



SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL EVALUATION OF NOVEL HETEROCYCLIC PYRIDINE BASED THIOPHENE DERIVATIVE OF TRANSITION METAL COMPLEXES

Boya Rajannagari Chaitanya Kumar, Kondra Sudhakar Babu* and Palyam Shabana

Department of Chemistry, Sri Krishnadevaraya University, Ananthapuramu- 515 003, Andhra Pradesh, India.

***Corresponding Author: Kondra Sudhakar Babu**

Department of Chemistry, Sri Krishnadevaraya University, Ananthapuramu- 515 003, Andhra Pradesh, India.

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ABSTRACT

The transition metal complexes (where [M = Co, Ni, and Cu]) with pyridine based thiophene derivative of 2-((E)-2-((5-bromothiophen-2-yl) methylene)hydrazinyl)-4-methyl-6-phenylpyridine-3-carbonitrile [BTHPC] ligand has been devised and synthesized. The physico-chemical, analytical data, UV-Vis, FT-IR, ¹H-NMR, and ESR spectrum methods were used to characterize all the complexes. Ligand and Metal complexes were screened for cytotoxicity on lung cancer cell lines and hepatic cancer cell lines A549 and HepG2 respectively, with MTT assay. Antibacterial studies were done against different pathogens of gram positive and negative bacteria. Copper complex has more significant cytotoxicity and antibacterial activity than Nickel and Cobalt complexes.

KEYWORDS: Pyridine-thiophene derivative, Transition metals, cytotoxicity studies, MTT assay, Antibacterial activity.

1. INTRODUCTION

A vast number of heterocyclic compounds having pyridine rings have been linked to a variety of pharmacological effects, including anticonvulsant,^[1] antimicrobial,^[2,3] antiviral,^[4] anticancer,^[5] and anti-HIV.^[6] Pyridine derivatives have been produced and employed as intermediates with the parent molecule 2-chloropyridine-3-carboxylic acid, and they display antifungal and anticancer properties. Recent synthetic methods to anticancer,^[7,8] medicines have shown that N-alkylated 2-pyridones are key intermediates in the production of polycyclic molecules of biological significance.

New pyridine derivatives have been synthesized, resulting in fascinating heterocyclic scaffolds that can be used to build various chemical libraries of drug-like compounds for biological screening. In the recent literature, Terpyridine derivatives showed promising cytotoxicity activities with A549, MCF7, and A2780 cell lines.^[9] Some of the pyridine derivatives (pyridine-2-carboxamidrazone), whose importance in terms of antimycobacterial activity of a number of derivatives has previously been described.^[10,11]

The development of new anticancer drugs is a dynamic area of research in chemical science. After the discovery of *cis*-platin by Rosenberg^[12] as an effective anticancer drug having various side effects, the fruitful results to

obtain alternative metal based drugs with no side-effects are still awaited and remained a challenge to bioinorganic chemists. The thiosemicarbazones derived from 2-benzoylpyridine and 2-acetylpyrazine and their transition metal complexes have shown significant antitumor activities.^[13-17]

The chemistry of coordination metal complexes with nitrogen-sulphur donor ligands has recently piqued the interest of researchers, with the majority of the focus being on transition metal complexes with Schiff base ligands. The presence of both nitrogen and sulphur donor atoms in the backbones of these ligands explains this.^[18-19] Schiff bases are advantageous because of their capacity to stabilize metal ions in various oxidation states, their use in a variety of catalytic and industrial applications, and their wide range of biological activities.^[20-21] The lone pair of electrons of azomethine (-C=N-) group bonding in the structure of stable metal complexes is owing to nitrogen's lone pair of electrons.^[22] Current breakthroughs in the realms of bioinorganic chemistry and medicine have heightened interest in transition metal complexes with various types of ligands.^[23] Due to their stability under a variety of oxidative and reductive conditions, as well as the fact that imine ligands are marginal between hard and soft Lewis bases, Schiff bases have played an important role as chelating ligands in main group and transition metal coordination chemistry over the years.^[24-25]

These ligands cytotoxic effects have improved when they are coordinated with Cu and Ni ions, and they can also improve their lipophilicity within the cell.^[26] The hydrazine-pyrrole-2-carboxaldehyde, hydrazine-furan-2-carboxaldehyde, and hydrazine-thiophene-2-carboxaldehyde and their phenyl derivatives, as well as their Co (II), Cu (II), and Ni (II) mixed complexes, were synthesized and described.^[27]

Because of the cooperative effectiveness, if thiosemicarbazone derivatives and transition metal elements are employed together to manufacture a novel medicine, it may have good biological activity. Some thiophene-2-carboxaldehyde thiosemicarbazones and their Ru(II) complexes showed promise against *E. histolytica* in previous research.^[28]

Several nitrogen and sulphur containing heterocyclic systems exhibit a wide range of therapeutic activities, which is why a recent study on the synthesis of new heterocycles of 2-hydrazinyl-4-methyl-6-phenylpyridine-3-carbonitrile condensed with 5-Bromothiophene-2-carbaldehyde was undertaken. This can result in the development of new biologically active compounds. We designed and synthesized new pyridine derivatives as well as their transition metal complexes, namely Co, Ni, and Cu. These compounds were characterized using various techniques, and they were then tested for cytotoxic and antibacterial activity.

