Synthesis, Characterization and Antimicrobial Studies of Co(II), Fe(II) and Ni(II) Tosylated 4-aminopyridine Complexes

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Abstract

The research investigates the synthesis of tosylated 4-aminopyridine complexed with cobalt(II), iron(II), and nickel(II) and its used as antibacterial agents. The purity of the ligand and its complexes was determined using melting point and thin-layer chromatography techniques. The chemical properties were assessed by the utilisation of Ultraviolet-Visible Spectroscopy (UV-VIS), Infrared (IR), Molar Conductivity, Electrospray Ionisation Mass Spectrometry (ESI-MS), and Nuclear Magnetic Resonance (NMR) techniques. The free imine nitrogen in the ligands vibrated at a higher frequency than the complexes' coordinated imine. This suggests the transfer of lone pair electrons from the free azomethine nitrogen to the metal ions. A variety of microorganisms was used to determine the antimicrobial potential of both ligand and their complexies. The findings revealed that the ligand had no effect on bacterial or fungal strains, whereas, the complexes were sensitivity on some microbes. The bioactivity of monotosylated 4-aminopyridine was greatly enhanced by its complexes. Among the clinical pathogens, S. cerevisiae is most affected by the iron(II) complex.

Keywords: *Antimicrobial, Metal Complexes, Monotosylated 4-aminopyridine, Synthesis*

Introduction

Numerous vital medications contain the chemical molecule aminopyridine, which comprises the heterocyclic aromatic pyridine along with an amine group (Morrison et al., 1992). Its ring structure provides biological building blocks, and many pharmaceuticals have pyridine and amine moieties; therefore, it evokes a broad spectrum of biological reactions in various animals (Clayden et al., 2012). According to Nagashree et al. (2013), Igwe and Okoro (2014), and Singh et al. (2006), compounds derived from aminopyridines have demonstrated strong pharmacological activity, such as antifungal, antibacterial, and insecticidal effects. Piroxicam, tenoxicam, and sulphasalazine are anti-inflammatory medications that contain aminopyridine residues.

Emergence of bacteria and fungi resistant to antibiotics is a major concern in clinical settings for public health. The worldwide health crisis is worsened since there are no effective ways to avoid it and not enough effective remedies. A rise of bacteria and fungi resistant to several drugs has been associated with insufficient and incorrect use of conventional antimicrobials.

(Choudhury et al., 2012; Abdul-Qadir et al., 2015; Morehead & Scarbrough, 2018; Nsude & Orie, 2022). Despite these obstacles, researchers have been working around the clock to create antimicrobial medicines that work in both living organisms and laboratory settings, with the hope of reducing the impact of multi-resistance to traditional antibiotics.

Some heterocyclic sulphonamides used as substrates or intermediates in the chemical and pharmaceutical industries are produced by the crucial tosylation of aminopyridine. Scientists have looked into the possibility of sulphonamides as antifungal, antibacterial, and anticancer agents. The biological significance of sulphonamides in some natural products that served as antibiotics has been understudy in N-(salicylidene) sulphadiazine (Vidya, 2016), ketene-N,S-acetal-substituted sulphonamide (Sani and Iliyasu, 2018), 4-(benzylideneamino)- and 4-(benzylamino)-benzenesulphonamide derivatives (Prabhakaran et al., 2004; Ostrowski & Ford, 2009), N-(quinolin-8-yl)various N-heterocyclic sulphonamide derivatives, 4-chloro-benzenesulphonamide (Kinali-Demirci et al., 2013; Sultana et al., 2010); alkyl-2-(4-(N-(substituted)sulphamoyl)phenyl)diazenylTwo-substituted phenyl-2-oxo-, two-hydroxyl-, and two-acylloxyethylsulphonamides (Amalraj et al., 2017) and 3-oxo-3-(2-henylhydrazinyl)propanoates (Kartal & Sahin, 2021).

