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

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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) dithiocarbamate-5-phenyl-1,3,4-thiadiazole, dibenzyl-N-(5-phenyl-1,3,4-thiadiazole-2yl)dithiocarbamid, difenacyl-N- (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 ^{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.

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-helicobacter 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-Hydroxybenzal)amino-5-phenyl-1,3,4-thiadiazole, 2-(N-cylohexzyl carbamyl methylthiocarbamate)-5-phenyl-1,3,4-thiadiazole, 2-(Allyl) dithiocarbamat-5-phenyl-1,3,4-thiadiazole, dibenzyl-N-(5-phenyl-1,3,4-thiadiazole-2-yl) dithiocarbamic, 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
Solvents were dried and distilled prior to use. Infrared spectra were recorded on a Mattson 1000 FT-IR System Spectrum. ^{1}H-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 ^{o}C). 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, $\delta\nu$(N=C-S-C) 682. ^{1}H-NMR (200 MHz, DMSO-d_6) δ/ppm 7.97-7.53 (m, 5H, aromatic protons), 4.61-4.57 (m, 2H, -O-CH_2-protons),

4.3 (s, 2H, -CH_2-S-protons), 1.34-1.26 (t, 3H, -CH_3 protons). Calcd.: C, 46.00; H, 3.86; N, 12.38; S, 28.34. Found: C, 46.83; H, 3.53; N, 12.04; S, 28.13.

2.1.2. Synthesis of 2-(2-Hydroxybenzal)amino-5-phenyl-1,3,4-thiadiazole

(0.35 g, 0.002 mole) 2- amino -5-phenyl-1,3,4- thiadiazole was added into a round 100 mL bottom flask and then added 25 mL isopropyl alcohol. To this solution, then (0.2 mL, 0.002 mole) salicylaldehyde was added dropwise, after added 0.7 mL icy acetic acid, was refluxed for 12 hours. Solution was cooled. Oily substance formed was extracted with chloroform. Chloroform phase was dried with $MgSO_4$. Solvent phase was evaporated until 10 mL. product was precipitated in hexane, and filtered, washed with ethyl alcohol (yield 52%, m.p:187-188 ^oC). ν(OH) 3336-3284, ν(aromatic C-H) 3048, ν(C=N) 1619, ν(N-H) 1529, ^{1}H-NMR (200 MHz, DMSO-d_6) δ/ppm 11.38-11.21(1H, OH protons), 9.27 (s, 1H, =CHproton), 7.99-7.02 (m, 9H, aromatic protons). Calcd.: 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-cylohexzyl 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 acetone was added. Then, (0.3 mL 0.005 mole) CS_2 at 0 ^oC 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 ^oC). IR(KBr, cm^{-1}) ν(NH) 3293, ν(aromatic C-H) 3064, ν(aliphatic C-H) 2929, 2854, ν(C=O) 1653, ν(C=N) 1589, δ(N-H) 1542, δ(C=S) 1036, δ(C-S-C) 981, ^{1}H-NMR (200 MHz, DMSO-d_6) δ/ppm 8.04-7.58 (m, 5H, aromatic protons), 3.95 (s, 2H, -S-CH_2-protons), 1.70-1.15 (m, 11H, -CH_2-protons), Calcd.: 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) dithiocarbamat-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 acetone was added. Then, (0.3 mL 0.005 mole) CS_2 at 0 ^oC 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 $MgSO_4$. 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 ^oC). IR(KBr, cm^{-1}) ν(aromatic C-H) 3005, ν(aliphatic C-H) 2918, ν(C=O) 1653, ν(C=N or C=C) 1592, δ(N-H) 1521, ν(C=S)) 1244, δ(C-S-C) 987, ^{1}H-NMR (200 MHz, DMSO-d_6) δ/ppm 8.01-7.50 (m, 5H, aromatic protons), 6.01-5.87 (m, 1H,=CH-proton), 5.39-5.12 (d, 2H, C=-CH_2-protons), 3.95-3.91 (d, 2H, -CH_2-protons), Calcd.: 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 acetone was added. Then, (0.3 mL 0.005 mole) CS_2 was added dropwise in 15 minutes at 0^{o}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^{o}C). IR(KBr, cm^{-1}) ν(aromatic C-H)) 3036, ν(aliphatic C-H)) 2967, ν(C=N) 1583. ^{1}H-NMR (200 MHz, DMSO-d_6) δ/ppm 7.93-7.25 (m, 15H, aromatic protons), 4.60 (s, 2H, -CH_2-protons), 4.45-4.44 (s, 2H, -CH_2-protons). Calcd.: 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 difenacyl-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 acetone was added. Then, (0.3 mL, 0.005 mole) CS_2 was added dropwise in 15 minutes at 0^{o}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 $MgSO_4$. 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 ^oC). IR(KBr, cm^{-1}) ν(aromatic C-H) 3050, ν(aliphatic C-H) 2923, ν(C=O) 1683, ν(C=N) 1592. ^{1}H-NMR (200 MHz, DMSO-d_6) δ/ppm, 8.12-7.30 (m, 15H, aromatic C-H protons), 5.19 (s, 2H, -CH_2-protons), 4.53-4.51(s, 2H, CH_2-protons). Calcd.: 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-di(dithiocarbamate-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 acetone was added . Then, (0.15 mL, 0.0025 mole) CS_2 was added dropwise in 15 minutes at 0 ^oC. After stirring for 30 minutes at room temperature, (0.16 g, 0.00125 mole) dichloroaceton

