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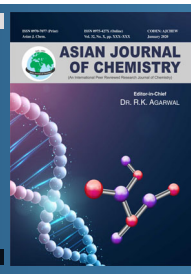

4-Aminoindane Derived Novel Schiff Base Metal Complexes: Synthesis, Characterization, DNA Binding and Molecular Docking Studies

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A novel Schiff base [SAL-L=2-((2,3-dihydro-1*H*-inden-4-ylimino)methyl phenol] was synthesized and used as ligand for the synthesis of Ni(II) and Co(II) complexes. The structural characterization of ligand and its Ni(II) and Co(II) complexes was determined using various spectroscopic methods. Based on spectral studies, a square planar and octahedral geometry have been proposed for Ni(II) and Co(II) complexes, respectively. DNA binding properties of these metal complexes with calf-thymus DNA in tris-hydrochloride buffer (pH 7.2) were investigated using UV- visible absorption studies. The binding constants were in the order of 10^5 M^{-1} suggested a good binding affinity towards CT-DNA. The synthesized ligand is docked on TSPO protein showing good binding energy and found to be a potent inhibitor of cancer.

Keywords: Schiff base, 4-Aminoindane, Complexes, Ni(II), Co(II), DNA binding, TSPO protein, Molecular docking.

INTRODUCTION

Schiff base ligands are an important class of organic compounds known for their complexation ability with transition metal ions [1]. Metal complexes of Schiff bases possess potent antibacterial, antifungal, anticancer activity and also has important role in catalysis [2,3]. Aminoindane and its derivatives are renowned bronchodilator analgesics, protease inhibitors and anticonvulsants, anti-HIV and anticancer agent [4-8]. They act as anti-Parkinsonian drugs and used in psychotherapy [9].

Literature survey revealed that antimicrobial and anticancer properties of some metal(II) complexes of nitrophenol and naphthalene-2-ol Schiff bases containing 4-aminoindane (4-AMD) moiety have been reported [10,11]. 4-Aminoindane derivatives are an important class of compounds due to their anticancer properties. This motivated us for the synthesis and characterization of Schiff base [SAL-L=2-((2,3-dihydro-1*H*-inden-4-ylimino)methyl phenol] which is derived from condensation of 2-hydroxy benzaldehyde with 4-aminoindane and its Ni(II) and Co(II) complexes were also synthesized and characterized by UV-vis, NMR, IR and mass spectrometry.

In recent years, the study of interactions between transition metal complexes of Schiff base and DNA have gained much importance due to their utility in design and development of synthetic restriction enzymes, chemotherapeutic agents, site specific cleavers, molecular photo switches and foot printing agents [12-17]. Metal complexes interact with the double helix DNA in either covalent or non-covalent way. The non-covalent way includes three modes of binding, *i.e.* electrostatic effects, groove binding and intercalation, among which intercalation is the most important binding mode [18]. Small molecules when bind to DNA through intercalation can damage DNA in cancer cells and hence can be used as anticancer drugs. Interested by the anticancerous property of 4-aminoindane derivatives we are reporting here the DNA binding studies of the metal complexes of SAL-L which have shown good binding constant (K_b) values which are in agreement with previous literature values [19-21].

Molecular docking is one of the most commonly used tool in structure-based drug designing, because of its capability to predict the binding-conformation of small molecule ligands to the specific correct target binding site. TSPO protein is a trans-membrane protein and called trans-locator protein which is present in external mitochondrial membrane involved in various cellular functions like cell proliferation, mitochondrial respiration and synthesis of steroids [22]. Increased levels of

TSPO protein are diagonised in various cancerous tissues whereas in normal human tissues low levels are observed, indicating the participation of TSPO in different types of cancers, hence it can be used as a biomarker in the stage-dependent diagnosis of cancer [23]. So docking process has been carried out on TSPO protein using the synthesized ligand (SAL-L) to confirm its anticancer activity.

