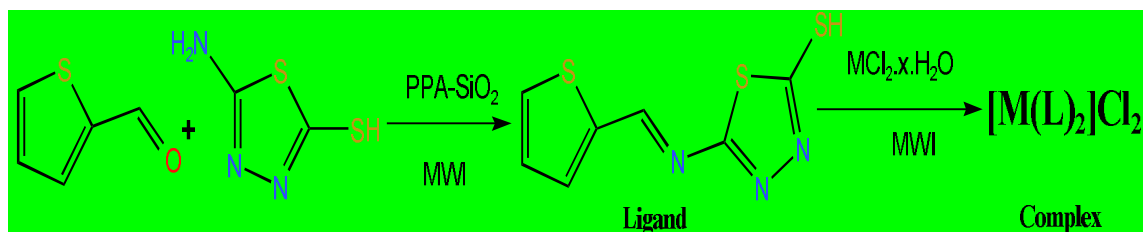


Eco-friendly Synthesis, Characterization, and Antimicrobial Evaluation of Transition Metal (II) Complexes with Thiophene-Derived Tridentate (S N N donor) Heterocyclic Schiff base Ligand

ABSTRACT

A new unsymmetric tridentate (SNN donor) Schiff base ligand was synthesized from the 1:1 M condensation of thiophene-2-carboxaldehyde with 5-amino-1,3,4-thiadiazol-2-thiol, under microwave irradiation in the presence of a green catalyst PPA-SiO₂. The bivalent 3d transition metal (M = Co²⁺, Ni²⁺ and Cu²⁺) complexes were obtained by the reaction of M(II) chloride with tridentate Schiff base ligand (L) in a 1:2 M ratio under microwave irradiation in aqueous ethanol medium. The Schiff base and its complexes have been characterised by FTIR, ¹H NMR, UV/Vis, elemental analyses, conductometry and magnetic measurements. The IR results showed that the Schiff base ligand acts as a neutral unsymmetrical tridentate with SNN donor sequence in E isomeric form towards the metal ion through azomethine-N, thiadiazole-N and thiophene-S. The electronic spectral results and magnetic measurement data revealed six coordinated octahedral geometries having the formula [M(L)₂]Cl₂ for the synthesised metal complexes. The melting point supported all the compounds' thermal stability and non-hygroscopic nature. The molar conductance data revealed the 1:1 electrolytic nature of the metal complexes. The *in vitro* biological activities of the free ligand and its metal complexes against a few bacteria and fungi were screened by the disc diffusion technique. The relative order of potency of antimicrobial activity against pathogens is Cu(II) > Co(II) > Ni(II) > Ligand.

Graphical Abstract



Keywords: Anti-microbial activity, Heterocyclic Schiff bases, Microwave irradiation, Octahedral geometry, Transition metal complexes,

1. INTRODUCTION

“Schiff base (SB), also known as imine or azomethine, ligands have attracted significant interest because of their remarkable synthetic and structural characteristics, excellent tunability, chemical selectivity concerning the central metal atom/ion, unique coordination, and structural properties” [1-3]. “These are regarded as highly promising ligands and commonly known as 'privileged ligands' due to their remarkable ligation ability with O, N and other donors that accommodate various geometries” [4, 5]. These complexes have been used as drugs and have been reported to have a wide variety of biological activities and have many biochemical, clinical and pharmacological applications [6]. These compounds are extensively researched because they have sigma donor capabilities towards metal cations and exhibit π acceptor characteristics at the imine nitrogen ($>C=N-$) atom, making them effective donor ligands in coordination chemistry [7]. Schiff bases, particularly those associated with heterocyclic structures, demonstrated a range of pharmacological and biological activities including antibacterial, cytotoxic, antifungal, antimalarial, anticonvulsant, antioxidant and anti-inflammatory properties [8]. Heterocyclic Schiff base ligands with multiple donor sites, containing both nitrogen and sulfur atoms, exhibit flexible coordination capabilities with different transition metal ions [9]. Consequently, they have garnered significant attention, especially in the creation and use of bioactive coordination compounds.

“Conventional chemical synthetic methods frequently utilize solvents and chemicals that can be hazardous, posing hazards to both environmental and human health. Instead, green synthesis approaches are made to use reagents that are less hazardous to the environment and select safer solvents, or even no solvents altogether. In addition to being environmentally friendly, “these methods can also lead to products that are more pure and plentiful” [10-12]. Microwave-assisted synthesis can increase yields and drastically reduce reaction times from hours to only a few minutes, making it a superior alternative to conventional reflux synthesis. Microwave heating is becoming increasingly popular with chemists due to its convenience and safety features. Therefore, microwave-assisted synthesis is considered an environmentally friendly or green synthetic method, essential for modern sustainable chemistry” [13-15].

“The literature survey indicates that transition metal complexes with tridentate Schiff base ligands have been extensively studied and have a variety of biological applications” [16]. However, little research has been done on the antimicrobial properties and green synthesis of transition metal complexes with thiophene-derived tridentate ligands [17]. “The main objective of this study is to elucidate the structure and evaluate the antimicrobial properties of some newly eco-friendly synthesized Co(II), Cu(II) and Ni(II) complexes with a new tridentate (SNN donor) Schiff base which was obtained by condensation of 2-thiophenecarboxaldehyde with 5-amino-1,3,4-thiadiazol-2-thiol, under microwave irradiation in the presence of green catalyst, silica gel-supported polyphosphoric acid (PPA-SiO₂)” [18]. This approach expands our earlier research [19] and accounts for the various biological activities associated with the new Schiff base and its complexes. Although, single crystal of the investigated complexes could not be isolated from any solutions; however, analytical, magnetic data and spectroscopic studies enable us to propose possible geometries of the undertaken complexes.

