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Synthesis and Characterization of Complexes Derived from Metals Mixed Ligands of Erythritol Sugar and 4-Aminoantipyrine or Salicylic acid as Antibiotic

Waseem M. Gameel Hasan [1], Samaa A. Raoof [2], Asem S. A.A. Albotani [3], Shakir M. Saied [4], Mohaned Y. Saleh[5], Rania Abd Elmohsen Abo El Nour [6&7] , M .A Abdelzaher [8*]

[1] *Department of pharmaceutical chemistry, College of Pharmacy, Ninevah University, Mosul- Iraq.*
[2] *Northern Technical University, Mosul Technical Institute, Department of Chemical Industry, Mosul, Iraq*
[3] *Department of Chemistry, College of Science, University of Mosul, Mosul, Iraq*
[4] *College of Pharmacy, Al-Noor University, Mosul city, Alshallalat Road.*
[5] *Department of Chemistry, College of Education for Pure Science, University of Mosul, Mosul, Iraq*
[6] *Community Health Nursing Department, Beni-Suef Health Technical Institute, Ministry of Health, Beni-Suef, 62511, Egypt*
[7] *Anesthesia Techniques Department, College of Health and Medical Techniques, Al-Mustaqbal University, 51001, Babylon, Iraq*
[8] *Environmental Science and Industrial Development Department, Faculty of Postgraduate Studies for Advanced Sciences, Beni-Suef University, Beni-Suef 62511, Egypt*

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Abstract

New antibiotic complexes were synthesized from cobalt, nickel, copper, and zinc, ions mixed with ligands of either erythritol (ER) with 4-aminoantipyrine (4AAP), complexes I(a-d) or erythritol (ER) with salicylic acid (SAL), complexes II(a-d). The general formulas for these two types complexes are $[M(ER)(4AAP)(H_2O)_2]$ and $K_2[M(ER)(SAL)(H_2O)_2]$, respectively. These complexes were characterized by various physical properties, including melting points, colors, and solubility, alongside elemental analysis via CHN device. Additional techniques employed for characterization included molar conductance measurements, Fourier-transform infrared spectroscopy (FTIR), Ultraviolet-Visible (UV-VIS) spectrophotometry, magnetic susceptibility tests and flame absorption. Both 4-aminoantipyrine (4AAP) and salicylic acid (SAL) serve as bidentate ligands, each contributing two donor atoms to form four coordinating bonds in the structure of these mixed ligand complexes (I and II). All synthesized complexes are non-electrolytes and are classified as octahedral. Some complexes demonstrated antibacterial potential; notably, complexes Ia and IId showed activity against E. coli at both tested concentrations, reaching 59.1% of the activity of ciprofloxacin, while their activity against Pseudomonas aeruginosa reached 58.3% and 58.4% respectively.

Keywords: 4-aminoantipyrine, Antibiotic activity, Erythritol, Metal complexes, Octahedral geometry, Salicylic acid.

*Email: mohseoud@gmail.com

تحضير وتشخيص معقدات مشتقة من معادن مختلفة مرتبطة بسكر إريثريتول و4-أمينوأنتيبيرين أو حمض الساليسيليك واستخدامها كمضاد حيوي

وسيم محمد جميل حسن [1]، سماء عدنان رؤوف [2]، عاصم س.أ. البوتاني [3]، شاكر محمد سعيد [4]، مهند يقضان صالح [5]، رانيا عبد المحسن أبو النور [6, 7] , محمد أبوالسعود عبد الظاهر [8]

[1] قسم الكيمياء الصيدلانية، كلية الصيدلة، جامعة نينوى، الموصل، العراق.

[2] الجامعة التقنية الشمالية، المعهد التقني الموصل، قسم الصناعات الكيميائية، الموصل، العراق.

[3]قسم الكيمياء، كلية العلوم، جامعة الموصل، الموصل، العراق.

[4] كلية الصيدلة، جامعة النور، مدينة الموصل، طريق الشلالات.

[5] قسم الكيمياء، كلية التربية للعلوم الصرفة، جامعة الموصل، الموصل، العراق.

[6] قسم تمريض صحة المجتمع، المعهد التقني الصحي بني سويف، وزارة الصحة، بني سويف، مصر.

