



Synthesis, Characterization, and Biological Activity of New Metal Ion Complexes with Schiff Base Derived from 2-Acetylthiophene and Isatin

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Abstract

This study describes the preparation of a new bidentate Schiff base derived from the condensation of Isatin-3-hydrazone with 2-acetylthiophene and the preparation of new series of complexes with a good yield. The prepared ligand was characterized by IR, UV-Vis, C, H, N, and S elemental analyses, ¹H and ¹³C NMR, LC-Mass spectrometry, and physical measurements. Its complexes were analyzed by C, H, N, and S elemental analyses, UV-Vis., FTIR, NMR, LC-Mass Spectra, atomic absorption spectroscopy, magnetic susceptibility, and conductivity measurements. The results from spectroscopy and measurement studies showed that the ligand coordinated to the metal ion as a bidentate ligand via oxygen and nitrogen, forming an octahedral geometry around it. *In vitro* antimicrobial activity of the prepared compounds was tested against *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Bacillus*, and *Candida* fungi by the agar well diffusion method. The ligand and its complexes have a good effect on the studied microorganisms' Gram-positive and Gram-negative strains and fungi.

Keywords: 2-Acetylthiophen, Isatin-3-Hydrazone, Biological activity, Schiff base complexes, Octahedral eometry

1. Introduction

Schiff bases are organic molecules that can be synthesized by the condensation reaction between primary amines and carbonyl compounds (aldehydes and ketones) in the presence of a suitable catalyst could be acid or base. These compounds are also known as imine or azomethine with structure (R-CH=N-R⁻) when R, R⁻ = alkyl or aryl [1]. They reveal a wide range of applications in biological activity, agrochemicals, modern technology such as optical computers, measure, and control intensity of irradiation, reversible optical memories, as well as a photodetector in biological systems, catalysis, and as modifiers for polymers [2-7]. Azomethine-containing compounds are coordinated to the metal ions through the nitrogen atom of azomethine moiety as well as various donor atoms such as nitrogen, oxygen, and sulfur depending on the substituted moieties [8]. So, these compounds are characterized by stabilizing different metal ions in various oxidation states, synthesizing simplicity, and flexibility with exceptional stability [9]. Lately, the great importance of complexes containing Schiff base is that they are used widely in biological activity [10-11], industrial [12], analytical applications [13], and as catalysts in various applications and organic reactions [13-14].

Thiophene and isatin Schiff bases and their complexes played a major role in the development of coordination chemistry as they form stable complexes with most of the metal ions [12-16].

Due to the dramatic raises of microbial against the presented drugs in the last years, the finding of new antimicrobials is biologically important. [17] So, this paper deals with the synthesis, elemental and spectral characterization of a newly bidentate ligand of 2-acetylthiophene and its corresponding complexes. Also, studying *in vitro* antimicrobial tendency against Gram-positive, and Gram-negative strains of bacteria and fungi.

2. Experimental

2.1. Materials

All reagents and chemicals used in this study were in the analytical grade and purchased from (Sigma-Aldrich). Isatin (1H-indole-2,3-dione) 97%, Hydrazine monohydrate 99%, 2-acetylthiophene 99%, MnCl₂.2H₂O 99%, NiCl₂.6H₂O 99%, CuCl₂.2H₂O 99%, CoCl₂.6H₂O 99%, and ZnCl₂ 98% were provided from BDH and used once received.

2.2. Instruments

Melting points of the prepared compounds were measured by Gallen Kampm F.B-60 Melting point

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Apparatus. FTIR-spectra of ligand and its complexes were recorded as a disk of KBr and CsI-pellets by IR Prestige-21, single beam, Fourier Transform Infrared Shimadzu spectrophotometer, Japan in the range (4000-400) cm^{-1} . A Shimadzu-1800, double-beam UV-Vis spectroscopy, Japan was used to record electronic absorption spectra of the prepared ligand and the metal complexes in 10-3M of DMF solution within (200-1100)nm. The magnetic susceptibility of the inorganic complexes was measured using a Bruker BM6 magnetic balance Bruker, Zürich, Switzerland. Also, elemental analyses of C, H, N, and S were carried out on the Vario EL III instrument (Analysis system GmbH, Hanau, Germany). Molar conductance of the complexes was measured in 10-3M DMF solution at RT using WTW ProfiLine Oxi3205 conventional portable meter-Xylem Inc., Weinheim, Germany. NMR spectra were carried out on a Bruker DRX300NMR spectrometry (Bruker, Zürich, Switzerland) at 107 MHz and DMSO- d_6 was used as a solvent for the measured samples. Also, LC-Mass spectrometry was used to determine the molecular weight for the prepared ligand recorded by MS QP50A: DI Analysis Shimadzu QP-2010-plus (E170Ev) spectrometer.