2. MATERIALS AND METHODS

2.1. Materials

Benzoyl acetone, cyanoacetamide, sodium ethoxide, triethylamine, phosphoryl chloride, hydrazine monohydrochloride, 5-Bromothiophene-2-carbaldehyde, copper (II) chloride, nickel (II) chloride, and cobalt (II) chloride were purchased from sigma Aldrich. All of the

other chemicals and solvents were analytical reagent grade and purchased from a commercial source.

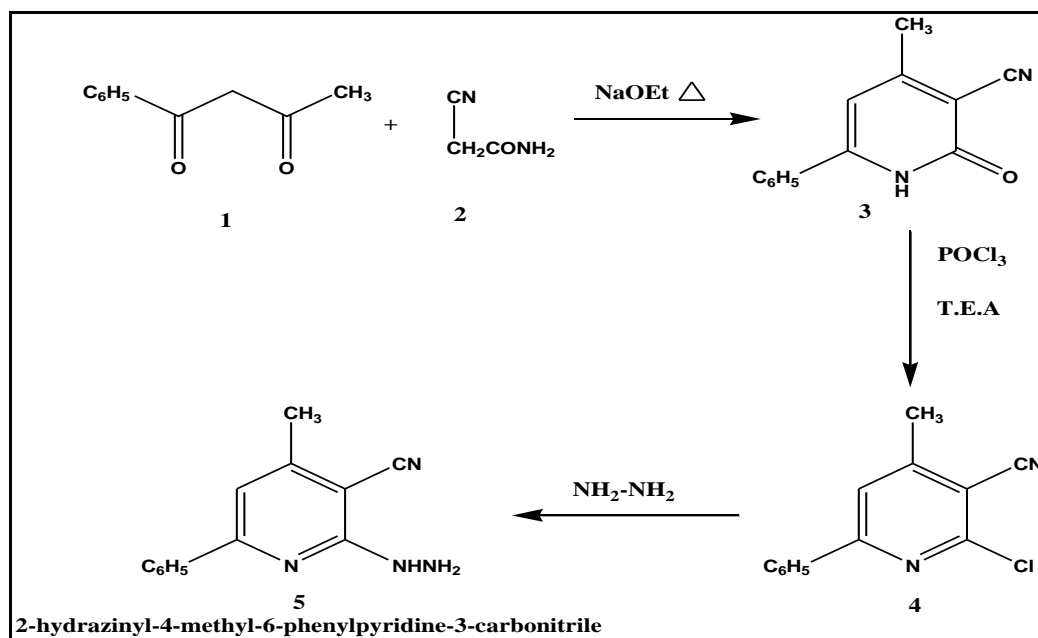
2.2. Physical measurements

The elemental analysis (C, H and N) was performed on a PerkinElmer 2400 CHN analyzer. Melting points were determined in open capillaries using a G LAB melting apparatus and were reported uncorrected. UV-visible spectra of DMF solutions were recorded on a UV-210 ELICO spectrometer in the spectral window of 200-800 nm. Infrared spectra (FT-IR) were recorder using a Bruker FT/IR vector 22 spectrometer in the form of KBr pellets. Proton NMR were recorded in solution state with AVANCE III 500 NMR spectrometer.

