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The spectra result showed that the hydrazone Schiff base ligand undergoes keto-enoltautomerism forming a bidentated ligand (N, N) towards Zn+2 (II) ions. It is very interesting that on sides of the two hydrazone Schiff base ligands which coordinate to the Zn+2 ions, an additional two thiosemicarbazine moiety were also coordinated with Zn+2 ions in the crystalline powder, resulting in a hexa coordinated distorted octahedral Zn (II) complex.

Prof. (Dr.) Richa Kothari working as a Dean Projects & Patents in ITM University, Gwalior (M.P.).

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Synthesis, Characterization & Antibacterial activities

of Zn(II) complexes derived from Schiff base ligand

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Abstract –

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Keywords: Hydrazones, Zinc (II) complex, XRD, Molecular docking, Antibacterial activity

1. Introduction-

Schiff bases derived from an amino and carbonyl compound are an important class of ligands that coordinate to metal ions via azomethine nitrogen and have been studied extensively [1]. In azomethine derivatives, the C=N linkage is essential for biological activity, several azomethines were reported to possess remarkable antibacterial, antifungal, anticancer and diuretic activities [2]. Schiff bases have wide applications in food industry, dye industry, analytical chemistry, catalysis, fungicidal, agrochemical and biological activities[3].With the increasing incidence of deep mycosis, there has been increasing emphasis on the screening of new and more effective antimicrobial drugs with low toxicity. Schiff-base complexes are considered to be among the most important stereochemical models in main group and transition metal coordination chemistry due to their preparative accessibility and structural variety [4]. A considerable number of Schiff-base complexes have potential biological interest, being used as more or less successful models of biological compounds [5]. Not only have they played a seminal role in the development of modern coordination chemistry, but also they can also be found at key points in the development of inorganic biochemistry, catalysis and optical materials [6].

Lately, there has been a very successful interaction between inorganic chemistry and biology. Schiff bases and their complexes in medicinal chemistry are an essential class of compounds [7, 8]. Schiff bases play a crucial role in coordination chemistry, since they form stable metal complexes [9–18].

The role of coordination compounds in detoxification of heavy metals is a complex subject that involves cooperation between numerous scientific branches. The primary contribution of chemistry to this subject is to produce both models of coordination and complex formation constants between chelating agents and metal ions, in a parliamentary procedure to compare the power of the formed complexes with their properties. Column 12 metal complexes are typically attractive in view of their marked differences in chemical and biological behaviours.

Zn is the human body's second most abundant trace metal [19] and can catalyze over 300 enzymes, such as those responsible for the synthesis of DNA and RNA [20]. It is also physiologically essential for bone metabolism, collagen synthesis, the integrity of the immune system, anti-inflammatory actions, and defense versus free radicals [21]. Therefore, Zn(II) is better removed by novel methods away from classical coordination methods used in vivo.Nevertheless, cadmium is a very toxic metal ion that poses both human and animal health hazards. Its toxicity is done by its easy localization inside the liver and then by the binding of metallothionein, which eventually forms a complex and is transmitted into the blood stream to be lodged in the kidney.

The cause of Cd toxicity is the negative effect on cell enzyme systems that are the consequences of metallic ion substitution (mainly Zn^{2+}, Cu^{2+}, and Ca^{2+}) into metalloenzymes and its strong interaction with thiol groups [22]. Zinc (II) replacement with Cd(II) ion usually causes apoprotein catalysis to break down [23,24]. Thus, substances that can form stable chelates with Cd may be produced in a significant research field as they can be used as detoxifying compounds. Referable to the broad scope of pharmacological properties of thiosemicarbazone ligands and their compounds, these compounds can also very well fit for this role.

Schiff-bases are a peculiar type of ligands possessing a diversity of donor atoms that exhibit remarkable coordination modes towards transition metals [25-27], with the existence of an azomethine linkage influencing biological activities [28–30]. An appreciable number of Schiff-bases starting from various amines have been investigated by different methods [31,32] and have been shown to have interesting applications in catalytic reactions, materials chemistry, and last but not least, in industry [33,34]. Due to the reason that the steric and electronic properties can be controlled by the amine/aldehydes basic, the salen type ligands, obtained after condensation of salicylaldehyde and the primary diamine, are stated as flexible ligands for coordination chemistry. This important type of ligands contains in their structure donor centers necessary for metal ions to project different geometries with other ligands [35]. Therefore, a numerous number of complexes were obtained by moving the metal ions in the salen-type ligand. These compounds have been considerably investigated in various domains of chemistry. The chelating activity of the tetradentate ligand with nitrogen-oxygen donor atoms gives it kinetic and thermodynamic stability, making it interesting for researchers. The presence of the nitrogen in the imine groups (C=N) in Schiff-bases and in their metallic complexes and their chelating properties are the reason for their many unique biological properties. Metallo-salens compounds constitute relevant parameters in the progress of current inorganic biochemistry [36–38], catalysis [39–41], magnetism [42], medical imaging [43], and not long ago in sensors [44,45], nonlinear optical (NLO) devices [46], solar cells [47], and as building motifs [48] or building blocks [49].

These compounds are easy to synthesize and can be bonded with quasi all metal ions in order to form the appropriate complexes; azomethine nitrogen being responsible for coordination with metal ions through it [50]. Quite a large number of these types of metal complexes with different coordination geometry and flexible oxidation states have been studied in depth [51–58], some of them being representative of the progress of inorganic biochemistry and catalysis. Copper is a biologically essential component, which is why many chemicals need it to function [59]. The coordination chemistry of copper has aroused the interest of numerous scientists due to its well-informed biological characteristics. A very large number of copper complexes based on Schiff-

bases have been successfully used as models in biological and supramolecular systems [60–61]. Beyond the last decades, there have been many scientific studies regarding applications, mainly in biology: the antimicrobial, redox, catalytic, and antioxidant activities. Therefore, a review accentuating the employment of the named ligands and their complexes is demanded. The significance of Schiff-base complexes in supramolecular chemistry, materials science and catalysis, coordination and separation processes, applications in biomedical fields, and the formation of new compounds with outstanding structures and properties, had been well studied and revised [62–68].

The biological activity of the metal complexes is higher than that of their ligands. The complexes of the Schiff-bases are of great consideration due to their stability, electron donating capacity, optical nonlinearity, catalytic, photochromic, and biological activity. These practical activities are all based on the coordination of Schiff-bases with the metal ions. An interesting class of Schiff-base complexes is that obtained starting from amino acids [69]. Amino acids are dynamically implicated in a part of biological processes and they possess the –NH2 and –COOH coordinating sites, which can be bonded with aldehydes/ketones for synthesize Schiff-bases which are easily coordinated with the metal ions (The majority of the ligands derived from the amino acids and their complexes with the appropriate metal present distinct activities as drugs. An important study focused on the analysis of complexes based on Schiff-bases of amino acid derivatives from the last five years was made by Ghanghas et al. [70]. The complexes made with these ligands have high thermal stability and antibacterial activity, making them suitable for medical applications. The different types of the metal, ion, and ligand, the surrounding of the complex, coordination sites, hydrophilicity, lipophilicity, and the presence of co-ligands, together with the concentration, all affect the antibacterial activity of these compounds [71–73]. Inclusion of polar and lipophilic substituents increases the antibacterial action. Heterocyclic ligands with multifunctionality, which can interact with nucleoside bases or specific biological metal ions, are good candidates for bactericides [74–76]. The heterocyclic ligands interfere with functional groups (enzymatic type) to get access to high coordination numbers. In a recent study, Ghanghas et al. presented the history of the evolution of different types of investigations used in order to improve the metal complexes of the Schiff-bases' biological activity, thus being of real help in projecting a new class of drugs starting from the named compounds. The research regarding the antimicrobial activity of the synthesized compounds has been considerably studied because there is a relevant issue to exploring the linking properties of the complexes with a large variety of metal ions.

