

Zn (II) Metal Complexes with Schiff-Bases (Ligand) Synthesis, Characterization and its Biological activity

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Abstract: In this study, metal ions of Zn (II) and Schiff-base ligand have been synthesised using a 2:1 molar ratio (2L:M). To confirm the metal (II) complexes were effectively synthesised, the compound was characterized through PNMR, EDX, Elemental analysis, FTIR, LCMS, magnetic susceptibility measurement, and UV-Vis. The obtained results demonstrated that the ligand and metal ion were regarded as bidentate ligands. Its molar conductivity confirmed the non ionic nature of the Zn (II) complex. For this complex, a tetrahedral geometry influence has been suggested for the Zn (II) complex based on the data displayed. These Schiff base ligand metal complexes have been used for the treatment of Alzheimer's disease. For which, we have taken HSA as a model protein, being a major carrier in humans, and its activity was checked by using different biophysical methods. As evident in the figure, when HSA was aggregated sufficiently, increasing concentrations of the Zinc (II) complex acted as an anti-aggregatory agent, as a result of which aggregation was inhibited. It is noteworthy that the highest inhibitory concentration was found to be 250 μ M. Beyond this concentration there was saturation, and hence it was concluded that a complex based upon this phenomenon would be beneficial in the treatment of neurodegenerative diseases.

Keywords: Schiff Base Ligand with metal Zn (II) complex, biological activity.

1. Introduction

The present study highlighted that the Schiff-base ligands are vital in coordination chemistry, serving as versatile building blocks for metal complex synthesis within applications of photochemistry, spanning catalysis, and biological systems [1]. Due to their anticancer, anti-Alzheimer's, antibacterial, and enzyme-blocking properties, these ligands have been used throughout to assist in the creation of metal-based remedies and evaluated their potential as therapeutic factors [2-8]. Schiff-base ligands are broadly used in medicinal and coordination chemistry because of their capacity to form chelating bonds with metal ions, especially through nitrogen and oxygen donor atoms [9-14]. Several different biological functions, like that of hemoglobin synthesis, brain growth, bone formation, tissue development, and regulating insulin interaction, depend on the zinc (II) complex, a trace element [3]. The antibacterial, radical-scavenging, anti-inflammatory, and antidiabetic activities of Zn(II) compounds have been studied [4-9]. The fact that their antibacterial processes remain unclear despite a great deal of investigation. Conventional chelating ligands, especially those containing nitrogen and oxygen donor atoms, have shown remarkable biological behaviour due to their natural capacity to bind metals [10]. To investigate the biological and physical characteristics of metallic ions, a variety of ligands, including Schiff-bases, amines, 2-aminobenzimidazole, and substituted salicylaldehydes corresponding derivatives, have been efficiently bonded to metal ions [11-15].

Thereby, several reports and publications publish in the past decade and current on the transition and non-transition metallic compounds with nitrogen-donor ligands, including Schiff-bases, N-heterocycles, ammonia, amines, and urea derivatives, remain a highly diverse and rapidly evolving class of compounds, with applications in materials science, medicinal chemistry, pharmaceuticals, organic and inorganic synthesis, semiconductors, polymers, ceramics, and bioinorganic chemistry

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[16–24]. As a consequence of durability together with adaptability, conventional Schiff base ligands, which are usually made by condensation reactions, are regarded as highly specialized ligands. The identification of co-ligands, the amount and configuration of molecule ligands, and the overall metallic stereochemistry process initially affect the characteristics and activation of nitrogen-based metallic complexes [25–26, 35]. The Schiff base metal complexes are being presently emphasized for their potential medicinal uses, such as antiviral activity against COVID-19, indicating their wide range of therapeutic possibilities [36–39]. In alignment with this research, novel Schiff base ligands derived from α -(1,3-Oxo-Indane-2yl)-Ethylidene-p-Toluidine were synthesized and coordinated to Zn(II) ions. Their structural features and anti-Alzheimer's activity were systematically investigated. Given their capacity to stabilize proteins and inhibit aggregation, these Schiff base ligands and their Zn(II) complexes represent promising candidates for the development of future Alzheimer's disease therapeutics. Human serum albumin (HSA) was employed as a protein model to evaluate the compounds' anti-aggregation and neuroprotective potential.

2. The Experimental Section

2.1. Methods and Chemicals

All reagents and solvents were of analytical grade (AR) and purchased from Sigma-Aldrich, including 2-acyl indan-1,3-dione and zinc chloride (ZnCl_2). UV–Vis absorption spectra were captured into ethanol at room temp. using a PerkinElmer Lambda 850 spectrophotometer over 300–600 nm. PNMR spectrum were obtained on a JNM-ECZ400S/L (400 MHz) spectrometer in D_6 -DMSO, with tetramethylsilane (TMS) as the internal standard. FTIR spectra were measured using a PerkinElmer 1600 spectrophotometer with KBr pellets in the $4000\text{--}400\text{ cm}^{-1}$ range to confirm metal coordination. Molar conductance (Λ_m) of 1 mM ethanol solutions was established at 25°C using a MK-509 conductivity meter. LC–MS was performed on a Triple TOF 5600+ spectrometer (Sciex), and elemental analysis (C, H, N) was conducted via energy-dispersive X-ray (EDX) using a JSM 6510 LV scanning electron microscope (SEM). Magnetic susceptibility of the Zn(II) complexes was measured by Gouy balance (Model 7641C), within $[\text{HgCo}(\text{SCN})_4]$ as the standard, at the Deptt. of Physics, AMU, Aligarh. Alzheimer's activity assays were performed at the Department of Biochemistry, AMU, Aligarh. Melting points were recorded uncorrected using a Kofler apparatus (Nagemann, Germany).

