Synthesis, Characterization and biological activity of new derivatives of 1,3,4-thiadiazol with some transitions metal ion


Department of chemistry, College of Science, Thi-Qar University, Iraq

Abstract

In the present study we prepared derivatives of 2,5-diacylhydrazino-1,3,4 thiadiazole and its, Cd (II) and Ni (II) complexes, compound (L₃) 2-cyano-N-(5-hydrazinyl-1,3,4-thiadiazol-2-ylyl)acetyhydrazide, compound (L₃) 2,2'-[1,3,4-thiadiazole-2,5-diyldi(hydrazine-2,1-diy)]bis(1,3-benzothiazole), all prepared compounds were diagnosed by spectra of H¹-NMR, mass, Fourier transform infrared (FTIR), as well as magnetic susceptibility, micro- elemental analysis(CHN) and molar electrical conductance measurements. The conductivity data of the complexes Confirmed their non-electrolytic. The magnetic studies suggest an tetrahedral and square planer geometry of the complexes, From results it was suggested square planer geometry for Cd(II) complex and tetrahedral geometry for Cd (II) complexes. The derivatives and its complexes has shown moderate to good activity against gram-positive bacteria (Staphylococcus aureus), gram-negative bacteria (Escherichia coli) when compared with standard antibiotic gentamycin.

Keywords: thiadiazole, 1,3,4-thiadiazole, synthesis, biological activities

INTRODUCTION

Thiadiazoles are an important class of heterocyclic compounds that exhibit diverse applications in organic synthesis, pharmaceutical and biological applications. Thiadiazole is a five-membered unsaturated ring structure having molecular formula C₂H₂N₂S [1], It is a clear to yellowish liquid with a pyridine like odor , It is soluble in alcohol and ether and slightly soluble in water. Thiadiazole is a five-membered unsaturated ring structure with molecular formula C₂H₂N₂S [1]. Thiadiazole is a polar symmetric molecule, the value of The dipole moment is equal 3.25D, its exhibiting pseudo aromatic character. Actually 1,3,4-thiadiazole molecule does not display a true aromatic behavior as do benzene, pyridine and thiophene [6]. 1,3,4-thiadiazole derivatives have demonstrated a broad spectrum of biological properties in both pharmaceutical and agrochemical fields. They have known to exhibit diverse biological activities such as Analgesic and Anti-inflammatory Activity [7-9], antibacterial and Antifungal [10], Antitubercular [11], Anticancer [12], Antidiabetics [13], Acaricidal [14]. They are also useful as oxidation inhibitors [15], dyes [16], anti-corrosion agents [17] and Liquid crystalline [18].

EXPERIMENTAL

Synthesis of 1,3,4-thiadiazole-2,5-dithiol (A)

A mixture of (8 ml,0.1mol) of hydrazine and (11.2gm,0.2 mol) potassium hydroxide was dissolved in (50ml) absolute ethanol, to this solution (15.2 ml, 0.2mol) of carbon disulfide was added. The resulting mixture was heated under reflux for (15 hours).The resultant mixture was concentrated, and carefully acidified with hydrochloric acid HCl(10%) to give yellow precipitate. The crude product was filtered and washed and recrystallized by ethanol absolute to give the desired product (A) , melting point 165°C, yield 83% [19]

Synthesis of 2,5-dihydrazino-1,3,4-thiadiazole (B):

2,5-dimercapto-1,3,4-thiadiazole (A) (10 gm,0.06 mol) dissolved in ethanol, hydrazine hydrate (8ml,0.13 mol) was added , and the mixture was then refluxed for (20 h), the mixture was evaporated to half volume , Filtered the resulting solid which was separated out on cooling and recrystallized from ethanol to give the desired product (B), the solid (B) was pale white, melting point 198°C, yield 77% [19].

Synthesis of 2-cyano-N¹-(5-hydrazinyl-1,3,4-thiadiazol-2-yl)acetohydrazide (L₁)

A mixture of (A) (5 gm, 0.03 mol) in absolute ethanol (50 mL) and (ethyl cyanoacetate) (3.6gm,0.03 mol) was refluxed (18 h). The product was isolated and recrystallized from ethanol to get yellow ligand(L₁) melting point 128°C, yield 79%.

Synthesis 2,2'-[1,3,4-thiadiazole-2,5-diyldi(hydrazine-2,1-diy)]bis(1,3-benzothiazole)(L₂)

The ligand(L₂) was synthesized by condensation of 2,5-dihydrazino-1,3,4-thiadiazole (B) and 2-Mercaptobenzothiazole in ethanol absolute (50ml), the product was isolated and recrystallized from tetrahydrofuran (THF), the solid (L₂) was light orange crystals, melting point 137°C, yield 66%.

