



Synthesis and Characterization of Metal Complexes of Mg(II) and Cu(II) Ions with N-(4-hydroxyphenyl) Acetamide

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

N-(4-hydroxyphenyl) acetamide or paracetamol is an acylated aromatic amide used as analgesic and antipyretic to relieve pain and reduce body temperature. In medicinal chemistry, there is a growing interest in the development of drugs based on metal complexes, which are of great importance in therapeutic and diagnostic possibilities. Selected metals, magnesium and copper are elements that are extremely important for the human body. In this research, complexes of Mg(II)

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and Cu(II)-ions with N-(4-hydroxyphenyl) acetamide were synthesized and confirmed with FTIR, UV and MS spectroscopy. The results of the analysis of the synthesized complexes spectra indicate interactions between N-(4-hydroxyphenyl) acetamide and metal Mg(II)-ions and Cu (II)-ions via O-donor and N-donor atoms.

Keywords: N-(4-hydroxyphenyl) acetamide; Mg(II)-ion; Cu (II)-ion; complexes; FTIR; MS.

1. INTRODUCTION

In coordination chemistry, one of the main interests is the study of the interactions of a central atom with surrounding atoms, ions, or molecules (Gebreyohannes et. al., 2016). The ions or molecules that bind to the metal to form coordination compounds are called ligands (Erkey, 2011). The synthesis of organic molecules as well as the formation of metal complexes with appropriate drugs has been of great interest in recent years in various branches of chemistry. Research has established that various metals significantly influence the structure of the corresponding drug and thereby improve the overall properties of the molecule. Metal complexes are significant precisely because of their biological uses, such as antifungal, antibacterial and antitumor activity (Farrell, 1989). Magnesium and copper complexes are attracting a lot of attention because of their therapeutic application. Generally, metals are essential components of cells chosen by nature (Frezza et.al., 2010). Magnesium, as one of the most abundant cations with special characteristics, is involved in numerous enzymatic reactions. It acts as a cofactor for more than 300 enzymes, regulating a number of fundamental functions such as muscle contraction, neuromuscular conduction, glycaemic control, myocardial contraction and blood pressure (Bertinato et.al., 2015 and Gröber et.al., 2015). Copper plays an important role in the biological process of living organisms, it plays in the process of binding oxygen, redox processes, electron transfer processes, and is part of the structure of numerous enzymes. Cu occurs in +1 and +2 oxidation states in biological systems and this polyvalent characteristic enables it to form complex compounds. Thanks to the multiple mechanism of action, complexes with copper can be effective in the treatment of inflammatory diseases, viral (Lebon et-al., 2002) and microbial infections (Gubte and Muruper, 2009). Due to their anticancer properties that they possess as a metal, they are a promising guide for the next generation of metal-based complexes against cancer, as well as their significant roles in

biological systems (Brett et.al., 2010 and Stanilla et.al., 2011). The paracetamol molecule is a derivative of 4-aminophenol whose molecular formula is $C_8H_9NO_2$ and molecular mass 151.16 g/mol (Fig. 1). It is one of the most commonly used pain killers and is the main ingredient of numerous cold and flu medications. The paracetamol results in serious side effects when overdosed and taken with alcohol or medications, can cause skin rashes, liver toxicity, kidney damage, liver failure, nephrotoxicity, inflammation of the pancreas and ultimately death (Blough and Wu, 2011., Mao et.al., 2015., Kumar et. al., 2016., Bharathi et. al., 2018. and Benssassi et.al., 2021). Paracetamol has potential electron donors present in its structure such as nitrogen (*N-donor*) from the amide group, *O-donor* from (OH) hydroxyl and carbonyl (C=O) groups. Interaction of various metal ions with antibiotics may enhance their antimicrobial activity as compared to that of free ligands (Prafulla et.al., 2012). The purpose of this research is to improve the biological properties of the drug (paracetamol) by synthesising its Mg(II) and Cu(II) complexes.

