

Anticancer and Antioxidant activity of Cobalt (ii) and Nickel (ii) complexes containing Benzimidazolyl Terpyridine

M. Kiruthika* and G. Krishnaveni

Department of Chemistry, Arignar Anna Government Arts College, Musiri-621 211, Tamilnadu, India

Abstract

Benzimidazole based terpyridine ligand has been prepared and cobalt and nickel complexes containing benzimidazolyl terpyridine have been synthesized. Spectral techniques such as UV-Vis, FT-IR and ESI-MS were employed to characterize the compound. Electrochemical behavior of the metal complexes has been studied using cyclic voltammetry method. DPPH free radical scavenging activity showed the complex with nickel atom shows better activity than that of the one with cobalt atom. In addition, the MTT assay was carried out to investigate the anticancer activity of the compounds with MCF7 breast cancer cell lines. Compound containing nickel atom showed the best activity than the ligand and cobalt compound.

Keywords: 1. Benzimidazole, 2. terpyridine, 3. DPPH, 4. MTT.

Introduction

The coordination chemistry of nitrogen donor ligands is an active and interesting area of research. Organic compounds containing pyridine rings play an important role in many biological reactions. Many transition metal and heavy metal cations also play an active role in various biological processes. Polypyridines are becoming increasingly important in many fields. ^[1] Over the past decades, hundreds of polypyridine metal complexes have been prepared and used. Among the polypyridines, the three-nitrogen terpyridine derivatives have been widely studied as tridentate ligands to coordinate with various transition metal ions. The coordination chemistry of 2,2':6',2''-terpyridines, particularly 4'-substituted terpyridines, has attracted increasing attention in many fields. ^[2] Due to their bioaccessible redox potential and relatively high nucleobase affinity, metal complexes are very popular for research as chemical nucleases. ^[3] Recent reports have shown that certain mononuclear, dinuclear and polynuclear metal complexes of Cu²⁺, Fe³⁺, Zn²⁺, Ru²⁺, Co³⁺ with pyridyl, benzimidazolyl, ferrocenyl, etc. exhibit strong chemical nuclease activity ^[4,5]. Over the past 30 years, more and more research has focused on the synthesis, spectroscopic characterization, electrochemical and biological properties of polypyridyl metal ion complexes. Terpyridine ligands are stiffer than bidentate ligands such as bipyridine and phenanthroline. ^[6-9] The physicochemical and biological properties of terpyridine metal complexes can be favorably tuned by placing appropriate substituents at the 4-position of the terpyridine. The interaction of transition metals (Mn, Fe, Cu) with molecular oxygen (in the presence of reducing agents) often generates reactive oxygen species that eventually cleave DNA. ^[10] Hammam et al ^[11] adopted a "metal complex" strategy to prepare a new mixed ligand of Cu²⁺, Fe³⁺, Ni²⁺ and Co²⁺ terpyridine (tpy) containing complexes of dithioacetate (dto) and thiosemicarbazide (tsc). The mixed ligand complexes were characterized by elemental analysis, molar conductivity, thermal analysis, and infrared and electronic spectroscopic measurements. It is assumed that the coordination mode of tpy changes from tridentate in the binary complex to bidentate in the triangular complex. Zohreh Naseri et al studied the first series of thienyl-substituted terpyridine transition metal complexes. The terpyridine - metal complexes also exhibit interesting photophysical properties. The terpyridines are highly useful building blocks for the creation of wide range of transition metal complexes with interesting photophysical, electrochemical and catalytic properties. Consequently metal-terpyridine complexes have been explored extensively for their use in desensitized solar cells, two-photon luminescent systems as well as light emitting devices. Metal complex [M(thiotpy)_m(X)_n] where thiotpy =

4'-(2-thienyl)-2,2':6,2''-terpyridine, $X = \text{NO}_3^-/\text{OAc}^-$ and $M = \text{Cr}^{\text{III}}, \text{Mn}^{\text{II}}, \text{Fe}^{\text{II}}, \text{Co}^{\text{II}}, \text{Ni}^{\text{II}}$ and Cu^{II} were characterized by elemental analysis, infrared and electron spectroscopy (UV-Vis, fluorescence) [12]. Medicinal inorganic chemistry has become an important research area since the validation of cisplatin as an effective anti-cancer agent in humans. The rich coordination chemistry of transition metal ions with organic ligands provides suitable candidates in the design of chemotherapeutic drugs for various diseases. Bioactivity studies showed that the complex has excellent antibacterial, antitumor and superoxide performance to synthesize and characterize the title compound 4'-(1H-benzimidazol-2-yl)-2,2':6,2''-terpyridine and its metal ion complexes, to determine their electrochemical properties and biological assessment activities.

