



Received on 18 January 2019; received in revised form, 24 April 2019; accepted, 24 September 2019; published 01 October 2019

SYNTHESIS, CHARACTERIZATION, AND DNA- BINDING INTERACTION STUDIES OF A NEW MANNICH BASE AND IT'S METAL COMPLEXES

Sivakami Sudhasankar

Department of Chemistry, SRMIST, Kattankulathur - 603203, Tamil Nadu, India.

Keywords:

Mannich base, DNA binding,
Fluorescence and viscosity
measurements

Correspondence to Author:

Sivakami Sudhasankar

Department of Chemistry,
SRMIST, Kattankulathur - 603203,
Tamil Nadu, India.

E-mail: sivakamisudhasankar@gmail.com

ABSTRACT: Cyclic imides such as succinimides, maleimides, phthalimide and their derivatives contain an imide ring and a general structure –CO-N(R)-CO- that confers hydrophobicity and neutral nature. Succinimide (pyrrolidine 2,5-dione) is a synthetically versatile substrate used for the synthesis of heterocyclic compounds and as a raw material for drug synthesis. Derivatives of succinimide are of important biological and pharmaceutical uses such as antibacterial, antifungal, anticonvulsant, antitumor and antinociceptive. In spite of these activities, much of their action mechanisms at molecular and cellular levels remain to be elucidated. A new series of nickel(II) and copper(II) complexes of a new mannichbase1-((2,5-dioxopyrrolidin-1-yl)(4-methoxyphenyl) methyl) thiourea (LIGAND) have been synthesized. The structures of newly synthesized compounds have been explicated on the basis of elemental analysis, molar conductance, IR, UV-Visible, NMR, Mass, and Magnetic measurements. The binding of the copper sulfate complex of the ligand with calf thymus DNA has been investigated using absorption spectroscopy, fluorescence spectroscopy, and viscosity measurements.

INTRODUCTION: Mannich reaction consists of an amino alkylation of an acidic proton placed next to a carbonyl group with formaldehyde and ammonia or any primary or secondary amine. The final product is a β -amino carbonyl compound. Reactions between imides and aromatic aldehydes have also been considered as Mannich reactions. A review of literature regarding Mannich reactions shows extensive volume on chemical, biological and toxicological feature of Mannich bases¹⁻³. Transition metals are essential for normal functioning of living organisms and are, therefore, of great interest as potential drugs⁴⁻⁷.

The coordination chemistry of nitrogen donor Ligands is an interesting area of research. A great deal of attention in this area has been focused on the complexes formed by 3d metals with bidentate Ligands using both the nitrogen atoms of the substrates. Several drugs showed increased activity as metal chelates rather than as organic compounds⁸⁻¹³. To the best of our knowledge, no work has been done on this class of metal complexes with the Mannich base Ligand.

In the continuation of our research work, herein, we report the synthesis of a new Mannich base derived from succinimide, methoxy benzaldehyde and thiourea (LIGAND) and the metal complexes with Ni(II) and Cu(II). The characterization studies of all the metal complexes have been done with appropriate methods. All the metal complexes were screened for antibacterial activities. The DNA binding and cleavage study of the copper complex containing the Ligand is reported.

<p>QUICK RESPONSE CODE</p> 	<p>DOI: 10.13040/IJPSR.0975-8232.10(10).4513-20</p> <hr/> <p>This article can be accessed online on www.ijpsr.com</p> <hr/> <p>DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(10).4513-20</p>
---	--

MATERIALS AND METHODS: All the reagents and solvents used for the synthesis of Ligand and the metal complexes were Analar grade of highest available purity and used as such without further purification.

Physical Measurements: Elemental analysis was performed using Carlo Erba 1108 analyzer and Coleman N analyzer and was found within $\pm 0.5\%$. The molar conductivities of the metal complexes were measured in approximately 10^{-3} mol ethanol solution using a Systronics direct reading digital conductivity meter -304 with dip type conductivity cell. The IR spectra were recorded as KBr pellets on Perkin- Elmer 1000 unit instrument. Absorbance in the UV-Visible region was recorded in DMF solution using UV-Visible spectrometer. The ^1H & ^{13}C NMR of the Ligand was recorded on a Bruker instrument employing TMS as internal reference and DMSO – DMF as solvent. The mass spectral study of the Ligand was carried out using LC mass spectrometer. Magnetic susceptibility measurements

at room temperature were made by using a Guoy magnetic balance

Preparation of Mannich base 1-((2,5-dioxopyrrolidin-1-yl)(4-methoxyphenyl) methyl) thiourea: A known weight of succinimide (1g, 0.01mol) and a known weight of thiourea (0.7g, 0.01mol) were dissolved in a small amount of distilled water and taken in a round-bottomed flask and fitted with a reflux condenser and a dropping funnel. The flask was heated in a water bath. A known weight of methoxy benzaldehyde (1.4g, 0.01 mol) was allowed to fall in drops from the dropping funnel into the flask and the contents are heated for about 30 min. The mixture is cooled and the contents are transferred into the beaker and stirred for 8-10 h. After a week, a solid product formed was filtered, washed with distilled water and dried in an air oven at 60°C and recrystallized using ethanol and chloroform in 1:1 ratio (Reaction scheme **Fig. 1**).

