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Synthesis, Characterizations and Biological Efficacy of Aminobenzofuran and 2-Methoxyphenylacetaldehyde and Its Co(II) and Zn(II) Complexes

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Abstract

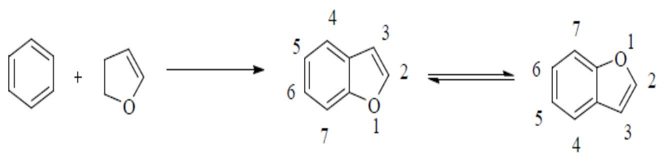
Metal complexes of some transition metal ions viz Co (II), and Zn (II) have been synthesized from a Schiff base (L) formed by the condensation of 2-amino-benzofuran and 2-methoxyphenylacetaldehyde. Synthesized compounds have been studied by various spectroscopic techniques and evaluated for their biological efficacy. From the FTIR result, A peak at 1566 cm^{-1} was assigned to azomethine v(C=N) stretching vibration, which shifted to 1640cm^{-1} and 1637cm^{-1} in cobalt (II) and, zinc (II) complexes respectively. Also, a broad band was observed in the Schiff base and the complexes at 3219cm^{-1} which indicate presence of water of crystallization to the complex structure. The complexes are non-electrolytic in nature and have high thermal stability. Job's method of continuous variation suggests 1:2 metal to ligand ratio. Antibacterial and antifungal study of ligand and its metal complexes have shown that the metal complexes are more active than their corresponding ligand.

Keywords: Aminobenzofuran, 2-Methoxyphenylacetaldehyde, Ligand, Characterization,

INTRODUCTION

Schiff base metal complexes have important application in medicinal chemistry. Medical science demands such types of drugs which are more potent, biologically active, easily absorbable and nontoxic, and show fast action for treatment of diseases. Extensive studies revealed that chelation makes the complex more stable and biologically more active in the presence of bio metal. Metal ions fix the complexes at the specific site of the proteins and enzymes of the host and show their potentiality (Chaudhary, 2013). Heterocyclic ring systems are the powerful backbones for many biological properties. Among the heterocyclic compounds, benzofuran is an important class of compounds occupied its place in numerous bioactive natural products and was first time synthesized by Perkin in 1870.

After that, the research and developments of benzofuran based biologically active compounds has been quite a rapidly developing and increasingly active field due to their wide potential applications as pharmaceuticals, agrochemicals, molecular electronic and functional polymers man-made materials, artificial acceptors, supramolecular ligands (Keay,et.al 2008). Most importantly, the applications of benzofuran derivatives in medicinal chemistry have achieved great progress. Many benzofuran anchored drugs play an important role in the treatment of various types of diseases, and new benzofuran derivatives with medicinal value are being actively explored worldwide. (Shimazu,et.al 2001). The accepted name for ring system **1** in chemical abstracts is benzo*(b)*furan. In order to shorten, *(b)* is conveniently dropped and it is commonly known by the generic name benzofuran



(1)

The vast range of biological effects associated with this scaffold has resulted in the benzofuran ring system being considered as a privileged structure. This has been strongly promoting much effort to focus on benzofuran based medicinal agents, and the expanding research and developments have become rapidly developing and increasingly active domains of research, and are almost extended to the whole range of medicinal field.

Nowadays a number of common and uncommon bacteria previously susceptible to common antimicrobials are reported to have developed resistance to diverse antibiotics. Initially, these bacteria caused significant nosocomial infections and were the cause of major morbidity and mortality in patients. More recently, they have spread to community, causing severe illnesses in previously healthy and otherwise non-vulnerable patients. Owing to this increased microbial resistance, new classes of antimicrobial agents with their mode of action are today's need to fight against the multidrug-resistant infections. (Mohamede, et,al 2013)

Metal ions play an important role in biochemical processes. Many biochemical reactions depend on the presence of metal ions, which are the part of coordination complexes. There has been an increasing attention in the biological applications of benzofuran based metal complexes including transition metals such as cobalt(II), nickel(II), copper(II) and zinc(II) in the last decade. Many of these complexes showed considerable antibacterial and anticancer properties in *invitro, invivo* and/or *insilico assays*. The choice of a suitable substitution on benzofuran based ligand system is found crucial in the design of novel target specific bioactive metal complexes.