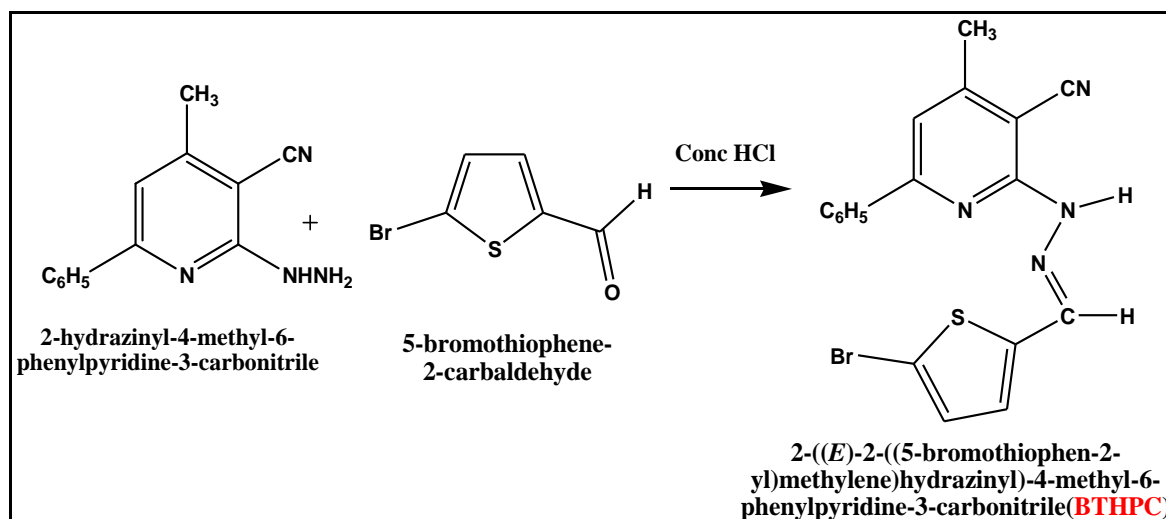
2.3. Synthesis of ligand

2-hydrazinyl-4-methyl-6-phenylpyridine-3-carbonitrile was synthesized early reported from^[29] was 2.4 g (0.01 mmol) dissolved in 20 mL methanol was added to 5-Bromothiophene-2-carbaldehyde 1 mL (0.01 mmol) in hot 10 mL methanolic solution with addition of few drops of concentrated hydrochloric acid. The reaction mixture was placed in a round bottom flask and allowed to reflux for two hours. The brown solid precipitate generated when the reaction mixture was cooled to room temperature was collected by filtration, and the solid product was washed with MeOH and dried under vacuum. Molecular formulae of ligand $C_{18}H_{13}N_4SBr$; Yield 73.65%; m.p.148-150 °C; IR cm^{-1} : 3332 (NH), 2256($C\equiv N$), 1632($C=N$), 1015(aromatic C-H); 1H -NMR; δ 2.45(s,3H CH_3), 6.97(d,1H, Thiophene-H), 7.43(d,1H Thiophene-H), 7.80-(s, 1H CH) 7.10 (s,1H, N-H), 7.73 (s,1H, Py-H), 7.53 - 7.95 (m,5H, Ar-H); MS m/z (%): 397.62;

The ligand is synthesized as illustrated in Scheme-1 & 2. Mass Spectrum of BTHPC ligand as shown in Fig.1.



Scheme 1 Synthesis of 2-hydrazinyl-4-methyl-6-phenylpyridine-3-carbonitrile.



Scheme 2: Synthesis of 2-((E)-2-((5-bromothiophen-2-yl)methylene)hydrazinyl)-4-methyl-6-phenylpyridine-3-carbonitrile [BTHPC]

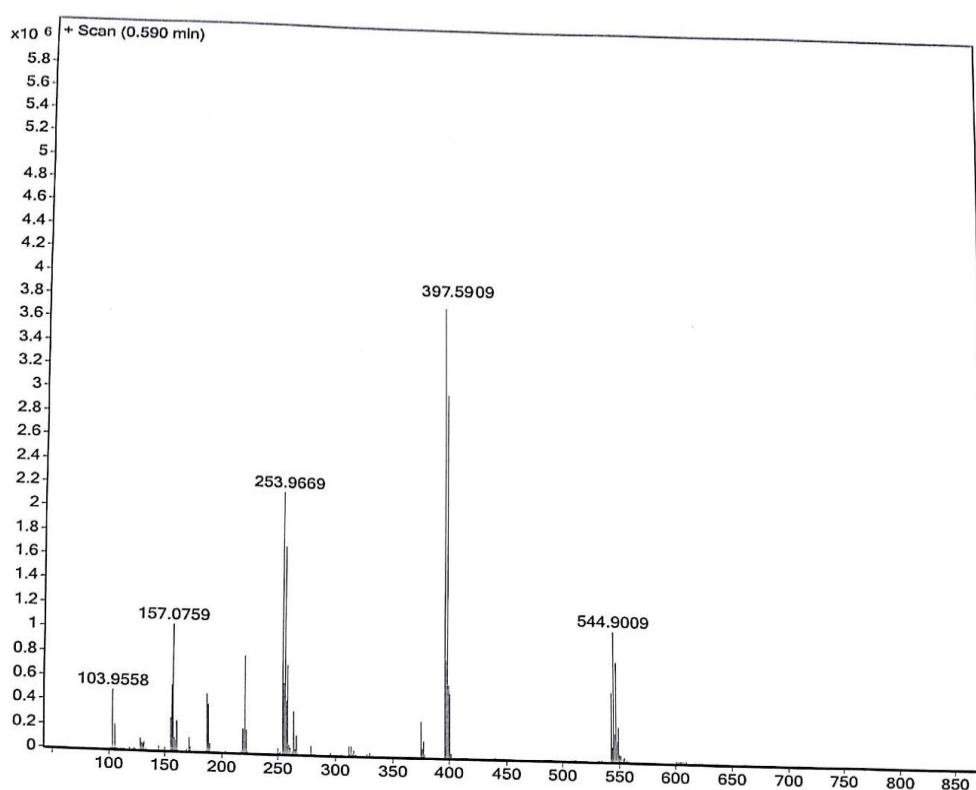
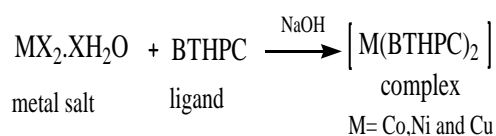


Fig. 1: Mass Spectrum of BTHPC ligand.

2.4. General procedures for the synthesis of complexes

A Hot methanolic solution (20 mL) of ligand mixture (3.52 g 0.1 mol) was added to a solution of Metal chlorides (M= Co, Ni and Cu) (0.05 mol) in H₂O (50 mL) with addition of 2 ml of 1M NaOH solution. The resulting colorless solution was refluxed for 2 h and then allowed to gently concentrate by evaporation at room temperature for a period of time, resulting in a solid substance that was washed with a tiny amount of MeOH and dried in the air. Synthesis of metal complex was

given in scheme 3. ESI-Mass Spectrum of [Cu (BTHPC)₂] Complex shown Fig.2.



Scheme 3: Synthesis of metal complexes.

