



## Interactions of Metal ions with Trimethoprim and Metformin

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**Abstract :** In this work, metal complexes of trimethoprim mixed metformin were synthesized and characterized by solubility studies, percentage metal analysis, UV-Vis spectroscopy, IR spectroscopy and magnetic susceptibility and conductivity measurements. The IR spectra showed that the trimethoprim coordinated as a monodentate ligand coordinating to the metal ions via the pyrimidine N(1), metformin acts as a bidentate ligand coordinating through the iminonitrogens. The infrared spectra bands at  $450\text{ cm}^{-1}$  and  $530\text{ cm}^{-1}$  is ascribed to M–N and M–O bond respectively indicating the formation of these complexes.

The magnetic moment data showed that all the complexes were paramagnetic with values ranging from 1.39 to 6.0 B.M, except  $[\text{Zn}(\text{TMP})(\text{MET})(\text{H}_2\text{O})\text{Cl}_2]$  which was diamagnetic. The conductivity results revealed that all the synthesised complexes were non-electrolytes, while the antibacterial studies of the mixed ligand complexes displayed moderate antimicrobial activity in comparison with the free ligands.

**Keywords :** Trimethoprim; Metformin; covalent; geometry; electronic structure; antibacterial.

### 1. Introduction

Trimethoprim (TMP) is an antibiotic drug used mainly in the treatment of bladder infections other uses include for middle ear infections and travellers' diarrhoea. TMP is a synthetic antibiotic that interferes with the production of tetrahydrofolic acid, a chemical that is necessary in order for bacteria and human cells to produce proteins<sup>[1,2]</sup>

Metformin (MET), marketed under the trade name Glucophage among others, is the first-line medication used in the treatment of non-insulin-dependent diabetes mellitus usually known as type 2 diabetes not responding to dietary medication. Metformin improves glycemic control by improving insulin sensitivity and decreasing intestinal absorption of glucose,<sup>[3]</sup> particularly in people who are overweight. It is used in the treatment of polycystic ovary syndrome. There is evidence that, the drug metformin may prevent cancer complication of diabetes and cardiovascular disease.<sup>[4]</sup> Several studies have been carried out on the complexes of trimethoprim.<sup>[5,6]</sup> Also in the same vein the structural elucidation of metformin complexes has also been reported.<sup>[7]</sup>

The synthesis and the structural elucidation of the mixed ligand complexes of trimethoprim has been widely reported<sup>[8]</sup> and the results have shown that the complexes exhibit higher antimicrobial activity than the free ligand.<sup>[9]</sup> This is in consonance with several studies that metal complexes possess higher activity than the ligand.<sup>[10,11]</sup>

However, work on the synthesis, structural elucidation and antibacterial activity of Co(II), Ni(II), Cu(II), and Zn(II), Fe(III), Mn(II) mixed ligand complexes trimethoprim with metformin has not been reported, this is the essence of this study. The results of this study are herein reported.

## 2. Experimental

### 2.1. Reagents and solvents

All the chemicals and solvents used in the study were obtained from Bond Pharmaceutical and BDH were used without further purification. They are methanol, copper(II) chloride dihydrate, manganese(II) chloride tetrahydrate, iron(III) chloride hexahydrate, cobalt (II) chloride hexahydrate, and nickel(II) chloride hexahydrate. The percentage metal content was determined by complexometric titration using EDTA and atomic absorption spectroscopy (AAS). The infrared spectra were recorded in the 4000–400 cm<sup>-1</sup> region with a Shimadzu FT-IR 8000 spectrophotometer using KBr pellets. UV-Visible spectra of the samples were measured in the range 800–200 nm using a Shimadzu UV-Vis 1800 spectrophotometer. Magnetic susceptibility measurements were carried out at room temperature using a Sherwood Scientific MXI model Gouy magnetic balance.

