Vanillin Pramipexole Schiff Base Metal Complexes: Synthesis, Characterization, And Dna Binding Studies

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ABSTRACT

In addition to being widely used in industry, Schiff bases and their complexes also exhibit a wide range of biological activities, such as antifungal, antibacterial, anti malarial, anti-proliferative, anti-inflammatory, antiviral, and antipyretic properties. These versatile compounds are created by condensation of an amino compound with carbonyl compounds. Numerous Schiff base complexes exhibit good catalytic activity in a variety of processes when moisture is present. Numerous studies on their use in homogeneous and heterogeneous catalysis have been published during the past few years. The study of these compounds' coordination behaviour has increased significantly as a result of the impact that some metals have on the biological activity of these substances as well as their inherent chemical interest as multidentate ligands. New chemotherapeutic Schiff bases and their metal complexes are currently garnering the attention of researchers. Medical chemists are now interested in developing novel chemotherapeutic Schiff bases and their metal complexes. The current study uses a modified version of Sand Mayer's approach to synthesise and characterise metal complexes of novel Schiff bases obtained from Pramipexole (4, 5, 6, 7-Tetrahydro-N6-propyl-2, 6-benzothiazolediamine) and Vanillin. Synthesized compounds were analysed using a variety of methods, including conductometric titrations, IR, 1HNMR, UV-visible, and UV-visible spectroscopy. According to infrared spectrum data, the core metal ion and ligand are coordinated by deprotonated phenolic oxygen and azomethine nitrogen. Additionally, the compounds were examined by the authors for DNA binding tests. These complexes were discovered to have significant binding capacities.

1. INTRODUCTION

A double bond connecting the carbon and nitrogen atoms in Schiff bases gives them their versatility, which is produced by the many ways they can be combined with different alkyl or aryl substituents. This kind of substance can be both found in nature and created in a lab. Various amino compounds with imine-derived aldehydes or ketones can be combined to create the versatile chemical molecule known as a schiff base. Due to their ease of condensation synthesis, schiff base ligands are regarded as favoured ligands. They have a wide range of applications in biology, industry, food packaging, dyes, polymers, and coordination chemistry in addition to being employed as an O2 detector. In recent years, coordination complexes have become more significant, particularly in the development of long-acting medications for metabolism. Because of their technical applications, the metal complexes from bidentate ligands have recently received a lot of attention. 1, 2, and applications for improving medication action 3,4. Transition metals are highly sought after as possible medications since they are

necessary for the normal functioning of living things. 5. Research is now being done on the coordination chemistry of nitrogen donor ligands. The complexes produced by metals with bidentate ligands containing both oxygen and nitrogen have received a lot of interest in this area. 6,7. An essential group of ligands in coordination chemistry are the Schiff bases. The imine nitrogen has pi-acceptor characteristics and is basic. Alkyl diamines and aromatic aldehydes are frequently the sources of the ligands. One of the first ligands utilised for asymmetric catalysis was chiral Schiff bases8. Understanding the structure and binding characteristics of different Schiff base complexes can be crucial for a deeper comprehension of the intricate biological process9. Vanillin-derived Schiff bases are well known for their intriguing ligation characteristics and unique applicability in several fields10. The propensity of Pramipexole-derived Schiff bases to generate metal complexes is well documented from the literature11. A literature review suggests that these complexes are potentially more physiologically active as a result of the interaction between these donor ligands and metal ions. Because of their wide biological activity, Schiff bases and their metal complexes have become quite popular in recent years12,13. The ligand VP Schiff base (L) has been created in continuation of our past research on transition metal complexes with Schiff bases, keeping in mind the aforementioned fact. The synthesis and characterisation of the ligand and its complexes with Cu (II) and Ru (II) are reported in the current article.

2. MATERIALS AND METHODS

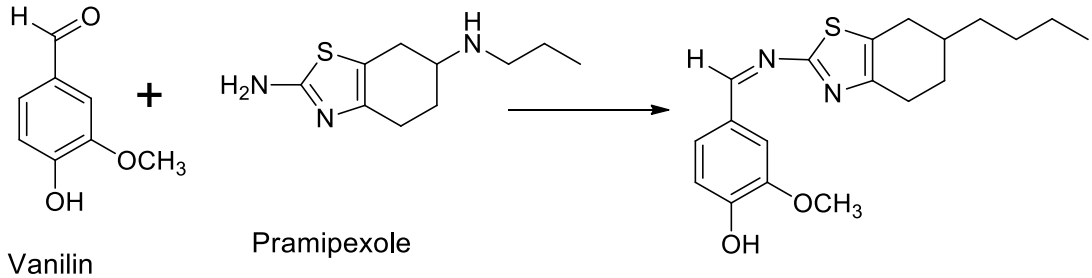
2.1 Instrumentation:

Using an element analyzer14 CHNO model Fison EA 1108, the element compositions (CHNO) for the compounds were calculated as a percentage. Using a JASCO FT/IR-5300, the infrared spectra were captured as potassium bromide (KBr) discs. The ACF200 Broker Germany Spectrometer was used to capture the 1H (400Hz) nuclear magnetic resonance spectra. Utilizing the Prekin-Elmer lab India UV-Vis Spectrometer, ultraviolet spectra were captured. The JES-FA Series and SPTQ600 PA were used to record electron spin resonance spectra, while the Perkin Elmer equipment in the thermal analysis centre was used to carry out thermo gravimetric analyses of the metal complexes 15. As a solvent, stick Cochin and ethyl alcohol were utilised. In the current experiment, only pure Aldrich compounds were employed.

2.2 Preparation of the ligand and its metal complexes:

2.2.1 Preparation of Vanillin Schiff base (VP) with Pramipexole:

In a 250 ml borosil refluction flask with 1 ml of tri ethyl amine, 4.22g of pramipexole (0.02 mole) and 3.04g of vanillin (0.02 mole) were dissolved in 50ml of methanol. After cooling to ambient temperature after being refluxed for three hours over a water bath, the mixture was separated into light yellow tinted crystals, which were then washed with methanol and dried in vacuum desiccators over CaCl2 anhydrous.



