Struct Chem (2010) 21:795–802
DOI 10.1007/s11224-010-9613-y

ORIGINAL RESEARCH

A joint theoretical and experimental structural study of two novel 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine derivatives

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Received: 19 February 2010 / Accepted: 12 April 2010 / Published online: 23 April 2010

Abstract In this study, two novel 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine derivatives, 3-[2-(4-methoxyphenyl)ethyl]-6-phenyl-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (compound **1**) and 3-[2-(3,4,5-trimethoxyphenyl)ethyl]-6-phenyl-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (compound **2**), having analgesic–anti-inflammatory activity were synthesized and characterized by IR, ^{1}H-NMR, and mass spectroscopic techniques besides elementary analysis. Additionally, the structures and molecular packings of the mentioned compounds have been investigated by X-ray single crystal diffraction. The six-membered thiadiazine ring adopts the screw boat conformation in both the compounds. In the crystal packings of the compounds **1** and **2**, C–H···N and C–H···O interactions link the molecules into a two-dimensional network and generate infinite chains. Furthermore, C–H···π intermolecular interactions provide further stability to the molecular packing in both the molecules. The conformers have been predicted by the potential energy surface scan employing the AM1 method. Geometry optimizations and electrostatic properties have been obtained using AM1 and ab initio quantum methods.

Keywords X-ray analysis · Triazolo[3,4-*b*]-1,3,4-thiadiazine · Theoretical calculations · Structural study

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Introduction

Development of new analgesic/anti-inflammatory compounds with safer and as effective as opioids for the treatment of pain and inflammation has been in interest of us for many years. In earlier studies, we have synthesized many substances derived from 1,2,4-triazole-5-thiones and tested their analgesic/anti-inflammatory activity. A considerable number of the prepared compounds have been found to have analgesic/anti-inflammatory activity comparable to or higher than the reference compounds besides lower ulcerogenic risks in the stomach [1–7]. Finally, we have synthesized a series of 4-amino-3-substituted-1,2,4-triazole-5-thiones and their corresponding condensed derivatives, 3,6-disubstituted 7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines, with possible anti-inflammatory–analgesic properties [8, 9]. The concerned compounds, 3-[2-(4-methoxyphenyl)ethyl]-6-phenyl-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (compound **1**) and 3-[2-(3,4,5-trimethoxyphenyl)ethyl]-6-phenyl-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (compound **2**), are two members of this series having analgesic/anti-inflammatory activity [9].

To the best of our knowledge, neither spectral data nor X-ray crystallographic analysis and theoretical calculations on these two compounds have been available till now. Here, we present synthesis and characterizations of the compounds **1** and **2** as well as X-ray crystallographic analysis and some theoretical calculations. In order to gain further information on the conformational features of the given compounds, a potential energy scan was performed by using the semi-empirical AM1 method. For the most stable conformations ab initio geometry optimization at restricted Hartree-Fock level using the 6-31G basis set was performed. The geometrical features predicted by AM1 and RHF/6-31G calculations and those determined by X-ray crystallographic analysis are compared and some other comparisons are also

made between several properties (dipole moments, frontier orbitals).

Experimental and computational procedures

Synthesis

Synthesis of the compounds was realized in two steps. In the first step, aminomercaptotriazoles required as starting material was prepared by heating 3-(4-methoxyphenyl)/(3,4,5-trimethoxyphenyl)propionic acids with thiocarbohydrazide at the melting temperature (160–170 °C) [8, 9]. Aminomercaptotriazoles were converted into 6-phenyl-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines in one step by reacting them with phenacyl bromide in anhydrous ethanol under reflux [9–11] (Scheme 1). The structures of the compounds are characterized by elementary analysis, IR, ^{1}H-NMR, and mass spectra. The spectral data are in good agreement with the proposed structures.

*3-[2-(4-Methoxyphenyl)ethyl]-6-phenyl-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine (compound **1**)*

Yield 64%; mp 142–143 °C (ethanol); IR (KBr): 1610 (C=N), 1300 (C–N), 1244 (C–O) cm^{-1}. ^{1}H-NMR δ (ppm): 3.11 (2H, t, C*H*$_2$CH$_2$), 3.28 (2H, t, CH$_2$C*H*$_2$), 3.70 (3H, s, OC*H*$_3$), 3.90 (2H, s, SC*H*$_2$), 6.75 (2H, d, arom. H-3, H-5), 7.11 (2H, d, arom. H-2, H-6), 7.52–7.59 (3H, m, arom. H-3′, H-4′, H-5′), 7.84 (2H, d, arom. H-2′, H-6′). MS (70 eV, EI): *m*/*z* (%): 352 ($M^{+\cdot}$+2, 5.26%), 350 ($M^{+\cdot}$, 66.67%), 335 ($M^{+\cdot}$–CH$_3$, 6.14%), 317 ($M^{+\cdot}$–SH, 1.75%), 247 ($M^{+\cdot}$–C$_6$H$_5$CN, 3.51%), 232 ([$M^{+\cdot}$–(C$_6$H$_5$CN+CH$_3$)], 48.25%), 134 (CH$_3$OC$_6$H$_4$CHCH$_2$, 16.23%), 121 (CH$_3$OC$_6$H$_4$CH$_2$, 100%), 77 (C$_6$H$_5$, 39.91%). Anal. Calcd for C$_{19}$H$_{18}$N$_4$OS: C, 65.12; H, 5.18; N, 15.99; S, 9.15. Found: C, 65.10; H, 4.93; N, 15.90; S, 9.38.