Reaction Scheme:

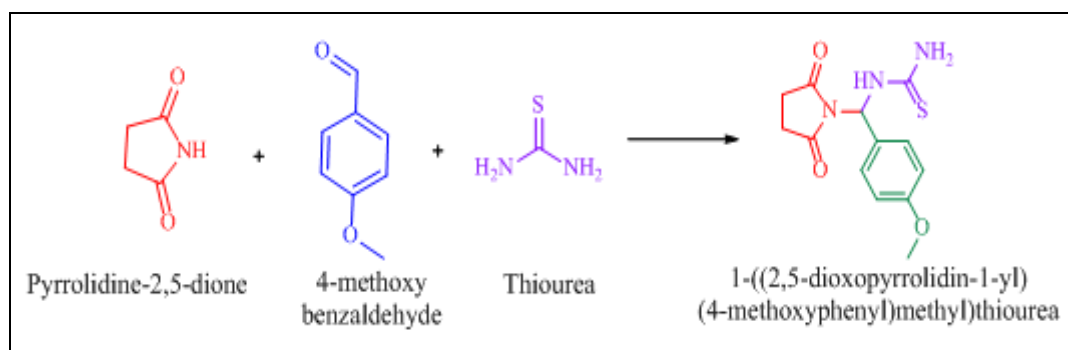


FIG. 1: PREPARATION OF MANNICH BASE 1-((2,5-dioxopyrrolidin-1-yl)(4-Methoxyphenyl) Methyl) THIOUREA (LIGAND)

Synthesis of Nickel Chloride Complex of Mannich Base: To a hot methanolic solution of Nickel chloride (0.08g, 3mmol), hot ethanolic solution of the Ligand (0.1g, 3m mol) was added dropwise under constant stirring at 60°C for 24 h. Then the solution was kept aside for evaporation of the solvent. After 10 days, dull green solid mass obtained was filtered, washed with methanol, and dried in vacuum **Fig. 2**.

Synthesis of Nickel Sulphate Complex of Mannich Base: The Nickel sulfate complex of LIGAND was prepared by refluxing a suspension of a hot methanolic solution of Nickel sulfate (0.09g, 3mmol) with hot ethanolic solution of the Ligand (0.1g, 3mmol) for 1 h to obtain a clear

solution. Green crystals of the metal complex were separated on evaporating the solution at room temperature for 2 weeks. The compound was filtered and washed with methanol and dried in vacuum **Fig. 2**.

Synthesis of Copper Chloride Complex of Mannich Base: To a hot methanolic solution of Copper chloride (0.05g, 3mmol), hot ethanolic solution of the Ligand (0.1g, 3mmol) was added dropwise under constant stirring for 24 h. Then the resulting mixture was kept aside for evaporation of the solvent. After 10 days, light green needle-shaped crystals were obtained. It was filtered, washed with methanol and dried in vacuum **Fig. 2**.

Synthesis of Copper Sulphate Complex of Mannich Base: The copper sulfate complex of the Ligand was prepared by stirring a suspension of a hot methanolic solution of Copper sulfate (0.08g, 3mmol) with hot ethanolic solution of the Ligand (0.1g, 3mmol) for 1 h in a magnetic stirrer at 60 °C

to obtain a clear solution. Blue crystals of the metal complex were separated on evaporating the solution at room temperature for 2 weeks. The compound was filtered and washed with methanol and dried in vacuum **Fig. 2**.

