

Article

Synthesis, characterization, and biological activity of new metal complexes derived from 1,2,4-triazole Schiff base ligand

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ABSTRACT

The present study involves the synthesis of a new Schiff base ligand (L) and its complexes (C1-C5) with Co (II), Ni (II), Cu (II), Pd (II), and Pt (IV). The ligand was synthesized by the condensation reaction of 4-Amino-5-(3,4,5-trimethoxy phenyl)-4H-1,2,4-triazole-3-thione (1) with 2-hydroxy-1-naphthaldehyde (2). The structures of the new ligand and its complexes were confirmed by FT-IR, UV-visible, ¹H NMR, ¹³C NMR, mass spectrometry, microelement analysis (CHNS), atomic absorption flame (AAF) spectrophotometry, conductivity, and magnetic susceptibility analysis. The antibacterial activity of the ligands (L) and their complexes (C1-C5) was examined in vitro against the gram-positive and gram-negative bacteria *Staphylococcus aureus* and *Escherichia coli*, with the (MIC) values being compared to two common antibiotics. Furthermore, *Aspergillus flavus* and *Penicillium* spp. were used as test subjects for the novel compounds' antifungal properties.

Keywords: Schiff base, triazole, metal complexes, antibacterial, antifungal.

INTRODUCTION

The heterocyclic chemistry can be considered a separate field in organic chemistry according to their many decades of history with a boundary spectrum of applications ¹. Triazoles are a class of five-membered ring heterocyclic compounds that contain two carbon and three nitrogen atoms. The connectivity of the five atoms in triazoles results in two sets of isomers, 1,2,3-triazole and 1,2,4-triazole. Each one of these isomers has two tautomers ². There are two types of 3-mercapto-1, 2, 4- triazoles. They can be in two tautomeric shapes, i.e., you can bind mobile hydrogen once to nitrogen (thione form) and once to sulfur (thiol form). The predominant form is thion. Therefore, the 3-mercapto-1,2,4-triazole derivatives are most of special interest ³. 3-Mercapto-1H-1,2,4-triazol-5-yl derivatives have been reported in numerous studies, a thiol-thione group leading to an increase in biological activity linked to the triazole moiety ⁴ Triazoles and their derivatives became main class of organic molecules which have wide range of applications in the fields of pharmaceutical chemistry, drug design and drug discovery⁵ Different triazole derivatives have been reported as antifungal ⁶, antioxidants ⁷, antitumor ⁸, insecticides ⁹, antibacterial ¹⁰, antiviral ¹¹, anti-

inflammatory ¹², antineoplastic ¹³, sedatives ¹⁴, anti convulsants ¹⁵, anti-histaminic [16], and CNS stimulants ¹⁷. Compounds with the structure of azomethine group(—C= N—) are known as Schiff bases, which are usually synthesized from the condensation of primary amines and compounds having active carbonyl groups.

Further, Schiffbases represent an important class of organic compounds, especially in the medicinal and pharmaceutical fields. The chemistry of Schiff bases derived from 1,2,4-triazole analogs has been an interesting field of study for a long time. It is well known from the literature that Schiff bases derived from 1,2,4-triazole displayed excellent biological properties. In particular, they show antibacterial, antifungal, antitubercular, antioxidant, antitumor, analgesic, anti-inflammatory, and pesticide properties. They are essential molecules in the medicinal and pharmaceutical fields, and it has been suggested that the azomethine linkage might be responsible for their biological activities ¹⁸. Their biological activity increases after chelation with metal ions ¹⁹. The scope of metal-based triazole-derived Schiff bases has expanded, as it has been acknowledged that most of these metal chelates may act as models for biologically significant species ²⁰. Now, novel diagnostic and therapeutic metal chelates strongly influence pharmaceutical practice ²¹. Furthermore, the developments in bio-inorganic chemistry are significant to improve the structural design of complexes and to understand their mechanisms of action with reduced toxic side effects ²².

