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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF SCHIFF BASE TRANSITION METAL COMPLEXES OF (E)-2-((2-METHOXYBENZYLIDENE)AMINO)PHENOL

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ABSTRACT

Annually several compounds are synthesized to find out potential chemotherapeutic agents to combat harmful microorganisms. Schiff bases and their corresponding complexes have wide applications as anticancer, antibacterial, antifungal, antimalarial and antiviral. Metal complexes are becoming indispensable in the design of drugs, thus, encouraging the study on metal-based drugs. Schiff Base derived from 2-amino phenol and 2-methoxybenzaldehyde was synthesized and characterized by different physicochemical techniques. The Schiff base and Mn(II), Fe(II) and Ni(II) complexes were synthesized and characterized by solubility test, decomposition temperature, molar conductance, infrared spectroscopy, UV-visible, elemental analysis and ^{1}H NMR. Melting point of the Schiff base was 110 $^{\circ}$C and decomposition temperatures of the complexes were in the range 131 - 140 ^{o}C. The IR spectrum of the Schiff base shows a strong absorption band at 1600 cm^{-1} due to ν(C= N). which was shifted in the spectra of the complexes to 1581-1698 cm^{-1} indicating complexation through nitrogen atom of azomethine group. Magnetic susceptibility revealed that all the complexes were paramagnetic. The molar conductance values of the complexes were between 17.07 and 28.37 $\Omega^{-1}cm^{-2}mol^{-1}$. The low values indicate non-electrolytic behaviour of the complexes. Elemental analysis result shows 1:2 metal to ligand ratio. The compounds were screened against bacterial and fungal species, ciprofloxacin and ketoconazole, used as control respectively. The results revealed that the complexes exhibit higher activities than the Schiff base but lower than the control.

Key words: Antibacterial, Antifungal, Complexes, 2-amino phenol, 2-methoxybenzaldehyde and Schiff base.

INTRODUCTION

Schiff base compounds are condensation products of primary amines and aldehydes or ketones [1, 2]. Schiff bases have an esteemed place in medicinal chemistry [3].

Schiff base derivatives have attracted the attention of many researchers due to their high potentials to bind metal ions and widespread range of applications [4, 5]. They have played a vital role in developing coordination chemistry [6,7]. Their synthesis have been widely explored [8]. They exhibit effective biological activities such as antibacterial [9], antifungal [10], anti-inflammatory [11], antiviral [12], antioxidant [13], antiproliferative [14] and anticancer [15].

Many drugs possess modified pharmacological and toxicological properties when administered in the form of metallic complexes [16, 17]. Drugs resistances are renowned condition that occurs when diseases become tolerant to chemotherapeutic agents. Even though, several classes of antibacterial and antifungal drugs are presently available, the resistance of microorganisms to these drugs is persisting. In order to address this serious medical problem, there is need to discover new drugs with novel mechanisms of action, higher activity and improved selectivity to address the severe challenges of multidrug resistance in treating deleterious diseases [18].

There has been considerable interest in the chemical properties, structures, coordination behaviours and diverse applications of Schiff base complexes. In view of the versatile applications of Schiff bases and their complexes, this research was aimed at synthesis, characterization and biological evaluation of transition metal complexes with Schiff base derived from 2-amino phenol and 2-methoxybenzaldehyde,

