Scientific paper

Biologically Active Tetraazamacrocyclic Complexes of Co(II), Ni(II), Cu(II) and Zn(II)

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Abstract

A new series of the macrocyclic complexes of type $[M(C_{16}H_{28}N_4)X_2]$, where M = Co(II), Ni(II), Cu(II), Zn(II) and X = Cl^{-1}, NO_3^{-1}, CH_3COO^{-1} has been synthesized by [2+2]condensation reaction of ethylenediamine with and acetonylacetone (diacetonyl) in the presence of divalent metal ions. The complexes have been characterized with the help of elemental analyses, conductance measurements, electronic, NMR and infrared spectral studies. On the basis of these studies, a six coordinate distorted octahedral geometry has been proposed for all the complexes. The complexes were tested for their *in vitro* antibacterial activity. Some of the complexes showed remarkable antibacterial activity against some selected bacterial strains.

Keywords: Antibacterial activity; minimum inhibitory concentration; macrocyclic complexes; infrared spectra.

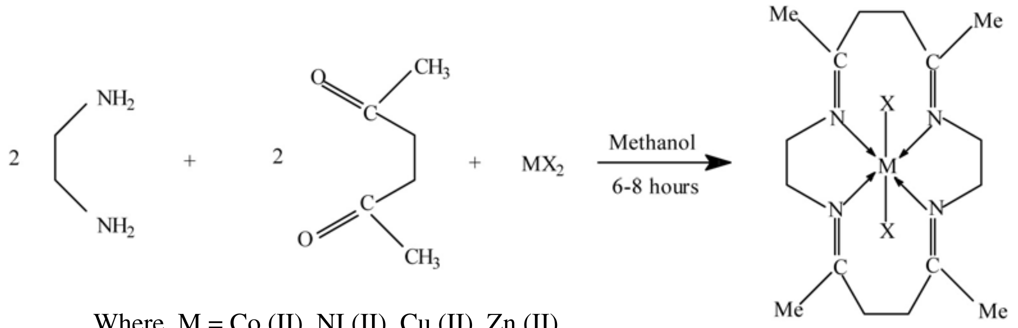
1. Introduction

The multifarious role played by the naturally occurring macrocycles in biological systems is well known. The chemistry of synthetic macrocyclic complexes is also of great importance due to their use as dyes and pigments, MRI contrast agents and models for naturally occurring macrocycles.[1–4] Macrocyclic nickel complexes find use in DNA recognition and oxidation[5] while macrocyclic copper complexes find use in DNA binding and cleavage.[6] Some macrocyclic complexes have been reported showing antibacterial, antifungal and anti-inflammatory activities.[7–8] Macrocyclic metal chelating agents (DOTA) are useful to detect tumor lesions.[9] Prompted by these, in the present paper a new series of macrocyclic complexes of Co(II), Ni(II), Cu(II) and Zn(II) (chloride, nitrate, acetate salt of cobalt, nickel, copper and acetate salt of zinc) obtained by template condensation reaction of ethylenediamine and acetonylacetone has been reported. The complexes have been characterized with the help of various physicochemical techniques like elemental analyses, IR, NMR, magnetic susceptibilities, electronic spectra and molar conductance. These macrocyclic complexes were also screened for their *in vitro* antibacterial activity against some pathogenic bacteria.

2. Experimental

2. 1. Chemistry

All the reported macrocyclic complexes were prepared by template method. To a stirring methanolic solution (~50 cm^3) of ethylenediamine (10 mmol) was added divalent cobalt, nickel copper and zinc salt (5 mmol) (chloride, nitrate, acetate for cobalt, nickel, copper and acetate for zinc) dissolved in methanol (~20 cm^3). The resulting solution was refluxed for 0.5 h. After that acetonylacetone (10 mmol) dissolved in ~20 cm^3 methanol was added in the refluxing mixture and again refluxed for 6–8 h. On overnight cooling coloured complexes formed, which were filtered, washed with methanol, acetone and ether and dried *in vacuo* (Yield 45–50%). Scheme-I present the template syntheses of the complexes. The complexes were soluble in DMF and DMSO, but were insoluble in common organic solvents and water. They were found thermally stable up to ~250 °C and then decomposed.



