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Physical-chemical characterization and bioactivity of Copper(II), Cobalt(II) and Nickl(II) complexes with 4,4,4-Trifluoro-1-(2-thienyl)-1,3-butanedione

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Abstract

The aim of this study is to synthesize, characterize and detect the potential biological activity of a complexes of selected biologically significant metals with 4,4,4-trifluoro-1-(2-thienyl)-1,3-butanedione (TTA). Spectroscopic methods were used for the structural characterization of the products. Crystal morphology was analyzed using a binocular microscope. In vitro antimicrobial activity was tested for reference strains from the ATCC collection using diffusion techniques, and antioxidant activity using DPPH and FRAP methods. The complexes show significant antimicrobial activity in vitro, which may contribute to further clinical studies of these compounds. This study did not confirm the significant effect of the complex against free radicals but highlights the potential biological significance of complexes with TTA, which should certainly be the subject of more detailed research in the coming period.

Keywords: TTA, complexes, DPPH, FRAP, antimicrobial activity

INTRODUCTION

Metal complexes with biological activity are of increasing importance in medicine as potential alternatives for biologically active organic compounds, which often show severe side effects (Schattschneider et al., 2019). With a wide range of potential ligands and diverse synthetic chemistry, metal complexes represent versatile scaffolds that can be tailored to overcome the specific limitations of a broad spectrum of drugs (Renfrew, 2014). The metal complexation of ligands containing oxygen, nitrogen or sulfur have been coordinated with metals like copper, zinc, cobalt and iron, showing enhanced antihypertensive, antimalarial, antimicrobial properties (Rehman et al., 2019). Therapeutic potential of metal complexes in cancer therapy has attracted a lot of interest mainly because metals exhibit unique characteristics, such as redox activity, variable coordination modes and reactivity toward the organic substrate. These properties become an attractive probe in the design of metal complexes that selectively bind to the biomolecular target with a resultant alteration in the cellular mechanism of proliferation (Ndagi et al., 2017).

4,4,4-trifluoro-1-(2-thienyl)-1,3-butanedione (2-thenoyltrifluoroacetone, TTA) is a classical inhibitor of the mitochondrial electron flux and mitochondria appear to play a significant role in the mechanisms of antitumor activity of complexes. Structure of the TTA is shown in Figure 1. TTA has been proven to be a valuable reagent for the solvent extraction of many metal ions. It has the property of achieving extraction from stronger acid solutions than other chelating agents.

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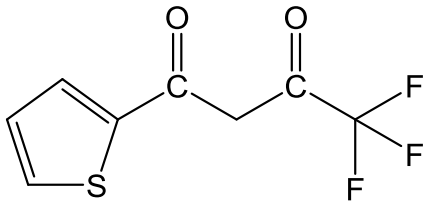

Fig. 1: Structure of TTA

Since many studies in the world are currently involved in the synthesis of potentially biologically active components, this study aims to synthesize complexes with TTAs and to determine their potential biological effects.

MATERIAL AND METHODS

Synthesis of the complexes

Complexes of biogenic metal with TTA were prepared according to published procedures (Horozić et al., 2019). Metal hydrate salts were used for the synthesis of complexes. The reactants were dissolved in a solvent mixture of ethanol: water (80:20 *v/v*) with M:L concentration ratio of 1:2. The reactant solutions were then mixed in the beaker in equal volume ratio. 1 mol/L NaOH solution was used to adjust the appropriate pH model of the system. The mixture was stirred for 60 minutes at 300 rpm and then left in the dark for seven days to precipitate the crystals of the complex. After filtration, the products were dried at 50 °C and then stored in a desiccator.

Spectral and morphological characterization

In order to determine the structure of the complex, samples were recorded on Nicolet iS10 FT-IR spectrophotometer - Thermo Fisher Scientific. The ATR technique was used for sample analysis. Samples were recorded in the range of 4000-650 cm^{-1}.