2.2.2 Preparation of Pramipexole and Vanillin Schiff base (VP) Metal Complexes:

Metal chloride salts were employed to prepare Cu (II) and Ru (II). 3.2947g (0.01 Mole) of the newly created ligand should be dissolved in enough methanol. Aqueous solutions of 1.3434 g (0.01 mole) and 1.718 g (0.01 mole) metal chlorides were added to this solution, along with 1 ml of sodium acetate. Dark green and dark brown sharp needles were separated from the mixture after it had been refluxed

for six hours in a water bath. The coloured metal complexes were cleaned with methanol and water before being recrystallized from ether and dried in vacuum desiccators on top of CaCl2 anhydrous. The recently created ligand metal complexes underwent an elemental examination. The ratios of the prepared metal complexes were 1:2. Analytical information about ligands and metal complexes was compiled in Table 1.

Table-1: Analytical data of the ligand and their metal complexes.

			Complex		
			VP	$Cu(VP)_2X_2$	$Ru(VP)_2X_2$
Molecular weight			345.474	789.48	828.01
Co lour			Light yellow	Dark green	Dark brown
Yield			72	73	70
M.P			260-262	272-274	280-282
Elemental Analysis	C %	Calculated	62.52	54.71	52.17
		Found	62.02	54.45	52.05
	H%	Calculated	6.65	6.33	6.03
		Found	6.34	6.11	5.74
	N %	Calculated	12.15	10.63	10.14
		Found	12.01	10.33	9.01
	O%	Calculated	9.26	8.10	7.72
		Found	9.03	8.01	7.53
	M%	Calculated	-	8.04	12.20
		Found	-	7.98	12.00

3. RESULT AND DISCUSSION

3.1 Infrared spectral analysis:-

Using KBr pellets, infrared spectra were captured using a JASCO FT/IR-5300 Spectrometer (4000-400cm-1). By using this spectroscopy, it is possible to shed light on the discovery made when examining the IR spectra of ligand and metal complexes that the compound contains significant functional groups. The figures 1, 2, and 3 show the usual IR spectra.

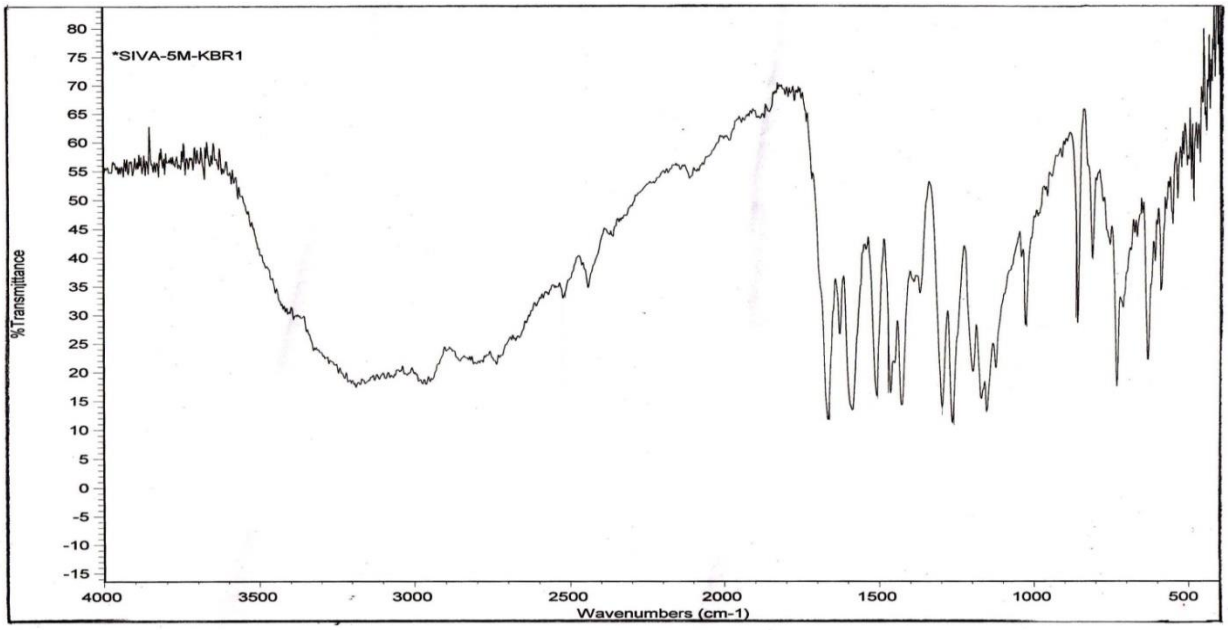


Fig-1: IR Spectrum of VP Ligand

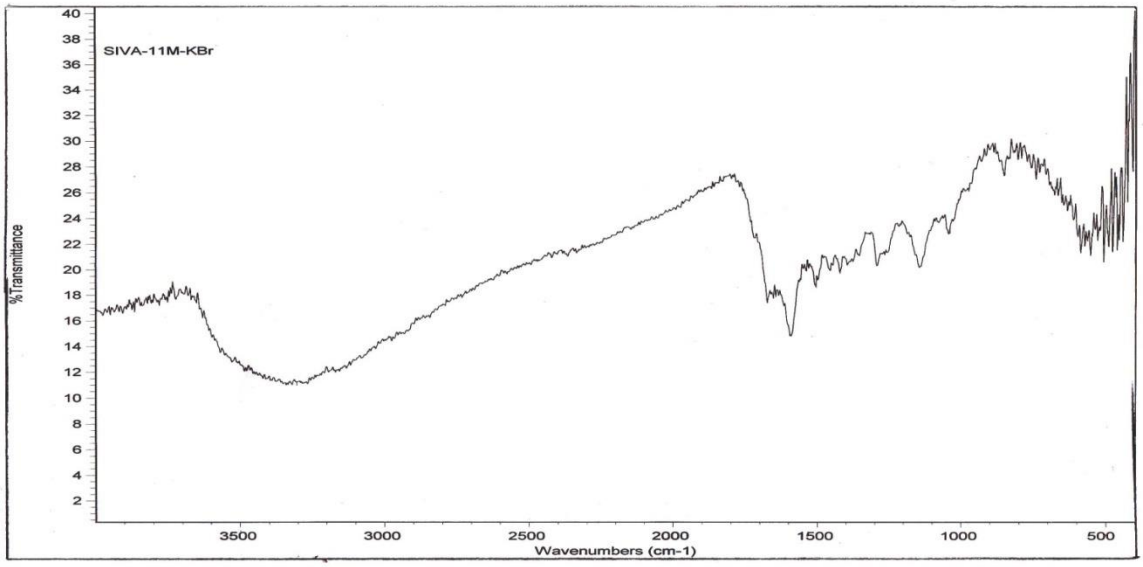


Fig-2: IR Spectrum of Cu $(VP)_2$ complex.