Scheme 1 Where, M = Co (II), NI (II), Cu (II), Zn (II)
$X = Cl^{-1}, NO_3^{-1}, CH_3COO^{-1}$

2. 2. In Vitro Antibacterial Activity (Biological assay)

The synthesized macrocyclic complexes were tested for *in vitro* antibacterial activity against some bacterial strains using spot-on-lawn on Muller Hinton Agar.[10]

2. 2. 1. Test Pathogens

Four test pathogenic bacterial strains viz *Bacillus cereus* (MTCC 1272), *Salmonella typhi* (MTCC 733), *Escherichia coli* (MTCC 739) and *Staphylococcus aureus* (MTCC 1144) were considered for determination of MIC (Minimum Inhibitory Concentration) of selected complexes.

2. 2. 2. Culture Conditions

The test pathogens were subcultured aerobically using Brain Heart Infusion Agar (HiMedia, Mumbai, India) at 37 °C/24 hrs. Working cultures were stored at 4 °C in Brain Heart Infusion (BHI) broth (HiMedia, Mumbai, India), while stock cultures were maintained at –70 °C in BHI broth containing 15% (v/v) glycerol (Qualigens, Mumbai, India). Organism was grown overnight in 10 ml BHI broth, centrifuged at 5,000g for 10 min and the pellet was suspended in 10 ml of phosphate buffer saline (PBS, pH 7.2). Optical density at 545 nm (OD-545) was adjusted to obtain 10^8 cfu/ml followed by plating serial dilution onto plate count agar (HiMedia, Mumbai, India).

2. 2. 3. Determination of Minimum Inhibitory Concentration

The minimum inhibitory concentration (MIC) is the lowest concentration of the antimicrobial agent that prevents the development of visable growth after overnight incubation. Antimicrobial activity of the compounds was evaluated using spot-on-lawn on Muller Hinton Agar (MHA, HiMedia, Mumbai, India). Soft agar was prepared by adding 0.75% agar in Muller Hinton Broth (HiMedia, Mumbai, India). Soft agar was inoculated with 1% of 10^8 Cfu/ml of the test pathogen and 10 ml was overlaid on MHA. From 1000X solution of compound (1mg/ml of DMSO) 1, 2, 4, 8, 16, 32, 64 and 128X solutions were prepared. Dilutions of standard antibiotics (Linezolid and Cefaclor) were also prepared in the same manner. 5l of the appropriate dilution was spotted on the soft agar and incubated at 37 °C for 24 hrs. **Pure DMSO with no compound was considered as negative control and the zone of inhibition for the compounds under investigation, was measured after subtraction of the zone observed with negative control.**

3. Analyses

The microanalysis of C, H, and N were recorded at Elementar Vario EL III (Carlo Erba 1108). These analyses were carried out at CDRI, Lucknow. Melting points were determined using capillaries in electrical melting point apparatus. The molecular weight was determined by rast camphor method. The metal contents were estimated using standard methods.[11]

4. Physical Measurements

Electronic spectra of metal complexes were recorded in the region 1100–200 nm on a Hitachi U-2000 spectrophotometer. IR spectra were recorded on Beckman IR-20 spectrophotometer in KBr/Nujol mull in the range 4000–200 cm^{-1}. Proton NMR spectra was recorded in DMSO (d6) on Brucker ACF 300 spectrometer at 300 MHz reference to Me_4Si (0.0 ppm). Magnetic moments studies were carried out at SAIF, IIT, Roorkee, on Vibrating Sample Magnetometer (Model PAR 155). The conductivity was measured on digital conductivity meter (HPG System, G-3001).

5. Results and Discussion

5. 1. Chemisry

The analytical data suggest the formula of macrocyclic complexes as: $[M(C_{16}H_{28}N_4)X_2]$ Where M = Co

Table 1: Analytical data of divalent cobalt, nickel, copper and zinc complexes derived from and ethylenediamine and acetonylacetone

