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Synthesis and Characterization of Potentially Bioactive Sulfamethoxazole Isatin Schiff Base and its Mn(II), Fe(II) and Ni (II) Complexes

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ABSTRACT

Sulfonamide and isatin were use for the synthesis of N-(5-Methyl-isoxazol-3-yl)-4-(2-oxo-1,2-dihydro-indol-3-ylideneamino)-benzenesulfonamide Schiff base ligand and its complexes with Mn(II), Fe(II) and Ni (II) have been synthesized and characterized by elemental analysis, conductivity measurement, magnetic measurement and spectroscopic analysis. Infrared spectra of the Schiff base revealed azomethine peak at 1639 cm^{-1} which shifted in the complexes to 1641 – 1687 cm^{-1} range, also a newpeak in the range of 717 – 786 cm^{-1} was observed for all the complexes. The values agree with the formation and chelation of the Schiff base through the azomethine nitrogen and ketonic oxygen. Conductance measurement (1.64 – 30.50 Ohm^{-1} cm^2 mol^{-1}) suggested the non-electrolytic nature of all the complexes. Magnetic susceptibility analysis of the complexes gave results in the range of 1.94 – 5.32 B.M. suggesting octahedral geometry for all the complexes.CHN Elemental analysis was in good agreement with the proposed formulation of the complexes suggesting the ligand-metal ratio to be 2:1. Decomposition temperature (165^{0}C – 215^{0}C) of the complexes implied relative stability of the complexes. The Schiff base and its metal chelates were screened for antimicrobial activity against six pathogenic microbes (*Staphyloccus aureus*, *Escherichia coli*, *Salmonella typhi*, *Aspergillus flavus*, *Aspergillus niger* and *Mucor indicus*), the Schiff base shows moderate activity, while the complexes show higher antimicrobial activity against the tested microbes.

Keywords: Antimicrobial, Characterization, Isatin, Schiff base, Sulfamethoxazole, Synthesis

INTRODUCTION

Schiff bases are compounds characterized by the presence of azomethine group (-HC=N-) formed by the condensation of ketones or aldehydes with amines. They have been an amazing discovery in chemistry and have contributed immensely to the development of coordination chemistry. They serve as ligands to most of the transition metals forming very stable complexes (Ghosh *et al*., 2020, Abu-Dief and Mohamed, 2015). Schiff bases have continued to play a key role in the development of medicinal and industrial chemistry with wide range of applications from radio-immunotherapy, cancer diagnosis and treatment, as antiviral agents, treatment of tumor, as catalystsetc (Abu-Dief and Mohamed, 2015, Noor *et al*., 2020). On the other hand, sulfa drugs have attracted huge attention due to their therapeutic recognition as they found application in many medical field (Bushra *et al* 2021, Sinem and Marianna, 2019), specifically sulfamethoxazole have been prescribed in combination with trimethoprim in the treatment of a variety of bacterial infections (Brogden*et al*, 1982). Many of the organic drugs can serve as ligands to form metallic complexes (Jurca*et al*, 2017, Damini*et al*., 2021) which may have the potential to surpass the potency of the non-complexed drug. The metal-drug complexes may combine the specific anti-bacterial tendencies of the sulfa drug and the antimicrobial activities of the metal ion producing some more powerful materials in medicine.

There are many literature reports on the study of antimicrobial activities of sulfamethoxazole and its complexes (Al-khodir 2015, Julia *et al* 2015, Siraj and Ado 2018, Shahnaz *et al*., 2019). However, research in the area is never exhausted as reports on the sulfa-drugs Schiff base and their complexes are still an area of ongoing investigation with many gaps to fill. The present work presents the synthesis, characterization and antimicrobial studies of sulfamethoxazole complexes and its Schiff base with isatin and its Mn(II), Fe(II) and Ni(II) complexes.

MATERIALS AND METHODS

All reagents and solvents used were of analytical grade and were used without further purification. Glass wares were washed with detergent, rinsed with distilled water and dried in an oven at 110^{o}C before use. Weighing was carried out on an electric Metler balance model H3OAR, melting points/decomposition temperature were determined using Galenkemp melting point apparatus. Molar conductance measurements were carried out in DMSO using Jenway conductivity meter 4010 model. Magnetic Susceptibility Measurement was conducted using Magnetic Susceptibility Balance MK1 model, infrared spectral analyses were recorded using a Fourier transform IR Genesis series model in the range of 650-4000cm^{-1}. Elemental analysis was carried out using D5201 test method at Petroleum Industry Laboratories Khartoom, Sudan.

