# Co(II) and Zn(II) Complexes of Ciprofloxacin Imine: Physicochemical and *In-Vitro* Biological Evaluation

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***Abstract:*** **- Schiff base ligand (HL) derived from ciprofloxacin and 2-aminopyridine was successfully synthesized and complexed with cobalt(II) chloride and zinc(II) acetate. The characterization was done base on molar conductance, infrared and electronic spectra. $^1$H NMR was also used for the ligands. The complexes were formed in moderate yields. The ligand and complexes are stable at room temperature. They are soluble in polar solvents (distilled water, ethanol and methanol) but slightly soluble in non-polar solvents (acetone, chloroform and n-hexane). The ligand has sharp melting point of 150 $^0$C while the range of those of the complexes indicate their purity. The molar conductivity measurements are in the range of 0.006-0.193 Scm$^2$mol$^{-1}$ indicating that the complexes are non-electrolytes. The percentage of the metals determined in the complexes are in close agreement with the theoretical values. Infrared spectra of the complexes agree with the coordination to the central metal atom through the nitrogen of the azomethine (C=N), pyridinium (azine) nitrogen hence the ligands are tridentate. The electronic spectra reveals the $\pi$-$\pi$* and n-$\pi$* transitions of the ligand while the $^1$H-NMR spectra of the ligand suggests the formation of the azomethine bond. The *in vitro* antimicrobial activity of all the compounds at different concentrations was screened against four bacterial pathogens, namely, *Staphylococcus aureus, Bacillus subtilis, Salmonella typhi and Escherichia coli* and also on fungal strain; *Aspergillusniger and Aspergillusfumigatus.* The complexes showed better activity of antibacterial strain compared to the parent and control drug but no activity on fungal strain. This is an indication that the synthesized compounds have broad spectrum activity.**

***Key words:*** **Ciprofloxacin, 2-aminopyridine, ciprofloxacin-imine, *in-vitro* antimicrobial activity, Schiff base ligand and metal complexes.**

## I. INTRODUCTION

The continual increase in the resistance of bacteria and fungi towards the action of most antibiotics especially floroquinolone and its members has been a challenge to the medicinal chemist and pharmacologist. Researches therefore have proved frequent modification in the activities of these antibiotics. A lot of Schiff bases have been synthesized to improve and modify the action of ciprofloxacin [1]. Ciprofloxacin is a broad spectrum antibiotic that was synthesized and introduced into the health system in 1987 [2]. It is the most widely used of the second-generation of quinolones, other second generation members include norfloxacin, lomefloxacin, ofloxacin and enoxacin. The World Health Organization has it in the list of essential medicines, the most effective and safe medicines needed in a health system. It is available as a generic medication and not very expensive [3]. Ciprofloxacin occupies an important role in treatment guidelines issued by major medical societies for the treatment of a number of bacterial infection which includes bone and joint infection serious infections, intra-abdominal infections, infectious diarrhea, respiratory tract infections, skin infections, typhoid fever and urinary tract infections [4].

Being a broad spectrum, it is active against wide variety of aerobic gram negative and gram positive bacteria in which its mechanism involves inhibition of bacteria DNA gyrase [5, 1].

From our earlier report it has been shown that Ciprofloxacin is an excellent Schiff base component when reacted with 2-amino pyridine to give ciprofloxacin imine compound. The Schiff base when complexed with metal(II) ion has remarkable potency against the tested microbes [6]. In line with the above, we report on the Synthesis, physicochemical and in vitro biological evaluation of Co(II) and Zn(II) complexes derived from ciprofloxacin and 2-aminopyridine.

Aminopyridine is an organic compound, cream to light yellow-beige crystalline powder. It is one of three isomericaminopyridines, used in the production of drugs [7].

