Synthesis and theoretical study of 5-phenyl-1,3,4-thiadiazole derivatives

H. Muglu1,*, C.D. Vurdu2,*, G. Sayiner3, M.S. Cavus2, F. Kandemirli2, M. Ahmedzade

1Department of Chemistry, Faculty of Science, Kastamonu University, Kastamonu, Turkey
2Biomedical Engineering Department, Faculty of Engineering and Architecture, Kastamonu University, Kastamonu, Turkey
3Gebze Institute of Technology, Department of Environmental Engineering, 41400, Kocaeli, Turkey

Received 19 April 2014; Revised 19 July 2014; Accepted 19 July 2014.
Corresponding Author. E-mail: hmuglu@kastamonu.edu.tr; Tel: (+903662801922)

Abstract
2-(ethyl xanthate) acetylamino-5-phenyl-1,3,4-thiadiazole, 2-(2-Hydroxybenal) amino-5-phenyl-1,3,4-thiadiazole, 2-(N-cylohexzyl carbamyl methylthiocarbamate)-5-phenyl-1,3,4- thiadiazole, 2-(Allyl) dithiocarabamate-5-phenyl-1,3,4-thiadiazole, dibenzyl-N-(5-phenyl-1,3,4-thiadiazole-2yl)dithiocarbamid, difenacil-5- (5-phenyl-1,3,4-thiadiazole-2-yl) dithiocarbamid, 1,3-di(dithiocarbamate-5-phenyl-1,3,4-thiadiazole)propane were synthesized. The characterization of all new synthesized compounds was carried out by the 1H-NMR, IR, mass spectroscopic data and elemental analyses. The quantum chemical calculations were obtained by means of the DFT/6-311G(d,p) method.

Keywords: Thiadiazole, UV, IR, DFT

1. Introduction
Thiadiazole having 5-membered ring system contains hydrogen-binding domain, and two-electron donor nitrogen system, sulfur atom and a wide variety of biological activity. 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole are isomeric forms of thiadiazole. Thiadiazole and its derivatives have been studied because of biological activities such as antibacterial and antifungal [1], anticancer [2], anti-inflammatory [3,4], anti-helico bacter pylori [5,6], antimicrobial [7], antitubercular [8,9], analgesic [10,11], antiviral [12], antiepileptic [13], antineoplastic [14] activity. A series of 2,5-disubstituted-1,3,4-thiadiazoles were synthesized, screened for the antituberculosis activity against Mycobacterium tuberculosis H37Rv and the relationships between the structures of compounds and their antituberculosis activity were studied by using the Electronic-Topological Method (ETM) and feed forward neural networks (FFNNs) trained with the back-propagation algorithm [15]. In this study 2-(ethyl xanthate) acetylamino-5-phenyl-1,3,4-thiadiazole, 2-(2-Hydroxybenal) amino-5-phenyl-1,3,4-thiadiazole, 2-(N-cylohexzyl carbamyl methylthiocarbamate)-5-phenyl-1,3,4-thiadiazole, 2-(Allyl) dithiocarabamate-5-phenyl-1,3,4-thiadiazole, dibenzyl-N-(5-phenyl-1,3,4-thiadiazole-2-yl) dithiocarbamid, difenacil-N-(5-phenyl-1,3,4-thiadiazole-2-il) dithiocarbamid, 1,3-di(dithiocarbamate-5-phenyl-1,3,4-thiadiazole)propane were synthesized, characterized and quantum chemical calculations were studied.

2. Materials and methods
2.1. Experimental Details
Solvens were dried and distilled prior to use. Infrared spectra were recorded on a Mattson 1000 FT-IR System Spectrum. 1H-NMR spectra were taken on GEMINI VARIAN 200 MHz spectrophotometer. The elemental analysis was carried out on CHNS-932 (LECO). Melting points were uncorrected and recorded on Gkampallen melting point apparatus.

