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Synthesis and Quantum Chemical Calculations 5-phenyl-1,3,4-dithiadiazole derivatives

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Abstract
1-phenyl-1,3,4-thiadiazole derivatives were synthesized and characterization was carried out by the elemental analyses, ^{1}H-NMR, IR spectroscopy were obtained by means of the DFT/6-311G(d,p) method were performed for the quantum chemical calculations.

Keywords: Thiadiazole, UV, IR, DFT

Introduction
1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole and 1,3,4-thiadiazole are isomers of thiadiazole. 1,3,4-Thiadiazole is the main isomer of thiadiazole series had a wide variety of biological activity such as anti-fungal[1], anti-bacterial [2-4], anti-inflammatory [5,6], anti-convulsant [7,8], anti-oxidant [9], anti-hypertensive [10], antitubercular[11,12], anti-cancer[13], anti-viral[14], analgesic [15,16], anti-helicobacter pylori [17,18], and antineoplastic [19] activities etc.

Antituberculosis activity against Mycobacterium tuberculosis H37Rv and Electronic-Topological Method (ETM) and feed forward neural networks (FFNNs) trained with the back-propagation algorithm for a series of 2,5-disubstituted-1,3,4-thiadiazoles were studied [20].

The molecular electronic structures of a wide range of organic molecules were used to explain the inhibitor mechanism, reactivity of the molecules and to provide of understanding on behaviour of the interactions [21]. There were some quantum chemical calculations to study inhibitory effect of organic and inorganic inhibitors [22-25].

In previous study synthesis, characterization and quantum chemical calculations for 2-(ethylxanthate) acetyl amino-5-phenyl-1,3,4-thiadiazole, 2-(2-Hydroxybenzal)amino-5-phenyl-1,3,4-thiadiazole, 2-(N-cylohexzyl carbamylmethylthiocarbamate)-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)dithiocarbamid, difenacil-N-(5-phenyl-1,3,4-thiadiazole-2-yl)dithio carbamid, 1,3-di(dithiocarbamate-5-phenyl-1,3,4-thiadiazole)propane were performed [26].

In this study, 1,2-di(2-chloroacetamido-1,3,4- thiadiazolyl) benzene (**1**), 1,2-di(2-acetamido-1,3,4- thiadiazolyl) benzene (**2**), 1,2-di(2-benzoatoacetylamino-1,3,4- thiadiazolyl)benzene (**3**), 1,2-di(2-N,N-diethylaminodithio carbamateacetylamino-1,3,4-thiadiazolyl)benzene (**4**), 1,2-di(2-acetate acetylamino-1,3,4-thidiazolyl)benzene (**5**), 1,2-di(2-pyrrolidine-dithiocarbamateacetylamino-1,3,4- thiadiazolyl)benzene (**6**), 1,2-di(2-piperidinedithio

carbamateacetylamino-1,3,4- thiadiazolyl)benzene (**7**), were synthesized and characterization was carried out by the elemental analyses, ^{1}H NMR and IR spectroscopies.

2. Materials and methods

2.1. Experimental Details

Solvents were dried and distilled before use. The elemental analysis was performed on CHNS-932 (LECO). Infrared spectra were recorded on a Mattson 1000 FT-IR System Spectrum. ^{1}H-NMR spectra were taken on GEMINI VARIAN 200 MHz spectrophotometer. Melting points were recorded using Gkampallen melting point apparatus and uncorrected.

1) Synthesis of 1,2-di(2-chloroacetamido-1,3,4-thiadiazolyl)benzene

2.76 g (0,01mole) 1,2-di(2-amino-1,3,4- thiadiazolyl) benzene and 25 mL dried acetone were added into a round bottom flask (250 mL) and stirred at 0^{o}C. Then, 1,6mL (0,02 mole) chloroacetylchloridewas added dropwise. After the solution was stirred at room temperature for three hours, it was neutralized with 10% $NaHCO_3$ solution, filtered and washed with water and dried.

