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Synthesis, Characterization and Antimicrobial Studies of Co(II) and Ni(II) Schiff Base Complexes Derived Furfuraldehyde and Sulfamethoxazole

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ABSTRACT

Complexes of Co(II)and Ni(II) with a Schiff base derived from sulfamethoxazole and furfural have been synthesized and characterized via physical characteristics, analytical data, FT-IR spectral studies and elemental analysis. Infrared spectral data of the Schiff base and that of the complexes concurs with the formation and chelation of the Schiff base through the azomethine nitrogen at 1629 cm^{-1} and aldehydic oxygen at 1288 cm^{-1}. Molar conductance measurement of 17.32 and 3.52 $Ohm^{-1}\ cm^2\ mol^{-1}$ suggested a non-electrolytic nature of the all complexes. Magnetic susceptibility data (4.33 and 3.00 BM) suggested octahedral structure for all the synthesized complexes. Elemental analysis suggested the ligand-metal ratio of 2:1 respectively. The Schiff base melted at 180°C and the complexes decomposed at 239°C and 241°C, this implies a good thermal stability. The Schiff base and the complexes have been screened for their antimicrobial activities against four pathogenic microbes; *Staphylococcus aureus*, *Escherichia coli, Aspergillus flavus* and *Candida albicans*. The ligand showed moderate activity with inhibition zone in the range of 8 – 14mm, while the metal complexes exhibited higher antimicrobial activity with inhibition zone of 8 – 15mm against the tested microbes.

Keywords : Schiff base, sulfamethoxazole, furfuraldehyde, spectroscopic study, antimicrobial activity

I. INTRODUCTION

Sulfa based drugs continued special attention is due to their historic therapeutic use in medicine as they were used against bacterial infections (Ana *et al.*, 2017; Chuang *et al.*, 2019; Muhammad *et al.*, 2020). The sulfonamide functional group in Sulfamethoxazole is probably responsible for its antimicrobial activities of these class of drugs (Chuang *et al.*, 2019). The therapeutic ability of most sulfa drugs can be enhanced based on addition or subtraction of substituents from the aromatic rings. The enhancement process became a necessity due to the global challenge of drug resistant bacteria and fungi.

Coordination compounds have proved to be more active in different filed of life (biological, industrial, chemical, agricultural etc) than the free ligand (Abu-Dief and Mohamed, 2015; Fawaz, 2017). These characteristics and properties were found to be dependent upon the nature of the metal ion as well as the ligand and its substituents. Therefore, complexing transition metals ion series into the sulfa containing Schiff base ring system (to form chelates) might significantly improve the efficacy of the sulfonamide drug families (Jurca *et al.*, 2017; Weaver *et al.*, 2016). Most of the reported sulfonamides Schiff base complexes in literature have demonstrated a wide range of applications, especially in anti-bacterial and anti-fungal activities (Radha *et al.*, 2016; Sudipa *et al.*, 2018; Mustafa *et al.*, 2019).

Sulfonamide group containing compounds have continued to be used as a drug for different microbial infections (Apaydin and Torok, 2019; Mary *et al.*, 2019). In continuation of our work (Siraj and Ado, 2018; Siraj and Yusuf, 2017) on sulfa drugs coordination compounds, we here in report synthesis, characterization and antimicrobial studies of Schiff base 4-{(E)- [(furan-2-yl)methylidene]amino}-N-(3-methyl-1,2-oxazol-4-yl)benzene-1-sulfonamide and its complexes with Co (II) and Ni (II) ions.

II. MATERIALS AND METHODS

All the reagents used in this research work were of analytical grade and the highest purity available. The glass wares were washed with detergent, rinsed throughout with distilled water and dried in Gallenkamp hot box oven at 110±0.5°C before use. Magnetic susceptibility balance Sherwood model MK1 was used to measure the magnetic properties of the synthesized complexes. Melting point of the Schiff base and thermal decomposition temperature of the complexes were determined using Gallenkamp melting point apparatus. Infrared spectral analyses of the Schiff base and the complexes were recorded using Agilent Technologist FTIR Cary 630 spectrophotometer. Molar conductance of the complexes were measured using Jenway 4010 model conductivity meter. Elemental Analysis was conducted at Micro Analytical Centre, Faculty of Science, Cairo University using CE Instrument (thermo) EA1110 Elemental Analyzer. Antimicrobial activity studies were carried out at the Department of Microbiology, Bayero University Kano.

