EFFICIENT ONE POT SYNTHESIS, *In-vitro* ANTIOXIDANT ACTIVITIES OF Zn(II) COMPLEX WITH (E)-N1[(E)-3-PHENYLALLYLIDENE]BENZENE-1,2-DIAMINE

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ABSTRACT

The Schiff base (E)-N1[(E)-3-phenylallylidene]benzene-1,2-diamine was derived from the condensation of orthophenylenediamine and cinnamaldehyde. The Schiff base and its Zn(II) complex were characterized based on microanalysis, conductivity, IR, UV-Visible, NMR spectral studies. The analytical data suggest the stoichiometry to be 1:1 (M:L). The molar conductance data reveal that the complex is non-electrolyte. Melting points support the thermal stability of the Schiff base. The UV spectral data support the square planar geometry of the complex. Coordination of ligand was confirmed by the constant change in FT-IR. The NMR (¹H & ¹³C) spectra of the Schiff base and its complex were confirmed by the geometry and magnetic property them. The *in-vitro* antibacterial activity of the synthesized ligand and Zn(II) complex were screened for bio-potential activity using some microorganisms by agar well diffusion method. The antibacterial activity further confirmed by its pharmacokinetics study using Swiss ADME computational study. The antioxidant activity of the Schiff base and Zn(II) complex was also assessed by DPPH free radical scavenging method. IC50 values are also predicted and compared with standard ascorbic acid.

Keywords: Cinnamaldehyde, Schiff base, Metal Complex, Antibacterial, Antioxidant, Pharmacokinetics

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INTRODUCTION

Schiff base is a multilateral ligand in which C=O group is replaced by C=N by the condensation of the nucleophilic nitrogen atom of amine attack to the electrophilic carbon atom of aldehyde or ketones.¹ Schiff base ligands are readily formed from aldehyde than that of the ketones. It was first discovered by Hugo Schiff in 1864.² This ligand is chemically and biologically very important due to the presence of Sp² hybridized nitrogen atom of azomethine group.³ Schiff base shows a vital role in organic and bioinorganic chemistry, they form the most stable complexes with transition and post-transition metal ions.⁴ They are important in the field of modern coordination chemistry because they have industrial, analytical, antibacterial, antifungal, anticancer, antiviral and antitubercular activities and it also shows chelating ability, catalytic and extraction properties.^{5,6} Antioxidants are the compounds that terminate the attack of free radicals and prevent it from aging and different diseases associate with oxidative damage inside the body system.⁷ Cinnamaldehyde is one of the main components of bark extract cinnamon. It is used in perfume especially natural, sweet and fruity scents they also used aroma compounds by the smell of cinnamon in almond, apricot and butterscotch.⁸ It is a potential anti-obesity drug due to its low toxicity, eco-friendly, food flavoring, medical herb and renowned strong adsorption properties.⁹ Orthophenylenediamine (OPD) is one the organic compound it undergoes condensation with carbonyl compounds (aldehyde and ketones) gives Schiff base which is used as an antioxidant in rubber product and also used in photo-luminescence, catalytic activity and pharmaceutical with various diketone.¹⁰ Zinc metal plays an important role in biologist such as absorption of calcium, formation of antibodies, thyroid gland and hormone function and it is present in brain, muscle, bones, kidney and liver.¹¹ The present view of this paper is to the synthesis of transition metal Zn²⁺) the complex of Schiff base from cinnamaldehyde and

Orthophenylenediamine (OPD) and characterized by various physicochemical, spectral and bio-potential studies.

EXPERIMENTAL

Materials

Orthophenylenediamine, cinnamaldehyde, potassium thiocyanate, zinc nitrate, solvent (AnalaR grade) used as it is purchased from a chemical company. The synthesized ligand and zinc complex are stable and stored for a long time at room temperature.

