

CHELATION, CHARACTERIZATION AND ANTIBACTERIAL ACTIVITIES OF SOME MIXED ISONICOTINIC ACID HYDRAZIDE - PARACETAMOL METAL DRUG COMPLEXES

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Abstract

The structural properties of new Zn(II), Cu(II), and Cd(II) complexes bearing isonicotinic acid hydrazide and paracetamol ligands have been investigated. The newly synthesized compounds were characterized by various techniques such as FT-IR, elemental analysis, atomic absorption spectroscopy, conductivity measurement, magnetic susceptibility, and powdered x-ray diffraction. Based on the FT-IR of the new complexes, it was observed that the ligands act as bidentate donors. Other spectral and analysis confirms the synthesis of the compounds and their coordination with the ligand. The as-synthesized compounds were screened for potential antibacterial activity against some isolated organisms: *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Based on the results obtained, the assay revealed broad-spectrum antibacterial agents. The complexes were found to exhibit higher potency than the free parent ligands with no activities. According to powdered XRD data, Zn and Cd complexes were found to possess hexagonal crystal except for Cu, which is face centred cubic.

Keywords: Isonicotinic acid hydrazide, paracetamol, metal-drug, complexes, antibacterial

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Introduction

Isonicotinic acid hydrazide is an anti-tuberculosis drug used as chemotherapy for the treatment of tuberculosis. It shows impact with the microbial cells (Marcos *et al.*, 2010). Research has created more interest in the utilization of metal drug complexes to cure different human diseases (Shazia *et al.*, 2010). It has been discovered in past years that the interaction of metal ions in complexes helps to enhance the effectiveness of the complexes as therapeutic agents (Warra, 2011; Baile *et al.*, 2015). Many drugs exhibit the pharmacological and toxicological properties when administered in the form of metal-drug complexes which is of great interest (Sedher and Agwal, 2010). Presence of metal ions helps to quicken the actions of the drug (Emma, 2011; Reena *et al.*, 2011). Also, the presence of transition metals in the environment is at a low concentration because human may inhale it and cause chronic diseases to the body system (Abu Dief and Nassr, 2015). Metal-drug complexes have increased their interest as potential therapeutic or diagnostic agents, most notably since the anti-cancer drug (cisplatin) was discovered. The properties of metal drug complexes are used for the production of agents with optimal properties for their biological functions. It has been observed that some metal drug complexes are used clinically (Emori and Gaynes, 1993).

More research is still on-going to discover new alternative drugs. Discovery of some antimicrobial agents is necessary because of the resistance acquired by different microorganisms. Increase in *Staphylococcus aureus* resistant to antituberculosis has increased to high levels in different of the nations. Furthermore, novel compounds are to be discovered in order to enhance antimicrobial activities of drugs against resistance menace as corroborated by Jegede (2005) and Alam *et al.* (2012). From previous researches, complexes with nitrogen and oxygen donor atoms play an important role in the antimicrobial and anticancer activities of the complexes with activities higher than the parent ligands (Mustapha *et al.*, 2014). In past studies, some compounds have been reported to exhibit antimicrobial and anticancer

activities higher than their parent drugs such as cis-platin and cloxacillin (Lawal and Obaleye, 2007; Harminder *et al.*, 2013). The aim of this research work is to synthesize Zn(II), Cu(II), and Cd(II) complexes bearing isonicotinic acid hydrazide and paracetamol ligands and evaluate their potential against disease control.

Materials and Methods

Isonicotinic acid hydrazide was obtained from Sigma Aldrich Chemical Company and paracetamol from Rajrab pharmaceutical company, Ilorin, Kwara State, Nigeria without further purifications. The metal salts were collected from the Chemistry Department, University of Ilorin, Ilorin, Nigeria. Chemicals and reagents used were of analytical grade without further purification. They were obtained from BDH Laboratory Supplies. Poole BH 151 TD, England.

The melting point of the ligands and the complexes were carried out using Stanford research system melting point apparatus at STEP B, the Department of Chemistry, University of Ilorin, Ilorin, Nigeria. The infra-red spectroscopy was carried out using KBr pellets within 4,000-400 cm^{-1} range spectrophotometer at Redeemer University, Ogun, Nigeria. Conductivity measurements were also done at the Department of Chemistry, University of Ilorin, Ilorin, Nigeria. It was done on Jenway 4510 conductivity meter with a cell constant 1.38. Elemental Analysis was done at Medac limited, Brunel science, Egham, United Kingdom to determine the percentage of chemical elements (C, H, N) present in the complexes. The PXRD was carried out at Ahmadu Bello Zaria using Rigaku-190E42.

