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Research Article

DNA BINDING AND ANTIBACTERIAL ACTIVITY OF TERNARY METAL COMPLEXES

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ABSTRACT

Bivalent metal complexes having the composition $M(Bpy)Cl_2$ (where, M= Cu(II), Ni(II) and Co(II); Bpy = 2,2-bipyridyl) were reacted with 2-acetylthiophene-4-ethyl-3-thiosemicarbazone (ATET) to produce ternary metal complexes with molecular formula $M(Bpy)(ATET)Cl_2$. The complexes are characterized using physical (molar conductivity) and spectral (mass spectra, infrared and electronic spectroscopes) methods. Electrochemical behaviour of complexes was uncovered using cyclic voltammetry. The complexes show quasi reversible cyclic voltammetric responses for the Cu(II)/Cu(I) couple. The DNA binding properties of the complexes are determined by using absorption UV-Visible spectro-photometry. Metal complexes are screened for their antibacterial activity by using agar well diffusion method against pathogenic bacterial strains *viz.* Gram-ve such as *Escherichia coli, Klebsiella Pneumonia* and Gram+ve such as *Staphylococcus aureus, Bacillus cereus*. Anti bacterial activity of the present complexes are comparable with the activity of Ciprofloxacin. The $Cu(Bpy)(ATET)]Cl_2$ complex inhibits bacteria more strongly than any other complex. The $[Cu(Bpy)(ATET)Cl_2]$ complex shows more activity than the parent complex, $Cu(Bpy)Cl_2$.

Keywords: Ternary complexes, Thiosemicarbazone, Bipyridyl, DNA binding, Antibacterial Activity.

1. INTRODUCTION

Transition metal complexes with assorted ligands containing hetero donor atoms (N, S) are known to exhibit interesting stereochemical, electrochemical, and electronic properties. Thiosemicarbazones are emerged as an important type of sulfur containing ligands particularly for transition metal ions. The importance of thiosemicarbazones is due to their ability to form stable complexes with transition metal ions. In coordination chemistry, Schiff bases are important class of ligands possessing wide range of applications [1]. Metal complexes of thiosemicarbazones have been reviewed [2-9].

The molecular features have been shown to be essential for biological activity. These features would also be expected to promote effective transition-metal chelating properties. It was observed that the presence of certain bulky groups at position N^4 of the thiosemicarbazone moiety greatly enhances antimalarial activity [10]. In the light of the above observations, it is considered to prepare N^4 substituted thiosemicarbzone. Structural and spectral studies on transition metal complexes with 2-acetylthiophene-4-ethyl-3-thiosemicarbazone (ATET) are very limited [11]. It is of interest to study ternary transition metal complexes. This is because they are the most general and probable form of coordination compounds in the biological system. Therefore studies of ternary complexes may serve as models for biochemical processes. They are also characterized [12-19], by their extreme stability and the properties of the central metal ion are more pronounced in these complexes. In the light of the above, Co(II), Ni(II) and Cu(II) complexes with 2,2- bipyridyl and 2-acetyl-thiophene-4-ethyl-3-thiosemicarbazone (ATET) have been synthesized and characterized. Antibacterial activity and DNA binding properties of complexes are investigated [20-26].

2. EXPERIMENTAL

2.1. Material and methods

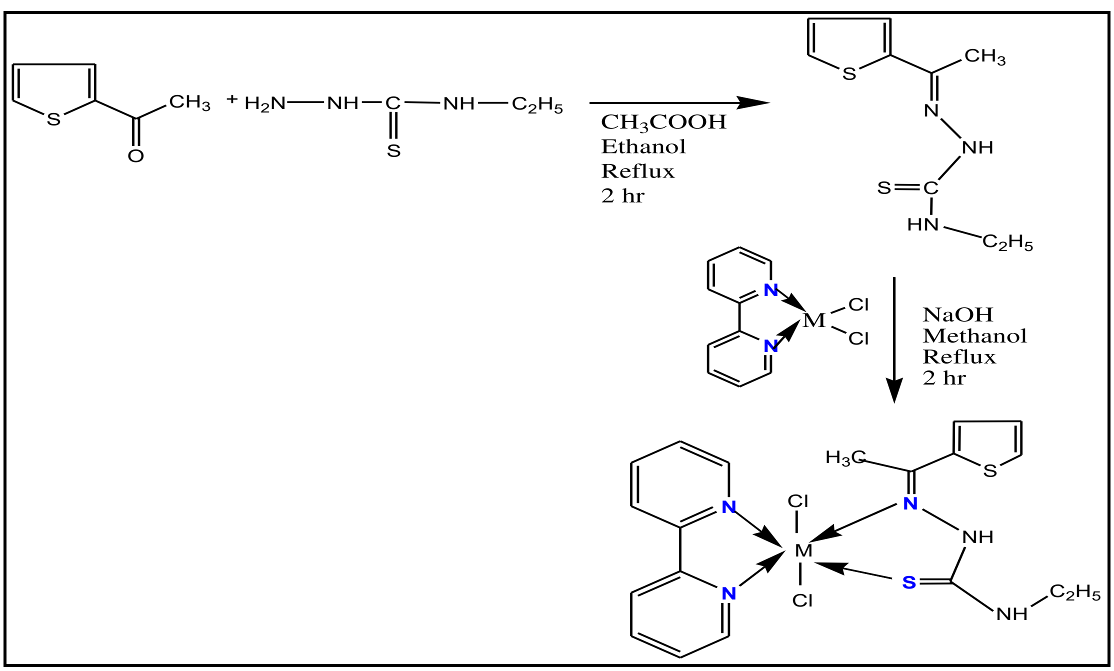
All chemicals were of AR grade and used as provided. 4-ethyl-3-thiosemicarbazide, 2-Acetylthiophene, 2,2-Bipyridyl, were purchased from Sigma-Aldrich. The solvents used for the synthesis were distilled before use. Calf-Thymus DNA (CT-DNA) was purchased from Genio Bio labs, Bangalore, India. Elemental analyses were carried out on a Heraeus Vario EL III Carlo Erba 1108 instrument. Molar conductivity measurements at 298±2K in dry and purified DMF were carried out using a CM model 162 conductivity cell (ELICO). The electronic spectra were recorded in DMSO with a UV lamda50 (Perkin-Elmer) spectrophotometer. IR spectra were recorded in the range 4,000-400 cm^{-1} with a Perkin-Elmer spectrum100 spectrometer on KBr discs. ESR spectra were recorded on a Varian E-112 X-band spectrophotometer at room temperature (RT) and liquid nitrogen temperature (LNT) in solution (DMF) state. Cyclic voltammetric measurements were taken on a CH instruments assembly equipped with an X-Y recorder. Measurements were taken on degassed (N_2 bubbling for 5 min) solutions (10^{-3} M) containing 0.1 M Bu_4NPF_6 as the supporting electrolyte. The three-electrode system consisted of glassy carbon (working), platinum wire (auxiliary) and Ag/AgCl (reference) electrodes.

