



P-ISSN: 2349-8528  
 E-ISSN: 2321-4902  
 IJCS 2019; 7(4): 222-227  
 © 2019 IJCS  
 Received: 14-05-2019  
 Accepted: 22-06-2019

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## Synthesis, characterization and Quantum Chemical Calculations of 2-chloroacetamido -5-(2-chloroacetamido-1, 3, 4-thiadiazolyl)-1, 3, 4-Thiadiazole Derivatives

**H Muglu and MS Çavuş**

### Abstract

2-chloroacetamido-5-(2-chloroacetamido-1,3, 4-thiadiazolyl)-1,3, 4-Thiadiazole, bis(2-chloroacetamido-1,3,4-thiadiazolyl)methane, 1,4-di(2-chloroacetamido -1,3,4- thiadiazolyl) benzene were synthesized, and molecular characterizations were carried out by the elemental analyses. Experimentally obtained <sup>1</sup>H NMR and FT-IR spectroscopic data were supported by DFT calculations using B3LYP/cc-pvtz method. Electronic parameters such as electronegativity, chemical hardness, polarizability and dipole moment were also calculated and analyzed. Experimental data of the compounds were compared with theoretical results. Intramolecular interactions of Cl-NH and S-O were performed using Bader's QTAIM approach.

**Keywords:** Thiadiazole, UV-Vis, FT-IR, DFT

### 1. Introduction

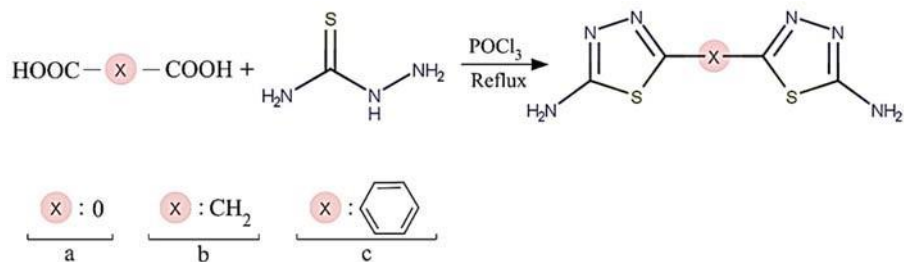
Although many antimicrobial drugs have been invented to prevent infectious diseases since ancient times, the change and resistance of microbes in the life cycle has improved [1]. The development of drug-resistant microorganisms has reached worldwide concern and the synthesis of new anti-infective compounds has become an urgent need for the treatment of microbial infections [2]. In recent years, heterocyclic ring systems have been of great interest in medical chemistry research because of interesting biological and synthetic applications [3]. Therefore, numerous heterocyclic compounds such as thiazoles, thiadiazoles, oxadiazoles and pyrroles; antibacterial, anticancer, antipyretic, hypoglycemic, antihypertensive, anti-inflammatory and anti-HIV4 reagents were synthesized. In addition, heterocyclic molecules are used in agriculture, plastics, polymers, dyes and textiles. Thus, heterocyclic chemistry continues to attract the attention of synthetic organic chemists [4-7].

Heterocyclic compounds such as thiadiazole is a five-membered ring system containing two nitrogen atoms and one sulphur atom with conjugated p and π electrons. They are present in four isomeric forms; 1,2,3-thiadiazole, 1,2,5-thiadiazole, 1,2,4-thiadiazole and 1,3,4-thiadiazole. 1,3,4-thiadiazoles, the most studied species, are used in agriculture and in many technological fields [8, 9].

In this study, 2-chloroacetamido -5-(2-chloroacetamido-1,3,4-thiadiazolyl)-1,3,4-Thiadiazole, bis(2-chloroacetamido-1,3,4-thiadiazolyl)methane, 1,4-di(2-chloroacetamido-1,3,4-thiadiazolyl) benzene were synthesized, and characterized experimentally and theoretically. The synthesized compounds were performed by using density functional theory (DFT) calculations and compared with the experimental results of FT-IR and <sup>1</sup>H NMR spectroscopies. Furthermore, intramolecular interactions of Cl-NH and S-O were analyzed by Bader's QTAIM approach.