2. 2. Preparation of ligand

The Schiff base was synthesized through refluxing p-toluidine and 2-acyl Indan-1,3-dione in an equimolar amount, which was mixed with 50 ml of ethanolic solutions. It is refluxed for 3-4 hours, a yellowish-colored precipitate was formed, and it was cooled at room temperature and dried. Analysis was done on the yield of 79.2% of the yellowish Schiff base product that was produced (m.p. 34.5°C). Anal. Calc. for $\text{C}_{18}\text{H}_{15}\text{O}_2\text{N}$: C = 77.96 (76.46); H = 5.45 (4.75); N = 5.05 (4.62) %. FT-IR (KBr, cm^{-1}): 1746 (C=O), 1620 (C=N) [27-29, 54-56]; $\lambda_{\text{max}} = 280\text{ nm}$ and $\lambda_{\text{max}} = 310\text{ nm}$ [29]; $^1\text{H NMR}$ (DMSO-d_6): 3.4 (s, 1H, H-2), 6.9 (m, 2H, H-4 & H-5), 7.1 (m, 2H, H-6 & H-7), 6.8 (m, 2H, H-2 & H-6), 6.5 (m, 2H, H-3 & H-5), 1.5 (s, CH_3), and 2.3 (s, CH_3).

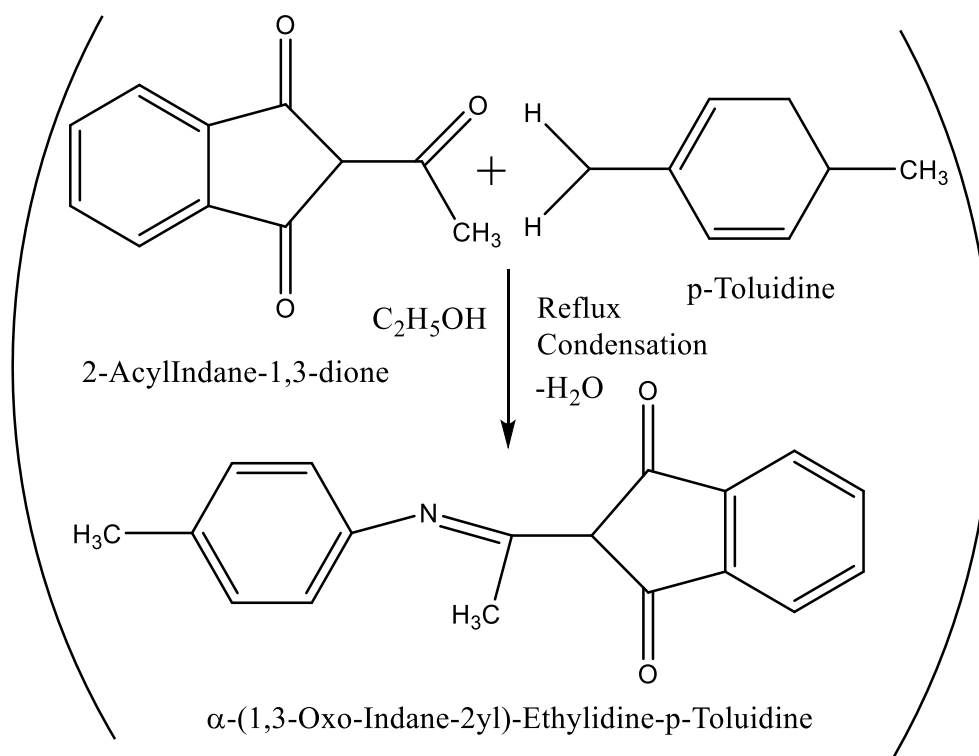


Fig 1: Schematic representation of Schiff base ligand

2. 3. Synthesis of metal complex

After dissolving 1.0 mol (0.70 g) of ZnCl_2 in 45 ml of ethanol, it was gradually added to the 2.0 mol (1.40 g) of ligand solution in 45 ml of ethanol. For three hours, the mixture was stirred. As the solvent evaporated, the end result observed was white precipitate (yield 1.4 g, 66.66%). M.p.: 22 °C. Anal. Calc. for $[(\text{C}_{18}\text{H}_{15}\text{O}_2\text{N})_2\text{Zn}]\text{Cl}_2$: C = 62.60 (61.10), H = 4.34 (3.90), N = 4.05 (3.91) %; μ_{eff} : 0.0 BM. The compound was soluble in ethanol and common organic solvents. FT-IR (KBr pellet cm^{-1}): 1714 (C=O), 1630 (C=N); λ_{max} = 340 & 475 nm [27-29]; ^1H NMR (DMSO-d_6): 3.5 (s, 1H, H-2), 7.9 (m, 4H, H-4, H-5, H-6 & H-7), 6.8 (m, 2H, H-2 & H-6), 6.5 (m, 2H, H-3 & H-5), and 2.3 & 2.1 (s, $2 \times \text{CH}_3$).

