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Research Article

Synthesis, characterization and investigation of biological activities of Schiff Base and its Ni(II) complex obtained from 2-Benzoylpyridine and 3-Hydroxy-2-naphthoic hydrazide

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Abstract

In this paper, a new aryl hydrazone and its Nickel (II) complex were synthesized from 2-benzoylpyridine and 3-Hydroxy-2-naphthoic hydrazide. The synthesized compounds were characterized by elemental analysis, UV-Visible, IR, ^{1}H and ^{13}C-NMR spectral studies and mass spectra.

Elemental analysis data show that the metal atom is coordinated by two ligands. Considering all the data, the ligand coordinates to the metal atom through carbonyl-O, azomethine-N and pyridyl-N atoms. This shows that the $[NiL_2]$ complex is octahedral. When tested against various reference bacterial strains and clinical isolates, it was discovered that the antibacterial activity of the $[NiL_2]$ complex was more effective than the ligand.

Keywords: Aryl hydrazone, Metal Complexes, Antimicrobial Studies, NNO Donor

2-Benzoilpiridin ve 3-Hidroksi-2-naftoik hidrazitten elde edilen Schiff bazı ve Ni(II) kompleksinin sentezi, karakterizasyonu ve biyolojik aktivitelerinin araştırılması

Öz

Bu yazıda, 2-Benzoilpiridin ve 3-Hidroksi-2-naftoik hidrazitten yeni bir aril hidrazon ve onun Nikel (II) kompleksi sentezlendi. Sentezlenen bileşikler element analiz, UV-Visible, IR, ^{1}H ve ^{13}C-NMR spektral çalışmaları ve kütle spektrumları ile karakterize edildi.

Element analizi verileri, metal atomunun iki ligand tarafından koordine edildiğini göstermektedir. Tüm veriler göz önüne alındığında ligandın metal atomuna karbonil-O, azometin-N ve piridil-N atomları aracılığıyla koordine olduğu görülmektedir. Bu, **$[NiL_2]$** kompleksinin oktahedral olduğunu gösterir. Çeşitli referans bakteri suşlarına ve klinik izolatlara karşı test edildiğinde, **$[NiL_2]$** kompleksinin antibakteriyel aktivitesinin liganddan daha etkili olduğu keşfedildi.

Anahtar Kelimeler: Aril Hidrazon, Metal Kompleksleri, Antimikrobiyal Çalışmalar, NNO Donör

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1. Introduction

Arylhydrazones exhibit a broad spectrum of biological activity properties and pronounced binding modifications to transition metal complexes. Therefore, the importance of these molecules in coordination chemistry is increasing. It is also recognized that arylhydrazone transition metal complexes provide a good model for elucidating their crucial biological functions [1]. Arylhydrazone metal complexes have been associated with a variety of biological effects, including antibacterial [2, 3], anticonvulsant [4], anti-tuberculosis [5], and anti-proliferation [6]. Due to keto-enol tautomerization, 2-benzoylpyridine arylhydrazone derivatives behave as a neutral or tridentate monobasic ligand. These ligands are capable of generating six coordinated octahedral geometries due to their tridentate binding modes. Furthermore, the heterocyclic ring in these ligands provides an additional binding site for metal ions, enhancing the pharmacological properties of the synthesized compounds [7]. The structural characteristics, biological functions, and cytotoxic effects of 2-benzoylpyridine Schiff metal complexes are all still being studied in depth.

In this study, we describe the synthesis, characterization, and biological activity of the new arylhydrazone **HL**, a novel 3-hydroxy-2-naphthoic acid hydrazide derivative, and its Ni(II) complex. The molecular structures of the **HL** ligand and the **[NiL$_2$]** complex were identified by IR, UV-Visible, ^{1}H and ^{13}C-NMR studies, elemental analyses, and mass spectra. The antibacterial activity of the compounds was investigated using yeast, Gram-positive, and Gram-negative bacteria as test organisms.

2. Material and Method

2.1. Chemicals and instrumentations

All chemicals used in this study were purchased from commercial suppliers (Sigma/Aldrich). All chemicals purchased from commercial suppliers were of reagent grade and were used immediately.

Elemental analyses were performed using the Thermo Flash 2000 CHNS Analyzer. A Thermo Scientific GENESYS 10S UV-Visible spectrophotometer operating between 200 and 1100 nm was used to record the UV spectra of the synthesized compounds in DMSO solution. The MXl instrument from Sherwood Scientific was used to identify the magnetic moment of the **[NiL$_2$]** complex at room temperature as Bohr Magneton (BM). Infrared spectra were recorded with the Thermo Scientific Nicolet iS10 using ATR. The ^{1}H and ^{13}C-NMR spectra of the ligand dissolved in DMSO-d$_6$ was recorded using an Agilent Premium Compact 600 MHz spectrometer. Mass spectra were collected using a Thermo Scientific TSQ Quantum Access Max.