### 2. Materials and methods

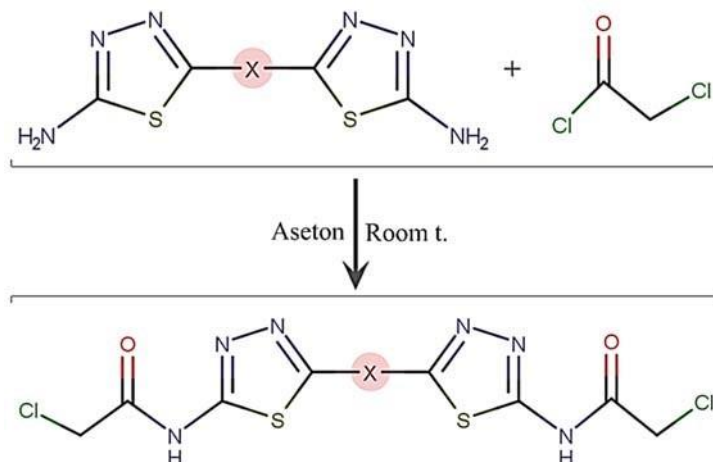
Di-(2- amino-1,3,4-thiadiazoles) were synthesized with the reaction of dicarboxylic acids and thiosemicarbazide in the presence of POCl<sub>3</sub>. The bands of IR spectra observed at 3370 cm<sup>-1</sup>, 3264 cm<sup>-1</sup> belonging to the N-H and 1636 cm<sup>-1</sup>, 1629cm<sup>-1</sup> belonging to the C=N stretching band and bending vibration respectively and H-NMR δ/ppm 7.70, 7.55, 7.19 (s, 4H, -NH<sub>2</sub> protons) supports that bis (2 amino-1,3,4-thiadiazole (Scheme 1).



**Scheme 1:** 1,2-di-(2-amino-1,3,4-thiadiazolyl)

2-chloroacetamido-5-(2-chloroacetamido-1,3,4-thiadiazolyl)-1,3,4-Thiadiazole was synthesized with the reaction of 2-amino-5-(2-amino-1,3,4-thiadiazolyl)-1,3,4-thiadiazole and chloroacetyl chloride in the room temperature dry acetone. The bands of IR spectra observed at 3156  $\text{cm}^{-1}$ , 1560  $\text{cm}^{-1}$  and 1712  $\text{cm}^{-1}$ , belonging to the N-H, C=N and C=O stretching

bands and bending vibration respectively and H-NMR  $\delta/\text{ppm}$  4.52-4.50 (s, 4H,  $-\text{CH}_2-$  protons) supports that 2-chloroacetamido-5-(2-chloroacetamido-1,3,4-thiadiazolyl)-1,3,4-Thiadiazole (X-a) was (Scheme 2).



**Scheme 2:** 2-chloroacetamido-5-(2-chloroacetamido-1,3,4-thiadiazolyl)-1,3,4-thiadiazole

Bis(2-chloroacetamido-1,3,4-thiadiazolyl) methane was synthesized with the reaction of Bis(2-amino-1,3,4-thiadiazolyl) methane and chloroacetyl chloride in the room temperature dry acetone. The bands of IR spectra observed at 3169  $\text{cm}^{-1}$ , 1640  $\text{cm}^{-1}$  and 1700  $\text{cm}^{-1}$ , belonging to the N-H, C=N and C=O stretching bands and bending vibration respectively, and H-NMR /ppm 4.46 (s, 4H,  $-\text{CH}_2\text{-Cl}$  protons), 4.09 (s, 2H,  $-\text{CH}_2-$  protons) supports that 2-chloroacetamido-5-(2-chloroacetamido-1,3,4-thiadiazolyl)-1,3,4-Thiadiazole (X-b) was obtained (Scheme 2).