Researchers have concentrated their efforts in recent years on producing and investigating a new category of ligands and their complexes, having tetramethyldisiloxane spacers between the

complexing groups (from 320 to 3249 structures in the Cambridge Crystallographic Data Centre (CCDC) database).

The tetramethyldisiloxane spacers are well known as flexible and hydrophobic, and these properties are of real interest. Thus, research activities focused primarily on the production of such ligands and their metal complexes of relevance for catalysis, biological activity, materials science, and nanoscience, reporting a vast number of such structures in the CCDC crystallographic database. The scientists have obtained and investigated around 259,536 Schiff-base ligands and their complexes, organized as a single crystal (the structures are presented in the CCDC Cambridge base) and more others in different forms.

The subject-the metal complexes starting from Schiff-bases has attracted the attention of researchers because of its biological activity, with the main goal of discovering straight and active therapeutic agents for the cure of various bacterial diseases. Research into biological and inorganic chemistry has been of particular concern to Schiff-base metal complexes, as it has been observed that a lot of the complexes can be used as models for biologically important species. Therefore, we report them hereunder. 2.1. Antimicrobial Activity (Antibacterial and Antifungal) Over the recent few years, from 2015 to present, the Schiff-base metal complexes have earned much attention due to the biological properties of them. A large number of studies have been published on their use in biological applications. Schiff-bases have been found as potentially effective antibacterial agents. The metal complexes of the Schiff-bases have much better antibacterial activity than their free ligands. The recently published literature emphasizes the notable potential for antimicrobial activity and progress in the field of other types of interesting topoisomerase complexes. It was demonstrated that the Cu(II)-picolinic acid complex is a significant delayer of gel electrophoresis. The thiosemicarbazone derivative of copper(II) has good activity in the killing of S. aureus, S. typhimurium and K. pneumoniae after 6 h of incubation . The antibacterial activity of a special class of complexes of transition metals bonded through coordination bonds in the N2O2 mode was investigated, with the Schiff-bases of the salen-type starting from the, 1,3-bis(3-propyl)tetramethyldisiloxane (AP0)—a diamine having a siloxane spacer commercially available, with various salicylic aldehyde derivatives.All the metal complexes studied were assessed for antifungal (in vitro with three types of fungi species (Aspergillus niger, Penicillium frequentans and Alternaria alternata) and antibacterial activity (with two types of bacteria—Gram-negative (P. aeruginosa) and Gram-positive bacteria (Bacillus)). The results of the antimicrobial activity tests showed a higher efficiency, closer to that of the reference compounds (in this case-Caspofungin and Kanamycin), in the case of the azomethines originating from substituted salicylaldehyde. The ligands derived from 5-chlorosalicylaldehyde and its metal complexes have been shown to present

the highest potential for biological applications (this could be caused by the presence of chlorine in the 5 position). The results of the antifungal and antibacterial activity measurements recommended some of the synthesized compounds as possible antimicrobial agents. In another study, Zaltariov et al. obtained and studied metal complexes starting from silicon-containing ligands (starting from a new amine-trimethylsylil-propyl-p-aminobenzoate). The Schiff-bases behave as bidentate (NO), tridentate (N2O), or tetradentate (N2O2) ligands, and they have a large diversity of interesting characteristics with applications in various domains like biological, analytical, or industrial applications. Many of these ligands and complexes have antibacterial, antifungal, antiviral, and antitumor properties. For projecting different types of ligands, it is really important to choose the appropriate carbonylic and aminic precursors. Homometallic and heterometallic complexes with trimethylsilyl groups in structure have demonstrated an amphiphilic character and they can self-assemble in solution as a function of solvent polarity. These special properties enhance the catalytic activity for the complexes in various substrates and affect the behavior in solution. The authors synthesized Cu(II) and Zn(II) complexes with two bidentate Schiff-bases having trimethylsilyl units. The ligands were prepared by the condensation reaction of a novel trimethylsilyl-propyl-p-aminobenzoate with o-vanillin and salicylaldehyde. Some of the complexes can be used as possible candidates for cellular imaging because of their absorbance in the visible region and because of their green emission. Complexes with different types of metals were estimated against various fungi species and some types of bacteria, and the analysis showed that they have a higher biological activity than the standard compounds Kanamycin and Caspofungin. Literature studies indicate that Schiff-bases having antibacterial activity are obtained from indole, pyridine, isatin, hydrazide, benzimidazole, thiazolidiones, thiazole, thiosemi-carbazone, lysine/curcumin, and siloxane.

Further study of the literature has shown an important increase in systemic fungal infections with life-threatening effects. Numerous studies show that Candida (albicans and non-albicans) and Aspergillus (Asp.) species are responsible for the most severe fungal infections. Thus, the progress of new antifungal species with decreased resistance and bigger efficacy is a priority. A number of lengthy and laborious investigations have been carried out, and some Schiff ligands have been found to be bright antifungal agents. The researchers also highlighted the existence of different groups such as methoxy, halogen, and naphthyl, which enhance the ligand's fungicidal activity. While very disseminated, new literature clearly accentuates the remarkable potential of antifungal drug research in the metal complex domain.

Currently, numbers of serious problems in clinics were caused by various bacterial infections. The multi-drug resistance limits the progress of conventional antimicrobial agents in the clinics. More and more antibiotics have been explored in order to overcome these issues. Some heavy metal ions

with biocidal action such as silver, zinc or copper, have been used as inorganic metal antibacterial materials. As most of the substances are toxic, zinc is one of essential dietary trace metals required for a number of physiological and biochemical functions in human body. Zinc deficiency can lead to series of hazardous influence to immune systems. Furthermore, zinc itself exhibits antibacterial efficacy. Zinc chloride can effectively inhibit the growth of almost all strains causative of halitosis and periodontal disease resulting in a direct decrease of the bacterial production. Zinc ion possibly inhibits the growth of plaque formation and exhibits a promising potential to be used as an antibacterial agent in future dentifrices and mouth rinses. Zinc containing wound dressings are commonly used for topical applications which enhance healing of chronic and acute wounds. Meanwhile, there are also many evidences that zinc can provide anti-infective action in the damaged skin or tissues with little side effects. Free zinc ion accelerates hospital acquired infections by increasing the virulence of *Streptococcus pyogenes* and inducing intercellular adhesion of *Staphylococcus epidermidis* and *Staphylococcus aureus*. Therefore, the development of biofilms chelated zinc represents a potential therapeutic approach for combating biofilm growth in a wide range of biofilm-related infections. Additionally, zinc ion has protein-precipitating action resulting in tissue contraction, corrosion and a chemical fixative effect. High concentrations of zinc chloride ingestion cause obstructive scarring in the pylorus and mild corrosion of oropharynx or oesophagus. Zinc chloride has an inherent degree of toxicity with a great ability to permeate tissues. Ingestion of zinc chloride might cause the stimulatory action on the mucous membranes of gastrointestinal tract with vomiting, abdominal pain, and diarrhea. In order to reduce the toxicity and irritation of free zinc ion, various zinc complexes come to wide attention.