Keywords: thiadiazole, 1,3,4-thiadiazole, synthesis, biological activities
The Ni(II), Cd(II) complexes were prepared by refluxing the respective hydrated metal chloride (0.14 gm, 9 mmol) and (0.21 gm, 9 mmol) in 15 ml ethanol with 50 ml of an ethanolic solution of the [L1] (0.2g, 9 m mol) for 3 hr. The resultant solids which separated were filtered, washed with ethanol and dried.

Preparation of L2 complexes
The Ni(II), Cd(II) complexes were prepared by refluxing the respective hydrated metal chloride (0.214 gm, 9 mmol) and (0.21 gm, 9 mmol) in 15 ml ethanol with 50 ml of an ethanolic solution of the [L2] (3.22g, 0.01mol) for 3 hr. The resultant solids which separated were filtered, washed with ethanol and dried.

RESULTS & DISCUSSION
The physical properties of ligands and its complexes are presented, magnetic susceptibility, and molar electrical conductivity in table 1. The Elemental microanalysis CHN shown in table 2.

<table>
<thead>
<tr>
<th>No</th>
<th>Compound</th>
<th>Molecular formula</th>
<th>M. wt</th>
<th>Color</th>
<th>( \Delta )Scm(^2) mol(^{-1})</th>
<th>Mel. Point °C</th>
<th>( \mu_{\text{eff}} ) B.M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>C(_5)H(_7)N(_7)OS</td>
<td>213</td>
<td>Black</td>
<td>-----</td>
<td>130-132</td>
<td>-----</td>
</tr>
<tr>
<td>2</td>
<td>[Ni(L1)Cl]_2</td>
<td>Ni(C(_5)H(_7)N(_7)OS)Cl(_2)</td>
<td>342</td>
<td>Brown</td>
<td>16</td>
<td>292-290</td>
<td>0.5</td>
</tr>
<tr>
<td>3</td>
<td>[Cd(L1)Cl]_2</td>
<td>C(<em>{16})H(</em>{12})N(_8)S(_3)Cl(_2)Cd</td>
<td>396</td>
<td>light Brown</td>
<td>14</td>
<td>360 d(^1)</td>
<td>0.83</td>
</tr>
<tr>
<td>4</td>
<td>L2</td>
<td>C(<em>{16})H(</em>{12})N(_8)S(_3)</td>
<td>412</td>
<td>light orange</td>
<td>-----</td>
<td>136-137</td>
<td>-----</td>
</tr>
<tr>
<td>5</td>
<td>[Ni(L2)Cl]_2</td>
<td>C(<em>{16})H(</em>{12})N(_8)S(_3)Cl(_2)Ni</td>
<td>541</td>
<td>light Yellow</td>
<td>8</td>
<td>120-122</td>
<td>0.61</td>
</tr>
<tr>
<td>6</td>
<td>[Cd(L2)Cl]_2</td>
<td>C(<em>{16})H(</em>{12})N(_8)S(_3)Cl(_2)Cd</td>
<td>596</td>
<td>Brown light</td>
<td>18</td>
<td>150-152</td>
<td>0.8</td>
</tr>
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</table>

Table 2. Elemental microanalysis CHN for the ligands

<table>
<thead>
<tr>
<th>Compound</th>
<th>Theoretical</th>
<th>Experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C(%)</td>
<td>H(%)</td>
</tr>
<tr>
<td>L1</td>
<td>28.16</td>
<td>3.28</td>
</tr>
<tr>
<td>L2</td>
<td>46.59</td>
<td>2.9</td>
</tr>
</tbody>
</table>
The FTIR spectrum for L1 shows a characteristic stretching absorption bands at 3474 cm⁻¹, 1624 cm⁻¹, 1457 cm⁻¹, 1280 cm⁻¹ assigned to v(N-H), v(C=O), v(C=N), v(C-O), asymmetrical and symmetrical C-S-C stretching respectively [21].

The FTIR spectrum for L2 shows a characteristic stretching absorption bands at 3259cm⁻¹, 3059 cm⁻¹, 1465 cm⁻¹, 1701 cm⁻¹, 1558 cm⁻¹, 1427 cm⁻¹, 1238 cm⁻¹ assigned to v(N-H), v(C-H), v(C=O) of benzothiazole, v(C=N) of thiadiazole, v(C=C), asymmetrical (C-S-C), symmetrical C-S-C stretching respectively [20-25]. The C=N and N-H stretching vibrations are important to predict the bonding mode of the ligand, these bands were shifted to the high or low frequencies in the spectra of complexes compared with ligand, observed changes are the evidences of complexion mode of the ligand, these bands were shifted to the high or low frequencies respectively [20-25].