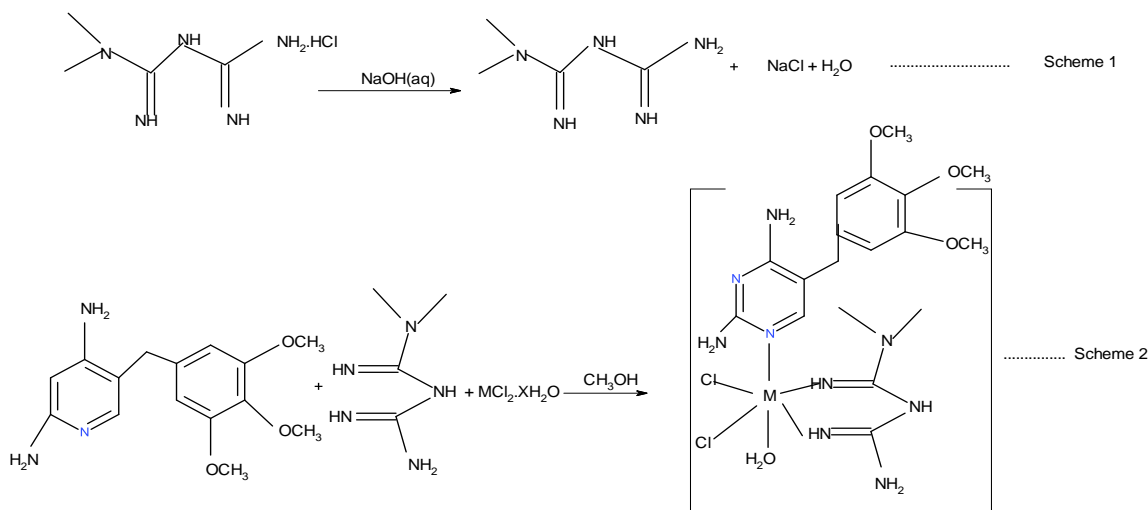
### 2.2. Synthesis of mixed ligand complexes

Solutions of each of the metal salts (1mmol of CoCl<sub>2</sub>.6H<sub>2</sub>O, CuCl<sub>2</sub>.2H<sub>2</sub>O, MnCl<sub>2</sub>.4H<sub>2</sub>O, ZnCl<sub>2</sub>, NiCl<sub>2</sub>.6H<sub>2</sub>O, FeCl<sub>2</sub>.4H<sub>2</sub>O) 10 ml of methanol was added drop wisely to the stirring methanolic NaOH solution of metformin hydrochloride (2 mmole). Trimethoprim (1 mmole) was added to the mixture. The resulting homogenous solution was stirred for one hour, thirty minutes during which precipitate was formed, the product was filtered, washed with ethanol and dried over anhydrous calcium chloride.

## 3. Results and discussion

### 3.1. Chemistry

Metformin hydrochloride is a salt whose electron donating capacity is hindered, the salt is treated with sodium hydroxide solution to release the base as shown in scheme 1.



**Scheme. Synthesis of mixed ligand metal complexes of trimethoprim and metformin**

The base metformin contains five nitrogen atoms, the tertiary, secondary, primary and the two imino groups which are electron rich in comparison to the amino nitrogen. The two iminonitrogens donate electron pair to the central metal ion through coordinate bonding. Trimethoprim as a base is capable of donating electron pair through the pyrimidine and amino nitrogen, the N2 pyrimidine is sterically hindered by other neighbouring substituents. In this study, the pyrimidine N1 donate electron pair to the central metal ion thereby acting as a monodentate ligand. The reaction of trimethoprim and metformin hydrochloride with hydrated metal salts in methanolicsodiumhydroxide produces the mixed ligand metal complexes shown in scheme 2.

### 3.2. Physicochemical parameters

The physicochemical properties of the synthesized compounds including the percentage yields are shown in Table 1. The mixed ligand complexes displayed high melting points and a variety of colours ranging from yellow to Tan brown except for the zinc complex which was white. The melting point of trimethoprim is 238-240. Most of the complexes have melting points above 300°C except for copper complex which melted at temperatures between 286-288 °C. The relatively high melting point of the metal complexes suggests high thermal stability.