1. Experimental section

1.1. Materials and methods

2-acetyl pyridine, cobalt(II) perchlorate hexahydrate and nickel(II) perchlorate hexahydrate were procured from Sigma Aldrich, USA and used as received. Other materials like sodium hydroxide, ammonium acetate and solvents like methanol, acetonitrile were of reagent grade. The ligand, bitpy (benzimidazolyl terpyridine) was prepared using published procedure.[13] UV-visible spectra of the complexes were recorded on a Perkin-Elmer Lambda 35 double beam spectrophotometer at 25°C. IR spectra were recorded as KBr pellets in the 400 - 4000 cm^{-1} region using a Shimadzu FT-IR 8000 spectrophotometer. Cyclic voltammetric studies of the complexes were carried out by using three electrode system in a single compartment comprising of glassy-carbon working electrode and potentials were referenced to standard calomel electrode. Positive ion electron ionization mass spectra of the complexes were obtained by using Thermo Finnigan LCQ 6000 advantage max ion trap mass spectrometer.

1.2. Synthesis of Metal Complexes

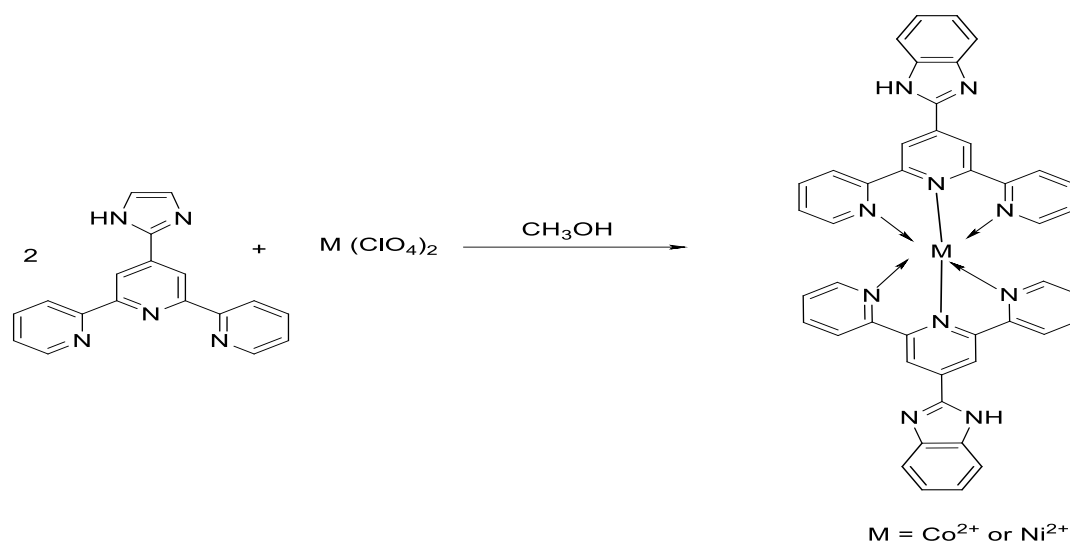
1.2.1. Synthesis of $[\text{Co}(\text{bitpy})_2](\text{ClO}_4)_2$ (1)

Caution! During handling of the perchlorate salts of metal complexes with organic ligands, care should be taken because of the possibility of explosion.

The ligand benzimidazolyl terpyridine (bitpy) was prepared by slight modification of the reported procedure[13] and the authenticity was confirmed from EI-MS, $m/z = 350$ [bitpy + H^+]. To a hot solution of $\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (50 mg, 0.1366 mmol) in methanol, bitpy (95.35mg, 0.2732 mmol) dissolved in methanol was added slowly and the mixture was refluxed for 4 h. The red coloured solid that separated out upon slow evaporation of solvent was filtered, washed with diethyl ether and dried. (Yield: 1.02 g, 88 %).