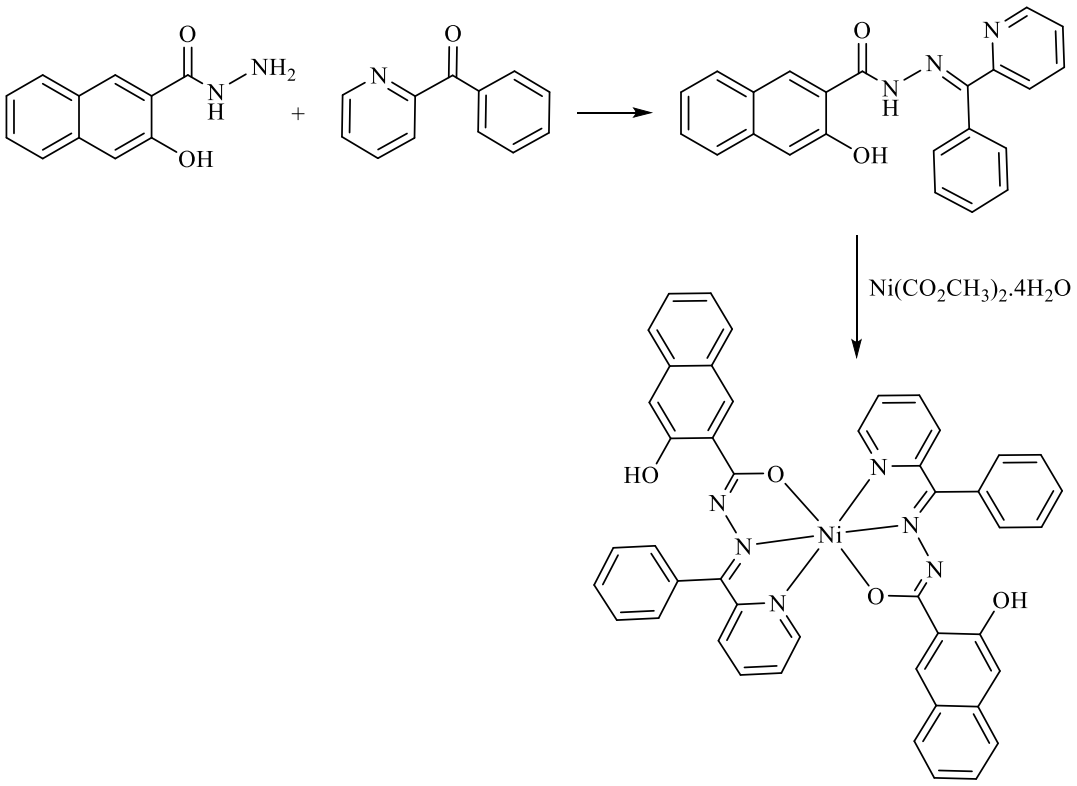
2.2. Preparation of the compounds

2.2.1. Synthesis of HL

To a solution of 3-hydroxy-2-naphthoic hydrazide (0.202 g, 1 mmol) in ethanol (20 mL) was added 2-benzoylpyridine solution (0.183 g, 1 mmol) dissolved in ethanol (20 mL) and refluxed for 4-5 hours. The filtered and ethanol-washed yellow product was dried in the air. Yield: 77%, Mp: 145 °C. Elemental Anal. Calcd. for $C_{23}H_{17}N_3O_2$ (367.41 g.mol^{-1}): C, 75.19; H, 4.66; N, 11.44; found: C, 74.25; H, 5.03; N, 10.31. ^{1}H-NMR (600 MHz, ppm, DMSO-d_6) δ=13.27 (Z), 11.61 (E) [O-H], 11.22 (Z), 11.07 (E) [N-H]. ^{13}C-NMR (600 MHz, solvent) δ= 162.05 (Z), 161.53 (E) [C13 (Z and E isomers)]; 154.23 (Z), 152.98 (E) [C5 (Z and E isomers)]; 152.69 (Z), 152.08 (E) [C6 (Z and E isomers)]; 150.21 (Z), 149.24 (E) [C1 (Z and E isomers)]; 138.48 (Z), 137.55 (E) [C3 (Z and E isomers)]; 137.18 (Z), 136.16 (E) [C4 (Z and E isomers)]; 133.60 (Z), 133.44 (E) [C5 (Z and E isomers)]. LC–MS/MS, m/z = 368.06 $[M+H]^+$, 391.11 $[M+Na]^+$.