The theoretical percentage metal in the mixed ligand complexes of trimethoprim with metformin showed a good correlation with the experimental values as shown in Table 1. All the complexes synthesized are soluble in dimethylsulfoxide (DMSO), while they show varying degrees of solubility in the other five common solvents. The insoluble nature of all the complexes in water suggests that, they are non-ionic in nature. The molar conductivity of the complexes were measured in DMSO, values obtained were in the range 2.71-18.17  $\Omega^{-1}\text{cm}^2\text{mol}^{-1}$  indicating the covalent nature of these complexes.<sup>[12]</sup> The results obtained are consistent and agrees with the commonly observed octahedral geometries of metal complexes.<sup>[13]</sup>

**Table 1. Physical Properties and Analytical Data for Compounds**

Compound	(Formula weight)	Colour	M.pt. (°C)	%metal found (calc)	Yield(%)	$\Lambda_m$ ( $\Omega^{-1}\text{cm}^2\text{mol}^{-1}$ )
Trimethoprim	(290.32)	White	238-240	-	-	-
Metformin HCl	(165.62)	White	222-226	-	-	-
[Mn(TMP)(MET)(H <sub>2</sub> O)Cl <sub>2</sub> ]	(563.41)	Tan brown	>300	10.10 (9.75)	83.25	18.17
[Fe(TMP)(MET)Cl <sub>3</sub> ]	(564.32)	Light yellow	>300	10.01 (9.60)	64.69	6.45
[Co(TMP)(MET)(H <sub>2</sub> O)Cl <sub>2</sub> ]	(567.47)	Green	>300	10.76 (10.39)	76.17	4.49
[Ni(TMP)(MET)(H <sub>2</sub> O)Cl <sub>2</sub> ]	(567.17)	Green	>300	10.55 (10.34)	71.00	2.50
[Cu(TMP)(MET)(H <sub>2</sub> O)Cl <sub>2</sub> ]	(572.02)	Pink	286-288	10.93 (11.10)	51.89	12.10
[Zn(TMP)(MET)(H <sub>2</sub> O)Cl <sub>2</sub> ]	(573.86)	White	>300	11.10 (11.39)	68.35	3.14

### 3.3. Infrared Spectroscopy

The IR spectra data of trimethoprim, metformin hydrochloride, and their mixed ligand complexes are presented in Table 2, while the representative infrared spectra are shown in Figure 1. The infrared spectra of the complexes were compared with those of the free ligand in order to determine the involvement of coordination sites.

TMP has characteristic band at 3471  $\text{cm}^{-1}$  and 3319  $\text{cm}^{-1}$  which account for  $\nu(\text{N-H})_{\text{asy}}$  and  $\nu(\text{N-H})_{\text{sym}}$  respectively. The N—H stretching frequencies of the pyrimidine NH<sub>2</sub> in the free trimethoprim shifted slightly in the metal complexes. It was observed in the same region, 3479-3379  $\text{cm}^{-1}$ , as seen in the free ligands. The slight shift is ascribed to hydrogen bonding and other noncovalent interactions in the metal complexes.<sup>[14]</sup> The bands observed in the complexes were compared with those of the ligands in order to establish