The field of coordination compounds and organometallics serves as a bridge between inorganic chemistry and medicine. It includes medicinally significant molecules based on metals, agents that sequester or mobilise metals, diagnostic tools that contain metals, and methods for medicinally recruiting endogenous metal ions. However, a wide variety of enzymes and protein cofactors comprise hundreds of inorganic complexes and metals that are vital to the proper functioning of the biological system and our bodies. Because of their biological importance and their crucial role in maintaining vital biological processes, chemists are drawn to the synthesis and application of coordination compounds and organometallics (Efthimiadou et al., 2008; Chohan et al., 2010; Uivarosi, 2013).

Among the many biological uses for metal complexes of aminopyridines and sulphonamide are their antimicrobial and antifungal properties. According to Jisha and Isac Sobana Raj (2017) and Don-Lawson et al. (2020), these complexes have various applications in the fields of corrosion and catalysis, as well as in therapeutic, analytical, and industrial settings. In contrast, medicinal chemists make use of metal-drug complexes, which can be formed by administering organic compounds that have altered pharmacological and toxicological characteristics (Dojer et al., 2015; Orie et al., 2015). Tosylated 4-aminopyridine and its complexes are the subject of this work, which details the synthesis and investigates their antibacterial potential.

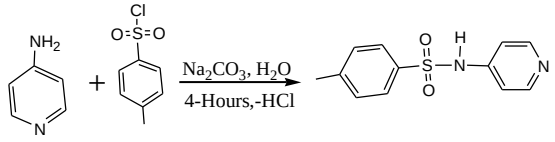
2.0 Materials and Methods

2.1. Materials used in this Study

The chemicals used were 2-aminopyridine, tosyl chloride, ethanol, acetic acid, acetone, sodium trioxocarbonate (IV), and others. The equipment used were TLC, Digital Melting Point Electrothermal(IA9300X1). The IR spectra, Liquid Chromatography/Mass Spectrometer, Proton Nuclear Magnetic Resonance (1HNMR) and Carbon-13 Nuclear Magnetic Resonance (13CNMR)

2.2.1 Synthesis of Monotosylated 4-aminopyridine

Abdul-Qadir et al. (2015) and Rehman et al. (2017), with slight modifications, provided the procedure that was used for the monotosylation of 4-aminopyridine. In a 250 mL round-bottom flask, agitated rapidly for 15 minutes in a fume chamber, 5-aminopyridine (0.053mol, 5g) and sodium trioxocarbonate (IV) (1M, 20ml) were added to 25ml of distilled water. Then, while the mixture was being agitated rapidly at room temperature for four hours, tosyl chloride (0.053mol, 10g) was added gradually. A shift from an alkaline to an acidic pH range and a TLC examination signalled the completion of the reaction. The product precipitated after being adjusted to an acidic pH with a few drops of strong hydrochloric acid; further washes with distilled water ensured that the product was free of acids; and finally, recrystallization was accomplished using a solvent system consisting of ethanol and water in a ratio of 1:5. The filtered crystal was then rinsed with distilled water and allowed to dry. (*Scheme 1*)



Scheme 1: Monotoosylated 4-aminopyridine

2.2.2 Complexation of Monotosylated 4-aminopyridine

For the complexation of monotosylated 4-aminopyridine, a procedure that was somewhat modified from that of Duru et al. (2014) and Orie et al. (2021) was used. The following solutions were added to separate 250 mL round-bottom flasks: a hot ethanolic sulphonylated aminopyridine solution (2.0g) and a boiled ethanolic solution of Ni(NO3)2.6H2O (404mmol, 1.19g), Fe(NO3)2.6H2O (403mmol, 1.16g), and Co(NO3)2.6H2O (402mmol, 1.17g). Two hours were spent stirring the concoction, and another two hours were spent letting it stand. The resulting precipitate underwent filtration and many ethanol washes. After being recrystallized using a solvent mixture of ethanol and dimethyl sulfoxide (1:6), the products were left to dry at room temperature. (*Scheme* 2).

