

## Synthesis of Ni(II), Cu(II) and Zn(II) coumarin-3-carboxylic acid derivatives and their physical-chemical properties

Síntese de derivados de ácido cumarina-3-carboxílico de Ni(II), Cu(II) e Zn(II) e suas propriedades físico-químicas

Síntesis de derivados del ácido cumarina-3-carboxílico de Ni(II), Cu(II) y Zn(II) y sus propiedades físico-químicas

Received: 03/01/2021 | Reviewed: 03/08/2021 | Accept: 03/16/2021 | Published: 03/22/2021

### Dirceu Aparecido Gonçalves de Souza

ORCID: <https://orcid.org/0000-0001-7754-0767>

Universidade Anhanguera de São Paulo, Brazil

E-mail: [dirceusouzacrif@gmail.com](mailto:dirceusouzacrif@gmail.com)

### Ricardo Luis Tranquilin

ORCID: <https://orcid.org/0000-0002-9556-337X>

Universidade Federal de São Carlos, Brazil

E-mail: [ricardotranquilin@gmail.com](mailto:ricardotranquilin@gmail.com)

### Marcio Luiz dos Santos

ORCID: <https://orcid.org/0000-0002-6607-1640>

Universidade Anhanguera de São Paulo, Brazil

E-mail: [marcio.l.santos@educadores.net.br](mailto:marcio.l.santos@educadores.net.br)

### Regina Mara Silva Pereira

ORCID: <https://orcid.org/0000-0001-9158-4555>

Universidade Anhanguera de São Paulo, Brazil

E-mail: [reginapereira1@anhanguera.com](mailto:reginapereira1@anhanguera.com)

### Abstract

In the search for new drugs, coumarins are an important class of compounds due to their chemical and biological properties, such as their potential to reduce cancer, diabetes, and cardiovascular diseases. They are heterocyclic compounds that contain oxygen in their structure and are found in plants. To improve the chemical and biological properties of the coumarin-3-carboxylic acid, were prepared metal transition complexes of Cu(II), Ni(II) and Zn(II) of coumarin-3-carboxylic acid by a new synthetic route. All complexes were characterized by Ultraviolet (UV), Infrared (FTIR), and Raman spectroscopy; Scanning electronic microscopy (SEM); X-Ray diffraction (XRD), as well as conductivity and elemental analysis. Electron microscopy and X-ray analysis showed that the degree of crystallinity of the complexes changes when compared with the precursor, 3-carboxy-coumarin acid, and the degree of crystallinity depends on the nature of the metal ion attached to coumarin. In addition, the antioxidant action of the complexes was evaluated by the DPPH method, and the results showed a higher activity of the complexes when compared with the precursor, suggesting that these complexes may present biological properties of interest.

**Keywords:** Coumarin; Synthesis; Complexes; Antioxidant; Coordination.

### Resumo

Na busca por novos medicamentos, as cumarinas são uma classe importante de compostos devido suas propriedades químicas e biológicas como, potencial de redução de doenças cancerígenas, diabetes e doenças cardiovasculares. São compostos heterocíclicos que contém oxigênio em sua estrutura e são encontrados em plantas. Com objetivo de melhorar as propriedades químicas e biológicas do ácido cumarina-3-carboxílico foram preparados complexos de transição de Cu(II), Ni(II), Zn(II), utilizando o ácido cumarina-3-carboxílico como precursor utilizando-se uma nova rota sintética. Todos os complexos foram caracterizados por espectroscopia de Ultravioleta (UV), Infravermelho (IV) e Raman; Microscopia eletrônica de varredura (MEV); Difractometria de raios-X (DRX), bem como condutividade e análise elementar. A microscopia eletrônica e as análises de raios-X mostraram que o grau de cristalinidade dos complexos muda quando comparado com o precursor, ácido 3-carboxi-cumarina, e sua cristalinidade depende da natureza do íon metálico ligado à cumarina. Além disso, avaliou-se a ação antioxidante dos complexos pelo método DPPH, cujos resultados indicaram uma maior atividade dos complexos quando comparados com o precursor, sugerindo que esses complexos podem ter potenciais propriedades biológicas de interesse.

**Palavras-chave:** Cumarina; Síntese; Complexos; Antioxidante; Coordenação.

## Resumen

En la búsqueda de nuevos fármacos, las cumarinas son una clase importante de compuestos debido a sus propiedades químicas y biológicas, como la reducción potencial de las enfermedades cancerosas, la diabetes y las enfermedades cardiovasculares. Son compuestos heterocíclicos que contienen oxígeno en su estructura y se encuentran en las plantas. Para mejorar las propiedades químicas y biológicas del ácido cumarínico-3-carboxílico, se prepararon complejos de transición de Cu(II), Ni(II), Zn(II), utilizando el ácido cumarínico-3-carboxílico como precursor utilizando una nueva ruta sintética. Todos los complejos se caracterizaron mediante espectroscopia Ultravioleta (UV), Infrarroja (FTIR) y Raman; Microscopía electrónica de barrido (MEB); Difracción de rayos X (DRX), así como conductividad y análisis elemental. Los análisis de microscopía electrónica y de rayos X mostraron que el grado de cristalinidad de los complejos cambia al compararlos con el precursor, el ácido 3-carboxi-cumarínico, y su cristalinidad depende de la naturaleza del ion metálico unido a la cumarina. Además, se evaluó la acción antioxidante de los complejos mediante el método DPPH, cuyos resultados indicaron una mayor actividad de los complejos en comparación con el precursor, lo que sugiere que estos complejos pueden tener potenciales propiedades biológicas de interés.

