

## Synthesis, Characterization, and Biological Investigation of Transition Metal (II) Complexes Based on 2-Alkyl-2-Oxazolin- $\alpha$ -D-glucopyranose Modified Derivatives

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**ABSTRACT** A transition metal complexes based on Fe(II), Co(II), Ni(II), and Zn(II) were developed in this study, utilizing ligands derivatives from 2-alkyl-2-oxazolin-3,4,6-tri-*O*-acetyl-1,2-dideoxy- $\alpha$ -D-glucopyranose derivatives. The elemental analyses suggested that the stoichiometry is (1:2) [Metal:(LD<sub>n</sub>)<sub>2</sub>]. The IR data confirmed the binding between the metal ion and the ligands. The crystallinity of the complexes formed was confirmed by the X-ray diffraction. The non-electrolyte nature of metal complexes was confirmed by molar conductance studies. The thermal study suggested the presence of coordinated water molecules in the complexes based on LD<sub>4</sub> [M(LD<sub>4</sub>)<sub>2</sub>.(OAc)<sub>2</sub>.xH<sub>2</sub>O]. The synthesized complexes and their corresponding ligands were tested for their antimicrobial activities against bacteria (*Escherichia coli* and *Pseudomonas aeruginosa* [Gram negative]) and (*Staphylococcus aureus* and *Streptococcus pneumonia* [Gram positive]). The complexes [(Zn(LD<sub>4</sub>)<sub>2</sub>.(OAc)<sub>2</sub>.2H<sub>2</sub>O] and [Ni(LD<sub>4</sub>)<sub>2</sub>.(OAc)<sub>2</sub>.4H<sub>2</sub>O] showed significant antibacterial activity compared to the corresponding ligands. The dosage with the radical DPPH at different concentrations for the complexes [(Ni(LD<sub>1</sub>)<sub>2</sub>.(OAc)<sub>2</sub>.4H<sub>2</sub>O] and [Ni(LD<sub>2</sub>)<sub>2</sub>.(OAc)<sub>2</sub>.4H<sub>2</sub>O] showed superior antioxidant activity than the corresponding ligands. The considerable results found proved that the ligands and their complexes are bioactive.

**KEYWORDS** 2-Alkyl-2-oxazolin-3,4,6-tri-*O*-acetyl-1,2-dideoxy- $\alpha$ -D-glucopyranose, Transition Metal(II) Complexes, Thermal study, *In vitro* biologic activity.

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### INTRODUCTION

The success of the heterocyclic fragments is the consequence of much researches, in the past decades, thanks to the synthesis of these active heterocyclic blocks, these are always conceding remarkable attention in the pharmaceutical industry due to their vast therapeutic applications.<sup>[1,2]</sup> Numerous studies are cited in the literature on different properties.<sup>[3-6]</sup> Among the most studied fragments, the 2-oxazolines or cyclic imino-ethers with five chains are a significant that helps to clarify the mechanisms of different chemical and biological reactions due to the presence of a

imino group (Schiff basis) in their structures,<sup>[7,8]</sup> they have an interesting structure, on which we can build a wide variety of natural or synthetic molecules with properties that make them interesting in many fields of application such as medical and pharmaceutical industries.<sup>[9-12]</sup> Among these natural substances, we were interested in 2-amino-2-deoxy-D-glucopyranose.<sup>[13-19]</sup> The majority of the work in the literature focuses on the synthesis of 2-alkyl-2-oxazolin-3,4,6-tri-*O*-acetyl-1,2-dideoxy- $\alpha$ -D-glucopyranose derivatives.<sup>[20-27]</sup> 2-Oxazolines free and/or bound had many reports of their applications in biology including antibacterial,<sup>[28,29]</sup> antifungal,<sup>[30]</sup> anti-cancer,<sup>[31]</sup>

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antitumor,<sup>[32]</sup> antioxidant,<sup>[33]</sup> anti-inflammatory activity,<sup>[34]</sup> antimalarial,<sup>[35]</sup> antiviral,<sup>[36]</sup> anti-tuberculosis,<sup>[37]</sup> and antibiotic<sup>[38,39]</sup>. In addition, they are used in the food industry,<sup>[40,41]</sup> medicine,<sup>[42,43]</sup> agriculture,<sup>[44]</sup> and polymers.<sup>[45]</sup> On the other hand, these derivatives were not very reactive and found only limited applications.<sup>[46-51]</sup> Furthermore, the problem of the stability of the Schiff basis function in the aqueous medium poses a problem in certain compounds, which makes their usefulness difficult and limited. For this purpose, a metal complex is formed to enhance the stability of these derivatives.

Metal complexes are gaining importance in recent years, especially in protracted drug design and metabolism. These monodentate ligands have often been studied recently due to their different applications<sup>[52,53]</sup> and applications in improving and/or increasing biological activity.<sup>[54]</sup> Transition metals or trace elements are essential for the normal functioning of the organism and are therefore of great interest as potential drugs. The various applications of transition elements make them materials of essential medicinal importance: this explains why they have been the subject of numerous researches.<sup>[55,56]</sup> The coordination chemistry of the nitrogen donor of heterocyclic ligands (oxazoline) to a metal center is a field of intense research.<sup>[50]</sup> In the light of all these observations, we made an intense bibliographic search, where we did not succeed in finding any work dealing with 2-oxazolidine based on native and/or protected *D*-glucosamine. About *D*-glucosamine-derived PYOX, we found reference in a work of Kraft,<sup>[15,56,57]</sup> in which they study the ability of the complexation by Pd(II) and similar work was published previously.<sup>[58,59]</sup> However, there is some information about our ligands, which are related to the methods of synthesis, the reactivity study, and the biological activity of oxazolines based on native and/or protected *D*-glucosamine, we mention for example the works of Tobias<sup>[60]</sup> (synthesis of Bis(oxazolines) based on *D*-glucosamine, Masato who synthesized in one step the oxazolines of *N*-acetyl-glucosamine<sup>[61,62]</sup>, Sommer,<sup>[18]</sup> Antony,<sup>[63]</sup> and Sergey.<sup>[64,65]</sup>

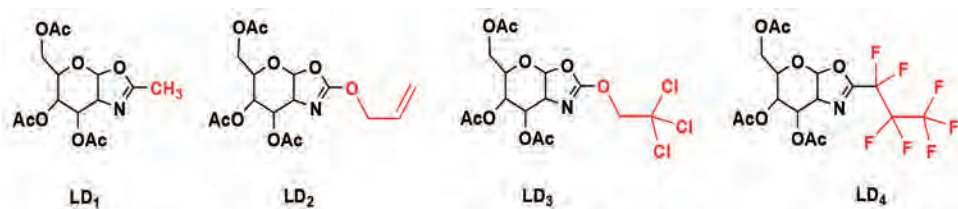
In line with our interests, we tried to introduce transition metals to form 2-alkyl-2-oxazolin-3,4,6-tri-*O*-acetyl-1,2-dideoxy- $\alpha$ -*D*-glucopyranose-based metal complexes to increase the selectivity, improve the stability, and the biological activity of these four derivatives (**LD<sub>1</sub>**, **LD<sub>2</sub>**, **LD<sub>3</sub>** and **LD<sub>4</sub>**). The structures of ligands are presented in **Figure 1**. In this article, we describe synthesis, characterization, and behavior of metal complexes based on 2-alkyl-2-oxazolin-3,4,6-tri-*O*-acetyl-1,2-dideoxy- $\alpha$ -*D*-glucopyranose derivatives. In addition, the biological activity of the four ligands and their complexes was examined.

