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One-step aldehyde group transformation by using guanidine and aminoguanidine: Synthetic, structural and computational studies

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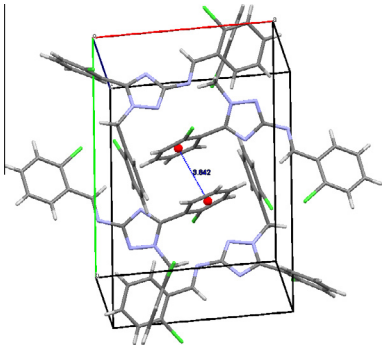
HIGHLIGHTS

- We report new synthetic methodologies of triazine derivatives.
- Structure of 1-(2-chlorobenzyl)-5-(2-chlorophenyl)-*N*-[(1*E*)-(2-chlorophenyl)methylene]-1,2,4-triazolidin-3-amine.
- 2,4-Diamino-3,6-dihydro-6-(2-chlorophenyl)-1,3,5-triazine was synthesized.
- Multinuclear NMR, X-ray and DFT characterization.
- High yield from low cost starting materials.

GRAPHICAL ABSTRACT



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ABSTRACT

New triazine derivatives 2,4-diamino-3,6-dihydro-6-(2-chlorophenyl)-1,3,5-triazine (**1**) and 1-(2-chlorobenzyl)-5-(2-chlorophenyl)-*N*-[(1*E*)-(2-chlorophenyl)methylene]-1,2,4-triazolidin-3-amine (**2**) were synthesized by a one-pot synthesis using 2-chlorobenzaldehyde, guanidine and aminoguanidine, respectively. The FTIR, multinuclear NMR, and single crystal X-ray characteristics of these compounds have been determined experimentally and rationalized on the basis of DFT calculation method.

1. Introduction

Aldehydes are a class of compounds of great interest from the synthetic, theoretical and application point of view. They can be transformed into a wide range of structures through applying a variety of reactions. Like ketones, aldehydes are sp^2 hybridized and could exist in the form of keto or enol tautomer. The equilibrium is strongly thermodynamically driven, and at room temperature the keto form is favored. The conversion between the two forms can be catalyzed by either acids or bases. As electrophiles, they are subject to be attacked by nucleophiles, and participate in many nucleophilic addition reactions.

In this paper, we reported the transformation of aldehyde group by guanidine and aminoguanidine to new triazine derivatives. Despite its potential value there are many papers describing this conversion. In most cases products are Schiff bases [1–13]. However, there are only few works showing the ring closure reaction

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similar to ours, all without NMR and X-ray characteristics [14]. The presented discussion is particularized by computational and spectroscopic studies. The triazines have been found broad applications in pharmaceutical and agrochemical industries [15–19]. They have also attracted considerable attentions due to their biological and medicinal activities, such as antileukemic, against resistant malarial strains, antitumor, diuretic, herbicides or in cancer therapy [20–26]. Triazine derivatives are cytotoxic to parasites since they offer excellent selectivity between parasites and host cells [27–29].

2. Experimental

2.1. General

NMR spectra were obtained with Bruker Avance 400 and 500 operating at 500.18 or 400.13 MHz (^{1}H), 125.78 or 100.5 MHz (^{13}C) at 21 °C. Chemical shifts referenced to ext. TMS (^{1}H, ^{13}C). Coupling constants are given in Hz. Mass spectra were obtained with a Varian 500 MS with applied ESI technique. Melting points were determined on MPA100 OptiMelt melting point apparatus and uncorrected. 2-Chlorobenzaldehyde, guanidine sulfate and aminoguanidine bicarbonate were purchased from Sigma–Aldrich, and were used without further purification.

