



Synthesis, Characterization and Biological Evaluation Study of Cephalexin (Ceph) and Isatin Schiff base and Its Complexation with Some Divalent Metal Ions

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Abstract

Background: In this paper, all the complexes with the general formulae I(a-e) $[MLCl_2H_2O]$ and II(a-e) $[ML_2]Cl_2$, were synthesized from divalent metal ions Co, Ni, Cu, Zn, or Mn with Schiff base (HL) which derived from cephalixin and isatin in the ratio of metal to ligand 1:1 for the primer and 1:2 for the later, this ligand Schiff base was tridentate NNO Schiff base. Complexes were characterized by elemental analysis, molar conductance and magnetic susceptibility measurements, electronic, FT-IR and ¹HNMR spectral studies.

Objective: The aim of this work was the synthesis of a novel Schiff base derived from cephalixin and isatin and synthesis of ten new complexes derived from this Schiff base and divalent metal ions (CO, Ni, Cu, Zn and Mn) in (1:1) for complexes I(a-e) and 1:2 for complexes II(a-e), ratio for complexes I(a-e) and (1-2) ratio for complexes II(a-e), and to test their antibacterial activity.

Methodology: The α -amino group of the cephalixin (Ceph) antibiotic was directly undergone nucleophilic addition into a Schiff base ligand when it was refluxed in ethanolic solution with isatin using an acid catalyst. This ligand was coordinated with divalent metal ions with ratio (1:1) and (1:2), by its refluxing in ethanolic solution to form the title complexes.

Results and Discussion: The chemical structures of the new ligand Schiff base and the neutral nonelectrolyte octahedral geometry of complexes I (a-e) and electrolyte octahedral geometry of complexes II(a-e) were confirmed through (¹HNR, FT-IR, U.V. and electronic spectra) in addition to elemental microanalysis, magnetic susceptibility and molar conductivity.

Conclusions: The Schiff bases ligand derived from Cephalixin (Ceph) with isatin and its complexation with divalent metal ions in (1:1) and (1:2) molar ratio of metal ion to ligand showed the interesting synthesis of simple procedures, high yields and good confirmation by all analysis methods with octahedral geometry and nonelectrolyte nature of complexes I(a-e) and electrolyte nature of complexes II(a-e). They have exhibited no antibacterial activity against Pseudomonas bacteria, but they exhibited minimum inhibitory concentration (MIC) ($\mu\text{g/ml}$) values against E.coli., especially those of complexes Ia and IIe, which displayed this activity at all concentrations.

Keywords: Cephalexin-Isatin, Schiff base, Divalent ions, Complexes

Introduction

It has been verified that the complexation of metallic elements with antibiotics increased their activity and decreased their toxicity.

At the end of the last century, the first-generation Cephalexin (Ceph) antibiotic which is active against Gram-positive and moderately active against Gram-negative [13] became too lost its activity due to the increase of β -lactamases resistance.

Many types of research to resolve this problem was detected by Mohler and colleagues who tested the

antimicrobial activity of complexes derived from Cu (II), Ag(I) or Zn (II) and β -lactam antibiotics and demonstrated that a coactive increase in the activity of the antibiotics and inhibition of β -lactamases responsible for resistance [23]. Another study provided serious information for understanding the ligand recognition and for advanced antibiotic development by studying the several crystal structures of L1 complexes with three different classes of β -lactam antibiotics (penicillin G, moxalactam, meropenem, and imipenem) [19]. Cephalexin (Ceph)

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show a variation in their antibiotic activity and toxicological properties when coordinated with metal as complexes, and this was due to the ability of chelate binding of these antibiotics to the metals [10].

At the same time, converted many antibiotics containing amino group moiety to Schiff bases using a bioactive famous chemical molecule 1H-indole-2,3-dione of the common name (isatin), which was literature informed to be wide spectrum antifungal and antibiotic activity [25],[21]

An example of increasing these antibiotic activities, many types of research were converted the amino group of cephalixin into Schiff bases, these Schiff bases derived from cephalixin showed substantially enhanced activity against *P. aeruginosa* as compared with the parent drug [18]