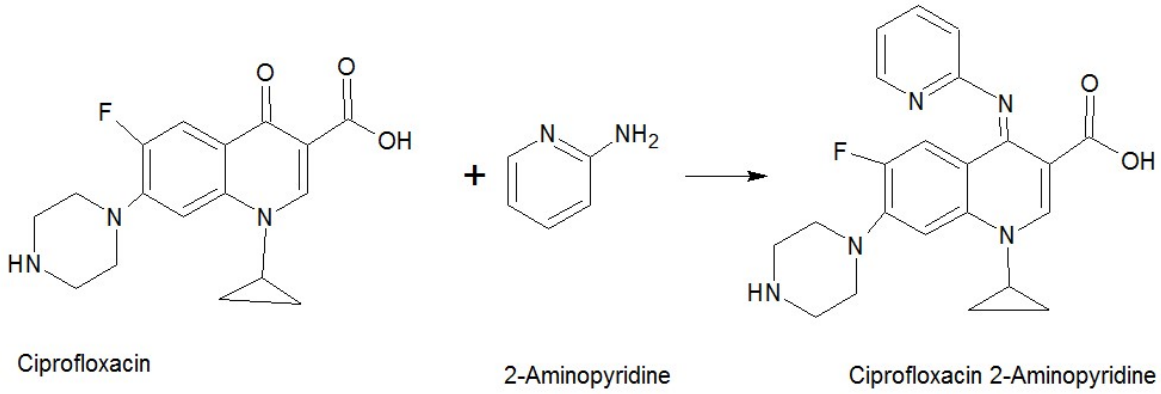
## II. MATERIALS AND METHODS

All chemicals used in the synthesis were of analytical reagent grade (AR) and were used without further purification. Ciprofloxacin antibiotics in pure (generic) form, 2-aminopyridine and ethanol were purchased from Sigma-Aldrich through Bristol Scientific Company, Lagos, Nigeria. Cobalt(II) chloride hexahydrate and zinc(II) acetate dihydrate were used. The rest of the reagents and solvents which include: acetic acid, methanol, ethanol, chloroform, n-hexane, benzene and acetone were of BDH and Merck products. Distilled water was used for all solution preparation.

### *Synthesis of the Ligand (Ciprofloxacin-Imines)*

The Schiff base ligand (HL) was synthesized with reference to a modification of literature procedures [1, 6, 8] Ciprofloxacin-imine (HL) was prepared by condensation of pure ciprofloxacin with 2-aminopyridine in ethanol. A 20 ml

ethanolic solution of ciprofloxacin (1mmol, 0.331g) and a 20 ml ethanolic solution of 2-aminopyridine (1mmol, 0.094g) were slowly mixed with constant stirring. The mixture was refluxed for 4 hours. The resulting solution was concentrated on a water bath and allowed to cool at $0^0$C (on ice chips). The whitish solid (HL) formed was filtered, washed with cold ethanol and dried in vacuo over calcium chloride.




**Scheme 1**: Synthesis of Ciprofloxacin 2-Aminopyridine

*Synthesis of Metal Complexes*

The ash/grey and whitish solid complexes of $Co(HL)_2$ and $Zn(HL)_2$ were prepared by dissolving (1mmol) of the Cobalt (II) chloride and Zinc (II) acetate separately in 20 ml hot ethanol and mixing with (2mmol) of ciprofloxacin imine ligand dissolved in 20 ml ethanol. The reaction mixtures were continuously stirred and refluxed for 4 hours. The resulting complexes were cooled, filtered, washed with ethanol and dried in a desiccator using calcium chloride.

*Antimicrobial Assay*

Test microorganisms includes two Gram positive bacteria: *Staphylococcus aureus, Bacillus subtilis* and two Gram negative bacteria*; Salmonella typhi, Escherichia coli,* and two fungal strain; *Aspergillusniger* and *Aspergillusfumigatus.* Method used is the Filter Paper Disc Diffusion Method as described elsewhere [1, 6, 9, and 10]. Disc of blotting papers impregnated with 30 or 20µg/ml concentrations of the test compounds were placed equidistant from the center in an inoculated petri dish and incubated. The zones of inhibition were then measured in mm as extent of activity of the test compound on the target microorganisms.

