

# Synthesis, spectroscopic characterization and antibacterial activities of mixed ligand metal(II) complexes of 4-amino-6-chloro-2-methylthiopyrimidine and 1,10-phenanthroline.

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**ABSTRACT:** Mixed ligand complexes of 4-amino-6-chloro-2-methylthiopyrimidine (L) and 1,10-phenanthroline (L<sup>1</sup>) with Mn(II), Fe(II), Ni(II), Pd(II), Cu(II) and Zn(II) ions were synthesized and characterized by infrared and electronic spectroscopies, room temperature magnetic moments, melting points and conductance measurements. Infrared spectra data confirmed that coordination was via the nitrogen atoms of the pyrimidine and phenanthroline rings respectively. Electronic spectra and room temperature magnetic moment data indicated that Mn(II), Fe(II), Ni(II) and Cu(II) complexes were octahedral and magnetically concentrated, exhibiting anti-ferromagnetism. In contrast, the Pd(II) and Zn(II) complexes assumed square planar and tetrahedral geometries, and were mononuclear and diamagnetic respectively. The conductance measurements in DMSO showed that the Ni(II), Zn(II) and Pd(II) complexes were 1:1/1:2 electrolytes. The in-vitro antibacterial studies of the complexes against *Bacillus cereus*, *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aureginosa*, *Klebsiella oxytoca* and *Staphylococcus aureus* revealed that the Mn(II) and Cu(II) complexes had broad-spectrum antibacterial activity with inhibitory zones range of 30.0-37.0 and 10.0-38.0 mm, proving their potentials as promising broad-spectrum antibacterial agents.

**Keywords:** antibacterial, antiferromagnetism, electrolyte, geometry, magnetically concentrated.

## Introduction

Nitrogen-containing heterocycles with their pronounced propensity of acting as ligands for metal ions have played a major role in the development of the field known as supramolecular and medicinal chemistry (Ajibade and Idemudia, 2013; Gulcan et al., 2012, Mostafa and Badria, 2008). The importance of metal ions in biological systems is well established (Goran et al., 2012). Moreover, pyrimidine and its derivatives have been extensively studied due to their occurrence in living cells (Gulcan et al., 2012, Isida et al., 1995). In addition, 1,10-Phenanthroline has a rigid structure with two aromatic nitrogens containing unshared electron pairs that can bind with metal ions. Most of the researches on the phenanthroline derivatives focus on their catalytic, redox, photoredox, biological activities, and their supramolecular chemistry (Prashanthi et al 2012; Ramankrishnan and Palaniandavar, 2005). Detailed literature search shows that mixed ligand metal(II) complexes of 4-amino-6-chloro-2-methylthiopyrimidine and 1,10-Phenanthroline have not yet been reported (Ajibade and Idemudia, 2013, Al-Ramadane et al., 2009, Anacona and Lopez, 2012, Beyramadi et al., 2011, Gulcan et al, 2012, Ishida et al., 1995, Li et al., 2008, Mostafa and Badria, 2008, Nazeeruddin et al., 2000, Onal et al 2011, Osanai et al., 2006, Osowole and Akpan, 2012, Osowole and Festus, 2013, Osowole et al., 2010). Thus, we synthesized and characterized the mixed ligand complexes of 4-amino-6-chloro-2-methylthiopyrimidine and 1,10-Phenanthroline, with the aims of investigating their potentials to exhibit ferro- and antiferromagnetism, and their suitability as lead complexes for further studies in drug development for infectious diseases. These complexes are new, being reported by us for the first time, as a continuation of our research on the use of metal complexes as treatments for infectious diseases and cancer (Osowole and Akpan, 2012, Osowole and Festus, 2013, Osowole et al., 2010, Osowole et al., 2011).

