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Synthesis and structural characterization of metal complexes derived from substituted guanidine-pyridine as potential antibacterial agents

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ABSTRACT

Two guanidine-pyridine ligands, namely 2-(6-aminopyridin-2-yl)-1,3-dimethylguanidine (**LI**) and 2-(6-aminopyridin-2-yl)-1,1,3,3-tetramethylguanidine (**LII**) were prepared. The ligands were characterized by nuclear magnetic resonance (^{1}H-NMR), Fourier-transform infrared (FTIR), Ultraviolet–visible (UV-Vis) and mass spectroscopy. Next, the corresponding Cu(II), Co(II) and Ni(II) metal complexes were synthesized and characterized by spectroscopic methods. The low molar conductance values of metal complexes indicating that the metal complexes are non-electronic. Based on spectroscopic methods square planar geometry is proposed for copper and nickel complexes, while octahedral geometry suggested for cobalt complexes.The ligands and metal complexes were screened for their anti-bacterial activity against *Escherichia coli*, *pseudomonas aeruginosa*, *staphylococcus aureus* and *enterococcus faecalis* using the agar well diffusion assay. On the basis of overall results, CoLI showed the highest activities against all four kinds of bacteria strains, while a weak antibacterial activity was observed from LII ligand. The CoLI complex was more affective against *staphylococcus aureus* with diameter inhibition zone of 18 mm.

Keywords: *guanidine-pyridine, square planar, octahedral, antibacterial activity, agar well diffusion.*

1. INTRODUCTION

It is known that metal-organic coordination compounds serve an important role in bioinorganic chemistry owing to such important applications as anti-cancer, anti-bacterial, anti-fungal, anti-oxidant, anti-diabetic and anti-leishmania properties [1-4]. Recently, heterocyclic compounds have been the focus of much attention in coordination chemistry owing to their numerous biological properties [5]. Among these compounds, pyridine derivatives have been applied in many areas of research due to their ability in using different coordination modes with metal ions [6]. During a relatively long period of time, pyridine group has been found in many different natural compounds, such that the importance of pyridine derivatives is clear to anyone in the field of biochemistry [7]. Since the time 2,2'-bipyridine was discovered near the end of the 19th century, it was widely utilized for the complexation of metal ions[8]. These compounds are of much interest as they have numerous biological and non-biological properties [9]. It has been shown that the heterocyclic ring of these compounds can have interaction with such biological molecules as enzymes, DNA and RNA; accordingly, pyridine compounds have been used for developing new drugs and many pyridine derivatives have been employed in medicinal chemistry, showing much success [10]. One of the most significant qualities of such compounds is intercalating ability; this is owing to presence of a lone pair of nitrogen atoms [11]. So, much research has been focused on the compounds which contain pyridine group ligand and their complexes due to their possible applications in biological processes [12]. Despite this, not much has been done regarding the synthesis of such ligands and their complexes.

This study reports the synthesis of guanidine-pyridine hybrid ligands. Species which contain the Y-shaped CN_3 unit have received much attention as ligands both electronically and sterically [13]. Recently, the exploration of the ligand properties of guanidine, particularly substituted guanidines and their anions, has been of much interest and the characterization of a wide variety of coordination modes has been done in complexes obtained from metals distributed all over the periodic table [14]. Accordingly, many natural and synthetic guanidine compounds with different biomedical properties have been explored [15]. The biological activity of such compounds is due to their flexible structure and the three nitrogen atoms of guanidine moiety [16]. It has been revealed that heterocyclic guanidine derivatives exhibit substantial antibacterial properties against both Gram-positive and Gram-negative bacterial strains [17].

Bacterial diseases have become very common all around the word, making bacteria drug resistance a growing concern [18]. To tackle this serious problem, finding new types of antimicrobial agents can be a very important but, at the same time, challenging task. In recent years, the studies have zoomed on the development of new antibacterial agents that can overcome the bacterial resistance [19]. In this regard, antimicrobial drugs with metal-based compounds can serve as effective strategies in the field of bioinorganic coordination chemistry [20]. In this work we report the synthesis of 2-(6-aminopyridin-2-yl)-methylguanidines and their Cu(Ⅱ), Co(Ⅱ) and Ni(Ⅱ) complexes. The ligands and metal complexes characterized by spectral analysis; and antibacterial activity were investigated for synthesized compounds.