EXPERIMENTAL

All chemicals used were of analytical purity 4-aminoindane, salicylaldehyde and triethylamine were obtained from E. Merck (Germany). Ethanol, acetic acid, nickel(II) nitrate hexahydrate, cobalt (II) chloride hexahydrate, dimethylsulphoxide and calf thymus-DNA were obtained from Aldrich Chemical Company Ltd.

Synthesis of Schiff base: Dissolved 4-aminoindane (1.13×10^{-2} mol) in 20 mL of 99 % pure ethanol and salicylaldehyde (1.13×10^{-2} mol) in 20 mL of 99 % pure ethanol separately. Mixed the solution of 4-aminoindane and salicylaldehyde in which a few drops of acetic acid was added and the mixture was refluxed for about 3 h. On cooling the product was collected in ice as orange-yellow product, which was filtered and recrystallized with ethanol (**Scheme-I**). Golden yellow crystals of the required Schiff base was obtained. ^{1}H NMR data (300 MHz, $CDCl_3$, δ in ppm) of SAL-L as 13.6 (s, 1H, OH), 8.39 (s, 1H, C=N), 6.76 (m, 3H, C5, C6, C7), indane ring: 7.22-7.06 (m, 4H, C-3′, C- 4′, C-5′, C-6′); 3.02 (t, 2H, C1), 2.15 (q, 2H, C2), 3.05 (t, 2H, C3). FTIR (KBr, cm^{-1}): 3429 ν(-OH) stretching and 1618 ν(C=N) stretching. Mass: *m/z* = 238.18 (M^+).

Synthesis of metal(II) complexes: Metal(II) complexes of Co(II) and Ni(II) were synthesized by refluxing the corresponding metal solutions with 0.60 mmol of Schiff base solution (SAL-L) along with 0.06 mmol of triethylamine in 30 mL ethanol for about 3 h. Coloured solid was filtered, washed with ethanol and dried in desiccator.

DNA binding studies: UV-Vis spectrophotometry was used to study the interactions of newly synthesized metal(II) complexes with CT-DNA. The binding of complexes with CT-DNA was measured in tris-HCl buffer solution (pH 7.2), prepared using 0.788 g of tris-HCl and 0.2925 g of NaCl followed by addition of 1-2 drops of 0.5 M of NaOH and was made to 50 mL with double distilled water to get pH 7.2. The concentration of CT-DNA used for binding studies was determined from its ratio of UV absorbance at 260 and 280 nm (A_{260}/A_{280}) of 1.9, indicating that CT-DNA is sufficiently free of protein [24-27]. The concentration of DNA was determined from the UV absorbance at 260 nm using the extinction coefficient ε_{260} = 6600 M^{-1} cm^{-1} [28]. Concentrated stock solutions of corresponding metal complexes were prepared by dissolving the complexes in DMSO and diluted suitably with the corresponding buffer. First of all, λ_{max} and absorbance of pure CT-DNA, in buffer solutions without complexes were recorded. To measure the absorption spectra of complexes, a proper amount of CT-DNA was added and absorption readings were noted for five successive readings. The binding constant K_b value were calculated from the data was fit to the following equation to obtain intrinsic binding constant K_b.

$$\frac{[DNA]}{[\varepsilon_a - \varepsilon_f]} = \frac{[DNA]}{[\varepsilon_b - \varepsilon_f]} + \frac{1}{K_b}[\varepsilon_b - \varepsilon_f] \quad (1)$$