Preparation of the Schiff base

Sulfamethoxazole (2.5328g, 0.01mol) and isatin (3.8239g, 0.01mol) solution in 50cm^3 ethanol was refluxed for three hours. The reaction mixture was cooled and allowed to stand for 24 hours. Precipitate obtained was filtered, washed with distilled water then diethyl ether and dried in desiccator over $CaCl_2$(Suraj et al 2012).

Synthesis of the Metal(II) Complexes

Chloride salts of Mn (II), Fe (II) and Ni (II) (0.01mol) were seperately mixed with the Schiff base (0.02mol) in ethanol (50cm^3) and refluxed for five hours to give the corresponding metal (II) Schiff base complexes. The reaction mixture was allowed to cool overnight and the precipitate obtained was filtered, washed thoroughly with cold ethanol then ether and dried in a desiccator over $CaCl_2$(Suraj et al 2012).

Antibacterial Activity Test

Clinical isolates of *Escherichia coli, Staphylococcus aureus,* and *Salmonella typhi* were obtained from the cultures collection of Microbiology Laboratory, Bayero University Kano, Nigeria. The isolates were identified at the Department of Microbiology using standard microbiological procedures described by Cheesbrough, 2002. The *in vitro* antibacterial activity was determined using Kirby-Bauer disc diffusion assay (CLSI, 2006). The inoculum was prepared by suspending overnight bacterial culture in saline solution (0.85%NaCl) and diluted to match the 0.5(10^{8}cells/mL) McFarland turbidity standard. The prepared inoculum was streaked with sterile cotton swab on to the surface of the nutrient agar (Yusha'u and Sadisu, 2011). The Schiff base and its complexes were dissolved separately in DMSO to have four different concentrations (100µg/ml, 200µg/ml, 300µg/ml and 400µg/ml) respectively by serial dilution. They were each transferred onto sterile paper disks (6.0 mm diameter). Commercial antibiotic (Amoxicillin) was used as a reference standard. The discs were placed onto the bacterial culture and growth inhibition zones (in mm) around the discs were observed and measured after 24 hours of incubation at 37 ^{o}C. The diameter of the zone of inhibition produced by the ligand and the complexes were compared with the standard (Yusha'u and Sadisu, 2011).

Antifungal Activity Test

Clinical isolates of *Aspergillus flavus, Aspergillus niger and Mucor inducus* were obtained from the cultures collection of Microbiology Laboratory, Bayero University Kano, Nigeria. The isolates were identified at the Department of Microbiology using standard microbiological procedures described by Cheesbrough, 2002. The *in vitro* antifungal activity was determined using Kirby-Bauer disc diffusion assay (CLSI, 2006). The inoculation method was as described by Hassan *et al*., (2006). The prepared inoculum was rubbed onto the surface of solidified Potato Dextrose Agar (PDA) already poured into Petri dishes. The ligand and its complexes were dissolved separately in DMSO to have four different concentrations (100µg/ml, 200µg/ml, 300µg/ml and 400µg/ml) per disc respectively by serial dilution method. They were placed on the surface of the culture media (potatoes dextrose agar) and incubated at room temperature for 48hrs. The diameter of zone of inhibition produced by the ligand and the complexes were compared with the standard antifungal Ketoconazole as reference (Hassan *et al*., 2006).

RESULTS AND DISCUSSION

General Studies

The N-(5-Methyl-isoxazol-3-yl)-4-(2-oxo-1,2-dihydro-indol-3-ylideneamino)-benzenesulfonamide Schiff base was prepared by adopting a literature method reported by Suraj et al 2012. The Schiff base was found to be light orange in colour which was clearly different from the colours of the sulfamethoxazole and that of isatin starting materials. The Schiff base was prepared as relatively stable compound with melting point of 121^{0}C (Table 1). The synthesized Schiff base was treated separately with Mn(II), Fe(II) and Ni(II) chloride, which afforded the corresponding metal(II) complexes in appreciable yield ranging from 76.44 to 87.74% (Table 1). The colours of the synthesized complexes were found to be varied and different from that of the Schiff base. The decomposition temperatures of the complexes were within the range of 165-182^{0}C displayinga significant increase to the melting point of the ligand which indicated that the Schiff base became more thermally stable upon complexation.