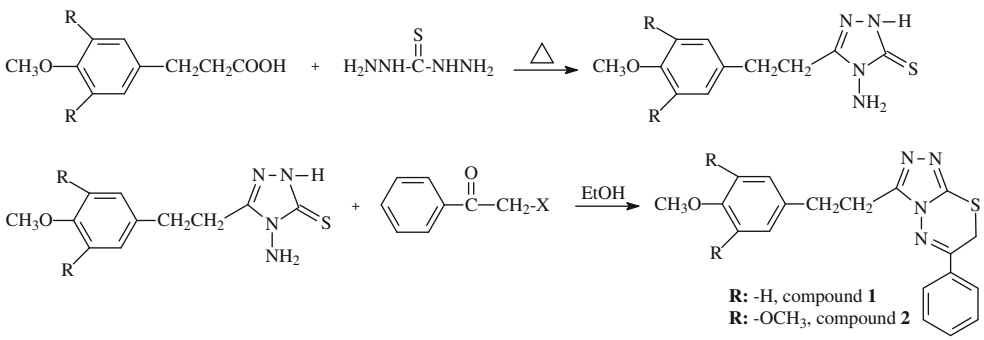
*3-[2-(3,4,5-Trimethoxyphenyl)ethyl]-6-phenyl-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine (compound **2**)*

Yield 34%; mp 158–159 °C (ethanol); IR (KBr): 1587 (C=N), 1305 (C–N), 1234 (C–O) cm^{-1}. ^{1}H-NMR δ (ppm): 2.96 (2H, t, C*H*$_2$CH$_2$), 3.17 (2H, t, CH$_2$C*H*$_2$), 3.49 (3H, s, OC*H*$_3$), 3.68 (6H, s, OC*H*$_3$), 4.29 (2H, s, SC*H*$_2$), 6.47 (2H, s, arom. H-2, H-6), 7.51–7.59 (3H, m, arom. H-3′, H-4′, H-5′), 7.95 (2H, d, arom H-2′, H-6′). MS (70 eV, EI): *m*/*z* (%): 412 ($M^{+\cdot}$+2, 2.86%), 410 ($M^{+\cdot}$, 37.86%), 395 ($M^{+\cdot}$–CH$_3$, 9.64%), 379 ($M^{+\cdot}$–OCH$_3$, 2.86%), 292 ([$M^{+\cdot}$–(C$_6$H$_5$CN+CH$_3$)], 7.86%), 181 ((CH$_3$O)$_3$C$_6$H$_2$CH$_2$, 100%), 77 (C$_6$H$_5$, 17.14%). Anal. Calcd. for C$_{21}$H$_{22}$N$_4$O$_3$S: C, 61.45; H, 5.40; N, 13.65; S, 7.81. Found: C, 61.71; H, 5.11; N, 13.81; S, 7.98.

Structure determination

Light yellow prismatic single crystals suitable for X-ray diffraction were chosen for the structure determination for compounds **1** and **2**. X-ray intensity data were collected at room temperature on an Enraf-Nonius CAD4 diffractometer [12] using graphite monochromated MoK$_\alpha$ radiation ($\lambda = 0.71073$ Å). w/2θ scan mode was applied for data collections. The cell parameters were refined from accurately determined 25 reflections in the range of $9.50 \leq \theta \leq 18.21°$ for compound **1** and $10.03 \leq \theta \leq 20.14°$ for compound **2**. Extinction correction was applied for compound **1**.

The structures were solved by direct methods using the SIR92 [13] for compound **1** and SHELXS-97 [14] for compound **2**. The positional parameters of non-H atoms were refined by a full-matrix least squares method with anisotropic thermal parameters using the program SHELXL-97 [15]. All hydrogen atoms were calculated on the basis of their stereochemical requirement at distances 0.93, 0.96, and 0.97 Å for aromatic, methylene, and methyl H atoms, respectively, and refined riding on their parent



Scheme 1 Synthesis of 3,6-disubstituted-7*H*-triazolo [3,4-*b*]-1,3,4-thiadiazines

atoms (for compounds **1** and **2**). Crystal data, a summary of intensity data collection and structure refinement, are given in Table 1. The dihedral angles were calculated using the PARST program [16], and the value of the dihedral angles for the planes (1, 2, 3) are given in Table 2. Ortep-3 [17] drawings with atom numbering are shown in Figs. 1 and 2 for compound **1** and **2**, respectively.

The additional material available from the Cambridge Crystallographic Data Centre (CCDC No. 699818 & 699819) comprises the final atomic coordinates for all atoms, thermal parameters and a complete listing of bond distances and angles (excluding structure factors). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK [Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Table 1 Crystal data and details of the structure determination of the title compounds