		(Found /calcd.), %						
Sr. No.	**Complexes**	**M**	**C**	**H**	**N**	**Colour**	**Mol. Wt.**	**Yield, (in %)**
(1)	$[Co(C_{16}H_{28}N_4)Cl_2]$	13.60(13.56)	47.28(47.29)	6.86(6.89)	13.77(13.79)	Pale brown	406	48
(2)	$[Co(C_{16}H_{28}N_4)\ (NO_3)_2]$	12.81(12.85)	41.79(41.83)	6.03(6.10)	18.22 (18.30)	brown	459	46
(3)	$[Co(C_{16}H_{28}N_4)(CH_3COO)_2]$	13.01(13.02)	52.88(52.98)	7.43(7.50)	12.28(12.36)	Light green	453	48
(4)	$[Ni\ (C_{16}H_{28}N_4)Cl_2]$	14.27(14.32)	47.32(47.40)	6.85(6.91)	13.80(13.82)	Brown	405	43
(5)	$[Ni(C_{16}H_{28}N_4)(NO_3)_2]$	12.63(12.66)	41.86(41.92)	6.08(6.11)	18.31(18.34)	Brown	458	47
(6)	$[Ni(C_{16}H_{28}N_4)(CH_3COO)_2]$	12.75(12.83)	53.11(53.09)	7.49(7.52)	12.37(12.38)	Brown	452	46
(7)	$[Cu(C_{16}H_{28}N_4)Cl_2]$	15.39(15.36)	46.79(46.82)	6.78(6.82)	13.68(13.65)	Green	410	49
(8)	$[Cu(C_{16}H_{28}N_4)(NO_3)_2]$	13.59(13.60)	41.42(41.46)	4.05(6.04)	18.12(18.14)	Violet	463	50
(9)	$[Cu(C_{16}H_{28}N_4)(CH_3COO)_2]$	13.72(13.78)	52.53(52.51)	7.39(7.43)	12.23(12.25)	Green	457	46
(10)	$[Zn(C_{16}H_{28}N_4)(CH_3COO)_2]$	14.12(14.16)	52.29(52.28)	7.39(7.40)	12.22(12.20)	cream	459	48

(II), Ni (II), Cu (II), Zn (II) and X = Cl^{-1}, NO_3^{-1}, CH_3COO^{-1}. The test for anions is positive after decomposing the complexes with conc. HNO_3, indicating their presence inside the coordination sphere. Conductivity measurements in DMSO indicate them to be non electrolytic in nature (10–20 $ohm^{-1}\ cm^2\ mol^{-1}$).[12] All compounds give satisfactory elemental analyses results as shown in **Table-1**.

Several attempts were unsuccessful to grow crystals of complexes in different solvents or mixture of solvents for the purpose of X-ray crystallography.

5. 1. 1. Infrared Spectra

A pair of the band at ~3230 cm^{-1} and ~3260 cm^{-1} of medium intensity was observed in the spectrum of ethylenediamine corresponding to $\nu(NH_2)$, but was found absent in the spectra of all the complexes. A strong peak was observed at ~1700 cm^{-1} of strong intensity in the spectrum of acetonylacetone which may be attributed due to >CO group. This peak was found absent in the spectra of all the complexes. This indicates the absence of >CO groups of acetonylacetone moiety in all complexes. This confirms the condensation of carbonyl groups of acetonylacetone and amino groups of ethylenediamine.[13,14] This fact is also supported by appearance of a new strong absorption band in the region ~1590–1615 cm^{-1} which may be attributed due to $\nu(C{=}N)$.[15,16] These results provide strong evidence for the formation of macrocyclic frame.[17] The lower values of $\nu(C{=}N)$ indicate coordination of azomethine nitrogens to metal.[18] The bands present at ~1350–1000 cm^{-1} of medium intensity may be assigned due to $\nu(C–N)$ vibration. The bands presents at ~2900–3130 cm^{-1} may be assigned due to various $\nu(C–H)$ vibrations.

The far infrared spectra show bands in the region ~420–460 cm^{-1} corresponding to $\nu(M–N)$ vibrations in all the complexes.[19–21] The presence of bands in all the complexes in region ~420–460 cm^{-1} originate from $\nu(M–N)$ azomethine vibration modes and gives an idea about coordination of azomethine nitrogen.[22] The bands present at ~300–310 cm^{-1} may be assigned as being due to $\nu(M–Cl)$ vibrations.[19,21] The bands present at ~ 210–250 cm^{-1} in all nitrato complexes are assignable to $\nu(M–O)$ vibrations of nitrato group.[19]

5. 1. 2. NMR Spectra

The ^1H NMR spectrum of zinc complex shows signal in the region 2.89 ppm (singlet) which may be assigned due to $–NC\mathbf{H_2}C\mathbf{H_2}N–$ protons (8H) while the protons of $–C\mathbf{CH_2CH_2C}–$moiety (8H) appear at 2.60 ppm (singlet). The $–C\mathbf{H_3}$ protons (12 H) appeared at 2.45 ppm.[23]