Table1: Physical Properties of Ligand and its Metal (II) Complexes

Compound	Colour	Decomposition temp (^{0}C)	Melting Point (^{0}C)	Percentage Yield%
Ligand	Light orange	-	121	90.70
$[MnL_2Cl_2]$	Brown	178		77.83
$[FeL_2Cl_2]$	Deep brown	182		76.44
$[NiL_2Cl_2]$	Reddish brown	165		87.74

L = ($C_{18}N_4H_{14}O_4S$)

Table 2 present the results of the solubility test of the Schiff base and the metal (II) complexes using the various solvents contained in the table. The results indicated that the Schiff base and all the complexes are soluble in DMSO, DMF, methanol and acetone, while most other complexes were found to be only fairly soluble in the other solvents tested. The molar conductance of the complexes was measured in DMSO. The values obtained for all the metal (II) complexes were found to be in the range of 1.64 – 30.50 Ohm^{-1} cm^2 mol^{-1} which were relatively low (Table 3), suggesting non-electrolytic nature of the complexes (Geary,1971). The results, indicated the absence of any counter ion outside the coordination sphere and therefore in good agreement with the proposed formulation of the metal complexes.

Table 2: Solubility test of Ligand and its Metal (II) Complexes

Compound	Distilled water	MeOH	EtOH	CH_3Cl	Acetone	Nitro Benzene	DMF	DMSO	Ether	Acetonitrile
Ligand	SS	S	S	SS	S	SS	S	S	IS	S
$[MnL_2Cl_2]$	SS	S	SS	IS	S	SS	S	S	IS	S
$[FeL_2Cl_2]$	SS	S	SS	SS	S	SS	S	S	IS	S
$[NiL_2Cl_2]$	SS	S	S	SS	S	SS	S	S	IS	S

Key: S-Soluble, SS- Slightly Soluble, IS- Insoluble

Table 3: Molar Conductivity test of Metal (II) Complexes

Complex	Concentration (Mol dm^{-3})	Specific conductance (Ohm^{-1} cm^{-1})	Molar conductance Ohm^{-1} cm^2 mol^{-1}
$[MnL_2Cl_2]$	1 X10^{-3}	2.27 x 10^{-6}	2.27
$[FeL_2Cl_2]$	1 X10^{-3}	5.57 x 10^{-6}	5.57
$[NiL_2Cl_2]$	1 X10^{-3}	2.38 x 10^{-6}	2.38

L = ($C_{18}N_4H_{14}O_4S$)

Infrared spectral data of the Schiff base and the complexes is contained in Table 4. A new vibrational peak at 1639 cm^{-1} was observed in the Schiff base, which was absent in the spectra of both sulfamethoxazole and isatin, as such can be assign to the newly formed azomethine bond. However, the azomethine peak had been shifted in the complexes to 1641- 1687cm^{-1} suggesting that the azomethine nitrogen participated in the coordination with the metal ions. In addition to the azomethine peak there was a carbonyl peak at 1730cm^{-1} in the Schiff base, which was observed to be shifted to 1737cm$^{-1,}$ 1739cm^{-1} and 1743cm^{-1} in the Mn(II), Fe(II) and Ni(II) complexes respectably, suggesting the participation of the carbonyl oxygen in the complexation. Absorption bands in the range 717 to 786 cm^{-1} observed in the complexes were attributed to metal – nitrogen (M-N) bond. Therefore, the data indicated that the Schiff base acted as bidentate ligand coordinating to the metal through azomethine nitrogen and the carbonyl oxygen atom.

Table 4: IR Spectral Data for Ligand and its Metal (II) Complexes

Compound	ʊ(C=N) cm^{-1}	ʊ(C=O) cm^{-1}	ʊ(M-N) cm^{-1}	ʊ(OH) cm^{-1}
L	1639	1730	-	
$[MnL_2Cl_2]$	1687	1737	786	3380
$[FeL_2Cl_2]$	1641	1739	717	3440
$[NiL_2Cl_2]$	1649	1743	761	3410

L = ($C_{18}N_4H_{14}O_4S$)

