Synthesis, Characterization of Metal Complexes of Mg(II) and Cu(II) ions with N-(4-hydroxyphenyl) acetamide

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) 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

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 [1]. Magnesium and copper complexes are attracting a lot of attention because of their therapeutic application. 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 [2,3]. Copper is the second selected element in this research. In the biological process of living organisms, it plays an important role in the process of binding oxygen, redox processes, electron transfer processes, and is part of the structure of numerous enzymes: enzymes for electron transfer and enzymes that participate in oxygenation processes [4,5]. In biological systems, it occurs in Cu (I) and Cu (II) oxidation state and its diverse role is, on the one hand, its polyvalence, and, on the other hand, the tendency of its ion to build complex compounds. The paracetamol molecule is a derivative of 4-aminophenol whose molecular formula is $C_8H_9NO_2$ and molecular mass 151.16 g/mol (Figure 1). It is one of the most commonly used pain killers and is the main ingredient of numerous cold and flu medications. N-(4-hydroxyphenyl) acetamide (paracetamol) as a drug was discovered over 100 years ago and is widely used in medical practice with similar analgesic and antipyretic properties as non-steroidal anti-inflammatory drugs. It is also known to be hepatotoxic to humans and various experimental animals at high concentrations [6,7,8]. The paracetamol results in serious side effects when overdosed and taken with alcohol or other medications, cancause skin rashes, liver toxicity, kidney damage, liverfailure, nephrotoxicity, inflammation of the pancreasand ultimately death [9-13]. Paracetamol has potential 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 [14]. The purpose of this research is to improve the biological properties of the drug (paracetamol).

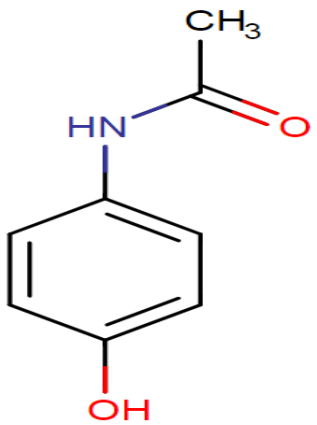


Figure 1. Structure of N-(4-hydroxyphenyl) acetamide

2. EXPERIMENTAL

2.1. Materials and methods

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)
- Distilled water

2.2. Synthesis of N-(4- hydroxyphenyl) acetamide -metal complexes

Solutions of the ligand N-(4-hydroxyphenyl) acetamide and the metal $MgCl_2 \cdot 6H_2O$, $CuCl_2 \cdot 2H_2O$ were prepared in the appropriate proportions of 0.91 g of the ligand and 0.51 g of the metal in distilled water in the ratio (2:1) and by adjusting the pH=7. Then the mixture was mixed for 6 hours and after completion it was left to rest for 48 hours in a darkened space until the formation of crystals of complexes with Mg(II) and Cu(II)-ions. The samples were filtered and left in an exsiccator until analysis.

FTIR spectroscopy:

The analysis of the formed metal complexes with Mg(II)-ion and Cu(II)-ion was performed on a Thermo Scientific Nicolet I S10 spectrometer in the ratio of 4000 to 450 cm^{-1}, with a resolution of 2 cm^{-1}. The samples were analysed in the laboratory of the pharmaceutical company Zada.

UV/VIS spectroscopy:

The synthesized complexes were analysed on a UV/VIS spectrometer in the wavelength range of 200-400 nm. The analysis was done in the laboratory of the Faculty of Mining, University of Tuzla.

Liquid chromatography-mass spectrometry (LC-MS)

Metal complexes were analysed on an Agilent Technologies LC/MS spectrometer, Ruđer Bošković Institute in Zagreb.

3. RESULTS AND DISCUSSION

Figure 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 [15]. 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.

Figure 3 shows paracetamol coordinating with metal Mg (II) through the O donor atom (hydroxyl group) and the N-donor atom (amino group).

