Synthesis, Characterization, DNA Binding Studies and Biological Activities of Cobalt (III) Complexes Containing 1,10 Phenanthroline and Semicarbazide & Thiosemicarbazide

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ABSTRACT

The new $[Co(Phen)_2(SC)](ClO_4)_2$ & $[Co(Phen)_2(TSC)](ClO_4)_3$ Cobalt(II) complexes (phen = 1,10-phenanthroline, SC = Semicarbazide & TSC = Thiosemicarbazide) have been synthesized and characterized by CHN analysis, molar conductance, electronic absorption, IR & NMR studies. They have been tested for their in vitro DNA binding activities by spectroscopic methods such as UV-Visible, Emission, Cyclic volumetric and viscosity measurements. Further complexes 1 & 2 were tested for their antimicrobial activities and it was found to have good antimicrobial activities.

INTRODUCTION

There is considerable interest in the design of small molecules, which react at specific sites along the DNA strand, as reactive models for protein-nucleic acid interactions, as probes of DNA structure, as an aid to drug design, and as tools of molecular biology[1-4]. The use of transition metal chelates is central in the effort to elucidate the mechanisms involved in the site specific recognition of DNA and to determine the principles governing the recognition.

Cancer is undoubtedly one of the main health concerns facing our society and one of the primary targets regarding medicinal chemistry. Even though platinum-based complexes had been in the primary focus of research on chemotherapy agents[5-7], the interests in this field have shifted to non-platinum based agents[8-15], in order to find different metal complexes with less side effects and similar, or better, cytotoxicity. Thus, a wide variety of metal complexes based on titanium, gallium, germanium, palladium, gold, copper, nickel, ruthenium and tin are being intensively studied as platinum replacements[16, 17]. Cobalt is an essential trace element in human, exhibiting many useful biological functions. Numerous compounds, naturally occurring and man-made, contain the cobalt at two common oxidation states Co(II) and Co(III). There is growing interest in investigating the cobalt and other transition metal complexes for their interaction with DNA[18-21]. Moreover, cobalt complexes appear to be very promising candidates for anticancer therapy; an idea supported by a considerable number of research articles describing the synthesis and cytotoxic activities of numerous cobalt complexes[12-19]. In addition, thiosemicarbazones are considered as an important class of nitrogen–sulfur donor ligands because of their highly interesting chemical, biological and medicinal properties, such as DNA binding, antioxidant, antibacterial, antiproliferative, antimalarial, anticancer and antitumor[30-36]. The presence of substituents at the 4-position have been shown to affect the activity of thiosemicarbazones and their metal complexes[17]. For example, metal complexes of 2-acetylpyridine thiosemicarbazones are found to exhibit increased antineoplastic activity when the N atom in the 4-position is part of a hexamethyleneiminyl ring instead of being a propyl- or dipropyl-carrying amine group. The variable coordination behavior of thiosemicarbazone ligands towards transition metals, as well as antitumor activity of the resulting complexes are studied by West et al[18–22]. We have previously reported the synthesis and biological studies of cadmium(II) complexes from 2-acetylpyridine thiosemicarbazones[23].

Citation: M. N. Arumugham et al. Ijppr.Human, 2019; Vol. 17 (1): 169-186.

170

MATERIALS AND METHODS

Synthesis of [Co(phen)$_2$Cl$_2$] Cl[24]

4.76g of Cobaltous chloride (CoCl$_2$.6H$_2$O) was dissolved in 12 mL of water and 7.92g of 1, 10 phenonthroline was added and heated in a round bottomed flask until solution become partly then it was cooled rapidly with constant stirring to yield fine pink crystal of [Co(phen)$_2$Cl$_2$]Cl. 3H$_2$O. With frequent stacking, chlorine gas was passed and it was gradually converted into dirty violet paste within 60-90 min. The product was separated, washed several times with 2M HCl and dried in air yields 8.4g. The cherry red solution heated with 25 ml of Con. HCl on the water bath. Dark violet crystal with greyish tinge in the form of prism gradually separated, more than 70% of the product was recrystallised.
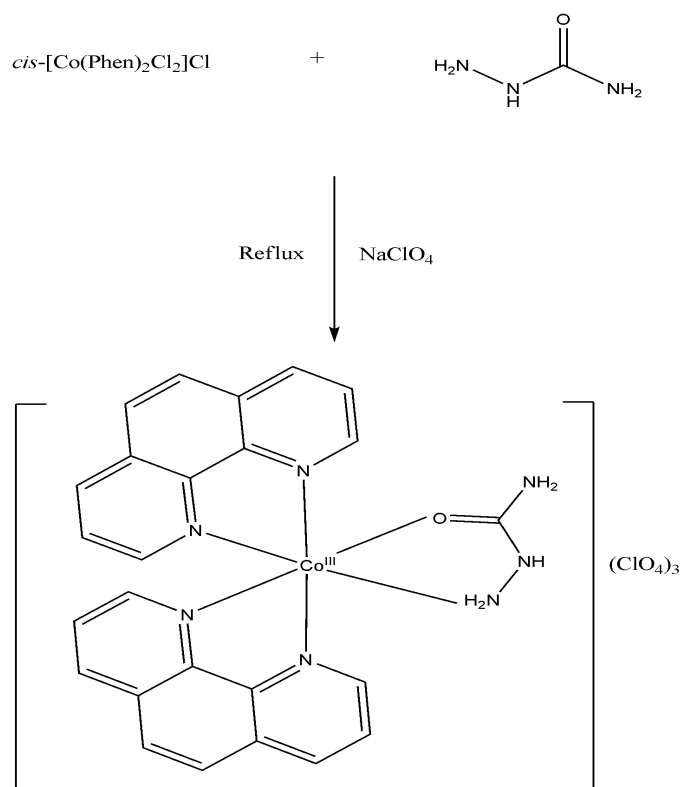
Synthesis of *cis*-[Co(Phen)$_2$(SC)](ClO$_4$)$_3$ (1)

