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CYTOTOXICITY AND ANTIBACTERIAL STUDIES OF NOVEL HETEROCYCLIC PYRIDINE-THIOPHENE DERIVATIVE AND ITS METAL COMPLEXES

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ABSTRACT

Tranistion metals [Co, Ni, and Cu] complexes of pyridine-thiophene derivative ligand 2-((E)-2-((5-methylthiophen-2-yl) methylene)hydrazinyl)-4-methyl-6-phenylpyridine-3-carbonitrile(MTHPC) have been synthesized and characterized with different spectral investigations viz. UV-Vis, FT-IR, 1H-NMR, and ESR. The ligand and metal complexes were screened for *in-vitro* cytotoxicity studies against two carcinoma cell lines A549 (Lung carcinoma cells) and HepG2 (Hepatocellular carcinoma cell). The results were found to possess cytotoxic effect. Nickel complex had shown high potent cytotoxic effect for A549 cell lines and Copper complex shown high cytotoxic effect for HepG2 cell lines. The ligand and metal complexes were tested *in vitro* against Gram -ve bacteria such *Pseudomonas desmolyticum*, *Escherichia coli*, and *Klebsiella aerogenes*, as well as Gram +ve bacteria like *Staphylococcus aureus*. Copper and Cobalt complex has modest antibacterial action at increasing concentrations, but Nickel complex has significant antibacterial activity.

Keywords: Transition Metals, Pyridine-Thiophene derivative, Cytotoxicity studies, Antibacterial activity.

1. INTRODUCTION

A wide range of pharmacological actions have been related to heterocyclic compounds with pyridine rings, including anticonvulsant [1], antibacterial [2-3], antiviral [4], anticancer [5], and anti-HIV [6]. Pyridine derivatives with antifungal and anticancer characteristics have been synthesized and used as intermediates with the parent molecule 2-chloropyridine-3-carboxylic acid. N-alkylated-2-pyridones are essential intermediates in the creation of polycyclic compounds of biological importance, according to recent synthetic techniques to anticancer [7-8] medications.

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 [9-10]. 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 [11-13]. 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 [14]. Current breakthroughs in the realms of bioinorganic chemistry and medicine have heightened interest in transition metal complexes with various types of ligands [15]. 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 [16-17].

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 [18]. 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 [19].

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 [20].

A recent investigation on the synthesis of novel heterocycles of 2-hydrazinyl-4-methyl-6-phenylpyridine -3-carbonitrile condensed with 5-Methylthiophene-2-carbaldehyde was done since several nitrogen and sulphur containing heterocyclic systems demonstrate a wide spectrum of medicinal actions. This could lead to the creation of novel physiologically active molecules. New pyridine compounds and their transition metal complexes, such as Co, Ni, and Cu, were developed and produced. These compounds were described using a variety of techniques, and their cytotoxic and antibacterial activity was subsequently investigated.

2. EXPERIMENTAL

2.1. Material

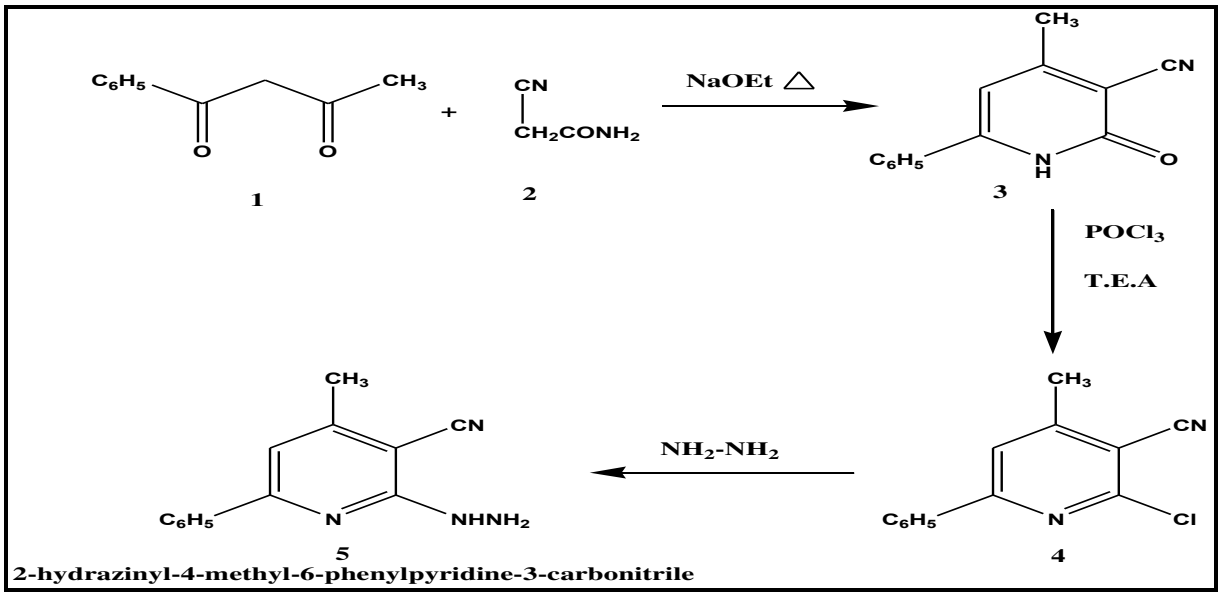
Benzoyl acetone, phosphoryl chloride, sodium ethoxide, triethylamine, hydrazine monohydrochloride, cyano-acetamide, 5-methylthiophene-2-carbaldehyde, Nickel (II) chloride, Cobalt(II) chloride, and Copper (II) chloride were purchased from Sigma Aldrich. All of the other chemicals and solvents were of analytical reagent grade and purchased from a commercial source.