	Compound **1**	Compound **2**
Formula	$C_{19}H_{18}N_4OS$	$C_{21}H_{22}N_4O_3S$
Formula weight	350.43	410.49
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
Cell constants		
a (Å)	13.238(3)	11.7272(12)
b (Å)	13.827(5)	7.6172(12)
c (Å)	9.889(4)	23.0201(19)
β (°)	70.93(3)	94.735(8)
Z; D_{calc} (g cm^{-3})	4; 1.361	2; 1.330
μ (MoK$_\alpha$) (mm^{-1})	0.204	0.188
Crystal size (mm)	0.30 × 0.36 × 0.60	0.18 × 0.30 × 0.60
Radiation	MoK$_\alpha$ (λ = 0.71073 Å)	MoK$_\alpha$ (λ = 0.71073 Å)
Temp. (K)	293(2)	293(2)
θ limits (°)	2.63–26.32	2.38–26.29
Index ranges	$-16 \le h \le 15$	$-14 \le h \le 14$
	$-17 \le k \le 17$	$0 \le k \le 9$
	$-12 \le l \le 0$	$-28 \le l \le 28$
Reflections collected	7189	8311
Reflections observed	2584 [$I > 2\sigma(I)$]	2566 [$I > 2\sigma(I)$]
Reflns. used in refinement	3475	4169
No. of refined parameters	227	261
Extinction coefficient	0.045(4)	–
R_{int}	0.0344	0.0589
R/R_w values	0.0559/0.1384	0.0406/0.1239
GOF	1.104	1.052
Final shift	0.000	0.000
$(\Delta\rho)_{min}$, $(\Delta\rho)_{max}$ (e Å^{-3})	−0.548, 0.558	−0.302, 0.267

Table 2 Dihedral angles (°) for compounds **1** and **2**

Plane	Compound **1**		Compound **2**	
	1	2	1	2
C1–C2–C3–C4–C5–C6				
N1–N2–C9–N3–C10	56.46(7)		12.52(7)	
C13–C14–C15–C16–C17–C18	62.87(7)	6.49(6)	37.64(8)	33.74(8)

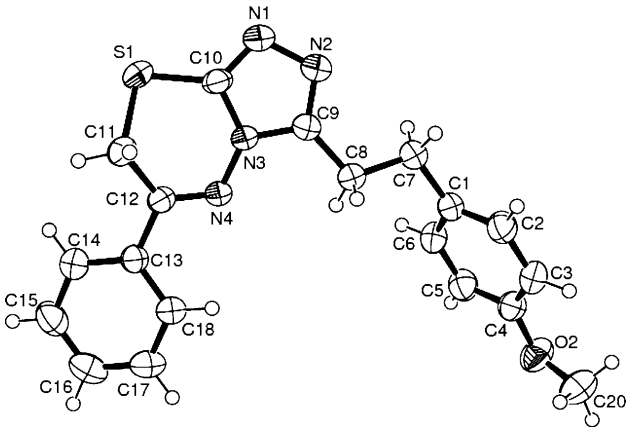


Fig. 1 ORTEP-3 view of the compound **1**, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level

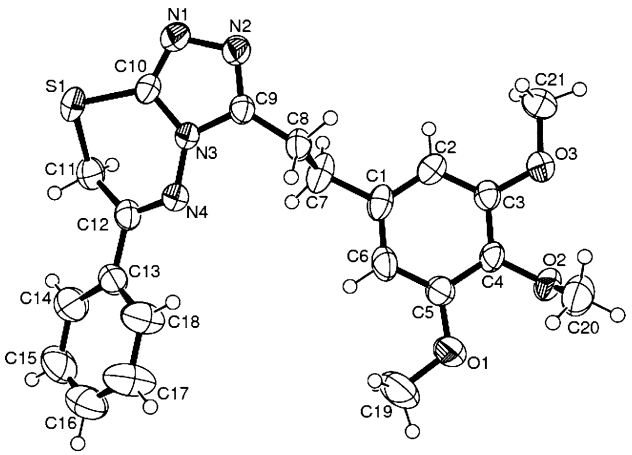


Fig. 2 ORTEP-3 view of the compound **2**, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level

Computational procedures

All calculations were carried out using Gaussian03W program [18]. For modeling, the initial guess of the molecules was obtained from the X-ray coordinates and transformed into the Gaussian Z-matrix format with Babel

program [19]. In order to explore the whole energy surfaces, conformational energies were calculated as a one-dimensional scan with rotation from −180° to +180° for φ_1(N2–C9–C8–C7), φ_2(C9–C8–C7–C1), φ_3(C8–C7–C1–C2), and φ_4(C11–C12–C13–C14) [φ_4(C11–C12–C13–C18) for compound **2**] torsion angles in 10° steps at the AM1 level. The minima obtained by the scan for the title compounds were optimized by AM1 method and at the ab initio restricted Hartree-Fock level of theory with the 6-31G basis set.

Result and discussions

Crystallography

The structures predicted from spectral analysis are confirmed by X-ray analysis of the single crystal. The X-ray structure analysis indicates that compound **1** consists of one methoxyphenyl ring, one phenyl ring, and a thiadiazine ring bearing the triazole ring. In compound **2**, there is trimethoxyphenyl ring instead of methoxyphenyl ring. The four rings do not share a common plane. The dihedral angles between the two phenyl rings are 62.87(7)° and 37.64(8)° for compounds **1** and **2**, respectively. The dihedral angle between the triazole ring and the benzene ring bearing the methoxy substituent is 6.49(6)° for compound **1** [33.74(8)° for compound **2**] (Table 2). In compound **1**, C1, C7, C8, C9 atoms are nearly linear and the related torsion angle is 173.4(2)°.

The triazole and phenyl rings are planar. The bond lengths and angles of the triazole ring are in good agreement with literature values [20, 21]. The O2 atom is located over the best plane of C1–C6 phenyl ring, while the C7 atom is oriented −0.114(2) Å below that ring for compound **1**. The orientation of the methoxy groups in compound **2** shows difference. While O1 and O2 atoms are above the best plane of the C1–C6 phenyl group, O3 atom is oriented to the downward. The C7 atom is almost in the best plane of the phenyl ring with −0.026(2) Å.

