



MECHANOCHEMICAL SYNTHESIS AND CHARACTERIZATION OF POTENTIALLY BIOACTIVE ISONICOTINIC ACID AND ITS Co (II), Cu(II) & Zn(II) COMPLEXES

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ABSTRACT

*Liquid assisted grinding of Isonicotinic acid with Co (II), Cu(II), and Zn(II) resulted in coloured metal (II) complexes with the formula $[M(INA)_2(OH)_2(H_2O)_2]$ ($M = Co (II), Cu(II), and Zn(II)$, INA = Isonicotinic acid). Elemental analysis, infrared spectroscopy, magnetic measurement, single crystal, and Powder x-ray diffraction were used to characterize the coordination compounds. The Infrared spectra of the ligand showed a strong band at 1695cm^{-1} and 1289cm^{-1} which corresponds to C=O and C-O stretching vibrations. A shift of the C=N stretching vibration from 1580cm^{-1} which was observed in the IR spectrum of the ligand to lower values in the spectra of the coordination compounds provides evidence of coordination to the central metal ion. This was further confirmed by the appearance of new bands in the spectra of the coordination compounds in the range ($550\text{-}500\text{cm}^{-1}$) which corresponds to (M-N) stretching vibrations. For all of the complexes, the effective magnetic moment values (5.11 and 1.71 for Co and Cu complexes respectively) suggest octahedral geometry. The CHN Elemental analysis agreed well with the calculated value, indicating a ligand-metal ratio of 2:1. The crystal is triclinic with a P-1 space group $a = 6.307\text{ \AA}$, $b = 6.798\text{ \AA}$, $c = 9.181\text{ \AA}$, and a distorted octahedral geometry. The experimental PXRD patterns of the coordination compounds matched those simulated from single-crystal data, indicating the phase purity of bulk samples. The antimicrobial activity of the ligand and its metal (II) complexes was tested against six pathogenic microorganisms (*Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi*, *Aspergillus flavus*, and *Aspergillus fumigatus*). Gentamycin and Ketoconazole were used as reference drugs for bacteria and fungi respectively. All the compounds demonstrated moderate antimicrobial activity.*

Keywords: Mechanochemistry, Isonicotinic acid, Antifungal, Crystal structure, Antibacterial.

INTRODUCTION

Solvent-less chemistry has gained popularity in both academic and industrial laboratories in recent years. The aim is to reduce the usage of solvents or, better yet, to perform synthetic reactions without them thus, reducing environmental contamination connected with solvent disposals and diminishing energy supplies (Tella *et al.*, 2011). The study of solid-state synthesis caused by mechanical energy, such as grinding in ball mills, is known as mechanochemistry. This technique is gaining a lot of attention since it can swiftly and quantitatively drive solid-solid reactions with no added solvent or just a minute amount of it (James *et al.*, 2012). Compared to traditional solvent-based synthetic processes, mechanochemical synthesis is more advantageous, safer, and eco-friendly (Owens *et*

al., 2015). Most crucially, it provides the possibility of attaining complexes that are either unfeasible or take a longer time to synthesize using traditional methods like solution chemistry (Kaupp *et al.*, 2001). For example, grinding $[Pd(NO_3)_2en]$ and a tripodal ligand (2,4,6-(tripyridyl)-1,3,5-triazine) at ambient temperature for ten minutes resulted in a Hexapalladium bowl-shaped cluster in quantitative yield, similar reaction using platinum took more than four weeks at 100°C in D_2O . (Orita *et al.*, 2002).

The mechanochemical ball-milling synthesis of two model organic pharmaceutical cocrystals of theobromine was reported by Karki *et al.*, (2007), the synthesis and structural determination using PXRD data and thermogravimetric analyses were completed in less than a day.

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In addition to the solvent-free mechanochemical process, Liquid-assisted grinding (LAG), a method that uses a tiny amount of liquid as an additive to improve or control reactivity has proven to be a very efficient and rapid procedure for the synthesis of coordination compounds (Friscic, *et al.*, 2012). For example, solution crystallization of cyanoguanidine and ZnCl_2 has previously produced two distinct complexes; $\text{Zn}(\text{cng})\text{Cl}_2$ and $\text{Zn}(\text{cng})_2\text{Cl}_2$. This is due to the ability of the simple and stiff ligand to act as a heteroditopic ligand, bridging the metal centers in one compound and acting as a terminal ligand in the other. Ball milling ZnCl_2 with cyanoguanidine in 1:1 and 1:2 ratios in an attempt to mechanochemically synthesize $\text{Zn}(\text{cng})\text{Cl}_2$ and $\text{Zn}(\text{cng})_2\text{Cl}_2$ resulted in a gluey and hygroscopic solid. However, repeating the experiments with a little amount of liquid phase as a catalyst resulted in white crystalline powders that were identified as $\text{Zn}(\text{cng})\text{Cl}_2$ and $\text{Zn}(\text{cng})_2\text{Cl}_2$ by PXRD, as expected (Strukil, *et al.*, 2010).

