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Synthesis, Characterization and Antimicrobial Activities of Pyrrolidin-2-ylidene-2,(4-chlorophenyl) Semicarbazone and Its Cd(II) Complex

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

A novel Schiff base ligand has been prepared by condensation between 4-chlorophenyl semicarbazide and 2-pyrrolidone in the presence of glacial acetic acid. The ligand and its Cd(II) complex were characterized using GC-MS, UV-Vis., IR, XRD, conductivity, melting point

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measurements and magnetic studies. The results of conductivity tests revealed that Cd(II) complex is good electrolyte while the ligand exists as a neutral molecule. Single crystal x-ray studies revealed that the ligand and its Cd(II) complex are pure crystals with respective space group symmetry of $p3_121$ and p63/mmc. The Cd(II) complex of the ligand is diamagnetic with square pyramidal geometry. Absorption bands for N^4-H and N^1-H stretches of amide and pyrrolidone moiety were observed at 3413 and 3310cm-1, while respective absorption bands at 1885, 1650, 1540, 1353 and 817cm^{-1} are indicative of the presence of C=C, C=O, C=N, C-H, C-Cl functional groups in the ligand. The emergence of infra red absorption bands at 427 and 411cm^{-1} in the complex revealed that the ligand is bidented and coordinates the metal ion through pyrrolidone nitrogen and the carbonyl oxygen. The ligand and its Cd(II) complex were tested at doses of 500 and 1000µg/ml in vitro antibacterial activities against *S. aureus*, *E. coli*, *K. pneumonia*, *B. subtilis* and antifungal activities againt *A. flavus* and *C. albicans* using ampicilin and fluoconazole as standard drugs and DMSO solution as control and solvent in all cases which revealed that the free ligand showed less inhibitory activities than the metal complex against gram positive (*S. aureus, B. subtilis),* gram negative*(E. coli, K. pneumonia)* bacteria and fungi*(C. albicans,A. flavus).*

Keywords: Schiff bases; metal complexes; pyrrolidone moiety; anti-bacterial activities; anti-fungal activities.

1. INTRODUCTION

Semicarbazones, a class of Schiff bases with the presence of imine group which impart biological activity, have proved the efficiency and efficacy in combating various diseases [1]. It is of great interest because of their chemistry and potentially beneficial biological activities such as anticonvulsant, antianhythmic [2], antiviral [3], antimalarial [4], antitubercular, cytotoxic, antibacterial and antifungal (Pandeya *et al*., 2000) activities. Recently, growing consideration have been paid to the preparation of N-heterocyclic compounds because of their beneficial pharmacological properties and their role as main intermediate and fine chemicals in pharmacological and organic chemistry [5] and are proper forerunner for unusual β-amino acids such as statin and its analogues. Many pyrrolidinones are the construction blocks of abundant natural products such as Pyrrocidine A, B [6], Ypaoamide [7], Lactacystin (Omura et al, 2003), (-)- Azaspirene [8] that is a new inhibitor of angiogenesis which was isolated from the fungus Neosartorya sp. Oteromycin, as a white powder, and also from two various strains of an unidentified fungus. Functionalized dihydro-2-oxypyrroles ring available in some of the alkaloids possesses broad pharmaceutical effect and they are also utilized as optoelectronic materials [9], HIV integrase inhibitors [10], receptors of vascular endothelial growth factor [11], antibacterial and antifungal, nootropic agents [12], peptidomimetic [13]. Cotinine is a common main 2-pyrrolidinone, an alkaloid reported in tobacco and is also the main metabolite of nicotine [14]. Ethosuximide is a succinimide anticonvulsant, utilized principally in the absence of seizures [15]. A great deal of information are available in the literature on the antibacterial and antitumor activities of 4,6-dimethoxy-1H-indole derivatives and on antibacterial and antioxidant activities of Schiff bases containing 1,2,3-triazole and tetrazole derivatives and related compounds [16,17]. This work is designed to explore the synthesis, characterization and antimicrobial activities of 4-chlorophenylsemicar- bazone having pyrrolidone moiety and some metal complexes.

2. EXPERIMENTAL

All reagents used in this work are of analytical grade and were obtained from directly from Aldrich Chemical Co. Inc. The reagents were used as starting materials for synthesis of more complex compounds without further purification. Metal salts were obtained from E. Merk and distilled water that was purchased from Chifok Scientific Co. (Nig.). Culture broths, Muller Hinton Agar, yeast, mould were obtained from Microbiology Department of Nnamdi Azikiwe University, Awka, Nigeria. Melting points were determined using capillary tube, Molar conductivity was measured in deionized water at 25^oC using a WTW conductivity meter. The infra red (FTIR) spectra were recorded using FTIR.8300 Shimadzu Spectrophotometer using CsI disc in the frequency range of 4000-400cm^{-1}. The ultra violet-visible spectra of the ligand and complexes will be recorded by using ultrospec. 2100 pro. ultra violet Spectrophotometer in the range of 200-800nm.Mass Spectra were recorded using gas chromatography-mass

spectrophotometer (QP2010 plus, shimadzu), crystallinity was measured using x-ray diffractometer (PANalytical X' pert PRO MPD), Magnetic susceptibility was measured using Sherwood scientific magnetic moment balance (MK1 model) and weights were measured using digital balance (Mettler Toledo PL 203).