5. 1. 3. Magnetic Measurements and Electronic Spectra

The magnetic moments of cobalt complexes at room temperature was found to be in the range of 4.82–4.85 μB. These data corresponds to three unpaired electrons. The electronic spectra of cobalt complexes show bands at ~8100–9100(ν_1), 12000–15550 (ν_2), and 18050–20220 cm^{-1} (ν_3) or (12.3–11) × 10^2 (ν_1), (8.3–6.4) × 10^2 (ν_2), (5.5–4.9) × 10^2 (ν_3) nm), respectively. The spectral data resemble to those reported to be octahedral.[24] Thus, assuming the effective symmetry to be D_{4h}, the various bands can be assigned to $^4T_{1g} \rightarrow {}^4T_{2g}$ (F), (ν_1), $^4T_{1g} \rightarrow {}^4A_{2g}$ (F), (ν_2), $^4T_{1g} \rightarrow {}^4T_{1g}$ (P), (ν_3) respectively. It appears that the symmetry of these complexes is not idealized octahedral but is D_{4h}. The assignment of the first spin-allowed band seems plausible since the first band appears approximately at half the energy of the visible band.[25]

The nickel complexes show magnetic moments in the 2.80–2.84 μB. range at room temperature showing octahedral environment around the divalent nickel ion in all complexes. The solution spectra of nickel complexes exhibit a well discernable band with a shoulder on the low energy side. The other two bands observed in the region at ~16700–17020 cm^{-1} or (6–5.9) × 10^2 nm)(ν_2), and 26800–28000 cm^{-1} or (3.7–3.6) × 10^2 nm (ν_3), are assigned to $^3A_{2g} \rightarrow {}^3T_{1g}$ (F) (ν_2), and $^3A_{2g} \rightarrow {}^3T_{1g}$ (P) (ν_3) respectively. The first two bands result from the splitting of one band ν_1, and are in the range at ~9700–10400 cm^{-1} or (10.3–9.6) × 10^2 nm and 11850–12500 cm^{-1} or (8.4–8) × 10^2 nm, which can be assigned to $^3B_{1g} \rightarrow {}^3E_g$ and $^3B_{1g} \rightarrow {}^3B_{2g}$, assuming the effective symmetry to be D_{4h} (component of $^3T_{2g}$ in O_h symmetry).[25] The intense higher energy band at ~35550 cm^{-1} or (2.8) × 10^2 nm may be due to a π–π transition of the (C=N) group. Various bands do not follow any regular pattern and seem to be anion independent. The spectra are consistent with distorted octahedral nature of these complexes.

The magnetic moments of copper complexes lie in the range 1.77–1.79 μB. The electronic spectra of the copper complexes exhibit bands in the region ~17400–19050 cm^{-1} or (5.7–5.2) × 10^2 nm with a shoulder on the low energy side at ~14,450–16,300 cm^{-1} or (6.9–6.1) × 10^2 nm, and show that these complexes are distorted octahedral.[24,25] Assuming tetragonal distortion in the molecule, the d-orbital energy level sequence for these complexes may be: $x^2–y^2 > z^2 > xy > xz > yz$ and the shoulder can be assigned to $z^2 \rightarrow x^2–y^2$ ($^2B_{1g} \rightarrow {}^2B_{2g}$) and the broad band contains both $xy \rightarrow x^2–y^2$ ($^2B_{1g} \rightarrow {}^2E_g$) and $xz, yz \rightarrow x^2–y^2$ ($^2B_{1g} \rightarrow {}^2A_{2g}$) transitions.[26] The band separation of the spectra of the complexes is the order 2500 cm^{-1} or (40) × 10^2 nm, which is consistent with proposed geometry of the complexes.[26] Therefore, it may be concluded that all the copper complexes are distorted octahedral.

5. 2. Biological Assay

The synthesized macrocyclic complexes were tested for their *in vitro* antibacterial activity against four test bacteria *Bacillus cereus* (MTCC 1272), *Salmonella typhi* (MTCC 733), *Escherichia coli* (MTCC 739) and *Staphylococcus aureus* (MTCC 1144). The MIC (minimum inhibitory concentration) shown by the complexes against these bacterial strains was compared with MIC shown by standard antibiotics *Linezolid* and *Cefaclor* (**Table-2, Fig.-1**).