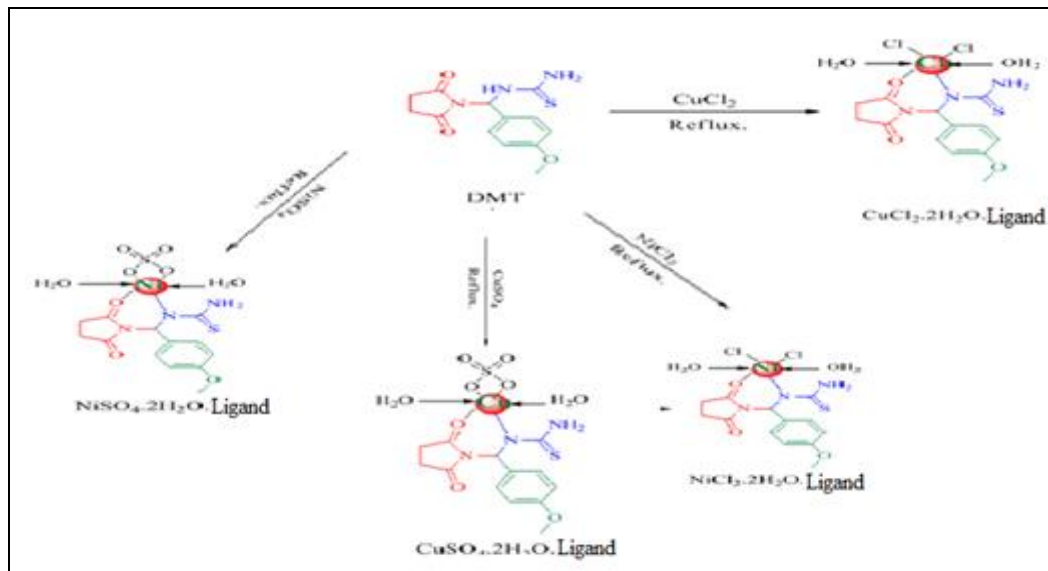


FIG. 2: SYNTHESIS OF COPPER SULPHATE COMPLEX OF MANNICH BASE

RESULTS AND DISCUSSION:

Physical Measurements: The physical properties and elemental analysis of the prepared Ligand and their metal complexes are described in **Table 1**. The structures of metal complexes were further confirmed by conductivity measurements and magnetic moment determinations **Table 1**.

UV-Vis Spectroscopic Studies: The Nickel chloride complex shows absorption bands at 10525 cm^{-1} , 15780 cm^{-1} and 24890 cm^{-1} and 35235 cm^{-1} for the transitions ${}^1A_{1g} \rightarrow {}^3T_{1g}$, ${}^1A_{1g} \rightarrow {}^3T_{2g}$, ${}^1A_{1g} \rightarrow {}^3T_{1g}$ and charges transfer transitions respectively. The μ_{eff} value was found to be 3.56 B.M suggestive of octahedral geometry ¹⁴.

The Nickel sulfate complex exhibits absorption bands at 10642 cm^{-1} , 16670 cm^{-1} , 23522 cm^{-1} and 35714 cm^{-1} due to ${}^1A_{1g} \rightarrow {}^3T_{1g}$, ${}^1A_{1g} \rightarrow {}^3T_{2g}$,

${}^1A_{1g} \rightarrow {}^3T_{1g}$ transitions respectively. The μ_{eff} value was found to be 1.48 B.M suggesting octahedral geometry ¹⁵.

The copper chloride complex registers absorption bands at 9275 cm^{-1} , 10374 cm^{-1} , 12357 cm^{-1} due to ${}^2B_{1g} \rightarrow {}^2A_{1g}$, ${}^2B_{1g} \rightarrow {}^2B_{2g}$, ${}^2E_g \rightarrow {}^2T_{2g}$ transitions respectively. The charge transfer transition bands occur at 24830 and 28327 cm^{-1} . The μ_{eff} value was found at 2.09 B.M suggesting octahedral geometry ¹⁶.

For the copper sulphate complex appears at 8240 cm^{-1} , 11325 cm^{-1} , 14653 cm^{-1} , 26391 cm^{-1} and 35670 cm^{-1} due to ${}^2B_{1g} \rightarrow {}^2A_{1g}$, ${}^2B_{1g} \rightarrow {}^2B_{2g}$, ${}^3E_g \rightarrow {}^2T_{2g}$ and CT transitions respectively. The μ_{eff} value was found to be 1.8 B.M in agreement with distorted octahedral geometry ¹⁷ **Table 1**.

TABLE 1: ANALYTICAL DATA & UV SPECTRAL DATA OF THE LIGAND SDBMTU & ITS METAL COMPLEXES

Compound	C	H	N	O	Δm ($\text{ohm}^{-1} \text{cm}^2$ mol^{-1}) & μ_{eff} (B.M)	λ_{max} (cm^{-1})	Transition Assignment	Geometry
LIGAND ($\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}_3\text{S}$)	53.20 (53.17)	5.10 (5.08)	14.27 (14.26)	16.32 (16.31)	-			
$\text{NiCl}_2 \cdot 2\text{H}_2\text{O} \cdot \text{LIGAND}$ ($\text{C}_{14}\text{H}_{20}\text{Cl}_2\text{N}_3\text{NiO}_5\text{S}$)	35.61 (35.58)	4.21 (4.20)	8.88 (8.86)	16.91 (16.89)	41 (3.56)	10525 15780	${}^1A_{1g} \rightarrow {}^3T_{1g}$ ${}^1A_{1g} \rightarrow {}^3T_{2g}$	Octahedral