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 ^{o}C). IR(KBr, cm^{-1}) ν(aromatic C-H) 3063, ν(aliphatic C-H) 2959, 2920, 2886, ν(C=O) 1712, δ(N-H) 1506, ν(C=S) 1070, ν(C-S-C) 976. ^{1}H-NMR (200 MHz, $CDCl_3$) δ/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-thiadiazole (molecule 1). 2-chloroacetamide-5-phenyl-1,3,4- thiadiazole (molecule 2) was synthesized with the reaction of 2-amino-5-phenyl-1,3,4- thiadiazole (molecule 1) and acetone in the presence of Na_2CO_3 at room temperature. With the reaction of dithiocarbamat and molecule 2 in acetone was synthesized 2-(ethyl xanthate acetylamino)-5-phenyl-1,3,4- thiadiazole. 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)amino-5-phenyl-1,3,4-thiadiazole 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-cylohexzil carbamil methylthiocarbamat)-5-phenyl-1,3,4-thiadiazole was synthesized from molecule 3 with cyclohexyl amide chloride. The presence of N-H stretching band at 32936 cm^{-1} and C=O stretching band at 1653 cm^{-1} IR spectrum 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. The presence of C-H stretching band at 2918 cm^{-1} and =CH proton at 6.01-5.87 and CH_2 protons at 3.95-3.91 supports that molecule 4 were obtained. The presence CH_2 protons at 4.60 ppm and 4.45 ppm supports that molecule 5 were obtained. The presence of C=O stretching band at 1683 cm^{-1} and CH_2 protons at 5.19 ppm, 4.52 ppm supports that molecule 6 were obtained. The presence of C=O stretching band at 1712 cm^{-1} and CH_2 protons at 3.85 supports that molecule 7 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_{HOMO} and E_{LUMO} reflects the chemical activity of the molecule. These orbital play part in chemical stability. E_{HOMO} and E_{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 mainly 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_{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.

$$\alpha = -\left(\frac{\partial^2 E}{\partial F_a \partial F_b} \right) a,b = x, y, z \qquad (1)$$

The observable quantity is defined by:

$$\langle \alpha \rangle = \frac{1}{3}\sum_{i} \alpha_{ii} \qquad (2)$$

Where, α_{ii} are the eigenvalues of the polarizibility tensor.