2.2. Physical measurements

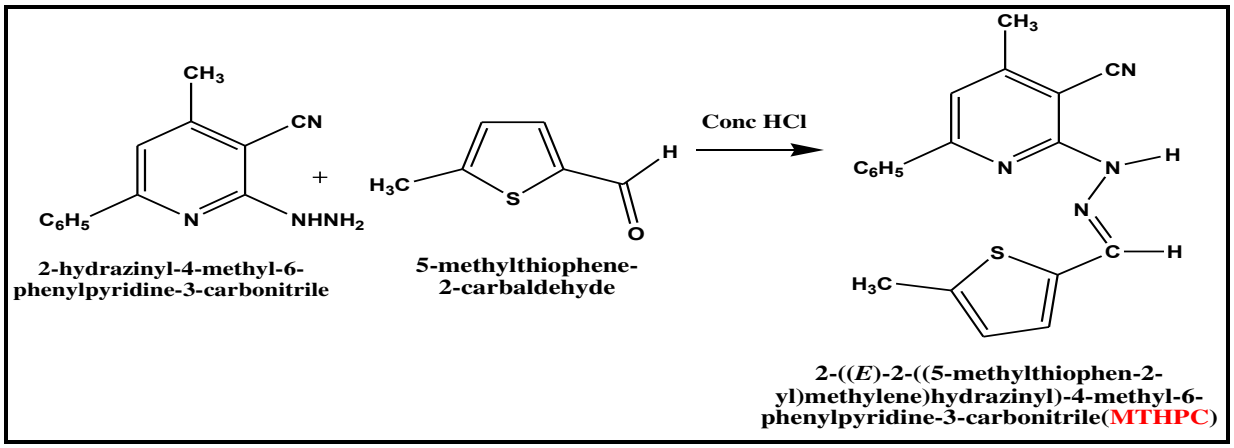
The elemental analysis (C, H and N) was performed on a PerkinElmer 2400 CHN analyzer. Melting points were determined in open capillaries using a G LAB melting apparatus and were reported uncorrected. UV-visible spectra of DMF solutions were recorded on a UV-210 ELICO spectrometer in the spectral window of 200-800 nm. Infrared spectra (FT-IR) were recorded 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 according to earlier reported method [21]. 2.4 g (0.01 mmol) of it was dissolved in 20 mL methanol and was added to 5-Methyl thiophene-2-carbaldehyde 1mL (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 $C_{19}H_{16}N_4S$; Yield 72.11%; m.p.192-194°C; IR cm^{-1}; 3340 (NH), 2235(C≡N), 1626(C=N), 1035(aromatic C-H); ^{1}H-NMR; δ 2.42(s,3H CH_3 pyridine), δ 2.26(s,3H CH_3 Thiophene), 7.14 (d,1H, Thiophene-H), 6.89(d,1H Thiophene-H), 7.81-(S, 1H CH) 7.28 (s,1H, N-H), 7.77 (s,1H, Py-H), 7.39-7.97 (m,5H, Ar-H); MS m/z(%): 334.11; The ligand is synthesized as illustrated in Scheme-1 & 2, and its mass spectrum was given in fig.1.



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



Scheme 2: synthesis of 2-((E)-2-((5-methylthiophen-2-yl)methylene)hydrazinyl)-4-methyl-6-phenyl-pyridine-3-carbonitrile(MTHPC)