**Palabras clave:** Cumarina; Síntesis; Complejos; Antioxidante; Coordinación.

## 1. Introduction

Coumarin is found in plants such as cinnamon, guaco, lavender, and peppermint. It is a simple oxygen-containing heterocycle that has received significant attention due to its biological properties including in medicine, food, the chemical industry, and botany (Wang et al., 2013), (Song et al., 2017), (Wang et al., 2019). Coumarins play a key role in natural products and act as a secondary metabolite in plants (Elhousseiny, Aazam, Al-Amri, 2014). They can be found in different concentrations and are distributed in fruits, roots, stems, and leaves as well as in bacteria and fungi (Patil et al., 2015). In nature, more than 3400 coumarins have been found, and these are distributed in 160 families (Musa, Cooperwood & Khan., 2008). The coumarins stand out for their biological properties, which is attributed to the functional groups present in their structure (Lv et al., 2015). Dicumarol was the first oral drug with oral anticoagulant action derived from warfarin (3-phenylacetyl ethyl, 4-hydroxycoumarin) (Mueller, 2004). Afraxetine (7,8-dihydroxy-6-methoxychromen-2-one) and dafnetin (7,8-dihydroxycoumarin) are known for their anti-inflammatory and antioxidant activity as superoxide radical scavengers. These are involved in various inflammatory processes. (Paya et al., 1994).

The properties of coumarins may be related to the effects of antioxidant activities along with other mechanisms of action such as anti-inflammatory action and interactions with enzymes (Borges Bubols et al., 2013), (Creaven et al., 2006).

It is well known that a variety of coumarin-derived complexes can be obtained through different coordination modes with varying spectroscopic properties and potential applications in different areas especially when coordinated to d-block transition metal ions (de Alcantara et al., 2015).

The biological action of coumarin-3-carboxylic acid (HCCA) can be potentiated by complexing with metals through different coordination modes with spectroscopic properties and potential applications (Creaven et al., 2011), (Islas et al., 2018). One example is an increase in the antimicrobial activity of the coordination of the silver (I)-HCCA complex versus free ligand as reported previously (Creaven et al., 2006). A series of complexes of HCCA with Zn, Co, Ni, and Mn ions were synthesized, and their molecular structure and spectroscopic studies were determined based on density functional theory (Creaven et al., 2011). However, more detailed analysis about the physicochemical properties and structure of the complexes for pharmaceutical applications has not been performed.

## 2. Methodology

### 2.1 Material

All of the chemicals including coumarin and the acetate salt of diphenyl picrylhydrazyl radical (DPPH) were obtained from Sigma-Aldrich and Merck. All solvents used were of PA grade.

## 2.2. Analytical instruments

IR spectra were obtained in solid state via reflectance between 4000 and 400  $\text{cm}^{-1}$  on a Nicolet–Nexus instrument, Raman spectra were collected using a Bruker RFS – 100/S; a 1064 nm YAG laser was used as the excitation source at 400 mW. The melting point was measured using QUIMIS equipment, and the UV/VIS spectra were obtained in a water solution between 200 and 500 nm with a Femto 800-XI spectrometer. The conductivity analysis was performed in DMF solution (3mM) and expressed in  $\Omega^{-1}\text{cm}^2 \text{mol}^{-1}$ . Analysis with scanning electron micrographs (SEM) was performed with a Supra 35-VP instrument (Carl Zeiss, Germany). The samples were evenly distributed on SEM specimen stubs with double adhesive tape. The micrographs were obtained with an accelerating potential of 2 kV. Monochromatic Cu Ka radiation (wavelength = 1.54056 Å) was produced by Rigaku-DMax/2500PC, Japan. The powdery samples were packed tightly in a rectangular aluminum cell prior to exposure to the X-ray beam. The scanning regions of the diffraction angle,  $2\theta$ , were 10 - 80°, and radiation was detected with a proportional detector.

## 2.3 General Synthesis of complexes

A methanol solution containing an equimolar amount of intended salt  $[\text{Cu}(\text{CH}_3\text{COO})_2\text{H}_2\text{O}]$ ,  $[\text{Ni}(\text{CH}_3\text{COO})_2\cdot 4\text{H}_2\text{O}]$  or  $[\text{Zn}(\text{CH}_3\text{COO})_2\cdot 2\text{H}_2\text{O}]$  (10 mL) was slowly added dropwise to a solution of 1.6 mmol of coumarin-3-carboxylic acid (HCCA) in 20 mL of methanol at 50°C. The mixture was stirred for 1 h. The solutions were stored at 5°C for 24 hours until precipitation. The precipitate was filtered and washed with cold methanol.

## 2.4 Antioxidant Activity

The solution contained 1mL of DPPH (diphenyl picrylhydrazyl radical) (60  $\mu\text{M}$ ) and different concentrations of complexes were prepared. For coumarin-3-carboxylic acid (HCCA) the concentrations varied from 100 to 1000  $\mu\text{M}$ , for Zn(II)-HCCA from 42 to 420  $\mu\text{M}$ , for Ni(II)-HCCA from 42 to 420  $\mu\text{M}$  and for Cu(II)-HCCA from 65 to 650  $\mu\text{M}$ . Ethanol PA was added to each solution until the volume of 2 mL and DPPH concentration of 30  $\mu\text{M}$ . The solutions were vigorously mixed and allowed to stand in the dark for 30 min at 25 °C. The absorbance of the resulting solutions was measured at 517 nm against a blank sample containing only DPPH (the negative control). Rutin was the reference (Ikeda et al., 2015).