For recording the UV spectra of the ethanol solutions of synthesized ligand and complexes is prepared at concentration 8 x 10^{-3} mg/mL, while the recording VIS spectra solution concentration was 0.2 mg/mL. Absorption spectra were recorded on a double-bean UV/Vis spectrophotometer Perkin Elmer λ25, in the wavelength range of 200-400 and 400-800 nm.

Before morphological characterization, solid complexes were treated with dimethyl sulfoxide. Microscopic analysis was performed in order to compare color, texture, ligand particle size. Shots were performed on the binocular microscope, the Leica DM 2500P mark.

In vitro antimicrobial activity assay

The antibacterial activity was investigated by diffusion method on reference bacterial strains *E. coli*, *E. faecalis*, *S. aureus*, *B. subtilis*, *L. monocytogenes* and *P. aeruginosa*. Antifungal activity of the complexes was tested on *Candida albicans*. From the microorganisms strains of overnight cultures, suspensions of 0.5 McFarland turbidity were prepared (density 10^7-10^8 CFU/mL). The strains were then placed on the surface of the nutrient substrate-Mueller-Hinton agar, dispersed in sterile Petri dishes. Substrate thickness was 4 mm. In the agar sterile drill-shaped holes were made ("wells"), into which 80 µL of complexes solutions in the concentration of 5 mg/mL were added. After the plates were left at room temperature for 15 minutes, the substance was diffused into agar, incubated at 37°C/24 h. After the incubation period, the size of the inhibitory zone was measured, and the sensitivity of the microorganisms was expressed in the manner described above (Pirvu et al., 2014).

In vitro antioxidant activity assay

The determination of ferric reducing antioxidant power or ferric reducing ability (FRAP assay) was performed as described earlier (Jiménez-Aspee et al., 2014). To prepare the calibration curve, solutions of $FeSO_4$ $7H_2O$ were prepared in the concentration range of 200-1000 µmol/L ($y = 0.001x + 0.0615$; $R^2 = 0.9907$). In each tube, 0.1 mL of complexes and 3 mL of FRAP reagent were added. The samples were incubated in an aqueous bath for 30 minutes at 37°C, and the absorbance was measured at 593 nm. 2,2-diphenyl-1-picryl-hydrazyl (DPPH) method was performed according to the earlier described method (Benvenuti et al., 2004). 500 µL of a solution of the complex (conc. 5 mg/mL) was transferred to a test tube and supplemented with methanol to 2 mL. 500 µL of DPPH solution was then added to the tube. The solutions were incubated in the dark for 30 minutes, and the absorbance was recorded at 517 nm. The radical scavenging effect (%) or percent inhibition of DPPH radical was calculated according to the equation:

[(Acontrol-Asample)/Acontrol] x 100

where A sample is the absorbance of the solution containing the sample and Control is the absorbance of the DPPH solution at 517 nm.

RESULTS AND DISCUSSION

The basic data in the isolated M-TTA products are shown in Table 1. The solubility of all products in methanol, dimethyl sulfoxide and dimethylformamide is excellent. Copper(II) and cobalt(II) complexes are well soluble in absolute ethanol, while

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nickel(II) complexes are poorly soluble in this solvent. All isolated reaction products of M(II) ions with TTA are insoluble in water. Considerable variations in melting point values have been observed. The melting point for TTA is 42 °C, while the complexes are characterized by a huge melting point (> 215 °C).

Table 1: Basic information on isolated products

Compound	Yield [%]	Color	Melting point [°C]
$Cu(TTA)_2$	67.3	dark green	243.0
$Co(TTA)_2(H_2O)_2$	75.5	yellow	215.5
$Ni(TTA)_2(H_2O)_2$	79.2	light green	306.0

Spectral characterization and structure of the complexes

The FTIR spectra of ligands and isolated products are relatively complex. An intense band at 1683 cm^{-1} is observed on the TTA spectrum, which corresponds to the vibrations of the carbonyl group. The high-intensity band characteristic of the C-F bond is observed at 1130 cm^{-1}. For the heteroaromatic ligand nucleus, bands at 680 cm^{-1} (C-S), 3099 cm^{-1} (C-H stretching vibrations) and 1571 cm^{-1} (C=C vibrations) were observed. Absence of a band characteristic of the carbonyl group is observed in the spectra of the complex, which indicates the involvement of π electrons in the formation of the M(II)-TTA bond.