Thiosemicarbazone is a multipurpose class of ligand having notable biological and chemical activities. Therefore, the design and preparation of new complexes with zinc and thiosemicarbazone, which aims to improve their proprieties through the discovery of new structures, is still a great scientific challenge. Further continuing research on our previous work, a novel zinc complex (ZnTC) was synthesized in this study by using Zn^{2+}, carbohydrazone and thiosemicarbazide hydrochloride. The structural, chemical components, characterization, acute toxicity and in situ intestinal absorption study of the complex was performed and evaluated. In order to investigate whether the complex formed, it was heated at 130 °C for 1 h, which resulted a fluorescence phenomenon observed under 365 nm ultraviolet light. The antibacterial activity was investigated and confirmed against both Gram-positive *Staphylococcus aureus* (*S. aureus*) and Gram-negative *Escherichia coli* (*E. coli*) strains. The ZnTC complex has a potential to be used as a candidate for zinc supplements and the application in antibiosis material in biomedical fields.

The use of metals for medicinal purposes has been exploited since very ancient times; for instance, silver has been used as a disinfectant agent for water and milk for thousands of years. Similarly, the application of gold in medicine can be dated back to 2500 BC and throughout the entire history of humanity it is possible to find traces of several applications of this noble metal to treat various diseases . Indeed, in the 19th century the complex dicyanoaurate(I) ($K[Au(CN)_2]$) was proposed by Koch for its bacteriostatic properties to fight tubercle bacillus, while in the 20th century, gold complexes were introduced to treat rheumatoid arthritis, leading to the approval of Auranofin by FDA in 1985. This latter compound is today the reference compound for gold complexes and, on the ground of the so-called repurposing strategy, has been proposed as promising anticancer agent and entered several clinical trials in US, some of which are still ongoing.

Beyond silver and gold, several bismuth, antimony and mercury compounds have been employed to combat bacterial and parasitic diseases. In this view, bismuth salts and antimony complexes have been proposed and used for eradication of Helicobacter pylori infection, and against leishmaniasis respectively . Also, arsenic, in the form of trioxide (As_2O_3), is nowadays one of the reference drugs for the treatment of acute promyelocytic leukemia. Several inorganic complexes are also used for diagnostic medicine as in the case of gadolinium-based contrast agents, ^{99m}Tc compounds for myocardial perfusion imaging and ^{64}Cu for PET imaging .

However, the most important impulse to the research of metal-based drugs with medicinal properties came from the serendipitous discovery of the antitumor features of cisplatin by Rosenberg and Loretta Van Camp in 1965. Cisplatin was approved in 1978 by the FDA, and this event triggered enormous efforts by scientists in search of innovative and ameliorated inorganic anticancer drugs, leading to the approval worldwide of carboplatin and oxaliplatin analogs. This makes platinum-based drugs an essential arsenal for first- and second-line anticancer chemotherapy used in about 50% of clinical protocols.

Metals complexes offer an extremely versatile and reliable tool for the development of improved medicinal compounds. Indeed, it is possible to finely tune the chemical properties of these complexes by controlling the metal centre oxidation state and selecting the most appropriate ligands for each application. Thus, it is not surprising that the challenge in the development of innovative and improved metal-based drugs largely overlaps with the development of innovative and ameliorated ligands for the functional metal element.

Among several ligands, thiosemicarbazones (TSCs), are a very attractive class of metal-chelating ligands, able to coordinate many transition metals through the sulfur as well as the azomethinic nitrogen atoms . They can act as N, S-multidentate ligands, and moreover, it is possible to modulate the binding properties/stoichiometries through the insertion of other heteroatoms into the backbone structure (i.e., phenolic or pyridyl moieties). They have a great variety of biological properties, both as free ligands and as metal complexes, and several studies have been published reporting on thiosemicarbazone-based complexes with medicinal applications.

Beyond TSCs, in recent years, there has been growing interest in the coordination chemistry of thiocarbohydrazones (TCHs) compounds that share the general formula depicted in and that can be considered the higher homologues of TSCs . The first synthesis of these systems is dated 1925 and described the condensation of ketones and aldehydes with thiocarbohydrazide. The earliest employ of this derivatives relied the hetero-ring closure of the aldehyde derived thiocarbohydrazones.

While TSC started to be used in the late sixties, the first report on the "*Preparation and fungistatic properties*" of neat TCH appeared only in the following decades, probably because the key thiocarbohydrazide intermediate was not commercially available until the late 1970s and should be synthesized from carbon sulfide and hydrazine. Until the first half of the nineties, however, most reports concerned the synthesis and characterization of ligands and their complexes with transition metals were reported. Only recently it was understood the potential of these systems: TCHs are able to act as metal-based drugs and their biological activities were investigated.

The analytical uses of TCHs as spectrophotometric reagents in metal determination has been reviewed in recent years and is continuously developing. However, despite their ability to coordinate metals and the remarkable biological properties of the resulting complexes, no general survey on the employment of TCHs as suitable ligand for the synthesis of metal-based drugs has yet reported. Here we give an overview of TCHs structures and tautomerism; the different biological activities as antibacterial, antimicrobial and anticancer agents of their metal complexes have been reported. Due to the huge variety of metal cations employed in biologically active TCH complexes (eighteen cationic species, ranging from the first-row transition metal cation to lanthanides, from organo-metal to oxo-metal cation, will be reported in this review) and to the different binding stoichiometries available for each cation, we decided to make use of a simpler classification based on the ligand backbone: the biological activity of the metal complexes derived from symmetric, macrocyclic and asymmetric TCHs has been discussed in three different section. Further sub-sections have been employed to describe the most common substituents used in the TCHs ligand

synthesis (R_1, R_2, R_3 and R_4 groups), namely salycilic, pyridyl, aromatic/heteroaromatic, ferrocenyl, isatin, coumarin, (and related) carbonyl compounds.

