Novel Bis-1,3,4-Thiadiazoles Derivatives: Synthesis, Spectroscopic Characterization, DFT Calculations and Evaluation of their Antimicrobial and Antioxidant Activities

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ABSTRACT

Two new, bis-1,3,4-thiadiazoles derivatives (I and II), were prepared by cyclization reaction of oxalic acid with N-alkyl/allyl thiosemicarbazides and phosphorous oxychloride (POCl3). Then the newly prepared products screened for their antimicrobial and antioxidant activities. The biological activity results shown that tested compounds exhibited effective antibacterial activity against six different bacteria. However, the compound II demonstrated greater ABTS+ scavenging ability. The characterization of the synthesized molecules was done by FT-IR, 1H NMR, 13C NMR spectroscopic methods and elemental analysis. Moreover, the experimental FT-IR and NMR spectra of the molecules were compared with the results calculated at the cc-pvtz, 6-311g(2d,2p), and 6-311+g(2d,2p) levels of theory. The effect of substituted groups on the spectral and electronic properties of the compounds was investigated. NCI and QTAIM analyses were performed to examine the effects of allyl group and intramolecular interactions on σ and π bonds. How the N-H bonds of the substituted groups affect the bond degrees was investigated using Fuzzy, Laplacian and Mayer approaches, and the relationship of the data with the antioxidant properties of the compounds was examined. In addition, the relationship between bond stretching force constant and intrinsic bond strength index, electron density, and delocalization index for some bonds was revealed.

Keywords: Bis-thiadiazoles, Biological activity, DFT, IBSI, Force constant (FC).

Research Article

Introduction

Thiadiazoles are five-membered heterocyclic compounds consisting of two nitrogen and one sulfur atom in the ring. Compounds having thiadiazole moiety possess medicinal characteristics and unique biological activity due to their strong aromaticity. When different functional groups that interact with biological receptors are added to this ring, moieties compounds with extraordinary properties are obtained. Thiadiazoles and their derivatives have various biological and medicinal characteristics such as antimicrobial [1], anticancer [2], antibacterial, antiviral [3], antifungal [4], antitubercular [5], antihypertensive [6], anticonvulsant [7], diuretic [8], antioxidant [9] properties. They are also used for various applications such as pesticides, herbicides, and insecticides in the agriculture field [10].

Accordingly, we have synthesized two new bis-1,3,4-thiadiazoles derivatives and investigated their antimicrobial and antioxidant characteristics. In vitro antimicrobial activity tests on the synthesized two new compounds were performed against six different bacteria and two fungi using the microdilution method (MIC). The results of the biological activity analyses reveal that these synthesized two new compounds show effective antibacterial activity against B. subtilis, S. aureus, E. faecalis, E. coli, K. pneumoniae, and P. aeruginosa. Besides, the antioxidant activities of these molecules were explored by employing ABTS radical scavenging method.

In the theoretical approaches, DFT calculations of the compounds were made first and the data were compared with the experimental results. Subsequently, the effects of intramolecular interactions on IR and NMR spectra were revealed. Quantum theory of the atom in the molecule (QTAIM) [11, 12] and non-covalent interaction (NCI) [13] analyses were performed to examine the relationship between intramolecular interactions, bond orders, and spectral data, depending on the electron charge distribution on the bonds. Furthermore, the relationship between properties such as bond length, Laplacian bond order (LBO), Fuzzy bond order (FBO), Mayer bond order (MBO) and bond stretching force constant (FC), Intrinsic bond strength index (IBSI), electron density (Rho) at the bond critical point (BCP), and DI were analyzed.

Materials and Methods

Instrumentation

All the reagents and solvents were acquired from Sigma Aldrich or Merck Chemical Company and were used without further purification. The melting points were...
determined using a Stuart SMP30 apparatus. Eurovector EA3000 elemental analyser was used to define elemental analysis. Infrared spectra were recorded with a Bruker Alpha Fourier transform FT-IR spectrometer. ¹H and ¹³C-NMR spectra were registered using a Bruker Avance DPX-400 spectrophotometer (400 and 101 MHz) in DMSO-d₆.

**General Synthesis Procedure for Novel bis-1,3,4-thiadiazoles (I and II)**

The mixture of oxalic acid (n mol) and N-alkyl/allyl thiosemicarbazide (2n mol) was chilled in a refrigerator and phosphorous oxychloride (3n mol) was added drop-wise by stirring. Then, refluxing was continued 90 °C for 4 h. After completion of the reaction, the mixture was cooled to room temperature, poured into ice-cold water with stirring, and then neutralized with ammonia. The final product was filtered, washed with water, and crystallized in a suitable solvent. These novel thiadiazoles were prepared according to the procedure [14] in Scheme 1.