2.9 g of [Co(phen)$_2$Cl$_2$]Cl complex was dissolved in equal ratio of 1:1mmol of (25ml) ethanol and water with constant stirring and added 0.38 g of Semicarbazide. The mixture was refluxed for 5 hours. On cooling the solution to ambient temperature, an aqueous solution of sodium perchlorate (12.244 g) was added and the mixture was refluxed for 30 minutes until the formation of brown precipitate which was filtered and washed with ethanol. Yield: ~64%.
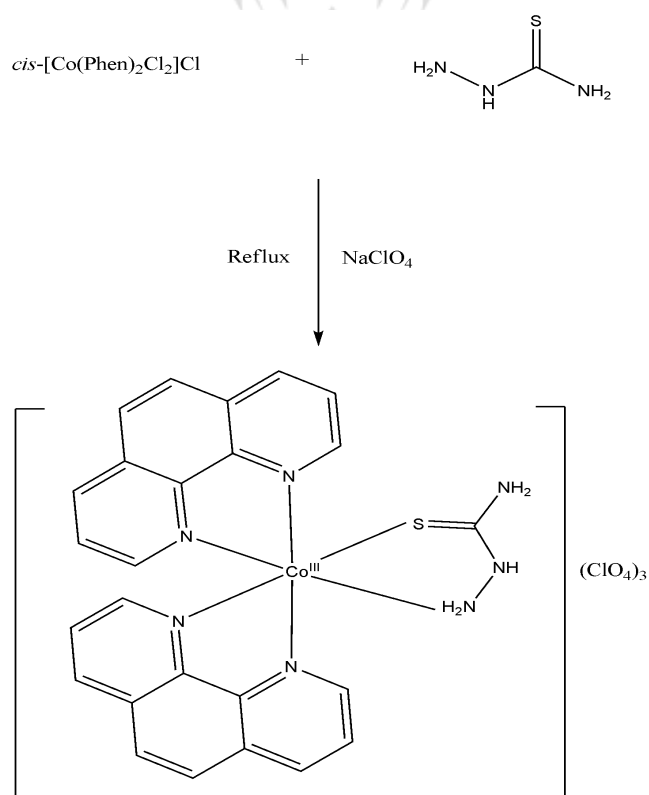
Caution! Although no problems were encountered in this work, perchlorate salts of transition metal complexes with organic ligands are potential explosives. Only small amount of material should be prepared and handled with caution.

Synthesis of *cis*-[Co(Phen)$_2$(TSC)](ClO$_4$)$_3$ (2)

2.9 g of [Co(phen)$_2$Cl$_2$]Cl complex was dissolved in equal ratio of 1:1mmol of (25ml) ethanol and water with constant stirring and added 0.45 g of thiosemicarbazide. The mixture was refluxed for 5 hours. On cooling the solution to ambient temperature, an aqueous solution of sodium perchlorate (12.244 g) was added and the mixture was refluxed for 30 minutes until the formation of brown precipitate which was filtered and washed with ethanol. Yield: ~57%.

Citation: M. N. Arumugham et al. Ijppr.Human, 2019; Vol. 17 (1): 169-186.

171

cis-[Co(Phen)$_2$Cl$_2$]Cl   +

Reflux | NaClO$_4$

$(ClO_4)_3$

Scheme 1: Synthesis of complex 1

cis-[Co(Phen)$_2$Cl$_2$]Cl   +

Reflux | NaClO$_4$

$(ClO_4)_3$

Scheme 2: Synthesis of complex 2

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172

RESULTS AND DISCUSSION

General Aspects

These complexes are stable in solid state and soluble in water and common organic solvents. The elemental analysis data of the cobalt (III) complexes (Table 1) agree with the theoretical values. The synthetic strategy of the complexes is outlined in Scheme **1** and 2.

The molar conductance measurement revealed[35, 36] that the cobalt (III) complexes behave as 1:3 electrolytes in aqueous medium.

Table 1: Elemental Analysis and Molar conductance complex 1 and complex 2

Complexes	Calcd (Found)			Molar Conductance (Sm^2mol^{-1})
	Carbon	**Hydrogen**	**Nitrogen**	
complex 1	37.88 (37.34)	2.67 (2.40)	12.37 (12.10)	396
complex **2**	37.12 (38.90)	2.62 (2.50)	12.12 (11.96)	379

Electronic Spectra

In the UV region, the complex presented (Fig 1 and 2) bands around 270 nm which can be attributed to $\pi \rightarrow \pi^*$ transition of the coordinated phenanthroline ligand[37], and the complexes **1** and **2** exhibit d-d band at The UV-Visible spectal data was given in table 2.