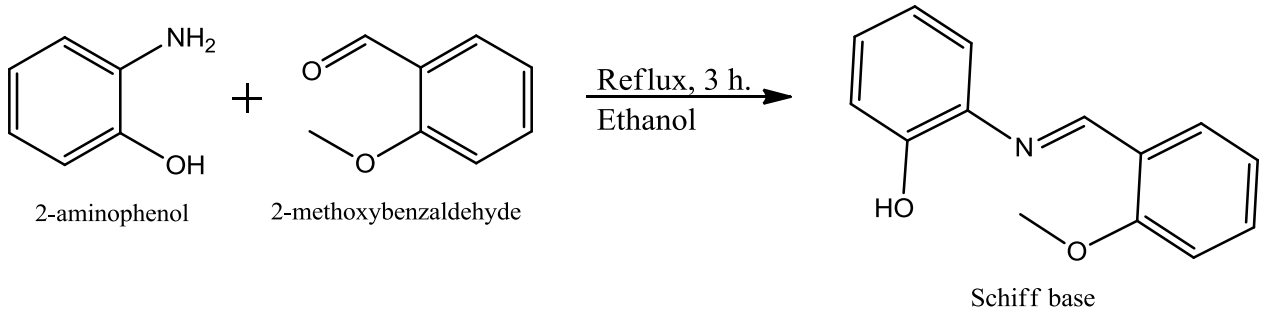
MATERIALS AND METHODS

All the chemicals were of analytical grade and were used without further purification. The transition metal salts and other chemicals were obtained from either Merck or Sigma Aldrich. All glassware were washed with detergent, rinsed with distilled water and dried in the oven at 110 ^{o}C. All weighing was carried out on electrical meter balance Toledo BI54. Melting point and decomposition temperatures were recorded using Gallenkamp melting point apparatus. Conductivity measurement was done using Jenway conductivity meter mode 4010. Infrared spectral analysis was recorded using Fourier Transform Infrared Spectrophotometer (FTIR) CARY 630 Agilent technology. Magnetic susceptibility measurements were conducted and recorded using Sherwood magnetic susceptibility balance. Elemental analyses were conducted using Flash EA 1112 series CHN (Thermo Finnigan) analyzer. The ^{1}H NMR was recorded on a Bruker 500MHz Avance III FT-NMR spectrometer at ambient temperature. Tetramethyl silane (TMS) was used as the internal standard. The *in vitro* antibacterial and

antifungal screening was performed by disc diffusion method on three bacterial species; *Staphylococcus aureus, Salmonella typhi,* and *Escherichia coli* and two fungal species; *Mucor spp* and *Aspergillus fumigitus,* at the Department of Microbiology Laboratory, Bayero University, Kano, Nigeria

Synthesis of Schiff Base

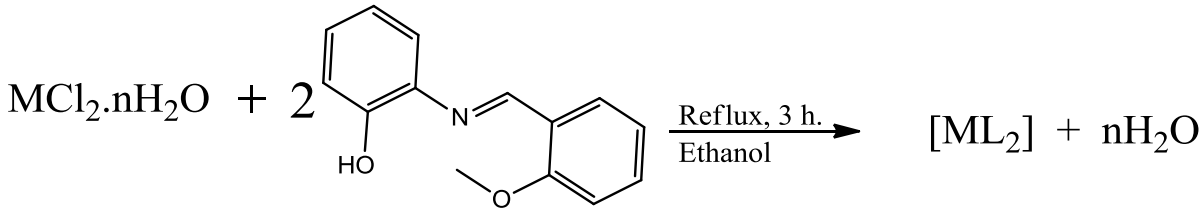
An ethanolic solution of 2-amino phenol (0.01 mol) and O-anisaldehyde (0.01 mol) were mixed gently and refluxed for 3 h. The volume of the resulting solution was reduced to half by evaporation and cooled to room temperature. The product obtained was filtered, washed with ethanol, dried and preserved in a dessicator over $CaCl_2$ for a week [19].



Equation 1: The scheme for the synthesis of the Schiff base

Synthesis of Complexes

An ethanolic solution of Schiff base (0.002 mol) and metal(II) chlorides (0.001 mol) were mixed gently and refluxed for 3 h. The volume of the resulting solution was reduced to half by evaporation and cooled to room temperature. The solid obtained was filtered, washed thoroughly with ethanol and dried in a dessicator over $CaCl_2$ for a week [19].



Equation 2: The scheme for the synthesis of the complexes.