# 3. Results and Discussion

## 3.1 Synthesis and Characterization of Complexes

The reactions of coumarin-3-carboxy acid (HCCA) and salt  $[\text{Cu}(\text{CH}_3\text{COO})_2\text{H}_2\text{O}]$ ,  $[\text{Ni}(\text{CH}_3\text{COO})_2\cdot 4\text{H}_2\text{O}]$  or  $[\text{Zn}(\text{CH}_3\text{COO})_2\cdot 2\text{H}_2\text{O}]$  produced new complexes Cu(II)-HCCA, Ni(II)-HCCA and Zn(II)-HCCA. These were characterized by melting point, elemental analyses, UV/Raman /FTIR spectroscopy, conductivity, X-ray diffraction (XRD), and scanning electronic microscopy (SEM). The color, melting point, conductivity, and elemental analysis are shown in Table 1.

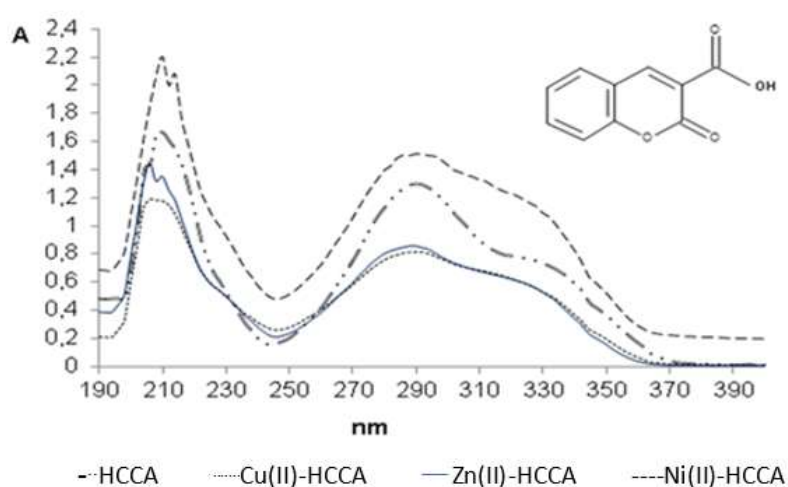
**Table 1.** Physico-chemical characteristics of Cu(II)-HCCA, Ni(II)-HCCA and Zn(II)-HCCA.

Complex	Color	Melting Point (°C)	Yield %	Elemental Analyses		Conductivity* ( $\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$ )
				%C Exp (Calc)	% H Exp (Calc)	
Cu(II)-HCCA	Light green	> 300	67.4	46.0 (46.1)	2.9 (2,9)	8.14
Ni(II)-HCCA	Green	> 300	48.1	49.2 (49.6)	3.2 (3.4)	5.42
Zn(II)-HCCA	White	> 300	47.1	50.0 (50.6)	2.7 (3,1)	5.55

\*3 mM. Source: Authors.

The elemental analysis data suggests a minimum molecular formula for the complexes of  $[\text{Cu}(\text{C}_{10}\text{H}_6\text{O}_4)(\text{CH}_3\text{COO})]$  to Cu(II)-HCCA,  $[\text{Ni}(\text{C}_{20}\text{H}_{11}\text{O}_8).(\text{CH}_3\text{COO})_2\text{H}_2\text{O}]$  to Ni(II)-HCCA, and  $[\text{Zn}(\text{C}_{20}\text{H}_{11}\text{O}_8).(\text{CH}_3\text{COO}).\text{H}_2\text{O}]$  to Zn(II)-HCCA. Although the formation of binuclear structures was considered, the elemental analysis data for the three complexes correlated better with a mononuclear structure (Table 1). However, the Ni(II)-HCCA and Zn(II)-HCCA has a ratio of two coumarin molecules to one metal center; Cu(II)-HCCA is one coumarin molecule to one copper ion (Fig 3). The experimental data of conductivity for Cu(II)-HCCA, Ni(II)-HCCA, and Zn(II)-HCCA (Table 1) showed that the complexes have low conductivity and are classified as non-ionic. According to the experiments conducted by El-Wahab, only complexes with a conductivity above  $54 \Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$  are considered ionic. The UV spectrum of HCCA has a maximum at 290 nm and a low intensity signal at 334 nm. The complexes of Cu(II)-HCCA, Ni(II)-HCCA, and Zn(II)-HCCA presented similar profiles of HCCA, however there was a small shift to 286 and 318 nm (Figure 1) indicating the interaction of metal ions with the conjugated ring. The peak at 286 nm could be related to the metal-ligand charge transfer transitions representing the HCCA( $\pi$ ) to a  $M(\text{d}y_z)/\text{HCC}(\pi^*)$  orbital transition. The shoulder at 318 nm corresponds to the transition from a  $M(\text{d}x_z)/\text{HCCA}(\pi)$  orbital to the HCCA( $\pi^*$ ) orbital (Creaven et al., 2011).

**Figure 1.** Spectra in ultraviolet region of HCCA, Cu(II)-HCCA, Ni(II)-HCCA and Zn(II)-HCCA.



Source: Authors.