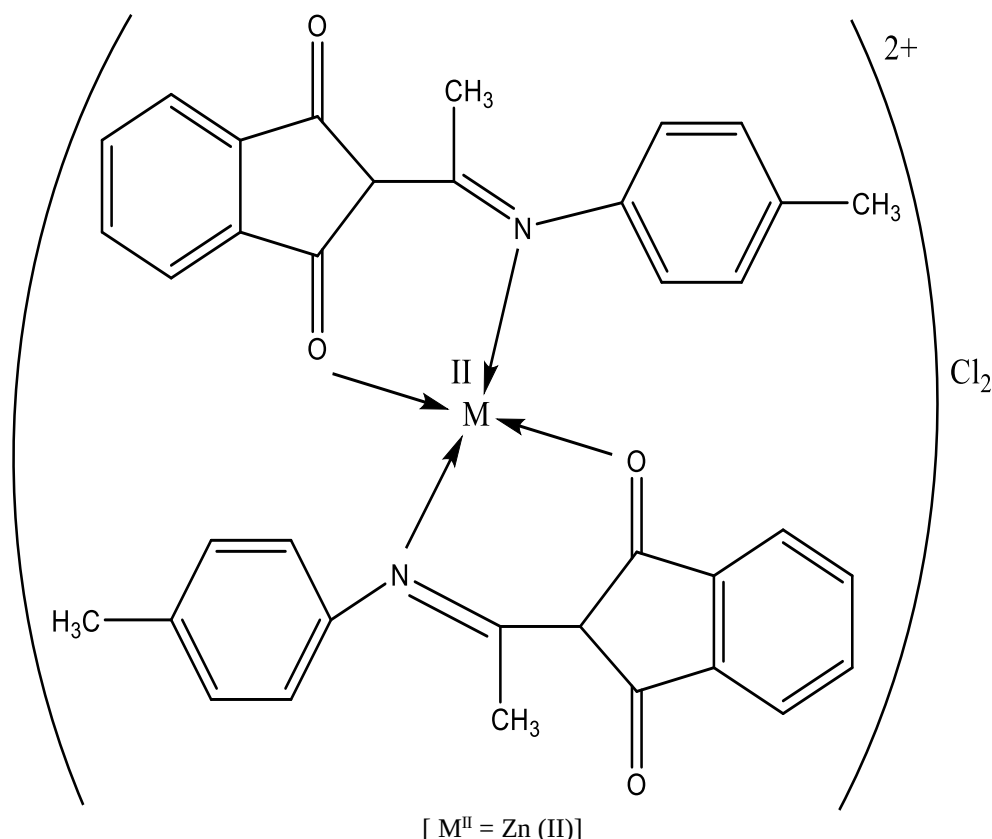


Fig 2: Schematic representation of Schiff base metal complex

2.4. Biological activity of synthesized compound

2.4.1. Protein Sample Preparation and Aggregation Studies

Human serum albumin (HSA) was selected as the model protein due to its well-characterized structure and critical role in drug transport; structural alterations in HSA can impair its biological functions. A stock solution of HSA (5 mg/mL) was prepared, and aliquots were taken as required for the experiments. Parallel sets of samples were prepared with increasing concentrations of the Zn(II) complex into evaluate its effect on protein aggregation. For the native control, HSA was subjected to elevated temperature (66°C) to induce aggregation. In samples treated with the Zn(II) complex, aggregation was observed to be inhibited, and the results were recorded accordingly [30].

2.4.2. Turbidity measurements at 360 nm for unfolding

The absorbance of HSA samples, either with or without the Zn(II) complex, was recorded at 360 nm using a 1 cm pathlength cuvette. Measurements were carried out on a PerkinElmer Lambda 25 double-beam UV-Vis spectrophotometer. The final protein concentration was maintained at 10 μM , and all measurements were performed in triplicate. Experiments were conducted using a sodium phosphate buffer at pH 7.4 [30].

2. 4. 3. Thioflavin T (ThT) assay

The Thioflavin T fluorescence assay was performed using a Shimadzu fluorescence spectrophotometer (model 5301 PC) connected to a Julabo Eyela water circulator. Fluorescence measurements were captured at a depolarization wavelength of 440 nm, with both excitatory and emission slit widths set to 5 nm. Emission spectra were collected over the range of 450–600 nm. The ThT concentration was determined at 412 nm using a molar extinction coefficient ($\epsilon = 36,000 \text{ M}^{-1} \text{ cm}^{-1}$). After the addition of ThT to the sample in a 1:2 ratio, the mixtures were incubated in the dark for 15 minutes prior to fluorescence measurement [31-32].

2. 4. 4. ANS fluorescence assay

ANS fluorescence measurements were conducted using a Shimadzu spectrophotometer (RF-5301 PC) coupled with a Julabo Eyela water circulator. The absorbance corresponding to the ANS concentration was determined at approximately 350 nm using a molar extinction coefficient ($\epsilon = 5,000 \text{ M}^{-1} \text{ cm}^{-1}$). Fluorescence emission spectra were recorded in the range of 400–600 nm, with an excitation wavelength set at 380 nm. Samples were incubated with ANS at a 1:50 molar ratio and kept in the dark at room temperature for approximately 30 minutes prior to measurement. The slit widths for both excitation and emission were maintained at 5 nm [33–34].

2. 4. 5. Rayleigh light scattering

Rayleigh light scattering (RLS) measurements were carried out using a Shimadzu fluorescence spectrophotometer (RF-5301 PC) equipped with a 1 cm pathlength quartz cuvette. The aliquots were gently agitated, and excitation was set near 350 nm. Emission spectrum were observed over the range of 300–400 nm, with both excitation and emission slit widths maintained at 1.5 nm [35].

2. 4. 6. Far UV CD measurement

Secondary structural alterations in HSA were evaluated using far-UV circular dichroism (CD) spectroscopy. Spectra were recorded at a scan speed of 50 nm/min within a response time of 2 seconds and a data pitch of 0.1 nm. The measurements were performed using a 0.1 cm pathlength quartz cuvette, maintaining a protein concentration of 10 μM and a spectral range of 190–250 nm. All observations were conducted at 25°C. The obtained CD data were expressed as mean residue ellipticity. (MRE, in $\text{deg} \cdot \text{cm}^2 \cdot \text{dmol}^{-1}$) using the following equation:

$$\text{MRE} = \frac{\theta_{\text{obs}}(\text{mdeg})}{c_p \times l \times n \times 10}$$

where θ_{obs} is the observed ellipticity in millidegrees, c_p is the molar concentration of the protein, l is the pathlength of the cuvette in centimeters, and n is the number of amino acid residues [36–37]

3. Result & Discussion

The Schiff base ligand was synthesized by refluxing equimolar amounts of 2-AcylIndane and p-toluidine in ethanol. The resulting compound was characterized using various analytical techniques, including FTIR, EDX, PNMN, LC–MS, UV–Vis spectroscopy, molar conductivity, and magnetic susceptibility measurements. The corresponding metal complex was subsequently prepared through a direct reaction between the synthesised ligand and the respective metal salt with a continuous stirrer at normal temperature.