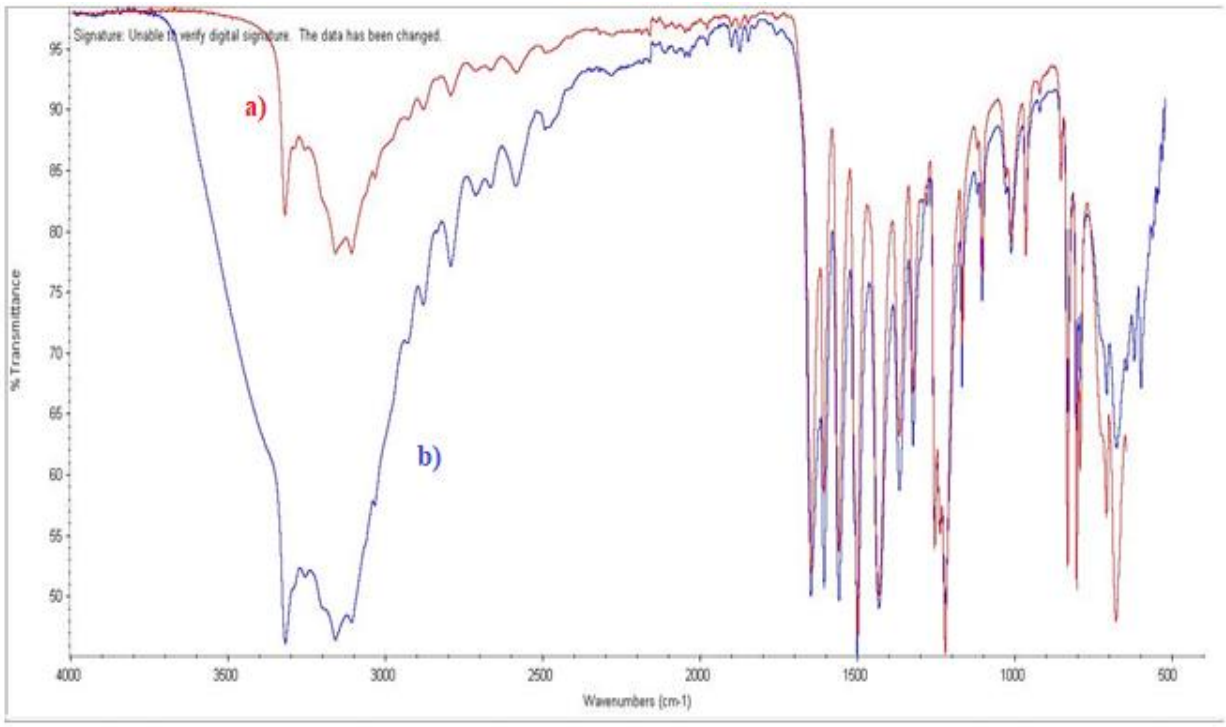


Figure 2. FTIR spectrum of a) pure N-(4-hydroxyphenyl) acetamide and b) formed complex Mg (II)-N-(4-hydroxyphenyl) acetamide

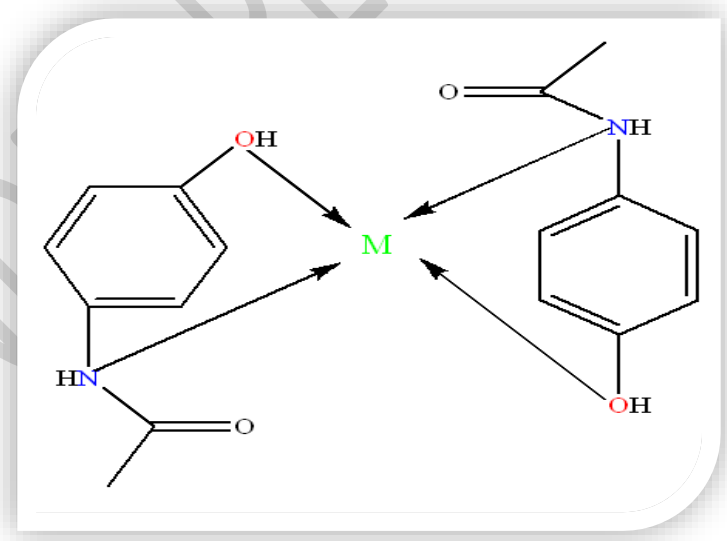


Figure 3. A proposed structure of N-(4-hydroxyphenyl) acetamide-Mg(II)

The *figure 4* shows the FTIR spectrum 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).

