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## Synthesis, characterization and antibacterial activity of copper(ii) and nickel(ii) complexes with 3, 10-dialkyl-1, 3, 5, 8, 10, 12 hexaazacyclotetradecane ligand

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### Abstract

14-membered hexaazamacrocyclic complexes were synthesized by the condensation reaction method of ethylenediamine, formaldehyde, and either butylamine or hexylamine using metal salt as Cu(II) and Ni(II) in a 2 : 4 : 2 : 1 mole ratio, respectively. The chemical formula of complexes was  $[\text{CuL}^1](\text{ClO}_4)_2$  (**1**),  $[\text{NiL}^1](\text{ClO}_4)_2$  (**2**),  $[\text{CuL}^2](\text{ClO}_4)_2$  (**3**), and  $[\text{NiL}^2](\text{ClO}_4)_2$  (**4**), where  $\text{L}^1 = 3,10\text{-dibutyl-1,3,5,8,10,12-hexaazacyclotetradecane}$  and  $\text{L}^2 = 3,10\text{-dihexyl-1,3,5,8,10,12-hexaazacyclotetradecane}$ . All complexes were characterized by Elemental analysis (% CHN), Fourier-Transform Infrared spectroscopy (FT-IR), UV-Visible spectroscopy (UV-Vis), and Liquid Chromatography-mass spectroscopy (LC-MS) techniques to confirm the complex structures. The results showed that the copper(II) and nickel(II) complexes were square-planar geometry, with four secondary amine nitrogen atoms of the macrocyclic ligand occupying in the equatorial plane and two oxygen atoms from perchlorate ions to be a weak bond as coordinated with copper(II) and nickel(II) ions in the axial position. These complexes were screened against different bacteria, *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*), and were compared with tetracycline as the standard drug by the agar diffusion method. The antibacterial activities of Cu(II) and Ni(II) complexes with hexaazamacrocyclic ligand showed good effective antibacterial activities but were lower than standard antibacterial drugs; the inhibitory effects of complexes were found to be against the microorganisms tested.

**Keywords:** 14-membered ring, transition metal complexes, spectroscopy techniques, condensation reaction

### 1. Introduction

The 14-membered hexaazamacrocyclic complexes were synthesized to be models for natural compounds such as metalloporphyrins and metallocorrins due to their favorable structural properties and potential applications in the areas of bio-inorganics<sup>[1]</sup>, magnetic properties<sup>[2]</sup>, catalytic activity<sup>[3]</sup>, and potentiometric sensors<sup>[4]</sup>. The preparation of hexaazamacrocyclic metal(II) complexes can change the side chain of several member rings. For example, Shakir, M. and et al.<sup>[5]</sup> studied these complexes using primary amine (amino group,  $-\text{NH}_2$ ) in which hydrazine was the side chain. In general, the hexaazamacrocyclic complexes were synthesized by a template reaction of the amine compounds method where ethylenediamine reacts with formaldehyde in the presence of the transition metals. In particular, formaldehyde is useful for causing cyclization<sup>[5]</sup>. For the hexaazamacrocyclic complexes, the antibacterial activity was studied. *S. aureus* as gram positive and gram negative bacterial such as *S. typhi*, *E. coli*, and *P. phaseolicola* were compared with standard drugs (streptomycin or nystatin). As a result, the antibacterial activity with the minimum inhibitory concentration (MIC) values was indicated against standard drugs<sup>[1]</sup>. Metal ion of hexaazamacrocyclic complexes uses partial sharing of the positive charge with nitrogen donor atoms leading to reduce polarity of the metal ion. This increase enhances the penetration of the hexaazamacrocyclic complexes into lipid membranes and blocking of the metal binding sites in the enzymes of microorganisms<sup>[6]</sup>.

In this work, we report the synthesis of 14-membered pendant arm hexaaza-macrocyclic complexes that were obtained by the condensation reaction of ethylenediamine, either butylamine or hexylamine and formaldehyde in the presence of metal (II) salts.

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## 2. Experimental

### 2.1 Materials and Methods

Copper chloride dihydrate, nickel chloride hexahydrate, ethylenediamine, formaldehyde, butylamine, hexylamine, and perchloric acid (70 %) were all purchased from commercial sources and used as received. IR spectra (4000-400  $\text{cm}^{-1}$ ) were recorded with FT-IR spectrophotometer as a KBr disk. The visible spectra were recorded with a Shimadzu Lambda-1600 UV-Vis spectrophotometer in DMSO. Elemental analysis of CHN was performed using a CE instruments Flash EA 1112 series, Thermo Quest analyzer. Mass spectra were recorded by an electro-spray ionization (ESI) technique operating in the positive ion mode by directly injecting the solution into a mass spectrometer (Waters Micromass).

