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# Synthesis, Characterization and Antimicrobial Studies of Mn(II) and Fe(II) Schiff Base Complexes Derived from 4-{(E)-[(furan-2-yl)methylidene]amino}-N-(3-methyl-1,2-oxazol-4-yl)benzene-1-sulfonamide

**Siraj I. T., *Sanusi S.**

Department of Pure and Industrial Chemistry,
Bayero University Kano.

**Email:** sulesanusi15@gmail.com

**Abstract**
*Complexes of Mn(II)and Fe(II) with Schiff based derived fromsulfamethoxazole andfurfural have been prepared and characterized on the basis of physical characteristics, analytical data, FTIR spectral studies and elemental analysis. Infrared spectra of the Schiff base and the complexes agrees 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 5.29 and 9.68 $Ohm^{-1}$ $cm^2$ $mol^{-1}$ suggesteda non-electrolytic nature of the complexes. Magnetic susceptibility data (5.84 and 5.12 BM)suggested octahedral structure for all the complexes. Elemental analysis suggested the ligand-metal ratio of2:1 respectively. The Schiff base melted at 180°C and the complexes decomposedat 232°C and 227°C implying thermal stability. The Schiff base and the complexes have been screened for their antimicrobial activity against four pathogenic microbes;Staphylococcus aureus, Escherichia coli, Aspergillus flavusand Candida albicans. The ligand showed moderate activity with inhibition zone in the range of 6 – 14mm, while the metal complexes exhibited higher antimicrobial activity with inhibition zone of 9 – 18mm against the tested microbes.*

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

## INTRODUCTION
Sulfa based drugs have continued to attract special attention due to their historic therapeutic importance as they were used against a wide spectrum of bacterial ailments (Ana *et al*., 2017;Chuang *et al*., 2019;Muhammad *et al*., 2020). The sulfonamide functional groups present in Sulfamethoxazole might be responsible for the antimicrobial activities of these types of drugs (Chuang *et al*., 2019). This important property of most sulfa drugs can be altered depending on the substituents added to or subtracted from the aromatic rings. The alteration of the properties became necessary due to increase in microbial resistance of the present antibiotic drugs including the sulfa drugs resulting in increase in infections across the globe presenting a serious health problem.

It is well established fact that most coordination compounds have shown more remarkable properties in different filed of life (biological, industrial, agricultural etc) than the free ligand (Abu-Dief and Mohamed 2015; Fawaz 2017). The characteristics and properties was found to be varied depending on the nature of the metal ion as well as the ligand and its substituents. Therefore, incorporation of transition metal ion 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).Some of the reported sulfonamides Schiff base complexes demonstrated wide range of application most especially antimicrobial activity (Radha *et al*, 2016;Sudipa et al., 2018; Mustafa *et al*., 2019).

Compounds containing sulfonamide group have continued to be used as a drug for different microbially induced diseases (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,

**Author for Correspondence*

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 Mn (II)and Fe (II) ions.

## MATERIALS AND METHODS

All the reagents used in this research were of analytical grade and were used without further purification. The glass wares were washed thoroughly with detergent, rinsed with distilled water and dried in gallenkamp hot box oven at 110±0.5 $^{o}$C before used. Magnetic susceptibility balance Sherwood MK1 was used to measure the magnetic properties of the complexes. Melting point of the Schiff base as well as the decomposition temperature of the complexes were determined using Gallenkamp melting point apparatus. Infrared spectral analyses were recorded using Agilent Technologist FTIRCary 630 spectrophotometer. Molar conductance of the complexes was measured using Jenway 4010 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 in50cm$^3$ ethanol was refluxed for four hours. The resulting solution was reduced to half of its original volume (concentration) and was left for two days. Yellow crystals of sulfamethoxazole Schiff's base were obtained, 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 product was concentrated, cooled and allowed to stand for two days. Solid crystalline compounds appeared and was filtered, washed with diethyl ether and dried over $CaCl_2$ in a desiccator (Bharti *et al*., 2013).