2. EXPERIMENTAL SECTION

Material and methods. All chemical and reagents here used were analytical grade and used without further purification unless mentioned. Solvents were dried with standard methods for 24h. All reactions were monitored by thin layer chromatography (TLC)

on silica gel poly gram SILG/UV 254 nm plates. Melting points of compounds were measured an Electrothermal type 9100 melting point apparatus and uncorrected. Mass spectra of compounds (m/z and intensity) were determined with Agilent technologies apparatus at 70 eV at 230 °C. ^{1}H-NMR (Nuclear magnetic resonance) spectra of ligands were performed on a Brucker AMX 500 MHz spectrometer at room temperature in DMSO-d_6 with tetramethylsilane (TMS) as internal standard. Chemical shifts and coupling constants are reported in δ and Hz respectively. Infrared Spectra (FT-IR) of compounds were taken in KBr pellets using Shimidzo 300 spectrometer. UV-Visible spectra were recorded on a Varian Cary 100 UV-Vis spectrophotometer. The molar conductance of metal complexes was recorded in DMSO (1×10^{-3} M solution) using Oakton ECTester 11 dual-range, conductivity tester.

Synthesis of Guanidine ligands. Fe_3O_4@L-arginine was prepared by chemical co-precipitation according to the previous literature [21]. Fe_3O_4@L-arginine (30 mg) was added to the mixture of 2,6-diaminopyridine (1 mmol) and urea derivative (1 mmol) in absolute ethanol. The mixture was heated to reflux in an oil bath at 80°C. Completion of reactions was monitored by TLC (n-hexane / ethyl acetate 40:60). After the proper reaction time, the mixture was cooled to room temperature. Ethanol was added and the catalyst was separated by magnetic decantation. The solution was evaporated under reduced pressure to give solid product.

2-(6-aminopyridin-2-yl)-1,3-dimethylguanidine (LI) Brown solid; 83%; M.p. 185-187 ºC; FT-IR(KBr, cm^{-1}): 3342, 3200, 2945, 2811, 1626, 1270; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ_{ppm} 7.00-6.97 (t, 1H, J= 15.0 Hz, Ar-H), 5.70 (s, 2H, NH_2), 5.60-5.59 (d, 2H, J= 5 Hz, Ar-H), 5.30 (s, 1H, N-H), 2.40 (s, 6H, CH_3); UV/Vis (DMSO): λ_{max} [nm] = 250, 310 nm.

2-(6-aminopyridin-2-yl)-1,1,3,3-tetramethylguanidine (LII) Creamy solid; 72%; M.p. 170-172 ºC; FT-IR(KBr, cm^{-1}): 3100, 2962, 2925, 1629, 1262; ^{1}H NMR (250 MHz, DMSO-d$_6$): δ_{ppm} 5.45 (s, 2H, NH_2), 5.31 (m, 3H, Ar-H), 2.50 (s, 12H, CH_3); UV/Vis (DMSO): λ_{max} [nm] = 250, 320 nm.

Synthesis of metal complexes. The metal complexes were prepared by treating 1 mmol warm dry methanol solution of chloride of Co(II), Ni(II), Cu(II) with 2 mmol corresponding ligands in the same solvent. The resulting mixture was refluxed for 3-4 h under inert atmosphere of nitrogen. After this period of time, precipitate was formed. The resulting products were filtered, washed with warm methanol, and finally dried in vacuum desiccator.

Bis (2-(6-aminopyridin-2-yl)-1,3-dimethylguanidine) copper (II) (CuLI) Dark brown solid; Yield: (87%); M.p. 157-159°C. Molar conductance Λ_m ($\Omega^{-1}cm^2mol^{-1}$) in DMSO: 10. Selected IR data (KBr, cm^{-1}): 3359, 2996, 2940, 1624, 1592, 1291, 569. UV-vis (DMSO): λ_{Max}= 280, 320, 450 nm. Mass: [m/z]$^+$ = 419.

Bis (2-(6-aminopyridin-2-yl)-1,3-dimethylguanidine) cobalt (II) (CoLI) Dark green solid; Yield: (92%); M.p. 157-159°C. Molar conductance Λ_m ($\Omega^{-1}cm^2mol^{-1}$) in DMSO: 10. Selected IR data (KBr, cm^{-1}): 3422, 2997, 2913, 1661, 1024, 669. UV-vis (DMSO): λ_{Max}= 270, 310, 550, 620 nm. Mass: [m/z]$^+$ = 451.