Table 2: UV-Visible spectral data of complex 1 and 2

Complex Name		$\lambda_{max(nm)}$	ε_{max} $(mol^{-1} cm^{-1})$
Complex **1**		225	89303
		267	77637
		574	174
Complex **2**	271	77499	
	577	176	

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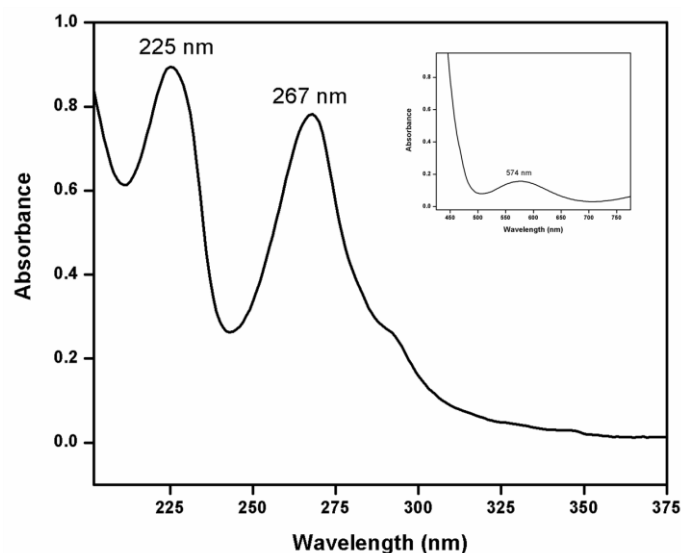
173

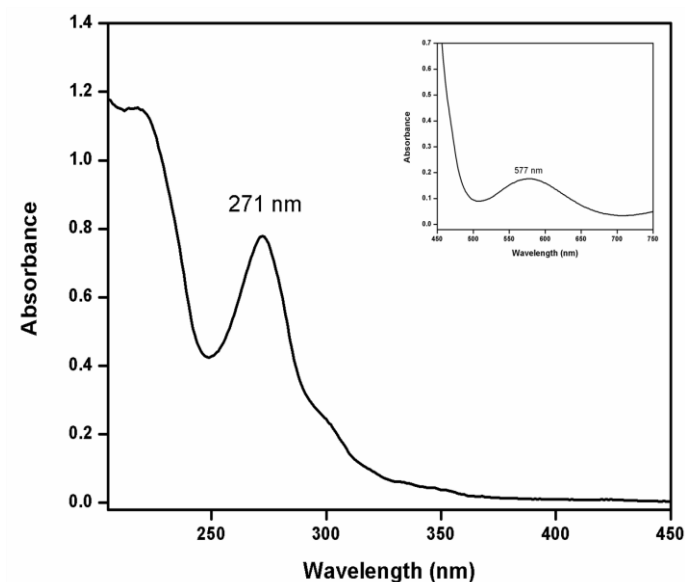**Figure 1: Electronic Spectrum of complex 1**

Figure 2: Electronic Spectrum of complex 2

Infrared spectra

Infrared spectrum of the complexes **1** and **2** was shown in Fig 3 and 4. The characteristic out-of-plane hydrogen bending modes of free phen observed at 853, 738 cm^{-1}, are red shifted to 842 and 714 cm^{-1} (**1**), 850 and 723 cm^{-1} (**2**) upon metal complexation. This shift can be explained on the basis of the fact that the nitrogen atoms of phenanthroline ligand donate a pair of electrons each to the central cobalt metal, forming a coordinate covalent bond. Besides, it is also confirmed by the shift of ν(C–N) of phenanthroline from about 1670 cm^{-1}

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174

in the free ligand to 1612cm^{-1}(**1**) and 1627cm^{-1}(2) after coordination[38]. For complex **1** a very strong band at 1080 cm^{-1} have been assigned to ν(Cl-O) of perchlorate anions. Perchlorate bands at 613 cm^{-1} belong to an ionic species; this means that this counter-ion is not involved in the cobalt–ligand coordination[39].
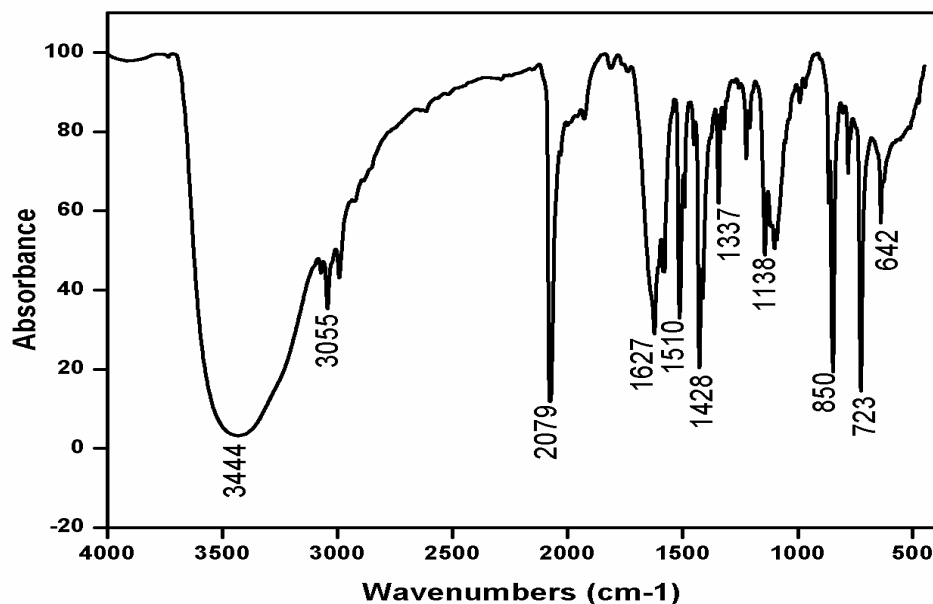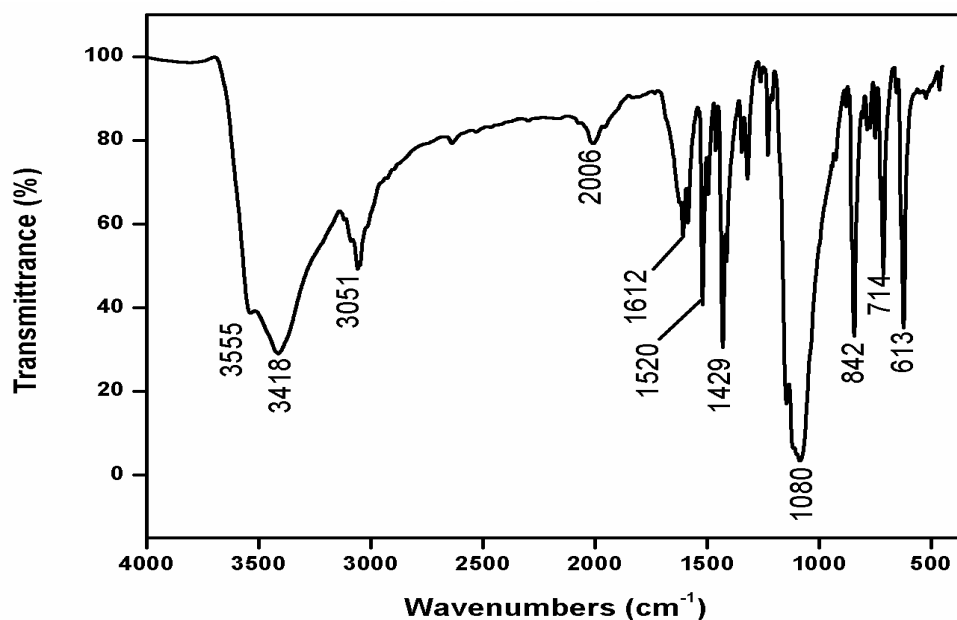