2.2.2. Synthesis of [NiL$_2$]

A heated ethanolic solution of **HL** (0.734 g, 2 mmol) (20 mL) was added to a ethanolic solution of $Ni(CO_2CH_3)_2$ $4H_2O$ (0.248 g, 1 mmol) (10 mL). For 3 to 4 hours, the reaction mixture was refluxed. Filtering and air drying were done on the precipitated dark brown product. Yield: 62 %, M.P. Decomposition: 297 °C. Elemental Anal. Calcd. for $C_{46}H_{32}N_6O_4Ni$ (791.49 g.mol^{-1}): C, 69.81; H, 4.08; N, 10.62; found: C, 69.09; H, 4.26; N, 9.61. LC–MS/MS, m/z = 792.97 $[M+H]^+$. Proposed structures of **HL** and **[NiL$_2$]** were given Scheme 1.



Scheme 1. Proposed structures of **HL** and **[NiL$_2$]**

2.3. Detection of antimicrobial activity

The minimum inhibitory concentration (MIC) was determined according to the previously mentioned method [8]. Clinical samples of *S. aureus* ATCC 25923*, E. coli* ATCC 25922*, P. aeruginosa* ATCC 27853*, L. monocytogenes* ATCC 19115*, B. cereus* ATCC 14579*, E. aerogenes* ATCC 1304 *and S.dysentery* ATCC from patients in the intensive care unit of the hospital were used in the study. These clinical strains are *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterococcus faecalis* and methicillin-resistant *Staphylococcus aureus* (MRSA). Clinical and type strains were developed using tryptone soy broth (TSB). Cultures were diluted to $1x10^6$ CFU/mL after one night of incubation at 37 ºC. **HL** and **[NiL_2]** were diluted 2-fold to a final concentration of 256-2 µM after dissolution in dimethyl sulfoxide (DMSO). The 96-well plate was then filled with an equivalent volume of the bacterial suspension and 50 µL of different concentrations of **HL** and **[NiL_2]** and incubated at 37 °C for 18 hours.

The lowest concentration at which no significant bacterial growth occurred was designated as MIC. In addition to gentamicin and ciprofloxacin, media containing metal-free bacteria was used as a negative control (Sigma Aldrich, USA) as a positive control [9].

3. Results and Discussion

3.1. NMR Spectra of HL

In the ^{1}H and ^{13}C-NMR spectra of **HL,** the signals of all hydrogens and carbons are duplicated, suggesting the existence of the E and Z configurations in DMSO-d_6 solution. Two signals of the azomethine proton (NH) group were observed at δ 11.22 and 11.07, which were attributed to the Z and E forms, respectively. Also, multiple signals may be seen in the ^{1}H-NMR spectrum of **HL** ligand in the 7.20-8.90 ppm range, which are indicative of aromatic ring protons of the E and Z isomers (Scheme 2) (Figure 1). Similarly, the signals of C13=O at δ 162.05 and 161.53 were attributed to the Z and E isomers, respectively. From the study of the ^{13}C-NMR spectrum of the **HL** ligand, C6=N signals were observed at δ 152.69 and 152.08 for the Z and E isomers, respectively (Figure 2) [10-13].