Magnetic susceptibility measurement at room temperature and the magnetic moment results (Table 5) showed that the metal (II) complexes are all paramagnetic. Manganese (II) complex recorded a magnetic moment value of 5.34B.M, which is similar to the 5.33BM reported in the literature by Weaver *et al* 2016 indicating high spin octahedral arrangement. The effective magnetic moment of 5.32B.M recorded for iron(II) complex is close to 5.6 – 5.9B.M usually observed for high spin octahedral iron (II) complexes (Figgis, 1978). The value of 3.12B.M for the nickel (II) complex is consistent with values for octahedral Ni (II) complexes (2.9 – 3.3B.M) reported in the literature (Greenwood and Earnshow 1984, Figgis, 1978, Angelica, 1977). All the magnetic moment values observed for the metal (II) complexes agreed with the expected octahedral geometry proposed for all the complexes prepared in this work. Two chlorine atoms from the metal salts were found to coordinate to the metal center to balance the coordination number. This was confirmed gravimetrically and was re-affirmed by the elemental analysis results.

Table 5: Magnetic Susceptibility value of the Metal (II) Complexes

Compound	Magnetic Susceptibility ($cm^3 g^{-1}$)	Molar Magnetic Susceptibility ($cm^3 mol^{-1}$)	B.M(μ_{eff})
$[MnL_2Cl_2]$	3.19×10^{-6}	2.91×10^{-3}	5.34
$[FeL_2Cl_2]$	4.81×10^{-6}	4.38×10^{-3}	5.32
$[NiL_2Cl_2]$	3.67×10^{-6}	3.36×10^{-3}	3.12

L = ($C_{18}N_4H_{14}O_4S$)

Elemental analysis (CHN) of the Schiff base and its metal (II) complexes was conducted to find the appropriate molecular formula of the compounds. The values obtained (Table 6) showed an excellent agreement between the calculated values and those observed using microanalytical instrument for the corresponding elements (CHN) and the result suggested 1:2 metal – Schiff base ratio in all the complexes (Table 6) which agrees with the proposed molecular formular of the corresponding compounds.

Table 6: Elemental analysis (CHN) of the Ligand and it's metal (II) complexes.

Compound	**C Observed (calculated)**	**H Observed (calculated)**	**N Observed (calculated)**
L	56.23 (56.50)	4.007 (3.66)	14.53 (14.62)
$[MnL_2Cl_2]$	47.47 (47.48)	3.27 (3.29)	12.32 (12.31)
$[FeL_2Cl_2]$	47.33 (47.43)	3.29 (3.30)	12.17 (12.19)
$[NiL_2Cl_2]$	47.27 (47.28)	3.24 (3.26)	12.27 (12.26)

L = ($C_{18}N_4H_{14}O_4S$)

Antimicrobial studies

The *in vitro* antibacterial and antifungal screening results are given in Table 7 and 8 respectively. DMSO was used as a negative control and amoxicillin was used as positive control for antibacterial and ketoconazole for antifungal activities. The results show that most of the complexes are more active than the Schiff base but much lower than the standard drugs used. In some cases, most especially in the antifungal screening, the Schiff base and the complexes have similar activities which are much lower than the ketoconazole standard. In the antibacterial, the Schiff base was found to show only mild activityagainst the isolates tested, only active at 400µg/disc against *Escherichia coli* with inhibition zone of 10mm. However, the complexes exhibited improved activity especially at higher concentrations than the uncordinated Schiff base. Fe(II) complex was found to have the highest anti *Staphylococcus aureus* activity (14mm) while Mn(II) and Ni(II) complexes has the highest growth inhibition (14mm) against *Escherichia coli* while the other compounds were only fairly active. *Salmonella typhi* was found to be resistant to both the Schiff base and the complexes except for Ni(II) which shows fairly good activity at higher concentration.

Table 7: Antibacterial Activity of Ligand and its Metal (II) Complexes

Test organism	Compound	Zone of Inhibition (mm)/Concentration (μg/disc)				Control (mm) Amoxicillin in 5 μg/disc
		400	300	200	100	30
Staphylococcus aureus	L	06	06	06	06	
	$[MnL_2Cl_2]$	11	06	06	06	
	$[FeL_2Cl_2]$	14	12	10	08	
	$[NiL_2Cl_2]$	11	09	08	06	
Escherichia coli	L	10	08	07	06	34
	$[MnL_2Cl_2]$	14	12	08	06	
	$[FeL_2Cl_2]$	13	11	09	07	
	$[NiL_2Cl_2]$	14	11	10	06	
Salmonella typhi	L	09	07	06	06	
	$[MnL_2Cl_2]$	06	06	06	06	
	$[FeL_2Cl_2]$	06	06	06	06	
	$[NiL_2Cl_2]$	12	10	09	08	30

L = ($C_{18}N_4H_{14}O_4S$)

The Schiff base was found be active against *Mucor inducus* and *Aspergillus flavus* but without any activity against *Aspergillus niger*. The complexes activity was fairly similar to those of the Schiff base, suggesting that the chelation has not have much impact on the isolates unlike in the bacterial isolates.