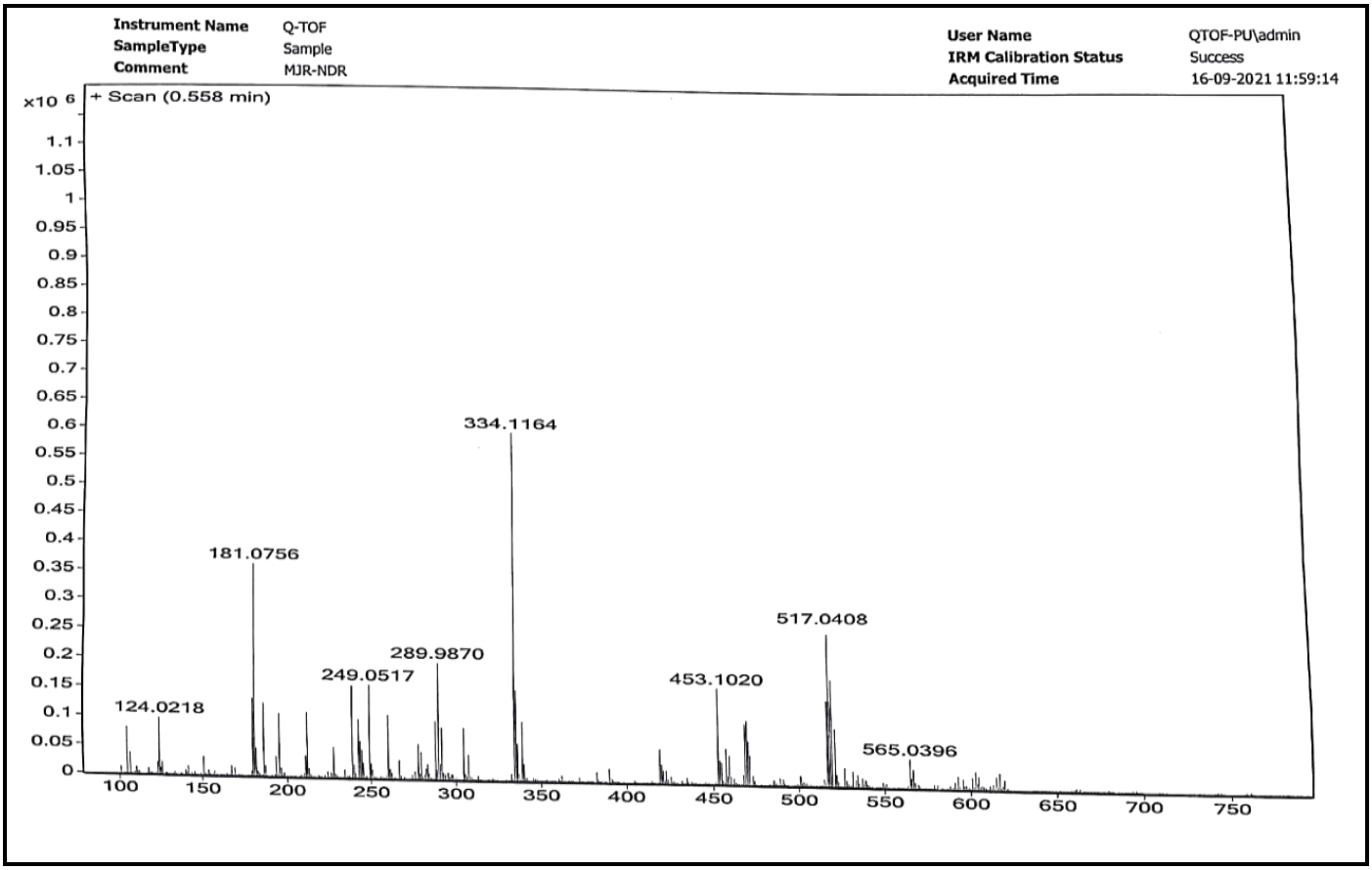


Fig. 1: Mass spectrum of MTHPC Ligand

2.4. General procedures for the synthesis of complexes

A hot methanolic solution (20 mL) of ligand mixture (3.52g 0.1 mol) was added to a solution of Metal chlorides (M= Co, Ni and Cu) (0.05 mol) in H_2O (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. The mass spectrum of Cobalt, Nickel and Copper complexes were given in fig. 2, 3, and 4 respectively.

$$\underset{\text{metal salt}}{MX_2.XH_2O} + \underset{\text{ligand}}{MTHPC} \xrightarrow{NaOH} \underset{\substack{\text{complex} \\ M= Co,Ni \text{ and } Cu}}{[\,M(MTHPC)_2\,]}$$