In view of the importance of the benzofuran Schiff base and its metal complexes in medicinal industry and in continuation of various searches for more resistance scaffold of benzofuran Schiff base and their metal complexes, herein we report new Schiff base formed by the fusion of biologically active heterocyclic aldehydes 2-methoxyphenylacetaldehyde and 2-amino-benzofuran could result in valuable chemical and biological properties. Furthermore, insertion of metal ions like Co (II), and Zn (II) could result in synthesizing biologically active compounds with a special significance in medicinal chemistry. In the present work, we report a synthesis, characterization, antibacterial and antifungal studies of a Schiff base derived from 2-aminobenzofuran and 2-methoxy phenyl acetaldehyde and its cobalt(II) and zinc(II) complexes.

MATERIALS AND METHODS

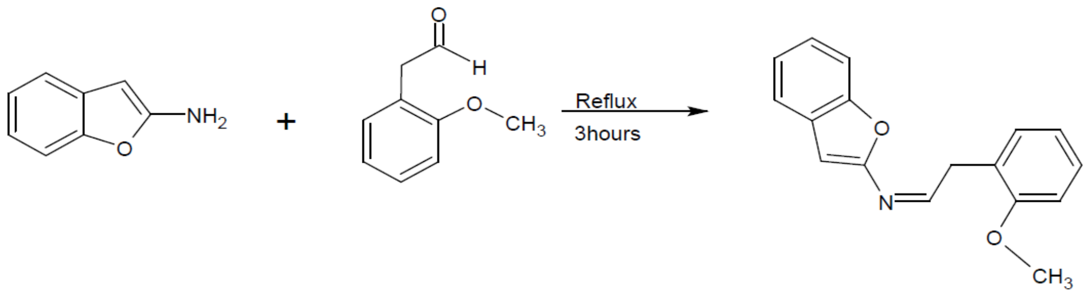
Chemicals of analytical grade purity were used. Melting point and decomposition temperature were determined on Gallenkamp melting point apparatus. Molar conductivity measurement was carried out using Jenway conductivity meter model 4010, while magnetic susceptibility measurement was done on Sherwood (29275) magnetic susceptibility balance at 25^oC. IR spectral analysis was carried out using FTIR Cary 630 (Agilent Technology) model in the range of 4000 - 600cm^{-1}.

Preparation of the Schiff base

The Schiff base formed from 2-aminobenzofuran and 2-methoxyphenylacetaldehyde was prepared by adding 20cm^3 ethanolic solution of 2-aminobenzofuran (1.00g, 0.00751mol) to the same volume of ethanolic solution of 2-methoxyphenylacetaldehyde (1.1278g, 0.00751 mol). The mixture was magnetically stirred at 70°C for 4hrs. The reaction mixture was concentrated, cooled to room temperature to afford a crude product which was allowed to stand for 72hr. The dark solid product obtained was filtered, re-crystallized with ethanol, and washed with distilled water and dried in desiccators over $CaCl_2$ for 24hours.

The percentage yield of the product was calculated using the equation shown below;

$$\% \text{ Yield} = \frac{Experimental\ Yield}{Theoretical\ Yield} * 100$$



Scheme 1: Preparation of Schiff base

Preparation of Schiff base Metal Complexes

The metal complexes were prepared by adding 20cm^3 of ethanolic solution of $MCl_2.nH_2O$ (where M = Co, or Zn) with ethanolic solutions of the prepared Schiff base in the ration of (1:2). The resulting mixture was magnetically stirred at 70^{0}C for 3hours. On cooling to room temperature, coloured solids were precipitated out. The product was filtered, re-crystallized with Sethanol, and washed with distilled water and dried in a dessicator over $CaCl_2$ for 24hours.

The percentage yield of the product was calculated using the equation (1) above;

Biological Efficacy

The biological efficacy of the Schiff base ligand and its metal complexes was carried out by using two bacterial isolates of *Staphylococcus aureus,* and *Escherichia coli* and *two fungi Candida* *albicans,* and *Aspergillus fumigatus*. The suspension of each microorganism was smeared on the surface of the solidified Muller-Hinton Agar (MHA) already poured into petri dishes. The Schiff base and the metal Complexes were separately dissolved in DMSO so as to have three distinct concentrations (250μg/disc, 125μg/disc and 62.5μg/disc) through serial dilution and placed on the surface of the culture media, incubated at 37ºC for 24 hours. Activities were determined by measuring (mm) the diameter of the zone of inhibition and compared with a standard drug (Ciprofloxacin) (Khan *et al.,* 2014).