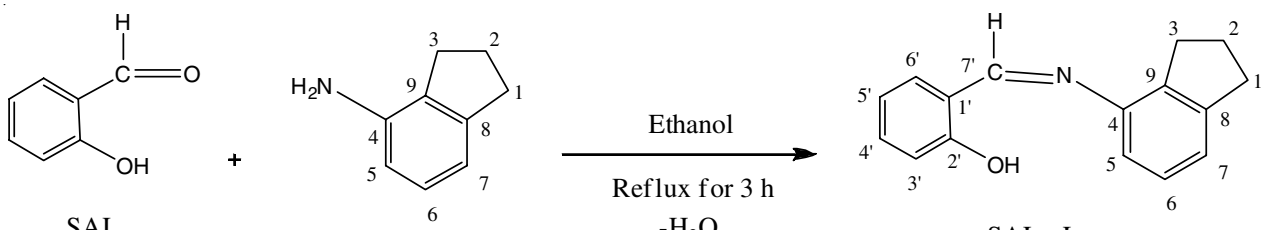
where [DNA] is the concentration of DNA in base pairs, ε_a is the extinction coefficient observed for MLCT absorption band at the given DNA concentration, ε_f is the extinction coefficient of complex free in solution and ε_b is the extinction coefficient of complex when fully bound to DNA.

A plot of $[DNA]/[\varepsilon_a - \varepsilon_f]$ *vs.* [DNA] gave a slope $1/[\varepsilon_a - \varepsilon_f]$ and Y intercept equal to $(1/K_b)[\varepsilon_b - \varepsilon_f]$, respectively. The intrinsic binding constant K_b is the ratio of the slope to the intercept [29].

Molecular docking: We have analyzed the 3D alignment of TSPO protein and its conformations while binding with SAL-L ligand and this analysis of docking processes gave valuable information regarding binding interactions. Software autodock uses a genetic algorithm to explore wide range of SAL-L ligand conformational flexibility and rotational flexibility of slected receptor. AutoDock tool has been used for docking the synthesized ligand SAL-L with TSPO protein [30,31]. The x, y, z coordinates have been taken from Mercury software for grid generation in docking process.

RESULTS AND DISCUSSION

Characterization of metal(II) complexes: The IR spectra of the metal complexes were compared with those of the free ligand in order to determine the coordination sites that may be involved in chelation. The metal-free ligand (SAL-L) has uncoordinated C=N stretching vibrations band at 1618 cm^{-1}. This band shifted to 1597.18 cm^{-1} in Co(II) metal complex and to 1475 cm^{-1} in Ni(II) metal complex. These shifts confirmed a coordination through the imine nitrogen atom. The strong bands at 3429 cm^{-1} in SAL-L is assigned as ν(OH) stretching frequency and was visibly absent in the spectra of both metal(II) complexes indicated the involvement of salicylaldehyde oxygen atom in chelation. The presence of bands due to ν(M-O) and ν(M-N) at 810-600 and 465-385 cm^{-1} in SAL-L metal(II)



2-((2,3-dihydro-1*H*-inden-4-ylimino)methyl)phenol

Scheme-I: Preparation of SAL-L

TABLE-1
KEY INFRARED SPECTRAL BANDS (cm^{-1}) OF SAL-L AND ITS METAL(II) COMPLEXES

Compounds	ν(O-H)	ν(C=N)	ν(C=C)	ν(C-N)	ν(M-N)	ν(M-O)
SAL-L	3429	1618	1572	1463	–	–
Co(II)-SAL-L	–	1597	1517	1469	418	690
Ni(II)-SAL-L	–	1475	1396	1440	464	806

complexes respectively, is the further proof of coordination [32,33]. The IR data of Schiff base ligand and its metal(II) complexes are presented in Table-1.

LC-MS spectra of metal(II) complexes: The LC-MS spectra of Ni(II) metal complex showed the molecular ion peak at *m/z* 533 (M-1) and Co(II) metal complex showed the molecular ion peak at *m/z* 606 (M+1).

Electronic spectra: The absorption spectra for ligand and its metal complexes was measured using pure DMSO in (Double Beam UV-VIS spectrophotometer:2201) ranging from 200 to 800 nm against the same solvent as a blank. SAL ligand gives two absorption bands at 276.8 and 348.4 nm (Fig. 1), these bands can be attributed to π-π* and n-π* transitions and Ni(II) complex show one intense absorption band at 238.4 nm, which may be attributed to the *d-d* transition while Co(II) complex shows three absorption bands at 260, 334.4 and 399.2 nm.