Preparation of Schiff's base

Sulfamethoxazole (2.5328g, 0.01mol) and furfuraldehyde (0.9608g, 0.01moI) solution in 50cm^3 ethanol was refluxed for four hours. The resulting solution after the reflux was reduced to half of its original volume (concentration) and was left for two days. Yellow crystals of sulfamethoxazole Schiff's base appeared, it was then filtered and washed with distilled water and diethyl ether, then dried in desiccator over $CaCl_2$ (Suraj*et al.*, 2012).

Preparation of Metal (II) Complexes

Metal(II) chloride (0.004mol) were mixed with the Schiff base (0.008mol) in ethanol (60cm^3) and refluxed for four hours. The resulting complex was concentrated, cooled and allowed to stand for two days as well. Solid crystalline compound appeared and was filtered, washed with cold diethyl ether and dried in a desiccator over $CaCl_2$ (Bharti *et al.*, 2013).

Antibacterial Activity Test

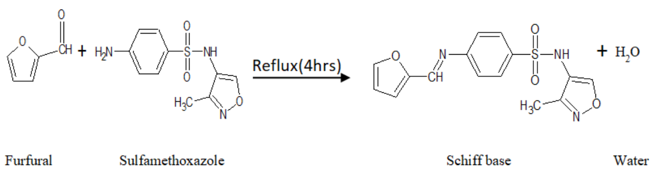
Clinical isolates of *Staphylococcus aureus* and *Escherichia coli* were obtained from Microbiology Laboratory, Bayero University Kano, Nigeria. The isolates were identified using standard microbiological technique as described by Cheesbrough, (2002). The *in vitro* antibacterial activity was determine using KirbyBauer 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(108cells/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 three different concentrations (15µg, 30µg and 60µg) respectively. They were each transferred onto sterile paper disks (6.0 mm diameter). Commercial antibiotic (Ciproflaxin) was used as a reference standard. The discs were placed onto the bacterial culture and growth inhibition zones (mm) around the discs were observed and measured after 24 hours of incubation at 37°C. The diameter of the zone of inhibition produced by the ligands and the complexes were compared with the standard (Yusha'u and Sadisu, 2011).

Antifungal Activity Test

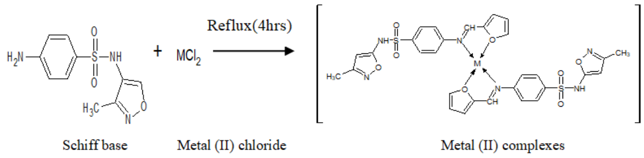
Clinical isolates of *Candida albican,* and *Aspergillus flavus* were obtained from the cultures collection of Microbiology Laboratory, Bayero University Kano, Nigeria and were identified using standard microbiological procedures described by Cheesbrough, (2002). The *in vitro* antifungal activity was 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 Schiff base and its complexes were dissolved separately in DMSO to have three different concentrations (15µg, 30µg and 60µg) per disc. 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).

III. RESULTS AND DISCUSSION

The Schiff base was synthesized by refluxing equimolar quantities of sulfamethoxazole and furfuraldehyde in ethanol (Scheme 1). A yellow colored product (Schiff base) was obtained in excellent yield. (Table 1). The observed melting point of the Schiff base is quite high, this means the Schiff base is thermally stable. The synthesized Schiff base was later on complexed separately with Co (II) and Ni (II) chloride (Scheme 2). The complexes obtained after the synthesis were colored products with higher decomposition temperature than the free Schiff base, this implies that the complexes exhibits higher thermal stability than the Schiff base. This was in agreement with our expected results as chelation tends to increase thermal stability. The analyzed physical data of the Schiff base and the complexes are presented in Table 1.



Scheme 1: Preparation of the Schiff base



Scheme 2: Preparation of metal (II) complexes

Table 1 : Physical characteristics of the Schiff base and its metal complexes

Ligand/Complexes	Color	Molecular Formula	M.P (°C)	Yield (%)
L	Yellow	$C_{15}H_{13}N_3O_4S$	180	94
$[CoL_2Cl_2].H_2O$	Burnt umber	$C_{30}H_{28}N_6O_9S_2Co$	239	85
$[NiL_2Cl_2].2H_2O$	Brick red	$C_{30}H_{30}N_6O_{10}S_2Ni$	241	96

L = Schiff base ($C_{15}H_{13}N_3O_4S$)

The molar conductance measurement carried out in DMSO were found to be 17.32 and 3.52 $ohm^{-1}\ cm^{-1}\ mol^{-1}$ for the Co(II) and Ni(II) complexes respectively (Table 2). The values obtained were less than 50 $ohm^{-1}\ cm^{-1}\ mol^{-1}$, so these lower values suggested that, the complexes are non-electrolytic in nature (Geary, 1971). Magnetic susceptibility results are presented in Table 3, the values obtained were 4.33 BM for Co(II) and 3.00 BM for Ni(II), these values suggested a paramagnetic nature of the complexes. The values obtained were well within the range of octahedral complexes as reported by Figgis *et al.*, (1960), (Co^{2+} octahedral complex, 4.3 - 5.2BM while Ni^{2+} is between 2.9 - 3.3BM).