Scheme 3: Synthesis of metal complexes

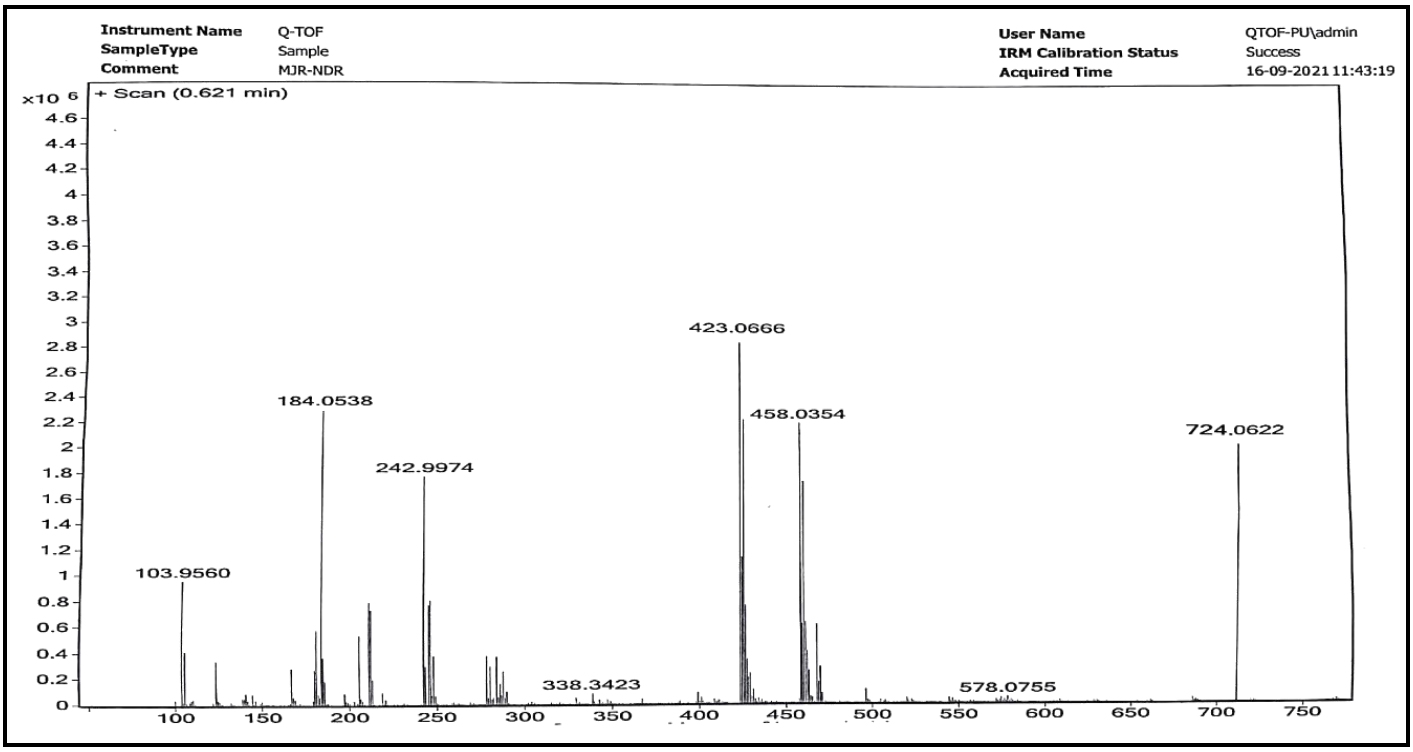


Fig. 2: ESI-Mass spectrum of [Co(MTHPC)$_2$] Complex

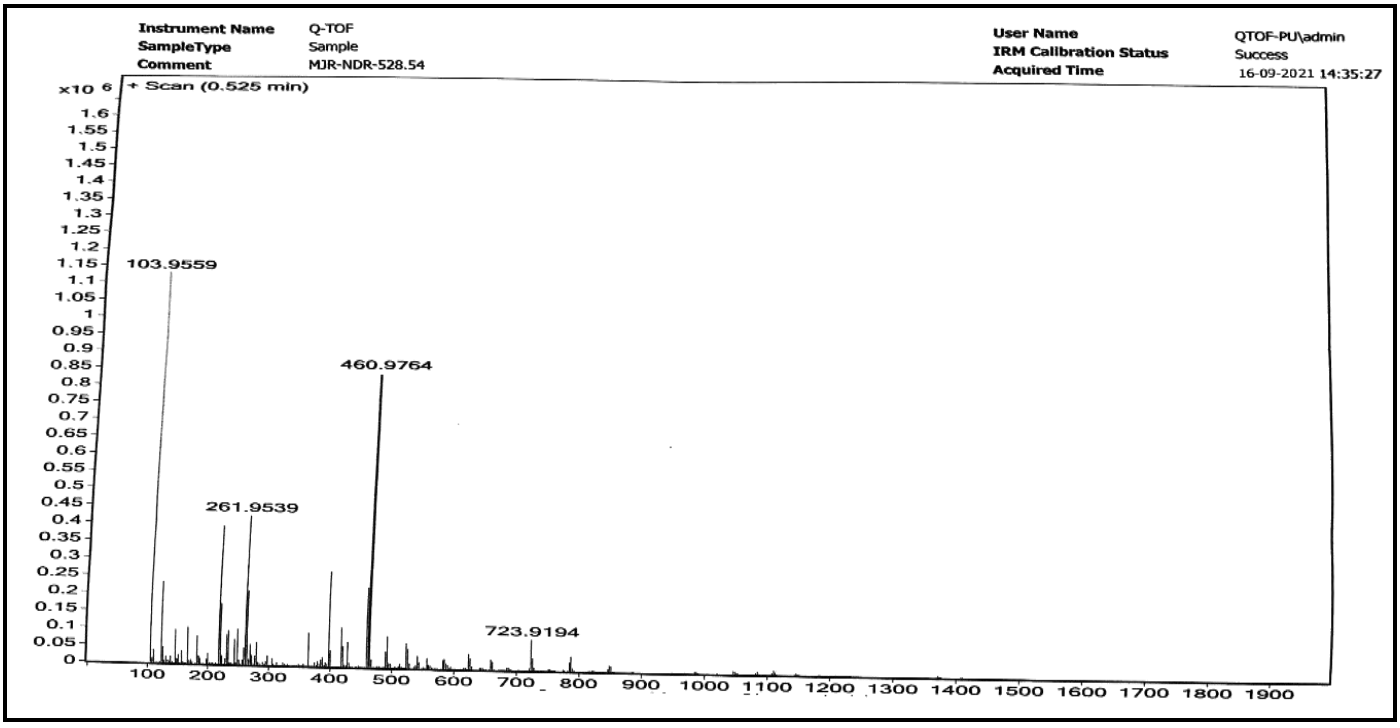


Fig. 3: ESI-Mass spectrum of [Ni(MTHPC)$_2$] Complex

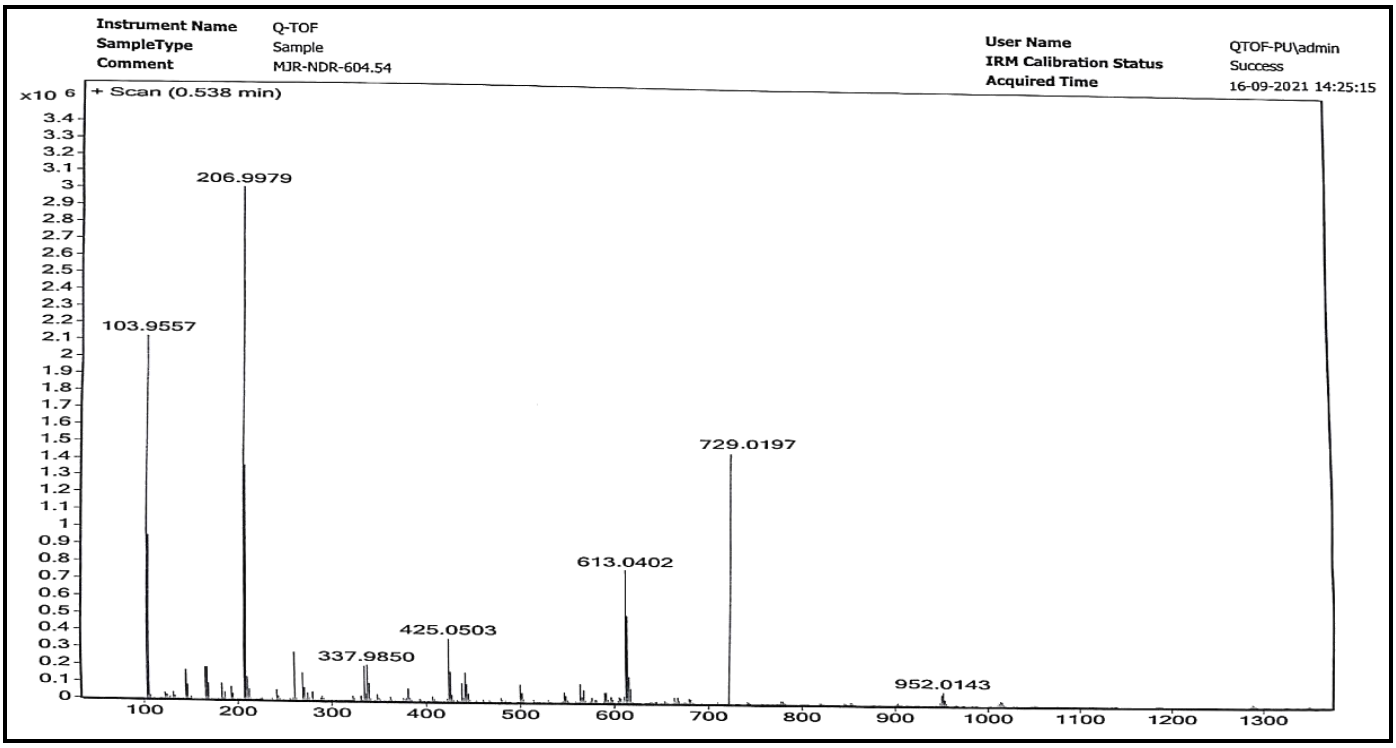


Fig. 4: ESI-Mass spectrum of [Cu(MTHPC)$_2$] Complex

2.5. Determination of cytotoxicity

Cell lines were grown in the presence of the following Dulbeccos Modified Eagles Medium (DMEM) with supplemented foetal bovine serum and antibiotics for 24 hours at 37°C in a humidified atmosphere of 5% CO_2. The cells were planted at a density of 25x103 cells per well in 96 well plates. The cytotoxicity of varied concentrations of metal complexes (25, 50, 100, 200 and 400µg/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.

2.6. 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 *Staphylococcus aureus* (NCIM-5022) strains (Purchased from National centre for cell science, Pune, India) by Agar well diffusion method. Different concentrations of metal complexes (100, 200, 300 and 400 µg/mL) were dispersed in 10% DMSO solution and while standard antibiotic Ciprofloxacin was used as a positive 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 millimetres. The antibacterial bacterial activity was determined in triplicate, preceded by the bactericidal activity of metal complexes.

3. RESULTS AND DISCUSSION

MTHPC, 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 (Λ_m = 18.80-26.43 Ω^{-1} cm^2 mol^{-1}) [22]. Physico-chemical and analytical data of ligand and its metal complexes were given in Table 1.

3.1. Electronic spectral bands

The electronic UV-Visible spectra obtained in DMF solutions, the electronic spectral data of the metal complexes are presented in Table 2. Electronic spectrum of complexes was given in Fig. 5. From the diffuse reflectance spectra it is observed that, the Cobalt complex exhibits a band at 30,303 cm^{-1}, which may be

