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Biologically Potent Complexes Derived from 1,3,4 Thiazole Derivative

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Abstract

A new Schiff base ligand, and its Zn (II), Cu(II), Co (II), complexes were synthesised and characterized by various spectroscopic techniques. Complexes were derived from condensation of heterocyclic aldehyde, acetyl acetone and substituted thiazole. New complexes were characterized by NMR, Infrared spectra, elemental analysis and magnetic moment reveal that metal ion is coordinated in tridentate nature. It was also studied using UV-Visible, TGA and XRD. TGA analysis used for thermodynamic and kinetic study. The antimicrobial activity of the ligand and its complexes was screened against a variety of pathogenic bacteria and fungi including *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans*. The data obtained revealed that the metal ion in the complexes enhanced the antimicrobial activity compared to the free ligand.

Keywords: Zn (II) complex, NMR, IR, TGA, Antimicrobial activity

1. Introduction

Researchers are continuing to explore a safe and effective metal based biologically active compound as potential antitumor drug which is of great urgency to overcome the drug-induced cellular resistance and the efficacy of each drug against certain cancers. The treatment involves the administration of multiple drugs as it is clear that chemotherapy leads to the development of resistance. As the first generation of the platinum based antitumor agent, cisplatin is widely used testicular, small lung cell and ovarian cancers [1-4]. In spite of its success, the clinical application of cisplatin is greatly restricted by its toxicity, low water-solubility, instinct and acquired drug resistance [5, 6]. Thousands of platinum compounds have been synthesized and screened for their antitumor activity, but little success has been achieved so far in finding novel platinum-based drugs active towards cisplatin resistant/refractory tumors [7, 8]. Non-platinum active compounds are likely to have mechanism of action, bio distribution and toxicity which are different from those of platinum drugs and might be effective against human cancers that are poor chemosensitive or have become resistant to conventional platinum drugs. Recently, there has been tremendous interest in studies related to the interaction of transition metal ions with nucleic acid because of their relevance in the development of new reagents for biotechnology and medicine [11]. These studies are also important to understand the toxicity of drugs containing metal ions [12]. β -Diketiminates are versatile ligand systems which have been known to form complexes with almost every metal ion. Earlier reports indicate that the attempts to prepare highly symmetrical and conjugated macrocyclic systems derived

from β -diketones condensed with organic amines have not led to the desired results. Condensation of the active methylene group of the β -diketone with an aldehydic group gives a non-enolisable Knoevenagel condensate, which can effectively react with amines to form Schiff bases [14]. Metal complexes of β -diketone derivatives have played an important role in coordination chemistry [15-17] and have been widely used in various aspects of industries, such as organic electroluminescent technology, luminescent materials and sensors for bioinorganic applications [18-20]. With an aim to develop cisplatin type anti-tumor response of β -diketone, different aromatic aldehydes are introduced in active methylene group by Knoevenagel condensation. β -Diketone derived complexes show antimicrobial, antimalarial and antitumorous activities, antioxidant, insecticidal activity. Recently transition metal complexes have received considerable interest in nucleic acid chemistry because of their chelating nature. The coordination behavior of β -diketimine also has significant influences in the relative stabilities of the Schiff base complexes as well as their use in biomedicine [21-24]. Thus, scientists are now engaged to explore the transition metal based complexes. Hence, the higher degree of conjugated versatile ligand systems of the Knoevenagel condensate β -diketimine as Schiff bases containing electron releasing/electron withdrawing groups and their low molecular weight copper(II) and zinc(II) complexes have been synthesized. It is therefore of interest to carryout investigations on model compounds to understand how a ligand environment could affect the redox properties of the central metal and thereby, the spectral properties and also

interested to explore the DNA binding and DNA cleavage activity of synthesized complexes.

2. Experimental

2.1. Materials

The standard quality chemicals were used in the preparation of Schiff bases and their metal complexes. The purity of chemicals was checked by melting point, boiling point, thin layer chromatography etc. Thiosemicarbazide Sigma Aldrich (AR), Acetoacetone Sigma Aldrich, Furfural Aldehyde Sigma Aldrich (AR), and metal salts Sigma Aldrich (AR) chemicals were used in the preparation of 2-amino-(5-substituted aryl) 1,3,4-thiadiazole, Schiff bases and their metal complexes.

All the solvents of HPLC grade were used for the preparation of Schiff bases and their metal complexes except for ethanol and methanol.