[7] قسم تقنيات التخدير، كلية التقنيات الصحية والطبية، جامعة المستقبل، بابل، العراق.

[8] قسم علوم البيئة والتنمية الصناعية، كلية الدراسات العليا للعلوم المتقدمة، جامعة بني سويف، بني سويف، مصر.

الخلاصة:

تم تحضير و دراسة خصائص معقدات جديدة ذات فعاليتها كمضادات حيوية مشتقة من ايونات فلزات ثنائية التكافؤ مناسبة (M^{+2}) مثل: الكوبلت والنيكل والزنك مع خلائط الاريثريتول (ER) مع 4-امين انتي بايرين (4AAP) ذو الصيغة العامة [M (ER)(4AAP)$(H_2O)_2$] او الاريثريتول (ER) مع حامض الساليسليك ذو الصيغة العامة K_2M [(ER)(SAL)$(H_2O)_2$] حيث تمت دراسة خصائصها من الصفات الفيزيائية (درجات الانصهار والألوان والاذابة) إضافة الى تحليل عناصر الكربون والهدروجين والنتروجين وحساب التوصيلية المولارية وطيف الاشعة تحت الحمراء وطيف الاشعة الفوق البنفسجية – المرئية وحساب المغناطيسية والامتصاص اللهبي الذري . ان لكل من الاريثريتول (ER) الممزوج مع احد لليكندات الاثنين وهما ال 4-امين انتي بايرين (4AAP) اوحامض الساليسليك (SAL) ذرتين مانحتين (ثنائيتا السن) والتي تشمل أربعة أواصر تناسقية لكل من هذه المعقدات الجديدة نوع (Ia-d) و(IIa-d). كل هذه المعقدات أظهرت صفات غيراليكتروليتية ولها اشكال هندسية ثمانية السطوح. بعض المعقدات الجديدة اثبتت فعالية مضادة للبكتيريا ،فقد بلغت هذه الفعالية للمعقدات (Ia و IId) ضد (*E-coli*) حوالي 59.1٪ من نشاط المضاد الحيوي Ciprofloxacin ، بينما وصل النشاط ضد *Pseudomonas aeruginosa* الى مايقرب 58.3٪ و 58.4٪ على التوالي.

1. Introduction

The synthesis of mixed-ligand coordination complexes has attracted increasing interest from inorganic chemists, especially when the ligands possess pharmaceutical activity [1-3]. This growing interest is due to the fact that these novel complexes exhibit variable properties and differ significantly from traditional complexes associated with the same metal ion. Moreover, these mixed-ligand complexes are often easier to synthesize and demonstrate enhanced pharmaceutical activity [4-8].

The primary ligand in this study is erythritol, a four-carbon polyol derived from blackstrap molasses and the reduced form of erythrose (one of the two reduced forms of erythrulose), as shown in Scheme (1), [9]. Erythritol was first commercially developed as a sweetener by Japanese companies in the 1990s, [10]. Additionally, many coordination complexes are utilized

as precursor materials in the preparation of nanometallic catalysts. Furthermore, numerous organometallic catalysts were synthesized by coordinating a metal with ligands such as alkaloids, chlorine, or selenate ions, and with coordination bonding to give very important homogeneous catalysts [11]. Recently, the European Food Safety Authority reconsidered the safety profile of erythritol, lowering its recommended daily intake to 0.5 grams per kg body weight, this lower limit was set to "safeguard against its laxative effect [12].

The second ligand utilized in this study is 4-aminoantipyrine, pyrazalone derivative as shown in Scheme (1). This heterocyclic compound, featuring an exocyclic carbonyl group at position (5) and the most active donating amine group at position (4), has attracted interest in diverse fields including biological, clinical, pharmacological, organic synthesis and inorganic coordination. It is also widely used in antipyretic medications [13-15]. third key ligand is salicylic acid, named after the Latin salix for willow tree, with it is famous ester, this acid is commonly used as skin remedy and skincare for (warts, psoriasis, acne vulgaris, ringworm, dandruff, and ichthyosis [16]. This phenolic compound contains an aromatic benzene ring with ortho hydroxyl group, making this molecule very important in organic synthesis and as an important ligand in inorganic complexations, as shown in Scheme (1), [17-18].