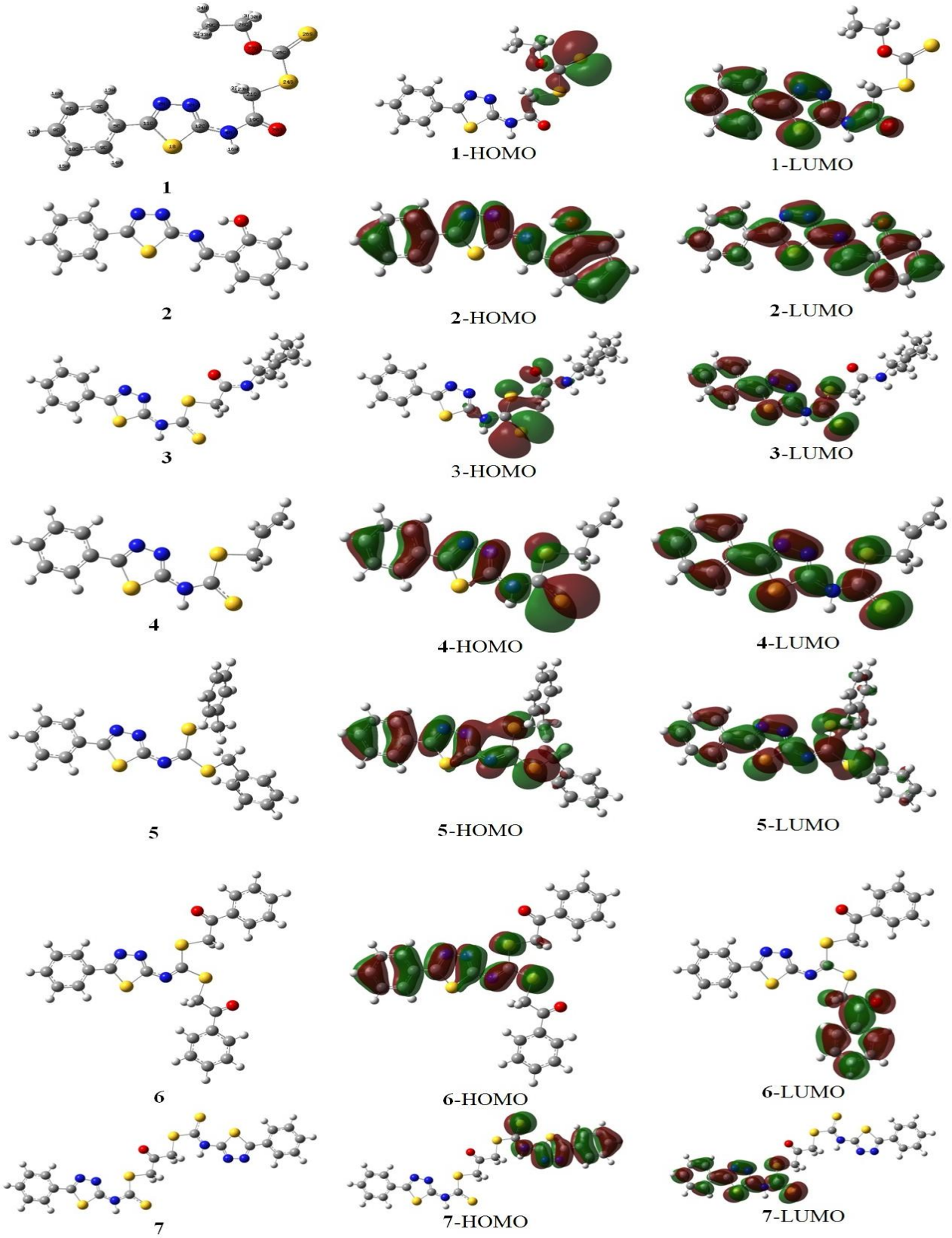

Figure 1: The optimized structures, HOMO and LUMO of the studied molecules.

Table 1: E_{HOMO} and E_{LUMO} and orbital Energy difference between HOMO and LUMO orbital referred as energy gap "ΔE", dipole moment "μ" and polarizibility and electronic energy of studies.

Molecules	Energy (RB3LYP) (a.u)	μ (Debye)	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (eV)	Polarizibility (a.u.)
1	-2012.74843	8.6380	-0.23019	-0.08092	0.14927	244
2	-1216.09136	4.9785	-0.23062	-0.10195	0.12867	257
3	-2148.96563	1.5454	-0.23207	-0.08146	0.15061	306
4	-1822.90585	3.1497	-0.23440	-0.08333	0.15107	240
5	-2247.00357	2.6158	-0.22287	-0.01784	0.14448	377
6	-2473.72799	5.2614	-0.22510	-0.07871	0.14639	398
7	-3603.12712	5.1173	-0.23709	-0.09144	0.14565	451

The molecules 1-7 have polarizibility equal 244, 257, 306, 240, 377, 398, and 451 a.u. Calculations showed that polarizibility values have dependence on the groups attached N4 atom.
Mulliken charges given in Table 2 are based on orbital occupancies, i.e., how much electron density is 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).

Table 2: Mulliken atomic charges of some atoms in studied molecules.