2.1.1 Synthesis of 2-(ethyl xanthate) acetylamino-5-phenyl-1,3,4- thiadiazole
(0.51 g, 0.002 mole) 2-chloro acetamid -5-phenyl-1,3,4- thiadiazole and (0.48 g, 0.003 mole) potassium ethyl xanthate was added into a round 100 mL bottom flask then 25 mL anhydrous acetone was added. The mixture was then refluxed for 3 hours. The excess of acetone was distilled off reduced pressure and resulting mixture was precipitated by adding water. The solid was filtered and washed with water. (Yield 61%, m.p:188-189 ºC). IR(KBr, cm−1) ν(NH) 3163, ν( aromatic C-H) 3025, ν(aliphatic C-H) 2882, ν(C=O) 1702, ν(C=N) 1565, δ(C=S) 1051, δ(O-C-S-C) 960, δ(N=C-S-C) 682. 1H-NMR (200 MHz, DMSO-d6) δ/ppm 7.97-7.53 (m, 5H, aromatic protons), 4.61-4.57 (m, 2H, -O-CH2- protons),
Lotassium hydroxide was added to 2.1.7. (m.p:155 and refluxed for 3 hours. Solution was cooled and added water into a round 100 mL flask then precipitated in hexane, and filtered, washed with ethyl alcohol (yield 52%, m.p:187-188 °C). ν(OH) 3336-3284, ν(aryl C-H) 3048, ν(C=N) 1619, ν(N-H) 1529, 1H-NMR (200 MHz, DMSO-d6) δ/ppm 11.38-11.21(1H, OH protons), 9.27 (s, 1H, =CH proton), 7.99-7.02 (m, 9H, aromatic protons). Calcld.: C, 64.04; H, 3.94; N, 14.94; S, 11.40. Found: C, 64.71; H, 4.03; N, 14.27; S, 11.86.

2.1.3. Synthesis of 2-(N-cylohexyl carbamyl methylthiocarbamate)-5-phenyl-1,3,4-thiadiazole
(0.44 g, 0.0025 mole) 2- amino -5-phenyl-1,3,4-thiadiazole and (0.14 g, 0.0025 mole) potassium hydroxide was added into a round 100 mL bottom flask then 25 mL anhydrous aceton was added. Then, (0.3 mL 0.005 mole) CS2 at 0 °C was added dropwise in 15 minutes. After stirring for 30 minutes at room temperature and (0.44 g, 0.0025 mole) cyclohexyl amide chloride was added and refluxed for 3 hours. Resulting solution was precipitated by adding water, the solid was filtered and washed with water and dried. (Yield 70%, m.p:215-216 °C). IR(KBr, cm⁻¹) ν(NH) 3293, ν(aryl C-H) 3064, ν(aliphatic C-H) 2929, 2854, ν(C=O) 1653, ν(aryl C-H) 1589, δ(N-H) 1542, δ(C=S) 1036, δ(C-S-C) 981. 1H-NMR (200 MHz, DMSO-d6) δ/ppm 8.04-7.58 (m, 5H, aromatic protons), 3.95 (s, 2H, -SH-2-protons), 1.70-1.15 (m, 11H, -CH₂-protons). Calcld.: C, 52.01; H, 5.13; N, 14.27; S, 24.50. Found: C, 51.75; H, 4.71; N, 14.89; S, 24.21.

2.1.4. Synthesis of 2-(allyl)dithiocarbamates-5-phenyl-1,3,4-thiadiazole
(0.44 g, 0.0025 mole) 2- amino -5-phenyl-1,3,4-thiadiazole and (0.14 g, 0.0025 mole) potassium hydroxide was added into a round 100 mL bottom flask then 25 mL anhydrous aceton was added. Then, (0.3 mL 0.005 mole) CS₂ at 0 °C was added dropwise in 15 minutes. After stirring for 30 minutes at room temperature and (0.22 mL, 0.0025 mole) allyl bromide was added dropwise and refluxed for 3 hours. Obtained oily substances were extracted with chloroform. Chloroform phase was dried with MgSO₄. The excess of solvent was evaporated under reduced pressure until 10 mL solution was remain then precipitated in hexane. And the solid was filtered and washed with water. (Yield 65%, m.p:193-194 °C). IR(KBr, cm⁻¹) ν(aryl C-H) 3005, ν(aliphatic C-H) 2918, ν(C=O) 1653, ν(aryl or C=C) 1592, δ(N-H) 1521, δ(C-S) 1244. 1H-NMR (200 MHz, DMSO-d6) δ/ppm 8.01-7.50 (m, 5H, aromatic protons), 6.51-5.87 (m, 1H, =CH-proton), 5.39-5.12 (d, 2H, C=CH₂protons), 3.95-3.91 (d, 2H, -CH₂-protons). Calcld.: C, 49.12; H, 3.78; N, 14.32; S, 32.78. Found: C, 50.02; H, 4.04; N, 14.38; S, 33.06.