An increase in antibacterial activity was also shown When Cephalixin (Ceph) was coordinated to tin (II) ion [8]. A new series of Schiff bases of cephalixin was synthesized by condensation of cephalixin with appropriate ketones or aldehydes, and many of these Schiff bases were found to hold moderate antibacterial and antifungal activity [9]. The complexes of bivalent metal ions and Schiff base (derived from cephalixin that contains amine functional group with carbonyl compound) were widely used for a broad range of biological activities which were usually increased by complexation [15][27], and this was encouraged to a considerable increase in the study of the development of new Schiff bases and their metal complexes for pharmacological attentions[3], [21]. At the same time, six different Schiff bases derived from ampicillin and amoxicillin with isatin, 5-bromoisatin and 5-nitrosation were linked directly through their α -amino group to the acyl side chain of isatin (or its derivatives) via nucleophilic addition using glacial acetic acid as a catalyst [1]

The complexes derived from these Schiff bases and transition metal compounds were extensively investigated and approved to have antimicrobial actions [1]. Schiff bases were initiated to be multipurpose active molecules for synthesizing many pharmacologically active compounds, as well as the study of their activities as antimicrobial or anti-fungus via their coordinating with metal and its prospects as a potential bioactive core [20]. As part of the continuous works fixed toward the preparation of novel significant organic compounds as ligands and their complexations with bivalent metals such as Co, Ni, Cu, Zn, or Mn [2, 11, 12] it was becoming of interest to investigate the preparative routes to synthesize the title Schiff base and to coordinating it with Co, Ni, Cu, Zn, or Mn to the synthesis of novel complexes.

2-Experimental

2.1. Materials and measurement

All Chemical reagents and metal (II) chlorides used were purchased from Fluka and used as provided.

The FT-IR spectra were recorded as caesium iodide disc on FT-IR 8300 Shimadzu Spectrophotometer.

The UV-Visible spectra were measured in Ethanol using Shimadzu UV-Vis. 160 A spectrophotometer in the range (200–1000) nm.

Magnetic susceptibility measurement for complexes was obtained at room temperature using (magnetic susceptibility balance model MSB-MKI).

Flame atomic absorption of the elemental analyzer, Shimadzu AA-670, was used for metal determination.

Elemental microanalysis was carried out using C.H.N.S elemental analyzer model 5500-Carlo Erba instrument. Gallen Kamp M.F.B.600.010 F.

Melting point apparatus was used to measure the melting point of all the prepared compounds.

2.2. General synthesis of the Schiff base ligand:

Equimolecular weight (500 mmoles) of cephalixin and isatin were mixed in ethanol(25ml.), and 2-3 drops of glacial acetic acid were added. The reaction mixture was refluxed for 3 hrs. and lifted to cool. The solvent was evaporated by vacuum and the product which precipitated was filtrated to afford the new Schiff base ligand. Physical, yields, melting points and elemental analyses were presented in Table(1).

2.3. General synthesis of the new Schiff base ligand-Bivalent Metal Complexes of 1:1 I(a-e):

Equimolecular weight (500mmoles) of Schiff base and appropriate metallic salt were mixed in ethanol (30ml.) as solvent. The reaction mixture was refluxed for 5 hrs. The product was cooled then filtrated. Physical, yields, melting points and elemental analyses were presented in Table (1).

2.4. General synthesis of the Schiff base ligand – Bivalent metal complexes of 1: 2 ratio II (a-e):

A mixture of Schiff base (500mmoles) and appropriate metallic salt (250mmoles) was mixed in ethanol (30ml.) as a solvent, and the mixture was worked up as procedure (2.3). Physical, yields, melting points and elemental analyses were presented in Table (2).

Table (1): Physical properties, CHN, metals % analysis of ligand and complexes, I (a-e)

No.	Compound	Colour	m.p °C	Molecular weight	Practical Theoretical			
					%C	%H	%N	%M
L	Ligand (Schiff base)	Brown	110	476.51	60.48 60.43	4.20 4.23	11.73 11.75	-----
a	[CoL.Cl ₂ .H ₂ O]	Green	82	666.44	42.19 43.21	3.36 3.40	8.48 8.4	8.89 8.83
b	[NiL.Cl ₂ .H ₂ O]	Dark Yellow	156	666.20	42.00 43.23	3.33 3.40	8.55 8.4	8.81 8.79
c	[CuL.Cl ₂ .H ₂ O]	Yellow	102	670.04	42.79 42.98	3.29 3.37	8.29 8.35	9.5 9.47
d	[ZnL.Cl ₂ .H ₂ O]	Yellow	180	672.88	42.69 42.8	3.29 3.36	8.20 8.32	9.75 9.71
e	[MnL.Cl ₂ .H ₂ O]	Brown	103	661.43	43.49 43.54	3.39 3.42	8.39 8.466	8.5 8.3