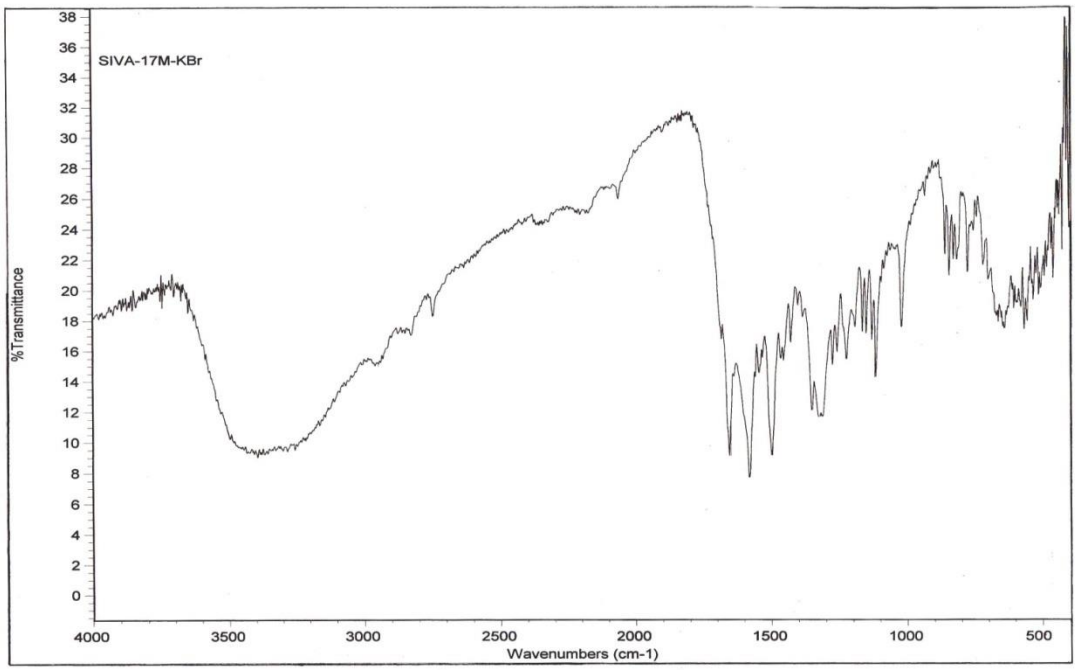


Fig-3: IR spectrum of Ru (VP) $_2$ Complex.

3.2 Interpretation of VP and Cu (II) and Ru (II) complexes:

Cu (II) and Ru (II) complex spectra were compared to the infrared spectrum of the ligand. The information was compiled in a table with their assignment.

Table-2: The important IR bands of the Ligand and Their Metal Complexes

Compound	OH(Water)	υOH (Phenolic)	υ C=N	υ N-H	υ M-O	υ M-N
VP	----	3285	1649	3348	-	-
$Cu(VP)_2$	3420	-	1630	3303	609	475
$Ru(VP)_2$	3435	-	1625	3315	690	490

Table 2 reveals that the IR spectra of the ligand exhibits a broad band at 1649 cm-1, which was attributed to the azomethine group's C=N stretching. This band was moved to lower areas in complexes, 1630 cm-1 for Cu (II) complexes and 1625 cm-1 for Ru (II) complexes, respectively. This indicates that the azomethine group (>C=N) group was involved in the complexation process. The decrease in electron density on nitrogen was the cause of this. By doing so, it shows how the nitrogen atoms and the metal are coordinated. The (OH)bond vanishes at 3285 cm-1 in the IR spectra of metal chelates. It shows that the phenolic (OH) group was displaced by a proton during complexation. As a result, the phenolic group's oxygen serves as a covalent connection that connects the metal ions to the ligands under study.

The broad band in the IR spectra of the Cu (II) and Ru (II) metal complexes can be attributed to the water molecules' (OH) groups, which are involved in the production of the complexes. For the complexes of Cu (II) and Ru (II), a wide band was visible at 3303 and 3315 cm-1, respectively. This can be attributed to the vibrations of the N-H stretching. In the complexes, new bands that were not seen in the ligand were seen. Stretching frequencies of (M-O) were assigned to the bands at 609 cm-1 and 690 cm-1, whereas stretching frequencies of (M-N) were given to the bands at 475 cm-1 and 490 cm-1, respectively.

3.3 NMR Spectrum of VP Ligand and its Metal complexes:

The ^{1}H NMR spectra of ligand and metal complexes in DMSO-d6 as solvent were given in Fig.4, 5 and6. The chemical shift values of the ligand and metal complexes were shown in Table-3.