## RESULTS AND DISCUSSION

### Synthesis of Metal Complexes

The reactions and proposed structures of the formed metal(II) complexes are schematized in **Figure 2**. The structures of these complexes have been studied by means of elementary analyses (C,H, N, and M), UV-Vis, FT-IR, and thermal analysis and conductivity measurements. All the synthesized metal complexes based on ligands (**LD<sub>1</sub>**, **LD<sub>2</sub>**, **LD<sub>3</sub>** and **LD<sub>4</sub>**) were purified by recrystallization and by flash chromatography in the form of crystals and/or colored powders. In most cases, the yields varied from 38% to 97%. The yields for the ligand-based complexes (**LD<sub>4</sub>** and **LD<sub>2</sub>**) are remarkable, while the yield values for the others are acceptable. It should be noted that melting points are lower than 350°C in all complexes, but we noted a decomposition in the two complexes [Zn(**LD<sub>1</sub>**)<sub>2</sub>·(OAc)<sub>2</sub>·2H<sub>2</sub>O] and [Zn(**LD<sub>3</sub>**)<sub>2</sub>·(OAc)<sub>2</sub>·2H<sub>2</sub>O]. In contrast, they are all stable in air and do not need special storage precautions and can be stored for a long time. The metal complexes obtained generally do not have characteristic odors. They are poorly soluble in petroleum ether and toluene; they are slightly soluble in acetone and in hexane at room temperature. They even precipitate in the hot medium. On the other hand, all the complexes are freely soluble in DMSO, DMF, methanol, and ethanol, while the solubility of the ligand-based complexes (**LD<sub>4</sub>** and **LD<sub>2</sub>**) is higher compared to the others. We also noticed that the color of the complexes is not the same as the corresponding ligands, which confirms the coordination of the ligand with the metal. This color change may be due to the metal-ligand interaction, which proves that the electronic properties of the complexes are distinct from the ligands used. Characteristics and physical properties of all the prepared metal complexes are reported in **Table 1**. The data of molar conductance of all metallic complexes measured in DMF at a concentration of 10<sup>-3</sup> mol.L<sup>-1</sup> at ambient temperature are in the order of 2.67–12.87 Ω<sup>-1</sup> cm<sup>2</sup> mol<sup>-1</sup>, which explains the non-electrolytic behavior of these complexes.<sup>[66,67]</sup> In addition, the results of the elemental analysis of all complexes obtained are in good agreement with those required by the proposed formulas of the complexes and indicate that the values found and calculated with an uncertainty equal to ±0.4% are within the limits; we have established the crude formulas of the proposed compounds (**Table 2**). The results for elemental analysis showed a stoichiometry (1:2) for the metal: ligand complex, that is, of the type [M:(**LD<sub>n</sub>**)<sub>2</sub>].

They have the general formula [M(**LD<sub>n</sub>**)<sub>2</sub>·(OAc)<sub>2</sub>·xH<sub>2</sub>O] where M(II): Fe, Co, Ni and/or Zn. The lattice water molecules were determined using thermal studies



**Figure 1:** The structures of ligands (**LD<sub>1</sub>**, **LD<sub>2</sub>**, **LD<sub>3</sub>** and **LD<sub>4</sub>**)

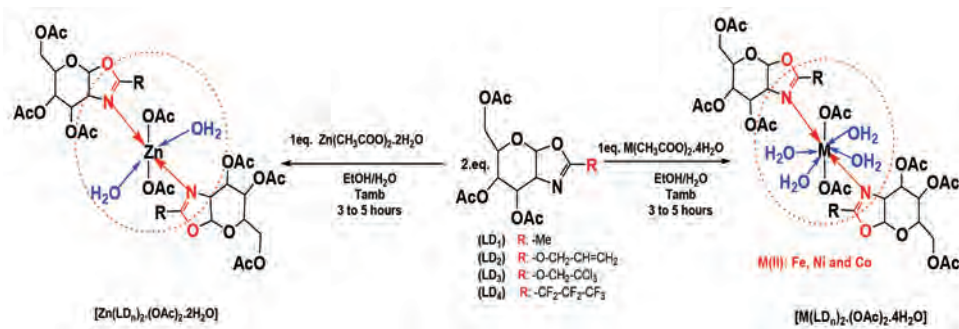


Figure 2: Synthesis of Metal(II)-2-alkyl-2-oxazolin-3,4,6-tri-O-acetyl-1,2-dideoxy- $\alpha$ -D-glucopyranose complexes

Table 1: Characteristics and physical properties of the free ligands and their complexes

Ligand/Complex	Color	Yield (%)	R <sub>f</sub>	m.p (°C)	$\Lambda_m^g$
<b>LD<sub>1</sub><sup>a</sup></b>	White	-----	0.52 <sup>d</sup>	198	-----
[Fe (LD <sub>1</sub> ) <sub>2</sub> ·(OAc) <sub>2</sub> ·4H <sub>2</sub> O]	Blue	44.2	0.41 <sup>e</sup>	255	7.60
[Co (LD <sub>1</sub> ) <sub>2</sub> ·(OAc) <sub>2</sub> ·4H <sub>2</sub> O]	p <sup>b</sup> Violet	62.7	0.39 <sup>d</sup>	251	6.51
[Zn (LD <sub>1</sub> ) <sub>2</sub> ·(OAc) <sub>2</sub> ·2H <sub>2</sub> O]	Golden-Yellow	71.5	0.40 <sup>d</sup>	209 <sup>e</sup>	2.67
[Ni (LD <sub>1</sub> ) <sub>2</sub> ·(OAc) <sub>2</sub> ·4H <sub>2</sub> O]	Light-Green	51.1	0.43 <sup>d</sup>	222	9.77
<b>LD<sub>2</sub><sup>a</sup></b>	White	-----	0.40 <sup>d</sup>	242	-----
[Fe (LD <sub>2</sub> ) <sub>2</sub> ·(OAc) <sub>2</sub> ·2H <sub>2</sub> O]	Red	72.5	0.33 <sup>e</sup>	275	8.80
[Co (LD <sub>2</sub> ) <sub>2</sub> ·(OAc) <sub>2</sub> ·4H <sub>2</sub> O]	p <sup>b</sup> Pink-Purple	82.2	0.34 <sup>d</sup>	268	7.70
[Zn (LD <sub>2</sub> ) <sub>2</sub> ·(OAc) <sub>2</sub> ·2H <sub>2</sub> O]	p <sup>b</sup> Yellow	91.9	0.35 <sup>e</sup>	235	4.78
[Ni (LD <sub>2</sub> ) <sub>2</sub> ·(OAc) <sub>2</sub> ·4H <sub>2</sub> O]	p <sup>b</sup> Dark-Green	94.2	0.37 <sup>e</sup>	245	11.98
<b>LD<sub>3</sub><sup>a</sup></b>	Pastel-Yellow	-----	0.38 <sup>d</sup>	250	-----
[Fe (LD <sub>3</sub> ) <sub>2</sub> ·(OAc) <sub>2</sub> ·4H <sub>2</sub> O]	Brown	65.7	0.29 <sup>e</sup>	288	11.33
[Co (LD <sub>3</sub> ) <sub>2</sub> ·(OAc) <sub>2</sub> ·4H <sub>2</sub> O]	p <sup>b</sup> Red	75.3	0.31 <sup>d</sup>	278	7.25
[Zn (LD <sub>3</sub> ) <sub>2</sub> ·(OAc) <sub>2</sub> ·2H <sub>2</sub> O]	Mustard yellow	41.5	0.33 <sup>d</sup>	255 <sup>e</sup>	4.14
[Ni (LD <sub>3</sub> ) <sub>2</sub> ·(OAc) <sub>2</sub> ·4H <sub>2</sub> O]	pb Yellow	38.7	0.34 <sup>e</sup>	275	10.25
<b>LD<sub>4</sub><sup>a</sup></b>	White	-----	0.50 <sup>e</sup>	220	-----
[Fe (LD <sub>4</sub> ) <sub>2</sub> ·(OAc) <sub>2</sub> ·4H <sub>2</sub> O]	Dark-Green	89.4	0.35 <sup>f</sup>	320	12.87
[Co (LD <sub>4</sub> ) <sub>2</sub> ·(OAc) <sub>2</sub> ·4H <sub>2</sub> O]	p <sup>b</sup> Blue-Violet	93.8	0.35 <sup>f</sup>	305	8.75
[Zn (LD <sub>4</sub> ) <sub>2</sub> ·(OAc) <sub>2</sub> ·2H <sub>2</sub> O]	Dark-Yellow	97.0	0.36 <sup>f</sup>	257	4.77
[Ni (LD <sub>4</sub> ) <sub>2</sub> ·(OAc) <sub>2</sub> ·4H <sub>2</sub> O]	Light-Green	75.5	0.38 <sup>f</sup>	280	11.55