Carbohydrazone Schiff base ligand plays an important role in inorganic chemistry stream because it can readily form stable complexes with a large number of transition metal ions like Cu+2, Fe+2, Ni+2, Co+2 etc. due to its flexibility to form keto-enol tautomerism. In coordination compounds the hydrazone Schiff base ligand normally exists in enol form in order to bind with the metal ions through the nitrogen atom from imine group and oxygen from hydroxyl group .Zn (II) metal ions generally have 4 - coordination number and predict a tetrahedral geometry for Zinc complexes. Because Zn has completely filled d-orbitals with ten electrons and forms a stable eighteen electrons complex can be formed through four coordination numbers with Schiff base ligands. Due to this reason, 5-6 coordinate Zn complex is considered unusual and expected to be unstable in nature. However, 5-6 coordinate Zn complex were previously reported .The oxidation state of Zn+2 ion in Zn complex is +2. However one reported by Song et al. is in the zero oxidation state. In this paper synthesis, characterization, molecular structure of Zn complex is reported. In addition, antibacterial activities and molecular docking studies of Zn complex and Carbohydrazone Schiff base have also been evaluated.

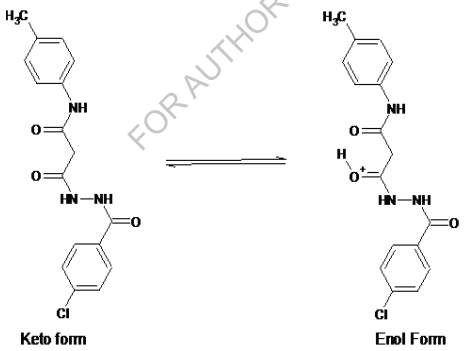


Figure1 -:Keto-enoltautomerization of a carbohydrazone Schiff base ligand

2. Experimental:

2.1 Instrumentation:

The IR Spectra of hydrazone Schiff base ligand L_1 and the Zn(II) complex were recorded in KBr disks by using Perkin Elmer FT-IR spectrophotometer with the wavelength range from 400 to 4000 cm^{-1}. Perkin Elmer UV/VIS lambda 25 UV-Visible spectrophotometer was used to record the electronic absorption spectra with Dichloromethane solvent. The elemental analysis of L_1 and its Zn(II) complex was conducted by using CHN Analyser, Thermo Flash EA1112 series at the temperature upto 900^o C and V_2O_5used as oxidizer to prevent inhibition caused by sulphur.X-ray measurements for the ligand and its Zn complex were performed on a Bruker axis D8 using Cuk α radiation (λ = 1.540 Å) over a 2θ collection range of 20 -80^o.

2.2 Chemicals

All the chemicals like Zinc chloride dihydrate ($ZnCl_2.2H_2O$), p-chloroacetophenone, Thiosemicarbazide, 4-methyl aniline, diethylmalonate, ethanol (C_2H_5OH) were purchased AR grade from Merck Pvt.India and were used as it is.

2.3 Synthesis

Ligand(L) and its Zn(II) complex were prepared in four stages

(i) Synthesis of Ester
(ii) Synthesis of hydrazide
(iii) Synthesis of hydrazoneSchriff base ligand (L)
(iv) Synthesis of Zn(II) complex using template route.

2.4 Synthesis of Ester

In the first stage, ligand(L) were prepared using refluxing method. 4-methyl aniline, diethylmalonate and ethanol were used for synthesis of ligand 0.05M of 4-methyl aniline is added in 10 ml of diethylmalonate. The solution is stirred continuous for 30 minutes at 50^o C. In another beaker, we have taken 30 ml ethanol and stirred for 15 minutes. Then both the solution mix together and refluxed for 70^o temperature for ½ hour. Cool the solution and poured into solid ice. A transparent precipitate was obtained. The precipitate was obtained after 24 hours aging process.

2.5 Synthesis of hydrazide:

In the second stage hydrazine hydrate was used for synthesis of hydrazide0.05 M of Ester is mixed with 0.05 M of hydrazine hydrate and stirred the solution continuously for one hours at 80^{o} C temperature. A colourless precipitate was obtained after 24 hours. of aging process.

2.6 Synthesis of Ligand (L)

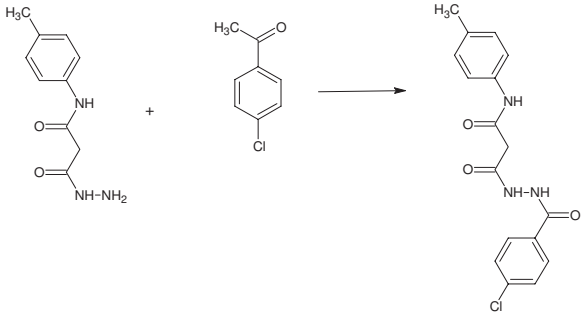
In the third stage, 1 mM of hydrazide dissolved in 50 ml ethanol and mixed with ethanolicsolution of 1 mMthiosemicarbazide and 1 mM hydrochloride solution and stirred the solution continuously for 4 hours at 80^{o} C temperature. A white precipitate was obtained after 36 hours of aging process.

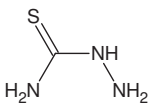
Yield- 2.20g (75.6%) and m.pt. :215^{0} - 220 ^{0}C.Anal. Calcd. for $C_{38}H_{37}N_{14}S_2Cl_2$: C, 67.06; H, 5.47; N, 8.76; S, 10.12, Cl, 17; Found(%) : C, 67.50; H, 5.68; N, 8.92;S, 11.11, Cl, 17.96.Characteristic IR absorption peaks are (KBr disk, cm^{-1}).: 3435(s), 3272(s),1610(s), 962 (m). H^{1}NMR [DMSO- d_6, δ] : 11.61 [S, 1Hz, N-H], 11.26 [S, 1 Hz , Ar-OH], 7.66 [d, 1Hz, J= 8 Hz, Ar- H] , 6.96 [m, 4Hz, Ar-H], 3.41 [s, 3Hz, CH_3]^{13}CNMR [CD_2Cl_2, δ] : 170.32, 163.28, 162.42, 160.86, 133.28, 130.49, 128.99, 128.60, 118.46, 117.36, 117.08, 114.86, 54.04, 41.44, 18.64.UV-Vis [DCM, λ_{max}]: 320 nm.

2.7 Synthesis of Zn(II) complex.

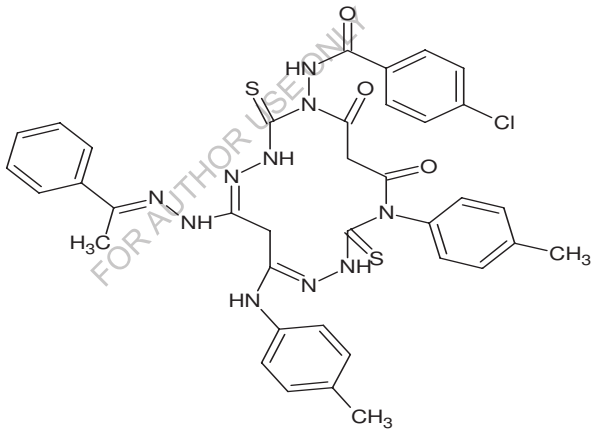
In the fourth stage, 1 mM of hydrazone dissolved in 50 ml ethanol and stirred the solution continuously for 1/2 hours at room temperature and slowly added 1 mM Zinc chloride dehydrate salt as a source of Zn^{2+} ion along with continuous stirring.(The precipitate was ultra sonicated for 2 hours at 80^{o} C temperature. After 24 hours aging precipitate obtains. After being refluxed for 24 hours the solution was cooled to room temperature followed by filtration and recrystallization from the mixture of DMSO and absolute ethanol. A yellow coloured crystal was obtained. After one week, which was then filtered and washed with DMSO.