## Experimental

### Materials And Reagents

Reagent grade 4-amino-6-chloro-2-methylthiopyrimidine, 1,10-phenanthroline, Copper(II)chloride tetrahydrate, Nickel(II) chloride hexahydrate, Palladium(II)chloride, Manganese(II)chloride tetrahydrate, Zinc(II)nitrate hexahydrate, and Iron(II) sulphate heptahydrate were obtained from Aldrich and BDH chemicals, and were used as received, and solvents were purified by distillation.

### Preparation of [Cu(L)(L<sup>1</sup>)Cl<sub>2</sub>]·H<sub>2</sub>O

This complex was prepared by the addition of 0.21g (1.14 x 10<sup>-3</sup> moles) of CuCl<sub>2</sub>·4H<sub>2</sub>O to a stirring solution of 1.14 x 10<sup>-3</sup> moles (0.20g, 4-amino-6-chloro-2-methylthiopyrimidine) and 1.14 x 10<sup>-3</sup> moles (0.21g 1,10-Phenanthroline) in 30 mL of ethanol. The resulting green solution's pH was raised to 9 with three drops of triethylamine, and was then refluxed for 3 hours. The dark green precipitate obtained was filtered, washed with ethanol and dried over silica gel. The same method was used for the preparation of the Mn(II), Fe(II), Ni(II), Zn(II) and Pd(II) complexes from their chloride, sulphate and nitrate salts respectively.

### Physical measurement

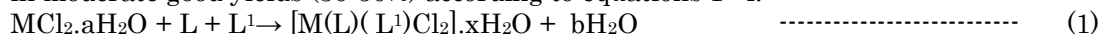
The solid reflectance spectra of the complexes were recorded on a Perkin-Elmer λ25 spectrophotometer and infrared spectra were recorded as KBr disc on a Perkin-Elmer FT-IR spectrum BX spectrometer in the range 4000-400 cm<sup>-1</sup>. The room temperature magnetic susceptibilities at 303K were measured on Sherwood Susceptibility Balance MSB Mark 1, melting points were determined with Mel-Temp electrothermal machine and molar conductivity measurements of 1 x 10<sup>-3</sup> M solutions in DMSO were obtained using electrochemical analyzer.

### Antibacterial assay

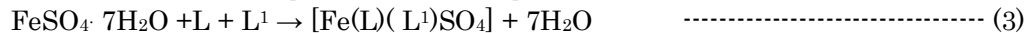
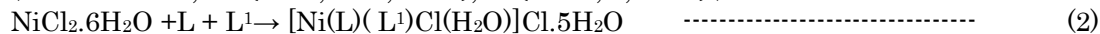
The antimicrobial activity of the synthesized compounds as well as their free ligands was studied using the agar diffusion technique. The bacterial used were identified laboratory strains of Bacillus cereus, Escherichia coli, Proteus mirabilis, Pseudomonias aureginosa, Klebsiella oxytoca and Staphylococcus aureus. The surface of the agar in a petri dish was uniformly inoculated with 0.2 mL of 18 hour old test bacterial culture. Using a sterile cork borer, 9 mm wells were bored into the agar. Then 0.06 mL of 10 mg/mL concentration of each metal complex in DMSO was introduced into the wells and the plates were allowed to stand on the bench for 30 minutes before incubation at 37°C for 24 hours after which inhibitory zones (in mm) were taken as a measure of antibacterial activity. The experiments were conducted in duplicates and Streptomycin was used as the reference drug.

### Results And Discussion

The reaction of the 4-amino-2,6-dichloropyrimidine (L), 1,10-phenanthroline(L<sup>1</sup>) with the metal(II) chlorides (Mn, Ni, Cu and Pd), FeSO<sub>4</sub>·7H<sub>2</sub>O and Zn(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O gave coloured complexes in moderate good yields (30-50%) according to equations 1- 4.