<sup>a</sup>Free ligand, <sup>b</sup>p Precipitate, <sup>d</sup>Decomposition, <sup>e</sup>(4 : 6 CH<sub>2</sub>Cl<sub>2</sub>/MeOH), <sup>f</sup>(7: 3EtOAc/MeOH), <sup>g</sup>(8: 2 hexane/EtOH), <sup>g</sup> $\Lambda_m$ : Molar conductance (at 25°C)  $\Lambda_m$  ( $\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$ )

(results presented for complexes based on ligand (**LD<sub>4</sub>**)). The thermogravimetric behavior and thermal stabilization of complexes based on ligand (**LD<sub>4</sub>**) have been evaluated from experimental data by thermal analysis. Thermal analysis showed that complexes are stable at temperature equals to 240°C, 285°C, 325°C, and 350°C for [Zn(**LD<sub>4</sub>**)<sub>2</sub>·(OAc)<sub>2</sub>·2H<sub>2</sub>O], [Ni(**LD<sub>4</sub>**)<sub>2</sub>·(OAc)<sub>2</sub>·4H<sub>2</sub>O], [Co(**LD<sub>4</sub>**)<sub>2</sub>·(OAc)<sub>2</sub>·4H<sub>2</sub>O], and [Fe(**LD<sub>4</sub>**)<sub>2</sub>·(OAc)<sub>2</sub>·4H<sub>2</sub>O], respectively, the resulting TGA thermogram for complexes is shown in **Figure 3**.

The corresponding mass losses at the various steps, which reflect the decomposition of the complexes, as well as the corresponding temperature ranges, are summarized in **Table 3**. From the plot, it is observed that [Ni(**LD<sub>4</sub>**)<sub>2</sub>·(OAc)<sub>2</sub>·4H<sub>2</sub>O] was the only complex that showed a horizontal level between 25 and 300°C with a mass loss of 81.80%.

This suggests that no water molecule (of hydration or of coordination) or no acetyloxy group is present in the structure of this complex. The same complex also shows another level located between 285 and 550°C that would reflect the disappearing of the acetic acid molecules and the departing of a single ligand molecule, with a weight loss of 20.10%, in perfect accord with the theoretical value calculated corresponding to the loss of NiO (calc. 19.96%).

The TGA curve of the [Fe(**LD<sub>4</sub>**)<sub>2</sub>·(OAc)<sub>2</sub>·4H<sub>2</sub>O] complex shows a weight loss corresponding to the departure of two molecules water of hydration between 110 and 150°C. A second plateau was observed between 150 and 350°C which would reflect the disappearance of two acetyloxy groups. The same curve reflects a third level between 350 and 550°C, probably indicating the departure of a single ligand molecule. The theoretical mass losses are also in accordance with the experimental ones. All results exclude the involvement of all the water molecules in central iron coordination.

Table 2: Elemental analysis data of free ligands and its complexes

Compound Brute formula	M (g/mol)	Analysis found (Calc) %			
		C	H	N	M
$C_{14}H_{19}NO_8^a$	329.11	51.06 (50.56)	5.82 (5.38)	4.2 (3.97)	-----
$C_{32}H_{52}FeN_2O_{24}$	904.23	44.25 (44.10)	5.57 (5.63)	3.23 (3.25)	6.43 (6.40)
$C_{32}H_{52}CoN_2O_{24}$	907.22	42.34 (41.49)	5.77 (5.75)	3.09 (2.97)	6.49 (6.52)
$C_{32}H_{48}ZnN_2O_{22}$	876.20	43.77 (43.58)	5.51 (5.55)	3.19 (3.20)	7.45 (7.87)
$C_{32}H_{52}NiN_2O_{24}$	906.23	42.35 (42.78)	5.78 (6.00)	3.09 (2.98)	6.47 (6.57)
$C_{16}H_{21}NO_9^b$	371.12	51.75 (51.23)	5.70 (5.66)	3.77 (3.45)	-----
$C_{36}H_{56}FeN_2O_{26}$	988.25	45.39 (45.17)	5.50 (5.49)	2.94 (3.02)	5.86 (5.77)
$C_{36}H_{56}CoN_2O_{26}$	991.25	43.60 (43.88)	5.69 (5.77)	2.82 (2.53)	5.98 (6.01)
$C_{36}H_{52}ZnN_2O_{24}$	960.22	44.94 (44.45)	5.45 (5.32)	2.91 (2.46)	6.80 (6.75)
$C_{36}H_{56}NiN_2O_{26}$	990.25	43.61 (42.55)	5.69 (4.72)	2.83 (3.10)	5.92 (6.34)
$C_{15}H_{18}Cl_3NO_9^c$	461.00	38.94 (39.00)	3.92 (3.87)	3.03 (2.98)	-----
$C_{34}H_{50}Cl_6FeN_2O_{26}$	1168.01	35.97 (35.84)	4.08 (4.00)	2.47 (2.44)	4.92 (4.89)
$C_{34}H_{50}Cl_6CoN_2O_{26}$	1171.01	34.77 (34.12)	4.29 (4.15)	2.39 (2.28)	5.02 (4.99)
$C_{34}H_{46}Cl_6ZnN_2O_{24}$	1139.99	35.67 (35.56)	4.05 (3.98)	2.45 (2.46)	5.71 (5.87)
$C_{34}H_{50}Cl_6NiN_2O_{26}$	1170.01	34.78 (33.00)	4.29 (3.08)	2.39 (2.37)	5.00 (5.13)
$C_{16}H_{16}F_7NO_8^d$	483.08	39.76 (39.25)	3.34 (3.12)	2.90 (2.56)	-----
$C_{36}H_{46}F_{14}FeN_2O_{24}$	1212.16	36.75 (36.63)	3.60 (6.37)	2.38 (2.15)	4.75 (4.55)
$C_{36}H_{46}F_{14}CoN_2O_{24}$	1215.15	35.57 (35.40)	3.81 (3.75)	2.30 (2.33)	4.85 (4.80)
$C_{36}H_{42}F_{14}N_2ZnO_{22}$	1184.13	36.45 (36.55)	3.57 (3.44)	2.36 (2.45)	5.51 (5.49)
$C_{36}H_{46}F_{14}NiO_{24}$	1214.16	35.57 (34.34)	3.81 (3.00)	2.30 (2.31)	4.83 (5.90)

<sup>a</sup>LD<sub>1</sub>, <sup>b</sup>LD<sub>2</sub>, <sup>c</sup>LD<sub>3</sub> et <sup>d</sup>LD<sub>4</sub> (free ligand)

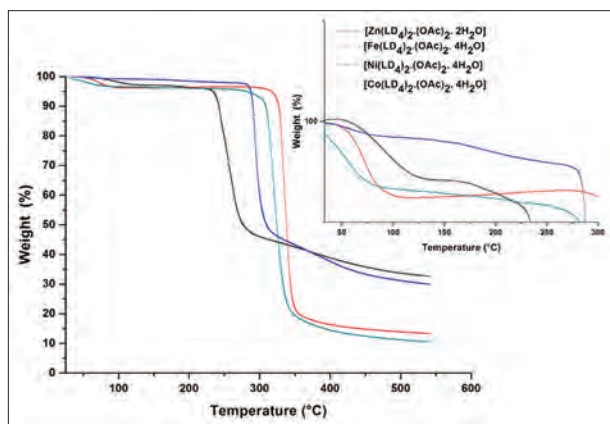


Figure 3: ATG thermogram of the four complexes based on the ligand (LD<sub>4</sub>)