### Antibacterial Activity Test

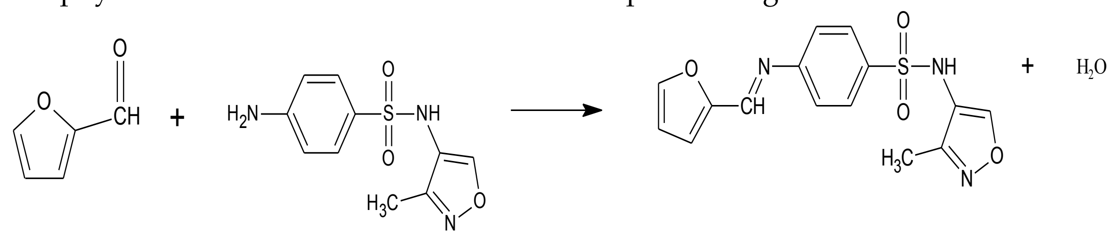
Clinical isolates of *Staphylococcus aureus* and *Escherichia coli* were obtained from the cultures collection of Microbiology Laboratory, Bayero University Kano, Nigeria and were identified using standard microbiological procedures described by Cheesbrough, 2002. The *in vitro* antibacterial activity 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 usedas 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$^{o}$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

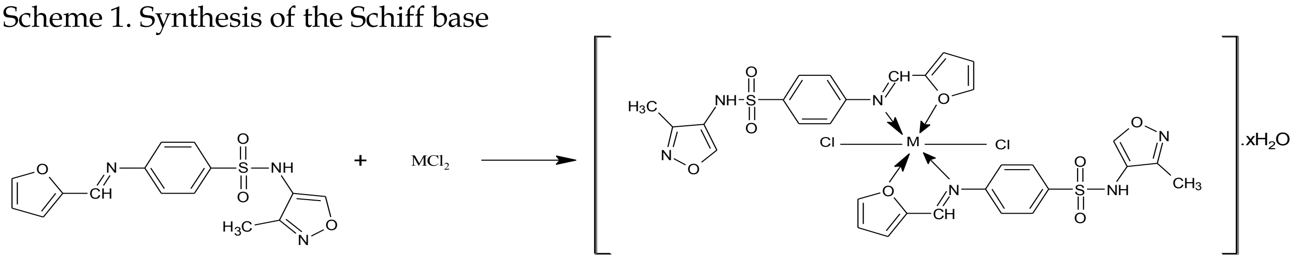
Clinical isolates of *Candida albican,* and *Aspergillus flavus* were obtained from the cultures collection of Microbiology Laboratory, Bayero University Kano, Nigeria and were identified using standard microbiological procedures described by Cheesbrough,2002. The *in vitro* antifungal activity was determined 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).

## RESULTS AND DISCUSSION

The Schiff base was synthesized by refluxing equimolar quantities of sulfamethoxazole and furfuraldehyde (Scheme 1)which afforded the expected yellow coloured sulfamethoxazole Schiff base in good yield (Table 1). The high melting point of the Schiff base shows its good thermal stability. The Schiff base was complexed separately with Mn (II) and Fe(II) chloride (Scheme 2). The coloured complexes were found to have higher decomposition temperature than the Schiff base suggesting that the complexes were even more thermally stable than the Schiff base. This was in line with our expected results as chelation increase thermal stability. The physical data of the Schiff base and the complexes are given in Table 1.



Scheme 1. Synthesis of the Schiff base



Scheme 2: Preparation of the complexes

Table 1: Physical characteristics of Schiff base and their metal complexes

| Compounds | Color | Molecular Formula | M.P (°C) | Yield (%) |
|---|---|---|---|---|
| L | Yellow | $C_{15}H_{13}N_3O_4S$ | 180 | 94 |
| $[MnL_2Cl_2].4H_2O$ | Red | $C_{30}H_{34}N_6O_{12}S_2Mn$ | 232 | 91 |
| $[FeL_2Cl_2].3H_2O$ | Brown | $C_{30}H_{32}N_6O_{11}S_2Fe$ | 227 | 92 |

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

The molar conductance measurement in DMSO carried out were found to be 5.29 and 9.68 ohm$^{-1}$ cm$^{-1}$ mol$^{-1}$ for the Mn(II) and Fe(II) complexes respectively (Table 2).These lower values suggested that, the complexes are non-electrolytes (Geary, 1971). Magnetic susceptibility results are presented in Table 3. The values obtained, 5.84BM for Mn(II) and 5.12BM for Fe(II) suggested paramagnetic complexes. These values were found to be within the range of octahedral complexes ($Mn^{2+}$ octahedral complex ,5.6 - 6.1BM while $Fe^{2+}$, 5.1 - 5.7BM) as reported by Figgis *et al.*, (1960).