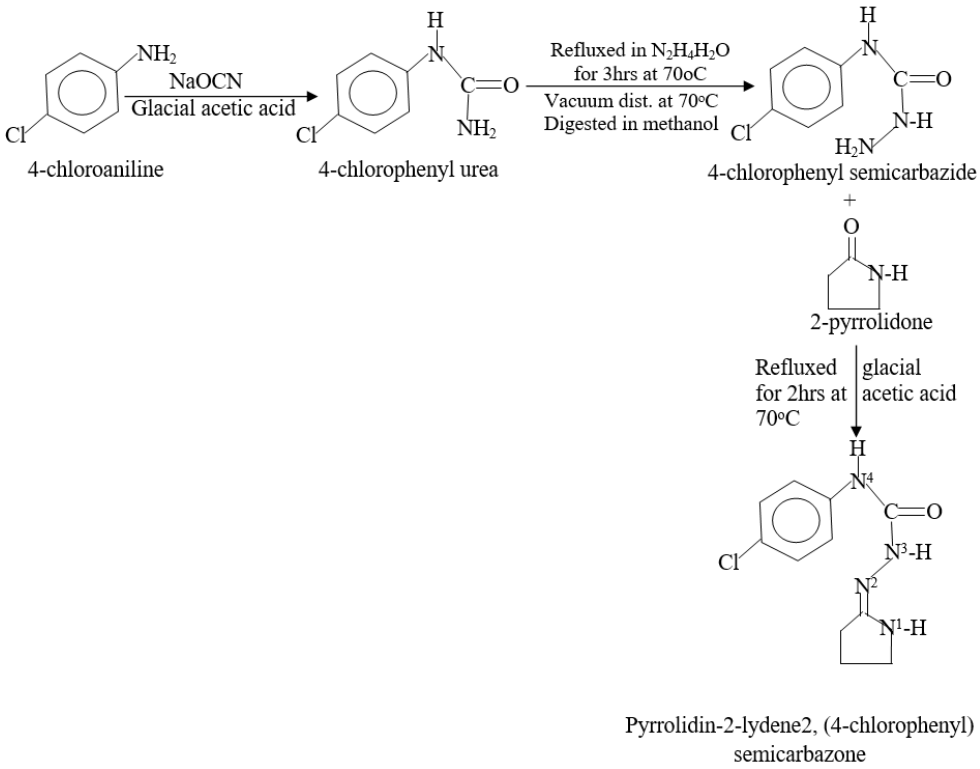
2.1 Synthesis of pyrrolidin-2-ylidene-2,(4-chlorophenyl)semicarbazone (L)

The ligand was synthesised according to the method used by Singh et al. [1] as follows:

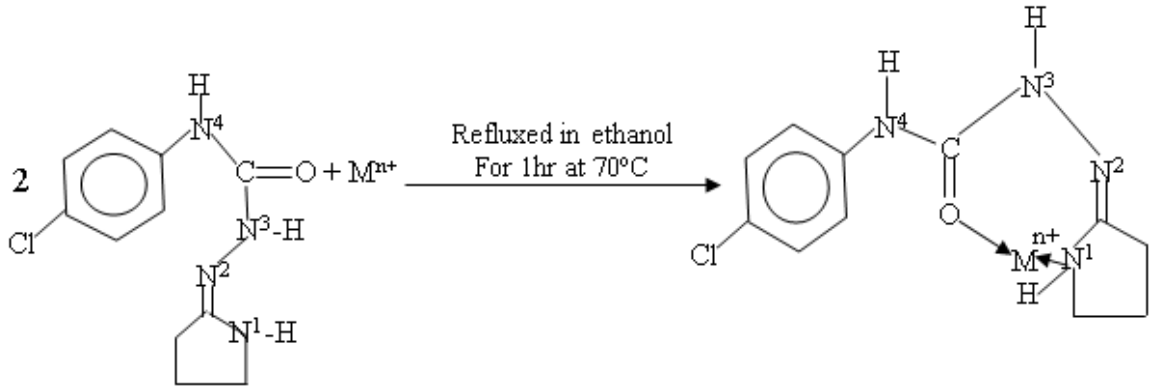
Step1: 4-chloroanaline (0.1M, 1.2757g) was dissolved in 10cm^3 of glacial acetic acid and diluted to 100cm^3 with distilled water. Equimolar quantity (0.1M, 0.33g) of sodium cyanate in 50cm^3 of warm water was added in the previous solution with stirring. The reaction mixture was allowed to stand for 30minutes, and crystals of 4-chlorophenylurea formed were filtered, washed, dried and recrystallised from boiling water.

Step2:60g of 4-chlorophenylurea in 100ml of hydrazine hydrate refluxed for 3hrs. Vacuum distilated at 70^{o}C, the product remaining in the flask was digested with 250ml methanol and refluxed for 45minutes, cooled to room temperature and filtered. The filterate obtained was cooled in ice bath to obtain 4-chlorophenylsemicarbazide crystals which were further purified by recrystallisation from ethanol.

Step3: A solution of the 4-chlorophenylsemicarbazide (0.1M, 2.22g) and equimolar quantity of pyrrolidne (0.1M) in 100cm^3 of ethanol will be refluxed at 70^{o}C for 2hours in the presence of glacial acetic acid (1cm^3). The product obtained after cooling was filtered and recrystallised from 95% ethanol to give pure Pyrrolidin-2-ylidene-2,(4-chlorophenyl) semicarbazone (L) ligand. Yield: 51%, M.p.: 198^{o}C, $C_{11}H_{13}ON_4Cl$(L), Anal. Found: C, 51.50; H, 5.07; O, 6.24; N.21.85; Cl, 13.85%. Calc. C, 52.23; H, 5.15; O,6.34; N, 22.18; Cl,14.06% IR (KBr, ν/cm^{-}): ν(C=O) 1650; ν(C=N) 1540; ν(N4-H) 3413; ν(N1-H) 3310; ν(C-N) 1248; ν(C-Cl) 817. UV-Vis.(DMSO) λ_{max}/cm^{-} 36,765, 31,447. XRD: cell dimension(Å) 4.91, 4.91, 5.43. interfacial angles (◦)90, 90, 120. Volume of unit cell (Å^3), 130.907. GC-MS (m/z): cal., 252.5; found, 256.3



Scheme 1. Synthesis of Pyrrolidin-2-ylidene-2,(4-chlorophenyl)semicarbazone(L)



