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SYNTHESIS, CHARACTERIZATION AND EVALUTION OF BIOLOGICAL ACTIVITY OF SOME SUBSTITUTED HETROCYCLIC COMPOUNDS AND THEIR METAL(II) COMPLEXES

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ABSTRACT. This work describes the preparation of some oxadiazole derivatives using the following steps: The first step involves preparing pyridine anhydride **1**, which was treated with carboxylic acid to form compound **2**. Ester **3**, which was formed in the second step, served as the substrate for the reaction with $N_2H_4.H_2O$ in the third step to give the benzohydrazide **4**, which had been reacted with benzaldehyde to obtain Schiff base (**5**). Furthermore, the acetylmethylation of (**5**) leads to the formation of 1,3,4-oxadiazole. IR, (^{1}H, ^{13}C) NMR spectroscopic, besides the C.H.N. analysis, gave us strong evidence of the structural clarity of the synthesized molecules (**1-6**), which were used as ligands in a 2:1 molar ratio with $CoCl_2.6H_2O$, $NiCl_2.6H_2O$ and $ZnCl_2$ to assemble **7-15**. Analytical methods, such as melting point, conductance dimensions, C.H.N., metal content, infrared, electronic spectra, nuclear magnetic resonance, magnetic characteristics, and thermal analysis, are associated with the characterization of the prepared complexes. Conductance dimensions suggested the non-conductive nature of all the compounds. Magnetic susceptibility and electronic spectra indicated an octahedral geometry for all complexes. Certain synthesized compounds have also counteracted the growth of four different species of bacteria. Some compounds have stronger antibacterial action than free ligands towards tested microbes.

KEY WORDS: Benzohydrazide, Biological activity, Schiff base, Heterocyclic compounds, Oxadiazole

INTRODUCTION

Over the last decade, nitrogen-containing heterocyclic systems have been of great interest owing to their potential uses in pyrotechnics, propellants, explosives, and particularly chemotherapy [1]. Pharmaceutical chemistry especially benefits from the 1,3,4-oxadiazole motif among these heterocycles [2]. For 1,3,4-oxadiazole, several synthetic pathways have been developed [3, 4]. The majority of these rely on diacylhydrazine cyclodehydration [5]. Moreover, attention has been directed to the synthetic and biologically significant properties of 1,2,4-triazoles and their heterocyclic derivatives [6-8]. Consequently, several ring systems that contain 1,2,4-triazoles have been used in various applications as synthetic dyes, corrosion inhibitors, polymers [9, 10], medicinal candidates and others,. Another significant class of chemical compounds with various applications and properties are the bicyclic nitrogen heterocycles called phthalimides. In recent times, they have been the subject of considerable biomedical research because of their significant biological effects. Generally, scientists use them as starting materials and intermediates to generate insecticides, a variety of alkaloids, and pharmacophores [11]. Synthesis of pesticides, and recently, because of their significant biological impacts, they have been deeply studied in biomedicine [12]. Based on the above information and our interest on the synthesis of some new complexes linked to various heterocycles. It was scheduled project to synthesize novel organic ligands (L1-L3) (**4-6**) starting from pyridine-2,3 dicarboxylic acid and confirm their structures by their physical properties and FTIR, ^{1}H NMR, and ^{13}C NMR spectroscopies. These ligands (**4-6**) were employed to prepare new complexes. The new complexes of cobalt(II) **7**, **10**, **13**, nickel(II) **8**, **11**, **14**, and zinc(II) **9**, **12**, **15** were characterized by elemental analysis (C.H.N.), thermal

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analysis along with spectroscopic techniques UV-Vis, FTIR, ^{1}H, ^{13}C-NMR, atomic absorption, and also conductivity and magnetic susceptibility. These newly synthesized complexes have a wide range of applications as catalysts and in the treatment of cancer.

EXPERIMENTAL

Materials

All chemicals and solvents were of analytical grade, and we utilized them without additional purification. Metal salts $CoCl_2.6H_2O$, $NiCl_2.6H_2O$, $ZnCl_2$ and pyridine 2,3-dicarboxylic acid were supplied by Sigma-Aldrich Company. Ethanol and dimethylformamide (DMF) were provided by Fluka Company.

Instrumentation

FT-IR spectra (υ_{max} (cm^{-1}) were measured using Shimadzu FT-IR84005 Spectrophotometer, Japan, at Education for Pure Sciences College, Tikrit University. The ^{1}H-NMR and ^{13}C-NMR tests were carried out at Sciences College, Basra University using Bruker-DRX system at 400 MHz, (TMS) as standard in DMSO-d_6. Electronic spectra measurements for ligands and their compounds at a concentration of 10^{-3} M in DMF as a solvent at 25 °C were conducted using the Shimadzu UV-Vis spectrophotometer Ultra Violet-1800Spectrophotometer at 190−1100 nm in Education for Pure Science College Mosul University. The GCMSQp2010 Ultra Gas Mass Chromatography Spectroscopy, Shimadzu measurement device was used to determine their molecular weight at Samarra University center laboratory .Element microanalyses were performed using a Leco 932 USA Elemental Analyzer (C.H.N.). The molar conductance of the synthesized compounds was measured using the HANNA EC214conductivity meter in dimethyl form amide at 25 °C in Education for Pure Science College, Mosul University. Metal ion analyses had been evaluated spectrophotometrically utilizing atomic absorption spectroscopy, Analytic Jena GmbH-novAA350 novAA350 at the College of Agriculture and Forestry, University of Mosul. Sherwood Scientific was used to assess the produced complexes' magnetic susceptibility at room temperature (MSB-MK) at chemistry department of Education for Pure Sciences College, Tikrit University.

Synthesis of ligands (L_1, L_2, L_3)

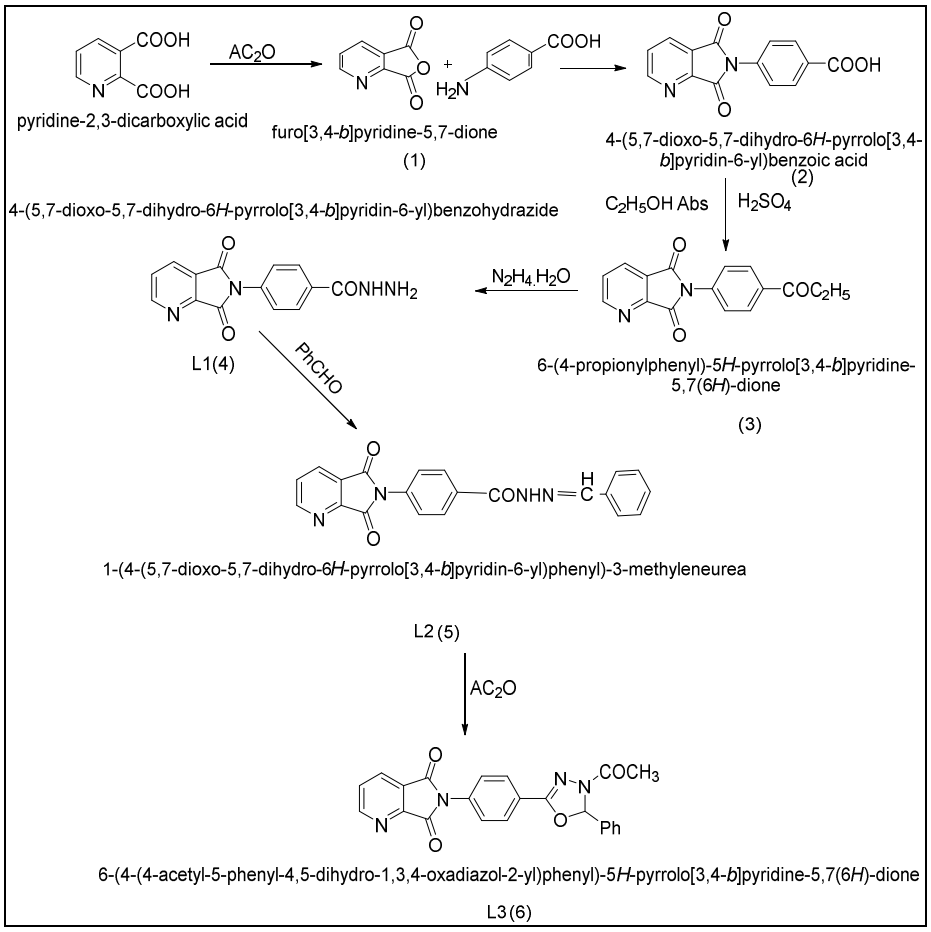
*Synthesis of Furo [3,4-b] pyridine-5,7-dione (**1**)*. It was obtained by dissolving pyridine 2,3-dicarboxylic acid (0.02 mol., 6.3 g) in acetic anhydride and then heating it under reflux for an hour. After the reaction was complete (checked by TLC), the solution was filtered under hot conditions as shown in Scheme 1. Yield: 90%.