2.1.5. Synthesis of dibenzyl-N-(5-phenyl-1,3,4-thiadiazole-2-yl) dithiocarbamid (0.44 g, 0.0025 mole) 2- amino -5-phenyl-1,3,4- thiadiazole and (0.28 g, 0.005 mole) potassium hydroxide was added into a round 100 mL bottom flask then 25 mL aceton was added. Then, (0.3 mL 0.005 mole) CS₂ was added dropwise in 15 minutes at 0°C. After stirring for 30 minutes at room temperature, (0.6 mL, 0.005 mole) benzyl chloride was added and refluxed for 3 hours. Resulting solution was precipitated by adding water, the solid was filtered and washed with water and dried (Yield 58%, m.p:209-210°C). IR(KBr, cm⁻¹) ν(aromatic C-H) 3036, ν(aliphatic C-H) 2967, ν(C=N) 1583. 1HNMR (200 MHz, DMSO-d6) δ/ppm 7.93-7.25 (m, 15H, aromatic protons), 4.60 (s, 2H, -CH₂-protons), 4.45-4.44 (s, 2H, -CH₂-protons). Calcld.: C, 63.71; H, 4.42; N, 9.69; S, 22.19. Found: C, 64.44; H, 4.58; N, 9.37; S, 21.01.

2.1.6. Synthesis of difenacil-N-(5-phenyl-1,3,4-thiadiazole-2-yl) dithiocarbamid (0.44 g, 0.0025 mole) 2- amino -5-phenyl-1,3,4-thiadiazole and (0.28 g, 0.005 mole) potassium hydroxide was added into a round 100 mL bottom flask then 25 mL aceton was added. Then, (0.3 mL, 0.005 mole) CS₂ was added dropwise in 15 minutes at 0°C. After stirring for 30 minutes at room temperature, (1.026 g, 0.005 mole) fenacil bromide was added and refluxed for 3 hours. Solution was cooled and added water. Obtained oily substances were extracted with chloroform. Chloroform phase was dried with MgSO₄. The excess of solvent was evaporated under reduced pressure until 10 mL solution was remaining then precipitated in hexane. And the solid was filtered and washed with water (yield 54%, m.p:155-156 °C). IR(KBr, cm⁻¹) ν(aromatic C-H) 3050, ν(aliphatic C-H) 2923, ν(C=O) 1683, ν(C=N) 1592. 1HNMR (200 MHz, DMSO-d6) δ/ppm 8.12-7.30 (m, 15H, aromatic C=H protons), 5.19 (s, 2H, -CH₂-protons), 4.53-4.51(s, 2H, CH₂-protons). Calcld.: C, 61.33; H, 3.91; N, 8.58; S, 19.65. Found: C, 60.17; H, 3.61; N, 8.14; S, 20.01.

2.1.7. 1,3-dithiocarbamates-5-phenyl-1,3,4-thiadiazole) propane-2-on
(0.44 g, 0.0025 mole) 2- amino -5-phenyl-1,3,4-thiadiazole and (0.14 g, 0.0025 mole) potassium hydroxide was added into a round 100 mL bottom flask then 25 mL aceton was added . Then, (0.15 mL, 0.0025 mole) CS₂ was added dropwise in 15 minutes at 0 °C. After stirring for 30 minutes at room temperature, (0.16 g, 0.00125 mole) dichloroacetone...
was added and refluxed for 3 hours. Solution was cooled and precipitated in water then the solid was filtered and washed with water (yield 64%, m.p:141-142 °C). IR(KBr, cm$^{-1}$) $\nu$(aromatic C-H) 3063, $\nu$(aliphatic C-H) 2959, 2920, 2886, $\nu$(C=O) 1712, $\delta$(N-H) 1506, $\nu$(C=S) 1070, $\nu$(C-S-C) 976. $^1$H-NMR (200 MHz, CDCl$_3$) $\delta$/ppm 7.94-7.44 (m, 10H, aromatic protons). 3.85 (d, 4H, -CH$_2$- protons). Calcd.: C, 44.98; H, 2.88; N, 14.99; S, 34.31. Found: C, 43.71; H, 2.70; N, 13.72; S, 33.54.

2.2. Calculation Methods

DFT calculations by means of the Gaussian 09 program [16] were performed with full geometry optimization for synthesized molecules Geometrical optimization were carried out with the B3LYP change-correlation corrected functional by using 6–311G(d,p) basis sets.