NiSO ₄ .2H ₂ O.LIGAND (C ₁₄ H ₂₀ N ₃ NiO ₉ S ₂)	36.17 (36.15)	3.12 (3.12)	8.99 (8.97)	24.27 (23.26)	44 (3.53)	24890	¹ A _{1g} → ¹ T _{1g}	Octahedral
						35235	CT	
						10642	¹ A _{1g} → ³ T _{1g}	
						16670	¹ A _{1g} → ³ T _{2g}	
						23522	¹ A _{1g} → ¹ T _{1g}	
CuCl ₂ .2H ₂ O.LIGAND (C ₁₄ H ₂₀ Cl ₂ CuN ₃ O ₅ S)	35.22 (35.21)	4.19 (4.18)	8.80 (8.79)	16.73 (16.72)	40 (2.09)	35714	CT	Octahedral
						9275	² B _{1g} → ² A _{1g}	
						10374	² B _{1g} → ² B _{2g}	
						12557	² E _g → ² T _{2g}	
						24330 & 28327	CT	
CuSO ₄ .2H ₂ O.LIGAND (C ₁₄ H ₁₆ CuN ₃ O ₇ S ₂)	36.00 (35.98)	3.16 (3.15)	8.99 (8.97)	23.91 (23.89)	43 (2.26)	8240	² B _{1g} → ² A _{1g}	Distorted Octahedral
						11325	² B _{1g} → ² B _{2g}	
						14653	² E _g → ² T _{2g}	
						26391 & 35670	CT	

IR Spectral Analysis of LIGAND and its Metal Complexes:

In order to study the binding mode of the ligand to metal in the complexes, the IR spectrum of the free ligand was compared with the corresponding metal complexes. Selected vibrational bands of the ligand and its metal complexes and their assignments are listed in **Table 2**. The IR spectrum the free ligand exhibited a strong band at 1690 cm⁻¹ which could be assigned to $\nu_{C=O}$ of the succinimide ring. A band around 3297cm⁻¹ could be attributed to stretching vibration of ν_{N-H} bond¹⁸. A strong band observed around 1392 cm⁻¹ could be assignable to $\nu_{C=S}$ vibration mode. In the metal complexes, the band

corresponding to $\nu_{C=O}$ of succinimide ring was shifted to lower frequency range suggesting the coordination of carbonyl group with the metal ion. There is no shifting of bands at 1400 cm⁻¹ and 750 cm⁻¹ indicating the absence of coordination of C=S group with the metal ion. The N-C-N stretching frequency of the ligand at 1472 cm⁻¹ was shifted towards lower values in all the complexes, indicating the involvement of the nitrogen of thiourea in coordination to the central metal ion. The participation of oxygen and nitrogen in coordination with the metal ion is further supported by the new band appearance of ν_{M-N} around 420-425 cm⁻¹ in the far-infrared region.

TABLE 2: CHARACTERISTIC IR SPECTRAL DATA (cm⁻¹) OF LIGAND AND IT'S METAL COMPLEXES

Compound	ν_{NH}	$\nu_{C=O}$	$\nu_{C=S}$	N-C-N	-OCH ₃	H ₂ O Coord	M-X	M-S
LIGAND	3297	1690	1392	1472	1272	-	-	-
NiCl ₂ . 2H ₂ O.LIGAND	3290	1683	1396	1463	1271	3747,1590,808	423	-
NiSO ₄ . 2H ₂ O.LIGAND	3320	1701	1381	1470	1294	3774,1624,817	-	427
CuCl ₂ . 2H ₂ O.LIGAND	3292	1687	1400	1466	1268	3377,1591,808	424	-
CuSO ₄ . 2H ₂ O.LIGAND	3384	1699	1385	1510	1273	3775,1626,816	-	423

¹H NMR Data of Ligand: (DMSO/TMS, 500 MHz) The ¹H NMR spectra of the ligand shows a singlet at δ 2.56 due to -CH₂ proton. The singlet for one proton at δ 3.7 is assigned to -OCH₃ proton. A multiplet in the range δ 6.41-7.78 is assigned for aromatic protons. The singlet for one proton at δ 10.10 is assigned to -NH₂ proton. Another singlet at δ 11.062 is assigned to -NH proton.

¹³C NMR Data of Ligand: (DMSO/TMS, 125 MHz) The number of signals of sharp peaks represents the number of carbons of the ligand which are not chemically equivalent. ¹³C NMR - δ 179.4, 156.9, 149.9, 139.5, 127.6, 120.9, 111.3, 108.2, 55.6, 40.0, 29.5.

LC Mass Data of LIGAND: Molecular formula: C₁₃H₁₅N₃O₃S, Observed $m/z=294.37$, Calculated $m/z=293.08$.

DNA Binding Studies:

Absorption Spectral Studies: The transition metal complex can bind to DNA via both covalent and/or non-covalent interactions. It is well known that electronic absorption spectroscopy is an effective method to examine the binding modes and binding extent of the metal complexes with DNA. In the UV region, the intense absorption bands observed in the region 300-360 nm were attributed to intra ligand $\pi-\pi^*$ transition. Increase in concentration of CT-DNA resulted in the hypochromism and blue-

shift in UV-Vis spectrum of the metal complexes of ligand. These spectral characteristics suggest that the metal complexes of ligand might bind to DNA by an interactive mode due to a strong stacking interaction between the aromatic chromophore of the complex and the base pairs of the DNA. After intercalating the base pairs of DNA, the π^* orbital of the intercalated ligand could couple with the π orbital of the base pairs, thus decreasing the π - π^* transition energy and further resulting in the blue shift.