![Scheme 1. Synthetic route for new bis-1,3,4-thiadiazoles compounds.](image)

**Detection of Antimicrobial Activity**

The antimicrobial activities were tested against the following eight microorganisms including Gram-staining-positive (*B. subtilis* ATCC 6633; *S. aureus* ATCC 25923; *E. faecalis* ATCC 29212), Gram-staining-negative (*E. coli* ATCC 25922; *K. pneumoniae* ATCC 70060; *P. aeruginosa* ATCC 27853) bacteria and fungi (*A. niger* ATCC 16404; *C. albicans* ATCC 1023). The antimicrobial screening activity was determined in nutrient broth for all the bacterial strains after 24 h of incubation at 37 °C. Fungi were maintained in nutrient broth after incubation for 24 h at 28 °C. Bacterial and fungi cells were homogenized in nutrient broth. The turbidity of bacterial and fungi suspensions was set at a concentration of approximately 10⁶ cells/ml. Only inoculated broth was used as controls. 100 mL suspension of each microorganism and 100 mL suspension of compound tested were added into the wells. The microplate with no growth of microorganism was recorded to represent the MIC enounced in μg/mL.

**Measurements of Antioxidant Activity**

ABTS⁺ radical scavenging activity of the samples were measured spectrophotometrically at 734 nm on the results of the oxidation of 2,2-azinobis-(3-ethylbenzothiozine-6-sulfonic acid) ammonium salt (ABTS²⁻) with of peroxydisulphate based on form ABTS⁺ radical and butylated hydroxyanisole (BHA), tert-butylhydroquinone (TBHQ) and α-tocopherol standards were used [16, 17]. IC₅₀ (μg/mL) values of the results were calculated.

**Theoretical Processes**

The ground state optimized geometries of the compounds and the calculations of the electronic parameters of these geometries were performed using the Gaussian 09 software package [18]. Becke three-parameter hybrid functional combined with Lee-Yang-Parr correlation functional (B3LYP) was used in the Kohn-Sham DFT [19, 20] calculations. Calculations were performed at the cc-pvDZ, 6-311g(2d,2p), and 6-311++g(2d,2p) levels of the theory without any geometry restrictions. The optimized geometries with minimum energy correspond to the actual minimum points on the potential energy surface, and no imaginary frequencies were observed in the calculations.

Frontier molecular orbital (FMO) energy eigenvalues and chemical reactivity parameters such as HOMO-LUMO energy gap, chemical hardness, electronegativity, electrophilic index depending on these eigenvalues were also calculated in the gas phase using the aforementioned basis sets.

IR calculations were performed in the gas phase for all three basis sets mentioned. NMR calculations were performed with the Gauge-Including Atomic Orbital (GIAO) approach, using conductor-like polarizable continuum model (CPCM) in the DMSO phase in accordance with the experiment. The calculated TMS values of ¹H and ¹³C NMR for cc-pvDZ, 6-311g(2d,2p), and 6-311++g(2d,2p) basis sets are 31.7450 and 184.4735; 31.8181 and 183.8257; 31.8149 and 183.7737, respectively.

QTAIM analyses, NCIs, electron density distributions, FBO and LBO, and IBSI [21, 22] calculations of the certain bonds were performed using Multiwfn [23] software. Bond stretching force constant (FC) were calculated separately with the mentioned three basis sets using Forcegen [24] software.
Results and Discussion

Analytical Data

Table 1. Analytical data for the synthesized compounds.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound’s Names</th>
<th>M. P. (°C)</th>
<th>Yields (%)</th>
<th>Colour</th>
<th>C%</th>
<th>H%</th>
<th>N%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>N5,N5’-dimethyl-[2,2’-bi(1,3,4-thiadiazole)]-5,5’-diamine</td>
<td>&gt;320</td>
<td>72</td>
<td>Light</td>
<td>31.57/31.69</td>
<td>3.53/3.55</td>
<td>36.81/36.76</td>
</tr>
<tr>
<td>II</td>
<td>N5,N5’-diallyl-[2,2’-bi(1,3,4-thiadiazole)]-5,5’-diamine</td>
<td>230-232</td>
<td>83</td>
<td>Yellow</td>
<td>42.84/42.93</td>
<td>4.31/4.34</td>
<td>29.98/29.92</td>
</tr>
</tbody>
</table>