(Yield 56%, m.p:262-263^{o}C). IR(KBr, cm^{-1}) ν(NH) 3177, ν(aromatic C-H) 3015, ν(aliphatic C-H) 2918, 2850, ν(C=O) 1700, ν(C=N) 1643, δ(N-H) 1585, δ(C-S-C) 699, ^{1}H-NMR (200 MHz, DMSO-d6) δ/ppm 7.96-7.71 (m, 4H, aromatic protons), 4.49-4.43 (s, 4H, -CH_2-protons), 12.9 (s, 2H, NH protons), Elemental analysis: Calcd: C, 39.18%; H,2.34%; N, 19.58%; S, 14.94%. Found: C, 39.32%; H, 2.978%; N, 17.63%; S, 15.47%.

2) Synthesis of 1,2-di(2-acetamido-1,3,4-thiadiazolyl)benzene

1.38 g (0,005mole) 1,2-di(2-amino-1,3,4- thiadiazolyl)benzene and 25 mL dried acetone were added into a round 100 mL bottom flask and stirred at 0^{o}C. Then, 0.78 mL (0,01mole) acetylchloride was added dropwise. After the solution was stirred at room temperature for three hours, it was neutralized with 10% NaHCO3 solution, filtered and washed with water and dried.

(Yield 56%, m.p:348-349^{o}C). IR(KBr, cm^{-1}) ν(NH) 3159, ν(aliphatic C-H) 2916, ν(C=O) 1697, δ(N-H) 1548, ^{1}H-NMR (200 MHz, DMSO-d6) δ/ppm 12.07 (s,2H, N-H protons),7.87-7.68 (m,4H,aromatic protons), 2.20 (s, 6H, -CH_3-protons), Elemental analysis:Calcd: C, 46.66%; H,3.35%; N, 23.32%; S, 17.79%. Found: C, 45.89%; H, 3.47%; N, 23.19 %, S, 17.56%.

3) Synthesis of 1,2-di(2-benzoatoacetylamino-1,3,4-thiadiazolyl) benzene

0.43 g (0,001mole) 1,2-di(2-chloroacetamido-1,3,4- thiadiazolyl) benzene, 0.43g (0.03 mole) sodium benzoate and 25 mL dried acetone were added into a round 250 mL bottom flask and stirred for three hours, the excess acetone was evaporated, and the remained solution was precipitated by adding water, filtered and washed with water and dried.

(Yield 53%, m.p:182-183^{o}C). IR(KBr, cm^{-1}) ν(NH) 3174, ν(aromatic C-H) 3045, ν(aliphatic C-H) 2929, ν(C=O) 1720, ν(C=N) 1542,ν(C-O-C-) 1270, 1H-NMR (200 MHz, DMSO-d6) δ/ppm): δ d 8.05-7.53 (m, 14H, aromatic protons), 5.11 (s, 4H, - CH_2-protons), 4.21 (s, 2H,NH protons), Elemental analysis Calcd: C, 55.99%; H,3.36%; N, 13.99%; S, 10.68%. Found: C, 56.79%; H, 3.27%; N, 13.16,%; S, 10.25%.

4) Synthesis of 1,2-di(2-N,N-diethylaminodithiocarbamateacetylamino-1,3,4-thiadiazolyl)benzene

0.43 g (0,001mole) 1,2-di(2-chloroacetamido-1,3,4- thiadiazolyl)benzene, 0.5g (0.003 mole) ammonium N,N-diethylthiocarbamate salt and 25 mL dried acetone were added into a round 100 mL bottom flask and stirred for three hours, the excess acetone was evaporated until 10 mL solution remains, and the remained solution was precipitated by adding water, filtered and washed with water and dried.