(when M = Mn, Cu {x = 1, a = 4, b = 3}, Pd {a = 0, x, b = 0} )



The ligands 4-amino-2,6-dichloropyrimidine (L), 1,10-phenanthroline(L<sup>1</sup>) melted at 138-140 and 98-100°C respectively, whereas their metal complexes mostly decomposed in the range 170-230°C, confirming coordination. The complexes were all slightly soluble in water, methanol, ethanol, nitromethane and methylene chloride but are soluble in DMSO. Single crystal of the complexes could not be isolated from any solution. Hence % metal, magnetic and spectroscopic data were used to propose possible structures, and the complexes are reported here for the first time. The colours, % metal, melting points, molar conductivity and room temperature magnetic moments for the complexes and proposed structure are presented in Table 1 and Figure 1 respectively.

### Conductance measurements

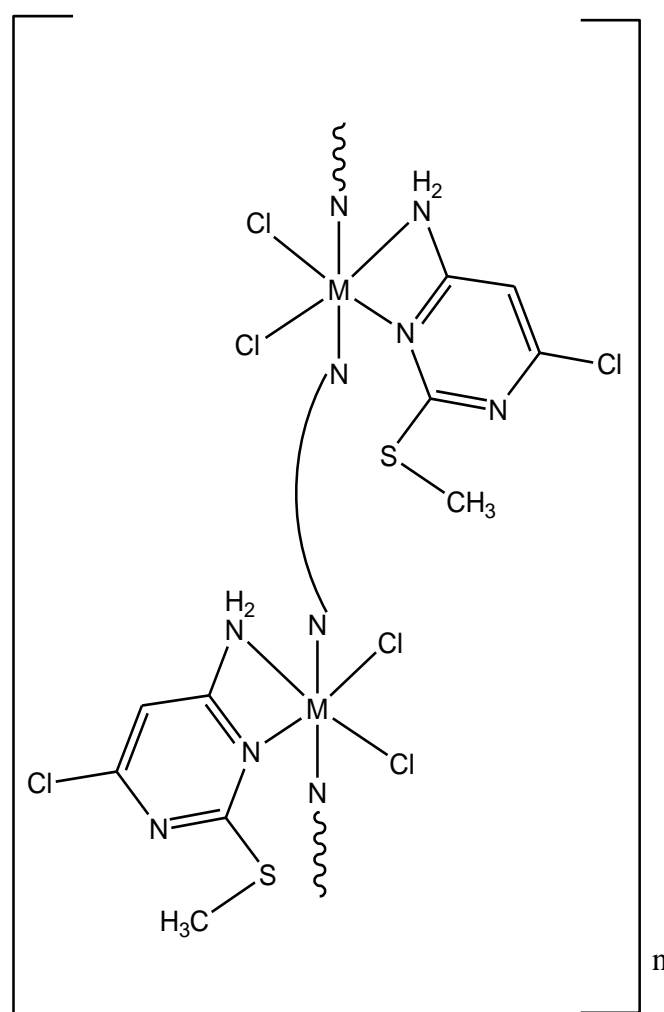
The molar conductance values of the complexes were in the range 6.63 - 31.4 Ω<sup>-1</sup>cm<sup>2</sup>mol<sup>-1</sup> indicating their non-electrolytic nature, with the exceptions of the Ni(II), Zn(II) and Pd(II) complexes with values of 40.3, 79.4 and 89.4 Ω<sup>-1</sup>cm<sup>2</sup>mol<sup>-1</sup> indicative of 1:1 and 1:2 electrolytes respectively (Gulcan et al., 2012).

### Electronic Spectra and Magnetic moments

The ultraviolet spectra of the compounds were characterized by strong absorption maxima between 28.57 kK, 32.26 - 38.46 kK and 40.0 kK respectively, assigned to  $n \rightarrow \pi^*$ ,  $\pi \rightarrow \pi^*$  and C.T transitions respectively (Table 2). The Mn(II) complex showed an absorption band at 24.88 kK assigned to  ${}^6A_{1g} \rightarrow {}^4E_{1g}$  transition, consistent with an octahedral geometry. The effective magnetic moment of Mn(II) complexes are expected to be close to the spin-only value of 5.90 B.M. since the ground term is  ${}^6A_{1g}$  and usually in the range 5.5-6.10 B.M since there is no orbital contribution. Consequently, an observed moment of 7.09 B.M is indicative of a high spin Mn(II) complex (Sakthilatha and Rajavel, 2013).

