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A Theoretical and Experimental Evaluation of Piprazine Ligand Mediated Zinc Complex Towards BSA Protein Binding

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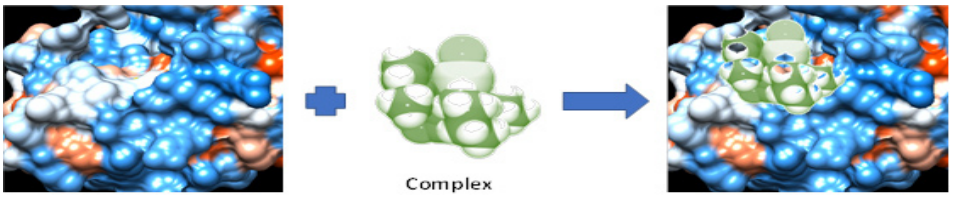
ABSTRACT

In this work, a Schiff base ligand namely 4-((2-(piprazine-1-yl)ethyl)pent-2-en-2-ol (HL) has been synthesized. Further the reaction between HL and $NiCl_{2.6}H_{20}$ salts has resulted in Schiff base complex with general formula [Zn(L)].Cl. The ligand HL and the corresponding Zn(II) complex was further characterized using various spectroscopic techniques, such as, FT-IR, ESI-MS, and elemental analysis. In the recent scenario, research in the field of protein dynamics is very crucial as these are the major part of the biological systems, and interactions of those macromolecules are responsible for various pathological diseases. Most of the metals inside the biological system shows some kind of affinity to bind with those macromolecules. Herein, it is our unmet need to address the issue by preparing some metal complexes. Therefore, fluorescence spectroscopy was introduced to check the protein binding study of BSA using Stern-Volmer equation.

Graphical Abstract



KEY WORDS: SCHIFF BASE, BIOLOGICAL SYSTEMS, METALS INSIDE THE BIOLOGICAL.

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INTRODUCTION

Biological processes drives to recognize the fundamental principles by the use of transition metals and its functionality due to its diverse nature in the quest of the scientist, which ultimately assistances to advance various structural and more significantly functional model systems.[1-3] Besides studying diverse biological procedures these metal ions are tend to retain the assets like antifungal, antibacterial, antiproliferative, antimicrobial and anticancer activity. These transition metal ions also perform a crucial part in terms of structural organization and overall functionality.[4-6].

Moreover, small metal complexes are quite interactive with essential protein is a current topic of main research as there is adequate potential for the progress of new therapeutic agents predominantly screening antitumor activities and the opportunity of conveying these molecules throughout the physiological organization. [6-10] Zinc and copper are two basic examples among the various transition metal ions, which have previously revealed promising capabilities in many of the above stated area.[11-15] The ability of the serum albumin to bind towards the diverse endogenous and exogenous samples delivers this plasma protein to achieve an effective character for conceivable drug delivery. Thus, the study of the interaction of small molecules with different types of serum albumin is also crucial for the understanding of metallo-pharmaceutical pharmacokinetics and structure–activity relationships. The studies on the interactions between proteins and zinc and copper were not studied much.[16-21]. Thus, we account the synthesis and characterization of a new mononuclear zinc complex [Zn(L)].Cl [where, ligand, HL=1-Phenyl-3-(2-piperazin-1-yl-ethylimino)-but-1-en-1-ol]. The interaction of Zn(II) complex with bovine serum albumin (BSA) also have been considered that displayed favorable consequences with effectual affinity towards the protein.