2.1.1. Synthesis of compounds

2.1.1.1. Synthesis of 2,4-diamino-3,6-dihydro-6-(2-chlorophenyl)-1,3,5-triazine (1). Guanidine sulfate (30.3 g, 0.28 mol) was partially dissolved in a mixture of methanol (300 mL) and DMSO (5 mL). Subsequently, K_2CO_3 (38.7 g, 0.28 mol) was added, and the reagents were heated under reflux for an hour, then 2-chlorobenzaldehyde (39.2 g, 0.28 mol) in a solution of methanol (50 mL) was added. After the addition, the reaction mixture was stirred under reflux overnight, followed by filtration. The solvent was evaporated from the resulting solution. The crude product was purified by extraction at Soxhlet apparatus using EtOH:

1; 32.47 g (0.146 mol; 52%); (white); m.p.$_{dec.}$ = 177–178 °C; ^{1}H NMR (DMSO-d_6; 400.2 MHz; 75 °C) δ = 5.44 (bs, 4H, N*H*), 5.99 (s, 1H, C*H*), 7.29 (d, *J* = 7.6 Hz, 1H, aromatic), 7.34 (t, *J* = 7.5 Hz, 1H, aromatic), 7.38 (d, *J* = 7.8 Hz, 1H, aromatic), 7.49 (d, *J* = 7.5 Hz, 1H, aromatic); ^{13}C{^{1}H} NMR (DMSO-d_6; 100.5 MHz; 60 °C) δ = 65.32, 126.87, 128.38, 128.60, 128.86, 131.01, 142.13 (bs), 158.15; MS (MeOH + AcOH): (ESI) $(M + H)^+$ = 224 (100% ^{35}Cl) and 226 (32% ^{37}Cl).

2.1.1.2. Synthesis of 1-(2-chlorobenzyl)-N-(2-chlorobenzylidene)-5-(2-chlorophenyl)-1H-1,2,4-triazol-3-amine (2). Aminoguanidine bicarbonate (38.1 g, 0.28 mol) was partially dissolved in water (100 mL). Subsequently, K_2CO_3 (38.7 g, 0.28 mol) was added, and the reagents were heated under reflux for an hour. Then the water was evaporated and 2-chlorobenzaldehyde (78.7 g, 0.56 mol) in solution of methanol (100 mL) was added. After the addition, the reaction mixture was stirred overnight (16 h), followed by filtration. The solvent was evaporated from the resulting solution. The crude product was purified by crystallization from MeOH:

2; 21.4 g (48.5 mmol; 26%); (beig); m.p. = 124–125 °C; ^{1}H NMR (DMSO-d_6; 500.18 MHz) δ = 3.34 (s, 2H, CH_2), 7.28–7.33 (m, 2H, aromatic), 7.34 (dd, *J* = 5.9, 2.9 Hz, 1H, aromatic), 7.41 (dd, *J* = 6.0, 2.9 Hz, 1H, aromatic), 7.48–7.55 (m, 2H, aromatic), 7.58–7.62 (m, 2H, aromatic), 7.65 (td, *J* = 7.2, 1.8 Hz, 2H, aromatic), 7.68 (dd, *J* = 8.0, 0.7 Hz, 1H, aromatic), 8.23 (d, *J* = 7.7 Hz, 1H, aromatic), 9.58 (s, 1H, C*H*N); ^{13}C{^{1}H} NMR (DMSO-d_6; 125.78 MHz) δ = 50.09, 126.83, 127.43, 127.60, 127.81, 128.35, 129.37, 129.86, 130.04, 130.22, 130.94, 131.89, 132.05, 132.45, 132.50, 132.53, 132.92, 133.85, 135.79, 152.66, 159.75, 164.72; MS: (ESI) $(M)^+$ = 441 (100%), 443 (100%), 442 (25%), 444 (25%) 445 (43%); CCDC 921074.

2.2. Crystallization

The crystal of **2** suitable for X-ray analysis was obtained from hot MeOH solution.

2.3. DFT calculations

The calculations were carried out by using Gaussian 09 [30] program. The DFT/B3LYP [31,32] method was used for the geometry optimization and electronic structure determination. The geometry optimization was made for gas phase molecule and a frequency calculation was carried out, verifying that the optimized molecular structure obtained corresponds to energy minimum, thus only positive frequencies were expected. The absence of the imaginary frequencies, as well as of negative eigenvalues of the second derivative matrix has been obtained in geometry optimization of all compounds. The calculations were performed using the polarization functions for all atoms: 6-31G** – carbon, nitrogen, oxygen, chloride and hydrogen. Natural charges were calculated with use of the NBO 5.0 package included in Gaussian 09.