2.3. Synthesis

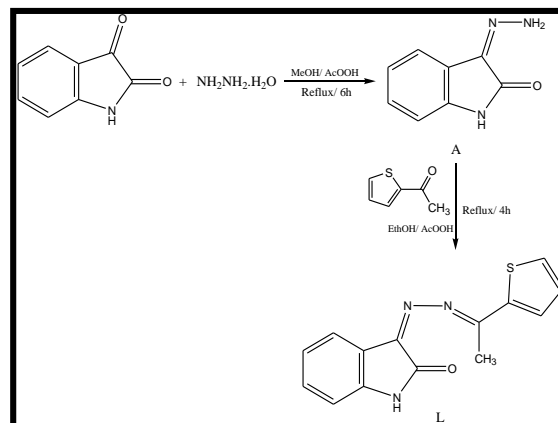
2.3.1. Synthesis of the ligand

Step I: Preparation of 3-Hydrazone-1,3-dihydro-indole-2-one (A)

Compound (A) was prepared as mentioned in [18]. In 50ml round bottom flask isatin-3-hydrazone solution (1gm, 0.0067mole in 10ml methanol) was added dropwise to a solution of hydrazine monohydrate (0.34gm, 0.0067mole in 10ml methanol) under stirring. The mixture of the reaction was refluxed for 6h. The yellow precipitate formed was filtered, washed with methanol, and dried at 50 °C. The yield of the prepared compound was 75%.

Step II: Preparation of Schiff base 3-[(1-Thiophen-2-yl-ethylidene)-hydrazono]-1,3-dihydro-indol-2-one (L)

A solution of 2-acetylthiophene (0.78gm, 0.0062mole in 10ml ethanol) was added dropwise to (1gm, 0.0062mole) of 3-hydrazone-1,3-dihydro-indole-2-one in 10ml of ethanol and 3drops of glacial acetic acid were allowed to react in a 50ml round bottom flask. The mixture was refluxed under stirring for 4h. An orange precipitate formed was collected by filtration, washed, and recrystallized with hot ethanol then dried at 50 °C. The yield was 55%. The preparation of L is shown in Scheme 1.



Scheme 1

2.3.2. Preparation of the Metal Complexes

New complexes were synthesized by mixing 10ml methanol of the metal salt as chloride metal salt (0.0018mole) (where $M^{2+} = Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+},$ and Zn^{2+}) with (0.0036mole) of the ligand (1:2) was dissolved in 10ml of methanol. The solution was stirred under heating at 50°C for 2h until the precipitate was formed. The colored complexes were separated by filtration, washed with methanol and ether, left to dry at 80°C, and recrystallized by hot methanol.

2.4. Biological Activity

All the synthesized ligand and its perspective metal (II) complexes were diagnosed *in vitro* against four types of bacteria (*Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumonia*, and *Bacillus*), and one fungus (*Candida*) by agar well method. A sterile metallic borer was used to dig the wells in the media with centers of at least 6mm diameter. A solution (200 μ l) of the synthesized samples 2mg/ml in DMSO was presented into the wells and one well was supplied by DMSO as a control. Immediately, the plates were incubated at 37°C for 24h. The inhibition activity of the tested compounds against the studied microbial was determined by measuring the diameter of the inhibition zones in millimeters (mm).

3. Result and Discussion:

The physical properties and elemental analysis of L and its complexes are shown in Table 1.

3.1. Infrared and NMR Spectral Measurements

Schiff base (A) was synthesized from the condensation of isatin with hydrazine monohydrate in a 1:1 mole ratio then reacted with one mole of 2-acetylthiophene to yield L. The reaction was carried out in ethanol in the presence of glacial acetic acid as

a catalyst. Fourier transforms infrared (FTIR) spectra for the prepared ligand and its complexes and assignments are tabulated in (Table 2).

Table 1: Physical data and elemental analysis of ligand and its metal complexes

Compound Formula	M.Wt gm/mol	m.p C ^o	Color	Elemental analysis experimental (Calculated)						
				%C	%H	%N	%S	%O	%Cl	%M
L C ₁₄ H ₁₁ N ₃ OS	269.7	234	Orange	62.10 (62.43)	4.00 (4.12)	15.77 (15.60)	11.89 (11.91)	5.60 (5.94)	-	-
[Mn L ₂ Cl ₂].4H ₂ O	736.6	213 dec.	Red Brown	45.13 (45.66)	3.78 (4.11)	11.17 (11.41)	8.65 (8.71)	13.15 (13.03)	9.50 (9.63)	7.70 (7.46)
[CoL ₂ Cl ₂].6H ₂ O	829.7	203 dec.	Dark Yellow	43.68 (43.31)	4.11 (4.41)	10.00 (10.82)	8.45 (8.26)	16.56 (16.48)	9.05 (9.13)	7.26 (7.59)
[Ni L ₂ Cl ₂]. 6H ₂ O	776.3	200 dec.	Yellow	43.40 (43.32)	4.25 (4.41)	10.46 (10.83)	8.12 (8.26)	16.40 (16.49)	9.02 (9.13)	7.42 (7.56)
[Cu L ₂ Cl ₂].2H ₂ O	709.1	177	Dark Brown	47.35 (47.42)	3.68 (3.70)	11.45 (11.85)	9.00 (9.04)	9.15 (9.02)	10.22 (10.00)	8.75 (8.96)
[Zn L ₂ Cl ₂]	674.94	218 dec.	Light Yellow	49.40 (49.83)	3.55 (3.29)	12.50 (12.45)	9.33 (9.50)	4.52 (4.74)	10.32 (10.51)	9.52 (9.69)