(Yield 53%, m.p:233-234^{o}C). IR(KBr, cm^{-1})ν(NH) 3185,ν(aromatic C-H) 3008,ν(aliphatic C-H) 2929, ν(C=O) 1700,δ(N-H) 1535, ν(C=S) 1089, ν(C-S-C) 983,^{1}H-NMR (200 MHz, DMSO-d_6) δ/ppm): 7.88-7.69 (s, 4H, aromatic protons), 4.40 (s, 4H, -CH_2-S protons), 3,96-3,73 (m, 8H, -CH_2-protons), 1.31-1.06 (m, 12H,-CH_3 protons). Elemental analysis Calcd: C, 44.01%; H,4.62%; N, 17.11%; S, 29.38%. Found:C, 44.28%; H, 4.08%; N, 16.65%, S, 27.53%.

5) Synthesis of 1,2-di(2-acetateacetylamino-1,3,4-thidiazolyl)benzene

0.43 g (0,001mole) 1,2-di(2-chloroacetamido-1,3,4- thiadiazolyl)benzene, 0.3g (0.003 mole) potassium acetate were added into a round 100mL bottom flask and then dried acetone was added. They were refluxed for three

hours, the excess acetone was evaporated until 10 mL solution remains, and the remained solution was precipitated by adding water, filtered and washed with water and dried.
(Yield 55%, m.p:287-288^{o}C). IR(KBr, cm-1) ν(NH) 3180, ν(aromatic C-H) 3034, ν(aliphatic C-H) 2934, ν(-O-C=O) 1752, ν (C= O) 1720, ν (C= N) 1571, ν (C-S-C) 1018, 1H-NMR (200 MHz, DMSOd6) δ/ppm 7.88-7.70 (m, 4H, aromatic protons), 4.84 (s, 4H, -CH_2-protons), 2.14 (s,6H,-CH_3 protons). Elemental analysis Calcd: C, 45.37**%**; H, 3.39**%**; N, 17.64**%**; S, 13.46**%**. Found: C, 46.18**%**; H, 3.21**%**; N, 17.89**%**,S, 13.72**%)**

6) Synthesis of 1,2-di(2-pyrrolidine-dithiocarbamateacetylamino-1,3,4-thiadiazolyl)benzene

0.43 g (0.001mole) 1,2-di(2-chloroacetylamido-1,3,4- thiadiazolyl) benzene, 0.5g (0.003 mole) ammonium pyrrolidinedithiocarbamate and 25 mL dried acetone were added into a round 100 mL bottom flask and were refluxed for three hours, the excess acetone was evaporated until 10mL solution remains, and the remained solution was precipitated by adding water, filtered and washed with water and dried.
(Yield 54%, m.p:290-291^{o}C). IR(KBr, cm^{-1}) ν(NH) 3175, ν(aromatic C-H) 3036, ν(aliphatic C-H) 2932, ν (C= O) 1720, ν (C= N) 1571, ^{1}H-NMR (200 MHz, DMSOd6) δ/ppm 7.87-7.69 (m, 4H, aromatic protons), 4.42 (s, 4H, -CH_2-S protons), 3.79-3-58(m,8H,-N-CH_2- protons), 2.09-1.89 (m,8H,C-CH_2-C protons), Elemental analysis Calcd: C, 44.29**%**; H,4.03**%**; N, 17.21**%**; S, 29.56**%**. Found: C, 44.10**%**; H, 4.29**%**; N, 17.94**%** S, 29.18**%.**

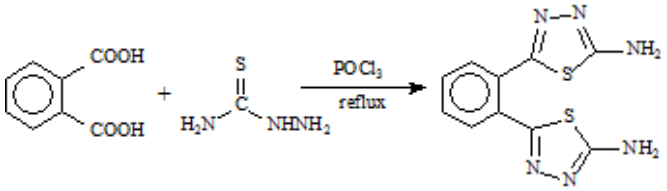
7) Synthesis of 1,2-di(2-piperidinedithiocarbamate acetylamino-1,3,4- thiadiazolyl) benzene