Synthesis and Characterization of The Complexes

The complexes $[\text{Zn}(\text{PCM})(\text{ISO})\text{Cl}_2]$, $[\text{Cu}(\text{PCM})(\text{ISO})\text{Cl}_2]$ and $[\text{Cd}(\text{PCM})(\text{ISO})\text{Cl}_2]$ were prepared from previous report with modifications (Tella 2008). 1 mmol of

paracetamol (PCM), 1 mmol of the metal salts and 1 mmol of isonicotinic acid hydrazide (ISO) were weighed into separate beakers and dissolved in 20 ml of acetone, 20 ml of distilled water and 20 ml of ethanol respectively. The three solutions were mixed, giving rise to a clear solution. The clear solution was then refluxed for 4 h, allowed to cool and left for days. The precipitate formed was filtered, washed, dried, and stored in a desiccator for further analysis.

Conductometric Measurements

Conductometric measurements were carried out using a Jenway 4510 conductivity meter at temperature a rate of 25°C in a DMSO solution (10^{-2} M). The undecomposed complexes in this solvent were utilized for determining the conductivity of these solutions for about 2 h of the dissolution and compared with the initial conductivity (Mariana *et al.*, 2013).

Antibacterial Screening

About seven gram of nutrient agar was measured into a sterilized H₂O (250 ml) and was thoroughly mixed. The mixed agar was heated for 15 minutes and then sterilized in an autoclave at 121°C for 24 h. The agar was transferred into the clean sterilized petri-dish and left to set. Holes were drilled in the prepared agar using a sterilized hole borer. Cotton wool swabs were deep inside the pure culture of the organisms and rubbed the surface of the agar. Different concentrations of the complexes in solution were introduced into the drilled hole and incubated at a degree of 37°C for 24 h. Zone of inhibitions was observed around the hole signifying the

antibacterial activity of the test compounds against the selected organisms (Bamigboye *et al.*, 2012).

Results and Discussion

Chemistry of the Compounds

The elemental analyses di in Table 1 are in good agreement with a 1:1 metal to ligand stoichiometry for all the complexes (Figure 1), giving rise to the complex type: [M(PCM)(ISO)Cl₂] (where M = Zn(II), Cu(II), Cd(II); PCM = paracetamol; ISO = isonicotinic acid hydrazide). They are stable in air. Based on the conductivity measurements in DMSO, the complexes are non-electrolytic in character, suggesting that the chloride ions are coordinated to the metal ion (Anacona and Gladys, 2005). The experimental percentage of the elemental analysis (C, H, N) of the complexes as listed in Table 1 corroborate to

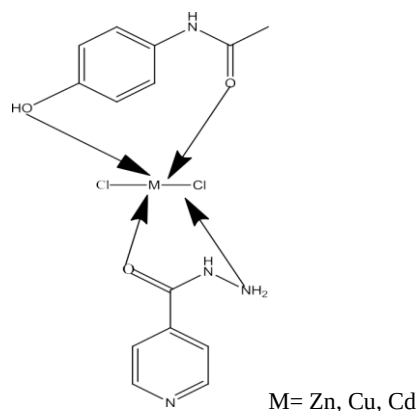


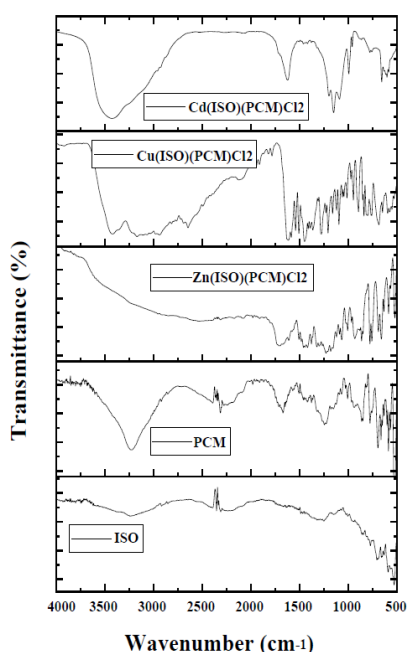
Figure 1. Proposed Structure of the complexes

Table 1. Analytical data of the mixed isonicotinic acid hydrazide - paracetamol complexes