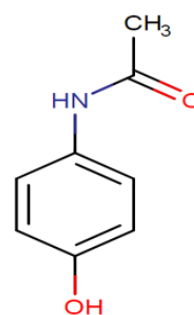


Fig. 1. Structure of N-(4-hydroxyphenyl) acetamide

2. MATERIALS AND METHODS

2.1 Materials

The chemicals used in the experimental research are: $MgCl_2 \cdot 6H_2O$ (Superlab), $CuCl_2 \cdot 2H_2O$ (Superlab), N-(4-hydroxyphenyl) acetamide (Kemig) and Distilled water.

2.2 Synthesis of N-(4- hydroxyphenyl) Acetamide-metal Complexes

Solutions of metal chlorides $MgCl_2 \cdot 6H_2O$ (0.91 g) and $CuCl_2 \cdot 2H_2O$ (0.91 g) were prepared in distilled water in a ratio (2:1) in favor of the ligand. After that, the pH of the corresponding solutions was adjusted to pH=7. The mixture was stirred for 6 hours and then left to stand for 48 hours in a dark place until crystals formed. The synthesized metal complexes were filtered. After that, they were left in a desiccator until analysis.

2.3 Metal Complex Characterization

2.3.1 FTIR spectroscopy

The synthesized metal complexes were analyzed in the laboratory on a Thermo Scientific Nicolet 10 spectrometer in the range (4000-450 cm^{-1}).

2.3.2 UV/VIS spectroscopy

The synthesized complexes were analysed on a UV/VIS spectrometer in the wavelength range of 200-400 nm.

2.3.3 Liquid chromatography-mass spectrometry (LC-MS)

Metal complexes were analysed on an Agilent Technologies LC/MS spectrometer.

3. RESULTS AND DISCUSSION

Fig. 2 shows the spectra of pure N-(4-hydroxyphenyl) acetamide and the formed Mg (II)-N-(4-hydroxyphenyl) acetamide complex. Comparing the spectrum of the formed complex with the spectrum of the N-(4-hydroxyphenyl) acetamide molecule, one can note that the spectrum of the interaction product shows an intense stretching band of (-OH) valence vibrations at 3323 cm^{-1} with a small wavenumber shift compared to the spectrum of N-(4-hydroxyphenyl) acetamide. The band at 3160.54 cm^{-1} , which originates from (-NH) valence vibrations, is not present in the formed complex, and the disappearance of this band indicates that the Mg(II) ion coordinates with the N-donor atom of the amino group (-NH) and is consistent with literature data (Refat et. al., 2013). The absorption band at 1654.78 cm^{-1} originates from valence (-C=O) vibrations and is shifted to a higher wavenumber by only 3 cm^{-1} compared to free N-(4-hydroxyphenyl) acetamide, which is not

enough for the possibility coordination of Mg(II) ions with the O-donor atom of the carbonyl (-C=O) group. The absorption band originating from out-of-plane deformation (-OH) vibrations occurs at 651.95 cm^{-1} and is shifted to a lower wavenumber by 30.88 cm^{-1} compared to the spectrum of N-(4-hydroxyphenyl) acetamide. This fact indicates that the Mg(II) ion coordinates with the O-donor atom of the hydroxyl (-OH) group of N-(4-hydroxyphenyl) acetamide. There is also a band at 796.67 cm^{-1} in the spectrum, which originates from deformation (-NH), then deformation (-C=O) vibrations at 831.85 cm^{-1} , which are shifted by 5 cm^{-1} towards lower values of the wave number relative to the band of free N-(4-hydroxyphenyl) acetamide. The present absorption band at 1556 cm^{-1} corresponds to the deformation vibrations of the amide (-CNH) group shifted to lower values of the wave number around 6 cm^{-1} compared to the spectrum of N-(4-hydroxyphenyl) acetamide. There are also aromatic (C=C) stretching vibrations at 1609.08 cm^{-1} , as well as valence (C-O) vibrations of the phenyl group at 1240.57 cm^{-1} , which are shifted to lower values of the wave number by 16 cm^{-1} in the formed to the Mg(II)-N-(4-hydroxyphenyl) acetamide complex. There are also (C-N) bending vibrations at 1325.33 cm^{-1} , slightly shifted to a lower wavenumber. Fig. 3 shows paracetamol coordinating with metal Mg (II) through the O donor atom (hydroxyl group) and the N-donor atom (amino group).