The Fe(II) complex had an absorption band at 19.23 kK typical of 6-coordinate, octahedral geometry and was assigned to  ${}^5T_{2g} \rightarrow {}^5E_g$  transitions. A moment of 5.0-5.5 B.M. is usually expected for octahedral Fe(II). In this study, a moment of 6.16 B.M was observed for this complex which was higher and indicative of a high spin octahedral complex (Salmom et al., 2009).

The Ni(II) complex showed two absorption bands at 16.66 kK and 22.22 kK typical of six coordinate octahedral geometry and were attributed to  ${}^3A_{2g} \rightarrow {}^3T_{1g}(F)$  and  ${}^3A_{2g} \rightarrow {}^3T_{1g}(P)$  transitions respectively. A room temperature magnetic moment of 3.94 B.M was observed, which indicated a high spin octahedral Ni(II) (Gulcan et al., 2013, Onal et al., 2011). The Cu(II) complex exhibited two absorption bands at 13.89 kK and 24.39 kK assigned to  ${}^2B_{1g} \rightarrow {}^2A_{1g}$  and  ${}^2B_{1g} \rightarrow {}^2E_{1g}$  transitions of a tetragonal (octahedral) geometry. A moment of 1.9-2.2 B.M. is usually observed for mononuclear copper(II) complexes, regardless of stereochemistry, expectedly higher than the spin only moment due to orbital contribution and spin-orbit coupling. The Cu(II) complex in this study, had a moment of 2.35 B. M which is slightly higher than expected (Beyramabadi et al., 2011, Reedy and Reddy, 2000).



Where M = Mn and Cu, N  N = 1,10-phenanthroline

Figure 1. Proposed structure for the Mn(II), Ni(II) and Cu(II) complexes

The Zn(II) complex showed M→L CT transitions at 23.04 kK, as no d-d transition was expected. This complex was diamagnetic and tetrahedral (Onaz et al., 2011). The spectrum of the Pd(II) complex showed an absorption band at 24.88 kK, typical of square planar geometry and was assigned to  $^1A_{1g} \rightarrow ^1E_{2g}$  transition. This complex was expectedly diamagnetic (Mostafa and Badria, 2008).

The consistent observation of higher room temperature magnetic moments for Mn(II), Fe(II), Ni(II) and Cu(II) octahedral complexes in this work was attributed to some antiferromagnetic interactions (Osanai et al., 2006) which we are unable to rationalize in the absence of viable crystals for single crystal X-ray structural investigation. This might indicate that these complexes were polymeric (Figure 1) with the 1,10-phenanthroline molecule bridging the metal centres, with each metal centre reinforcing the overall magnetic susceptibility of the complexes (Ishida et al., 1995).