Figure No. 3: IR spectra of complex 1

Figure 4: IR spectra of complex 2

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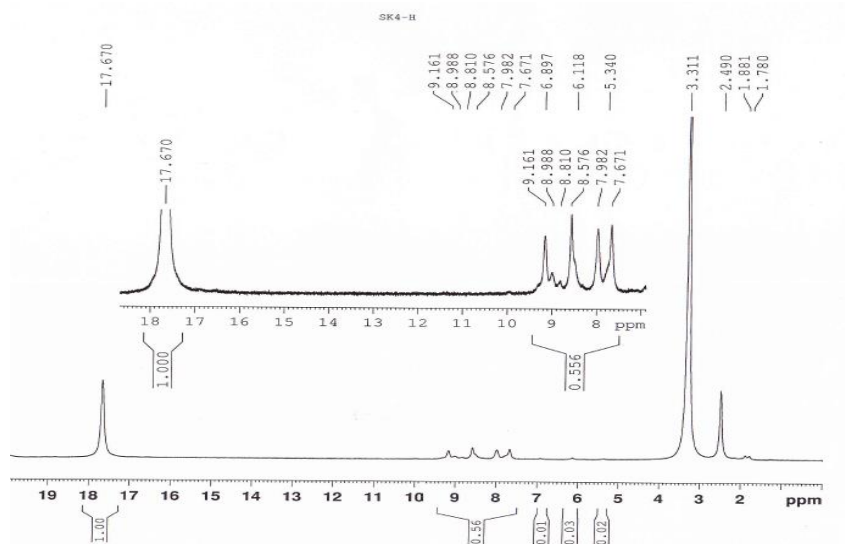
175

Figure 5: NMR spectra of complex 1

The electronic environment of many aromatic hydrogen atoms is similar and hence their ^{1}H NMR signals appear in a narrow chemical shift range. Infact, the aromatic regions of the spectra of this complex (Fig 5) complicated due to the overlapping of several signals, which have precluded the identification of individual resonance. However, from the direct comparison of the intensity of the aromatic protons with that of the observable azomethine proton (–CH=N–) in the downfield [d (–CH=N–), δ 9.1], the number of aromatic protons expected for these complex was confirmed. The singlet due to the azomethine proton in the complexes is considerably deshielded (δ > 9 ppm) relative to that of the free ligands, (δ 8.81 ppm) as a consequence of electron donation to the metal due to the coordination of the azomethine nitrogen[39].

DNA binding studies

UV-Vis absorption spectra

Electronic absorption spectra were initially employed to study the binding of cobalt(III) complexes with CT-DNA. The absorption spectra in aqueous buffer media of cobalt(III) complexes (**1** and **2)** in the absence and in the presence of CT-DNA are given in Fig 5 and 6. As the concentration of DNA increased, the absorption band of cobalt(III) complex at 270 nm exhibits hyperchromism and blue shift. A similar hyperchromism has been observed for the soret bands of certain prophyrins when incteracted with DNA, but have not yet been clearly explained[40]. The cobalt(III) complexes can bind to the double stranded DNA in different

Citation: M. N. Arumugham et al. Ijppr.Human, 2019; Vol. 17 (1): 169-186.

