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Synthesis, characterization and biological activity of ruthenium (III) complexes of 2-(2-(4-X-phenylhydrazono)-2-(1H-benzo[1,2,3]triazol-1-yl)-1-phenylethanone

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ABSTRACT

New air stable low spin Ru(III) complexes have been synthesized, from the reaction of 2-(2-(4-X-phenylhydrazono)-2-(1H-benzo[1,2,3]triazol-1-yl)-1-phenylethanone, X=H, F, Cl, Br, NO2, OCH3 and CH3 with RuCl3.3H2O in ethanol in presence of KOH in the media. The resulted complexes are studied by elemental analysis, molar conductivity, thermal analysis magnetic and spectral (UV-Vis., FTIR, EPR) studies. The redox behavior of the complexes is investigated by cyclic voltammetry method. The magnetic and spectral studies showed that binuclear structure of the complexes in the general form of $[[Ru_2(L^{1-7})_4Cl_2].nH_2O$. Some antibacterial activities of the ligands and their complexes have also been studied

KEYWORDS Benzotriazole,Ru(III) complexes, Antimicrobial activity.

Introduction

Compounds containing triazole have attracted much interest because of their biological applications [1–4], exhibiting plant growth regulating activity [1]. Furthermore, triazoles appear frequently in the structures of various natural products and biologically active compounds [5]. Triazole-containing com-pounds appear in many metabolic products of fungi and prim-itive marine animals. Many triazoles having different function-alities are used as dyes and as photographic chemicals [6]. In addition, polymers derived from triazoles are very important practical application of this heterocyclic system [3, 4]. The ben-zo-fused azoles such as benzotriazols have been studied for their importance in biological activities and medicinal chemistry [7, 8].

The coordination chemistry of triazole and benzotriazole derivatives was studied due to their importance in industry and agriculture and their biological activity. It is well known that the existence of a metal ion bonded to biologically active materials may enhance their activity by changing electronic and geometrical structures. The chemistry of ruthenium is also very interesting [5], because of the fascinating photochemical, photo physical and redox properties exhibited by complexes of this metal. Ruthenium complexes were used in the antitumor therapy, and believed to have great potential as alternative drugs to ***cis***-platin due to their low toxicity and good selectivity for solid tumor metastasis [9]. Similar to platinum anticancer drugs, the ruthenium ion forms a covalent bond with DNA [10], affecting the replication and transcription, and leads to cell death eventually, as all these properties are primarily directed by the coordination environment around the metal center. However, The biological activity of metal complexes is governed by several factors such as the chelate effect of the ligands, the nature of donor atoms, the nature of the metal ion, the total charge on the complex ion, the nature of the counter ions that the neutralize the complex if there is any [11]. A series of poly functional benzotriazole derivatives and their metal complexes were studied [12]. The benzotriazole hydrazone derivatives and some of their metal complexes showed interesting stereochemical, magnetic and spectral properties [13-17].In this work we aim to synthesize and characterize some ruthenium complexes of benzotriazole hydrazone ligands and study their biological activities.

Experimental

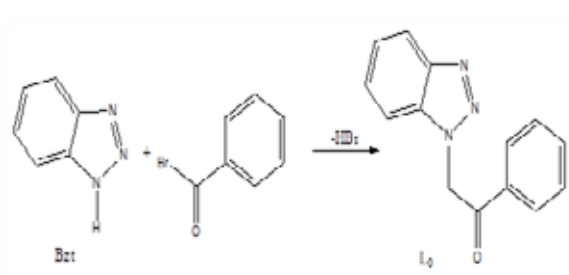
Materials:

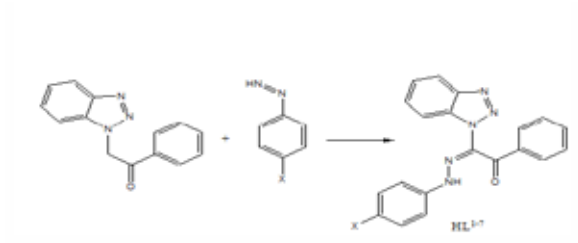
All chemicals were reagent grade quality obtained from Fluka and Aldrich Chemical Companies, and used as received. All solvents used were of high analytical reagent grade and used without further purification.