**Safety note:** Perchlorate salts of metal complexes are potentially explosive. Only a small amount material should be prepared, and it should be handled with care.

### 2.2 Syntheses

#### 2.2.1 Synthesis of $[\text{CuL}^1](\text{ClO}_4)_2$ (1) and $[\text{NiL}^1](\text{ClO}_4)_2$ (2)

To make 99.9 % absolute ethanol (10 mL) of  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (1.7048 g, 10 mmol), 99 % ethylenediamine (1.3 mL, 20 mmol) was added to the 99.9 % absolute ethanol (10 mL). After the mixture was a completely clear purple solution, 37 % formaldehyde (2.2 mL, 40 mmol) was added stirring until the mixture was a completely dark blue solution and then butylamine (2.0 mL, 20 mmol) was added with continuous stirring. The mixture of reactants was refluxed for 24 h and the purple-red solution was cooled to room temperature and filtered to remove any insoluble solids. After the amount of concentrated perchloric acid was added dropwise, the mixture was filtered and stored at room temperature to form purple-red solids.

Complex 2, the synthetic procedure is similar to that complex 1 except  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (2.3058 g, 10 mmol) was used instead of  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  to obtain yellow solids.

#### 2.2.2 Synthesis of $[\text{CuL}^2](\text{ClO}_4)_2$ (3) and $[\text{NiL}^2](\text{ClO}_4)_2$ (4)

For complexes 3 and 4, the synthetic procedure was similar to the one mentioned above, but it has been used hexylamine instead of butylamine (2.6 mL, 20 mmol) for both complexes. Both  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (1.7048 g, 10 mmol) and  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (2.3058 g, 10 mmol) were used for complex 3 and complex 4, respectively.

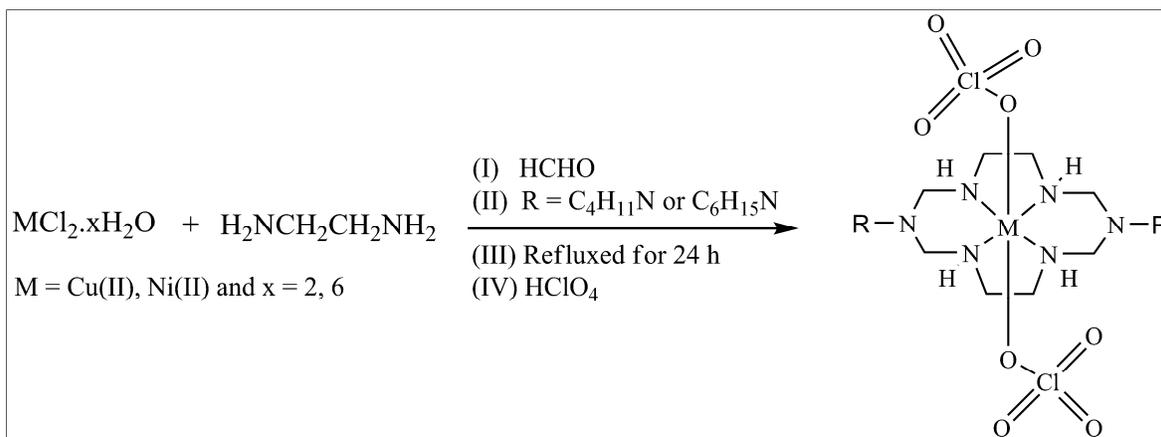
### 2.3 *In vitro* antibacterial activity

The *in vitro* antibacterial activity of the complexes was carried out against two bacterial strains, *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*), using the agar diffusion method by spreading the bacteria inoculum on the media plate. Wells ( $\phi = 6$  mm) were punched in the agar and loaded with 25, 50, and 100  $\text{mg} \cdot \text{mL}^{-1}$  of each complex. Blank containing neat DMSO solvent (negative control) was also run parallel in the same plate. The plates were incubated at 37 °C for 24 h and antibacterial determined by measuring inhibition zone diameter. The relative antibacterial potency of the given preparation was calculated by comparing its zone of inhibition with that of the blank and tetracycline drug.