MATERIALS AND METHODS

The chemicals used in this study were obtained from commercial sources. The melting points were recorded on the melting point apparatus (Stuart SMP30). The ¹H and ¹³C NMR spectra were recorded on Bruker Bio-Spin GmbH (400 MHz for the ¹H NMR and 100 MHz for the ¹³C NMR). The FT-IR spectra were recorded on Bruker, Tensor II spectrophotometer with ATR technique. The electrolytic conductivity values of the metal complexes (10⁻³M solutions in DMF) were measured at 25°C using a WTW Cond 7300 digital conductivity meter. The UV-Vis spectra of the ligands and their metal complexes were recorded on a SHIMADZU 1800-UV spectrophotometer. The magnetic susceptibilities tests were done using a Sherwood Scientific Magnetic Susceptibility Balance. The metal content analyses were assessed using (FL Aspect LS 131 RC1). The elemental analyses were recorded on Vario ELV5 CHNS Mode, S. No.: 11086109.

Synthesis of 4-(((2-hydroxy naphthalene-1-yl)methylene)amino)-5-(3,4,5-trimethoxy phenyl) -2,4-dihydro-3H-1,2,4-triazole-3-thione (L)

-4Amino-5-(3,4,5-trimethoxy phenyl)-4H-1,2,4-triazole-3-thione (1) was synthesized according to the literature procedure [23]. A hot solution of 1 (0.282 gm., 0.001 moles) in 25 mL ethanol was gradually added to a solution of 2-hydroxy-1-naphthaldehyde (2) (0.0172 gm., 0.001 moles) in the presence of 5–6 drops of glacial acetic acid. The mixture was refluxed for 6 hours. After completion of the reaction, the solution was poured into crushed ice. The precipitated product (L) was filtered, washed with ethanol and dried.

Synthesis of the metal complexes

The ligand **L** (0.872 g, 2 mmol) was dissolved in 30 ml of hot ethanol. Solutions of the metal salts (1 mmol, CoCl₂.6H₂O for **C1**, NiCl₂.6H₂O for **C2**, CuCl₂.2H₂O for **C3**, PdCl₂ for **C4**, and H₂PtCl₆.6H₂O for **C5**; 1 mmol) were prepared by dissolving the salts in 20 ml hot ethanol (except for PdCl₂ was dissolved in 0.02 M HCl [24] and added to the solution of **L**. The mixtures were refluxed for 6 hours (except for **C4**, which was heated up in the water bath at 75 °C), then cooled, and 10 mL of diethyl ether was added to precipitate the solid complex.

The products were filtered, washed with cold water and ethanol, dried, and recrystallized from ethanol.

RESULTS

The ligand **L** has been synthesized by the condensation reaction (Schiff base chemistry) of 4-amino-5-(3,4,5-trimethoxyphenyl)-4H-1,2,4-triazole-3-thione (**1**) with 2-hydroxy-1-naphthaldehyde (**2**) in the presence of catalytic amount of glacial acetic acid, Scheme 1. The structure of the product (**L**) was confirmed by elemental (CHNS) analysis, FT-IR, ^1H NMR, and ^{13}C NMR spectroscopy. The metal complexes **C1-C5** have been synthesized by the reaction of **L** with the proper metal salt as shown in Scheme 2.

The formulas, physical parameters, and elemental and metal content analyses of the ligand **L** and its metal complexes **C1-C5** are shown in Table 1. The elemental and metal content analyses indicated that complexes **C1**, **C2**, **C3** and **C5** have molar ratios of 1:2 (metal: ligand), while **C4** has a molar ratio of 1:1 (metal: ligand). The solubility of the metal complexes in typical organic solvents was examined, and it was found that all of the complexes were substantially soluble in DMSO, DMF, and chloroform, but they were only moderately soluble in methanol, ethanol, and chloromethane.

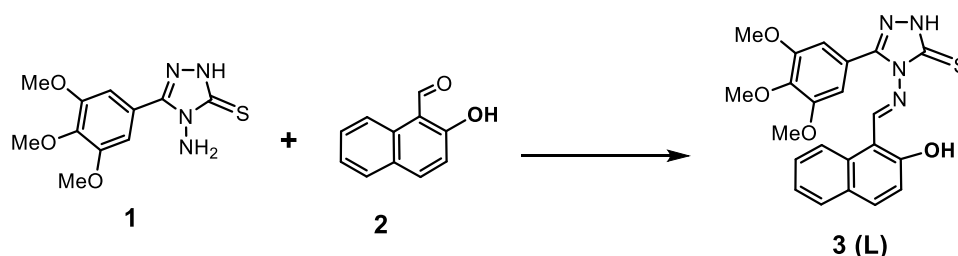


Figure 1. Synthesis of the ligand **L** (reagents and conditions: glacial acetic acid (catalytic amount), ethanol (solvent), reflux (5-6 hours)).