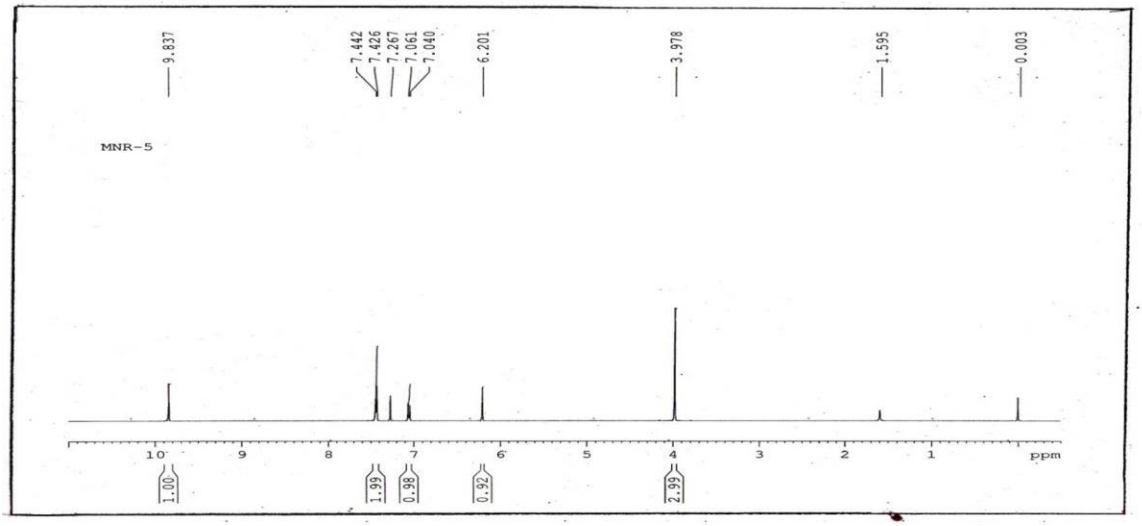


Fig-4: NMR Spectrum of VP

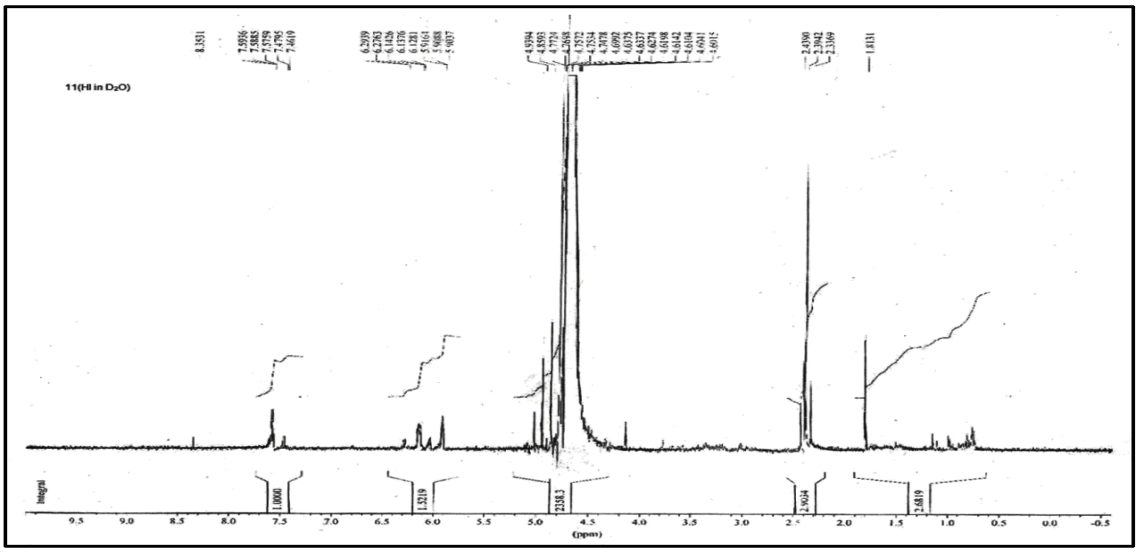


Fig-5: NMR Spectrum of Cu (VP) $_2$ complex

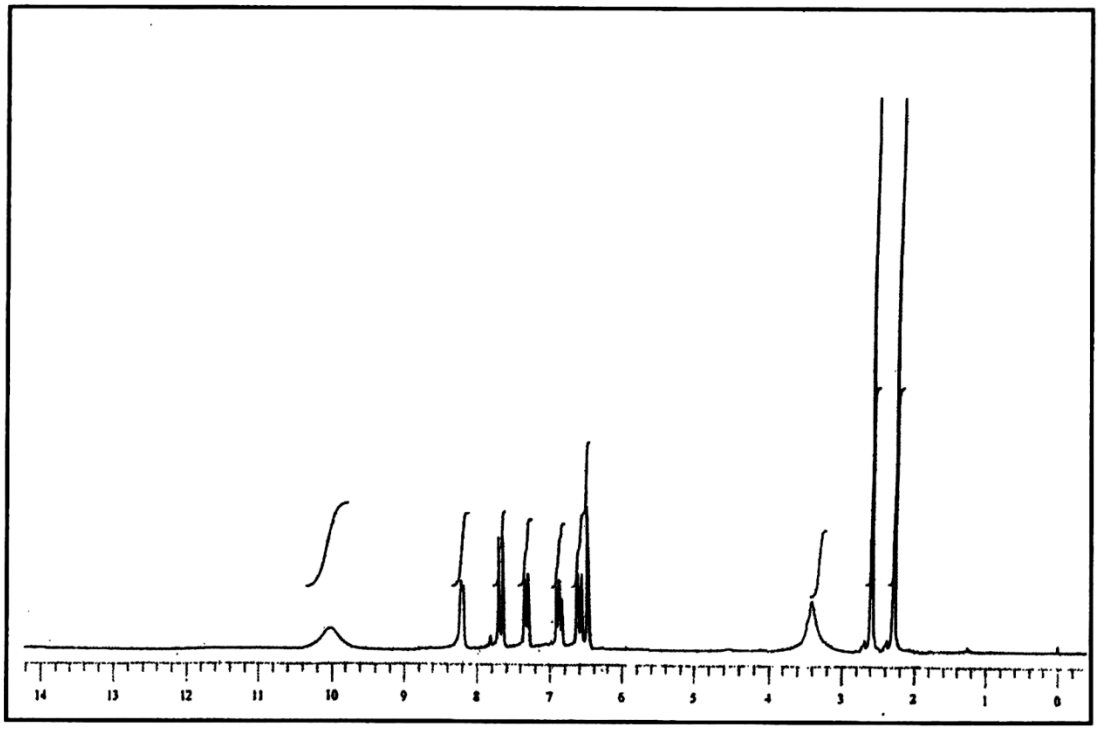


Fig-6: NMR Spectrum of Ru (VP) $_2$ complex

Table-3: ^{1}H NMR Spectrum of the ligands and its metal complexes in DMSO-d6 in ppm