## 3. Results and discussion

### 3.1 Description of syntheses

The hexaazamacrocyclic complexes were synthesized in a condensation reaction from the starting materials: copper(II) chloride dihydrate (or nickel(II) chloride hexahydrate), ethylenediamine, formaldehyde, and butylamine or hexylamine with in a 1 : 2 : 4 : 2 mol ratio according to Scheme 1. The powder products were soluble in organic solvents such as DMSO, MeCN, DMF, and acetone. Unfortunately, all efforts failed to grow single crystal suitable for X-ray crystallography.



**Scheme 1:** The preparation of the complexes.

These complexes were investigated and characterized by using FT-IR, LC-MS, and UV-Vis techniques. Melting point,

color, and elemental analyses (Table 1) agree well with the proposed structures of the complexes.

**Table 1:** Formula weight, melting point, yield (%), and analytical data for the complexes.

Complexes	Formula weight	Melting point (°C)	Yield (%)	Found (Calc.) %		
				C	H	N
$[\text{Cu}(\text{C}_{16}\text{H}_{38}\text{N}_6)](\text{ClO}_4)_2$ (1)	576.99	242-245	73	32.06 (32.10)	6.30 (6.60)	14.33 (14.44)
$[\text{Ni}(\text{C}_{16}\text{H}_{38}\text{N}_6)](\text{ClO}_4)_2$ (2)	572.13	221-223	56	28.36 (28.40)	6.12 (6.20)	14.42 (14.45)
$[\text{Cu}(\text{C}_{20}\text{H}_{46}\text{N}_6)](\text{ClO}_4)_2$ (3)	633.07	269-271	65	37.31 (37.94)	7.10 (7.32)	13.17 (13.27)
$[\text{Ni}(\text{C}_{20}\text{H}_{46}\text{N}_6)](\text{ClO}_4)_2$ (4)	628.22	250-252	58	38.54 (38.24)	7.30 (7.38)	13.41 (13.38)

### 3.2 FT-IR spectra of complexes

The preliminary investigation of the hexaazamacrocyclic complexes was done from their FT-IR spectra (Fig 1). The FT-IR complexes showed the absence of a strong band in the range of 1720-1740  $\text{cm}^{-1}$  to be assignable to the carbonyl group of aldehydic moiety confirming the condensation reaction [5]. All complexes, which have a weak band in the range between 1631-1650  $\text{cm}^{-1}$ , were assigned to  $\delta(\text{O-H})$  of the moisture. The complexes showed the presence of a sharp

band around 3238 and 3208  $\text{cm}^{-1}$  corresponding to  $\nu(\text{N-H})$  of the coordinated secondary amine of the complexes. A medium intensity band appearing in the range between 2963-2877  $\text{cm}^{-1}$  was assigned to  $\nu(\text{sp}^3 \text{C-H})$ .<sup>1</sup> In the region of 1100  $\text{cm}^{-1}$ , splitting into two peaks at 1144-1121 and 1089-1120  $\text{cm}^{-1}$ , could be assigned to perchlorate ions. The splitting of this peak clearly explained the presence of coordinated perchlorate ions. In all complexes, a band seen at 485-441  $\text{cm}^{-1}$  was probably due to the formation of M-N bonds [7].

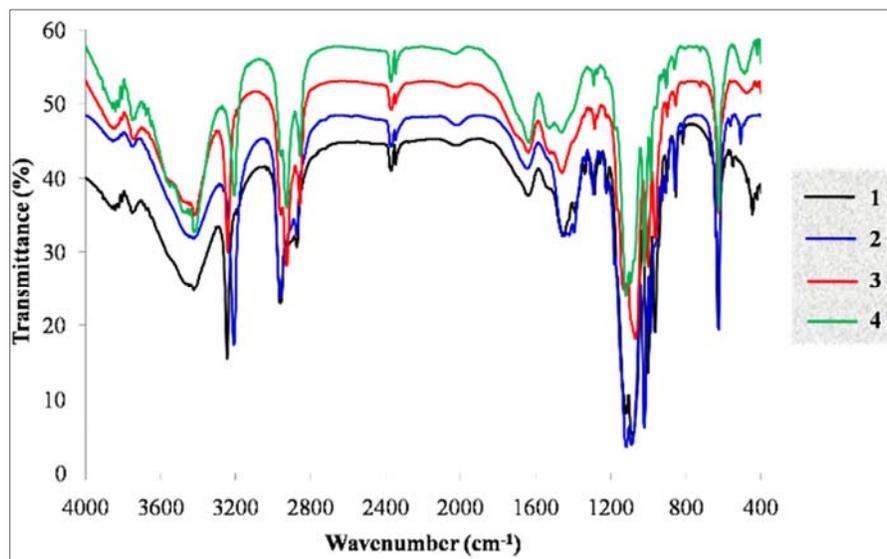


Fig 1: The FT-IR spectra of complexes.

