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# Spectroscopic Investigations of Co(II) and Cu(II) Interaction with Imatinib Mesylate and Capecitabine

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**Abstract:** Cobalt and copper are present as trace elements in biological systems and they are very important for the activity of many enzymes with different functions in the body. Their biological functions derive from the possibility of potential interaction of their M(II) ions with O, N and S donor atoms of various ligands and biomolecules in the living organisam. Capecitabine and imatinib mesylate (ImM) are synthetic organic compounds which are used in a treatment of some oncological diseases thus disturbing homeostasis of biological system. In this study, UV and FTIR spectroscopic methods are used to investigate metalligand interactions and products of their interaction at physiological conditions using model test systems. FTIR spectrum of Co(II)-capecitabine model systems show lack of absorption bands characteristic for -OH (at 3230 $cm^{-1}$) and C=O groups positioned at pyrimidine cycle (at 1718 $cm^{-1}$) for pure capecitabine. It indicates interaction of Co(II) ion with capecitabine via O-donor atoms. FTIR spectrum of pure ImM deviates from spectrum of Co(II)-ImM system at 1250-1050 $cm^{-1}$ wavelength region. This region corresponds to peaks characteristic for mesylate ions ($O_3S$-$CH_3$), which indicates on interaction between Co(II) and donor atoms containing molecule ligands (O and/or S).
UV results for model systems of M(II) with capecitabine and ImM show similar absorption bands as those of pure ligand, while absobances are different (except for Cu(II)-ImM). Since these investigations are done at approximately at physiological conditions, it is expected that, after application of these ligands as pharmacological agents, the same interactions are happening in the human body.

## INTRODUCTION

Cobalt and copper are present as trace elements in biological systems and are very important for the activity of many enzymes with different functions in human body. Biological functions of these metal ions derive from possible interaction of Co(II) and Cu(II) ions with O, N and S donor atoms of various ligands and biomolecules in human organism. (Krstić et al., 2015). Capecitabine (CPC) is an orally-administered chemotherapeutic agent used in the treatment of metastatic breast, stomach, pancreas and colorectal cancers (Kathiravan and Pandey, 2014). CPC (5-deoxy-5-flouro-N-[(pentyloxy)carbonyl]-cytidine), is fluoropyrimidine carbamate pro-drug of 5-fluorouracil (5-FU) and its absorption is higher than 5-FU (Kandimalla and Nagavalli, 2012; Sunkara et al., 2013). Structure of CPC is presented at Figure 1.

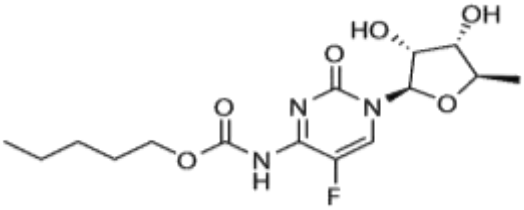


**Figure 1.** Structure of Capecitabine

Imatinib mesylate (ImM) is a tyrosine kinase inhibitor, that was found to be one of the most recent drugs used for the treatment of chronic myeloid leukemia and gastro-intestinal stromal tumor (Zaharieva et al., 2013). Structure of ImM is presented at Figure 2.

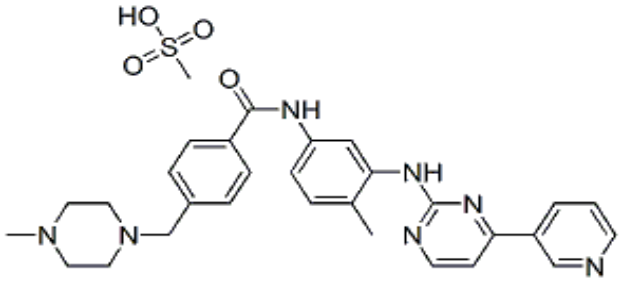

**Figure 2.** Structure of Imatinib Mesylate

Complexes of Cu(II) and Co(II) with these reagents were synthesized and characterized.