Yield: 0.18 g (92.10%) and m.pt.: 285.5^{0} - 220 ^{0}C. Anal. Calcd. for Zn($C_{38}H_{37}N_{14}S_2Cl_2$) : C, 57.61; H, 5.14; N, 7.89; S, 10.16, Cl, 17.36; Found(%) : C, 57.78; H, 5.26; N, 8.12; S,11.28, Cl ,17.90.Characteristic IR absorption peaks are (KBr disk, cm^{-1}).: 3446(s), 1620(s), 962 (m), 994(w), 660(m). H^{1}NMR [CD_2Cl_2, δ] : 8.10 [Cl, 1H, J=6.1 Hz, Ar-H], 6.92 [d & t , 2H , J=7 Hz, Ar-H], 6.72 [d, 2H, J= 9 Hz, Ar- H] , 6.96 [d & t, 2H, J= 7 Hz, Ar-H], 6.74 [d , 2H, J= 9 Hz, Ar-H], 3.66 [s, CH_3 , 3H].^{13}CNMR [CD_2Cl_2, δ] : 172.36, 164.88, 162.20, 160.58, 133.20, 130.49, 129.86, 128.50, 118.89, 117.39, 117.40, 114.39, 54.06, 44.46.UV-Vis [DCM, λ_{max}]: 345 nm.

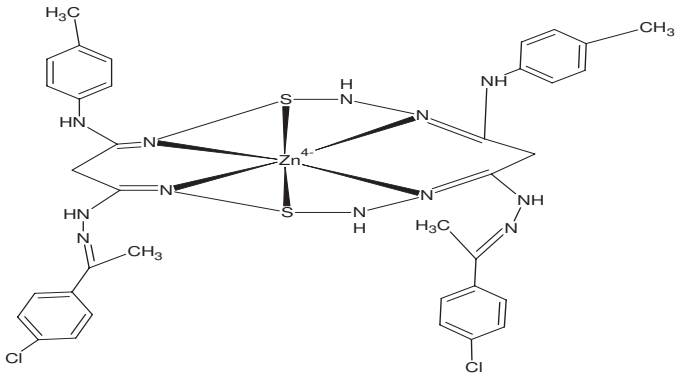




Abs. EtOH, Reflex 4 Hrs.



ZnCl2.2H2O. Abs
EtOH+DMSO, Reflud 24 Hrs



Scheme 1: Synthetic Pathway of Ligand (L) and its hexa coordinate Zn (II) Complex

2.8 Molecular Docking Studies

In this research work, antibacterial activities were evaluated on two microorganisms i.e. E.coli and S.aureus, therefore crystal structures of molecular targets i.e. DNA gyrase subunit b (PDB ID: 1KZN) and topoisomerase II (PDB ID: 1JIJ) related to microbial potential of those mentioned microorganisms were retrieved from protein data bank. Before performing the molecular docking study, molecular targets were refined (removal of native ligands and water atoms). Macromolecules processed further into the AutoDock execution window and saved as target.pdbqt after adding hydrogens and charges were automatically assigned on the macromolecules. Zn complex and ligand were prepared through ChemDraw Ultra 8.0 and optimized for energy minimization using MM2 force field and converted into .pdb format by OpenBable -2.3.2software. The Zn complex and ligand were also processed into AutoDock execution window and their torsions along with rotatable bonds are assigned and the files are saved as Zn complex.pdbqt and ligand.pdbqt respectively. The binding modes of zinc complex and ligand with targets were obtained via AutoDockVina software and blind docking was carried out to identify actual binding modes of zinc complex and ligand in the targets. The nine different conformers were fabricated of Zn complex and ligand and conformers which showed lowest binding energy and better interactions with molecular targets were discussed. In case of topoisomerase II, The docking parameters were defined as coordinates of the center of binding site with x = -10.686, y = 20.282, z = 91.742 and in case of DNA gyrase, the docking parameters were x = 20.538, y = 19.166, z = 43.283 and binding radius = 1.000 Å and The

grid dimension used for all the three (3) proteins are 47.25 × 47.25 × 47.25 Å (grid size) with point separated by 1.000 Å (grid-point spacing).

2.9Antibacterial Study of the Compounds

The antibacterial study was carried out on hydrazine ligand L and its Zn(II) complex using disc two diffusion method.(17) One colony of eachE.Coli (MTCC-1687), E.faecalis(MTCC-439), S. aureus (MTCC-737) and indigenous methicillin resistant S.aureus from a streak plate was inoculated in 20 ml of LB broth after 16 hours of incubation, the optical density of the inoculums were measured and further diluted to achieve McFarland standard of 0.5 using sterile cotton swab, again plates were uniformly swabbed with diluted inoculums of bacterial cultures. After that sterile filter paper (6 mm) which were impregnated with different concentration.(i.e. 50, 25, 12.5, 6.25 and 3.125 µg/µl using dichloromethane as the solvent) of ligand (L_1) and its Zn(II) complex were placed the again. The inhibitory zones in millimetres were measured after 24 hours of incubation. All the antibacterial assays were performing in triplicates.

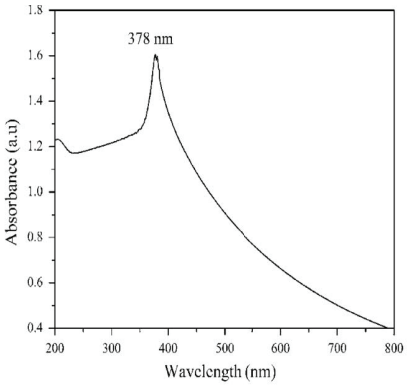
3. Results and Discussion

3.1 Synthesis and characterisations of ligand and its Zn (II) complex

Hydrazone ligand (L) was successfully synthesised through condensationprocess between hydrazide and 4- chloroacetophenone under reflux for 24 hours at 80^{o} C. The colour remained unchanged even after the addition of hot ethanolic hydrazide into ethanolic solution of 4- chloroacetophenone with stirring and heating A colourless precipitate started to form after 12 hours of refluxing with the yield of 75%. The synthesized ligand L was thenreacted with Zn(II) chloride under reflux condition for 28 hours. Upon completion of the reaction the dark yellow solution was filtered as Paleyellow crystal after 2-3 weeks.