Compound	**H-C=N**	**Ar-H**	**CH_2**	**Ar-OH**	**N-H**	**H_2O-OH**
VP	6.2	7.04-7.44	1.595	5.71	9.8	–
VP-Cu	6.5	6.39-7.66	1.65	7.28	10.1	5.05
VP-Ru	6.7	6.50-7.50	1.58	7.2	9.8	4.60

Ligand exhibits a singlet at 6.2 ppm 21, which is caused by protons bound to the Schiff base group, as seen in Table 3. This band was moved to the low field areas of 6.5 ppm and 6.7 ppm for the Cu (II) and Ru (II) complexes, respectively, during complexation. The deshielding of the azomethine proton on coordination through the nitrogen atom of the azomethine group is indicated by this down field shift. Methylene protons create a singlet in the region of 1.595ppm, while the aromatic ring protons form a multiplet in the range of 7.04–7.44ppm. The singlet caused by the methelene protons in the cyclohexane ring ligand, which was initially discovered at 1.595 ppm, is now found at 1.65 ppm for the Cu complex .At 7.28 ppm, a signal caused by the para position of the phenolic group's OH proton became visible. The shift in the multiplet from 6.37 to 6.41 ppm for the ligand's aromatic protons to 6.39 to 7.66 ppm for the copper complex may be the result of ring electrons wandering in the direction of the metal ion. In the case of the Cu (II) complex, a new signal is seen as a singlet at 5.05 ppm that denotes the existence of water molecules coordinated to

the metal atom. The signal in the ligand owing to the N-H proton is moved to 10.1 ppm for the Cu complex. The multiplet associated with the aromatic C-H protons of the phenyl ring in the area 6.50–7.50 ppm for the Ru complex may be the result of a ring of electrons migrating in the direction of the metal ion. In the instance of the Ru complex, a new signal is seen as a singlet at 4.60 ppm, suggesting the existence of water molecules coordinated to the metal atom. a signal from an N-H proton for the Ru complex was detected at 9.8 ppm.

3.4 Conductivity measurements:

The molar conductance of complexes in DMF (~10-3 M) was determined at 27+20C using Systronic 303 direct reading conductivity bridge. A known amount of solid complexes is transferred into 25ml standard flask and dissolved in dimethyl formamide (DMF). The content complies with DMF standards. A 100ml beaker that is clean, dry, and empty is used to hold the complicated solution. These residual metal complexes' molar conductance values are listed in Table 4.

Table-4: Conductance data for Metal-2, 4 DHAPP Complexes: Cell constant: 1.00

S.No.	Metal Complex	Conductance Ohm^{-1}	Specific Conductance Ohm^{-1} cm^{-1}	Molar Conductance Ohm^{-1} cm2 mol^{-1}
1.	$Cu(VP)_2$	0.00021 x 10^{-3}	0.00021 x 10^{-3}	21
2.	$Ru(VP)_2$	0.00020 x 10^{-3}	0.00020 x 10^{-3}	20

Table 4 shows that the complexes' molar conductances were less than 25 Ohm-1 cm2 mol-1, demonstrating their non-electrolytic character.

3.5 Electronic spectra:

The transitions in UV-visible electromagnetic radiation are connected to the molecule under study's electrical energy levels. On a Thermo SpectronicHeylosa spectrophotometer, the electronic spectra were captured. The transition metal ions can be found in many structural settings. The electrical structures are incredibly diverse as a result. UV-visible spectroscopy was used to identify the electrical structures.

Table-5: Electronic spectral data

Compound	**λ_{max} of compound**
VP	245
VP-Cu	321
VP-Ru	341

The transition for the ligand happened at 245 nm, as shown in Table.5. However, new bands at 321 nm and 341 nm, respectively, corresponding to the transitional charge transfer from the ligand to the various metal ions, emerged upon complexation with the various metal ions like Cu and Ru. Bands for two compounds that appeared in the 321-341 nm range are attributed to charge transfer transitions (L-M). The octahedral structure for the Cu and teraheradal structure for Ru complexes is suggested in light of the findings.

3.6 Magnetic susceptibility measurements of copper (II) and Ruthenium (II) complexes:

Data on an EG and G-155 magnetometer were recorded on magnetic susceptibility. Before being inserted into the magneto meter, the powdered samples of the compounds were packed in capsules and preserved in a glove box with an inert atmosphere. Using a palladium reference provided via quantum design, the calibration was performed at 2980 K. At room temperature, the susceptibility value's independence from the applied field was examined. Vibrating sample magnetometer VSM-155 for use in practical research, with fields of 0.3 to 0.8 T. The saturated moment of 99.999% highly pure nickel is used to calibrate the VSM. The material is finally pulverized into a powder, typically weighing 50 mg, and deposited in a homogenous, uniform magnetic field. When sinusoidal motion is induced in the sample. Using Pascal's constants, the output values are adjusted to account for the sample holder's diamagnetism as well as the underlying diamagnetism of the ligand's component atoms. Using the moment captured at various field intensities, Bohr magneton μ_{eff} may be calculated.

$$\mu_{eff} = 2.84 \quad \frac{\sqrt{\text{Magnetic moment} \times \text{molecular weight} \times T}}{\sqrt{\text{Weight sample} \times \text{magnetic field strength}}}$$

The values of each complex's effective magnetic moment are shown in Table 7. At ambient temperature, the octahedral complex has a sizable orbital contribution and effective magnetic moments.

Table-7: Magnetic moments of cupper and Ruthenium

S.No.	Metal Complexes	Effect. In B.M.	
		Theoretical	Observed
1.	$Cu(VP)_2$	4.90	4.80
2.	$Ru(VP)_2$	5.20	5.21

Table 7 shows that. The current Cu(VP)2 complex has a magnetic moment of 4.80 B.M., which is less than the spin-only value and exhibits reduced Para magnetism, suggesting the creation of a low-spin complex with octahedral geometry. The current Ru(VP)2 complex has a magnetic moment of 5.21 B.M., which is higher than the spin-only value and suggests the creation of a high-spin complex with a tetrahedral structure.