Determination of Melting Point and Decomposition Temperature

The melting point of the Schiff base as well as the decomposition temperatures of the metal complexes were determined by introducing a pinch of each into a capillary tube and then inserted into the Gallenkamp apparatus; The temperature at which the ligand melts and that which the complexes decompose were recorded. The result is shown in Table 1.

Solubility Test

The Schiff base and its metal complexes were subjected to solubility test in some common solvents: Acetone, deionize water, methanol, ethanol, nitrobenze, carbontetrachloride, chloroform, DMSO, DMF and benzene. The result is shown in (Table 2).

Molar Conductivity Measurement

Three millimole of each metal complex was dissolved in 10 mL of DMSO and the corresponding conductance values recorded, molar conductance of each metal complex was then evaluated. The result is shown in Table 3.

Infrared Spectral Analysis

Infrared spectral analysis was recorded using Fourier Transform Infrared Spectrophotometer (FTIR) CARY 630 Agilent technology. The spectral data was shown in Table 4 and all the spectra were displayed in Figures 4–7.

CHN Elemental Analysis

Elemental analyses were conducted using Flash EA 1112 series CHN (Thermo Finnigan 300) analyzer. Acetanilide was used as a reference standard. The microanalytical data of the Schiff base and its metal(II) complexes were shown in Table 5.

^{1}H Nuclear Magnetic Resonance (NMR)

The ^{1}H NMR was recorded on a Bruker 500MHz Avance III FT-NMR spectrometer at ambient temperature. Tetramethyl silane (TMS) was used as the internal standard while recording the spectrum. The ^{1}H NMR spectrum of the new Schiff base was taken in DMSO-d_6 solvent at 2.50 ppm. The spectral data was reported as: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet) in ppm and the values were shown in Table 6.

Magnetic Susceptibility Measurement

The synthesized complexes were introduced in to a given capillary tube up to a given mark and the reading recorded using the magnetic susceptibility balance. The gram magnetic moment was calculated from which effective magnetic moment was computed.

Antibacterial and Antifungal Test

The antibacterial and antifungal tests of the Schiff base and metal complexes were carried out by disc diffusion method. The bacterial species used in the screening were *Staphylococcus aureus*, *Escherichia coli* and *Salmonella typhi*. The fungal species were *Mucor spp* and

Aspergillus fumigatus. Three different concentrations 60 µg/disc, 30 µg/disc and 15 µg/disc of each metal complex and ligand were prepared in DMSO. About 0.06 g of each of the complexes and the ligand was dissolved in 1 ml of the solvent separately. About 0.5 mL of each solution was introduced into 50 sterile discs in the bijou bottles respectively to make 60 µg/disc concentrations. About 0.5 ml of DMSO was added into the remaining stock solution, making 1 ml. About 0.5 ml was taken and placed into other bottles containing 50 discs to make the 30 µg/disc concentrations. About 0.5 ml of DMSO was added to the stock solution and another 0.5 ml was taken and added to 50 discs in the bottles to make the 15 µg/disc concentration [20]. The results are presented in Figure 1.

Standard innocula of the isolates were swabbed onto to the surface of the prepared and solidified nutrient Agar in separate petri-dishes. The prepared discs of the complexes and standard antibiotic discs were placed on the surface of the inoculated media at interval. The standards used for the antibacterial tests was ciprofloxacin and for the antifungal test was ketoconazole. The plates were incubated at 37 ^{o}C for 24 hours before observation and measurement of inhibition zone. The same procedure was used for the fungal isolates using potato dextro agar and the plates were incubated at room temperature for 48 hours. The results are presented in Figure 2.

RESULTS AND DISCUSSION

Percentage yield and some physical properties of the Schiff base and that of the complexes were shown in Table 1.