Where $M^{n+} = Cd^{2+}$

Scheme 2. Synthesis of Cd(II) Complex of Pyrrolidin-2-ylidene-2,(4-chlorophenyl)semicarbazone(L)

2.2 Synthesis of Cd (II) Complex of Pyrrolidin-2-ylidene-2,(4-chlorophenyl)semicarbazone(L)

Cadmium (II) Complex of Pyrrolidin-2-ylidene-2,(4-chlorophenyl)semicarbazone was synthesized according to the method used by Yousif et al. [18] as follows:50cm^{3}of 0.25M ethanolic solution of Cadmium (II) trioxonitrate (V) tetrahydrate [$Cd(NO_3)_2.4H_2O$]. was added to 50cm^{3}of 0.5M ethanolic solution of pyrrolidin-2-ylidene-2,(4-cholrophenyl)semicabarzone and heated under refluxed at 70^{o}C for 1hour and cooled in ice. The product was washed with distilled water and recrystallized from 95% ethanol..Yield: 47%, M.p.: 260^{o}C, $CdL(NO_3)_3$: Anal. Found: C, 26.98; H, 2.66; O, 32.71; N, 20.03; Cl, 7.26; Cd, 10.36%. calc. C, 27.00; H, 2.66; O, 32.73; N, 20.03; Cl, 7.26, Cd, 10.31% IR (KBr, ν/cm$^-$): ν(C=O) 1648; ν(C=N) 1541; ν(N4-H) 3413; ν(N1-H) 3309; ν(C-N) 1248; ν(C-Cl) 817,ν(Cd-N),427; ν(Cd-O), 411. UV-Vis.(DMSO) λ_{max}/cm$^-$: 34,013. XRD: cell dimension (Å) 5.98, 5.98, 9.76. interfacial angles (◦)90, 90, 120. Volume of unit cell (Å^3), 349.022. conductivity(µs/cm), 200; effective magnetic moment, diamagnetic. GC-MS (m/z): cal., 488.9; found, 489.2.

3. RESULTS AND DISCUSSION

The reaction of 4-cholorophenylsemicarbazide with 2-pyrrolidone in the presence of glacial acetic acid yielded the ligand (L); Pyrrolidin-2-ylidene-2,(4-chlorophenyl)semicarbazone (Scheme 1). The reaction of the ligand (L); Pyrrolidin-2-ylidene-2,(4-chlorophenyl)semi carbazone with cadmium trioxonitrate (V) tetrahydrate [$Cd(NO_3)_2.4H_2O$] in 2:1 ligand to metal ratio which yielded the corresponding cadmium (II) complex, $CdL(NO_3)_3$. The ligand and its cadmium (II) complex were isolated as air stable microcrystalline solids in good percentage yield of 51 and 47% respectively (Table 1). While the white colouration of the ligand is seen to result from less conjugated nature of the compound, white colour of the complex is attributed to completely filled d-orbital (d^{10}) configuration in the complex. The melting points of the ligand and complexes suggest that the synthesized compounds are air and moisture stable (Table 1). Observed increase in solubility in water and increase in the melting point of the ligand from 198 to 260^{o}C upon complexation with Cd(II) ion is indicative of metal-ligand bond formation [19]. The complex is a monometallic centred compound. This was deduced from the results of percentage elemental analysis which are in good agreement with the assigned formulations. The theoretically calculated percentage values of elements in the ligand and in complexes are in close agreement with experimental values obtained from the results of gas chromatography-mass spectroscopic analyses.

The infra red spectra of the ligand are almost the same in the regions of 3413cm^{-1} -1540cm^{-1} to those of the corresponding metal complexes. This suggests that the molecular functional groups in both the ligand and the complexes are identical. In Cd(II) complex, the most feasible coordination option is bonding through N^1-H and C=O. This is suggested by variations in the absorption frequencies in the complex (N^1-H at 3309cm-1, C=O at 1648cm^{-1}) compared to that of

the ligand (N^1-H at 3310cm^{-1}, C=O at 1650cm^{-1}). It was also inferred from the infra red results that approach of the ligand was electrostatic [20], thereby compressing the crystal structure of the complex directly through N^1-H and C=O axes, shortening the bond length, strengthening and increasing the bond energies of N^1-H and C=O bonds leading to the observed increase in the absorption frequencies as compared to that of the free ligand.