Methods

Using Vario make EL-III model instrument at 950-1200°C temperature, predict the elemental analysis of the Schiff and complex. After decomposing the complex with a known weight, the metal ion was estimated by the gravimetric method. Melting point(°C) was measured using Ajay melting point instrument in an open capillary tube. Molar conductance of the Schiff base and complex was measured in acetonitrile solution at 10^{-3} M concentration at room temperature by the use of Systronic Conductivity Bridge. UV-Visible spectra of complex and Schiff base were recorded in solid-state spectra (DRS method) on JASCO-V650 made spectrometer in the range of 200-800 nm. Using Shimadzu, FT-IR-4100 type-A model IR spectrometer, IR spectral study of ligand and its metal complex were recorded in the range of 4000 to 400cm^{-1} as KBr pellet method. The Far IR spectra of the complex were recorded in a Bruker, Germany makes 3000 Hyperion Microscope with Vertex 80 FTIR system model instruments. Using Bruker instrument in DMSO-d₆, the ^1H and ^{13}C -NMR spectra of Schiff base and its diamagnetic Zn(II) complex were carried.

Synthesis of Schiff Base

The goal of green chemistry is to develop Eco-friendly synthetic reactions. Green chemistry involves the use of microwave technology, sonochemistry, phase transfer catalysis, ionic liquids, and many other techniques. The green chemical one-pot multicomponent condensation reaction of 0.486g (4.40 mmol) of Orthophenylenediamine (10 ml ethanol) and 0.624g (4.70 mmol) of cinnamaldehyde (10 ml diethyl ether) using water as a green solvent and stirred continuously for about 10-15 min at room temperature, the shiny powdered yellow color precipitate was formed.¹² The obtained complex was purified by simple filtration followed by washing with water and drying in desiccators and the yield was (73.33%) Scheme-1. This method is experimentally simple, clean, high-yielding, and green, with reduced reaction times.

Synthesis of Zn(II) Complex

Green route one-pot multicomponent reactions of a Schiff base, 0.75g, (3.36 mmol) in 20 ml ethanol solution was mixed with zinc nitrate (1g, 3.36 mmol in 10 ml of methanol) and add anionic ligand viz., potassium thiocyanate (0.65 g, 6.72 mmol in 10 ml of water) was added. Then water used as a green solvent and stirred continuously for 10-15 min at room temperature yellow color precipitate was formed. The product was purified by simple filtration followed by washing with water and drying in desiccators and the yield was (87.87%) Scheme-2.

Evaluation of Antibacterial Activity: Antibacterial activities of synthetic compounds such as Schiff base and its metal complex evaluated using well diffusion method with MHA. Under aseptic conditions, the MHA plates were inoculated. The test samples in the well were incubated at 37°C for 24 hours. After the incubation period, the diameter of the growth inhibition zones was measured. The antibacterial activity of the given compound was assessed against five bacterial species: *Staphylococcus aureus*, *Escherichia coli*, *Vibrio parahaemolyticus*, *Pseudomonas aeruginosa* and, *Enterococcus* and *Candida albicans* by agar well diffusion method. Each bacterial culture was grown in nutrient broth (bacterial) and potato dextrose broth (fungal) medium for 12 hours at 37°C. Then, each grown culture was swabbed on nutrient agar medium and well were cut about 5 mm using a cork borer. Each well was added with 80 μl of sample and incubated at 37°C for 18 hours. After incubation, the plates were observed for the zone of inhibition and it was measured.

Antioxidant (DPPH Free Radical Method)

The free radical scavenging capacity of the plant extract was measured based on the method delineate by Brand-Williams *et al* (1995) with slight modification. 1ml of 0.1mM DPPH solution in methanol was mixed with 1ml of plant extract solution of varying concentrations (10, 100, 500 and 1000 µg/ml). Blank samples were prepared and L-Ascorbic acid was used as standard. These tubes were thoroughly mixed and kept in the dark for 30 min and their absorbance was measured at 517 nm using UV-Visible spectrophotometer. The inhibition % was calculated using the following formula:

$$\text{Inhibition \%} = \frac{A_c - A_s}{A_c} \times 100$$

RESULTS AND DISCUSSION

Analytical Data

The elemental analysis (C, H, N) of the Schiff base and its complex is shown in Table-1, the data which are in good agreement with calculated values. Based on the metal estimation of complex the stoichiometry and molecular formulae of the Schiff base and its complex are assessed as $[\text{Zn}(\text{SB})(\text{SCN})_2]$. The molar conductance of 10^{-3} M Zn(II) complex shows the non-electrolytic (1:0 type) nature and no more anion and cations are present on its coordination sphere outside.¹³