The vibrational FTIR and Raman spectra of Cu(II)-HCCA, Ni(II)-HCCA, and Zn(II)-HCCA were measured and compared with the HCCA (Figure 2). In the region between 3300 and 2500  $\text{cm}^{-1}$ , there were broad and weak bands corresponding to  $\nu\text{O-H}$  stretching. Between 1440 and 1395  $\text{cm}^{-1}$  there was medium  $\nu\text{C-O}$  bending of the carboxylic acid group. These data indicate the permanence of the hydrogen atom in HCCA (Table 2); These results were confirmed by Raman spectroscopy (Figure 2), whose characteristic stretching frequency of  $\nu\text{O-H}$  at 3080  $\text{cm}^{-1}$  was observed for all HCCA binders and all complexes. Metal ions interact with coumarin molecules via the carboxylic and carbonyl groups, and those interactions promote a polarization of the bond leaving the  $\nu\text{C=O}$  bond. This in turn promotes a shift of the  $\nu\text{C=O}$  band to lower frequencies versus the HCCA bands (Table 2). The  $\nu\text{M-O}$  bond is observed at 594, 592, and 594  $\text{cm}^{-1}$  for Cu(II)-HCCA, Zn(II)-HCCA, and Ni(II)-HCCA respectively. According to Patil et al. (2015) the copper complexes of 6-formyl-7, 8-dihydroxy-4-methyl coumarin and o-toluidine-3-aminobenzotrifluoride have a  $\nu\text{M-O}$  stretch near 580  $\text{cm}^{-1}$  corroborating our assignment of  $\nu\text{Cu-O}$  of Cu(II)-HCCA.

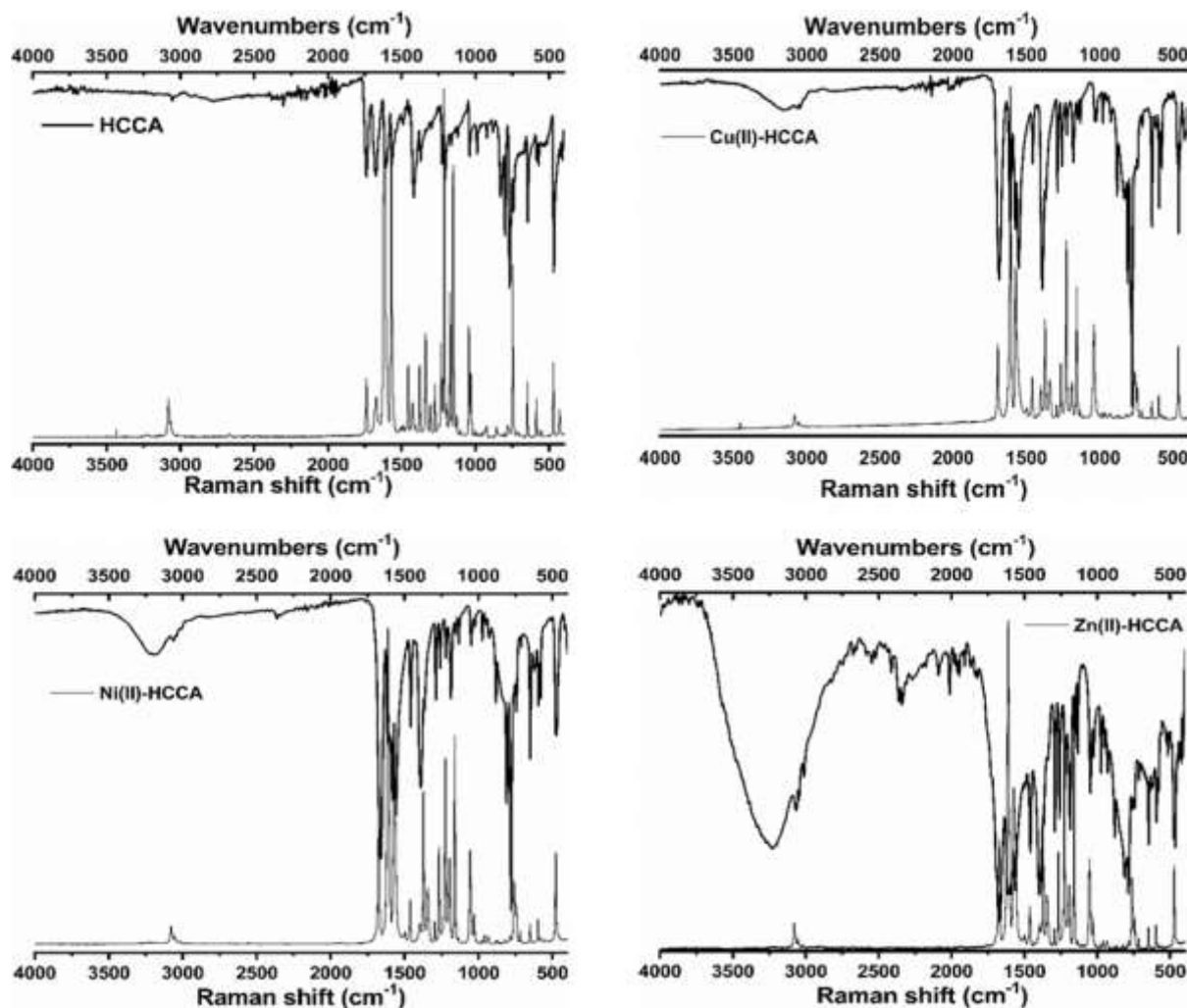
**Table 2.** Principal bands ( $\text{cm}^{-1}$ ) of the IR spectra for HCCA, Cu(II)-HCCA, Ni(II)-HCCA and Zn(II)-HCCA.