M^{2+}+ L_A $[M(L_A)_2]$ L_A= Methyl-*N*-(pyridin-4-yl)benzene sulphonamide

M^{2+}= Fe^{2+}, Ni^{2+} and Co^{2+},

Scheme 2: Complexation of monotosylated 4-aminopyridine

2.2.3 Pathogen Isolation

The pathogens used for the bioactivity of this study were three bacteria strains (*Escherichia coli, Salmonella typhi, Staphylococcus aureus*) and three fungi strains (*Aspergillus flavus, Aspergillus niger and Saccharomyces cerevisiae*). These pathogens were isolated and confirmed in the Department of Microbiology, University of Port Harcourt. The antimicrobial activities of the ligand and its complexes were investigated using disc diffusion.

3.3.3 Preparation of Agar Solution

The nutritional agar was made by dissolving 28 grammes of solid nutrient agar in 1 litre of distilled water. The produced agar solution was homogenised before being sterilised in an

autoclave at 121oC for 15 minutes, cooled to 47oC, and poured onto Petri plates. The plate contents were then allowed to cool and solidify (Donlawson et al., 2020).

3.3.4 Preparation of Antimicrobial Sample Solution

A stock solution of each synthesized compound was prepared by dissolving 1000 mg of the ligands/complexes in 2.0 mL of DMSO. Other concentrations (500 mg/mL, 250 mg/mL, 125 mg/mL, 62.5 mg/mL and 31.25 mg/mL) of the antimicrobial test agents were prepared using serial dilution method with 50%v/v DMSO contained in different sterile test tubes and labelled appropriately. The serial dilution of the stock solutions was achieved *via* the formula:

$$V_s = \frac{C_d V_d}{C_s}$$

3.3.6 Antimicrobial Sensitivity Test

The well-in-agar diffusion approach adopted was consistent with Andrews (2001). The bacteria pathogens were streaked over a newly prepared agar medium and let to suspend overnight at 37 oC to renew them before marching to 0.5 McFarland standards. To make holes in the material, a sterile corkborer was employed. Then, the synthesised chemicals were added to the wells in varying quantities. After inoculation, the medium was kept at 37 °C for a full day. At last, the plates were examined, and millimetres (mm) were measured for the diameters of the inhibition zones surrounding the wells.

3.0 Results and Discussions

3.1. Solubility Analysis of Ligand, and its Complexes

Monotosylated 4-aminopyridine and related derivatives were tested for solubility in eight different solvents. Water, hexane, acetone, and ethyl acetate did not dissolve this monotosylated 4-aminopyridine, however DMSO, DMF, acetic acid, and ethanol did. In contrast to ethanol, DMSO, DMF, and hexane, the complexes did not dissolve water, hexane, or ethyl acetate. The solubility results were supported by research conducted by Abdul-Qadir et al. (2015) and Orie et al. (2021). There was evidence that polar solvents including acetic acid, DMSO, and DMF might dissolve sulphonamide derivatives in the solubility experiments. The interaction between the synthetic compounds' hydrogen atoms and the solvents' very electronegative atoms proved the formation of a hydrogen bond (Duru et al., 2014).).

3.2. Physicochemical Analysis of Monotosylated 4-aminopyridine and Complexes

Table 1 displays the results of the physicochemical study of four-aminopyridine that has been monotosylated and its complexes. As confirmed by a single spot in the TLC investigation using several solvent mixes, the melting point values fall within the purity limit. According to Abdul-Qadir et al. (2015) for amidine and benzene sulphonamides and Orie et al. (2021) for complexes of monotosylated 4-aminopyridine, the values were in agreement with the melting points. In DMSO (10-3M), the complexes' molar conductances varied between 8.0 and 13.0 Ω-1cm-2mol-1. Unless otherwise specified, all of the complexes have values that rule out the presence of anions beyond the coordination sphere. According to Al-Khodir (2015), this indicates that the chemicals that were synthesised do not undergo electrolysis. Rehman et al. (2017) reported a successful synthesis of monotosylated 4-aminopyridine and its metal (II)

complexes with a yield ranging from 50 to 57%. The expected molecular weight of the ligand and its complexes matched the molecular ion peaks seen in the ESI-MS study.