the binding site.<sup>[15]</sup> Three (-OCH<sub>3</sub> aromatic groups) has vibrations bands at 1128 cm<sup>-1</sup><sup>[16]</sup>. The band for stretching vibration of (C=N) showed at 1633 and 1508 cm<sup>-1</sup>.<sup>[17]</sup> The absorption bands at 1263 and 1236 cm<sup>-1</sup> are ascribed to C-O-C<sub>(asy.)</sub> and C-O-C<sub>(sym.)</sub> respectively. The significant shifts in frequency band for all the complexes suggest the coordination of the metal ion to the TMP ligand through the pyrimidine nitrogen N(1).<sup>[18]</sup> Interestingly, the spectra of the complexes also showed a moderate weak sharp bands around 450 cm<sup>-1</sup> and 690 cm<sup>-1</sup> which are completely absent in the spectrum of the free ligands (trimethoprim and metformin HCl) has been assigned to  $\nu$ M-N and  $\nu$ M-Cl bonds respectively.<sup>[14]</sup> Most of the deformational modes were found in similar ranges as in the free ligand. OCH<sub>3</sub> aromatic groups did not show any significant change, which is an indication that it does not involve in coordination with metals in all the complexes. The band at 1509 cm<sup>-1</sup> corresponding to  $\nu$ (C=N) exhibits no remarkable shift upon complexation thus supporting the coordination of metal ion to the trimethoprim through the pyrimidine nitrogen. TMP acts as a monodentate ligand while MET acts as a bidentate ligand. The absorption band for stretching vibration C-N single bond in all the metal complexes appeared at (1236, 1238, 1240, 1236, 1236) cm<sup>-1</sup> for Cu(II), Co(II), Mn(II), Ni(II), and Zn(II) complexes respectively. It was also observed that there is coordination between (H<sub>2</sub>O) molecules and the (M<sup>+2</sup>) which resulted in the appearance of vibrational bands at range 702 -771 cm<sup>-1</sup> (M-OH<sub>2</sub>) in the complexes.<sup>[17]</sup> It may be noted that, these vibrational bands are absent in the spectra of the ligands (trimethoprim and metformin HCl). Whereas in the case of metformin. HCl ligand, the new strong bands in the range 1670-1630 cm<sup>-1</sup> are assigned to the coordinated imino groups.<sup>[19]</sup> The formation of a chelate ring is supported by the appearance of a new band at (1365-1200 cm<sup>-1</sup>) assigned to ring vibration.<sup>[14]</sup> The spectra data of the complexes of trimethoprim mixed with metformin is shown in Table 2, while the spectrum is displayed in Figure 1.

**Table 2. Infrared Spectra Data of Complexes of Trimethoprim mixed with Metformin**

Compounds	$\nu$ (NH <sub>2</sub> )	$\nu$ (N-H)	$\nu$ (N-CH <sub>3</sub> )	$\nu$ (C=N)	$\nu$ C=N)(py)	$\nu$ (M-N)	$\nu$ (M-O)
TMP	3478, 3363	-	-	-	1633, 1508	-	-
MET	-	3419, 2931	1381	1739	-	-	-
[Mn(TMP)(MET)(H <sub>2</sub> O)Cl <sub>2</sub> ]	3368, 3196	3271, 2943	1342	1681	1643, 1516	468	702
[Fe(TMP)(MET)Cl <sub>3</sub> ]	3408, 3167	3325, 3895	1342	1680	1643,	530	
[Co(TMP)(MET)(H <sub>2</sub> O)Cl <sub>2</sub> ]	3470, 3122	3319, 2931	1344	1633	1597, 1508	439	769
[Ni(TMP)(MET)(H <sub>2</sub> O)Cl <sub>2</sub> ]	3470, 3157	3319, 2937	1334	1635	1597, 1508	451	769
[Cu(TMP)(MET)(H <sub>2</sub> O)Cl <sub>2</sub> ]	3470, 3252	3369, 3196	1344	1670	1626, 1508	491	719
[Zn(TMP)(MET)(H <sub>2</sub> O)Cl <sub>2</sub> ]	3470, 3122	3319, 2931	1344	1633	1595, 1508	441	769