Ligands/Complexes	Percentage Yield	Melting Point	Colour	Elemental Analysis			Metal contents	Magnetic Moment (BM)
				% Theoretical	(Expt.)			
				C	H	N		
Isonicotinic acid hydrazide	-	340	White	-	-	-	-	-
Paracetamol	-	169	White	-	-	-	-	-
[Zn(PCM)(ISO)Cl ₂]	75	>360	White	39.82	3.75	13.24	15.37	0.48
				(39.45)	(3.32)	(13.31)	(15.00)	
[Cu(PCM)(ISO)Cl ₂]	70	>360	Blue	39.72	3.78	13.27	15.13	1.73
				(39.23)	(3.84)	(13.44)	(15.98)	
[Cd(PCM)(ISO)Cl ₂]	40	>360	White	35.67	3.39	11.89	23.78	1.22
				(35.93)	(3.42)	(11.99)	(23.13)	

Table 2. Infrared data of the mixed Isonicotinic Acid Hydrazide - Paracetamol complexes

Ligands/Complexes	$\nu(\text{O-H})$	$\nu(\text{C=N})$	$\nu(\text{C=O})$	$\nu(\text{N-H})$	$\nu(\text{M-O})$	$\nu(\text{M-N})$
Isonicotinic acid Hydrazide	-	1,555	1,625	3,398		
Paracetamol	3,400	-	1,618	3,380	-	-
[Zn(PCM)(ISO)Cl ₂]	3,481	1,525	1,671	3,430	536	619
[Cu(PCM)(ISO)Cl ₂]	3,462	1,529	1,634	3,491	625	628
[Cd(PCM)(ISO)Cl ₂]	3,428	1,503	1,644	3,320	516	530

**Figure 2. FT-IR spectra of the ligands and their complexes**

the calculated values. The metal contents in each of the compounds were estimated using the atomic absorption spectroscopy ranging from 15.00% to 23.78%. These are in good agreement with the proposed structure for all the complexes. Melting point values of the complexes were observed to be higher than those of the ligands, indicating the formation of complexes.

FT-IR Analysis of the Compounds

The IR spectra of the complexes and their parent ligands are shown in Table 2. The results demonstrate a shift in the $\nu(\text{C=N})$ band, observed at 1,555 cm^{-1} in the isonicotinic acid

hydrazide (Figure 2), to 1,525 cm^{-1} in [Zn(PCM)(ISO)Cl₂], 1,529 cm^{-1} in [Cu(PCM)(ISO)Cl₂], and 1,503 cm^{-1} in [Cd(PCM)(ISO)Cl₂]. The $\nu(\text{O-H})$ band observed at 3,400 cm^{-1} in the paracetamol were observed to shift to higher values in the three complexes formed. The $\nu(\text{M-O})$ bands were observed at 536 cm^{-1} , 625 cm^{-1} and 516 cm^{-1} in the [Zn(PCM)(ISO)Cl₂], [Cu(PCM)(ISO)Cl₂], and [Cd(PCM)(ISO)Cl₂] complexes respectively while the $\nu(\text{M-N})$ were observed at 619 cm^{-1} , 628 cm^{-1} , and 530 cm^{-1} in the [Zn(PCM)(ISO)Cl₂], [Cu(PCM)(ISO)Cl₂], and [Cd(PCM)(ISO)Cl₂] respectively (Ejidike and Ajibade, 2015). From the spectra of the chloride complexes, it indicates that a broadband in the region 3,428-3,481 cm^{-1} due to stretching vibration of O-H group (Bamigboye *et al.*, 2012; Ejidike and Ajibade, 2015). The stretching vibration of $\nu(\text{N-H})$ group observed around 3,398 cm^{-1} and 3,380 cm^{-1} in the isonicotinic acid hydrazide and paracetamol respectively, were observed around regions 3,320-3,4891 cm^{-1} (Figure 2) in the complexes (Bamigboye *et al.*, 2012; Ejidike and Ajibade, 2015). Presence of chloride ion in the complexes was tested using silver nitrate, it was observed that no precipitate of silver halide occurred. This confirms the presence of chloride ion in the coordination sphere of the complexes (Tella, 2013). Octahedral geometry has been proposed for all the complexes. With paracetamol, coordination occurred through the oxygen of the hydroxyl group and carbonyl group, while the binding site was vis the oxygen of the carbonyl group and nitrogen of the amine group with isoniazid ligand. The conductometric measurement of the complexes was measured in DMSO, as shown in Table 3. The results obtained confirmed that they are covalent in nature (Zayed and Abdullah, 2005).

Conductivity Measurement and Magnetic Susceptibility

According to previous reports, the conductivity measurement obtained for all the complexes are in good agreement with the assigned formula for a 1:1 electrolyte in DMSO (Adriano *et al.*, 2004; Osanai *et al.*, 2006). The conductivity was carried out in the same solutions after 48 h, and no significant

changes were observed showing that the complexes are stable.