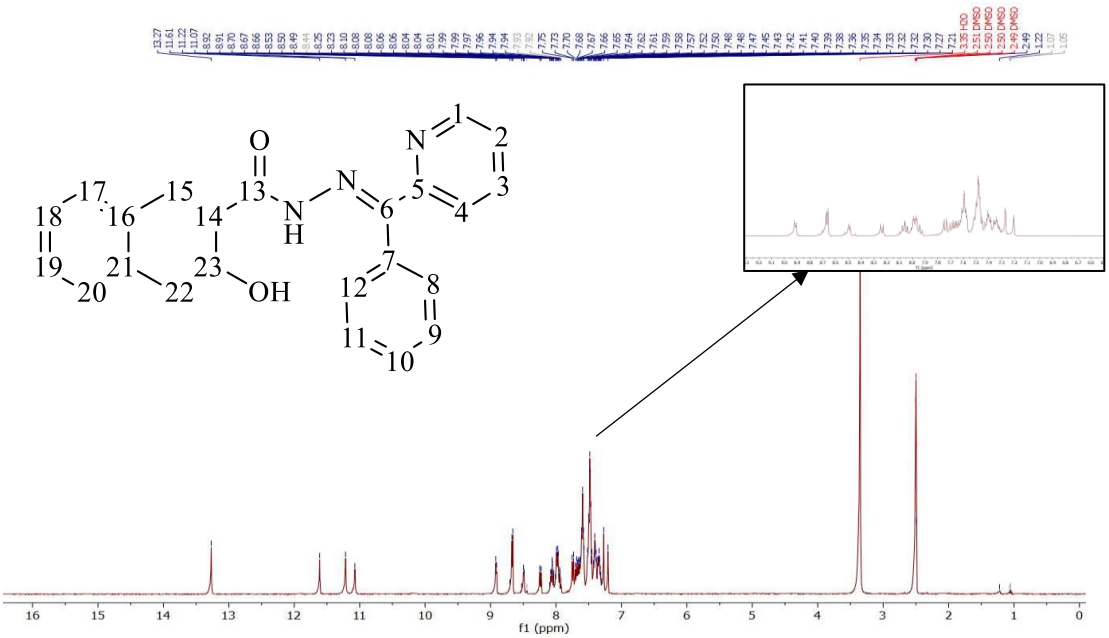


Figure 1. ^{1}H-NMR spectrum of the **HL**

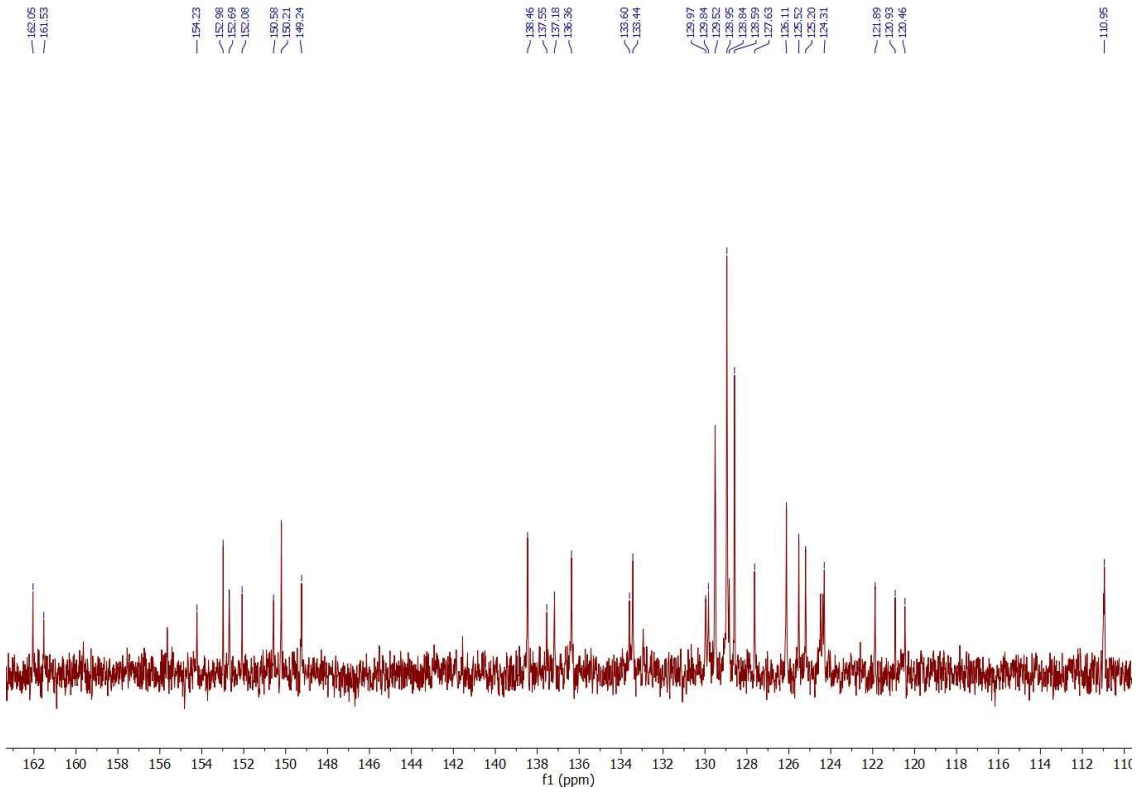
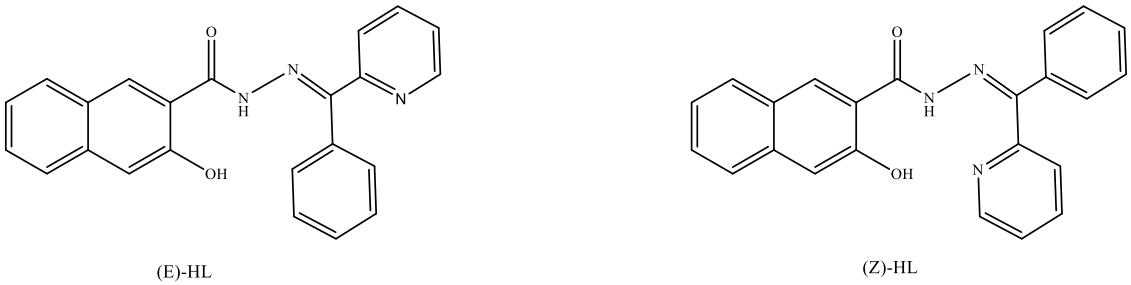