The purpose of this study, as part of an ongoing program directed toward the study of important biologically active agents [19-21], it to present the synthesis, characterization of eight mixed complexes comprising metal ions combined with mixed ligands—erythritol and either 4-aminoantipyrine or salicylic acid—as novel antibiotic-active compounds.
These new complexes were characterized by using physical properties of color, melting points, CHN elemental analysis, molar conductance, magnetic measurements and spectral techniques such as IR and UV-Vis spectroscopy.

2. Experimental

The three ligands of erythritol (ER), 4-aminoantipyrine (4AAP) and salicylic acid (SAL) as well as the four metal salts ($CoCl_2.6H_2O$, $NiCl_2.6H_2O$, $CuCl_2.2H_2O$ and $ZnCl_2$) were from Merck. The Philips PW-Digital Conductance meter was used to measure conductivity of the compounds dissolved in DMF (10^{-3} M/L) at 25°C. The Euro vector EA 3000 single V.3.O. was used to utilize the elemental analysis (C, H, N). An auto magnetic susceptibility was measured at 25°C using Sherwood equipment. A Shimadzu A.A-160A Atomic Absorption / Flame emission spectrophotometer was used to measured atomic absorption. The UV-Vis- spectrum was recorded by UV-Vis 160A spectrophotometer. Finally, the infrared spectra were performed on a Shimadzu FTIR-8400S Fourier transform infrared spectrophotometer in the range 400-4000 cm^{-1}.

3.1 Synthesis of [M (ER)(4AAP) (H_2O)2], I(a-d): [22]

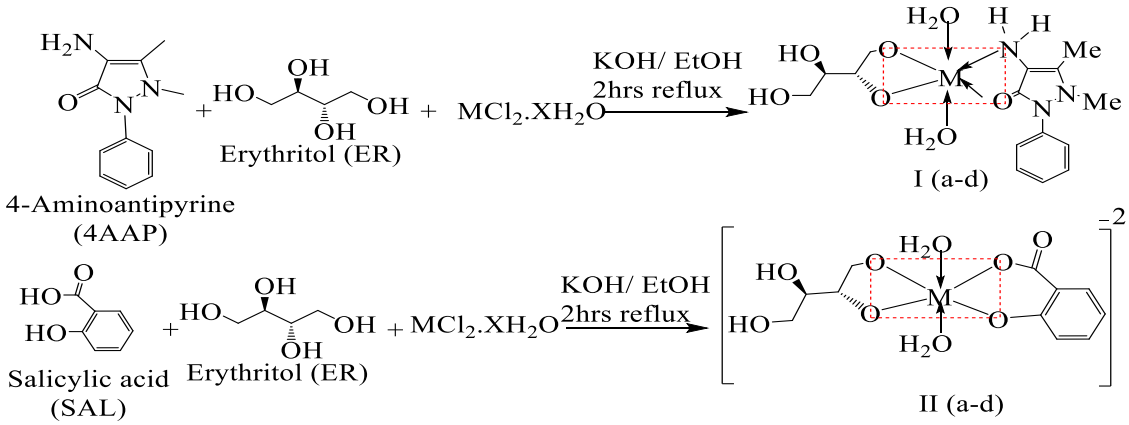
A mixture of erythritol (0.122 gm,0.001 mol) and 4-aminoantipyrine(4AAP) (0.203 gm, 0.001 mol) was gradually added to the KOH solution (0.5M). The result mixture was refluxed using a magnetic stirrer with the appropriate MCl2 (0.001 mole) of [0.237g , $CoCl_2.6H_2O$; 0.237g , $NiCl_2.6H_2O$; 0.170g , $CuCl_2.2H_2O$; 0.136g ,$ZnCl_2$] for 2 hours to ensure the completion of the complexation reaction. The resulting solid was filtered, washed with 20 ml of diethyl ether and dried under vacuum for several hours. The physical characterizations of these complexes, elemental analyses (CHN) and molecular weight are presented in Table (1).

3.2 Synthesis of K2 [M (ER)(SAL) (H_2O)2], II(a-d): [1]

An ethanolic solution containing erythritol (0.122 gm,0.001 mol) and salicylic acid (SAL) (0.138 gm, 0.001 mol) was gradually added to the KOH solution (0.5M). The resulting mixture was then processed identically to the first experiment. The physical characteristics of these complexes, the elemental analyses (CHN) and molecular weight are presented in Table 1).