1		2		3		4		5		6		7	
Atom	(ē)	Atom	(ē)	Atom	(ē)	Atom	(ē)	Atom	(ē)	Atom	(ē)	Atom	(ē)
S1	0.226	S1	0.212	S1	0.222	S1	0.224	S1	0.238	S1	0.214	S1	0.231
N2	-0.191	N2	-0.194	N2	-0.190	N2	-0.192	N2	-0.205	N2	-0.200	N2	-0.189
N3	-0.233	N3	-0.159	N3	-0.205	N3	-0.207	N3	-0.181	N3	-0.195	N3	-0.209
N4	-0.429	C10	-0.028	N4	-0.382	N4	-0.376	N4	-0.300	N4	-0.384	N4	-0.382
C11	0.000	C11	0.129	C11	0.001	C11	0.001	C11	-0.009	C11	-0.010	C11	0.003
C12	0.209	N17	-0.431	C12	0.213	C12	0.214	C12	0.137	C12	0.161	C12	0.212
C19	0.352	C18	0.226	C19	-0.140	C19	-0.149	C18	-0.161	C18	-0.135	C19	-0.136
O20	-0.306	C21	0.231	S20	-0.202	S20	-0.180	S19	0.193	S19	0.323	S20	-0.181
C21	-0.403	O29	-0.340	S21	0.325	S21	0.281	S20	0.250	C20	-0.500	S21	0.320
S24	0.265			C22	-0.451	C22	-0.378	C21	-0.399	C23	0.268	C22	-0.420
C25	-0.114			C25	0.385			C35	-0.360	O24	-0.281	C25	0.236
S26	-0.139			O26	-0.360					S36	0.235	O26	-0.248
O27	-0.292			N27	-0.408					C37	-0.412	S30	0.311
C28	-0.035									C40	0.264	C31	-0.165
										O41	-0.292	S32	-0.104
												N33	-0.351
												C34	0.157
												S35	0.348
												N36	-0.213
												C37	-0.050
												N38	-0.197

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 the 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.

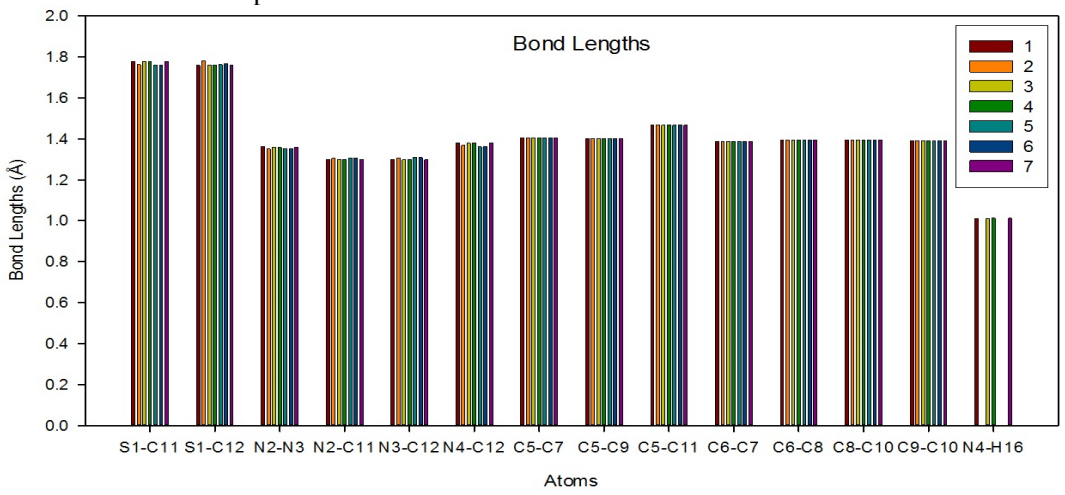

Figure 2: Comparisons of the calculated bond lengths for studied molecules.

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

		ν(OH)	ν(NH)	ν(C=O)	ν(C=N)	δ(NH)	ν(C-N-C)	δ(OH)	ν(C=S)	ν(C-S-C)	δ (O-C -S-C)	δ(N=C-S -C)
1	Exp.		3163	1702	1565	1495			1051		960	682
	Theo.		3596	1781	1542	1509			1055		1018	687
2	Exp.	3336, 3284			1619			1529				
	Theo.	3305			1654			1606				
3	Exp.		3293	1653	1589	1542			1036	981		
	Theo.		3609, 3580	1754	1545	1530			1154	1038		
4	Exp.				1592	1521			1244	987		
	Theo.		3579		1539	1530			1164, 1272	1154		
5	Exp.				1583							
	Theo.				1573							
6	Exp.			1683	1592							
	Theo.			1750, 1758	1561							
7	Exp.			1712	1596	1506			1070			
	Theo.		3576, 3581	1804	1469, 1498	1417, 1531, 1534, 1558	1348		1172			

Conclusion

5-phenyl-1,3,4-thiadiazole, derivatives were synthesized and characterized by ^{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.

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