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Novel dinuclear metal complexes of guanidine-pyridine hybrid ligand: synthesis, structural characterization and biological activity

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ABSTRACT

A novel series of metal complexes of guanidine-pyridine hybrid ligand derived from condensation of N, N' dimethylurea and 2-aminopyridine in present of $POCl_3$ have been synthesized. The complexes are characterized by IR, UV-Vis, molar conductance and mass spectroscopy. The low molar conductance values indicate that the complexes are non-electrolytes. Substituted guanidine acts as bidentate ligand toward metal ions. Spectroscopic studies confirmed that the ligand bonded to the metals through the nitrogen atoms. Coordination number of copper complex is four with square planner geometry, while the nickel and cobalt complexes have distorted octahedral geometry. All the synthesized compounds were tested against Gram-negative bacteria; *Escherichia coli*, *Serratia marcescens* and Gram-positive bacteria; *Bacillus sabtilis* and *Staphylococcus aureus* by disc diffusion and micro-broth dilution methods. Guanidine ligand was most effective against *serratia marcescens* (diameters inhabitation zone ranged of ligand between 8-20 mm). The most antibacterial activity of synthesized compounds belong to CoL complex. Its minimal inhibitory concentrations (MICs) against *E. Coli*, *S. aureus*, *B. sabtilis* and *S. marcescens* were 62.5, 125, 125 and 15.62µg/mL respectively. The results of these studies showed that the metal complexes have more antibacterial against species compared to the non-complexed ligand.

Keywords: *guanidine-pyridine hybrid ligand, bidentate ligand, square planner geometry, distorted octahedral geometry, gram-negative bacteria, gram-positive, antibacterial activity.*

1. INTRODUCTION

Guanidines are a class of N donor ligands with high nucleophilic and basicity properties [1-4]. The species containing a Y-shaped CN_3 unit is classified as guanidine [5-7]. These compounds are similar to carbonic acids in which the C=O group has been replaced by a C=NH group and each OH group has been replaced by a NH_2 group [8-10]. In comparison with other nitrogen-containing compounds such as urea, amidine and amide, the coordination chemistry of guanidine has developed slowly, possibly because of its high basicity and consequent ready formation of guanidium cation in the aqueous media of guanidine and its derivatives [11]. Guanidine can coordinate with metals through the unshared electron pair of nitrogen and form stable complexes [12-16].

In recent years, the syntheses of many guanidine complexes have been reported [16-18]. They possess antibacterial, antifungal, anti-cancer, anti-oxidant, anti-diabetic, anti-leishmania and other biological activities [19-24]. These compounds have been intensely investigated in bioinorganic coordination chemistry [25].

A large number of natural and synthetic guanidine-pyridine hybrid compounds are used as therapeutic compounds with a broad spectrum of medicinal activity [26-28]. The heterocyclic ring of these compounds can interact with biological molecules such as enzymes, DNA and RNA; thus, these compounds have been employed in the design of new drugs and many guanidine derivatives are successfully used in medicinal chemistry [29-35]. Therefore many chemists have carried out research on the compounds containing guanidine-pyridine hybrid ligand and their metal complexes [36, 37].

Different modes of coordination of transition metals with these compounds can be envisaged [38, 39]. Guanidine ligands can be classified as either guanidine derivatives with no additional donor atoms or guanidine derivatives with additional donor atoms [40-43]. The difference between these two classes is that when no additional donor atoms are present, the guanidine acts as a monodentate ligand; however, when guanidine derivatives have additional donor atoms, there is a tendency for the molecule to act as a bidentate ligand [44, 45].

Bacterial diseases and bacterial drug resistance are very common all around the world [46]. In order to inhibit this serious medicinal problem; the discovery of new types of antibacterial agents is a very important task. Antimicrobial drugs with metal-based compounds are effective strategies in bioinorganic coordination chemistry [47]. Reports on the synthesis of such kind of compounds still remain essentially missing.

The present study reports on the synthesis of guanidine ligand and their Cu (II), Ni (II) and Co (II) complexes. The identities of synthesized compounds were performed by various spectroscopy methods. The antibacterial activities of compounds were also studied.