Table 1: Physical Properties of Ligand and Complexes

Compound	Colour	Mol. weight	Melting point, °C	% Yield	Molar conductivity $\Omega^{-1}cm^{-2}mol^{-1}$	TLC Analysis	
						R_F Value	Solvent mixture/ ratio
$C_{12}H_{12}N_2O_2S$	Offwhite	249.0	210-212	50	8.5	0.80	AA:ETOH:H_2O (2:1:1)
$[Fe(C_{12}H_{12}N_2O_2S)_2]$	Yellow	554.81	190-192	56	12.0	0.83	AA:ACE (1:2)
$[Ni(C_{12}H_{12}N_2O_2S)_2]$	white	556.30	195-197	55	12.5	0.86	AA:ACE (2:1)
$[Co(C_{12}H_{12}N_2O_2S)_2]$	Yellow	557.93	184-186	57	13.0	0.75	AA:ACE (2:1)

3.3 ^{1}H NMR Analysis of Monotosylated 4-aminopyridine

The chemical shift, coupling constant, and peak characteristics are displayed in Table 2. The sulphonamide (O=S-N-H) was determined to have a chemical shift of 14.37 ppm (1H, s), which proved that the reactants condensed. The chemical shift of the sulphonamide of tosylated amidine, according to Abdul-Qadir et al. (2015), is 11.45 ppm in deuterated ethanol solvent. In a DMSO solvent, Orie et al. (2021) measured 12.40 ppm for the proton of the sulphonamide with 2-aminopyridine. Possible explanations for the observed variation in the proton chemical shift of sulphonamide include variations in the sulphonamide derivatives' substituents and the solvents employed in the 1HNMR investigation. In the aromatic zone, you can find the chemical shift between 6.95 and 7.47 ppm. The aromatic zone, which includes values of 6.95 ppm to 7.47 ppm, is supported by studies conducted by Zhang et al. (2016), Sumrra et al. (2020), and Zahan et al. (2015). The presence of the benzene and pyridine rings in monotosylated 4-aminopyridine has been confirmed. The toluene methyl group was identified as the peak with a chemical shift value of 2.11 ppm (Duru et al., 2014). The presence of an aromatic ring can be confirmed by a carbon-12 chemical shift of 114.32-152.89 ppm, and the presence of a methyl group linked to the aromatic ring can be inferred from a shift of 21.33 ppm (Alsughayer et al., 2014; Rehman et al., 2017).

Table 2: NMR **Data 4-Methyl-*N*-(pyridin-4-yl)benzene sulphonamide**

Experimental		Literature	
^{1}H (δ ppm)	^{13}C (δ ppm)	^{1}H (δ ppm)	^{13}C (δ ppm)
14.37 (br, s, one H, NH),8.05 (dd, J=5.63 Hz, 1.88 Hz, one H), 7.76 (m, J=8.41Hz, one H), 7.15 (d, J=7.85.11 Hz, one H), 7.19 (d, J=8.8.68Hz, one H), 7.33 (d, J=8.03Hz one H) 7.52(m, one H),6.91 (ddd, J=6.83 Hz,5.63 Hz, 1.88 Hz, one H), 2.32-2.29 (s, three H)	21.43, 114.37, 117.60, 126.94, 126.50, 126-129.65, 139.13, 141.31, 143.13, 145.14,152.89	12.40, (br, s, 1H, NH), 7.97(d, *J* = 8.11Hz, 1H, CH),7.61 (d, *J* = 8.31 Hz,1H, CH), 7.25 (t, *J* = 7.21Hz, 1H, CH), 7.20 (s, 1H, CH), 7.11(t, *J* = 8.41Hz, 1H, CH), 7.15 (d, *J* = 8.39 Hz, 1H, CH), 2.48 (s, 3H, CH3) Abdul-Qadir *et al.* (2015), Duru *et al.* (2014	22, 113, 117, 125 138, 148, 150 Chohan *et al.* (2010) Rehman *et al.* 2017)

J=Coupling constant, s=Singlet, d=Doublet, t=Triplet, br=Broad, m=medium, dd= Double of doublet, ddd= Double of doublet of doublet