Table (2): Physical properties, CHN, metals % analysis of ligand and complexes, II (a-e)

No. II	Compound	Colour	m.p. °C	Molecular weight	Practical Theoretical			
					%C	%H	%N	%M
a	[CoL _v] Cl ₂	Green	135	1054.03	54.12 54.64	3.77 3.79	11.00 10.62	5.25 5.2
b	[NiL _v] Cl ₂	Dark yellow	132	1053.79	54.07 54.65	3.77 3.79	11.12 10.62	5.6 5.56
c	[CuL _v] Cl ₂	Yellow	118	1058.21	53.80 54.43	3.77 8.78	11.07 10.53	6.19 6.00
d	[ZnL _v] Cl ₂	Yellow	120	1060.48	53.70 54.33	3.79 3.77	11.00 10.56	6.24 6.16
e	[MnL _v] Cl ₂	Brown	130	1050.03	53.30 54.85	3.80 5.81	11.44 10.66	5.3 5.22

3. Results and discussion:

Cephalexin, the parent ligand in this work has many basic atoms or groups that are bonded to the central metal atom or ions by donating its lone pair of the electron to the central bidentate metal of highly positive charge atom, which is Co, Ni, Cu, Zn, or Mn. The chemical structure of this ligand and its suggested donor sites were tridentate ligand coordinated to the metal through primary amino, β -lactamic carbonyl (exocyclic carbonyl group), carboxylate and/or even the amide nitrogen as shown in fig (1).

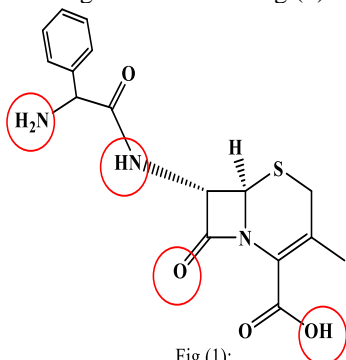


Fig (1):
Cephalexin chemical structure and its suggested donor sites

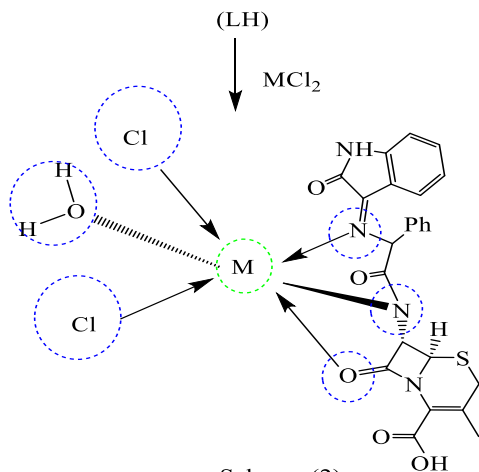
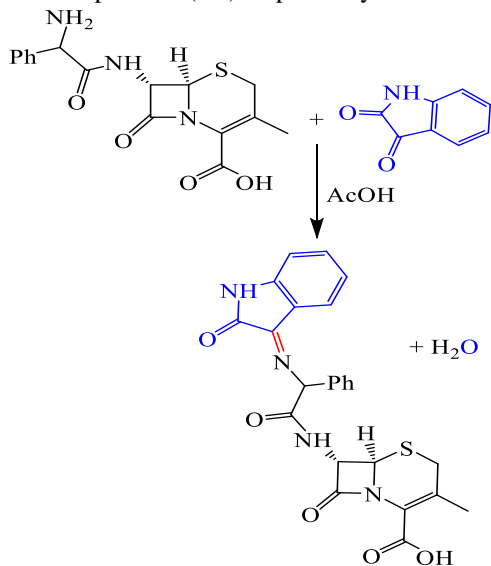
The Schiff base ligand was synthesised via the condensation of the primary amine group of the cephalosporin antibiotic with the isatin carbonyl group using acetic acid as catalyst, Scheme (1). The formation of the imine ($-C=N-$) functional group provides many uses in medicinal, industrial, catalytic activity and as important ligands in coordination compounds[14]. This Schiff base ligand was characterized by spectroscopic analysis (FT-I.R), (U.V-vis) and (¹H.NMR) spectra in addition to physical properties of colour and melting points. Complexes I(a-e) and II (a-e) were obtained by the reaction of bivalent metal ions Co (II), Ni (II), Cu (II) Zn (II) or Mn (II) and the Schiff base ligand in mole ratio (1:1) and (1:2) respectively. These complexes were very stable at room temperature in the solid state and generally soluble in hot DMF and DMSO.