3. 1. FTIR Spectroscopy of Metal Complex

The FTIR spectrum of the Schiff-bases ligand and its corresponding metal complex are presented into Fig. 1. A strong and distinct absorption band observed at 1746 cm^{-1} corresponds to the $\nu(\text{C=O})$ stretching vibration, confirming the presence of the Schiff base functional group. The imine (C=N) stretching band appeared at 1620 cm^{-1} [38–40]. In the metal complexes, this imine band shifted to lower frequencies (1544 and 1601 cm^{-1}), indicating the coordinating of the imine nitrogen atom with the metal center. Additionally, the appearance of $\nu(\text{C=O})$ and $\nu(\text{C=N})$ vibrations at 1714 cm^{-1} and 1630 cm^{-1} , respectively, in the complex spectra supports metal–ligand coordination. These observations suggest that both the nitrogen and oxygen atoms of the imine group participate in coordination with the Zn(II) ion, confirming complex formation [41–43].

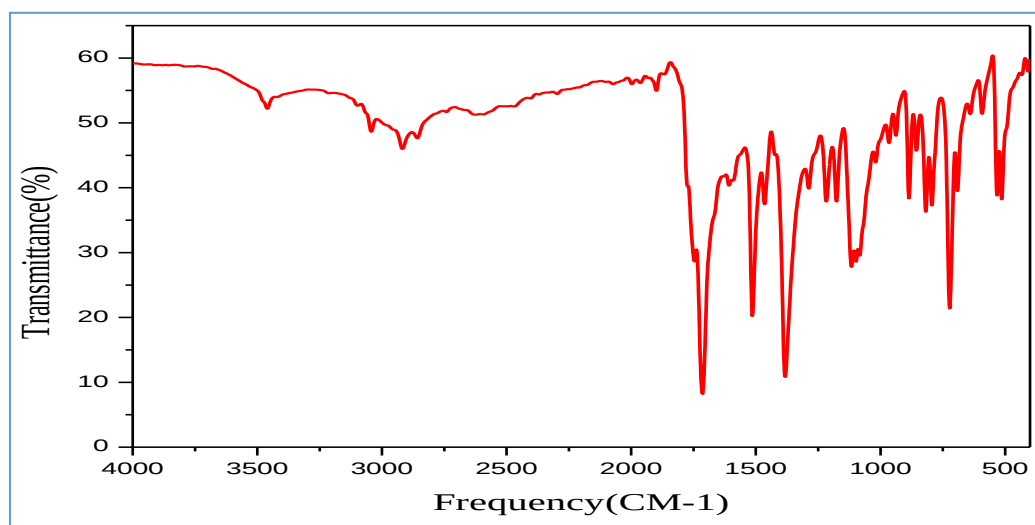


Fig.3: Schematic representation of FTIR analysis of Schiff base (Ligand)