On the other hand, the coupling of the π orbital was partially filled by electrons, thus decreasing the transition probabilities and concomitantly, resulting in the hypochromism.

The spectroscopic methods were used to ascertain the interaction mode of the metal complexes NiCl_2 .Ligand, NiSO_4 . Ligand, CuCl_2 . Ligand and CuSO_4 . Ligand with CT-DNA. The metal complexes exhibited intense absorption bands around 260 nm which are assigned to intraligand charge transfer transition of aromatic Chromophore and at 370 nm which are attributed to metal-ligand charge transfer bands¹⁹⁻²². The absorption spectra of complexes in the absence and presence of CT-DNA are shown in **Fig. 3** and **4**.

Addition of increasing amounts of CT-DNA resulted in an appreciable decrease in absorption intensity of complexes and redshift in wavelength. In order to compare quantitatively the affinity of the metal complexes of LIGAND towards CT-DNA, the intrinsic binding constants K_b of the complexes with CT-DNA were obtained by monitoring the changes in absorbance with increasing concentration of CT-DNA.

The binding constant K_b of the complexes NiCl_2 .Ligand, NiSO_4 . Ligand, CuCl_2 . Ligand and CuSO_4 . Ligand are 1.3×10^4 , 1.8×10^4 , 2.6×10^4 , 2.8×10^4 and $2.4 \times 10^4 \text{ M}^{-1}$ respectively **Table 3**. The hypochromism and redshift are associated with the binding of the metal complexes to the DNA helix, due to the intercalative mode involving a strong stacking interaction between the aromatic chromophore of the complexes and the base pairs of DNA. The values suggest that the copper sulfate complex has stronger binding affinity than the other complexes.

TABLE 3: BINDING PARAMETERS OF LIGAND AND METAL COMPLEXES WITH DNA

Complexes	DNA		
	$K_b \times 10^4$ (M^{-1})	$K_{sv} \times 10^4$ (M^{-1})	$K_{app} \times 10^6$ (M^{-1})
NiCl_2 .LIGAND	1.3	2.08	1.33
NiSO_4 .LIGAND	1.8	2.1	1.42
CuCl_2 .LIGAND	2.6	3.15	1.51
CuSO_4 .LIGAND	2.8	4.9	2.2

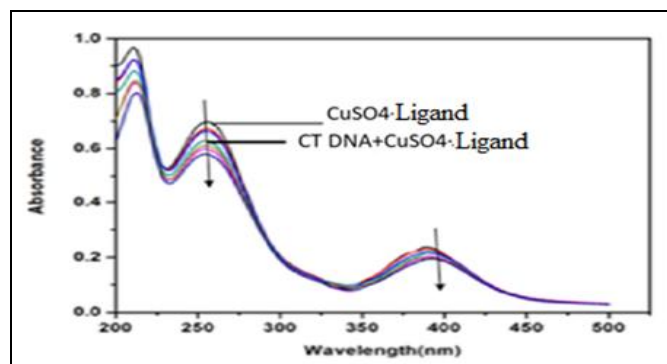


FIG. 3: ABSORPTION SPECTRA OF THE COPPER COMPLEX OF LIGAND IN THE ABSENCE AND PRESENCE OF INCREASING AMOUNTS OF CT-DNA (0-200 μM) IN TRIS-HCL BUFFER

Fluorescence Spectral Studies: In order to investigate further the interaction modes between these metal complexes and CT-DNA, the ethidiumbromide (EB) fluorescence displacement experiments were further used. In general, the intrinsic fluorescence intensity of DNA is very low, and that of EB in Tris buffer is also not high due to quenching by the solvent molecules. However, on the addition of DNA, the fluorescence intensity of EB will be enhanced because of its intercalation into the DNA. Thus, EB can be used to probe the interaction of complexes with DNA. The fluorescence intensity of EB can be quenched by the addition of another molecular due to decreasing of the binding sites of DNA available for EB. Thus fluorescence spectral method is used to study the relative binding of the synthesized complexes and ethidium bromide (EB) with CT-DNA.

Complexes are non-emissive both in the presence and absence of CT-DNA. EB emit intense fluorescence at about 600 nm in the presence of CT DNA because of its strong interaction between the adjacent DNA base pairs (Fernandez et al., 2001). If the metal complex intercalates into DNA, it leads to a decrease in the binding sites of DNA available for EB and a decrease in the fluorescence intensity of the EB-DNA system²³.