2.2. Physical Measurements

The colors of the all ligands are yellow to buff in color. Obtained ligands were characterized by various analytical techniques. The melting point was recorded on Cotech digital melting point apparatus. Elemental C, H, N, and S analysis was carried out on a Fison EA1108 analyzer. NMR spectra recorded on a Bruker 400 MHz FT-NMR instrument using solvent DMSO- d_6 . The UV-vis spectra of the ligand and its metal complex were recorded in DMSO using V-530 UV-vis Spectrophotometer (Path-length: 1 cm). The IR spectra were recorded using Perkin-Elmer FT-IR spectrometer (RX-1) in the range 400-4000 cm^{-1} using KBr pallets.

2.3. Preparation of 2-amino-5-(Substituted phenyl)1,3,4-thiadiazole

The commercially purchased all reagents and solvents of analytical grade were used without any purification. 2-amino-5-(substituted phenyl)1,3,4-thiadiazole was prepared 5-7 in laboratory by alkanoylation of thiosemicarbazide followed by dehydration. The reaction progress was screened by thin layer chromatography (TLC). Molecular structure of derived moiety is as shown in figure 1.

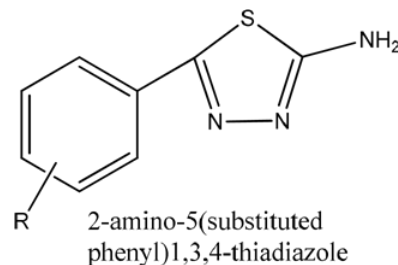


Fig 1: 2-amino-5-(substituted phenyl)1,3,4-thiadiazole

2.4. Synthesis of Schiff base Ligand

A round bottom flask charged with substituted aromatic aldehyde, aceto acetone (10mmol) each and along with 10 mole % solid supported Morpholine in methanol (20ml) are refluxed at 70 $^{\circ}C$ by for 3 hours. The progress of reaction was monitored by using pet ether and ethyl acetate system (7:3 v/v). After that 2-amino-5-(substituted aryl) thiadiazole (10mmol) added and continued refluxing for 1 hour. The progress of reaction was monitored by benzene, acetone system (7:3 v/v). The reaction mixture was poured on flaks of ice. The obtained solid yellow precipitate of expected ligand was filtered, dried and recrystallized in methanol.

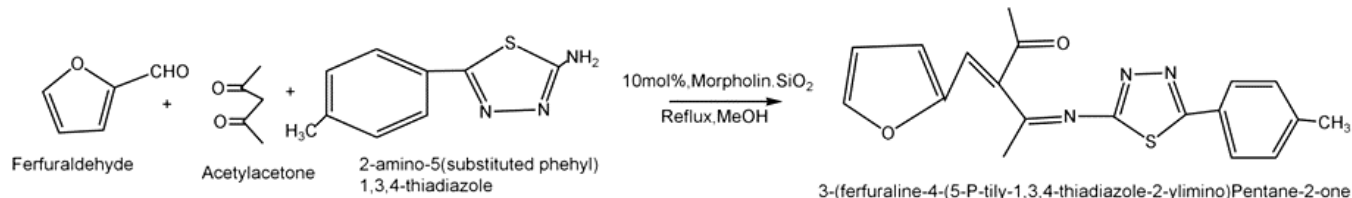


Fig 2:

2.5. Synthesis of Metal Complex

The metal ion solution was refluxed with ligand and metal salts (1:1) at 85 $^{\circ}C$ for 1 hour in methanol and morpholine as a catalyst. The formation of the expected complex was monitored by TLC. The obtained complex was dissolved in DMF and filtered. The filtrate was then concentrated under reduced pressure to afford shiny redish black complex used for various analytical tool screening. On analytical data and color of complex, it is confirmed that the sulphur taking part in coordination on these data the expected structure of the complex will be as shown in figure 3.

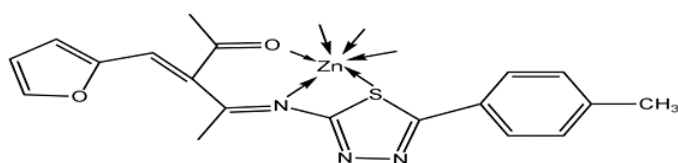


Fig 3

3. Result and Discussion

The synthesized ligand and its Zn (II) complex is represented in figure 1 and 2 respectively.