Based on the IR spectra of ligand (L) and its Zn(II) complex the absence of ν(N-H) and ν (C=0) peak in the IR spectrum of Zn(II) complex indicates enolization of Keto group in Ligand , which coordinate to the Zn metal ion through azonmethine nitrogen atoms. The changes of frequency of IR spectra of ν (C=N) , chemical shift from 1606 to 1608 cm^{-1} were rather insignificant after the complexation process. This result of the IR spectra is equivalent to the finding from Tay et al,(15) where the IR frequency of C =N was also shifted by only 2 cm^{-1} from 1621 cm^{-1} to 1619 cm^{-1} after their ligand bis-2' –hydroxy Schiff base compound bound to Zn^{2+} ion. The IR spectral data of ligand and its Zn(II) complex is supported by the UV-Vis results where the n-> π* transition in C=N bond shifted from 325 nm to 345 nm after binding to the Zn^{2+} ion. The bathochromic shift was aroused due to the backbonding from Zn metal ion to the C= N bond in ligand and sulesequently weakend the bond energy of C=N.

The ^{1}HNMR spectra of Zn(II) complex also shows some differences compared to ligand(L_1). A broad HNMR signal at 11.82 ppm and a singlet present at 11.26 ppm of ligand L_1 are assigned to the N-H of azomethine and phenolic proton present in Schiff base ligand respectively. These two HNMR signals showed that ligand in present in KETO form. This is also supported by the IR spectra of Schiff base ligand L_1 with the presence of ν (N-H) and ν (C=0) at 3272 and 1606 cm^{-1} respectively. The two NMR signals at 11.82 and 11.30 ppm disappeared after complexation with Zn^{2+} ion, indicating that the structure of ligand shows Keto- enol isomerizationand the N of the ligand has bound to the Zn^{2+} ion.



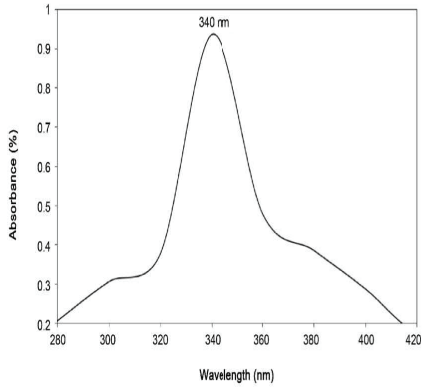


Figure 1– UV- Visible spectra of Ligand (L) Figure 2. UV –Visible spectra of Zinc(II) complex

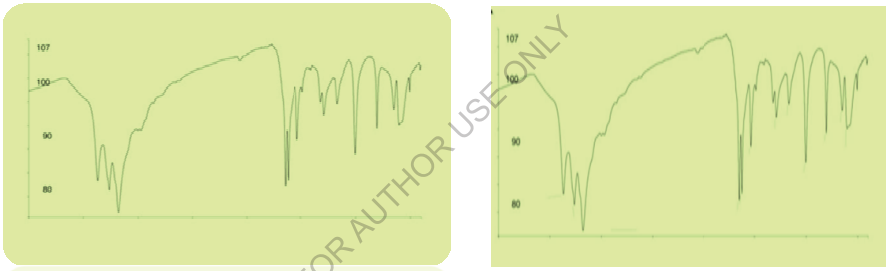


Figure -3 FT-IR Spectra of ligand and its synthesized Zinc (II) complex

X -ray diffraction is a popular analytical technique which has been used for the analysis of test molecular and crystal structures. Samples were readily synthesized in alcoholic solution. Fig 3&4 show the XRD pattern of ligand and its zinc complex powder deposited from the alcoholic solution, which is in agreement with that of the standard powder diffraction of compounds with a hexagonal structure. The diffraction lines are indexed as its zinc complex as 101,102,103,110 phases [JCPDSNO-06-04]. From the full width at half maximum of diffraction peaks (111) is employed to calculate the average crystalline size using Debye- Scherer's equation .i.e.,

$$D = 0.9 \times \frac{\lambda}{\beta . \cos\theta}$$

Where,

D = Crystalline size

λ = wavelength of X- Rays

β= Full width at half maximum of the diffraction peak

θ = Bragg's angle

The estimated particle size was below 100nm (Calculated by using Debye Scherer equation) the width of the peaks obtained in XRD pattern is cognate to the crystalline size of the particle. The small size of nanoparticles indicated the high surface area and high surface area to volume ratio.(16)

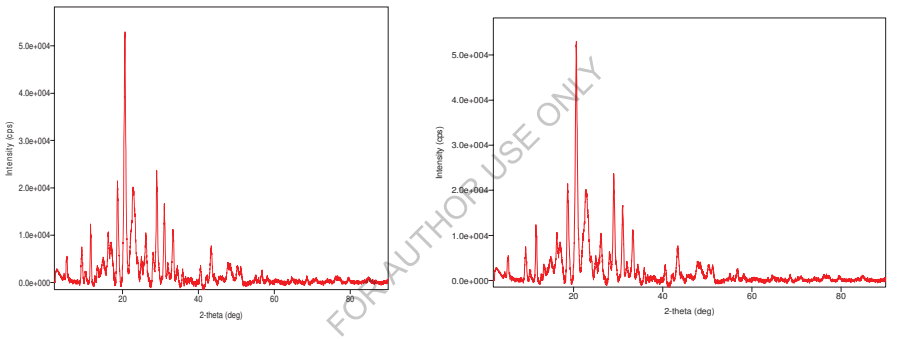


Figure 3&4 XRD Spectra of Ligand and its Zinc (II) Complex

The estimated particle size was below 100 nm, the wilder of the peaks obtained in XRD pattern is cognate to the crystalline size of zinc complex .The small size of complex indicated the high surface area to volume ratio.

EDX studies confirms the presence of zinc & sulphur elements in complex. The other impurities is found such as carbon &oxygen was identified because of the interaction with the leaf extract duringbioprocessing process.

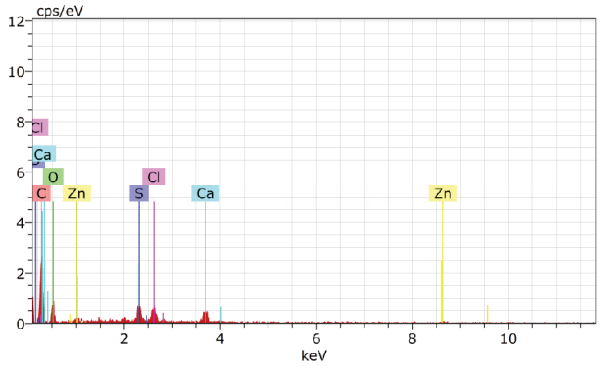


Figure5. EDX spectra of Zinc Complex which shows the presence of Zn, S, C,OElements

Spectrum: test 5165

Table 1 - Element Series unn. C norm. C Atom. C Error (3 Sigma)
[wt.%] [wt.%] [at.%] [wt.%]

Carbon K-series 45.92 59.96 73.48 27.73
Oxygen K-series 16.74 21.86 20.11 14.29
SulfurK-series 2.46 3.21 1.47 0.54
Calcium K-series 4.37 5.71 2.10 0.85
ChlorineK-series 3.04 3.98 1.65 0.63
Zinc K-series 4.04 5.28 1.19 2.00

Total: 76.58 100.00 100.00e

TEM images of Zinc(II) complex

The TEM images of the zinc complex are show in figure 6. According to the picture, light coloured zinc complex are arranged in a cluster form, approximately 100nm in size, which are expected to the binding with ligand after the generation, and prevent their further growth also fig 6. show the size distribution of zinc complex having arrangement of equispaced particles. The TEM images

shows that zinc complex particles are not combined but are separated by equal interspace between the particles, which was confirmed by microscopy visualising under the higher resolution. The TEM images explains that the zinc complex arebounded with the ligand.