The observed quenching of EB-DNA fluorescence intensity upon addition of complex into EB-DNA system suggest that the complex may displace EB from the EB-DNA and complex can interact with CT-DNA probably by the intercalative mode **Fig. 5**. The Stern-Volmer quenching constant K_{sv} values of the complexes NiCl₂.Ligand(1), NiSO₄.Ligand (2), CuCl₂.Ligand(3) and CuSO₄.Ligand(4) were calculated as 2.08×10^4 , 2.1×10^4 , 3.15×10^4 and 4.9×10^4 respectively. On the other hand, it is noteworthy that 50% of EB molecules were replaced from DNA-bound EB at a concentration ratio of [complex] / [EB] = 21 and the apparent binding constant (K_{app}) of complexes can be calculated by using the following equation

$$K_{app} = K_{EB}[EB]_{50\%} / [complex]_{50\%}$$

Where K_{EB} is the DNA-binding constant of EB, and $[EB]_{50\%}$ and $[complex]_{50\%}$ are EB and complex concentrations at 50% fluorescence. K_{EB} is known as $1.0 \times 10^7 \text{ M}^{-1}$. The K_{app} values of the complexes were calculated as 1.33×10^6 , 1.42×10^6 , 1.51×10^6 and $2.2 \times 10^6 \text{ M}^{-1}$ respectively. From this spectral data, it is seen that the copper complex binds well through intercalative than the other complexes.

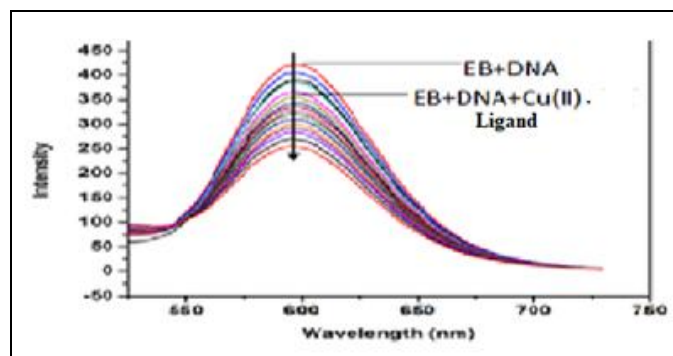


FIG. 4: EMISSION SPECTRA OF EB BOUND TO DNA IN TRIS-HCL BUFFER (pH 7.2) IN THE ABSENCE AND PRESENCE OF THE COPPER COMPLEX. [EB]= 4 μ M, [DNA] = 0 μ M, Cu(II).LIGAND] = 0 to 160 μ M. (λ_{ex} = 520nm)

Viscosity Measurements: Viscosity measurements were carried out to further clarify the mode of interaction of metal complexes to DNA. A classical intercalative mode causes a significant increase in viscosity of DNA solution due to an increase in the separation of base pairs at intercalation sites and hence an increase in the overall DNA length. With increasing [complexes] / [DNA] ratios from 0.02 to 0.12, the complexes NiCl₂.Ligand(1), NiSO₄.

Ligand(2), CuCl₂.Ligand(3) and CuSO₄.Ligand(4) exhibits a tendency of increasing relative viscosity of the [complexes-DNA] system, which strongly suggests the intercalation as the main binding mode of these complexes with CT-DNA.

DNA Cleavage Studies: Complexes can cleave DNA via hydrolytic and/or oxidative pathways. In the oxidative pathway, they have been shown to react with molecular oxygen or H₂O₂ to produce a variety of reactive oxidative species (ROS). The cleavage mechanism was studied by using a series of scavengers that could inhibit production of the ROSs. For example, DMSO and t-BuOH can be used as a scavenger of HO \cdot radical, while NaN₃ can be used as singlet-oxygen scavenger.

The cleavage of supercoiled pBR322 DNA was studied in a medium of 50 mM Tris-HCl/NaCl Buffer (pH = 7.2) in the presence of H₂O₂. All the metal complexes of Ligand showed remarkable cleavage. **Fig. 5** shows the results of the gel electrophoretic separations of plasmid pBR322 DNA by the complexes in the presence of H₂O₂. Under similar conditions, no cleavage of pBR322 DNA occurred for free H₂O₂ (40 μ M) or complex (30 μ M). All the complexes showed the cleavage at 30 μ M concentrations in presence of H₂O₂ at 40 μ M. Hence, it is reasonable to suggest that the higher DNA cleavage activity of the complex is due to the presence of aromatic group in the Ligand, which enhances the binding and cleavage ability of the molecule.

The cleavage mechanism of pBR322 DNA induced by complex was investigated and clarified in the presence of hydroxyl radical scavenger 0.4 M DMSO, SOD (3 & 4 units) and EDTA as a chelating agent under aerobic conditions. As shown in **Fig. 5** the DNA cleavage mechanism by complex is shown as follows: both DMSO and SOD are completely ineffective, this rules out the possibility of cleavage by hydroxyl radical and superoxide. The singlet oxygen scavenger NaN₃ did not show inhibition of DNA cleavage suggesting that ¹O₂ did not take part in the cleavage mechanism. The EDTA can efficiently inhibit the activity of the compounds^{24, 25}.