3.4 Electronic Analysis of Monotosylated 4-aminopyridine and its Complexes

Using a DMSO solution, the electronic spectra of both the pure monotosylated 4-aminopyridine and its complexes were recorded at room temperature within the 200–1100 nm range. The tosylated 4-aminopyridine and benzene rings show absorptions at 290-253 nm and 341-300 nm, respectively, which were attributed to the π → π* and n → π* transitions, respectively. The absorbance band at 220-200 nm, on the other hand, corresponds to the π → π* transition. The ligand-metal charge transfer transition (LMCT) was determined to be the cause of the band observed at 300-420 nm (Table 2). According to Hossain et al. (2018), who studied the coordination of Schiff bases of 2-aminopyridine derivatives with several metal complexes, the transition bands were in agreement.

Table 2: Selected UV-VIS Absorption Bands for Monotosylated 4-aminopyridine and Complexes.

compound	Adsorption nm	Band assignment
$C_{12}H_{12}N_2O_2SN_2O_2S$	220–200, 290–253,341-300	π →π*,n → π*
$[Fe(C_{12}H_{12}N_2O_2S)_2]$	375–305	π → π*, n → π*
$[Ni(C_{12}H_{12}N_2O_2S)_2]$	410–308	π → π*, n → π*
$[Co(C_{12}H_{12}N_2O_2S)_2]$	390-315	π → π*, n → π*

π →π*, n → π*, Electronic transition from highest occupied molecular orbital(HOMO) to lowest unoccupied molecular orbital(LUMO)

3.4 FTIR Analysis of Monotosylated 4-aminopyridine and its Complexes

Table 3 shows the binding sites and IR active sites of the ligand and its metal complexes. According to Pervaiz et al. (2020) and Orie et al. (2021), the most probable locations for coordination are the imine nitrogen and the sulphonamide, which consists of oxygen and nitrogen. The pyridine nitrogen was given the vibration frequency at 1688.10 cm^{-1} (Sobola & Watkins, 2018). Vibrational frequencies of 1674.27 cm^{-1} were given to the coordination of imine to iron(II) ions, 1651.12 cm^{-1} to nickel(II), and 1643.41 cm^{-1} to cobalt(II) ions. Jisha and Isac Sobana raj (2017) and Sobola and Watkins (2018) estimated the frequency range of azomethine (C = N) to be 1683.41 -1575 cm^{-1}, and this observation supports their findings. The ligand and its complexes are displayed in Table 3 along with their other frequency ranges.

Table 3. Selected FT IR Absorption Bands for Ligand and complexes.

	Experimental	**Literature (ref)**
Ligand/Complex	Vibration Frequency (cm^{-1})	Vibration Frequency (cm^{-1})
$C_{12}H_{12}N_2O_2S$	3286.81, 3510.86 NH, 2416.47 CH, 1688.10, C=N, 1519.96 C=C, 1134.38 C – N, 1003.02 S=O, 933.58, 848.71 aromatic C=C	3328 (NH), 1665 (C=N), 1019(S=O), 1161 (-N- S=O), 1455 (C=C), Abdul Qadir *et al.*(2015); Deng, & Mani,(2006)
$[Fe(C_{12}H_{12}N_2O_2S)_2]$	3317.67, 3618.58 NH, 2908.75 CH, 1674.27 C=N, 1527.67 C=C, 1010.73, S=O	3461 (NH),1648 (C=N),1558 (C=C), 1155(-N- S=O), 1261(C–N) (Duru *et al.* (2014); Pervaiz *et al.*,(2020)
$[Ni(C_{12}H_{12}N_2O_2S)_2]$	3356.25, 3603.15 NH, 2931.30 CH, 1651.12, C=N, 1519.06 C=C, 1134.18 C – N, 1010.73 S=O, 925.88, aromatic C=C	3380(NH), 1620(C=N), 1573 (C=C), 1157 (-N- S=O), Al-Noor,(2012); Sobola & Watkins, (2018)
$[Co(C_{12}H_{12}N_2O_2S)_2]$	3618.58, 3718.88 NH, 2918.47 CH, 1643.41 C=N, 1273.06 C –N, 1550.82 C=C, 1064.74 S=O, 810.13 aromatic C=C	3653.15 NH, 1655.22, C=N, 1589.06 C=C, 1134.18 (-N- S=O), 1010.73 S=O Pervaiz *et al.*,(2020)