Table 2: Minimum Inhibitory Concentration (MIC) shown by Complexes against test bacteria by using agar dilution assay

Sr. No.	Complexes	MIC (μg/ml) a	b	c	d
(1)	$[Co(C_{16}H_{28}N_4)Cl_2]$	64	4	32	–
(2)	$[Co(C_{16}H_{28}N_4)\ (NO_3)_2]$	128	–	64	–
(3)	$[Co(C_{16}H_{28}N_4)(CH_3COO)_2]$	> 128	128	64	64
(4)	$[Ni\ C_{16}H_{28}N_4)Cl_2]$	16	8	16	64
(5)	$[Ni(C_{16}H_{28}N_4)(NO_3)_2]$	–	–	> 128	64
(6)	$[Ni(C_{16}H_{28}N_4)(CH_3COO)_2]$	8	16	32	32
(7)	$[Cu(C_{16}H_{28}N_4)Cl_2]$	64	32	128	32
(8)	$[Cu(C_{16}H_{28}N_4)(NO_3)_2]$	32	32	–	64
(9)	$[Cu(C_{16}H_{28}N_4)(CH_3COO)_2]$	64	64	128	–
(10)	$[Zn(C_{16}H_{28}N_4)(CH_3COO)_2]$	16	64	32	–
	Cefaclor	8	2	8	16
	Linezolid	4	4	16	32

(–) No avtivity
a – *Bacillus cereus* (MTCC 1272)
b – *Staphylococcus aureus* (MTCC 1144)
c – *Escherichia coli* (MTCC 739)
d – *Salmonella typhi* (MTCC 733)
Cefaclor and Linezolid are standard antibiotics.

Complex 1 showed minimum inhibitory concentration of 4 μg/ml against bacterial strain *Staphylococcus aureus* (MTCC 1144) which is equal to MIC shown by standard antibiotic Linezolid against the same bacterial strain. A minimum inhibitory concentration of 16 μg/ml was registered by Complex 4 against bacterial strain *Escherichia coli* (MTCC 739) which is equal to that of shown by standard antibiotic Linezolid against the same bacterial strain. Complex 6 and 7 registered a minimum inhibitory con-

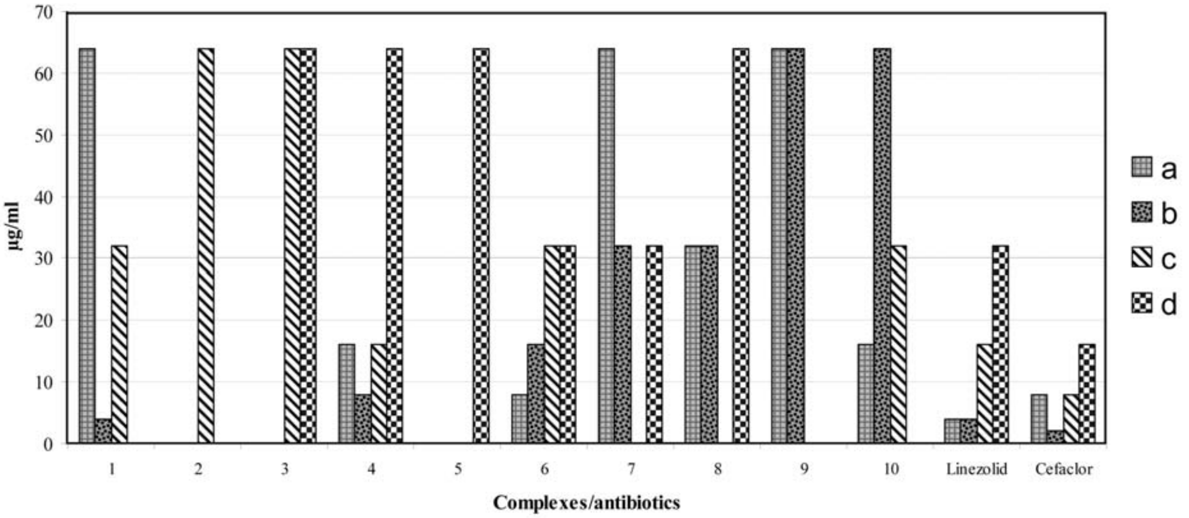
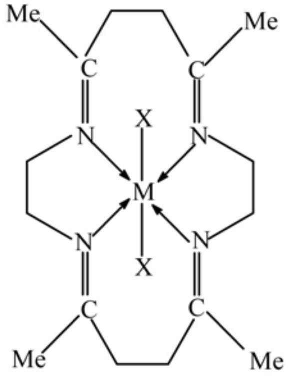