## III. RESULTS AND DISCUSSION

From Table 1, the colour of the Co(II) and Zn(II) complexes and that of the Schiff base ligand ranges from ash to white. Ciprofloxacin imine on interaction with Co(II) chloride and Zn(II) acetate yielded complexes corresponding to the general formula $ML_2$ [11,12]. The corresponding molar conductivity value of 0.143 and 0.006 $Scm^2mol^{-1}$ for Co(II) and Zn(II) complexes suggest that the newly synthesized compounds are non-electrolyte. The newly synthesized compounds are soluble in polar solvents and slightly soluble in non-polar solvents. Melting point of Co(II) and Zn(II) are of range; 178-180 and 180-183$^0$C respectively, an indication that the complexes are probably pure. They are also stable at room temperature. Moderate yields of 65 and 79% for the complexes were obtained. Furthermore, using EDTA complexometric titration, the theoretical and experimental percentage metal estimate are in close agreement. Metal to ligand ratio is shown to be 1:2 and this is in agreement with findings of [6, 13, 14 and 15].

*Electronic Spectra:* This is summarized in Table 2. The absorption spectra of ciprofloxacin 2-aminopyridine displayed two bands appeared at 282nm (35461$cm^{-1}$) and 320nm (31250 $cm^{-1}$) and the assignments are as follows; $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions. However, additional bands in the higher wavelength region were observed in the complexes which signify metal ligand coordination. Cobalt(II) complex exhibited two distinct bands at 280 and 330 nm ( 35714 and 30303 $cm^{-1}$). These transitions in the UV region correspond to $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ [16]. The shift to longer wavelength (bathochromic shift) together with colour change authenticates complex formation [1]. Similarly, the electronic absorption spectra of zinc(II) complex also showed two outstanding intense bands 280 and 325 nm (35714 and 30769 $cm^{-1}$) which are as well assigned to $\pi\rightarrow\pi^*$and $n\rightarrow\pi^*$ respectively [17]. The shift to longer wavelength; bathochromic shift in nature is a suggestive of complex formation [8]

*Infrared:* The infrared spectra of the free ciprofloxacin 2-aminopyridine and the metal(II) complexes measured as KBr discs are shown in Table 2. The bands attributed to υ ($NH_2$) group of 2-aminopyridine and υ (C=O) of ciprofloxacin were significantly absent in the spectra of the newly synthesized Schiff base, instead, newly formed broad bands at 1622 $cm^{-1}$

and 1541 $cm^{-1}$ which are attributed to υ(C=N) stretching vibration were obtained. This suggests the complete condensation of the amino groups with keto group [18, 19]. The IR of the Schiff base ligand was compared with the spectra of metal(II) complexes in order to study the binding mode of the newly synthesized compounds. .It was observed that the position or intensities of the peaks changed upon complexation. Characteristics changes were observed in the IR of the metal(II) complexes as compared with the spectrum of the ligand, suggesting complexation. Co(II) and Zn(II) complexes showed shifts to higher frequencies between 1629-1632 $cm^{-1}$ (7-10 $cm^{-1}$ shift) and 1530-1570 $cm^{-1}$ for azo and azi ring respectively. The shift in the frequencies revealed coordination of the Schiff base to metal(II) ions through the azomethine nitrogen [1, 6 and 18] and azine ring of the pyridine [17]. The higher υ(C=N) values observed in the metal(II) complexes indicate the possibility of M →L π bonding; which increases the bond order and consequently leads to a higher frequency of absorption. The involvement of the pyridine-N in metal coordination depends largely on its position relative to the imine-N [17]