A transition metal complex, also known as a coordination complex, is an entity made up of a central metal atom or ion connected to a fixed number of ions or molecules known as ligands that are arranged in a definite geometrical arrangement surrounded by a square bracket known as a coordination sphere (Bagchi *et al.*, 2015).

The ligands may compose of multiple tiny independent sets of atoms (or single atoms) or a more complex arrangement of atoms connecting those that are directly attached to or coordinated to the central atom (Warra, 2011). Coordination compounds have proven to be useful in various fields with a wide range of applications. For example, Transition metal complexes have been used as sensor materials for the detection of volatile organic compounds (VOC) (Belviso, *et al.*, 2021). They are used as a catalyst in various material syntheses, they have applications in photochemistry and biological systems. They also exhibit various chemical, optical and magnetic properties.

It is possible to form a stable chelate ring by coordination using ligands having electron donor atoms, such as N, O, S, and P. the chemistry of metal-nitrogen bonds in transition metal compounds has garnered a lot of attention in recent years (Bagchi *et al.*, 2015). Chelation often affects the biological properties of the ligand and the metal ion, in many cases, it synergistically improves the bioactivity of both the ligand and the metal ion. As a result, it is possible to design novel metal-based anti-microbial to curb the level of resistance of these microbes to existing drugs (Rafique *et al.*, 2010).

Among the nitrogen-containing ligands, isonicotinic acid and its analogues have piqued interest because they act as bidentate ligands, functioning both as chelating and/or bridging ligands (Syaima, *et al.*, 2018). The compounds have drug-like properties thus playing a significant role in biology. For instance, nicotinic acid, commonly known as niacin, is a type of vitamin B₃ present in a variety of foods such as chicken, beef, and fish, and it aids in the prevention of cardiovascular diseases (Khan *et al.*, 2017). Isonicotinic acid hydrazide is used to treat tuberculosis. Several studies have been reported on the antibacterial and antifungal properties of mixed ligand metal complexes with isoniazid and hydrazone derivatives (Kriza *et al.*, 2010). In view of the versatile importance of isonicotinic acid as a source of possible new drugs, we herein describe the liquid-assisted synthesis, characterization, and antimicrobial studies of isonicotinic acid with Co(II), Cu(II), and Zn(II) transition metal complexes.

MATERIALS AND METHODS

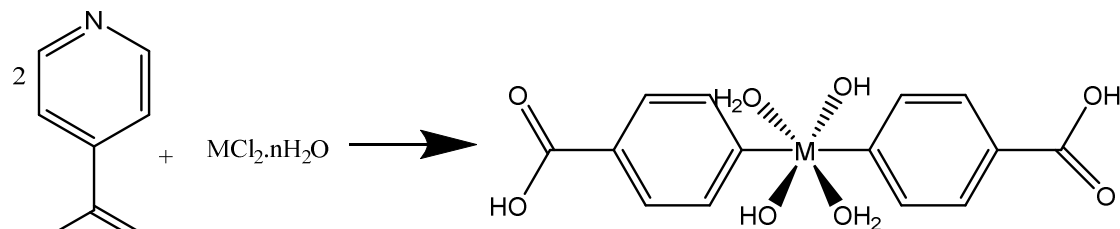
The reactions were carried out by grinding in an agate mortar and pestle. All chemicals used in this research work were obtained from Sigma Aldrich UK in >95% purity and were used without further purification. Samples were weighed using an electric meter balance model AB 54. IR spectral analysis was recorded using a Perkin-Elmer FT-IR spectrophotometer in the range 4000 – 400 cm^{-1} . Magnetic susceptibility measurements were carried out on a Sherwood Scientific Auto Magnetic susceptibility balance. PXRD measurements were carried out on a PANalytical Empyrean X'Pert Pro X-ray diffractometer. Copper was used as the X-ray source with a wavelength of 1.5405 Å. Elemental microanalysis (C, H, and N) was determined using a Perkin-Elmer CHNS/O 2400 series II elemental analyzer. Single crystal X-ray diffraction was performed on a Bruker Kappa APEX2 diffractometer with a MoK α ($\lambda = 0.71073$ Å) I μ S microfocus source at 293 K. before data collection, each single crystal sample was kept in a small volume of the appropriate mother liquor in which dissolution-recrystallization occurred prior to data collection.