The absence of inhibition of DNA cleavage performed by the complex clearly suggests that the

DNA scission mechanism might follow a hydrolytic pathway rather than oxidative pathway. The complexes cleave DNA even in the absence of oxygen, approximately to the same extent as under aerobic conditions. It is thus concluded that the complexes are likely to cleave DNA by a hydrolytic mechanism.



FIG. 5(A): CLEAVAGE OF SC pBR322 DNA (0.2 μ g, 33 μ M) by NiCl₂.LIGAND, NiSO₄.LIGAND, CuCl₂.LIGAND AND CuSO₄.LIGAND (30 μ M) IN PRESENCE OF H₂O₂ (40 μ M) IN 50 mMTris-HCl / NaCl BUFFER (pH 7.2). LANES 1, DNA CONTROL; 2, DNA + H₂O₂ +NiCl₂.LIGAND (30 μ M); 3, DNA + H₂O₂ + NiSO₄.LIGAND (30 μ M); 4, DNA + H₂O₂ + CuCl₂.LIGAND (30 μ M); 5, DNA + H₂O₂ + CuSO₄.LIGAND (50 μ M)

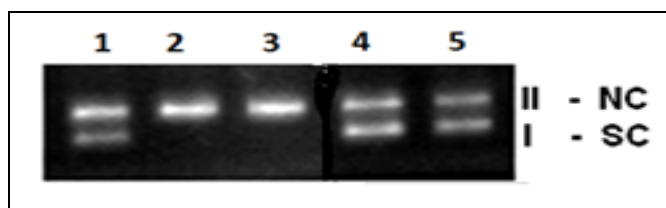


FIG. 5(B): CLEAVAGE MECHANISM OF SC pBR322 DNA (33 μ M) BY THE METAL COMPLEXES OF LIGAND (50 μ M) IN THE PRESENCE OF H₂O₂ (40 μ M) IN 50 mMTris-HCl / NaCl Buffer (pH 7.2). LANES 1, DNA CONTROL; 2, DNA + H₂O₂ + NiCl₂ COMPLEX + SOD (4 UNITS); 3, DNA + H₂O₂ + NiSO₄ COMPLEX + SOD (4 UNITS); 4, DNA + H₂O₂ + CuCl₂ COMPLEX + DMSO (70 mM) AND 5, DNA + CuSO₄ COMPLEX + NaN₃ (70 mM)

CONCLUSION: In this paper coordination chemistry of a Mannich base ligand obtained from the reaction of succinimide, methoxy benzaldehyde and thiourea is described. Ni(II), and Cu(II) complexes have been synthesized using the above Mannich base ligand and characterized on the basis of analytical, magnetic and spectral data. The Mannich base coordinates through its thiourea nitrogen and oxygen of succinimide to the metal ion and acts as a neutral bidentate ligand. All the complexes exhibit octahedral geometry. The ligand and its metal complexes have shown significant antibacterial activity. The Cu(II) metal complex showed efficient DNA binding ability, and the binding constant value is consistent with other typical intercalators. The nuclease activity of the

synthesized Cu(II) complex was effective which could induce scission of pBr322 supercoiled DNA effectively to linear form in presence of H₂O₂ as oxidising agent.

ACKNOWLEDGEMENT: The author wishes to thank Biogenics, Hubli for the DNA cleavage studies, Madras University for DNA binding studies and viscosity measurements and ISISM, SRMIST for spectral studies.

CONFLICT OF INTEREST: The authors declared no competing interests.

REFERENCES:

- Chen HL, Chang CY, Lee HT, Lin HH, Lu PJ, Yang CN, Shaiu CW and Shaw AY: Synthesis and pharmacological exploitation of clioquinol-derived copper-binding apoptosis inducers triggering reactive oxygen species generation and MAPK pathway activation. *Bioorganic Medicinal Chemistry* 2009; 17(20): 7239-47.
- Karpenko AS, Shibinskaya MO, Zholobak NM, Olevinskaya ZM, Lyakhov SA, Litvinova, LA, Spivak MY and Andronati SA: Synthesis, DNA binding and intferon-inducing properties of isatin and benzoisatin-hydrazones. *Pharmaceutical Chemistry Journal* 2006; 40(11): 595-02.
- Lev E: Medicinal exploitation of inorganic substances in the Levent in the Medieval and early Ottoman periods. *Adler Museum Bulletin* 2012; 28(2): 11-16.
- Seklon BS and Gandhi L: Medicinal uses of inorganic compounds- 1. *Resonance* 2006; 11(4): 75-89.
- Vidyavatreddy S, Nirdoshpatil M, Tukaramreddy A and Angadi SD: Synthesis and characterization of Cu (II),Co(II),Ni(II) complexes with Schiff bases derived from 3-(4-chloro phenoxy methyl)-4-amino 5mercapto-1,2,4-triazole. *Journal of Chemistry* 2008; 5(3): 529-38.
- Jayaseelan P, Prasad S, Vedanayaki S and Rajavel R: Synthesis, characterization, antimicrobial, DNA binding and cleavage studies of Schiff base metal complexes. *Arabian Journal of Chemistry* 2016; 9(1): 668-77.
- Frerickson CJ, Koh JY and Bush AI: The neuro biology of Zinc in health and disease, *Nature Reviews. Neuroscience*, 2005; 6(6): 449-62.
- Thomas DD, Ridnour LA, Isenberg JS, Flores-Santana W, Switzer, CH, Donzelli S, Hussain P, Vecoli C, Paolucci, N, Ambs S, Colton CA, Harris CC, Roberts DD and Wink DA: The chemical biology of nitric oxide : implications in cellular signaling. *Free Radical Biology and Medicine* 2008; 45(1): 18-31.
- Chen PR and He C: Selective recognition of metal ions by metallo regulatory proteins. *Current Opinion in Chemical Biology* 2008; 12(2): 214-21.
- Pennella MA and Giedroc DP: Structural determinations of metal selectivity in prokaryotic metal responsive transcriptional regulators. *Biometals* 2005; 18(4): 413-28.
- Cowan JA, Bertini I, Gray HB, Stiefel EI and Valentine JS: *Structure and Reactivity: Biological Inorganic Chemistry*, 3, University Science Books, Sausalito 2007, 8(2): 175181.
- Jameel A and Syed Ali Padusha MSA: Synthesis, characterization and antimicrobial activities of some novel