*Synthesis of [4-(5,7-dioxo-5,7-hydro-6H-pyrrolo [3,4-b] pyridine-6-yl] benzoic acid (**2**)*. (0.02 mol, 3 g) of compound 1 and(0.02 mol, 2.8 g) of 4-aminobenzoic acid, in 30 mL acetic acid had been refluxed for an hour; this was filtered under hot conditions, evaporated, cooled, and precipitated by ethyl acetate. The formed precipitate was filtered and recrystallized using acetic acid [13] (Scheme 1). Yield: 87%.

*Synthesis of 6-(4-propionyl phenyl-5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione] (**3**)*. Compound **2** (0.02 mol, 5.36 g) was dissolved in absolute ethanol and then the solution of concentration sulfuric acid (3-5 mL) was added. The reaction mixture had been refluxed for 6 h. Ending of the reaction was monitored by TLC, followed by pouring the product into ice-cold water, neutralized by sodium bicarbonate, washed, and separated into ester (Scheme 1). Yield: 79%.

*Synthesis of benzohydrazide (**4**) (**L_1**)*. (0.02 mol., 3 mL) of compound **3** and hydrazine hydrate

(0.02 mol, 3 mL) in 30 mL ethanol had been refluxed for 5 h. This was allowed to remain for about 24 h at room temperature to obtain the precipitation. The resulting particles were filtered and recrystallized from ethanol to yield compound **4** (Scheme 1). This compound resulted in 79% yield as a white (m.p. 257 °C). FTIR (KBr, cm^{-1}) 3394, 3275 cm^{-1} ($NHNH_2$), other absorption bands at 1774, 1720, 1658, 1643, and 1307 cm^{-1} (C=O asym. imide), (C=O amide), (C=C aromatic), and (C–N imide) [14].



Scheme 1. Synthesis of L_1, L_2, L_3.

*Synthesis of benzohydrazide (Schiff base) (**5**) (**L_2**)*. A mixture of benzohydrazide L_1 (0.001 mol, 0.3 g) with (0.001 mol, 4 mL) of benzaldehyde dissolved in absolute ethanol containing two drops of glacial acetic acid was refluxed with stirring for 3 h [15]. After the reaction was completed, the solution was concentrated to half its volume. The formed precipitate was filtered, washed with ether dried and recrystallized using ethanol (Scheme 1). This compound gives an in 81% yield as an off-white powder (m.p. 310 °C). FTIR (KBr, υ, cm^{-1}) 3417, 1782, 1728, 1681, 1620, and 1571 cm^{-1} (N-H asym amide) (C=O sym imide), (C=O imide), (C=O amide), (C=N) and (C=C arom.) [15]. ^{1}H NMR (ppm) (DMSO d_6, 400 MHz) δ: (7.5–8.8) aromatic protons and NH proton, and at

(8.7) imine proton. CHNS elemental analysis calculated for ($C_{21}H_{14}N_4O_3$): C, 68.10%; H, 3.81%; N, 15.13%; O, 12.96%. Found: C, 67.88; H, 3.32; N, 14.91; O, 12.74%.

Synthesis of 1,3,4-oxadiazol ***(6)*** *(**L_3**)*. Schiff base L_2 (0.003 mol, 0.55 g), with acetic anhydride (10 mL) was refluxed for 4 h. This was allowed to remain for about 24 h. at room temperature to obtain the precipitation. Excess acetic anhydride was removed by the addition of water and then stirred for further 30 min. The formed product was filtered, washed with water, and recrystallized using ethanol (Scheme 1). This compound results in 65% yield as a light yellow powder (m.p. 305 °C). FTIR (KBr, υ, cm^{-1}) showed multiple absorption bands at 1760, 1724, and 1705 cm^{-1} (C=O asym. imide), (C=O) sym. imide), and (C=O amide); other at 1620, 1573, 1338, 1211, and 1153 cm^{-1} (C=N arom) (C–N imide) and (C–O–C asym. and sym.) [16]. ^{1}H NMR (ppm): ($DMSOd_6$, 400 MHz) δ: (2.7, 4.2) (CH_3) and (CH_2) protons and the proton in the oxadiazole ring, at δ: (7.8-8.2) aromatic protons. The ^{13}C NMR spectrum showed peaks at 22.49, 64, 82 (CH_3, CH_2, and carbon in the oxadiazole ring. Other bands at (125.9-134) and 161 aromatic carbons (C=N) and (C=O). CHNS elemental analysis calculated for ($C_{23}H_{16}N_4O_4$): C, 66.99%; H, 3.91%; N, 13.59%; O, 15.52%. Found: C, 66.79; H, 3.74; N, 13.35; O, 15.10% [17].

*General procedure of preparation of complexes in a ratio of (2:1) (L:M) (**7-15**)*

A mixture of (0.002 mol) of the prepared ligand (**4-6**) in 25 mL of absolute ethanol was added to a solution consisting of dissolving (0.001 mol) of the metal salt ($CoCl_2.6H_2O$) in absolute ethanol (10 mL), and add (0.001 mol, 0.060 g) to the mixture of tri ethyl amine dissolved in 10 mL of absolute ethanol. The mixture was heated with stirring for three hours. The solution was cooled, and the resulting precipitate was filtered, washed, and recrystallized using ethanol. All complexes were prepared in this way, using special weights for each ligand and metal according to its molecular weight of the prepared complexes [18].

*Complex (**7**)*. It was prepared from ligand (**1**) with ($CoCl_2.6H_2O$) and result in 75% as a light purple powder (m.p. 265d ºC), FTIR (KBr, υ, cm^{-1}) 3410 (N-H), 1691 (C=N), 1520 (C-N asym.), 1342 (C-N sym.), 1101 (C-O-C asym.), 1006 (C-O-C sym.), 502 (Co-N), 410 (Co-O), and 227 (Co-Cl). CHNS elemental analysis calculated for $C_{28}H_{20}Cl_2N_8O_8Co$: C, 48.43%; H, 2.90%; N, 16.14%; Cl, 10.21%; Co, 8.49. Found: C, 45.90%; H, 2.80%; N, 15.14%; Co, 9.42%.