2.2. Synthesis of ATET

The ligand, 2-acetylthiophene-4-ethyl-3-thiosemicarbazone (ATET) was prepared using 4-ethyl-3-thiosemicarbazide and carbonyl compound viz 2-Acetylthiophene. A ethanolic solution of 4-ethyl-3-thiosemicarbazide (5mmol), carbonyl compound (5mmol) in ethanol was mixed in a round bottom flask. Two drops of CH_3COOH were added to the reaction mixture. This reaction mixture was refluxed for 3 hours and the reaction mixture was cooled to room temperature. The ligand ATET was obtained as shiny milk white crystalline product, which are subsequently used for the synthesis of metal complexes. Yield 80%, M.Pt. 118-120°C, IR spectra (cm^{-1}) 3178, 1592. 1201 cm^{-1} are assigned to ν(N-H asym), ν(C=N) and ν(C=S) stretching vibrations respectively. NMR spectra (δ) 8.77 (singlet 1H), 7.03-7.37 (multiplet 3H), 3.49 (quartet 2H), 0.9 (triplet 3H), are assigned to >NH, thiophene H, and CH_2, CH_3 protons respectively. Molecular weight of ATET ligand is 227. The preparation of ligand and their metal complexes are shown in fig.1.

2.3. Preparation of metal complexes

A 1.2 g of ATET ligand (0.006 moles) was dissolved in 15 mL of 0.05 N NaOH in methanol solvent in 100-mL beaker. A 1.0 g Cu $(bpy)_2$ Cl_2 (0.003 moles) was dissolved in 15 mL of methanol solvent in 100 mL beaker. Ligand solution and $Cu(bpy)_2Cl_2$ solution were transferred into 100 mL round bottom flask and heated under reflux for 1hr. On cooling the contents of flask, light green coloured complex was formed. It was collected by filtration, washed with small quantities of methanol and dried in air. Ni (Bpy)(ATET)Cl_2 and Co(Bpy)(ATET)Cl_2 complexes were prepared similarly.



[Where, M= Cu(II), Co(II) and Ni(II)]

Fig. 1: **Scheme for the synthesis of ATET ligand and its metal complexes**

3. RESULTS AND DISCUSSION

3.1. Physicochemical properties

Metal complexes having the composition M(Bpy)Cl_2 (where, M= Cu(II), Ni(II) and Co(II); Bpy = 2,2-bipyridyl) are reacted with 2-acetylthiophene-4-ethyl-3-thiosemicarbazone (ATET) to produce heteroleptic transition metal complexes with molecular formula M(Bpy) (ATET) Cl_2. All the complexes are stable at room temperature, non-hygroscopic, insoluble in water, slightly soluble in methanol and ethanol but readily soluble in DMF and DMSO. The physico-chemical data for the complexes are summarized in table 1.

3.2. Conductivity measurements

The complexes are readily soluble in dimethyl formamide (DMF), For 1:1 electrolyte the molar conductivity values are in the range 65-90 $\Omega^{-1}.cm^2.mol^{-1}$ in dimethylformamide [27]. Molar conductivity data of complexes are summarized in table 1. The observed values are less than lower limit (65 $\Omega^{-1}.cm^2.mol^{-1}$) and data indicates non-electrolytic nature of complexes.