Similarly, the bands in the region 1725-1730 $cm^{-1}$ assignable to the COOH group in the IR spectra of the ciprofloxacin 2-aminopyridine were absent in the metal complexes. This suggests the deprotonation of the -COOH group on complexation [1]. The IR spectra of the ligand (HL) showed a broad band at 3438 $cm^{-1}$ due to the stretching vibration of carboxylic hydroxyl, the broadness is due to intermolecular hydrogen bonding between the -COOH groups and the azomethine group [19]. The broad band at 3438 $cm^{-1}$ shifted to lower frequencies at 3401 and 3410 $cm^{-1}$ for Co(II) and Zn(II) complex respectively, the shift is a suggestive of coordination of the hydroxyl group with the metal ion this is in agreement to the findings of [1]

Furthermore, characteristic non ligands band were observed at 548 $cm^{-1}$ and 624 $cm^{-1}$ which is assignable to ν(M−N) are absent in the spectra of the ciprofloxacin 2-aminopyridine. In the same vein, the bands at 506 and 497 $cm^{-1}$ for Co(II) and Zn(II) complexes respectively are also absent in the spectra of the (HL) ligand, which is assignable to ν(M−O). These non-ligand spectra bands are indicators to the possible coordination of the azomethine nitrogen, azine nitrogen and the carboxylate oxygen to the metal ions [20].

Finally, the ciprofloxacin 2-aminopyridine is observed as a tridendate ligand complexing through the azomethine –N, pyridinium (azine) –N and O-atom of the hydroxyl group [6, 17].

*The proton NMR of the Ciprofloxacin 2-aminopyridine*

To further confirm the formation of the azomethine bonds and ascertain the position of the hydrogen bonds, $^1H$ NMR spectra of the Schiff base ligand (HL) recorded in MeOD against tetramethylsilane (TMS) as internal reference was carried out (Table 4). This showed a characteristic singlet at δ 3.15-3.50 ppm to the proton of ($CH_3$) of the MeOD. Multiplet signal of cyclo propane –$CH_2$.$CH_2$-was observed at 1.15ppm while signals appearing in the range δ 7.7-8.0 ppm are attributed to aromatic proton (Ar-H) [16]. Furthermore, the singlet signal displayed at δ 8.88 ppm is suggestive to amine proton which are implicated in hydrogen bond interaction [21]. The positions of the peaks showed an absence of sharp signals at 2.2-2.9 ppm in ligand, this can be attributed to deprotonation of the amine group in the formation of the azomethine bond hence a confirmation of the formation of the Schiff base [6].

*Antimicrobial Studies*

Two Gram positive bacterial strains: *Staphylococcus aureus, Bacillus subtilis,* two Gram negative bacterial strains: *Salmonella typhi and Escherichia coli* and two fungal strains; *Asperigillusniger and Aspergillusfumigatu* as shown in (Table 5) were used to investigate the *in vitro* biological screening effects of the newly synthesized compounds. Studies were also conducted based on the minimum inhibition concentration (MIC) and minimum bacterial concentration (MBC) activity of the compounds. Minimum inhibition concentrations (MIC) is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation. Minimum bactericidal concentration (MBC) was also carried to determine the lowest concentration in µg/ml of the antimicrobial agent that results in more than 99.9% killing of bacteria being tested. The results suggest an enhanced antibacterial activity of the ligand (HL) and metal(II) complexes. An excellent activity was shown by the ligand which is far greater than those of parent drug; ciprofloxacin and control drug; ketoconazole at higher concentrations [6]. This is due to interference in the normal cell process of organism caused by the formation of hydrogen bond through the azomethine group with the active center of cell constituents [12]. On the fungal strain assay no activity was shown on the tested ligand and its metal(II) complexes. The metal complexes have increasing activity when compared with the free ligand ciprofloxacin-imine. This may be attributed to the basis of oxidation state, overtone concept and chelation theory [23] which reduces the polarity of the metal ion by partial sharing of the positive charge with donor atom of the ligand (imine and oxygen). Sequel to the overtone concept of cell permeability, the lipid membrane that surrounds the cell favors the passage of only lipid-soluble materials in which liposolubility is an important factor that controls the antimicrobial activity. On chelation the polarity of the metal ion will be reduced to a greater extent due to overlap of ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Furthermore, it increases the delocalization of π-electrons over the whole chelate ring and enhances the lipophilicity of complexes. This increased lipophilicity enhances the penetration of complexes into the lipid membranes and blocks the metal binding sites in enzymes of microorganisms. The respiration process of the cell is being obstructed by the complexes, thus blocking the