### 3.3 UV-Vis spectra of complexes

All complexes are soluble in DMSO. The electronic spectral data (Fig 2) of purple-red complexes **1** and **3**, and other yellow complexes **2** and **4** showed a visible absorption

maximum at 512, 452, 514 and 450 nm for complexes **1**, **2**, **3** and **4**, respectively. It could be seen that those absorption spectra at the  $\lambda_{\text{max}}$  512, 452, 514 and 450 nm which were assigned to d-d transition of Cu(II) and Ni(II) ions [8, 9].

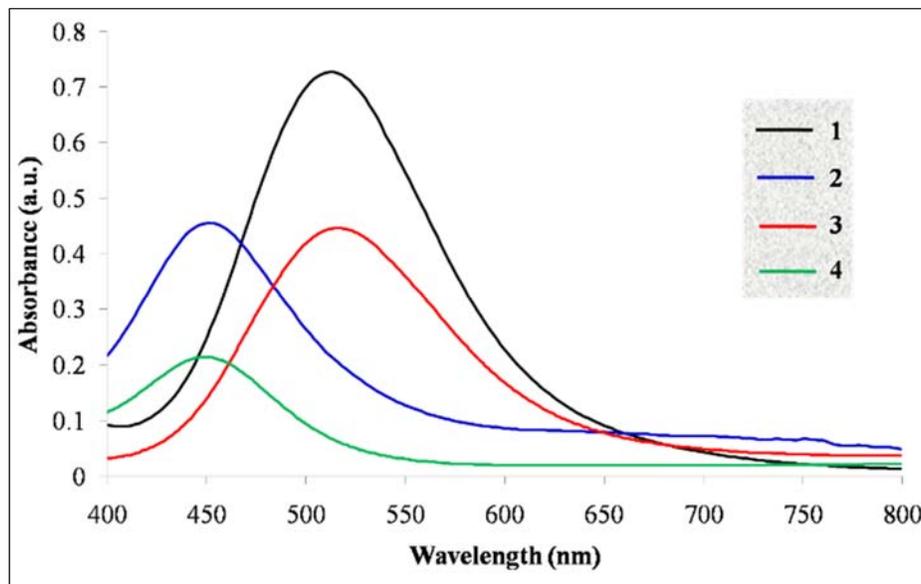


Fig 2: The electronic spectra of complexes.

### 3.4 Mass spectra of complexes

Electron spray ionization (ESI) mass data of the complex **1** showed the molecular ion peak at  $m/z = 577$  which was assigned to  $[\text{CuL}^1 + 2\text{ClO}_4]$  and the fragmentation of one molecule and a perchlorate ion occurred base peak at  $m/z =$

476.2 (100 %) corresponding to  $[\text{CuL}^1 + \text{ClO}_4]^+$  and weak isotopic species at  $m/z = 478.2$ . Also, the spectrum exhibited fragments at  $m/z = 188.6, 190.0, 233.1, 247.1, 291.2, 325.2, 376.2$  and  $412.2 \text{ amu}$  [10-14].

Electron spray ionization (ESI) mass data of the complex **2** indicated that the molecular ion peak at  $m/z = 571$  corresponding to  $[\text{NiL}^1 + 2\text{ClO}_4]$  and the fragmentation of one molecule and a perchlorate ion that represented the base peak at  $m/z = 471.2$  (100 %) which was assigned to  $[\text{NiL}^1 + \text{ClO}_4]^+$  and weak isotopic species at  $m/z = 473.2$ . Moreover, the spectrum also exhibited fragments at  $m/z = 186.1, 201.1, 286.2, 386.1$  and  $407.2$  amu.

Electron spray ionization (ESI) mass data of the complex **3** in which the molecular ion peak was observed at  $m/z = 632.2$  related to the fragment  $[\text{CuL}^2 + 2\text{ClO}_4]$  and the fragmentation of one molecule and a perchlorate ion that represent the base peak at  $m/z = 532.2$  (100 %) which was assigned to  $[\text{CuL}^2 + \text{ClO}_4]^+$  and weak isotopic species at  $m/z = 534.2$  and there were other peaks at  $m/z = 176.1, 190.0, 219.1, 261.1, 275.1, 319.2, 419.2$  and  $468.3$  amu.