The six-membered thiadiazine ring, N3/N4/C12/C11/S1/C10, is distorted from planarity, with maximum r.m.s. deviation of −0.555(2) and −0.635(2) Å for compounds **1** and **2**, respectively. Structural results show that thiadiazine ring adopts the screw boat conformation in both compounds having spherical polar set values [22] $Q = 0.5533(17)$ Å, $\theta = 66.76(18)°$ and $\varphi = 326.1(2)°$ for compound **1** and $Q = 0.6027(18)$ Å, $\theta = 115.13(18)°$ and $\varphi = 148.3(2)°$ for compound **2**. Atoms C11 and C12 are displaced from the S1/C10/N3/N4 mean plane by −0.946(2) and −0.378(2) Å, respectively, for compound **1**. In compound **2**, C11 and C12 atoms are located above the best plane of S1/C10/N3/N4 by 1.024(2) and 0.424(2) Å, respectively. Both S–C [with a mean distance 1.770(2) Å] and C–N [with a mean distance 1.327(2) Å] bond lengths are comparable to those in related compounds [23, 24].

Table 3 Hydrogen bonding geometry (Å, °) for compounds **1** and **2**

D–H···A	D–H	H···A	D···A	D–H···A
Compound **1**				
C11–H11B···N2^{i}	0.97	2.610	3.318(3)	130
C20–H20C···Cg(3)^{ii}	0.96	2.665	3.605(3)	122
Compound **2**				
C19–H19···O1^{iii}	0.96	2.350	3.190(3)	146
C21–H21C···N2^{iv}	0.96	2.580	3.413(3)	146
C21–H21B···Cg(3)^{v}	0.96	2.840	3.687(2)	148

Cg(3): C1–C2–C3–C4–C5–C6

Symmetry code: (i) $-x$, $1/2 + y$, $1/2 - z$, (ii) x, $-1/2 - y$, $1/2 + z$, (iii) x, $1 + y$, z, (iv) $2 - x$, $-1/2 + y$, $1/2 - z$, (v) $2 - x$, $1 - y$, $-z$

In the crystal structures, weak C–H···N and C–H···O intermolecular hydrogen-bonding interactions link the molecules into a two-dimensional network and generate infinite chains (Table 3; Figs. 3, 4). Furthermore, C–H···π intermolecular interactions lend further stability to the molecular packing in both molecules.

Theoretical computations

In order to find all the conformers of 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine derivatives, AM1 method has been used for the potential energy surface scan. The potential energy surface maps are shown in Figs. 5 and 6.

Compound **1**

The rotations around N2–C9–C8–C7 (φ_1), C9–C8–C7–C1 (φ_2), and C8–C7–C1–C2 (φ_3) show several conformations. The X-ray structure shows the φ_1, φ_2, and φ_3 torsion

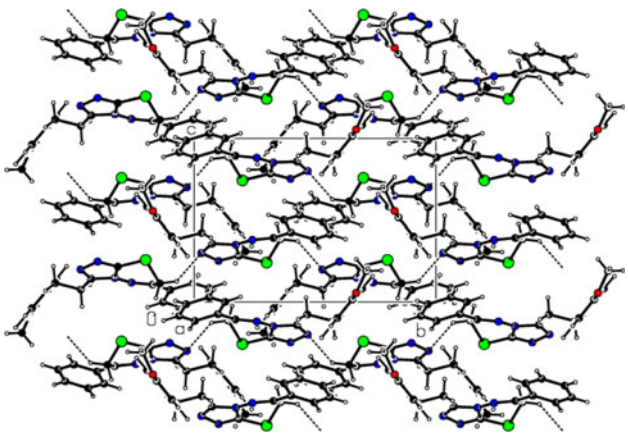


Fig. 3 Crystal packing of the compound **1** projected onto bc plane. The *dashed lines* indicate the intermolecular hydrogen bonds

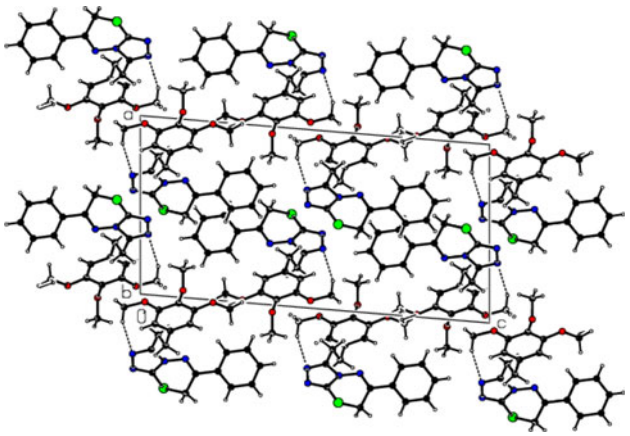


Fig. 4 Crystal packing of the compound **2** projected onto ac plane. The *dashed lines* indicate the intermolecular hydrogen bonds

angles to be −16.9(3)°, 167.7(2)°, and −109.1(2)°; while the theoretical calculations found for φ_1 to be −5.6° at semi-empirical AM1 level and 174.4° at RHF/6-31G level. For φ_2 and φ_3, full optimized AM1 geometry found to be −178.7° and −107.5°, respectively. In the case of ab initio calculations, φ_2 and φ_3 torsion angles are found as 179.1° and 82.9°, respectively. When compared with the X-ray results, the RHF/6-31G optimization indicates different conformation for φ_1. Rotation around C12–C13 bond shows large plateau and the barrier at −150°. This result suggests that phenyl moiety can rotate around 1,2,4-triazolo-1,3,4-thiadiazine moiety. The RHF level of theory could not predict the minimum energy structure. However, AM1 method has predicted the most stable conformation.