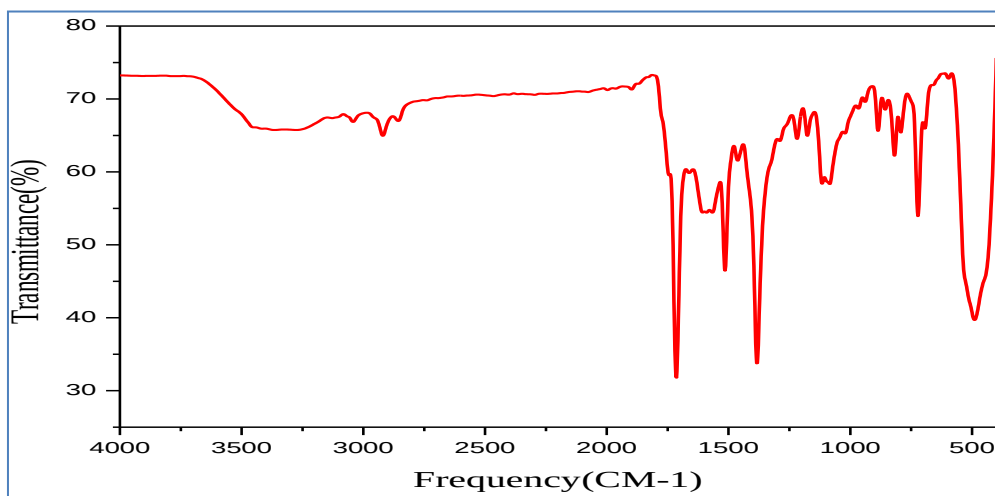


Fig.4: Schematic representation of FTIR analysis of Zn(II) complex

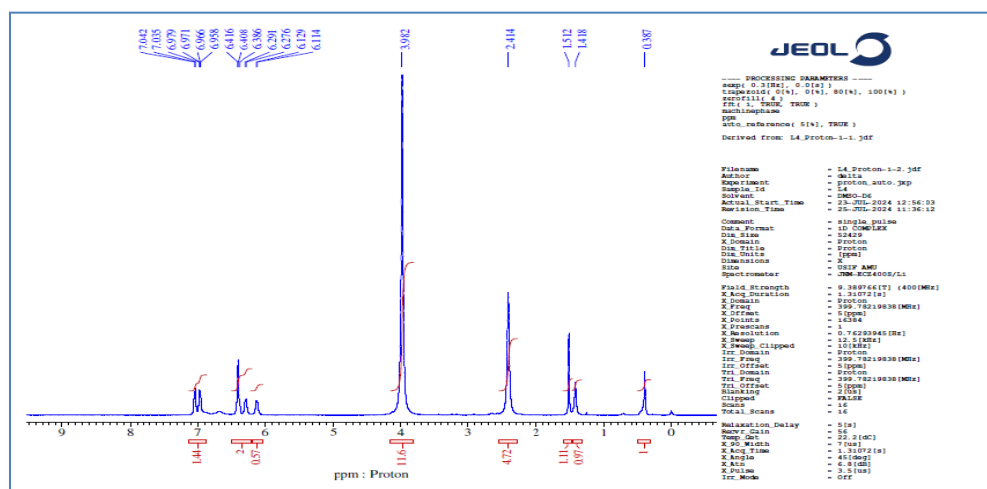
3. 2. Electronic spectral studies

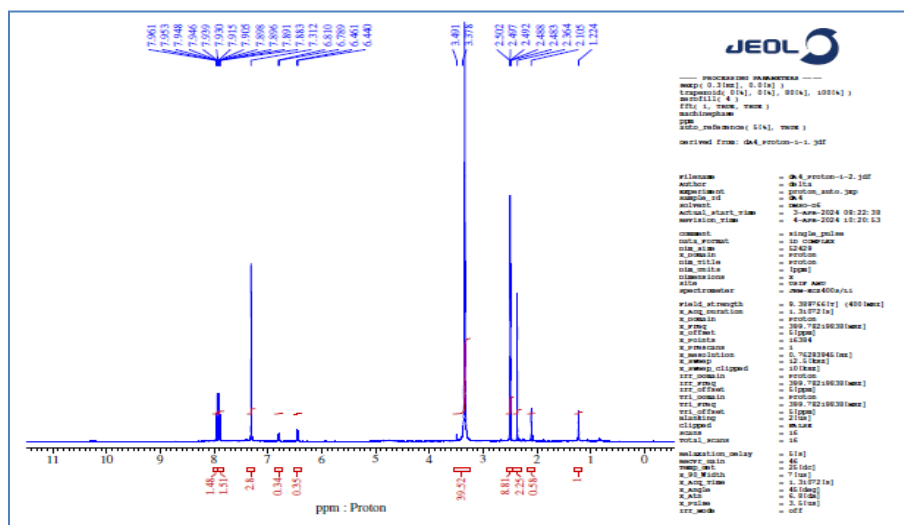
The electronic spectrum data and magnetic moment values of the synthesized complex provide insights into its structural geometry. The complex exhibited diamagnetic behavior, with a magnetic moment of zero [44], which is consistent with a completely filled 3d orbital configuration. The corresponding electronic spectra, presented in Fig. 2, display the maximum absorption wavelength (λ_{max}) values along with their respective transitions. At room temperature, the UV–Vis absorption spectrum of the ligand and its complex were recorded in the 200–700 nm range. The free ligand exhibited characteristic $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions at $\lambda_{\text{max}} = 280$ nm and 310 nm, respectively, attributed to the imine chromophore. Upon complexation, the $n \rightarrow \pi^*$ transition shifted to longer wavelengths (410–475 nm), indicating the involvement of the imine nitrogen in coordination. The Zn–ligand complex (ZnL) also displayed bands corresponding to ligand-to-metal charge transfer (LMCT) transitions.

In combination with the FTIR and metal analysis results, these findings suggest that the Zn(II) complex exhibits a four-coordinate geometry, consistent with a square planar configuration. Although Zn(II) ions can theoretically adopt a tetrahedral geometry through sp^3 hybridization [69–71], the steric constraints and donor atom arrangement within the ligand system favor a square planar geometry. Moreover, spectral observations confirm that the ligand acts as a bidentate donor, coordinating to the metal ion through both nitrogen and oxygen atoms [44–46].

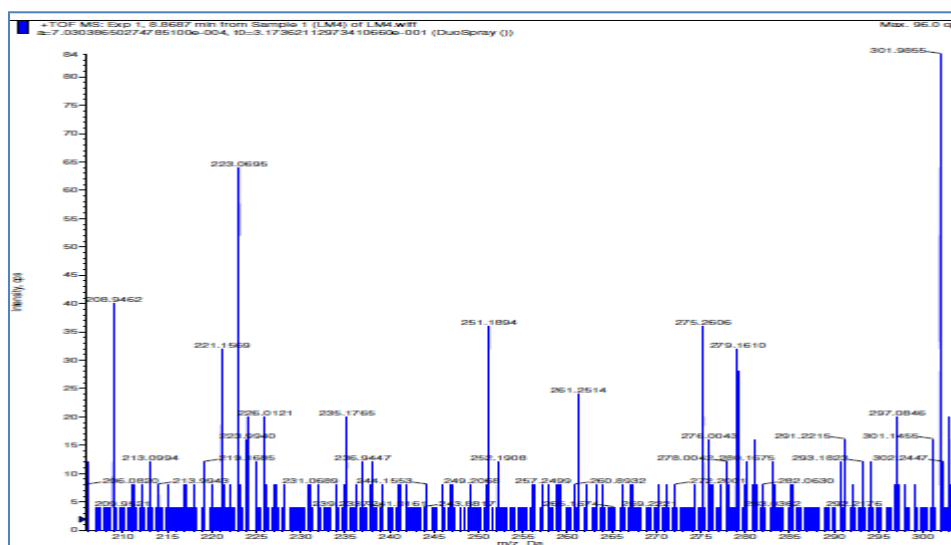
3.4. PNMR

The PNMR spectral data, along with the corresponding experimental assignments, are presented in Fig. (5 & 6). All proton signals appeared within their expected chemical shift regions [48], supporting the proposed bonding mode inferred from FTIR analysis. The Zn(II) complex displayed downfield shifts in several proton resonances compared to the free ligand, indicating coordinating of the imine nitrogen and carbonyl oxygen atoms to the Zn(II) ion. The integration of the proton peaks corresponded well with the theoretically calculated values based on the elemental (C, H, and N) analysis, confirming the stoichiometry of the complex. Furthermore, the coordinating solvent DMSO exhibited negligible influence on the PNMR spectra of both the ligand and its corresponding Zn(II) complex [49].