*Complex (**8**)*. It was prepared from ligand (**1**) with ($NiCl_2.6H_2O$) and result in 75% as a light green powder (m.p. 255d ºC), FTIR (KBr, υ, cm^{-1}) 3523 (N-H), 1671 (C=N), 1159 (C-O-C asym.), 1009 (C-O-C sym.), 431 (Ni-N), 402 (Ni-O) and 291(Ni-Cl). CHNS elemental analysis calculated for $C_{28}H_{20}Cl_2N_8O_8Ni$: C, 48.45%; H, 2.90%; N, 16.14%; Ni, 8.46%. Found: C, 47.21%; H, 2.99%; N, 15.37%; Ni, 9.21%.

*Complex (**9**)*. It was prepared from ligand (**1**) with ($ZnCl_2$) and result in 79% as a white powder (m.p. 257d ºC), FTIR (KBr, υ, cm^{-1}) 3359 (N-H), 3107, 1662 (C=N), 1101 (C-O-C asym.), 1006 (C-O-C sym.), 436 (Zn-N) 421 (Zn-O) and 279 (Zn-Cl). CHNS elemental analysis calculated for $C_{28}H_{20}Cl_2N_8O_8$ Zn: C, 47.99%; H, 2.88%; N, 15.99%; O, 13.70; Zn, 9.33%. Found: C, 45.99%; H, 2.75%; N, 15.80%; Zn, 10.78%.

*Complex (**10**)*. It was prepared from ligand (**2**) with ($CoCl_2.6H_2O$) and result in 66% as a violet green powder (m.p. 288d ºC), FTIR (KBr, υ, cm^{-1}) 3414 (N-H), 1689 (C=N), 1525 (C-N asym.), 1340 (C-N sym.), 1099 (C-O-C asym.), 1005 (C-O-C sym.), 500 (Co-N) and 412 (Co-O). CHNS elemental analysis calculated for $C_{42}H_{28}C_{l2}N_8O_6Co$: C, 47.95%; H, 3.24%; N, 12.87%; Cl, 8.14%; O, 11.03%; Co, 6.77%. Found: C, 46.90%; H, 2.99%; N, 14.95%; O, 10.65%; Co, 7.42%.

*Complex (**11**)*. It was prepared from ligand (**2**) with ($NiCl_2.6H_2O$) and result in 64% as a light

green powder (m.p. 286d ºC), FTIR (KBr, ν, cm^{-1}) 3530 (N-H), 1675 (C=N), 1161 (C-O-C asym.), 1006 (C-O-C) sym., 429 (Ni-N) and 401 (Ni-O). CHNS elemental analysis calculated for $C_{42}H_{28}C_{l2}N_8O_6$ Ni: C, 47.96%; H, 3.24%; N, 12.88%; Cl, 8.15%; O, 11.03%; Ni, 6.74%. Found: C, 47.70%; H, 2.98%; N, 14.77%; Cl, 8.50%; O, 10.70%; Ni, 11.20%.

*Complex (**12**)*. It was prepared from ligand (**2**) with ($ZnCl_2$) and result in 70% as a yellow brown powder (m.p. 292d ºC), FTIR (K Br, υ, cm^{-1}) 3340 (N-H), 1660 (C=N), 1105 (C-O-C asym.), 1004 (C-O-C sym.), 434 (Zn-N) and 422 (Zn-O). CHNS elemental analysis calculated for $C_{42}H_{28}C_{l2}N_8O_6$ Zn: C, 57.52%; H, 3.22%; N, 12.78%; Cl, 8.08%; O, 10.95%; Zn, 7.45%. Found: C, 56.70%; H, 2.90%; N, 14.80%; C l, 9.22%; O, 10.70%; Zn, 9.77%.

*Complex (**13**)*. It was prepared from ligand (**3**) with ($CoCl_2.6H_2O$) and result in 70% as a light purple powder (m.p. > 300d ºC), FTIR (KBr, υ, cm^{-1}) 3413 (N-H), 1690 (C=N), 1519 (C-N asym.), 1340 (C-N sym.), 1100 (C-O-C asym.), 1003 (C-O-C sym.), 501 (Co-N) and 401 (Co-O). CHNS elemental analysis calculated for $C_{46}H_{32}Cl_2N_8O_8Co$: C, 57.88%; H, 3.38%; N, 11.74%; Cl, 7.43%; O, 13.41; Co, 6.17%. Found: C, 46.90%; H, 3.11%; N, 12.14%; Co, 8.42%.

*Complex (**14**)*. It was prepared from ligand (**3**) with ($NiCl_2.6H_2O$) and result in 71% as a light green powder (m.p. > 300d ºC), FTIR (KBr, υ, cm^{-1}) 3521 (N-H), 1675 (C=N), 1161 (C-O-C asym.), 1008 (C-O-C sym.), 430 (Ni-N) and 400 (Ni-O) .CHNS elemental analysis calculated for $C_{42}H_{28}C_{l2}N_8O_6$ Ni: C, 57.88%; H, 3.38%; N, 11.74%; Cl, 7.43%; O, 13.41; Co, 6.17%. Found: C, 46.90%; H, 3.11%; N, 12.14%; Co, 8.42%.

*Complex (**15**)*. It was prepared from ligand (**3**) with ($ZnCl_2$) and result in 72.5% as a light brown powder (m.p. > 300d ºC), FTIR (KBr, υ, cm^{-1}) 3356 (N-H), 1660 (C=N), 1100 (C-O-C asym.), 1005 (C-O-C sym.), 434 (Zn-N) and 419 (Zn-O). CHNS elemental analysis calculated for $C_{42}H_{28}C_{l2}N_8O_6$ Zn: C, 57.49%; H, 3.36%; N, 11.66%; Cl, 7.38%; O, 13.32; Zn, 6.80%. Found: C, 56.99%; H, 3.03%; N, 11.22%; C l, 8.02%; Zn, 7.78%.

Biological study

The biological impact of several prepared compounds (**1-15**) has been studied against four types of bacteria, both Gram-positive and Gram-negative bacteria; these bacteria are *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*, and *Salmonella typhi*, obtained from the laboratories of the Department of Life Sciences, College of Pure Science, University of Mosul. Inhibition activity test was done by the Levne method [19], which is based on the Vandepitte method [20], was followed. Nutrientsaline medium was injected with individual colonies of the mentioned bacteria separately. The bacteria were then incubated at a temperature of 37 ºC for 18-24 hours. Subsequently, a series of dilutions were made with normal saline solution to obtain a concentration equivalent to 108 cells/cm^3, compared to tube number 1 of Macferland standard tubes. To study the antibacterial effect of the prepared compounds, filter paper discs with an adiameter of 6 mm were saturated with specific concentrations of the compounds dissolved in DMSO, which were selected. Then, the discs were placed on the surface of agar plates using sterilized forceps and incubated at a temperature of 37 ºC for 18-24 hours. Afterward, the inhibition zone diameter was measured and compared to some plates with standard antibiotics (tetracycline) as standard samples.

RESULTS AND DISCUSSION

Preparation of 1,3,4-oxadiazole compounds

The present study focuses on the synthesis of novel heterocyclic derivatives by incorporating **1**, 3,4-oxadiazole cycles into the pyridine 2,3-dicarboxlic acid ring through the multistep synthesis,

which included the production of pyridine 2,3-phthalic via a reaction of pyridine 2,3-dicarboxlic acid with acetic anhydride.

The structure of compound **1** was assigned based on FTIR, NMR, and spectral data. The FT-IR spectrum shows the dispersion of the block (OH) from 135 °C, which agrees with the literature. Compound (**1**) is the primary key compound used in this study to prepare all newly synthesized compounds. As a result, compound (**3**) is the first derivative of compound **1**. Compound **3** was synthesized in two stages.