Table 2: The characteristic IR (cm⁻¹) bands of L and complexes

Compound Formula	$\nu(\text{N-H})$	$\nu(\text{C=O})$	$\nu(\text{C=N})$	$\nu(\text{O-H})$	$\nu(\text{M-O})$	$\nu(\text{M-N})$	$\nu(\text{M-Cl})$
L	3201s	1687s	1612s	-	-	-	-
[Mn L ₂ Cl ₂].4H ₂ O	3161	1762	1658	3360m	524w	501m	289
[CoL ₂ Cl ₂].6H ₂ O	3217	1685	1658	3361m	501m	443m	379
[Ni L ₂ Cl ₂]. 6H ₂ O	3163	1730	1658	3360m	524w	501m	289
[Cu L ₂ Cl ₂].2H ₂ O	3196	1732	1618	3450m	480w	457m	277
[Zn L ₂ Cl ₂]	3161	1658	1591	3360m	524w	501m	289

In the IR-spectra of the ligand, a stretching band at 3201 cm⁻¹ was assigned to the stretching mode of (NH) of isatin moiety as observed in Figure 1. In the double bond region, two noticeable bands presented at 1687 cm⁻¹ and 1612 cm⁻¹ attributed to the stretching band modes of carbonyl of the isatin moiety and imine functional groups respectively [14-16]. Due to the formation of the complexes, the IR-spectra of the ligand exhibited an appropriate shift. The $\nu(\text{C=O})$ of the isatin and $\nu(\text{C=N})$ imine functional groups bands are observed in the range 1685-1730 and 1618-1658 cm⁻¹ respectively, compared with the bands that detected in the free ligand. This shift was indicative of the coordination of the carbonyl oxygen and the imine nitrogen to the metal ions and supporting the formation of M-O and M-N bonds respectively. Also, broadbands were observed around 3360-3450 cm⁻¹ belonging to the $\nu(\text{O-H})$ of water molecules, indicating for coordination of the water to the central metal ions [17-19]. New bands appeared at low intensity with

lower wavenumbers in the IR spectrum of the complexes in the regions (524-480) cm⁻¹, (501-443) cm⁻¹ and (379-277) cm⁻¹ assigned to $\nu(\text{M-O})$, $\nu(\text{M-N})$ and $\nu(\text{M-Cl})$ respectively [19-22].

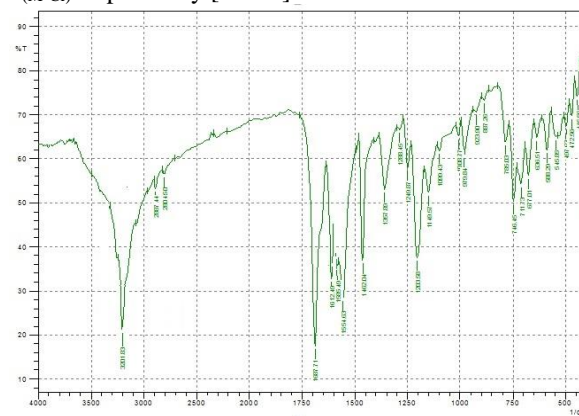
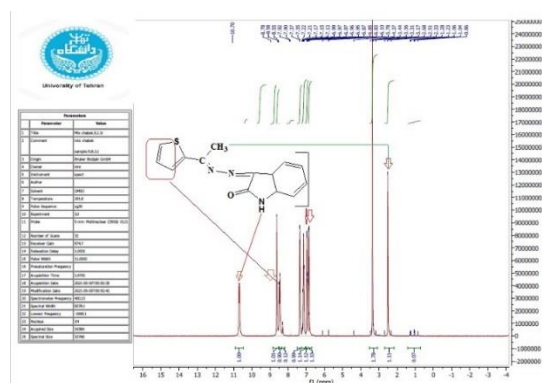
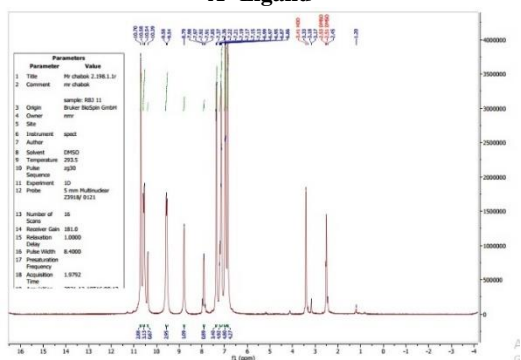
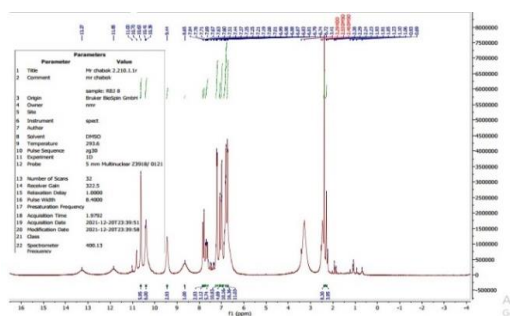
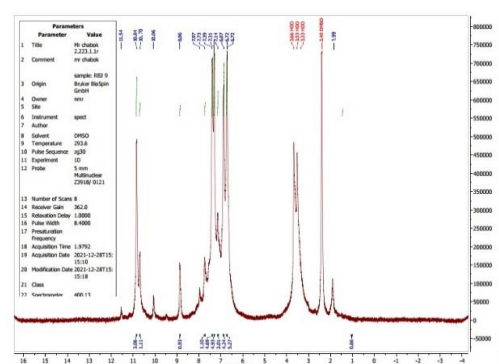
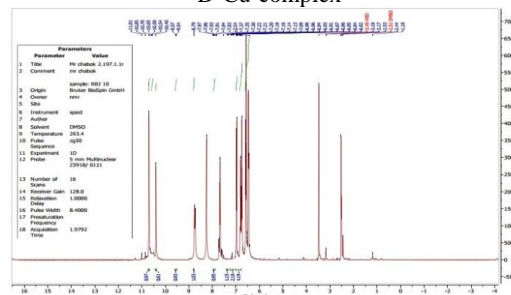