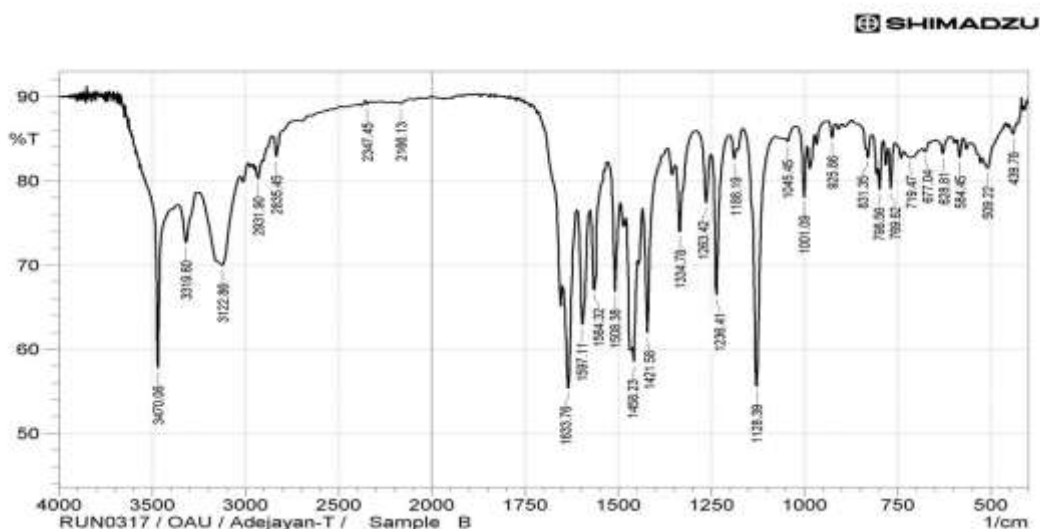


Figure 1. Infrared spectrum of mixed metformin and trimethoprim copper(II) complex

### 3.4. Electronic spectroscopy and Magnetic susceptibility measurement

The electronic spectral data of the free ligands and their complexes are summarized in Table 3. The UV-Vis spectrum of TMP in DMSO solvent appeared with high intense absorption band at 257 nm which is attributed to  $[\pi \rightarrow \pi^*/n \rightarrow \pi^*]$  (overlap of the two peaks) of the aromatic ring, metformin showed two bands at 245 and 288 nm assigned to intraligand  $\pi \rightarrow \pi^*$  and  $n \rightarrow \pi^*$  transitions respectively. It is found that these bands were shifted to lower energy on complexation. The shifts are positive shifts toward longer wavelength. The electronic spectra also contain broad bands having relatively high intensities, which are attributed to charge transfer bands and other bands in the visible region which are due to d-d transitions which are responsible for the various colours displayed by these complexes. On coordination, the electronic transitions of the ligands exhibited a positive shift towards longer wavelength with values ranging from 230-343 nm suggesting the coordination of the ligands to the metal ions.

The spectrum of the Co(II) complex of TMP mixed with MET shows three absorption bands within the range 250-300 nm attributable to  $\pi \rightarrow \pi^*$  and  $n \rightarrow \pi^*$  transitions. Bands around 525-800 nm attributed to the  ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ ,  ${}^4T_{1g}(F) \rightarrow {}^4A_{1g}(F)$ ,  ${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ . These transitions are characteristic of Co(II) complexes in an octahedral environment.<sup>[20,21]</sup> The spectrum of the Ni(II) complex in the UV region shows absorption bands at 253 nm which is attributed to the charge transfer transition and three absorption bands in the visible region at 638, 690 and 658 nm for complexes of TMP with MET which are assignable to  ${}^3A_{2g} \rightarrow {}^3A_{1g}(P)$ ,  ${}^3A_{2g} \rightarrow {}^3T_{1g}$  and  ${}^3A_{2g} \rightarrow {}^3T_{2g}$ .<sup>[21-23]</sup> The visible electronic absorption spectrum for Cu(II) complex shows an absorption band at about 550-720 nm and a shoulder assigned to  ${}^2E_g \rightarrow {}^2T_{2g}$  while the shoulder is as a result of Jahn-Teller distortion of the octahedral geometry.<sup>[24,25]</sup> The uv-visible spectra are displayed in Figure 2. Mn(II) complex of TMP mixed with MET displays bands at 560, 594, 785, and 860 nm assigned to  ${}^2T_{2g} \rightarrow ({}^2A_{2g}, {}^2T_{1g})$ ,  ${}^2T_{2g} \rightarrow {}^2E_g$ ,  ${}^2T_{2g} \rightarrow {}^2A_{1g}$  d-d transitions, which supports low spin Mn(II) complexes in an octahedral field.<sup>26</sup> The iron complex of the TMP mixed with MET showed many bands at 717, 735 and 754 nm in the visible region. These bands are due to overlap of the charge transfer bands, consistent with an octahedral geometry. The Zn(II) complex of TMP with MET displayed bands within the uv region which are assignable to  $\pi \rightarrow \pi^*$  and  $n \rightarrow \pi^*$ .