Figure 2. ^{13}C-NMR spectrum of the **HL**



Scheme 2. E and Z isomers of the **HL**

3.2. IR Studies of HL and [NiL_2]

The bands at 3415 cm^{-1} and 3216 cm^{-1} in the IR spectrum of **HL** are caused by (O-H) and (N-H), respectively. The complex spectrum did not contain the (N-H) band. For **[NiL_2]**, the OH band was seen at 3452 cm^{-1}. This shows that the OH group is uncoordinated and the NH group is coordinated with the metal ion. The IR spectrum of the **HL** exhibits three absorption bands with wavelengths of 1650, 1623, and 1513 cm^{-1} that are caused, respectively, by υ(C=O), $(C=N)_{imine}$, and $(C=N)_{pyridine}$. In comparison to the ligand, the IR spectrum of **[NiL_2]** complex shows considerable modifications. The (C-O) band was recorded in 1360 cm^{-1} for the complex spectrum, but the (C=O) band was not seen. And also new band due to the conjugate system υ(>C=N-N=C<) appeared at 1575 cm^{-1}, for **[NiL_2]** (Figure 3) [14].

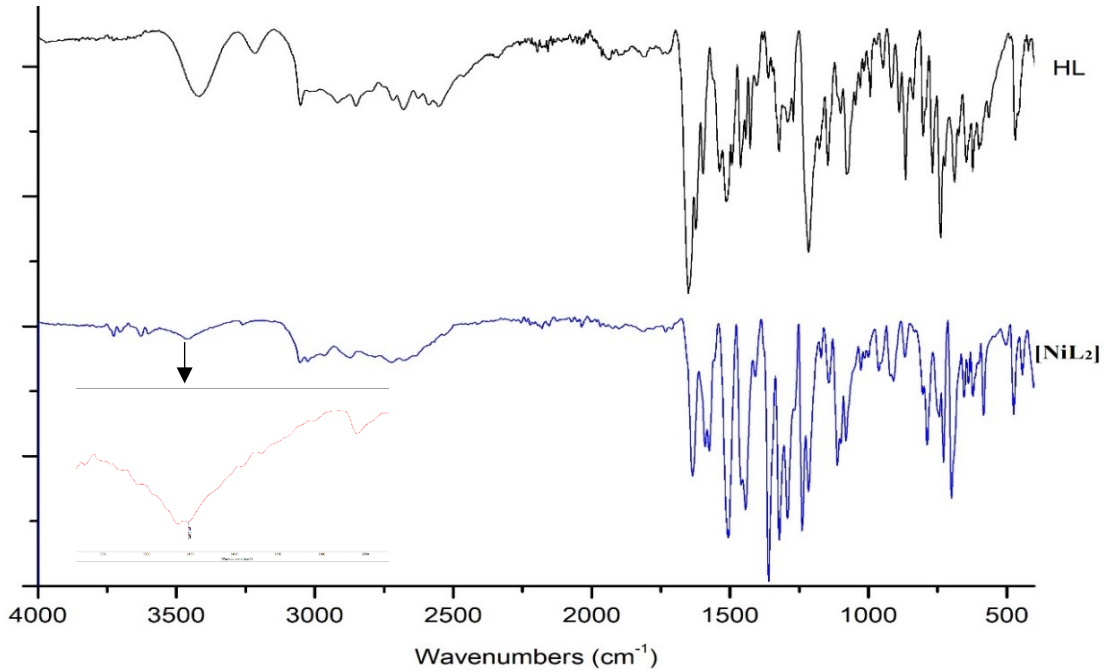


Figure 3. Infrared spectra of the **HL** and **[NiL_2]**

3.3. UV-Visible and magnetic measurement studies

In DMSO (10^{-4} M), the electronic spectrum of **HL** (Figure 4) shows a band at 318 nm associated with the n→π* transition of the carbonyl group. The aromatic rings and azomethine moiety are attributed to the π→π* transitions that are seen as a band and a shoulder at 289 nm. There is a slight shift in these bands during complexation. In the UV-Visible spectrum of the **[NiL$_2$]** complex (Figure 5), charge-transfer transitions for the **[NiL$_2$]** complex were observed at 393 nm. Two electronic absorption bands at 413 and 826 nm, which stand for the $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ (ν_2) and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)(\nu_2)$ transitions, respectively, were visible in the electronic spectra of the synthesized **[NiL$_2$]** complex [15]. These transitions demonstrated the octahedral geometry of the **[NiL$_2$]** complex. The **[NiL$_2$]** complex showed the magnetic moment value 3.5 BM. This value is consistent with the values expected for Ni(II) cations in octahedral geometries with two unpaired electrons [15, 16].