Figure 1: Comparison of MIC of complexes with standard antibiotics up to the concentration of 64 μg/ml
a – *Bacillus cereus* (MTCC 1272); b – *Staphylococcus aureus* (MTCC 1144); c – *Escherichia coli* (MTCC 739); d – *Salmonella typhi* (MTCC 733). Cefaclor and Linezolid are standard antibiotics.

centration of 32 μg/ml against bacterial strain *Salmonella typhi* (MTCC 733), which is equal to MIC shown by standard antibiotic Linezolid against the same bacterial strain. Further complex 6 also showed a minimum inhibitory concentration of 8 μg/ml against bacterial strain *Bacillus cereus* (MTCC 1272), which is equal to MIC shown by standard antibiotic Cefaclor against the same bacterial strain. Complex 2, 3, 5, 8, 9 and 10 showed poor antibacterial activity against all bacterial strains among the whole series under test. However complex 6 was found most potent out of all complexes which showed MIC ranging from 8–32 μg/ml. Complex 1, 4 and 7 also showed satisfactory antibacterial activity.

6. Conclusions

The macrocyclic complexes synthesized by [2 + 2] condensation reaction of ethylenediamine with and acetonylacetone in presence of metal ion have been characterized with the help of elemental analyses, conductance measurements, electronic, NMR and infrared spectral studies. Based these studies, a six coordinate distorted octahedral geometry (**Fig.2)** has been proposed for all the complexes.



Where, M = Co(II), Ni(II), Cu(II), Zn(II)
X = Cl^{-1}, NO_3^{-1}, CH_3COO^{-1}

The complexes were tested for their *in vitro* antibacterial activity. Some of the complexes showed remarkable antibacterial activity against some selected bacterial strains. It has been suggested that chelation/coordination reduces the polarity of the metal ion mainly because of partial sharing of its positive charge with donor group within the whole chelate ring system. This process of chelation thus increases the lipophilic nature of the central metal atom, which in turn, favours its permeation through the lipoid layer of the membrane thus causing the metal complex to cross the bacterial membrane more effectively thus increasing the activity of the complexes. Besides from this many other factors such as solubility, dipole moment, conductivity influenced by metal ion may be possible reasons for remarkable antibacterial activities of these complexes.[27–29] It also has been observed that some moieties such as azomethine linkage or heteroaromatic nucleus introduced into such compounds exhibit extensive biological activities that may be responsible for the increase in hydrophobic character and liposolubility of the molecules in crossing the cell membrane of the microorganism and enhance biological utilization ratio and activity of complexes.[30–33]

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8. Abbreviations:

MIC-Minimum Inhibitory Concentration, MTCC-Microbial Type Culture Collection, MHA -Muller Hinton Agar, CFU-Colony Forming Unit, DMF -N,N-dimethylformamide, DMSO-Dimethylsulphoxide, BHI-Brain Heart Infusion

9. References

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Povzetek

Nova vrsta makrocikličnih kompleksov tipa $[M(C_{16}H_{28}N_4)]X_2$, kjer je M = Co(II), Ni(II), Cu(II), Zn(II) and X = Cl^{-1}, NO_3^{-1}, CH_3COO^{-1}, je bila sintetizirana z reakcijo [2+2] kondenzacije etilendiamina z acetonilacetonom (Diacetonyl) v prisotnosti divalentnih kovinskih ionov. Kompleksi so bili ovrednoteni z analizo elementov, meritvami prevodnosti, ter elektronskimi, NMR in infrardečimi spektralnimi študijami. Glede na rezultate teh študij smo za vse komplekse predlagali a six coordinate distorted octahedral geometry. Komplekse smo testirali *in vitro* na antibakterijsko aktivnost. Nekateri izmed kompleksov so pokazali visoko antibakterijsko aktivnost proti izbranimi bakterijskim sevom.