synthesis of proteins, hence further growth of the bacteria is impeded [1, 24].

Table 1: Physico-analytical Data for Ciprofloxacin Schiff base and its Metal(II) complexes

| Compound | Proposed formula/ (F. Weight) | Colour | Conductivity ($Scm^2mol^{-1}$) | M.P ($^0C$) | Yield (%) | Metal (%) (Cal)/ Found |
|---|---|---|---|---|---|---|
| HL | $C_{22}H_{22}FN_5O_2$ 407.45 | White | 0.018 | 150 | 88 | - |
| $Co(HL)_2$ | $Co(C_{22}H_{22}FN_5O_2)_2$ 873.83 | Light green | 0.143 | 178-180 | 65 | 6.70 (6.74) |
| $Zn(HL)_2$ | $Cu(C_{22}H_{22}FN_5O_2)_2$ 880.27 | White | 0.006 | 180-183 | 79 | 7.90 (7.42) |

Table 2: Relevant Infrared Spectra of the HL Ligand and its Metal(II) Complexes ($cm^{-1}$)

| Compounds | υ(OH) | υ(C=N) azo | υ(C=N) azi | υ(M-N) | υ(M-O) |
|---|---|---|---|---|---|
| HL | 3438b | 1626sh | 1541sh | | |
| $Co(HL)_2$ | 3401b | 1632sh | 1572sh | 548w | 506w |
| $Zn(HL)_2$ | 3410sh | 1629m | 1530sh | 624w | 497w |

Where: sh = sharp, m = medium, b = broad, w = weak, s = strong

Table 3: $^1$H NMR of the Ligand (Chemical Shift in ppm)

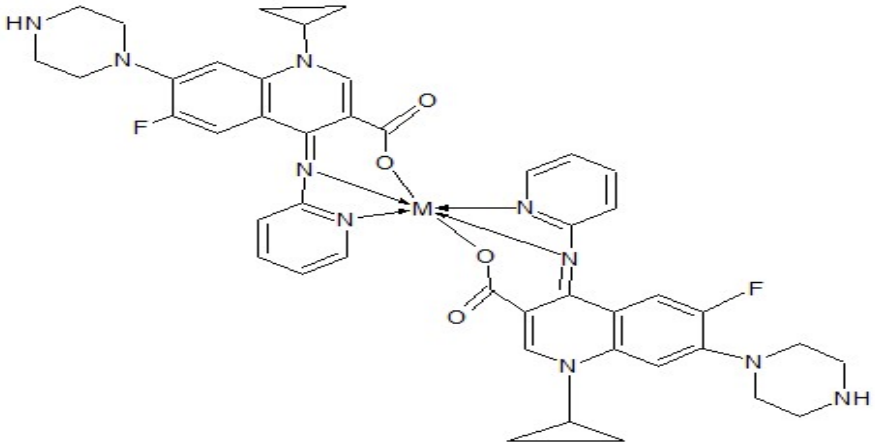
| Ligand | Aryl-H δ | Cyclopropane δ-H | Amine δ N-H | **S**olvent MeOD δ $CH_3$ |
|---|---|---|---|---|
| HL | 7.7–8.0 (m,5H) | 1.2-1.5 (m,5H) | 8.85 (s,1H) | 3.15-3.50 (s,4H) |