Table 2: Conductivity data of the complexes

| Compounds | Concentration (mol dm$^{-3}$) | Specific conductance (Ohm$^{-1}$ cm$^{-1}$) | Molar conductance (Ohm$^{-1}$ cm$^2$ mol$^{-1}$) |
|---|---|---|---|
| $[MnL_2Cl_2].4H_2O$ | $1 \times 10^{-3}$ | $5.29 \times 10^{-6}$ | 5.29 |
| $[FeL_2Cl_2].3H_2O$ | $1 \times 10^{-3}$ | $9.68 \times 10^{-6}$ | 9.68 |

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 ($\mu_{eff}$) |
|---|---|---|---|
| $[MnL_2Cl_2].4H_2O$ | $199.25 \times 10^{-7}$ | $14.293 \times 10^{-6}$ | 5.84 |
| $[FeL_2Cl_2].3H_2O$ | $153.32 \times 10^{-7}$ | $1.101 \times 10^{-6}$ | 5.12 |

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

The elemental analysis (CHN) of the Schiff base and the complexes were determined to find the appropriate metal to ligand ratio of the compounds. The values obtained (Table 4) showed a good agreement with the calculated values for the corresponding elements and is very supportive of the targeted formulation of the compounds confirming 1:2 metal - Schiff base ratio for all the complexes.

Table 4: Elemental analysis (CHN) of the Ligand and it's 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 |
| $[MnL_2Cl_2].4H_2O$ | (41.87) 41.58 | (3.98) 4.03 | (9.77) 10.16 |
| $[FeL_2Cl_2].3H_2O$ | (42.72) 42.65 | (3.82) 3.59 | (9.96) 10.24 |

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

Two chloride ions were found to be present in all the complexes. They were found to be inside the coordination sphere by simple 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 suggesting the presence of the chloride ions. Similar observation was reported by Aderoju *et al.*, (2015) and Fatima (2015).

Infrared spectra of sulfamethoxazole show peaks at 3378cm$^{-1}$ and 3298cm$^{-1}$ due to stretching frequencies of free -$NH_2$.Disappearance of these peaks in the spectra of the ligand and the appearance of a new band at 1629cm$^{-1}$ of -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, which indicated that complexation have taken place through the nitrogen atom of azomethine group. Bands at 585 - 611cm$^{-1}$ and 448 - 491 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 Ligand and its Metal (II) Complexes

| Compounds | √(C=N)cm$^{-1}$ | √(C-O)cm$^{-1}$ | √(M-N) cm$^{-1}$ | √ (M-O) cm$^{-1}$ |
|---|---|---|---|---|
| L | 1629 | 1288 | - | - |
| [$MnL_2Cl_2$].$4H_2O$ | 1614 | 1272 | 604 | 448 |
| [$FeL_2Cl_2$].$3H_2O$ | 1618 | 1272 | 585 | 481 |

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

The antibacterial activity of the Schiff base and the complexes hasbeen determined. The diameter of inhibition zone (mm) was measured for each treatment. Inhibition zone of ciproflaxin 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 Mn(II) complex was observed to exhibit highest activity of 16 mm against all the two bacterial isolate tested while iron(II) complex was found to have lower activity of 14 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 Mn(II) complex exhibiting highest activity of 18 mm and Fe (II) complex showing milder activity (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.