The first step consisted of converting compound **1** into its carboxylic acid **2**. The obtained product **2** was subjected to a reaction with absolute ethanol under reflux in the second step, which yielded compound **3**. This substituted side chain (-CH_2CO_2Et) has the excellent leaving group (-OEt), which we will work on in the following step. The FTIR spectra of compound **3** showed the disappearance of a band at 3212 cm^{-1} that belongs to υ(OH) and the emergence of typical absorption bands at 1684/1740 cm^{-1}, 1238 cm^{-1}, and 1131 cm^{-1} belonging to υ(C=O, asym. ester), υ(C–O ester), and υ(C–O sym. ester), respectively. These bands are excellent evidence for the success of ester compound (**3**) formation. Other bands appeared at 1770, 1720 and 1581 cm^{-1}, which belong to υ(C=O asym. and sym. imide) and υ(C=C arom.) [16, 17]. The FTIR spectra of compound **4** revealed the absence of the absorption bands that belonged to both υ(C=O) and υ(C–O ester), and the appearance of two characteristic absorption bands at 3394 and 3275 cm^{-1} that belonged to υ ($NHNH_2$). These two points are critical evidence of the success of compound's (**4**) benzo hydrazide formation. Absorption bonds at 1774, 1720, 1658, 1643, and 1307 cm^{-1} are attributed to υ(C=O asym.), υ(C=O sym imide), υ(C=O amide), υ(C=C arom.), and υ(C–N imide), respectively [17]. The next step contained the introduction of compound (**4**) in several synthetic routes, yielding numerous novel heterocyclic (1,3,4-oxadizole), all of which contain pyridine 2,3-di carboxylic acid. Another synthesis method in the present work consisted mixing compound **4** with benzaldehyde in ethanol with a few drops of the glacial acetic acid under reflux, resulting in the novel Schiff base (**5**). The FTIR spectra of compound **5** showed absorption bonds at 3417, 1782, 1728, 1681, 1620, and 1573 cm^{-1} due to υ(N-H asym. amide), υ(C=O sym. imide), υ(C=O imide), υ(C=O amide), υ(C=N), and υ(C=C arom.) [21]. ^{1}H NMR spectra of compound **5** showed CH_2 protons at δ = 4.8 ppm, aromatic and NH protons at δ = 7.5-8.8 ppm, and imine protons at δ = 7.95 ppm (Figure 1).

It is well known that Schiff bases can be successfully introduced in reaction with many chemicals via an active imine group. Therefore, under reflux, the prepared new Schiff base **5** reacted with acetic anhydride to yield compound **6**. The reaction was a nucleophilic attack of the Schiff base's imine nitrogen on the acetic anhydride's carbonyl group, followed by a nucleophilic attack of the amide carbonyl group through the oxygen atom on the positive carbon, leading to ring closure and finally resulting compound **6** [22, 23].

The infrared spectrum compound (**6**) L_3 showed frequency bands in the range 1650-1691 cm^{-1} that belong to the frequency of the stretch group (C=N) in the oxazole ring. These frequencies did not have a clear change after coordination with the metal ion, and this confirms that they do not participate in coordination, as The spectrum gave absorption frequency bands in the range 3393-3593 cm^{-1} that belong to the stretch bands of the (N–H) group. After coordination with the metal ion, it was observed that the frequency was shifted to a lower wavelength, indicating the participation of the electron pair on the nitrogen atom in the formation of the complex, and the appearance of bands at a frequency of 375 cm^{-1} indicated that the metal is compatible with oxygen (M–O) [24, 25].

The ^{1}H-NMR spectrum of the prepared compounds was also studied for L_3, which gave a multiple signal of medium intensity at the site (6.41-6.96 ppm) belonging to the (2H) protons of the CH g aliphatic roup, and another single signal of low intensity at the site (7.73 ppm) is due to the (1H) protons of the carbon atom of the oxazole ring adjacent to the oxygen atom, and multiple low-intensity signals are due to the (4H) protons at the site (7.73-8.10 ppm) belonging to the aromatic ring.

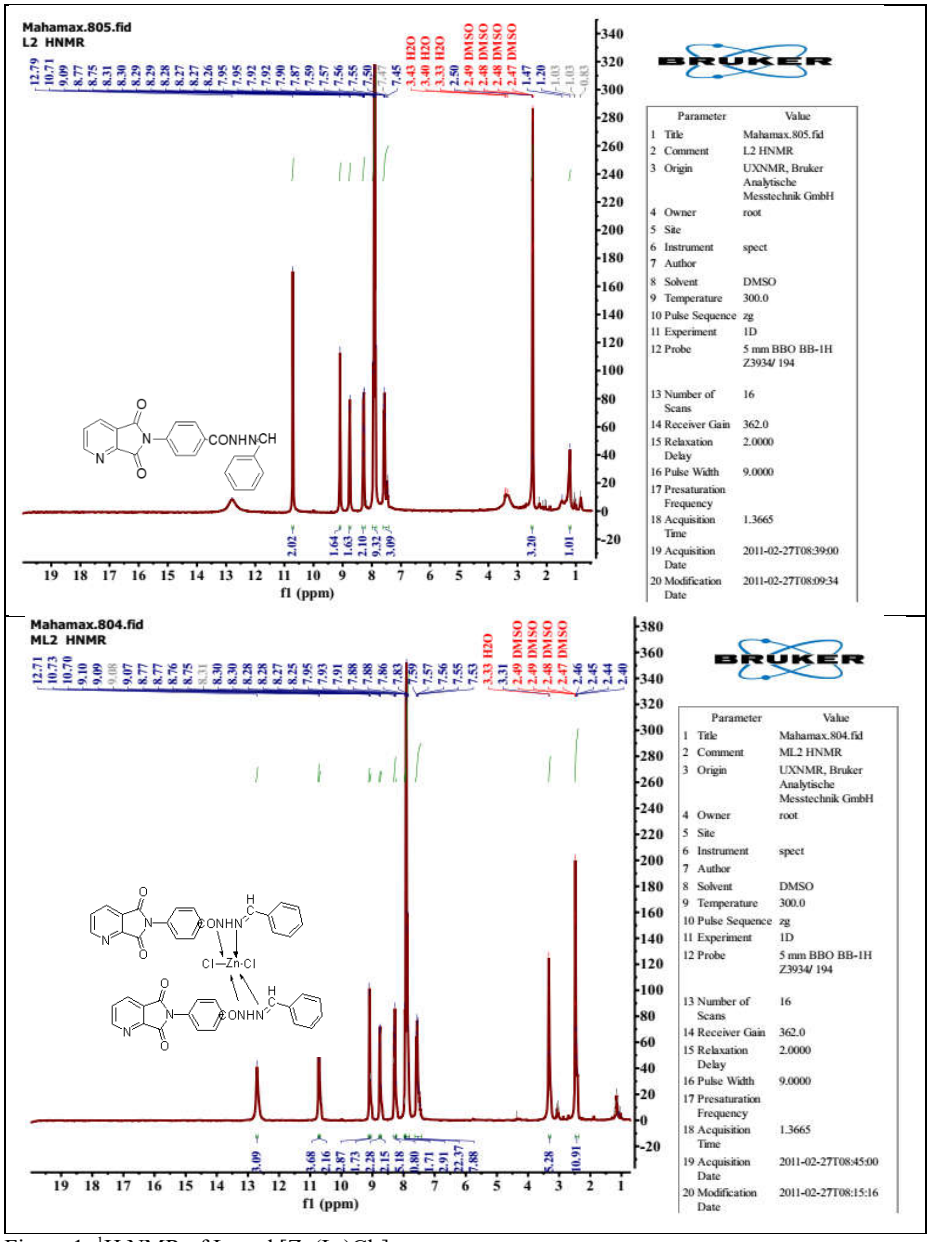


Figure 1. ^{1}H NMR of L_2 and $[Zn(L_2)Cl_2]$.