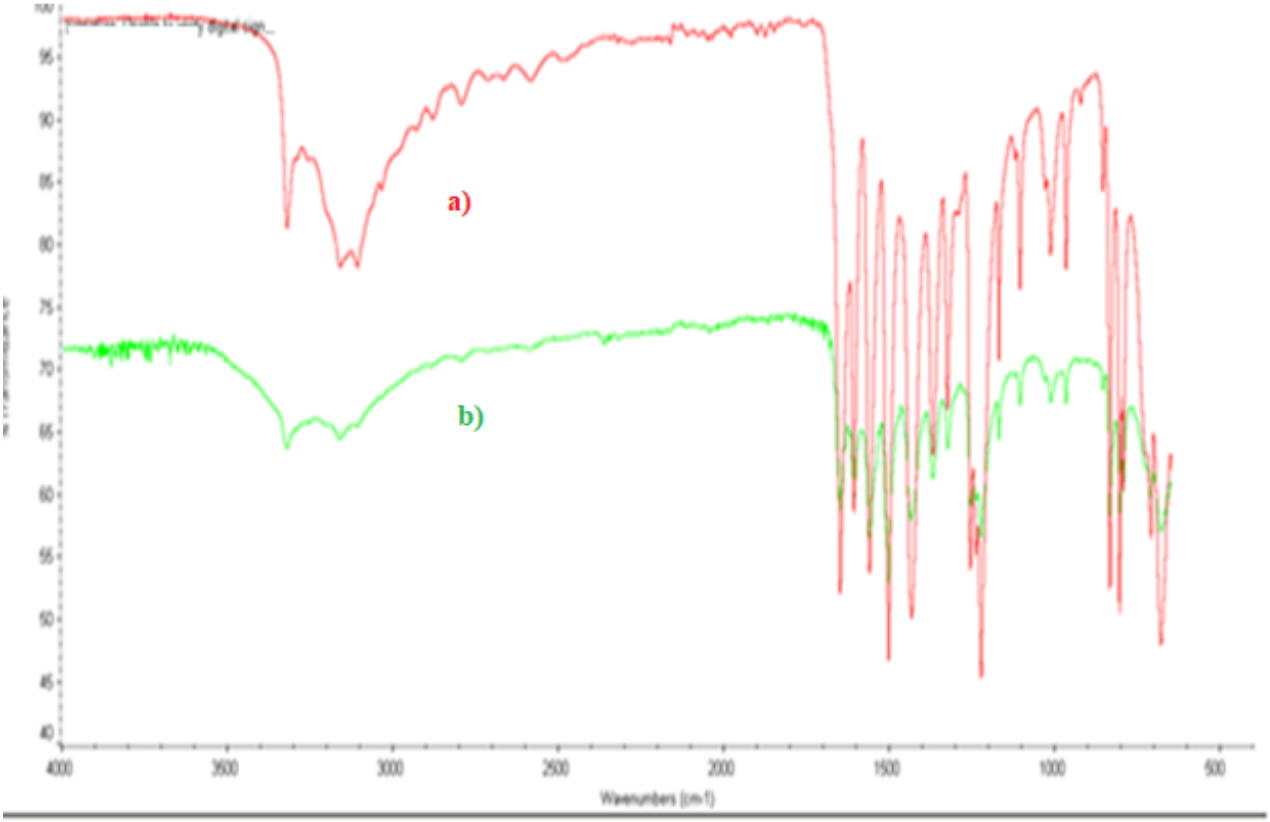


Figure 4. FTIR spectrum of a) pure N-(4-hydroxyphenyl) acetamide and b) formed complex Cu (II)-N-(4-hydroxyphenyl) acetamide

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

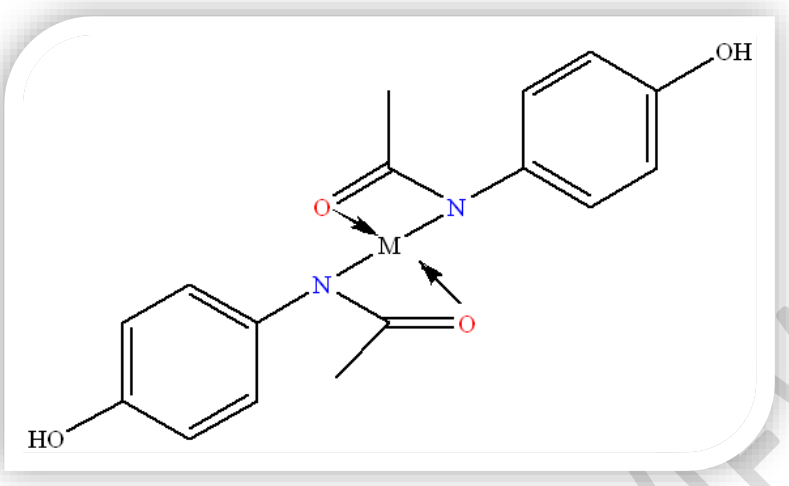


Figure 5. A proposed structure of N-(4-hydroxyphenyl) acetamide-Cu(II)