Fig.1: IR-spectrum of L

Table 3: ^1H - and ^{13}C -NMR data of **L** and its complexes

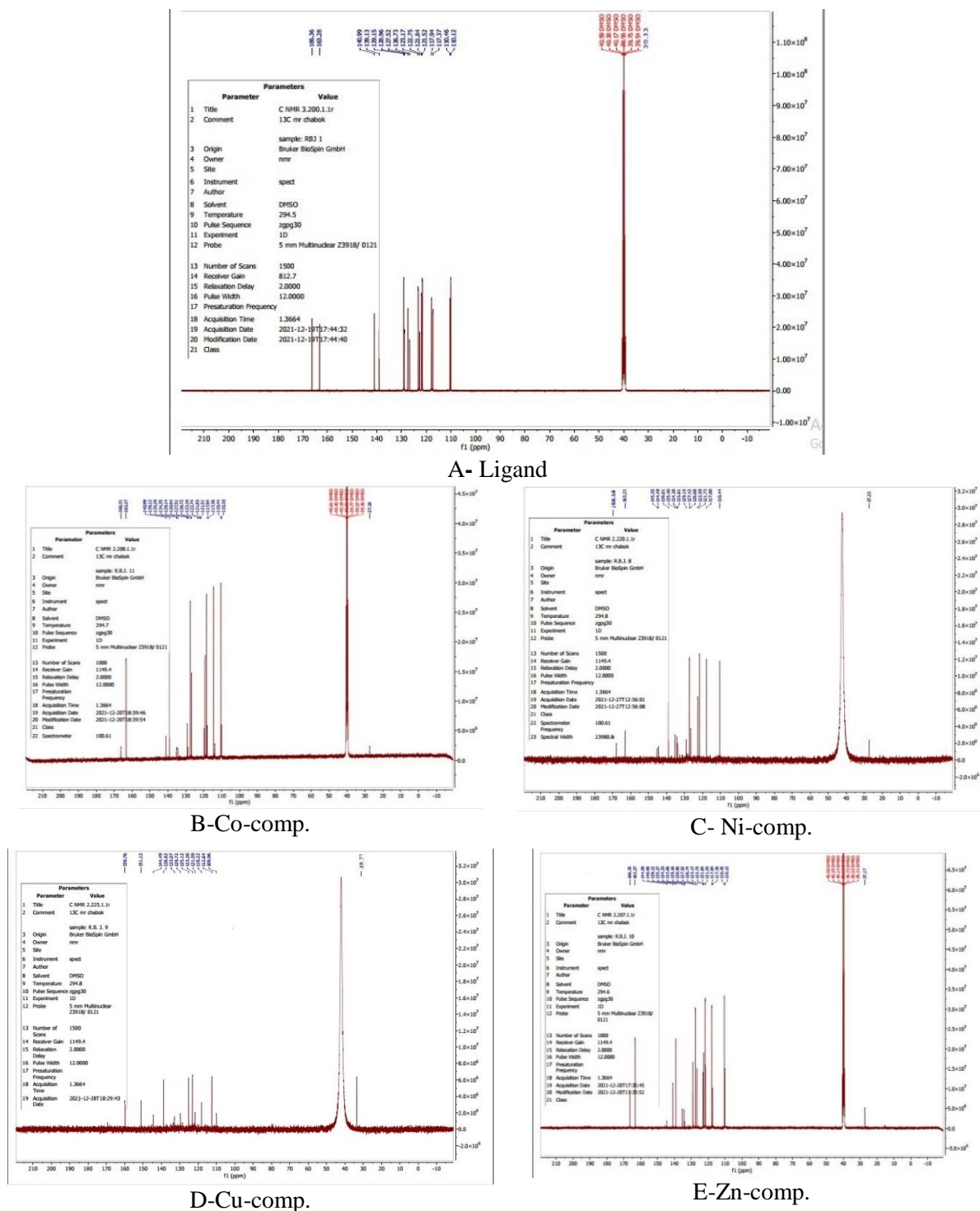
Compound	^1H -NMR (ppm)	^{13}C -NMR (ppm)
L	$\delta=2.51$ (s, 3H, CH_3), 6.97-7.22 (m, 4H, Ar-H), 8.55-8.78 (d, 3H, Thiophene moiety), 10.70 (s, 1H, NH)	$\delta=39.33$ (3C, CH_3), 110.12-121.84 (6C, Ph), 122.73-127.52 (4C, Thiophene), 166.36 (C=O), 163.28 (C=N)
$[\text{CoL}_2\text{Cl}_2] \cdot 6\text{H}_2\text{O}$	$\delta=2.45$ (s, 3H, CH_3), 6.86-6.97 (m, 4H, Ar-H), 7.19-7.22 (d, 3H, Thiophene moiety), 10.70 (s, 1H, NH)	$\delta=27.18$ (3C, CH_3), 110.10-121.83 (6C, Ph), 127.51-134.35 (4C, Thiophene), 166.31 (C=O), 163.27 (C=N)
$[\text{NiL}_2\text{Cl}_2] \cdot 6\text{H}_2\text{O}$	$\delta=2.38$ (s, 3H, CH_3), 6.72-6.81 (m, 4H, Ar-H), 7.51-7.63 (d, 3H, Thiophene moiety), 10.70 (s, 1H, NH)	$\delta=27.23$ (3C, CH_3), 110.44-127.42 (6C, Ph), 133.81-139.01 (4C, Thiophene), 168.56 (C=O), 163.21 (C=N)
$[\text{CuL}_2\text{Cl}_2] \cdot 2\text{H}_2\text{O}$	$\delta=1.98$ ppm (s, 3H, CH_3), 6.72-7.31 (m, 4H, Ar-H), 7.39-7.97 (d, 3H, Thiophene moiety), 10.70 (s, 1H, NH)	$\delta=39.77$ (3C, CH_3), 109.96-125.12 (6C, Ph), 129.72-144.49 (4C, Thiophene), 159.76 (C=O), 151.12 (C=N)
$[\text{ZnL}_2\text{Cl}_2]$	$\delta=2.18$ (s, 3H, CH_3), 6.82-6.91 (m, 4H, Ar-H), 7.54-7.84 (d, 3H, Thiophene moiety), 10.70 (s, 1H, NH)	$\delta=27.17$ (3C, CH_3), 110.12-122.73 (6C, Ph), 126.74-129.15 (4C, Thiophene), 166.36 (C=O), 163.27 (C=N)