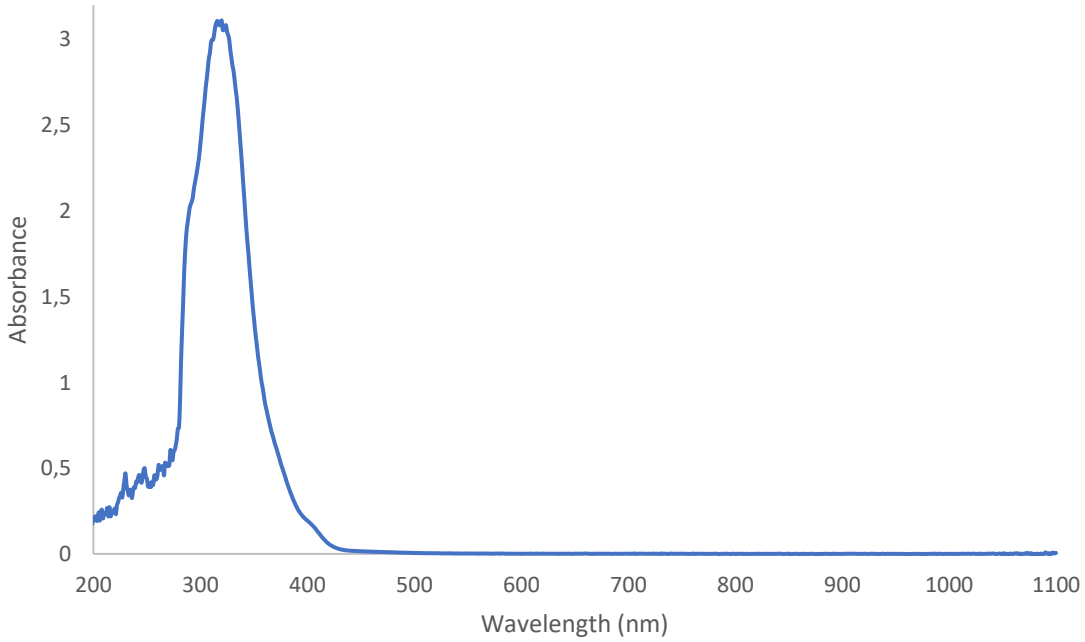


Figure 4. Absorption spectrum of the **HL**

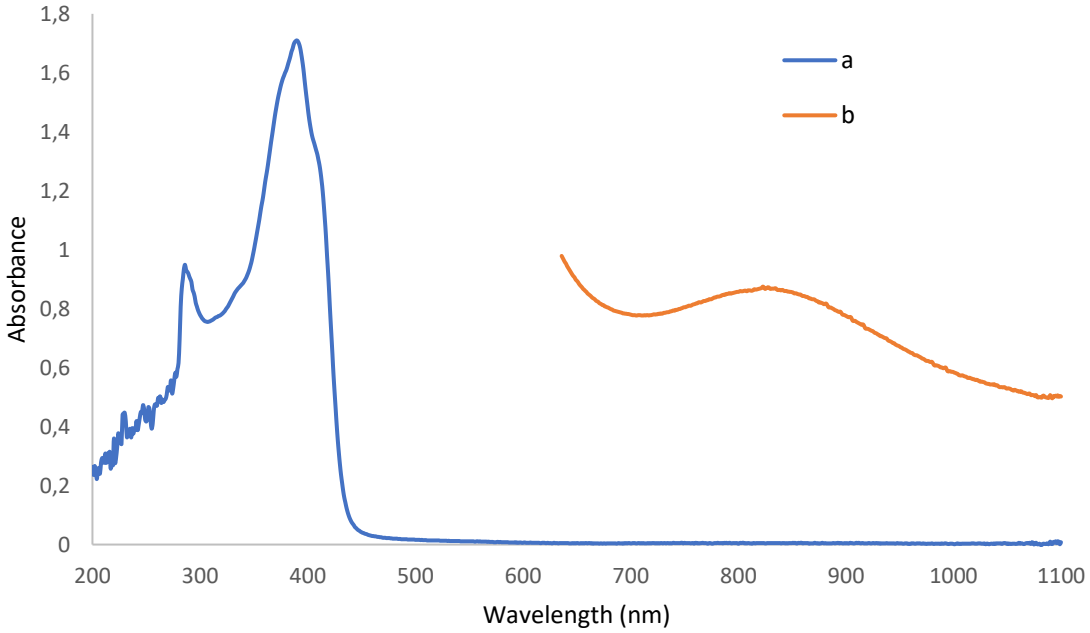


Figure 5. Absorption spectra of **[NiL$_2$]** complex a) 10^{-4} M, b) 10^{-2} M

3.4. Mass spectral analysis of HL and [NiL$_2$]

The ESI-MS spectra of the **HL** and **[NiL$_2$]** complex are presented Figure 6. The mass spectra of **HL** and **[NiL$_2$]** complex confirmed the identity of the structures. The **HL** ligand spectrum gave two m/z signals of 368.06 and 391.11 for $[M+H]^+$, $[M+Na]^+$, respectively, which were in agreement with the calculated values of 368.42 and 390.40. ESI-MS of the **[NiL$_2$]** complex