2.4. Crystal structure determination and refinement

The crystal of **2** was mounted in turn on a Gemini A Ultra, Oxford Diffraction automatic diffractometer equipped with a CCD detector for data collection. X-ray intensity data were collected with graphite monochromated Mo K_α radiation ($\lambda = 0.71073$Å) at temperature of 295.0(2) K **2**, with ω scan mode. Ewald sphere reflections were collected up to $2\theta = 50.10$. Details of crystal data and refinement are gathered in Table 1, and selected bond lengths and angles for compounds are listed in Table 2. During the data

Table 1
Crystal data and structure refinement details for **2**.

	2
Empirical formula	$C_{22}H_{15}Cl_3N_4$
Formula weight	441.73
Temperature (K)	295.0(2) K
Radiation	Mo K_α λ = 0.71073 Å
Color, habit	Colorless, plate
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	
a (Å)	10.8119(9)
b (Å)	13.4154(9)
c (Å)	15.4186(13)
β (°)	110.016(9)
Volume (Å^3)	2101.3(3)
Z	4
Calculated density (Mg/m^3)	1.396
Absorption coefficient (mm^{-1})	0.452
F(000)	904
Crystal dimensions (mm)	0.27 × 0.19 × 0.06
θ range for data collection (°)	3.35–25.05
Index ranges	$-8 \leqslant h \leqslant 12$ $-15 \leqslant k \leqslant 13$ $-18 \leqslant l \leqslant 15$
Reflections collected	7993
Independent reflections	3714 [$R_{(int)}$ = 0.0326]
Data/restraints/parameters	3714/0/262
Goodness-of-fit on F^2	1.073
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0528 wR_2 = 0.1190
R indices (all data)	R_1 = 0.0944 wR_2 = 0.1524
Largest diff. Peak and hole (e Å^{-3})	0.765 and −0.501
CCDC number	921074

Table 2
Selected bond lengths and angles for **2** (Å and °).

Exp.			Calc.	
Bond lengths (Å)				
Cl(1)–C(9)	1.740(5)		1.84	
Cl(2)–C(15)	1.691(5)		1.83	
Cl(3)–C(22)	1.744(4)		1.84	
N(1)–C(2)	1.343(5)		1.34	
N(1)–N(2)	1.352(4)		1.38	
N(1)–C(3)	1.463(5)		1.39	
N(2)–C(1)	1.312(5)		1.34	
N(3)–C(2)	1.315(5)		1.35	
N(3)–C(1)	1.353(5)		1.38	
N(4)–C(16)	1.266(5)		1.30	
N(4)–C(1)	1.398(5)		1.38	
Angles [°]				
C(2)–N(1)–N(2)	109.7(3)		110.0	
C(2)–N(1)–C(3)	128.5(3)		126.4	
N(2)–N(1)–C(3)	121.7(3)		119.2	
C(1)–N(1)–N(2)	102.5(3)		102.9	
C(2)–N(3)–C(1)	103.1(3)		104.3	
C(16)–N(4)–C(1)	115.7(3)		120.3	
N(2)–C(1)–N(3)	114.8(3)		113.6	
N(2)–C(1)–N(4)	121.5(3)		120.4	
N(3)–C(1)–N(4)	123.7(3)		125.9	
Hydrogen bonds				
D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
C(8)–H(8)···N(3) #1	0.93	2.58	3.488(6)	167.0
C(16)–H(16)···Cl(3)	0.93	2.68	3.042(4)	104.2
C(16)–H(16)···N(3)	0.93	2.35	2.723(5)	103.8

Symmetry transformations used to generate equivalent atoms: $1 1/2−*x*, 1/2 + *y*, 1/2−*z*.