2. EXPERIMENTAL STUDY

2.1: Materials and Methods

The starting materials 2-thiophenecarboxaldehyde and a heterocyclic amine (5-amino-1,3,4-thiadiazol-2-thiol) were obtained from Aldrich. The 3d transition metal (II) salt ($\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ and $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$) and other chemicals used in this research project were obtained from Aldrich and stored in controllable conditions in a glovebox. Solvents like ethanol (EtOH), N, N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetone and molecular sieves (0.4 nm) were purchased from Merck.

A modified microwave oven model 2001 ETB (Bajaj Electricals Limited, Mumbai, India) with a rotating tray and a power source 230V, microwave energy put out 800W and microwave frequency 2450 MHz was used for green synthesis of ligand as well as undertaken M(II) complexes. The progress of the synthetic reaction was monitored by performing TLC using Al sheets precoated with Merck 60 F₂₅₄ that was visualised using a UV lamp.

With the EA-1106 elemental analyzer (Carlo-Erba) the elemental analysis of C, H, and N content and empirical formulas of the compounds/complexes were determined. The metal contents were estimated using standard methods. The chloride content in the complexes was determined gravimetrically as a silver nitrate test.

Molar conductance (10^{-3} M) was measured by an Elico-conductivity bridge at room temperature. The magnetic susceptibility measurements were carried out on a Gouy balance at room temperature using $\text{Hg}[\text{Co}(\text{SCN})_4]$ as the calibrant. Electronic spectra were recorded (in DMSO at 10^{-3} M) on a Shimadzu UV-Vis-160A spectrophotometer. Shimadzu 8400-S FT-IR spectrophotometer ($\lambda = 4000\text{-}400\text{ cm}^{-1}$) was used to record the infrared spectra using KBr pellets. Bruker Avance Digital 500-NMR spectrometer (operating at 500 MHz) was used for recording the ^1H NMR spectra in DMSO- d_6 using TMS as an internal standard. The chemical shift was measured in ppm on the δ scale and the coupling constants were measured in Hertz.

2.2: Preparation of Green Catalyst (PPA-SiO₂)

SiO₂ (5g 200-400 mesh) was added to the polyphosphoric acid (PPA) solution in chloroform at 320K and stirred for one hour until solid formation. To remove the unused chloroform, a rotary evaporator was used and the resulting solid was dried under vacuum at 298K [20].

2.3: Green Synthesis of Heterocyclic Schiff Base Ligands

A mixture in equimolar proportions of 2-thiophenecarboxaldehyde (I) and a 0.01 molar ethanolic solution of heterocyclic amine [5-amino-1,3,4-thiadiazole-2-thiol (II)] along with PPA-SiO₂ in each scenario was exposed to microwave irradiation for 10 minutes at 360W and 360K, with the reaction process being tracked using TLC. (scheme-1). The reaction mixture was maintained at room temperature and then cooled with water while stirring for a few minutes, resulting in the production of a bright yellow powder solid product that was collected by suction filtration. The pure form of the ligand was obtained by recrystallization with aqueous ethanol and identified or characterized by spectral studies and the melting point determination [yield = 95% (conventional 82%)].

2.4: Green Synthesis of Transition Metal (II) Complexes

An aqueous-ethanolic solution of the ligand (L) and the respective transition metal (II) chloride was thoroughly mixed in a 1:2 (metal: ligand) stoichiometric ratio and irradiated in the microwave oven adding 0.1% ethanolic KOH solution to maintain the pH within the range of 7-8 for 5-7 minutes, which produced the better yield (80-85%) of the respective metal (II) complexes (scheme-1) compared to the conventional method (55-60%). Thus, obtained coloured solid products were filtered and recrystallized from DMF, washed with ethyl acetate, and then dried under reduced pressure over anhydrous CaCl₂ in a desiccator.

2.5: Antimicrobial Activity of Ligands and Metal (II) Complexes

“The *in vitro* antimicrobial (anti-bacterial and anti-fungal) activities of the investigated ligand and its transition metal (II) complexes were evaluated by the disc-diffusion method” [21-23]. The *in vitro* antibacterial activity of the undertaken compounds was achieved against two Gram-positive bacteria {*Staphylococcus aureus* (SA) and *Bacillus subtilis* (BS)} and two Gram-negative bacteria {*Escherichia coli* (EC) and *Salmonella typhi* (ST)} using chloramphenicol as standard reference. The anti-fungal activity of the undertaken compounds was performed against fungal strains {*Candida albicans* (CA) and *Aspergillus niger* (AN)} using griseofulvin as a standard reference of the same concentration (20 µg/mL) under identical conditions.

Accurately weighed 10 mg each of the green synthesized ligand and its transition metal (II) complexes were dissolved separately in DMSO and volume made up to 10 mL in a volumetric flask (1.0mg/mL). These solutions were further diluted with DMSO to the appropriate concentration (100 µg/mL). Similarly, solutions of 20 µg/mL of concentration of each chloramphenicol and griseofulvin were prepared from their stock solutions. Nutrient broth, for antibacterial activity, has a composition of 2.0 g yeast extract, 1.0 g beef extract, 5.0 g peptone and 5.0 g of NaCl in distilled water and volume made up to 1L. Nutrient Agar medium was obtained by adding 2.0% of agar to nutrient broth at 7.4 pH. For antifungal activity, Sabouraud dextrose medium has a composition of 10.0 g peptone, and 40.0 g dextrose in 1.0 L distilled water at 5.7 pH and agar medium was obtained by adding 1.5% of agar to it.

The sterile disks were drenched in investigated test compounds and were carefully placed on an incubated agar surface separately. The petri dishes were incubated for 24 hours at 37 K for bacteria and for 48 hours at 37K for fungal strains. Finally, the zone of inhibition (in mm) was carefully measured separately for each compound tested by comparing them with standard drugs. Each test was performed in triplicate in an individual experiment, and the mean was reported (Table 4). “The various concentrations of test compounds in DMSO like 50, 30, and 20 µg/mL were first prepared and tested for inhibition. Further dilutions were made and tested till the concentration inhibition was observed. The broth dilution method was used to determine the minimum inhibitory concentration (MIC) against the mentioned bacteria” [24]. The observations related to MIC are presented in Table 5.