From the curve of the  $[Zn(LD_4)_2(OAc)_2 \cdot 2H_2O]$  complex, we observe the disappearance of two water molecules. Indeed, the curve reveals a plateau in the range 50–310°C and two others between 310–350°C and 350–550°C, which probably reflect the departure of the hydration water molecules, of the two acetyloxy groups (OAc) of the metal, and of a ligand molecule, respectively. Theoretical values of the mass losses confirm again the values found experimentally. The TGA curve of the  $[Co(LD_4)_2(OAc)_2 \cdot 4H_2O]$  complex reflects the disappearance of two water hydration molecules between 85 and 330°C, with a small weight loss of about 1.58%. The degradation of organic entity as well as the other two coordinating water

molecules and the two acetyloxy groups (OAc) of the metal takes place at 350°C, but the metal continues until about 550°C, where a quasi-horizontal plateau extends to the end of the thermal treatment, corresponding to the degradation of the final metal oxide (FeO, NiO, ZnO and CoO). Above mentioned, all complexes are thermally stable toward the ligand (LD<sub>4</sub>) and this result is in keeping with literature.<sup>[68-71]</sup> In the end, all the thermogravimetric results obtained remain completely in accordance with the data from the elemental analysis and thus with the structures proposed for the different complexes. IR spectral investigation is a useful technique to confirm the binding mode of a metal ion to ligand. The analogy of the IR spectra of all ligands with the complexes enables us to identify the functions of the complex involved in complexation and to get information on the internal vibrational movements of the molecules. The displacement and appearance of new vibrational bands of the complex imply the coordination of metal ion to ligand. In the four free ligands (LD<sub>1</sub>, LD<sub>2</sub>, LD<sub>3</sub>, and LD<sub>4</sub>), intense absorption bands are located range of 1619–1660 cm<sup>-1</sup>, corresponding to the imino-group  $\nu(C=N)$ , which has shifted to lower wavenumbers in all metal complexes. This band shift to a lower frequency occurred due to the donating of nitrogen electrons to the vacant metal atom orbitals.<sup>[68,69]</sup> In this way, it was able to confirm the coordination of the metal atoms with the nitrogen. In spectrum of all complexes, an appearance of a new absorption band of low intensity was observed in region 457–480 cm<sup>-1</sup>, which was attributed to  $\nu(M-N)$ .<sup>[70]</sup> The appearance of a new band located between 3225 and 3477 cm<sup>-1</sup> which was attributed to



**Table 3: Thermogravimetric analysis data of the ligand-based complexes (LD<sub>4</sub>)**

Compound	T (°C) <sup>b</sup>	TG weight loss		Residue (Color)
		Found	(calc) %	
<b>LD<sub>4</sub><sup>a</sup></b>	219–222	-----		Decomposition of LD <sub>4</sub>
[Fe (LD <sub>4</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·4H <sub>2</sub> O]	110–150	1.28	(1.22)	FeO (black powder)
	150–350	75.60	(74.97)	Iron (II) oxide
	350–550	6.86	(6.28)	
[Ni (LD <sub>4</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·4H <sub>2</sub> O]	25–300	81.80	(81.20)	NiO (gray-green powder)
	300–550	20.10	(19.96)	Nickel (II) oxide
[Zn (LD <sub>4</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·2H <sub>2</sub> O]	50–310	4.95	(4.88)	ZnO (white powder)
	310–350	92.78	(92.54)	Zinc (II) oxide
	350–550	0.20	(0.15)	
[Co (LD <sub>4</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·4H <sub>2</sub> O]	85–330	1.58	(1.46)	CoO (grey powder)
	330–355	88.98	(89.0)	Cobalt (II) oxide
	355–550	0.95	(1.00)	

<sup>a</sup>Free ligand, <sup>b</sup>Temperature range (°C)**Table 4: The characteristic FT-IR wavenumbers (cm<sup>-1</sup>) of the free ligands (LD<sub>1</sub>, LD<sub>2</sub>, LD<sub>3</sub>, and LD<sub>4</sub>) and their complexes**

Compounds	$\nu$ (C=N)	$\nu$ (H <sub>2</sub> O)	$\nu$ (M–N)	$\nu_{\text{asym}}$ (COO <sup>-</sup> )	$\nu_{\text{sym}}$ (COO <sup>-</sup> )	$\Delta\nu^b$
<b>LD<sub>1</sub><sup>a</sup></b>	1635	----	----	----	----	----
[Fe (LD <sub>1</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·4H <sub>2</sub> O]	1632	3373	457	1554	1395	159
[Co (LD <sub>1</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·4H <sub>2</sub> O]	1622	3470	469	1596	1414	182
[Zn (LD <sub>1</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·2H <sub>2</sub> O]	1617	3422	471	1599	1400	199
[Ni (LD <sub>1</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·4H <sub>2</sub> O]	1620	3355	470	1595	1407	188
<b>LD<sub>2</sub><sup>a</sup></b>	1644	----	----	----	----	----
[Fe (LD <sub>2</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·4H <sub>2</sub> O]	1641	3380	473	1546	1395	151
[Co (LD <sub>2</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·4H <sub>2</sub> O]	1638	3477	475	1547	1400	147
[Zn (LD <sub>2</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·2H <sub>2</sub> O]	1622	3462	480	1568	1415	153
[Ni (LD <sub>2</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·4H <sub>2</sub> O]	1630	3369	478	1557	1436	121
<b>LD<sub>3</sub><sup>a</sup></b>	1650	----	----	----	----	----
[Fe (LD <sub>3</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·4H <sub>2</sub> O]	1645	3379	454	1574	1389	185
[Co (LD <sub>3</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·4H <sub>2</sub> O]	1639	3355	459	1570	1390	180
[Zn (LD <sub>3</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·2H <sub>2</sub> O]	1630	3312	468	1593	1398	195
[Ni (LD <sub>3</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·4H <sub>2</sub> O]	1633	3345	461	1590	1400	190
<b>LD<sub>4</sub><sup>a</sup></b>	1660	----	----	----	----	----
[Fe (LD <sub>4</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·4H <sub>2</sub> O]	1650	3250	467	1540	1345	195
[Co (LD <sub>4</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·4H <sub>2</sub> O]	1645	3345	471	1452	1350	102
[Zn (LD <sub>4</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·2H <sub>2</sub> O]	1639	3420	477	1562	1400	152
[Ni (LD <sub>4</sub> ) <sub>2</sub> (OAc) <sub>2</sub> ·4H <sub>2</sub> O]	1647	3233	470	1555	1415	140

<sup>a</sup>Free ligand, <sup>b</sup> $\Delta\nu = \nu_{\text{asymétrique}}(\text{COO}^-) - \nu_{\text{symétrique}}(\text{COO}^-)$ 

$\nu(\text{H}_2\text{O})$  highlighted the existence of water of hydration and coordination molecules that were observed in the metal-based complexes. In addition, the appearance of the two new non-ligand absorption bands located between 1599–1462 cm<sup>-1</sup> and 1312–1415 cm<sup>-1</sup> have been attributed to the metal associated carboxylate (COO<sup>-</sup>) groups: asymmetric and symmetric. The values of the frequency deviation between asymmetric and symmetric bands ( $\Delta\nu$ ) varied between 131 and 199 cm<sup>-1</sup>, which implied monodentate coordination with the metal (II) complexes, because it was <200 cm<sup>-1</sup> ( $\Delta\nu < 200$  cm<sup>-1</sup>).<sup>[71–73]</sup> The spectroscopic characteristics of

the synthesized metal complexes based on the ligand (LD<sub>1</sub>, LD<sub>2</sub>, LD<sub>3</sub>, and LD<sub>4</sub>) are collected in **Table 4**. On the other hand, the UV-Vis absorption spectrum of the ligand (LD<sub>4</sub>) and their corresponding complexes is shown in **Figure 4**. A bathochromic shift was observed for the complexes with respect to their corresponding ligand (LD<sub>4</sub>). This phenomenon is mainly associated with the ligand-metal charge transfer, which consists of a non-binding doublet transfer from the nitrogen to the vacant slot of the (*d*) orbital of the metal, to form the coordination bond.<sup>[74–76]</sup> This spectrum is recorded in the range 250–300 nm. The spectrum



of the ligand ( $\text{LD}_4$ ) shows a band at 268 nm attributed to the  $n-\pi^*$  transitions of the imino-group in 2-oxazoline chromophore. On complexation, the electronic transition of the imino-group shifts to a higher wavelength,<sup>[72]</sup> this shows the coordination between the ligand and the metal.<sup>[77-79]</sup> According to **Figure 4**, it can be observed that the spectrum of the complexes presents slightly different appearances and band shifts toward the higher energy compared to the free ligand. This can be assigned to the conjugation that occurs after the complexation of the central ion and the nitrogen electrons of the imino-group in 2-oxazoline. These results are in accord with the FT-IR, so the electronic spectra give further confirmation of coordination of the transition metals with the tested ligand. The essential results and spectrum data are grouped in **Table 5**.