RESULTS AND DISCUSSION

The ligand prepared is crystalline dark brown, it is soluble in common organic solvents but insoluble in water. The cobalt(II) and zinc(II) Schiff base complexes prepared are crystalline brown and have decomposition temperatures 243ºC and 210ºC for the cobalt(II) and zinc(II) complexes respectively. These high decomposition temperatures revealed the stability of the complex compounds which is common with such complexes (Table 1). The solubility tests carried out on the ligand and its cobalt(II) and zinc(II) complexes showed that they are soluble in most common organic solvents but insoluble in water, indicating that the compounds are not ionic (Table 2). The differences in the solubility of the ligand and their corresponding complexes further proved that the synthesized complexes are different from their parental ligand.

The presence of broad peak around *3219cm*$^{-1}$ in the IR spectra of the complexes indicates water of hydration in the complexes. Further studies revealed four water molecules for cobalt(II) complex and two water molecules for zinc(II) complex (Table 3 & 4).. Jobs method of continuous variation was used to confirm the metal ligand reacting ratio and the results obtained from the Job's plot giving in figures 1 and 2, the number of coordinated ligand was determined which indicate a 1:2 metal ligand ratio for the two metal complexes.

The IR spectral data of the ligand showed a band at 1707cm^{-1}, which is assigned to v(C=N) stretching vibration, a feature found in Schiff bases (Jezowska et al, 1988). This band is also observable in the complex compounds, at lower frequency in both complexes. 1640cm^{-1} and 1637cm^{-1} in cobalt (II) and Zinc(II) complexes respectively (Table 4). Suggesting that the ligand is coordinated to the respective metal ions, resulting in the formation of the two complexes (Prabhu and Dodwad, 1986). Coordination of the Schiff base to the metal ions through the nitrogen atom is expected to reduce electron density in the azomethine link and lower the (C=N) stretching absorption frequency. This band shifted to a lower wave number side in all the complexes indicates the participation of the azomethine nitrogen in coordination with metal ions. This feature was also observed by Halli, et,al 2015 and Shaishta, et,al 2014, in their similar synthesis. The bands in the region 1031–1247 cm^{-1} are assigned to the v(C–O–C) stretching vibrations of furan moiety. It was also reported by Halli, et,al 2015 and Shaishta, et,al 2014 in their literature that (C–O–C) stretching vibration is observed at 1206 cm^{-1}, this study similarly observed (C–O–C) stretching vibrations in the region of 1108 cm^{-1} which remains unaltered in the metal complexes, indicating non-participation of the furan ring oxygen atom in bonding with the metal ions (Shaishta, et,al 2014).

The peak at 1242 cm^{-1} which shifted to 1292cm^{-1} in Co (II), and 1201cm^{-1} in Zn (II) complexes respectively were assigned to C-O bond of the methoxy group (Abdel-Latif *et al.,*2006). The bands in the regions 743cm^{-1} ,765cm^{-1} and 680cm^{-1} -683cm^{-1} are attributed to v(M-N) and v(M-O) stretching vibrations respectively, confirming the coordination of the Schiff base to the respective metal ions.

Table 1. Physicochemical Characterization of the Schiff base and its metal (ii) complexes

Compounds/ Complex	Molecular weight	Colour	Percentage Yield	Melting Point	Decomposition Temperature
Ligand	265.00	Brown	89.32	187	
$[CoL_2Cl_2]$	660.41	Brown	65.14	_	243
$[ZnL_2Cl_2]$	666.51	Brown	82.88	_	210
L = Ligand, $C_{17}H_{15}NO_2$ Mol. weight = 265					

Table 2. Solubility Test of the Schiff base and its Metal (II) Complexes

Ligand/Complexes	Distilled water	Ethanol	Methanol	Acetone	Pet. ether	DMF	DMSO
Ligand	IS	S	S	S	IS	S	S
$[CoL_2]$	IS	S	SS	SS	IS	S	S
$[ZnL_2]$	IS	S	SS	SS	IS	S	S
L=Ligand $C_{17}H_{15}NO_2$ Mol. weight=265 DMF=Dimethylformamide, DMSO=Dimethylsulfoxide, S= Soluble SS= Slightly Soluble IS= Insoluble							

Table 3. Percentage of Water of Crystallization

Complexes	Initial Weight (g)	Weight loss (g)	% Water of Crystallization	Number of Water of Crystallization
Co (ii)	0.2	0.0196	9.8	4
Zn (ii)	0.2	0.0104	5.2	2