1,4-di(2-chloroacetamido-1,3,4-thiadiazolyl) benzene was synthesized with the reaction of 1,4-di(2-amino-1,3,4-thiadiazolyl) benzene and chloroacetyl chloride in the room temperature dry acetone.

The bands of IR spectra observed at 3170  $\text{cm}^{-1}$ , 1573  $\text{cm}^{-1}$  and 1704  $\text{cm}^{-1}$ , belonging to the N-H, C=N and C=O stretching bands and bending vibration respectively and H-NMR /ppm 8.05 (s, 4H, aromatic protons), 4.51 (s, 4H,  $-\text{CH}_2\text{-Cl}$  protons) supports that 2-chloroacetamido-5-(2-chloroacetamido-1,3,4-thiadiazolyl)-1,3,4-Thiadiazole (X-c) was obtained (Scheme 2).

## 2.1. Synthesis of the compounds

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.  $^1\text{H-NMR}$  spectra were taken on GEMINI VARIAN

200 MHz spectrophotometer. Melting points were recorded using Gkampallen melting point apparatus and uncorrected.

### 2.1.1 Synthesis of 2-chloroacetamido-5-(2-chloroacetamido-1,3,4-thiadiazolyl)-1,3,4-Thiadiazole (compound I)

2.00 g (0,01mole) 2-amino-5-(2-amino-1,3,4-thiadiazolyl)-1,3,4-thiadiazolyl and 25 ml dried acetone was added into a round 100 mL bottom flask and stirred at 0 °C. Then, 1.6 ml (0,02mole) Chloroacetyl chloride was added dropwise. After the solution was stirred at room temperature for three hours, it was neutralized with 10%  $\text{NaHCO}_3$  solution, filtered and washed with water and dried.

(Yield 57%, m.p:320-321°C). IR(KBr,  $\text{cm}^{-1}$ )  $\nu(\text{NH})$  3156,  $\nu(\text{aliphatic C-H})$  3016,2937,  $\nu(\text{C=O})$  1712,  $\nu(\text{C=N})$  1560,  $^1\text{H-NMR}$  (200 MHz,  $\text{DMSO-d}_6$ )  $\delta/\text{ppm}$ : 4.52-4.50 (s, 4H,  $-\text{CH}_2-$  protons), 13.8-13.2 (2H,  $-\text{NH}$ -protons), Calcd: C, 27.20; H, 1.71; N, 23.79; S, 18.16. Found: C, 27.34; H, 1.80; N, 23.39 S, 17.22.

### 2.1.2 Synthesis of Bis(2-chloroacetamido-1,3,4-thiadiazolyl) methane (compound II)

2.14 g (0,01mole) Bis(2-amino-1,3,4-thiadiazolyl) methane and 25 ml dried acetone was added into a round 100 ml bottom flask and were stirred at 0°C. Then, 1,6 ml (0,02 mole) chloroacetyl chloride was added dropwise. After the solution was stirred at room temperature for three hours, it was

neutralized with 10% NaHCO<sub>3</sub> solution, filtered and washed with water and dried.

(Yield 51%, m.p:260-261 °C). IR(KBr, cm<sup>-1</sup>)  $\nu$ (NH) 3169,  $\nu$ (aliphatic C-H) 2938,  $\nu$ (C=O) 1700,  $\nu$ (C=N) 1640,  $\nu$ (N-H) 1550, <sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>)  $\delta$ /ppm: 4.46 (s, 4H, -CH<sub>2</sub>-Cl protons), 4.09 (s, 2H, -CH<sub>2</sub>-protons), Calcd: C, 29.44; H,2.19; N, 22.88; S,17.46. Found: C, 29.91; H, 2.50; N, 22.82 S, 16.25.