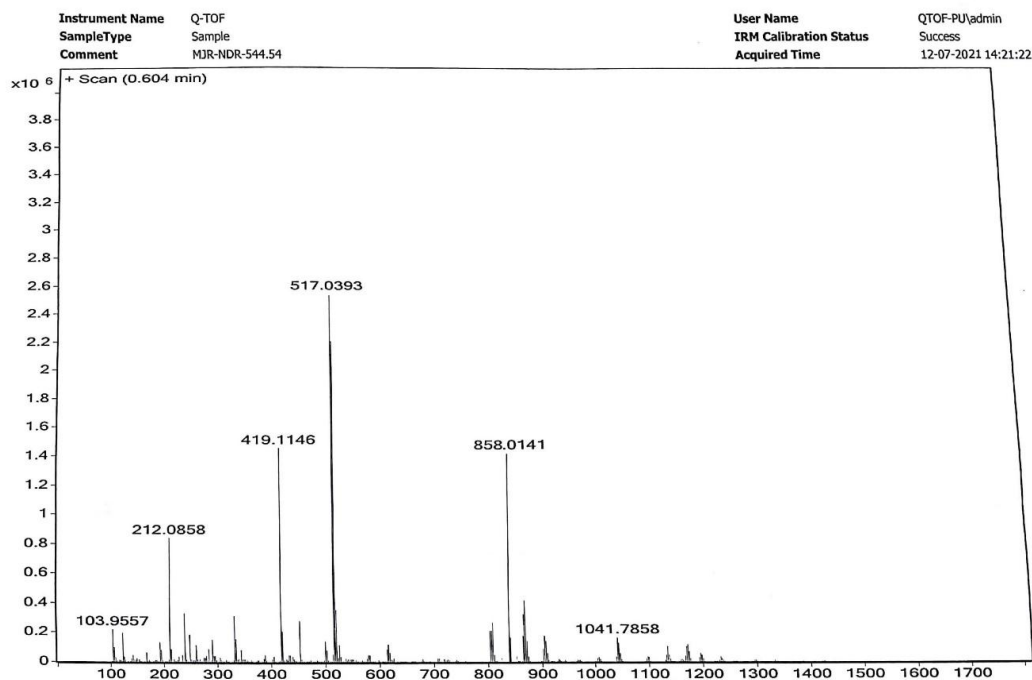


Fig. 2: ESI-Mass Spectrum of $[\text{Cu} (\text{BTHPC})_2]$ Complex.

2.5. ESR spectrometry

Electron spin resonance (ESR) is a potent non-destructive and non-instructive analytical approach. The copper complexes were determined using a JES-FA200 ESR spectrometer (ESR-JEOL, Japan) with a standard frequency (X band) of 8.75-9.65 GHz, sensitivity of 7×10^9 spin/0.1 mT, resolution of -2.35(micro)T, and temperature range of +200 °C to liquid nitrogen temperature.

2.6. Determination of cytotoxicity

Cytotoxicity is the toxicity caused due to the action of chemotherapeutic agents on living cells. Ligand and their metal complexes cytotoxicity in human lung cancer (A549) and human hepato carcinoma (HepG2) cell lines were examined in MTT assay (National centre for cell science, Pune, India). The cytotoxicity of varied concentrations of metal complexes (25, 50, 100, 200 and 400 $\mu\text{g/mL}$) against human cancer cell lines were examined in MTT assay. MTT is a yellow dye that is reduced into purple crystals in the presence of activity in the mitochondrial succinate dehydrogenase enzyme in viable cells. The IC_{50} value was determined after a statistical analysis of the cytotoxicity of metal complexes against cancer lines in the presence of MTT.

2.7. Antibacterial activity

The antibacterial activity of metal complexes against different pathogenic bacterial strains both Gram -ve bacteria *Pseudomonas desmolyticum* [NCIM-2028], *Escherichia coli* [NCIM-5051], and *Klebsiella aerogenes* [NCIM-2098] and Gram +ve bacteria *Staphylococcus*

aureus [NCIM-5022] strains (Purchased from National centre for cell science, Pune, India) by Agar well diffusion method. Then after, different concentration of metal complexes (100, 200, 300 and 400 $\mu\text{g/mL}$) was dispersed in 10% DMSO solution and while standard antibiotic Ciprofloxacin used as a positive control and control in to the wells. The plates were incubated for 24 hours at 37°C. Following the incubation period, the zone of inhibition around the wells was measured in millimeters. The antibacterial bacterial activity was determined in triplicate, preceded by the bactericidal activity of metal complexes.

3. RESULTS AND DISCUSSION

BTHPC, a newly synthesized Schiff base ligand, and its complexes 1–4 were found to be very stable at room temperature. In DMF, they were soluble. Elemental analysis values were in good agreement for complexes with a ratio of 1:2. All of them were neutral and non-conducting compounds ($\Lambda_m = 20.16\text{--}28.25 \Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$).^[30] Physico-chemical and analytical data of ligand and its metal complexes were given in Table-1.

Table 1: Analytical and Physical Characterization data for Ligand and its Metal complexes.