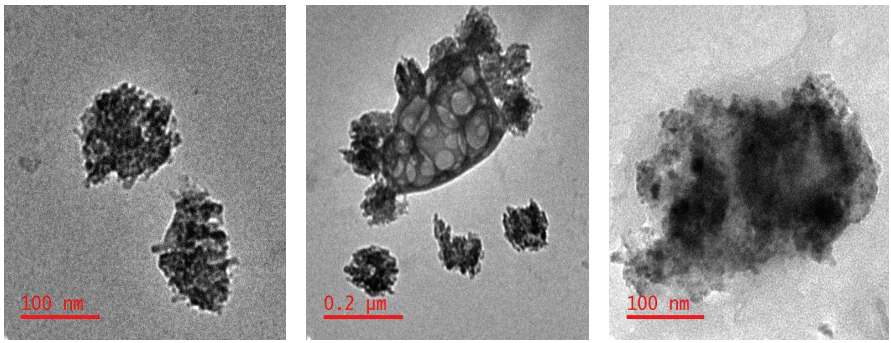
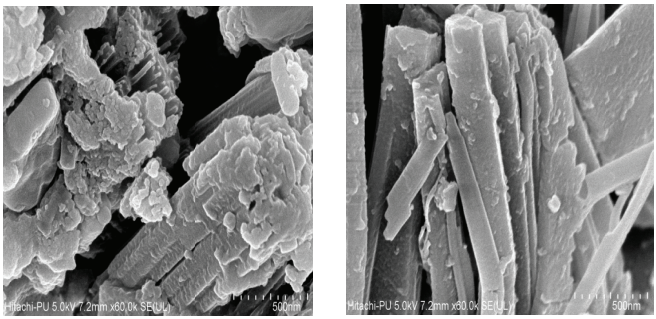


Figure 6. TEM Images of Zinc (II) Complex

SEM images of Zinc (II) Complex

SEM monographs in figure 7 explains well dispersed, versatile and spherical shape of zinc complex when added to the ethanolic solution of ligand, does not change the shape of zinc complex particles but it increases the size of particles mostly in higher concentrations. The zinc complex particles are were assembled into a very open and quasi- linear structure than a dense closely packed assembly.



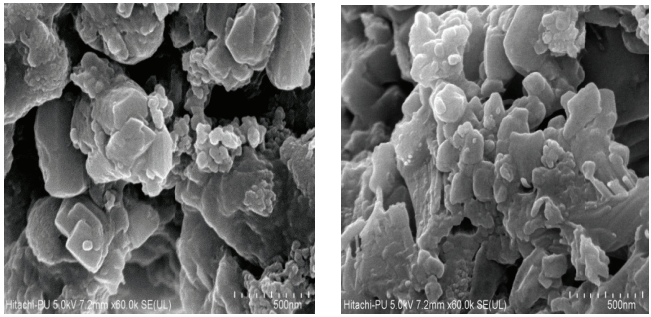


Figure 7–SEM Images of Zinc (II) Complex

TGA Analysis of Ligand & its Zinc (II) Complex

The TGA figure 8& 9 .indicate that the graphs ligand and its Zinc (II)complex begin to decompose at 276.93℃,259℃,respectively.Comparison of the decomposition temperature of the compounds shows that zinc complex decompose at higher temperature than its ligand. The TGA curve for zinc complex displays 8.626 mg weight loss within the temperature range of 150-800℃ and exhibent a man loss of 93.7% The curve of ligand displays 7.26 mg weight loss within the temperature.

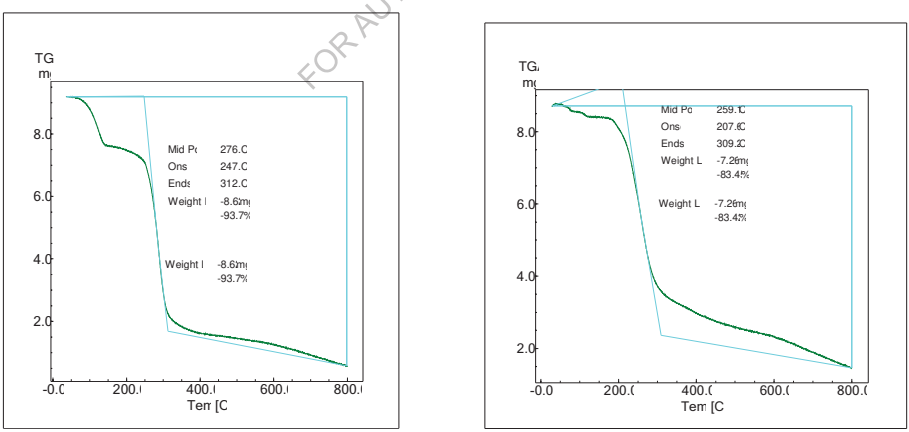


Figure 8&9TGA Spectra of Ligand and its Zinc (II) Complex

3.2 Antibacterial Screening of Ligand and its Zinc (II) complex

The antibacterial activity of hydrazone Schiff base ligand L and Zn(II) complex was examined using disc diffusion method and the results were summarized in Table 2 and fig7. .The results show that both ligand And its Zn(II) complex are considered non- toxic to gram positive and gram negative bacteria. Results show that Zn(II) complex are more reactive than its ligand(L); even the concentration was increased up to **6.25µg/ µl** to **100 µg/ µl** the possible reason for this could be the absence of ling hydrocarbon chains in both the structures of carbohydrazone and its Zn(II) complex.

Table 2 : Inhibition of standard drug Vancomycin- HCl against all test microbes.