### 2.1.3 Synthesis of 1,4-di(2-chloroacetamido -1,3,4-thiadiazolyl) benzene (compound III)

2.76 g (0,01mole) 1,4-di(2-amino-1,3,4- thiadiazolyl)benzene and 25 mL dried acetone was added into a round 100 ml bottom flask and were stirred at 0 °C and 1,6 mL (0,02mole) chloroacetyl chloride was added dropwise. After the solution was stirred at room temperature for three hours, it was neutralized with 10% NaHCO<sub>3</sub> solution, filtered and washed with water and dried.

(Yield 64%, m.p:318-319 °C). IR(KBr, cm<sup>-1</sup>)  $\nu$ (NH) 3170,  $\nu$ (aromatic C-H) 3027, $\nu$ (aliphatic C-H) 2940,  $\nu$ (C=O) 1704,  $\nu$ (C=N) 1573,  $\nu$ (C-S-C) 630, <sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>)  $\delta$ /ppm 8.05 (s,4H,aromatic protons), 4.51 (s, 4H, -CH<sub>2</sub>-Cl

protons), Calcd: C, 29.17; H,2.35; N, 19.58; S, 14.94. Found: C, 28.32; H, 2.23; N, 20.42 S, 15.26.

### 2.2 Computational methods

Structural optimization of the compounds (ground-state geometries), FT-IR and <sup>1</sup>H NMR calculations were performed by Kohn-Sham density functional theory [10, 11] calculations without any geometric restriction. Optimization processes of the compounds were performed using the exchange–correlation hybrid functional B3LYP (three-parameter exchange functional of Becke B3 combined with the Lee–Yang–Parr correlation functional LYP) method with cc-pvtz (valence triple zeta with polarization) basis set. As a result of the optimizations, a local minimum values were reached on the potential energy surfaces, that is, imaginary frequencies are not available for optimized structures.

Compound I was dihedrally scanned between the thiadiazole rings and the C-N bond to determine the minimum energy level conformation of the compounds, performing total of 169 steps with rotation of 30 degree (Figure 1). The same calculation procedure was used for the geometric optimization of compounds II and III.

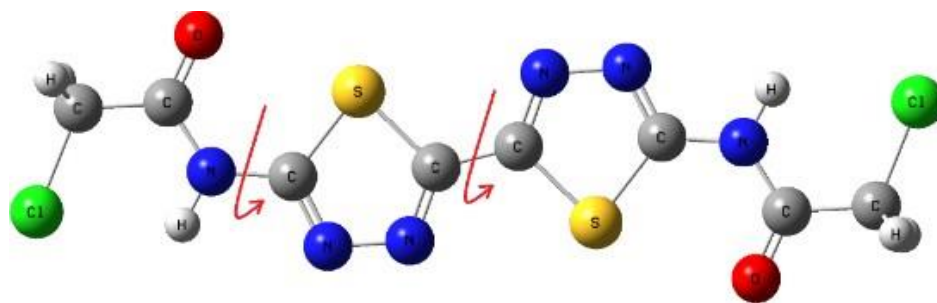


Fig 1: Dihedral scanning of compound I.

Energetically most favorable structures of the compounds I and III were obtained for approximate planar geometries. In

the compound II, the bending angle of the molecule was calculated to be 114.25 degrees (Figure 2-b).