FT-IR Spectral Analysis

In the IR spectra data of the compounds, the corresponds to carboxylic acid (-COOH) absorption bands of the starting material were not observed at approximately 3500-2800 cm⁻¹. Furthermore, asymmetric and symmetric stretching absorption bands of the NH₂ group were not appeared around 3400–3150 cm⁻¹. For compounds I and II, the peaks of the -NH were showed at 3188 and 3189 cm⁻¹, the -C=N stretching frequencies of thiadiazole ring were observed at 1556 and 1576 cm⁻¹; the -C=N stretching frequencies were showed at 1158 and 1143 cm⁻¹; the -C=S signals of aryl ring were observed at 697 and 691 cm⁻¹, respectively as shown in Figure 1. These frequency values of the target compounds were nearly in accordance with the literature [25-27]. The IR stretching vibration frequencies of the compounds are summarized in Table 2.

Table 2. Experimental and calculated IR values of the target compounds (cm⁻¹).

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Comp.</th>
<th>-NH</th>
<th>Aliph. CH</th>
<th>C=N</th>
<th>C-N</th>
<th>C-S</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3188</td>
<td>2978-2863</td>
<td>1556</td>
<td>158</td>
<td>697</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>3189</td>
<td>2928-2827</td>
<td>1576</td>
<td>1143</td>
<td>691</td>
<td></td>
</tr>
<tr>
<td>BS1</td>
<td>I</td>
<td>3647.7</td>
<td>3131.4-3021.9</td>
<td>1476.7</td>
<td>1560.4</td>
<td>731.8</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>3621.9</td>
<td>3216.2-3007.8</td>
<td>1476.9</td>
<td>1537.2</td>
<td>730.5</td>
</tr>
<tr>
<td>BS2</td>
<td>I</td>
<td>3641.3</td>
<td>3139.8-3026.1</td>
<td>1478.0</td>
<td>1558.1</td>
<td>727.5</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>3621.1</td>
<td>3218.7-3014.3</td>
<td>1478.2</td>
<td>1534.0</td>
<td>725.9</td>
</tr>
<tr>
<td>BS3</td>
<td>I</td>
<td>3649.1</td>
<td>3140.0-3032.5</td>
<td>1472.7</td>
<td>1553.5</td>
<td>728.1</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>3621.8</td>
<td>3221.3-3020.2</td>
<td>1472.7</td>
<td>1526.9</td>
<td>726.8</td>
</tr>
</tbody>
</table>

BS1: B3lyp/cc-pvtz, BS2: B3lyp/6-311g(2d,2p), BS3: B3lyp/6 311++g(2d,2p).

H NMR Spectral Analysis

The ¹H NMR spectra of the compounds are given in Figure 2. For compound I, the proton signal of –NH was detected as a quartet at 8.13-8.09 ppm. The methoxy group (OCH₃) peak on the aryl ring was resonated as a doublet at 2.95-2.94 ppm. For compound II, the proton...
Signal of –NH was detected as a triplet at 8.37–8.35 ppm. The methylene (–N–CH₃) group peak on the aryl ring was observed as a triplet at 4.00–3.97 ppm. The methine (–C=CH=) group peak on the aryl ring was observed as a multiplet at 5.96–5.89 ppm. The methylene (–C=CH₂) group peak on the aryl ring was appeared as a multiplet at 5.30–5.14 ppm. DMSO-d₆ and water in DMSO (HOD, H₂O) signals are shown around at 2.00, 2.50 (quintet) and 3.30 ppm, respectively [28]. These observed are compatible with the literature [25-27]. The chemical shift values are presented in Table 3.

Table 3. ¹H NMR values of the compounds (δ, ppm, in nDMSO-d₆).