Synthesis

a. Synthesis of organic ligands

2-(2-(4-X-phenylhydrazono)-2-(1H-benzo[1,2,3]tri-azol-1-yl)-1-phenylethanone, X=H, F, Cl, Br, NO_2, OCH_3 and CH_3 are synthesized by the reaction of 2-bromoacetophenone with 1H-benzotriazole [18,19] then to a cold solution of the above products (0.01mol) in ethanol (100 mL), 2.0 g sodium hydroxide is added. The mixture is then treated gradually with stirring at room temperature with a solution of aryl-diazonium salt (prepared from 0.01 mol of aryl amine and appropriate quantity of hydrochloric acid and sodium nitrite) [20].





Scheme 1. Synthesis of organic ligands

	X
HL^1	H
HL^2	F
HL^3	Cl
HL^4	Br
HL^5	NO_2
HL^6	CH_3
HL^7	CH_3O

b. Synthesis of complexes:
The reaction of the monobasic anion of the organic ligands with Ru(III) metal ions through mixing stoichiometric amount of $RuCl_3.3H_2O$ and ligands, in ethanolic solution and boiled under reflux for 2-3 hours, cooling and the complex was obtained as powder. Complete precipitation was achieved by the addition of diethyl ether to the cold reaction mixture. The solvent was evaporated under vacuum. The residue was washed several times with hot petroleum ether (60–80 °C) and recrystallized from benzene/ethanol.

Physical measurements
Elemental Analysis
Carbon, hydrogen and nitrogen were determined using Perkin Elmer 2400 CHN elemental analyzer.

Electronic Spectra
The electronic spectra of the reported compounds were recorded on UV-Vis recording spectrophotometer, Shimadzu.

Infrared spectra
FT-IR spectra were recorded in a KBr matrix using a shimadzu model 8108 spectrophotometer at room temperature.

Electron Paramagnetic Resonance Spectra (EPR)
The EPR spectra for Ru(III) complexes were scanned on a Radio-pan varian spectrometer at 100.0000 KHz at different G mod-ulation amplitude with rectangular TE 102 cavity and 100 KHz modulation field. Resonance conditions were found at ca. 9.7 GHz (X-band) at room temperature only. The field was calibrated using a powder of diphenylpicrylhydrazyl as the g-marker (DPPH; g = 2.0037).

Redox Measurements
The cyclic voltametric studies were performed at room temperature, using eDAQ-potentiostate and in conjugation with a three microelectrodes fitted with a purged dinitrogen gas inlet and outlet and all the potentials were referred to Ag/AgCl. All the measurements were performed at room temperature in methylene chloride solvent containing 0.1 M TBAP, $1.0x10^{-3}$ M (complex) under O_2 free conditions.

Magnetic Susceptibility
The magnetic susceptibility measurements were made on Gouy balance at room temperature using $Hg[Co(SCN)_4]$ as calibrant.

Conductivity Measurements
Molar conductance of the complexes are measured for $1.0x10^{-3}$ M DMSO solutions at 25±1°C using Professional EC/TDS bench meter, AD3000.

Biological Activity
The antimicrobial activity of synthesized ligands and their corresponding complexes against five strains of Gram negative bacteria, (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Proteus mirabilis* and *Salmonella typhemearium*) and three strains of Gram positive bacteria, (*Staphylococcus*, *aureus*, *Streptococcus*, *Pyogenes and Bacillus anthracis*), using the disk diffusion method as previously described [21, 22].

Results and discussion
General
The reactions of Ru(III) with organic ligands (HL^{1-7}) in ethanol afforded new hexa-coordinated low spin Ru(III) Schiff base complexes. Elemental analyses and some physical properties of the reported ligands and their Ru(III) complexes are listed in Table 1. The proposed molecular formulae for all the complexes are in good agreement with the stoichiometries concluded from their analytical data. The complexes are stable in atmospheric conditions for extended periods and easily soluble in DMF and DMSO; slightly soluble in ethanol, methanol and acetone; insoluble in benzene, water and diethyl ether. The molar conductivity values of prepared solutions as $1.0x10^{-3}$ M DMF solutions indicate the non-electrolytic nature of these complexes [23].