The ^{13}C-NMR spectrum of compound L_3 showed signals at the positions (120.23-124.97 ppm) belonging to the four symmetric carbon atoms of the aromatic ring. Also, it showed a band at the position 131.67 ppm that belongs to the carbon atom of the oxazole ring, which is directly attached to oxygen. The band at the position of 132.31 ppm is attributed to a carbon atom of the oxazole

ring, which is attached to phenyl, and a band appeared at the position of 146.1 ppm goes to carbon atom of 2-pyridine ring, Figure 2.

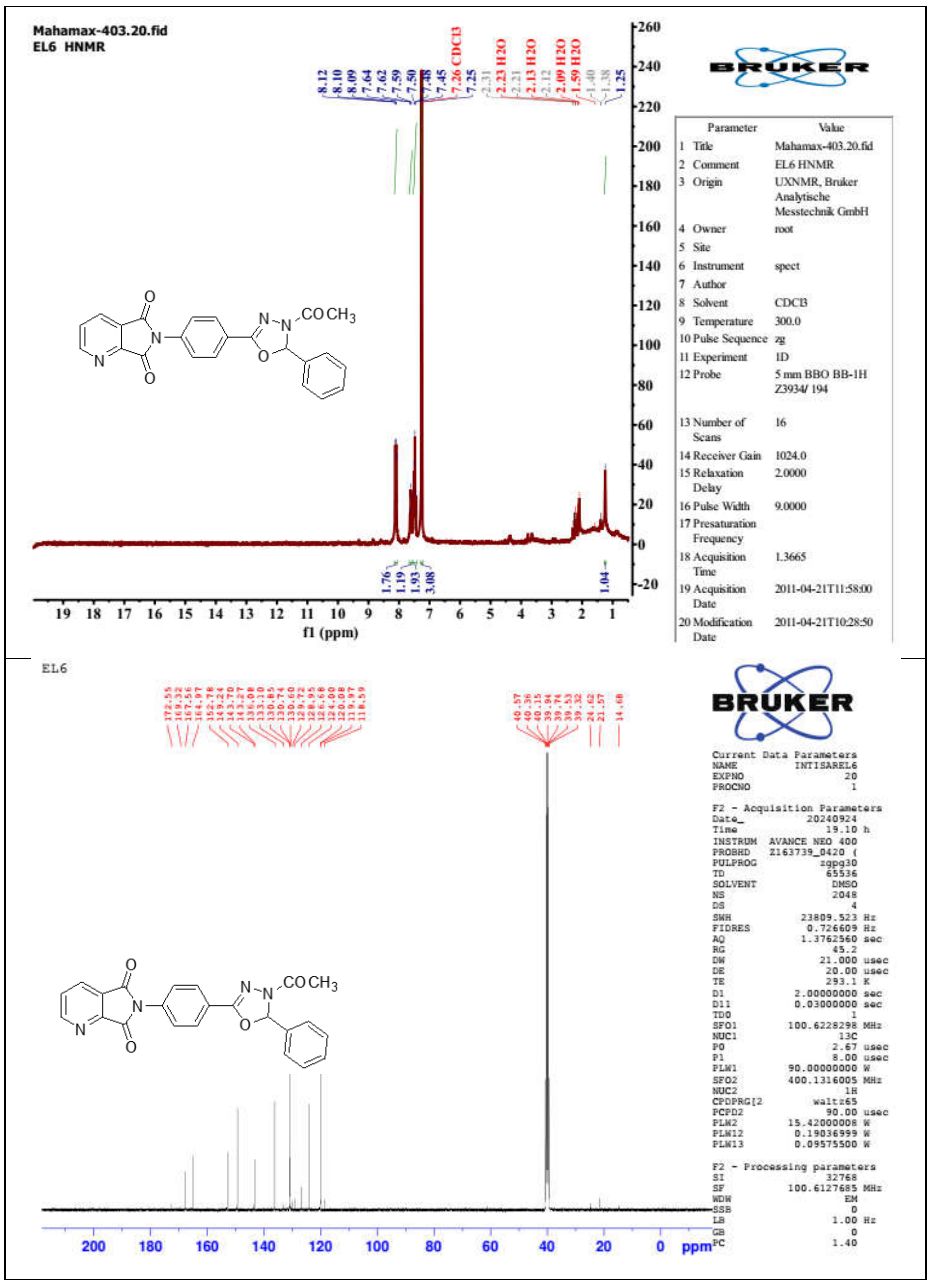


Figure 2. ^{1}H and ^{13}C NMR of L_3.

Magnetic measurements and electronic spectra

The prepared cobalt(II) complexes that possess the cobalt(II) system (d^7) gave the electronic arrangement t_2g^5 eg^2 and have magnetic moment values ranging between (3.96-4.93) B.M. (Table 1), which is due to the presence of three individual electrons in the (d^7) system. The value of the effective magnetic moment is due to the value higher than the theoretically calculated value, which indicates the presence of the orbital contribution, and this is consistent with the values of the magnetic moment for the hexagonal cobalt(II) complexes with a highly twisted octahedral geometric shape [26, 27]. The electronic spectra of the cobalt complexes(II) shown in Table 1 showed that the complexes (**1**, **4**, **7**) show three bands: the first band is υ_1 located in the range υ_1 (12845-15728) cm^{-1}, the second band υ_2 is in the range 17421-18150 cm^{-1}, and the third band υ_3 (24941-30472) cm^{-1} of the spectrum, in addition to the charge transfer band, which appears above (30000) cm^{-1} (Table 1). The appearance of bands υ_1, υ_2, and υ_3 confirms that these transitions are permissible. It goes back to octahedral cobalt complexes [28]. For Ni(II) complexes, the μ_{obs} values are higher than the μ_{eff} values when comparing the μ_{eff} and μ_{obs} values. The possible values of the μ_{obs} value is 4.11-4.65 B.M.

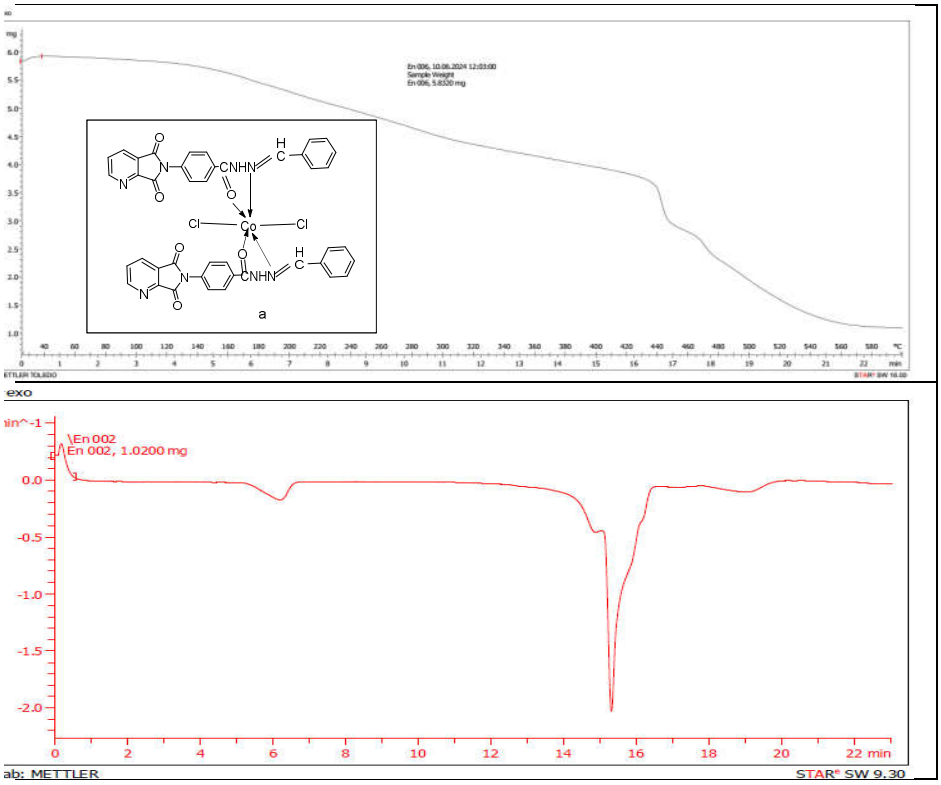
Table 1. Shows the electronic spectra and magnetic properties of complexes metal(II).