The Fig. 4 shows the FTIR spectral of N-(4-hydroxyphenyl) acetamide a) and the Cu(II)- ion-N-(4-hydroxyphenyl) acetamide interaction product b). The characteristic band present at 3321.00 cm^{-1} originates from the valence (-OH) vibrations of the metal-ligand interaction product, with the same wave number as in the spectrum of N-(4-hydroxyphenyl) acetamide. On the spectrum of the formed complex Cu(II)-N-(4-hydroxyphenyl) acetamide, there is also a band of lower intensity at 3161.77 cm^{-1} , which originates from valence (-NH) vibrations compared to the intensity of the band of the spectrum of N-(4- hydroxyphenyl) acetamide. An absorption band originating from valence (-C=O) vibrations is present at 1652.01 cm^{-1} with a weaker intensity in the formed Cu(II)-N-(4-hydroxyphenyl) acetamide complex compared to the spectrum of N-(4-hydroxyphenyl) of acetamide. The band at 1558.95 cm^{-1} corresponds to the deformation vibrations of the amide (-CNH) group and is shifted to lower values in relation to the spectrum band of N-(4-hydroxyphenyl) acetamide. There is also a band

of valence (C-O) vibrations of the phenyl group at 1258.55 cm^{-1} , which is shifted to a higher wave number by 17 cm^{-1} compared to the band of the spectrum of N-(4-hydroxyphenyl) acetamide. Bands of valence (C-N) bending vibrations are present at 1327.01 cm^{-1} , as well as aromatic (C=C) vibrations at 1608.86 cm^{-1} . The deformation (-OH) vibration band is present at 682.78 cm^{-1} , the deformation (-NH) vibration at 796.01 cm^{-1} and the deformation (-C=O) vibration at 835.96 cm^{-1} . Based on the research results, a weaker interaction between the Cu(II)-ion and the N-(4-hydroxyphenyl) acetamide molecule can be assumed, through the O-donor atom of the

carbonyl (-C=O) and the N-donor atom of the amino group (-NH).

Based on the obtained data, paracetamol acts as a bidentate ligand (Fig. 5) with the metal ion Cu(II) through an O-donor (carbonyl group) and an N-donor (amino group).

The Fig. 6 shows the UV spectrum of the complex between N-(4-hydroxyphenyl) acetamide and Mg(II)-ion. The UV spectrum contains an intense band originating from the formed complex between N-(4-hydroxyphenyl) acetamide and Mg(II)-ion.