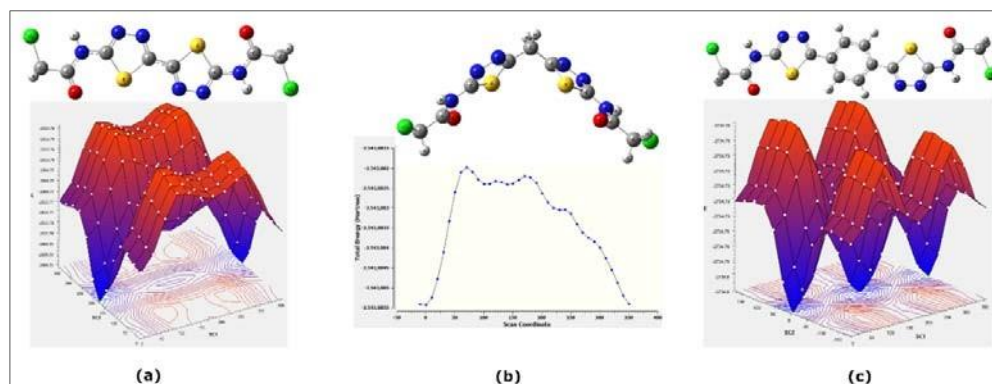


Fig 2: Molecular geometries of the compounds, obtained by dihedral scanning.

The FT-IR and <sup>1</sup>H NMR calculations were performed using optimized geometries. The self-consistent reaction field (SCRf) method and the conductor-polarizable continuum model (CPCM) were used for <sup>1</sup>H NMR calculations, in dimethyl sulfoxide (DMSO) solvent. The frontier molecular orbital (FMO) energies were also calculated with same method and basis set. The HOMO and LUMO energy eigenvalues were used to calculate the energy gap  $\Delta E$ , chemical hardness and electronegativity. HOMO-LUMO and molecular electrostatic potential (MEP) surfaces of the

optimized compounds were also examined using the theoretical results. All calculations were performed using the GAUSSIAN 09 software package program [12].

Furthermore, Bader's theory of atoms in molecules [13–15] (QTAIM) was used for analysing the electron density in the compounds, which is also widely used to predict the properties and reactivity of molecules. QTAIM analysis was also performed to determine the intramolecular interactions and to determine the ring-critical points (RCPs) of the charge density distribution and the bond-critical points (BCPs) of the

electron density between two atoms (especially between C–NH and S–O) forming a chemical bond. Furthermore, the electron delocalization indices (DIs) between the atoms was calculated.

### 3. Results and discussion

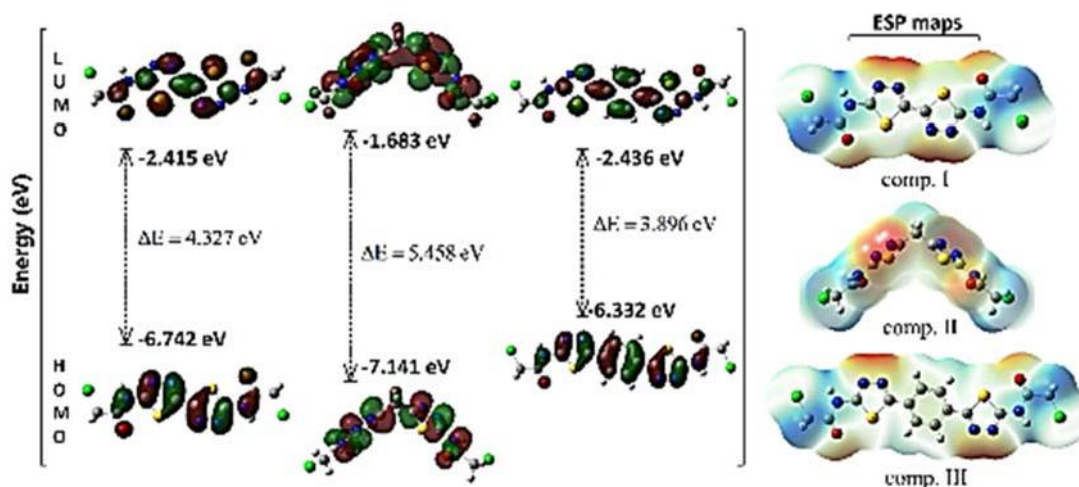
Several calculated electronic parameters are given in Table 1 such as minimum molecular energy ( $E$ ), HOMO energy ( $E_{\text{HOMO}}$ ), LUMO energy ( $E_{\text{LUMO}}$ ), HOMO-LUMO energy gap ( $\Delta E$ ), chemical hardness ( $\eta$ ), electronegativity ( $\chi$ ), polarizability ( $\alpha$ ) and dipole moment ( $\mu$ ). The electrical dipole moment is a measure of the separation of positive and negative charge centers within a system and determines the polarity of the system. Moreover, the ability of a molecule to interact with surrounding environments (atoms or molecular structures) is proportional to the total dipole moment. [16]. Dipole moments of the compounds I and III was calculated to be 0.00 Debye. This result showed that the negative and positive charge centers of compounds I and III were coincident and that their molecular structures were planar symmetric. The dipole moment of compound II was calculated as 2.29 Debye and as shown in Table 1, the HOMO-LUMO energy gap  $\Delta E$  was higher than that of the other compounds, indicating that its chemical reactivity is