Comp. No.	Comp. formula	ν_1	ν_2	ν_3	C.T. (cm^{-1})	μeff B.M.	Suggested structure
7	$[Co(L_1)_2Cl_2]$	14830 $^4T_1g(F)\rightarrow$ $^4T_2g(F)$	18015 $^4T_1g(F)\rightarrow$ $^4A_2g(F$	30121 $^4T_1g(F)\rightarrow$ $^4T_1g(P)$	34650	4.83	Oh
8	$[Ni(L_1)_2Cl_2]$	15740 $^3A_2g \rightarrow {}^3T_1g(P)$	17430 $^3A_2g \rightarrow {}^3T_1g(F)$	30475 $^3A_2g \rightarrow {}^3T_2g(F)$	35135	4.62	Oh
9	$[Zn(L_1)_2Cl_2]$	-----	-----	-----	34080	-----	Oh
10	$[Co(L_2)_2Cl_2]$	14673 $^4T1g(F)\rightarrow$ $^4T_2g(F)$	18008 $^4T_1g(F)\rightarrow$ $^4A_2g(F)$	30120 $^4T_1g(F)\rightarrow$ $^4T_1g(P)$	34655	4.63	Oh
11	$[Ni(L_2)_2Cl_2]$	15728 $^3A_{2g} \rightarrow {}^3T_{1g(P)}$	17421 $^3A_{2g} \rightarrow {}^3T_{1g(F)}$	30472 $^3A_{2g} \rightarrow {}^3T_{2g(F)}$	35137	4.65	Oh
12	$[Zn(L_2)_2Cl_2]$	-----	-----	-----	34081	-----	Oh
13	$[Co(L_3)_2Cl_2]$	14666 $^4T_1g(F)\rightarrow$ $^4T_2g(F)$	18012 $^4T_1g(F)\rightarrow$ $^4A_2g(F)$	30119 $^4T_1g(F)\rightarrow$ $^4T_1g(P)$	34649	4.20	Oh
14	$[Ni(L_3)_2Cl_2]$	15735 $^3A_{2g} \rightarrow {}^3T_{1g(P)}$	17425 $^3A_{2g} \rightarrow {}^3T_{1g(F)}$	304733 $^3A_{2g} \rightarrow {}^3T_{2g(F)}$	35133	4.11	Oh
15	$[Zn(L_3)_2Cl_2]$	-----	------	------	34079	-----	Oh

This could be explained by the following factors: The spin-orbit coupling is larger due to the positive value of α, Δ, and the negative value of λ, and the orbital angular momentum is quenched for $(t_2g)^6$ $(eg)^2$ configurations. Therefore, the magnetic moment observed is greater than the calculated value. In the present investigation, three absorption bands observed for the nickel(II) complexes **8**, **11** and **14** (Table 1) are in general assigned to the following three transitions. The electronic spectra and magnetic moments of the complexes show that they have an octahedral shape and are spin free [27, 29]. Zinc(II) complexes' electronic spectra did not exhibit an absorption band for the (d-d) transition since the d orbital is a field (d^{10}-system). Display the shift in the band position caused by the charge transfer between Zn(II) and the ligand in comparison to the free ligand given in Table 1 [30]. The molar electrical conductivity of the prepared complexes was measured at a concentration (M 10^{-3}) using the solvent dimethyl sulfoxide (DMSO). It was found from the molar electrical conductivity measurements that it agrees with the proposed structural formulas for the prepared complexes of the type (1:2), as it was found that cobalt complexes All of the preparations fall within the range of complexes with neutral behavior, non-electrolytes, or weak conductors, and the molar electrical conductivity values of these complexes in the solvent (DMSO) ranged between 3-20 ($cm^2.ohm^{-1}.mol^{-1}$) [31].

Differential and gravimetric thermal analysis of complexes

We observed from the results of the thermogravimetric analysis (TGA, DTA) measurement of the complex $[Co(L_2)Cl_2]$ that there are three main changes. The first change starts within the range (160-180 ºC), which is attributed to the loss of CO_2 due to dissociation of carbonyl group within this range, and its percentage was 30%. The second is within the temperature range (380–430 ºC), which is attributed to the beginning of ligand decomposition with a weight loss of approximately (20%). The third decomposition, which falls within the range (440-520 ºC), is due to the complete ligand decomposition, resulting in a total weight loss of around 20%. It's worth noting that these changes match and align with differential thermal analysis (DTA) (Figure 3). Thermogravimetric analysis of the complex $[Ni(L_3)Cl_2]$ was also studied, as we notice through the thermogravimetric analysis (TGA) that the complex began to lose weight after a temperature of 140 ºC. This indicates that the complex does not contain water molecules, and at a temperature of (420 ºC) with a weight loss of approximately 50% results from the process of changing from solid to liquid or the beginning of ligand decomposition, which takes place in three steps, the first at (440 ºC) and the second at (460-480 ºC), the percentage of weight loss continued to increase until the temperature reached (540 ºC), and at a temperature of (560 ºC) the percentage of weight loss reached more than 80% (Figure 3). There is clear consistency and alignment between both gravimetric thermal analysis and differential thermal analysis (DTA) (Figure 3) [32, 33].