Concludes, that the IR data are proven by the UV-Vis results where the  $n-\pi^*$  transition in the carbon-nitrogen bond shifted from 268 nm to the strong field depending on the bonded metal after complexation at the center of the metal. The bathochromic shift is due to the retrodonation  $\pi$  of the metal-nitrogen bond in all characterized complexes and the subsequent weakening of the metal-nitrogen bond energy.<sup>[80]</sup> In contrast, the X-ray diffraction (XRD) diagram of the Ni(II), Zn(II), Co(II), and Fe(II) complexes and the free ligand ( $\text{LD}_4$ ) is shown in **Figure 5**. XRD diagram of metal complexes shows well-defined crystal peaks indicating that the samples were in crystal phase. The metal complexes reveal clear crystalline XRD patterns, with varying of intensities from metal to the other and this is confirmed by the main positioned peaks, which differ considerably from those of the ligand which shows an amorphous profile. The occurrence of crystallinity in formed complexes is due to the complexation of metal- $\text{LD}_4$ .

## Biological Activity

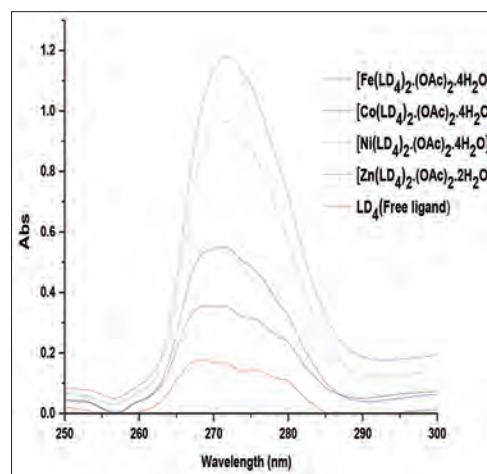
### Antimicrobial testing of the free ligands and their metal complexes

*In vitro* antimicrobial activity examined against two Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and two Gram-positive bacteria (*Staphylococcus aureus* and *Streptococcus pneumoniae*) using the disk diffusion method; this method is designed to determine the existence or the absence of inhibition zone in comparison with gentamicin (standard antibiotic). The results showed that certain free ligands and/or complexes are very effective on certain microorganisms. The results obtained are shown in **Table 6**. The inhibition zone for (*S. aureus* and *S. pneumoniae*) was found in the range of 6–20 mm and for (*E. coli* and *P. aeruginosa*) was found in the range of 7–25 mm. It was observed that the complex based on the ligand ( $\text{LD}_4$ ) [ $\text{Ni}(\text{LD}_4)_2(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ ] was very effective against *E. coli* with inhibition zone of 25mm, *P. aeruginosa* with inhibition zone of 23mm, *S. aureus* with inhibition zone of 19 mm, and against *S. pneumoniae* with an inhibition zone of 17 mm; on the other hand, the [ $\text{Zn}(\text{LD}_4)_2(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ ] complex was very reactive against *E. coli* with an inhibition zone of 23mm and against *P. aeruginosa* with an inhibition zone of 24 mm, *S. aureus* with an inhibition zone of 20mm, and *S. pneumoniae* with inhibition zone of 19mm, but this

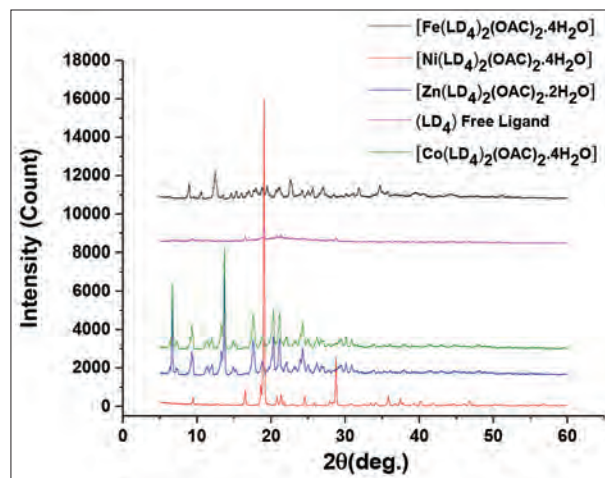
**Table 5: Electronic spectrum data of ligand ( $\text{LD}_4$ ) and their metal complexation EtOH**

Compounds	$\lambda_{\text{max}}$ (nm)	Abs	$\epsilon_{\text{max}}^d$
$\text{LD}_4^a$	268	0.177	177
$\text{Fe}(\text{LD}_4)_2^b$	269	0.358	358
$\text{Co}(\text{LD}_4)_2^b$	271	0.549	549
$\text{Ni}(\text{LD}_4)_2^b$	272	0.970	970
$\text{Zn}(\text{LD}_4)_2^c$	272	1.185	1185

<sup>a</sup>(Free ligand); <sup>b</sup>[ $\text{M}(\text{LD}_4)_2(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ ]; <sup>c</sup>[ $\text{Zn}(\text{LD}_4)_2(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ ]; <sup>d</sup>Molar absorption coefficient ( $\text{L} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$ )



**Figure 4: UV absorption spectrum of free ligand ( $\text{LD}_4$ ) and synthesized metal complexes in EtOH, pH = 7,  $C=10^{-3} \text{ mol} \cdot \text{L}^{-1}$ ,  $T = 25^\circ \text{C}$**



**Figure 5: X-ray diffraction patterns of free ligand ( $\text{LD}_4$ ) and their metal complexes**

activity remains lower than that obtained with the standard antibiotic, which is gentamicin which provides inhibition diameters of 33mm, 29 mm, and 30 mm with *E. coli*, *P. aeruginosa*, and *S. aureus*, respectively, it shows a low activity with *S. pneumoniae* with inhibition zone of 10mm, we can say that this antibiotic has a low activity against this strain, compared to [ $\text{Zn}(\text{LD}_4)_2(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ ], and [ $\text{Ni}(\text{LD}_4)_2(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ ] complexes which showed a strong inhibition effect against all G-positive and G-negative bacteria.

**Table 6: Antibacterial activity of free ligands and their metal complexes at 500 µg/disk concentration**

Compound	Zone of inhibition (mm) <sup>b</sup>			
	<i>E. coli</i> <sup>c</sup>	<i>P. aeruginosa</i> <sup>c</sup>	<i>S. aureus</i> <sup>d</sup>	<i>S. pneumoniae</i> <sup>d</sup>
<b>LD<sub>1</sub></b> <sup>a</sup>	7	6	8	6
[Fe (LD <sub>1</sub> ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	8	7	8	8
[Co (LD <sub>1</sub> ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	8	7	10	7
[Zn (LD <sub>1</sub> ) <sub>2</sub> .(OAc) <sub>2</sub> .2H <sub>2</sub> O]	12	12	14	8
[Ni (LD <sub>1</sub> ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	10	12	15	9
<b>LD<sub>2</sub></b> <sup>a</sup>	10	9	7	6
[Fe (LD <sub>2</sub> ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	10	9	8	6
[Co (LD <sub>2</sub> ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	10	9	8	6
[Zn (LD <sub>2</sub> ) <sub>2</sub> .(OAc) <sub>2</sub> .2H <sub>2</sub> O]	14	13	13	10
[Ni (LD <sub>2</sub> ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	16	10	15	9
<b>LD<sub>3</sub></b> <sup>a</sup>	7	10	8	6
[Fe (LD <sub>3</sub> ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	11	12	9	7
[Co (LD <sub>3</sub> ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	10	12	10	8
[Zn (LD <sub>3</sub> ) <sub>2</sub> .(OAc) <sub>2</sub> .2H <sub>2</sub> O]	13	15	12	8
[Ni (LD <sub>3</sub> ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	14	19	12	8
<b>LD<sub>4</sub></b> <sup>a</sup>	14	13	17	13
[Fe (LD <sub>4</sub> ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	20	18	12	11
[Co (LD <sub>4</sub> ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	21	19	15	12
[Zn (LD <sub>4</sub> ) <sub>2</sub> .(OAc) <sub>2</sub> .2H <sub>2</sub> O]	23	24	20	19
[Ni (LD <sub>4</sub> ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	25	23	19	17
(Gentamicin) Reference drug	33	29	30	10