Table 1: Physical properties of the ligand and its metal (II) complexes

Compound	Colour	B.M (μ_{eff})	Decomposition Temperature($^{\circ}$C)	Melting Point ($^{\circ}$C)	Percentage yield%
Ligand	Light Brown	–	–	110	82.57
[Mn L_2]	Dark Brown	5.87	140	–	70.70
[Fe L_2]	Dark Red	5.42	134	–	65.66
[Ni L_2]	Brown	3.42	131	–	79.83

Table: 2: Solubility tests of the Ligand and its metal (II) complexes

Compound	Deionize H_2O	MeOH	EtOH	Chloroform	Acetone	Nitro Benzene	CCl_4	Benzene	DMF	DMSO
Ligand	IS	S	S	SS	SS	S	IS	SS	S	S
[Mn L_2]	IS	SS	SS	S	SS	SS	IS	SS	S	S
[Fe L_2]	IS	SS	SS	SS	SS	S	IS	SS	S	S
[Ni L_2]	IS	SS	SS	SS	SS	SS	IS	SS	S	S

KEY: S = Soluble, SS = Slightly Soluble, IS = Insoluble

Table: 3: Molar Conductivity Measurement of the Complexes in DMSO

Complex	Concentration moldm^{-3}	Specific Conductance Ohm^{-1}cm^{-1}	Molar conductance Ohm^{-1} cm^2 mol^{-1}
[Mn L_2]	3×10^{-3}	85.1×10^{-6}	28.37
[Fe L_2]	3×10^{-3}	53.6×10^{-6}	17.87
[Ni L_2]	3×10^{-3}	51.2×10^{-6}	17.07

Table: 4: Infrared spectral data of the Ligand and its metal (II) complexes

Compound	υ(OH) cm^{-1}	υ(C=N) cm^{-1}	υ(M – N) cm^{-1}	υ(M-O) cm^{-1}
Ligand	3304	1600	–	–
[Mn L]	–	1590	752	456
[Fe L_2]	–	1581	750	407
[Ni L_2]	–	1698	748	459

Table 5: Microanalytical Data of the Schiff base and its Metal(II) Complexes.

Compounds	Percentage of Elements Calculated (Found)		
	C	H	N
Ligand	73.99 (72.95)	5.77 (5.71)	6.16 (6.10)
[MnL_2Cl_2]	66.27 (65.69)	4.77 (4.12)	5.52 (5.32)
[FeL_2Cl_2]	66.16 (66.10)	4.76 (4.42)	5.51 (5.29)
[NiL_2Cl_2]	65.79 (64.99)	4.73 (.433)	5.48 (5.01)

Where Ligand is; $C_{14}H_{13}NO_2$

Table 6: Proton NMR Spectral Data of (E)-2-((2-methoxybenzylidene)aminophenol

Chemical Formula	Name	^{1}H NMR (500 MHz, DMSO-d_6, TMS) (ppm)
$C_{14}H_{13}NO_2$		7.28 (q, 1H), 7.01 (q, 1H), 6.95 (d, 1H), 7.16 (d, 1H), 5.35 (s, 1H), 3.83 (s, 3H), 8.87 (s, 1H), 7.08 (q 1H), 7.68 (q, 1H), 7.26 (d, 1H), 7.72 (d 1H)