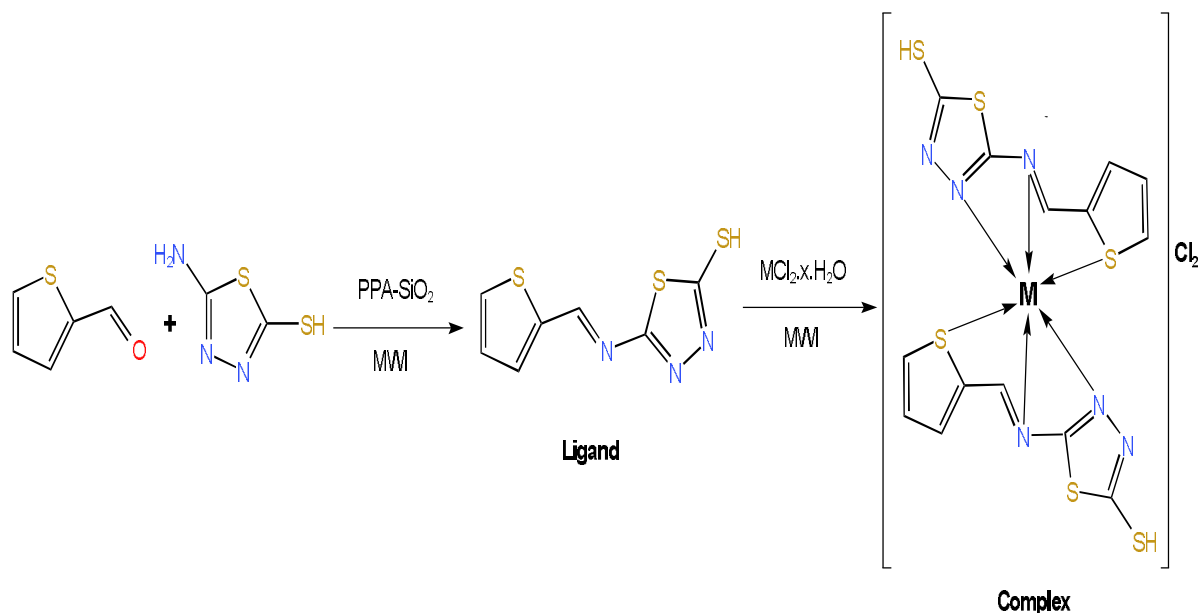
3. RESULTS AND DISCUSSION

3.1: Synthesis and Characterization

“The heterocyclic Schiff base (L) was synthesised using a microwave-assisted green approach by condensation of heterocyclic aldehyde (2-thiophene carboxaldehyde, I) with thiadiazole amine [(II)] in the presence of PPA-SiO₂ as a solid acid catalyst under clean and environmentally benign conditions. The condensation involves the nucleophilic attack of the NH₂ group on the electrophilic H-C=O group followed by dehydration to form corresponding Schiff bases. The used catalyst (PPA-SiO₂) was recycled by simple filtration and can be used repeatedly; therefore, it acts as a green catalyst and the present synthetic approach complies with the principle of sustainable chemistry” [25]. The M(II) complexes were formed by direct ligation of ligand (L) in the appropriate molar to metal precursors ratio 1:2 (metal: ligand) and furnished the corresponding complexes in better yields (80-85% from 57-60%). This is probably due to the increased homogeneity of the reaction mixture by rotation of the reaction platform tray in the microwave oven. The microwave-assisted synthesis of the mentioned ligand and its respective M (II) complexes was completed in a shorter time with higher yields compared to the conventional synthetic methods. The synthetic reaction completion time and the yields of the products using a green synthetic approach and conventional method are presented in **Table -1** for comparison.

3.2: Physico-Analytical Studies

“The heteronuclear Schiff base and all the eco-friendly synthesized transition metal (II) complexes are stable and non-hygroscopic coloured solids at room temperature. The complexes have a range of melting points or decomposition temperatures. The complexes are insoluble in common organic solvents but soluble in DMF and DMSO. The elemental analysis of the synthesized M(II) complexes {[ML₂]Cl₂} also verifies % composition of C, H, and N constituents, and agrees with the proposed structures corresponding to {1:2 (metal: ligand)} stoichiometry and mononuclear nature. The values of observed molar conductance of the metal (II) complexes (88.54 to 98.60 ohm⁻¹cm²mol⁻¹) were appreciable and account for their any dissociation in DMF at room temperature, which revealed their 1:1 electrolytic nature” [26].



Where M = Co(II), Ni(II) & Cu(II)

Scheme-1: Microwave-assisted green synthesis of ligand and its metal(II) complexes

Table 1: Microanalytical and physical data with the comparative results of conventional and green synthetic methods of the investigated compounds

The molecular formula of compounds (colour)	Molecular wt. (g mol ⁻¹)	Melting Pt. (K)	Elemental analysis % calculated (found)				Molar Conductance (ohm ⁻¹ cm ² mol ⁻¹)	Reaction Time CM (GM)	% Yield CM (GM)
			C	H	N	M			
C ₇ H ₅ N ₃ S ₃ Bright yellow	227.3	457-459	37.0 (37.2)	2.2 (2.5)	18.5 (18.6)	-	-	2 h (10 min.)	80 (92)
[CoL ₂]Cl ₂ Light pink	584.0	489-491	28.8 (28.5)	1.7 (1.5)	14.4 (14.5)	10.09 (10.0)	93	1h (5 min.)	58 (85)
[NiL ₂]Cl ₂ Light green	583.7	493-495	28.8 (28.5)	1.7 (1.9)	14.4 (14.5)	10.05 (10.02)	96	1h (6 min.)	56 (82)
[CuL ₂]Cl ₂ Green	588.5	485-487	28.5 (28.4)	1.7 (1.5)	14.3 (14.5)	10.79 (10.80)	90	1h (7 min.)	55 (80)

CM = Conventional method, time in hours; GM = Green method, time in minutes

3.3: Spectroscopic Characterization

3.3.1: Infrared Spectral Studies

The infrared spectral (FTIR) data of the investigated compounds {ligand and metal(II) complexes} are presented in **Table 2**. Comparison of the FTIR spectra of the ligand and that of metal (II) complexes reveals the involvement of coordination sites in chelation. The FTIR spectral data of the metal (II) complexes contained all the major absorption bands of the ligand and some new bands indicative of the tridentate coordination of the ligand with the metal (II) ions in the complexes.