3.6 Antimicribial Activity of Tosylated Aminopyridine and its complexes

Figure 1 illustrates the heightened susceptibility of certain monotosylated 4-aminopyridine complexes to bacterial activity. At a concentration of 1000 mg/mL, the Co(II) complexes exhibited activity against *S. typhi* and *E. coli*, as shown by the presence of inhibition zones of 10mm and 20mm, respectively. The Ni complex exhibited activity against *S. aureus*, *S. typhi*, and *E. coli*, with inhibition zones measuring 9mm, 13mm, and 19mm, respectively. On the other hand, the Fe(II) complex showed sensitivity against *S. aureus*, *S. typhi*, and *E. coli*, with inhibition zones measuring 5mm, 8mm, and 11mm, respectively. The ligant exhibited little activity against the three clinical pathogens but became active upon complexation.

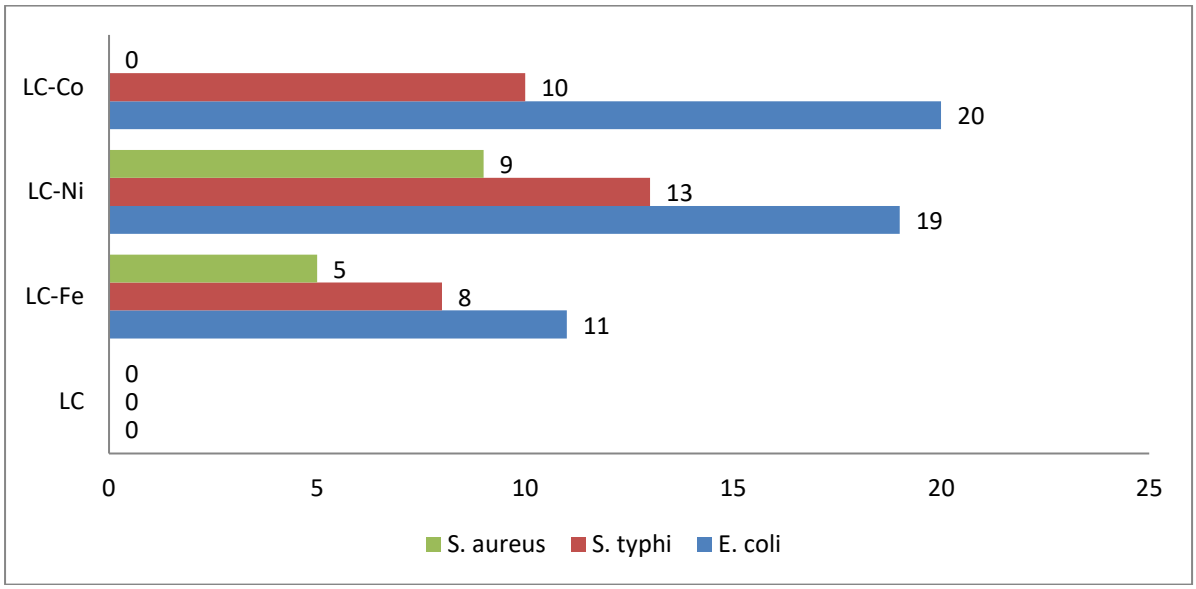


Figure 1 Antibacterial Activity of monotosylated 4-aminopyridine and its complexes

Results from the antibacterial study corroborated those from earlier studies that analysed activity. Imidazole derivative complexes were determined to be more bioactive than their ligand counterparts by Duru et al. (2014). The maximum zone inhibition for Gram(-) *E. coli* (34 mm), Gram(-) *S. typhi* (36 mm), and Gram(+) *S. aureus* (37 mm) when ciprofloxacin is utilized as a reference. This suggests that the synthetic chemical was less effective than the traditional medication against all bacterial strains. The results of the phenyl sulphonamide sensitivity test that Ijeomah and Tseeka (2021) performed were in agreement with this finding. When tested against Gram(+) *E. coli*, the synthetic chemical proved less effective than the gold standard medication, ciprofloxacin.