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Comp.</th>
<th>NH</th>
<th>H1</th>
<th>H2</th>
<th>H3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>8.13–8.09 (q)</td>
<td>2.95–2.94 (d)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>8.37–8.35 (t)</td>
<td>4.00–3.97 (t)</td>
<td>5.96–5.89 (m)</td>
<td>5.30–5.14 (m)</td>
</tr>
<tr>
<td>BS1</td>
<td>I</td>
<td>5.17</td>
<td>3.17, 3.01</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>4.75</td>
<td>4.76, 3.78</td>
<td>6.41</td>
<td>5.75, 5.58</td>
</tr>
<tr>
<td>BS2</td>
<td>I</td>
<td>4.97</td>
<td>3.23–2.92</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>4.60</td>
<td>4.73, 3.71</td>
<td>6.37</td>
<td>5.73, 5.58</td>
</tr>
<tr>
<td>BS3</td>
<td>I</td>
<td>5.19</td>
<td>3.27–3.03</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>4.76</td>
<td>4.69, 3.82</td>
<td>6.52</td>
<td>5.81, 5.64</td>
</tr>
</tbody>
</table>

d: doublet, t: triplet, q: quartet, m: multiplied.
BS1: B3lyp/cc-pvtz, BS2: B3lyp/6-311g(2d,2p), BS3: B3lyp/6-311++g(2d,2p).

Figure 2. ¹H NMR spectra of compounds I and II.


**13C NMR Spectral Analysis**

The $^{13}$C NMR spectra of the compounds I and II recorded in DMSO-d$_6$ showed 3 and 5 different carbon atoms resonances respectively, in good agreement with the proposed structure as shown in Figure 3. The chemical shift results are given in Table 4.

In compound I, the carbon signals (C1 and C2) of thiadiazole ring were detected at 148.79 and 169.74 ppm, respectively. The C2 carbon (C2-NH) is shifted down-field (high values, $\delta$) at 169.74 ppm due to the presence of amino group (NH). The carbon atom of methyl (N-CH$_3$) group on the aryl ring was observed at 31.88 ppm.

For compound II, the carbon signals (C1 and C2) of thiadiazole ring were detected at 149.04 and 168.90 ppm, respectively. The C2 carbon (C1-NH) is shifted down-field (high values, $\delta$) at 168.90 ppm due to the presence of amino group (NH). The carbon atom of methyle (N-CH$_2$) group on the aryl ring was observed at 47.45 ppm. The carbon atom of methine group (-CH=) was detected at 134.44 ppm. The methylene (–C=CH$_2$) carbon atom was resonated at 116.99 ppm. These spectroscopic data are in agreement with values previously reported in the literature [25].

**Table 4. $^{13}$C NMR values of the title compounds ($\delta$, ppm, in DMSO-d$_6$)**

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Comp.</th>
<th>C$_1$</th>
<th>C$_2$</th>
<th>C$_3$</th>
<th>C$_4$</th>
<th>C$_5$</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>148.79</td>
<td>169.74</td>
<td>31.88</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>149.04</td>
<td>168.90</td>
<td>47.45</td>
<td>134.44</td>
<td>116.99</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BS1</td>
<td>I</td>
<td>158.99</td>
<td>175.84</td>
<td>32.62</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>159.52</td>
<td>175.83</td>
<td>52.41</td>
<td>142.67</td>
<td>124.91</td>
</tr>
<tr>
<td>BS2</td>
<td>I</td>
<td>157.97</td>
<td>175.55</td>
<td>32.58</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>158.27</td>
<td>175.04</td>
<td>52.22</td>
<td>142.19</td>
<td>125.02</td>
</tr>
<tr>
<td>BS3</td>
<td>I</td>
<td>160.08</td>
<td>177.47</td>
<td>32.67</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>160.64</td>
<td>177.30</td>
<td>52.59</td>
<td>143.81</td>
<td>125.88</td>
</tr>
</tbody>
</table>

**Antimicrobial Evaluation**

Antimicrobial activity tests of the compounds were performed against six different bacteria and two fungi using the microdilution method (MIC). In this study based on serial dilution, MIC value for DMSO used as a control was found to be > 4000 μg/mL. When the effect of the one compound on bacteria is examined, it is seen that MIC values are 1000 μg/ml for B.subtilis, 1000 μg/ml for S.aureus, 500 μg/ml for E.faecalis, 500 μg/ml for E.coli, 1000 μg/ml for K.pneumonia and 1000 μg/ml for P.aeruginosa. Likewise, when the effect of the second compound on bacteria is examined, it is seen that MIC values are 250 μg/ml for B.subtilis, 500 μg/ml for S.aureus, 500 μg/ml for E.faecalis, 125 μg/ml for E.coli, 250 μg/ml for K.pneumonia and 1000 μg/ml for P.aeruginosa. Two new compounds synthesised did not show antifungal activity against A.niger and C.albicans. The MIC values were showed in Table 5.
Table 5. The minimum inhibition concentrations (MIC’s) of the tested compounds.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Gram-staining-positive</th>
<th>Gram-staining-negative</th>
<th>Fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B. subtilis</td>
<td>S. aureus</td>
<td>E. faecalis</td>
</tr>
<tr>
<td>Compound I</td>
<td>1000</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>Compound II</td>
<td>250</td>
<td>500</td>
<td>125</td>
</tr>
</tbody>
</table>