The IR spectrum of the undertaken Schiff base (L) exhibited the azomethine (HC=N) and thiadiazole stretching at 1640 and 1620 cm^{-1} respectively. The thiol (S-H) stretching appeared in the 2590 cm^{-1} region along with a band resulting from the thiophene ring ($\nu_{\text{C-S-C}}$) stretching of thiophene moiety at 850 cm^{-1} [27].

“A comparison of the infrared spectra of the Schiff base ligand was performed as a reference and their metal (II) complexes showed that the ligand was principally tridentate coordinated with the central metal (II) ions. The absorption band appearing at 1640 cm^{-1} due to azomethine stretching vibration is shifted to a lower frequency, indicating the participation of azomethine nitrogen in complexation” [28]. “The absorption band at 1620 cm^{-1} assigned to the thiadiazole ring (C=N) vibration is also shifted to a lower frequency, which is indicative of the involvement of the thiadiazole ring in complexation” [29]. Furthermore, an absorption band at 850 cm^{-1} attributed to thiophene ring C-S-C in the ligands shifted to a lower frequency in the respective metal (II) complexes. This shows the sulfur in the thiophene is coordinated in the complexation. Finally, conclusive evidence of coordination of the ligand with metal atoms was established by far IR spectra in which new absorption bands at 525, 530 and 540 cm^{-1} assigned to M-N (azomethine), M-N (thiadiazole), and M-S (thiophene S) were observed in the spectra of the metal (II) complexes, which were not present in the infrared spectra of the ligand.

Table-2: Observed IR bands (cm^{-1}) of Schiff bases and its metal (II) complexes

<i>Compound</i>	$\nu(\text{HC=N})_{\text{azomethine}}$	$\nu(\text{C=N})_{\text{thiadiazole}}$	$\nu(\text{S-H})_{\text{thiophene}}$	$\nu(\text{N-M})_{\text{azomethine}}$	$\nu(\text{N-M})_{\text{thiadiazole}}$	$\nu(\text{S-M})_{\text{thiophene}}$
(L)	1635	1620	850	-	-	-
[Co(L) ₂]Cl ₂	1625	1610	835	525	525	360
[Ni(L) ₂]Cl ₂	1625	1610	835	530	530	365
[Cu(L) ₂]Cl ₂	1620	1605	835	525	525	365

The infrared spectral studies of the ligand and its M(II) complexes revealed that the investigated Schiff base ligand acted as a neutral tridentate (designated as SNN donor) ligand.

3.3.2: ¹H NMR Spectral Studies

The ¹H NMR spectra of the investigated Schiff base displayed the SH proton as a singlet at δ 13.12 ppm and the azomethine (HC = N) proton appeared as a singlet at δ 9.05 ppm. C₅-H and C₃-H of the thiophene moiety appeared as doublets at δ 7.59 ppm and δ

7.82ppm respectively. Similarly, C₄-H appeared as a double doublet at δ 7.127ppm. (Figures 1 and 2).