Table 2: Conductivity data of the complexes

Complexes	Concentration (mol dm^{-3})	Specific conductance ($Ohm^{-1}\ cm^{-1}$)	Molar conductance ($Ohm^{-1}\ cm^2\ mol^{-1}$)
$[CoL_2Cl_2].H_2O$	1×10^{-3}	17.32×10^{-6}	17.32
$[NiL_2Cl_2].2H_2O$	1×10^{-3}	3.52×10^{-6}	3.52

L = Schiff base ($C_{15}H_{13}N_3O_4S$)

Table 3: Magnetic Susceptibility data of the complexes

Complexes	Magnetic susceptibility ($cm^3\ g^{-1}$)	Molar susceptibility ($cm^3\ mol^{-1}$)	B.M (μ_{eff})
$[CoL_2Cl_2].H_2O$	109.36×10^{-7}	78.881×10^{-6}	4.33
$[NiL_2Cl_2].2H_2O$	52.62×10^{-7}	37.943×10^{-6}	3.00

L = Schiff base ($C_{15}H_{13}N_3O_4S$)

The elemental analysis (CHN) data of the Schiff base its metal complexes were determined to find the appropriate metal to ligand ratio of the compounds. The values obtained (Table 4) were in consensus with the calculated values for the corresponding elements (CHN) and thus confirmed the proposed formulation of the compounds in 1:2 metal - Schiff base ratio for all the complexes.

Table 4: Elemental analysis (CHN) of the Ligand and its metal (II) complexes

Compound	C observed (calculated)	H observed (calculated)	N observed (calculated)
L	(54.37) 53.19	(3.95) 4.29	(12.68) 12.61
$[CoL_2Cl_2].H_2O$	(44.45) 44.84	(3.48) 3.96	(10.37) 11.31
$[NiL_2Cl_2].2H_2O$	(43.50) 43.53	(3.65) 3.96	(10.15) 10.59

L = Schiff base ($C_{15}H_{13}N_3O_4S$)

Two chloride ions were found to be present in all the complexes synthesized. They were found to be inside the coordination sphere by silver nitrate test. No precipitation was first observed upon addition of silver nitrate to the solution of the complexes. However, after digestion with nitric acid, the silver nitrate test gave a positive result by precipitating, this suggests the presence of the chloride ions inside the coordination sphere. Similar observation was reported by Aderoju *et al.*, (2015) and Fatima, (2015).

Infrared spectra of sulfamethoxazole has two peaks at 3378cm^{-1} and 3298cm^{-1} due to stretching frequencies of free -NH_2. Disappearance of these peaks in the spectra of the Schiff base and the appearance of a new band at 1629cm^{-1} which was assigned for -C=N- group clearly indicated that, the amine group was involved in the formation of the azomethine bond of the Schiff base. However, this band was observed to shift by (11 - 17 cm^{-1}) towards the lower frequency in the spectra of all complexes, this indicated that complexation have taken place through the nitrogen atom of azomethine group. Bands at 592 - 596cm^{-1} and 478 - 485 cm^{-1} in the complexes were attributed to metal – nitrogen (M - N) and metal - oxygen (M - O) bond respectively (Table 5).

Table 5: IR spectral Data for the Ligand and its Metal (II) Complexes

Ligand/Complexes	C=N	C-O	M-N	M-O
L	1629	1288	-	-
$[CoL_2Cl_2].H_2O$	1612	1272	592	485
$[NiL_2Cl_2].2H_2O$	1614	1272	596	478

L = Schiff base ($C_{15}H_{13}N_3O_4S$)

The antibacterial activity of the Schiff base and the complexes has been evaluated. The diameter of inhibition zone in mm was measured for each treatment. Inhibition zone of ciproflaxin (standard) was also determined as positive control. The Schiff base was found to be active against the bacterial isolates at all concentration and the activity increases with increase in the concentration. The activity of the Schiff base as expected increases on coordination with metal ion. Chelation is attributed to be largely responsible, it reduces the polarity of the compounds which enhances lipophilicity of the complexes and consequently increases antimicrobial activity of the complexes. Similar trend was reported for many other Schiff base complexes (Kumble *et al.,* 2017, Muhammad *et al.*, 2020). The Co(II) complex was observed to exhibit highest activity of 15 mm against all the two bacterial isolate tested while Ni(II) complex was found to have lower activity of 08 mm(Figure 1 and 2). However, the activity for both compounds were found to be lower than the control drug, ciproflaxin.