## EXPERIMENTAL

### Materials and methods

***Modeling System for UV spectroscopy:*** In the case of testing interactions of M(II) ions with natural and synthetic ligands, distilled water and ethanol-water solutions were used as solvents in ratios between 50/50 and 80/20 (v/v.) Concentrations of metal and ligand solutions were in order of $10^{-6}$ molL$^{-1}$. After stirring samples in 1: 1 volume ratio, the same have being left to stand for about one hour. After that, absorption spectra of prepared solutions were recorded on Perkin Elmer λ25 UV/Vis spectrophotometer, in the wavelength region of 200-400 nm at room temperature (T = 25°C) in the quartz cuvette, the optical path length l = 1.0 cm, with deuterium lamp as a source of light. Measurements were performed in the laboratory of Department of Physical Chemistry and Electrochemistry at Faculty of Technology, University of Tuzla.

***Modeling System for FTIR spectroscopy:*** Metal and ligand were mixed in 1: 2 (n/n) molar ratio. Solution of dissolved metal (15 mL) and solution of ligand (15 mL) were mixed in a beaker and stirred with a magnetic stirrer without heating, with the appropriate adjustments of pH values in solutions. pH-values were measured on Mettler Toledo MP 220 pH-meter. In order to extract solid products of M-L interactions, stock solutions were prepared by adjusting pH values after stirring for 30 minutes and then left in a dark area for three days at room temperature. After that, if precipitation occurred*, solid phases were separated from solutions by filtration on filter paper (blue ribbon) and thereafter dried in an oven at temperatures between 40-50 °C. Isolated solid products of M-L interactions were prepared as KBr pellet to record FTIR spectra on FTIR Spectrum BX, Perkin Elmer, in wavelength region 450-4000 cm$^{-1}$, resolution of 2 cm$^{-1}$ at room temperature (in Laboratory of Faculty of Pharmacy, University of Tuzla).

* Because of the extremely small quantities of separated precipitates in the case of model systems Cu(II)-CPC and Cu(II)-ImM, the same could not be subjected to FTIR analysis.

## RESULTS AND DISCUSSION

### UV spectroscopic characterization

UV spectra of pure CPC and Co(II)-CPC model system are showed at Figure 3. UV spectrum of CPC shows several absorption maxima at 214, ~ 240 and 305 nm, which completely corresponds to literature data (Piórkowska, 2014). The binary system of Co(II)-CPC shows maximum peak at low absorbance values. There is hypo-chromic shift in comparison to the spectrum of pure CPC, in which the last peak (with the highest $\lambda_{max}$) is not clearly defined as in the case of pure CPC. It can be concluded that the Co(II) ions interacted with the CPC. Calculated value of energy splitting for Co(II)-CPC system is 559 kJmol$^{-1}$.

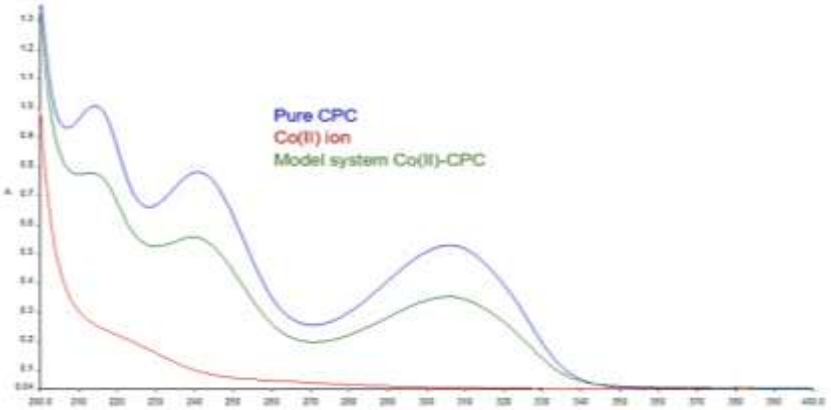


**Figure 3.** UV spectra of CPC and model system Co(II)-CPC

UV spectra of pure ImM and Co(II)-ImM model system are showed at Figure 4. ImM spectrum shows an absorption maximum at about 255 nm which corresponds to the literature data (Kumar Raja, 2010). The product of interaction Co(II)-ImM gives new hypo-chromic shifted spectrum with absorption maximum slightly dislocated toward longer wavelengths at ~ 258 nm. Calculated value of energy splitting for Co(II)-ImM system is 464 kJmol$^{-1}$.