The magnetic moment values as displayed in Table 3, shows that all the complexes are paramagnetic, except the Zn(II) complex which was diamagnetic. The copper(II) complex gave a value of 1.43 BM, the low value of magnetic moment is as a result of antiferromagnetism.<sup>[13]</sup> The magnetic susceptibility values for cobalt(II), iron(III) and Ni(II) complexes supports an octahedral geometry. The magnetic moment value of 1.84 BM displayed by the Mn(II) complex is attributed to the presence of one unpaired electron indicating a paramagnetic nature of Mn(II) in a low spin octahedral environment. This report is consistent and in agreement with the report of.<sup>[21,22]</sup>

Table 3. Electronic Spectra Data of Compounds

Complex	Intraligand (nm)	Ligand Field (nm)	Assignment	$\mu_{\text{eff.}}$ (BM)
Trimethoprim	257	-	-	-
Metformin	245, 388	-	-	-
[Mn(TMP)(MET)(H <sub>2</sub> O)Cl <sub>2</sub> ]	293	560, 594 785 860	${}^2T_{2g} \rightarrow ({}^2A_{2g}, {}^2T_{1g})$ ${}^2T_{2g} \rightarrow {}^2E_g$ ${}^2T_{2g} \rightarrow {}^2A_{1g}$	1.84
[Fe(TMP)(MET)Cl <sub>2</sub> ]	243, 253, 295	717, 735, 754	Forbidden transitions	5.74
[Co(TMP)(MET)(H <sub>2</sub> O)Cl <sub>2</sub> ]	255, 280, 295	525 625 775	${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ , ${}^4T_{1g}(F) \rightarrow A_{1g}(F)$ , ${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ .	3.51
[Ni(TMP)(MET)(H <sub>2</sub> O)Cl <sub>2</sub> ]	253, 295	638 658 690	${}^3A_{2g} \rightarrow {}^3A_{1g}(P)$ , ${}^3A_{2g} \rightarrow {}^3T_{1g}$ ${}^3A_{2g} \rightarrow {}^3T_{2g}$	2.78
[Cu(TMP)(MET)(H <sub>2</sub> O)Cl <sub>2</sub> ]	243, 292	580, 618(sh)	${}^2E_g \rightarrow {}^2T_{2g}$	1.43
[Zn(TMP)(MET)(H <sub>2</sub> O)Cl <sub>2</sub> ]	261, 328	-	MLCT	0.16

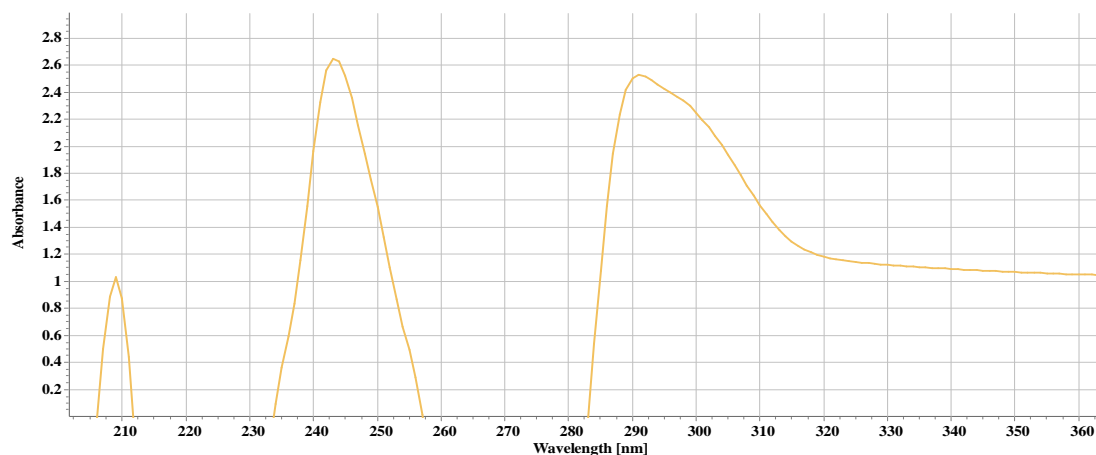


Figure 2a. UV spectrum of [Cu(TMP)(MET)(H<sub>2</sub>O)Cl<sub>2</sub>]