0.43 g (0,001mole) 1,2-di(2-chloroacetamido-1,3,4-thiadiazolyl)benzene, 0.6g (0.003mole) piperidine-dithiocarbamate salt and 25 mL dried acetone was added into a round 100 mL bottom flask and were refluxed for three hours, the excess acetone was evaporated until 10mL solution remains, and the remained solution was precipitated by adding water, filtered and washed with water and dried.
(Yield 54%, m.p:253-254^{o}C). IR(KBr, cm^{-1}) ν(NH) 3179, ν(aromatic C-H) 3030, ν(aliphatic C-H) 2936,2851 ν (C= O) 1710, ν (C= N) 1560, ν (C= S) 1111, ν (C-S-C),1010 ,1H-NMR (200 MHz, DMSOd6) δ/ppm 7.87-7.68 (m, 4H, aromatic protons), 4.41 (s, 4H, -CH_2-S protons), 4.18-3.87(d,8H,-N-CH_2-C protons),1,63 (s,12H,C-CH_2-C protons). Calcd: C, 45.99**%**; H,4.45**%**; N, 16.50**%**; S, 28.34**%**. Found: C, 46.11**%**; H, 4.82**%**; N, 15.89**%** S, 28.73**%.**

2.2. Calculation Methods
Density functional theoretical (DFT) computations were performed by using B3LYP [27,28] functionals in combination with 6-311G(d,p) basis set by means of the Gaussian 09 program [29] to derive the complete geometry optimization. The calculated harmonic vibrational wavenumbers were not scaled down.

3. Results and discussion

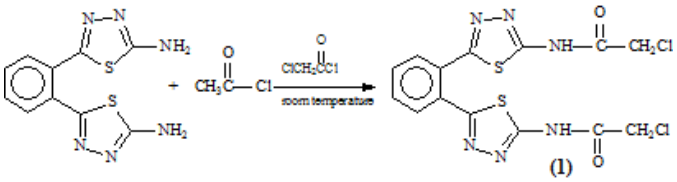
1,2-di-(2-amino-1,3,4-thiadiazole) was synthesized with the reaction of phthalic acid and thiosemicarbazide in the presence of $POCl_3$ (Scheme 1.) and then ,2-di(2-chloroacetamido-1,3,4-thiadiazolyl)benzene were obtained with the reaction chloroacetylchloride and 1,2-di-(2-amino-1,3,4-thiadiazole). The bands observed at 3323 cm^{-1} and 1610 cm^{-1} and 1508 cm^{-1} belonging to the N-H and C=N stretching bands and bending vibration, respectively, supports that 1,2- di-(2-amino-1,3,4-thiadiazole (2) was obtained (Scheme 2). Amide derivatives (3,4,5,6,7) were obtained with the reaction of compound 1 and several salts (Scheme 3 and 4). IR spectra belonging to 3,4,5,6,7 are showed that disappearing of C-Cl stretching vibration observed at 781 cm^{-1} and observing C=O band at 1720 cm^{-1} and CH_3-CH_2- protons confirm that amid chloride derivatives were synthesized.



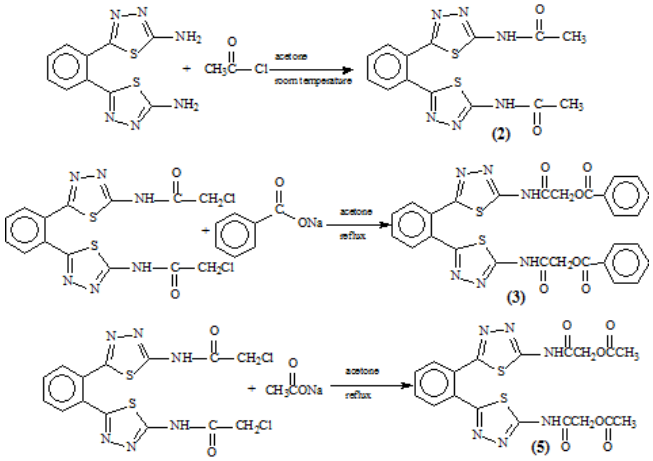
Scheme 1. 1,2-di-(2-amino-1,3,4-thiadiazole)