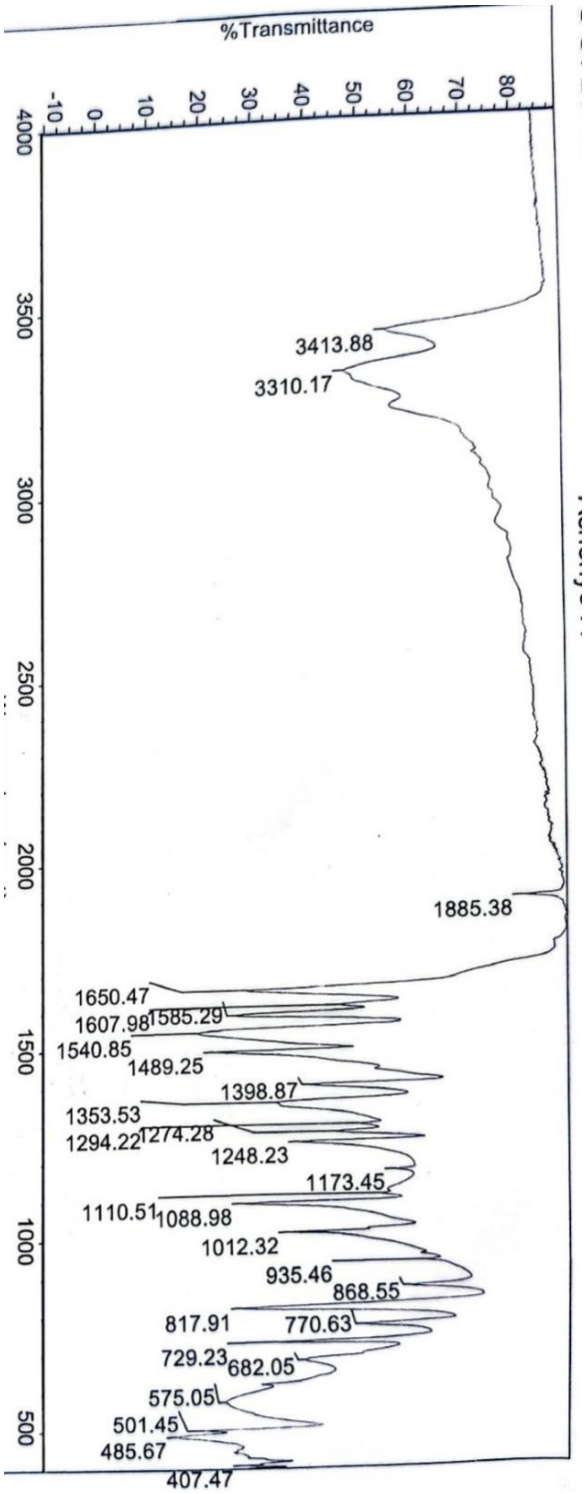


Fig. 1. Infra Red Spectrum of pyrrolidin-2-ylidene-2,(4-chlorophenyl)semicarbazone (L)

Table 1. Physicochemical Properties pyrrolidin-2-ylidene-2,(4-chlorophenyl)semicarbazone (L) and its Cadmium (II) Complex

						% Element found (% calculated)					
S/N	**Compounds**	**Colours**	**Melting Points (°C)**	**Yield (%)**	**Molar mass g/mol**	**%C**	**%H**	**%O**	**%N**	**%CL**	**%M**
1	$C_{11}H_{13}ON_4Cl$(L)	White	198	51	256.3 (252.5)	51.50 (52.23)	5.07 (5.15)	6.24 (6.34)	21.85 (22.18)	1385 (14.06)	- -
2.	$CdL(H_2O)_3\ NO_3$	White	260	41	489.2 (488.9)	26.98 (27.00)	2.66 (2.66)	32.71 (32.73)	20.03 (20.04)	7.26 (7.26)	10.36 (10.31)

Table 2. Selected Infra Red Data of pyrrolidin-2-ylidene-2,(4-chlorophenyl)semicarbazone (L) and its Cadmium (II) Complex

S/N	**Compounds**	**(N^1-H)**	**(N^4-H)**	**(C=O)**	**(C=N)**	**(M-N)**	**(M-O)**
1.	$C_{11}H_{13}ON_4Cl$(L)	3413	3310	1650	1540	-	-
2.	$CdL(H_2O)_3\ NO_3$	3413	3309	1648	1541	427	411

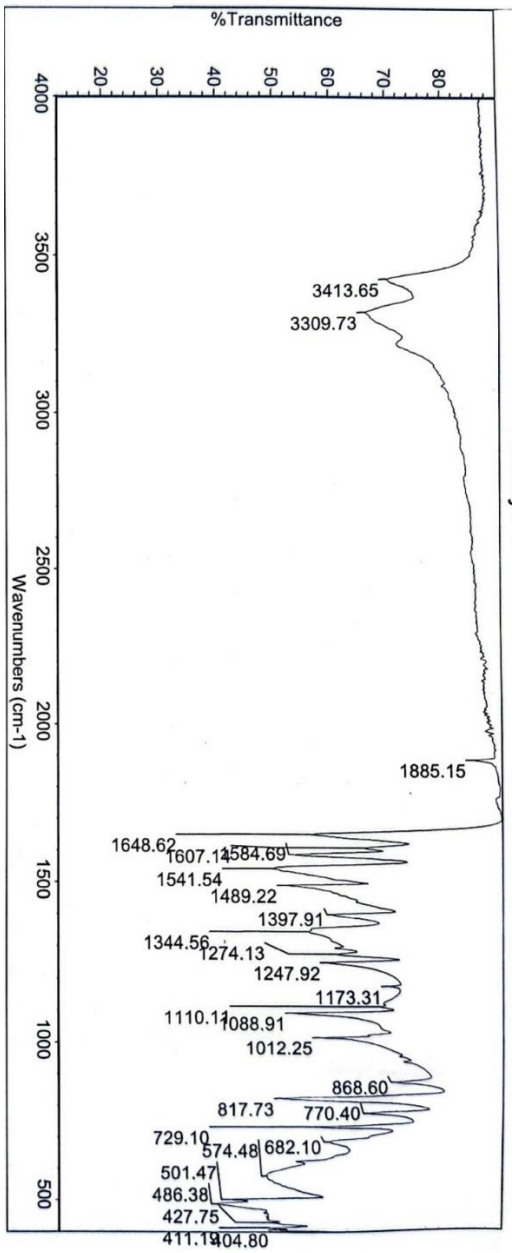


Fig. 2. Cadmium (II) Complex of pyrrolidin-2-ylidene-2,(4-chlorophenyl)semicarbazone (L)

Gas chromatogram of the ligand showed peaks at m/z 429.2, 355.1, 284.3 and 252.5, with at m/z 429.2 result from the interaction between the already formed ligand with 2-pyrrolidone dimer present in the reaction medium. This interaction was necessitated by high tendency of intermolecular hydrogen bond formation between the ligand and coupled 2-pyrrolidone molecules [21]. Upon fragmentation, the two pyrrole rings that make up the 2-pyrrolidone dimer are lost gradually in two step mechanisms. At first, one pyrrole ring is detached leaving behind a cation with m/z 355.1, in the second step, another pyrrole ring fragments out resulting to a cation with m/z 284.3. The fragment with m/z 284.3 then loses an hydroxyl ion and an atom of oxygen to give the ligand peak m/z 256.3. All the observed fragments possess m/z values are in agreement with the calculated values confirming the ligand formation (Fig.3).