3.1. Characterization of Ligand and Complex

The synthesized ligand and its corresponding metal complex have been screened by various analytical and spectroscopic techniques such as IR, 1H NMR, UV-vis, Molar conductance, etc. The synthesized ligand and its corresponding metal complex are moisture insensitive, air stable and soluble in DMSO. The analytical data are in good agreement with calculated values and are consistent with formation of mononuclear complex having metal to ligand ratio 1:1.

3.2. Physical Observation and Molar Conductance

The color of synthesized ligand was yellow and icoomplex was redish black. Physical parameters of ligand and metal complex are shown in table-1. The synthesized Zn (II) complex was dissolved in DMSO solvent and molar conductance of 10^{-3} solution was measured at room temperature. The value of molar conductance indicates that the metal complex is non-electrolyte⁸.

3.3. NMR Spectra

The 1H NMR spectra of the synthesized ligand, 3-(Ferfuraline-4-(5-P-tilyl-1,3,4 thiadiazole-2-ylimino)Pentane-

2-oneImine is shown in figure 4. It showed a singlet at 9.17 ppm due to azomethine proton (-CH=N-). The signal at 10.29 ppm is because of hydroxyl proton (-OH).

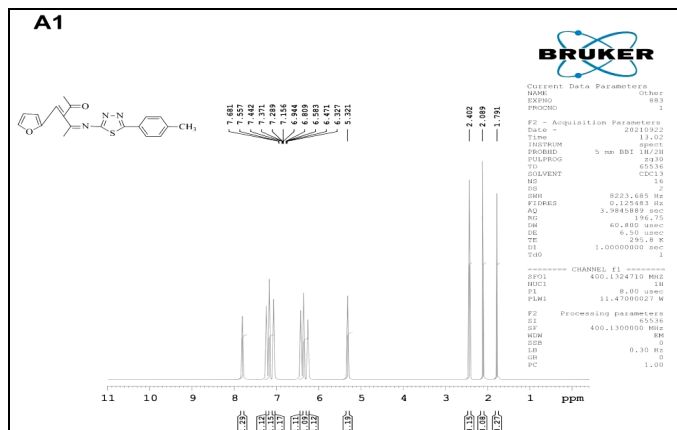


Fig 4

3.4. Infrared Spectra

The metal ion and ligand coordination has been studied using IR data of ligand and its Zn(II) complex. The IR spectra of synthesized ligand and its Zn(II) complex are shown in figure 4a and 4b respectively. The shifts in the stretching frequencies of Zn(II) complex compared with free ligand. The ligand shows a characteristic strong band at 1708 cm⁻¹ due to ν(-C=O) this band shift to 1585 cm⁻¹ in the complex, indicating participation of oxygen in complexation. A band at 1633 cm⁻¹ due to ν(-C=N) of ligand this band shift to 1514 cm⁻¹ in the complex, indicating participation of nitrogen in complexation. A band at 945 cm⁻¹ due to ν(-C-S) of ligand this band shift to 883 cm⁻¹ in the complex, indicating participation of sulphur in complexation. Therefore from the above data and elemental analysis together indicates that the synthesized imines is tridentate coordinate to Zn(II) with N, O and S. The complex possibly has tetrahedral geometry due to d¹⁰ configuration of Zn (II) ion⁹.

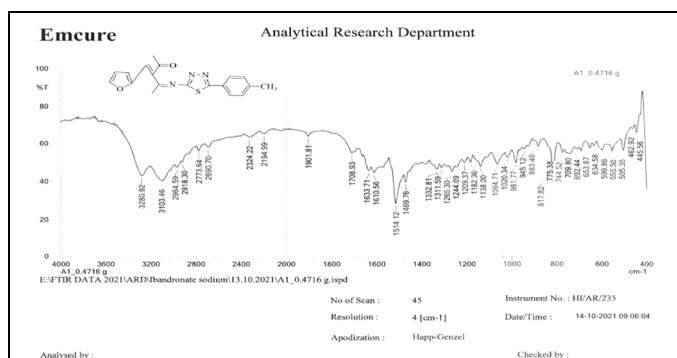


Fig 5

Thermogravimetric Analysis

The synthesized metal complex ((C₁₉H₁₇N₃O₂SZn)) was analyzed through TGA with heating rate 20°C min⁻¹. The TG analysis predicts the nature of volatile compounds produced while heating^{10, 11}. In the first phase temperature range 50°C to 200°C weight loss was found due to dehydration of the complex. In the further heating weight loss of complex found gradually due to combustion of moieties present out of sphere

and inner sphere. It was confirmed that above temperature 800°C the final product occurred ZnO. It predicts the calcination temperature was 800°C. The TGA curves are shown in figure-6 using this curves the thermodynamic parameters are calculated.