Antifungal activity of the Schiff base and the complexes have also been determined and Ketoconazole was used as positive control. The Schiff base was found to be active against the fungal isolates even at lower concentration but the activity increases with increase in concentration. Similarly, the activities of the complexes were found to be higher with Co(II) complex exhibiting highest activity of 18 mm and Ni(II) complex showing milder activity at 15 mm (Figures 3 and 4). The higher activity of the complexes compared to the uncoordinated Schiff base might also be attributed to the chelation factor. Similar observations on antifungal activity of other related Schiff base complexes were reported by many literatures (Muhammad *et al.,* 2020, Abu-Dief and Muhammad 2015). The control drug ketoconazole use was much higher in activity than both Schiff base and the complexes.

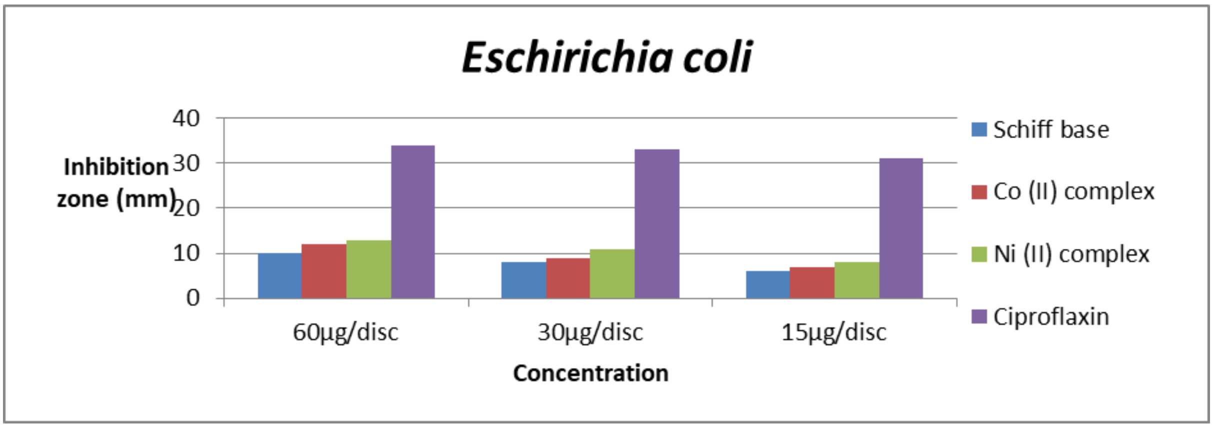


Fig. 1: Antibacterial activity inhibition zones of the Schiff base and its metal (II) complexes against *Escherichia coli.*

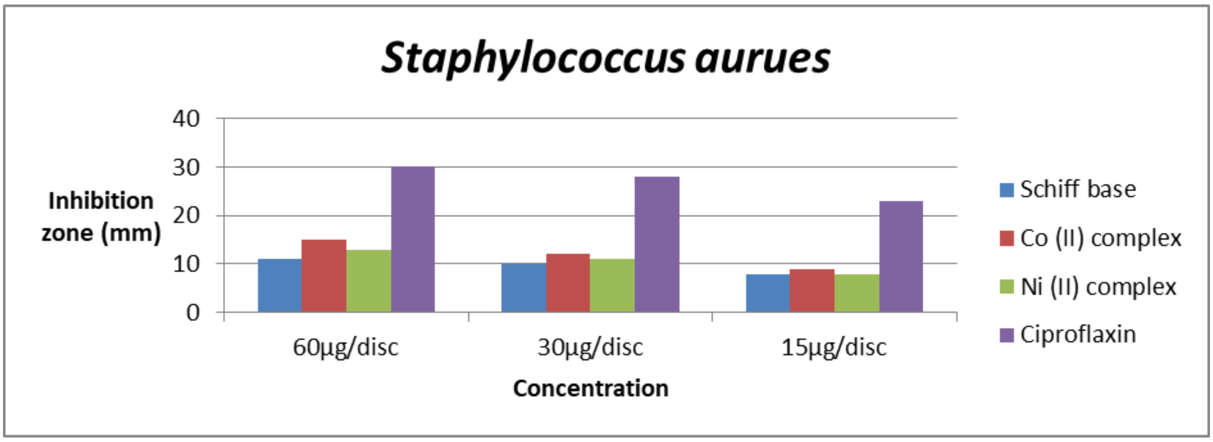


Fig. 2: Antibacterial activity inhibition zones of the Schiff base and its metal (II) complexes against *Staphylococcus aureus.*