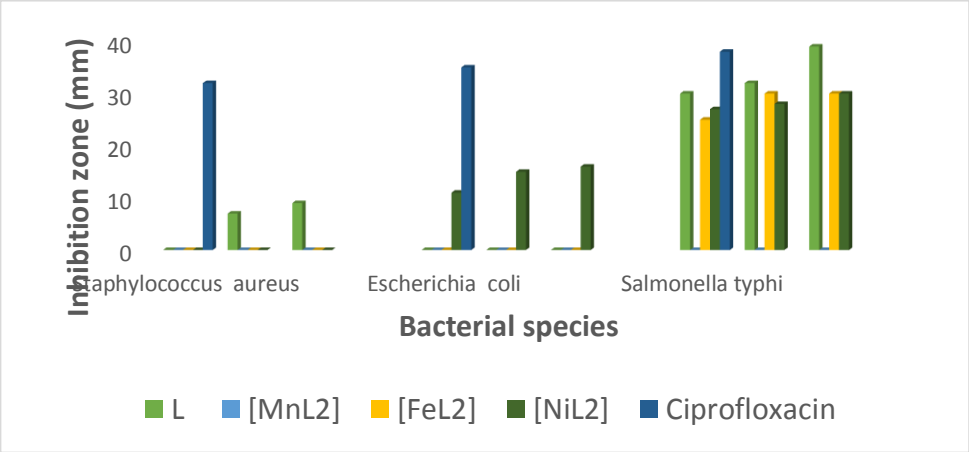


Fig. 1: Chart showing the antibacterial activities of the Schiff base and the complexes.

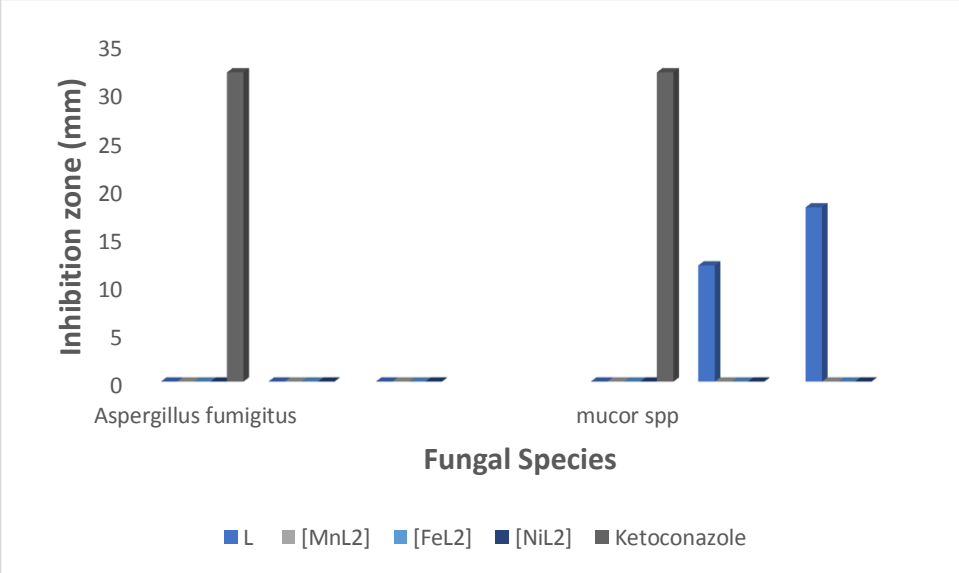


Fig. 2: Chart showing the antifungal activities of the Schiff base and the complexes.

The Schiff base was synthesized by condensation of 2-aminophenol and 2-methoxybenzaldehyde. It was brown in colour with high yield (82.57%). The high yield indicates that the reaction is economically feasible and promising, with a melting point of 110 $^{\circ}$C. The values of melting point precisely indicate that the Schiff base is thermally stable. The complexes formed from the reaction of the Schiff base and the corresponding metal(II) chlorides were of various colours (Table 1) due to chromophores and electronic transitions in the d-orbitals of the metal ions in the complexes.

All the complexes formed have an appreciable percentage yield in the range of 65.66 - 79.83% indicating the feasibility of the process for their synthesis. This is similar to the result reported by Sadi *et al.*[21].

Decomposition temperatures of the complexes were in the range 131-140 $^{\circ}$C. These values indicated that the complexes are stable are more thermally stable than the free Schiff base due to presence of metal ion. This result is in good agreement with the result reported [21-22].

Solubility test for the Schiff base and its corresponding complexes were carried out in order to identify the best solvent used for the purification and other spectroscopic and analytical measurements as shown in Table 2. The result indicated that the Schiff base and its corresponding complexes were insoluble in water. All the compounds were slightly soluble in moderately polar solvents and soluble in methanol, ethanol and readily soluble in DMSO and DMF due to their high dielectric constant. The solubility in these solvents might be due to the presence of polar ends of the compounds. This agrees with the results reported by Sayeed *et al.,* [22]. The molar conductance measurement in DMSO carried out on the metal(II) complexes were in the range 17.07 – 28.37 $Ohm^{-1}cm^{2}mol^{-1}$ which were relatively low suggesting non-electrolytic nature of the complexes [23].

