid of the pyridine ring (C5/C6/C7/N7/C8/C9); Symmetry codes: (i)  $x + 1/2, -y + 1/2, z + 1/2$ ; (ii)  $-x - 1/2, y + 1/2, -z + 1/2$ ; (iii)  $-x, -y, 1-z$ .

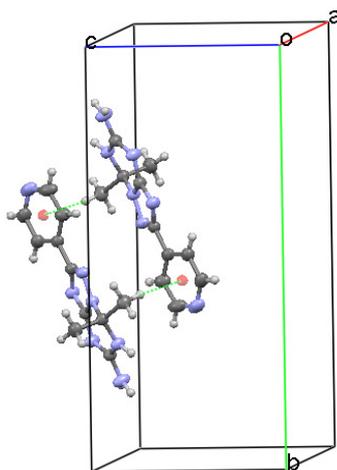
**Figure 3.** A view of the crystal packing in **1** along the  $c$  axis, showing the  $C(4)C(6)$  chain of molecules formed by the  $\text{NH}\cdots\text{N}$  hydrogen bonds running parallel to the  $[101]$  direction.



**Figure 4.** A view of the crystal packing in **1** along the  $c$  axis, showing the  $C(11)$  chain of molecules formed by the  $\text{NH}\cdots\text{N}$  hydrogen bonds running parallel to the  $[010]$  direction.



**Figure 5.** A dimer formed by the molecules **1** via the  $\text{CH}\cdots\pi$  interactions.



### 3. Experimental Section

The X-ray diffraction data for the compound were measured at room temperature on a Bruker SMART APEX CCD diffractometer using  $\text{Mo } K\alpha$  ( $\lambda = 0.71073 \text{ \AA}$ ) radiation. The empirical absorption

corrections were applied by the multi-scan method using SADABS [21]. Intensity data were collected in the  $\omega$ - $\phi$  scan mode using SMART [22] and were reduced using SAINT [22]. The structure was solved by direct methods using SHELXS97 [23] and difference Fourier synthesis using SHELXL97 [23]. The positions and anisotropic displacement parameters of all non-hydrogen atoms were included in the full-matrix least-square refinement using SHELXL97 [23] and the procedures were carried out for a few cycles until convergence was reached. A total of 8323 reflections were collected, resulting in 2736 ( $R_{\text{int}} = 0.037$ ) independent reflections of which the number of reflections satisfying  $I > 2\sigma(I)$  criteria was 2282. All the N-bound hydrogen atoms were located in a difference map and refined freely. The hydrogen atoms attached to the carbon atoms were placed in calculated positions (0.94 Å for C<sub>aryl</sub>-H and 0.97 Å for the methyl groups) and included in the final cycles of refinement using a riding model, with  $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C}_{\text{aryl}})$  and  $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C}_{\text{methyl}})$ . A rotating group model was used for the methyl groups. The  $R$  factor for observed data finally converged to  $R_1 = 0.0476$  with  $wR_2 = 0.1188$  in the compound. The maximum and minimum values of residual electron density were 0.268 and  $-0.213 \text{ e}\text{\AA}^{-3}$ . The geometry calculations were performed using PLATON [24]. SHELXTL [23] and MERCURY [25] were used for the diagram generation.

#### 4. Conclusions

The molecular structure of 7,7-dimethyl-2-pyridin-4-yl-6,7-dihydro-1,2,4-triazolo[1,5-*a*][1,3,5]triazin-5-amine has been determined and compared with structurally similar molecules. The classical NH $\cdots$ N hydrogen bonds and C-H $\cdots$  $\pi$  interactions stabilizing packing of the molecules in the crystal has been described.

#### Acknowledgments

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