Where HLis Ciprofloxacin 2-Aminopyridine, s = singlet, m = multiplet

Table 4: The *in vitro* Antimicrobial Activities of the Schiff base Ligand HL and its Metal(II) Complexes

| **Compound** | **Conc. (µg/ml)** | ***S. aureus*** | ***B. subtilis*** | ***S. typhi*** | ***E. coli*** | ***A.niger*** | ***A. Fumigatus*** |
|---|---|---|---|---|---|---|---|
| HL | 30<br>20 | $36.66\pm0.33^{a}$<br>$29.33\pm0.33^{b}$ | $30.00\pm0.00^{a,a'}$<br>$24.33\pm0.33^{b,b'}$ | $37.33\pm0.33^{a,a'}$<br>$31.33\pm0.33^{b}$ | $30.00\pm0.00^{a}$<br>$24.33\pm0.33^{b,b'}$ | R<br>R | R<br>R |
| $Co(HL)_2$ | 30<br>20 | $30.00\pm0.00^{b}$<br>$23.33\pm0.33^{g,c'e'}$ | $30.00\pm0.00^{a}$<br>$24.33\pm0.00^{b,b'}$ | $26.66\pm0.33^{i}$<br>$20.33\pm0.33^{j}$ | $40.00\pm0.00^{g}$<br>$33.33\pm0.33^{c,b'}$ | R<br>R | R<br>R |
| $Zn(HL)_2$ | 30<br>20 | $27.66\pm0.33^{h,b'}$<br>$21.33\pm0.33^{i,c'}$ | $29.66\pm0.33^{a}$<br>$26.00\pm0.33^{g,b'}$ | $37.33\pm0.33^{a}$<br>$31.33\pm0.33^{f,d'}$ | $33.00\pm0.00^{e,b'}$<br>$25.33\pm0.33^{b}$ | R<br>R | R<br>R |
| Ciprofloxacin | 30<br>20 | $30.00\pm0.00^{b}$<br>$24.33\pm0.33^{f.c',e'}$ | $30.00\pm0.33^{a,b'.a'}$<br>$24.33\pm0.33^{b}$ | $35.00\pm0.00^{k,c',a'}$<br>$29.00\pm0.00^{f,d'}$ | $37.66\pm0.33^{h,c'}$<br>$30.66\pm0.33^{a}$ | -<br>- | -<br>- |
| Ketoconazole | 30<br>20 | -<br>- | -<br>- | -<br>- | -<br>- | 30.33±0.00 | 30.33±0.00 |

Different superscripted letters along the same column are significantly (P<0.05) different




Metal(II) Complex of Ciprofloxacin -2-Aminopyridine

Figure 1: Proposed Structure for the metal(II) complex

Where M is Co(II) or Zn(II)

## IV. CONCLUSION

The novel ligand; ciprofloxacin 2-aminopyridine and its metal(II) complexes were successfully synthesized. Physicochemical analysis of the new compound were evaluated using molar conductance, electronic spectra and IR. $^1$H NMR was used to probe the hydrogen bonding of the ligand. The conductivity measurement suggested that the synthesized compounds are non-electrolytes and are soluble in most polar solvents. The sharp melting point of the ligand and the metal(II) complexes gave an indication that they are probably pure. The analytical data with some physical properties show that the ligand on interaction with Co(II) chloride or Zn(II) acetate formed complexes corresponding to the general formula [$ML_2$]. An outstanding tridentate nature of the ligand was confirmed by the spectroscopic IR evaluation. The $^1$H NMR of the ligand suggests the formation of the azomethine bond while the electronic spectra of the Schiff base ligand (HL) also showed evidences of the non-bonding electrons present on the nitrogen of the azomethine group. The obtained results are similar to the our earlier report of complexation with Cu(II), Ni(II) and Mn(II) [6]. Finally, the *in vitro* biological screening of the newly synthesized compounds suggest greater and excellent activity against the tested microbes than the parent and control drug hence essentially relevant for development of new antibiotic ingredients

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