Electronic Spectral study
The electronic absorption spectra of Ru(III) complexes in DMF are studied in the range (200-900) nm . Ruthenium(III) ground state is $^2T_{2g}$ and the first excited doublet levels in the order of increasing energy are $^2A_{2g}$ and $^2T_{1g}$, which arise from $(t_{2g})^4 (e_g)^1$ configuration [30]. Transitions of ligands are ranged within 25641–37736 cm^{-1}, these bands are attributable to π-π* and n-π* transitions of the aryl rings and the nonbonding electrons on the N and O atoms. The Ru(III) ion, with a d^5 electronic configuration, has relatively high oxidizing properties which obscures the weaker bands due to d-d transitions [24-26]. The band in the 17000–22200 cm^{-1} region have been assigned to the $^2T_{2g}$ -$^2A_{2g}$ transition, which is in conformity with the assignments made for similar ruthenium(III) complexes [27]. The electronic spectra for Ru(III) complexes suggests the octahedral environment around the ruthenium(III) ion [26].

Magnetic data
Generally high spin Ru(III) complexes have room temperature magnetic moment near to the spin only value (5.9 B.M) with ground state whereas the low spin complexes have room temperature magnetic moment more than the spin only value (2.4 B.M) with ground state and this may be attributed to the orbital contribution to their magnetic moments [28, 29].

Sometimes, the magnetic values can lay between (2.0-5.92) B.M, where the ligand field strength is comparable with the mean electronic pairing energy of the d^5 configuration, and ground states. In the prepared complexes the values lie between 3.80 and 3.84 B.M. which is between the high spin and low spin magnetic moments suggesting an intermediate spin (3/2) or the presence of magnetic exchange interaction [30].

Infrared spectra
The interaction of azo group, with transition metal salts maybe produced from nitrogen -donor bonds or π - bond of azo group [31].

The spectra of the Ru(III) complexes display broad medium to strong band at 3455-3400 cm^{-1} characteristic of water of crystallization. The CO stretching vibration suggests the azo-enol form as it exhibits medium band at (1420-1470) cm^{-1}. The triazole medium to strong band at (1554-1592)cm^{-1} in the free ligand appeared at frequency (1550-1590) cm^{-1} and this indicate that the triazol nitrogen atoms are not participating in coordination to metal ion. The spectra of all complexes exhibit a medium band at (1390-1409) cm^{-1} characteristic of coordinated azo group through one nitrogen [16, 32]. This is further supported by the appearance of the band corresponding

to the (Ru-N) stretching vibration at (590–610) cm^{-1}. Furthermore, the appearance of bands at 460– 490 cm^{-1} due to Ru-O stretching in the complexes and weak bands at 320-340 cm^{-1} due to Ru-Cl stretching vibration [31]. However, comparing the infrared spectra of free organic ligands and their ruthenium (III) complexes indicate that these ligands are monobasic bidentate and the coordination to Ru(III) is formed through metal-chelate rings in NNO .

Electron Paramagnetic Resonance

The EPR spectral data are listed in Table (2). Fig. (1), represents solid state X-band EPR spectrum for $[Ru_2(L^3)_4Cl_2].9H_2O$ complex. The spectra of all complexes showed axial spectra with almost the same g- values, indicating that these complexes have rhombic distortion [27]. All the Ru(III) complexes have similar anisotropic spectra with almost the same, indicating that the bonding in all the complexes is similar, whatever the substituent in the ligand was.

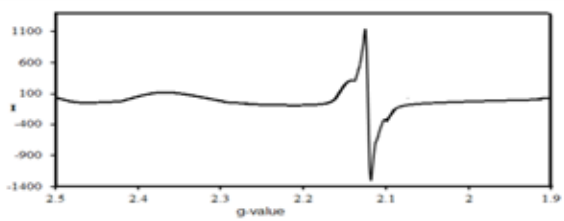


Fig. 1 Room temperature solid state X-band EPR spectrum for $[Ru_2(L^3)_4Cl_2].9H_2O$