Table 4. Percentage Compositions and Empirical Formula of the Complexes

Complexes	% of Metal	% of Chlorine	% of ligand	%of Water	M:L ratio	Empirical Formulae
Co (ii)	8.04	9.69	72.37	9.8	1:2:2	$[CoL_2CL_2].4H_2O$
Zn (ii)	9.25	10.10	75.44	5.2	1:2:2	$[ZnL_2CL_2].2H_2O$

Table 5. Selected infrared spectral data of the Schiff base and its metal (ii) complexes

Compound	u(C=N) cm^{-1}	u(-OCH3) cm^{-1}	u(C=C) cm^{-1} aromatic	u(C-N)cm^{-1}	u(M-N)cm^{-1}	u(M-O)cm^{-1}
Ligand	1707	1242	1443	1328	-	-
$[CoL_2]$	1640	1292	1495	1383	765	680
$[ZnL_2]$	1637	1201	1447	1346	743	683
L = Ligand, $C_{17}H_{15}NO_2$						

Table 6: Molar magnetic susceptibility, gram magnetic susceptibility and effective magnetic moments of the complexes

Complex	Xg ($ergG^{-2}g^{-1}$)	Xm ($ergG^{-2}mol^{-1}$)	μeff (B.M)
$[CoL_2]$	4.50×10^{-10}	2.97×10^{-8}	4.8
$[ZnL_2]$	-4.02×10^{-10}	-2.68×10^{-8}	-

Gram magnetic susceptibility and the effective magnetic moment of the cobalt(II) complex as determined from the magnetic susceptibility was 4.8MB which indicate that its paramagnetic because of its positive value and suggest high spin complex with octahedral geometry. While zinc(II) complex was negative which indicate diamagnetic. (Table 6).

Molar conductance of the complexes as determined from the electrical conductance in 0.003M DMSO solution of the complexes. The values obtained were 32.71ohm^{-1}cm^{2}mol^{-1} and 10.55 ohm^{-1}cm^{2}mol^{-1} for cobalt(II) and zinc (II) complexes respectively (Table 7) which are relatively low, and suggests none electrolytic nature of the complexes indicating that the two chlorides ions are present in the coordination sphere.

The antimicrobial efficacy of the Schiff base and its metal complexes were tested against bacterial strains *(Staphylococcus aureus* and *Escherichia coli)* and fungal isolates *(Aspergillus flavus* and *Mucor species)*. The diameter of the inhibition zones were measured and recorded as shown in (Table 9 and 10). The results of the tests indicated moderate antimicrobial activity against the tested microorganisms when compared with the standards (Ciprofloxacin and Ketoconazole), and this activity increases by increasing concentration. And also the metal complexes showed higher activity than free ligand, due to the effect of metal ions on the normal metabolic function of the cell. These findings are similar to that reported by Halli *et al*., 2015

Table 7. Conductivity Measurement Data of 10^{-3} M Metal (II) Complexes in DMSO

Complexes	Electrical Conductivity (ohm^{-1} cm^{-1})×10^{-6}	Molar Conductance (ohm^{-1} cm^{2}mol^{-1})
[CoL_2]	32.71	10.9
[ZnL_2]	10.55	3.51

Table 8 Antibacterial Screening of the ligand and its complexes

Complexes	Concentration (ug/ml)/ Zone of inhibition (mm)						
	Staphylococcus Aureus				***Escherichia Coli***		
	250	125	62.5		250	125	62.5
Ligand	17	14	10		16	13	11
[CoL_2]	21	19	14		19	15	12
[ZnL_2]	24	19	15		20	18	14
Standard	32				27		

L = Ligand, $C_{17}H_{15}NO_2$ **Standard = Ciprofloxacin**

Table 9 Antifungal sensitivity test of the Schiff base and its metal (ii) complexes

Complexes	**Concentration (ug/ml)/ Zone of inhibition (mm)**						
	Candida albican				***Mucur specie***		
	250	125	62.5		250	125	62.5
Ligand	18	16	15		17	16	13
[CoL_2]	21	19	14		19	15	12
[ZnL_2]	16	12	10		18	17	13
Standard	38				36		

