JOTCS A
Journal of the Turkish Chemical Society
Section: A
Chemistry

TURKISH CHEMICAL SOCIETY

(This article was presented to the 28th National Chemistry Congress and submitted to JOTCSA as a full manuscript)

Synthesis and Characterization of N-((6-methylpyridin-2-yl)carbamothioyl)thiophene-2-carboxamide and its Co(II), Ni(II) and Cu(II) Complexes: Calculation of the Molecular Orbitals and Antioxidant and Antitumor Activities

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Abstract: N-((6-methylpyridin-2-yl)carbamothioyl)thiophene-2-carboxamide, $C_{12}H_{11}N_3OS_2$ (HL) and its Co(II), Ni(II) and Cu(II) complexes (ML_2 type) have been synthesized and characterized by elemental analysis, FT-IR ,^{1}H-NMR and HR-MS methods. Moreover, HL was characterized by single crystal X-ray diffraction method. The HL crystallizes in the monoclinic crystal system with $P\ 1\ 2_1/c\ 1$ space group, Z=4, a=7.2326(8) Å, b=18.3492(16) Å, c=9.7724(9) Å. The [ML_2] complex structures were optimized by using B97D/TZVP level. Molecular orbitals of HL ligand were calculated at the same level. Antioxidant activities of the complexes were determined via DPPH and ABTS assays. Anticancer activity of the complex was studied via MTT assay in MCF-7 breast cancer cells.

Keywords: Thiourea; thiophene; anticancer activity, crystal structure; molecular orbital.
Cite this: Yeşilkaynak T. Synthesis And Characterization of N-((6-methylpyridin-2-yl)carbamothioyl)thiophene-2-carboxamide and Its Co(II), Ni(II) and Cu(II) Complexes: Calculation of the Molecular Orbitals and Antioxidant and Antitumor Activities. Journal of the Turkish Chemical Society, Section A: Chemistry. 2016;3(3):1–14.

Submitted: June 27, 2016. **Accepted:** July 9, 2016.

DOI: 10.18596/jotcsa.80465.

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INTRODUCTION

Thiourea derivatives are important compounds due to their wide range of applications. They have a long history as functional ligands in coordination chemistry and they coordinate to metals via both O and S atoms [1]. Benzoylthioureas have been reported as extractants for various valuable metals such as Ni, Co, Ag, Pd and Au [2–4]. In previous studies, metal complexes of benzoylthiourea derivatives were synthesized and their properties were reported [5–7]. It is known that thiourea derivatives show antibacterial, antifungal, antitubercular, antithyroid, and insecticidal properties [8].

Therefore, this study is focused on the synthesis, characterization, and crystal structure of new thiourea derivatives (Figure 1) and their metal complexes. Quantum chemical computations were performed to investigate molecular orbitals of HL ligand and optimized geometries of ML_2 complexes. Also, antioxidant and anticancer activity of all complexes and electrochemical behavior of the Cu complex were investigated.

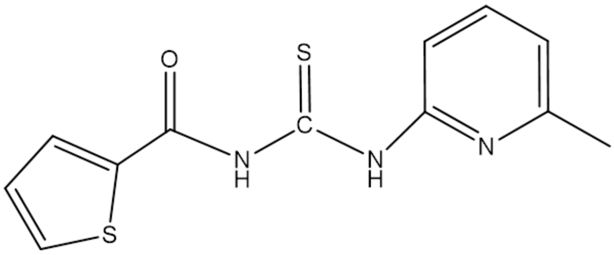


Figure 1 Molecular structures of the HL.