Synthesis of the Metal (II) Complexes

The compounds were synthesized according to the literature procedure (Adams *et al.*, 2008) with little modification. 1mmol of Isonicotinic acid and 0.5mmol of the metal salt were carefully weighed into an agate mortar and pestle. A few drops of water were added and the mixture was ground for 30 minutes.

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A coloured paste that gradually turned into a powder upon grinding was obtained. The powder was washed with ethanol and dried in a vacuum.



Scheme of the Reaction

Antibacterial Activity Test

The *in vitro* antibacterial activity of the ligand and its metal (II) complexes were performed using the agar well diffusion method. The ligand and the metal complexes were separately dissolved in dimethylsulphoxide. Three different concentrations (60 µg/ml, 30 µg/ml, and 15 µg/ml) were obtained using the serial dilution method. The standard Inocula of *Staphylococcus aureus*, *Salmonella typhi*, and *Escherichia coli* isolates were obtained from Microbiology Laboratory, Bayero University Kano, Nigeria. The inoculum was made by suspending overnight bacterial culture in saline solution and diluting to match the McFarland turbidity standard of 0.5(108 cells/mL). Using a sterile cotton bud, the bacterial inocula were dispersed on the top of the nutrient agar. (Yusha'u and Sadius, 2011). A sterile metallic borer was used to dig the wells (6mm in diameter). In each well, the appropriate concentration of the test sample was added. As a reference standard, a commercial antibiotic (Gentamycin, 15 µg/ml) was used. The plates

were incubated at 37°C for 24 h. The activity was determined by measuring the diameter (mm) of zones showing complete inhibition.

Antifungal Activity Test

The *in vitro* antifungal activity of the ligand and its complexes against *Aspergillus flavus*, *Aspergillus niger*, and *Mucor spp* was also determined in the same manner using potato dextrose as the media and Ketoconazole as the reference drug. After 48 hours of incubation at room temperature, the width of the zone of inhibition induced by the ligand and the complexes was evaluated to determine their potency. (Hassan et al., 2006).

RESULTS AND DISCUSSION

The liquid assisted grinding (LAG) of Isonicotinic acid with Co(II), Cu(II) and Zn(II) afforded coloured crystalline solids with an appreciable percentage yield (Table 1). The coordination compounds have high decomposition temperatures thus indicating good stability.

Table 1: Physical Properties of the Ligand and its Metal (II) Complexes.

Compound	Colour	Decomposition Temp. (°C)	Yield (%)
INA			
[Co(INA) ₂ (OH) ₂ (H ₂ O) ₂]	Lavender magenta	263	93.2
[Cu(INA) ₂ (OH) ₂ (H ₂ O) ₂]	Medium aquamarine	231	88.5
[Zn(INA) ₂ (OH) ₂ (H ₂ O) ₂]	White	248	90.2

INA = Isonicotinic Acid.

The solubility of the Coordination Compounds was determined in different solvents, from the results obtained (Table 2) the compounds were found to be soluble only in DMF and DMSO, but slightly soluble in water. The molecular formula of the metal (II) complexes was determined using

elemental analysis (CHN). The calculated values (Table 3) are in excellent agreement with those observed using a micro-analytical instrument, and the result suggested a 1:2 metal-ligand ratio in all the complexes.

Table 2: Solubility test of the Metal (II) Complexes

Compound	DMF	DMSO	Acetonitrile	MeOH	EtOH	Chloroform	H ₂ O
[Co(INA) ₂ (OH) ₂ (H ₂ O) ₂]	S	S	IS	IS	IS	IS	SS
[Cu(INA) ₂ (OH) ₂ (H ₂ O) ₂]	S	S	IS	IS	IS	IS	SS
[Zn(INA) ₂ (OH) ₂ (H ₂ O) ₂]	S	S	IS	IS	IS	IS	SS

INA = Isonicotinic Acid.

Table 3: Elemental analysis (CHN) of the Ligand and its metal (II) complexes.