3. Results and discussion

Benzoic acid reacts with thiosemicarbazide in presence of POCl$_3$ to give 2- amino-5-phenyl-1,3,4-thiazidazole (molecule 1). 2-chloroacetamide-5-phenyl-1,3,4-thiazidazole (molecule 2) was synthesized with the reaction of 2-amino-5-phenyl-1,3,4-thiazidazole (molecule 1) and acetone in the presence of Na$_2$CO$_3$ at room temperature. With the reaction of dithiocarbamat and molecule 2 in acetone was synthesized 2-(ethyl xanthate acetyl amino)-5-phenyl-1,3,4-thiazidazole. Disappearing of C-Cl stretching vibration observed at 781 cm$^{-1}$ molecule 2 and N-alkyl protons shows molecule 1 were formed. 2-(2-Hydroxybenzyl)aminio-5-phenyl-1,3,4-thiazidazole was obtained with the reaction of molecule 1 and salicylaldehyde in the presence of icy acetic acid in isopropyl alcohol. The presence of O-H stretching band at 3284-3336 cm$^{-1}$ in IR spectrum and O-H proton at 11.38-11.21 pm and =CH protons at 9.27 ppm supports that molecule 2 were obtained.

Potassium dithiocarbamate salts (molecule 3) were prepared from molecule 1 with KOH and CS$_2$ in acetone. 2-(N-cylohexyl carbamyl methylthiocarbamat)-5-phenyl-1,3,4-thiazidazole was synthesized from molecule 3 with cyclohexyl amide chloride. The presence of N-H stretching band at 3293 cm$^{-1}$ and CH$_2$ protons at 3.95 ppm and CH$_2$ protons of cyclohexzane at 1.70-1.15 ppm supports that molecule 3 were obtained.

In addition, molecular geometry optimization, vibrational spectra, Mulliken charges, HOMO and LUMO energies were performed with the Gaussian 09 software package [16] by using density functional theory (DFT) methods with B3LYP hybrid exchange-correlation functional [17-19] and the standard 6–311G(d,p) basis set. No imaginary frequencies were obtained for vibrational frequencies computations at the optimized geometry. This ensures that it corresponds to a local minimum on the potential-energy surface. Fig. 1 shows the optimized form and HOMO, LUMO of studied molecules calculated using DFT method. The highest occupied molecular orbital (HOMO) could act as an electron donor, due to its outermost (highest energy) orbital containing electrons and the lowest unoccupied molecular orbital (LUMO) could act as the electron acceptor, due to its innermost (lowest energy) orbital that has room to accept electrons. The energy gap of $E_{\text{HOMO}}$ and $E_{\text{LUMO}}$ reflects the chemical activity of the molecule. These orbital play part in chemical stability. $E_{\text{HOMO}}$ and $E_{\text{LUMO}}$ and orbital energy difference between HOMO and LUMO orbital referred as energy gap, dipole moment and polarizibility and electronic energy of studies molecules are given in Table 1. The HOMO levels are dominated by orbitals from the ethyl xanthate ring for molecule 1, distributed whole molecule except S atom for molecule 2; are mainly consist of sulphur atom of dithiocarbamate functional group for molecule 3; are distributes to phenyl ring, thiadiazole ring and S atoms of dithiocarbamate functional group for molecules 4-6; and are mainly consist of phenyl-1,3,4-thiadiazole ring. $E_{\text{HOMO}}$ energies of molecules 1-7 are -0.23019, -0.23062, -0.23207, -0.23440, -0.22287, -0.22510, -0.23709 au, respectively, and energy gap of those are 0.14927, 0.12867, 0.15061, 0.15107, 0.14448, 0.14639, 0.14565 au.

As seen from here, the energy range from 0.12867 to 0.14927 au for studied molecules is needed to reach to excited state. The electric dipole polarizibility, representing a second-order variation in the energy is a measure of the linear response of the electron density in the presence of an infinitesimal electric field, F, and is given as the following equation.

$$\alpha = -\left(\frac{\partial^2 E}{\partial F_a \partial F_b}\right)_{\alpha, \beta = x, y, z}$$

186
The observable quantity is defined by:

$$\langle \alpha \rangle = \frac{1}{3} \sum_{i} \alpha_{ii}$$

(2)

Where, $\alpha_{ii}$ are the eigenvalues of the polarizibility tensor.

**Figure 1:** The optimized structures, HOMO and LUMO of the studied molecules.
Calculations showed that Mulliken charges associated with each atom’s orbitals. Mulliken charges and the bond length of 2-amino-5-phenyl-1,3,4-thiadiazole ring molecules 1-7 were carried and respective graphs were plotted. The atomic charges on C atoms of phenyl ring are almost identical, however S and N heteroatom belonging to 2-amino-5-phenyl-1,3,4-thiadiazole ring are slightly different. For example charge of 4N atom of molecule 1-7 are -0.429, -0.431, -0.382, -0.376, -0.300, -0.384 and -0.382 ē (shown in Table 2).