ESI Mass Spectra

ESI mass spectrum of Schiff base recorded at room temperature. It is proposed that the empirical formula of the Schiff base and also support the stability of them. From the data of m/z the value at 222 confirmed the molecular formulae of Schiff base ($\text{C}_{15}\text{H}_{14}\text{N}_2$) but the fragments at 105 and 117 correspond to the $\text{C}_6\text{H}_6\text{N}_2^+$ and C_9H_8^+ respectively.¹⁴

Table-1: Physico-chemical Data of Schiff Base Complex

S. No.	Schiff base/ Complex	Molecular Weight (g/mol)	MP (°C)	Color	Elemental Analysis					Molar Conductance ($\text{Ohm}^{-1}\text{cm}^2\text{mol}^{-1}$)
					%C	%H	%N	%S	%M	
1	Schiff base	222.30	117	Shiny yellow	80.97 (80.19)	6.29 (6.30)	12.59 (12.52)	-	-	20.00
2	$[\text{Zn}(\text{SB})(\text{SCN})_2]$	403.83	230	Pale Yellow	50.51 (50.10)	3.46 (3.19)	13.86 (13.50)	15.84 (15.19)	16.18 (16.90)	14.28

UV Spectra

The electronic spectra of Schiff base exhibit one broadband at the transition of $25,575\text{cm}^{-1}$ shows the $\pi \rightarrow \pi^*$ whereas in the complex this transition present with related values confirming the imine bond of the Schiff base. The Zn(II) complex is diamagnetic its filled 'd' shell shows only $n \rightarrow \pi^*$ transition is also as being due to C=N bond which is C-T (charge transfer) band at $27,397\text{cm}^{-1}$ confirming the square planar geometry.¹⁵

IR and Far-IR Spectra

IR spectra are the main tool to find out the functional group present in the ligand and its entry into the coordination sphere. Determine the binding site of Schiff base to the metal ion in the complex. IR spectrum of the free ligand was compared with the spectrum of the metal complex (Fig.-1). The spectral data of the Schiff base showed the appearance of a new band at 1595cm^{-1} due to the Schiff base azomethine linkage formation. In Zn(II) complex the $\nu(\text{C}=\text{N})$ stretching frequency shifted to higher values at 1628cm^{-1} indicate the metal ions are coordinate with the free Schiff base through an azomethine nitrogen atom. There are two aromatic rings $\nu(\text{C}-\text{H})$ are present in the Schiff base at 3371 and 3142cm^{-1} . In complexes, one of the values are shifted to the lower region at 3206cm^{-1} but the other frequencies were also changed at 3186cm^{-1} due to the effective coordination through the imine nitrogen atom which is attached in one aromatic ring, the other amine group chelated to metal ions is confirmed by the $\nu(\text{N}-\text{H})$ at 3500cm^{-1} while in complex these values shifted to 3437cm^{-1} . The C-N stretching frequency of Schiff base is at 1398cm^{-1} which is also shifting to the higher frequency at 1402cm^{-1} in a metal complex which is further evidence of coordination of metal ion through imine nitrogen.^{16, 17} The mixed anionic ligand thiocyanate ion coordinated through nitrogen or Sulphur to the metal ion. If it is coordinated through "N" it is N-bonded at below 2100cm^{-1} whereas through "S" it is above 2100cm^{-1} . In metal complexes, the $\nu(\text{SCN})$ stretching frequency at 2068cm^{-1} was confirmed by the coordination of metal ions through the 'N' atom of thiocyanate ion and not from its Sulphur atom.¹⁸ In far-IR spectra, the low frequencies at 419cm^{-1} and 526cm^{-1} corresponding to the M-N coordination bonds of imine and amino group of Schiff base to the metal complex. The frequency at 489cm^{-1} shows the M-N coordination bond of thiocyanate additional ligand in the complex.¹⁹