assigned to the Charge transition in octahedral geometry of the complex. The region at 14,771 and 16,420 cm^{-1} refers to the d-d transition. The solid reflectance spectrum of the Nickel complex gives two bands at 28,985 and 36,630 cm^{-1} wave number regions. The region at 28,985 and 36,630 cm^{-1} refers to the charge transfer band and $\pi\text{-}\longrightarrow\pi^*$ transition. The reflectance spectrum of Copper chelate consists of a broad, low intensity shoulder band centered at 16,920 and 28,818 cm^{-1}. This assignment is in agreement with the general observation that Copper has d–d transitions are normally close in energy. A moderately intense peak observed in the range 28,818 cm^{-1} is due to ligand-metal charge transfer transition [23-26]. Electronic spectrum of metal complexes is given in fig.5.

Table 1: Physicochemical and analytical data of ligand and their metal complexes

Compound	Molecular Weight Found (Calculated)	Melting point (°C)	Colour Yield (%)	Elemental analysis Found (calculated)			Molar conductivity
				C(%)	H(%)	N(%)	
MTHPC	334.11 (332.37)	192-194	Brown (72.11)	68.47 (68.64)	4.78 (4.85)	16.75 (16.85)	-
[Co(MTHPC)$_2$]	724.05 (723.67)	212-214	Black (73.48)	63.54 (63.05)	4.52 (4.45)	15.46 (15.48)	20.11
[Ni(MTHPC)$_2$]	723.87 (723.43)	237-239	Dark Brown (82.69)	63.14 (63.08)	4.52 (4.45)	15.46 (15.48)	18.80
[Cu(MTHPC)$_2$]	729.08 (728.28)	254-256	Black (69.97)	62.09 (62.65)	4.49 (4.42)	15.41 (15.38)	26.43

Table 2: UV-Visible spectra of metal complexes with MTHPC ligand

Complex	Wavelength λ max (nm)	Frequency (cm^{-1})	Assignment
[Co(MTHPC)$_2$]	330	30,303	CT transition
	609	16,420	d-d transition
	677	14,771	d-d transition
[Ni(MTHPC)$_2$]	273	36,630	$\pi\text{-}\longrightarrow\pi^*$ transition
	345	28,985	CT transition
[Cu(MTHPC)$_2$]	347	28,818	CT transition
	591	16,920	d-d transition