**A- Ligand****B- Co-complex****C- Ni-complex****D- Cu-complex****E- Zn-complex****Fig.2:** ^1H NMR spectra of ligand and complexes

^1H and ^{13}C -NMR-spectra of the ligand and complexes in DMSO-d_6 gave an additional confirmation about the formation of the prepared compounds in this study [7-8,25-26]. $[\text{MnL}_2\text{Cl}_2] \cdot 2\text{H}_2\text{O}$ didn't show spectrum. The expected chemical shifts of **L** and its complexes are illustrated in Table 3 and in Figures 3 and 4.

3.2. The Mass Spectral Studies:

The mass spectra of the prepared ligand were consistent with the proposed structural formula $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_5$ as shown in Figure 2. Three bands are revealed in the mass spectra of the ligand resulting from the successive fragmentation of **L**. The peak detected at 269.7 m/z related to the molecular ion of the **L**. Additional distinct peaks were associated with other fragments.

Fig.3: ^{13}C NMR of ligand and complexes

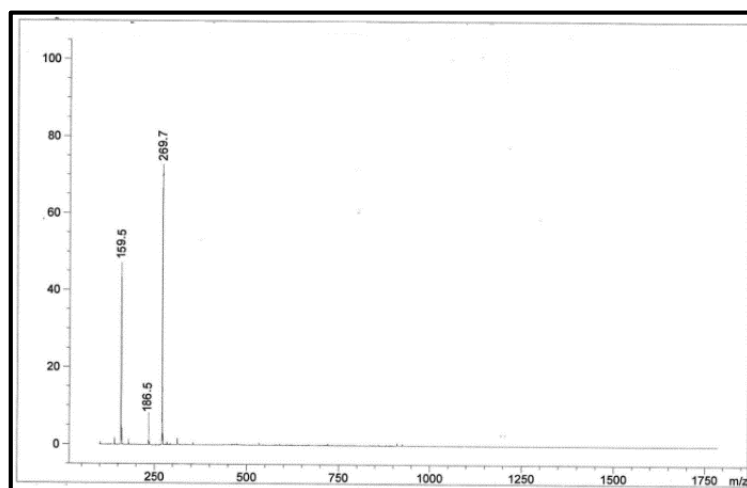


Fig.4: LC-Mass Spectra of L

3.3. Electronic Absorption Spectra Magnetic Moment, and molar conductivity:

The electronic spectra of L and its complexes were recorded in 10^{-3} M in DMF solution at room temperature in the range (200-1100) and data were presented in Table 3. The UV-V. spectra of the L revealed two strong intensity absorption bands at 249 and 313 nm ascribed to intra-ligand $\pi-\pi^*$ and $n-\pi^*$ transitions of azomethine and carbonyl chromophores, respectively [14]. Changes in positions of absorption bands were observed in the spectrum of the complexes indicating the coordination of the metal ions through azomethine and carbonyl functional groups. The electronic spectrum of Co(II) complex in DMF gave bands at 275 nm and 289 nm in the UV. region due to $\pi-\pi^*$ and $n-\pi^*$ transitions in the ligand field. New bands displayed of Co(II) spectrum about 625 nm and 495 nm in the visible area assigned to ${}^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ and ${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$

belongs to (d-d) transitions. Also, an intense and sharp band was detected about 320 nm belongs to LMCT. The magnetic moment 4.35 BM and the detected electronic spectrum of Co(II) complex give the probability of the formation of high-spin octahedral geometry [26-27].