L = Ligand, $C_{17}H_{15}NO_2$ **Standard = Ketoconazole**

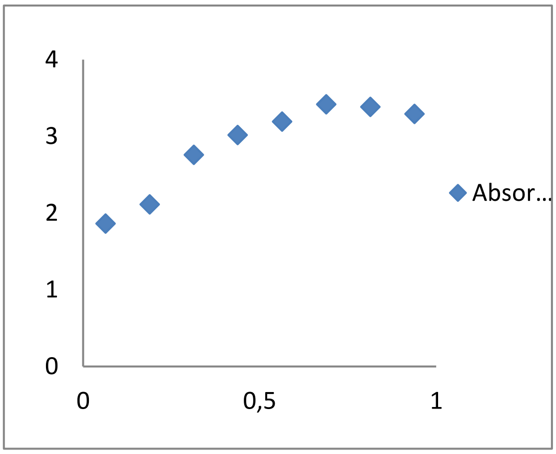


Fig. 1: Plot of absorbance against ligand mole fraction at 635nm for Zn(II) complex

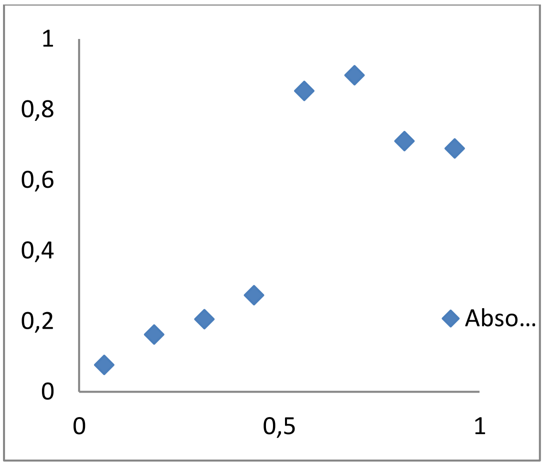


Fig. 2: Plot of absorbance against ligand mole fraction at 545nm for Co(II) complex

CONCLUSION

The Schiff base and its corresponding metal complexes of Co(II), and Zn(II) were synthesized and characterized successfully by various analytical techniques. The complexes are non-electrolytes in DMSO solvent. The decomposition temperature of the metal (II) complexes indicated that complexation has taken places. Based on magnetic susceptibility data, Co(II) complex is paramagnetic while Zn(II)complex diamagnetic. Vibration stretching of furan v(C–O–C) moiety was observed around 1108 cm^{-1} which remains unaltered in the metal complexes, indicating non-participation of the furan ring oxygen atom in bonding with the metal ions.

Based on the spectral studies, conductance data and magnetic susceptibility data, the synthesized ligand and its complexes are neutral bidentate, coordinating through the Oxygen of the methoxy group and Nitrogen of the azomethine group. The antimicrobial efficacy results indicate that the complexes showed higher efficacy than free ligand, due to the effect of metal ions on the normal metabolic function of the cell. Based on the analytical and spectral studies, we propose octahedral geometry to the complexes (Figure. 3 and 4).

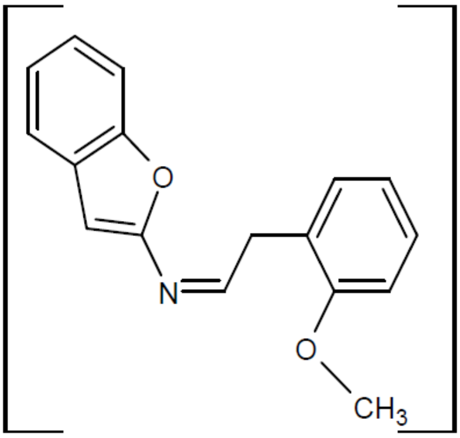


Fig. 3: Proposed structure of the Schiff base

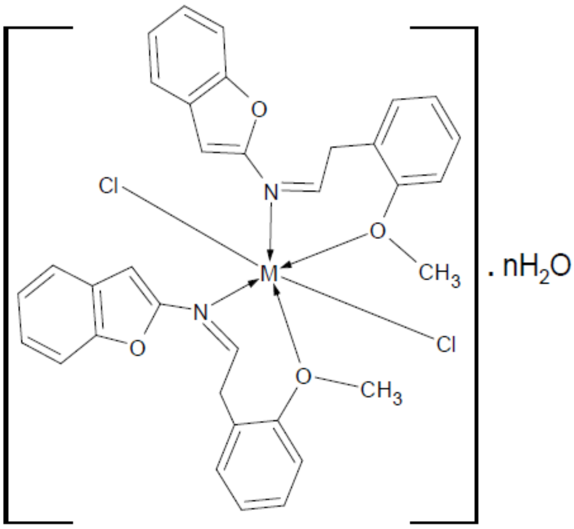


Fig. 4: Proposed structure of the metal (II) complex of Co(II) and Zn(II) of the Schiff Base.

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