**Compound I**: N5,N5’-dimethyl-[2,2’-bi(1,3,4-thiadiazole)]-5,5’-diamine;  
**Compound II**: N5,N5’-diallyl-[2,2’-bi(1,3,4-thiadiazole)]-5,5’-diamine.

In 2009 Demirbaş et al. [29] conducted a similar study. They synthesized some new 1,3,4-thiadiazol-2-ylmethyl-1,2,4-triazole derivatives and found them to moderate activity against all the tested microorganisms (E. coli, Y. pseudotuberculosis, P. aeruginosa, E. faecalis, S. aureus, B. cereus) except C. tropicalis and C. albicans. Muglu et al. (2018) [14] synthesized new 1,3,4-thiadiazole compound and all the tested compounds showed good antimicrobial activities against S. aureus.

**Antioxidant Evaluation**

The antioxidant activities of the samples (I and II) were determined through the ABTS⁺ scavenging activity test. In the present study, the ABTS⁺ scavenging activity results of the tested compounds have shown in Table 6. The compound II (IC₅₀ value of 68.93±0.79 µg/mL) was found to be the most active with comparison to compound I. It was even found to have activity close to the α-tocopherol standard. This effect may be owing to its role of the allyl group (-CH₂CH=CH₂) and activating the bithiadiazole rings [30]. In compound I, the methyl group (-CH₃) at position 2,2’ of the bis- 1,3,4-thiadiazole nucleus is substituted whereas in II this has an allyl group. This indicates that the allyl group on the bithiadiazole rings enhances the activity. As result, the ABTS⁺ scavenging activity was significantly ameliorated when the methyl groups were replaced by allyl groups. According to the IC₅₀ values, the antioxidant capacities of the tested compounds were observed lower than that of the standards products. The ABTS⁺ scavenging effect of the title compounds and standards decreased in the following order: TBHQ> BHA> α-tocopherol> II> I.

**Theoretical Calculations**

Calculations reveal that the allyl group decreases the $E_{HOMO}$ and $E_{LUMO}$ energies of the compound while increasing the energy gap $\Delta E=E_{LUMO}-E_{HOMO}$ (Figure 4).

Figure 4. HOMO-ESP and LUMO surface of comp. I (BS3). The graph shows the HOMO-LUMO energy eigenvalues and Energy gap, $\Delta E$, values of the compounds calculated by the basis sets BS1, BS2, and BS3.

In this context, we can say that compound I is more reactive. In parallel, the chemical hardness of compound I is lower. Contrary to these data, compound II was both more electronegative and had higher electrophilic index (Figure 5). However, there are many variables that dominate chemical reactions, and such static variables of the whole molecular structure can be partially helpful in predicting reaction mechanisms, but it can be misleading.

Table 6. IC₅₀ values for the compounds.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>ABTS radical scavenging activity, IC₅₀* (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound I</td>
<td>103.26±1.39</td>
</tr>
<tr>
<td>Compound II</td>
<td>68.93±0.79</td>
</tr>
<tr>
<td>BHA</td>
<td>33.91±2.09</td>
</tr>
<tr>
<td>TBHQ</td>
<td>32.09±2.02</td>
</tr>
<tr>
<td>α-tocopherol</td>
<td>64.86±3.28</td>
</tr>
</tbody>
</table>

Values are expressed as means (n = 3).  
*IC₅₀ = the concentration (µg/mL) exhibiting 50% inhibition of ABTS radical.  