While for Cd(II) complex of the ligand,$CdL(NO_3)_3$, the observed $M^{+\cdot}$ism/z 489.2 and the calculated molecular mass is 488.9gmol^{-1}, this shows total agreement between the observed and the calculated molecular masses for the complex.

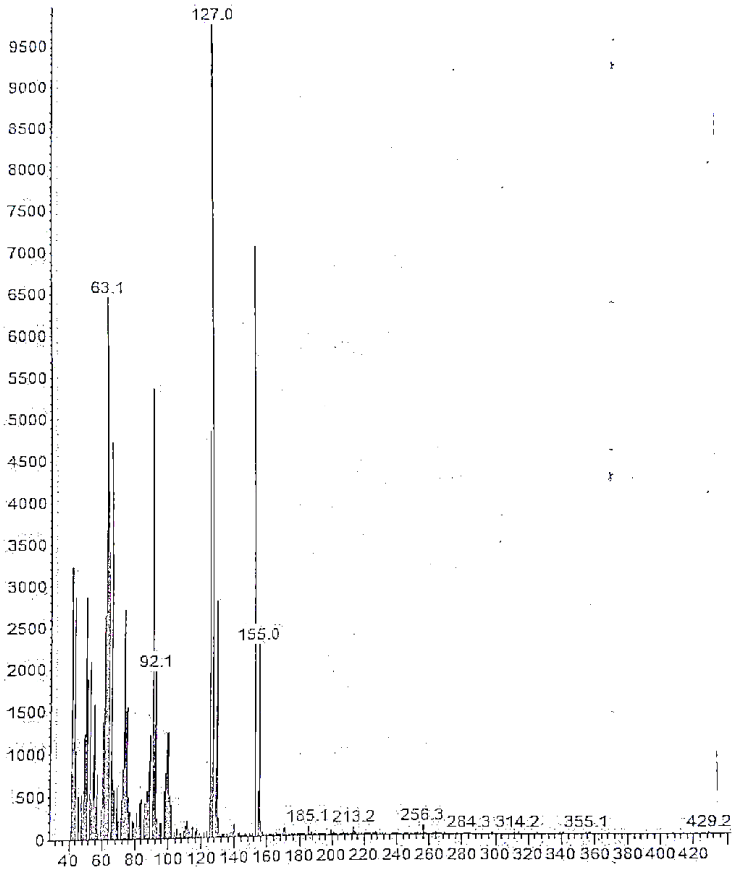


Fig. 3. GC-MS Spectrum of The Ligand

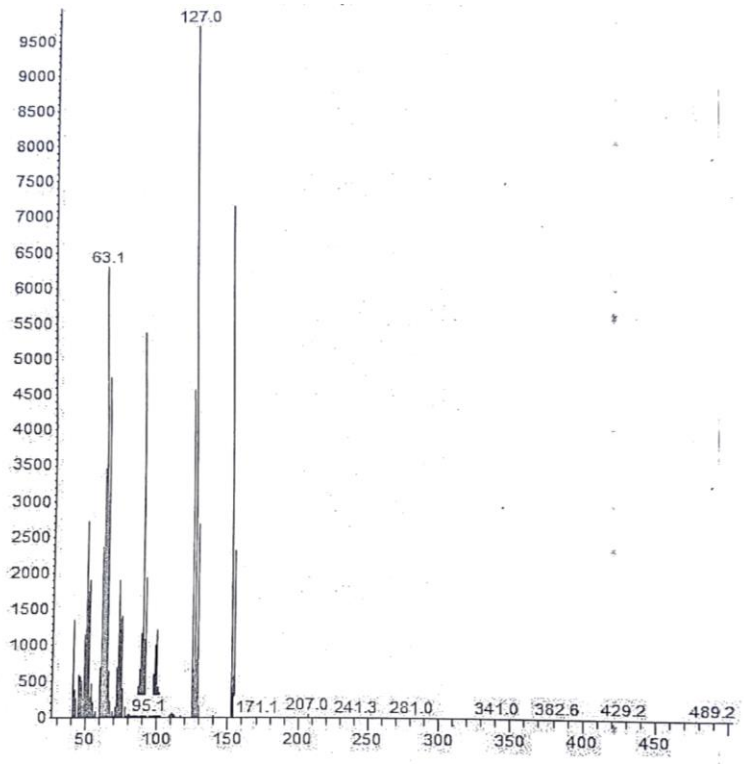


Fig.4. GC-MS Spectrum of Cd(II) Complex of The Ligand

Sharp peaks obtained from the single crystal x-ray analysis of the compounds confirmed that both the ligand and its Cd (II) complex exist as pure crystals. The spectra obtained in this work were interpreted by matching with standard libraries and similar materials in the literature. The ligand was identified to be of $p3_121$symmetry and in trigonal crystal system while Cd (II) complexes of the ligand possessed a symmetry of p63/mmc and hexagonal in shape.