<sup>a</sup>Free ligand, <sup>b</sup>Values including disk diameter (6 mm Ø) are averages of three replicates, <sup>c</sup>Gram-negative, <sup>d</sup>Gram-positive, concentration of sample (500 µg/disc). *E. coli*: *Escherichia coli*, *P. aeruginosa*: *Pseudomonas aeruginosa*, *S. aureus*: *Staphylococcus aureus*, *S. pneumoniae*: *Streptococcus pneumoniae*

This can be due to the structure of ligand (**LD<sub>4</sub>**) (fluorinated group carries on 2-oxazoline) which helps the metal to restrict bacterial mobility or to the inhibition of active sites and can be commonly explained by the complexation of ligand (**LD<sub>4</sub>**) with Zinc(II) and Nickel(II), because the metal complexes have at the same time polar and non-polar characteristics.<sup>[81,82]</sup> This makes them well suited for penetration into the cell. The metal ion's polarity is decreased due to the partial division of positive charge of this metal ion with donor groups, like nitrogen on ligands. Complexation enhances its penetration in lipid membranes by improving the delocalization of p-electrons through the chelate ring.<sup>[83,84]</sup> Lipophilicity, that controls the rate of molecules entry to the cell, is changed by coordination. It is possible that both complexes of [Zn(**LD<sub>4</sub>**)<sub>2</sub>.(OAc)<sub>2</sub>.2H<sub>2</sub>O] and [Ni(**LD<sub>4</sub>**)<sub>2</sub>.(OAc)<sub>2</sub>.4H<sub>2</sub>O] have been shown promising activity against all the strains in comparison to other complexes. In brief, this study indicated that the observed antibacterial activity was reinforced for metal complexes as compared to single metal salts or their corresponding ligands. Therefore, the complexation favored antibacterial activity, which may be explained through the chelation theory. In this theory, it is stated that coordination has reduced the metal ion polarity by partitioning positive charge with the ligand's donor groups, resulting in the delocalization of electron density over the entire coordination sphere, which subsequently induces an increase in the lipophilic character of the complex, ensuring better penetration through the cell's lipid membrane.<sup>[85]</sup>

Finally, we can conclude that all the same conclusions have also been found in the literature.<sup>[86,87]</sup>

#### Evaluation of antioxidant activity

The assessment of ligand antioxidant activity and of their complexes was determined against BHT as a positive standard. We plotted the curves representing the percentage of inhibition as a function of concentration. The results of the DPPH• free radical scavenging test of free ligands and their metal complexes are reported in Figures 6-9 below.

The acquired results show that the inhibition percentage of the DPPH free radical increases with the increase of the concentration for both the free ligands and the metal complexes. We observed that the percentage of inhibition of nickel complex is higher in all cases and for all concentrations; however, the percentage of inhibition of this latter is greater than the corresponding ligands for concentrations above 50 µg/mL. This notice that is in accord with those reported in the literature.<sup>[88-90]</sup> The results of the antioxidant activity of free ligands and their metal complexes show that the percentage of inhibition of the free radical DPPH of these compounds presents an activity to trap the free radical higher than 30% from the concentration 150 µg/mL in the cases of the complexes, while the ligands (**LD<sub>1</sub>**, **LD<sub>2</sub>**, **LD<sub>3</sub>**, and **LD<sub>4</sub>**) are inactive. Better antioxidant activity is observed with the Ni(II) complex in all cases of the ligands, the latter having a percentage higher than 60% at concentrations around 350 µg/mL as a free radical

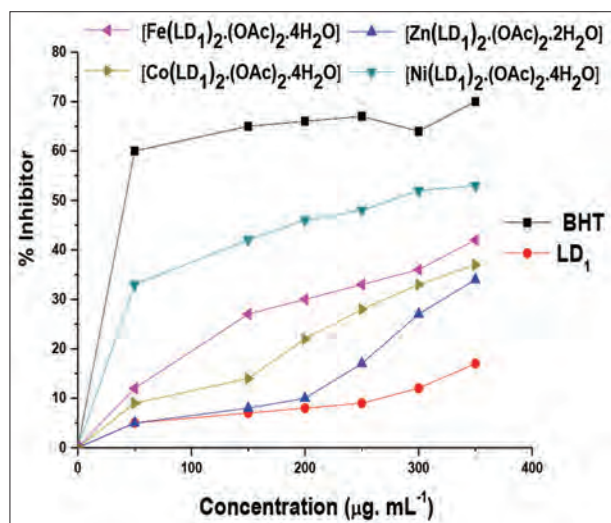
scavenger compared to the other complexes. The action of the synthesized complexes may be related to their capacity to give electrons to neutralize the free radicals.

The results represented in **Table 7** below, show the  $IC_{50}$  variation ( $\mu\text{g/mL}$ ) of free four ligands and their complexes in compare to BHT. The  $IC_{50}$  value of nickel complex based on ligands ( $LD_1$ ,  $LD_2$ ,  $LD_3$ , and  $LD_4$ ) is (2.423, 2.583,

**Table 7: DPPH radical scavenging activities of ligands and metal complexes at an inhibitory concentration ( $IC_{50}$ )**

Compounds	$IC_{50}$ ( $\mu\text{g/mL}$ ) <sup>b</sup>	$R^{2c}$
$LD_1^a$	12.301	0.913
[Fe ( $LD_1$ ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	12.309	0.958
[Co ( $LD_1$ ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	4.703	0.984
[Zn ( $LD_1$ ) <sub>2</sub> .(OAc) <sub>2</sub> .2H <sub>2</sub> O]	4.039	0.944
[Ni ( $LD_1$ ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	2.423	0.938
$LD_2^a$	9.278	0.900
[Fe ( $LD_2$ ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	4.365	0.882
[Co ( $LD_2$ ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	5.948	0.975
[Zn ( $LD_2$ ) <sub>2</sub> .(OAc) <sub>2</sub> .2H <sub>2</sub> O]	9.256	0.890
[Ni ( $LD_2$ ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	2.583	0.845
$LD_3^a$	4.424	0.968
[Fe ( $LD_3$ ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	4.072	0.523
[Co ( $LD_3$ ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	4.308	0.968
[Zn ( $LD_3$ ) <sub>2</sub> .(OAc) <sub>2</sub> .2H <sub>2</sub> O]	3.549	0.881
[Ni ( $LD_3$ ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	3.267	0.949
$LD_4^a$	10.802	0.957
[Fe ( $LD_4$ ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	8.250	0.833
[Co ( $LD_4$ ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	7.727	0.962
[Zn ( $LD_4$ ) <sub>2</sub> .(OAc) <sub>2</sub> .2H <sub>2</sub> O]	4.256	0.922
[Ni ( $LD_4$ ) <sub>2</sub> .(OAc) <sub>2</sub> .4H <sub>2</sub> O]	3.577	0.868
BHTindex	1.421	0.978

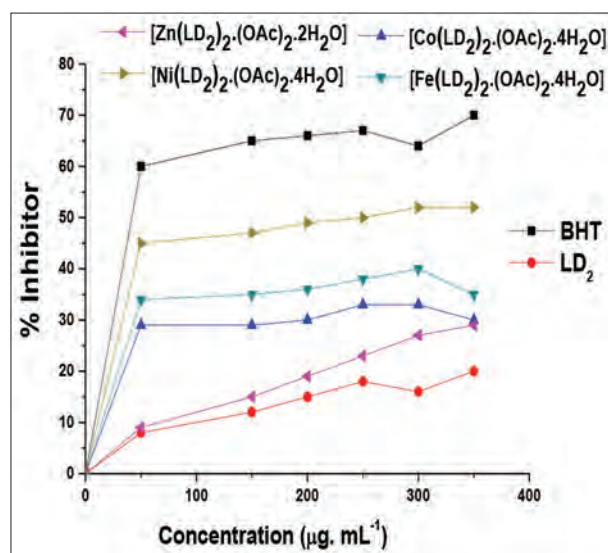
<sup>a</sup>Free ligand, <sup>b</sup> $IC_{50}$ -Inhibitory concentration; <sup>c</sup> $R^2$ : Correlation coefficient; <sup>d</sup>Reference standard