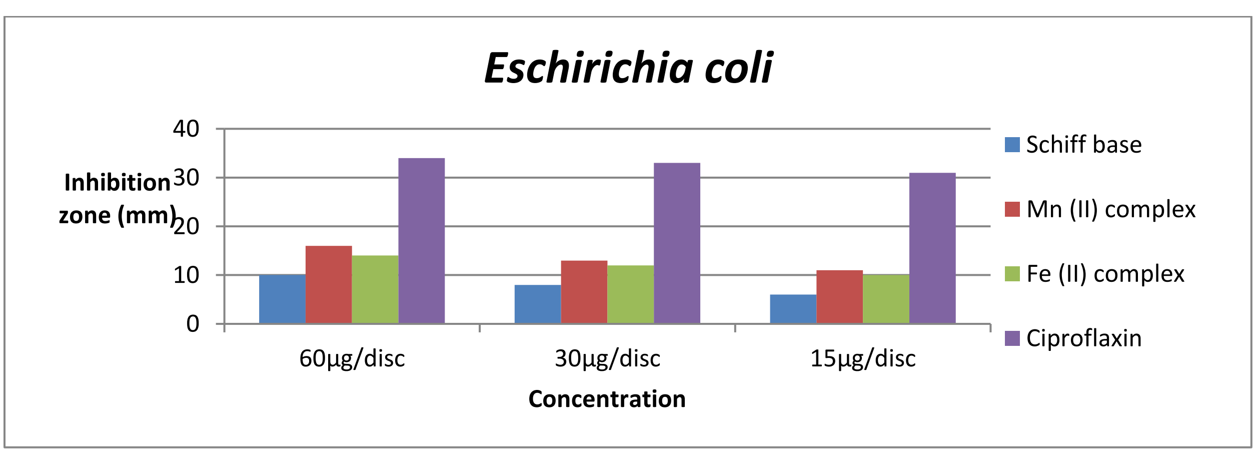



Fig. 1: Antibacterial activity inhibition zones of the Schiff base and its metal (II) complexes against *Escherichia coli*.

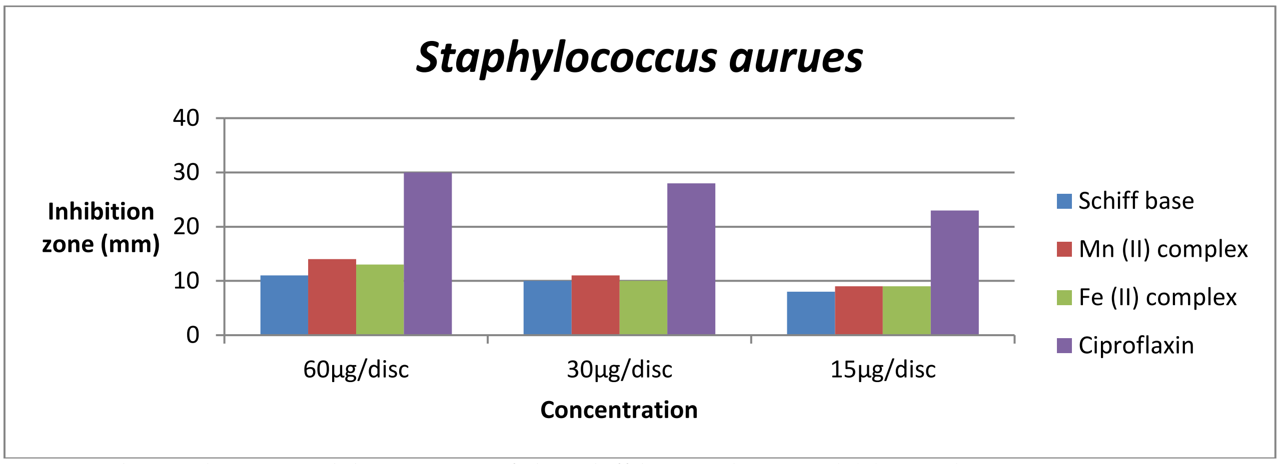



Fig 2: Antibacterial activity inhibition zones of the Schiff base and its metal (II) complexes against *Staphylococcus aureus*.