The figure 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. According to literature data, compounds with an aromatic core in the UV spectrum have two characteristic transitions, namely π→ π* (around 202 nm) and π→ π* (around 255 nm), depending on the R-residue [16]. 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 (*Figure 7*). Based on these research results, the occurrence of interaction between Cu(II)-ion and N-(4-hydroxyphenyl) acetamide cannot be confirmed with certainty.

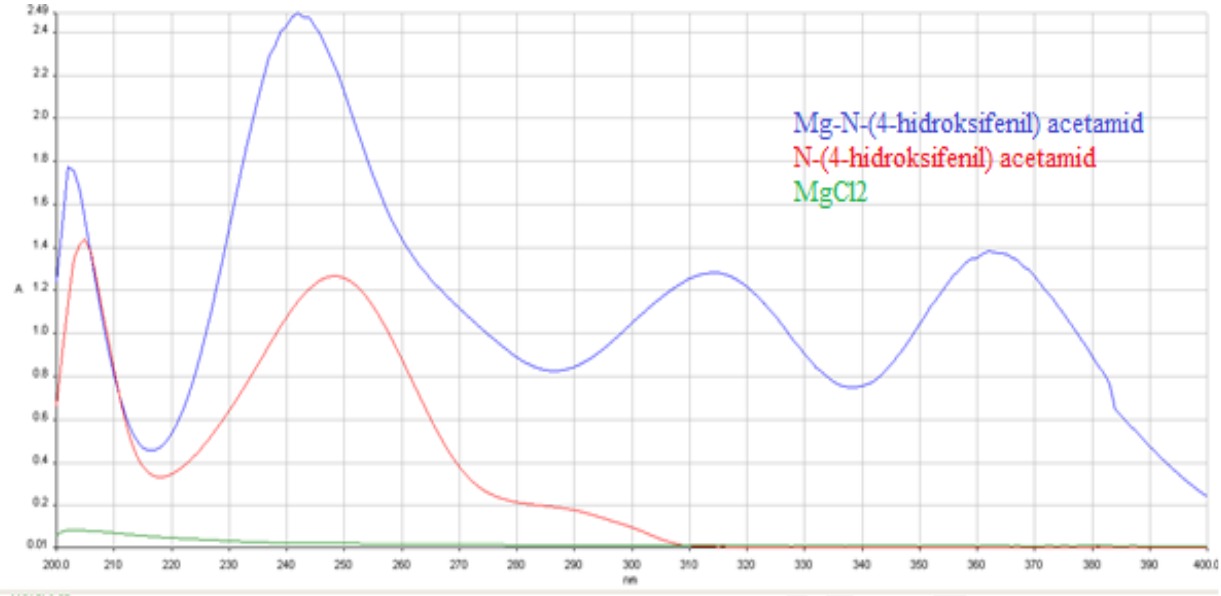


Figure 6. UV spectrum of the formed complex a) Mg-N(-4-hydroxyphenyl) acetamide b) N-(4-hydroxyphenyl) acetamide and c) $MgCl_2$