The absorption spectra of d^9 Cu(II) complex exhibited bands at 211 nm, 268 nm, and 380 nm attributed to $\pi-\pi^*$, $n-\pi^*$ transitions, and charge transfer type LMCT respectively. Six coordinates around Cu(II) as expected in the presence of broadband centered on the 635 nm which attributed to ${}^2E_g \rightarrow {}^2T_{2g}$ in which belongs to ${}^2B_{1g} \rightarrow {}^2A_{1g}$, ${}^2B_{1g} \rightarrow {}^2B_{2g}$. These d-d bands were strongly indicative of the distorted octahedral

geometry around the metal ion. This is further supported by the magnetic susceptibility value of 1.89BM. [27].

The bands in the UV-region of the spectrum of Mn(II) complex at 267 nm and 317 nm can be attributed to intraligand $\pi-\pi^*$ and $n-\pi^*$ transitions. Because of multiplicities in the ground and excited states are different Mn(II) complex didn't show any d-d transitions except one band at 395 nm ascribed to LMCT. These findings agree with the value of $\mu_{\text{eff}} = 6.26\text{BM}$ indicating an octahedral geometry of ligands around Mn(II) ions [27-29].

The spectrum of Ni(II) [26,28-29] complex revealed the electronic absorption bands of the ligand moiety at 260 nm and 312 nm assigned to $\pi-\pi^*$ and $n-\pi^*$ transitions respectively. Three bands in the visible region were observed about 400, 500, 810 nm attributed to the spin-allowed transitions ${}^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$, ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$, and ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ respectively. The

observed value of the magnetic moment of Ni(II) complex in the normal range for octahedral arrangement is equal to 3.68BM.

The electronic spectra of the d^{10} Zn(II) complex showed a charge transfer band at 407 nm as well as two bands at 275 nm and 329 nm corresponding The electronic spectra of the d^{10} Zn(II) complex showed a charge transfer band at 407 nm as well as two bands at 275 nm and 329 nm corresponding to $\pi-\pi^*$, $n-\pi^*$ transitions [29-31]. The molar conductivities indicate that the complexes are non-electrolyte. Figure 5 represents the electronic spectra of the prepared ligand and its complexes. Depending on the obtained results, the proposed structure of the prepared complexes is observed in Figure 6.

Table 4: Electronic spectra, magnetic moments, and molar conductivity for the prepared compounds

Compound	Conductivity Ohm ¹ .cm ² .mol ⁻¹	μ_{eff} BM	Band Position λ (nm)	Assignments
L	-	-	249 313	$\pi-\pi^*$ $n-\pi^*$
[Mn L ₂ Cl ₂].2H ₂ O	10	6.26	267 317 395	$\pi-\pi^*$ $n-\pi^*$ C.T
[Co L ₂ Cl ₂].6H ₂ O	36	4.35	275 289 495 625	$\pi-\pi^*$ $n-\pi^*$ ${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ ${}^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$
[Ni L ₂ Cl ₂].6H ₂ O	20	3.68	260 312 400 500 810	$\pi-\pi^*$ $n-\pi^*$ ${}^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$ ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$
[Cu L ₂ Cl ₂].4H ₂ O	32	1.89	211 268 380 635	$\pi-\pi^*$ $n-\pi^*$ C.T ${}^2B_{1g} \rightarrow {}^2B_{2g}$
[Zn L ₂ Cl ₂]	3	Diamagnetic	275 329 407	$\pi-\pi^*$ $n-\pi^*$ C.T

C.T= Charge Transfer

3.4. Biological Activity:

The *in vitro* results of Schiff base THD and its metallic(II) chelates were diagnosed against *E. coli* (G⁻), *S. aureus* (G⁺), *Klebsiella pneumonia* (G⁻) and *Bacillus* (G⁺) bacterial strains and *Candida* fungi to evaluate their antimicrobial susceptibility using the agar diffusion method, as shown in Table 4 and Figure 7. DMSO was used as a controller for both antibacterial and antifungal activity. In general, the prepared ligand and its complexes were active against the studied cultures at the selected concentration of 2mg/ml. The ligand L exhibited a high inhibition against the gram-negative strains. Cobalt and copper complexes showed significantly the highest activity against both Gram-negative and Gram-positive of the tested strains. On the other hand, the Mn, Ni and Zn-complexes revealed a moderate inhibition against the tested bacterial strains. The potential of the prepared 2-acetylthiophene based compounds was screened against *Candida* fungal species and observed an

excellent activity against the studied fungal. The ligand and its complexes were displayed very high activity against the bacterial strains and fungi under this study [31-32].