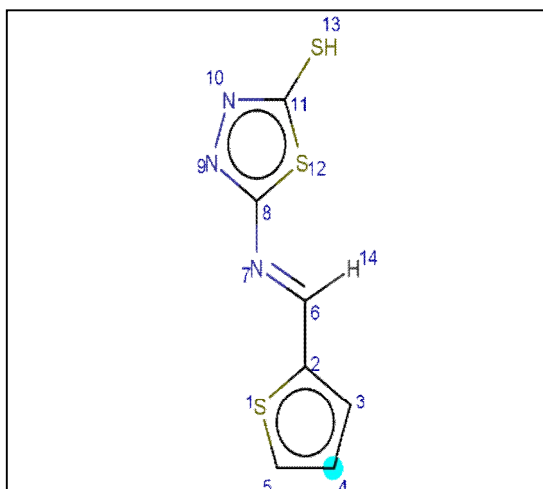


Figure 1: Structure of the ligand

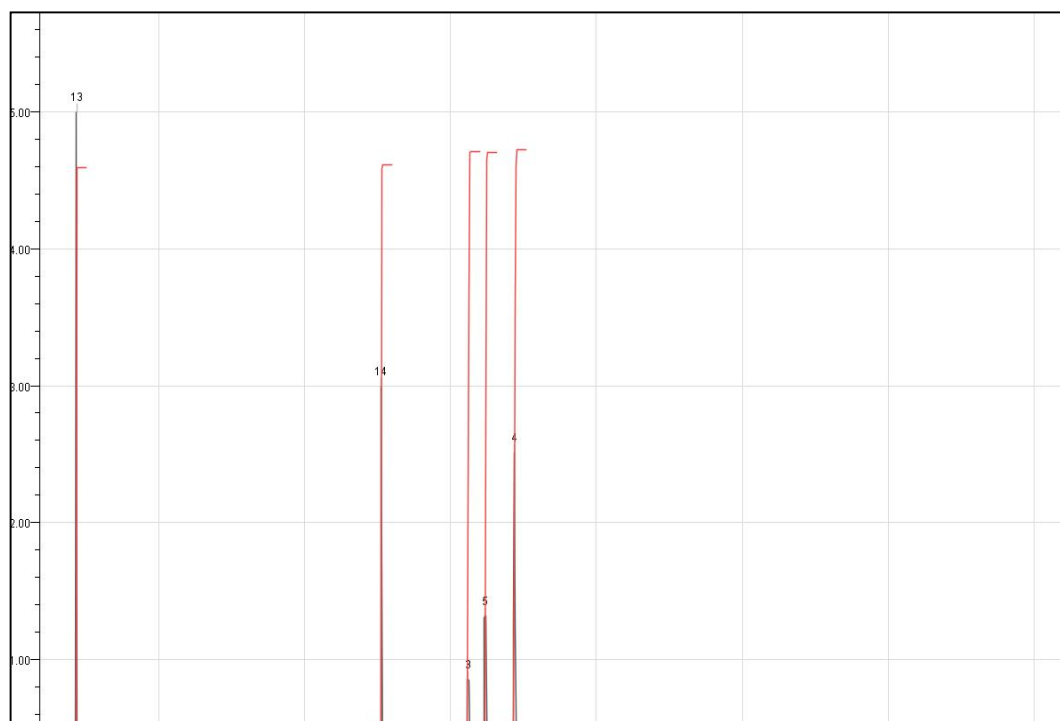


Figure-2: ^1H NMR spectrum of the investigated Schiff base (L)

3.3.3: Magnetic Property and Electronic Spectral Studies

Electronic absorption (UV-vis) spectral studies along with the observed magnetic moment values of the metal (II) complexes are quite useful for the nature of the ligand field around the metal ion and thus can be used for the prediction of probable geometry or stereochemistry in association with other spectroscopic methods. It is well well-established fact that the extension of the absorption spectra from the UV region to the visible region is due to ligand-to-metal charge transfer (LMCT) and d-d transition bands of the metal in the complexes. The structure of the coordination complexes can be assigned based on the position and number of peaks of the *d-d* transitions in their electronic spectra. The observed *d-d* transitions and determined magnetic moment values of the investigated metal (II) complexes with their plausible geometry are presented in Table 3.

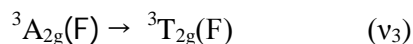
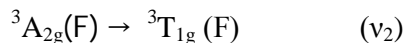
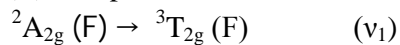
The ligands show two bands at absorption bands at 252 and 310 nm assigned for $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ electronic transitions respectively.

Table 3: Observed electronic bands, magnetic moments and geometry of M(II)-complexes

M-complexes	d-d transition bands (nm)	μ_{eff} (BM)	Stereochemistry of M(II) Complexes
$[\text{Co}(\text{L})_2]\text{Cl}_2$	328, 548, 1141	4.4	Octahedral
$[\text{Ni}(\text{L})_2]\text{Cl}_2$	352, 616, 987	3.4	Octahedral
$[\text{Cu}(\text{L})_2]\text{Cl}_2$	326, 448	1.4	Distorted octahedral

The electronic spectra of the investigated Co(II) complex show three absorption bands corresponding to the $^4\text{T}_{1g} \rightarrow ^4\text{T}_{2g}$ (F), $^4\text{T}_{1g} \rightarrow ^4\text{T}_{2g}$ (P) and $^4\text{T}_{1g} \rightarrow ^3\text{A}_{2g}$ (F) electronic transitions respectively suggesting the octahedral geometry which is substantiated by the observed magnetic moment value (4.4 BM) corresponding to three unpaired electrons per Co(II) ion in an octahedral environment [30].

The electronic spectra of Ni(II) complex showed three electronic absorption bands assigned for



electronic transitions which suggested the octahedral geometry of the metal complex. The determined magnetic moment value of the Ni (II) complexes were 3.4 BM which correspond to two unpaired electrons per Ni²⁺ ion for the ideal six-coordinated octahedral configuration [31].

“The electronic spectrum of the investigated Cu(II) complex showed broad absorption bands between the 10Dq band for octahedral geometry corresponding to the ²E_g → ²T_{2g} transition. The determined magnetic moment values of the Cu(II) complex was 1.4 BM, which is indicative of one unpaired electron per Cu²⁺ ion suggesting that the investigated complex had structure within the range consistent with spin-free distorted octahedral geometry” [32].

3.4: Proposed Structure of the M(II)-Complexes

Based on the aforesaid experimental evidence, we tentatively propose the octahedral /distorted octahedral structure of the investigated M(II)-complexes (where M = Co, Ni and Cu) in which the heterocyclic Schiff base ligands act as a neutral tridentate (SNN Donor) ligand. **Figure 3** presents the common tentative octahedral geometry/structure of the complexes.