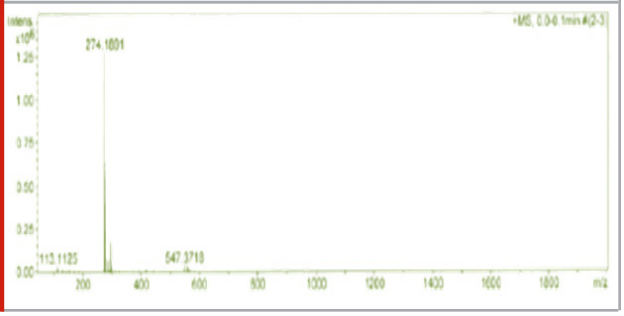
Experimental Section

MATERIAL AND METHODS

We used the chemicals from Sigma aldrich and applied without additional refinement. A BRUKER TENSOR 27 instrument were recorded Infrared spectra (4000 to 500 cm^{-1}) with using KBr pellets. We used Bruker-Daltonics Mass spectrometric microTOF-Q II mass spectrometer for study. Moreover, the elemental analyses were done with a ThermoFlash 2000 elemental analyzer. Emission spectroscopy were measured in a Horiba JobinYvon (Model: FM-100) made Fluoromax-4p spectrofluorometer from using a 1 cm path length-based quartz cuvette. UV-Visible (200 to 800 nm) spectra were recorded in 0.1 cm path length cell (Hellma, Muellheim/Baden, Germany) using a scan rate of 20 nm min–1 and band width of 1 nm. The ligand, HL and corresponding complexes were characterized using various spectroscopic techniques, such as, FT-IR, ESI-MS, and elemental analysis.

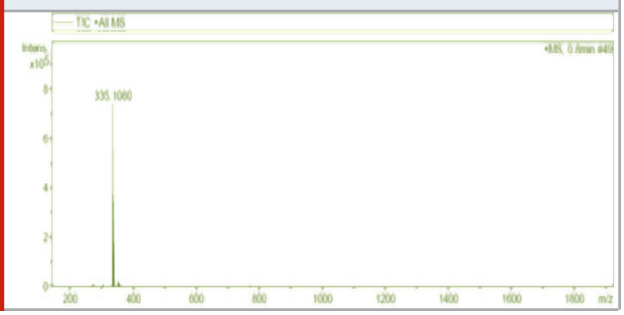
Synthesis of 4-((2-(piperazin-1-yl)ethyl)imino)pent-2-en- 2-ol (HL): 0.65 g of amino ethyl piperazine (5 mmol) poured into 25 mL of MeOH was mixed with a solution of 0.50 g (5 mmol) of acetyl acetone in 20 mL of methanol. The mixture was then refluxed for 4 h at 60 degree centigrade. A yellow oily compound is formed after evaporating the volatile solvent. Yield: 84%. Anal. Cacl (%): $C16H_{23}N_3O$: H, 8.48; C, 70.30; N, 15.37; O, 5.85. Found (%): C, 71.08; N, 15.88; O, 6.02. $[C16H_{23}N_3O + H]^+$ (m/z) Calculated- 274.18 (m + H)+; obtained- 274.18 $(m + H)^+$ (Figure 1).

Figure 1: ESI-MS of Schiff base ligand (HL)



Synthesis of complex, [Zn(L)].Cl: Ligand, HL (0.062 g, 0.25 mmol) and $ZnCl_{2.6}H_{20}$ (0.61 g, 0.25 mmol) containing 15 mL of MeOH solution was stirred at refluxing condition for 4 h and the producing light green coloured solution. After that, the solution was concentrated by evaporating the methanol solvent. Green needle shaped crystals were finally obtained after two or three days by keeping the reaction mixture to the slow evaporation at room temperature. Yield: 85%. Anal. Calcd (%): $C16H_{21}ClN_3ZnO_5$: H, 4.93; C, 44.74; N, 9.78. Found (%):H, 5.07; C, 44.64; N, 9.26. $[C16H_{21}N_3ZnO]^+$ (m/z in positive ESI-MS mode) calculated – 335.05 $(m)^+$; obtained – 335.10 $(m)^+$ for $[Zn(L)]^+$. Designated infra-red data on KBr pallets (ν/cm^{-1}): 160_3-160_4 (C=N), 2951 (N-H) (Figure 2).