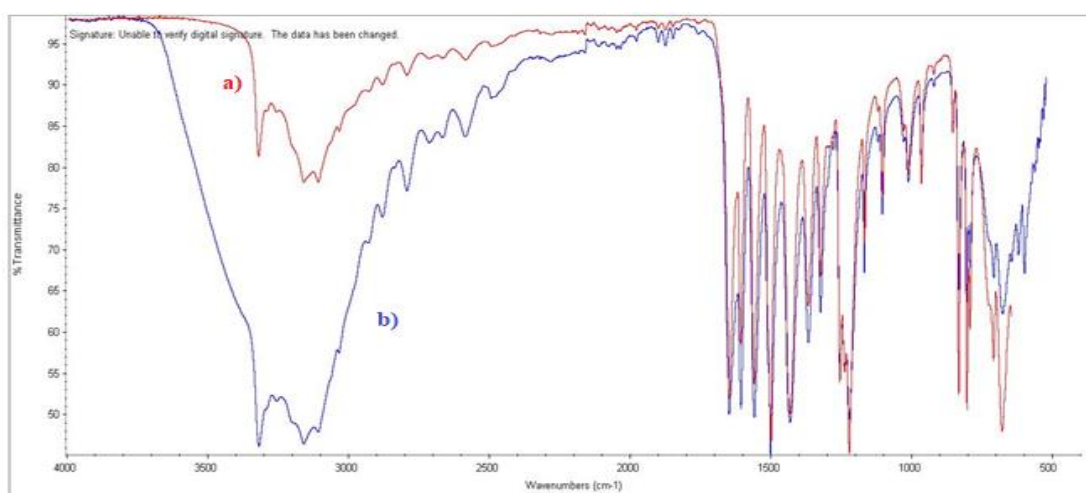


Fig. 2. FTIR spectrum of a) pure N-(4-hydroxyphenyl) acetamide and b) formed complex Mg (II)-N-(4-hydroxyphenyl) acetamide

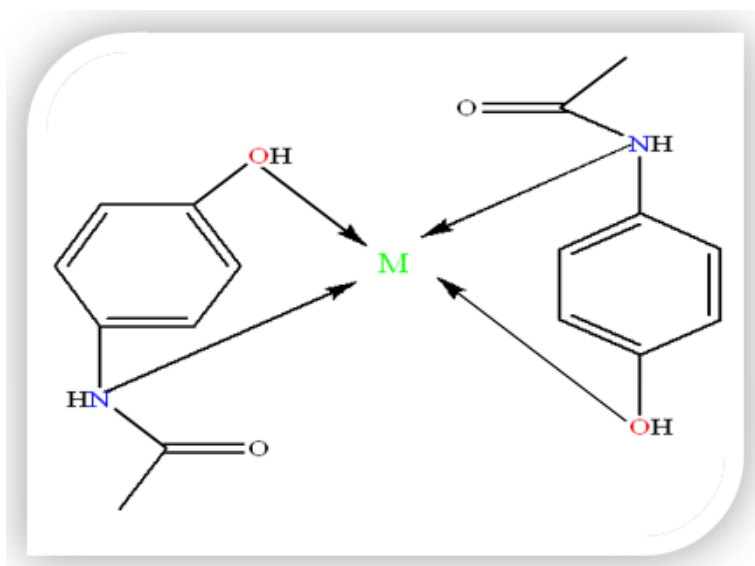


Fig. 3. A proposed structure of N-(4-hydroxyphenyl) acetamide-Mg(II)

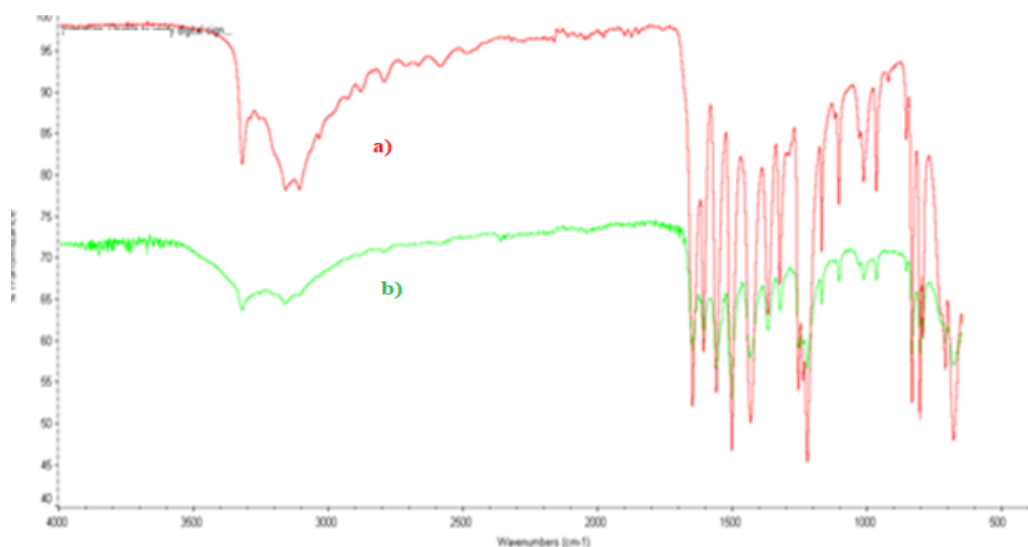


Fig. 4. FTIR spectrum of a) pure N-(4-hydroxyphenyl) acetamide and b) formed complex Cu(II)-N-(4-hydroxyphenyl) acetamide