1.2.2. Synthesis of $[\text{Ni}(\text{bitpy})_2](\text{ClO}_4)_2$ (2)

Hot solution of $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (50 mg, 0.1367 mmol) and bitpy (95.43 mg, 0.2734mmol) in methanol were mixed and the mixture was stirred for 4 h. The pale green solid that separated out upon slow evaporation of the solvent was filtered, washed with diethyl ether and dried. (Yield: 1.09 g, (80 %).



2.2.2. Antioxidant Activity

1,1-Diphenyl-2-picrylhydrazyl (DPPH) is a stable free radical having maximum optical absorbance at 517 nm. A stock solution (1 mg/mL) was diluted to final concentrations of 20-100 $\mu\text{g/mL}$. An ethanolic DPPH solution was added to sample solutions in DMSO at various concentrations (20-100 $\mu\text{g/mL}$). The test tubes were kept at an ambient temperature for 30 minutes. The absorbance of the sample solutions containing ligands and their ruthenium complexes were measured at 517 nm using UV-Visible spectrophotometer. These measurements were run in triplicate. The percentage of scavenging activity was calculated as follows:

$$\text{Scavenging activity (\%)} = [(A_{\text{DPPH}} - A_{\text{TEST}})/A_{\text{DPPH}}] \times 100$$

Where, A_{DPPH} is the absorbance of DPPH without test sample (control) and A_{TEST} is the absorbance of DPPH in the presence of test sample.

1.2.3. Anticancer Activity

3-[4,5-dimethylthiazol-2-yl]2,5-diphenyltetrazolium bromide (MTT) is a yellow water soluble tetrazolium salt. A mitochondrial enzyme in living cells, succinate-dehydrogenase, cleaves the tetrazolium ring, converting the MTT to an insoluble purple formazan. Therefore, the amount of formazan produced is directly proportional to the number of viable cells.

The human breast cancer cell line (MCF 7) was obtained from National Centre for Cell Science (NCCS), Pune and grown in Eagles Minimum Essential Medium (EMEM) containing 10 % fetal bovine serum (FBS). All cells were maintained at 37°C, 5 % CO₂, 95 % air and 100 % relative humidity. For screening experiments, the cells were seeded into 96-well plates in 100 μL of the respective medium containing 10 % FBS, at a plating density of 10000 cells/well and incubated at 37 °C, 5 % CO₂, 95 % air and 100 % relative humidity for 24 h prior to the addition of compounds. The compounds were dissolved in DMSO and diluted in the respective medium containing 1 % FBS. After 24 h, the medium was replaced with the respective medium with 1 % FBS containing the compounds at various concentrations and incubated at 37°C, 5 % CO₂, 95 % air and 100 % relative humidity for 48 h. Experiments were performed in triplicate and the medium without the compounds served as control. After 48 h, 15 μL of MTT (5 mg mL⁻¹) in phosphate buffered saline (PBS) was added to each well and incubated at 37°C for 4 h. The medium with MTT was then removed and the formed formazan crystals were dissolved in 100 μL of DMSO and the absorbance measured at 570 nm using a micro plate reader. The % cell inhibition was determined using the following formula, and a graph was plotted between % of cell inhibition and concentration. From this plot, the IC₅₀ value was calculated. The % cell inhibition was determined using the following formula.

$$\% \text{ Cell Inhibition} = 100 - \text{Abs (sample)}/\text{Abs (control)} \times 100.$$

Nonlinear regression graph was plotted between % Cell inhibition and Log concentration and IC₅₀ was determined using GraphPad Prism software.

2. Results and discussion

2.1. Synthesis and spectral characterization

The results of the elemental analysis, conductance and magnetic moment data obtained for the metal(II) perchlorato complexes with bitpy are furnished in Table 1.

Table 1
Electronic Spectral and Electrical Conductance Values of Ligand and Manganese(II) Complexes

Compound	Colour	Effective magnetic moment (BM)	Absorption maxima (cm ⁻¹)
bitpy(L1)	Colourless	--	40486 35336 31949
[Co(bitpy) ₂](ClO ₄) ₂ 1	Red	4.4	20460 17036 30488
[Ni(bitpy) ₂](ClO ₄) ₂ 2	Pale Green	2.98	28028 17094 350450

2.2. Infrared Spectral Studies on bitpy and its Metal (II) Complexes

The assignments of various absorption frequencies of bitpy and its complexes are listed in Table 2. The NH stretching vibration of the benzimidazole moiety in L1 appears at 3399 cm⁻¹. The CH stretching vibrations appear at 3057 - 2855 cm⁻¹. The aromatic ring C=C and C=N stretching (skeletal) vibrations are observed at 1523 – 1431 cm⁻¹. The CH out - of -plane bending vibrations are seen at 791 and 737 cm⁻¹. The in-plane ring deformation is observed at 624 cm⁻¹, while the out- of-plane ring deformation is found at 434 cm⁻¹.