Compound	% Carbon		% Hydrogen		% Nitrogen	
	Found	(Calculated)	Found	(Calculated)	Found	(Calculated)
[Co(INA) ₂ (OH) ₂ (H ₂ O) ₂]	38.40	(38.42)	4.23	(4.30)	7.41	(7.47)
[Cu(INA) ₂ (OH) ₂ (H ₂ O) ₂]	38.94	(38.44)	4.32	(4.25)	7.38	(7.68)
[Zn(INA) ₂ (OH) ₂ (H ₂ O) ₂]	36.23	(37.77)	4.13	(4.23)	7.11	(7.34)

INA = Isonicotinic Acid.

Some chosen IR frequencies of the free Ligand and its Coordination compounds are provided in Table 4. The Infrared spectrum of the free monocarboxylic acid showed a strong band at 1695cm⁻¹ and 1289cm⁻¹ which corresponds to C=O and C-O stretching vibrations. Similar peaks were present in the IR spectra of the coordination compounds. However, a significant shift in the frequency of the C=N stretching vibration was observed between the IR spectra of the Isonicotinic acid free ligand (1580 cm⁻¹) and that of its metal (II) complexes to lower wavenumbers indicating coordination to the central metal ion is

through nitrogen. In addition, the appearance of additional bands in the range (550-500cm⁻¹) in the spectra of the metal complexes which correspond to (M-N) stretching vibrations provided further confirmation that coordination to the central atom occurs through the pyridine nitrogen and not the carbonyl group. Strong, broadbands in the range (3600-2500cm⁻¹) and those at about 1400cm⁻¹ belong to O-H stretching and bending vibrations. The overall spectral patterns of the free ligands are consistent with theoretical discussions given by Max & Chapados (2004), Li & Zhong (2014).

Table 4: Infrared spectral data of the Ligand and its Metal (II) Complexes.

Compound	$\nu(\text{O-H})$ cm ⁻¹	$\nu(\text{C-H})$ cm ⁻¹	$\nu(\text{C=O})$ cm ⁻¹	$\nu(\text{C=C})$ cm ⁻¹	$\nu(\text{C=N})$ cm ⁻¹	$\nu(\text{M-N})$ cm ⁻¹
INA	2409	3058	1695	1609	1580	—
[Co(INA) ₂ (OH) ₂ (H ₂ O) ₂]	3372	3064	1703	1612	1560	545
[Cu(INA) ₂ (OH) ₂ (H ₂ O) ₂]	3673	3065	1699	1614	1559	540
[Zn(INA) ₂ (OH) ₂ (H ₂ O) ₂]	3639	3086	1703	1611	1562	549

INA = Isonicotinic acid

The Magnetic susceptibility of the Coordination compounds was measured at room temperature and the effective magnetic moments of each compound were calculated as shown in Table 5. The effective magnetic moment value of the

coordination compounds shows the compounds to be high spin, paramagnetic, octahedral Compounds except for Zn (II) compound which is diamagnetic.

Table 5: Magnetic Susceptibility values of the Metal (II) Complexes

Compound	Mass Susceptibility Xg (erg.G ⁻² g ⁻¹)	Molar Susceptibility Xm (erg.G ⁻² mol ⁻¹)	Magnetic Moment μ_{eff}
[Co(INA) ₂ (OH) ₂ (H ₂ O) ₂]	2.887 X 10 ⁻⁵	1.083 X 10 ⁻²	5.11
[Cu(INA) ₂ (OH) ₂ (H ₂ O) ₂]	3.430 X 10 ⁻⁵	1.303X 10 ⁻²	1.71
[Zn(INA) ₂ (OH) ₂ (H ₂ O) ₂]	Diamagnetic	—	—

INA = Isonicotinic acid

A single crystal of Cu (II) Isonicotinic acid coordination compound was obtained by slow evaporation of the compound dissolved in DMSO. The lattice parameters at ambient temperature suggest a triclinic, P-1 space group (Table 6).

Similar Crystal has been reported (CCDC number: 1841691) by Yuan *et al.*, (2018). The crystal was obtained by slow evaporation of DMSO solution containing CuCl₂ and Isonicotinic acid.

Table 6: Crystallographic Data.

