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Full Length Research Paper

Synthesis, structure elucidation and DFT studies of new thiadiazoles

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A series of previously unavailable derivatives of coumarins were synthesized via the reaction of 4-hydroxycoumarin with ethyl bromoacetate which were then cyclized with thiosemicarbazide. The structures of all synthesized compounds were confirmed by nuclear magnetic resonance (NMR) and infra red (IR) spectroscopic techniques in addition to the use of elemental analysis method (CHN). Selected optimized geometrical parameters, have been reported and highest occupied molecular orbital (HOMO) - lowest unoccupied molecular orbital (LUMO) energies and structures were elucidation.

Key words: DFT, HOMO-LUMO energies, 4-hydroxycoumarin, ethyl bromoacetate, nitrous acid, thiosemicarbazide.

INTRODUCTION

Coumarin is a phytochemical compound found in many plants such as Tonka bean, lavender, sweet clover grass, licorice, strawberries, apricots, cherries, and cinnamon (Datta et al, 2011). Coumarin derivatives have been observed to act as anti-coagulants (Suttie, 1990; Al-Amiery and Al-Bayati, 2011), antibacterial agents (Bedair et al., 2000), antifungal agents (Gnerre et al., 2000), and biological inhibitors (Mihaylov et al., 2008), chemo-therapeutics (Gregory et al., 2003; Budzisz et al., 2004) as well as bio-analytical reagents (Jiménez et al., 2000). These are useful antioxidants and have shown to exhibit antitumour activity (Koshy et al., 2000) and cytotoxicity (Monajjemi et al., 2011; Thati et al., 2007; Ouahouo et al., 2004; Camacho-Corona et al., 2009; Finn et al., 2001).

4-hydroxycoumarin and its derivatives have been effectively used as anticoagulants for the treatment of disorders in which there is excessive or undesirable cloterting, such as thrombophlebitis (Janget et al., 2007), pulmonary embolism (El-Agrodyet et al., 2001), and certain cardiac conditions (Dittmer et al., 2005). A number of comparative pharmacological investigations of the 4-hydroxycoumarin derivatives have shown good anticoagulant activity combined with minimum side effects and low toxicity (Verdía et al., 2011). Thiazolidinones substituted in the 2-position, which its derivatives and analogues exhibit unusually high *in vitro* activity against Mycobacterium tuberculosis (Jung and Park, 2009).

Recently, density functional theory (DFT) has been accepted by the quantum chemistry community as a cost effective approach for the computation of molecular structure, vibration frequencies, and energies of chemical reactions. Many studies have shown that the molecular structures and vibration frequencies calculated by DFT methods are more reliable than MP2 methods (Monajjemi et al., 2011; Beyramabadi and Morsali, 2011). While there is sufficient evidence that DFT provides accurate description of the electronic and structural properties of solids, interfaces and small molecules, relatively little is known about the symmetric performance of DFT applications to their molecular associates.

In view of the high degree of bio-activity shown by both thiazolidinones and coumarin heterocyclic analogs, we

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Abbreviations: NMR, Nuclear magnetic resonance; **IR,** infra red; **DFT,** density functional theory; **HOMO,** highest occupied molecular orbital; **LUMO,** lowest unoccupied molecular orbital; **TLC,** thin layer chromatography; **m.p.,** melting point; **FT-IR,** Fourier transform infrared spectroscopy.

have focused on the design of novel structural entities that incorporate both of these structural moieties into a single molecular scaffold.

EXPERIMENTAL

The chemicals used during synthesis was supplied by Sigma-Aldrich with purity of the compounds was checked on thin layer chromatography (TLC) plates (Silica gel G) in the solvent system consist of benzene:ethylacetate:methanol (40:30:30,v/v/v) and toluene:acetone (75:25,v/v). The TLC spots were located under UV light 254 and 365nm. The IR spectra was obtained on Fourier transform infrared spectroscopy (FT-IR) spectrometer (without out KBr pellets), Thermo Scientific, NICOLET 6700 FTIR. The NMR spectra were measured on a JEOLJNM-ECP 400, FT. NMR system and NMR (600 MHz). Elemental micro analysis was carried out using CHN elemental analyzer model 5500-Carlo Erba instrument. Gallen Kamp M.F.B.600.010 F melting point apparatus was used to measure the melting point of all the prepared compounds.