3.7 Thermal analysis:

In the thermal analysis centre IICT Hyderabad, thermo gravimetric analyses of the metal complexes were performed utilising the METTLER TOLEDO STAR System. All reasonable measures were made to ensure that the conditions were ideal for conducting the Thermo gravimetric analysis studies.

Although many techniques are employed in thermoanalytical analysis, differential thermal analysis (DTA) and gravimetric analysis (TGA) are the most effective techniques utilised in coordination chemistry. the information collected in the form of constantly recorded curves that are comparable to thermal spectra.

These thermograms describe a system, whether it has one or more components, according to how its thermodynamic properties change with temperature. A system's weight may fluctuate during a thermo gravimetric study as the temperature is raised at a predetermined rate. In differential thermal analysis, the temperature difference between the sample under study and a thermally inert reference chemical is used to measure changes in heat content; In this way, the endo and exo thermal bands and peaks that occur in the thermo grams are used to detect enthalpy changes, such as melting and chemical changes, and thermo gravimetric analysis is used to determine the related weight changes. These complexes are subjected to thermal investigations in order to determine their stability during thermal decomposition as well as the various byproducts that result from it that have novel catalytic capabilities. In Table.8, thermo analytical information about metal complexes was provided. Figures 8 and 9 displayed representative thermo grams.

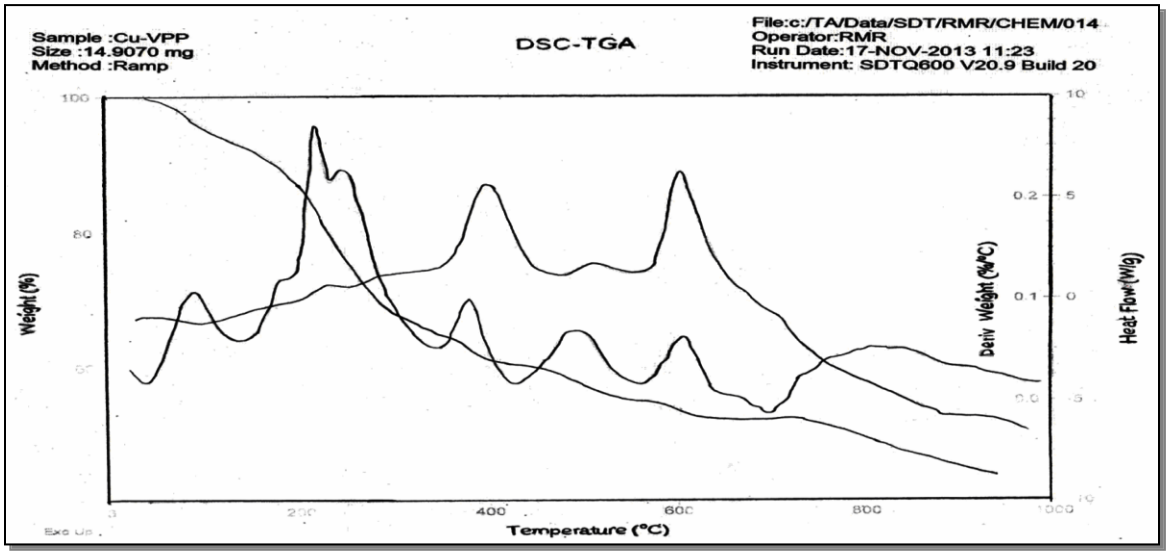


Fig-8: TG & DTA Spectrum of Cu $(VP)_2$ complex

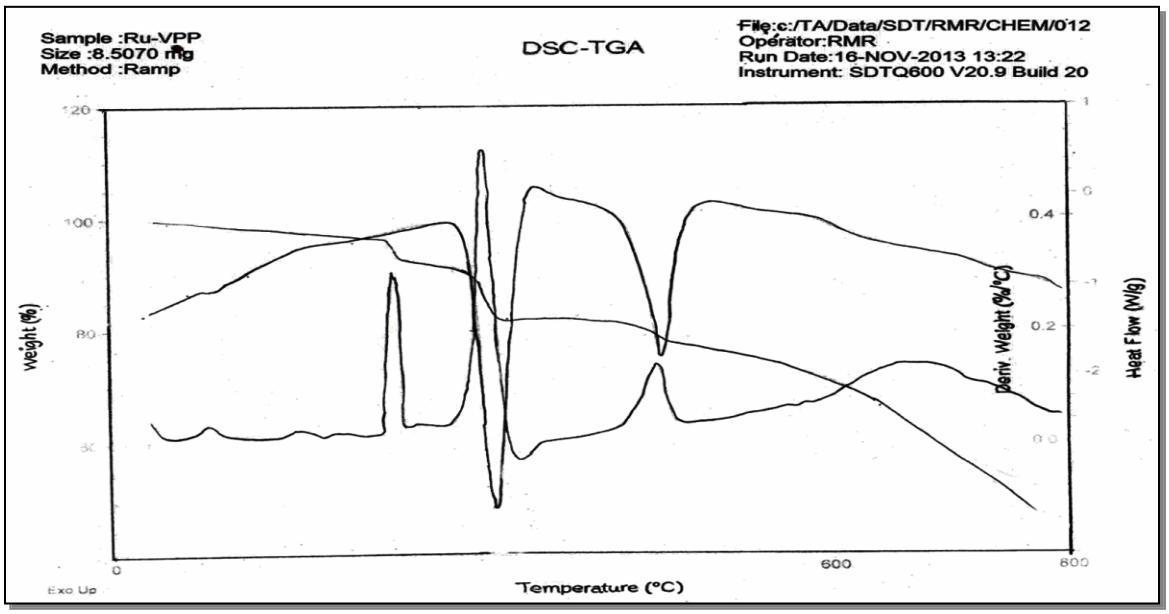


Fig-9: TG & DTA spectrum of Ru $(VP)_2$ complex

3.8 Study of VP and its Cu (II) and Ru (II)metal complexes by TGA-DTA spectra:

In Table.8, thermoanalytical information about metal complexes was provided. The Cu complexes are thermally stable up to 90^0C, as shown in Table 8. The two lattice water molecules are lost during the complex's initial breakdown stage, which takes place between 90 and 190^0 C, resulting in an anhydrous complex27. The stable intermediate, which was generated between 200 and 290 ^{0}C28-29, is the second breakdown stage with two endothermic reactions. At a high temperature, specifically above 550^0C, exothermic decomposition expresses to provide the appropriate metal oxides as the final decomposition product. In a nitrogen atmosphere, the complexes' breakdown behavior was observed.