Compounds	$\nu_{\text{O-H}}$	$\nu_{\text{C=O}}$ (carboxylic)	$\nu_{\text{C=O}}$ (carbonyl)	$\nu_{\text{C=C}}$	$\nu_{\text{O-H}}$	$\nu_{\text{M-O}}$
HCCA	-	1738	1673	1607;1565	1417	-
Cu(II)-HCCA	3160	1686	1610	1576; 1552	1339	594
Ni(II)-HCCA	3219	1663	1616	1584;1561	1394	594
Zn(II)-HCCA	3198	1662	1608	1584;1560	1390	592

Source: Authors.

The Raman spectra for HCCA and complexes Cu(II)-HCCA, Ni(II)-HCCA and Zn(II)-HCCA, exhibited a weak peak at 3080  $\text{cm}^{-1}$  was assigned to the  $\nu\text{O-H}$ , indicating the permanence of the hydrogen acid in all complexes. The peaks at 1476 and 1380  $\text{cm}^{-1}$  are medium  $\nu\text{O-H}$  bending of the carboxylic acid group stretching (due to the coupling of the angular deformation in the plane of the  $\nu\text{O-H}$  and the axial deformation of  $\nu\text{C-O}$ , confirming the presence of carbonilic hydrogen in de complexes. The bands assigned to the  $\nu\text{C=O}$  (stretching) and  $\nu\text{C=C}$  aromatic (stretching) was also confirmed by the Raman spectra in Figure2.

**Figure 2.** IR and Raman spectra of HCCA, Cu(II)-HCCA, Ni(II)-HCCA and Zn(II)-HCCA.

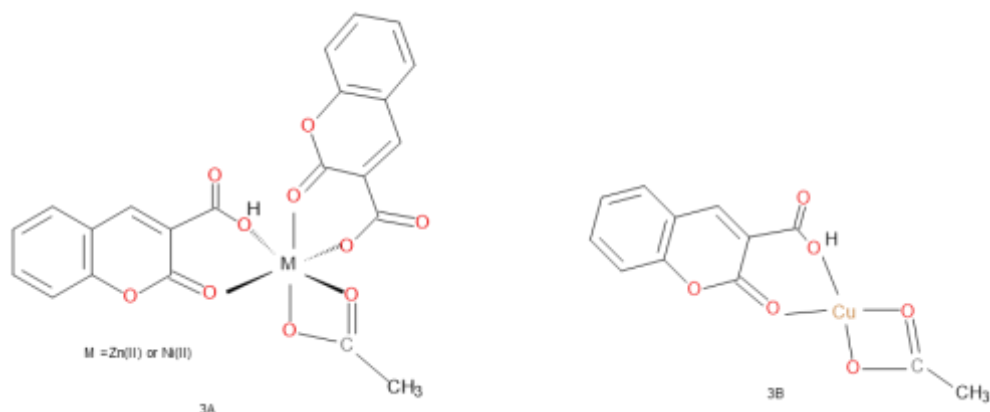


Source: Authors.

According to the IR and Raman data, the coordination of the metal ions occurred through the carboxylic and carbonyl group at positions 2 and 4 of the heterocycle for all complexes. The  $\nu_{\text{H-O}}$  of the carbonyl group is present in all complexes. Raman and IR data for all complexes indicate coumarin-3-carboxy acid (HCCA) binder H carboxylic remains in the molecule after metallic coordination. According to the conductivity data (Table 1) all the synthesized complexes are neutral suggesting the presence of two negatively charged binders coordinated to Cu(II), Zn(II), and Ni(II) ions, forming the respective complexes. Therefore, based on spectroscopic data (Table 2 and Figure 2), conductivity and elemental analysis (Table 1) it is suggested an octahedral structure for Ni(II)-HCCA and Zn(II)-HCCA. There is coordination of two molecules of coumarin-3-carboxy acid occurred, but there is deprotonation of only one HCCA and interaction of one molecule of ethyl acetate leaving the complexes neutral (Figure 3A). For the Cu(II)-HCCA complex, it is suggested a square planar structure with coordination of only one molecule of coumarin-3-carboxy acid, which does not suffer deprotonation and the coordination of one molecule of acetate (Figure 3B).



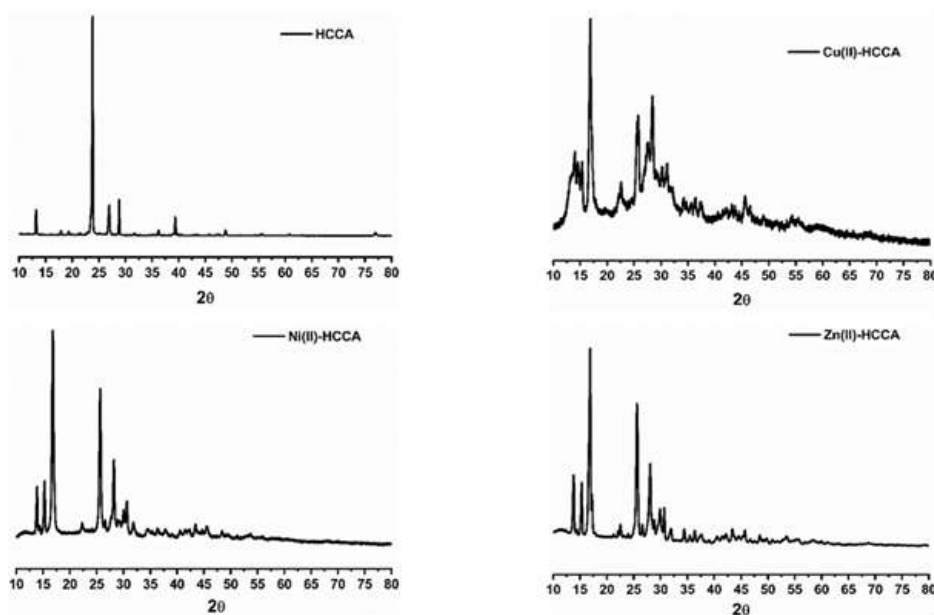
**Figure 3.** Structures suggested (A) to Ni(II)-HCCA and Zn(II)-HCCA; (B) to Cu(II)-HCCA.