NMR Spectra of Ligand and Zn(II) Complex

Proton NMR

Proton NMR spectrum of Schiff base was carried out in DMSO they appeared signal of the aromatic proton was found to be in the expected region of them. The azomethine $\text{N}=\text{C}-\text{H}$ proton shows the chemical shift

value at 8.42 to 8.43 ppm and NH_2 proton appeared at 5.05 ppm. The aromatic chemical shift values of Schiff base are 7.44 ppm (C--H₁), 7.38 ppm (C--H₂), 7.65 -7.66ppm (C--H₃) 7.17 ppm (C--H₄) 7.11ppm (C--H₅) 6.69-6.70 ppm (C--H₈) 6.57-6.58 ppm (C--H₉) 6.97 -6.98ppm (C--H₁₀) and 7.0-7.03 (C--H₁₁). In Zn(II) complex all the chemical shift values of the proton slightly shifted to a down or up-field (Fig.-2 and 4) due to the de-shielding and increasing the conjugation in the chelates ring.²⁰

¹³C- NMR

¹³C-NMR spectrum of Schiff base gives the chemical shift values of different carbon atoms. Azomethine carbon atom found at 158.79 ppm whereas Zn(II) complex is slightly shifted to 158.93 ppm, the N_H_2 carbon atom chemical shift value in Schiff base is 144.02ppm in Zn(II) complex it is shifted to upfield region at 143.84 ppm. (Fig.-3 and 5) All the other chemical shift values of carbon atom slightly shifted to down or upfield.²¹

Fig.-1: FT-IR Spectra of Free Ligand and Zn(II) Complex

AS-3590-A-IN DMSO-D6-PROTON NMR

Fig.-2: ¹H-NMR Spectrum of (E)-N1[(E)-3-phenylallylidene]benzene-1,2-diamine

Fig.-3: ^{13}C -NMR Spectrum of (E)-N1[(E)-3-phenylallylidene]benzene-1,2-diamine

Fig.-4: ^1H -NMR Spectrum of diamagnetic Zn(II) Complex

Fig.-5: ^{13}C -NMR Spectrum of Diamagnetic Zn(II) Complex

Antibacterial and Antifungal Activities

The synthesized Schiff base metal(II) complex were subjected to in-vitro biological activities viz., antibacterial and antifungal using bacterial and fungal strains viz., *S. Aureus* and *Enterococcus*, three-gram negative bacteria such as *E.coli*, *Vibrio parahaemolyticus* and *P.aeruginosa* and *C. albicans* by Agar well diffusion method (Fig.-6). The MIC values (Table-2) of the microorganisms predicted which indicating the Schiff base and its Zn(II) complex exhibit bio-potential activity. The antibacterial and antifungal activity of the Zn(II) complex is highly active for *S. Aureus* and *C. albicans* but moderately active for the other microorganisms than the Schiff base. The increased activity of the metal chelates may be explained on basis of Tweedy chelation theory. The chelation of metal complexes acts as a powerful and bactericidal agent. That chelation killing more bacteria, the positive charge on the metal ion is partially shared with the ligand. There may be a π electron delocalization in the chelates ring is present which increase the lipophilicity which increases the enhanced bio-potential activities, solubility, conductivity and bond parameters are also increase the activity of metal complexes.²²

Fig.-6: Antibacterial and Antifungal Comparative Study Schiff base and Zn(II) complex

Table-2: Bio-potential Activities of Free Ligand and its Complex

S. No.	Compound	<i>S. aureus</i> (mm)	<i>E. coli</i> (mm)	<i>Vibrio</i> <i>parahaemolyticus</i> (mm)	<i>P. aeruginosa</i> (mm)	<i>Enterococcus</i> (mm)	<i>C. albicans</i> (mm)
1	Schiff base	08	14	12	08	14	28
2	Zn(II) Complex	12	12	10	10	08	22