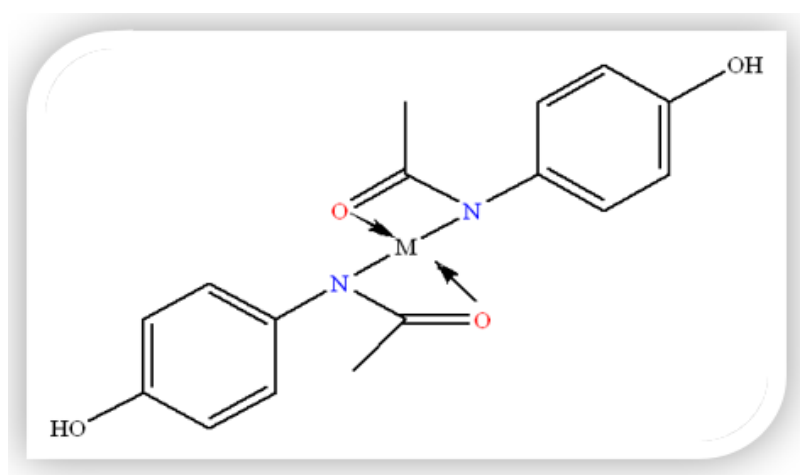


Fig. 5. A proposed structure of N-(4-hydroxyphenyl) acetamide-Cu(II)

According to literature data, compounds with an aromatic core in the UV spectrum have two characteristic transitions, namely $\pi \rightarrow \pi^*$ (around 202 nm) and $n \rightarrow \pi^*$ (around 255 nm), depending on the R-residue (Pašalić, 2013). In the UV spectrum, a band at 248.10 nm is observed, which corresponds to electronic transitions in the ligand N-(4-hydroxyphenyl) acetamide. That there is a possible interaction between Mg(II)-ion and N-(4-hydroxyphenyl) acetamide as a potential O-donor and N-donor ligand is indicated by changes in the UV spectrum with the presence of an intense band that is slightly shifted towards lower wavelength values (hypochromic shift) at 242.19 nm and most likely

originates from Mg(II)-N-(4-hydroxyphenyl) acetamide interactions, i.e. the formation of a coordination bond. The UV spectrum of the formed Cu(II)-N-(4-hydroxyphenyl) acetamide complex shows an extremely intense band (hyperchromic effect) at 248.44 nm, which may originate from electronic transitions of the chromophore (-C=O) due to the interaction with the O-donor atom of the carbonyl group (-C=O) in relation to the spectrum of N-(4-hydroxyphenyl) acetamide (Fig. 7). Based on these research results, the occurrence of interaction between Cu(II)-ion and N-(4-hydroxyphenyl) acetamide cannot be confirmed with certainty.