3.3. Electronic spectra

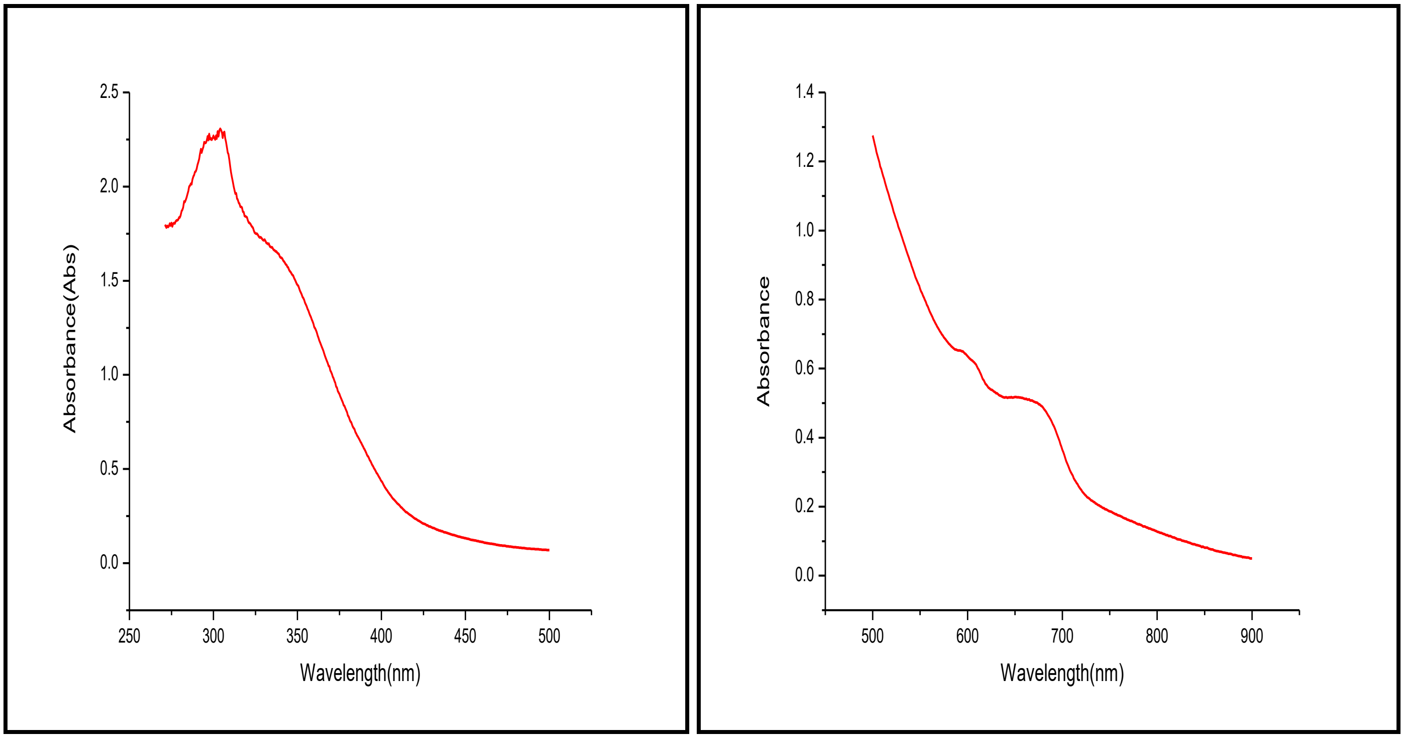
The electronic spectra of the complexes are recorded in DMF. The significant bands obtained from electronic spectral data are presented in table 2. A strong sharp band is observed in the region of 36,496-31,847 cm^{-1} for the metal complexes is associated with $\pi \rightarrow \pi^*$ transition of aromatic chromophore [28]. Medium intensity band is observed in the range of 29,154-29,069 cm^{-1} which corresponds to charge transfer spectra caused by ligand to the metal ion [29]. A weak band in the 16,835-13,106 cm^{-1} region may be assigned to d-d transition. The electronic spectra of Co (Bpy) (ATET) Cl_2 complex is shown in fig. 2.

Table 1: Physicochemical and analytical data of metal complexes

Complex	ESI-MS (F.W)	Melting Point (˚C)	Colour (Yield %)	Molar Conductivity
Cu(Bpy)Cl_2	289.40 (291)	Above 300	Light Green (71.56%)	30.90
Cu(Bpy)(ATET)Cl_2	517.03 (517.62)	286-287	Light green (84.32%)	18.75
Ni(Bpy)Cl_2	281.30 (285)	Above 300	Parrot Green (81.93%)	27.75
Ni(Bpy)(ATET)Cl_2	512.00 (512.77)	275-276	Black (83.49%)	18.58
Co(Bpy)Cl_2	282.32 (286)	Above 300	Blue (72.77%)	46.05
Co(Bpy)(ATET)Cl_2	515.00 (513.01)	263-264	Black (84.75%)	17.25

Table 2: Electronic spectral data for complexes

Complex	Wavelength λ max (nm)	Frequency (cm^{-1})	Assignment
Cu(Bpy)Cl_2	301	33,222	π-→π* transition
	312	32,015	CT transition
	763	13,106	d-d transition
Cu(Bpy)(ATET)Cl_2	314	31,847	π-→π* transition
	343	29,154	CT transition
	606	16,501	d-d transition
Ni(Bpy)Cl_2	298	33,557	π-→π* transition
	305	32,786	CT transition
	615	16,260	d-d transition
Ni(Bpy)(ATET)Cl_2	274	36,496	π-→π* transition
	344	29,069	CT transition
Co(Bpy)Cl_2	295	33,898	π-→π* transition
	518	19,305	CT transition
	675	14,814	d-d transition
	990	10,101	d-d transition
Co(Bpy)(ATET)Cl_2	303	33,003	π-→π* transition
	594	16,835	d-d transition
	670	14,925	d-d transition



(A) Low Concentration (Uv spectrum) (B) High Concentration (visible spectrum)

Fig. 2: Electronic spectra of Co (Bpy)(ATET) Cl_2. Complex.

3.4. Infrared spectra

IR spectral data of ligand, 2-acetylthiophene-4-ethyl-3-thiosemicarbazone (ATET) and its metal complexes along with assignment of peaks are given in table 3.