### Infrared Spectra

The relevant bands are presented in Table 2. The medium bands at  $3373\text{ cm}^{-1}$  and  $3402\text{ cm}^{-1}$  in 4-amino-6-chloro-2-methylthiopyrimidine and 1,10-Phenanthroline were assigned as  $\nu(\text{NH}_2)$  and  $\nu(\text{OH})$  bands (Ajibade and Idemudia, 2013, Nazeeruddin et al., 2000). These bands appeared mainly as lone band in the complexes, with the exception of the Fe(II) complex which still retained the two bands at  $3547\text{--}3425\text{ cm}^{-1}$ . This confirmed non deprotonation of the amino hydrogen and its coordination to the metal(II) ions. The sharp bands at  $1648$  and  $1654\text{ cm}^{-1}$  in the ligands were assigned as  $\nu\text{ C}=\text{N}$  stretching vibrations and were shifted to  $1656\text{--}1660\text{ cm}^{-1}$  in the spectra of the metal(II) complexes confirming coordination through the nitrogen atoms of the pyrimidine and 1,10-Phenanthroline rings (Prashanti et al., 2012). The non appearance of  $\nu(\text{C}-\text{S})$  and  $\nu(\text{M}-\text{S})$  stretching vibrations confirmed the non involvement of the S- atom of the thiopyrimidine in complexation. Furthermore, the new bands in the range  $590\text{--}530\text{ cm}^{-1}$  were absent in the ligands and were assigned to  $\nu(\text{M}-\text{N})$  indicative of coordination of the N-atoms of the 4-amino-6-chloro-2-methylthiopyrimidine and 1,10-Phenanthroline to metal ions (Prashanti et al., 2012, Ramakrishnan and Palaniandavar, 2005). Similarly, the bands at  $358\text{--}389\text{ cm}^{-1}$  were absent in the spectra of the ligands, and were assigned to  $\nu(\text{M}-\text{O})$  and  $\nu(\text{M}-\text{Cl})$  respectively, confirming the involvement of oxygen of the sulphate/water and chlorine atoms in complexation with the metal atoms (Nazeeruddin et al., 2000).

### Antibacterial activities

4-amino-6-chloro-2-methylthiopyrimidine (L) was inactive against all the tested bacteria, while 1,10-phenanthroline (L<sup>1</sup>) was very active against all the bacteria with inhibitory zones range of 34.0-48.0 mm. However, their metal complexes generally were more active than the former and less active than the latter. The best activity of 1,10-phenanthroline was attributed to its ability to form hydrogen bond with the cellular content of the bacteria thereby causing the death of the organism (Anacona and Lopez, 2012). In addition, metal(II) complexes are expected to be generally more effective than the free ligand, due to chelation, which reduces the polarity of the metal atom mainly because of partial sharing of its positive charge with donor groups of the ligand and possible  $\pi$ -electron delocalization over the aromatic rings. This increases lipophilic character, favouring its permeation through lipid layers of the bacterial membrane (Ajibade and Idemudia, 2013, Anacona and Lopez, 2012).

### Conclusion

Mixed ligand complexes of 4-amino-6-chloro-2-methylthiopyrimidine (L) and 1,10-phenanthroline (L<sup>1</sup>) with Mn(II), Fe(II), Ni(II), Pd(II), Cu(II) and Zn(II) ions were synthesized and characterized by infrared and electronic spectroscopies, room temperature magnetic moments, melting points and conductance measurements. Electronic spectra and room temperature magnetic moment data indicated that Mn(II), Fe(II), Ni(II) and Cu(II) complexes were octahedral, the Pd(II) complex was square planar and the Zn(II) complex assumed a tetrahedral geometry. The conductance measurements in DMSO showed that the complexes were all covalent with the exceptions of the Ni(II), Zn(II) and Pd(II) complexes which were 1:1/1:2 electrolytes. The in-vitro antibacterial studies of the complexes against *Bacillus cereus*, *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aureginosa*, *Klebsiella oxytoca* and *Staphylococcus aureus* were generally good.