2. EXPERIMENTAL SECTION

2.1. Materials and Instruments. All chemicals and solvents purchased from Merck and Aldrich Company and were used without further purification, otherwise mentioned. The complexion reactions were carried out under inert atmosphere of

nitrogen but the reaction for the synthesis of ligand performed on ambient condition. The solvents used in reactions were dried by standard methods. The UV-Vis spectra measured on a Cary 100 spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra of ligand were recorded on a Brucker 300 MHz spectrometer in DMS-d_6 and $CDCl_3$ using tetramethylsilane as internal standard. The IR spectra were taken with a Shimidzo 300 spectrometer using KBr pellets. Melting points of compounds were measured by an electrothermal melting point apparatus and were not corrected. The molar conductance of the complexes in DMSO (1×10^{-3} M solution) was performed at 25 °C using oakton ECTestr 11 dual-range, conductivity tester. The Mass spectra were run at 70 eV at 230 °C with Agilent technologies. Thin-layer chromatography (TLC) was performed for determination of purity of the synthesized compounds till observation of new spot and disappearance of starting materials using n-hexane/EtOAC (1:2) as an eluent.

2.2. Synthesis of 1, 1'-((pyridin-2-ylimino)methylene)bis(3-methyl-1-(pyridin-2-yl)urea (HL). $POCl_3$ (0. 2 mol) was added to a solution of N, N'-dimethylurea (0. 1 mol) in dry benzene. The mixture was stirred in room temperature overnight, then a solution of 2-aminopyridine (0. 15) in dry benzen added in several portions. After heating under reflux (24h) and cooling to room temperature, the precipitate solved in water and 2N NaOH to bring the pH about 14. The resulting mixture extracted with benzene. The organic layer evaporated in vacuum.

(HL): yellow. Yield :(68%). Melting point: 140-142 °C. Anal. calc. for $C_{20}H_{20}N_8O_2$: IR (KBr, υ_{max} [cm^{-1}]:3421, 3170, 2924, 1700, 1636, 1581, 1342; ^{1}H- NMR (300 MHz, DMSO-d_6)δ: 2. 77(6H, s), 5. 85(2H, s), 6. 41-6. 46 (t, 3H, Ar-H), 6. 56-6. 60(t, 1H, Ar-H), 6. 65-6. 68(d, 1H, Ar-H), 7. 29-7. 43(m, 3H, Ar-H), 7. 86-7. 88(m, 2H, Ar-H), 7. 99-8. 01(m, 1H, Ar-H); ^{13}C-NMR(75 MHz, $CDCl_3$): δ= 163. 34, 158. 42, 156. 67, 148. 00, 145. 34, 137. 73, 136. 98, 120. 01, 114. 40, 113. 90, 108. 59, 27. 77; UV-Vis (DMSO): λ_{Max}= 240 nm.

2.3. General preparation of metal complexes. Reaction of ligand with metal (Ⅱ) ions in the molar ratios 1:2 (1ligand: 2metal) afforded the corresponding metal complexes, as follow:

Cobalt (Ⅱ), Nickel (Ⅱ) and Copper (Ⅱ) complexes were prepared by the same general method. To a solution of 2 mmol of the appropriate metal chloride in 15 mL dry methanol, was slowly added with stirring a solution of 1 mmol HL in 10 mL of dry methanol. The resulting mixture was refluxed for 2-3 h under inert atmosphere of nitrogen. The stirring was continued at room temperature for 24 h to ensure the completion of reaction. The solid product was filtered with methanol and dried in vacuum desiccator.

Complex[Cu_2(1, 1'-((pyridin-2-ylimino)methylene)bis(3-methyl-1-(pyridin-2-yl)urea)(H_2O)$_4$] (CuL): Dark green solid. Yield (72%). Melting point: 127-129°C. Anal. calc. for $C_{20}H_{26}Cu_2N_8O_6$: IR (KBr, υ_{max} [cm^{-1}]): 3422, 3100, 2900, 1368, 1567, 1417, 1335, 521, 439; UV-Vis (DMSO): λ_{Max}= 290, 650 nm. Mass: $[m/z]^+$ = 600.