Bis (2-(6-aminopyridin-2-yl)-1,3-dimethylguanidine) nickel (II) (NiLI) Yellow solid; Yield: (65%); M.p. 153-155°C. Molar conductance Λ_m ($\Omega^{-1}cm^2mol^{-1}$) in DMSO: 12. Selected IR data (KBr, cm^{-1}): 3423, 2997, 2913, 1664, 1017, 669. UV-vis (DMSO): λ_{Max}= 250, 300, 405 nm. Mass: [m/z]$^+$ = 415.

Bis (2-(6-aminopyridin-2-yl)-1,1,3,3-tetramethylguanidine) copper (II) (CuLII) Brown solid; Yield: (75%); M.p. 136-138°C. Molar conductance Λ_m ($\Omega^{-1}cm^2mol^{-1}$) in DMSO: 20. Selected IR data (KBr, cm^{-1}): 3411, 2985, 2910, 1636, 1028, 562, 483. UV-vis (DMSO): λ_{Max}= 280, 310, 410 nm. Mass: [m/z]$^+$ = 475.

Bis (2-(6-aminopyridin-2-yl)-1,1,3,3-tetramethylguanidine) cobalt (II) (CoLII) Purple solid; Yield: (80%); M.p. 145-147°C. Molar conductance Λ_m ($\Omega^{-1}cm^2mol^{-1}$) in DMSO: 14. Selected IR data (KBr, cm^{-1}): 3440, 2998, 2913, 1661, 1237, 525. UV-vis (DMSO): λ_{Max}= 250, 310, 505, 580 nm. Mass: [m/z]$^+$ = 507.

Bis (2-(6-aminopyridin-2-yl)-1,1,3,3-tetramethylguanidine) nickel (II) (NiLII) Dark yellow solid; Yield: (73%); M.p. 140-142°C. Molar conductance Λ_m ($\Omega^{-1}cm^2mol^{-1}$) in DMSO: 12. Selected IR data (KBr, cm^{-1}): 3437, 2996, 2913, 1656, 1212, 524. UV-vis (DMSO): λ_{Max}= 260, 313, 420 nm. Mass: [m/z]$^+$ = 471.

Antibacterial activity: All the synthesized compounds were screened for their *in vitro* antibacterial activity against two Gram-negative (*Escherichia coli* (ATCC 25922), *pseudomonas aeruginosa* (ATCC 27853)) and two Gram-positive (*staphylococcus aureus* (ATCC 25923), *enterococcus faecalis* (ATCC 51299)) bacteria strains by applying agar well-diffusion method. The tests were executed using the methodology designated in the procedures of the National Committee for Clinical Laboratory Standards (NCCLS) [22]. Each of the bacterial strain was cultured onto Muller-Hinton agar (MHA) medium and incubated for 18-24 h at 37 °C. The tests compounds were dissolved in DMSO (100 µg/ml); So DMSO was used as a negative control for all the samples. Suspensions of each bacteria strain were achieved from their 24 h cultures to obtain approximately 1.5×10^8 CFU/ml (colony forming units) and controlled with 0.5 McFarland turbidity standard. In the agar well-diffusion test, an amount of 20 ml sterile Muller Hinton Agar and 100 µl of suspension of each bacteria were transferred to sterile petri dishes and allowed to solidify. The wells were dug in the culture plates by using a sterile cork borer (8 mm in diameter) and 100 µl of sample solution was charged to individual wells. Standard antibiotic drug (Gentamycin) was also used as positive control. The petri dishes were incubated for 18-24h 37 °C. After this period of time, results were determined by measuring inhibition zones formed around each well as millimeters (mm) diameter. The experiments were repeated three times. Results are given in Figure 3.

3. RESULTS SECTION

The method for the synthesis of guanidine ligands (**LI, LII**) were illustrated in Figure 1. Firstly, urea derivatives (*N*,*N*′-dimethylurea and 1,1,3,3-tetramethylurea) were treated with 2,6-diaminopyridine in the presence of Fe_3O_4@L-arginine nanoparticles under reflux condition. Fe_3O_4@L-arginine was prepared according to the reported literature. In the next step, from reaction of guanidine ligands with metal salts in molar ratio 2:1 metal complexes were prepared (Figure2). All the ligands and complexes were obtained in good yield. The synthesized compounds were characterized by ^{1}H-NMR, FT-IR, UV-Vis and mass spectroscopy, also molar conductance were measured. Analytical and physical data of ligands and their metal complexes are presented in Table1.