Compound 3 and 5 is obtained in 53 and 55 % yield with the reaction of compound 1 and sodium carboxylate salts in acetone. Compounds 3 and 5 were confirmed by disappearing the IR peak of C-Cl occured at 781 cm^{-1} and IR spectral data showing characteristic bands at around 1720 and 1750 cm^{-1}, indicating the presence of two C=O band.

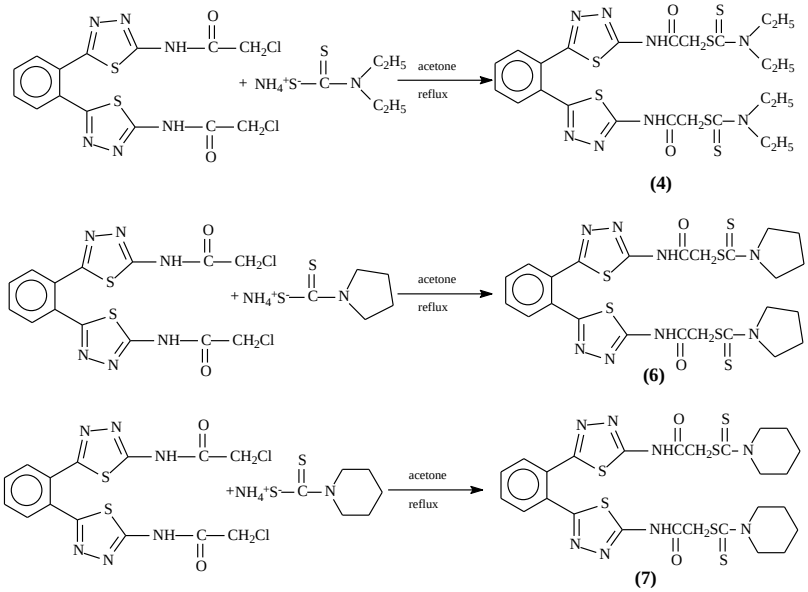
The derivative of Compound 1 was obtained with the boiling up in dry acetone of compound and dithiocarbamate salts with a yield of 50-55%. Compounds 4, 6 and 7 were confirmed by disappearing the IR peak of C-Cl appearing at 781 cm^{-1} and IR spectral data showing characteristic bands at around 1720 and 1750 cm^{-1}, indicating the presence of two C=O bands.



Scheme 2. Scheme for 1,2-di(2-chloroacetamido-1,3,4-thiadiazolyl)benzene



Scheme 3. 2,3 and 5 compounds obtained using Acetyl chloride and carboxylate salts



Scheme 4. 4,6 and 7 compounds obtained using dithiocarbamate salts

All computational studies were performed with the Gaussian 09 series of programs [29] by using density functional theory (DFT) methods with B3LYP hybrid exchange-correlation functional [27,28] with the standard 6-311G(d,p) basis set. No imaginary frequencies were obtained for vibrational frequencies computations at the optimized. Vibrational frequencies were determined by the FREQ calculations on the stationary points obtained after the optimization to check if there were true minima. The contour plots of the frontier orbitals for the ground state of molecule 1-7 are shown in Figure 1, including the highest occupied molecular orbital (HOMO) acting as an electron donor, due to its outermost (highest energy) orbital containing electrons and the lowest unoccupied molecular orbital (LUMO) acting as the electron acceptor

It can be seen from the Figure 1 that the HOMO orbitals are located on the phenyl, thiadiazole ring and nitrogen atom attached to thiadiazole ring for molecule 1-5, and on the Sulphur atoms of the chain for molecules 6 and 7,. while LUMO orbitals are mainly located on the phenyl and thiadiazole ring for all the studied molecules.