lower than other compounds. HOMO energy is related to ionization potential (IP) given by Koopmanns' theorem in molecular orbital theory approaches and LUMO energy is also used to estimate electron affinity (EA) [17]. The difference between the lowest neutral state energy of a molecule and the lowest state energy of its corresponding negative ion is defined as the EA [18]. It was calculated that the EA of compound II was weaker than those of compounds I and III, but the IP was higher. Moreover, the polarizability of compound II was calculated as the lowest, but  $\Delta E$  to be the highest. The HOMO-LUMO surfaces and electrostatic potential (ESP) maps of the compounds are given in Figure 3. Furthermore, Electronegativity ( $\chi$ ) and Chemical hardness ( $\eta$ ) values of the compounds were also calculated. Electronegativity, which is the measure of the power of an electron or group of atoms to attract electrons towards itself [19], is a very useful tool for understanding chemical reactivity. Electronegativity is given by  $\chi = -(E_{\text{HOMO}} + E_{\text{LUMO}})/2$ . The chemical hardness measures the resistance of an atom to a charge transfer [20] and it is given by the equation  $\eta = (E_{\text{HOMO}} - E_{\text{LUMO}})/2$ , where  $E$ ,  $N$  and  $V$  are the energy, number of electrons and the constant external potential, respectively.

**Table 1:** Calculated electronic parameters of the compounds I-III.

Comp.	$E$ (au)	$E_{\text{HOMO}}$ (eV)	$E_{\text{LUMO}}$ (eV)	$\Delta E$ (eV)	$\eta$ (eV)	$\chi$ (eV)	$\alpha$ (au)	$\mu$ Debye
I	-2504.601	-6.742	-2.415	4.327	2.164	4.579	225.4	0.00
II	-2543.926	-7.14	-1.683	5.458	2.729	4.412	216.4	2.29
III	-2735.738	-6.332	-2.436	3.896	1.948	4.384	325.0	0.00

$E$ : Energy,  $\Delta E$ :  $E_{\text{LUMO}} - E_{\text{HOMO}}$ ,  $\eta$ : Chemical Hardness,  $\chi$ : Electronegativity,  $\alpha$ : Polarizability,  $\mu$ : Dipole moment



**Fig 3:** HOMO-LUMO surfaces and ESP maps of compounds I-III.

#### 3.1. Spectral analysis

Theoretical and experimental IR results showed compatibility with each other. However, as the intermolecular interactions were not taken into account in the theoretical processes, the calculated vibrations were obtained higher than the experimental results. The N-H stretching peaks of the compounds were assigned at 3170-3156  $\text{cm}^{-1}$  and the corresponding theoretical values were 3562-3559  $\text{cm}^{-1}$ . In our study, aliphatic C-H peaks of the compounds were observed

that 3016-2937  $\text{cm}^{-1}$ , and at 1496-1547  $\text{cm}^{-1}$  in the calculation. The C=O peaks were observed in the range of 1712-1704  $\text{cm}^{-1}$  (theoretically 1749-1746  $\text{cm}^{-1}$ ), while C-N peaks were in the range of 1640-1560  $\text{cm}^{-1}$  (theoretically 1527-1461  $\text{cm}^{-1}$ ). The aromatic C-H peaks of Compound III were experimentally 3027  $\text{cm}^{-1}$  and theoretically 3172  $\text{cm}^{-1}$ . Experimental and theoretical IR spectrum data are presented in more detail in Table 2.