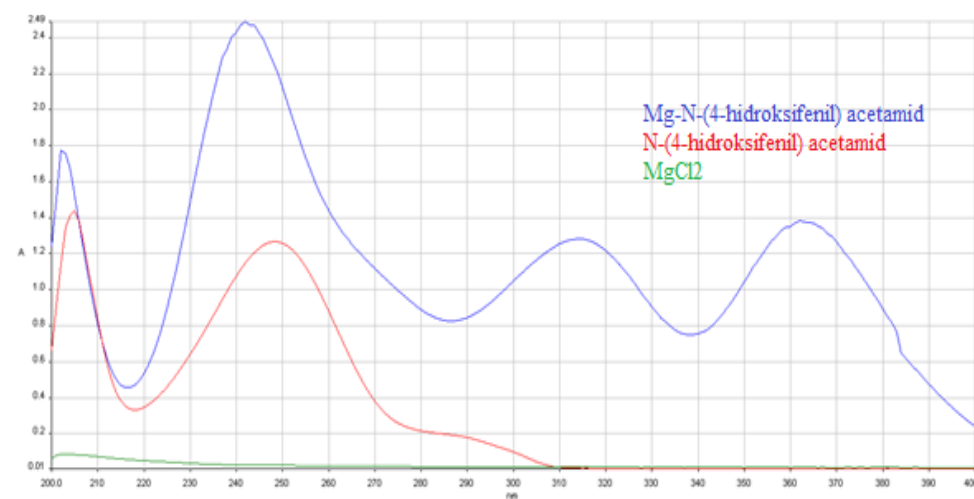


Fig. 6. UV spectrum of the formed complex a) Mg-N-(4-hydroxyphenyl) acetamide b) N-(4-hydroxyphenyl) acetamide and c) MgCl₂

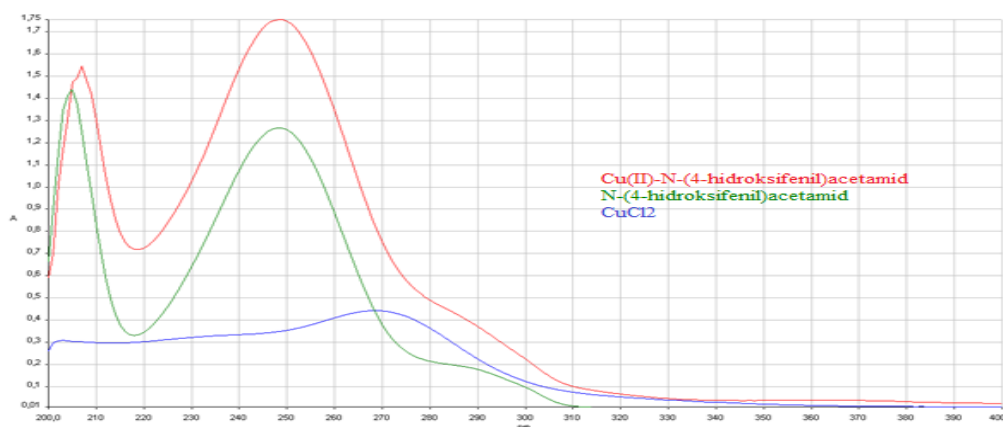


Fig. 7. UV spectrum of the formed complex a) Cu-N-(4-hydroxyphenyl) acetamide b) N-(4-hydroxyphenyl) acetamide and c) CuCl₂

The results of mass spectrophotometry research are shown in Fig. 8a. in negative ionization and 8b. in the positive ionization of the instrument. The basic peak of low intensity $m/z = 494.0$ may originate from the formed complex (2 : 1) in favour of the ligand N-(4-hydroxyphenyl) acetamide and MgCl₂ salt. On the mass spectrum (Fig. 8a.) there is also an intense peak $m/z = 129.1$ which, with the assumption, originates from the fragmentation of the resulting complex. The present peaks $m/z = 675.7$ $m/z = 934.8$, $m/z = 1110.2$, $m/z = 1293.6$ and $m/z = 1651.0$ most likely originate from the impurities present and the prize adduct ions formed upon ionization. Fig. 8b. shows an intense peak $m/z = 163.5$ which may originate from the molecular ion of N-(4-hydroxyphenyl) acetamide and a low intensity peak $m/z = 361.8$ which is the result of the fragment ion of the resulting complex. The

results of mass spectrometry research for the formed Cu(II)-N(4-hydroxyphenyl) acetamide complex are shown in Figs. 9a and 9b. The present peak at $m/z = 448.1$ (Fig. 9a) in the negative ionization ratio (2:1), with the assumption, originates from the formation of a complex between Cu(II)-ion and N-(4-hydroxyphenyl) acetamide, as well as peak at $m/z = 597.1$.

A peak of low intensity arises due to the ionization process. The intense peak at $m/z = 299.1$ may originate from the fragmentation of the resulting complex. A peak of lower intensity is present at $m/z = 107$ and is due to the process of fragmentation of the N-(4-hydroxyphenyl) acetamide molecule. The positive ionization spectrum (Fig. 9b) shows an intense peak at $m/z = 152.1$ originating from the molecular ion of N-

(4-hydroxyphenyl) acetamide. The present peak of lower intensity at $m/z = 301.1$ may originate from the process of fragmentation of the formed Cu(II)-N-(4-hydroxyphenyl) acetamide complex.