3. Results and Discussion

These eight novel complexes were synthesized by refluxing the two bidentate ligands of erythritol and 4-aminoantipyrine(4AAP) or salicylic acid (SAL) with the corresponding metal chloride of cobalt, nickel, copper or zinc in presence of an ethanolic solution of potassium hydroxide. The synthetic route of the designed complexes (I and II) is shown in Scheme (1)



Scheme (1): The synthetic routs of the designed new complexes I and II

M = Co, Ni, Cu or Zn

The physical properties of these complexes, including melting points, colors and elemental analysis, are presented in Table 1). All these complexes were soluble in ethanol, di-methyl sulphoxide and dimethyl formamide [23].

Table 1: The novel Complexes Physical Properties

Complex No.	Molecular Formula/ Molecular Weight	m.p. °C	Color	CHN Analysis Theo. Pract.			
				C	**H**	**N**	**M**
Ia	$C_{15}H_{25}N_3O_7Co$ 417.93	108-110	Brown	43.06 43.13	5.98 5.87	10.05 10.07	14.1 14.06
Ib	$C_{15}H_{25}N_3O_7Ni$ 417.69	158-160	Green	43.09 43.02	5.98 5.86	10.05 10.11	14.05 14.14
Ic	$C_{15}H_{25}N_3O_7Cu$ 422.55	98-100	Brown	42.59 42.64	5.91 5.85	9.93 9.86	15.03 15.00
Id	$C_{15}H_{25}N_3O_7Zn$ 424.38	143-145	White	42.41 42.35	5.89 5.93	9.89 9.92	15.40 15.44
IIa	$K_2[C_{11}H_{16}O_9Co]$ 428.93	178-180	Violet	30.77 30.68	3.73 3.65	----	13.73 13.70
IIb	$K_2[C_{11}H_{16}O_9Ni]$ 428.69	134-136	Green	30.79 30.83	3.73 3.69	----	13.69 13.74
IIc	$K_2[C_{11}H_{16}O_9Cu]$ 433.55	103-105	Green	30.44 30.37	3.69 3.58	----	14.65 14.60
IId	$K_2[C_{11}H_{16}O_9Zn]$ 435.38	107-109	cocoa	30.31 30.25	3.67 3.70	----	15.01 15.04

The solubility and melting points of these novel complexes suggest that they are non-polymeric in nature [24-25]. Molar conductance measurements of the complexes in DMF

(Table 2) indicated that they behave as non-electrolytes. These complexes can be formulated as [M (ER)(4AAP) $(H_2O)^2$] and K2[M (ER)(SAL) $(H_2O)_2$] where M= Co(II),Ni(II),Cu(II) or Z(II) [21, 22]. The presence of "K^+ ions" of the K2[M (ER)(SAL) $(H^2O)_2$] complex result in reduced conductivity significantly and limiting of this complex to dissociate in DMF due to this complex stability and solvent property [26-27].

Table 2: Molar conductance measurements

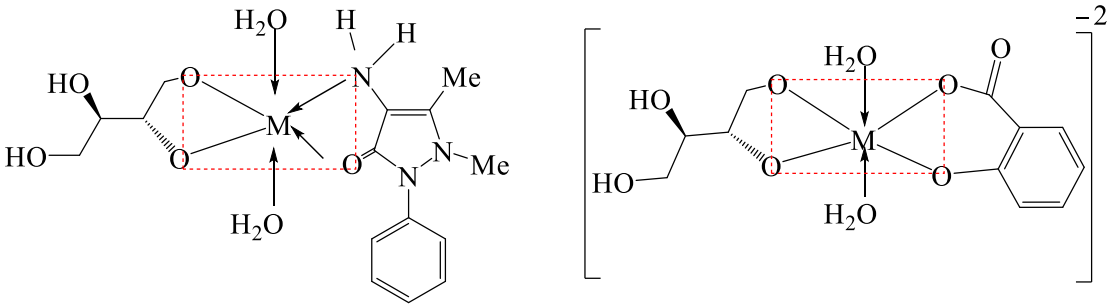
No	Molar conductance in DMF $\Omega^{-1}cm^2mol^{-1}$
Ia	11.5
Ib	19
Ic	17
Id	21.5
IIa	13.4
IIb	20
IIc	10.8
IId	14.2

The functional groups in the structures of these novel complex were identified by Fourier transform infrared spectroscopy (FTIR) (Table 3), revealing various different absorption bands, all detected signals align with the values previously documented in the literature [28-30].