A low-intensity band at ~ 3400 cm^{-1} was recorded on the spectra of Co(II) and Ni(II) complexes, which could indicate the presence of water molecule/s bound to the metal centre.

Figure 2 shows the UV/Vis spectra of the TTA and M(II) complexes. Absorption bands of ligands and complexes were not recorded in the 400-800 range. There are several bands in the UV region with λmax at about 337 nm in the case of all compounds. The difference is observed in the intensity of the bands. For M(II) complexes, a hyperchromic shift was observed at about ~ 202 nm and at λmax, relative to the parent ligand band. Differences are also observed in the range of 261-276 nm, where the slight shift of the band of the copper(II) complex towards larger wavelengths (bathochromic shift) and hypochromic shift of the cobalt(II) complex are observed, relative to the parent ligand. The slightly pronounced band at 289 nm characteristic of the TTA spectra is not visible in the spectra of the complexes.

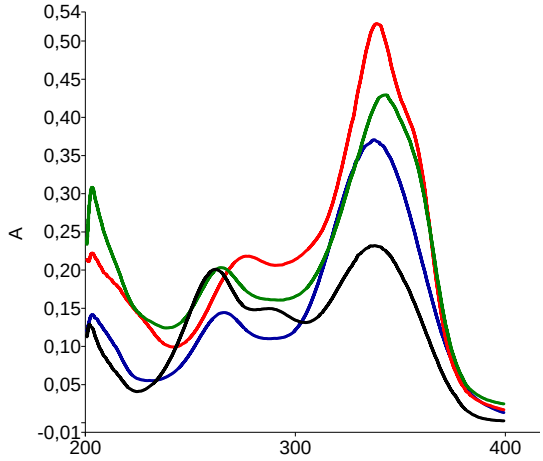

Fig. 2: UV spectra of TTA and M(II) complexes

The absorbances at 337 nm correspond to π → π * transitions originating from the carbonyl group and the presence of double bonds in the heterocyclic ring of the ligand molecule. The absorption at a lower wavelength (~ 261 nm) corresponds to n → σ * transitions resulting from the presence of a free sulfur electron pair in the heteroaromatic part of TTA. The ligand and complexes do not absorb in the visible part of spectra.

Based on the obtained spectral data, the reaction scheme and the assumed structure of the obtained complexes are presented (Figure 3). It is assumed that the TTA coordinate metal ions such as bidentate O-donor ligands. Two carbonyl groups of TTA are involved in bond formation, forming a square-planar geometry complex (in the case of the copper complex). It is assumed that two water molecules are attached to the metal center in the cobalt and nickel complexes, thus forming octahedral complexes.

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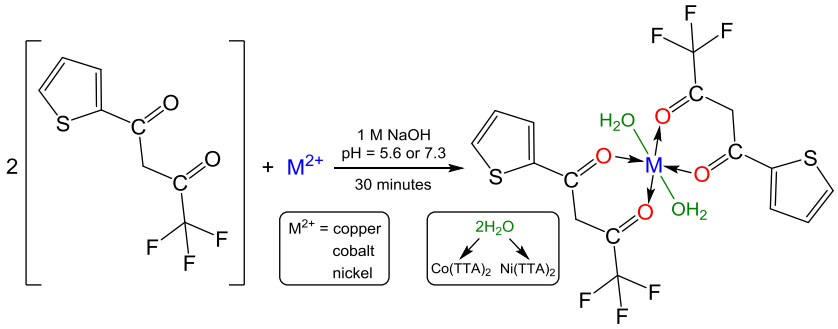