Complex[Co_2(1, 1'-((pyridin-2-ylimino)methylene)bis(3-methyl-1-(pyridin-2-yl)urea)(H_2O)$_8$] (CoL): purple solid. Yield (65%). Melting point: 120-122°C. Anal. calc. for $C_{20}H_{34}Co_2N_8O_{10}$: IR (KBr, υ_{max} [cm^{-1}]: 3440, 2998, 2913, 1661, 1437, 525; UV-Vis (DMSO): λ_{Max}= 260, 590, 680 nm. Mass: $[m/z]^+$ = 664.

Complex[Ni_2(1, 1'-((pyridin-2-ylimino)methylene)bis(3-methyl-1-(pyridin-2-yl)urea)(H_2O)$_8$] (NiL): light green solid. Yield (70%). 130-132°C. Anal. calc. for $C_{20}H_{340}Ni_2N_8O_{10}$: IR (KBr, υ_{max} [cm^{-1}]): 3437, 2996, 2913, 1656, 1437, 1312, 524; UV-Vis (DMSO): λ_{Max}= 290, 410, 710 nm. Mass: $[m/z]^+$ = 662.

2.3. *In vitro* antibacterial activity. Four microorganisms were used to test the antibacterial activity of the ligand and its metal complexes. They were: *Escherichia coli (ATCC: 25922) and Serratia marcescens* (ATCC: 13880) as gram negative bacteria and *Bacillus sabtilis* (ATCC: 6633) and *Staphylococcus aureus* (ATCC: 6838) as gram positive bacteria. The antibacterial activity of the synthesized compounds was determined with two methods: the disc diffusion and micro broth dilution methods. These methods recommended by the National Committee for Clinical Laboratory Standards (NCCLS) [47]. Each of the bacterial strains were cultured onto Muller-Hinton agar plate and incubated for 18 to 24 hours at 35 °C. The density of bacteria culture require for the tests was adjusted to 0. 5 McFarland (1. 5×10^8 CFU/ml) (CFU = Colony Forming Unit). The tests were repeated three times to ensure reliability.

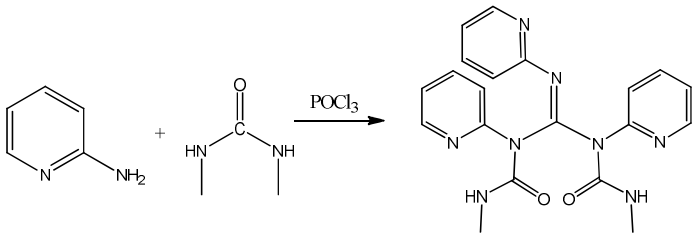
2.3.1. *Disc diffusion method.* Disc diffusion method for antibacterial susceptibility was carried out according to standard method to presence antibacterial activity of synthesized compounds [48]. The compounds (0. 02 g) were dissolved in 1 mL DMSO. A bacterial culture (which has been adjusted to 0. 5 McFarland) was used to lawn Hinton agar plates using a sterile swab. The discs had been impregnated with synthesized compounds were placed on the Muller-Hinton agar surface. Tetracycline, impeneme and cephradine were used as standards for antibacterial measurements. DMSO showed no activity against any bacterial strains. After incubation for 18-24 h at 35 °C, the diameter of each zone of inhabitation was measured (mm). The results presented in Table 3.

2.3.2. *Micro-broth dilution method for determination of Minimal Inhibitory Concentration (MIC).* The Minimal Inhibitory Concentrations (MICs) of the ligand and complexes were also determined for the bacterial strains. MIC is the lowest concentration of antimicrobial compound, which inhibits the visible growth of a microorganism after overnight incubation. In this method the various concentrations of synthesized compounds were made from 2000 to 1. 95µg/ml in sterile tube. A 1 ml sterile Muller Hinton Broth (MHB) was poured in each sterile tube followed by addition of 1 ml test compound in tube 1. Two fold serial dilutions were carried out from all the tubes and excess broth (1ml) was discarded from the last tube. To each tube 0. 1 ml of standard microorganism (1. 5×10^8 CFU/ml) was added. Turbidity was observed after incubating the inoculated tubes at 35 °C for 24 h. the MIC values of free ligand and complexes are presented in Table 4.