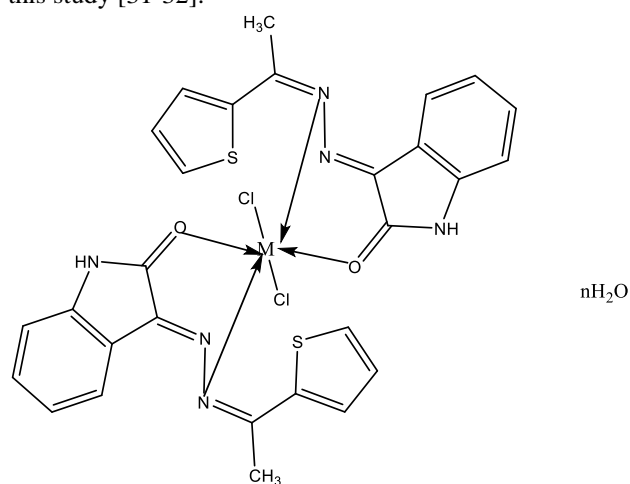


Fig. 6. The proposed geometry of the prepared complexes

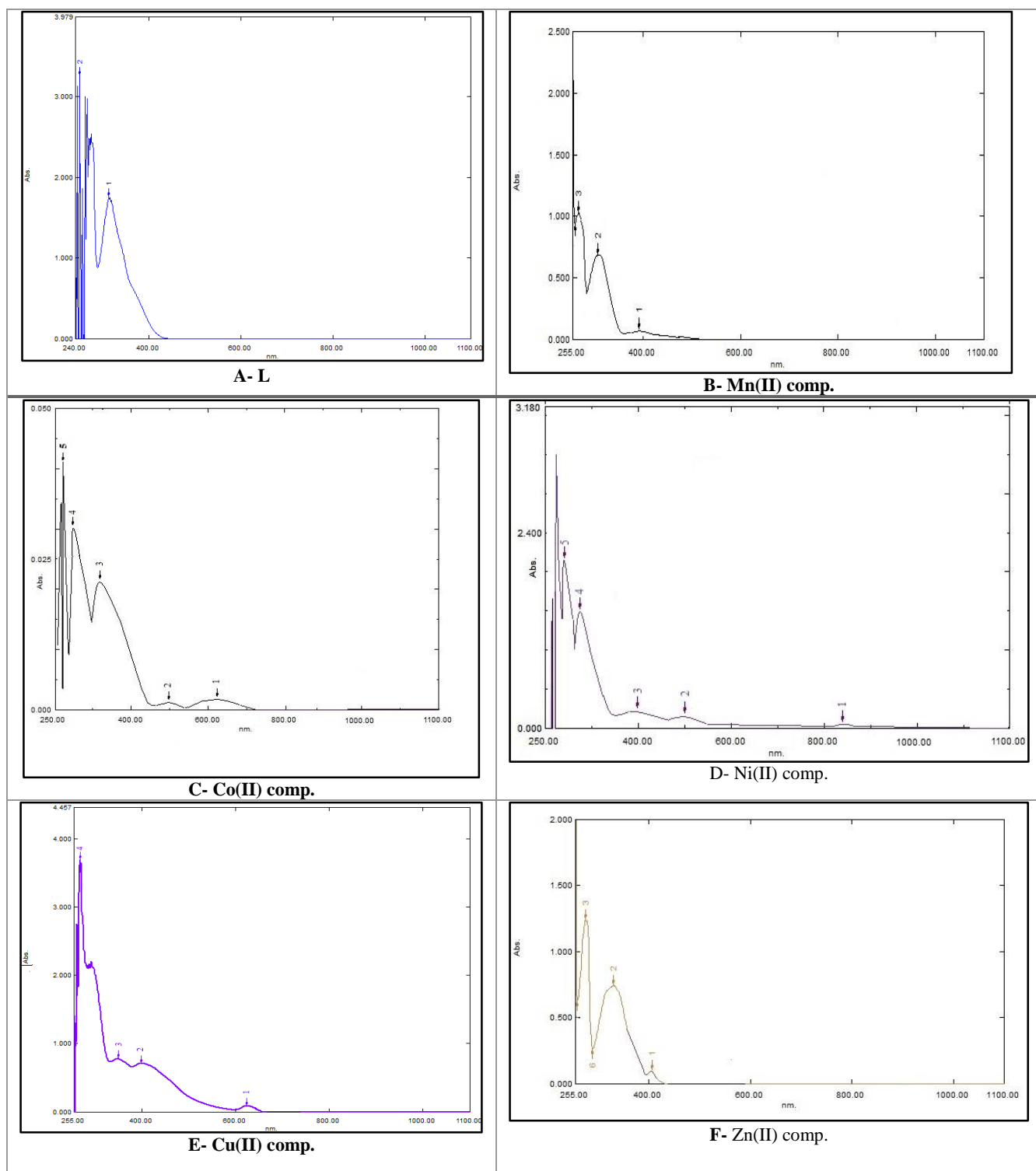


Fig. 5: The electronic spectra of ligand and complexes

Table 5: Antibacterial and antifungal activity data for L and its complexes

Compound	<i>E. coli</i>	<i>S. aureus</i>	<i>Klebsiella pneumoniae</i>	<i>Bacillus</i>	<i>Candida</i>
	-	+	-	+	
L	19	14	20	15	24
[Mn L ₂ Cl ₂].4H ₂ O	11	13	17	11	23
[Co L ₂ Cl ₂].6H ₂ O	21	21	19	20	25
[Ni L ₂ Cl ₂]. 6H ₂ O	12	14	13	13	29
[Cu L ₂ Cl ₂].2H ₂ O	23	24	24	22	33
[Zn L ₂ Cl ₂]	15	16	13	15	21
DMSO	-ve	-ve	-ve	-ve	15