176

binding modes on the basis of their structure and charge and type of ligands. The cobalt(III) complexes containing phenanthroline ligands can bind to DNA by intercalation mode between these phen and thymine groups. The hyperchromism effect may due to intercalation mode between positively charged complex and negatively charged phosphate backbone at the periphery of the double helix CT DNA[40]. Structurally, intercalation to DNA may be one of the binding patterns, since the cobalt(III) complexes contain phen ligands which should provide aromatic moiety extending from the center through which overlapping occurs in base pairs of DNA by an electrostatic binding mode. The intrinsic binding constant (K_b) was determined from the following equation:

$$[DNA]/(\varepsilon_a-\varepsilon_f) =[DNA]/(\varepsilon_b-\varepsilon_f)+1/K_b(\varepsilon_b-\varepsilon_f)$$

The apparent extinction coefficient(ε_a) was obtained by calculating $A_{obsd}/[Co]$. The terms ε_f and ε_a correspond to the extinction coefficients of free (unbound) and fully bound complex, respectively. A plot of $[DNA]/(\varepsilon_a-\varepsilon_f)$ Vs K_b is the ratio of the slope and intercept. The intrinsic binding constant (K_b) for the association of the complexes with CT DNA (inset of Figure 6 and 7) was determined as 1.24 and 2.27 respectively.

The K_b value is classically higher than earlier reported. This indicates that complexes have effective binding affinity with DNA.
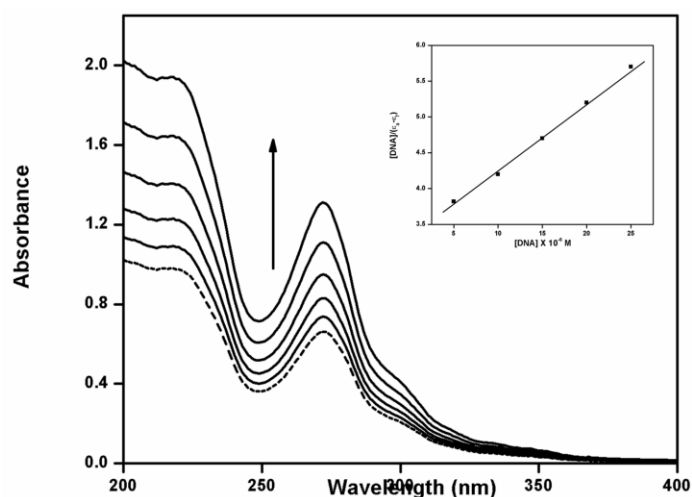

Figure 6: Electronic spectra of 5.0x10⁻⁵M complex 1, in the absence (---)and presence (—) of increasing amount of CT DNA at the ratio r = 0.3, 0.5, 0.7, 1.0. Arrow (↑) shows the absorbance changes upon increasing DNA concentration. Inset: linear plot for the calculation of the intrinsic DNA binding constant.

Citation: M. N. Arumugham et al. Ijppr.Human, 2019; Vol. 17 (1): 169-186.

177

Figure 7: Electronic spectra of 5.0x10^{-5}M complex 2, in the absence (---)and presence (—) of increasing amount of CT DNA at the ratio r = 0.3, 0.5, 0.7, 1.0. Arrow (↑) shows the absorbance changes upon increasing DNA concentration. Inset: linear plot for the calculation of the intrinsic DNA binding constant.
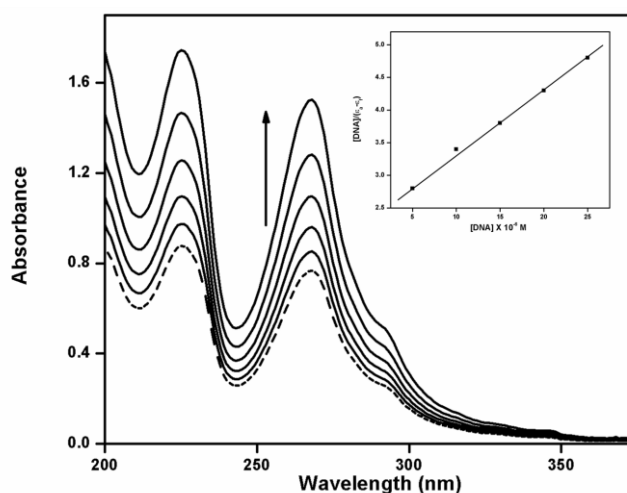
Fluorescence spectra

Competitive binding studies using DNA with bound ethidium bromide (EtBr) was carried out for complex 1 and 2. The extent of fluorescence quenching of ethidium bromide (EB) by competitive displacement from DNA is a measure of the strength of interaction between the second molecule and DNA. The results in (Fig. 8 and 9) showed that the fluorescence intensity of CT-DNA-EB decreased remarkably with the addition of cobalt complexes, which indicated that the complex can bind to DNA and replace EB from the CT-DNA-EB system. The above data was analyzed by means of the Stern-Volmer equation[55]. The quenching plots (Fig 8 and 9) illustrates that the fluorescence quenching of EB bound to DNA by the complexes are in linear agreement with the Stern-Volmer relationship, which corroborates that the complex bind to DNA. In the plot I_0/I vs [complex]/[DNA], K_{sq} value for the complexes are 0.324 (**1**) and 0.422 (**2**).
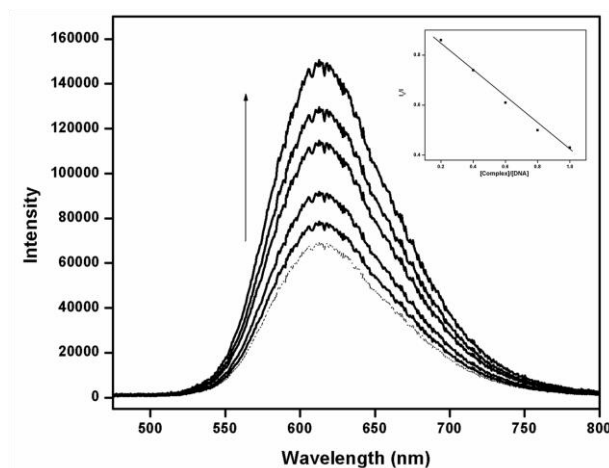
Citation: M. N. Arumugham et al. Ijppr.Human, 2019; Vol. 17 (1): 169-186.

