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Synthesis, Characterization, and Biological Investigation of Transition Metal (II) Complexes Based on 2-Alkyl-2-Oxazolin-*α*-*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-dideosy-*α*-*D*-glucopyranose derivatives. The elemental analyses suggested that the stoichiometry is (1:2) [Metal:$(\mathbf{LD_n})_2$]. 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 $\mathbf{LD_4}$ [$M(\mathbf{LD_4})_2.(OAc)_2.xH_2O$]. 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 [$(Zn(\mathbf{LD_4})_2.(OAc)_2.2H_2O$] and [$Ni(\mathbf{LD_4})_2.(OAc)_2.4H_2O$] showed significant antibacterial activity compared to the corresponding ligands. The dosage with the radical DPPH at different concentrations for the complexes [$(Ni(\mathbf{LD_1})_2.(OAc)_2.4H_2O$] and [$Ni(\mathbf{LD_2})_2.(OAc)_2.4H_2O$] 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-dideosy-α-*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.[1,2] Numerous studies are cited in the literature on different properties.[3-6] 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,[7,8] 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.[9-12] Among these natural substances, we were interested in 2-amino-2-deoxy-*D*-glucopyranose.[13-19] 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-dideosy-α-*D*-glucopyranose derivatives.[20-27] 2-Oxazolines free and/or bound had many reports of their applications in biology including antibacterial,[28,29] antifungal,[30] anti-cancer,[31]

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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,[99] where 0.3 mL of solution of each ligand (**LD_1**, **LD_2**, **LD_3**, and **LD_4**) 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.[100]

$$\% \text{ Scavenging activity} = \left|\frac{Abs_{517\text{ nm of control}} - Abs_{517\text{nm of sample}}}{Abs_{517\text{ nm of control}}}\right| \times 100$$

Statistical Analysis

The obtained experimental data of biological activity evaluations were expressed as an average. The IC_{50} 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-dideosy-α-*D*-glucopyranoses (ligands) derivatives that we studied are: 2-Methyl-3,4,6-tri-*O*-acetyl-1,2-dideoxy-(2-amino-2-deoxy-*α*-*D*-glucopyrano)-[2,1-*d*]-2-oxazoline (**LD_1**); 2-Allyloxy-3,4,6-tri-*O*-acetyl-1,2-dideoxy-(2-amino-2-deoxy-*α*-*D*-glucopyrano)-[2,1-*d*]-2-oxazoline (**LD_2**); 2-(2,2,2-Trichloroethoxy)-3,4,6-tri-*O*-acetyl-1,2-dideoxy-(2-amino-2-deoxy-*α*-*D*-glucopyrano)-[2,1-*d*]-2-oxazoline (**LD_3**); and 2-(2,2,3,3,4,4,4-Heptafluorobutoxy)-3,4,6-tri-*O*-acetyl-1,2-dideoxy-(2-amino-2-deoxy-*α*-*D*-glucopyrano)-[2,1-*d*]-2-oxazoline (**LD_4**).

Preparation of Metal (II) Complexes

A series of Metal(II)-2-alkyl-2-oxazolin-3,4,6-tri-*O*-acetyl-1,2-dideosy-α-*D*-glucopyranose (1:2) complexes was synthesized as described in the literature.[101,102] The complexes based on Zn(II), Fe(II), Ni(II), and Co(II) and the ligands (**LD_1**, **LD_2**, **LD_3** and **LD_4**) 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 $Zn(CH_3COO)_2.2H_2O$, $Fe(CH_3COO)_2.4H_2O$, $Ni(CH_3COO)_2.4H_2O$, and/or $Co(CH_3COO)_2.4H_2O$ 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-dideosy-α-*D*-glucopyranose, which were taken as free ligands (**LD_1**, **LD_2**, **LD_3**, and **LD_4**). 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):$(\mathbf{LD_n})_2$]. 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 mondentate 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_4**-based metal complexes. Antimicrobial tests showed that the $[Zn(\mathbf{LD_4})_2.(OAc)_2.2H_2O]$ and $[Ni(\mathbf{LD_4})_2.(OAc)_2.4H_2O]$ complexes recorded antibacterial efficiencies. Significantly, a study of the free radical scavenging properties of the compounds revealed that the $[Ni(\mathbf{LD_1})_2.(OAc)_2.4H_2O]$ and $[Ni(\mathbf{LD_2})_2.(OAc)_2.4H_2O]$ 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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