Compound **2**

In compound **2**, similar torsion angles are effective in the conformation of the molecule. The rotation around C8–C9 bond shows two minima occurring at −105° and the other at 75°. In both conformations, 1,2,4-triazolo-1,3,4-thiadiazine moiety is parallel to the trimethoxyphenyl ring. However, the only difference is the trimethoxyphenyl ring located on the mirror image side with respect to C8–C9 bond (Fig. 7). The conformational energy versus the C9–C8–C7–C1 torsion angle diagram predicts four conformers (Fig. 8). The most stable conformation is predicted at 175°. Rotation around C7–C1 is obtained with plateau between 150° and 180°. The energy curve φ_4 shows that a minimal energy is obtained for −170°, with a plateau between −180° and 50° and another between 75° and 180°. The minimum energy structure for compound **2** predicted by AM1 and RHF/6-31G methods compare in general quite well with the experimental data.

The geometrical features predicted by AM1 and RHF/6-31G calculations and those determined by X-ray crystallography analysis are listed in Tables 4 and 5, showing the most relevant bond distances, valence angles, and torsion angles of compounds **1** and **2**. It has been noticed that the level of RHF/6-31G theory estimate the bond lengths C=N

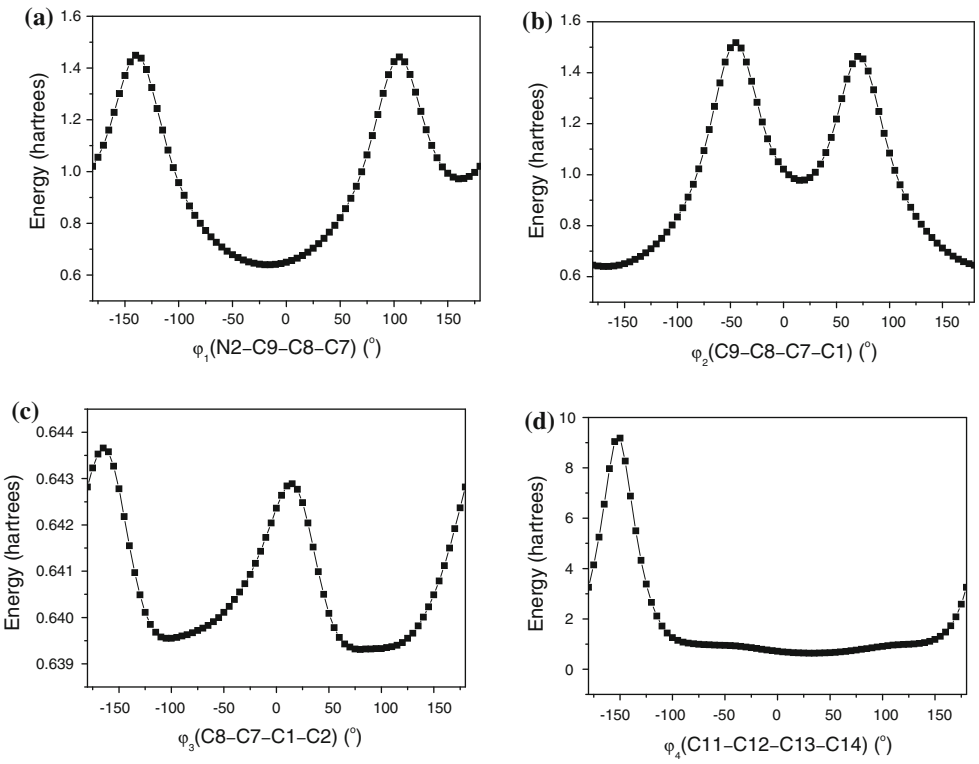


Fig. 5 AM1 calculated conformation energies for X-ray starting geometry of compound **1** versus the **a** φ_1(N2–C9–C8–C7), **b** φ_2(C9–C8–C7–C1), **c** φ_3(C8–C7–C1–C2), **d** φ_4(C11–C12–C13–C14)