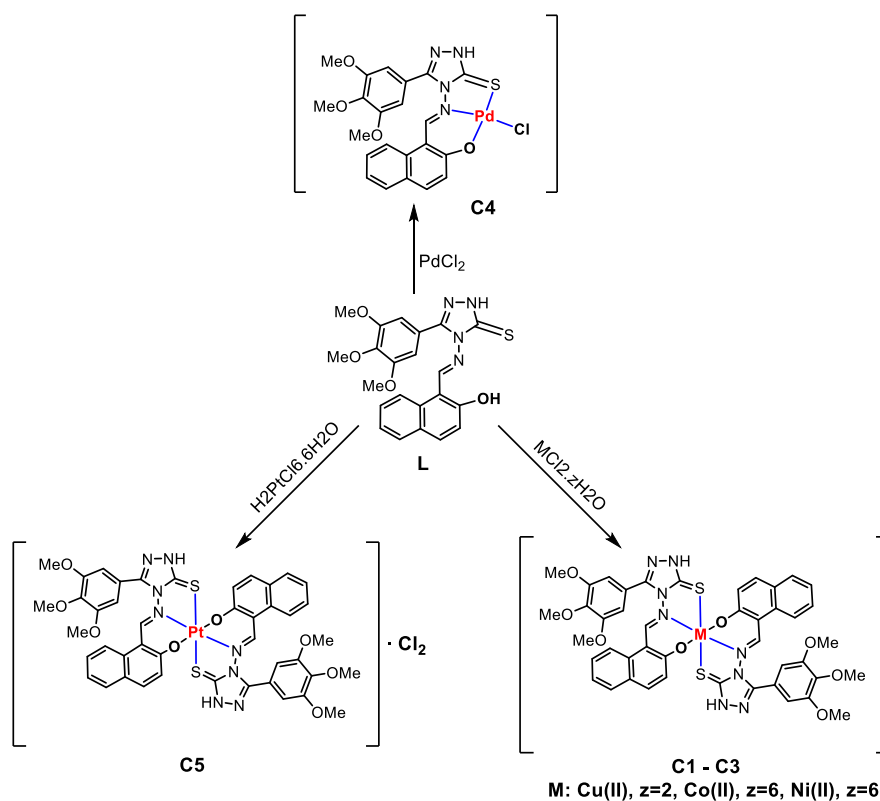


Figure 2. Synthesis of the metal complexes (**C1-C5**).

Co mp sym.	Experimental Formula	color	M.wt (g/mo l)	Yiel d	M.p c°	Elemental analysis %				Metal con- tent Foun d (calc.)
						Experimental (theoretical)				
						C	H	N	S	
L3	C ₂₂ H ₂₀ N ₄ O ₄ S	yel- low	436.49	89	234-236	60.61 (60.48)	4.79 (4.58)	13.33 (12.82)	7.52 (7.34)	-----
L3Co	[Co(C ₂₂ H ₁₉ N ₄ O ₄ S) ₂]	brown	929.91	70	226-228	57.13 (56.77)	4.39 (4.08)	12.20 (12.04)	7.08 (6.89)	7.223 (6.337)
L3Ni	[Ni(C ₂₂ H ₁₉ N ₄ O ₄ S) ₂]	brown	929.67	72	230-232	57.08 (56.79)	4.36 (4.08)	12.16 (12.04)	7.03 (6.89)	6.909 (6.313)
L3Cu	[Cu(C ₂₂ H ₁₉ N ₄ O ₄ S) ₂]	greeni sh nutty	934.52	62	196-198	56.64 (56.49)	4.35 (4.06)	12.26 (11.98)	7.14 (6.86)	7.701 (6.799)
L3Pd	[Pd(C ₂₂ H ₁₉ N ₄ O ₄ S) ₂ Cl]	brown	577.36	79	218-220	46.12 (45.76)	3.72 (3.29)	10.21 (9.71)	5.72 (5.55)	17.776 (18.432)
L3Pt	[Pt(C ₂₂ H ₁₉ N ₄ O ₄ S) ₂ .Cl ₂]	dark yel- low	1136.96	75	222-224	46.66 (46.48)	3.57 (3.34)	10.14 (9.86)	5.81 (5.63)	16.364 (17.158)

Table 1. Elemental analyses and physical characteristics of the ligand (L) and its metal complexes (C1-C5).