Source: Authors.

X-ray diffraction data of the three complexes Cu(II)-HCCA, Ni(II)-HCCA, and Zn(II)-HCCA were compared with the HCCA (Figure 4). All peaks corresponding to the HCCA (#: 50-2380, a:11.383, b:5.544, c:13.887, system: monoclinic) were identified. The Cu(II)-HCCA complexes exhibited line broadening of the crystalline diffraction peak and showed lower crystallinity. The Ni(II)-HCCA and Zn(II)-HCCA complexes exhibit sharp peaks while no peaks were observed for the rest of the complexes indicating their higher crystallinity. The crystallographic nature of the complexes was indicated by comparing the diffractograms of the ligand and the complexes. The literature suggests this may be due to the incorporation of water molecules into the coordination sphere (Khan et al., 2013). Although single crystal X-ray crystallography is the most precise source of information regarding the structure of a complex, the difficulty in obtaining suitable crystals in a proper symmetric form has rendered this method unsuitable for such a study.

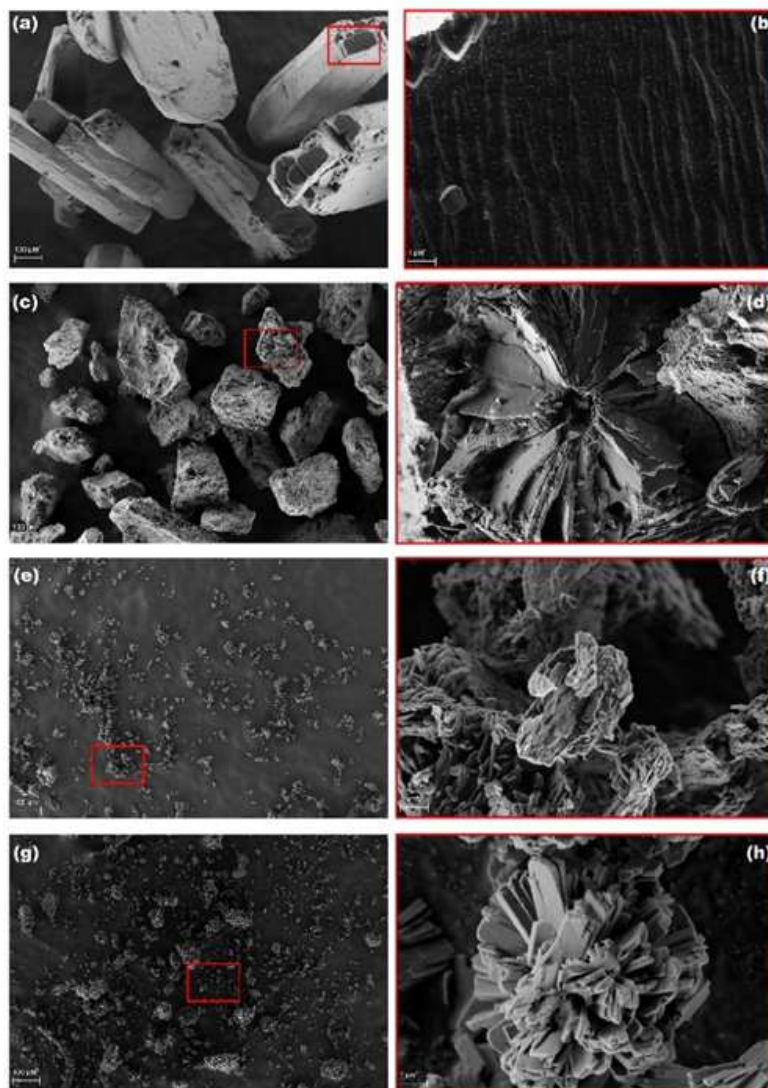
**Figure 4.** X-ray diffraction analysis of HCCA, Cu(II)-HCCA, Ni(II)-HCCA and Zn(II)-HCCA.



Source: Authors.

Scanning electron micrographs of the HCCA, Cu(II)-HCCA, Ni(II)-HCCA, and Zn(II)-HCCA samples are presented in Figure 5(a-h). Figure 5(a) shows that the HCCA particles have irregular sizes, but with a structure that is regularly scattered (Figure 5b). Figure 5(c-d) shows that the Cu(II)-HCCA grains are small with similar sizes. The micrographs of Ni(II)-HCCA and Zn(II)-HCCA (Figure 5(e-f, g-h)) indicated the presence of defined crystals free of any sign of the metal ion. In the metal complexes, crystals grew via agglomerates of plates of various sizes (Khan et al., 2013).

**Figure 5.** Scanning electron micrographs of (a, b) HCCA, (c, d) Cu(II)-HCCA, (e, f) Ni(II)-HCCA and (g, h) Zn(II)-HCCA. Magnitude: 200 X and 20000X.



Source: Authors.