A strong band is observed in the IR spectrum of ATET at 1592 cm^{-1} which is assigned to ν(C=N) group. In all the complexes, this band is shifted to lower frequency indicating the participation of azomethine nitrogen atom in coordination [30]. A medium band is appeared in the spectrum of ATET ligand at 1201 cm^{-1}, which is assigned to ν(C=S) group. In all the complexes, this peak is shifted lower wave numbers suggesting participation of thioketo sulphur in chelation. The thiophene ring deformation modes are observed in 620 and 752 cm^{-1} regions respectively. These bands are shifted to higher wave number indicating coordination of sulphur to metal atom. In far IR region, new peaks are observed in 581-473 and 462-441 cm^{-1} regions which are assigned to υM-N and υM-S vibrations [31] respectively.

3.5. ESR spectra

The ESR spectra of copper complexes were recorded in DMF solution at room temperature and at liquid nitrogen temperature. A typical ESR spectrum of Cu (Bpy)(ATET)Cl_2 recorded at LNT is shown in fig. 3. The spin Hamiltonian, orbital reduction and bonding parameters of complexes are given in table 4.

The $g_{||}$ and $g_\perp$ are computed from the spectra using TCNE free radicals as g marker. The observed $g_{||}$ values for complexes are less than 2.3 suggesting significant covalent character of metal ligand bond in agreement with observation of Kivelson [32]. The $g_{||}$ and $g_\perp$ were more than 2, corresponding to an axial symmetry. The trend the $g_{||} > g_\perp > g_e$ (2.0023) observed for these complexes suggests that the unpaired electron is localized in the $d_{x^2-y^2}$ orbital [33] of the copper ion. The axial symmetry parameter G is defined as [33]

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

The calculated G values for these complexes are less than 4.0 which indicates the presence of small exchange coupling and misalignment of molecular axes. The $g_{||}$, $g_\perp$, $A_\|$, $A_\perp$ of complexes and the energies of the d-d transitions are used to calculate the orbital reduction parameters ($K_\|$, $K_\perp$), the bonding parameter(α^2). The factor α^2 which is usually taken as a measure of covalency and it is evaluated by the expression:

$\alpha^2 = A_\| / p + (g_{||} - 2.0023)+3/7(g_\perp - 2.0023)+ 0.004$

Hathaway pointed out that for pure σ bonding $K_\| \approx K_\perp \approx$ 0.77, for in-plane π-bonding $K_\| < K_\perp$, while out of plane π-bonding $K_\parallel > K_\perp$ the following simplified expressions were used to calculate $K_\parallel$ and $K_\perp$:

$$K_\parallel^2 = \frac{(g_\parallel - 2.0023)}{8x\ \lambda_0} \text{ X d-d transition}$$

$$K_\perp^2 = \frac{(g_\perp - 2.0023)}{8x\ \lambda_0} \text{ X d-d transition}$$

The observed $K_\parallel < K_\perp$ relation for Cu(Bpy)Cl_2 complex indicates the significant in- plane π-bonding.

Table 3: IR spectral data (cm^{-1}) of complexes with Bipyridine and ATET

ATET	Cu(Bpy)(ATET)Cl_2	Ni(Bpy)(ATET)Cl_2	Co(Bpy)(ATET)Cl_2	Assignment
1592	1554 1513	1563	1575	υC=N (Azomethine)
	1464 1234	1489 1316	1431 1350	υC-C (thiophene)
1201	1079	1072	1092	υC=S (thione)
	752	744	760	Thiophene
	620	623	637	Thiophene
	473	474	581	υM-N
	441	462	451	υM-S

Table 4: ESR spectral data of copper complexes in DMF solvent

Parameter	Cu(Bpy) Cl_2		Cu(Bpy)(ATET)Cl_2	
	LNT	RT	LNT	RT
$g_{\|\|}$	2.28	2.14	2.23	2.09
$g_\perp$	2.05	2.08	2.01	2.03
g_{avg}	2.13	2.10	2.08	2.05
G	3.87	1.74	2.78	1.66
$A_\parallel$ x 10^{-5}	0.0016	-	0.0013	-
$A_\perp$ x 10^{-5}	--	-	0.00035	-
$K_\parallel$	0.995	-	0.990	-
$K_\perp$	1.027	-	1.267	-
λ	463	-	488	-
α	0.2997	-	0.2395	-