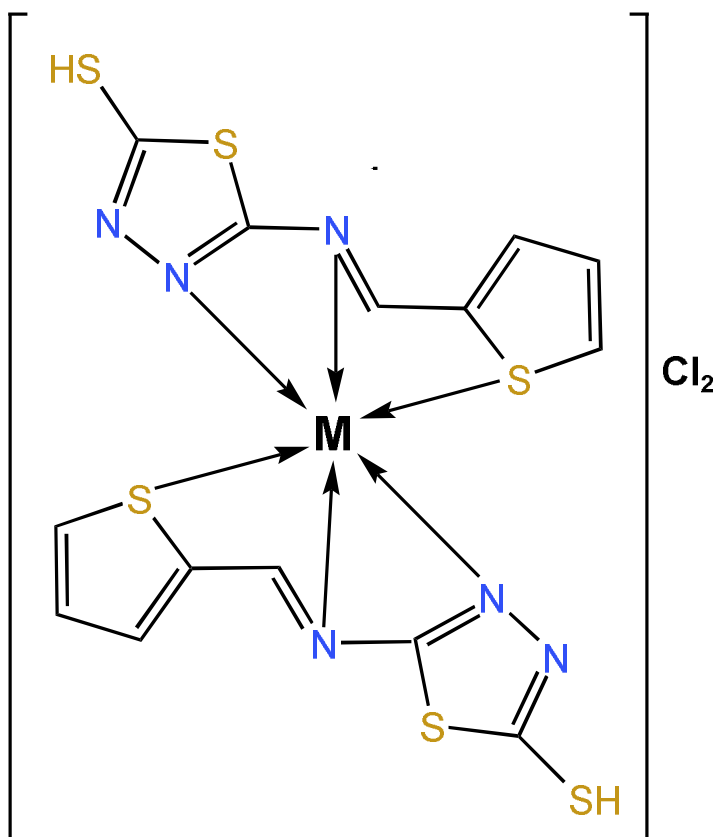


Figure-3: Proposed octahedral structure of the investigated M(II) complexes

3.5: Antimicrobial Activities

The experimental results of the antimicrobial activity of the undertaken heterocyclic Schiff base ligand and the transition metal (II) complexes are presented in Table 4 and Table 5.

Table 4: Determined zone of inhibition (in nm) of investigated compounds against pathogens

Compound	Concentration	Zone of inhibition in nm					
		Gram-(+)-bacteria		Gram-(-)-bacteria		Fungi	
		SA	BS	EC	ST	CA	AN
Ligand	100 µg/mL	13	14	12	11	9	10
[Co(L) ₂]Cl ₂	100 µg/mL	16	17	17	14	10	11
[Ni(L) ₂] Cl ₂	100 µg/mL	14	15	15	13	9	11
[Cu(L) ₂] Cl ₂	100 µg/mL	18	17	17	15	12	13
Chloramphenicol	20 µg/mL	20	21	22	20	-	-
Griseofulvin	20 µg/mL	-	-	-	-	21	22
DMSO	-	-	-	-	-	-	-

Figure 4: Zone of inhibition

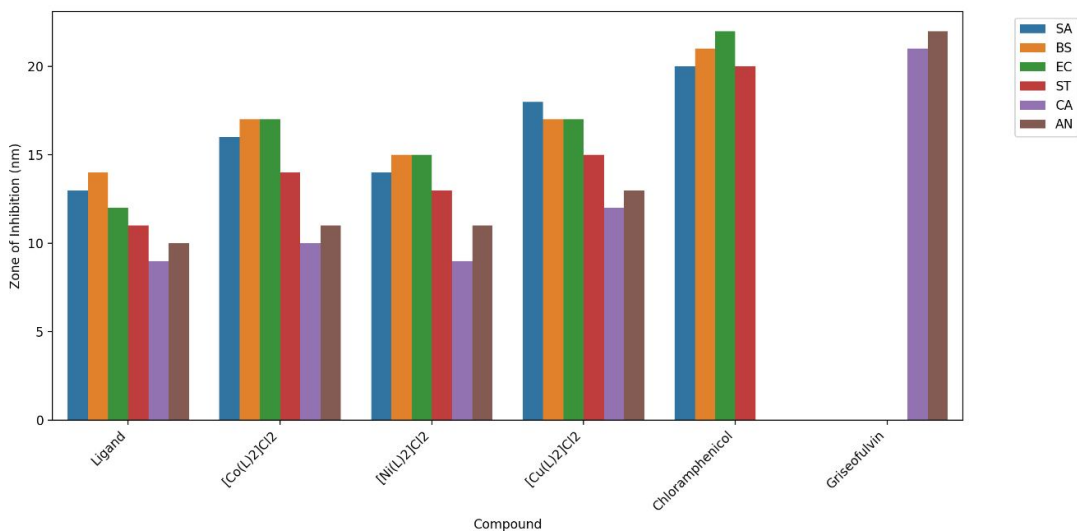
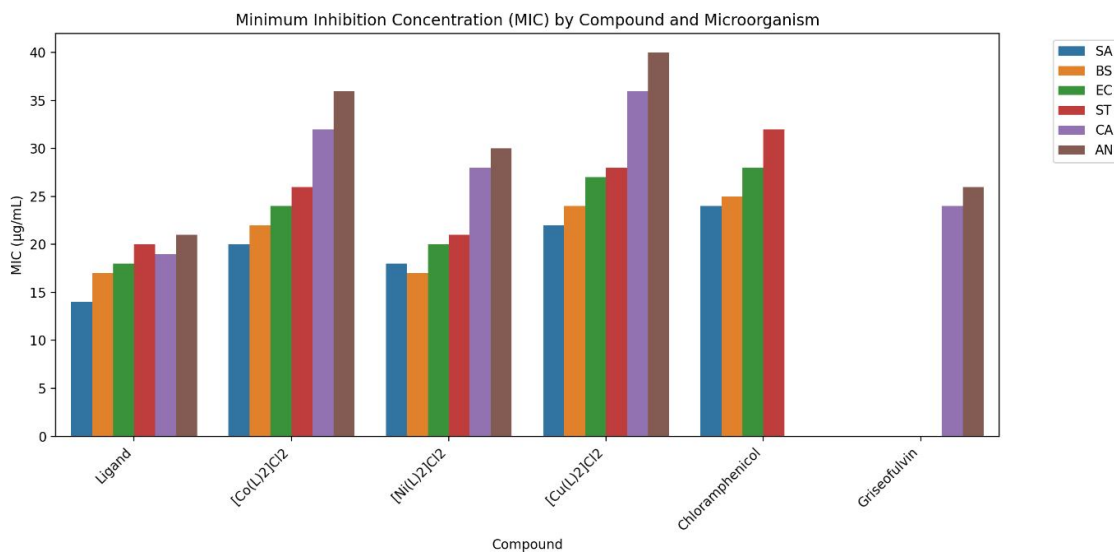