Redox Chemistry

Cyclic voltammetry (CV) measurements for Ru(III) complexes have been measured versus Ag/Ag^+ as a reference electrode in 0.1M tetrabutylammoniumperchlorate (TBAP) in methylene chloride as non-aqueous reference electrode, the data are collected in Table (4) and Fig. (2), shows the redox behavior of $[Ru_2(L^4)_4Cl_2].8H_2O$ complex. Successive metal-based couples for, Ru^{III}–Ru^{III} → Ru^{III}–Ru^{IV} and Ru^{III}–Ru^{IV} → Ru^{IV}–Ru^{IV}, appear in the range (0.32-0.35) V and (0.72-0.76) V. In addition, two reversible reductions in the range (–0.24 to-0.0.26)V and (–0.67 to -0.69)V , one-electron reduction of Ru^{III}–Ru^{III} → Ru^{III}–Ru^{II} (E_{pc} ≈–0.30 V, E_{pa} ≈ –0.24 V) and Ru^{III}–Ru^{II} to Ru^{II}–Ru^{II} (E_{pc} ≈–0.75 V, E_{pa} ≈ –0.66V); both of the reduction processes are reversible with peak-to-peak separation (ΔE_p) values of about 80 and 90 mV, respectively, and I_{pa}/I_{pc} ≈ 1, which are characteristic of a single-step, one-electron transfer [32, 33].

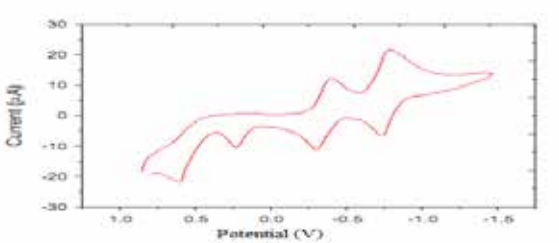


Fig. 2 Cyclic voltammogram of 1×10^{-3} M of $[Ru_2(L^4)_4Cl_2].8H_2O$ in 0.1 M TBAP in CH_2Cl_2 solvent at a Pt working electrode vs. Ag /Ag^+ reference electrode at room temperature and scan rate 100 mV/Sec .

Thermal analysis

The thermal analyses of ruthenium complexes under study were carried out to clarify the content and bonding of water in the complexes. The TG analyses display three steps of change. The first step characterizes the removal of water in the range of 35 -180°C. The second and third steps characterize de-chlorination and some decompositions within the temperature range 180 – 600°C. The thermal analysis showed mixed endothermic-exothermic character, denoting elimination of water of hydration (endothermic process) and a partial decomposition of the organic ligand (exothermic process). The last species at about 600°C does not correspond to metal oxides or metallic ruthenium, even at 800°C, indicating that the decomposition of the organic moiety remains incomplete even at this temperature.

Antimicrobial assay

Antibiotic resistance is a growing problem, some of this is due to the overuse of antibiotics in human, but some of it is probably due to the use of antibiotics as growth promoters in food of animals. So, there is a growing demand for new antibiotics. The synthesized new complexes are evaluated for their in vitro antimicrobial activity against five strains of Gram-negative bacteria (*Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus mirabilis and Sallmonela typhemarium) and three strains of Gram-positive bacteria (Staphylococcus aureus, Streptococcus mutans and Bacillus anthracis)*. Table 4 shows the susceptibility of the synthesized ligands and their Ru(III) complexes beside the benzotriazole (Bzt) and 2-(1-H-benzotriazol-1-yl)-1-phenyl ethanone (L_0), indicating that some of the compounds were not effective with the tested bacteria. Based on the results of zone of inhibition, data in Table 5 revealed that the effective compounds have about one third efficiency of that of Amikacin antibiotic compounds 30mg which produced 36mm inhibition zone in inhibiting the growth of the tested bacterial strains. Since the biological activity of metal complexes is governed by some factors such as the geometrical structure, nature of donor atoms, the chelate effect of ligands and the nature of metal ions [12]. We can notice from the results the different behavior of the synthesized complexes relative to each other and even for the ligands. Since the complexes have same structure as expected from spectral and electrochemical studies, the only different is in the substituted group in the aniline part of the ligand which may affect the strength of the Ru-Ligand bond.

Conclusion

The interaction between the $RuCl_3.3H_2O$ and the organic ligands, 2-(2-(4-substituted-phenyl) hydrazono)-2-(1H-benzo [1, 2, 3] triazol-1-yl)-1-phenylethanone resulted in the same stoichiometry whatever the reactant mole ratio is structutres of the ligands and thier Ru(III) complexes were characterized using spectroscopic and analytical techniques. The structures of the complexes were found to be distorted octahedral of binuclear ruthenium complexes having Cl as bridging ligand.