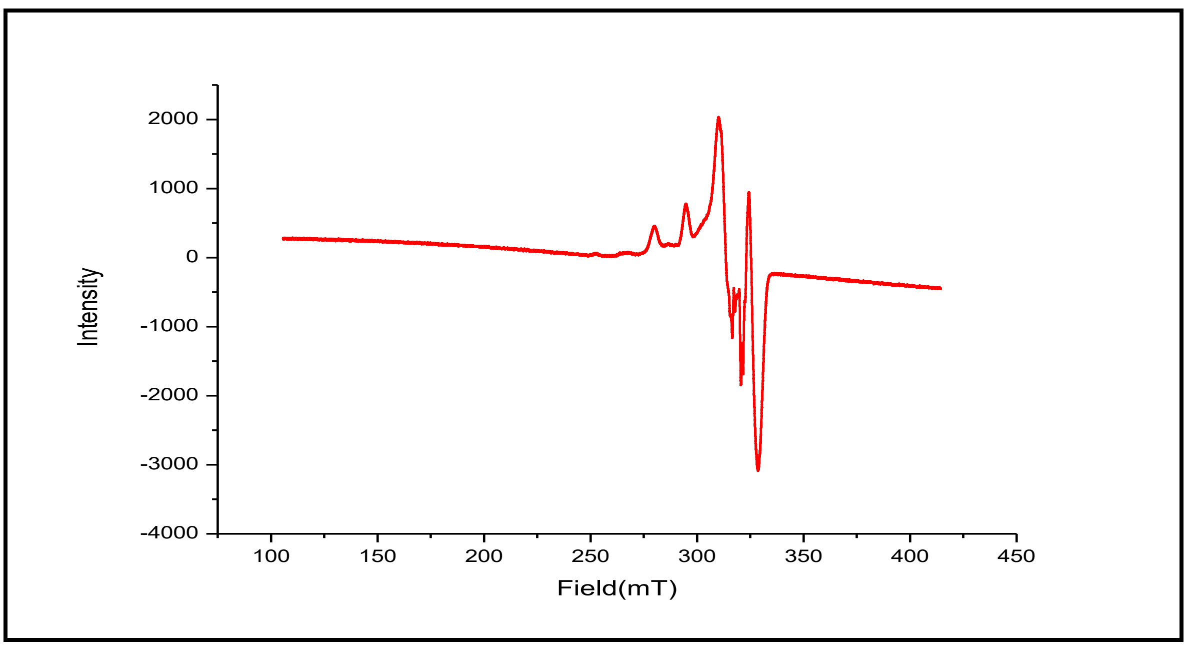


Fig. 3: ESR Spectrum of Cu (Bpy) (ATET) Cl_2 Complex at LNT

3.6. Cyclicvoltammetric studies

The redox behaviour of the complexes has been investigated by cyclic voltammetry in DMF using 0.1M tetrabutylammonium hexafluorophosphate as supporting electrolyte. The cyclic voltammogram of Ni (Bpy)(ATET)Cl_2 complex is shown in fig. 4 and the electrochemical data of complexes are summarized in table 5.

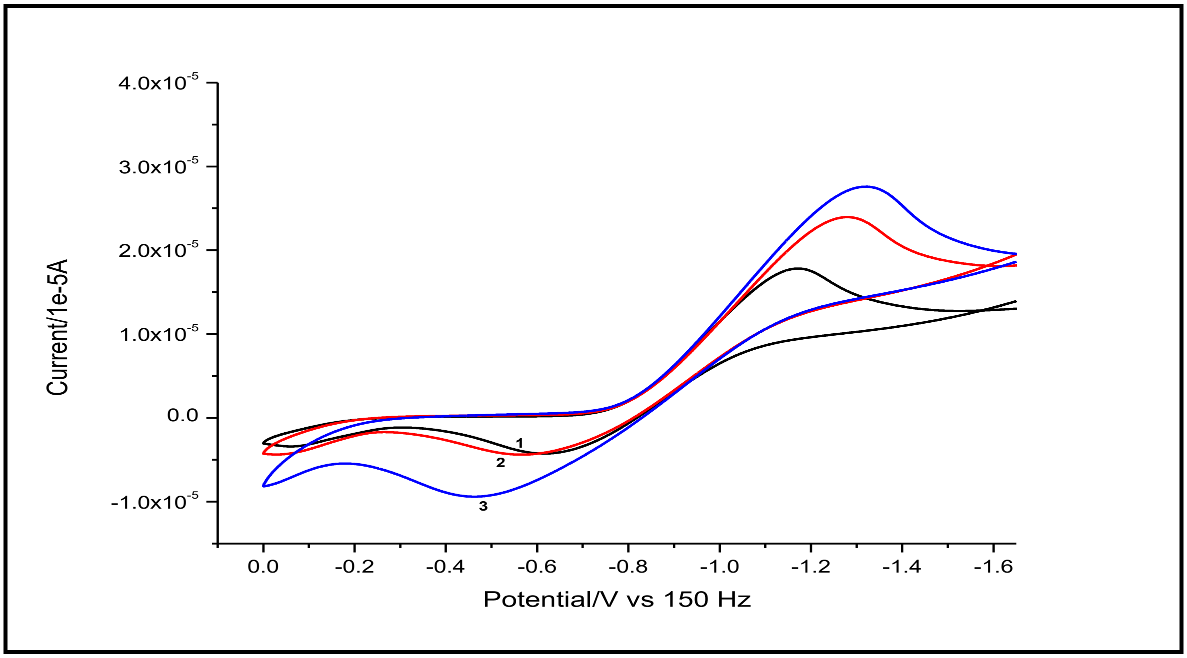


Fig. 4: Cyclic voltammogram of Ni (Bpy)(ATET) Cl_2 at different scan rates (1) 0.05; (2) 0.1 and (3) 0.2 mVs^{-1}

Table 5: CV data of Cu(II), Ni(II) and Co(II) complex

Complex	E_{pc}	E_{pa}	ΔEp (mV)	$E_{1/2}$(V)	$-i_c/i_a$	LogKc[a]	-ΔG[b]
Cu(Bpy)Cl_2	-0.047	0.488	535	0.267	1.510	0.062	362
Cu(Bpy)(ATET)Cl_2	-0.192	0.549	741	0.371	1.938	0.094	542
Ni(Bpy)Cl_2	-1.291	-0.743	548	-1.017	2.740	0.061	354
Ni(Bpy)(ATET)Cl_2	-1.170	-0.630	540	-0.900	2.417	0.062	359
Co(Bpy)Cl_2	-1.034	-0.726	308	-0.880	0.895	0.010	629
Co(Bpy)(ATET)Cl_2	-0.991	-0.685	306	-0.838	2.137	0.110	635

[a]$\log K_c = 0.434ZF/RT\Delta E_p$; [b]$\Delta G^o = -2.303RT\log K_c$

The cathodic peak current function values were found to be independent of the scan rate. Repeated scans at various scan rates suggest that the presence of stable redox species in solution. It has been observed that cathodic (Ip_c) and anodic (Ip_a) peak currents were not equal. The $E_{1/2}$ values of copper(II) complexes are noticed in potential range of 0.267-0.371 V. It may be concluded that all the bivalent metal complexes undergo one electron reduction to their respective M(I) complexes.