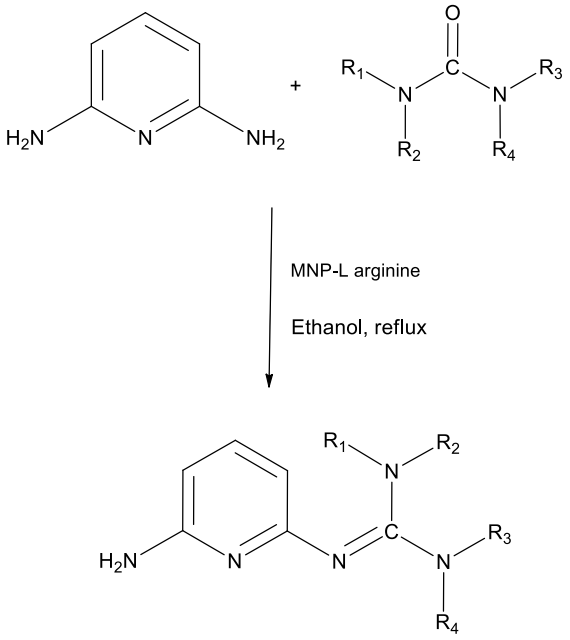


Figure 1. Method for synthesis of Guanidine ligands

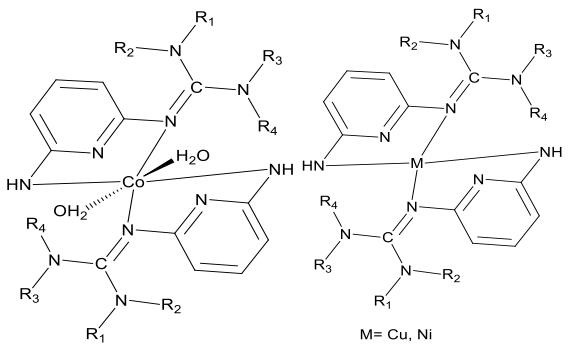


Figure 2. Proposed structure for the metal complexes

The molar conductivity of metal complexes was measured using the conductometric method by $\Lambda_m = \frac{\kappa}{C}$ equation. Where, κ is the measured conductivity and C is the concentration of the solutions. The low molar conductance values of all the complexes indicated that these complexes were non-electrolytes.

Table 1. Analytical and physical data of ligands and their metal complexes

compounds	M.W. (g/mol)	Color	Yield (%)	Molar conductance	M.P (°C)
LI	179.23	Brown	83	-	185-187
LII	207.29	Creamy	72	-	170-172
CuLI	420	Dark brown	87	12	160-162
CoLI	451	Dark green	92	10	157-159
NiLI	415	Yellow	65	12	153-155
CuLII	476	Brown	75	20	136-138
CoLII	507.52	purple	80	14	145-147
NiLII	471	Dark yellow	73	12	140-142

Characterization of Ligands. In the ^{1}H-NMR spectra of guanidine ligands the CH_3 groups of LI and LII can be found at 2.40 and 2.50 ppm, respectively. The signals of aromatic protons appear in the range 7.00-5.45 ppm. In the ^{1}H-NMR spectra of LI NH_2 group shows signal at 5.72ppm while in the LII Ligand shows signal at 5.62 ppm. The NH protons in the LI compound were also seen at 5.29 ppm.

The FTIR technique was also used to confirm the functionalities in the compounds. The FTIR spectra of LI showed a strong peak at 3342 cm^{-1} indicating the N-H group, as well as NH_2 band was seen at 3210 cm^{-1}. The C-H $_{(aromatic)}$ and C-H $_{(aliphatic)}$ stretching bands are appearing at 2945 and 2811, respectively. The absence of a sharp peak in the range 1700-1720 cm^{-1} (C=O) and the presence of peaks at 1626 cm^{-1} (C=N) and 1270 cm^{-1} (C-N) confirm the formation of guanidine ligand. The C=N and C-N stretching frequencies for LII are observed in 1636 and 1262 cm^{-1} respectively, which indicate resonance character in CN_3 unit; also C-H $_{(aromatic)}$ and C-H $_{(aliphatic)}$ bands are observed in 2962 and 2854 cm^{-1}. The NH_2 functional group in LII is also shows at 3200 cm^{-1}.