reduction, the decay of the correction coefficient was taken into account. Lorentz, polarization and empirical absorption correction using spherical harmonics implemented in SCALE3 ABSPACK scaling algorithm [33] were applied. The structures were solved by direct method. All the non-hydrogen atoms were refined anisotropically using full-matrix, least-squares technique on F^2. All the hydrogen atoms were found from the difference of the Fourier synthesis after four cycles of anisotropic refinement, and refined as "riding" on the adjacent atom with individual isotropic temperature factor equal to 1.2 times the value of equivalent temperature factor of the parent atom, with geometry idealization after each cycle. The Olex2 [34] and SHELXS97, SHELXL97 [35] programs were used for all the calculations. Atomic scattering factors were those incorporated in the computer programs.

2.5. X-ray and DFT studies

2 Crystallizes in monoclinic $P2_1/n$ space group and its molecular structure is displayed as ORTEP representation in Fig. 1.

The heterocyclic triazole ring is planar within experimental error and the N(2)–C(1) and N(3)–C(2) distances of 1.312(5) Å and 1.315(5) Å, respectively, clearly indicate they are double bonds. The N(1)–N(2) bond (1.352(4) Å) is somewhat shorter than the standard ordinary bond N–N (1.451 Å), which can be explained by the delocalization of double bond in the triazole fragment. The bond's lengths of triazole molecule are the same with the tabulated values. The C–N–N angles in the ring show large deviations from the value of 120° usually found in the trigonal planar arrangement, which is common in five-membered rings. The angles between the planes defined by the triazole cycle and the benzene rings are 37.21°, 66.85° and 84.85°, respectively. In the molecule of **2** can be found intra- and intermolecular short contact (Table 2) which, according to Desiraju & Steiner, can be classified as weak hydrogen bond [36]. However the hydrogen bonds do not form any substructures. Nevertheless some electronic interactions

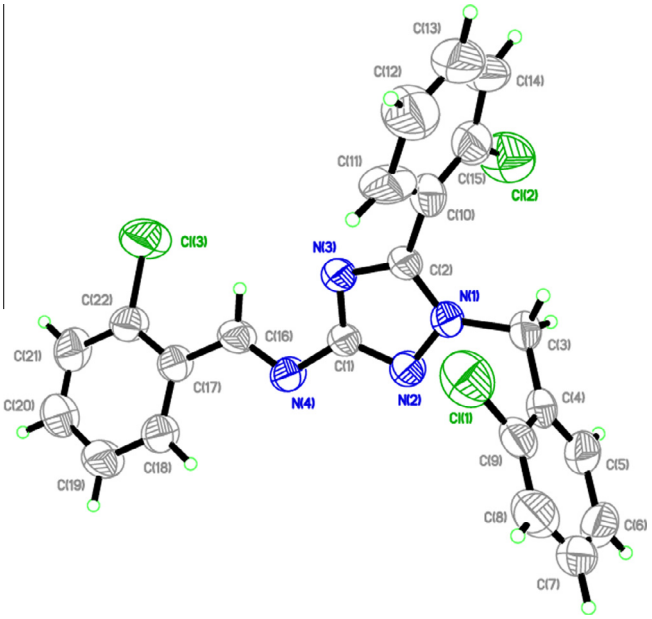


Fig. 1. ORTEP drawing of molecule 2 with 50% probability displacement ellipsoids.

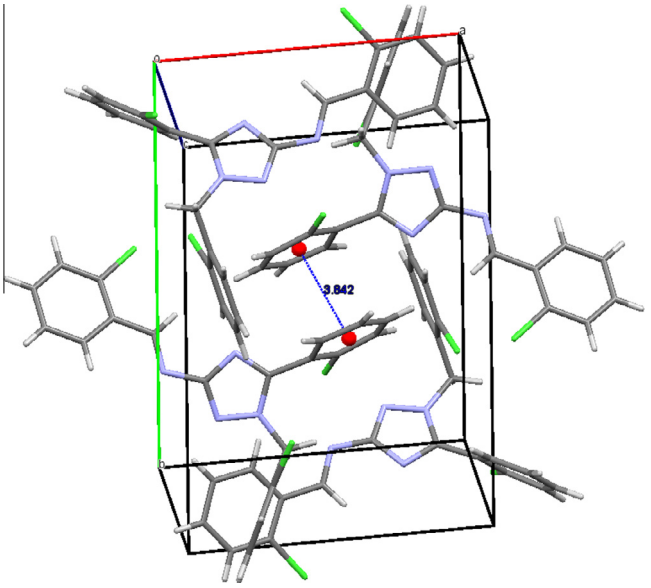


Fig. 2. Interaction between parallel phenyl rings in the unit cell of 2.