Infrared studies

The FT-IR spectrum of the new Schiff base ligand L shows an absorption band at 3444 cm⁻¹ for the (O-H) phenolic group. However, the band disappeared after complex formation, indicating the deprotonation of phenol -OH during complex formation²⁵. The C=N (imine group) appears as a sharp band at 1624 cm⁻¹. The appearance of a band at 3114 cm⁻¹ due to ν (N-H) was observed due to the tautomerism in the H-N-C=S groups in the triazole ring that leads to increasing the bond order of the C=S bond, and the band is shifted to the lower frequency due to complexation^{26,27}. FT-IR spectral data of Schiff base ligand L and its complexes are shown in Table. 2 and in Figure. 1

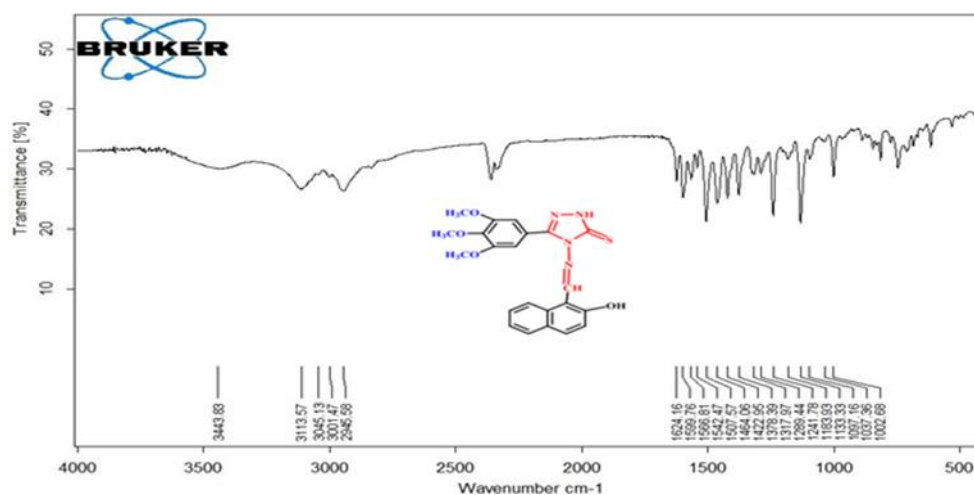


Figure 3. The FT-IR spectrum of the ligand L.

Comp.	ν _{O-H}	ν _{N-H}	ν _{C-O}	□C=S	ν _{C=N} N imine	ν _{M-O}	ν _{M-N}	ν _{M-S}	ν _{M-Cl}
L3	3444	3114	1289	1242	1623	---	---	---	---
L3Co	---	3109	1240	1185	1618	490	532	434	---
L3Ni	---	3112	1242	1185	1623	490	533	434	---
L3Cu	---	3109	1241	1126	1617	502	532	461	---
L3Pd	---	3108	1241	1183	1622	506	533	488	390
L3Pt	---	3115	1242	1133	1622	508	533	432	---

Table 2. The characteristic absorption bands in the FT-IR spectra of ligand L, C1-C5.

Nuclear Magnetic Resonance (¹H NMR and ¹³C NMR) Spectra of Ligand (L)

The ¹H NMR spectrum of ligand L showed all the expected signals. It showed a broad singlet signal at 14.13 ppm corresponding to 1 H of the NH, a singlet signal at 10.29 ppm corresponding to 1 H of the OH, singlet signal at 8.80 ppm for 1 H of the azomethine group, doublet signal at 8.06 (d, J = 9.0 Hz, 1H, aromatic), doublet signal at 7.90 (d, J = 9.0 Hz, 1 H, aromatic), multiplet signals in the range 7.56-7.25 correspond to 6 H (aromatic). In the aliphatic region of the spectrum (up-field), a signal corresponding to 9 H belonging to the protons of the 3 OMe groups was observed.