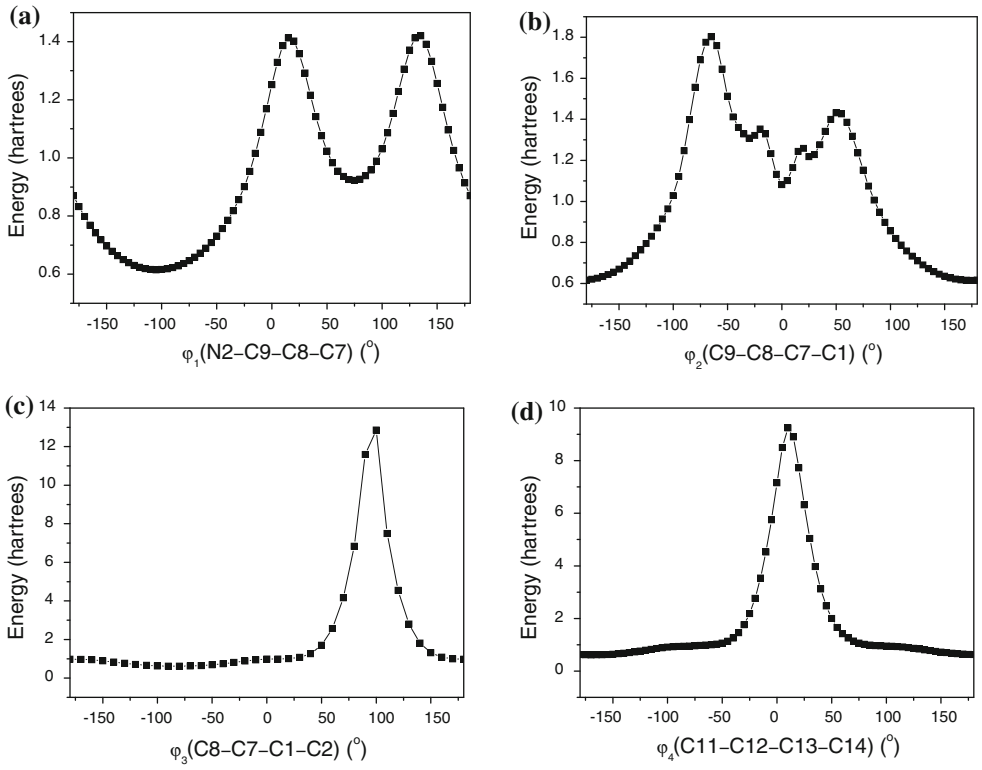


Fig. 6 AM1 calculated conformation energies for X-ray starting geometry of compound **2** versus the **a** φ_1(N2–C9–C8–C7), **b** φ_2(C9–C8–C7–C1), **c** φ_3(C8–C7–C1–C2), **d** φ_4(C11–C12–C13–C14)

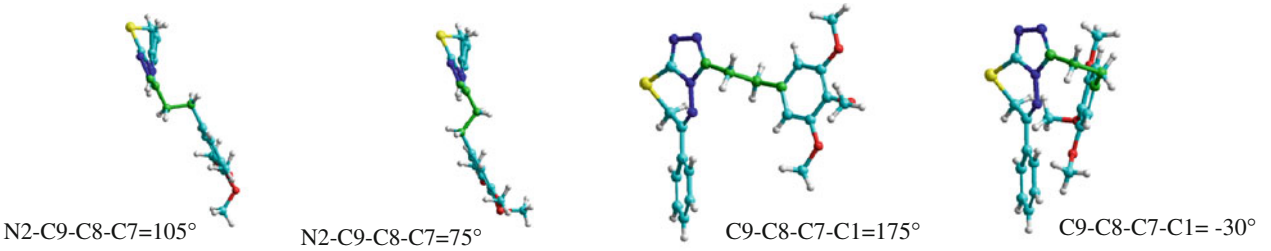


Fig. 7 Two different conformations of compound **2** predicted by AM1 theoretical calculations for the rotation about C8–C9 bond

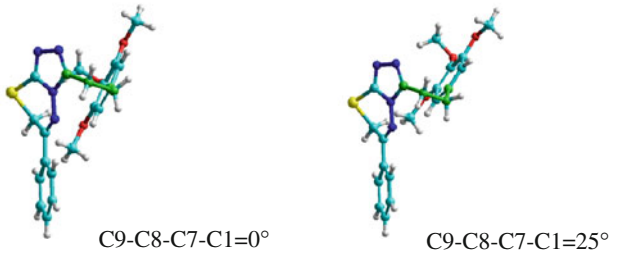


Fig. 8 Four different conformations of compound **2** predicted by AM1 theoretical calculations for the rotation about C8–C7 bond

and N–N accurately. Comparing the values of bond angles between RHF/6-31G calculated geometry and experimental geometry, it is observed that the bond angles in 1,2,4-triazole ring are predicted by 0.2° on the average for compound **1** (0.5° for compound **2**) at the RHF/6-31G level. For the 1,3,4-thiadiazine ring, the bond angles are predicted on the average 1.0° for compound **1** (1.1° for compound **2**) at the RHF/6-31G level. Comparisons of experimental bond lengths with the calculated values show that for RHF/6-31G method, the biggest bond difference is 0.075 Å for C11–S1 bond for compound **1** (0.072 Å for C11–S1 bond for compound **2**). In view of the bond angles difference between the experimental and calculated values, the biggest bond angle difference is 3.0° for C12–N4–N3 bond angle for compound **1** (3.4° for C12–N4–N3 bond angle for compound **2**). In both the cases, AM1 method gives biggest difference, and RHF/6-31G method predicts bond lengths and angles better than AM1 method. In spite of the differences, both methods give satisfactory calculational precision, which shows that the optimized geometries calculated by AM1 and RHF/6-31G methods can well reproduce the crystal structure of the title compounds.

Inspection of Fig. 9 reveals the similarity between the X-ray and RHF/6-31G geometries that were obtained by using the overlay procedure in HyperChem [25] with