between parallel phenyl C(10)–C(15) rings, with centroid–centroid distance 3.842 Å and shift distance equal to 1.114 Å, (Fig. 2) also exert influence on the crystal structure of the compound.

2.6. DFT

The geometry of the compound **2** was optimized in singlet states using the DFT method with the B3LYP functional and the predicted bond lengths and angles are over-estimated by about 0.1 Å and 5°, respectively.

The calculated IR frequencies of the compound **2** show good agreement with the experimental spectrum (see Fig. 3); the differences can be explained by the neglect of intermolecular interactions for the gas phase. From the data collected in Table 2, the major differences between the experimental and calculated

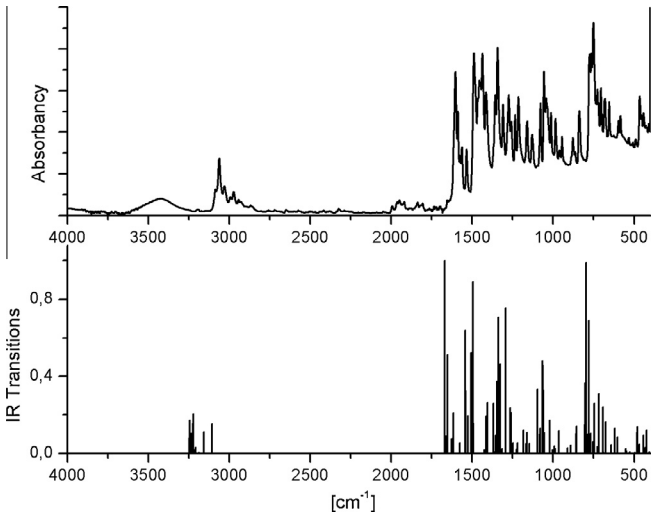


Fig. 3. IR spectroscopic data of **2**.

geometries are found in the Cl(2)–C(15) distance (~0.13 Å) and C(16)–N(4)–C(1) angle (4.6°).

The atomic charge calculations can give a feature for the relocation of the electron density of the compounds, but the local concentration and local depletion of electron charge density allow us to determine whether the nucleophile or electrophile can be attracted.

Fig. 4 presents the plots of the electrostatic potential for **2**. The isoelectronic contour is plotted at 0.05 a.u. (13 kJ/mol). The color code of the map is in the range of 0.05 a.u. (deepest red) to −0.05 a.u. (deepest blue), where blue indicates the strongest attraction and red indicates the strongest repulsion. Regions of negative $V(r)$ are usually associated with the lone pair of electronegative atoms. The negative potentials (−0.5 to −0.2) are mainly localized on the nitrogen atoms. Chlorine substituents have charges close to zero (−0.04) similarly to our previous results [37–39]. The natural charges of nitrogen and chloride atoms in molecule of **2** compounds are collected in Table 3 and as one can see the triazole N(3) and azomethine N(4) atoms have comparable most negative charges.

3. Results and discussion

We report herein an efficient one-pot conversion of an aldehyde group into triazine derivatives. In literature there was only one paper describing reaction between benzaldehyde with excess of guanidine freshly liberated from the corresponding hydrochloride salt in methanol leading to triazine derivatives [40].

We carried out analogous reaction between 2-chlorobenzaldehyde with excess of guanidine freshly liberated from the corresponding sulfate salt in methanol. Conversion was unambiguous and leads to **1** (Scheme 1). Our studies demonstrated that there were three possible tautomeric forms; two symmetric A, B and one unsymmetrical C (Scheme 2).