S. No.	Compound	Molecular Weight Found (Calculated)	Melting point (°C)	Colour Yield (%)	Elemental analysis Found (calculated)			Molar conductivity $\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$
					C(%)	H(%)	N(%)	
1	BTHPC	397.59 (397.25)	148-150	Brown (73.65)	54.39 (54.41)	3.33 (3.29)	14.08 (14.10)	-
2	[Co(BTHPC) ₂]	853.17 (853.43)	243-245	Black (88.21)	50.74 (50.65)	3.15 (3.06)	13.01 (13.12)	20.16
3	[Ni(BTHPC) ₂]	853.74 (853.19)	260-262	Black (71.23)	50.77 (50.67)	3.18 (3.07)	13.06 (13.13)	23.36
4	[Cu(BTHPC) ₂]	858.01 (858.04)	224-226	Dark Brown (76.27)	50.65 (50.38)	3.14 (3.05)	13.12 (13.05)	28.25

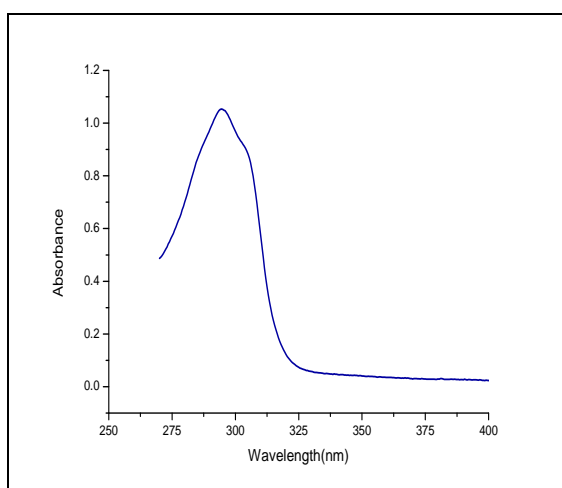
3.1. Electronic spectral bands

The electronic UV–Visible spectra obtained in DMF solutions exhibit one very broad absorption band in the 16,722 cm^{-1} region it is due to d–d transitions, a medium intense band at 27,932 cm^{-1} region for charge transition, and a strong sharp band at 34,013–37,174 cm^{-1} region for

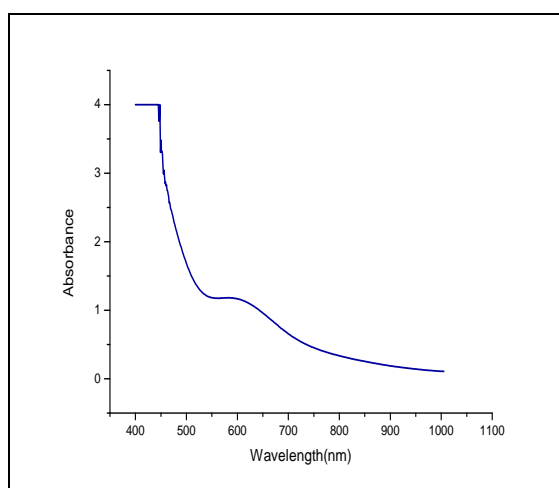
$\pi \rightarrow \pi^*$ transition.^[31–34] The electronic spectral data of the metal (II) complexes are presented in Table-2. Electronic spectrum of [Cu (BTHPC)₂] in high concentration (visible region) and low concentration (UV region) was given in Fig.3.

Table 2: UV-VISIBLE data of Metal Complexes.

S. No.	Complex	Wavelength λ_{max} (nm)	Frequency (cm^{-1})	Assignment
1	[Co (BTHPC) ₂]	277	36,101	$\pi \rightarrow \pi^*$ transition
		358	27,932	CT transition
2	[Ni (BTHPC) ₂]	269	37,174	$\pi \rightarrow \pi^*$ transition
		290	34,482	$\pi \rightarrow \pi^*$ transition
3	[Cu (BTHPC) ₂]	294	34,013	$\pi \rightarrow \pi^*$ transition
		598	16,722	d-d transition



(A)



(B)

Fig. 3: Electronic spectrum of [Cu (BTHPC)₂] (A) Low concentration (UV region) (B) high concentration (Visible region).

3.2. IR spectral bands

One of the most extensively used instruments for detecting functional groups in pure compounds and mixtures, as well as the type of atom binding in metal complexes, is infrared spectroscopy. IR spectral data of the ligand [BTHPC] and its metal (II) complexes are shown in Table-3. A medium intensity band around 3332 cm^{-1} due to ν (N-H). These observations suggest the non-

involvement of atom N-H in coordination. The IR spectrum of the ligand display at 1632 cm^{-1} , which may be assigned due to the ν (C=N) azomethine. When compared to complex this band is shift lower frequency (1606 to 1585 cm^{-1}) indicates the coordination of nitrogen in the complex formation. The participation of nitrogen in coordination with the metal ion is further supported by the new band appearance of ν (M-N) at

559-532 cm^{-1} . A new band appearance of ν (M-S) at 480-469 cm^{-1} respectively in the infrared region.^[35-39]

Table 3: IR Spectral data (cm^{-1}) of the ligand and its Metal Complexes.