Table 5: Minimum Inhibitory Concentration (MIC) of compounds against pathogens

Compound	Minimum inhibition Concentration (MIC) in $\mu\text{g/mL}$					
	Gram-(+)-bacteria		Gram-(-)-bacteria		Fungi	
	SA	BS	EC	ST	CA	AN
Ligand	14	17	18	20	19	21
[Co(L) ₂]Cl ₂	20	22	24	26	32	36
[Ni(L) ₂]Cl ₂	18	17	20	21	28	30
[Cu(L) ₂]Cl ₂	22	24	27	28	36	40
Chloramphenicol	24	25	28	32	-	-
Griseofulvin	-	-	-	-	24	26

Figure .5: Minimum Inhibitory Concentration (MIC) of compounds against pathogens



“The data and bar plots of antimicrobial activities of the investigated compounds showed that the metal complexes have enhanced activity compared to the free ligand against the same micro-organisms under identical experimental conditions. The metal complexes show moderate activity compared to standard drugs despite being at higher concentrations” [33]. [Cu(L)₂]Cl₂ shows the best overall antimicrobial activity among the metal complexes. The order of activity for metal complexes is :



Furthermore, the gram-positive bacteria (SA and BS) show slightly higher susceptibility than gram-negative bacteria (EC and AN) and fungi (CA and AN) generally show lower zones of inhibition compared to bacteria.

“The metal complexes maintain activity across all tested organisms, showing broad-spectrum antimicrobial properties. The enhancement in antimicrobial activity of metal complexes compared to the free ligand suggests successful coordination and improved bioactivity through complexation”[34]. Apart from this, other factors such as solubility, conductivity and dipole moment (influenced by the presence of metal ions) may also be the possible reasons for enhancing their antimicrobial activity [35].

CONCLUSIONS

An efficient and facile synthesis of a new pharmaco-active ligand in a single step by PPA-SiO₂-catalysed condensation of 2-thiophenecarboxaldehyde with 5-amino-1,3,4-thiodiazol-2-thiol in an ethanolic solution as a green solvent and its bivalent transition metal complexes bearing possible pharmacophore were obtained under microwave irradiation with higher yields in less time compared to conventional heating. The ligand coordinated to the M(II) ion in a neutral tridentate (SNN donor) mode. The octahedral geometry of the metal complexes { [M(L)₂]Cl₂ } has been proposed based on elemental analyses, molar conductance, magnetic measurement and electronic spectral studies. The antimicrobial activity studies indicated that the M (II) complexes possess comparatively higher activities than the free ligand owing to enhanced lipophilicity by chelation. The order of antimicrobial activity for compounds is :



The newly synthesized compounds were found to be more active against Gram-positive than Gram-negative bacteria. The results of these analyses indicated the substantial potential of green synthesized metal complexes in the biological field as future drugs.

The present eco-friendly synthetic procedure represents an alternative to the existing methods for the synthesis of bioactive thiophene-derived Schiff base ligand and its metal (II) complexes under microwave irradiation. This article describes a simple, proficient, and sustainable approach to synthesis with easy workup, higher yield, and economic viability compared to other methodologies.

DATA AVAILABILITY STATEMENT

The data that have been used are presented here.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors hereby declare that no generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of manuscript.

REFERENCES

1. Qin W, Long S, Panunzio M, Biondi S. Schiff bases: A short survey on an evergreen chemistry tool. *Molecules*. **2013**;18:12264-12289.
<https://doi.org/10.3390/molecules181012264>
2. Jia Y, Li J. Molecular assembly of Schiff base interactions: construction and application. *Chem. Rev.* **2015**;115:1597-1621.
<https://doi.org/10.1021/CR400559G>
3. Fabbrizzi Luigi. Beauty in chemistry: Making artistic molecules with Schiff bases. *J. Org. Chem.* **2020**; 85:12212–12226.
<https://doi.org/10.1021/acs.joc.0c01420>
4. Raczuk E, Dmochowska B, Samaszko-Fiertek J, Madaj J. Different Schiff Bases-Structure, Importance and Classification, *Molecules*. **2022**; 27:787.
<https://doi.org/10.3390/molecules27030787>
5. Shanty AA, Philip JE, Sneha EJ, Kurup MRP, Balachandran S, Mohanan PV. Synthesis, characterization, and biological studies of Schiff bases derived from heterocyclic moiety. *Bioorganic Chemistry*. **2017**, *70*, 67-73.
<https://doi.org/10.1016/j.bioorg.2016.11.009>
6. Uddin MN, Ahmed SS, Alam SMR, REVIEW: Biomedical applications of Schiff base metal complexes. *Journal of Coordination Chemistry*, **2020**, 73(23), 3109–3149.
<https://doi.org/10.1080/00958972.2020.1854745>
7. Hameed A, al-Rashida M, Uroos M, Abid Ali S, Khan K M. Schiff bases in medicinal chemistry: a patent review (2010-2015). *Expert Opinion on Therapeutic Patents*, **2016**, 27(1), 63–79.
<https://doi.org/10.1080/13543776.2017.1252752>
8. ZoubiWA, Mohamed SG, Al-Hamdani AAS, Mahendradhanya AP and Ko YG. Acyclic and cyclic imines and their metal complexes: recent progress in biomaterials and corrosion applications. *RSC Adv.*, **2018**, 8, 23294-23318
<https://doi.org/10.1039/c8ra01890a>
9. Fonkui TY, Ikhile MI, Ndinteh DT, Njobeh PB. Microbial activity of some heterocyclic Schiff bases and metal complexes: A review, *Tropical Journal of Pharmaceutical Research*. **2018**; 17 (12): 2507-2518.
<http://dx.doi.org/10.4314/tjpr.v17i12.29>
10. Paul Anastas, Nicolas Eghbali, Green chemistry: Principles and practice, *Chem. Soc. Rev.* **2010**;39:301-312.
<https://doi.org/10.1039/B918763B>