The simplicity of ^{1}H NMR and ^{13}C NMR characteristics ruled out the presence of unsymmetrical C tautomer. Similarly to Ujjinamatada and Hosmane [40], our compound possesses characteristic methine signal showing a single resonance at $\delta(^{1}H) = 5.99$ and $\delta(^{13}C) = 65.32$ ppm (Table 4). The analysis of the trend in ^{1}H NMR and ^{13}C NMR chemical shifts of **1** and their literature analogues revealed that the presence of chloride atom in phenyl ring significantly decreased the shielding effect (downfield effect, larger δ) (Table 4) [40]. One of the interpretations could be the existence

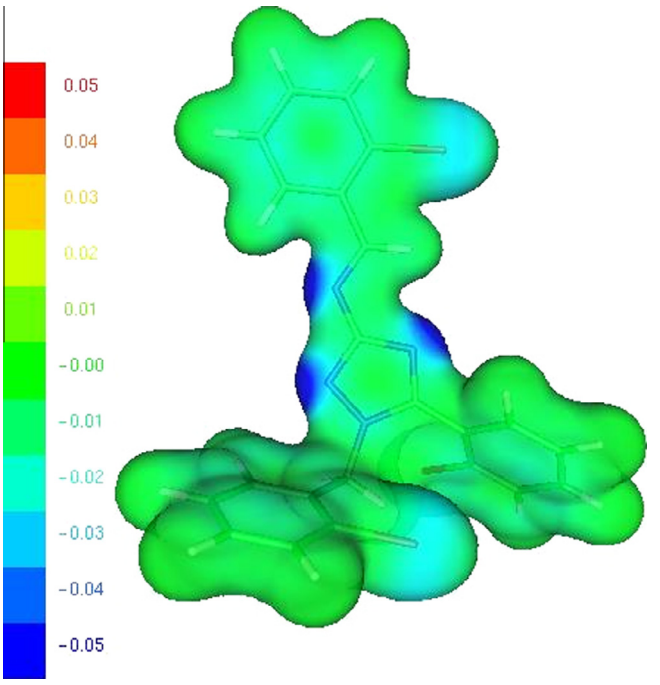


Fig. 4. The electrostatic potential (ESP) surface for **2** plotted with use of gOpenmol program.

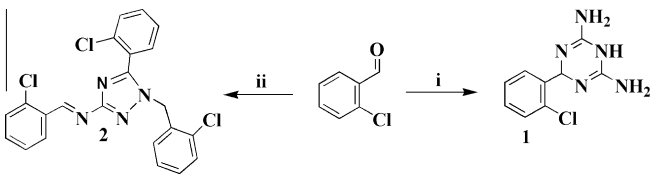
Table 3
The natural charges of selected atoms in molecule of **2**.

Atom	N(1)	N(2)	N(3)	N(4)	Cl(1)	Cl(2)	Cl(3)
Natural charge	−0.19	−0.27	−0.51	−0.46	−0.05	−0.04	−0.04

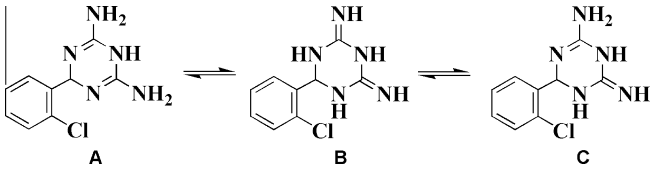
of intramolecular hydrogen bonds between >NH and chloride which could make the methine carbon atom slightly more positive. The existence of intramolecular hydrogen bonds in constitution of similar triazines has been already demonstrated by Rihn et al. [41]. This in consequence should support the presence of tautomer "B" rather than postulated by Ujjinamatada and Hosmane "A" [40].

Another ring closure reaction was presented during the syntheses of **2**. The protocol was based on previously described synthesis of **1**. Reaction between 2-chlorobenzaldehyde with excess of aminoguanidine freshly liberated from the corresponding bicarbonate salt in methanol smoothly led to **2**. Product was quantitatively prepared and characterized by MS, and multinuclear NMR spectroscopy together with their X-ray structure (Fig. 1).