**Table 2:** Experimental and calculated IR results.

	Comp.	V(NH) Stretching/Bending	V(aromatic C-H)	V(aliphatic C-H)	V(C=O)	V(C=N)
Exp.	I	3156	-	3016, 2937	1712	1560
	II	3169	-	2938	1700	1640
	III	3170	3027	2940	1704	1573
Calc.	I	3559 / 1551	-	3101	1749	1461
	II	3562 / 1565	-	3101-3055	1749, 1749	1527, 1509
	III	3561 / 1558	3172	3100	1746	1493

The  $^1\text{H-NMR}$  spectra of compounds are obtained in  $d_6$ -DMSO and TMS using as a internal standards, and obtained data are given in Table 3. Theoretical data are good agreement with the experimental values. The N-H protons of all compounds were observed at 13.8-12.9 ppm in the experiment as a singlet peak, and theoretically at 10.33-10.15 ppm. The aromatic protons of compound III were observed at 8.05 ppm (theoretically at 9.02 and 8.31 ppm). Experimental  $^1\text{H-NMR}$

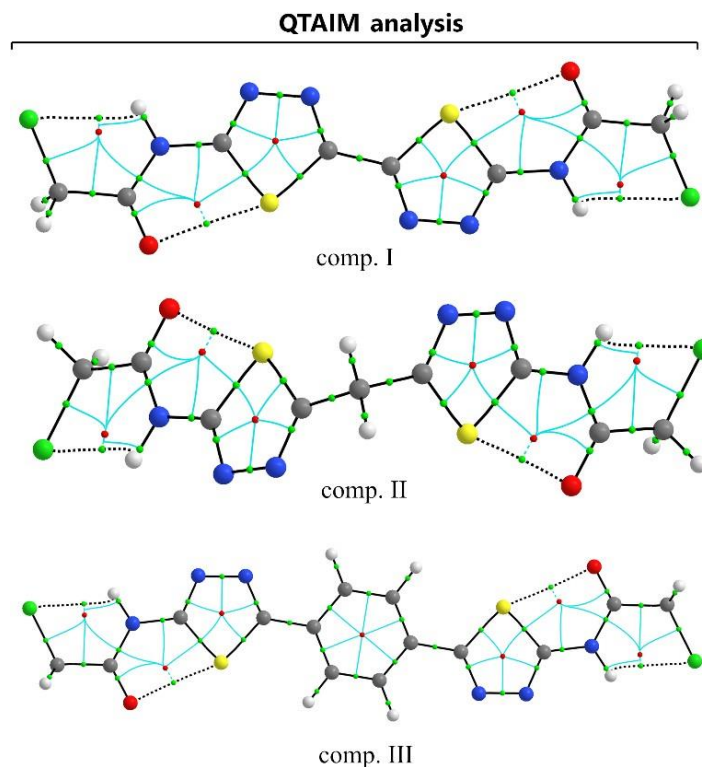
spectra of compounds showed that, for compound I,  $-\text{CH}_2\text{-Cl}$  protons gave peaks between 4.52 and 4.00 ppm, as the compounds II and III gave 4.46 and 4.51 ppm, respectively. The theoretical results were between 4.69-4.60 ppm in the form of a singlet. The C-H proton chemical shift, for compound II, was experimentally obtained as 4.09 ppm and 5.06 ppm as theoretically.