All these complexes elemental microanalysis was in agreement with the anticipated stoichiometry of the complexes (the calculated and found values were obeyed with the accepted limits), Tables (1 and 2).

Schiff base ligand had melting point at 110°C, while all complexes were melted at (82-180) °C. The dye colours of the Schiff base ligand and the novel complexes (I and II) indicated the high molar

extinction constant [24], these physical properties and elemental microanalysis of Schiff base ligand and complexes I and II were found in good agreement with the expected values and were listed in Tables (1) and (2) respectively.

Scheme (1,2 and 3) showed the synthetic pathways of new Schiff base ligand, complexes I(a-e) and complexes II(a-e) respectively.

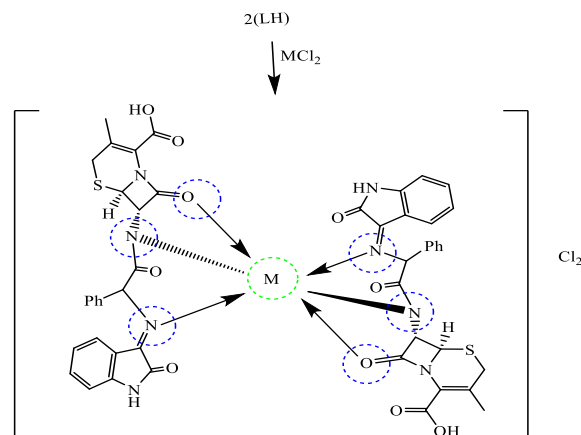


M = Co, Ni, Zn , or Mn

3.1. Ligand 1HNMR

The NMR spectra of Schiff base ligand, fig (2) was recorded in DMSO-d₆, exhibited a single peak appeared at 12ppm was assigned for OH of cephalixin

carboxylic proton. Another peak that appeared at 7.96ppm was assigned to the amino group proton of the isatin ring, and all nine aromatic protons appeared at 7.48-7.94ppm.



M = Co, Ni, Zn , or Mn

3.2. Infrared Spectral Analysis:

The FT-IR spectrum of the new ligand (HL) is comprised of the main absorption peaks of the Schiff base free ligand (Table1). The characteristic band was shown at (1699.76 cm⁻¹) for ν(C=N) azomethine, bands at (3270cm⁻¹) for ν (NH) amide and band at (1618cm⁻¹) for ν(C=O) of β lactam exocyclic carbonyl functional group respectively, Table (3) and fig (3).[26,27,28]

The FT-IR spectra of the complexes I of formula [MLCl₂H₂O] showed numerous guide peaks in which their absorptions were expected to be shifted upon complexation and they were involved in chelation.

These absorptions were shifted to lower frequencies of the different metals coordinating to azomethine (C=N) groups at (1630-1667.10cm⁻¹) and amide (NH) groups around (3170-3179cm⁻¹) and to β-lactam (C=O) groups around (1610-1615.85cm⁻¹) respectively which were a good indication that the ligand was coordinated with the two atoms of chloride and one molecule of water at one side and metal ions through the (N-N-O) atoms at the other side as shown in Scheme (2).

Also, the frequencies of the (M-OH₂) and (M-Cl) bands around ν(2888cm⁻¹) and ν(507cm⁻¹) were assigned to the structures of these complexes with a 1:1 ratio. The FT-IR of complex I(a), Fig (4) was the representative for complexes I(a-e). The FT-IR spectra of the complexes II(a-e) of formula [ML₂]Cl₂, Table (4) displayed ligand bands with the proper shifts due to complexes formation.

The lower frequency of the azomethine (C=N) groups at (1628-1633.81 cm^{-1}) was a good indication that the ligand was coordinated with the metal ions through the (N) azomethine group, and the lower frequencies of the amide (NH) groups around (3170-3177 cm^{-1}), and the β -lactam (C=O) groups around (1698-1615 cm^{-1}), respectively.

Also, the absence of the two frequencies of the (M-OH₂) and (M-Cl) bands was assigned to the structures of these complexes with a 1:2 ratio that coordinated to the (N, N, O) atoms with the two sides.