In vitro antimicrobial studies have shown that, most compounds were found to be very active towards Gram positive bacteria, few other compounds showed higher activity towards Gram-negative bacteria whereas some compound exhibited a higher activity against fungi among the series. These findings give some idea about further research on those species with hope to get biologically active agents.

Acknowledgement

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Table 1. Micro analysis, molar conductivity and magnetic moment data for Ru(III) complexes.

Complex	Found (Calc.) (%)			Λ_M ($\Omega^{-1}cm^2mol^{-1}$)	$\mu_{eff.\ (B.M)}$
	%C	%H	%N		
$[Ru_2(L^1)_4Cl_2].7H_2O$	54.58(54.39)	4.01(4.30)	15.91(16.13)	4.32	3.80
$[Ru_2(L^2)_4Cl_2].9H_2O$	51.42(52.35)	3.78(3.64)	14.99(14.89)	4.58	3.83
$[Ru_2(L^3)_4Cl_2].9H_2O$	49.67(49.24)	3.65(3.32)	14.48(14.36)	18.2	3.83

$[Ru_2(L^4)_4Cl_2].8H_2O$	45.88(41.23)	3.27(3.05)	13.38(13.14)	4.20	3.84
$[Ru_2(L^5)_4Cl_2].8H_2O$	49.06(48.92)	3.62(3.58)	16.34(16.60)	4.00	3.80
$[Ru_2(L^6)_4Cl_2].6H_2O$	50.09(51.31)	4.26 (4.07)	15.57(16.62)	8.32	3.82
$[Ru_2(L^7)_4Cl_2].6H_2O$	54.16(53.99)	4.11 (3.98)	15.04(15.00)	3.98	3.84

Table 2. EPR and electronic spectral data for Ru(III) complexes in DMF at room temperature.

Complex	Electronic transitions (cm^{-1})	EPR parameters			
		g_1	g_2	g_3	$g_{av.}$
$[Ru_2(L^1)_4Cl_2].7H_2O$	37315,25200,22200	2.35	2.15	2.12	2.21
$[Ru_2(L^2)_4Cl_2].9H_2O$	39215,26385,22222	2.36	2.16	2.12	2.21
$[Ru_2(L^3)_4Cl_2].9H_2O$	38116,26280,22100	2.36	2.16	2.12	2.21
$[Ru_2(L^4)_4Cl_2].8H_2O$	38200,25460,20350	2.38	2.15	2.13	2.22
$[Ru_2(L^5)_4Cl_2].8H_2O$	37736,25641,16949	2.39	2.17	2.13	2.23
$[Ru_2(L^6)_4Cl_2].6H_2O$	37250,26230,17960	2.38	2.17	2.12	2.22
$[Ru_2(L^7)_4Cl_2].6H_2O$	37736,25641,19950	2.38	2.17	2.12	2.23

Table3. The infrared spectral data of the reported Ru(III) complexes.

Complex	IR spectra(cm^{-1})					
	$\upsilon_{(H_2O)}$	$\upsilon_{(C-O)}$	$\upsilon_{(N=N)}$	$\upsilon_{(Ru-N)}$	$\upsilon_{(Ru-O)}$	$\upsilon_{(Ru-Cl)}$
$[Ru_2(L^1)_4Cl_2].7H_2O$	3440	1420	1405	598	460	320
$[Ru_2(L^2)_4Cl_2].9H_2O$	3454	1449	1383	590	477	320
$[Ru_2(L^3)_4Cl_2].9H_2O$	3441	1426	1390	599	485	325
$[Ru_2(L^4)_4Cl_2].8H_2O$	3428	1452	1409	601	470	328
$[Ru_2(L^5)_4Cl_2].8H_2O$	3460	1440	1395	599	469	340
$[Ru_2(L^6)_4Cl_2].6H_2O$	3467	1461	1407	605	475	333
$[Ru_2(L^7)_4Cl_2].6H_2O$	3470	1440	1400	600	488	327

Table 4. Cyclic voltammetry data for 1x10^{-3} M Ru(III) complexes at a scan rate 50 mV/Sec at room temperature in 0.1 M TBAP in CH_2Cl_2.