The ¹³C NMR spectrum of L showed all the expected 21 signal for the different types of carbons in the structure, it showed signals at 166.58, 162.89, 160.89, 153.33, 148.56, 148.27, 139.84, 136.65, 132.24, 129.48, 129.10, 128.47, 124.47, 123.99, 121.08, 118.87, 108.64, 106.39, 60.60, 56.36 and 56.32 ppm. Figure 1 shows the ¹H NMR (A) and ¹³C NMR (B) spectra of L.

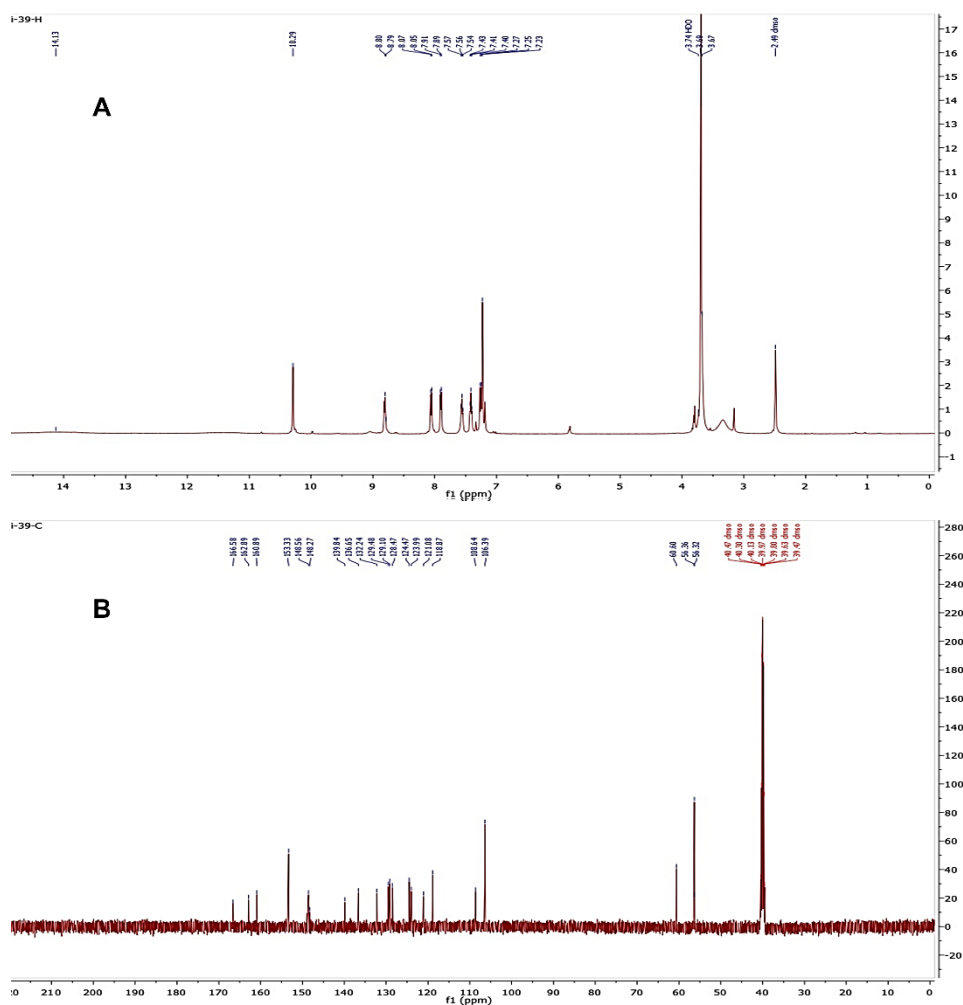


Figure 4. ^1H NMR (A) and ^{13}C NMR (B) spectra of L.

Electronic Spectra, Conductivity Measurements, and Magnetic Susceptibility

The (U.V-Vis) spectrum of ligand (L) in absolute ethanol exhibited Two absorption bands at (322 nm, 31055cm^{-1}) and (367 nm, 27247cm^{-1}) were assigned to ($\pi \rightarrow \pi^*$) and ($n \rightarrow \pi^*$) transitions ³¹. Complexation of (L) with metal ions appearance a new band in the visible and UV. These bands were attributed to M-L charge transfer and ligand field transitions. Table 3 describes bands of maximum absorption of complexes in chloroform with their assignments.