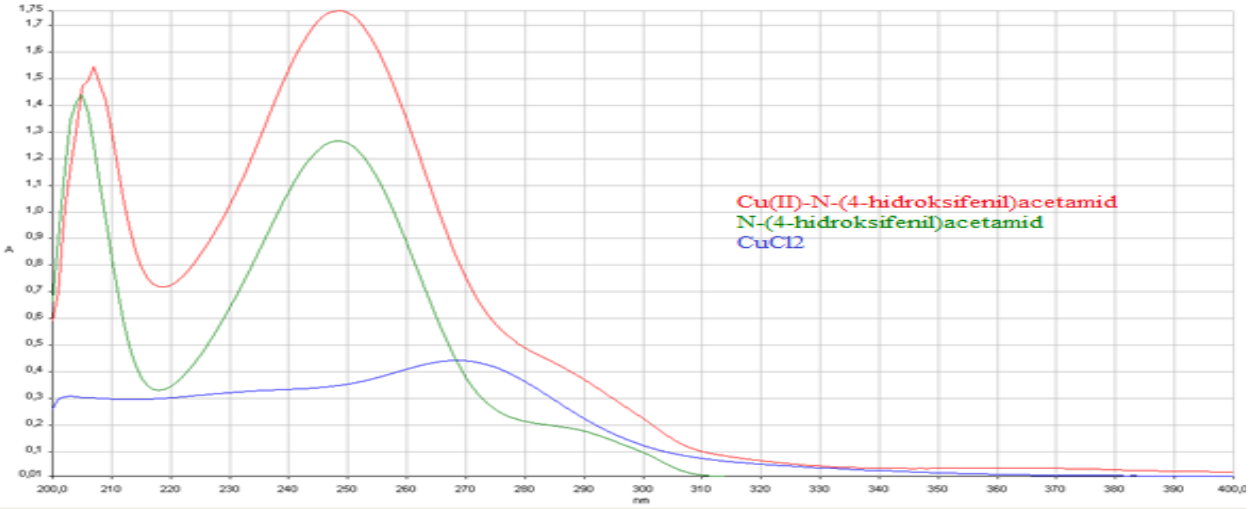
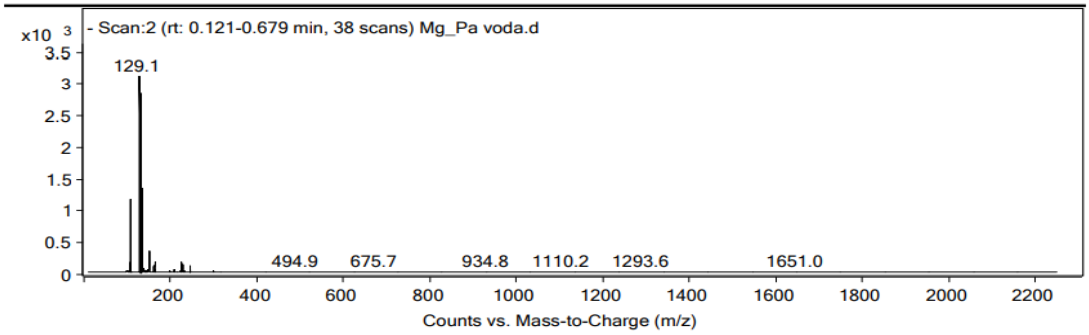


Figure 7. UV spectrum of the formed complex a) Cu-N(-4-hydroxyphenyl) acetamide b) N-(4-hydroxyphenyl) acetamide and c) $CuCl_2$

The results of mass spectrophotometry research are shown in *Figure 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 $MgCl_2$ salt. On the mass spectrum (*Figure 8a.*) there is also an intense peak *m/z* = 129.1 which, with the assumption, originates from the fragmentation of the resulting complex.

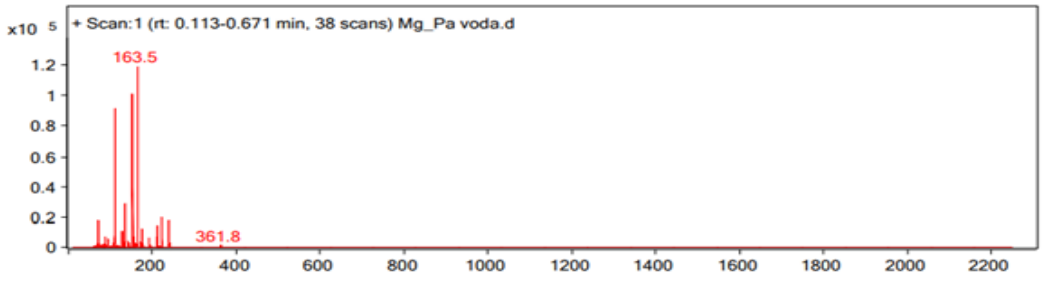
The present peaks *m/z* = 675.7 *m/z* = 934.8, *m/z* = 1110.2, *m/z* = 1293.6 and *m/z* =1651.0 most likely originate from the impurities present and the prize adduct ions formed upon ionization. *Figure 8b.* shows an intense peak *m/z* = 163.5 which may originate from the molecular ion of N-(4-hydroxyphenyl) 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 Figures 9a and 9b. The present peak at *m/z* = 448.1 (Figure 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 (*Figure 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.