Fig.5: Schematic representation of ^1H NMR of Schiff base (Ligand)



3. 5. Liquid Chromatography Mass Spectra



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The structural confirmation of the synthesised Schiff-base ligand and its Zn(II) complex was carried out using liquid chromatography–mass spectrometry (LC–MS). The experimental molecular ion peaks (m/z values) were found to be consistent with the calculated molecular weights, thereby supporting the proposed molecular formulas of the compounds. The LC–MS spectra of the free Schiff-base ligand exhibited a prominent molecular ion peak at $m/z = 278.0042$ (Fig.7), corresponding to the ligand molecular ion (M^+). In the case of the Zn(II) complex, the LC–MS spectrum displayed a molecular ion peak at $m/z = 690.5303$, along with an additional isotopic peak at $m/z = 691.5334$ (Fig. 8). The observed fragmentation pattern was in good agreement with the predicted structure, confirming the successful formation of the Zn(II) complex and validating the proposed molecular composition [27].

3. 6. Analysis of Molar Conductivity

The molar conductivity of the Zn (II) complex was measured at room temperature using a 10^{-3} M solution prepared in ethanol. The observed molar conductivity value of $17.73 \pm 0.11 \text{ S} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$ indicates that the complex exhibits non-electrolytic behavior. This relatively low conductivity value, compared with standard electrolyte solutions, suggests limited ion dissociation of the complex in ethanol, confirming its neutral or weakly associated nature in solution.

3. 7. Turbidity measurements for unfolding of HAS

Turbidity measurements were used to monitor the unfolding and aggregation of HSA. Increased turbidity reflects greater aggregation, which occurs when hydrophobic residues buried within the polypeptide chains become partially or fully exposed at elevated temperatures, leading to increased absorbance. As shown in Fig. 9, incubation of the protein in the absence of any complex resulted in enhanced absorbance, consistent with exposure of hydrophobic residues. In contrast, co-incubation of HSA within the Zn(II) complex led to a decrease in absorbance, indicating the inhibitory effect of the complex on protein aggregation. The inhibition reached a plateau at a certain concentration, with no significant further reduction in absorbance beyond $250 \mu\text{M}$, suggesting this as the maximum inhibitory concentration. This effect is likely due to the interaction of the Zn(II) complex with the hydrophobic regions of the polypeptide, stabilizing the protein and preventing aggregation [50–54].

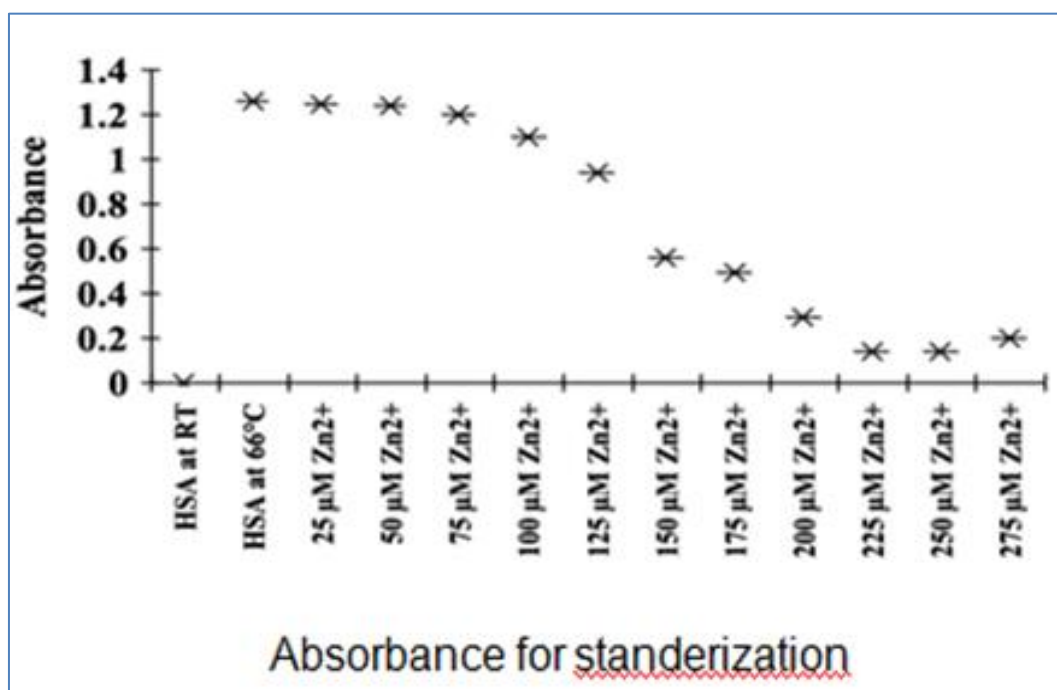


Fig.9: Absorbance for standerization of Zn(II) metal complex

3. 8. ThT measurements

Thioflavin T (ThT) is an aggregate-specific dye that binds to exposed hydrophobic residues, resulting in enhanced fluorescence. As illustrated in Fig. 10, HSA alone exhibited low fluorescence intensity; however, incubation at elevated temperature (66°C) led to a marked increase in fluorescence, indicating aggregate formation. Upon addition of the Zn(II) complex, a significant reduction in fluorescence intensity was determined, demonstrating the inhibitory effect of the complex on thermally induced HSA aggregation. These results are consistent with previous observations, showing that a concentration of $250 \mu\text{M}$ Zn(II) complex provides maximal inhibition. The reduction in fluorescence is likely due to stabilization of the polypeptide chains through hydrophobic interactions, which limits aggregate formation [55–58].