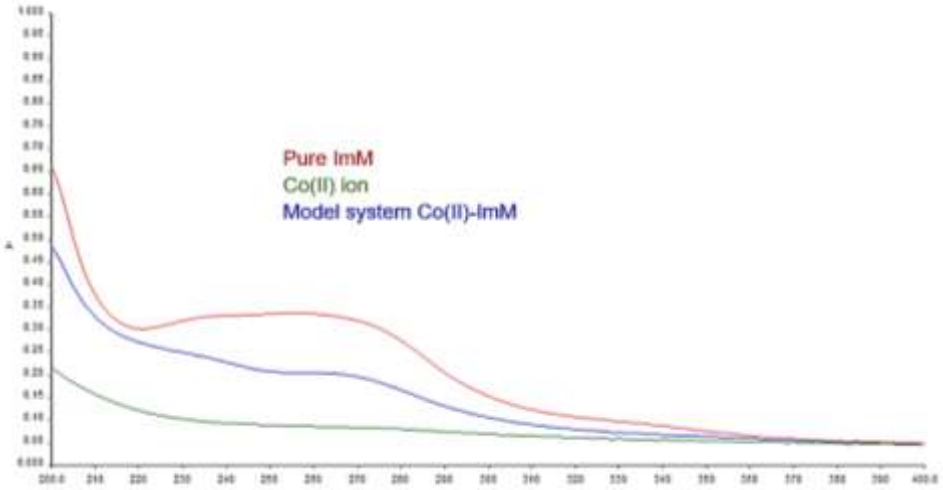


**Figure 4.** UV spectra of ImM and model system Co(II)-ImM

UV spectra of pure CPC and Cu(II)-CPC model system are showed at Figure 5. Spectrum of CPC and spectrum of Cu(II)-CPC binary system have very similar profiles of absorption bands, but different in the absorbance intensity. Significant absorption values for model system Cu(II)-CPC are less comparable to that of pure CPC. Spectra of Cu(II) and Cu(II)-CPC are almost identical, but with a very small deviations of the absorbance values. The value of energy d-splitting is also 559 kJmol$^{-1}$.

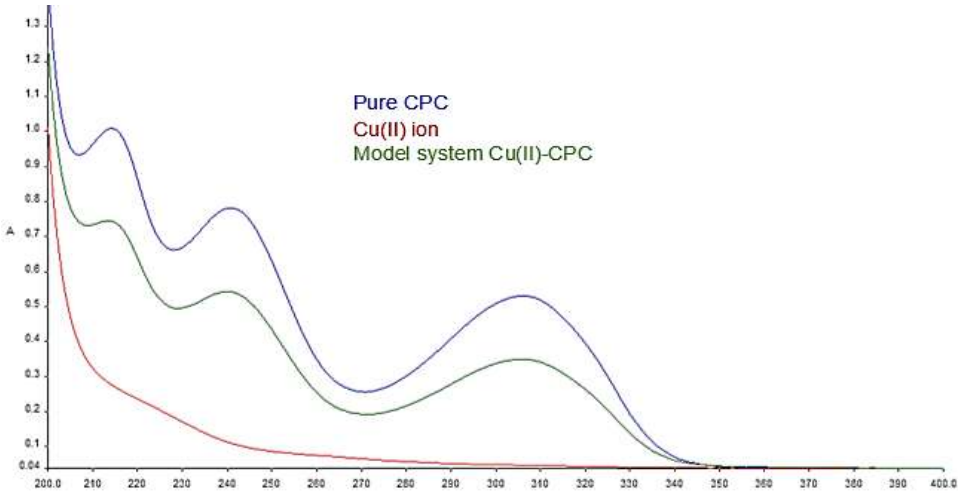


**Figure 5**. UV spectrum of CPC and model system Cu(II)-CPC

UV spectra of pure ImM and Cu(II)-ImM model system are showed at Figure 6. Spectrum of pure ImM and spectrum of binary system Cu(II)-ImM shows significantly different absorption bands with a positive difference from 200 to 255 nm and a negative difference from 255 to ~ 286 nm, and again positive difference to 400 nm.