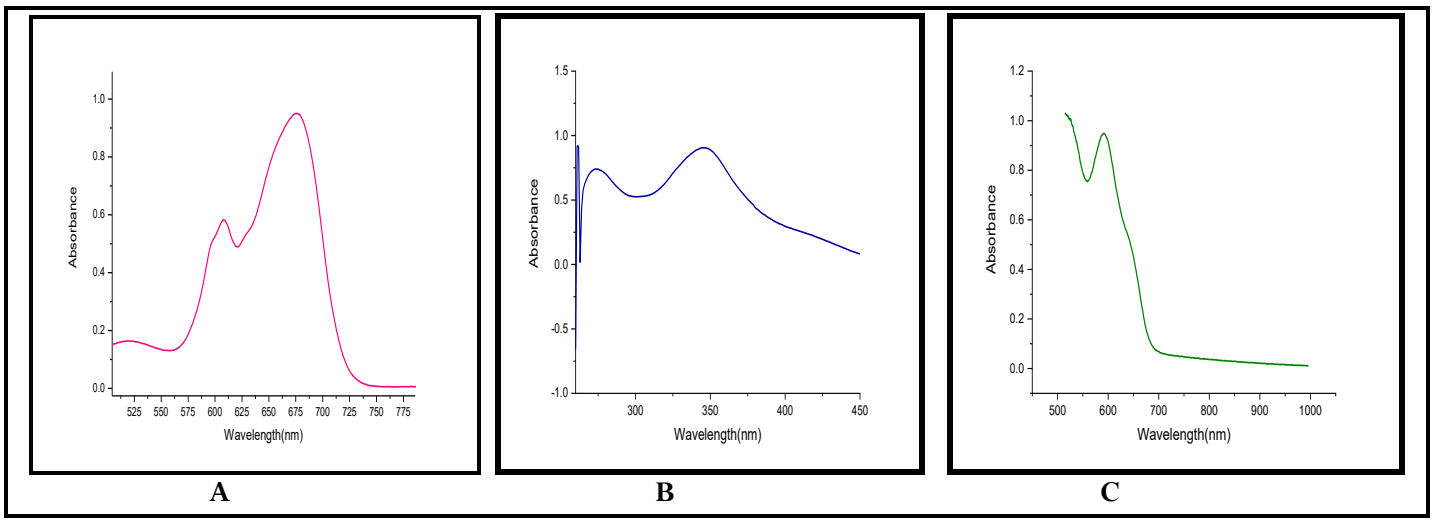


Fig. 5: Electronic spectrum of [Co (MTHPC)$_2$] Visible region(A); [Ni (MTHPC)$_2$] UV region (B); and [Cu (MTHPC)$_2$] Visible region (C).

3.2. IR spectral bands

The IR data of the MTHPC Schiff base and its complexes are listed in Table 3. The IR spectra of the complexes are compared with those of the free ligand in order to determine the coordination sites that may involve in chelation. There are some guide peaks, in the spectra of the ligand, which are of good help for achieving this goal. The position and/or the intensities of these peaks are expected to be changed upon chelation. These guide peaks are listed in Table 3. Upon comparison it was found that the ν (C=N) of the azomethine stretching vibration is found in the free ligand at 1626 cm^{-1}. This band is shifted to lower 1592-1575cm^{-1} wavenumbers in the complexes indicating the participation of the azomethine nitrogen in coordination (M-N). New bands are found in the spectra of the complexes in the regions 538-562 and 462-483 which are assigned to ν (M-N) and ν (M-S) stretching vibrations [27-31].

3.3. ESR analysis of copper complex

The ESR spectrum of copper (II) complex are recorded in DMF at 300 and 77 K and the spin Halmiltonian parameters of the complexes are listed in Table 4 (fig.6.) 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 2.32, characteristic of mono nuclear configuration which also suggests that the exchange coupling is present and misalignment is appreciable [32-36].

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

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

It has an octahedral geometry, according to the physico-chemical and spectral data. It was shown in fig. 7.

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 [37-38].

Table 3: IR data of Ligand (MTHPC) and their metal complexes

MTHPC	$[Co(MTHPC)_2]$	$[Ni(MTHPC)_2]$	$[Cu(MTHPC)_2]$	Assignment
3340	3276	3284	3318	N-H
2245	2239	2240	2236	CN
1626	1581	1575	1592	C==N
1035	961	987	990	Aromatic CH
	542	538	562	M-N
	470	462	483	M-S