S. No.	Test Microbes	Diameter of Zone of Inhibition(in mm) at different drug concentration				
		50 µg/ µl	**25 µg/ µl**	**12.5 µg/ µl**	**6.25 µg/ µl**	**3.125 µg/ µl**
1.	E. Coli (MTCC-1687)	11 mm	10 mm	Nil	Nil	Nil
2.	E. Faecalis (MTCC-439)	30 mm	28 mm	25 mm	23 mm	20 mm
3.	S.aureus (MTCC-737)	27 mm	26 mm	24 mm	22 mm	21 mm
4.	M.R.S.aureus (Indigenous)	22 mm	21 mm	19 mm	19 mm	18 mm

Table 3 : Results of antibacterial actibity of carbohydrazone Schiff base ligand (L_1) and its Zn(II) complex. :

S. No.	Concentration (µg/µl) in Dichloromethane	E. Coli (MTCC-1687)		S.aureus (MTCC-737)		E. Faecalis (MTCC-439	
		Ligand L_1	**Zn(II) complex**	**Ligand L_1**	**Zn(II) complex**	**Ligand L_1**	**Zn(II) complex**
1.	**100 µg/ µl**	10	20	15	25	08	13
2.	**50 µg/ µl**	12	19	12	19	09	13
3.	**25 µg/ µl**	11	18	08	14	10	12
4.	**12.5 µg/ µl**	6.25	13	06	12	06	10
5.	**6.25 µg/ µl**	5.5	10	05	10	nil	nil

Figure 10 – Anti bacterial activity of ligand and its Zinc (II) complexes

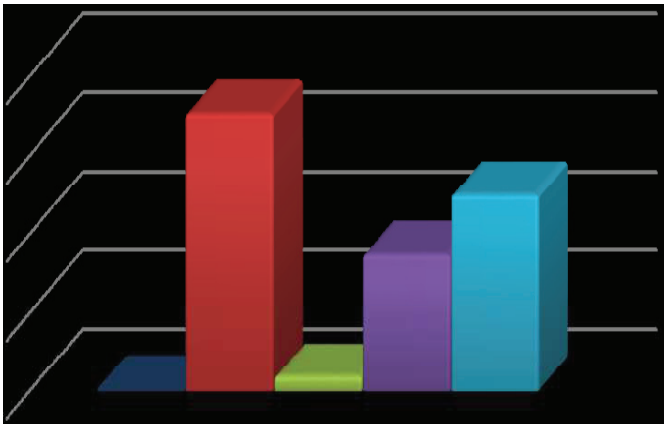


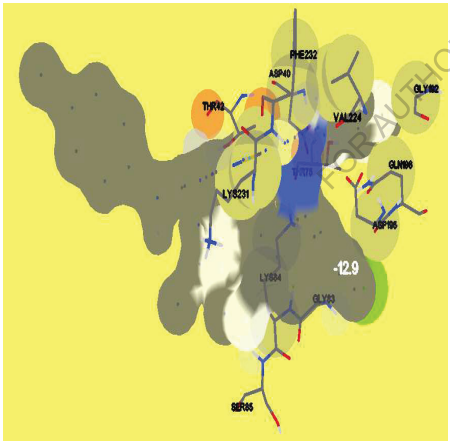
Figure 11- Graphical representation for antibacterial activity potential of ligand and its Zn(II) Complex in comparison to activity of standard vancomycin antibiotic

3.3 Molecular Docking Analysis

The molecular docking studies revealed that Zinc complex and ligand both got accessed into the active pockets of molecular targets and interacted with amino acids responsible for target inhibition. Although Zinc complex interacted with amino acid residues more efficiently in terms of binding affinity rather than ligand but Zn complex could not afford the hydrogen bond formation with active site residue in both targets whereas ligand could afford the formation of hydrogen bond with each target (Table no.). These results decipher here that significant binding affinity of zinc complex to topoisomerase II enzyme than that to DNA gyrase enzyme confirms that Zn complex is more effective against *S.aureus*.

Table 4 . Result of docking studies of Zn complexes and ligand

Name	Binding Affinities (kcal/mol)with targets		Amino acids Involved in the interactions		H-bond with Distance	
	PDB=IJIJ	PDB=IKZN	PDB=IJIJ	PDB=IKZN	PDB=IJIJ	PDB=IKZN
Zn complex	-12.9	-11.2	Asp40, Thr42, Thr75, Gly83, Lys84, Ser85, Gly192, Asp195, Gln196, Val224 and Phe232	Met25, Asn46, Glu50, Ile78, His95, Glu117, His118, Val120 and Leu197	NIL	NIL
Ligand	-8.9	-7.9	Gly38, Ala39, His50, Leu70, Asp195, Gln196	Val43, Asn46, Glu50, Ile78, Ala96 and Val120	Asp195 (2.242 Å)	Asn46 (1.897Å)



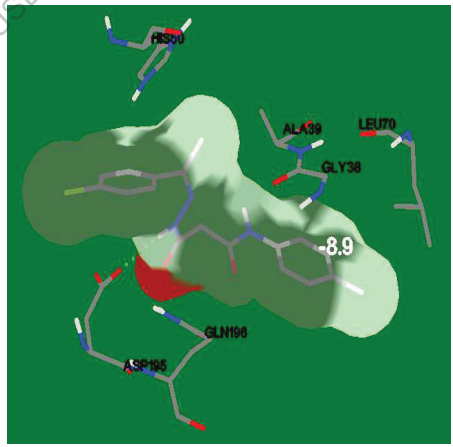


Figure12: A binding mode of Zinc complex with topoisomerase II (3D model of interactions between ligand and target)

Figure13: A binding mode of ligand with topoisomerase II (3D model of interactions between ligand and target)

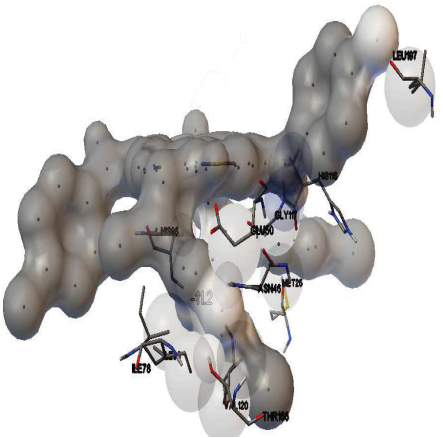


Figure14: A binding mode of Zinc complex with DNA Gyrase (3D model of interactions between ligand and target)

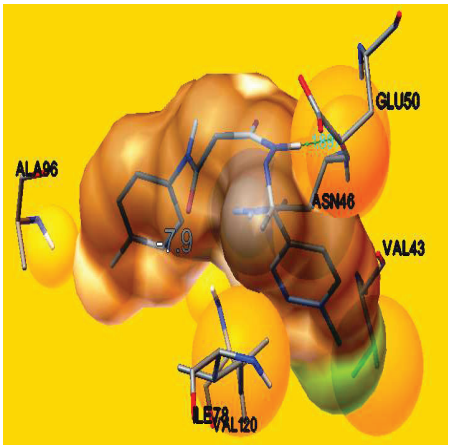


Figure15: A binding mode of ligand with DNA Gyrase (3D model of interactions between ligand and target)

4. CONCLUSION:

The synthesis and molecular structure of **Synthesis, Characterization, Molecular docking and Antibacterial activities of Bis-[(E)-3{2-(1-4-chlorophenyl) ethylidiene] hydrazinyl}-N-(4-methylphenyl)-3-oxo propanamide Zinc (II) complex** reported. The molecular structure of ligand and its Zn(II) complex are in agreement with the from CHN elemental analysis and HNMR spectroscopy results. In UV-Visible spectra, the bathochromic shift of C=N wavelength absorption spectra indicates the binding of azomethine nitrogen atoms from C=N to zinc $^{2+}$ ion. From the result of antibacterial study, both ligand and its zinc complex are explained the nontoxic behaviour towards both gram positive and gram negative bacteria. Molecular docking studies also reveal that zinc complex showed excellent binding to the receptor responsible for antibacterial effect.

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