UV-vis spectra of ligands and metal complexes were recorded in DMSO (Table 2). In the electronic spectra of LI and LII two intense bands in the range 250-320 were observed. The first one can be assigned to $\pi\rightarrow\pi^*$ transition of aromatic ring and the second one is due to the $n\rightarrow\pi^*$ of –C=N group.

Characterization of complexes. The IR spectra of metal complexes show that the stretching frequency of the C=N and C-N bonds were shifted to the lower wavenumbers when compared to the free ligand which is due to the coordination of nitrogen atom to the metal ions. The disappearance of the NH_2 group of ligands in all the metal complexes were also indicate the NH_2 group of ligand has been deprotonated and coordinate to the metals; so the guanidine-pyridine ligands act as bidentate ligands. The coordination of ligands to the metal centers was also demonstrated by the $\upsilon_{(M-N)}$ vibrations appearing in the range 483-669 cm^{-1}.

The UV-Vis spectra of complexes were compared to ligands. In all the metal complexes $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions of the free ligands were shifted to the lower frequencies through the coordination of ligands to the metal center. The features of the UV-Vis spectra of Cu(II) complexes are very comparable to each

other and they are show the square planar geometry for these complexes. Based on electron confirmation of cu^{2+} complexes, one spin-allowed band are expected in the square planar geometry, *i.e.* $^2B_1g \rightarrow {}^2B_2g$. The Co(II) complexes exhibited two peaks in the range 400-800 nm. They are typical for octahedral geometry. These bands assigned to $^4T_1g \rightarrow {}^4T_1g(p)$ and $^4T_1g \rightarrow {}^4A_2g$ d-d transitions. The UV-Vis spectra of Ni(II) complexes were also show similarities which indicate similar geometry in their structures. The absorption bands in the range 260-313 nm are due to the intra ligand bands. The appearance a new peak in 405 and 420 nm for NiLI and NiLII assigned to the $^3A_2g \rightarrow {}^3Eg$ transition of central metal ion.

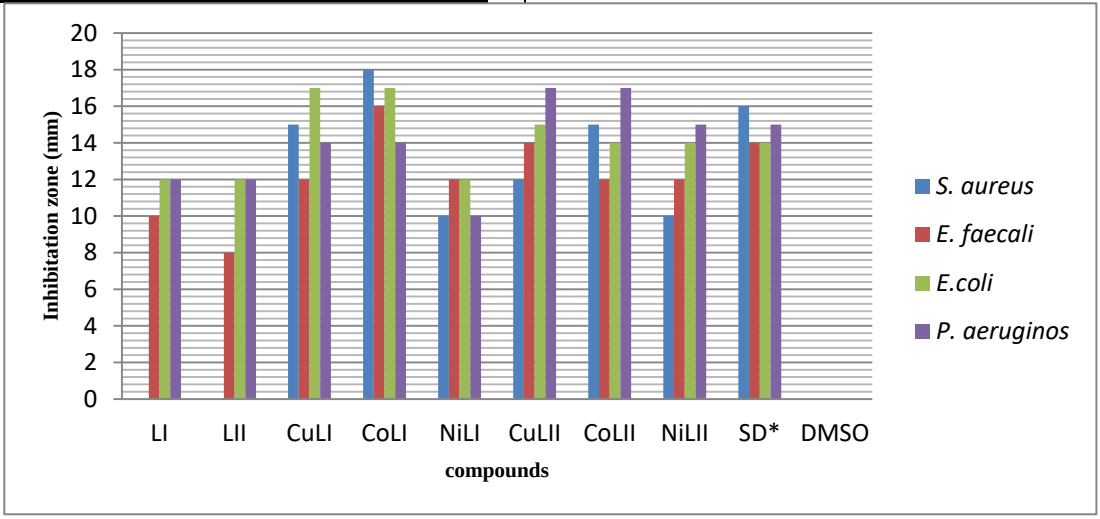
Table 2. UV-Visible data of ligands and their metal complexes