Ethyl 2-(2-oxo-2H-chromen-4-yloxy) acetate (2)

A suspension of 4-hydroxycoumarin (1) (6.17 mmol) in acetone (30 mL) was refluxed with ethyl bromoacetate (9.15 mmol) and K_2CO_3 (4.69 g, 33.91 mmol) for 12 h. After cooling, the mixture was evaporated to dryness and the residue was separated between $CHCl_3$ (50 mL) and water (50 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was dried and recrystallized from acetone with yield of 92%, melting point (m.p.) 99°C; ^{1}H-NMR ($CDCl_3$): δ 5.780 (s, 1H, –C=C-H),δ 4.91 and δ 5.25 (d, 2H, t, 2H, for OCH_2), δ 7.20–7.80 (m, 1H, C-H aromatic ring), δ 3.22 (t, 3H) and δ 3.85 (q, 2H); ^{13}C-NMR: 167.2; 165.1; 163.4, 155.9; 134.2; 121.8; 121.1; 119.0; 113.8; 100.9; 65.3; 54.7; 22.12; IR: 3089.5 cm^{-1} (C-H, aromatic), 2987.3 (C-H alkane); 1759.3 cm^{-1} (C=O, lactone), 1717.6 cm^{-1} (C=O, ester), 1629.2(C=C, alkene), 1577.3 (C=C Aromatic); Anal. Calcd. for $C_{12}H_9N_3O_3S$: C 62.90%, H 4.87%. Experimentally: C 60.91% and H 3.22%.

Synthesis of 2-(2-oxo-2H-chromen-4-yloxy) acetic acid (3)

A solution of compound (2) (2.7 mmol) and sodium hydroxide 5% (2.16 ml) in ethanol (15 ml) was stirred and reflux for 2 h. After removal of the solvent, the residue was dissolved in water and acidified with HCl 6 M. The white solid collected by filtration was washed with cool water, dried, recrystallized from ethanol as white powder with yield of 84% and m.p. 219°C; ^{1}H-NMR ($CDCl_3$): δ 5.69 (s, 1H, –C=C-H), δ 4.98 and δ 5.31 (d, 2H, t, 2H, for OCH_2), δ 7.38–7.91 (m, 1H, C-H aromatic ring), δ 3.22 (t, 3H) and δ 3.85 (q, 2H); ^{13}C-NMR: 174.1; 162.3; 158.8; 151.2; 134.3, 123.1; 122.5; 119.4; 114.3; 99.8; 65.7; IR: 2835-3280 cm^{-1} (O-H, hydroxyl), 1755.3 cm^{-1} (C=O, lactone), 1720.6 cm^{-1} (C=O, ester), 1617 cm^{-1}(C=C, alkene), 1581.9 cm^{-1} (C=C Aromatic); Anal. Calcd.for $C_{12}H_9N_3O_3S$: C 60.00%, H 3.66%. Experimentally: C 58.77% and H 3.51%.

Synthesis of 4-[(5-amino-1, 3, 4-thiadiazol-2-yl)methoxy]-2H-chromen-2-one (4)

Phosphorus oxychloride (20 ml) was added to compound (3) (0.05mol) and the mixture was stirred for I h at room temperature**.** Thiosemicarbazide (4.56 g, 0.05 mol) was added and the mixture was heated and reflux for 5 h. On cooling, the mixture was poured on to ice. After 4 h. stir for 15 min. to decompose the excess phosphorusoxychloride, then heated under reflux for 30 min, cooling, the mixture was neutralized by 5% potassium hydroxide, the precipitated was filtered, washed with water, dried and crystallized. Recrystallization from dichloromethane yields 55%, m.p. 99 °C; ^{1}H-NMR ($CDCl_3$): δ 5.62 (s, 1H, –C=C-H), δ 4.91 and δ 5.33 (d, 2H, t, 2H, for OCH_2), δ 7.23–7.87 (m, 1H, C-H aromatic ring), δ5.21 (s, NH_2); IR: 3314.5 and 3375.1 cm^{-1} (s, H, amine), 291.2(C-H alkane); 3079.1 (C-H aromatic),1752.3 cm^{-1} (C=O, lactone), 1591.1 cm^{-1}(C=N, imine), 1635.3 cm^{-1} (C=C aromatic); Anal. Calcd. for $C_{12}H_9N_3O_3S$: C 52.36%, H 3.30%, N 15.26%. Experimentally: C 51.64% H 2.92% and N 14.94%.