Absorption band of model system shows hyper-chromic shift, with absorption maximum shifted towards smaller wavelengths. Based on the absorption maximum at about 216 nm, calculated energy splitting value is 554 kJmol$^{-1}$

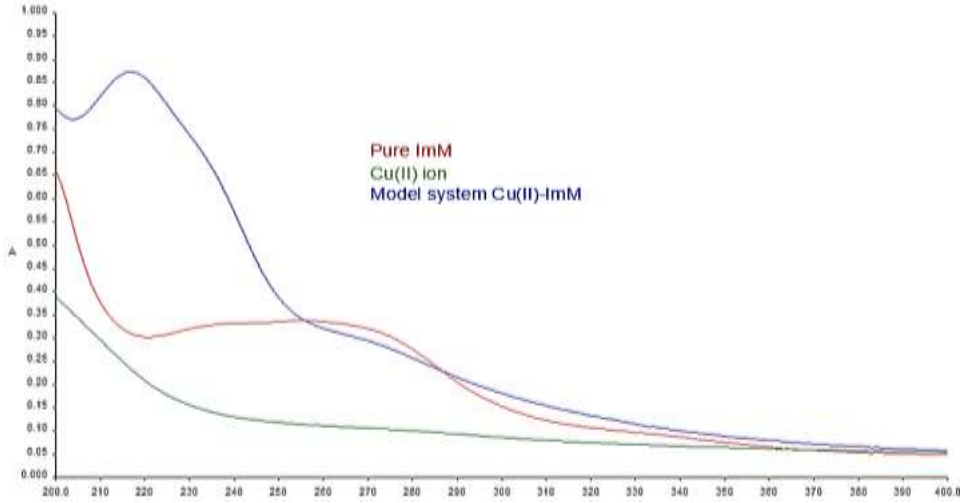


**Figure 6.** UV spectrum of ImM and model system Cu(II)-ImM

The spectrum of pure ImM and the spectrum of binary system Cu(II)-ImM shows significantly different absorption bands with a positive difference at 200 - 255 nm and negative difference at 255 to ~ 286 nm, and after that positive difference to 400 nm. Absorption band of the model system shows hyper-chromic shift, with the absorption maximum shifted towards smaller wavelengths. Based on the absorption maximum at about 216 nm, calculated energy splitting value is 554 kJmol$^{-1}$.

**FTIR spectroscopic characterization**

FTIR spectra of pure CPC and Co(II)-CPC model system are showed at Figure 7. Comparison of these FTIR spectra clearly shows a number of differences which indicates on the interaction of Co(II) ion with CPC. Wide, medium sharp peak at 3230 cm$^{-1}$ in CPC, characteristic for free -OH group is not visible at FTIR spectrum of Co(II)-CPC model system indicating on a link between oxygen atom as electron-donor and Co(II) ion. Very intense peak at 1718 cm$^{-1}$ visible at CPC spectrum corresponds to the carbonyl group positioned on pyrimidine ring. This peak is not visible for Co(II)-CPC model system which points on the interaction between metal ion and oxygen atom, which could cause delocalization of electron pair of double bond to oxygen.