### 3.1 Antioxidant activity of Complexes

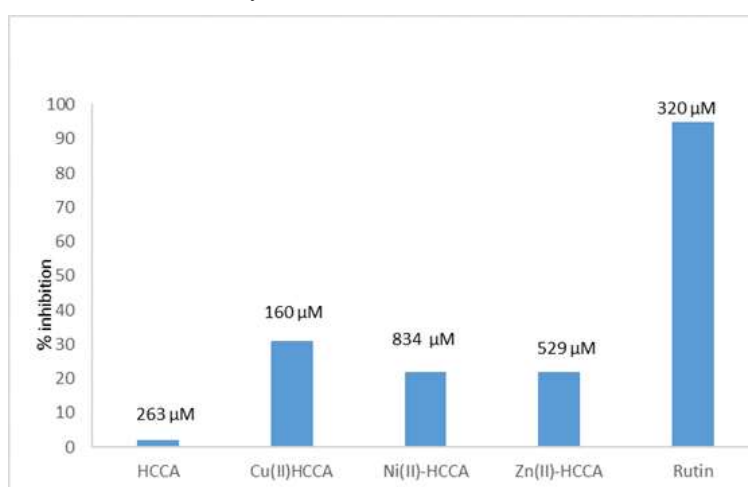
The antioxidant potential of the complexes was evaluated via the DPPH method (Halli et al., 2012) at concentrations ranging from 100 to 1000  $\mu\text{M}$  (Figure 6). Cu(II)-HCCA had the best correlation between percentage of free radical inhibition and concentration (31% at 160  $\mu\text{M}$ ) while HCCA inhibits 2% at a concentration of 236  $\mu\text{M}$ , Zn(II)-HCCA 22% at 529  $\mu\text{M}$  and Ni(II)-HCCA 22% at 834  $\mu\text{M}$ . However, when the antioxidant activity of the complexes is compared with the antioxidant activity of rutin, this is still much lower than the positive control, 95% of inhibition at 320  $\mu\text{M}$  (Figure 6).



According to the literature, the transition metal complexes derived from coumarins show greater antioxidant action than their respective precursors (de Alcantara et al, 2015). Comparing the antioxidant activity results obtained from Cu(II)-HCCA and Ni(II)-HCCA with Cu(II) and Ni(II) complexes derived from 3-aminocoumarin, the latter showed 1.6 and 5 times higher activity, respectively, than Cu(II)-HCCA and Ni(II)-HCCA complexes (Kadhun et al, 2011). However, no comparative study of the antioxidant action of 3-aminocoumarin and its complexes has been shown.

The increased antioxidant activity of these complexes can be attributed to the electron withdrawing effect of the Zn(II), Ni(II) and Cu(II) ions, which facilitates the release of hydrogen carboxylic to reduce the DPPH radical (Ejidike & Ajibade, 2015). The DPPH radical scavenging ability of the test samples can thus be ranked in the order Rutin > Cu(II)-HCCA > Ni(II)-HCCA > Zn(II)-HCCA > HCCA.

**Figure 6.** Maxima % of antioxidant activity of HCCA, Cu(II)-HCCA, Ni(II)-HCCA, Zn(II)-HCCA and Rutin.



Source: Authors.

#### 4. Conclusion

A new method has been developed for the synthesis of Cu(II)-HCCA, Ni(II)-HCCA, and Zn(II)-HCCA. The SEM and XRD analyses showed that the degree of crystallinity of the complex depends on the nature of the metal ion bound to HCCA. Ni(II)-HCCA and Zn(II)-HCCA showed higher crystallinity than Cu(II)-HCCA. All complexes presented better antioxidant activity than the HCCA precursor.

#### Acknowledgments

This work was supported by the FAPESP under grant (2012/14159-9); The Center for the Development of Functional Materials – CDMF/São Paulo Research Foundation – FAPESP under grant (Process 2013/07296-2)

#### References

- Borges Bubols, G., da Rocha Vianna, D., Medina-Rejon, A., von Poser, G., Maria Lamuela-Raventos, R., Lucia Eiffler-Lima, V., & Cristina Garcia, S. (2013). The Antioxidant Activity of Coumarins and Flavonoids. *Mini-Reviews in Medicinal Chemistry*, 13(3), 318–334. <https://doi.org/10.2174/1389557511313030002>
- Creaven, B. S., Devereux, M., Georgieva, I., Karcz, D., McCann, M., Trendafilova, N., & Walsh, M. (2011). Molecular structure and spectroscopic studies on novel complexes of coumarin-3-carboxylic acid with Ni(II), Co(II), Zn(II) and Mn(II) ions based on density functional theory. *Spectrochimica Acta - Part A: Molecular and Biomolecular Spectroscopy*, 84(1), 275–285. <https://doi.org/10.1016/j.saa.2011.09.041>
- Creaven, Bernadette S., Egan, D. A., Kavanagh, K., McCann, M., Noble, A., Thati, B., & Walsh, M. (2006). Synthesis, characterization and antimicrobial activity of a series of substituted coumarin-3-carboxylatosilver(I) complexes. *Inorganica Chimica Acta*, 359(12), 3976–3984. <https://doi.org/10.1016/j.ica.2006.04.006>