178

Figure 8: Emission spectra of EB bound to DNA. complex 1 [EB]= 40 μM, [DNA] = 40 μM, [Complex] = (0-50 μM). Arrow (↓) shows the intensity changes upon increasing the concentration of the complex. Inset: Stern-Volmer quenching curves.

Figure 9: Emission spectra of EB bound to DNA. complex 2 [EB]= 40 μM, [DNA] = 40 μM, [Complex] = (0-50 μM). Arrow (↓) shows the intensity changes upon increasing the concentration of the complex. Inset: Stern-Volmer quenching curves.

Viscosity measurements
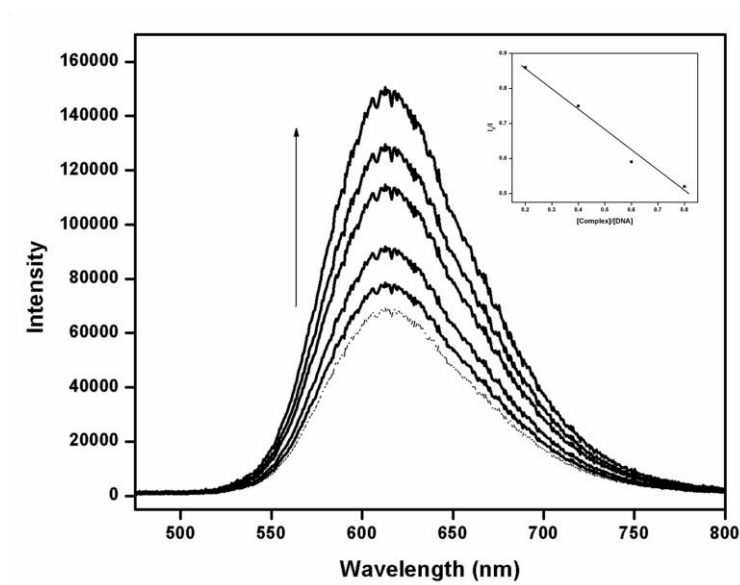
Mode of interaction between the metal complexes and DNA was clarified by viscosity measurements. Hydrodynamic measurements are sensitive to the length change (i.e., viscosity and sedimentation) are regarded as the least ambiguous and the most critical test of binding in solution. A classical intercalation mode demands that the DNA helix lengthens as

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179

base pairs are separated to accommodate the bound ligand, leading to the increase of DNA viscosity. In contrast, a partial non-classical intercalation of ligand could bend the DNA helix, reduce its effective length and concomitantly its viscosity. The effect of the complexes **1** and **2** on the viscosity of rod like DNA is shown in Fig. 10 and 11. The viscosity of DNA is increased with the increase of the concentration of the complexes, in contrast to that of proven DNA intercalator EtBr. Based on the viscosity results, it was observed that these complexes bind with DNA through intercalation mode.
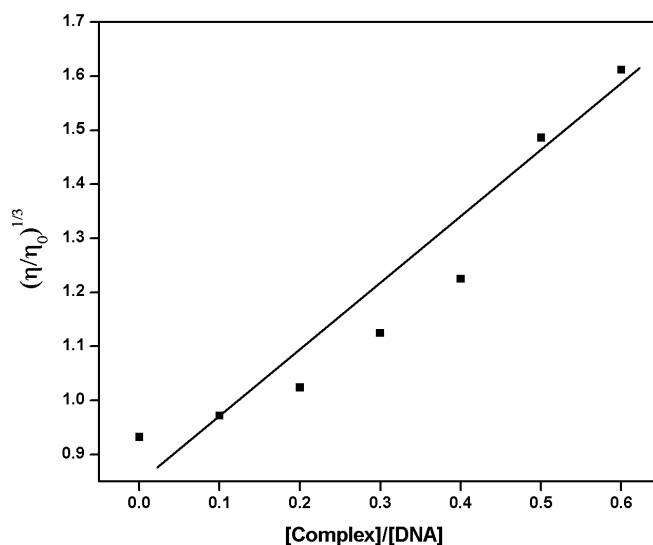
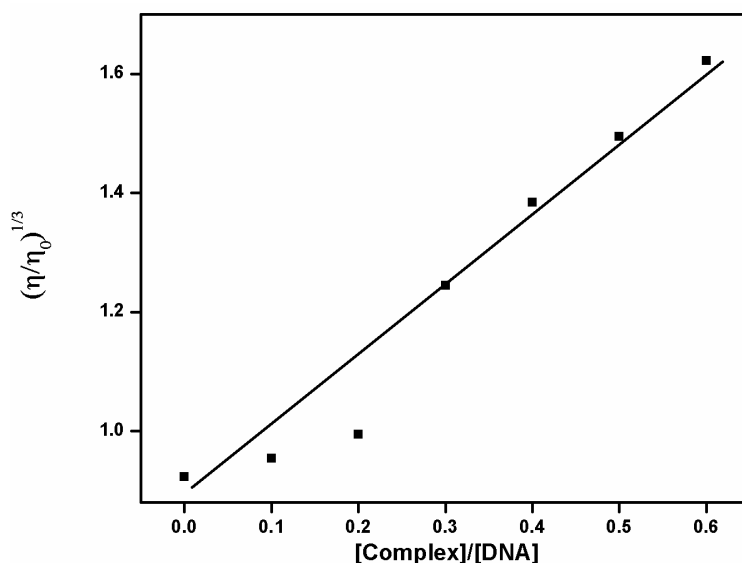**Figure 10: Effects of increasing amounts of complex 1 on the relative viscosities of CT DNA at 25^{0}C:**

Figure 11: Effects of increasing amounts of complex 2 on the relative viscosities of CT DNA at 25^{0}C:

Citation: M. N. Arumugham et al. Ijppr.Human, 2019; Vol. 17 (1): 169-186.