Table 2
IR Absorption Frequencies (cm⁻¹) for bitpy (L1) and its Complexes (1&2)

In the IR spectrum of the cobalt(II) complex, i.e. [Co(bitpy)₂](ClO₄)₂, the skeletal vibrations of

Sl. No	Compound	ν_{NH}	ν_{CH}	$\nu_{\text{C=N}}$ & $\nu_{\text{C=C}}$ of Terpyridine	ν_{ClO_4}	ν_{MO} & ν_{MN}
1	bitpy(L1)	3399	3057 - 2855	1523 - 1431	-	-
2	[Co(bitpy) ₂](ClO ₄) ₂ 1	3381	3094	1516 - 1447	1117 1082	500
3	[Ni(bitpy) ₂](ClO ₄) ₂ 2	3391	3057	1562 - 1447	1115 1084	516

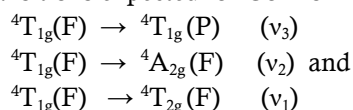
the aromatic heterocyclic rings are observed at 1516 – 1447 cm⁻¹, while in the ligand spectrum they are found at 1523 – 1431 cm⁻¹. The position of these vibrational bands suggests the binding of the pyridyl nitrogen atoms to the metal ion^[14]. The in-plane ring deformation vibration appears in the complex

spectrum at 629 cm^{-1} where as in the ligand spectrum it appears at a lower value of 624 cm^{-1} , indicating the binding of two pyridyl nitrogens at 1 and 1'' positions to the metal ion. The IR spectrum of Complex 2 also suggests the coordination of the perchlorate groups to the metal centre. Absorptions appearing at $1117 - 1082\text{ cm}^{-1}$ are due to the unidentate coordination of the perchlorate ions to the metal atom.

A perusal of the IR spectrum of Complex 2 i.e. $[\text{Ni}(\text{bitpy})_2(\text{ClO}_4)_2]$ reveals the appearance of skeletal vibrations of the aromatic heterocyclic rings at $1562 - 1447\text{ cm}^{-1}$, while in the ligand spectrum they appear at $1523 - 1431\text{ cm}^{-1}$. The upward shifting of these skeletal vibrations may be due to the binding of the terpyridine nitrogen atoms to the metal ion. Also the in-plane ring deformation seen at 624 cm^{-1} in the ligand spectrum has shifted positively to 632 cm^{-1} pointing to the coordination of two terpyridine nitrogen atoms at 1 and 1'' positions. Further the out-of-plane ring deformation located at 434 cm^{-1} in the ligand has shifted to 516 cm^{-1} due to two equivalent pyridyl nitrogen coordination. Strong absorptions observed at 1115 and 1084 cm^{-1} are due to the perchlorate groups which have coordinated to the nickel(II) ion.

3.3. Electronic Spectral and Magnetic Studies on bitpy (L1) and its Metal complexes

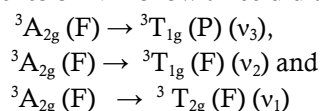
The benzimidazolyl terpyridine ligand (bitpy, L1) shows UV absorption at 40486 and 35336 cm^{-1} which are due to the aromatic $\pi-\pi^*$ transitions and another absorption at 31949 cm^{-1} which is assigned to $n-\pi^*$ transition. Generally compounds containing hetero atoms such as nitrogen, oxygen, sulphur etc., have nonbonding electrons (n) in addition to σ and π electrons. Thus the terpyridine derivative shows both $\pi-\pi^*$ and $n-\pi^*$ transitions in its UV spectrum. Cotton et al have made a detailed study of the electronic spectra of cobalt (II) complexes. The ground term arising from the $t_{2g}^5 e_g^2$ configuration in an octahedral field is $^4T_{1g}(F)$. The three d-d transitions expected for Co^{II} ion in an octahedral ligand field are



These transitions generally occur in the regions $21000-20000$, $18000-15000$ and $9000-8000\text{ cm}^{-1}$. The v_1 transition occurs in the near IR region.