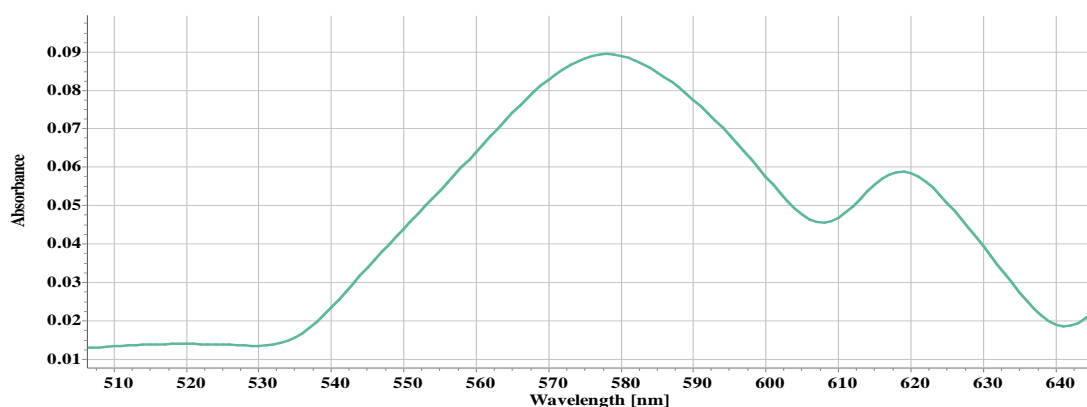


Figure 2b. Visible spectrum of [Cu(TMP)(MET)(H<sub>2</sub>O)Cl<sub>2</sub>]

### 3.5. Antimicrobial Activity

The ligands and synthesized metal complexes were screened for their antimicrobial activity by well plate method in nutrient agar. The activities were expressed in terms of millimeter (mm) by measuring inhibition zone (IZ) and compared with the standard [27].

The free ligands showed no activity against the tested micro-organisms except for trimethoprim which showed activity against *Staphylococcus aureus*, *B.cereus* and *Klebsiella pneumonia* with 12, 11 and 14 mm zones of inhibition respectively, which suggests that trimethoprim is more active than metformin. However, the positive standard (Streptomycin) had an activity in all the tested microorganisms. The mixed ligand complexes of the free ligands displayed variety of antibacterial activity against the tested microorganisms.  $[\text{Co}(\text{TMP})(\text{MET})(\text{H}_2\text{O})\text{Cl}_2]$ ,  $[\text{Ni}(\text{TMP})(\text{MET})(\text{H}_2\text{O})\text{Cl}_2]$ , exhibited a broad spectrum antimicrobial activity as they are active in almost all selected bacterial isolates except *B.subtilis*, *E.coli*, and *Pseudomonas aeruginosa*. They have also shown a stronger antibacterial activity than the free ligands as well as the control (Streptomycin). The investigation of antibacterial screening data revealed that most of the synthesized complexes were found to possess various antimicrobial activities toward *Shigella species* microorganism.

The better activity of the metal complexes was due to chelation, which reduces polarity of the metal atom and increases lipophilic character, favouring its permeation through lipid layers of the organism membrane while, the inactivity of some of the metal(II) complexes in this study may be attributed their probable lipophobic nature and / microbe strain.<sup>[15]</sup> Conclusively, all the metal complexes and their ligands showed good to excellent activity against all the microbes. The zone of inhibition of the ligands and mixed ligand complexes are shown in Table 4.

**Table 4. Zone of inhibition of the ligands and mixed ligand complexes**

Compounds/Bacteria	MET	TMP	Co complex	Ni complex	Cu complex
<i>Shigella spp</i>	0	0	8	0	8
<i>Enterococcus faecalis</i>	0	0	0	12	0
<i>Proteus vulgaris</i>	0	0	8	12	0
<i>Staphylococcus aureus</i>	0	12	0	12	0
<i>B.subtilis</i>	0	0	0	8	0
<i>Micrococcus luteus</i>	0	0	13	8	8
<i>E.coli</i>	0	0	0	0	0
<i>B.cereus</i>	0	11	0	10	0
<i>Kleb. pneumoniae</i>	0	14	12	0	0
<i>Pseud. aeruginosa</i>	0	0	0	0	0

### 4. Conclusion

Six complexes of trimethoprim mixed with metformin have been prepared and characterized by physical and chemical methods. The complexes show colour ranging from pink to brown. The complexes are generally soluble in DMSO they also had a high melting point which revealed a thermal stability for the compounds.