The Zn complex is diamagnetic in character exhibiting octahedral geometry with magnetic moment of 0.48 BM (Raman *et al.*, 2004). Cu complex has a magnetic moment of 1.73 BM and octahedral geometry, indicating anti-ferromagnetism (Ndahi and Wakil, 2015).

Antibacterial Activities of the Compounds

Table 4 shows the result of the antibacterial activity of the synthesized metal complexes ($[\text{Cd}(\text{PCM})(\text{ISO})\text{Cl}_2]$, $[\text{Cu}(\text{PCM})(\text{ISO})\text{Cl}_2]$ and $[\text{Zn}(\text{PCM})(\text{ISO})\text{Cl}_2]$) evaluated by measuring the zone of inhibition for each bacterial against each complex. The results show that the metal complexes were effective against the gram-positive and gram-negative bacteria used (Figure 3). The highest activity was observed for $[\text{Cu}(\text{PCM})(\text{ISO})\text{Cl}_2]$ against *Bacillus subtilis* while the least activity was observed for $[\text{Zn}(\text{PCM})(\text{ISO})\text{Cl}_2]$ against *Staphylococcus aureus*. $[\text{Cu}(\text{PCM})(\text{ISO})\text{Cl}_2]$ complex exhibited the highest antibacterial activity against *Staphylococcus aureus*. The synthesized complexes generally showed lower activity against the 40 ppm solution of *Staphylococcus aureus* as compared to the activity against the 20 ppm solution. Paracetamol and isoniazid exhibited no inhibition against the isolated microorganisms (More and Sontakke, 2013). All the metal complexes were found to be highly effective antimicrobial agents against the tested organisms (Osanai *et al.*, 2006). The above funding confirms the potentials of the tested compounds as a broad-spectrum antibacterial agent. From previous research, metal complexes are more effective than their parent ligands because of coordination,

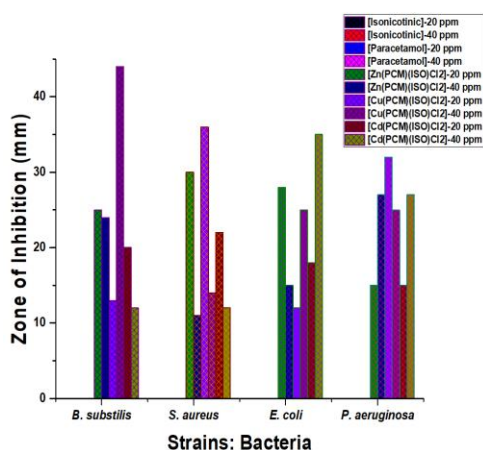


Figure 3. Antibacterial activities of the ligands and their complexes

Table 3. Conductivity ($\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$) in DMSO at 25°C of mixed Isoniazid-Paracetamol complexes

Complexes	Conductivity ($\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$) at 25°C
$[\text{Zn}(\text{PCM})(\text{ISO})\text{Cl}_2]$	25
$[\text{Cu}(\text{PCM})(\text{ISO})\text{Cl}_2]$	27
$[\text{Cd}(\text{PCM})(\text{ISO})\text{Cl}_2]$	31

Table 4 Antibacterial activities of the mixed Isonicotinic Acid Hydrazide – Paracetamol complexes

	<i>Bacillus subtilis</i> (ppm)		<i>Staphylococcus aureus</i> (ppm)		<i>Escherichia coli</i> (ppm)		<i>Pseudomonas aeruginosa</i> (ppm)	
	20	40	20	40	20	40	20	40
Isonicotinic acid hydrazide	0	0	0	0	0	0	0	0
Paracetamol	0	0	0	0	0	0	0	0
$[\text{Zn}(\text{PCM})(\text{ISO})\text{Cl}_2]$	25	24	30	11	28	15	15	27
$[\text{Cu}(\text{PCM})(\text{ISO})\text{Cl}_2]$	13	44	36	14	12	25	32	25
$[\text{Cd}(\text{PCM})(\text{ISO})\text{Cl}_2]$	20	12	22	12	18	35	15	27

which helped to reduce the polarity of the metal atom present (Ejidike, 2018). All the complexes are effective against all the organisms. It has been observed that all the compounds may show some useful way of understanding the antibacterial mechanism of the ligands on these organisms (Adriano *et al.*, 2004). The non-effect of paracetamol and isoniazid against the tested organisms showed that they are harmless at the concentrations of 20 ppm and 40 ppm. This confirms the activity

of the ligands as pain killer (Harminster *et al.*, 2013). The findings from this study demonstrate that at a low concentration (20 ppm) of metal complexes, it can select resistant towards *B. subtilis*, *S. aureus*, *E. coli* and *P. aeruginosa* variations, and the selective effects varied among strains and species. These inconsistencies could be partly elucidated by the dissimilar genetic backgrounds of the strains, types of mutations conferring resistance, resistance features at type and species levels, and costs of fitness (defined as reduced competitiveness in the absence of test compounds) connected with the mutations (Andersson and Hughes, 2012; Bernier and Surette, 2013).