180

Cyclic voltammetry studies

The Cyclic Voltammetric (CV) response for $[Co(phen)(SC)]^{3+}$ in Tris-HCl buffer (pH 7.28) in the presence and absence of CT DNA is shown in (Fig.12 and 13). In the forward scan, a single cathodic peak was observed, which corresponds to the reduction of complex. In the reverse scan, no anodic peak was observed, which indicates that the process is irreversible.

When CT-DNA is added to a solution of complex, marked decrease in the peak current and potential values was observed. The cyclic voltammetric behavior was not affected by the addition of very large excess of DNA, indicating that the decrease of peak current of complex after the addition of DNA due to the binding of $[Co(phen)(SC)]^{3+}$ complex to the DNA. When the concentration of DNA increased the changes in peak current and potential become slow. This reveals that the complexes were interact with CT-DNA.[41]
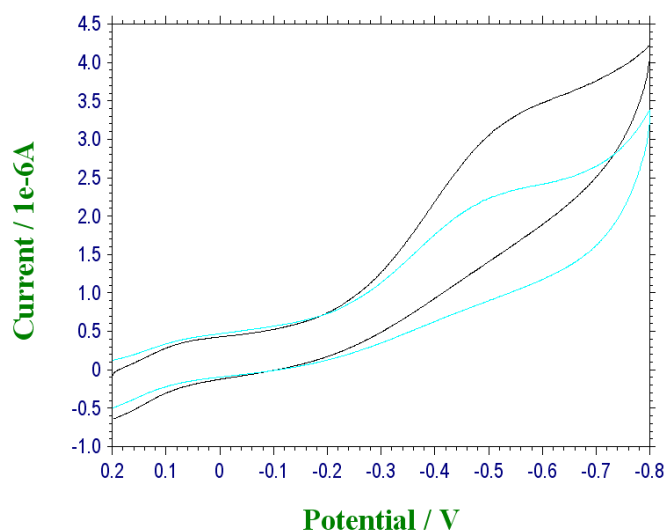

Figure 12: Cyclic voltammogram of 0.5 mM complex 1, in the absence (—) and presence (---) of 2.5 mM DNA.
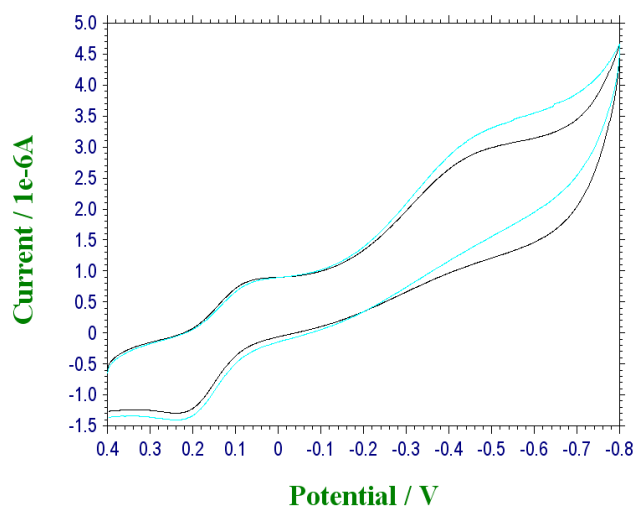
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181

Figure 13: Effects of increasing amounts of complexes on the relative viscosities of CT DNA at 25^{0}C: complex 2.

Antibacterial and antifungal screening

The cobalt(III) complex was screened in vitro for their microbial activity (Fig 14 and 15) against certain pathogenic bacterial and fungal species using disc diffusion method. This complex was found to exhibit considerable activity against Gram positive (*Staphylococcus aureus* and *Bacillus Cereus*) and Gram negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and the pathogenic yeast *Candida albicans*. The test solutions were prepared in dimethyl sulphoxide (1%) and the results of the antimicrobial activities are summarized in Table 3. The cobalt (III) complex showed significant microbial activity against Gram positive, Gram negative bacteria and fungus. In our biological experiments, using cobalt(III) complex, we have observed high antibacterial activity against Gram positive bacteria (*Staphylococcus aureus* and *Bacillus cereus*) than Gram negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*). The cobalt (III) complexes are also very active against the yeast *Candida albicans*.

Citation: M. N. Arumugham et al. Ijppr.Human, 2019; Vol. 17 (1): 169-186.