Table 4 Selected geometric parameters (Å, °) for compound **1**

Compound 1			
	X-ray	AM1	RHF/6-31G
C1–C7	1.506(3)	1.488	1.512
C7–C8	1.525(3)	1.519	1.538
C8–C9	1.484(3)	1.485	1.488
C9–N2	1.303(2)	1.359	1.297
C9–N3	1.373(2)	1.432	1.375
C10–N1	1.301(3)	1.36	1.286
C10–N3	1.369(2)	1.433	1.372
C10–S1	1.733(2)	1.679	1.792
C11–C12	1.507(3)	1.496	1.507
C11–S1	1.806(2)	1.773	1.881
C12–N4	1.283(2)	1.316	1.275
C12–C13	1.479(3)	1.476	1.483
N1–N2	1.405(2)	1.322	1.402
N3–N4	1.385(2)	1.333	1.373
C1–C7–C8	110.91(16)	110.8	111.7
C9–C8–C7	113.84(16)	112	112.5
N4–C12–C13	115.89(16)	118.5	117.1
N1–C10–S1	129.41(15)	129.7	129.9
N2–C9–C8	128.51(18)	129.7	127.5
C6–C1–C7	120.96(19)	120.1	120.9
N4–C12–C11	123.59(17)	126.4	123
C14–C13–C12–C11	32.4(3)	57.2	28.7
C9–C8–C7–C1	−167.7(2)	−178.7	179.1
C8–C7–C1–C2	−109.1(2)	−107.5	82.9
N2–C9–C8–C7	−16.9(3)	−5.6	174.4
C20–O2–C4–C5	−164.3(2)	178.5	178.4

Table 5 Selected geometric parameters (Å, °) for compound **2**

Compound 2			
	X-ray	AM1	RHF/6-31G
C1–C7	1.509(3)	1.49	1.512
C7–C8	1.528(3)	1.52	1.545
C8–C9	1.482(3)	1.485	1.485
C9–N2	1.303(2)	1.36	1.297
C9–N3	1.371(2)	1.43	1.375
C10–N1	1.303(2)	1.361	1.287
C10–N3	1.372(2)	1.433	1.371
C10–S1	1.730(2)	1.679	1.79
C11–C12	1.509(3)	1.498	1.509
C11–S1	1.809(2)	1.772	1.881
C12–N4	1.286(2)	1.317	1.275
C12–C13	1.478(3)	1.475	1.482
N1–N2	1.410(2)	1.321	1.402
N3–N4	1.385(2)	1.333	1.371
C1–C7–C8	112.52(17)	110.8	111.8
C9–C8–C7	112.31(17)	110.9	112.5
N4–C12–C13	116.67(19)	118.8	117
N1–C10–S1	129.93(16)	129.8	129.9
N2–C9–C8	127.54(17)	128.4	126.9
C6–C1–C7	120.3(2)	119.9	120.2
N4–C12–C11	122.17(18)	126	123.5
C18–C13–C12–C11	−170.6(2)	−155.6	−138.4
C9–C8–C7–C1	173.4(2)	175.6	−179.5
C8–C7–C1–C2	−83.0(3)	−76.4	−87.7
N2–C9–C8–C7	−105.3(2)	−100.2	−102
C20–O2–C4–C5	−87.6(2)	−76.1	−93.2
C19–O1–C5–C4	−179.3(2)	−171.5	−171.7
C21–O3–C3–C2	4.1(3)	−8.6	−7.4

default parameters. Agreement between the calculated structures and the experimentally determined X-ray crystal structures were excellent (RMS values 5.5×10^{-3} Å for compound **1** and 5.7×10^{-3} Å for compound **2**).

No experimental dipole moments have been reported for the compounds covered by this article. Using the ab initio calculations, the electric dipole moments were obtained from both Mulliken and molecular electrostatic potential charges for both the compounds. The theoretical calculations indicate similar values for both the compounds ($\mu = 6.11$ D for compound **1** and $\mu = 5.85$ D for compound **2**).

The energies of the wave functions associated with the frontier (and those close in energy) molecular orbitals were calculated at the RHF/6-31G level and are given in Table 6. The respective energies associated with the frontier orbitals (HOMO and LUMO) for both compounds at the optimized structures are similar. Figures 10 and 11 show the wave function associated with the HOMO and LUMO. The population analyses based on the RHF/6-31G

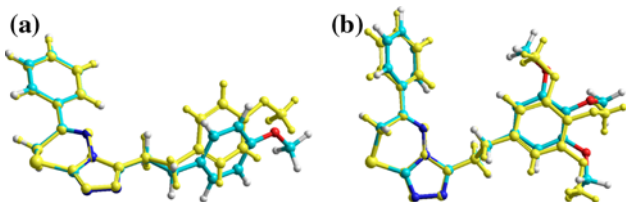


Fig. 9 An overlay of the X-ray (*yellow*) and RHF/6-31G optimized geometries of compound **1** (**a**) and **2** (**b**)

optimized geometry indicate that the frontier molecular orbitals are mainly composed of *s* orbitals. As seen from Figs. 10 and 11, in the HOMO, electrons are mainly delocalized on the methoxyphenyl-ethyl group in compound **1** and trimethoxyphenyl-ethyl group in compound **2**. However, when electron transitions take place, some electrons will enter into the LUMO, then, in the LUMO, the electrons will mainly be delocalized on triazole ring, thiadiazine ring, and phenyl rings as well as the O atoms.