Peak List

m/z	z	Abund
107.2		1181.38
129.1	1	3130.86
130.1	1	229.29
131.2	1	2848.94
132		253.91
133.1		1356.84
135		201.54
150.3		372.56
163		190.32
225.1		188.62

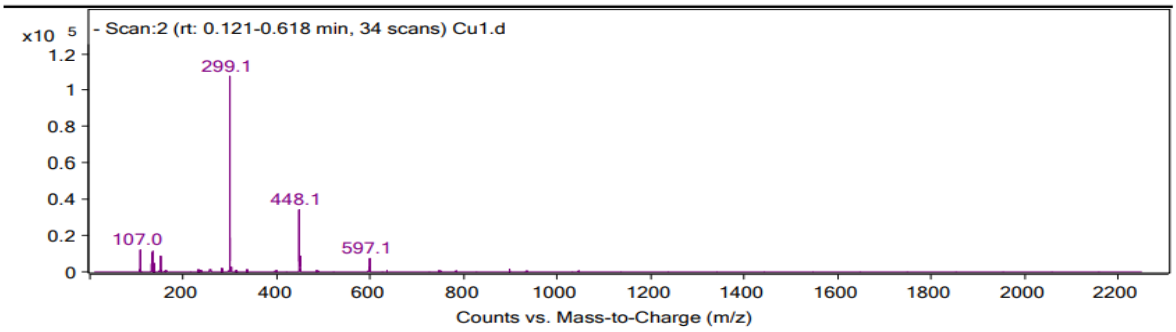
Figures 8a). Mass spectrum Mg(II) -N- (4-hydroxyphenil) acetamide in negative ionization



Peak List

m/z	z	Abund
69.2		17978.96
110.3	1	91738.1
127.3	1	11061.5
134.4	1	28955.66
152.5	1	100992.34
163.5	2	118678.9
174.5	2	12444.38
210.5	1	15090.16
220.6	2	19784.51
239.2	1	17486.26

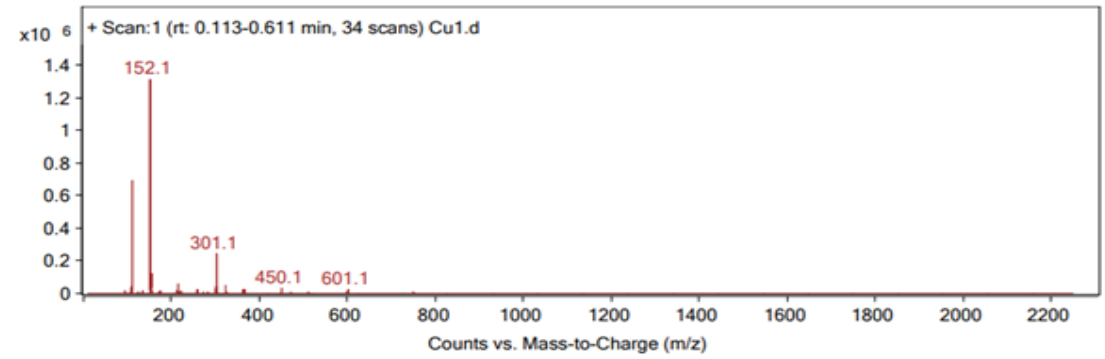
Figure 8b). Mass spectrum Mg(II)-N-(4-hydroxyphenil) acetamide in positive ionization



Peak List

m/z	z	Abund
107	1	11813.13
132.9		11062.9
134.9		11316.99
136.8		4496.4
150		8462.91
299.1	1	107725.94
300.1	1	18870.81
448.1	1	34284.54
449.1	1	8516.31
597.1	1	7503.41

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



Peak List

m/z	z	Abund
109.1		39006.82
110.1	1	691636.5
111.1	1	48826.55

152.1	1	1313621.5
153.1	1	120366.42
214		54931.9
301.1	1	245752
302.1	1	46601.72
323.1		52423.33
450.1		30818.1

Figures 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 the metal and the selected molecule through the corresponding O-and N-donor atoms. Research that is increasingly in the direction of metal complexes gives results that improve the overall properties of molecules that are of particular importance for therapeutic applications in medicine.

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