The mass spectra of ligand (L1) appeared molecular ion peak at m/z 541 (+), 396 (+) which is in conformity with the molecular mass of the complex. The mass spectrum shows fragment ion peak with loss two chlorine atom at m/z (361,324) due to [Cd(L1)]⁺ and [Cd(L1)]⁻ respectively as shown in Figure (10,11).

The magnetic momentum for each metal complex is listed in Table 3. These magnetic measurements give an idea about the electronic state of the transition metal ion of the complexes and type of ligand. The observed magnetic momentum value of L1Ni (II) complex was 0.5 BM, expected for square planer geometry. The magnetic momentum value was 0.83 BM for L1Cd (II) complex expected for tetrahedral geometry, the value 0.61 BM for L2Ni (II) suggesting square planer geometry while the value 0.8 BM for L2Cd suggesting tetrahedral geometry[25] we conclude that the ligand works as strong ligand (strong field).

The FTIR spectrum of the complex [Ni(L1) Cl2] shows a molecular ion peak at m/z (342) which is equivalent to molecular mass of the complex the complex spectrum shows fragment ion peak with loss two chlorine atom at m/z (306,271) due to [Ni(L1)]⁺ and [Ni(L1)]⁻ respectively. The mass spectrum of the complex [Cd(L1) Cl2] shows a molecular ion peak at m/z (396) which is equivalent to molecular mass of the complex. The complex shows fragment ion peak with loss two chlorine atom at m/z (361,324) due to [Cd(L1)]⁺ and [Cd(L1)]⁻ respectively as shown in Figure (10,11).

The mass spectra of the complexes are shown in Table (3) and figure (1-6). lists the stretching frequency (υ) for some of the characteristics groups exhibited by the (L1-L2) and complexes.

### Nuclear magnetic resonance

The H¹-NMR spectral data for the L1 exhibit a singlet signals at (12.06 ppm, 1H), (5.29 ppm, 4H) and (2.54 ppm, 2H) due to N-H amide protons N-H protons and C-H moment value was 0.83 BM for L1Cd (II) complex expected for tetrahedral geometry, the value 0.61 BM for L2Ni (II) suggesting square planer geometry while the value 0.8 BM for L2Cd suggesting tetrahedral geometry. The observed magnetic momentum value of L1Ni (II) complex was 0.5 BM, expected for square planer geometry. The magnetic momentum value was 0.83 BM for L1Cd (II) complex expected for tetrahedral geometry, the value 0.61 BM for L2Ni (II) suggesting square planer geometry while the value 0.8 BM for L2Cd suggesting tetrahedral geometry.

### Magnetic Susceptibility

The magnetic momentum for each metal complex is listed in Table 3. These magnetic measurements give an idea about the electronic state of the transition metal ion of the complexes and type of ligand. The observed magnetic momentum value of L1Ni (II) complex was 0.5 BM, expected for square planer geometry. The magnetic momentum value was 0.83 BM for L1Cd (II) complex expected for tetrahedral geometry, the value 0.61 BM for L2Ni (II) suggesting square planer geometry while the value 0.8 BM for L2Cd suggesting tetrahedral geometry. The magnetic momentum value was 0.83 BM for L1Cd (II) complex expected for tetrahedral geometry, the value 0.61 BM for L2Ni (II) suggesting square planer geometry while the value 0.8 BM for L2Cd suggesting tetrahedral geometry.

### Molecular Electrostatic Potential (MEP)

Electrostatic potential is very important in finding the active site in the molecule system with a positive point charge. The species that have positive charge tend to attack a molecule where the electrostatic potential is strongly negative (electrophilic attack) Electrostatic potential of free