The present peaks of low intensity at $m/z = 450.1$ and $m/z = 501.1$ may originate from the formed metal-ligand complex, the ratio (2 : 1) in favour of the ligand.

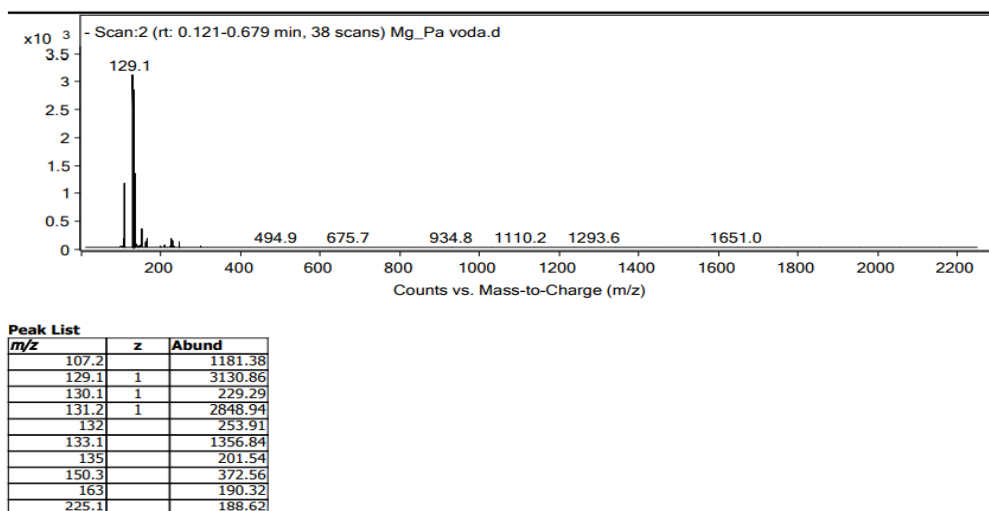


Fig. 8a. Mass spectrum Mg(II) -N- (4-hydroxyphenil) acetamide in negative ionization

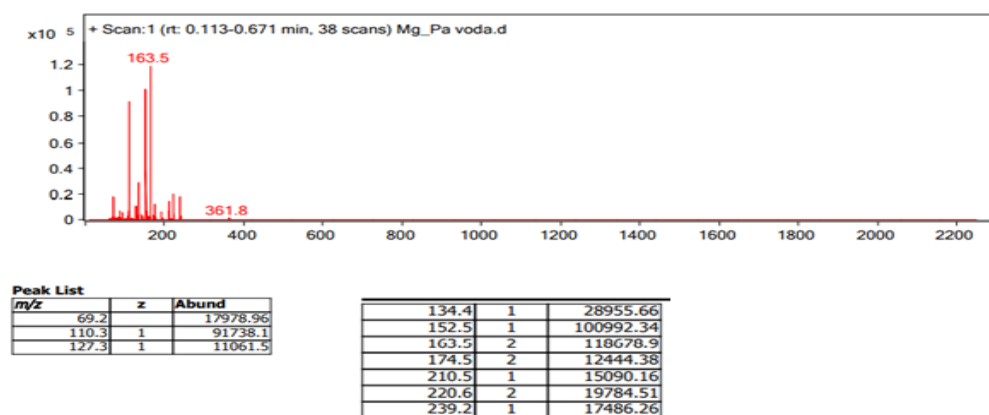


Fig. 8b. Mass spectrum Mg(II)-N-(4-hydroxyphenil) acetamide in positive ionization