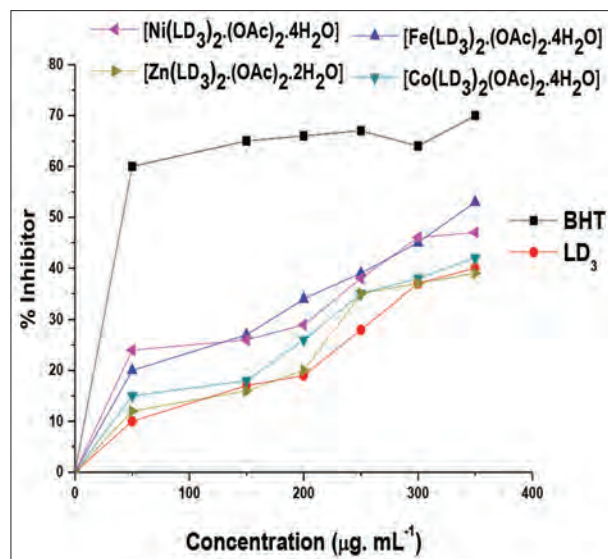
**Figure 6: Antioxidant activity (DPPH scavenging) of BHT and the free ligand ( $LD_1$ ) and its complexes**

3.267, and 3.577)  $\mu\text{g/mL}$ , respectively, showing a very high activity which is relatively similar to BHT (1.42  $\mu\text{g/mL}$ ) compared to the other compounds, while the  $IC_{50}$  values of the free ligands ( $LD_1$ ,  $LD_2$ , and  $LD_4$ ) (12.310, 9.278, and 10.802  $\mu\text{g/mL}$ ), respectively, also remain low, on the other hand, the  $IC_{50}$  value for  $LD_3$  is greater compared to the other ligands. For this, the presence of the coordinated metal ions changes the corresponding ligands structure, which affects the antioxidant activity.

Moreover, it is possible to conclude a relationship between the antioxidant activity and the functional groups that are present in their structures. In this context, the presence of methyl, allyloxy, trichloroethoxy, and heptafluorobutoxy groups at the 2-oxazoline of the ligands ( $LD_1$ ,  $LD_2$ ,  $LD_3$ , and  $LD_4$ ), respectively, have a great effect on the activity of the complexes, while the free ligands show a low activity.

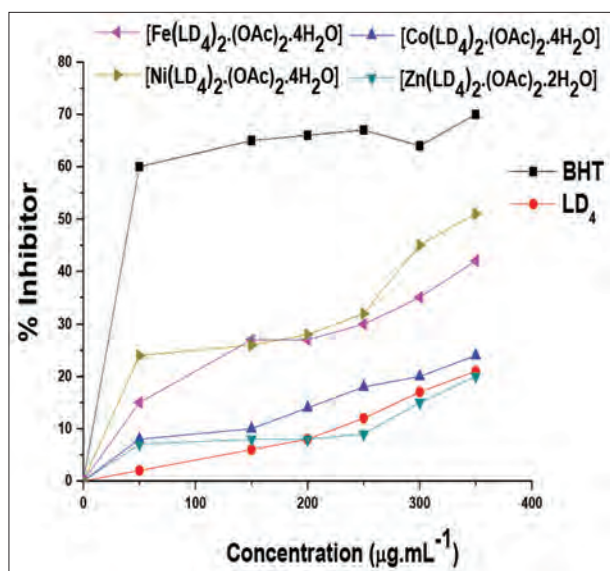


**Figure 7: Antioxidant activity (DPPH scavenging) of BHT and the free ligand ( $LD_2$ ) and its complexes**



**Figure 8: Antioxidant activity (DPPH scavenging) of BHT and the free ligand ( $LD_3$ ) and its complexes**





**Figure 9: Antioxidant activity (DPPH scavenging) of BHT and the free ligand (LD<sub>4</sub>) and its complexes**

Furthermore, the antioxidant activity increases with the type and oxidation degree of the metal in the case of Ni(II). From these results, it is proved that [Ni(LD<sub>1</sub>)<sub>2</sub>(OAc)<sub>2</sub>.4H<sub>2</sub>O] complex and [Ni(LD<sub>2</sub>)<sub>2</sub>(OAc)<sub>2</sub>.4H<sub>2</sub>O] complex are active antioxidants varying between 2.423 µg/mL and 2.583 µg/mL of inhibition with DPPH compared to other compounds tested, this important activity mainly associates with the presence of nickel metal and methyl and allyloxy groups to 2-oxazoline.

Finally, these values are in accordance with prior studies of the metal complexes,<sup>[91,92]</sup> in which the complex metals are more active than their corresponding ligands.

## EXPERIMENTAL SECTION

### Materials and Methods

The sensitive reactions were performed in solvents and reactants that were freshly distilled, or that were purified by us following the usual procedures.<sup>[93,94]</sup> The used solvents (99.8%) ethanol, absolute methanol, diethyl ether, chloroform, dimethylformamide (DMF), and dimethylsulfoxide (DMSO) were obtained from Prolabo. Metal acetate salt (Sigma-Aldrich): Iron(II) acetate tetrahydrate Fe(CH<sub>3</sub>COO)<sub>2</sub>.4H<sub>2</sub>O, 95%), Zinc(II) acetate dihydrate, (Zn(CH<sub>3</sub>COO)<sub>2</sub>.2H<sub>2</sub>O, 98%), Cobalt acetate tetrahydrate (CoCH<sub>3</sub>COO)<sub>2</sub>.4H<sub>2</sub>O, 98%), Nickel(II) acetate tetrahydrate (Ni(CH<sub>3</sub>COO)<sub>2</sub>.4H<sub>2</sub>O, 98%), 2,2-Diphenyl-1-picrylhydrazyl (DPPH), 95% (Sigma-Aldrich), Gentamicin (GEN) (Sigma-Aldrich), and Butylhydroxytoluene (BHT) are provided by Sigma-Aldrich.

### Precautions of Manipulation

All four ligands (LD<sub>1</sub>, LD<sub>2</sub>, LD<sub>3</sub>, and LD<sub>4</sub>) have sensitivity to acidic conditions as well as to heating. Under these conditions, the four ligands undergo a degradation made by the hydrolysis of the carbon-nitrogen double bond. To avoid this degradation, most of the reactions are done

in anhydrous, neutral medium, and at a temperature not exceeding 50°C. The solvent is evaporated under vacuum in a hot water bath at a temperature not higher than 45°C.

### Instrumental Methods (Techniques and Equipment Used)

The ultraviolet-visible spectra of complexes were recorded on a UV-Vis spectrophotometer (Shimadzu UV mini-1240). The samples for analysis were solubilized in the absolute ethanol at room temperature, using quartz cells of 1 cm of thickness between 500 and 200 nm at a concentration of 10<sup>-3</sup> M. FT-IR spectra were recorded with a Shimadzu FT-IR-470 spectrometer in the wavenumbers range from 4000 to 400 cm<sup>-1</sup>, using standard KBr beam splitter. The XRD spectra of the free ligand (LD<sub>4</sub>) and their complexes were carried out within the Solid State Physics Laboratory at the University of M'sila. The data were collected on AXS D8. ADVANCE Bruker (XRD) diffractometer with a copper anticathode (K $\alpha$  line;  $\lambda = 1.5418\text{\AA}$ ) at a voltage of 40 kV and an intensity of 40 mA. The 2 $\theta$  scanning was performed between 1° and 69.99°, with a step of 0.02°/s, the time was 0.25 s. The molar conductance for complexes was determined using a WTW Cond 7110 laboratory conductivity meter. The melting point was determined using a Kofler bench type of WME. The simultaneous TGA analysis of the free ligand (LD<sub>4</sub>) and its metal complexes was studied, where the heating rates were suitably controlled at 10°C min<sup>-1</sup> under argon and the weight loss was measured from ambient temperature to 550°C. pH measurements were carried out using a Hanna H1-2211 pH-ORP. The elemental analysis (C, N, H, and M) was done on a Carlo Erba 1106. For biological activity, an autoclave (Hirayama, Japan) was employed for the sterilization.