In the present study, $[\text{Co}(\text{bitpy})_2(\text{ClO}_4)_2]$ exhibits absorptions at 17036 cm^{-1} (v_2) and at 20460 cm^{-1} (v_3) and a charge transfer transition at 30488 cm^{-1} . The v_1 absorption in the near IR region was not measured. This red coloured complex records a magnetic moment of 4.4 BM at room temperature. Thus based on colour, magnetic moment and electronic absorption energy positions, an octahedral geometry for Complex 1 is proposed^[15].

The stereochemistry of the Ni^{II} complex can also be decided based on absorptions due to ligand field transitions and the measured effective magnetic moment. The nickel (II) ion has the $3d^8$ outer electronic configuration. The ground term arising from the $t_{2g}^6 e_g^2$ configuration in an octahedral field is $^3A_{2g}(F)$. The octahedral complexes of $\text{Ni}^{(II)}$ are mostly green in colour. Rarely may they be yellow and red also. The octahedral complexes of Ni^{II} show three d-d transitions. They are



They normally appear at $19000-28000$ (v_3), $13000-19000$ (v_2) and $7000 - 13000\text{ cm}^{-1}$ (v_1) respectively.

In the present study the pale green coloured complex, $[\text{Ni}(\text{bitpy})_2(\text{ClO}_4)_2]$ exhibits electronic absorptions at 28028 cm^{-1} (v_3), 17094 cm^{-1} (v_2) and 30450 cm^{-1} (CT). The strong absorption band at the energy position 30450 cm^{-1} is assigned to a charge transfer transition. This pale green complex measures an effective magnetic moment of 2.98 BM at room temperature. Thus based on the colour, magnetic moment and the spectral features, Complex 2 is proposed to have the octahedral structure.

3.4. Electrochemical Studies on Complexes

Electrochemical studies have been carried out on $[\text{Co}(\text{bitpy})_2(\text{ClO}_4)_2]$ and $[\text{Ni}(\text{bitpy})_2(\text{ClO}_4)_2]$. The cyclic voltammograms have been recorded at three different scan rates (V) viz. 50 , 100 and 200 mVs^{-1} . The values of anodic peak potentials (E_{pa}) indicate the energy required for oxidation of the central metal ion in

the complex species while the values of cathodic peak potential (E_{pc}) indicate the energy required for reduction of the metal ion.

Redox Behaviour of $[Co(bitpy)_2(ClO_4)_2]$, Complex 1

This complex in its cyclic voltammograms (Fig. 2) scanned at 50, 100 and 200 mVs^{-1} records cathodic peak potentials (E_{pc}) at 1.0026, 1.099 and 1.361 V respectively featuring the reduction of Co^{II} to Co^I species, while the anodic peak potential values measured at 1.379, 1.548 and 1.649 V respectively feature the re-oxidation of Co^I species to Co^{II} species on reversing the scan. The peak potential separations have been calculated at 376, 449 and 288 mV for the scans operated at 50, 100 and 200 mVs^{-1} respectively. The calculated peak separation values are higher than 200 mV for this cobalt (II) complex revealing that an irreversible redox process is involving a Co^{II} / Co^I redox couple. The peak current ratios (I_{pa}/I_{pc}) have been measured at 0.508, 0.418 and 1.924 when scanned at 50, 100 and 200 mVs^{-1} respectively