Fig. 3: Reaction scheme and proposed structure of the complexes

Morphology of the complexes

The morphology of the crystals of the synthesized complexes is shown in Figure 4. The $Cu(TTA)_2$ (A-1 and A-2) crystals are elongated prismatically and interfering in first-order green colour. The crystal sizes range from 0.35-0.40 mm (A-1) and 0.2 mm (A-2). The $Co(TTA)_2(H_2O)_2$ complex (sub-images B-1 and B-2) is characterized by radial-ray aggregates (articulated-fin and spherical-ray). Crystal sizes range from 0.5-0.7 mm (larger crystals) and 0.3-0.5 mm (spherical forms). $Ni(TTA)_2(H_2O)_2$ crystals evolved in the form of radial-ray aggregates (called rosettes). The crystal size ranges from 0.25-0.40 mm (C-1 and C-2).

***In vitro* antioxidant activity**

The DPPH method showed a weak $Co(TTA)_2(H_2O)_2$ and $Cu(TTA)_2$ inhibitory capacity of 5.22 and 5.40%, respectively. The nickel complex showed no inhibitory activity. No reduction of the $Cu(TTA)_2$ and $Ni(TTA)_2(H_2O)_2$ complexes at the tested concentration of 5 mg/mL was observed using the FRAP method. The FRAP value for the cobalt complex at a concentration of 5 mg/mL is 1158.5 µmol/L Fe^{2+}. The stated value is significantly lower than the FRAP value for vitamin C, which at the same concentration (5 mg/mL) is 71 250 µmol/L Fe^{2+}.

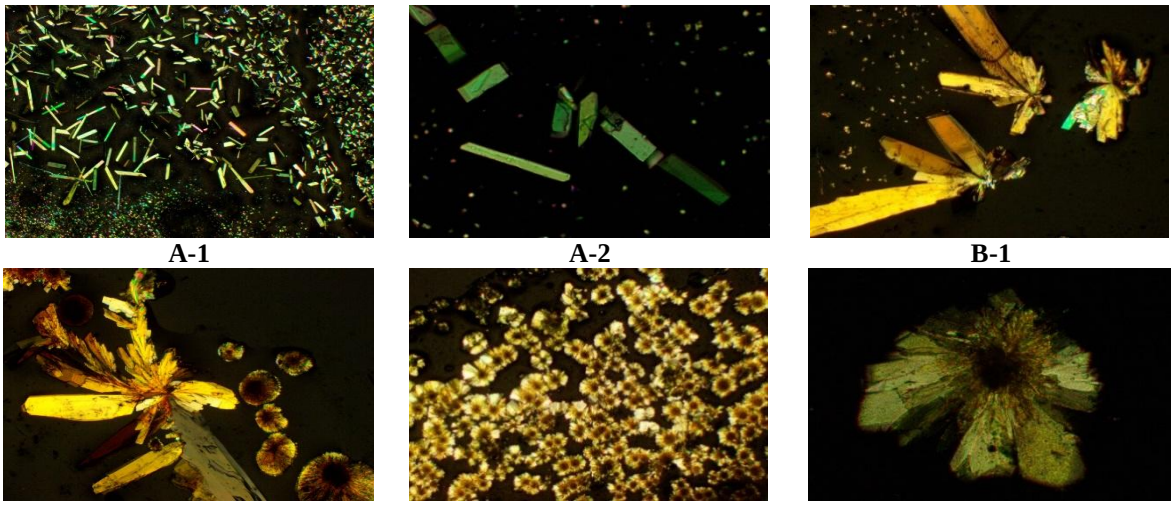

Fig. 4: Cristal morphology of the complexes

***In vitro* antimicrobial activity**

The results of the antimicrobial activity obtained by the diffusion technique are shown in Table 2. $Cu(TTA)_2$ showed high antimicrobial activity in the case of all strains tested. The cobalt complex has similar zones of inhibition as the copper complex, except in the case of *E. faecalis* where the complete absence of antimicrobial activity was observed. $Ni(TTA)_2(H_2O)_2$ showed satisfactory antibacterial activity in the case of *E. coli*, *B. subtilis* and *L. monocytogenes*.