Electronic spectrum of (C1) exhibits three bands observed at (888 nm, 11261cm^{-1}) due to $^4\text{T}_{1g} \rightarrow ^4\text{T}_{2g}$ (F) (ν_1), (670 nm, 14925cm^{-1}) due to $^4\text{T}_{1g} \rightarrow ^4\text{A}_{2g}$ (F) (ν_2) and (nm, cm^{-1}) for $^4\text{T}_{1g} \rightarrow ^4\text{T}_{1g}$ (P) (ν_3) ³². these values are good evidence that octahedral geometry around two Co(II) ions [33]. The magnetic susceptibility and molar conductivity measurement indicated that the complex is paramagnetic 4.24 BM and is non-electrolytic [34]. Can be suggested octahedral structure for the binuclear complex (C1).

The electronic spectrum of (C2) shows three spin-allowed bands at (693 nm, 14430cm^{-1}), (633 nm, 15797cm^{-1}) and (587 nm, 17035cm^{-1}) assigned to $^3\text{A}_{2g} \rightarrow ^3\text{T}_{2g}$ (F) (ν_1), $^3\text{A}_{2g} \rightarrow ^3\text{T}_{1g}$ (F) (ν_2) and $^3\text{A}_{2g} \rightarrow ^3\text{T}_{1g}$ (P) (ν_3) transitions respectively [3031] This indicated geometry was octahedral for Ni(II) ion, the calculated values of magnetic moment were (2.8 BM). and it is about in the range of (2.8-3.5) BM. This is approved with octahedral geometry for Ni(II) ion ³².

The UV-visible spectrum of (C3), shows one broad band at (673 nm, 14858 cm⁻¹) assigned to ²E_g → ²T_{2g} transition³⁸, and the shoulder band at (nm, cm⁻¹) may be assigned to the charge transfer transitions LMCT. The position of this band is in good agreement with an octahedral configuration. The value of magnetic moment at room temperature was found to be (1.74B.M), which agrees well with distorted octahedral geometry around Cu (II) complex³². The conductance measurements in DMF indicate the non-ionic behavior of this complex.

The electronic spectrum of the (C4) complex shows two bands at (450 nm, 22222cm⁻¹), (425nm, 23529cm⁻¹), which are assigned to ¹A_{1g} → ¹B_{1g} and ¹A_{1g} → ¹E_g transitions, respectively[36]. The complex may have square-planar coordination with the central metal ion by the surrounding ligands. The magnetic moment data of the Pd(II) complex (0.21 BM) indicate that this complex is diamagnetic. This agrees with square-planar geometry around Pd(II) ion³⁹. The conductance measurements in DMF indicate the non-ionic behavior of this complex.

The electronic spectrum of the (C5) complex shows bands at (nm, cm⁻¹), (449 nm, 22271 cm⁻¹) and (420 nm, 23809 cm⁻¹) assigned to ¹A_{1g} → ³T_{1g}, ¹A_{1g} → ³T_{2g} and ligand to metal charge transfer (LMCT) respectively³⁹. The complexes may have an octahedral coordination of the central metal ion by the surrounding ligands. The magnetic value (0.08 BM) for Pt(IV) is observed. This agrees with octahedral geometry around Pt(IV)ion⁴⁰. The conductance measurements indicate the ionic behavior of this complex.

No	λ_{\max} nm (ν cm ⁻¹)	Assignment	ohm ⁻¹ cm ² mol ⁻¹	μ BM. found	Suggested Structure
L3	367(27247) 322(31055)	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$	---	---	---
L3Co	888(11261) 670(14925) 535(18691)	⁴ T _{1g} → ⁴ T _{2g} (F) ⁴ T _{1g} → ⁴ A _{2g} (F) ⁴ T _{1g} → ⁴ T _{1g} (P)	10.68	4.24	Octahedral
L3Ni	892(11210) 633(15797) 587(17035)	³ A _{2g} → ³ T _{2g} (F) ³ A _{2g} → ³ T _{1g} (F) ³ A _{2g} → ³ T _{1g} (P)	11.98	2.8	Octahedral
L3Cu	674(14836) 432(23148)	² E _g → ² T _{2g} LMCT	12.11	1.74	Octahedral
L3Pd	450(22222) 425(23529)	¹ A _{1g} → ¹ B _{1g} ¹ A _{1g} → ¹ E _g	10.28	Zero(0.21)	Square planer
L3Pt	530(18867) 449(22271) 420(23809)	¹ A _{1g} → ³ T _{1g} ¹ A _{1g} → ³ T _{2g} LMCT	170.33	Zero(0.08)	Octahedral