11. Sheldon RA. Matrices of green chemistry and sustainability: Past, present & future; *ACS Sustainable Chem. Eng.* **2018**; 6:32-48.
<https://doi.org/10.1021/acssuschemeng.7b03505>
12. Schmink JR, Leadbeater NE. Microwave heating as a tool for sustainable chemistry: An introduction, microwave heating as a tool for sustainable chemistry; CRC Press: Boca Raton, FL, USA. **2011**:1–24.
13. Mahato AK, Sahoo BM, Banik BK, Mohanta BC. Microwave-assisted synthesis: Paradigm of green chemistry. *J. Indian Chem. Soc.* **2018**; 95:1327–1339.
14. Díaz-Ortiz Á, Carrillo JR. Microwaves in green and sustainable chemistry. *In Microwave Chemistry*; Cravotto G, Carnaroglio D, Eds. De Gruyter: Berlin, Germany. **2017**;167–183.
15. Katre SD. Microwaves in organic synthetic chemistry-a greener approach to environmental protection: an overview. *Asian Journal of Green Chemistry.* **2024**; (8)68-80. <https://doi.org/10.48309/ajgc.2024.392833.1387>
16. Demirtas G, Dege N, Sekerci M, Servi S, Dincer M, (E)-5-Phenyl-N-(2-thienylmethylene)-1,3,4-thiadiazole-2-amine, *Acta Cryst.* **2009**. E65, o1668
<http://doi.org/10.1107/S1600536809023447>
17. Chohan ZH. Biologically active Co(II) and Ni(II) complexes of N-(2-thienylmethylene)-2-aminothiadiazole. *Metal Based Drugs*, **2002**, 8,6, 323-327.
18. Kantevari S, Bantu R, Nagarapu L. HClO₄-SiO₂ and PPA-SiO₂ catalyzed efficient one-pot Knoevenagel Condensation, Michael addition and cyclodehydration of Dimedone and aldehydes in acetonitrile, aqueous and solvent-free conditions: scope and limitations. *Journal of Molecular Catalysis A: Chemical*, 2007, 269, 53-57.
<http://dx.doi.org/10.1016/j.molcata.2006.12.039>
19. Shalinee, Sanjay Kumar. “Heterocyclic Schiff base complexes of bivalent transition metals: Microwave- assisted green synthesis, structure elucidation and antimicrobial studies”. *Chemical Science International Journal* 2024. 33 (5):41-51.
<https://doi.org/10.9734/CSJI/2024/v33i5915>.
20. Davoodnia A, Razavi B, Tavakoli-Hoseini N; An efficient and green procedure for the synthesis of 2,4,6-triarylpyridines using PPA-SiO₂ as a reusable heterogeneous catalyst under solvent-free conditions, *E-Journal of Chemistry*, **2012**, 9(4), 2037-2043.
<https://doi.org/10.1155/2012/743513>
21. Collee JG, Duguid JP, Farser AG, Marmion BD. (Eds.), *Practical medical microbiology*, Churchill Livingstone, NY;1989.
22. Kokare C. *Pharmaceutical Microbiology: Experiments and Techniques*, 2nd ed. Career Publications, Nashik, India, 138, 2007
23. Dickert H, Machka K, Braveny I. The uses and limitations of disc diffusion in the antibiotic sensitivity testing of bacteria. *Infection.* 1981; 9(1):18–24.
<https://doi.org/10.1007/BF01640803>.
24. Schwalbe R, Steele-Moore L, Goodwin AC. *Antimicrobial susceptibility testing protocols*. CRC Press; 2007.
25. Srivastava KP, Singh R, Kumar N. Environmentally benign synthesis, characterization, and evaluation of biological activities of some novel N-substituted imines of indoles, *Inter. J. Green Herb. Chem.* 2019; 8 (1):143-152.
<https://doi.org.10.24214/IJGHC/GC/8/1/14352>

26. Geary WJ. The use of conductivity measurements in organic solvents for the characterisation of coordination compounds, *Coord. Chem. Rev.* 1971; 7(1):81-122. [https://doi.org/10.1016/S0010-8545\(00\)80009-0](https://doi.org/10.1016/S0010-8545(00)80009-0)
27. Bellamy LJ. *The infrared spectra of complex molecules*, 3rd edn., Chapman & Hall, London. 1975; 233.
28. Coates J. *Interpretation of infrared spectra-a practical approach: Encyclopedia of analytical chemistry*, John Wiley & Sons Ltd., Chichester, USA. 2000; 10815-10837.
29. Nakamoto K. *Infrared spectra of inorganic and coordination compounds*, 6th Edn. Wiley-Interscience, N Y; 2009.
30. Carlin RL, Vandrynevedt AJ. *Magnetic properties of transition metal compounds*, Springer-Verlag, New York; 1997.
31. Figgis BN, *Introduction to Ligand Fields*, Wiley Eastern Ltd., New Delhi. 1976; 279.
32. El-Sherif A A, Shehata MR, Shoukry MM, Barakat MH, Synthesis, characterization, equilibrium study and biological activity of Cu(II), Ni(II) and Co(II) complexes of polydentate Schiff base ligand, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, **2012**, 96, 889–897 <http://dx.doi.org/10.1016/j.saa.2012.07.047>
33. Tweedy GB. *Phytopathology*, Plant extracts with metal ions as potential antimicrobial agents. 1964; 55:910-919.
34. Hossain TJ, Methods for screening and evaluation of antimicrobial activity: A review of protocols, advantages, and limitations. *European Journal of Microbiology and Immunology*. 2024, 14, 2, 97–115 <https://doi.org/10.1556/1886.2024.00035>
35. Balouiri M, Sadiki M, Ibsouda SK. Methods for in vitro evaluating antimicrobial activity: A review. *Journal of Pharmaceutical Analysis*, 2016. 6. 71–79 <http://dx.doi.org/10.1016/j.jpha.2015.11.005>