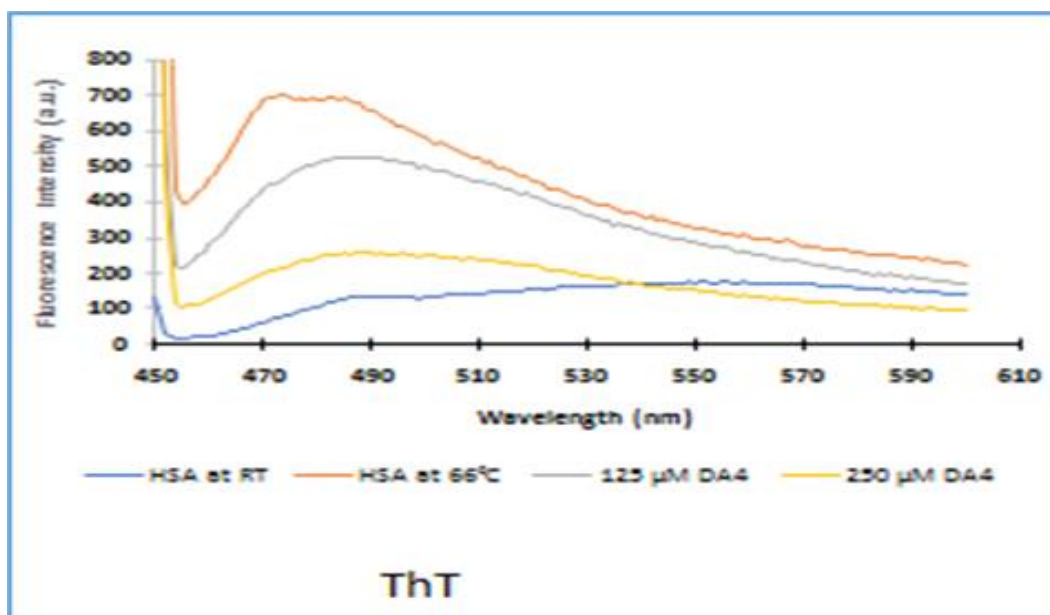


Fig10: ThT spectra in the absence & presence of Zn(II) metal complex

3. 9. ANS measurements

8-Anilino-1-naphthalene-sulfonic acid (ANS), a dye specific for hydrophobic patches, binds to exposed hydrophobic regions of proteins. As shown in Fig. 11, the fluorescence intensity decreased in the presence of the Zn(II) complex, indicating its inhibitory effect on protein aggregation. The complex likely intercalates into the polypeptide backbone and forms hydrophobic interactions, thereby stabilizing the protein and preventing aggregation under elevated temperatures. These results are consistent with previous observations, with the maximum inhibitory effect occurring at a concentration of 250 µM [59-61].

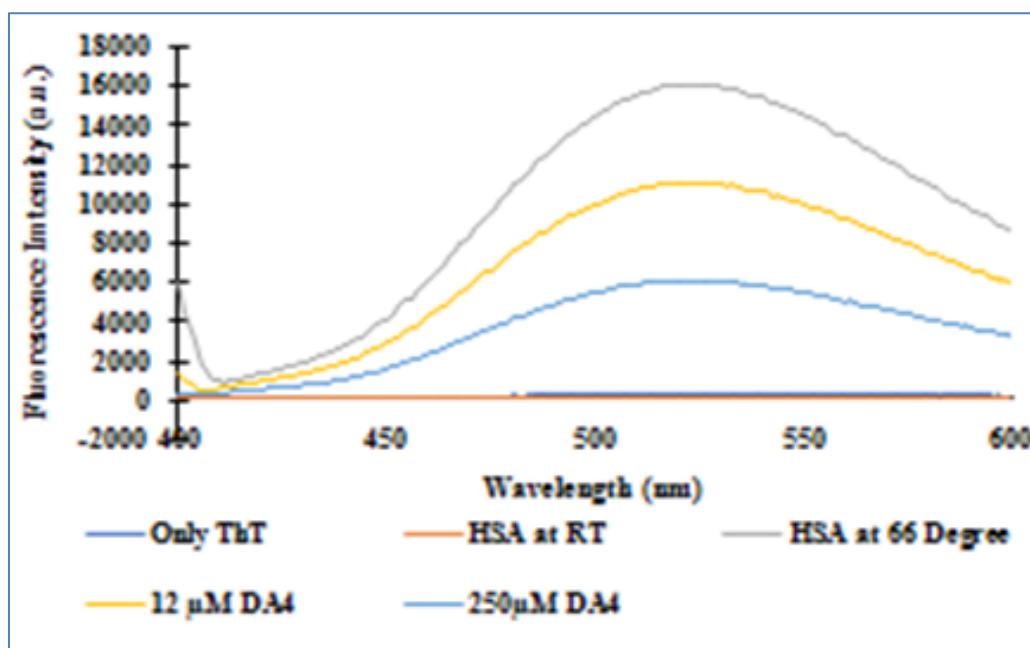


Fig.11: ANS spectra in the absence & presence of Zn (II) metal complex

3. 10. Rayleigh scattering

Rayleigh light scattering measurements were performed to support previous findings regarding the reduction in fluorescence intensity in the presence of the Zn(II) complex. A dose-dependent decrease in synchronous spectra was observed, confirming the inhibitory effect of the Zn(II) complex across multiple biophysical assays. As illustrated in Fig. 12, samples incubated at elevated temperatures showed no increase in fluorescence intensity upon addition of the Zn(II) complex, highlighting the stabilizing and protective effect of the synthesized compound on protein aggregation [62-64].