gave m/z signal at790.85 which corresponded to the calculated value of 792.50 for $[NiL_2+H]^+$. The mass spectrum of the Ni(II) complex was evidence for the chelation of the two ligand molecules to the Ni (II) center.

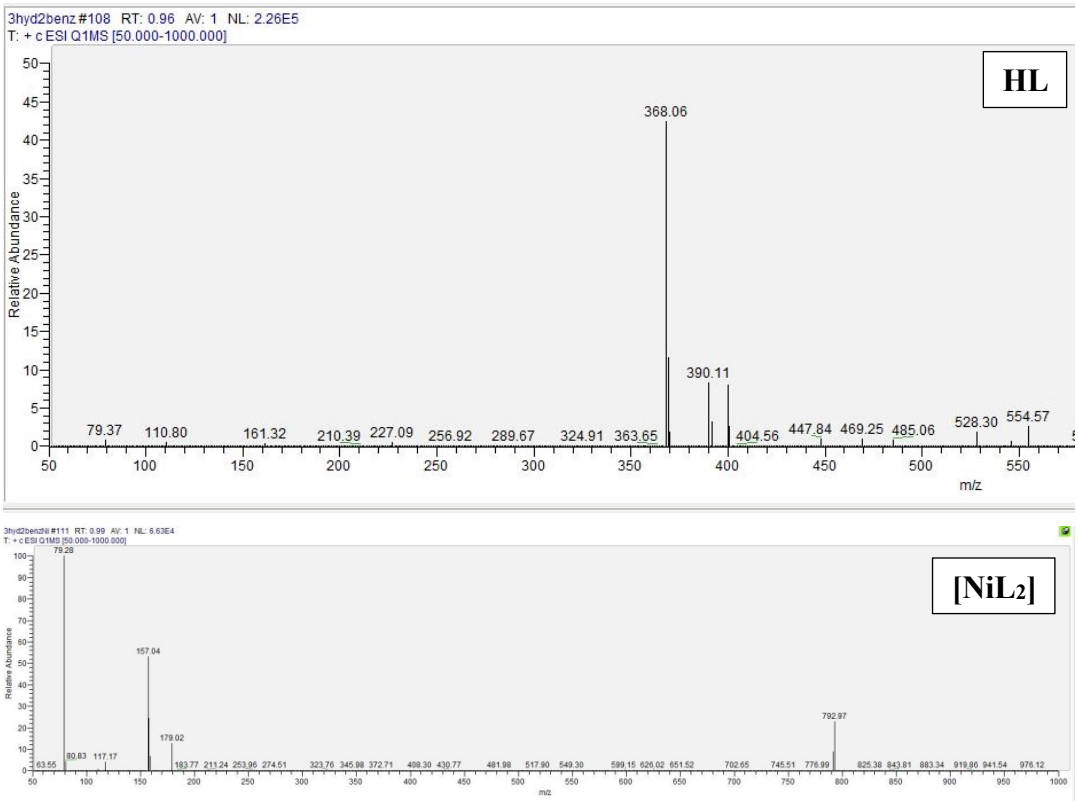


Figure 6. Mass spectra of the **HL** and **[NiL$_2$]**

3.5. Biological activity of HL and [NiL$_2$]

The antibacterial activity of the newly synthesized compounds **HL** and **[NiL$_2$]** was evaluated using broth microdilution technique against various reference bacterial strains and clinical isolates. The outcomes demonstrated that these substances have potent antibacterial action.