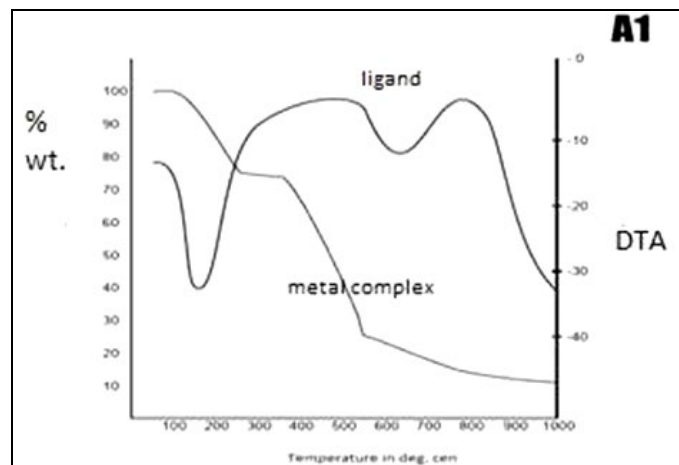


Fig 6

3.4.1. Calculation of Kinetic and Thermodynamic Parameters from TGA Data

The kinetic and thermodynamic parameters were calculated by considering the decomposition thermal reaction as first order reaction. Rate equation of first order reaction is shown in equation 1.

$$- \ln(1 - x) = kt \tag{1}$$

Where

$$x = \frac{w_i - w_t}{w_i - w_f} \tag{2}$$

And w_i is the initial weight, w_t of sample at particular time t and w_f is final weight. Equation (1) can be written as

$$\ln(1 - x) = -kt \tag{3}$$

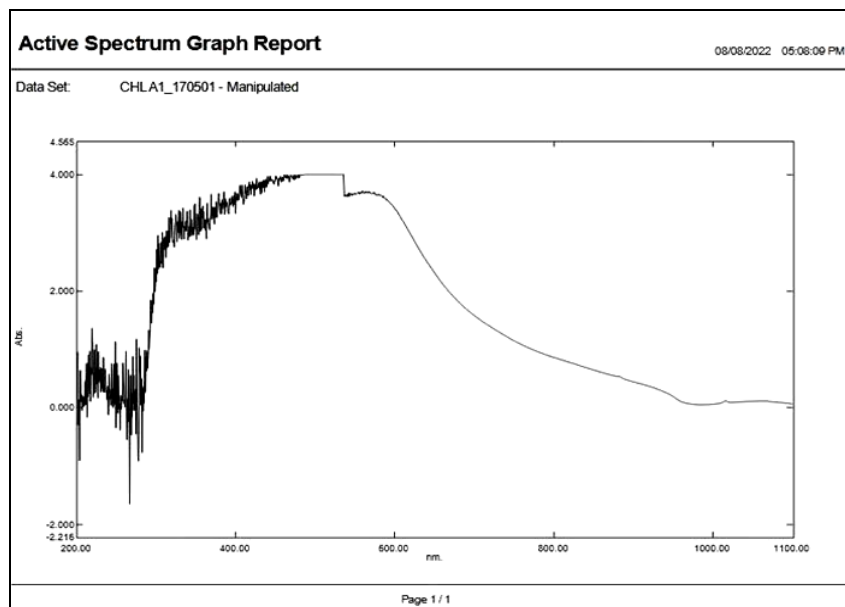
Using equation (3) graph was plotted; the value of slope of obtained straight line is equal to rate constant (k). The half-life period (t_{1/2}) was determined by using equation (4).