The IR spectral data of the Schiff base ligand (Table 4) showed vibrational peak at 1600 cm^{-1} which may be attributed to the azomethine υ(C=N) [21]. This indicates the condensation reaction between 2-methoxybenzaldehyde and 2-aminophenol. The band in the range1581-1698 $cm^{-1}$are observable in the spectra of the complexes which is an indication of the participation the metal(II) ions in the formation of the complexes. This is similar to the results Ahmed *et al.* [24]. New absorption bonds at 748-752 cm^{-1} and 407-459 cm^{-1} in the metal(II) complexes indicate the formation of M-N and M-O bonds respectively which indicated that the ligand is coordinated to the metal ions through these groups as reported by

Ayman *et al.*, [25]. The IR spectra of the complexes and that of the Schiff base were displayed in Figures 4-7.

Magnetic susceptibility measurement at room temperature showed that the metal(II) complexes are all paramagnetic in nature. All the metal(II) complexes synthesized have effective magnetic moment values between 3.42 - 5.87 BM. The values suggested octahedral geometries for the complexes [21,26].

The elemental analysis results of the Schiff base and the metal (II) complexes are presented in Table 5. The results were in good agreement between the calculated percentages of C, H and N in the compound and the experimental values (found) with slight differences. This agrees with the proposed structures of the complexes; Hence, 1:2 metal to ligand ratio is proposed [23, 24].

The quartet peaks at 7.28 and 7.01 ppm were assigned to meta and para protons of phenol ring respectively, likewise, the doublet peaks at 6.95 and 7.16 ppm were due to auto and meta protons of phenol ring in the same order. This is similar to the results of Ahmed *et al.* [24]. The singlet peak at 5.35 ppm is attributed to phenolic proton. Similarly, the sharp and intense singlet peak at 3.83 ppm is due to three methoxy protons which are at the same chemical environment. The singlet peak at 8.87 was assigned to HC=N proton. The quartet peaks at 7.68 and 7.08 ppm were assignable to aromatic protons that are meta and para to methoxy group. The doublet peaks at 7.26 and 7.72 ppm were assignable to auto C-H aromatic protons auto and meta to methoxy groups correspondingly. This agrees with the results reported by Ayman *et al* [25]. Therefore, the structures of the complexes proposed in Figure 3.

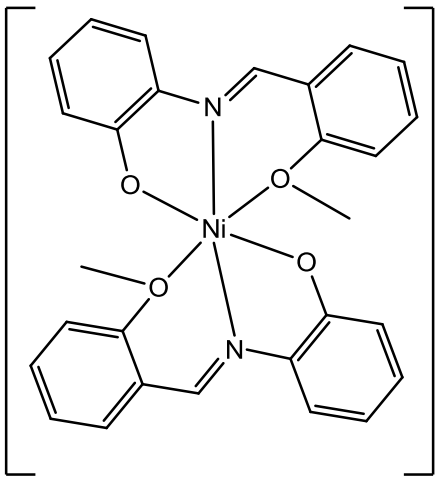


Fig 3: Proposed structure of the complex

The antibacterial and antifungal activity for the Schiff base and its metal(II) complexes were determined using the disc diffusion method. The diameters of zone of inhibition (mm) were measured for each treatment. The ligand showed little activity against *Staphylococcus aureus* and *Mucor spp.* Lit. showed a very good activity on *Salmonella typhi* and no activity against *Escherichia coli* and *Aspergellus fumigates.* Fe(II) complex showed a good activity against *Salmonella typhi* with no activity against all tested bacteria and fungi species. Mn(II) complex showed no activity against all fungi and bacterial species. Ni(II) complex showed activity against *Escherichia coli* and *Salmonella typhi* only. The highest concentration (60µg/disc) has most activity on *Escharichia coli* and on the case of *salmonella typhi*, the highest concentration is 60 µg/disc. This result is in good agreement with the one reported by Caramella *et al.* [27].