Compound	[Cu(INA) ₂ (OH) ₂ (H ₂ O) ₂]
Empirical Formula	[Cu(C ₁₂ H ₁₀ N ₂) ₂ (OH) ₂ (H ₂ O) ₂]
Molecular weight	379.81
Crystal System	Triclinic
Space group No.	P-1
Temperature (K)	293
a/Å	6.307
b/Å	6.798
c/Å	9.181
α/°	99.06
β/°	105.73
γ/°	108.70

The compound has been reported to have a distorted octahedral geometry, Cu(II) lies on an inversion centre where the transpositions are occupied by nitrogen atoms of the two pyridine rings (Cu – N 2.0036(Å)) while, Oxygen atoms of the two hydroxyls (Cu – O1 1.986(Å)) and two water molecules (Cu – O2 2.415(Å)) occupy the remaining positions.

The Cu – N, Cu – O1, and Cu – O2 distances agree well with the corresponding distances in related Copper(II) complexes: e.g. [Cu–N 2.010(2)(Å)], [Cu – O1 1.984(2)(Å)] and [Cu – O2 2.452(2)(Å)] in trans- tetra aqua-bis(pyridine-4-carboxylate-N)copper (II) (waizump *et al.*, 1998).



Fig. 1(a): Connectivity and coordination environment of Cu in [Cu(INA)₂(OH)₂(H₂O)₂]. (Cu = Blue, O = Red, N = Grey, C = Brown, H = Pink). (b): Microscope of [Cu(INA)₂(OH)₂(H₂O)₂]

An appreciable difference in the X-ray powder diffraction patterns of the starting materials and product was observed. This provides an evidence in the conversion of the starting material to product. A comparison of the calculated X-ray powder diffraction pattern from the single crystal data with experimentally observed powder pattern at room temperature (Fig. 2) showed that

the compounds are Isostructural with high similarity and only slight changes in the intensity of the peaks. Thus, the powder pattern of the bulk sample corresponds to the simulated pattern calculated from the single crystal data indicating that the obtained products are highly crystalline and phase pure without additional polymorphs

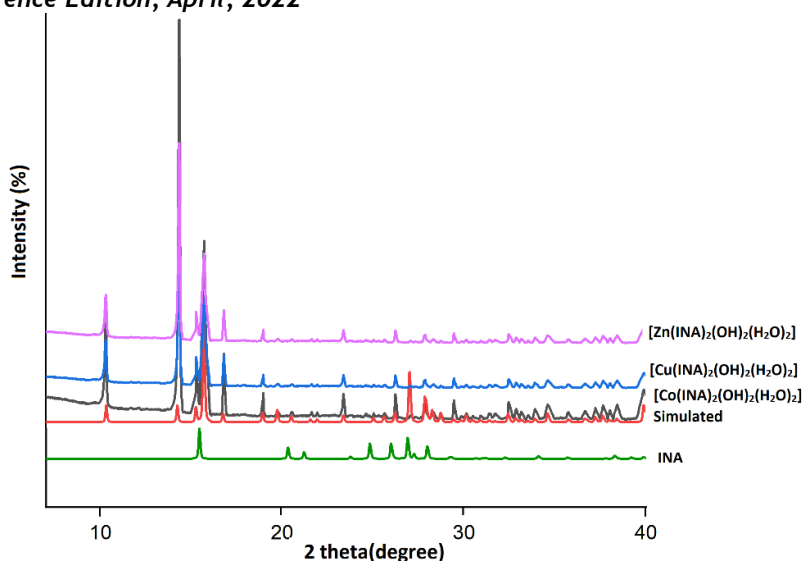


Fig. 2: PXRD Pattern of Isonicotinic acid and its Coordination Compounds

The *in vitro* antibacterial and antifungal activity of the ligand and its metal (II) complexes were investigated using the agar well diffusion method. Gentamycin and ketoconazole were used as a positive control for antibacterial and antifungal activities respectively. Three different strains of

bacteria which include both gram-positive (*Staphylococcus aureus*) and gram-negative (*Salmonella* and *Escherichia coli*) and three fungal isolates (*Aspergillus flavus*, *Aspergillus fumigatus*, and *Mucor species*) were tested.