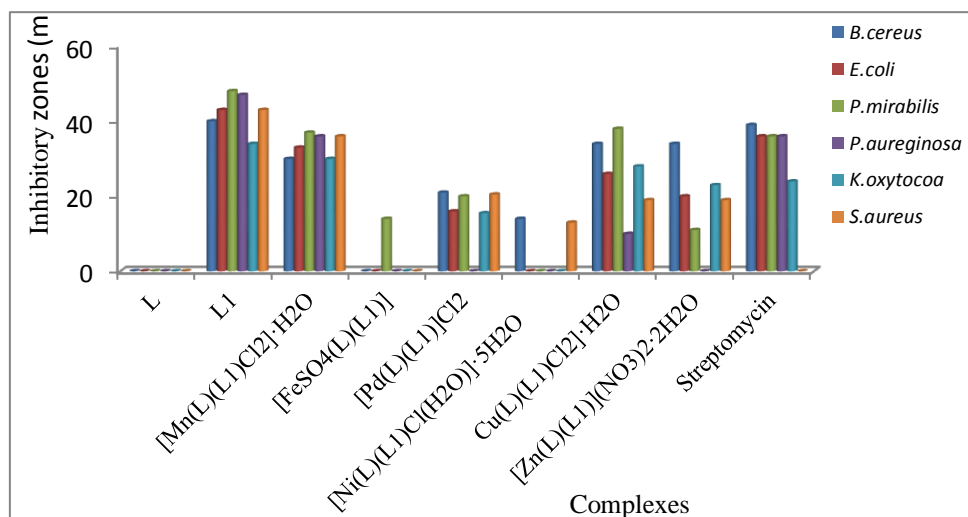


Figure 2. Histogram of the antibacterial activities of the legends and their complexes

The Fe(II) complex had the least activity, being active against only *P. mirabilis* with inhibitory zone of 14.0 mm. This was followed by the Ni(II) complex with activity against only the Gram positive *S. aureus* and *B. cereus* with inhibitory zones of 13.0 and 14.0 mm respectively. Furthermore, the Pd(II), and Zn(II) complexes had moderate activity against all the bacteria used with the exception of *P. aureginosa* with inhibitory zones range of 15.5 - 21.0 and 11.0 - 34.0 mm respectively.

The Mn(II) and Cu(II) complexes had the best activity, been active against all tested bacteria with inhibitory zones range of 30.0-37.0 mm and 10.0-38.0 mm respectively, proving their usefulness as potential broad-spectrum antibacterial agents.

Interestingly,  $L^1$  (1,10-phenanthroline) was more active (34.0-48.0 mm) than streptomycin (24.0-36.0 mm) against all the Gram negative bacteria. On the contrary,  $L^1$  (40.0 mm) had about same activity with streptomycin (39.0 mm) against *B. cereus* but lesser activity (43.0 mm) than streptomycin (50.0 mm) against *S. aureus*.

Table 1. Analytical data of the ligands and their metal(II) complexes.

Complexes	Formula mass	Colour	M.pt (°C)	%M (Exp)	%Y	$\chi_m$ ( $\Omega^{-1}\text{cm}^2\text{mol}^{-1}$ )	$\mu_{\text{eff}}$ (B.M)
L	175.64	Cream	138-140	-		-	-
$L^1$	180.21	White	98-100	-		-	-
$[\text{Mn}(\text{L})(\text{L}^1)\text{Cl}_2]\cdot\text{H}_2\text{O}$	481.68	Brown	+255	12.17 (11.41)	30	26.0	7.09
$[\text{FeSO}_4(\text{L})(\text{L}^1)]$	507.72	Red	+236	11.36 (11.00)	45	6.63	6.16
$*[\text{Ni}(\text{L})(\text{L}^1)\text{Cl}(\text{H}_2\text{O})]\text{Cl}\cdot 5\text{H}_2\text{O}$	593.54	Green	228-230	9.86 (9.89)	10	40.3	3.94
$[\text{Pd}(\text{L})(\text{L}^1)]\text{Cl}_2$	533.18	Cream	+222	20.27 (19.96)	30	89.4	0.75
$[\text{Cu}(\text{L})(\text{L}^1)\text{Cl}_2]\cdot\text{H}_2\text{O}$	508.31	Green	+218	12.27 (12.50)	50	31.4	2.35
$[\text{Zn}(\text{L})(\text{L}^1)](\text{NO}_3)_2\cdot 2\text{H}_2\text{O}$	581.26	White	+170	10.96 (11.25)	30	79.4	D

key: L = 4-amino-6-chloro-2-methylthiopyrimidine;  $L^1$  = 1, 10-Phenanthroline; Y = yield; + = Decomposition; D = Diamagnetic; \* = hygroscopic; Exp = Experimental.