- de Alcantara, F. C., Lozano, V. F., Vale Velosa, A. S., dos Santos, M. R. M., & Pereira, R. M. S. (2015). New coumarin complexes of Zn, Cu, Ni and Fe with antiparasitic activity. *Polyhedron*, 101, 165–170. <https://doi.org/10.1016/J.POLY.2015.09.010>
- El-Wahab, Z. H. A., Mashaly, M. M., Salman, A. A., El-Shetary, B. A., & Faheim, A. A. (2004). Co(II), Ce(III) and UO<sub>2</sub>(VI) bis-salicylatothiosemicarbazide complexes. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 60(12), 2861–2873. <https://doi.org/10.1016/j.saa.2004.01.021>
- Elhousseiny, A. F., Aazam, E. S., & Al-Amri, H. M. (2014). Synthesis of new microbial pesticide metal complexes derived from coumarin-imine ligand. *Spectrochimica Acta - Part A: Molecular and Biomolecular Spectroscopy*, 128, 852–863. <https://doi.org/10.1016/j.saa.2014.03.003>
- Halli, M. B., Sumathi, R. B., & Kinni, M. (2012). Synthesis, spectroscopic characterization and biological evaluation studies of Schiff's base derived from naphthofuran-2-carbohydrazide with 8-formyl-7-hydroxy-4-methyl coumarin and its metal complexes. *Spectrochimica Acta - Part A: Molecular and Biomolecular Spectroscopy*, 99, 46–56. <https://doi.org/10.1016/j.saa.2012.08.089>
- Ikeda, N. E. A., Novak, E. M., Maria, D. A., Velosa, A. S., & Pereira, R. M. S. (2015). Synthesis, characterization and biological evaluation of Rutin–zinc(II) flavonoid-metal complex. *Chemico-Biological Interactions*, 239, 184–191. <https://doi.org/10.1016/j.cbi.2015.06.011>
- Islas, M. S., Martínez Medina, J. J., Piro, O. E., Echeverría, G. A., Ferrer, E. G., & Williams, P. A. M. (2018). Comparisons of the spectroscopic and microbiological activities among coumarin-3-carboxylate, o-phenanthroline and zinc(II) complexes. *Spectrochimica Acta - Part A: Molecular and Biomolecular Spectroscopy*, 198(Ii), 212–221. <https://doi.org/10.1016/j.saa.2018.03.003>
- Kadhun, A. A. H., Mohamad, A. B., Al-Amri, A. A., & Takriff, M. S. (2011). Antimicrobial and antioxidant activities of new metal complexes derived from 3-aminocoumarin. *Molecules*, 16(8), 6969–6984. <https://doi.org/10.3390/molecules16086969>
- Khan, M. I., Khan, A., Hussain, I., Khan, M. A., Gul, S., Iqbal, M., Inayat-Ur-Rahman, & Khuda, F. (2013). Spectral, XRD, SEM and biological properties of new mononuclear Schiff base transition metal complexes. *Inorganic Chemistry Communications*, 35, 104–109. <https://doi.org/10.1016/j.inoche.2013.06.014>
- Lv, H. N., Wang, S., Zeng, K. W., Li, J., Guo, X. Y., Ferreira, D., Zjawiony, J. K., Tu, P. F., & Jiang, Y. (2015). Anti-inflammatory coumarin and benzocoumarin derivatives from *Murraya alata*. *Journal of Natural Products*, 78(2), 279–285. <https://doi.org/10.1021/np500861u>
- Mueller, R. L. (2004). First-generation agents: Aspirin, heparin and coumarins. *Best Practice and Research: Clinical Haematology*, 17(1), 23–53. <https://doi.org/10.1016/j.beha.2004.03.003>
- Musa, M., Cooperwood, J., & Khan, M. O. (2008). A Review of Coumarin Derivatives in Pharmacotherapy of Breast Cancer. In *Current Medicinal Chemistry* 15(26). <https://doi.org/10.2174/092986708786242877>
- Patil, S. A., Prabhakara, C. T., Halasangi, B. M., Toragalmath, S. S., & Badami, P. S. (2015). DNA cleavage, antibacterial, antifungal and anthelmintic studies of Co(II), Ni(II) and Cu(II) complexes of coumarin Schiff bases: Synthesis and spectral approach. *Spectrochimica Acta - Part A: Molecular and Biomolecular Spectroscopy*, 137, 641–651. <https://doi.org/10.1016/j.saa.2014.08.028>
- Paya, M., Goodwin, P. A., De Las Heras, B., & Hoult, J. R. S. (1994). Superoxide scavenging activity in leukocytes and absence of cellular toxicity of a series of coumarins. *Biochemical Pharmacology*, 48(3), 445–451. [https://doi.org/10.1016/0006-2952\(94\)90273-9](https://doi.org/10.1016/0006-2952(94)90273-9)
- Song, P. P., Zhao, J., Liu, Z. L., Duan, Y. B., Hou, Y. P., Zhao, C. Q., Wu, M., Wei, M., Wang, N. H., Lv, Y., & Han, Z. J. (2017). Evaluation of antifungal activities and structure–activity relationships of coumarin derivatives. *Pest Management Science*, 73(1), 94–101. <https://doi.org/10.1002/ps.4422>
- Wang, T., Peng, T., We, X., Wang, G., Sun, Y., Liu, S., Zhang, S., & Wang, L. (2019). Design, synthesis and preliminary biological evaluation of benzylsulfone coumarin derivatives as anti-cancer agents. *Molecules*, 24(22). <https://doi.org/10.3390/molecules24224034>
- Wang, Y. H., Avula, B., Nanayakkara, N. P. D., Zhao, J., & Khan, I. A. (2013). Cassia cinnamon as a source of coumarin in cinnamon-flavored food and food SUPPLEments in the United States. *Journal of Agricultural and Food Chemistry*, 61(18), 4470–4476. <https://doi.org/10.1021/jf4005862>