The non-equivalent current in cathodic and anodic peaks indicates quasi-reversible behaviour [34]. The difference, ΔEp in all the complexes is better than the Nerstian requirement 59/n mV (n = number of electrons involved in oxidation reduction) which demonstrate quasi-reversible character of electron transfer [35]. The complexes show large separation between anodic and cathodic peaks indicating quasi-reversible character. The ΔG° values of mixed ligand complexes both ligands are higher than respective parent complexes. These data suggest that ternary complexes are more stable than parent complexes containing one bpy ligand.

Based on analytical, physicochemical and spectral data, a general structure (fig. 5) is proposed for the complexes.

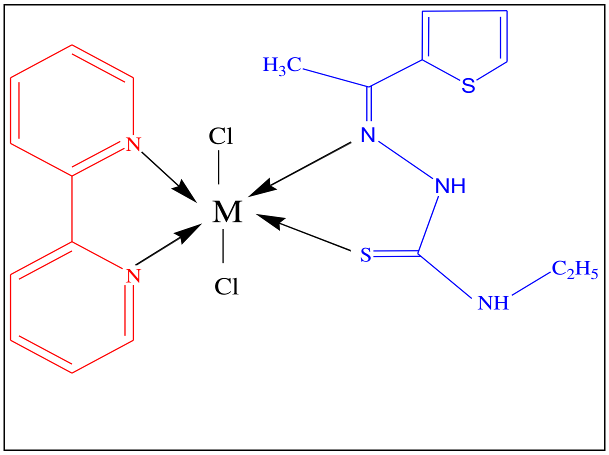


Fig. 5: Structure of [M (Bpy) (ATET)Cl_2] Complex [M= Cu(II), Ni(II) and Co(II)

3.7. DNA binding studies

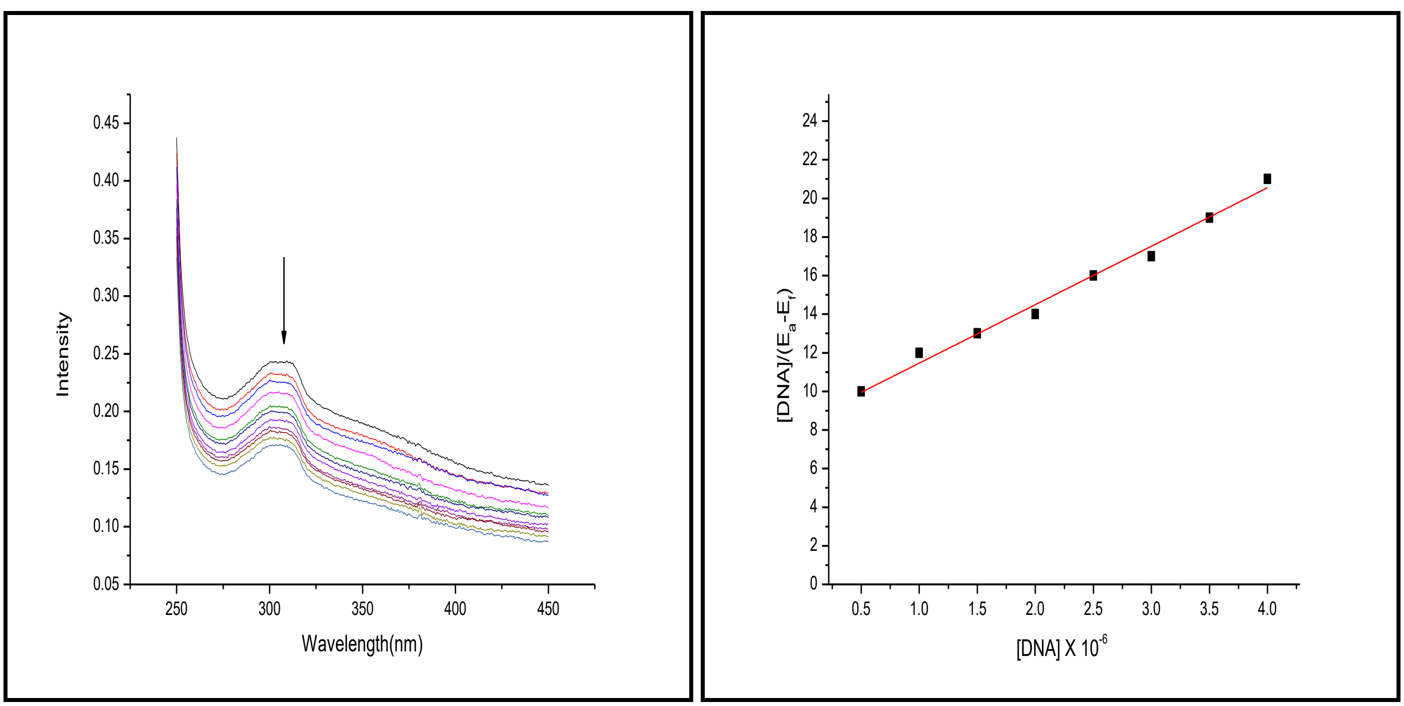
The binding interaction of the complexes with DNA was monitored by comparing their absorption spectra with and without CT-DNA. Typical absorption spectra of Cu(Bpy)(ATET)Cl_2 complex in the absence and in the presence of CT DNA are shown in fig. 6.