Synthesis of 5-[(2-oxo-2H-chromen-4-yloxy) methyl]-1,3,4-thiadiazol-2(3H)-one (4)

A mixture of compound 2 (2.0 mmole), and tiose-micarbazide (2.2 mmole) in polyphosphoric acid (7 ml) were refluxed for 10h., at 70-80°C. After cooling poured in to ice then the precipitate collect and recrystallized from dichloromethan, yield 32%, m.p. 102°C.

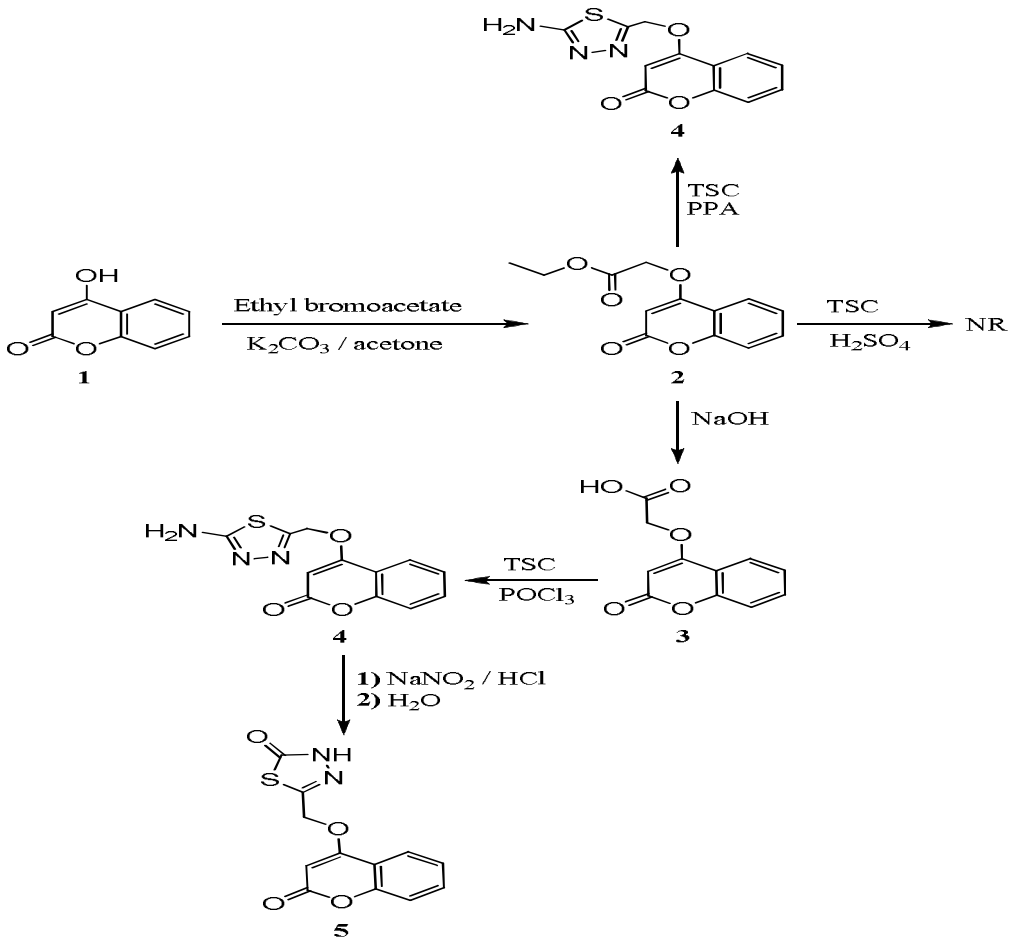
Synthesis of 5-[(2-oxo-2H-chromen-4-yloxy) methyl]-1, 3, 4-thiadiazol-2(3H)-one (5)