BTHPC	[Co(BTHPC) ₂]	[Ni(BTHPC) ₂]	[Cu(BTHPC) ₂]	Assignment
3332	3285	3291	3330	N-H
2256	2250	2248	2244	CN
1632	1592	1585	1606	C=N
1015	972	981	998	Aromatic CH
	532	545	559	M-N
	480	475	469	M-S

3.3. ESR analysis of copper complexes

The ESR spectrum of copper (II) complex are recorded in DMF at 300 and 77 K given in Fig.4. and the spin Hamiltonian parameters of the complexes are listed in Table-4. The observed spectral parameters reveals that $g_{\parallel} > g_{\perp}$ characteristic of an axially elongated octahedral geometry. The g_{avg} value is less than 2.28 indicating the covalent character of the metal-ligand bond. Further, it is supported from the fact that the unpaired electrons lies predominantly in the dx^2-y^2 orbital. The observed

value of G for copper complex is 4.24, characteristic of mono nuclear configuration which also suggests that the exchange coupling is present and misalignment is appreciable.^[40-44]

$$g_{\text{avg}} = \frac{[g_{\parallel} + 2g_{\perp}]}{3}$$

$$G = \frac{[g_{\parallel} - 2.0023]}{[g_{\perp} - 2.0023]}$$

Table 4: ESR Spectral data of copper complexes at RT and LNT.

Complex	g_{\parallel}	g_{\perp}	g_{avg}	G	$A_{\parallel} \times 10^{-5}$	$A_{\perp} \times 10^{-5}$	K_{\parallel}	K_{\perp}	λ	α
[Cu(BTHPC) ₂] (RT)	2.12	2.03	2.06	4.24	-	-	-	-	-	-
[Cu(BTHPC) ₂] (LNT)	2.10	2.01	2.04	12.68	-	-	-	-	-	-

*RT=Room Temperature; LNT= Liquid Nitrogen temperature

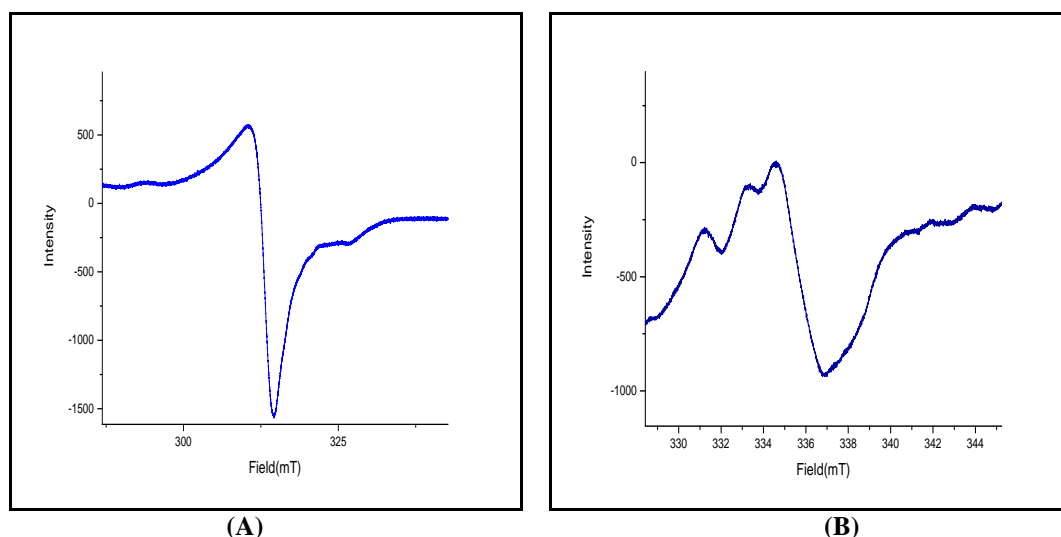


Fig. 4: ESR spectra of Copper complex recorded at LNT (A) and RT (B)

It has an octahedral geometry, according to the physico-chemical and spectral data. It was shown in Fig. 5.

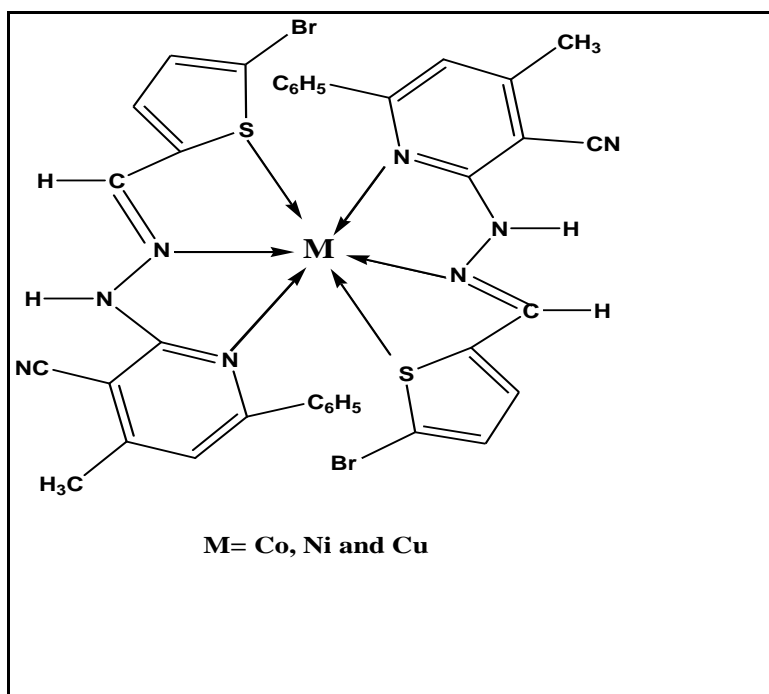


Fig. 5: Proposed structure of metal complexes.