Table 8 : Thermal analytical data of the Ligand and their metal complexes

Complex X=H_2O	Temperature range in °C	Probable assignment	Mass loss (%)	Total mass loss (%)
CuL_2X_2 L=$C_{18}H_{23}N_3SO_2$	90-190	Loss of $2H_2O$ molecules	11.14	84.07
	200-290	Decomposition of L	66.11	
	Above-550	Formation of CuO	7.22	
RuL_2X_2 L=$C_{18}H_{23}N_3SO_2$	230-240	Loss of $2H_2O$ molecules	6.78	65.13
	290-460	Decomposition of L	52.11	
	Above-660	Formation of RuO	6.24	

The Ru compounds are thermally stable up to 230^0C, as shown in Table 8. The two lattice water molecules are lost during the complex's initial step of disintegration, which occurs during exothermic dehydration, between 230 and 240^0 degrees Celsius to produce anhydrous complexes. Stable intermediate is the second breakdown stage that has two exothermic reactions and forms between 290 and 460^0 degrees Celsius. At a high temperature, specifically above 660^0C, exothermic decomposition expresses to provide the appropriate metal oxides as the final decomposition product.

In a nitrogen atmosphere, the complexes' breakdown behavior was observed. The appropriate metal oxides were produced as stable byproducts at high temperatures. Comparisons were made between all experimental percentage mass losses and computed weights. Thermal measurements demonstrated that the complexes' stability order was Cu (II)> Ru (II).

DNA Binding studies of newly synthesized Metal complexes:

Present Studies:

In the current study, DNA interactions were investigated using freshly synthesised Cu and Ru VP complexes, and the results are shown below.

Method Employed

UV-visible spectral studies were used to keep track of how each freshly manufactured complex interacted with the others. The most effective method for examining how compounds interact with DNA is UV-visible spectroscopy. Studies on DNA drug interactions are crucial for a number of reasons. If a metal complex serves as a DNA probe, binding to DNA should alter its spectroscopic characteristics. These changes in spectroscopic characteristics offer great information about DNA structure and conformation. The unique distinguishing characteristics of DNA interactions include hypochromicity in absorption, the formation of isobestic points, a red-shift in the absorption maxima, and an increase in luminescence. In some situations, adding calf-thymus DNA to the complexes repeatedly caused a hyperchromic shift to be seen. The fact that the absorbance changed when DNA was added suggests that the complexes had bound to the DNA.

Chemical required: Calf thymus DNA, Buffer solution, DMSO, Newly synthesized complexes
Maintenance and Sterility:

Prior to usage, all necessary equipment was sanitized, and every conceivable measure was taken to prevent contamination throughout the procedure..

Procedure:

DNA from the calf thymus was preserved as a disodium salt at 5°C. DNA dissolved in a buffer of 45 mM NaCl/5 mM Tris HC1 (pH 7.1) in water produced UV absorbance at 260 and 280 nm that was 1:9. The ratio of A260/A280 shows that the DNA is adequately free of protein [28]. Following 1:100 dilutions, the coefficient of DNA at 260 nm (6600 Cm-1) was used to calculate the concentration.

By dissolving in DMSO and dilution appropriately with the appropriate buffer to the requisite concentrations for all the studies, concentrated stock solutions of the complexes were created. Absorption spectra in the 240–400 range were captured. The ranges that saw the greatest change in absorption after DNA insertion were chosen.

Experimental studies:

Complexes' absorption spectra in the presence and absence of CT-DNA were contrasted. The spectra of complexes revealed a sharp drop (hypochromicity) in intensity together with a shift in the absorption maxima towards longer (red-shift) wavelengths in the presence of increasing amounts of DNA. Due to the strong stacking interaction between the aromatic chromophore of the ligand and DNA base pairs, the binding of intercalative molecules to DNA has been well described by large hypochromism and significant red-shift, with the extent of hypochromism and red shift typically consistent with the strength of intercalative interaction.

The intrinsic binding constants Kb of the complexes for binding with CT DNA were obtained by solving the equation in order to enable quantitative comparison of the DNA binding affinities. $[DNA]/(\varepsilon_a - \varepsilon_f) = [DNA] / (\varepsilon_b - \varepsilon_f) + 1\ K_b\ (\varepsilon_b - \varepsilon_f)$

Where [DNA] is the concentration of DNA in base–pairs, ε_a is the apparent extinction coefficient obtained by calculating A_{obs} / [complex], ε_f corresponds to the extinction coefficient of the complex in its free form and ε_b refers to the extinction coefficient of the complex in the bound form. Each set of data, when fitted to the above equation, gave a straight line with a slope of $1/ (\varepsilon_a - \varepsilon_f)$ and a y–intercept of $1/K_b\ (\varepsilon_b - \varepsilon_f)$ and K_b was determined from the ratio of the slope to intercept. The intrinsic binding constants K_b, obtained for the complexes.

Analysis:

The table below contains the electronic absorption spectral data after CT-DNA addition along with binding constants. In IX.2, it became clear that these complexes bind DNA with a high degree of affinity; their estimated binding constants are in the vicinity of 105–106 M-1. This might be caused by the pyridine ring's pi-stacking in the ligand moiety, as seen in Figures IX.1 to IX.18 and in Table IX.2.