It has been observed that molar absorptivity of complexes decreases (hypochromism, $\Delta\varepsilon$, +17.77 to +38.8%, (table 6) for each addition of CT-DNA, of the π-π^* absorption band as well as a hypsochromic shift in the case of Cu(II) complexes and bathochromic shift for Ni(II) and Co(II) complexes of a few nanometers (0.5-2.0nm). The intrinsic binding constants (K_b), were determined by using the equation.

$$\frac{[DNA]}{\varepsilon_a-\varepsilon_f} = \frac{[DNA]}{\varepsilon_a-\varepsilon_f} + \frac{1}{K_b}\,(\varepsilon_a - \varepsilon_f) \quad \text{------------- (1)}$$

The intrinsic binding constants of complexes are given in table 6.

Hyperchromic effect and hypochromic effect are the special features of DNA concerning its double helix structure. Hypochromism results from the contraction of DNA in the helix axis as well as from the change in conformation on DNA while hyperchromism emerges from the damage of the double helix structure [36]. Hypochromism was observed due to intercalative mode involving strong stacking interactions between aromatic chromophore of metal complexes and nitrogenous bases of DNA [37]. Hypochromism and bathochromic shift in spectra of complexes [except Cu (Bpy)Cl_2] suggest that these complexes bind DNA through intercalation involving a strong π-stacking interaction between the aromatic chromophore and base pairs of DNA.



(A) **(B)**

Fig. 6: (A) Absorption Spectra of Cu(Bpy)(ATET)Cl_2 In the absence and in the presence of increasing concentration of CT-DNA; *[The Top most spectrum is recorded in the absence of CT-DNA and below spectra on addition 20µl DNA each time.]* **(B) A plot [DNA]/ (E_a-E_f) vs [DNA] X 10^{-6}**

3.8. Antibacterial activity

Metal complexes are screened for their antibacterial activity by using agar well diffusion method. The diameters of inhibition of zone were measured with Verniercallipers in mm and its values are depicted in the table 7.

Antibacterial activities of present complexes are quite comparable to the standard compound (fig. 7). $Cu(Bpy)(ATET)Cl_2$ complex inhibits bacteria more strongly than any other complex. The Cu(Bpy) (ATET) Cl_2 complex shows more activity than the parent complex $Cu(Bpy)Cl_2$. The mixed ligand complexes show higher activity than the parent complexes possibly due to synergistic interactions of two organic ligands with bacteria.

Table 6: Electronic absorption data upon addition of C T-DNA to the complexes

Complex	λ max (nm)		Δ λ	H%	K_b [M^{-1}]
	Free	Bound			
$Cu(Bpy)Cl_2$	300.5	300	0.5	38.80	3.5 X10^5
$Cu(Bpy)(ATET)Cl_2$	308	309	1.0	22.76	4.1 X10^5
$Ni(Bpy)Cl_2$	306	306.5	0.5	36.60	3.56 X10^5
$Ni(Bpy)(ATET)Cl_2$	325.5	326.5	1.0	38.14	3.98 X10^5
$Co(Bpy)Cl_2$	295	296.5	1.5	17.77	3.12 X10^5
$Co(Bpy)(ATET)Cl_2$	303	304.5	1.5	20.13	3.25X10^5