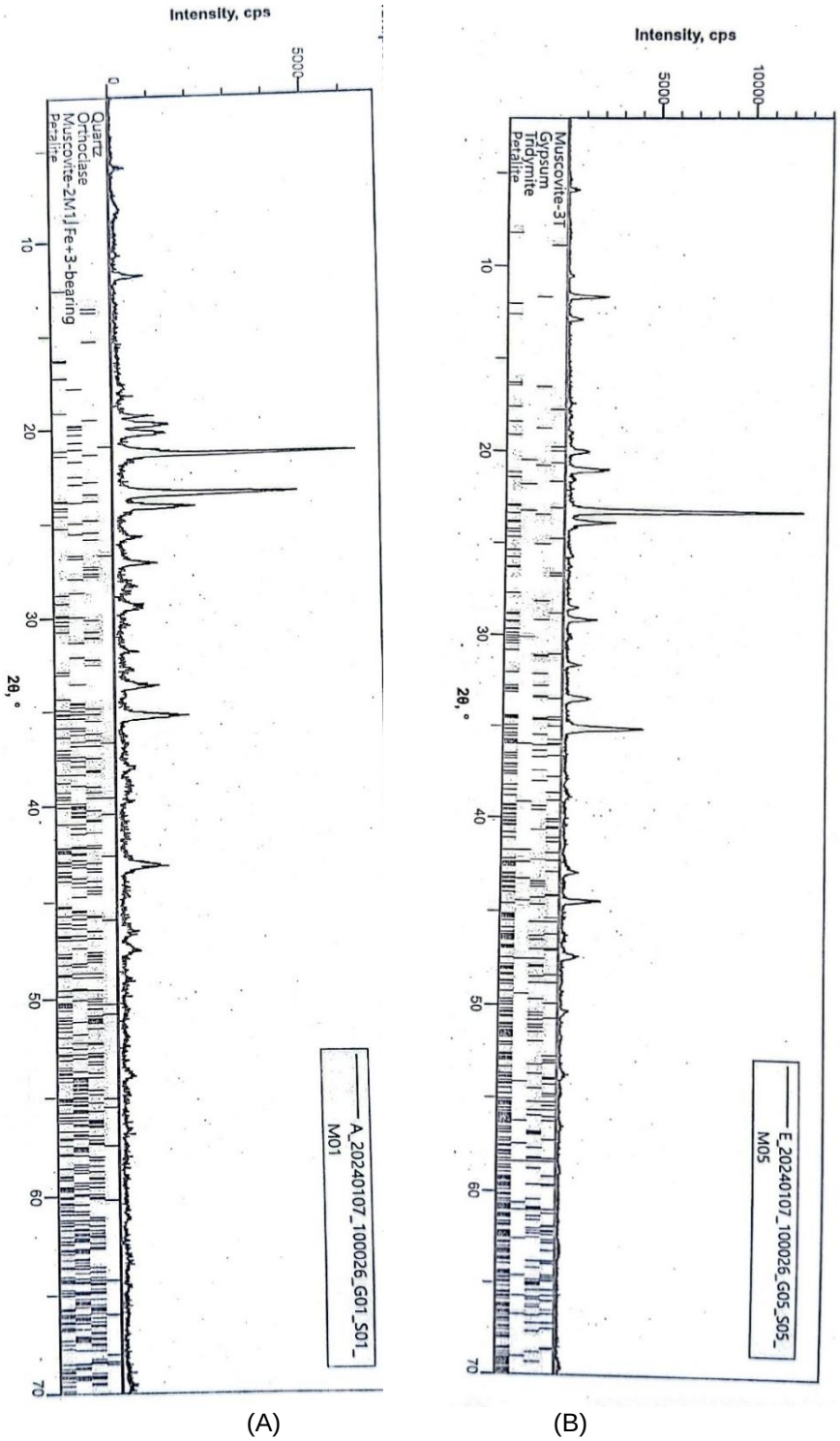


Fig. 5. XRD Spectra of The Ligand (A) and its Cd(II) Complex(B)

Table 3. XRD Data of Pyrrolidin-2-ylidene-2,(4-chlorophenyl)semicarbazone (L) and its Copper(II) Complex

Parameters	$C_{11}H_{13}ON_4Cl(L)$	$CdL(NO_3)_3$
Emperical formula	$C_{11}H_{13}N_4OCl$	$CdC_{11}H_{13}O_{10}N_7Cl$
Formula weight (g/mol)	252.5	489.2
Temperature (K)	298	298
Wavelenght(Mo Kα)(Å)	0.71073	0.71073
Crystal system	Trigonal	Hexagonal
Space group	$P3_121$	P63/mmc
Lattice constant		
a(Å)	4.91	5.98
b(Å)	4.91	5.98
c(Å)	5.43	9.76
α(º)	90	90
β(º)	90	90
γ(º)	120	120
Volume($Å^3$)	130.907	349.022

Spectra of the ligand showed peaks at 36,765cm^{-1} (272nm) and 31,447cm^{-1} (318nm) assignable to π → π* and n → π* transitions respectively. The former transition band arose from the excitation of pi-elections to the next higher energy level which is attributed to the presence of double bonds of the benzene ring that are in conjugation with lone pair of electrons of the anilinic nitrogen group, while the later transition band occurring at 31,447cm (318nm) revealed the excitation of non-bonding electrons to pi antibonding orbitals of the imine ($C=N^2$) functional group. The observed variation in the transitions occurring in the free ligand and those of its metal complexes is indicative of metal-ligand bond formation resulting from complexation [19]. High molar conductivity value of the complex suggests that it can function as a good electrolyte, while the ligand showed no signal on conductivity. This signals the presence of metal ions in the complex which is indicative of complex formation, while the ligand on the basis of its conductivity value could be regarded as neutral molecule.

Proposed Structures of Pyrrolidin-2-ylidene-2,(4-chlorophenyl)semicarbazone (L) and its Copper(II) Complex: From the elemental analysis, observed magnetic moment and the spectral data, structures of the synthesized compounds are suggested as shown in Fig. 3 The structures assigned to these compounds are confirmed by the IR, GC-MS, XRD and UV-Vis. Spectroscopic data and by analysis of the analogous structures available in the literature (Turdor et al., 2007).

Antimicrobial Activitites of Pyrrolidin-2-ylidene-2,(4-chlorophenyl)-semicarbazone and its Cd(II) complex: Pyrrolidin-2-ylidene-2,(4-chlorophenyl)-semicarbazone and its Cd(II) complex were tested in vitro growth the inhibitory activities two gram positive bacteria (*A. Aureus* and*B. Subtilis*), two gram negative bacteria (*E. coli* and *K. Pneumonae**)*** and two fungi (*C. albicans* and *A.flavus*) by standard disc diffusion technique using 100% DMSO as solvent. Effectiveness of antimicrobial agent was based on the diameter of inhibition. Antimcrobial agents were considered effective when the diameter of inhibited zone is 9mm and above, but ineffective or negative when the diameter of inhibited zone is less than 9mm as was adopted from Joseph et al. [22].