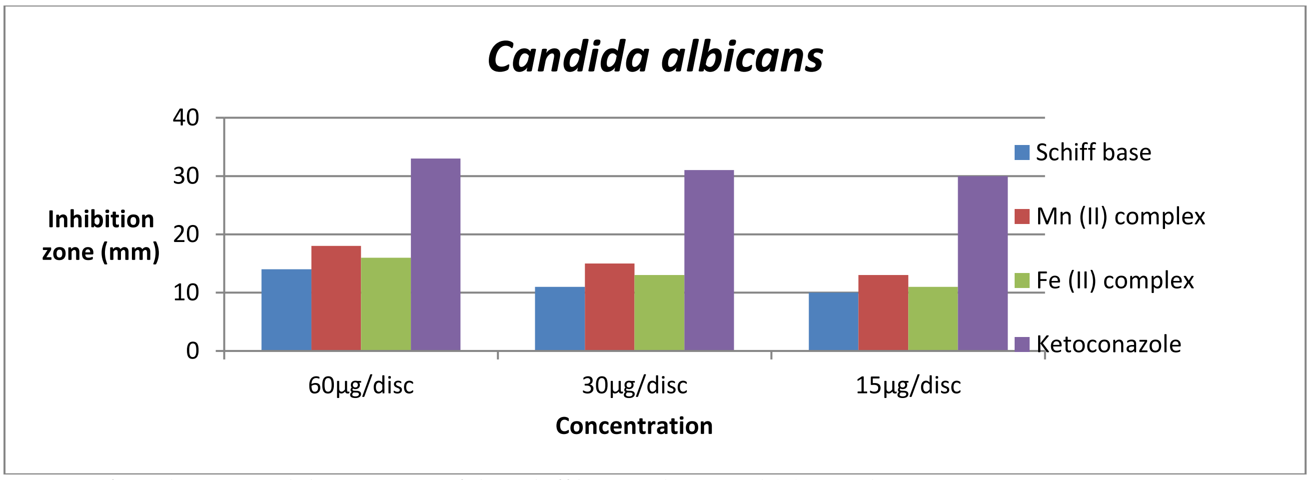



Fig 3:Antifungal activity inhibition zones of the Schiff base and its metal (II) complexes against *Candida albicans*.

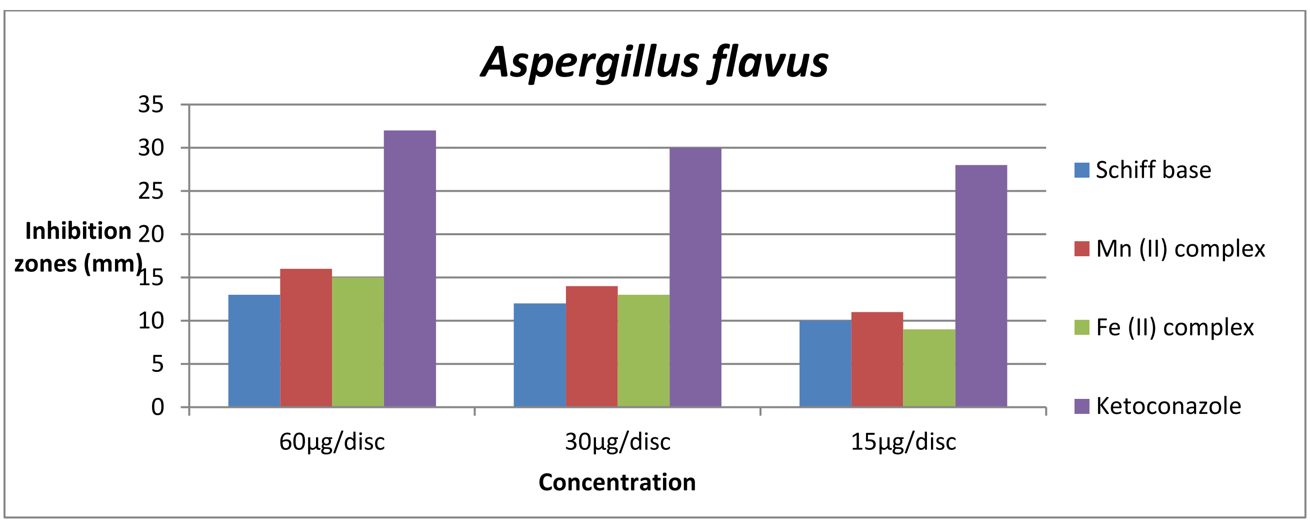



Fig 4: Antifungal activity inhibition zones of the Schiff base and the complexes against *Aspergillus flavus*.

## CONCLUSION

The target Schiff base was prepared in stable form by condensation of furfural and sulfamethoxazole. The corresponding Fe(II) and Mn(II) complexes were also prepared from the reaction of the ethanolic solution of the Schiff base and the respective metal (II) chlorides. Spectral data revealed that the Schiff base was coordinated in a bidentate manner through azomethine nitrogen and the oxygen of the furfural group, giving octahedral complexes. Elemental analysis showed that the ligand metal ratio is 2:1.The Schiff base was found to be active against the fungal isolates. It was further observed that the compounds are more active against the fungal isolates but generally lower than the complexes.

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