In order to improve the understanding of the chemical behavior or the structure of species like **1** or **2**, and similar molecules, it would be desirable if one could employ a technique or a method rather than an execution of experiments which could require complex synthesis and a consumption of expensive materials.



Scheme 1. The synthesis of **1** and **2;** *Reagents and conditions:* (i) guanidine, MeOH, reflux; (ii) aminoguanidine, MeOH, reflux.



Scheme 2. Tautomers of **1**.

Table 4
The experimental ^{1}H and ^{13}C chemical shifts of methine signal of **1** and their literature analogues.

Compound	Solvent	^{1}H NMR	^{13}C NMR	Substituent
1	DMSO-d_6	5.99	65.32	Cl in 2 position
[40]	DMSO-d_6	5.77	62.4	only H
[40]	DMSO-d_6	5.74 or 5.73	59.7	OCH_3 in 2 and 4 position

Table 5
NICS(0) and NICS(1) values for symmetric A and B tautomers of **1** obtained with use of the GIAO procedure at B3LYP/6-31G** level.

	A	B
NICS(0)	−2.51	− 0.67
NICS(1)	− 5.99	− 1.33

The aromaticity is an important parameter used frequently as a measure of reactivity of many organic compounds. The majority of organic compounds may be characterized by more or less pronounced aromatic character, which is especially important for heterocyclic compounds. Many theoretical criteria for aromaticity have been proposed, but resonance energy was the first quantitative measure of aromatic character and still provides useful characteristics of aromaticity [42]. Magnetic properties of organic molecules arise from the diamagnetic ring currents of aromatic systems. The nucleus independent chemical shift (NICS) was defined by Schleyer et al. as a negative value of the absolute magnetic shielding computed in the centers of ring or 1 Å above the molecular plane [43]. NICS at an empty point in space equals to zero and in principle does not require reference molecules and calibrating (homodesmotic) equations for evaluation of aromaticity. Negative values of NICS indicate shielding-presence of induced diatropic ring currents understood as aromaticity at specific point. On the contrary, its positive values are interpreted as deshielded—paratropic ring currents and antiaromaticity. Schleyer et al. after studies on an extensive set of heterocyclic compounds, proved that there are very good linear correlations between geometric, energetic, and magnetic properties providing straightforward interpretation of the electronic structures and properties of organic molecules [42]. Despite the fact that it is not obvious localization of maximum shielding, the distance of 1 Å above the molecule geometric center is commonly accepted as a reference point. Such value denoted as NICS(1) is then a measure of aromaticity [42–45].

The calculated aromaticity for tautomers of **1** suggests a stronger stability of tautomer **A** due to significantly more aromatic compared to the tautomer **B** (planar structure of triazine ring was retained) as one can see from data collected in Table 5.

Nevertheless, the requirement of triazine ring planarity in the case of tautomer **B** led to form not in minimum on the potential energy surface; the corresponding minimum energy structure is non-planar. Therefore the concept of aromaticity applied to the settlement of the isomers problem gives rather inconclusive result.

4. Conclusions

The presented research focused on the synthesis of selected crystalline triazine derivatives containing chloro substituent, which showed high yield of products. The compounds were further characterized by analytical methods and rationalized on the basis of DFT calculation method with B3LYP functional. Chlorine substituents have charges close to zero similarly to our previous results. For future studies, we plan to extend this work and investigate the efficiency of the synthesis of triazine derivatives for various biomedical applications.

Acknowledgments

The GAUSSIAN 09 calculations were carried out in the Wrocław Centre for Networking and Supercomputing, WCSS, Wrocław, Poland (http://www.wcss.wroc.pl Grant Number 18).

Appendix A. Supplementary data

CCDC 921074 for **2** contains the supplementary crystallographic data for the compound. These data can be obtained free of charge from http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk. Calculations have been carried out in Wroclaw Centre for Networking and Supercomputing (http://www.wcss.wroc.pl).

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