Table 2: Results of in vitro antimicrobial activity

Microorganism	ATCC	Inhibition zone [mm]		
		$Cu(TTA)_2$	$Co(TTA)_2(H_2O)_2$	$Ni(TTA)_2(H_2O)_2$
Escherichia coli	25922	20 (++)	22 (+++)	19 (++)
Staphylococcus aureus	25923	20 (++)	18 (++)	-
Bacillus subtilis	6633	20 (++)	20 (++)	16 (++)
Enterococcus faecalis	51299	20 (++)	-	-
Listeria monocytogenes	19118	25 (+++)	23 (+++)	13 (+)
Pseudomonas aeruginosa	27853	17 (++)	16 (++)	-
Candida albicans	2091	19 (++)	19 (++)	-

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CONCLUSION

The interaction of divalent biometals (copper, cobalt and nickel) with TTA forms complexes of square-planar and octahedral geometry, with significant antimicrobial activity and extremely low antioxidant activity. Through further studies, it is necessary to investigate in detail the structure of the complex, among other things, due to the assumption that the metal centres are bound to water molecules.

REFERENCES

Benvenuti, S., Pellati, F., Melegari, M. and Bertelli, D., 2004. Polyphenols, Anthocyanins, Ascorbic Acid and Radical Scavenging Activity of Rubus, Ribes and Aronia. Journal of Food Science, 69(3):164-169. DOI: 10.1111/j.1365-2621.2004.tb13352.x

Horozić, E., Ademović, Z., Suljagić, J., Cipurković, A., Roša, E., Sejfić, A., Husejnagić, D. and Hodžić, S., 2019. Synthesis, spectral characterization, antibacterial and antifungal activity of Copper(II)-pABA complex. Technologica Acta, 12(1):27-30. DOI: 10.5281/zenodo.3268784

Jiménez-Aspee, F., Quispe, C., Soriano, C. M. P., Fuentes Gonzalez, J., Hüneke, E., Theoduloz, C. and Schmeda-Hirschmann, G., 2014. Antioxidant activity and characterization of constituents in copao fruits (Eulychnia acida Phil., Cactaceae) by HPLC-DAD-MS/MS^n. Food Research International, 62:286-298. DOI: 10.1016/j.foodres.2014.03.013

Ndagi, U., Mhlongo, N. and Soliman, M.E., 2017. Metal complexes in cancer therapy - an update from drug design perspective. Drug Design, Development and Therapy, 11:599-616. DOI: 10.2147/DDDT.S119488

Pirvu, L., Hlevca, C., Nicu, I. and Bubueanu, C., 2014. Comparative analytical, antioxidant and antimicrobial activity studies on a series of vegetal extracts prepared from eight plant species growing in Romania. JPC - Journal of Planar Chromatography - Modern TLC, 27(5):346-356. DOI: 10.1556/JPC.27.2014.5.4

Rehman, S., Ikram, M., Subhan, F., Sinnokrot, M., Khan, W., 2019. Antibacterial Activities of Transition Metal complexes of Mesocyclic Amidine 1,4-diazacycloheptane (DACH). Open Chemistry, 17(1):936–942. DOI: 10.1515/chem-2019-0108

Renfrew, A.K., 2014. Transition metal complexes with bioactive ligands: mechanisms for selective ligand release and applications for drug delivery. Metallomics, 6:1324-1335. DOI: 10.1039/C4MT00069B

Schattschneider, C., Kettenmann, S.D., Hinojosa, S., Heinrich, J. and Kulak, N., 2019. Biological activity of amphiphilic metal complexes. Coordination Chemistry Reviews, 385:191-207. DOI: 10.1016/j.ccr.2018.12.007