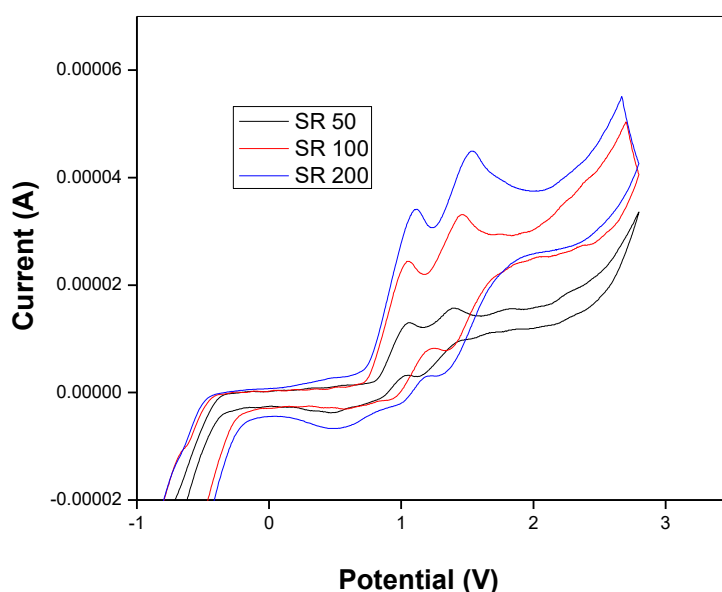


Fig. 2. Cyclic Voltammograms of Complex 1 at 50,100 and 200 mVs^{-1}

These peak current ratios measured at 50 and 100 mVs^{-1} which are less than unity indicate that the electron transfer is followed by chemical reaction i.e. EC mechanism is followed in the process but, at 200 mVs^{-1} it is not so. For this complex the $E_{1/2}$ values have been determined at 1.191, 1.324 and 1.505 V at 50,100 and 200 mVs^{-1} respectively. These positive values of $E_{1/2}$ suggest that the benzimidazolyl terpyridine (bitpy) ligand exhibits considerable σ -donating ability so as to form a stable chelate complex^[16]. Hence reduction of Co^{II} species become very difficult.

Redox behavior of $[Ni(bitpy)_2(ClO_4)_2]$, Complex 2

When scanned at 50,100 and 200 mVs^{-1} the nickel (II) complex with bitpy ligand registers cathodic peak potentials at 1.744, 1.972 and 1.767 V respectively featuring the reduction of Ni^{II} to Ni^I species. The anodic peak potentials measured at 1.424, 1.551 and 1.607 V respectively feature the reoxidation of Ni^I to Ni^{II} upon scan reversal. The peak potential separations have been calculated at -319.8, -421 and -160 mV for the scans carried out at 50,100 and 200 mVs^{-1} respectively. They are higher than 200 mV suggesting an irreversible redox process involving Ni^{II} / Ni^I couple. The peak current ratios (I_{pa}/I_{pc}) have been measured at 1.533, 1.299 and 1.729 for the scans carried out at 50,100 and 200 mVs^{-1} respectively. These ratios are higher than unity and indicate that the electron transfer is not followed by a chemical reaction. The voltammetric $E_{1/2}$ values have been determined at 1.583, 1.761 and 1.687 V for the scans operated at 50,100 and 200 mVs^{-1} respectively. These

positive values of $E_{1/2}$ suggest that the benzimidazolyl terpyridine (bitpy) ligand has formed very stable chelate complex with Ni^{II} ion due to its high σ -donating ability and hence the reduction of Ni^{II} species becomes very difficult.

3.5. Antioxidant Activity

The synthetic ligand bitpy and its metal complexes were screened for the reduction of DPPH at concentrations of 05-20 $\mu\text{g/mL}$. The present compound (test agent) has been observed to scavenge free radicals in a concentration dependent manner. Table 3 provides the scavenging activities of DPPH measured and compares them to those of standard vitamin C. Lower absorbance values of the reaction mixture indicate higher radical scavenging activity. It should be noted that over the concentration range of 05 to 20 $\mu\text{g/mL}$, the activity of the tested drug was comparable to that of standard L-ascorbic acid in the concentration range of 2.0-3.5 g/ml. The activity was found to increase with increasing concentration. The concentration of the test agent with maximum activity was about 20 $\mu\text{g/ml}$, while the concentration of the standard was 3.5 $\mu\text{g/ml}$. This means the tests mean, i.e. bitpy and its complexes (1&2) were 5.7 times less active than standard antioxidant vitamin C at the same concentration. It was concluded that bitpy-metal complexes were not efficient enough to scavenge free radical DPPH species. However, based on the percentage of antioxidant activity determined for these compounds tested, it was observed that bitpy ligand and complex 2 exhibited the same activity at 94.74%. Therefore, the order of antioxidant activity of the drugs tested was bitpy \sim Complex 2 $>$ Complex 1.