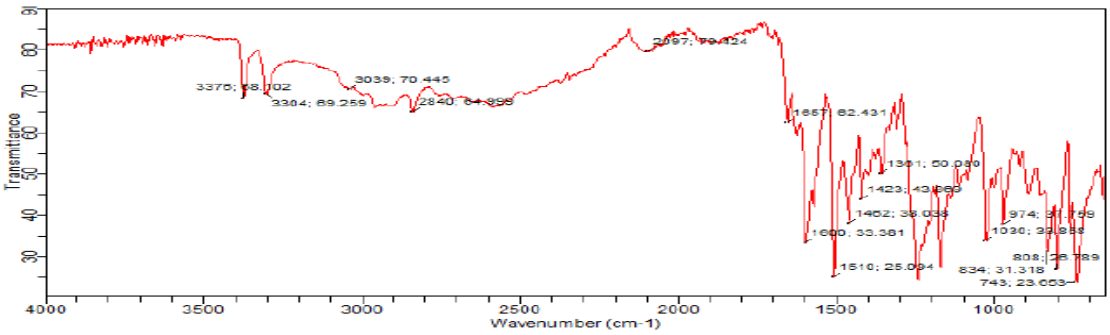


Fig. 4: IR Spectrum of the Schiff Base

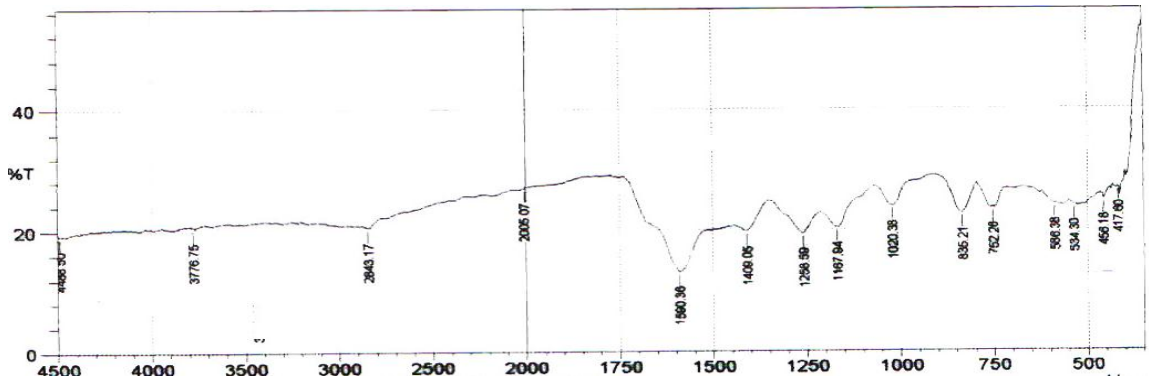


Fig. 5: IR Spectrum of Manganese Complex

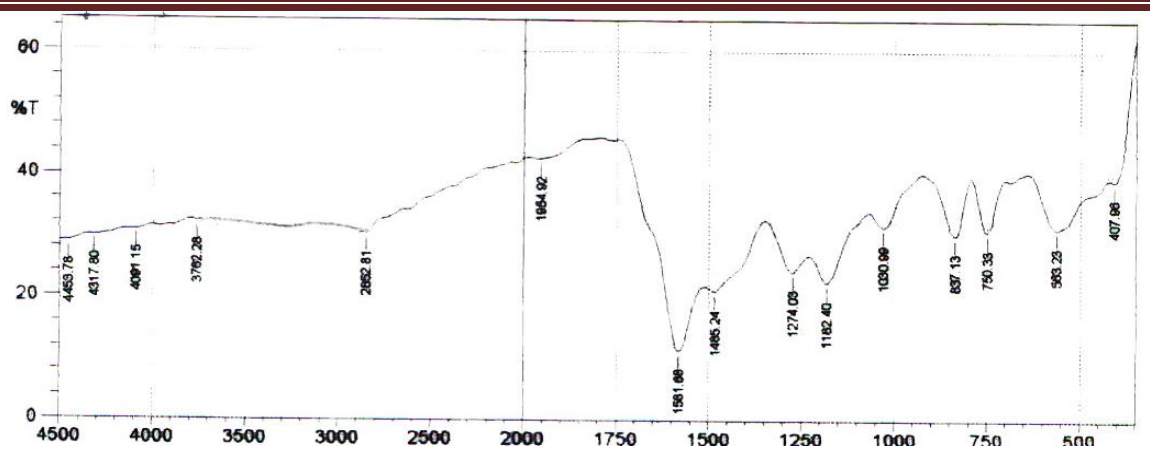


Fig. 6: IR Spectrum of Iron Complex

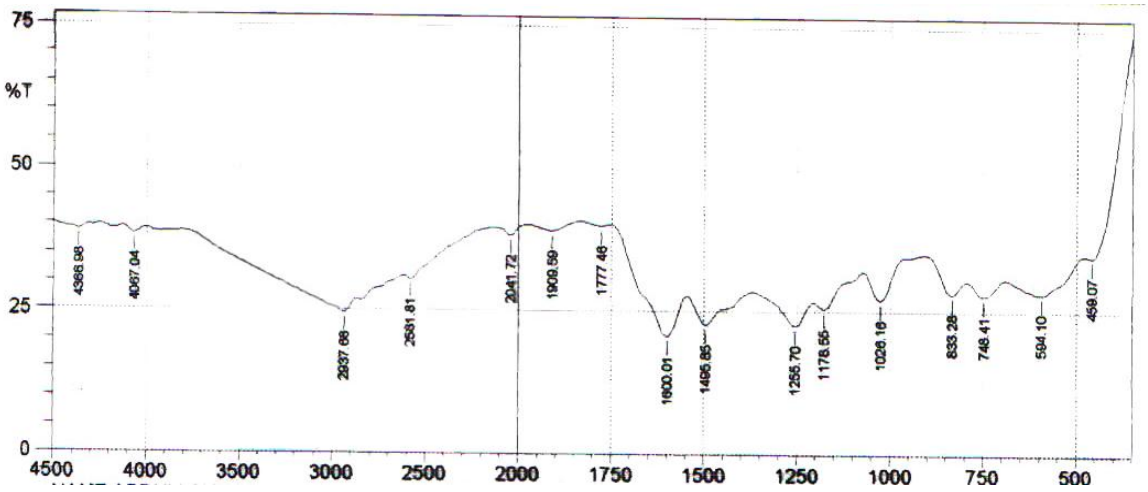


Fig. 7: IR Spectrum of Nickel Complex

CONCLUSION

The Schiff base was prepared by condensation of 2-aminophenol with 2-methoxybenzaldehyde. The corresponding Mn(II), Fe(II) and Ni(II) complexes were also synthesized from the reaction of the ethanolic solution of the Schiff base and metal(II) chlorides. All the complexes were non-electrolytic. The decomposition temperature of the complexes showed that they are thermally stable. The complexes and the ligand are soluble in dimethylformamide and dimethylsulfoxide probably due to their high dielectric constant and high solvation effects. IR spectroscopy showed the Schiff base was coordinated to the central metal ions in a tridentate manner through the N-atom of the azomethine and two oxygen of the phenol and ether (methoxy group). Elemental analysis confirmed that the, ligand metal

ratio is 2:1. Few of the compounds showed significant antibacterial and antifungal activity at high concentration. While most of the compounds showed no activity against the tested organisms. All compounds have no effect on *Aspergillus fumigitus.*

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