Chemical activity of the molecules is related with the energy gap of E_{HOMO} and E_{LUMO} The sum of electronic and zero-point energies, of the dipole moment, the average polarizability, the HOMO energy, the LUMO, The energy gap is given in Table 1. E_{HOMO} energies of molecules 1-7 are -0.09360 au, -0.08241au, -0.08617au, -0.07237au, -0.08708au, -0.07027au, -0.07119 au, respectively, and the energy required to transfer electron from HOMO to LUMO for the studied molecules of those are 0.16359au, 0.16222au, 0.16268au, 0.14039au, 0.16261au, 0.14223au, 0.14188, au.

Table 1: E_{HOMO} and $E_{LUMO,}$ energy gap dipole moment "μ" and polarizability and electronic energy of molecules under sdudy

Molecules	SEZPE[a] (RB3LYP) (a.u)	μ (Debye)	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (eV)	Polarizability (a.u)
1	-2735.320084	9.57	-0.25719	-0.09360	0.16359	275
2	-1816.078046	5.42	-0.24463	-0.08241	0.16222	252
3	-2655.319900	4.65	-0.24885	-0.08617	0.16268	421
4	-3910.202439	2.29	-0.21276	-0.07237	0.14039	468
5	-2271.862477	5.55	-0.24969	-0.08708	0.16261	310
6	-3907.831510	2.98	-0.21250	-0.07027	0.14223	463
7	-3986.418852	2.83	-0.21307	-0.07119	0.14188	488

[a]*Sum of electronic and zero-point Energies*

The electric dipole polarizability is given by the following formula

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

The observable quantity is defined as below.:

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

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

The polarizability of the molecules 1-7 equal to 275a.u, 252a.u, 421a.u, 468a.u, 310a.u, 463a.u, 488 a.u. Calculations showed that thio groups have the biggest polarizability values.

Mulliken charges arising from the Mulliken population analysis provide a means of estimating partial atomic charges from quantum chemical calculations.

Mulliken charges and the bond length of 2-amino-5-phenyl-1,3,4-thiadiazole ring molecules 1-7 were presented on Tables2 and 3, respectively. S and N heteroatom belonging to 2-amino-5-phenyl-1,3,4-thiadiazole ring are slightly different. The atomic charges on S of thidiazole ring for molecule 1-7, and are 0.243ē, 0.236ē, 0.247ē, 0.284ē, 0.249ē, 0.289ē, 0.288 ē, respectively; those on N2 are -0.169ē, -0.175ē, -0.171ē, -0.170ē, -0.173ē, -0.173ē, -0.172ē, respectively; those on N3 atomsare -0.241ē, -0.231ē, -0.239ē, -0.227ē, -0.237ē, -0.228ē, -0.225ē, respectively.