Complex	Ru (III-IV)		Ru (III-II)					
	E_1 [a]	E_2 [b]	E_{pa1}	E_{pc1}	E_{pa2}	E_{pc2}	ΔE_{p1}	ΔE_{p2}
$[Ru_2(L^1)_4Cl_2].7H_2O$	0.32	0.72	-0.24	-0.32	-0.66	-0.75	0.08	0.09
$[Ru_2(L^2)_4Cl_2].9H_2O$	0.32	0.72	-0.24	-0.32	-0.65	-0.74	0.08	0.09
$[Ru_2(L^3)_4Cl_2].9H_2O$	0.33	0.73	-0.25	-0.33	-0.67	-0.76	0.08	0.09
$[Ru_2(L^4)_4Cl_2].8H_2O$	0.31	0.73	-0.23	-0.31	-0.68	-0.77	0.08	0.09
$[Ru_2(L^5)_4Cl_2].8H_2O$	0.32	0.72	-0.24	-0.32	-0.66	-0.75	0.08	0.09
$[Ru_2(L^6)_4Cl_2].6H_2O$	0.35	0.76	-0.25	-0.33	-0.68	-0.77	0.08	0.09
$[Ru_2(L^7)_4Cl_2].6H_2O$	0.35	0.76	-0.26	-0.34	-0.67	-0.76	0.08	0.09

[a]: *E_1=oxidation potential for Ru ^{III}-Ru ^{III} → Ru IV-Ru III;* [b]: *$E_{2=}$ oxidation potential for Ru IV-Ru III →Ru IV-Ru IV; $E_{pa=}$ anodic reduction potential; E_{pc} = cathodic reduction potential.*

Table 5 The susceptibility of some selected compounds against 8 pathogenic bacteria using Amikcin 30 mg as a standard antibiotic.

Compound	*E.coli*	*K.Pneumonia*	*P.auerginosa*	*P.mirabilus*	*S.typhaemirum*	*B.anthracius*	*St.aureus*	*St.Pyogenus*
Bzt	S	S	S	S	S	S	S	S
L_0	S	S	S	S	S	S	S	S
HL^1	S	S	S	S	S	S	S	S
HL^2	N	N	N	N	N	N	N	N
HL^3	N	N	N	N	N	N	N	N
HL^4	S	S	S	S	S	S	S	S
HL^5	S	S	S	S	S	S	S	N
HL^6	S	N	S	S	S	S	S	N
HL^7	N	N	N	N	N	N	N	N
$[Ru_2(L^1)_4Cl_2].7H_2O$	S	S	S	S	S	S	S	S
$[Ru_2(L^2)_4Cl_2].9H_2O$	N	N	N	N	N	N	N	N
$[Ru_2(L^3)_4Cl_2].9H_2O$	S	N	S	S	S	N	S	N
$[Ru_2(L^4)_4Cl_2].8H_2O$	N	N	N	N	N	N	N	N
$[Ru_2(L^5)_4Cl_2].8H_2O$	S	S	S	S	S	S	S	S
$[Ru_2(L^6)_4Cl_2].6H_2O$	S	S	S	S	S	S	S	S
$[Ru_2(L^7)_4Cl_2].6H_2O$	N	N	N	N	N	N	N	N

S; Susceptible , N; Non-susceptible

Table 6 The inhibition zone by minimum inhibitory concentration in millimeter

Compound	*E. coli*	*K. Pneumonia*	*P. auerginosa*	*P. mirabilus*	*S. typhaemirum*	*B. anthracius*	*St. aureus*	*St. Pyogenus*
Bzt	8	9	7	11	10	9	8	7
L_0	8	8	10	9	9	9	8	10
HL_1	8	7	8	10	9	7	8	6
HL_4	6	6	7	6	6	7	8	6
HL_5	8	8	7	8	7	7	6	N
HL_6	10	N	7	6	7	6	6	N
$[Ru_2(L^1)_4Cl_2]$.$7H_2O$	8	6	7	6	6	6	7	7
$[Ru_2 (L^5)_4Cl_2].9H_2O$	6	N	6	6	6	N	6	N
$[Ru_2 (L^5)_4Cl_2].8H_2O$	7	N	8	10	8	10	10	8
$[Ru_2 (L^6)_4Cl_2].6H_2O$	8	6	8	7	8	9	9	7

The inhibition zone for standard Amikacin is about ± 36 mm

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