3.4. Cytotoxicity

On the basis of in-vitro analysis, the cytotoxicity of synthesized ligands and metal complexes against A549 and HepG2 cell line cancer cells was assessed. The ligand and metal complexes were tested against cell lines with Cis-platin as the positive control. As a result, as shown in Tables 5 and 6, the viability assay of cytotoxicity of ligand and metal complexes against A549 and HepG2 cancer cell lines. The decrease in cell viability with increasing metal complex concentrations has shown significant cytotoxicity to accumulate internal cells and higher stress, eventually leading to apoptosis.^[45,46]

Even though the concentrations were increased, the ligand alone had little effect. The activity increased dramatically as the quantities of metal complexes increased. Copper complexes had the most activity, whereas Nickel and Cobalt complexes had moderate activity with the A549 cell lines. For HepG2 cell lines the activity show a slight different for metal complexes, although the copper complex has the highest activity, Nickel complex has a similar activity with copper complex at 200µg/mL. After that, there is a drastic difference in activity, as seen in the graphical representations. Fig. 6 (A) & (B).

Table 5: Cytotoxicity of ligand and metal complexes against A549 cancer cell lines.

	A549 cell line					
	Concentrations (µg/mL)					
	25	50	100	200	400	IC ₅₀
Standard (Cis-Platin)	49.09	-	-	-	-	-
BTHPC	95.45	90.64	84.36	80.42	76.38	-
[Co (BTHPC) ₂]	94.48	82.31	69.54	60.26	45.78	342
[Ni (BTHPC) ₂]	91.52	80.28	65.32	59.92	43.84	323
[Cu (BTHPC) ₂]	90.96	78.84	70.66	58.24	40.46	292

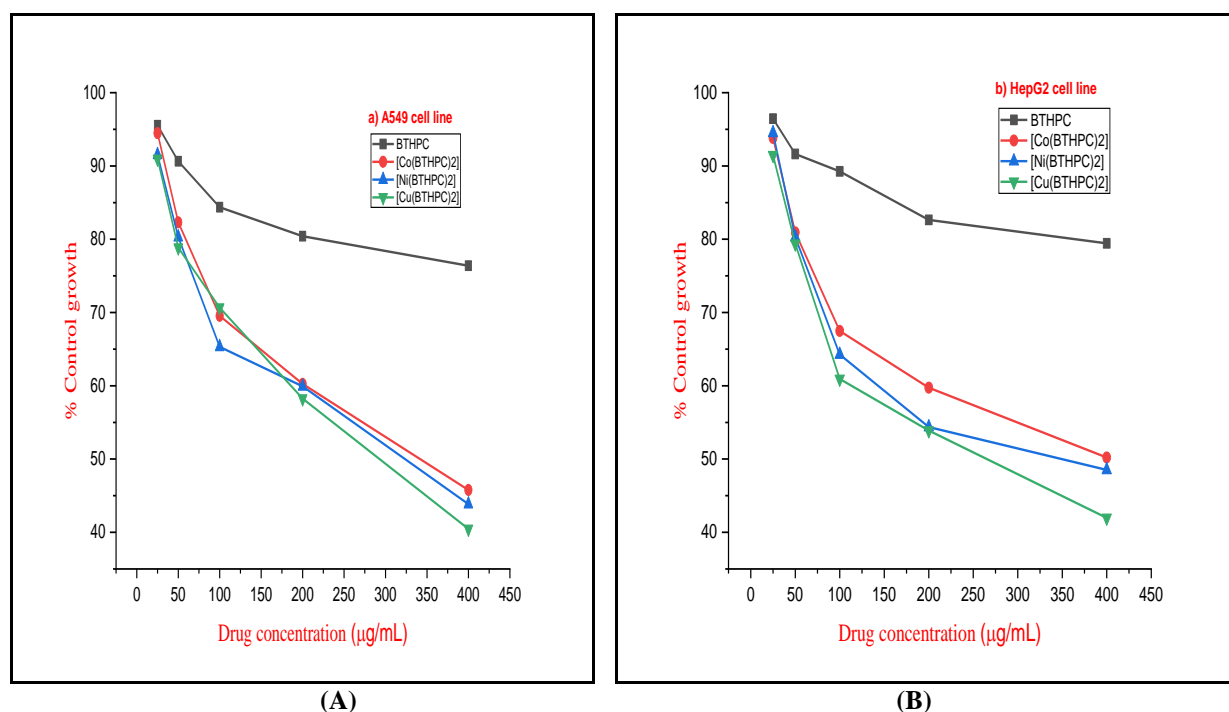


Fig. 6: Graphical representation of metal complexes with cytotoxicity effect on A549 cell lines (A) and HepG2 cell lines (B).

Table 6: Cytotoxicity of ligand and metal complexes against HepG2 cancer cell lines.