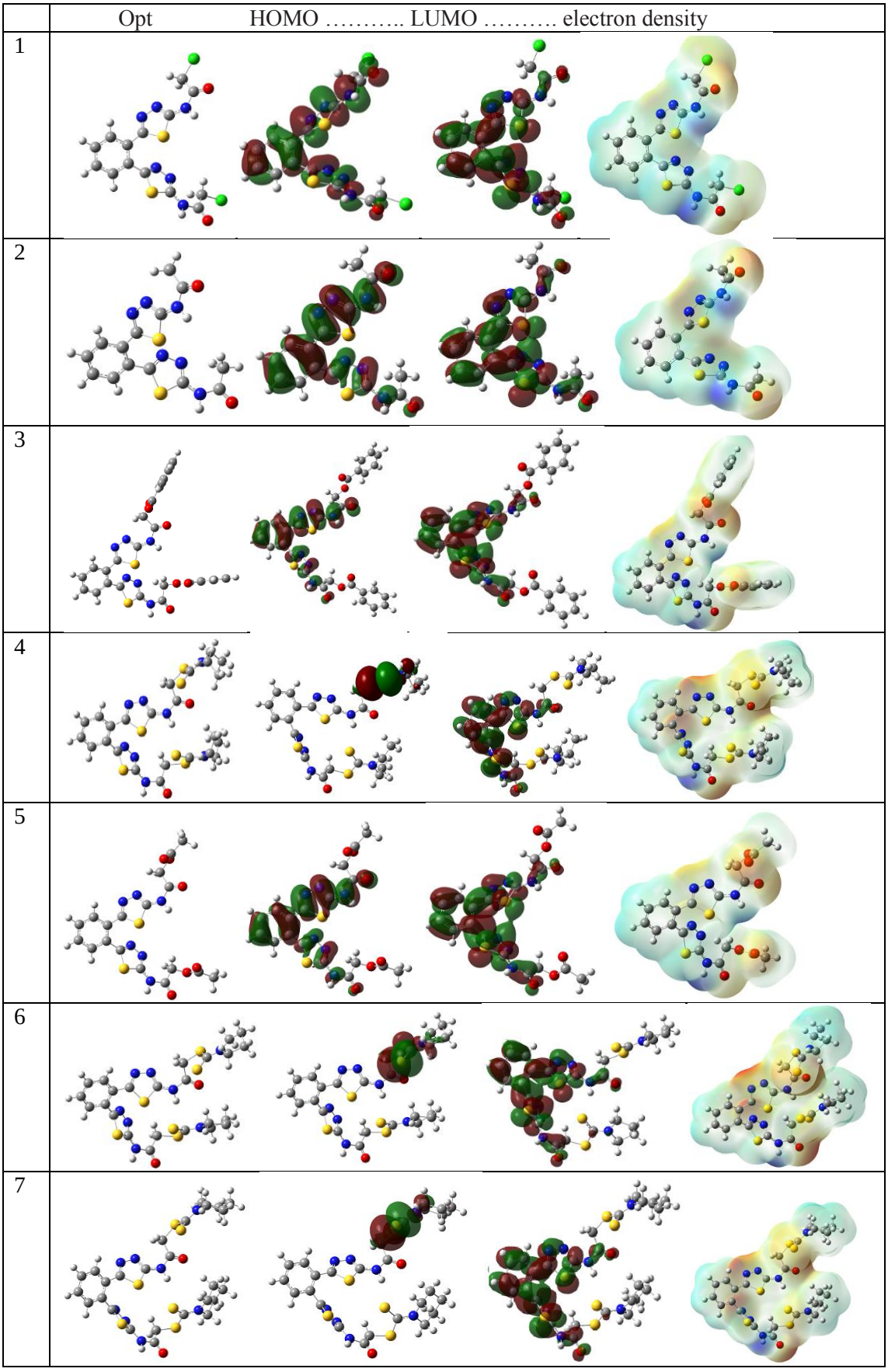


Figure 1: The optimized structures, HOMO and LUMO and electrondensity of the studied molecules.

Table 2: Mulliken charges (ē) of some atoms for molecules under study.

	S1	C12	N3	N2	C11	N4	C25	O26
1	0.243	0.225	-0.241	-0.169	-0.049	-0.435	0.357	-0.289
2	0.236	0.220	-0.231	-0.175	-0.048	-0.427	0.299	-0.324
3	0.247	0.226	-0.239	-0.171	-0.051	-0.189	0.331	-0.309
4	0.284	0.208	-0.227	-0.170	-0.091	-0.425	0.403	-0.316
5	0.249	0.223	-0.237	-0.173	-0.048	-0.437	0.334	-0.314
6	0.289	0.205	-0.228	-0.173	-0.088	-0.421	0.410	-0.324
7	0.288	0.204	-0.225	-0.172	-0.089	-0.156	0.404	-0.317

Table 3: Calculated bond lengths between some atoms for molecules under study.