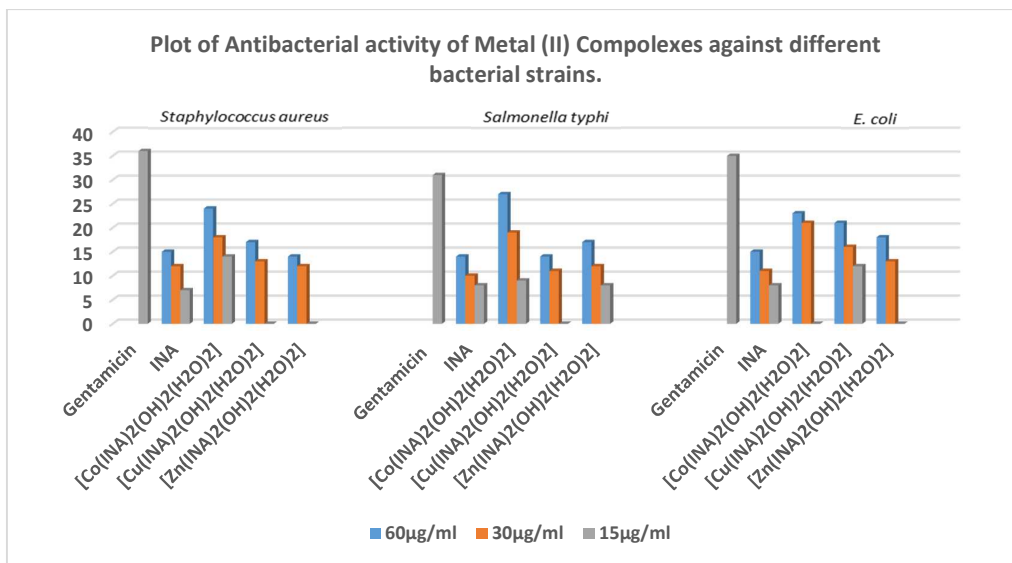


Fig. 3: Plot of Antibacterial Activity of Metal (II) Complexes against *Staphylococcus aureus*, *Salmonella typhi* & *Escherichia coli*.

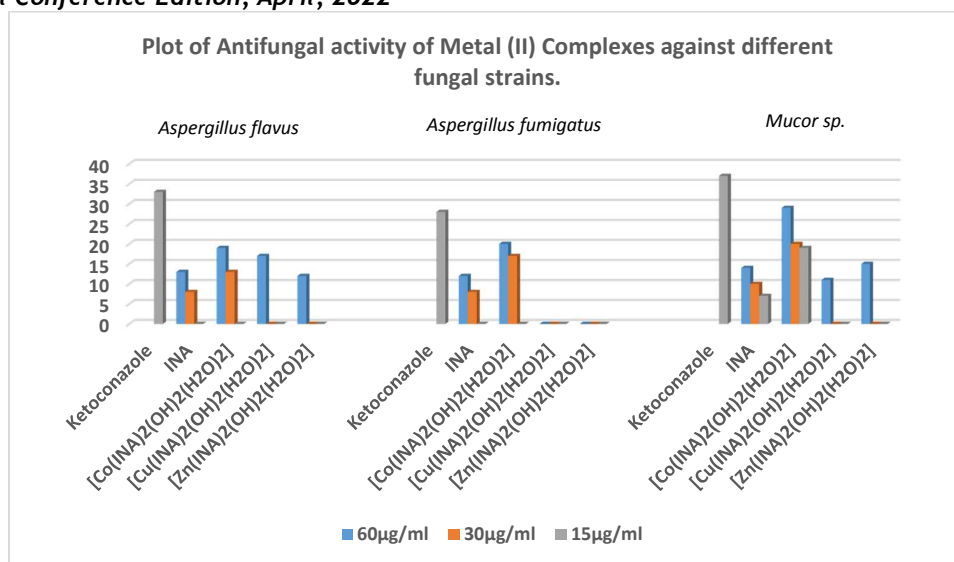


Fig. 4: Plot of Antifungal Activity of Metal (II) Complexes against *Aspergillus flavus*, *Aspergillus fumigatus* and *Mucor specie*.

As expected, the ligand was found to be active against all bacterial and fungal strains. Furthermore, the metal (II) complexes showed an increase in activity compared to the free ligand (Fig. 3 and 4). This indicates that the increase in activity is a result of a synergistic effect between the biologically active Isonicotinic acid coupled with bioactive metal ions.

CONCLUSION

Liquid-assisted grinding of Isonicotinic acid with Co (II), Cu(II), and Zn(II) resulted in colored metal (II) complexes with a distorted octahedral geometry. The isonicotinic acid served as a

monodentate ligand, binding through the nitrogen of the pyridine ring in the transposition. While oxygen atoms of the two hydroxyls and two water molecules occupy the axial position. The antimicrobial test conducted revealed that the ligand and its metal (II) complexes are all potent and biologically active against the tested pathogens. This is even more impressive because the metal complexes have shown more activity than the free ligand, which is even more remarkable. Indicating the effectiveness of metal chelation in enhancing the biological activity of bactericidal agents and prescription drugs.

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