$$t_{1/2} = \frac{\ln 2}{k} \tag{4}$$

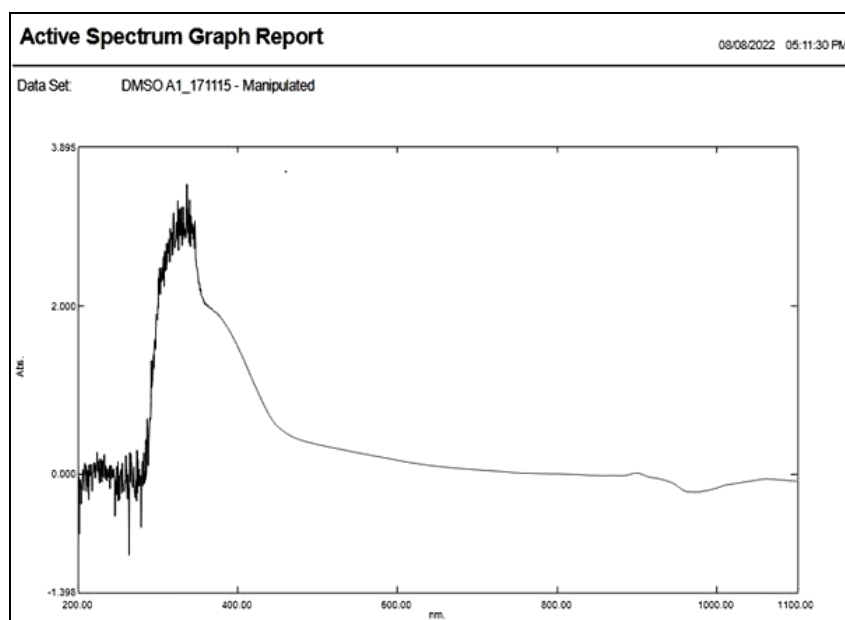
The thermodynamic parameters were calculated by using basic thermodynamic equations. Both parameters are shown in Table-2. On the TGA data, it is confirmed that the decomposition of metal complex reaction is endothermic in nature. The positive values of ΔH and ΔG and negative value of ΔS reveals that the reaction is non-spontaneous.

3.5. Electronic Spectra

The UV-Vis absorption spectra of synthesized ligand in chloroform and its Zn(II) metal complex were recorded in DMSO (10⁻⁵M) at room temperature and are shown in Figure-7a and 7b. The electronic absorption spectrum of imines contain three bands at 380 nm, 450 nm and 480.



(a)



(b)

Fig 7(a, b)

The electronics spectrum of the ligand shows the absorption maxima $n \rightarrow \pi^*$ Transition at 10682 cm^{-1} and $\pi \rightarrow \pi^*$ Transition at 9960 cm^{-1} the latter being more intense bands in the respective of complex, the $n \rightarrow \pi^*$ band is blue shifted to 11135 cm^{-1} . In the low and high energy $\pi \rightarrow \pi^*$ band also blue shifted 10626 cm^{-1} respectively. The band observed in UV visible region with absorption maximum at 28751 and 27027 cm^{-1} . In all complexes may be conjugated to strong ligand to metal charge transfer transition. 4 4 4 4

$T_{1g}(F) \rightarrow T_{2g}(F)$ & $T_{1g}(F) \rightarrow T_{1g}(F)$ with high spin octahedral geometry (Chohan, 2001). On the basis of all these complexes shows octahedral geometry in which ligand act as trident it and stability is found in complexes.

Powder XRD diffractogram of Zn(II) complex were recorded in the range $22-80^\circ$ at wavelength 1.540 \AA . The diffractogram and associated data depict the 2θ value of each peak, relative intensity and inter planer spacing major relaxes were used to determine corresponding interplaner distance. The X-ray diffraction pattern of Zn(II) Complex with respect to major peaks having relative intensity greater than 10% has

been indexed by using computer program. Miller indices, unit cell parameters and unit cell volume were also obtained from above indexing method. The unit cell of Zn(II) complex yield value of lattice constants $a=11.2235$, $b=7.5331$, $c=5.0391$ and unit cell volume 425.44 \AA^3 . Also the condition as $a \neq b \neq c$ and $\alpha = \gamma = 90^\circ \neq \beta$ for a sample to be monoclinic were tested and found satisfactory. Hence Zn(II) complex have monoclinic crystal system.