Antioxidant Activity

Antioxidant activity of Schiff base and Zn(II) complex was determined by DPPH free radical scavenging method. The free radical scavenging activity of compounds was carried out at different concentrations (10-1000 μ g/ml). L-Ascorbic acid is used as a standard. The percentage inhibition was measured from the absorption of control and samples. The result of scavenging activity shows the maximum free radical scavenging activity at 74.10% and 72.30%. The IC₅₀ value of the Schiff base is 359.3 but in Zn(II) complex it is 357.0 (Fig.-7) which is higher than the standard. Comparing the standard Schiff base and complex shows antioxidant activity at higher concentrations. It is observed that they have 50% scavenging activity.^{23, 24}

Physico-chemical and General Computational Methodology

The SMILES for Schiff base and Zn(II) complex generate structure file generator from online tool Swiss ADME web page. Using the web tool the physicochemical descriptors, such as the molecular weight (MW),

molecular refractivity (MR), count of specific atom types and the topological polar surface area (TPSA), the latter proven as a useful descriptor in many models for estimation of membrane diffusion, ADME and pharmacokinetic behavior. The lipophilicity was assessed using five alternative predictive models; *i.e.* XlogP; WlogP; MlogP; SILICOS-IT, ilogP, together with a consensus logP estimation, based on the average value of the different computational parameters (Table-3,4 and 5).

Fig.-7: Antioxidant % Inhibition of Schiff base and Zn(II) Complex

Table-3: Physico-chemical Parameters

S. No.	Parameters	Schiff base	[Zn(SB)(SCN) ₂]
1	Formula	C ₁₅ H ₁₄ N ₂	C ₁₇ H ₁₄ N ₄ S ₂ Zn
2	Molecular weight	222.29 g/mol	403.83 g/mol
3	Num. heavy atoms	17	24
4	Num. atom. heavy atoms	12	12
5	Fraction Csp3	0.00	0.00
6	Num. rotatable bonds	3	3
7	Num. H-bond acceptors	1	3

Table-4: Lipophilicity

1	GI absorption	High	High
2	BBB permeant	Yes	No
3	P-gp substrate	No	Yes
4	CYP1A2 inhibitor	Yes	No
5	CYP2C19 inhibitor	Yes	No
6	CYP2C9 inhibitor	Yes	No
7	CYP2D6 inhibitor	No	No
8	CYP3A4 inhibitor	Yes	No
9	Log K _p (skin permeation)	-5.55 cm/s	-5.85 cm/s

The medicinal chemistry and drug properties of the compounds were also assessed and the results indicating the Schiff base and its complex are used as a drug in the field of medicinal chemistry. In Pharmacokinetics study the blood-brain barrier is absent but GI absorption is high which leads to high lipophilicity of the compounds shows high Pharmacokinetics and drug likeliness properties.²⁵⁻²⁷

Table-5: Pharmacokinetics

1	Log $P_{o/w}$ (ilogP)	2.61	-44.74
2	Log $P_{o/w}$ (XlogP3)	2.97	4.10
3	Log $P_{o/w}$ (WlogP)	3.58	3.61
4	Log $P_{o/w}$ (MlogP)	3.05	1.66
5	Log $P_{o/w}$ (SILICOS-IT)	3.67	3.67
6	Consensus log $P_{o/w}$	3.18	-6.34

CONCLUSION

The Schiff base (E)-N1[(E)-3-phenylallylidene]benzene-1,2-diamine and Zn(II) complex was synthesized by high efficient green route method with a higher yield. The Schiff base coordinated to the metal ion through its imine and amino nitrogen by bidentate mode to form metal chelates, based on the analytical and spectral data (UV-Visible, IR, Far-IR, Mass spectra and NMR) reports confirmed the mononuclear, non-electrolytic and square planar geometry of Zn(II) complex. The Schiff base is high potential to the screened microorganisms but the complexes are highly active for some microorganisms and moderately active against the growth of other microorganisms. The antioxidant activity of the Schiff base and Zn(II) complex shows 50% scavenging activity.

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