Electron spray ionization (ESI) mass data of the complex **4** in which the molecular ion peak showed a peak at  $m/z = 627.2$  corresponding to the fragment  $[\text{NiL}^2 + 2\text{ClO}_4]$  and the fragmentation of one molecule and a perchlorate ion occurred base peak at  $m/z = 527.2$  (100 %) corresponding to the  $[\text{NiL}^2 + \text{ClO}_4]^+$  species and isotopic species at  $m/z = 529.3$ . Other fragments were observed at  $m/z = 158.0, 199.1, 201.1, 314.2, 414.2$  and  $4463.3$  amu.

As a result, mass spectra of all complexes are consistent with the proposed formulas for those complexes as confirmed from the observed peaks in these spectra which correspond to fragments resulting from the expected fragmentations of the complexes.

### 3.5 *In vitro* antibacterial activity

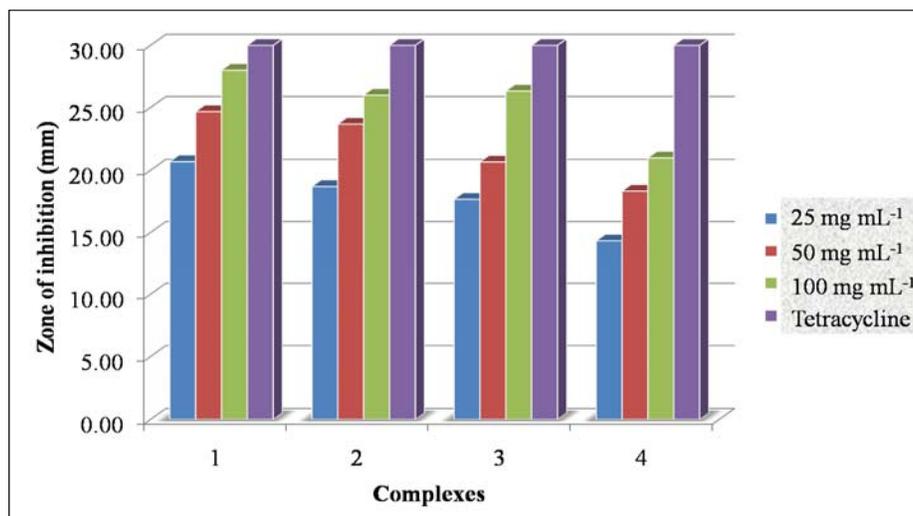
The antibacterial activity of hexaazamacrocyclic complexes and a standard drug (Tetracycline) were checked against *E. coli* and *S. Aureus* and tested using the agar diffusion method. As a result, the antimicrobial screening of hexaazamacrocyclic complexes is shown in Tables 2 and 3. The present work (Figs 3 and 4) reveals that the copper(II) complex was more effective against bacteria than nickel(II) complexes. The overall results indicated that the present complexes were more against *E. coli* as gram negative than *S. aureus* as gram positive due to the fact that gram negative bacteria has thin cells wall and the complexes can penetrate into the cells of *E. coli*. The influence factor of the antibacterial activity of the complexes were shown in the following: (i) chelating of the ligands, (ii) the nature of *N*-donor ligands, (iii) net charge of the complexes, (iv) the presence and nature of the ion in the complex, and (v) nuclearity of center metal atom in the complexes.<sup>12</sup> From Tweedy's chelation theory<sup>[15]</sup>, the polarity of the copper(II) or nickel(II) ion will be reduced to a greater extent due to the overlap of the ligand orbitals and partial sharing of the positive charge of the copper(II) or nickel(II) ion with donor groups. This increased lipophilicity enhances the penetration of the complexes into lipid membranes and blocking of the metal binding sites in the enzymes of microorganisms<sup>[16-19]</sup>.