Table 4. Electrical Data of Pyrrohdin-2-hydene-2-, (4-chlorophenyl) Semicarbonzone and Its Cd (II) Complex

S/N	Compounds	Conductivity μS/CM	Magnetic Moment (BM)	Absorption Bands (CM^{-1})	Assigned Transitions	Geometry
1.	$C_{11}H_{13}ON_4Cl(L)$	-	-	36,765, 31,447	𝜋→ 𝜋*, n→ 𝜋*	-
2.	$CdL(NO_3)_3$	200	Diamagnetic	34,103	L→Cd(CT)	Square Pyramidal

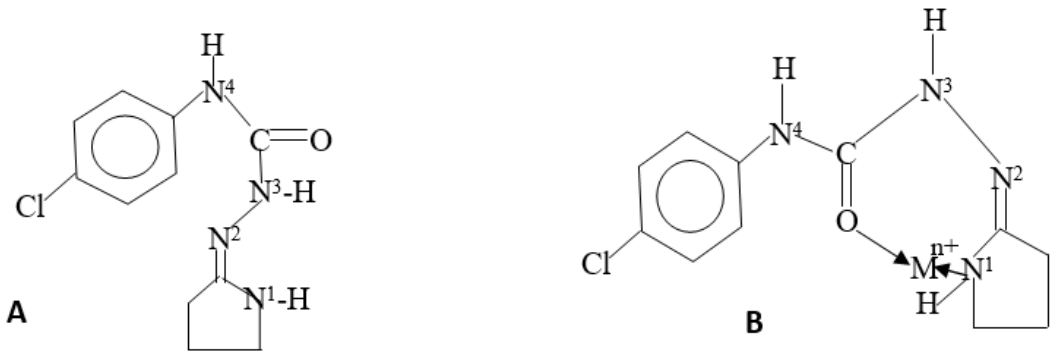


Fig. 6. Proposed Structures of Pyrrolidin-2-ylidene-2,(4-chlorophenyl)semicarbazone (L) and its Cadmium(II) Complex

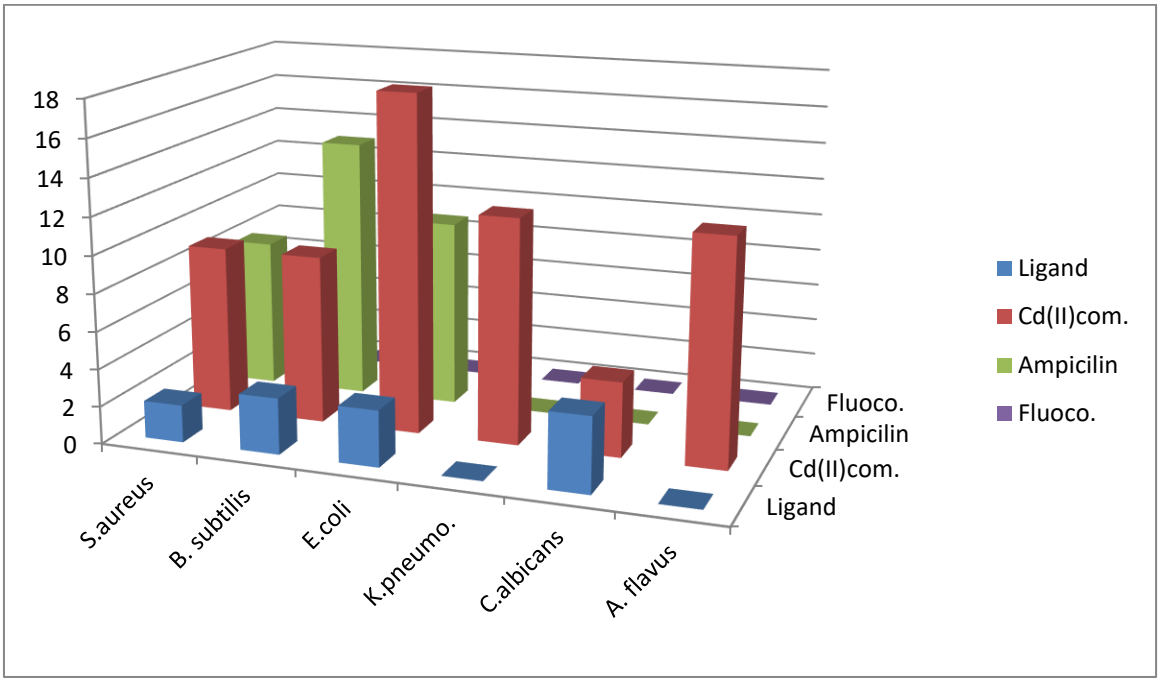


Fig. 7. Antimicrobial Activities of Pyrrolidin-2-ylidene-2,(4-chlorophenyl)semicarbazone (L) and its Cd(II) Complex at 1000µg/ml Dosage