Table 4: ESR spectral data of Copper Complex

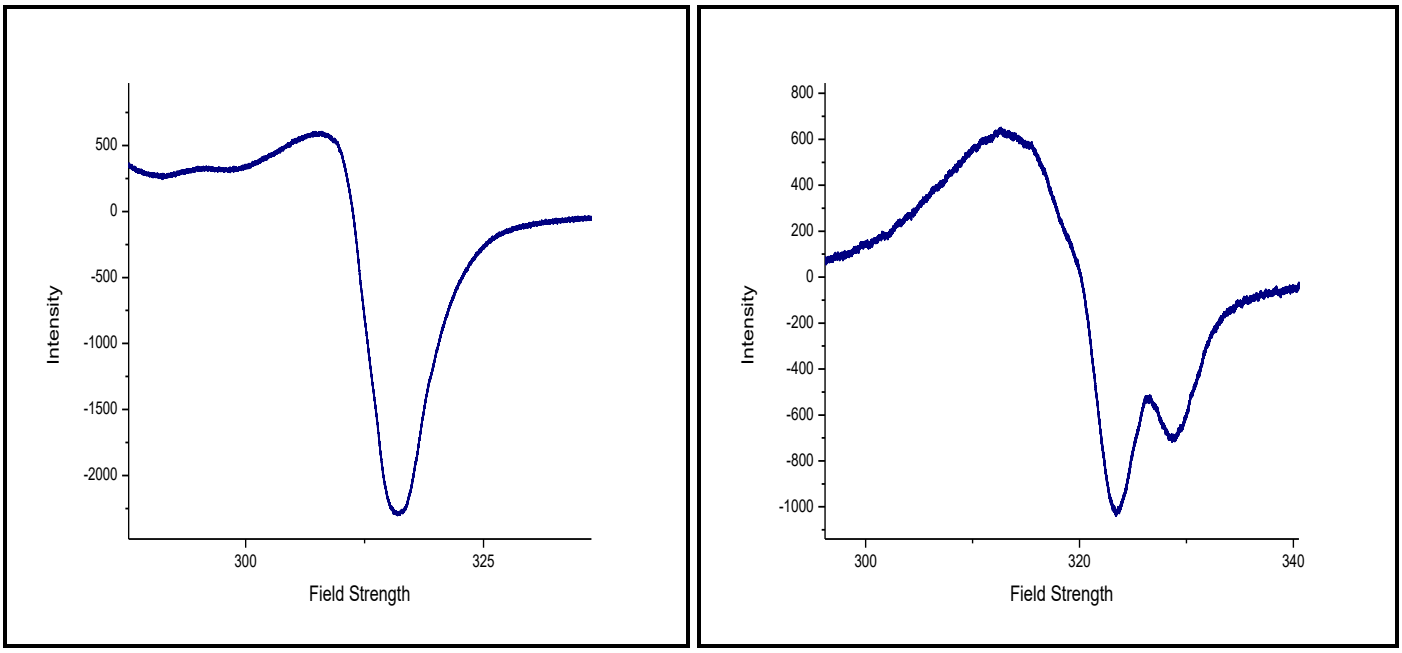
Complex		$g\|\|$	$g^{\perp}$,	g_{avg}	G	$A_{\parallel}$ x 10^{-5}	$A^{\perp}$ x 10^{-5}	$K_{\parallel}$	$K^{\perp}$	λ	α
$[Cu(MTHPC)_2]$	(RT)	2.14	2.07	2.09	2.03	-	-	-	-	-	-
$[Cu(MTHPC)_2]$	(LNT)	2.09	2.04	2.05	2.32	-	-	-	-	-	-

**RT=Room Temperature; LNT= Liquid Nitrogen temperature*

Even though the concentrations were increased, the ligand alone had little effect. The activity increased dramatically as the quantities of metal complexes increased. Nickel complexes had the most activity with A549 cell lines, whereas Copper complexes had most activity with HepG2 cell lines. The order of cytotoxic effect on A549 cell is Ni > Cu > Co and for HepG2 cell line is Cu > Ni > Co. It was shown in fig. 8 & 9.

Table 5: Cytotoxicity of Ligand and metal complexes with Lung cancer cell lines A549

	A549 cell line					
	Concentrations (µg/mL)					
	25	50	100	200	400	IC_{50}
Standard (Cis-Platin)	49.09	-	-	-	-	-
MTHPC	96.46	91.45	86.24	82.30	78.66	-
$[Co(MTHPC)_2]$	95.12	81.85	73.82	61.54	48.70	376
$[Ni(MTHPC)_2]$	92.06	78.56	69.76	56.92	45.24	320
$[Cu(MTHPC)_2]$	91.48	80.26	72.18	60.46	47.86	365



(a) (b)

Fig. 6: ESR spectra of Copper complex recorded at LNT (a) and RT (b)

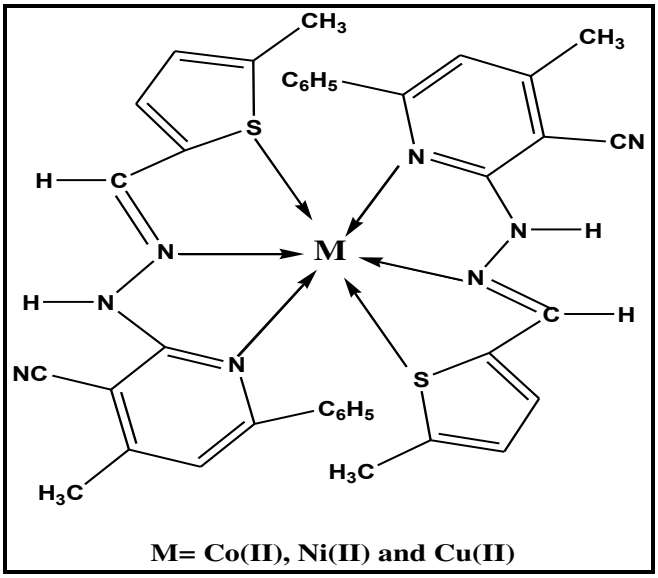


Fig. 7: Proposed structure of metal complexes

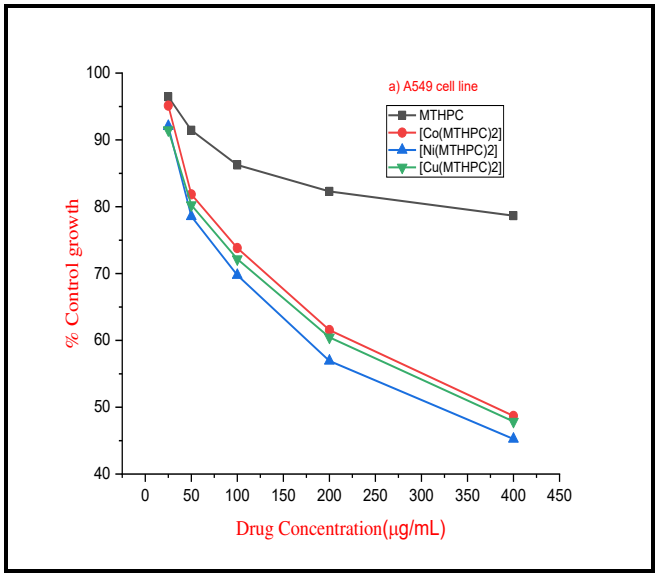


Fig. 8: Graphical representation of metal complexes with cytotoxicity effect on A549 cell lines