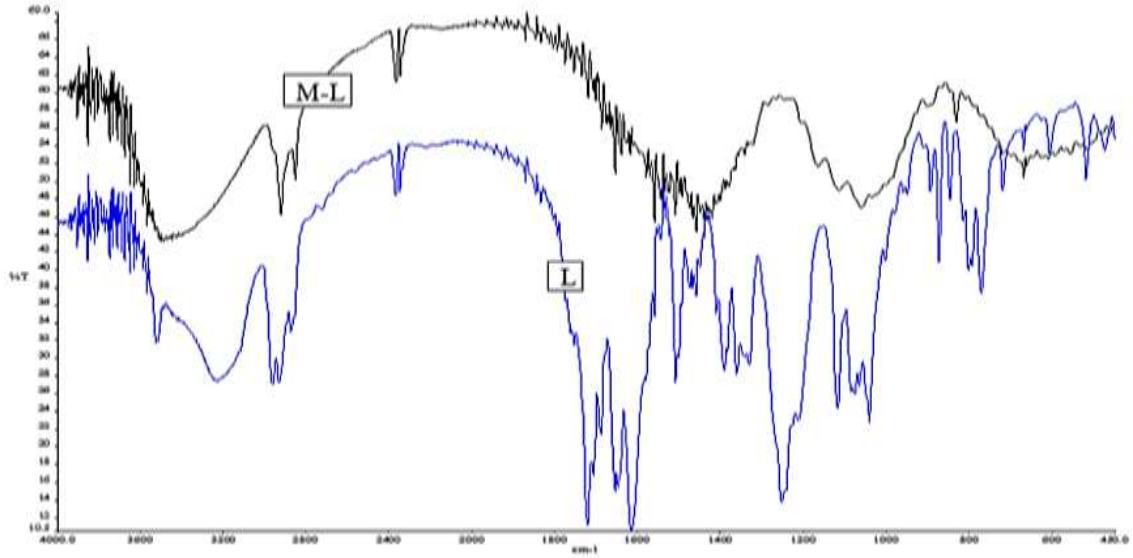


**Figure 7.** FTIR spectrum of pure CPC and model system Co(II)-CPC

Peaks visible at CPC spectrum at the 1000-1600 cm$^{-1}$ wavelengths range obviously change because of the interaction of Co(II) ion and ligand so the most of peaks are lost or changed intensity (peaks of high intensity become less pronounced and stretched).

Very intensive peak at 1647 $cm^{-1}$ which corresponds to the C = N group of CPC (Sunkara, 2013) is also not visible in Co(II)-CPC system suggesting on some changes in the structure of pyrimidine ring after chemical reaction.

FTIR spectra of pure ImM and Co(II)-ImM model system are showed at Figure 8.