Table 3: FTIR measurements

No	C-N	NH_2	C=O	C-O	C-OH aliphatic	CO_2 sym	CO_2 asym	M-OH_2	M-O	M-N
ER	----	----	----	1178 m	3224 s	----	----	----	----	----
4AAP	1294 m	3339m	1676 s	----	----	----	----	----	----	----
SAL	----		----	1156 m	----	1386 s	1662 w	----	----	----
Ia	1274 m	3260m	1647 s	1145 m	3228 s	----	----	759 m	677 m	470 m
Ib	1270 m	3246m	1653 s	1140 m	3231 s	----	----	765 m	630 m	441 m
Ic	1271 m	3309m	1653 s	1143 m	3230 s	----	----	756 m	613 m	428 m
Id	1253 m	3234m	1668 s	1145 m	3233 s	----	----	766 m	618 m	426 m
IIa	----		----	1123 m	3221 s	1373 s	1606 w	785 m	669 m	474 m
IIb	----		----	1110 m	3230 s	1377 s	1622 w	752 m	632 m	433 m
IIc	----		----	1130 m	3226 s	1375 s	1645 w	746 m	613 m	425 m
IId	----		----	1129 m	3229 s	1357 s	1624 w	758 m	620 m	426 m
The ligands abbreviations are: ER= Erythritol; 4AAP= 4-aminoantipyrine and SAL= Salicylic acid										

The general chemical structures of new complexes I(a-d) and II (a-d) are shown in scheme (2).



Complexes I (a-d) Complexes II (a-d)

Scheme (2): The general chemical structures of new compmlexes I(a-d) and II(a-d)

All the FTIR characteristic absorption bands of the free erythritol (ER) coordinated in the new complexes I and I (a-d) were observed between 850-1200 cm^{-1}, corresponding to M-C-O-H of this ligand sugar [3-33A closer examination revealed two absorption peaks around 1662 and 1386 cm^{-1}, which is attributed to the characteristic of the asymmetric (COOH) stretching and the symmetric (COOH) stretching of the free salicylic acid (SAL) which were decreased to 1606-1645 and 1357-1377 cm^{-1} which is attributed to the characteristic of the asymmetric (COO–) stretching and the symmetric (COO–) stretching of the coordinated acid [34-35]. Finally, the two peaks of free 4-aminoantipyrine (4AAP) primary 4-amine group and the exocyclic carbonyl group at 5-position were 3339 and 1676 cm^{-1} respectively, this absorption peaks were decreased in the coordination to 3233-3228cm^{-1} and 1647-1668cm^{-1} for the coordinating 4-amine and 5- carbonyl respectively, [36-38].

The key theoretical measurement is the spin-only magnetic moment, calculated using the Bohr Magneton (BM) aformula. This model assumes negligible orbital angular momentum contribution, an assumption that is often valid for first-row transition metal complexes:

$\mu_{eff} = \sqrt{n(n+2)}$

, Where: μ_{eff} is the effective magnetic moment and n is the number of unpaired electrons, [32]. While that for the practical measurements where related to magnetic susceptibility measurements, particularly in the context of diamagnetic corrections and experimental determination of magnetic susceptibility using methods like the Gouy or Evans balance: $\chi A = KM * MWt$

$\chi A = \chi M - D$

where (χM): Molar Magnetic Susceptibility,

χ : Volume susceptibility (dimensionless) and n : Number of moles per unit volume,[39]