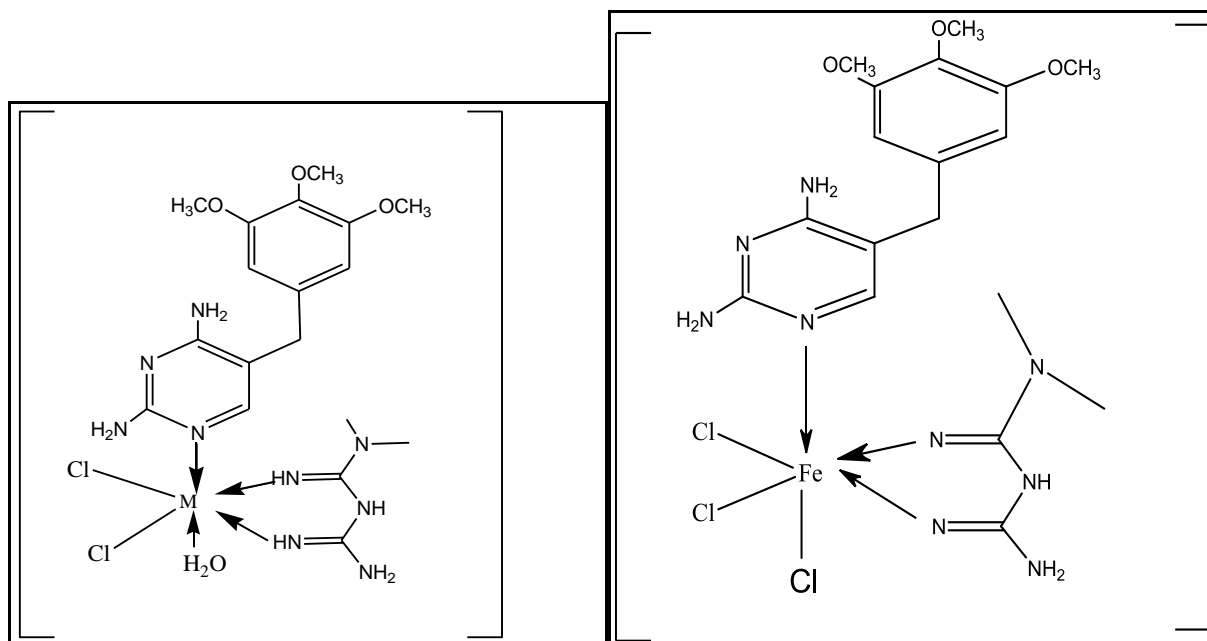
The IR spectra revealed that Trimethoprim acts as a monodentate ligand that coordinating to the metal ions via the pyrimidine nitrogen N(1), while metformin acts as a bidentate ligand coordinating through the iminonitrogens. The infrared spectra bands at  $450\text{ cm}^{-1}$  and  $530\text{ cm}^{-1}$  is ascribed to M-N and M-O bond respectively indicating the formation of these complexes.

The electronic spectra and magnetic moments predicted a number of transitions and number of unpaired electrons which are consistent with octahedral geometry, hence, octahedral geometry is being proposed for all the complexes.

The molar conductivity value of  $2.71\text{--}18.17\ \Omega^{-1}\text{cm}^2\text{mol}^{-1}$  are indicative of the non-electrolytic nature of these complexes. The stoichiometry of the complexes are 1:1:1 corresponding to TMP: MET: M as found in the



metal analysis. The synthesized complexes all show stronger antibacterial activity when compared with the free drugs.



M = Mn, Co, Ni, Cu and Zn

**Figure 3. Proposed Structure for Complexes of Trimethoprim mixed with metformin**

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