Table 6: Cytotoxicity of Ligand and metal complexes with Lung cancer cell lines HepG2

	HepG2 cell line					
	Concentrations (µg/mL)					
	25	50	100	200	400	IC_{50}
Standard (Cis-Platin)	54.48	-	-	-	-	-
MTHPC	97.38	92.59	87.46	80.10	76.42	-
$[Co(MTHPC)_2]$	96.46	80.88	72.56	63.28	46.08	354
$[Ni(MTHPC)_2]$	95.82	80.62	73.98	60.54	45.26	335
$[Cu(MTHPC)_2]$	92.75	79.16	70.82	59.16	42.54	310

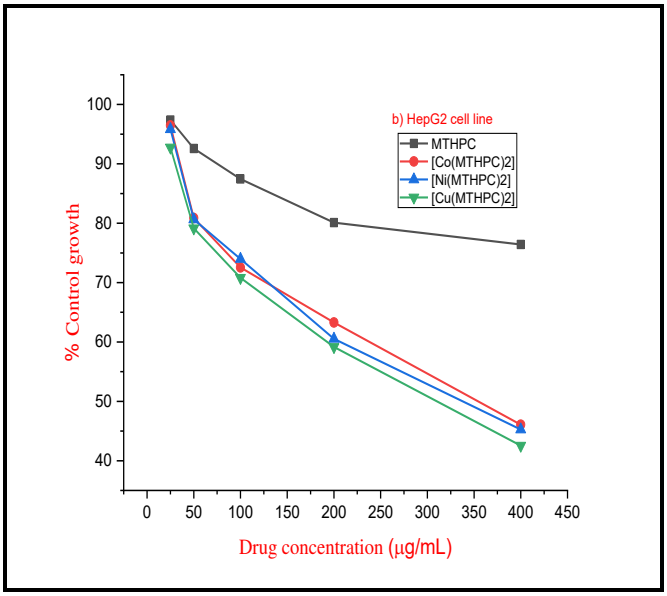


Fig. 9: Graphical representation of metal complexes with cytotoxicity effect on HepG2 cell lines

3.5. Antibacterial activity

The antibacterial activity of the ligand MTHPC and its metal (II) complexes was investigated. The zone of inhibition was measured in millimetres, and the values of the substances studied are listed in Table 7. In testing of antibacterial activity of these compounds, we used more than one test organism. All of the tested compounds showed a remarkable biological activity against different types of Gram-positive and Gram-negative bacteria. On comparing the biological activity of the Ligand (MTHPC) and its metal complexes with the standard Ciprofloxacin, the following results are obtained.

It is obvious from the results that the metal complexes have greater antibacterial action than the free ligand MTHPC. The biological activity of the complexes follow the order Ni > Cu > Co Also, the data in Table 7. 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 [39-42]. 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 Table 7.

Table 7: Antibacterial activity of Ligand and Metal complexes with different pathogenic strains

	Treatment				
Sample	**Concentration(µg/mL)**	***S. aureus***	***E. coli***	***P. desmolyticum***	***K. aerogenes***
Ciprofloxacin	10	14.10	11.45	11.52	12.06
MTHPC	100	0.98	1.06	0.82	1.02
$[Co(MTHPC)_2]$	100	2.32	2.64	2.04	2.52
	200	3.54	3.68	3.26	3.48
	300	4.46	4.82	3.98	4.24
	400	6.42	6.88	6.05	6.76
$[Ni(MTHPC)_2]$	100	2.74	2.82	2.16	2.94
	200	4.36	3.91	3.83	4.02
	300	5.54	5.64	4.14	5.46
	400	7.92	8.16	7.83	7.84
$[Cu(MTHPC)_2]$	100	2.48	2.51	2.26	2.64
	200	3.94	3.75	3.74	3.93
	300	4.82	5.18	4.42	5.28
	400	7.16	7.28	7.64	7.56

4. CONCLUSION

A novel pyridine derivative of the ligand [MTHPC] and their transition metal complexes (where M = Cu, Co, and Ni) have been synthesized and described. The complexes' stoichiometry and composition were determined using elemental, conductivity, and mass spectrometry studies. FT-IR, UV-Vis, 1H NMR, and ESR spectrum data were used to corroborate the bonding properties of the aforesaid ligand and metal complexes. Copper complex ESR values show that the complex has an octahedral geometry, based on the observations. Increased metal complex concentrations have caused significant cytotoxicity, resulting in the buildup of internal cells and increased stress, eventually leading to apoptosis. The cytotoxicity of metal complexes is higher than that of free ligand. For A549 cell lines, Nickel complexes had the maximum activity, whereas Copper complexes had the highest activity for HepG2 cell lines. The ligand (MTHPC) and its metal complexes have antibacterial activity *in vitro*, indicating that the complexes are more effective than the free ligand. Copper and Cobalt complexes have moderate antibacterial activity, but Nickel complexes have significant antibacterial activity.

5. ACKNOWLEDGEMENTS

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Conflict of interest

The authors have no conflicts of interest regarding this investigation.

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