**Table 3:** Theoretical  $^1\text{H NMR}$  results.

	Comp.	(s, 4H, $-\text{CH}_2\text{-Cl}$ protons)	(2H, $-\text{NH}$ -protons)	(s, 2H, $-\text{CH}_2$ -protons)	(s,4H,aromatic protons)
Exp.	I	4.52-4.50	13.8, 13.2	-	-
	II	4.46	13.6, 12.9	4.09	-
	III	4.51	13.5, 13.2	-	8.05
Calc.	I	4.69	10.33	-	-
	II	4.60	10,15	5.06	-
	III	4.68	10.26	-	9.02, 8.31

For a detailed analysis of intramolecular interactions, Bader's QTAIM analysis was used on optimized structures. The topological parameters including the bond critical points (BCP), ring critical points (RCP), delocalization index (DI), ellipticity of the bond ( $\epsilon$ ), the total electron energy density at

BCP ( $H_{\text{BCP}}$ ), the local kinetic energy density ( $G_{\text{BCP}}$ ) and the local potential energy density ( $V_{\text{BCP}}$ ) were calculated. The results are given in Table 4. The dashed lines indicate the interactions of the respective atoms.

**Fig 4:** QTAIM visualisation of compounds I-III; green points: BCPs, red points: RCPs.

**Table 4:** Topological parameters of total charge density ( $\rho$ ), delocalization index (DI), ellipticity of the bond ( $\epsilon$ ), potential energy density ( $V_{BCP}$ ), kinetic energy density ( $G_{BCP}$ ) calculated at the B3LYP/cc-pvtz level.

Comp.	Bonding	$\rho$ (au)	DI	$\epsilon$	$G_{BCP}$ (au)	$V_{BCP}$ (au)
I	Cl ... NH	0.016978 <sup>a,b</sup>	517869524 517869521	0.667244 <sup>a,b</sup>	0.013841 <sup>a,b</sup>	-0.011279 <sup>a,b</sup>
	O ... S	0.016983 <sup>a,b</sup>	1202237397 1202240849	0.249257 <sup>a,b</sup>	0.013485 0.249257	-0.011267 <sup>a,b</sup>
II	Cl ... NH	0.016925 <sup>a</sup> 0.016944 <sup>b</sup>	518186954 <sup>a</sup> 517730410 <sup>b</sup>	0.673174 <sup>a</sup> 0.669762 <sup>b</sup>	0.013805 <sup>a</sup> 0.013817 <sup>b</sup>	-0.011243 <sup>a</sup> -0.011257 <sup>b</sup>
	O ... S	0.016688 <sup>a</sup> 0.016686 <sup>b</sup>	1179330391 <sup>a</sup> 1179401487 <sup>b</sup>	0.268259 <sup>a</sup> 0.268152 <sup>b</sup>	0.013236 <sup>a</sup> 0.013235 <sup>b</sup>	-0.011023 <sup>a</sup> -0.011021 <sup>b</sup>
III	Cl ... NH	0.017021 <sup>a,b</sup>	520824095.80 520824095.82	0.660055 <sup>a,b</sup>	0.013872 <sup>a,b</sup>	-0.011316 <sup>a,b</sup>
	O ... S	0.016522 <sup>a,b</sup>	1169446501,6 1169446255,1	0.270832 <sup>a,b</sup>	0.013094 <sup>a,b</sup>	-0.010893 <sup>a,b</sup>

<sup>a</sup> left side of compound, <sup>b</sup> right side of compound (see Figure 4).

#### 4. Conclusion

2-chloroacetamido-5-(2-chloroacetamido-1,3,4-thiadiazolyl)-1,3,4-thiadiazole derivatives were synthesized and characterized by <sup>1</sup>H-NMR, IR and elemental analyses.

Elemental analysis and spectroscopic methods support that the accuracy of synthesized compounds. B3LYP/cc-pvtz method were used for the quantum chemical calculations. QTAIM analysis was used to elucidate the structure of intramolecular interactions.

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