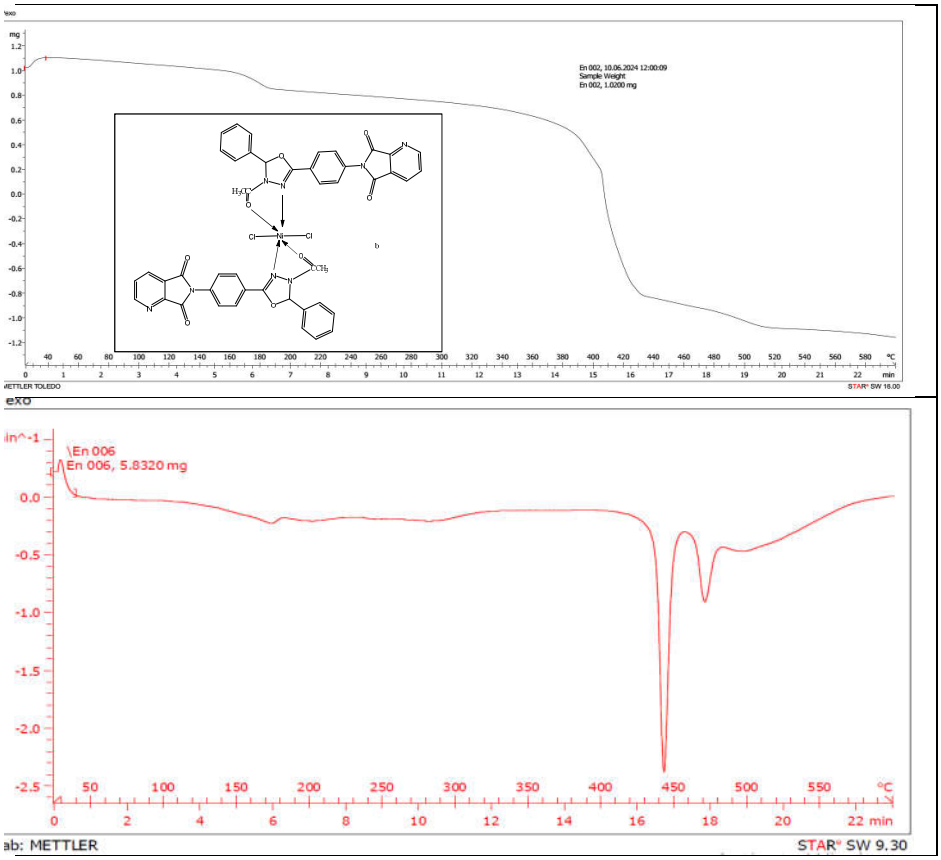


Figure 3. TGA and DTA of a: $[Co(L_2)Cl_2]$ and b: $[Ni\ (L_3)Cl_2]$ curves.

Table 2. Biological properties of tested compounds.

Compound No.	*Staphylococcus aureus* (10 mg/mL)	*Eschershia coli* (10 mg/mL)	*Klebsiella pneumonia* (10 mg/mL)	*Salmonella* (10 mg/mL)
$[Co(L_1)Cl_2]$ (**1**)	13	13	20	2
$[Ni(L_1)Cl]$ (**2**)	17	17	17	18
$[Zn(L_2)]Cl_2$ (**3**)	15	15	13	15
$[Co(L_2)Cl_2]$ (**4**)	14	17	18	18
$[Co(L_3)Cl_2]$ (**5**)	13	16	3	15
$[Zn(L_3)\ Cl_2]$ (**6**)	14	17	18	17
Tetracycline (C1)	30	25	24	20

Biological activity

The bacteria were selected due to their significance in the medical field, as they are responsible for various diseases and exhibit varying levels of resistance to antibiotics and different drugs. The

inhibitory results are given in Table 2. It indicates that some of the prepared compounds have potential inhibition activity against the growth of the bacteria under test. The data obtained for the inhibitory activity reveals that (**2**, **4**, **10**) were highly effective against tested bacteria [21, 34].

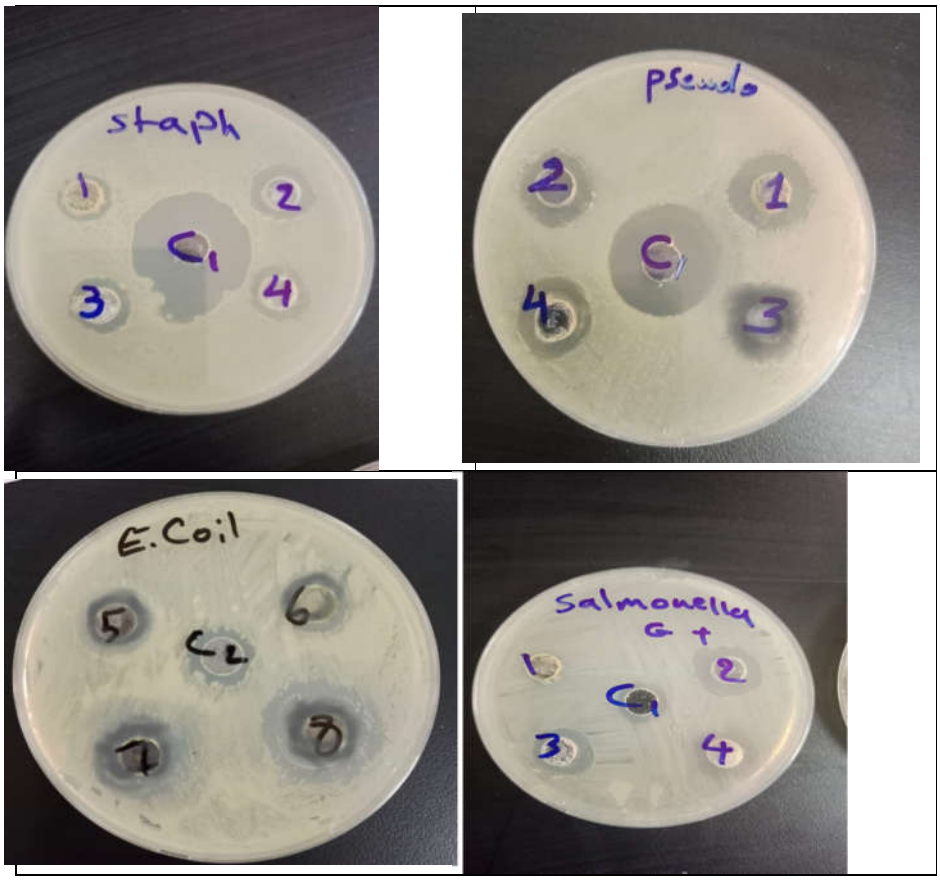


Figure 4. Inhibition zones (mm) of complexes with ligands for four types of bacteria.

Inhibition levels are categorized as follows: Levels between 1 and 6 mm are classified as low inhibition; those ranging from 6 to 12 mm indicate moderate inhibition; and levels exceeding 12 mm are indicative of high impact and inhibition inhibition zone.

Molecular docking studies

Docking was carried out on a molecular target, which is the penicillin-binding protein of *Staphylococcus aureus,* which was downloaded from the protein data bank available at https://www.rcsb.org/structure/3VSK. Designated PDB ID:3VSK using the on-line server CB-dock2 [35] which can be accessed via https://cadd.labshare.cn/cb-dock2/php/index.php. The control was Pencillin G (PDB ID: PNM) according to method [35]. Interactions were visualized using the LigPlot tool [36]. Table 3 shows the docking scores of the synthesized compounds with

their interactions as hydrogen bonds and hydrophobic interactions and share the same residue of Penicillin G, Arg504, Figure 5.