The FT-IR of complex II(a), Fig (5) was the representative for complexes I(a-e).[26]

3.3. Molar conductivity

All complexes I(a-e) were neutral in their nature, non-electrolytes and non-conductance due to low molar conductance values in ethanol solution which were (14-19) ($1 \times 10^{-3}\text{M}$) $\Omega^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$, Table (5), [6]. The molar conductance data of complexes II(a-e) were (70-88) ($1 \times 10^{-3}\text{M}$) $\Omega^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$ demonstrating that they were electrolytic, [16][17].Table (5).

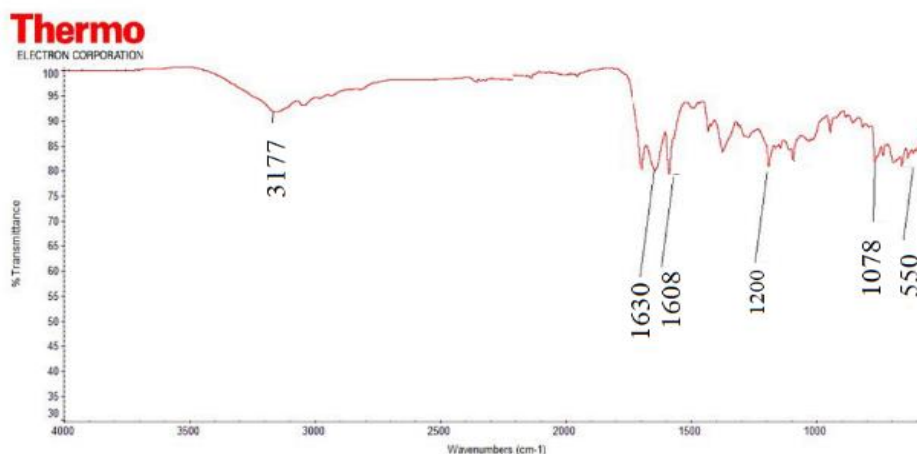


Fig (5)

Table (5): Conductivity data of the ligand and complexes I and II.

No. I	Complexes	Conductivity in Ethanol $\Omega^{-1} \text{cm}^2 \cdot \text{mol}^{-1}$	No. II	Complexes	Conductivity in Ethanol $\Omega^{-1} \text{cm}^2 \cdot \text{mol}^{-1}$
a	[CoLCl ₂ H ₂ O]	14	a	[CoL ₂]Cl ₂	70
b	[NiLCl ₂ H ₂ O]	19	b	[NiL ₂]Cl ₂	88
c	[CuLCl ₂ H ₂ O]	12	c	[CuL ₂]Cl ₂	81
d	[ZnLCl ₂ H ₂ O]	16	d	[ZnL ₂]Cl ₂	79
e	[MnLCl ₂ H ₂ O]	15	e	[MnL ₂]Cl ₂	77

3.4. Electronic spectra

The Schiff bases ligand active spectrum graph report that its electronic spectrum exhibited intense absorption at 357.5, 315.5 and 234 nm attributed to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ respectively. The electronic spectrum of Co (II) complex I(a) showed three peaks at 658, 303.5, 237.5 and 231 nm assigned to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ respectively, suggesting an octahedral geometry.

The electronic spectrum of Ni (II) complex I(b) showed five peaks at 390, 364, 699.5, 362.5 and 343.5 nm assigned to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ respectively, suggesting the same configuration octahedral geometry, [4]. The second set of complexes II(a-e) of metal: ligand 1:2, the [CoL₂. H₂O] complex II(a) electronic spectrum showed five peaks at 397, 318.5,

578.5, 328.5 and 304 nm assigned to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$. These complexes were, therefore, said to have also octahedral geometry, while the [CuL₂. 2H₂O] was shown the exceptional square planar geometry, all these values were shown in Table (6).

3.5. Magnetic Susceptibility:

All the absorption bands of these complexes were shown in Table (5) in which the magnetic susceptibility for divalent metals complexes I(a-e) of [ML.Cl₂.H₂O] were 2.5-5.6 respectively.

Complexes II(a-e) of [ML₂] Cl₂ were 2.5-5.5 respectively which confirmed the octahedral geometry for all these complexes. Scheme (2) and (3) [22] [27] and [5].