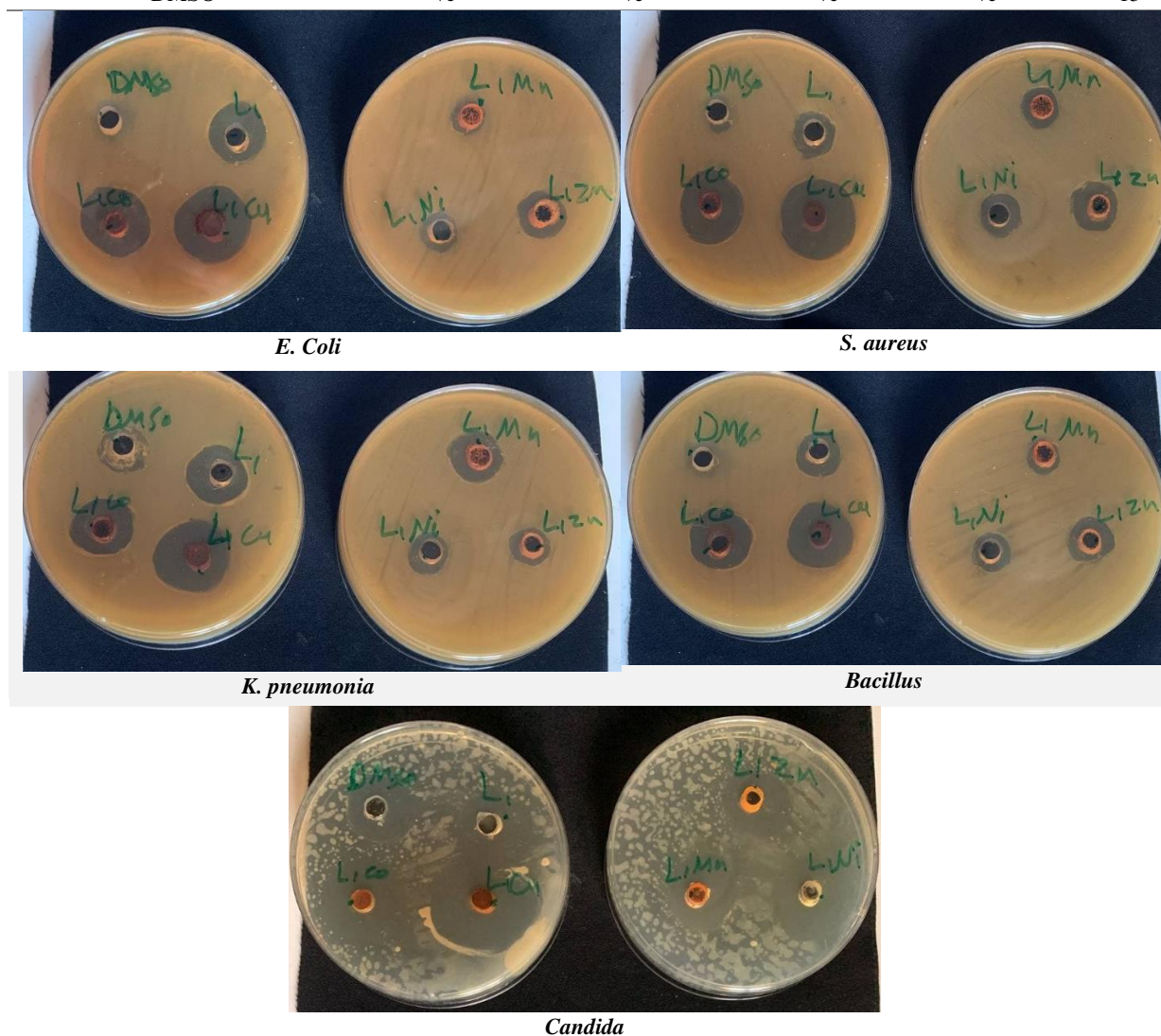


Fig.7. Antibacterial and antifungal activity of L and its complexes

4. Conclusion:

Schiff base L was synthesized in a two-step procedure from the condensation between isatin and hydrazine monohydrate to yield A which reacted with 2-acetyl thiophene then was characterized by FTIR, UV. V., C.H.N. elemental analysis, NMR, and Mass spectroscopy. The prepared ligand form stable complexes with the first series of transition metals were confirmed their structure by physical, elemental,

and spectroscopic studies. Also, the biological activity of the free ligand and its complexes were studied and showed that the prepared compounds have a good ability to be used as antibacterial and antifungal.

5. Conflicts of interest

We have no conflicts of interest to declare.

6. Formatting of funding sources

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