Table 3. Electronic spectra, molar conductivity, effective magnetic moments (μ_{eff}), and suggested geometry of complexes

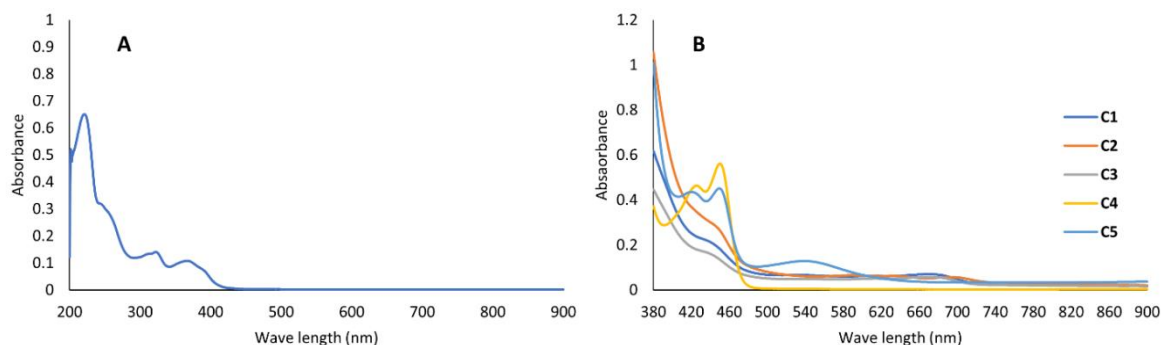


Figure 5. The UV-Vis spectrum of ligand L (A) and the metal complexes C1-C5 (B).

The antibacterial and antifungal activities of the ligand L and its complexes C1-C5

The synthesized ligand (L) and its metal complexes have been tested for their antibacterial activity against *Escherichia coli* (gram-negative bacteria), *Staphylococcus aureus* (gram-positive bacteria), and antifungal activity against *Aspergillus flavus*, and *Penicillium spp.* Fungi. Samples were prepared by dissolving the test compounds ($10^{-3}\mu\text{gm.ml}^{-1}$) in DMSO, which was used as a control as well. The disc sensitivity test protocol has been implemented; the growth inhibition zones were determined for microorganisms treated with discs of the test compounds on agar plate⁴¹. The plates were incubated at 37 °C for 24 hours, and the zone of inhibition around the disc was measured. Using the tube dilution method⁴², the minimum inhibitory concentration (MIC) of each test compound was determined. By incubating tubes with various concentrations of L, C1-C5 at 37 °C for 45 hours, the minimum inhibitory concentration (MIC) of L, C1-C5 against each bacterium was identified. Ampicillin and amoxicillin, two well-known antibiotics, were employed as conventional treatments. Evaluation of the antifungal efficacy for the new ligand (L) and its metal complexes C1-C5 was done against the pathogenic fungus (*Aspergillus flavus* and *Penicillium spp.*). The fungus was cultivated on potato dextrose agar medium and incubated at 30 °C for 72 hours. Solutions of the test compounds in DMSO (10^{-3}M) were used. The inhibition percentage of fungal growth (based on the growth in test plates relative to the appropriate control plates) was calculated according to the following equation⁴³:

$$\text{Inhibition \%} = 100 (C - T) / C$$

Where C is the diameter of fungal growth on the control plate, and T is the diameter of fungal growth on the test plate. Table. 4 also shows the antibacterial and antifungal activities for L and C1-C5, the order of activities for the test compounds against *E. coli*: C5>C4>C3>C2>C1>L; against *Staph. Aureus*: C5>C3>C4>C1= L>C1.