Table 6 Energy (eV) of the wave function associated with the frontier (and those close in energy) molecular orbitals for the optimized compounds **1** and **2** molecules

MO	Compound **1** E(eV)	Compound **2**
+3	+7.51	+7.48
+2	+7.33	+7.13
+1	+6.86	+6.77
HOMO	+4.98	+4.86
LUMO	−6.41	−6.31
−1	−7.12	−6.49
−2	−7.44	−7.22
−3	−7.76	−7.46

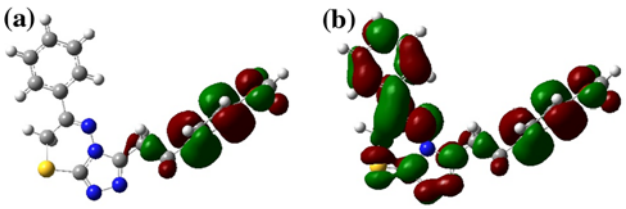


Fig. 10 Surfaces of **a** HOMO and **b** LUMO for the compound **1**

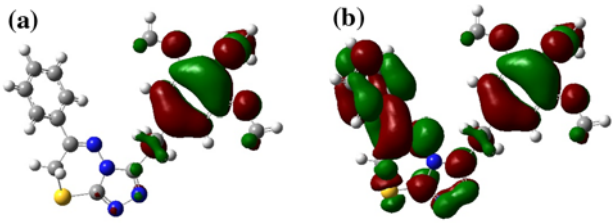


Fig. 11 Surfaces of **a** HOMO and **b** LUMO for the compound **2**

Conclusions

Two novel 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine derivatives, 3-[2-(4-methoxyphenyl)ethyl]-6-phenyl-7*H*-1,2,4-triazolo [3,4-*b*]-1,3,4-thiadiazine (compound **1**) and 3-[2-(3,4,5-trimethoxyphenyl)ethyl]-6-phenyl-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (compound **2**), having analgesic–anti-inflammatory activity were synthesized and characterized by IR, ^{1}H-NMR, mass spectroscopic techniques, and X-ray single crystal diffraction. Potential energy surface scans were drawn. AM1 and RHF/6-31G calculations for the title compounds show that the optimized geometries resemble the crystal structure. RHF/6-31G level of theory has predicted geometrical features better than AM1.

Acknowledgment The authors would like to acknowledge the support of Hacettepe University Research Fund (project no: 030260 2001 and 0701301001).

References

1. Tozkoparan B, Ayhan-Kılcıgil G, Ertan R, Ertan M, Kelicen P, Demirdamar R (1999) Arzneimittel-Forschung 49(12):1006–1016
2. Tozkoparan B, Gökhan N, Aktay G, Yeşilada E, Ertan M (2000) Eur J Med Chem 35(7):743–750
3. Tozkoparan B, Aktay G, Yeşilada E, Ertan M (2001) Arzneimittel-Forschung 51(6):470–477
4. Tozkoparan B, Aktay G, Yeşilada E (2002) Il Farmaco 57(2): 145–152
5. Tozkoparan B, Gökhan N, Küpeli E, Yeşilada E, Ertan M (2004) Arzneimittel-Forschung 54(1):35–41
6. Tozkoparan B, Küpeli E, Yeşilada E, Ertan M (2007) Bioorg Med Chem 15(4):1808–1821
7. Doğdaş E, Tozkoparan B, Kaynak FB, Eriksson L, Küpeli E, Yeşilada E, Ertan M (2007) Arzneimittel-Forschung 57(4):196–202
8. Tozkoparan B, Aytaç SP, Aktay G (2009) Arch Pharm 342:291–298
9. Aytaç SP, Tozkoparan B, Kaynak FB, Aktay G, Göktaş Ö, Ünüvar S (2009) Eur J Med Chem 44(11):4528–4538
10. Prasad AR, Ramalingam T, Rao AB, Diwan PV, Sattur PB (1989) Eur J Med Chem 24:199–201
11. Karegoudar P, Prasad DJ, Ashok M, Mahalinga M, Poojary B, Holla BS (2008) Eur J Med Chem 43(4):808–822
12. Enraf-Nonius (1994) CAD-4 Express Software. Enraf-Nonius, Delft, The Netherlands
13. Altomare A, Cascarano G, Giacovazzo C, Guagliardi A, Burla MC, Polidori G, Camalli M (1994) SIR92—a program for automatic solution of crystal structures by direct methods. J Appl Cryst 27:435
14. Sheldrick GM (1997) SHELXS97. Program for the solution of crystal structure. University of Göttingen, Germany
15. Sheldrick GM (1997) SHELXL97. Program for the refinement of crystal structures. University of Göttingen, Germany
16. Nardelli MJ (1995) Appl Cryst 28:659
17. Farrugia LJ (1997) ORTEP-3 for Windows. J Appl Cryst 30:565
18. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery JA, Stratmann RE Jr, Burant JC, Dapprich S, Millam JM, Daniels AD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson GA, Ayala PY, Cui Q, Morokuma K, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Cioslowski J, Ortiz JV, Baboul AG, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Gomperts R, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Gonzalez C, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Andres JL, Gonzalez C, Head-Gordon M, Replogle ES, Pople JA (2003) GAUSSIAN 03. Gaussian Inc., Pittsburgh, PA
19. Walters P, Stahl M (1994) Babel, version 1.1. Department of Chemistry, University of Arizona, Tucson, AZ
20. Zhang L-X, Zhou S-N, Zhang A-J, Lei X-X, Cai C-X (2005) Acta Cryst E61:o4058–o4059
21. Jin J-Y, Zhang L-X, Zhou S-N, Xiao H-P, Zhang A-J (2006) Acta Cryst E62:o713–o714
22. Cremer D, Pople JAJ (1975) Am Chem Soc 97:1354–1358
23. Zhang L-X, Zhang Z-Y, Zeng F-L (1990) Chem J Chin Univ 11:148–151
24. Zou K-H, Cai L-Q, Chen J-X, Zhang L-X, Zhang A-J, Hu ML (2004) Acta Cryst E60:o1736–o1738
25. HyperChem 7.5 (2003), Hypercube Inc