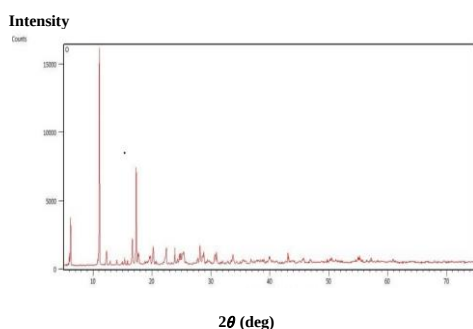


Figure 4. Powdered X-ray diffraction of Cu complex Intensity

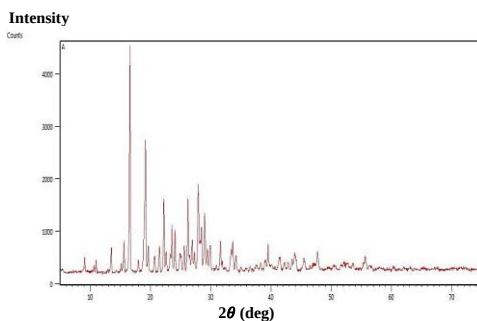


Figure 5. Powdered X-ray diffraction of Cd complex

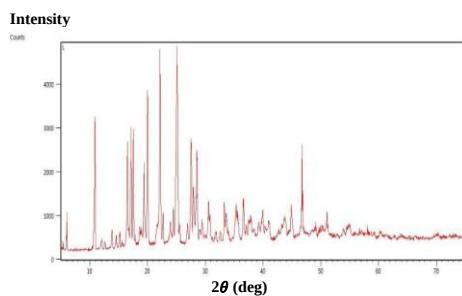


Figure 6. Powdered X-ray diffraction of Zn complex

Powdered X-ray Diffraction

The X-ray diffraction of the complexes is crystalline in character. The purpose of the study is to obtain evidence of the structure and geometry of the metal drug complexes (More and Sontakke, 2013). The powdered X-ray diffraction of the compounds was analyzed using X-ray diffractometer with copper as anode material, K- alpha. The powdered XRD diffractogram for Cu, Cd, and Zn complexes are presented in Figures 4-6. The X-ray diffraction pattern showed the crystalline nature of the compounds. They showed sharp peaks with crystalline phases (Ejidike and Ajibade, 2015). The value of $\sin 2\theta$ for each of the peaks were obtained by cell parameter. Based on the diffractogram, it was observed that ligands are quite different from their complexes which are assigned to a crystalline form. The compounds have a crystalline size of 35 nm, 39 nm, and 30 nm respectively. It indicates that the complexes are in crystalline form. The average size of the crystalline structure was determined using Scherer's formula (Oberoi *et al.*, 2005; Ejidike, 2018).

$$d_{\text{XRD}} = \frac{0.9 \lambda}{\beta(\cos \theta)}$$

This diffraction patterns of the peaks showed a relative intensity above 10%. The XRD is very dependable to give information of solid systems based on the interaction between materials. The interactions result in new

diffraction peaks when compared to the constituent element (Neelima *et al.*, 2016). From the previous report, the XRD peaks was indexed as a figure of merit to be 8.0. The density of the compound has been evaluated by floatation method in sodium chloride solution (Yuliandra *et al.*, 2018).

Conclusions

Mixed metal drug complexes of paracetamol and isoniazid were synthesized in 1:1 mole ratio (M:L). The synthesized complexes were characterized using different techniques such as melting point, conductivity measurements, infrared, atomic absorption spectroscopy and elemental analysis and magnetic moments. The infrared spectral studies showed that the coordination of the ligands to the complexes occurred through nitrogen and oxygen atoms. Magnetic moment data corroborated an octahedral geometry for the metal complexes. The conductance measurements of the complexes in DMSO showed that they are non-electrolyte. The complexes were found to be crystalline in nature as revealed by PXRD. The antibacterial activities of the compounds against the isolated organisms indicated that the complexes showed a broad spectrum against the microorganisms.

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