**Table 2:** Inhibition zone (mm  $\pm$  SD) of complexes in *E. coli* bacterial gram-negative.

Complexes	25 mg mL <sup>-1</sup>	50 mg mL <sup>-1</sup>	100 mg mL <sup>-1</sup>	Tetracycline
$[\text{Cu}(\text{C}_{16}\text{H}_{38}\text{N}_6)](\text{ClO}_4)_2$ (1)	20.70 $\pm$ 0.58	24.67 $\pm$ 0.58	28.00 $\pm$ 0.00	30.00 $\pm$ 0.00
$[\text{Ni}(\text{C}_{16}\text{H}_{38}\text{N}_6)](\text{ClO}_4)_2$ (2)	18.70 $\pm$ 0.58	23.67 $\pm$ 0.58	26.00 $\pm$ 0.00	30.00 $\pm$ 0.00
$[\text{Cu}(\text{C}_{20}\text{H}_{46}\text{N}_6)](\text{ClO}_4)_2$ (3)	17.67 $\pm$ 0.47	20.67 $\pm$ 0.47	26.33 $\pm$ 0.47	30.00 $\pm$ 0.00
$[\text{Ni}(\text{C}_{20}\text{H}_{46}\text{N}_6)](\text{ClO}_4)_2$ (4)	14.33 $\pm$ 0.47	18.33 $\pm$ 0.47	21.00 $\pm$ 0.00	30.00 $\pm$ 0.00

**Table 3:** Inhibition zone (mm  $\pm$  SD) of complexes in *S. aureus* bacterial gram-positive.

Complexes	25 mg mL <sup>-1</sup>	50 mg mL <sup>-1</sup>	100 mg mL <sup>-1</sup>	Tetracycline
$[\text{Cu}(\text{C}_{16}\text{H}_{38}\text{N}_6)](\text{ClO}_4)_2$ (1)	12.00 $\pm$ 0.00	19.00 $\pm$ 0.00	23.00 $\pm$ 0.00	30.00 $\pm$ 0.00
$[\text{Ni}(\text{C}_{16}\text{H}_{38}\text{N}_6)](\text{ClO}_4)_2$ (2)	11.00 $\pm$ 0.00	20.00 $\pm$ 0.00	21.00 $\pm$ 0.00	30.00 $\pm$ 0.00
$[\text{Cu}(\text{C}_{20}\text{H}_{46}\text{N}_6)](\text{ClO}_4)_2$ (3)	15.33 $\pm$ 0.47	17.67 $\pm$ 0.47	19.67 $\pm$ 0.47	30.00 $\pm$ 0.00
$[\text{Ni}(\text{C}_{20}\text{H}_{46}\text{N}_6)](\text{ClO}_4)_2$ (4)	12.67 $\pm$ 0.47	15.00 $\pm$ 0.47	16.33 $\pm$ 0.47	30.00 $\pm$ 0.00



**Fig 3:** The antibacterial activity of *E. coli* of complexes.

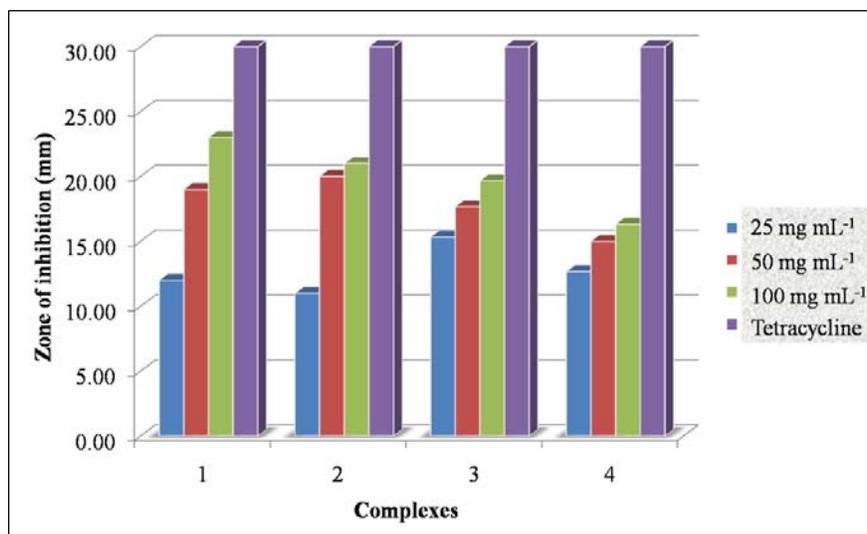


Fig 4: The antibacterial activity of *S. aureus* of complexes.

#### 4. Conclusion

The copper(II) and nickel(II) complexes containing hexaazamacrocyclic ligand were synthesized by a condensation reaction from the reaction of ethylenediamine, formaldehyde, and either butylamine or hexylamine. All complexes were characterized by FT-IR, UV-Vis, LC-MS and CHN analysis. Preliminary studies of the antibacterial activity of these complexes were compared with tetracycline as the standard drug indicating that all complexes are active against a series of pathogens.

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