As demonstrated in Figure 2, the antibacterial activity of monotosylated 4-aminopyridine and its complexes on fungi was investigated. The iron(II) complex exhibited the greatest zone inhibition for *S. cerevisiae* (26 mm), in contrast to the monotosylated 4-aminopyridine, which was insensitive to most fungi.

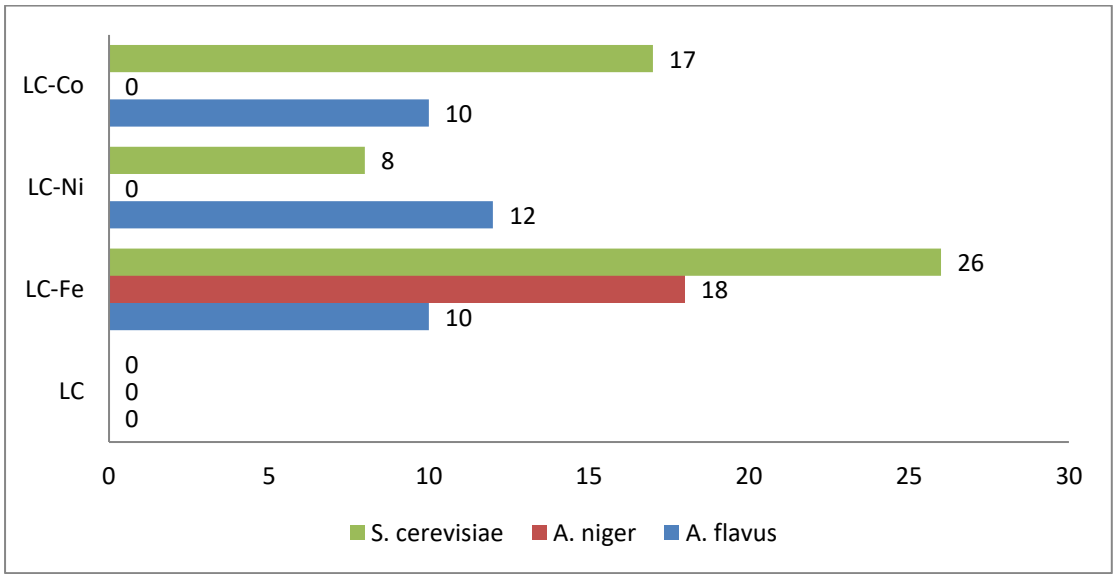


Figure 1: Antifungal Activity of Monotosylated 4-aminopyridine and its Complexes

The results show that ketoconazole has a zone inhibition of 20 mm on *A. flavus*, 26 mm for *A. niger*, and 16 mm for *S. cerevisiae*, when compared to the activity of the complexes on the fungi. At 1000 mg/mL, ketoconazole showed improved effectiveness against all tested fungal strains, with the exception of the iron(II) complex, which exhibited the greatest zone of inhibition. This result corroborated previous findings that the conventional medication was superior to aniline sulphonamide derivatives, as reported by Andrew (2001) and Lakrout et al. (2014).

4.0 Conclusion

The synthesis and characterization of tosylated 4-aminopyridine and its complexes(Fe(II), Co(II), and Ni(II)) were reported in this study. The complexation of tosylated 4-aminopyridines shows that the imine of aminopyridines is the possible site for metal coordination.

The results of the bioactivity assessment indicate that monotosylated 4-aminopyridine did not exhibit any activity against the bacterial and fungal strains investigatef. However, some of the metal complexes deplayed an effective inhibitory actions at a minimum inhibitory concentration (MIC) of 1000 mg/mL. The conventional antibacterial and antifungal agents employed in this study have shown superior efficacy compared to the synthesized compounds.

The result revealed that the antimicrobial activity of tosylated 4-aminopyridine can be enhanced upon complexation with Co(II), Fe(II) and Ni(II) ions. As a recommendation, the ligand and its complexes should be investigated on other clinical pathogens.

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