The μ_{eff} (Practical) for each complex is listed in Table (4), the μ_{eff} (Practical) for Co(II) complexes (Ia, IIa) are (1.80,1.83 B.M) respectively, these values suggested the presence of one unpaired electron and agreed with low spin octahedral geometry, [40]. While Ni(II) complexes (Ib,IIb) were (2.83,2.81 B.M) , these values suggested the presence of two unpaired electron and agreed with high spin octahedral geometry, for Cu(II) complexes (Ic,IIc) are (1.91,1.93 B.M), these values suggest presence one unpaired electron and agree with octahedral

geometry, The observed spectral data were in agreement with an octahedral geometry around the Co(II) ion. This further supports the conclusion drawn from the magnetic measurements that, the Co(II) complexes were found to adopt a low-spin configuration, consistent with prior reports. The observed spectral data were in agreement with an octahedral geometry around the Co(II) ion and this further supported the conclusion drawn from the magnetic measurements that the Co(II) complexes adopt a low-spin configuration as we will see,[41], However, the potential for a spin-state distribution in mixed-ligand complexes means some high-spin species could also be present, ,[25]. While Zn (II) complexes (Id,IId) are diamagnetic (0 B.M) because d10 are full of electrons and have an octahedral geometry.

Table 4: Magnetic measurements

No	μ_{eff} (Theoretical)	μ_{eff} (Practical)
Ia	1.73	1.80
Ib	2.83	2.83
Ic	1.73	1.91
Id	0	0
IIa	1.73	1.83
IIb	2.83	2.81
IIc	1.73	1.93
IId	0	0

The UV–Visible spectrum of Co complexes (Ia,IIa) shows bands at (11363,16393,20408,29850) (11337,14705,19230,34482) respectively, these bands are assigned to ^4T_1g (F) $\rightarrow ^4T_2g$ (F) (υ_1), ^4T_1g (F) $\rightarrow ^4A_2g$(F) (υ_2), ^4T_1g (F) $\rightarrow ^4T_1g$(P) (υ_3) transitions and charge transfer bands, these bands were agreed with octahedral geometry. The electronic spectra for Ni(II) complexes (Ib,IIb) show bands at (11441,19762,25641,32015)(11074,15503,26881,33783) respectively, these bands are assigned to ^3A_2g (F) $\rightarrow$ ^3T_2g (F) υ_1, ^3A_2g (F) $\rightarrow$ ^3T_1g (F) υ_2, ^3A_2g (F) $\rightarrow$ ^3T_1g (P) υ_3 transitions and charge transfer bands, these bands agree with octahedral geometry. The spectrum of Cu(II) complexes (Ic,IIc) shows broad bands at (18867,30303) (16583,30769) respectively, these bands are assigned to $^2B_1g \rightarrow ^2A_1g$ (υ_1), $^2B_1g \rightarrow ^2B_2g$ (υ_2), $^2B_1g \rightarrow ^2Eg$ (υ_3) transitions and charge transfer bands, these bands agree with octahedral geometry. The electronic spectra of Zn (II) complexes (Id,IId) do not show any d-d bands and no transitions because of Zn(II) has the electron configuration [Ar] $3d^{10}$ (d^{10} system), and all five d-orbitals are filled with 10 electrons,[42].

The summary of Wavelength(λ) observations of the d-d Transitions which occur at longer wavelengths (610–903 nm, visible to NIR region), and lower energy with weaker absorption (low molar absorptivity, $\varepsilon \approx 10–300$ $L \cdot mol^{-1} \cdot cm^{-1}$), while the charge transfer (CT) bands were occurred at shorter wavelengths (290–372 nm, UV region) and higher energy with strong absorption (high $\varepsilon \approx 1{,}000–50{,}000$ $L \cdot mol^{-1} \cdot cm^{-1}$), finally, the Zn(II) complexes (Id, IId) showed only high-energy bands (310–322 nm) with ligand-centered/CT transitions (no d-d bands) [43-44]. The electronic spectra were recorded at 10-3 M solution in DMF, and the results are listed in Table 5, [45-49].