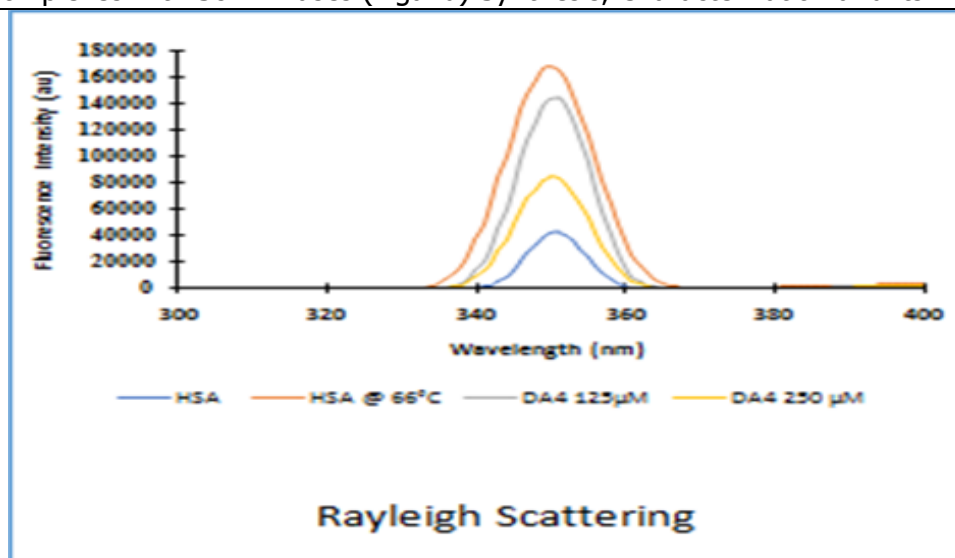


Fig.12: Rayleigh Scattering measurements of Zn (II) metal complex

3. 12. Measurements of far UV CD

Far-UV circular dichroism (CD) spectroscopy, a well-established technique for monitoring protein secondary structure, was employed to assess structural changes under elevated temperature conditions. As shown in Fig. 13, HSA exposed to high temperature exhibited a negative peak at 217 nm, indicative of predominant β -sheet formation. Upon incubation with the Zn(II) complex, two new peaks appeared, reflecting a shift toward native-like α -helical conformation. This demonstrates that the Zn(II) complex effectively inhibits thermal aggregation at a specific concentration, with maximal inhibition observed at 250 μ M. Beyond this concentration, no further significant reduction in β -sheet content was detected, confirming that 250 μ M represents the optimal inhibitory concentration [65-66].

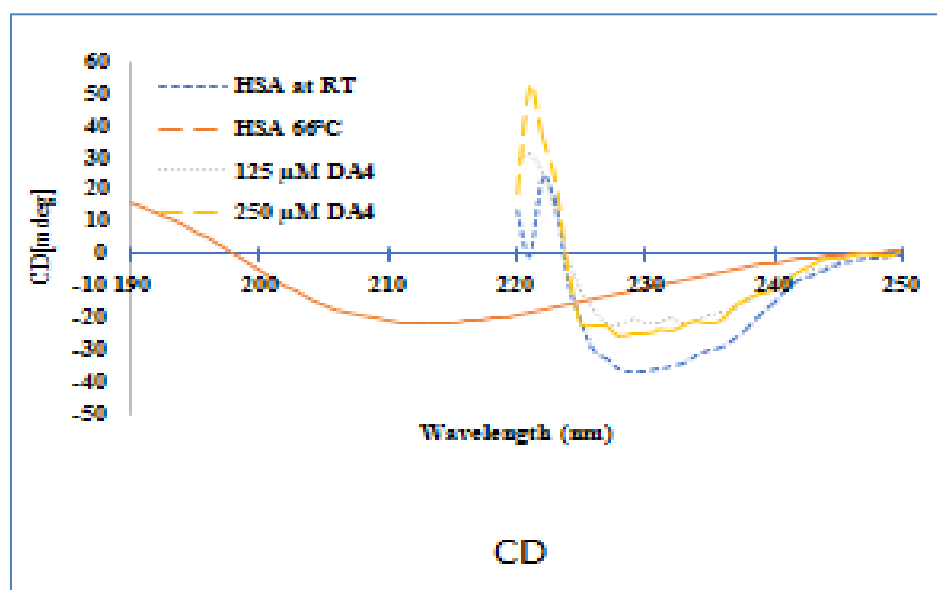


Fig.13: Far UV-CD spectra in the absence & presence of Zn (II) metal complex

4. Conclusions

In this work, zinc chloride is reacted with a lot of indane ethylidene-p-toluidine aniline to establish Schiff-base ligands under optimal circumstances. Characterization of the resulting Zn(II) complexes indicated reduced hydration compared to the free ligands, with ligand properties significantly influencing complex formation. Analyses using Ft-IR, LCMS, magnetic susceptibility, PNMR, and molar conductance confirmed the presence of coordination sites, while electronic spectral data suggested a tetrahedral geometry for the Zn(II) complexes, and the structure of the ligand and metal complex was confirmed. Schiff base metal complexes represent a significant and compelling area of research due to their ease of synthesis, cost-effectiveness, and versatile chemistry. Biological evaluation through various biophysical assays demonstrated that the Zn(II) complexes exhibit anti-Alzheimer's activity, with maximal inhibitory effects observed at 250 μ M, effectively preventing protein aggregation. These findings suggest that molecules derived from such complexes may have potential therapeutic applications for Alzheimer's disease, a neurodegenerative disorder. Nevertheless, further validation under in vivo conditions is warranted to confirm their efficacy.

5. Acknowledgement

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Abbreviation

Human Serum Albumin = HSA, Tioflavin T = ThT, Circular dichroism = CD, Liquid Chromatography Mass Spectra = LC-MS, Energy dispersive X-Ray = EDX, Doublet = d, Singlet = s, Multiplet = m, Fourier Transform Infrared Spectroscopy = FTIR, α -(1,3-Oxo-Indane-2yl)-Ethylidene-p-Toluidine = IEPT, 8-Anilino-1-naphthalene-sulphonic acid = ANS, RB = Round bottom flask, and Ultraviolet-Visible Spectroscopy = UV.

Declaration

Conflict of interest / COI statement

The authors report no conflicts of interest concerning the publication of this manuscript.

Ethical approval: N/A.

Consent to Publish: All authors have reviewed and approved the final manuscript.

Authorship contribution statement

V. K. S.: Supervision, resources, investigation, editing, and writing review. D. K. S.: Writing, conceptualization, original draft, result analysis, methodology. B. B. S.: Editing and formal analysis.

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