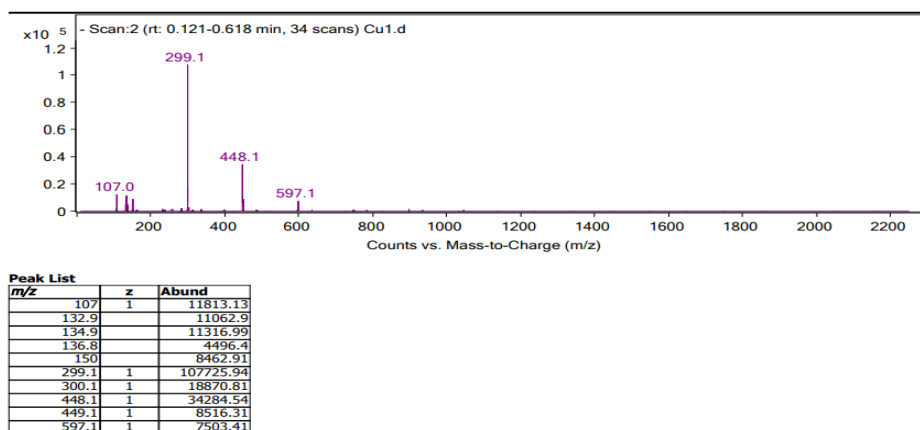


Fig. 9a. Mass spectrum Cu (II) -N- (4-hydroxyphenil) acetamide in negative ionization

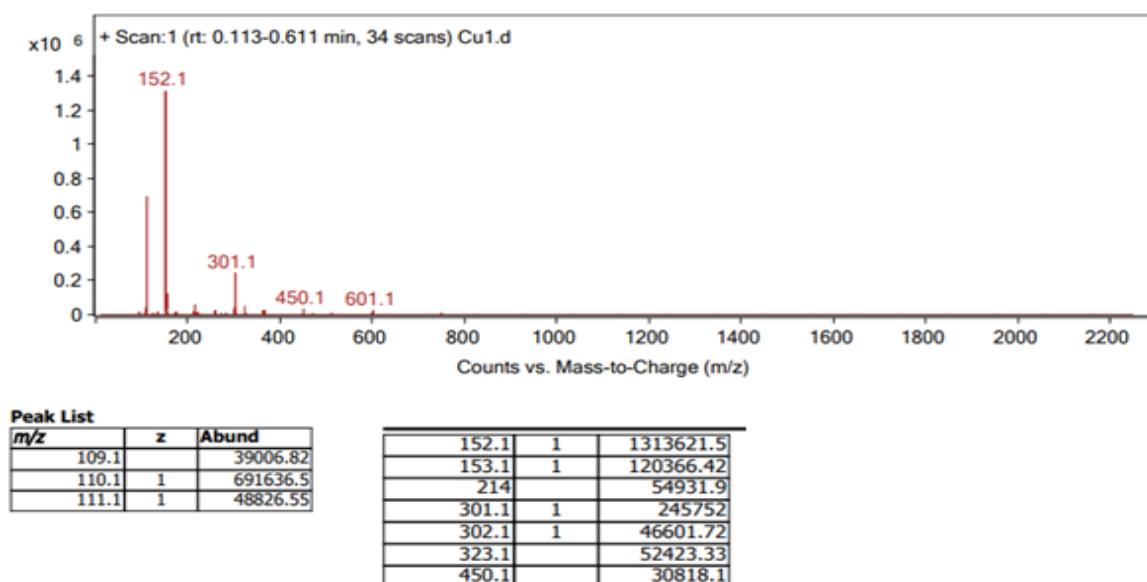


Fig. 9b. Mass spectrum Cu (II)-N-(4-hydroxyphenil) acetamide in positive ionization

4. CONCLUSION

This paper presents the synthesis of a complex between the N-(4-hydroxyphenyl) acetamide molecule and Mg(II) and Cu(II) ions. After synthesis, the synthesized complexes were analysed with FTIR, UV and MS methods. Coordination is achieved between Mg(II) and Cu(II) ions and N-(4-hydroxyphenyl) acetamide through the corresponding O-and N-donor atoms. In the last few years, the demand for metal-based compounds in cancer treatment has increased due to their biological activity compared to their free ligands. For this reason, increasing attention of scientists has been directed to the research of metal complexes.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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