Table 5: The UV– Visible spectra measurements

Complexes No.	Wavelength(λ) nm	Wavenumber($\bar{v}$) cm^{-1}	molar absorptivity $L \cdot mol^{-1} \cdot cm^{-1}$	transitions
Ia	880, 610, 490, 335	11363,16393,20408,29850	(10–300)	$^4T_1g(F) \rightarrow {}^4T_2g(F)(\upsilon_1)$, $4T1g(F) \rightarrow 4A_2g(F)(\upsilon_2)$, $^4T_1g(F) \rightarrow {}^4T_1g(P)$ (υ_3)
Ib	874,506,390, 312	11441,19762,25641,32015	(10–300)	$^3A_2g(F) \rightarrow {}^3T_2g(F)$ υ_1, $^3A_2g(F) \rightarrow {}^3T_1g(F)$ υ_2, $^3A_2g(F) \rightarrow {}^3T_1g(P)$ υ_3
Ic	530,330	18867,30303	(10–300)	$^2B_1g \rightarrow {}^2A_1g$ (υ_1) $^2B_1g \rightarrow {}^2B_2g$ (υ_2) $^2B_1g \rightarrow {}^2Eg$ (υ_3)
Id	310	32258	>1,000	-
IIa	882,680,520,290	11337,14705,19230,34482	(10–300)	$^4T_1g(F) \rightarrow {}^4T_2g(F)(\upsilon_1)$, $4T1g(F) \rightarrow 4A_2g(F)(\upsilon_2)$, $^4T_1g(F) \rightarrow {}^4T_1g(P)$ (υ_3)
IIb	903,645,372, 296	11074,15503,26881,33783	(10–300)	$^3A_2g(F) \rightarrow {}^3T_2g(F)$ υ_1, $^3A_2g(F) \rightarrow {}^3T_1g(F)$ υ_2, $^3A_2g(F) \rightarrow {}^3T_1g(P)$ υ_3
IIc	603, 325	16583,30769	(10–300)	$^2B_1g \rightarrow {}^2A_1g$ (υ_1) $^2B_1g \rightarrow {}^2B_2g$ (υ_2) $^2B_1g \rightarrow {}^2Eg$ (υ_3)
IId	322	31055	>1,000	-

4. The Antibiotic Activity

The antibiotic properties of complexes against two Gram-negative bacteria (*E-coli and Pseudomonas aeruginosa)* were evaluated by Agar well diffusion technique. Ciprofloxacin was used as the reference antibiotic. The results showed that some of the complexes have potential to act as antibacterial agents, this activity was reached in some novel complexes (Ia and IId) against E-coli of both two concentrations to 59.1% of Ciprofloxacin antibiotic activity, while the activity of the same complexes (Ia and IId) against Pseudomonas aeruginosa was reached to 58.3% and 58.4% respectively, Table (6).

Table 6 : The Antibiotic Activities Zone of inhibition, diameter in mm

Complex No.	*E. coli* 1ml.gm/disc	*E. coli* 2ml.gm/disc	*Pseudomonas aeruginosa* 1ml.gm/disc	*Pseudomonas aeruginosa* 2ml.gm/disc
I a	8	13	5	14
I b	6	7	0	5
I c	9	13	6	8
I d	10	11	0	10
II a	5	13	6	15
II b	6	11	9	9
II c	11	11	8	11
II d	7	13	10	12
Cip	22	22	24	24

Conclusion

Eight novel mixed-ligand complexes derived from erythritol (ER) paired with 4-aminoantipyrine (4AAP) or salicylic acid (SAL), coordinated with Co(II), Ni(II), Cu(II), and Zn(II) ions were successfully synthesized and characterized. The complexes were formulated as $[M(ER)(4AAP)(H_2O)_2]$ for the first type and $K_2[M(ER)(SAL)(H_2O)_2]$ for the second type. They were comprehensively characterized through elemental analysis, molar conductivity, FTIR, UV-Vis spectroscopy, magnetic susceptibility, and flame atomic absorption. The FTIR spectra confirmed the bidentate coordination of ER (via hydroxyl O-atoms), 4AAP (via amine N and carbonyl O), and SAL (via carboxylate O-atoms), while the magnetic moments and electronic spectra supported octahedral geometry for all complexes, with Co(II) and Ni(II) exhibiting high-spin configurations, Cu(II) showing distorted octahedral symmetry, and Zn(II) being diamagnetic. Molar conductance (10–21 $\Omega^{-1}cm^2mol^{-1}$) confirmed their non-electrolytic nature. The antibiotic efficacy of complexes Ia (Co(II)-4AAP) and IId (Zn(II)-SAL) was significant. Against E. coli, both complexes exhibited activity reaching 59.1% of the standard antibiotic Ciprofloxacin's effectiveness at both tested concentrations. Against Pseudomonas aeruginosa, the activity reached 58.3% and 58.4% for complexes Ia and IId, respectively.

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