Table 5 shows the results of the MIC investigations; it is obvious that L and C1-C5 are more effective than the standard antibiotics ampicillin and amoxicillin since all of them have lower MIC values, C1-C5 have MIC values ($0.05\mu\text{gm. ml}^{-1}$) against *Escherichia coli*, while against *Staphylococcus aureus* C2 was found to have the lowest MIC value ($0.025\mu\text{gm. ml}^{-1}$), C1 and C3 have MIC value of $0.05\mu\text{gm. ml}^{-1}$, C4 and C5 have MIC values of $0.25\mu\text{gm. ml}^{-1}$.

Comp. No.	<i>E. coli</i> *	<i>Staph. Aureus</i> *	<i>Asp. Flavus spp</i> **	<i>Penci. spp</i> **
DMSO	---	---	---	---
L	5	6	30	37
C1	7	6	24	27
C2	8	5	26	29
C3	10	12	19	24
C4	12	8	16	25
C5	17	14	18	20

*6-8 (+), 8-10(++) and > 10 (+++).
**10-20 (++++), 20-30 (+++++) and 30-40 (++++).

Table 4. Antibacterial and antifungal activities for free ligand (L) and its metal complexes C1-C5 ($10^{-3}\mu\text{g.m.l}^{-1}$)

Compound	<i>Escherichia coli</i>								<i>Staphylococcus aureus</i>							
	Concentration (MGM. ml ⁻¹)								Concentration (MGM. ml ⁻¹)							
	0.02 5	0.05	0. 1	0.25	0. 5	1	2.5	5	0.02 5	0.05	0. 1	0.25	0. 5	1	2. 5	5
L	+	+	+	MI C	-	-	-	-	+	+	+	MI C	-	-	-	-
C1	+	MI C	-	-	-	-	-	-	+	MI C	-	-	-	-	-	-
C2	+	MI C	-	-	-	-	-	-	MIC	-	-	-	-	-	-	-
C3	+	MI C	-	-	-	-	-	-	+	MI C	-	-	-	-	-	-
C4	+	MI C	-	-	-	-	-	-	+	+	+	MI C	-	-	-	-
C5	+	MI C	-	-	-	-	-	-	+	+	+	MI C	-	-	-	-
Ampicillin	+	+	+	+	+	MI C	-	-	+	+	+	+	+	MI C	-	-
Amoxicillin	+	+	+	+	+	+	MI C	+	+	+	+	+	+	MI C	-	-

(+): growth, (MIC):99%, (-): No growth

Table 5. Minimum inhibitory concentrations (MIC) of L and C1-C5.

DISCUSSION

The disappearance of stretching vibration of phenolic group ν (O-H) and the shift of ν (C-O) 1242 cm^{-1} to lower frequencies indicate the replacement of the phenolic proton by metal cations. Furthermore, shifts in ν (C=S) and ν (C=N) values, their positions and changes in their shapes or intensities when compared with the free ligand L attributable to the coordination of this ligand with the metal

ions and indicate that the complexes are formed ²⁸, so the Schiff base ligand behaves as mono basic tridentate, can link with the metal ion at either by oxygen of phenolic group, sulfur of thione group and nitrogen of azomethine (imine) group. The bands in the range 600-200 cm⁻¹ refer to (M-O), (M-N), (M-S) and (M-Cl) in complexes ^{29,30}.

Studies on the antifungal activity of L and C1-C5 revealed that the metal complexes were superior to the free ligand L in these tests. The increased antifungal activity of metal complexes may be explained by the effect of the metal ion on the regular cell function. According to Tweed's Chelation Theory ⁴⁴, chelation reduces the polarity of the metal atom primarily because its positive charge is partially shared with the donor groups of the ligand, which makes it easier for the complex to pass through the lipid layer of the cell membrane ⁴⁵.

CONCLUSION

New 1,2,4-triazole Schiff base ligand (L) and its Co (II), Ni (II), Cu (II), Pd (II), and Pt (IV) complexes (C1-C5) have been synthesized. Different techniques confirmed their structures. The results from spectra and elemental analyses indicated the octahedral geometry around Co, Ni, Cu, and Pt atoms and square planar geometry around the Pd atom. The new ligand and its metal complexes have excellent antibacterial and antifungal activities. They can be considered as promising antimicrobial agents.

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