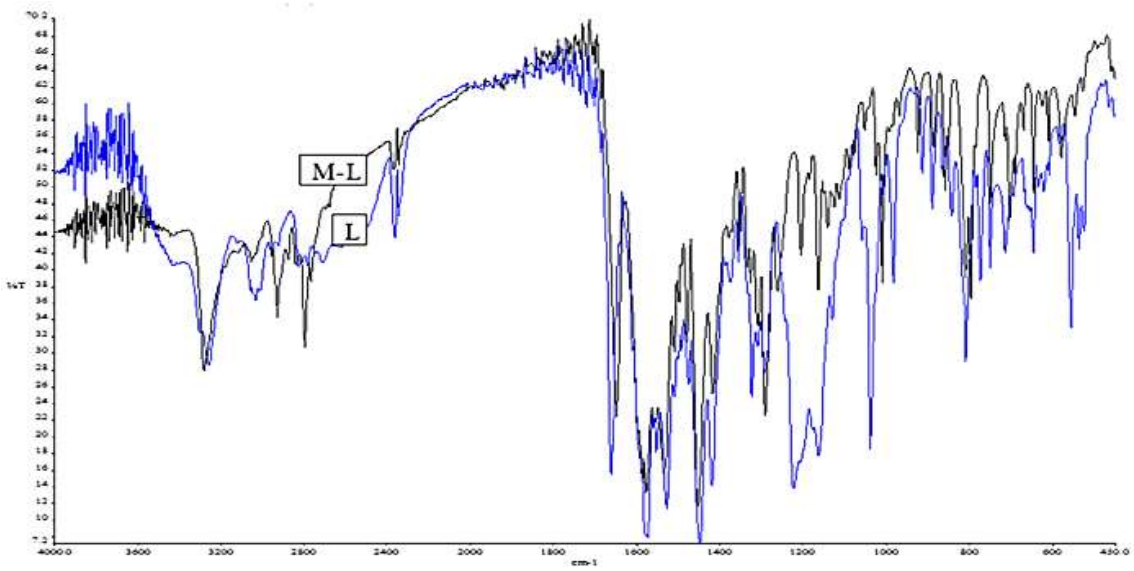


**Figure 8.** FTIR spectrum of pure ImM and model system Co(II)-ImM

FTIR spectrum of pure ImM is very complicated. There is an intensive series of bands, especially at wavelengths <1700 $cm^{-1}$. On the other hand, FTIR spectrum of model system Co(II) - ImM differs from the spectrum of pure ImM, indicating the interaction of ions with this ligand. The greatest changes in these spectra are observed in the areas of 3200-2800 $cm^{-1}$ and 1300-1000 $cm^{-1}$. The spectrum of pure ImM and Co(II)-ImM system at 3258 $cm^{-1}$ is characterized by a medium intense peak of secondary amino-group. Very intense peak in the spectrum of ImM visible at about 1660 $cm^{-1}$ which corresponds to a C = O stretching vibration of amide group, is shifted toward lower values in the spectrum of complex. Several more intense peaks of pure ImM in the area of 1450-1200 $cm^{-1}$ are characteristic of $SO_2$ groups of mesylate ion. These peaks are not clearly visible at the spectrum of model system Co(II)-ImM, which shows possible interactions of Co(II) ions with O- or S- donor atoms of mesylate ion. Aromatic amine moiety of ImM molecule shows C–N vibration stretching in the area of 1342-1266 $cm^{-1}$ which is caused by the increase of the force in C–N connections due to the resonance in the ring.

### Microscopic characterization of solid products of M-L interaction

Microscope images of pure ligands and their solid products with Co(II)-ions are showed at Figure 9.

Comparing microscopic images of ImM and the product of its interaction with Co(II) ions, it can be observed that there are differences in sizes and colors of their crystals. Crystals of pure ImM are not clearly visible, while the product of Co(II)-ImM interaction is characterized by clearly defined crystals, predominantly pink color, which indicates the presence of Co(II) ions. Ligand CPC and Co(II)-CPC interaction product are of fine-grounded crystal structure, with visible differences between crystals (crystals of product are clearly visible).

## CONCLUSION

The results obtained by UV and FTIR spectroscopy clearly indicated on chemical interactions between metal ions, Co(II) and Cu(II), and investigated ligands, capecitabine and imatinib mesylate. These interactions were probably achieved via O-donor atoms of both ligands. Microscopic images confirmed the results obtained with spectroscopic methods. There are noticeable differences in sizes and colors of crystals. Biological activities and cytotoxicity of these compounds have not been thoroughly investigated yet.

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## Summary/Sažetak

Kobalt i bakar su kao elementi u tragu prisutni u biološkim sistemima i veoma su značajni za aktivnost mnogih enzima sa različitim funkcijama u tijelu. Njihova biološka funkcija proističe iz potencijalne interakcije njihovih dvovalentnih iona sa O, N i S donorskim atomima različitih liganda i biomolekula u organizmu. Kapecitabin i imatinib mesilat su sintetski organski spojevi koji se koriste u tretmanu nekih onkoloških bolesti i pri tome narušavaju homeostazu biološkog sistema. U ovom radu korištene su UV i FTIR spektroskopske metode za ispitivanje metal-ligand interakcija i produkata njihove interakcije pri fiziološkim uslovima, korištenjem modelnih test sistema. FTIR spektar model sistema Co(II)-kapecitabin pokazuje izostanak apsorpcionih traka karakterističnih za -OH (na 3230 cm-1) i C=O (na 1718 cm-1) grupe smještene na pirimidinskom prstenu čistog kapecitabina. To ukazuje na interakciju Co(II) iona sa kapecitabinom preko O-donorskih atoma. FTIR spektar čistog ImM razlikuje se od spektra model sistema Co(II)-ImM u oblasti talasnih dužina od 1250 do 1050 cm-1. Ovo područje odgovara pikovima karakterističnim za mesilatne ione (O3S-CH3), što ukazuje na interakciju između Co(II) i atoma donora koje sadrže molekule liganda (O i/ili S). UV rezultati za model sisteme M(II) sa CPC i ImM pokazuju slične apsorpcione trake kao i čisti ligandi, dok su apsorbance različite (osim za Cu(II)-ImM). S obzirom da su ova istraživanja izvedena pri približno fiziološkim uslovima, može se očekivati da će se nakon primjene ovih liganada kao farmakoloških reagenasa iste interakcije odvijati u ljudskom tijelu.