Figure 2: Electrospray ionisation mass spectrometry data of [Zn(L)].Cl



RESULTS AND DISCUSSION

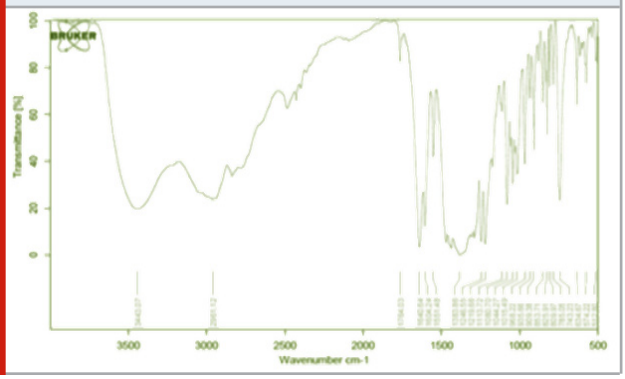
Synthesis of ligand and complex: The reaction of 1 : 1 molar ratio of amino ethyl piperazine with 1-phenyl-1,3-butanedione in methanol directed to the development of Schiff base ligand, HL (Scheme 1). The ligand can

behave as a tetradentate ligand or as a tridentate ligand depending upon its conformation. That is why these types of ligand may be called as flexidentate ligand. Upon reaction of HL with zinc per chlorate in MeOH, a light green colour medium was found. The solution was then dried to the rotary evaporator and the solid compound was collected. A pinch of the sample compound was then dissolved in the acetone for get the nice crystals of [Zn(L)].Cl within 3-4 days at room temperature (Scheme 1).

Scheme 1. Formation of zinc complex with the piperazine moiety.

FTIR Spectroscopy: The IR spectra of zinc complex (Figure 3) have a prominent band around 1603 and 1604 cm−1 detectable to ν(C=N) stretching mode respectively. Furthermore, Zn(II) complex shows intermediate intensity bands in the range of 2951 to 3443 cm^{-1} because of ν(N–H) stretching.

Figure 3: FTIR of complex, [Zn(L)].Cl.



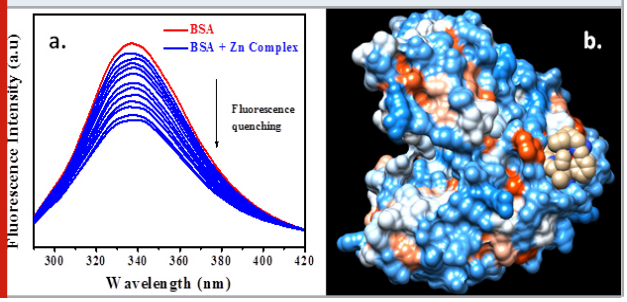
BSA binding study: Interaction of transition metal complexes with BSA protein are generally checked by the intrinsic fluorescence intensity. Generally, tryptophan, tyrosine, and phenylalanine residues are the main intrinsic component for showing emission intensity of a protein. The fluorescence spectrum of complex (Figure 4) with BSA shows that there is a sequential decrease in the fluorescence intensity. The Stern–Volmer equation is given in the following for determination of various parameters.

$$\frac{F_0}{F} = 1 + k_q \tau_0 [Q] = 1 + K_{SV}[Q]$$

where F and F0 are the emission intensities in the presence and the absence of a quencher, k_q is the rate constant for the bimolecular quenching, τ_0 is the fluorophore's average life time when the quencher is not present and [Q] is quencher (here complex) concentration. K_{SV} is the Stern-Volmer quenching constant in M^{-1}.

To corroborate the experimental results, the fluorescence quenching affinity further docked with BSA protein (PDB ID: 3V03). The prominent interactions were found with several amino acids of the protein chain, which are basically joined through hydrogen and van der Walls bonding. Thus, we can say that the experimental results are very much similar to the theoretical interpretation.

Figure 4: Quenching of the fluorescence of bovine serum albumin BSA by Zn(II) complex.



CONCLUSION

In summary, a new zinc complex [Zn(L)].Cl having square planer geometry with Schiff base ligand HL have been synthesized and characterized. All the synthesized ligand and complexes are well characterized using several analytical techniques. The interaction of Zn(II) complex with BSA protein, which displayed strong interaction with high fluorescence quenching and that is responsible for the interplay between the metal complex and protein.

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