3.6. Antimicrobial Activity

The *in vitro* antifungal and anti-microbial activities¹³ of synthesized Schiff bases have been studied by disc diffusion method. The antifungal and antimicrobial activities were done at $100 \mu\text{g/mL}$ concentration in chloroform solvent using four fungal and bacterial strains. *Aspergillus Niger*, *Candida albicans*, *Chrysogenum*, *Rhizopus* and *Shigella*, *Staphylococcus aureus*, *Escherichia coli*, *Bacillus megaterium* by minimum inhibitory concentration method (MIC). These fungal and bacterial strains were incubated for 24 h at 28°C . Standard fluconazole and streptomycin drugs were used for

comparison under similar condition. Activity was determined by measuring the diameter of the zone of inhibition (mm). It was observed that, the ligands are more active against the fungal and bacterial strains *Aspergillus niger* and *Staphylococcus aureus* as compare to other fungal and bacterial strains. The metal complex of the ligand shows moderate antifungal and antimicrobial activity against these four fungal and bacterial strains.

The Zn (II) complex powder XRD diffractogram was recorded at wavelength 1.540 \AA , with a range of $22-80^\circ$. The 2θ value of each peak is shown in the diffractogram and related data, and major relaxes in the interplaner spacing and relative intensity were utilized to calculate the appropriate interplaner distance. Using a computer program, the Zn (II) Complex's X-ray diffraction pattern has been indexed with regard to main peaks that have relative intensities larger than 10%. From the aforesaid indexing method, Miller indices, unit cell characteristics, and unit cell volume were also derived. The lattice constants $a=11.2235$, $b=7.5331$, $c=$

5.0391 , and unit cell volume 425.44 \AA^3 produce the Zn (II) complex unit cell value. The requirements for a sample to be monoclinic, namely $a \neq b \neq c$ and $\alpha = \gamma = 90^\circ \neq \beta$, were also examined and found to be sufficient. Therefore Zn(II) complex have monoclinic crystal system.

The absorption peaks $n \rightarrow \pi^*$ Transition at 10682 cm^{-1} and $\pi \rightarrow \pi^*$ Transition at 9960 cm^{-1} are visible in the ligand's electronics spectrum. The $n \rightarrow \pi^*$ band is blue shifted to 11135 cm^{-1} , with the latter having more intense bands in the corresponding complex. Blue shifts of 10626 cm^{-1} were also seen in the low and high energy $\pi \rightarrow \pi^*$ band, respectively. The band, which has an absorption maximum at 28751 and 27027 cm^{-1} , was seen in the UV visible area. Conjugated to strong ligand to metal charge transfer transition is possible in all complexes.

With high spin octahedral geometry, $4T_{1g}(F) \rightarrow 4T_{2g}(F)$ & $4T_{1g}(F) \rightarrow 4T_{1g}(F)$ (Chohan, 2001). The octahedral geometry of all these complexes, where the ligand functions as a trident, indicates that stability exists in complexes.

Table 1: Melting Points, Elemental Analytical data (%) and m/z values of ligand and its Zn (II) complex

Compound	$\Lambda_m \Omega^{-1} \text{ mol}^{-1} \text{ cm}^{-1}$	Color	M.P. ($^\circ\text{C}$)	C	Elements (%)			S	m/z
					H	N	O		
C19H17N3O2S (A1)	--	Yellow	107	63.70	5.05	12.38	9.43	9.45	351
[Zn (A1)] (C19H17N3O2SZn)	15.14	Redish black	>250	55.5	4.89	9.71	7.39	7.41	432

Table 2: Kinetic and Thermodynamic parameters of [Zn (A1)]/(C19H17N3O2SZn)

Metal Complexes	Temp (K)	K (min^{-1})	t1/2 (min)	E_a (Jmol^{-1})	ΔH (Jmol^{-1})($\times 10^3$)	ΔS ($\text{Jmol}^{-1}\text{K}^{-1}$)	ΔG (Jmol^{-1})($\times 10^4$)
[Zn (A1)] (C19H17N3O2SZn)	623	0.3	2.31	2.4942	5.1821	-281.0401	18.02701

4. Conclusion

A novel 2,3,4-thiadiazole derivative containing Schiff bases & their complexes have been synthesized and characterized by various analytical tools the electronic and IR spectra indicate a square planner geometry of the complexes the DNA binding studies of ligands and their complexes you will reveal that the complexes shows higher binding ability than ligand towards DNA. The DNA cleavage activity of complexes is increased in presence of oxidant DNA cleavage is not inhibited indicates that hydroxyl radical is not involved in cleavage which shows the intermediate mode of binding. The antifungal and antibacterial activity of ligands and their complexes have been studied and the copper containing complexes shows significant activity than other metal containing complexes. The kinetic and thermodynamic parameter indicates that the reaction is first order behaviour

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