10% aqueous sodium nitrite solution (10 ml) was added drop wise to an ice-bath suspension of compound (4) (0.01 mol) and hydrochloric acid (5 ml) in cold water (20 ml), with continuous stirring over a period of 20 min. The temperature was then allowed to rise to room temperature and the mixture was heated to boiling for 10 min, cooled and allowed to stand overnight. The separated crude product was filtered, washed with water, dried and crystallized then recrystallized from ethanol to yield 40% product with m.p. 112°C; ^{1}H-NMR ($CDCl_3$):δ 5.85 (s, 1H, –C=C-H), δ 4.93 and δ 5.33 (d, 2H, t, 2H, for OCH_2), δ 7.30–7.86 (m, 1H, C-H aromatic ring), δ 5.42 (s, H, amine); IR: 3201 cm^{-1} (N-H, amine), 1758.1 cm^{-1} (C=O, lactone), 1588.9 cm^{-1} (C=N, imine),2891 cm^{-1} (C-H alkane); 3078.9 cm^{-1} (C-H aromatic), 1715.2 cm^{-1} (C=O lactame), 1619.2 (C=C); Anal. Calcd. for $C_{12}H_9N_3O_3S$: C 52.17%, H 2.92 and 10.14%. Experimentally: C 50.99% H 2.71 and 9.46%.

RESULTS AND DISCUSSION

For the synthesis of 4-hydroxycoumarin derivatives, the reaction sequence is out lined in Scheme 1, started from 4-hydroxycoumarins which is commercially available or, alternatively, readily accessible (Shi and Cheng, 2011). Synthesis of ethyl 2-(2-oxo-2H-chromen-4-yloxy) acetate (2) was obtained by the reflux of ethyl bromoacetate with 4-hydroxycoumarin (1) in the presence of anhydrous potassium carbonate in anhydrous acetone. Hydrolysis of ester group was performed by the addition of 5% sodium hydroxide to yield compound (3), which was cyclized with thiosemicarbazide in presence of phosphorousoxychloride to produce compound (4), that was converted to compound (5) by using nitrous acid. It has been reported that the diazotation of amino thiadiazoles results in the substitution of the amino group with keto group (Al-Amiery et al., 2011). Several methods and catalysts for producing of compound (4) from compound (2) were used in the initial assessment but, only polyphosphoric acid was successively for producing compound (4) with low yield (Scheme 1).

Although two types of tautomer, ketone or enol,



Scheme 1. Synthesis of compounds (2-5).

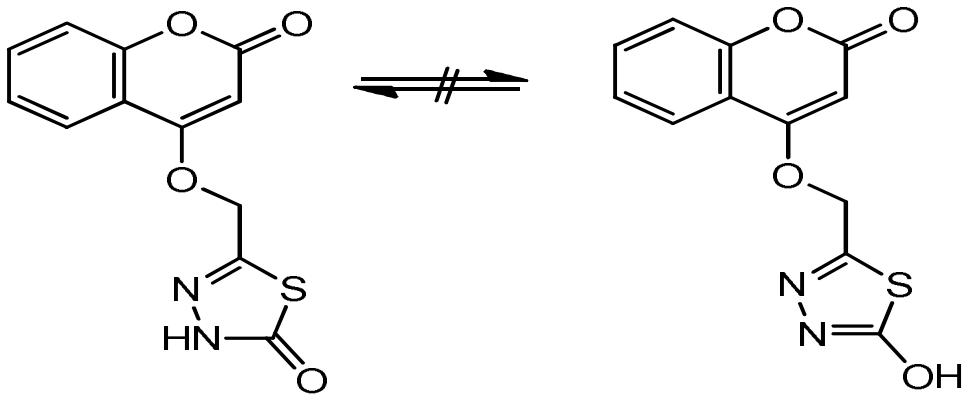
(Scheme 2) could be expected from the reaction of compound (4) with nitrous acid under acidic conditions, only the ketone type compound (5) was observed. The existence of the ketone form predominantly in the solid state is demonstrated by the presence of two absorption bands at 1715.2 and 3201 cm^{-1} belonging to the $U_{C=O}$ and U_{NH} groups, respectively, and by absence of U_{OH}.