The bond lengths of between C and C atoms of phenyl ring are almost identical; however bond lengths between the atoms of thiadiazole ring are slightly different (see Fig. 2.). The bond lengths of N4-C12 atoms of molecule 1-7 are 1.380, 1.368, 1.379, 1.379, 1.361, 1.361, 1.381 Å.
Moreover, the experimental FT-IR spectra (4000–400 cm⁻¹) for molecules 1-7 were done. The some important functional vibrational frequencies calculated for molecules 1-7 with the theory B3LYP using 6-311 with together experimental values are collected in Table 3. Molecule 1, 3, 6 and 7 showed vibrational frequency around 1702, 1653, 1683, 1712 cm⁻¹ which was assigned for C=O group as experimental and 1781, 1754, 1750 and 1804 cm⁻¹. The υ(C=N) bands have been observed at 1562, 1610, 1589, 1592, 1583, 1592 and 1596 cm⁻¹ for molecules 1-7 (Table 3). These were assigned as at 1542, 1654, 1545, 1539, 1573, 1561, 1491 cm⁻¹ with B3LYP method. For molecules 2 a broad band has appeared at the region 3336-3284 which confirms the presence of hydroxyl group (–OH). Aromatic C–H are assigned at 3085–3005 cm⁻¹ and aliphatic C–H are assigned at 2986–2851 cm⁻¹ were also observed. C=S signal for molecule 1, 3, 4 and 7 were observed at 1051, 1036, 1154 and 1070 cm⁻¹ as experimental.

**Figure 2:** Comparisons of the calculated bond lengths for studied molecules.

**Table 3:** Comparisons of the experimental and the theoretical values of some important functional vibrational frequencies for molecules 1-7.

<table>
<thead>
<tr>
<th></th>
<th>υ(OH)</th>
<th>υ(NH)</th>
<th>υ(C=O)</th>
<th>υ(C=N)</th>
<th>δ(NH)</th>
<th>υ(C-N-C)</th>
<th>δ(OH)</th>
<th>υ(C=S)</th>
<th>υ(C-S-C)</th>
<th>δ(O-C-S-C)</th>
<th>δ(N=C-S-C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Exp.</td>
<td>3163</td>
<td>1702</td>
<td>1565</td>
<td>1495</td>
<td>1051</td>
<td>960</td>
<td>682</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Theo.</td>
<td>3596</td>
<td>1781</td>
<td>1542</td>
<td>1509</td>
<td>1055</td>
<td>1018</td>
<td>687</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Exp.</td>
<td>3336, 3284</td>
<td>1619</td>
<td></td>
<td>1529</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Theo.</td>
<td>3305</td>
<td>1654</td>
<td>1606</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Exp.</td>
<td>3293</td>
<td>1653</td>
<td>1589</td>
<td>1542</td>
<td>1036</td>
<td>981</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Theo.</td>
<td>3609, 3580</td>
<td>1754</td>
<td>1545</td>
<td>1530</td>
<td>1154</td>
<td>1038</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Exp.</td>
<td>1592</td>
<td>1521</td>
<td></td>
<td>1244</td>
<td>987</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Theo.</td>
<td>3579</td>
<td>1539</td>
<td>1530</td>
<td>1164, 1272</td>
<td>1154</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Exp.</td>
<td>1583</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Theo.</td>
<td>1573</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Exp.</td>
<td>1683</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Theo.</td>
<td>1750, 1758</td>
<td>1561</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Exp.</td>
<td>1712</td>
<td>1596</td>
<td>1506</td>
<td></td>
<td>1070</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Theo.</td>
<td>3576, 3581</td>
<td>1804</td>
<td>1469, 1498</td>
<td>1417, 1531, 1534, 1558</td>
<td>1348</td>
<td>1172</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusion
5-phenyl-1,3,4-thiadiazole, derivatives were synthesized and characterized by \textsuperscript{1}H-NMR, IR, mass spectroscopic data and elemental analyses. The quantum chemical calculations were obtained by means of the DFT/6-311G(d,p) method. The data obtained from quantum chemical calculations give useful information about the reactivity and give information about the regions which undergo nucleophilic substitution or electrophilic substitution reactions. The Polarizibility of studied molecules values plays an important role in activity.

References

(2015); http://www.jmaterenvironscis.com/