### Biological Evaluation

#### Evaluation of antibacterial activity

The evaluations of antibacterial activity of all ligands and their metal complexes *in vitro* were performed using two Gram-positive bacteria *S. aureus* (ATCC 29213) and *S. pneumoniae* (ATCC 49619) and two Gram-negative bacteria *P. aeruginos* (ATCC 27853) and *E. coli* (ATCC 25922) by the disk diffusion technique in Mueller-Hinton (MH) agar medium.<sup>[95-97]</sup> The free ligands and their complexes were solubilized in DMF (6%), which was previously tested for antibacterial activity against all bacteria and was confirmed to have no antibacterial activity, then, using 10 µL of suspension of the tested bacteria, at 2.10<sup>8</sup> CFU/mL. The MH media was dispensed into sterile Petri dishes (15 mL). Sterile filter paper (whatman) disks (6 mm  $\phi$ ) were individually impregnated with 5 µL of free ligands and their metal complexes (500 µg/disk) concentration and then placed on the surface of agar media already inoculated with the tested bacteria. Petri dishes were kept at 4°C for 2 h and then incubated at 37°C for 24 h. The diameters of the inhibition zones (mm) were measured, including disk diameter.<sup>[98]</sup> Gentamicin (500 µg/disk) concentration was used as a control. The choice of the latter is due to the analogous structures of the ligands used. Gentamicin was solubilized in DMF (6%), to be used as positive control. The

obtained results are given as mean standard deviations of three determinations.

#### Evaluation of antioxidant activity

DPPH is generally the preferred substrate for the rapid and direct evaluation of antioxidant activity due to its stability as free radicals and the simplicity of the analysis. DPPH absorbs in the visible range at 517 nm wavelength. The followed experimental protocol for studying DPPH free radical scavenging activity is that described in the literature with some modifications,<sup>[99]</sup> where 0.3 mL of solution of each ligand (**LD**<sub>1</sub>, **LD**<sub>2</sub>, **LD**<sub>3</sub>, and **LD**<sub>4</sub>) and its methanolic complexes tested at different concentrations 0–350 µg/mL were mixed with 75 µL of a methanolic solution of DPPH (1.3 mg/mL), after an incubation period for 30 min at room temperature, the absorbance is measured at the wavelength of 517 nm. Free radical inhibition by BHT was also tested at the same concentration for comparison purposes. All tests were performed three times to check reproducibility. The ability of DPPH scavenging of the free ligands and their metal complexes was calculated using the following equation.<sup>[100]</sup>

$$\% \text{ Scavenging activity} = \frac{|\text{Abs}_{517 \text{ nm of control}} - \text{Abs}_{517 \text{ nm of sample}}|}{\text{Abs}_{517 \text{ nm of control}}} \times 100$$

#### Statistical Analysis

The obtained experimental data of biological activity evaluations were expressed as an average. The IC<sub>50</sub> values are calculated by a linear regression method from the curve (Inhibition % = f [concentration]). The correlation coefficient of the different properties was determined using the programs Origin 9 and Excel 2010.

#### Synthesis of Ligands

The derivatives used in this work have already been synthesized and characterized at the Laboratory of Organic Chemistry 2-Glycochemistry (CO2-GLCO) of the University Claude Bernard-Lyon 1 France. The four 2-alkyl-2-oxazolin-3,4,6-tri-*O*-acetyl-1,2-dideoxy- $\alpha$ -*D*-glucopyranoses (ligands) derivatives that we studied are: 2-Methyl-3,4,6-tri-*O*-acetyl-1,2-dideoxy-(2-amino-2-deoxy- $\alpha$ -*D*-glucopyrano)-[2,1-*d*]-2-oxazoline (**LD**<sub>1</sub>); 2-Allyloxy-3,4,6-tri-*O*-acetyl-1,2-dideoxy-(2-amino-2-deoxy- $\alpha$ -*D*-glucopyrano)-[2,1-*d*]-2-oxazoline (**LD**<sub>2</sub>); 2-(2,2,2-Trichloroethoxy)-3,4,6-tri-*O*-acetyl-1,2-dideoxy-(2-amino-2-deoxy- $\alpha$ -*D*-glucopyrano)-[2,1-*d*]-2-oxazoline (**LD**<sub>3</sub>); and 2-(2,2,3,3,4,4,4-Heptafluorobutoxy)-3,4,6-tri-*O*-acetyl-1,2-dideoxy-(2-amino-2-deoxy- $\alpha$ -*D*-glucopyrano)-[2,1-*d*]-2-oxazoline (**LD**<sub>4</sub>).

#### Preparation of Metal (II) Complexes

A series of Metal(II)-2-alkyl-2-oxazolin-3,4,6-tri-*O*-acetyl-1,2-dideoxy- $\alpha$ -*D*-glucopyranose (1:2) complexes was synthesized as described in the literature.<sup>[101,102]</sup> The complexes based on Zn(II), Fe(II), Ni(II), and Co(II) and the ligands (**LD**<sub>1</sub>, **LD**<sub>2</sub>, **LD**<sub>3</sub> and **LD**<sub>4</sub>) were synthesized by the precipitation reaction of 2 mmol of the dissolved ligand in 10 mL of

absolute ethanol/distilled water (1:1) (v/v) with 1 mmol of metal acetate salt Zn(CH<sub>3</sub>COO)<sub>2</sub>·2H<sub>2</sub>O, Fe(CH<sub>3</sub>COO)<sub>2</sub>·4H<sub>2</sub>O, Ni(CH<sub>3</sub>COO)<sub>2</sub>·4H<sub>2</sub>O, and/or Co(CH<sub>3</sub>COO)<sub>2</sub>·4H<sub>2</sub>O dissolved in the same solvent. At ambient temperature, the reaction mixtures were maintained under magnetic stirring for 3–5 h to obtain a better yield. The mixtures were left to stand for 24 h. The precipitates obtained were filtered, washed with a water-ethanol mixture (1:1), and finally dried at 50°C.

#### CONCLUSION

This research focused on the derivatives of 2-alkyl-2-oxazolin-3,4,6-tri-*O*-acetyl-1,2-dideoxy- $\alpha$ -*D*-glucopyranose, which were taken as free ligands (**LD**<sub>1</sub>, **LD**<sub>2</sub>, **LD**<sub>3</sub>, and **LD**<sub>4</sub>). The metal (II) complexes of Fe, Ni, Co, and Zn were produced using the coordination reaction with metal salts, giving naissance of new symmetrical metal complexes with the molar ratio (1:2) [M(II):(LD<sub>n</sub>)<sub>2</sub>]. The obtained complexes are stable solids and with a different color. The obtained metal complex structures were confirmed using elemental analysis, FT-IR, UV-Vis, and TGA. Molar conductivity measurements indicate that all complexes are non-electrolyte in DMF. Structural study by FT-IR eventually revealed the monodentate coordination of tested ligands and further showed the lowest frequency shift after coordination of the metal ions to the ligand; X-ray diffraction analysis suggests a crystal system in all **LD**<sub>4</sub>-based metal complexes. Antimicrobial tests showed that the [Zn(**LD**<sub>4</sub>)<sub>2</sub>·(OAc)<sub>2</sub>·2H<sub>2</sub>O] and [Ni(**LD**<sub>4</sub>)<sub>2</sub>·(OAc)<sub>2</sub>·4H<sub>2</sub>O] complexes recorded antibacterial efficiencies. Significantly, a study of the free radical scavenging properties of the compounds revealed that the [Ni(**LD**<sub>1</sub>)<sub>2</sub>·(OAc)<sub>2</sub>·4H<sub>2</sub>O] and [Ni(**LD**<sub>2</sub>)<sub>2</sub>·(OAc)<sub>2</sub>·4H<sub>2</sub>O] complexes possessed considerable antioxidant activities. The results obtained indicated that ligands as well as their metallic complexes have a potential for exploration as active substances that could be interesting in the pharmaceutical field. Finally, our results can be used in future work, namely, biological assays, to study their cytotoxic and antifungal activities.

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