- derivatives of phenol. *Asian Journal of Chemistry* 2010; 22(12): 3422-48.
13. Anupama B, Sunuta M, Leela DS, Ushaiah and Kumari CG: Synthesis, spectral characterization, DNA binding studies and antimicrobial activity of Co(II), Ni(II), Zn(II), Fe(III) and VO(IV) complexes with 4-aminoantipyrine Schiff base. *Journal of Fluorescence* 2014; 24(4): 1067-76.
 14. Lv J, Liu T, Cai S, Wang X, Liu L and Wang Y: Synthesis, structure and biological activity of cobalt(II) and copper(II) complexes of valinederived Schiff bases. *Journal of Inorganic Biochemistry* 2006; 100(3): 1888-96.
 15. Sawyer TK: Chemical biology and drug design: three dimensional, dynamic and mechanistic nature of two multi disciplinary fields. *Chemical Biology and Drug Design* 2016; 67(3): 196-00.
 16. Stockwell BR: Exploring biology with small organic molecules. *Nature* 2017; 43: 504-07.
 17. Fricker SP: Metal based drugs from serendipity to design. *Dalton Transactions* 2007; 43: 4903-17.
 18. Vijey Anandhi M, Verma AK, Sujatha R and Raj K: Synthesis and characterization of novel Mannich bases of benzimidazole derivatives for antibacterial and antifungal activity. *International Journal of Pharmacy and Pharmaceutical Sciences* 2013; 5(2): 295-97.
 19. Yunus U, Bhatti MH, Rahman N, Mussarat N, Asghar S and Massod B: Synthesis, characterization and biological activity of novel Schiff and Mannich bases of 4-amino-3-(N-phthalimidomethyl)-1,2,4-triazole-5-thione, *Journal of Chemistry* 2013; 2013, 163-71.
 20. Babbar R, Pathak DP and Jain S: Synthesis and anti-inflammatory activity of Mannich bases of Nicotinamide with diclofenac and mefenamic acid, *Der Pharma Chmeica* 2012; 4(5): 2024-28.
 21. Sunita M, Padmaja M, Anupama B and Kumari CG: Synthesis, characterization, DNA binding and cleavage of mixed-ligand Cu(II) complexes of 2,6-bis (benzimidazole-2-yl) pyridine. *Jou of Fluorescence* 2012; 22(3): 1003-12.
 22. Cohen SM: New approaches for medicinal applications of bioinorganic chemistry. *Current Opinion in Chemical Biology* 2017; 11(2): 115-20.
 23. Bala S, Sharma N, Kajal A, Kamboj S and Saini V: Mannich bases: An important Pharmacophore in present scenario, *International Journal of Medicinal Chemistry*, 2014; 15(1): 497-15.
 24. Lian X, Lin L, Fu K, Ma B, Liu X and Feng X: A new approach to the asymmetric Mannich reaction catalysed by chiral N,N'-dioxide-metal complexes, *Chemical Sciences* 2016; 8(2): 1238-42.

How to cite this article:

Sudhasankar S: Synthesis, characterization and DNA- binding interaction studies of a new mannich base and its metal complexes. *Int J Pharm Sci & Res* 2019; 10(10): 4513-20. doi: 10.13040/IJPSR.0975-8232.10(10).4513-20.

All © 2013 are reserved by International Journal of Pharmaceutical Sciences and Research. This Journal licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License.

This article can be downloaded to **Android OS** based mobile. Scan QR Code using Code/Bar Scanner from your mobile. (Scanners are available on Google Playstore)