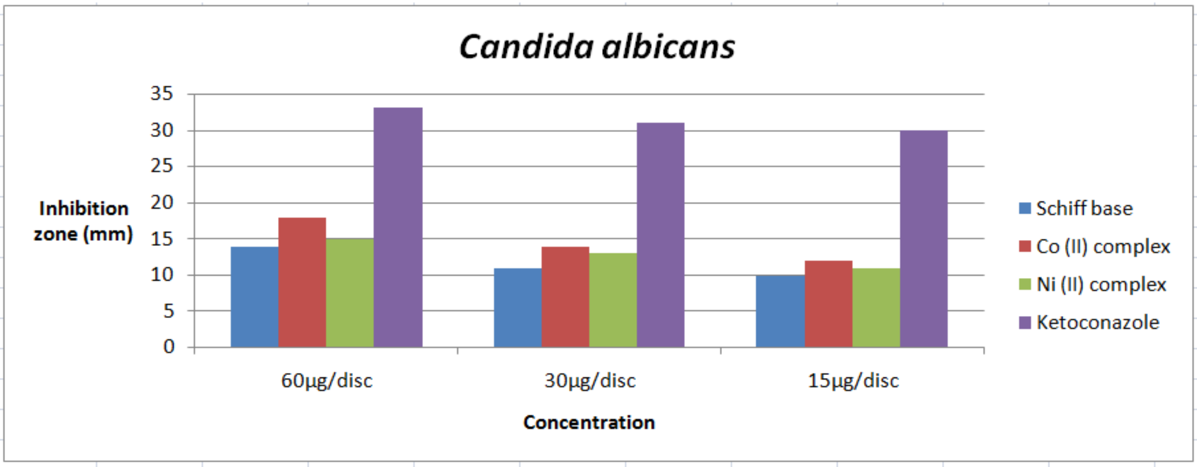


Fig 3: Antifungal activity inhibition zones of the ligand and its metal (II) complexes against *Candida albicans.*

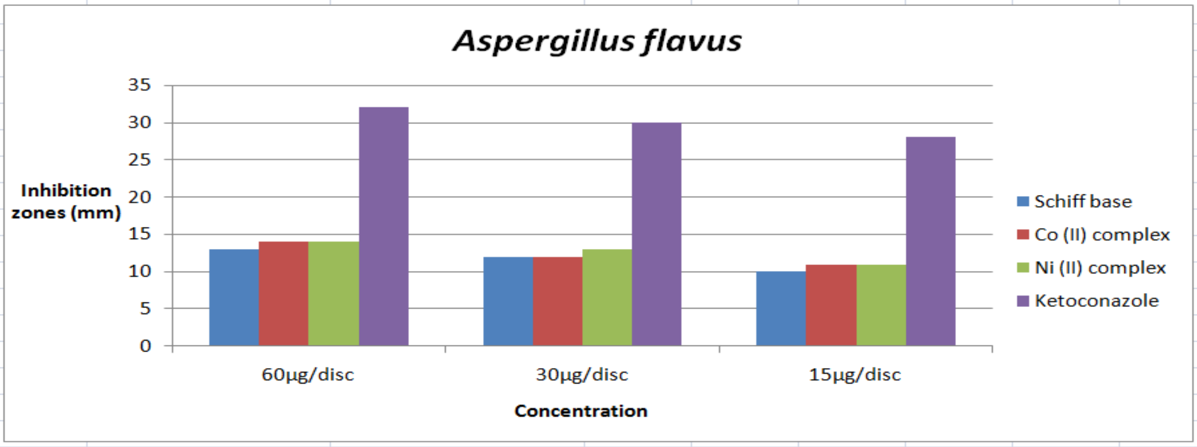


Fig 4: Antifungal activity inhibition zones of the ligand and its metal (II) complexes against *Aspergillus flavus.*

IV. CONCLUSION

The proposed Schiff base ligand was synthesized successfully in stable form by condensation of furfural and sulfamethoxazole in ethanol. Metal complexes of Co(II) and Ni(II) were subsequently synthesized by reaction of the ethanolic solution of the Schiff base and the metal (II) chlorides of cobalt and nickel. Spectral data revealed that the Schiff base was coordinated in a bidentate form through azomethine nitrogen and the oxygen of the furfural group, giving octahedral complexes. Elemental analysis data showed 2:1 ligand-metal ratio. The Schiff base was found to be moderately active against the bacterial and fungal isolates used. The complexes were found to exhibit higher activity against the isolates but generally lower than the control.

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