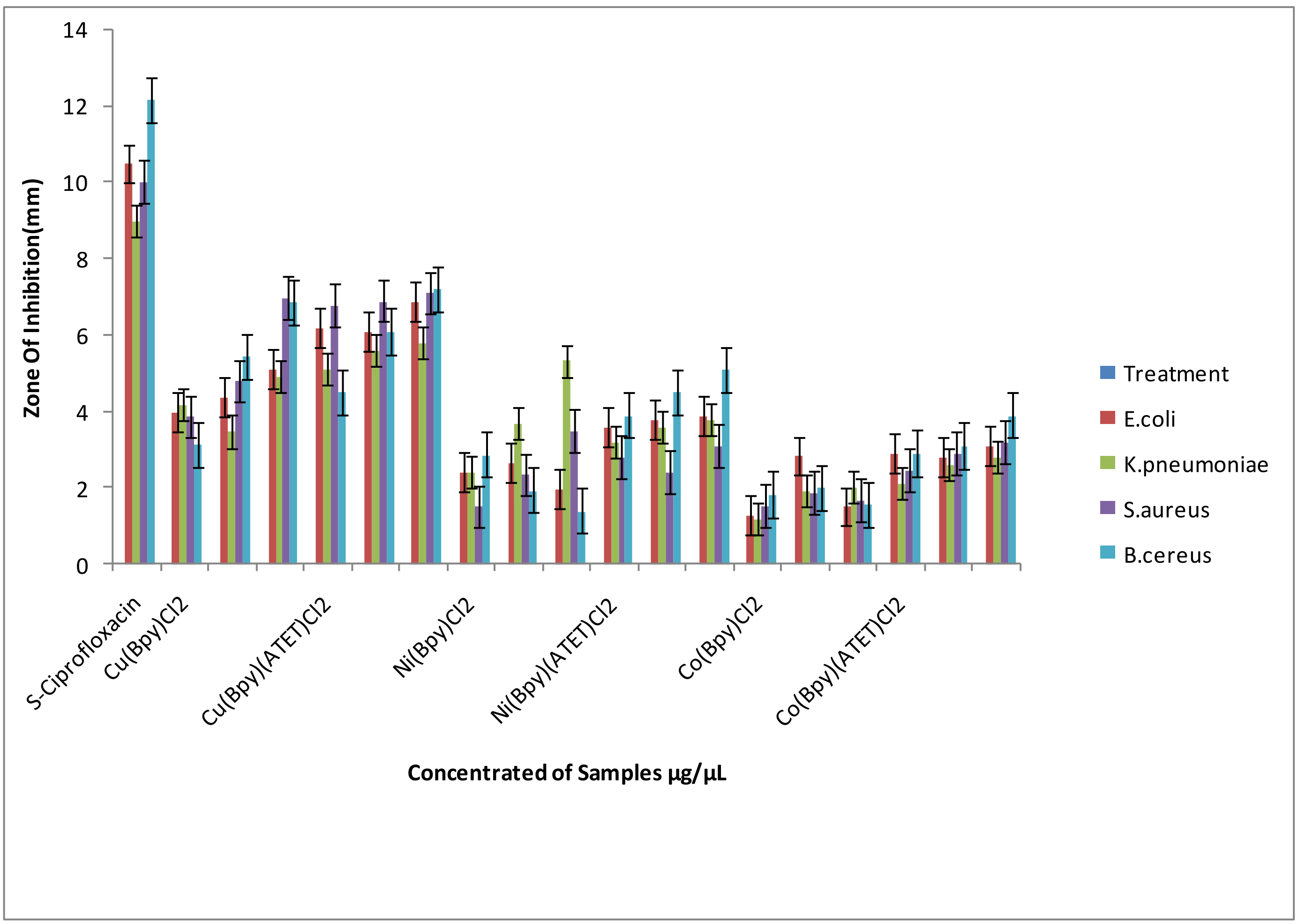


Fig. 7: Graphical representation of antibacterial activity of metal complexes against pathogenic bacterial strains

Table 7: Antibacterial activity of Metal Complexes against pathogenic bacterial strains

Sample	Treatment (Concentration)	*E. coli* (Mean±SE)	*K. pneumoniae* (Mean±SE)	*S. aureus* (Mean±SE)	*B.cereus* (Mean±SE)
S-Ciprofloxacin	(5µg/µL)	10.5 ±0.02	8.98 ±0.09	10.03±0.03	12.16±0.05
$Cu(Bpy)Cl_2$	100µg/µL	3.98 ±0.14	4.17 ±0.17	3.87±0.18	3.14±0.25
	200µg/µL	4.37±0.47	3.47±0.47	4.8±0.32	5.45±0.75
	300µg/µL	5.12±0.8	4.93±0.3	6.97±0.06	6.87±0.36
$Cu(Bpy)(ATET)Cl_2$	100µg/µL	6.2±0.02	5.1±0.07	6.8±0.03	4.5±0.09
	200µg/µL	6.1±0.03	5.6±0.08	6.9±0.08	6.1±0.42
	300µg/µL	6.9±0.04	5.8±0.01	7.1±0.06	7.2±0.65
$Ni(Bpy)Cl_2$	100µg/µL	2.4±0.11	2.4±0.17	1.5±0.28	2.87±0.16
	200µg/µL	2.67±0.09	3.67±0.17	2.34±0.15	1.93±0.26
	300µg/µL	1.98±0.06	5.33±0.17	3.5±0.63	1.4±0.32
$Ni(Bpy)(ATET)Cl_2$	100µg/µL	3.6±0.06	3.2±0.45	2.8±0.84	3.9±0.32
	200µg/µL	3.8±0.08	3.6±0.75	2.4±0.57	4.5±0.65
	300µg/µL	3.9±0.07	3.8±0.69	3.1±0.39	5.1±0.09
$Co(Bpy)Cl_2$	100µg/µL	1.3±0.15	1.2±0.18	1.53±0.3	1.83±0.01
	200µg/µL	2.83±0.17	1.93±0.13	1.87±0.87	2.01±0.34
	300µg/µL	1.5±0.29	2.01±0.15	1.69±0.23	1.57±0.36
$Co(Bpy)(ATET)Cl_2$	100µg/µL	2.9±0.07	2.1±0.04	2.47±0.02	2.9±0.75
	200µg/µL	2.8±0.09	2.6±0.05	2.9±0.06	3.1±0.84
	300µg/µL	3.1±0.05	2.8±0.09	3.2±0.04	3.9±0.95

Values are the mean ± SE of inhibition zone in mm.

4. CONCLUSION

Ternary transition metal complexes with 2,2-bipyridyl and 2-acetylthiophene-4-ethyl-3-thiosemicarbazone (ATET) were synthesized and characterized on the basis of mass spectra, molar conductivity, infrared and electronic spectra. Electrochemical properties of these complexes are uncovered by using cyclic voltammetry. The complexes show quasi reversible cyclic voltammetric responses for the M(II)/M(I) couple. The binding properties of these complexes with calf-thymus DNA are investigated by using absorption spectro-photometry. Ternary metal complexes show high binding affinity towards DNA. Metal complexes are screened for their antibacterial activities by using agar well diffusion method against pathogenic bacterial strains.. Among all coordination compounds, copper complexes show higher activity.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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