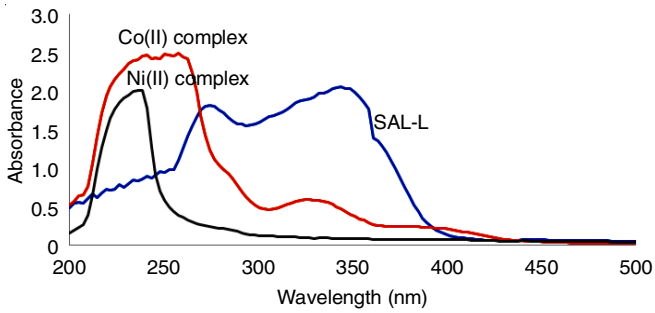


Fig. 1. UV-visible spectra of SAL-L and its metal(II) complexes

DNA binding studies: In the present study, both metal(II) complexes show hypochromism and bathochromism with the increase in concentration of DNA indicating the binding of the complexes through intercalation, which involves the insertion of planar aromatic chromophore of the ligand in between the base pairs of DNA. The extent of hypochromism is consistent with the strength of intercalative interaction.

There are many different spectroscopic techniques that can be used to determine the binding modes of metal complexes with DNA, but among all absorption spectra of the metal complexes is most widely preferred method to monitor change in absorbtion of complex with DNA and also to determine binding constant. Covalent binding involves the replacement of labile ligand by a nitrogen base of DNA, whereas the non-covalent includes three other modes like electrostatic, grove binding and intercalation. In case of intercalation of a complex to DNA, hypochromism along with red or blue shift is observed which involves binding between the aromatic chromophore of complex and the base pairs of DNA. The extent of hypochromism suggests the strength of intercalation. A strong π-π interaction between the DNA base pairs and the aromatic ring of ligand results in hypochromism. So, it was observed that in case of SAL-L-Ni(II) and SAL-L-Co(II) complexes showed hypochromic shift with red shift (Fig. 2). A quantitative comparison of the metal complexes were made using calculations of their intrinsic binding constants (K_b) with Ct-DNA. The changes in the absorption were monitored by increasing the concentration of Ct-DNA and K_b values were found to be $K_b = 3.04 \times 10^5$ for SAL-L-Ni(II) complex and $K_b = 2.06 \times 10^5$ for SAL-L Co(II) complex, which were in accordance with the expected values.

Geometry of SAL-L metal(II) complexes: Based on spectral data, the proposed geometry of Ni(II) and Co(II) complexes of SAL-L are square planar and octahedral, respectively (Fig. 3).

Molecular docking: Docking process was carried out by generating grid box by taking X, Y, Z as 1.327, -2.909 and -1.709 coordinates, respectively. Docking interactions of TSPO protein with synthesized SAL-L ligands molecule shows strong interactions with amino acids at active site residues VAL28, SER23, VAL110, LEU114, TRP53, TRP143, THR147, GLY50 and LEU49 of TSPO protein (Fig. 4), which might be important for binding of inhibitors. Docking is carried out for the SAL-L ligand using AutoDock tool. The synthesized ligand molecule binding energy and its interactions with TSPO protein were measured. As the ligand SAL-L shows the binding energy of -6.47, hence it is expected to be more stable and act as good inhibitor. SAL-L ligand is having more drugable activity of the inhibition of TSPO protein, normal range of RMSD value 2.4.