These results further demonstrated that the structure of the products and electronic effects of groups/substituents in the structures plays an important role of antioxidant activity [31].
to determine the reactivity of a compound in a particular reaction by considering these values. Certain reaction
mechanisms are directly related to specific local regions of
the compounds. For example, the antioxidant behavior of
synthesized thiadiazole derivative compounds is closely
dependent on both the conformational and electronic
properties of the N–H bond. Although these are not the
only parameters that determine the antioxidant reactions,
an analysis of the static and dynamic parameters of the N–
H bond is a useful method to predict the antioxidant
property of the compound. Intramolecular interactions
are among the factors that affect bond dissociation
energy, and in polyatomic molecules, treating two atoms
in a particular bond in isolation from other bonds and
atoms can yield false results. In addition, bond strengths
(or bond force constants) are strongly dependent on bond
order of the bonded atoms and molecular conformation,
which affects intramolecular interactions and thus charge
distribution. NCI analysis shows that the non-covalent
interaction of the allyl moiety with the thiadiazole region
is stronger than that of the methyl group (Figure 6). This
may result in compound II retaining its current
conformation more than compound I. In addition, both
the allyl group and intramolecular interactions affected
the electronic data of the bonds in the reactive region in
parallel in terms of IBSI, FC, Rho, and DI variables.

Although the electronic variables considered for
compound II were generally compatible with each other
for the bonds of interest, the FBO and DI values did not
change in parallel with the other variables, especially in
the N–H and C–S bonds (Figure 7). FC values of sigma
bonds B1, B3, and B5 were calculated lower than FC of
electronnegative atom groups and π bond (H2C=CH–), but
there is no linear relationship between FCs of σ and π
bonds.

Although the prediction of antioxidant properties of
the target compounds has difficulties due to the dynamic
nature of the reactions, the bond stretching FC data reveal
that compound II will exhibit higher antioxidant
properties. It has been determined that the Allyl group
weakens the N–H bond (the bond length also increased
from 1.004 to 1.006 Å), that is, it causes bond strength
reducing effects and therefore reduces the bond
dissociation energy.
Furthermore, it was observed that the electron density of the N–H bond, which plays an active role in antioxidant reactions, in BCP decreased (0.352 e/Bohr³ for compound I, 0.350 e/Bohr³ for compound II), and accordingly, both IBSI and bond stretching FC values also decreased (IBSI and FC values for compound I were calculated as 0.449 and 431.666 kcal/mol Å², respectively; 0.446 and 420.014 kcal/mol Å² for compound II). It can be said that this decrease in the bond strength and force constant of N–H bond results in easier breakage of the bond and therefore an increase in antioxidant properties. It is also a useful tool as the degree of a bond is usually related to the number of electrons forming the bond, and hence the bond strength; and overall, greater proportionality between bond strength and LBO emerged compared to the Fuzzy and Mayer approaches. MBO calculations increased the degree of =N= bond above 2 by adding the diffuse functions to the calculations. Especially adding the diffuse functions to the calculations may give wrong results in terms of MBO calculations. Moreover, there is a close relationship between IBSI and bond stretching FC, and it can be predicted that these parameters can be used to describe the chemical reactivity of compounds with desirable reactive sites.

Conclusions

In this study, new bis-1,3,4-thiadiazole compounds were prepared in excellent yields of 72–83%. The compounds were characterized by IR, ¹H NMR, ¹³C NMR and elemental analysis. In the next step, the compounds screened for their in vitro for their antimicrobial and antioxidant activities. The results of microbial activity studies show that the two synthesized compound exhibited effective antibacterial activity against B. subtilis, S. aureus, E. faecalis, E. coli, K. pneumoniae, and P. aeruginosa. Among the tested molecules, compound II exhibited greater ABTS⁺ radical scavenging ability. This effect can be explained with in presence of the allyl group in the structures. Therefore, the new two synthesized compounds can be considered as bioactive substances for pharmacological and medical applications.

Although HOMO-LUMO energy eigenvalues of molecules and parameters such as energy gap, chemical hardness, and electronegativity obtained from these eigenvalues are useful, they are insufficient to explain the reaction mechanisms in which local regions are reactive because they are obtained from the molecular orbital approach. Calculations on selected bonds of compounds reveal that parameter such as LBO, IBSI, and bond stretching FC can be helpful tools in understanding antioxidant reaction mechanisms. An inverse relationship was observed between the IBSI and bond stretching FC values of the N–H bond and its reactivity in antioxidant reactions, that is, the IBSI and FC values of the N–H bond of the compound decreased while the antioxidant property increased. QTAIM analysis plays an especially important role in correlating the charge densities (Rho) of the bonds in the BCP and the DI data with the strength of the bond. By which atomic groups the bonds are formed affects the way these analyses are used. LBO calculations yielded more consistent results for bonds with electronegative atoms, and a close relationship was also observed between LBO, IBSI and FC.

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Conflicts of interest

The authors declare that they have no conflict of interest.

References