### Table 3: Infrared spectra of L and its metal complexes (υ cm⁻¹)

<table>
<thead>
<tr>
<th>No</th>
<th>υ(N-H)</th>
<th>υ(C≡N)</th>
<th>Asy(C-S-C)</th>
<th>Sy (C≡S-C)</th>
<th>Stru. Move.</th>
<th>Other bands</th>
<th>M-N</th>
<th>M-Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3474</td>
<td>1624</td>
<td>1457</td>
<td>1280</td>
<td>1010</td>
<td>C=O 1651</td>
<td>CN 2300</td>
<td>C-H 2965</td>
</tr>
<tr>
<td>2</td>
<td>3348</td>
<td>1496</td>
<td>1427</td>
<td>1300</td>
<td>1049</td>
<td>C=O 1608</td>
<td>CN 2106</td>
<td>C-H 2900</td>
</tr>
<tr>
<td>3</td>
<td>3379</td>
<td>1604</td>
<td>1419</td>
<td>1237</td>
<td>1056</td>
<td>C=O 1651</td>
<td>CN 2206</td>
<td>C-H 2954</td>
</tr>
<tr>
<td>4</td>
<td>3259</td>
<td>1701</td>
<td>1427</td>
<td>1238</td>
<td>1006</td>
<td>C=O 1558</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>5</td>
<td>3113</td>
<td>1611</td>
<td>1427</td>
<td>1242</td>
<td>1005</td>
<td>C=O 1558</td>
<td>667</td>
<td>289</td>
</tr>
<tr>
<td>6</td>
<td>3417</td>
<td>1666</td>
<td>1427</td>
<td>1234</td>
<td>1000</td>
<td>1620</td>
<td>532</td>
<td>310</td>
</tr>
</tbody>
</table>

### FT-IR Spectral

- The FTIR spectrum for L1 shows a characteristic stretching absorption bands at 3474 cm⁻¹, 2300, 1651 cm⁻¹, 1427 cm⁻¹, 1457, 1280 cm⁻¹ assigned to v(N-H), v(C=O), v(C≡N), v(C-O), asymmetrical and symmetrical C-S-C stretching respectively [21].
- The FTIR spectrum for L2 shows a characteristic stretching absorption bands at 3259cm⁻¹, 3059 cm⁻¹, 1465 cm⁻¹, 1701 cm⁻¹, 1558 cm⁻¹, 1427 cm⁻¹, 1238 cm⁻¹ assigned to v(N-H), v(C-H), v(C=O) of benzothiazole, v(C≡N) of thiadiazole, v(C=C), asymmetrical (C-S-C), symmetrical C-S-C stretching respectively [20-25].
ligands were measured and plotted as 2D contour to find the active site of molecule as shown in figures (15-22)

**Biological Activity**

The ligand and its transition metal ions complexes were evaluated for antimicrobial activity against gram positive bacteria such as Staphylococcus aureus and gram negative bacteria Escherichia coli, by using agar well diffusion method. All the microbial cultures were adjusted to 0.5 McFarland standard, dimethyl sulphoxide (DMSO) were used to prepared all the test solution. The area of inhibition was measured in millimeter. nutrient agar used as culture medium.

| Table 4: Anti-bacterial data of ligand and its complexes |
|-----------------|-----------------|-----------------|
| **Compound**    | **Escherichia coli** | **Staphylococcus Aurens** |
| Gentamycin      | 20               | 23               |
| L₁              | 12               | 10               |
| [Cr(L₁)Cl₂]Cl₂  | 25               | 25               |
| [Cd(L₁)Cl₂]     | 18               | 20               |
| L₂              | 20               | 18               |
| [Ni(L₂)Cl₂]     | 20               | 25               |
| [Cd(L₂)Cl₂]     | 20               | 20               |
Figure 4: IR spectra of L$_2$

Figure 5: IR spectra of [Ni(L$_2$)Cl$_2$]

Figure 6: IR spectra of [Cd(L$_2$)Cl$_2$]
Figure 7. $^1$H NMR spectra of the ligand $L_1$

Figure 8. $^1$H NMR spectra of the ligand $L_2$

Figure 9. Mass spectra of ligand $L_1$
Figure 10. Mass spectra of [Ni(L1)Cl2]

Figure 11. Mass spectra of [Cd(L1)Cl2]

Figure 12. Mass spectra of ligand L2
Figure 13: Mass spectra of [Ni(L2)Cl2]

Figure 14: Mass spectra of [Cd(L1)Cl2]

Figure 15: Graphical presentation of stereochemistry of L1

Figure 16: Electrostatic potential 2D of L1

Figure 17: Graphical presentation of stereochemistry of [NiL1Cl2]

Figure 18: Graphical presentation of stereochemistry of [CdL1Cl2]
Figure 20: Electrostatic potential 2D of $L_2$

Figure 19: Graphical presentation of stereochemistry of $L_2$

Figure 22: Graphical presentation of stereochemistry of $[\text{CdL}_1\text{Cl}_2]$.

Figure 21: Graphical presentation of stereochemistry of $[\text{NiL}_2\text{Cl}_2]$.

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