Compounds	Transitions	Assignment	Geometry
LI	250	$\pi \rightarrow \pi^*$	-
	310	$n \rightarrow \pi^*$	
LII	250	$\pi \rightarrow \pi^*$	-
	320	$n \rightarrow \pi^*$	
CuLI	280	$\pi \rightarrow \pi^*$	Square planar
	320	$n \rightarrow \pi^*$	
	450	$^2B_1g \rightarrow {}^2B_2g$	
CoLI	270	$\pi \rightarrow \pi^*$	Octahedral
	310	$n \rightarrow \pi^*$	
	550	$^4T_1g \rightarrow {}^4T_1g(p)$	
	620	$^4T_1g \rightarrow {}^4A_2g$	
NiLI	250	$\pi \rightarrow \pi^*$	Square planar
	300	$n \rightarrow \pi^*$	
	405	$^3A_2g \rightarrow {}^3Eg$	
CuLII	280	$\pi \rightarrow \pi^*$	Square planar
	310	$n \rightarrow \pi^*$	
	410	$^2B_1g \rightarrow {}^2B_2g$	
CoLII	250	$\pi \rightarrow \pi^*$	Octahedral
	310	$n \rightarrow \pi^*$	
	505	$^4T_1g \rightarrow {}^4T_1g(p)$	
	580	$^4T_1g \rightarrow {}^4A_2g$	
NiLII	260	$\pi \rightarrow \pi^*$	Square planar
	313	$n \rightarrow \pi^*$	
	420	$^3A_2g \rightarrow {}^3Eg$	

The Mass spectra of ligands and their metal complexes are in good agreement with the suggested structures. The LI and LII compounds showed the parent peaks at m/z 179 and 207, respectively which compares well with the formula weight of the compounds. The molecular ion peak for the CuLI, NiLI, CuLII and NiLII complexes observed at *m/z*= 420, 415, 476 and 471 respectively, which are equivalent to the molecular weight of these complexes. In the mass spectra of CoLI and CoLII complexes molecular ion peak at *m/z*= 451 and 507 were observed which confirm the octahedral geometry for these complexes.

Antibacterial study. The antibacterial activity of the ligands and their Cu (II), Ni (II) and Co (II) metal complexes are assayed against Gram-positive bacteria: *enterococcus faecalis*, *Staphylococcus aureus* and Gram-negative bacteria: *Pseudomonus aeruginosa*, *Escherichia coli* using standard drug Gentamycin by well diffusion method with the concentration of 100 µg/ml in DMSO. The activity is also assayed for the pure solvent DMSO and the standard gentamycin for each bacteria strain. The results of antibacterial activity are shown in Figure 3. From the data, it is clear that the metal complexes exhibit much higher antimicrobial activity when compared to the free ligands. In compare to other metal complexes the CoLI are found to be better inhibiting the growth of bacteria strains. A possible explanation for this phenomenon can be suggested in the light of chelation theory [23]. It is suggested that the chelation considerably reduces the charge of the metal ion mainly because of partial sharing of its positive charge with the donor groups and possible π- electron delocalization over the whole chelate ring. This increases the lipophilic character of the metal chelate which favors its penetration through lipoid layers of cell membranes.

The results given in Figure3 demonstrated that the inhibition zone values of compounds are in the order CoLI>CuLI=CoLII>CuLII>NiLI=NiLII against *S. aureus.* The ligands showed no antibacterial activity against this microorganism. The inhibition zone against *E. faecali* are in order CoLI>CuLII>CuLI=CoLII=NiLII=CuLII>LI>LII, against *E.coli* CuLI=CoLI>CuLII>CoLII=NiLII>NiLI>LI=LII and CuLII=CoLII.NiLII.CuLI=CoLI>LI=LII>NiLI against *P. aeruginos* bacteria.



*Standard Drug= Gentamycin

Figure 3. Graphical presentation of antibacterial activity as inhibition zone diameters (mm) of synthesized compound.

4. CONCLUSIONS

The guanidine-pyridine hybrid ligands, 2-(6-aminopyridin-2-yl)-1,3-dimethylguanidine **(LI)** and 2-(6-aminopyridin-2-yl)-1,1,3,3-tetramethylguanidine **(LII)** were synthesized by condensation of *N,N′*-dimethylurea and 1,1,3,3-tetramethylurea with 2,6-diaminopyridine in the presence of Fe_3O_4@L-arginine in high yield up to 72%. The copper(II),

cobalt(II) and nickel(II) complexes were prepared by reaction of corresponding ligands and metal salts in molar ratio 2:1 in good yields. The synthesized compounds were characterized by several spectroscopic methods. The results showed that the Cu and Ni complexes have square planar geometry while the Co complexes have octahedral geometry. All the ligands and complexes were screened for their antibacterial activity against Gram-positive and Gram-negative microorganisms. The CoLI complex showed highest antibacterial activity compared to other compounds.

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