Atomic charges for compound (5)

These data show that the atomic charge has been affected by the presence of substituent of rings (Kadhumet et al., 2011; Al-Amiery et al., 2011; Kadhumand Wasmi, 2011) as shown in the Table 1. As a reference compound (5), the data for minimized geometry and the 3D-geometrical structure (Figure 1) is shown in. The data obtained show that the high estatomic charge in ligand molecule is at [O(6) -0.818)] the next charge value is at [N(1) -0.30619] and [C(10) (-0. 30129)].These data show clearly that these three atoms are the most reactive toward the substitution reactions or bonding with the metals. The determined bond angle and twist angle and 3D geometrical structure, indicate that this molecule is not planar.

Density function theory (DFT)

DFT calculations were performed for compounds (5). Optimized molecular structure of the most stable form is shown in Figure 1. Molecular orbital calculations provide a detailed description of orbitals including spatial characteristics, nodal patterns and individual atom contributions. The contour plots of the frontier orbitals for the ground state of (5) is shown in Figure 2, including the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) (Kadhum et al, 2011). It is interesting to see that both orbitals are substantially distributed over the conjugation plane. It can be seen from the Figure 2 that the HOMO orbitals are located on the substituted molecule while LUMO orbitals resemble those obtained for the unsubstituted molecule and therefore the substitution has an influence on the electron donation ability, but only a small impact on



Scheme 2. Tautomerization of compound (5).

Table 1. Atomic charges of synthesized compound (5).

Atom	Atom type (MM2)	Charge (MM2)	Charge Huckel	Atom	Atom type (MM2)	Charge (MM2)	Charge Huckel
S(1)	S Thiophene	0	0.39220	C(15)	C Alkene	0	-0.02148
C(2)	C Carbonyl	0	0.24402	C(16)	C Alkene	0	-0.10120
N(3)	N Amide	0	0.37904	C(17)	C Alkene	0	0.26049
N(4)	N Imine	0	-0.30619	O(18)	O Carboxyl	0	-0.060915
C(5)	C Alkene	0	0.037840	O(19)	O Carbonyl	0	-0.65322
O(6)	O Carbonyl	0	-0.83124	H(20)	H Amide	0	0.08594
C(7)	C Alkane	0	0.12432	H(21)	H	0	0.025617
O(8)	O Enol	0	-0.13114	H(22)	H	0	0.02513
C(9)	C Carbonyl	0	0.52645	H(23)	H	0	0.042154
C(10)	C Alkene	0	-0.30129	H(24)	H	0	0.022763
C(11)	C Alkene	0	0.30415	H(25)	H	0	0.025346
C(12)	C Alkene	0	-0.037840	H(26)	H	0	0.024938
C(13)	C Alkene	0	-0.026214	H(27)	H	0	0.028177
C(14)	C Alkene	0	-0.07787				

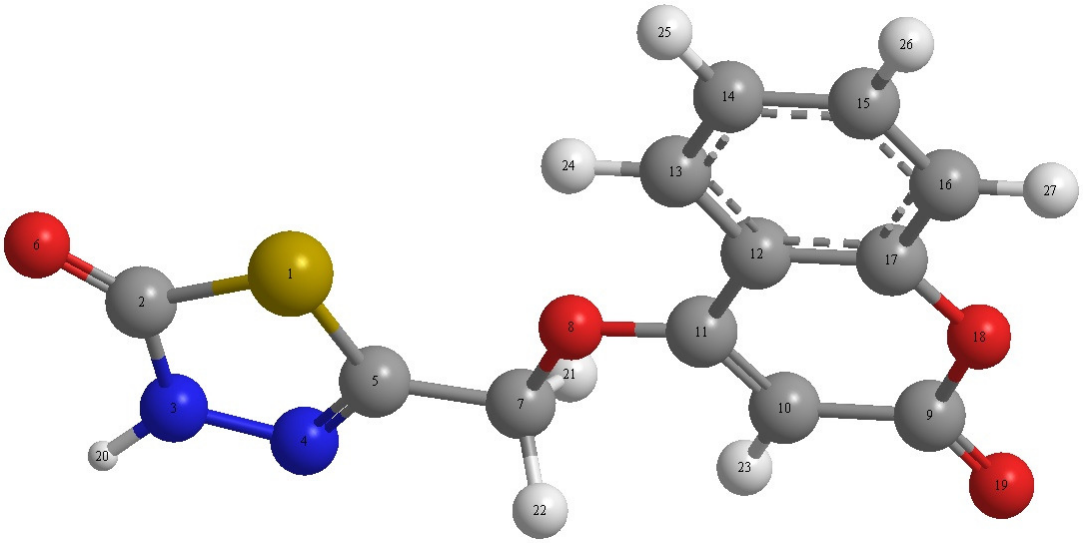


Figure 1. The 3D structure of compound (5).