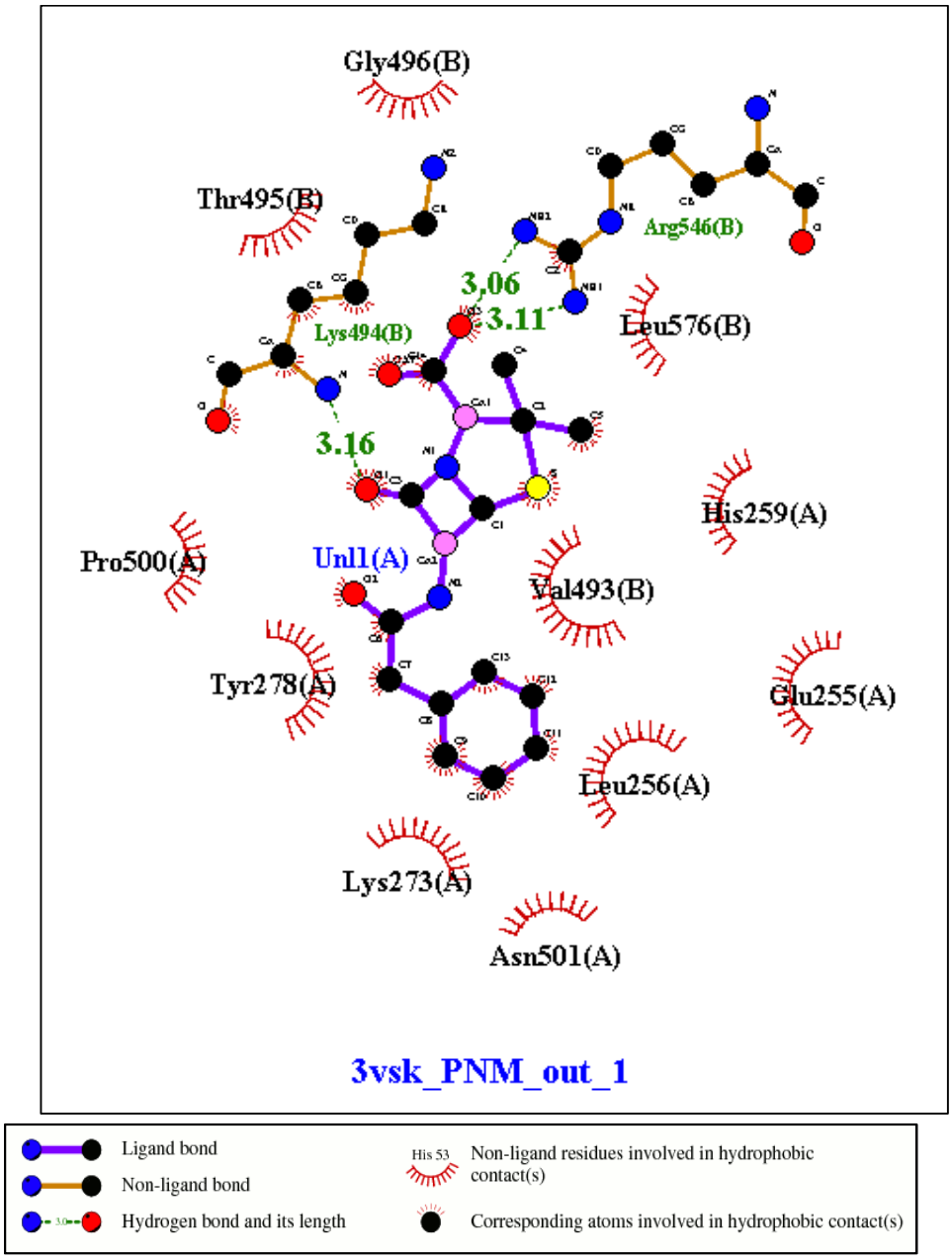


Figure 5. Interaction of Penicillin G with the molecular target 3VSK.

Table 3. Docking scores and interactions of the compounds.

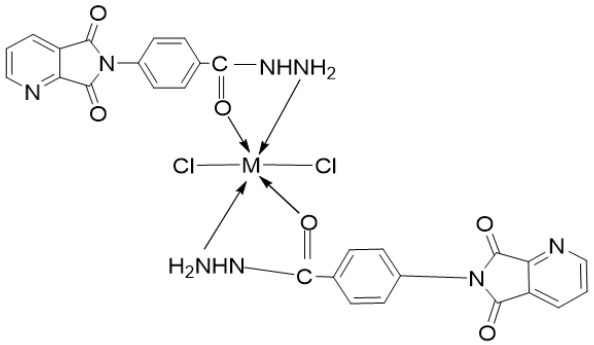
Compound	Docking score	Hydrogen bonding	Hydrophobic interactions
PNM	-7.8	Arg546,Lys494	Gly496,Thr495,Pro500,Tyr 278, Lys273,Asn501,Leu256,Glu255,Val493, His259,Leu576
L_1	-3.8	Thr385,Gln387	Thr503, Thr503, Ser386,Gln387, Gln506,Gly505
L_2	-3.4	Lys273,Asn501	Ser274,Tyr278,Pro500
L_3	-3.2	-----	Phe384,Thr383,Ile497,Asp361, Val353,Leu531

Due to increasing antimicrobial resistance, scientists began to look for new alternative targets for antimicrobial action, such as the isoprenoid biosynthetic pathway, the shikimate synthesis pathway, plasmid partition systems, and the cytoskeleton, so these elements can be exploited by screening chemical compounds or natural products that inhibit enzymes essential for bacterial metabolism [37, 38]. Studied several molecular targets in bacteria using compounds of mushrooms as possible antibacterial agents, including penicillin-binding protein. Docking was performed using Pencillin binding protein against compounds extracted from *Germainum kaempferol*. Germacrene A and elatine had binding affinities of -7.9, -7.1, and elatine -9.2 kcal/mol, respectively [39].

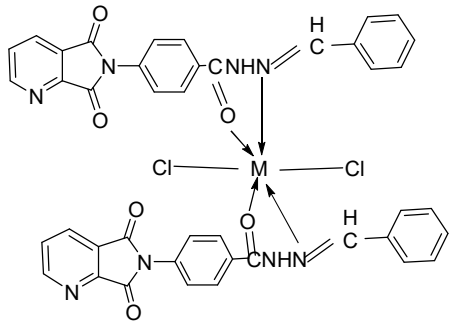
Structure for prepared compounds

According to the results discussed in our paper, compounds can be illustrated as

a



b



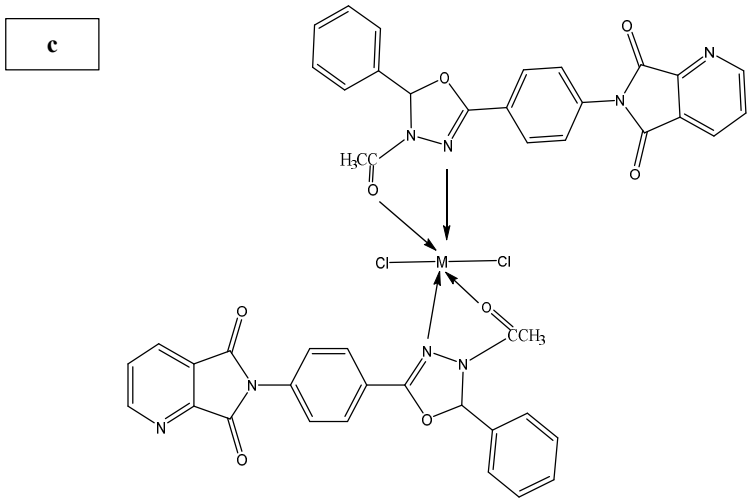


Figure 6. (a,b,c) Proposed structure of complexes (M = Co(II), Ni(II), Zn(II)).

CONCLUSION

In this research we have successfully synthesized substituted membered heterocyclic compounds. These ligand compounds are converted to cobalt, nickel, and zinc complexes. From the various physico- and spectroscopic studies mentioned earlier, the following conclusions can be drawn. Firstly, the ligands prepared for cobalt chloride, nickel chloride, and zinc chloride complexes exhibit identical ligand behavior. L_1 coordinate through the two nitrogen atoms of hydrazine groups. As for the Schiff base ligand L_2, they coordinate with cobalt, nickel and zinc in a bidentate manner through the nitrogen atom of azomethine group and the oxygen atom of carbonyl group. Regarding the oxadiazole ligand, coordination takes place in a bidentate manner through the nitrogen atom in the oxa diazole ring and oxygen atom of acetate group. Secondly, from the results of magnetic measurements and spectroscopic studies conducted on the prepared complexes, it can be inferred that they exhibit octahedral geometries. The biological study of some compounds revealed that a number of compounds have excellent inhibition against the bacteria, while others showed moderate to weak activity.

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