HepG2 cell line						
	Concentrations (µg/mL)					
	25	50	100	200	400	IC ₅₀
Standard (Cis-Platin)	54.48	-	-	-	-	-
BTHPC	96.45	91.63	89.26	82.63	79.44	-
[Co (BTHPC) ₂]	93.82	80.92	67.48	59.74	50.22	398
[Ni (BTHPC) ₂]	94.52	80.26	54.27	54.36	48.52	344
[Cu (BTHPC) ₂]	91.46	79.38	60.94	53.89	41.98	268

3.5. Antibacterial activity

The antibacterial activity of the ligand BTHPC and its metal complexes was investigated. The zone of inhibition was measured in millimetres, and the values of the substances studied are listed in Table-7. It is obvious from the results that the metal complexes have greater antibacterial action than the free ligand BTHPC. This is most likely owing to the complexes increased lipophilicity. The increased activity of metal (II) complexes can be explained using Overton's concept and Chelation theory.^[46-49] One possible explanation for the

observed increased activity after chelation is that the positive charge of the metal in the chelated complex is partially shared with the ligand donor atoms, resulting in electron delocalization throughout the chelate ring. This, in turn, increases the lipophilicity of the metal chelate and facilitates its permeation through the lipid layers of bacterial membranes. Antibacterial activity at various concentrations of the Ligand and their complexes with different pathogenic strains were given in Fig. 7. Copper complex, when compared to other metal complexes, has the highest antibacterial activity.

Table 7: Antibacterial activity of Ligand and its complexes against pathogenic bacterial Strains.

Treatment		Bacterial Strains			
Sample	Concentration (µg/mL)	<i>S. aureus</i>	<i>E. coli</i>	<i>P. desmolyticum</i>	<i>K. aerogenes</i>
Ciprofloxacin	10	14.10	11.45	11.52	12.06
BTHPC	100	1.04	1.12	0.97	0.91
[Co(BTHPC) ₂]	100	2.46	2.14	2.26	2.38
	200	3.62	3.22	3.36	3.14
	300	4.12	3.84	3.92	4.06
	400	4.86	4.95	5.16	5.32
[Ni(BTHPC) ₂]	100	2.52	2.38	2.54	2.76
	200	3.78	3.42	3.56	3.48

[Cu(BTHPC) ₂]	300	4.26	4.18	4.30	4.12
	400	5.14	5.26	5.22	5.62
	100	2.96	2.80	2.74	2.92
	200	4.12	4.02	3.98	4.22
	300	5.84	6.12	5.92	6.04
	400	8.82	9.04	8.92	8.74

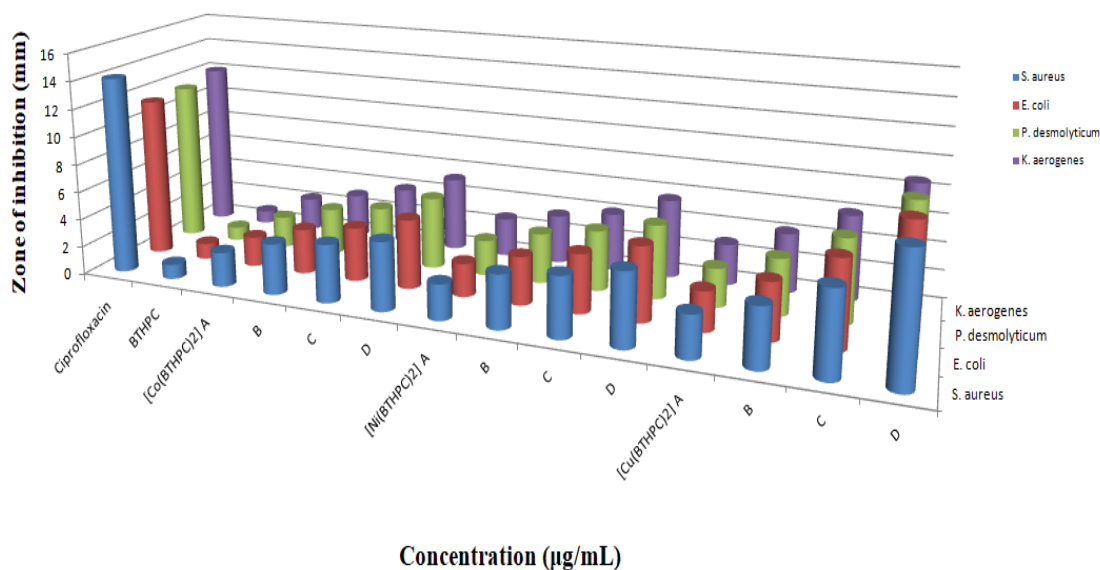


Fig. 7: Antibacterial activity at various concentrations of the Ligand and their complexes with different pathogenic strains.

4. CONCLUSIONS

The pyridine derivative of the ligand [BTHPC] as well as their transition metal complexes (where M = Co, Ni and Cu) have been synthesized and characterized. Elemental, conductivity, and mass spectrometry analyses revealed the complexes stoichiometry and composition. The bonding properties of the above ligand and metal complexes were confirmed by FT-IR, UV-Vis, ¹H NMR, and ESR spectral data. Based on the findings of Copper complex ESR parameters suggest that the complex has an octahedral geometry. The decrease in cell viability associated with increasing metal complex concentrations has resulted in considerable cytotoxicity, resulting in the accumulation of internal cells and increased stress, finally leading to apoptosis. Metal complexes have high cytotoxicity than free ligand. Copper complexes had the highest activity, while Nickel and Cobalt complexes had the moderate activity for A549 and HepG2 cell lines. The antibacterial activity of the ligand (BTHPC) and its metal complexes in vitro suggests that the complexes are more effective than the free ligand. When compared to other metal complexes, copper complex has the most antibacterial action.

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