Molecules	1	2	3	4	5	6	7
Atoms	Bond Lengths (Å)						
S1-C11	1.770	1.769	1.770	1.764	1.770	1.762	1.763
S1-C12	1.756	1.759	1.756	1.753	1.755	1.753	1.753
N2-N3	1.361	1.361	1.361	1.362	1.360	1.363	1.362
N2-C11	1.297	1.298	1.298	1.299	1.298	1.300	1.300
N3-C12	1.300	1.301	1.300	1.303	1.301	1.303	1.303
N4-C12	1.379	1.378	1.378	1.379	1.378	1.379	1.379
C5-C7	1.402	1.403	1.402	1.401	1.403	1.402	1.402
C5-C9	1.413	1.413	1.413	1.413	1.413	1.413	1.413
C5-C11	1.475	1.475	1.476	1.475	1.475	1.475	1.475
N4-H16	1.011	1.011	1.011	1.019	1.011	1.022	1.020
S18-C17	1.776	1.774	1.775	1.769	1.775	1.770	1.769
S18-C20	1.758	1.762	1.758	1.759	1.758	1.760	1.760
N19-N21	1.361	1.361	1.361	1.360	1.361	1.360	1.360
N19-C17	1.295	1.295	1.295	1.296	1.295	1.296	1.296
N21-C20	1.302	1.302	1.302	1.301	1.302	1.301	1.301
N22-C20	1.377	1.376	1.377	1.381	1.377	1.381	1.381
N22-H24	1.377	1.011	1.011	1.011	1.011	1.012	1.012

The some important functional vibrational frequencies calculated for molecules 1-7 with B3LYP functionals by using 6-311 basis set together with the experimental values are collected in Table 3. Molecules 1-7 showed vibrational frequency around 1700, 1697, 1720, 1700, 1720, 1720, 1710 cm^{-1} which was assigned for C=O group as experimental and 1781, 1754, 1750 and 1804 cm^{-1} as theoretical. The υ(C=N) bands have been observed at 1562, 1610, 1589, 1592, 1583, 1592 and 1596 cm–1 for molecules 1-7. 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.

Table 4: Comparison of the experimental and the theoretical values of some important functional vibrational frequencies for molecules 1-7.

		ν(NH)	ν(aromatic CH)	ν(aliphatic C-H)	ν(-O-C=O)	ν(C=O)	ν(C=N)	δ(N-H)	ν(C-O-C-)	ν(C=S)	δ(C-S-C)
1	Exp.	3177	3015	2918, 2850		1700	1643,	1585			699
	Theo	3597	3196	3106		1810	1543	1535			766
2	Exp.	3159	-	2916		1697		1548			
	The.	3597	3210	3158		1796	1544	1505			885
3	Exp.	3174	3045	2929		1720	1542		1270		
	Theo.	3596	3187	3096		1809	1543	1505	1291		772
4	Exp.	3185	3008	2929		1700		1535		1089	
	Theo.	3591	3194	3130		1796	1540	1525		1165	
5	Exp.	3180	3034	2934	1752	1720	1571				1018
	Theo.	3595	3195	3158	1825	1802	1543	1501			1093
6	Exp.	3175	3036	2932		1720	1571				
	Theo.	3591	3193	3172		1797	1547	1496		1018	
7	Exp.	3179	3030	2936,2851		1710	1560			1111	1010
	Theo.	3591	3193	3137,3093		1797	1540	1495		1152	1021

Conclusion

5-phenyl-1,3,4-di thiadiazole derivatives synthesized were characterized by ^{1}H-NMR, IR, mass spectroscopic data and elemental analyses. DFT/6-311G(d,p) method were used for the quantum chemical calculations.
The HOMO of the title compound is mainly located on the 1,2,3-thiadiazole ring, and nitrogen atom attached to thiadiazole ring for molecule 1-5, and on the sulphur atoms of the chain for molecules 6 and 7. The results obtained with the theoretical calculations indicate that the HOMO and LUMO energies polarizability change with the changing of the substituent.

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