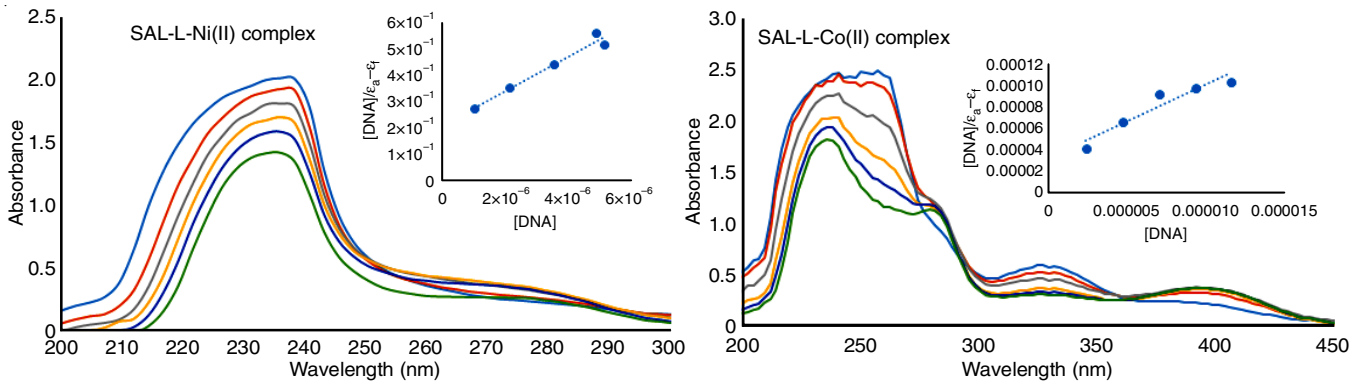


Fig. 2. DNA binding absorption spectra of SAL-L Ni(II) and Co(II) complexes

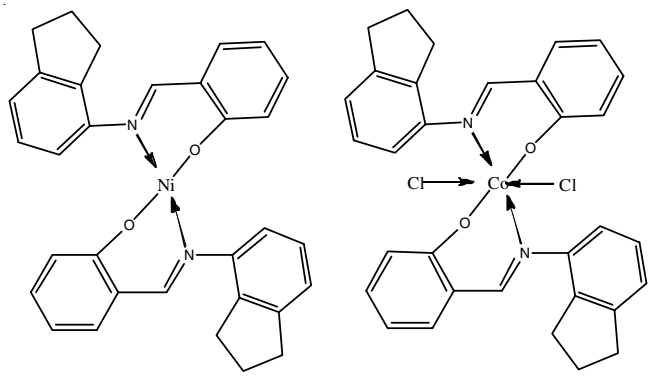


Fig. 3. Geometry of Ni(II) and Co(II) complexes

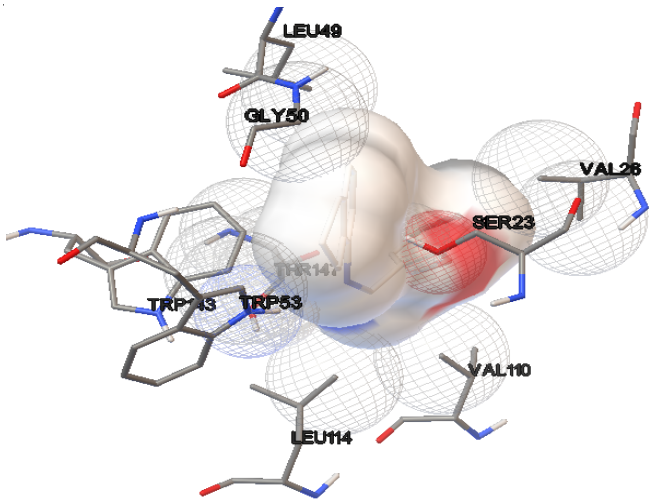


Fig. 4. Binding interactions of SAL-L ligand with TSPO protein

Conclusion

A Schiff base, 2-((2,3-dihydro-1*H*-inden-4-ylimino)-methyl phenol) (SAL-L) using 4-aminoindane and salicylaldehyde and its Ni(II) and Co(II) complexes were synthesized and characterized. The DNA-binding affinity of complexes were studied by UV-Vis absorption spectroscopy. Results confirmed that both the complexes bind to CT-DNA by an intercalative mode. The binding mode of ligand with TSPO protein active sites were predicted using docking technique. The binding energy value of ligand showed a good correlation with their inhibitory anticancer activity.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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