Table 3
Antioxidant Activities of bitpy (L1) and its Complexes

S.No.	Test Drug	Concentration ($\mu\text{g/mL}$)	Absorbance	%DPPH Scavenging Activity
1	Bitpy L1	05	0.19	50.00
		10	0.10	73.68
		15	0.05	86.84
		20	0.02	94.74
2	[Co(bitpy) ₂ (ClO ₄) ₂] 1	05	0.19	50.00
		10	0.10	73.68
		15	0.07	81.58
		20	0.03	92.11
3	[Ni(bitpy) ₂ (ClO ₄) ₂] 2	05	0.17	55.26
		10	0.09	76.32
		15	0.04	89.47
		20	0.02	94.74

3.6. Anticancer Activity Screening

This study investigated the efficacy of Ligand-1 and its complexes in inhibiting the human breast cancer cell line (MCF-7) after 24 hours by MTT assay. Treat the cells with five different concentrations ranging from 0.25 to 100 μM . Both the free ligand and the complex inhibit the growth of breast cancer cell lines in a dose-dependent manner. Maximum cell inhibition is 92. At 100 μM , complex-2, complex-1 and free ligand (L1) showed 13, 83.56 and 68.21% inhibition, respectively, with the lowest inhibition (2.03, 3.48, 6. For complex-2, free ligand (L1) and complex-1, 36, 6.62 and 22.24% were observed at a concentration of 0.25 M, respectively. IC_{50} values for MCF-7 cells treated with free ligand (L1), Co II and Ni II complexes were obtained at 51 to .09 $\mu\text{g/mL}$, respectively. In general, lower IC_{50} values were found for Ni II complexes, suggesting that Ni II may exert very potent antiproliferative effects compared to free

ligand and other complexes tested in breast cancer cell lines at low doses. Test agents with IC_{50} values greater than $30 \mu\text{g/ml}$ were considered inactive [17-19]. Compounds with an IC_{50} of $5.0 \mu\text{g/ml}$ or less were considered highly active, while compounds with IC_{50} values $5 - 10.0 \mu\text{g/ml}$ is associated with moderate activity. The benzimidazole ligand terpyridine (L1) has an IC_{50} value of $17.85 \mu\text{g/ml}$, which is considered to have a weak antiproliferative effect on breast cancer cell lines.

Table 4
 IC_{50} Values Determined for bitpy (L1) and Complexes 1 and 2

S. No.	Compound	IC_{50} (μM)
1	Bitpy L1	51.16
2	$[\text{Co}(\text{bitpy})_2(\text{ClO}_4)_2]$ 1	34.06
3	$[\text{Ni}(\text{bitpy})_2(\text{ClO}_4)_2]$ 2	13.7

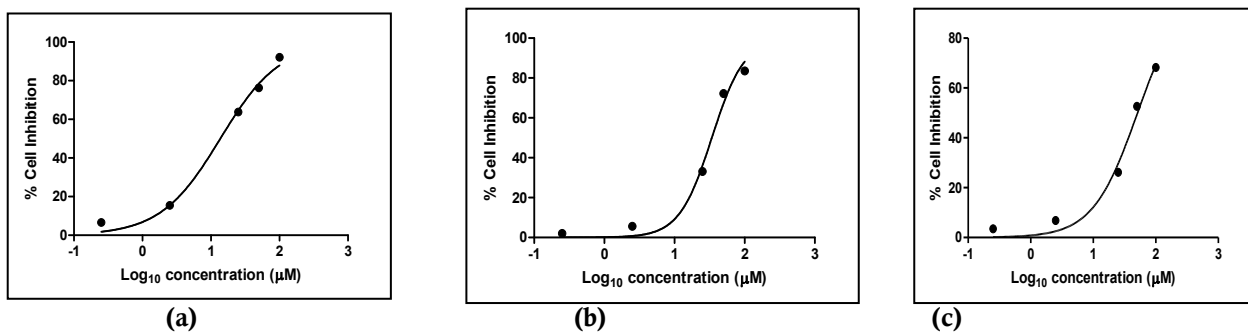


Fig.3. Antiproliferative Nonlinear Regression Graphs for (a) L1, (b) Complex 1, (c) Complex 2

3. Conclusions

We have prepared two complexes **1** and **2** having 4'-(benzimidazolyl)-2,2':6',2''-terpyridine ligand with a metal to heterocyclic base ratio as 1:2. Both the complexes were characterized by various physico-chemical techniques and a six coordinated distorted octahedral environment has been proposed for the complexes. DPPH free radical scavenging activity shows that the antioxidant activity of complex **2** is found to be higher than that of complex **1**. Similarly complex **2** containing nickel atom exhibits better anticancer activity than complex **1**.

Acknowledgement

The authors thank the Head, Department of Chemistry, AAGAC, Musiri for providing Laboratory facilities.

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