The improved activity of the metal complexes when compared with the free Schiff base in the antibacterial test may be linked to the influence of the metal ion in the cell membrane of the isolates. In addition, chelation may also play a role as it provides both the polar and non-polar properties together, needed for permeation to both the cells and the tissues. Also, lipophilicity is modified by coordination, which may make the complexes more active than the free Schiff base (Farrel, 2007). Though, in some cases complexation improves activity, it was found to be lower than the activity of the standards (positive control) for both the antibacterial and antifungal screening.

Table 8: Antifungal activity of ligand and its metal(II) complexes

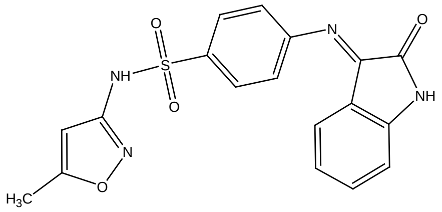
Test organism	Compound	Zone of Inhibition (mm)/Concentration (μg/disc)				Control (mm) Ketoconazole in 5 μg/disc
		400	300	200	100	
Aspergillus flavus	L	11	09	07	06	
	$[MnL_2Cl_2]$	11	09	06	06	
	$[FeL_2Cl_2]$	10	08	07	06	28
	$[NiL_2Cl_2]$	11	09	07	06	
Aspergillus niger	L	06	06	06	06	
	$[MnL_2Cl_2]$	12	06	06	06	
	$[FeL_2Cl_2]$	09	07	06	06	
	$[NiL_2Cl_2]$	06	06	06	06	31
Mucor inducus	L	14	12	10	09	
	$[MnL_2Cl_2]$	11	09	07	06	
	$[FeL_2Cl_2]$	11	10	08	06	
	$[NiL_2Cl_2]$	06	06	06	06	28

L = ($C_{18}N_4H_{14}O_4S$)

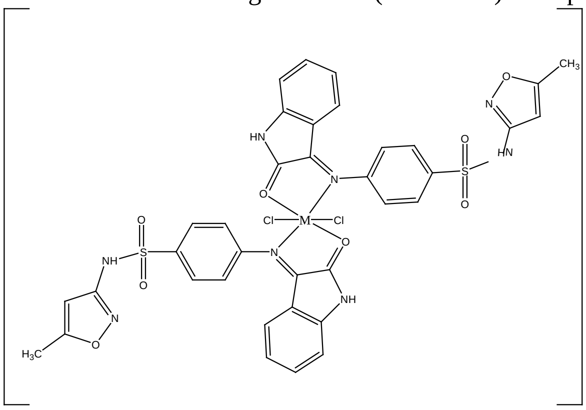
CONCLUSION

Schiff base derived from sulfamethoxazole and isatin has been succesfully prepared and its complexes with Mn(II), Fe(II) and Ni(II) ions have also been synthesized and characterized using conductance measurement, magnetic susceptibility analysis, infrared spectral studies and magnetic moment studies. The conductivity data indicated that, the complexes are non-electrolyte, infrared spectral data indicated that the Schiff base acted as bidentate ligand coordinating through azomethine nitrogen and the carbonyl oxygen atom. Magnetic studies reveal octahedral geometry for all the complexes while elemental analysis revealed 2:1 ligand to metal ration with two chlorine atoms balancing the octahedral sites. The antimicrobial activity data revealed that, the complexes are fairly more active than the free Schiff base against the bacterial isolates tested while the complexes and the Schiff base are almost similar in activity against the fungal isolates tested in the present work.

From the results of conductance measurement, magnetic susceptibility analysis, infrared spectral studies and magnetic moment studies, the structure of the Schiff base and the complexes are proposed as in Figure 1 (a & b) respectively.



(a)



Where M = Mn (II), Fe (II) or Ni (II)

(b)

Figure 1: The proposed molecular structure of (a) the Schiff base and (b) the metal(II) Schiff base complexes

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