The free ligand did not show appreciable inhibition activity against all bacteria tested while Cd(II) complex caused inhibition of *S.aureus, B. Subtilis*, *E.coli*, *K. Pneumonae*. From the antibacterial activities data, the complex is more potent antimicrobial agent than the free ligand against one or more microorganisms. This is attributable to the hydrophobic nature of the Schiff base ligand, which restricts its permeation to the cells and tissues. In addition, chelation enhances biochemical potential of bioactive organic species (Nair et al. 2012). Cd(II) complex showed high inhibition activity against Gram negative bacteria *(E. coli and K. Pneumonae*) at both low and high doses. This suggests that apart from being a chelate, Cd(II) complex of the ligand possessed some sort of lipophilic characteristics in order to enhance membrane permeability into the outer lipopolysaccharides layers of Gram-negative bacteria (Raman *et al*., 2009).The results of antifungal activities revealed that the ligand showed no observable activity against the test organisms (*C. albicans* and *A. flavus*), while Cd(II)complex of the ligand was only active against *A. flavus* at high dose. In the case of *A. flavus,* the observed resistance against the ligand and its Cd(II) complex (at low dose of 500mg) could be attributed to the development of biofilms which provide temporary antifungal drug resistance and protects the

pathogen in the hostile environment, this is a very common behavior among Aspergillus spp (Paul et al., 2017). The underlying mechanism of resistance in *C. albicans* as observed against the ligand could be attributed to the ability of the organism to bring about alterations in drug targets, due to mutation in target which reduces binding of drug to the target (Sanglard, 2016). The high activities of Cd(II) complex against *C. albicans* and *A. flavus* over the free ligand could be attributed to the presence of metal ions, and its effect on the normal cell membrane. Metal chelates bear polar and nonpolar properties together; this makes them suitable for permeation to the cells and tissues. This is possible because the cell wall is essential for the survival of many organisms and some antibiotics are able to kill them by inhibiting a step in the synthesis of peptidoglycan [23]. Cd(II) complex showed positive activity at respective MIC and MBC of 62.5 and 125 against *S.aureus, E. coli, A. flavous.* In comparison with the ligand which is rated inactive against all organisms studied due to its higher MIC and MBC values, potent bateriacidal behavior of the metal complex can be attributed to the fact that chilation increases solubility, conductivity and π-electron delocalization in metal complexes [19].

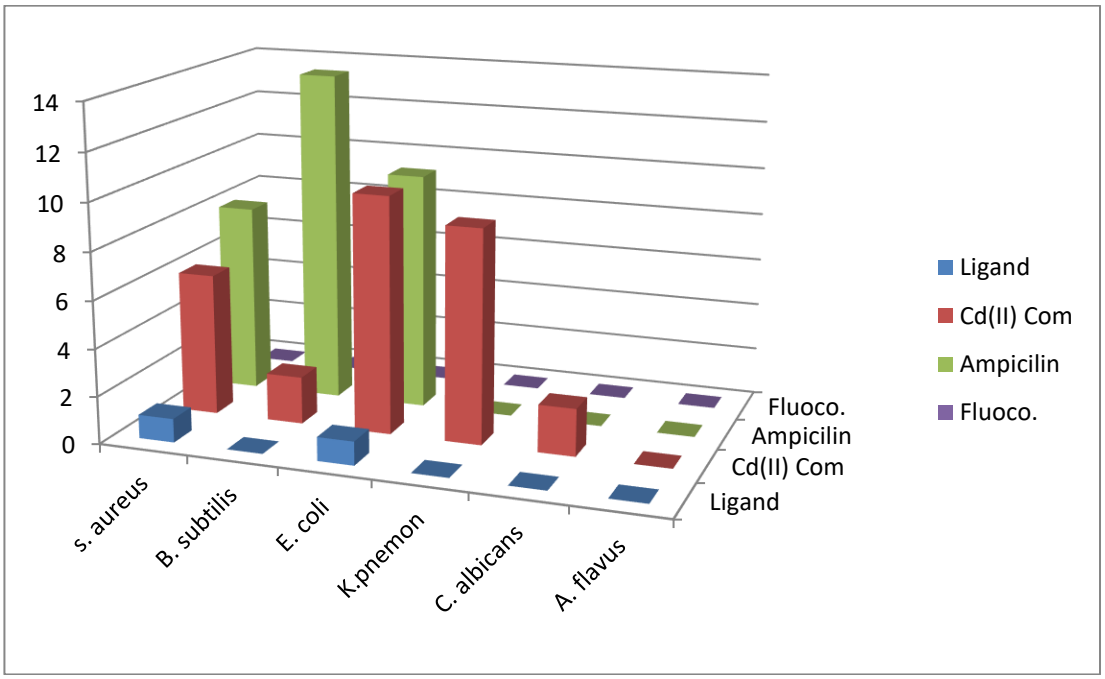


Fig. 8. Antimicrobial Activities of Pyrrolidin-2-ylidene-2,(4-chlorophenyl)semicarbazone (L) and its Cd(II) Complex at 500µg/ml Dosage

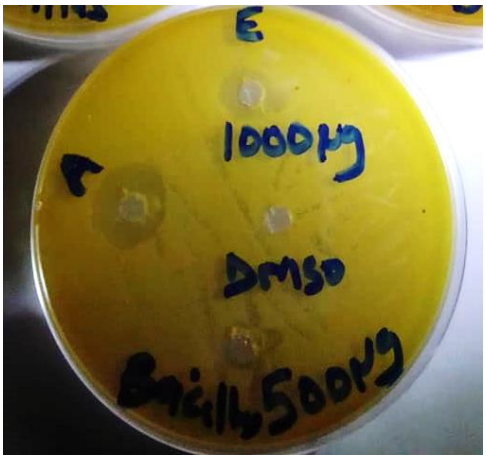


Fig. 9. Bacterial Activities of the ligand(A) and its Cd(II)(B) against *B. subtilis* by disc diffusion method

4. CONCLUSION

The ligand Pyrrolidin-2-ylidene-2,(4-chlorophenyl) semicarbazone (L) and its Cd(II) complex were synthesized and fully characterized. The ligand coordinated to the Cadmium (II) ion through metal-oxygen and metal-nitrogen bond formation to afford the complex. The metal ion was five coordinated in the complex and possessed square pyramidal geometry. Antimicrobial studies on the ligand and its Cd(II) complex revealed that the free ligand showed less inhibitory activities than the metal complex against gram positive (*S. aureus, B. subtilis),* gram negative*(E. coli, K. pneumonia)* bacteria and fungi *(C. albicans,A. flavus).*

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Arthors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during writing or editing of this manuscript.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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