Table 2. Relevant infrared and electronic spectra data of the Complexes.

Compound	$\nu(\text{OH})/\nu(\text{NH}_2)$	$\nu(\text{C}=\text{N})$	$\nu(\text{C}=\text{C})$	$\nu(\text{M}-\text{N})$	$\nu(\text{M}-\text{O})/\nu(\text{M}-\text{Cl})$	Electronic spectra (kK)	
L	3373m	1648s 1570	1420s	-	-	32.89	37.04
L <sup>1</sup>	-	1654s 1503s	1421s	-	-	32.26	38.46
[Mn(L)(L <sup>1</sup> )Cl <sub>2</sub> ].H <sub>2</sub> O	3425b	1656s	1422s	590w	378s	24.88	40.0
[FeSO <sub>4</sub> (L)(L <sup>1</sup> )]	3547s 3365b	1656s	1422s	617b	390m	19.23 36.50	24.88 33.33
*[Ni(L)(L <sup>1</sup> )Cl(H <sub>2</sub> O)]Cl.5H <sub>2</sub> O	3427m	1658s	1423s	575b	358s	16.00	22.22 34.00
[Pd(L)(L <sup>1</sup> )Cl <sub>2</sub> ]	3489m	1660m	1424s	530b	-	24.88 33.56	28.57
[Cu(L)(L <sup>1</sup> )Cl <sub>2</sub> ].H <sub>2</sub> O	3451m	1660s	1424s	541b	381s	13.89	24.39 37.58
[Zn(L)(L <sup>1</sup> )](NO <sub>3</sub> ) <sub>2</sub> .2H <sub>2</sub> O	3489m	1659s	1424s	535b	353s	23.04	35.21

L = 4-amino-6-chloro-2-methylthiopyrimidine, L<sup>1</sup>= 1, 10-Phenanthroline b = broad, s= strong, m= medium; 1kK = 1000cm<sup>-1</sup>

Table 3. Antibacterial activities of the Ligands and their complexes

Compound	<i>B. cereus</i>	<i>E. coli</i>	<i>P. mirabilis</i>	<i>P. aureginosa</i>	<i>K. oxytoca</i>	<i>S. aureus</i>
L	R	R	R	R	R	R
L <sup>1</sup>	40.0±1.4	43.0±2.8	48.0±1.4	47.0±2.8	34.0±1.4	43.0±2.8
[Mn(L)(L <sup>1</sup> )Cl <sub>2</sub> ].H <sub>2</sub> O	30.0±1.4	33.0±0	37.0±5.7	36.0±1.4	30.0±1.4	36.0±1.4
[FeSO <sub>4</sub> (L)(L <sup>1</sup> )]	R	R	14.0±1.4	R	R	R
[Ni(L)(L <sup>1</sup> )Cl(H <sub>2</sub> O)]Cl.5H <sub>2</sub> O	14.0±7.0	R	R	R	R	13.0±5.6
[Pd(L)(L <sup>1</sup> )Cl <sub>2</sub> ]	21.0±2.8	16.0±1.4	20.0±1.4	R	15.5±0.7	20.5±2.1
[Cu(L)(L <sup>1</sup> )Cl <sub>2</sub> ].H <sub>2</sub> O	34.0±4.2	26.0±4.2	38.0±1.4	10.0±1.4	28.0±1.4	19.0±0
[Zn(L)(L <sup>1</sup> )](NO <sub>3</sub> ) <sub>2</sub> .2H <sub>2</sub> O	34.0±4.2	20.0±4.2	11.0±2.8	R	23.0±0	19.0±0
Streptomycin	39.0±0	36.0±1.4	36.0±1.4	36.0±1.4	24.0±1.4	50.0±1.4

R = resistance

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