Table (6): Electronic spectra data for complexes

No.	complexes	$\nu_{1(\text{cm}^{-1})}$	$\nu_{2(\text{cm}^{-1})}$	$\nu_{3(\text{cm}^{-1})}$	$\nu_{4(\text{cm}^{-1})}$
	Ligand	14256	27972	31695	42735
Ia	[CoLCl ₂ H ₂ O]	15186	25250	32948	42105, 43290
Ib	[NiLCl ₂ H ₂ O]	14306	25641, 27472	-----	-----
Ic	[CuLCl ₂ H ₂ O]	13250	22350	32154	-----
Id	[ZnLCl ₂ H ₂ O]	14255	25580	33112	-----
Ie	[MnLCl ₂ H ₂ O]	19334	21088	35273	49504
IIa	[CoL ₂]Cl ₂	15430	25188	31397	-----
IIb	[NiL ₂]Cl ₂	15197	22471, 25000	-----	-----
IIc	[CuL ₂]Cl ₂	19330	24783, 28943	-----	44052, 46511
IId	[ZnL ₂]Cl ₂	19990	25940, 27624	30030	-----
IIe	[MnL ₂]Cl ₂	19249	21180	31746	42735

Table (7): Magnetic susceptibility measurements

No.I	μ_{eff} (practical)	No.II	μ_{eff} (practical)
Ia	5	IIa	5.2
Ib	2.8	IIb	3.1
Ic	4.5	IIc	4.9
Id	3.7	IId	2.5
Ie	4.7	IIe	5.5

3.6. Antibacterial Activity

The new complexes derived from the Schiff base and the transition metals were play dynamic roles in the antibacterial study; most of these were studied for their antibacterial activity. This work suggested that all the metal complexes of the functional groups return to the cephalixin moiety or the important azo methane group have comparatively more biological activity.

Antibacterial activities of the free Schiff ligand, complexes (I-II) and standard drug were screened by disc diffusion method in DMSO as solvent. The results of the antibacterial study were given in Table (8).

The antibacterial activity was estimated based on the size of the inhibition zone in the discs. Under identical conditions neither free Schiff base nor the new complexes I and II were exhibited any antibacterial activity against Pseudomonas bacteria, but they exhibited minimum inhibitory concentration (MIC) ($\mu\text{g/ml}$) values against E. coli., especially those of manganese complexes I (e) and II (e), which displayed this activity at all concentrations.

4. CONCLUSION

The novel Schiff base which derived from cephalixin and isatin with all these new complexes (I and II) derived from divalent metal ions and this Schiff base in (1:1) and (1:2) molar ratio of ligand to metal ion showed were successfully synthesized.

¹HNMR, FT-IR, UV and electronic spectral with molar conductivity measurement and magnetic susceptibility measurements suggested the non-electrolytic nature of complexes I(a-e) and electrolytic nature of the complexes II(a-e) which all have octahedral geometry. Further under

identical conditions neither free Schiff base nor the new complexes I and II have exhibited any antibacterial activity against Pseudomonas bacteria, but they exhibited minimum inhibitory concentration (MIC) ($\mu\text{g/ml}$) values against E. coli., especially those of manganese complexes I (e) and II (e), which displayed this activity at all concentrations.

Table (8): The antibacterial activity of free ligand and complexes I and II against Pseudomonas and E.coli:

Free ligand and Complexes	10 ⁻³ M		10 ⁻⁴ M		10 ⁻⁵ M		10 ⁻⁶ M	
	*	**	*	**	*	**	*	**
Ligand	+	-	+	-	-	-	-	-
Ia. [CoLCl ₂ H ₂ O]	+	-	-	-	-	-	-	-
Ib. [NiLCl ₂ H ₂ O]	+	-	+	-	-	-	-	-
Ic. [CuLCl ₂ H ₂ O]	+	-	-	-	-	-	-	-
Id. [ZnLCl ₂ H ₂ O]	-	-	-	-	-	-	-	-
Ie. MnLCl ₂ H ₂ O]	+	-	+	-	+	-	+	-
IIa. [CoL ₂]Cl ₂	-	-	-	-	+	-	+	-
IIb. [NiL ₂]Cl ₂	+	-	-	-	-	-	-	-
IIc. [CuL ₂]Cl ₂	+	-	-	-	-	-	-	-
IId. [ZnL ₂]Cl ₂	-	-	-	-	-	-	-	-
IIe. [MnL ₂]Cl ₂	+	-	+	-	+	-	+	-

*E.coli, ** Pseudomonas

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