3. RESULTS SECTION

The method of synthesis for 1, 1'-((pyridin-2-ylimino) methylene) bis (3-methyl-1-(pyridin-2-yl) urea) is illustrated in Scheme1. N, N'-dimethylurea was treated with 2-Aminopyridine in present of $POCl_3$ to get substituted guanidine. The ligand consists of tree pyridine rings which are bonded to a CN_3 unit. The ligand characterized by IR, ^{1}H-NMR, ^{13}C-NMR and UV-Vis spectroscopy.

Reaction of the ligand with Cu (Ⅱ), Ni (Ⅱ) and Co (Ⅱ) salts in 1:2 M ratio gave colored complexes in good yields. The proposed structure for the metal complexes is shown in Figure1. The characterization of complexes was established by molar conductance, IR, UV-Vis Mass spectroscopy analysis. All of the complexes are stable in room temperature and insoluble in common organic solvents, but soluble in DMF and DMSO.



Scheme 1. Preparation of ligand.

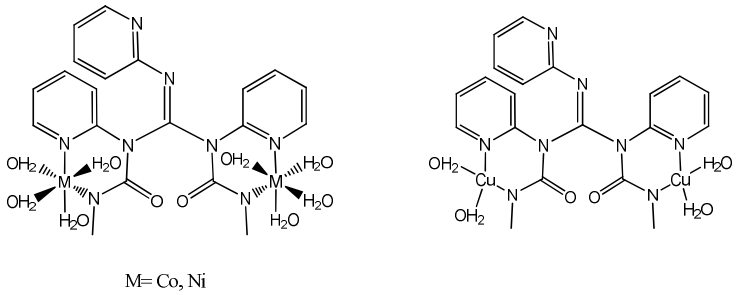


Figure 1. Proposed structure for metal complexes.

3.1. NMR spectroscopy. In the ^{1}H-NMR spectra of the HL, appearance of a singlet at 5. 85 ppm refers to NH protons. Aromatic protons signals are observed at 8. 01-6. 41 ppm as multiples, while CH_3 aliphatic protons appearance as singlet in 2. 77 ppm. The ^{13}C-NMR spectrum shows signal for carbon atom of CH_3 groups at 27. 77 ppm. The carbon atom of azomethine appears at 163. 34 ppm, while the carbonyl groups appeared at 158. 42. Aromatic carbon signals are observed between 108. 59-156. 67 ppm.

3.2. IR spectroscopy. The IR spectra were taken for ligand and all the complexes. The IR spectra of complexes were compared with the free ligand to determine the coordination site. The IR spectra of the free ligand shows a band in 1700 cm^{-1} which can attributed to the C=O stretching. The C=N stretching frequency for ligand are observed in 1636 cm^{-1} which indicate resonance character in CN_3 unit. The FT-IR spectra shows C=C band in 1581 cm^{-1} and also shows C-H $_{(aromatic)}$ and C-H $_{(aliphatic)}$ bands in 3100 and 2924 cm^{-1} respectively. The C-N groups appeared in the 1299-1342 cm^{-1}. A comparative absorption pattern of the complexes with free ligand shows that the coordination of guanidine ligand to metals has effect on υ (N-H) and υ (C-N) frequencies. In all the complexes the N-H frequency is disappearance and that confirmed the ligand bonded to the metals through NH site. The stretching frequencies of C-N group in all complexes are shift to lower wavenumbers compared to free ligand, confirming the coordination of the guanidine ligand to the metals. The coordination of H_2O to the metals is supported by the presence of broad bands of υ (OH) in the range 3422-3440 cm^{-1}. The Cu-N, Co-N and Ni-N frequencies are observed in 521, 525 and 524 cm^{-1} respectively.

3.3. UV-Vis spectroscopy. The UV-Vis spectra of guanidine ligand and its metal complexes were recorded in DMSO. The ligand shows band in 240 nm witch is assigned to $\pi \rightarrow \pi^*$ transition. In the electronic spectra of complexes slight shifts are observed in the position of this band as compared to the ligand. The Cu (Ⅱ) complex shows bands at 290, and 650 nm due to the $^2A_1g \rightarrow {}^2B_1g$ transition that support square planner geometry. The Ni (Ⅱ) complex shows bands at 290, 410 and 710 nm. These bands correspond to $^3A_2g \rightarrow {}^3T_1g$ and $^3A_2g \rightarrow {}^3T_1g$ transitions. The transition bands were found at 260, 590 and 680 nm in UV-Vis spectrum of Co (Ⅱ) complex. These are probably due to the ^4T_1g (F) $\rightarrow {}^4T_1g$ (P) and $^4T_1g \rightarrow {}^4T_2g$ transitions. In Co and Ni complexes these d-d transitions show octahedral geometry.