182

Gram positive bacteria

B. cereus

M. luteus

S. aureus

Gram negative bacteria

E. coli

K. pneumoniae

P. aeruginosa

Fungi

A. flavus

A. niger

C. albicans
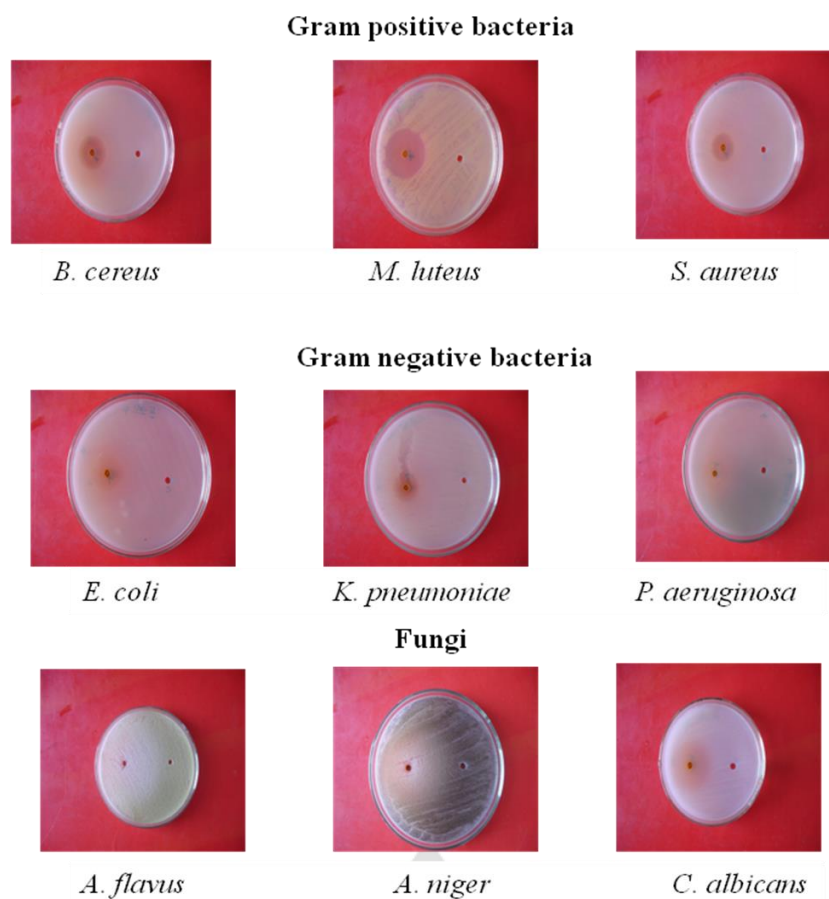
Figure 14: Antimicrobial activity of complex 1

Gram positive bacteria

B. cereus

M. luteus

S. aureus

Gram negative bacteria

E. coli

K. pneumoniae

P. aeruginosa

Fungi

A. flavus
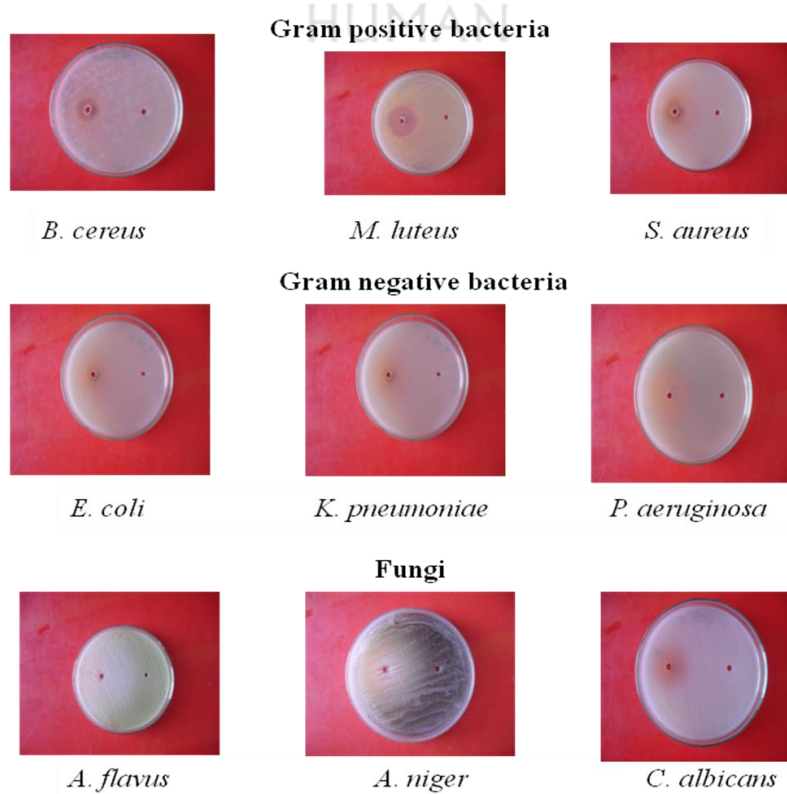
A. niger

C. albicans

Figure 15: Antimicrobial activity of complex 2

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183

Table 3: Biological activity of complexes 1 and 2

Name of the Organism	Diameter Zone of Inhibition (mm) Ciproflaxacin/ Amphotericin-B	
	Complex **1**	Complex **2**
A. flavus	-	-
A. niger	5	-
B. cereus	13	14
C. albicans	-	-
E. coli	11	-
K. pheumoniae	8	-
M. luteus	27	25
P. aeruginosa	-	-
S.aureus	13	12

CONCLUSION

In this study a new cobalt (III) complexes having N,N-donor 1,10-phenanthroline has been prepared and characterized. The planarity and extended conjugation of the phenanthroline base has a profound effect on the DNA binding complex. The effectiveness of binding induced changes in absorption and fluorescence spectroscopy along with viscosity measurements and cyclic voltammetric studies, confirm the interclative mode of interaction.

ACKNOWLEDGMENT

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184

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185

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186