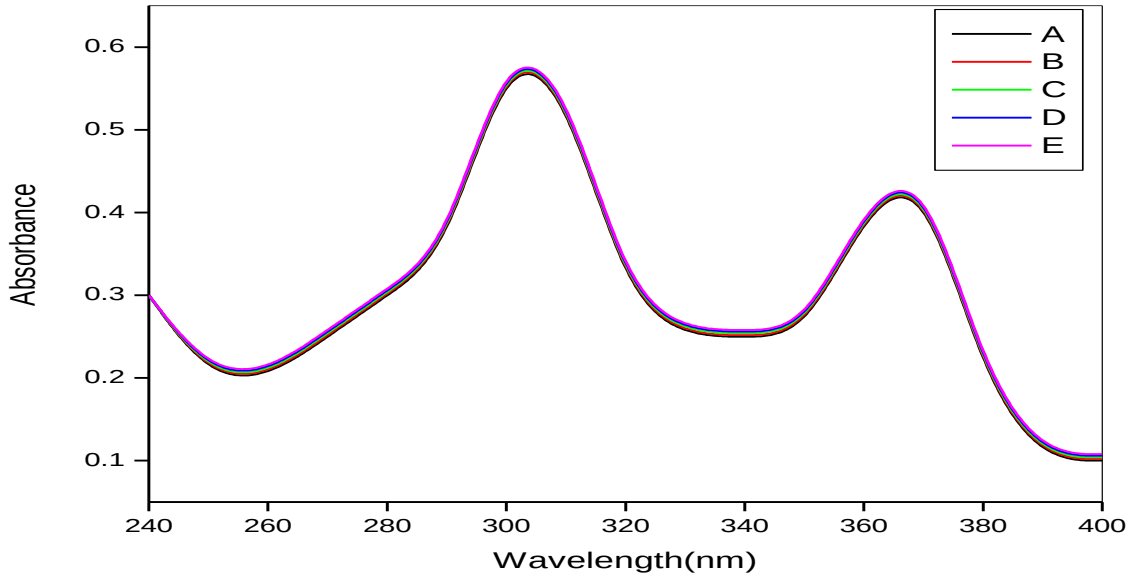


Fig.IX.9.DNA Binding interaction of Cu [VP]

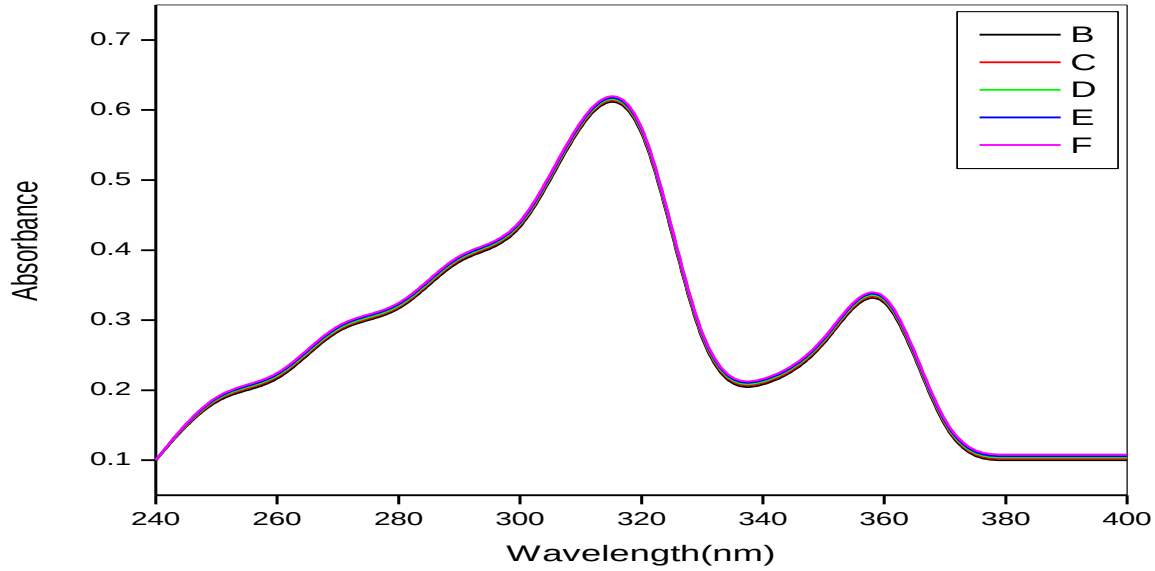


Fig.IX.9.DNA Binding interaction of Cu [VP]

Table.IX.2. DNA binding constants of metal complexes

S.No	Complex (X= H_2O)	λmax nm	Δλ nm	H%	$K_b(M^{-1})$

		Free	Bound			
1	[Cu $(VP)_2X_2$]	302	305	3	6.65	$2.03 \times l0^5$
2	[$Ru(VP)_2 X_2$]	314	317	3	6.33	$3.33\times l0^5$

It is clear from Table 9 that these complexes bind DNA with a high degree of affinity, and their estimated binding constants are in the neighbourhood of 105-106 M-1. This might be as a result of the pyridine ring in the ligand moiety pi-stacking.

5. CONCLUSION

The stoichiometry of the complexes, as determined by elemental analysis and Conductometric measurements, is confirmed by the aforementioned findings to be 1:2 [M: L]. The ligand appears to behave as a bidentate and coordinates to the central metal ion via the azomethine nitrogen and phenolic -OH group, according to IR spectra. The results of NMR spectrum research have further supported this. The complexes are thus discovered to have antibacterial capabilities in comparison to the respective ligand and the parent drug on the basis of the aforementioned physicochemical and spectral analyses, which in some ways justifies the goal of the research endeavour. The current work will be expanded upon to include the synthesis of metal complexes with the use of other biologically active metals and the assessment of their biological activity. The metal complexes are all thermally stable and conduct electricity. As a result, no one technique can anticipate the complexes' final architecture independently.

6. AUTHOR CONTRIBUTION STATEMENT

T. Noorjahan Begum came up with the idea and collected the information for this study. Dr. K. Aruna compiled the biological activity data, and the required suggestions were made for the manuscript's design. Each author contributed to the final manuscript and discussed the technique and findings.

7. ACKNOWLEDGEMENT

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8. CONFLICT OF INTEREST

Conflict of interest declared none

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