3.4. Molar conductance. By using the relation $\Lambda_m = \frac{\kappa}{c}$, the molar conductance of metal complexes can be calculated. The complexes were dissolved in DMSO and molar conductivities of 10^{-3} M of their solutions in 25 °C were measured. Table 1 shows the molar conductance values of the complexes. The molar conductances values of metal complexes are in the range of 10-12 $\Omega^{-1}mol^{-1}cm^2$. The results indicate that the complexes are non-electrolytes in DMSO.

Table 1. Analytical and physical data of ligand and its metal complexes.

Compounds	Molecular formula	Color	Yiel d%	Molar conductance	m. p. °C
L	$C_{20}H_{20}N_8O_2$	yellow	65	-	140-142
CuL	$C_{20}H_{26}Cu_2N_8O_6$	dark green	70	12	127-129
NiL	$C_{20}H_{34}Ni_2N_8O_{10}$	Light green	65	10	130-132
CoL	$C_{20}H_{34}Co_2N_8O_{10}$	purple	68	10	120-122

3.5. Mass spectroscopy. The Mass spectra of the synthesized compounds are in good agreement with the proposed structures. The molecular ion peak for the Cu (Ⅱ), Ni (Ⅱ) and Co (Ⅱ) complexes were observed at *m/z*= 600, 590 and 592 respectively, which are equal to their molecular mass. The other peaks in the mass spectrum were attributed to the fragmentation of complex inside the molecule.

3.6. Antibacterial activity. The antibacterial activity of all the synthesized compounds was investigated against four microorganisms to find out their biological activity by disk

diffusion and micro-broth dilution methods. The strains of bacteria used were *Escherichia coli*, *Serratia marcescens (*gram-negative*)* and *Bacillus sabtilis, Staphylococcus aureus* (gram-positive). Tetracycline, imipeneme and cephradine were used as standard antibiotics. The results are listed in Table 2 and 3. The results indicate that all the synthesized compounds exhibit moderate activity against all the bacteria. The CoL' complex showed the lowest MIC value against *seratia marcescens*. The CoL complex showed the highest MIC against *Staphylococcus aureu*s and *Bacillus sabtili*s. A comparison study between guanidine ligand and its metal complexes shows that the metal complexes have more antibacterial activity against bacteria strains than the free ligand. The increased antibacterial activity of the complexes can be explained based on the Tweedy chelation theory [49]. According to Tweedy's theory, chelation reduces the polarity of the metals. Thus, chelation enhances the penetration of the complexes in to lipid membranes and blocks the metal binding sits in the enzyme of microorganisms.

Table 2. Inhibitaion zone of ligand and metal complexes against bacterial and fungi strains.

Compounds	Bacteria			
	Escherichia coli	*Staphylococcus aureus*	*Bacillus sabtilis*	*Serratia marcescens*
	Inhabitation zone (mm)			
HL	10	8	10	20
CuL	12	11	16	30
CoL	15	12	12	34
NiL	10	8	10	24
Tetracycline	12	21	10	9
Imipeneme	30	20	30	25
Cephradine	16	24	10	30
DMSO	0	0	0	0

4. CONCLUSIONS

The Cu (II), Ni (II) and Co (II) complexes with 1, 1'-((pyridin-2-ylimino)methylene)bis(3-methyl-1-(pyridin-2-yl)urea) (HL) were synthesized. They were characterized by spectral data. Square planner geometry was assigned for Cu complexes, while Co and Ni complexes have distorted octahedral geometry. The antibacterial activities were screened for all the compounds. The Co complex demonstrated higher antibacterial activity compared to other compounds.

Table 3. Minimal Inhibitory Concentration, µg/ml of ligand and complexes against bacterial strains.

Compounds	Bacteria			
	Escherichia coli	*Staphylococcus aureus*	*Bacillus sabtilis*	*Serratia marcescens*
HL	250	500	1000	250
CuL	250	125	250	15.62
CoL	62.5	125	125	15.62
NiL	250	500	500	125

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