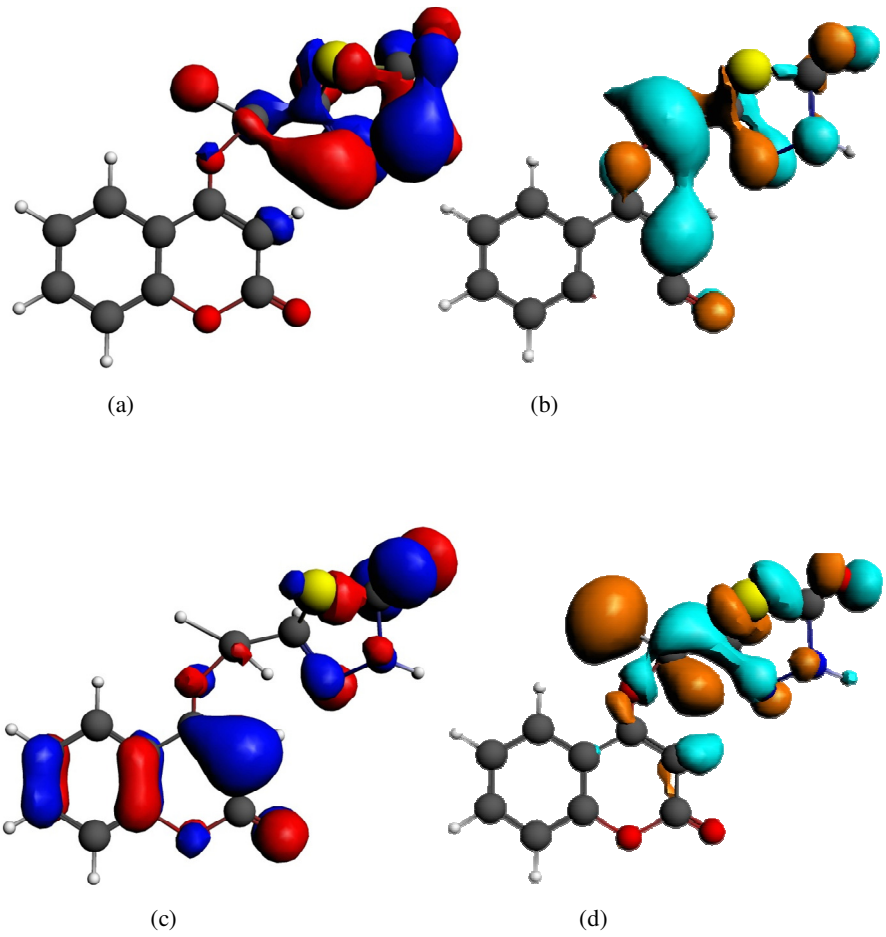


Figure 2. HOMO-LUMO energies for compound **5.** (a) HOMO -0.2178 Hartree: (b) LUMO -0.2175 Hartree: (c) HOMO-1 -0.2517 Hartree: (d) LUMO+1 -0.2021 Hartree.

electron acceptance ability. The orbital energy levels of HOMO and LUMO of compound5is listed. It can be seen that the energy gaps between HOMO and LUMO is -0.0003 Hartree for the compound (5). The lower value in the HOMO and LUMO energy gap explain the eventual charge transfer interaction taking place within the molecules.

Conclusions

In this study, compounds (2–5) were successively synthesized and characterized using various spectroscopic methods and elemental analysis. In all of the synthesis, thiosemicarbazide can be cyclized with carboxylic acid esters by using concentrated sulphuric acid, except compound (2) where the cyclization could not take place even by using different temperatures. Poly phosphoric acid is the only acid that can be used for cyclization of compound (2). The synthesized compounds were studied theoretically and the atomic charges, heat of formation and stereochemistry were estimated, and it was found that compound (5) is non-planar.

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