The data presented in Table 1 show that between both novel compounds, the **[NiL$_2$]** complex has higher antibacterial activity compared to the **HL** ligand. However, it can be said that **[NiL$_2$]** complex is more active on *S. aureus* 25923 and *E. faecalis* bacteria. When the Minimum Inhibitory Concentration (MIC) values of the compounds tested with positive control substances such as gentamicin and streptomycin are compared in the study, it is observed that these values are similar. MIC values indicate that the **[NiL$_2$]** complex is active at a lower concentration than the **HL** ligand. The data as a whole indicate that the test chemicals were more effective at killing Gram-negative bacteria than Gram-positive bacteria [17,18].

Table 1. Minimum inhibitory concentration with antimicrobial activity of **HL** and **[NiL$_2$]**

Compounds	Antimicrobial zone diameters												
	Gram-negative								Gram-positive				
	***E. coli* 25922**	***E. coli***	***PA* 27853**	***PA***	***KP***	***EA* 1304**	***SD* 11456b**		***LM* 19115**	***S. aureus* 25923**	***S. aureus* (MRSA)**	***B. cereus* 14579**	***E. faecalis***
[NiL$_2$]	16	15	15	17	14	17	15		14	16	16	17	17
HL	12	13	n.d[b]	n.d	13	12	14		11	14	n.d	14	n.d
GN	19	18	15	16	18	21	19		n.d	18	19	23	n.d
CIP	22	24	25	27	22	18	21		n.d.	22	21	19	20
	MIC[a] (µM)												
[NiL$_2$]	32	16	8	16	8	8	16		64	8	16	32	8
HL	64	128	n.d[b]	n.d.	2	64	32		>256	64	64	8	n.d.
GN	1	2	1	2	1	0.5			n.d	1		2	n.d
CIP	0.5	0.5	1	0.5	0.5	2	0.5		n.d	0.5	1	0.5	0.5

[a]The lowest peptide concentration that prevented bacterial growth was identified as the minimum inhibitory concentration (MIC) in three separate experiments carried out in triplicate. Abbreviations:PA: *P. aeruginosa*, KP: *Klebsiella pneumoniae*, EA: *Enterobacter aerogenes*, SD: *Shigella dysenteriae*, LM: *Listeria monocytogenes*, GN: Gentamisin, CIP: Siprofloksasin.

[b]n.d: Not detected

4. Conclusion

In this work, the synthesis and characterization of a novel 3-hydroxy-2-naphthoic acid hydrazide derivative, the hydrazone ligand **HL** and its Ni(II) complex was reported. Elemental analyzes, spectroscopic studies and magnetic measurements were performed to characterize the structural properties of the prepared compounds. ^{1}H-NMR and ^{13}C-NMR confirmed the structure of **HL**. The metal-to-ligand ratio of the **[NiL$_2$]** complex, determined by elemental analysis and mass spectra, was 1:2. The O-H and C=O bands observed in the IR spectrum of HL were not observed in the spectrum of the complex. In addition, shifts in the $(C=N)_{imine}$ and $(C=N)_{pyridine}$ bands were observed. The duplicating of the signals in the ^{1}H-NMR and ^{13}C-NMR spectra of the ligand indicates the presence of E and Z isomers of the ligand in DMSO-d_6 solution. These data show that the ligand in the E-isomer form coordinates to the metal atom via carbonyl-O, azomethine-N, and pyridyl-N atoms. When the antibacterial activity of the newly synthesized **HL** and **[NiL$_2$]** was tested on clinically important isolates and pathogenic strains, it was found that the **[NiL$_2$]** complex exhibited a wider zone width than the ligand in all microorganisms tested. It is of crucial importance for clinical microbiology as it has a stronger antibacterial effect against Gram-negative bacteria than against Gram-positive bacteria and also plays an effective role against resistant germs. The fact that the tested compounds have strong antimicrobial activity against microorganisms such as *E. coli*, *P. aeruginosa*, and *S. aureus*, which cause serious diseases in outpatient groups and cause death in intensive care patients, as well as resistant microorganisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), indicates that they may be antibiotic alternatives in the future. Furthermore, the chemicals examined have strong antibacterial action against *E. faecalis*, a Gram-positive bacteria prevalent in the gastrointestinal system. When the antibacterial activity of the new synthesized products are compared to the antibiotics utilized as positive controls, the compounds show promise as an alternative to antibiotics.

Ethics in Publishing

There are no ethical issues regarding the publication of this study.

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