MATERIAL and METHODS

Experimental

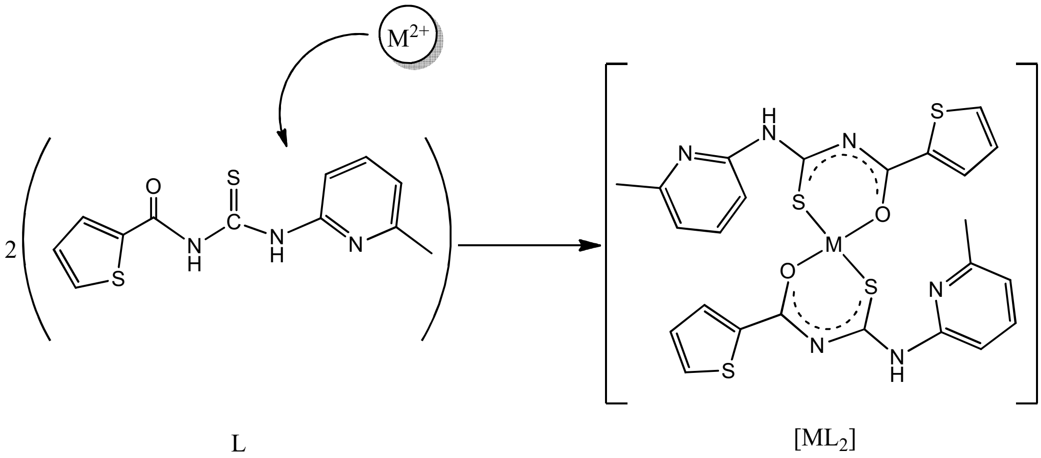
Synthesis of the ligand

All chemical reagents used for the synthesis were analytical purity. A solution of an appropriately substituted thiophenecarboxylic acid chloride (0.01 mole) in acetone (50 cm^3) was dropwise added to a solution of KSCN (0.01 mole) in acetone (30 cm^3). The reaction mixtures were heated under reflux for 30 min. Then they were cooled to room temperature. Solutions of 2-amino-6-methylpyridine (0.01 mole) in acetone (10 cm^3) were added and the resulting mixtures were stirred for 2 h. The resulting mixture was poured into HCl (0.1 N, 300 cm^3) solution and was filtered. The obtained solid product was washed with H_2O and was purified by recrystallization from $EtOH/CH_2Cl_2$ [9].

N-((6-methylpyridin-2-yl)carbamothioyl)thiophene-2-carboxamide, HL: Light Yellow. Yield: 88%, m.p. 155–157 °C. (*Anal.*: C, 51.5; H, 3.9; N, 15.0; S, 22.9; $C_{12}H_{11}N_3OS_2$ *calc.*: C, 52.0; H, 4.0; N, 15.2; S, 23.1%.). FT-IR (ATR, cm^{-1}): υ(N-H) 3181, υ(C-H *aro.*) 3013, υ(CH_3) 2810,1354, υ(C=O) 1695 (s), υ(C=S) 1155. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 8.37 (s, 1H, NH), 7.25–6.96 (m, 6H, Ar-H.).

Synthesis of the complexes, [ML_2]

Complexes were synthesized according to the following method: $MCl_2.xH_2O$ (0.001 mole) (M:Co^{2+}, Ni^{2+} and Cu^{2+}) in ethanol (10 cm^3) were added drop wise to into the solution containing the ligand (0.002 mole) dissolved in ethanol (40 cm^3) in the presence of a few drops of Et_3N under constant stirring for 30 min. The sediment was filtered, washed with a small amount of cold ethanol and was dried in desiccator [10].



Bis(N-((6-methylpyridin-2-yl)carbamothioyl)thiophene-2-carboxamide)cobalt(II), [CoL_2]: Pale green. Yield: 89%, *Anal.*: C, 46.9; H, 3.1; N, 13.2; S, 21.3; $C_{24}H_{20}N_6O_2S_4Co$, *calc.*: C, 47.1; H, 3.3; N, 13.7; S, 21.0%. FT-IR (ATR, cm^{-1}): υ(C=N) 1567 (s). HR-MS (ES$^+$), *m/z* (calc./found): 611.6478/611.6589.

Bis(N-((6-methylpyridin-2-yl)carbamothioyl)thiophene-2-carboxamide)nickel(II), [NiL_2]: Green. Yield: 77%, *Anal.*: C, C, 47.3; H, 3.4; N, 13.3; S, 21.5; $C_{24}H_{20}N_6O_2S_4Ni$, *calc.*: C, 47.2; H, 3.3; N, 13.8; S, 21.0%. FT-IR (ATR, cm^{-1}): υ(C=N) 1536 (s). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 7.21–6.87 (m, 12H, Ar-H), 4.34 (m, 1H, N-H). HR-MS (ES$^+$), *m/z* (calc./found): 611.4080/611.4164.

Bis(N-((6-methylpyridin-2-yl)carbamothioyl)thiophene-2-carboxamide)copper(II),[CuL_2]: Brown. Yield: 82%, *Anal.*: C, 46.0; H, 3.5; N, 13.3; S, 20.3, $C_{24}H_{20}N_6O_2S_4Cu$, *calc.*: C, 46.8; H, 3.3; N, 13.6; S, 20.8%. FT-IR (ATR, cm^{-1}): υ(C=N) 1520 (s). HR-MS (ES^{+}), *m/z* (calc./found): 616.2606/616.2690.

Instrumental

FT-IR measurements were performed via a Perkin Elmer LX-125000B FT-IR spectrometer with an ATR component (4000–30 cm^{-1}). ^{1}H-NMR spectra were recorded on a Bruker Avance III 400 MHz NMR spectrometer, using $CDCl_3$ as solvent and TMS as internal standard. ^{1}H-NMR signals were recorded with the aid of 2D COSY spectra where necessary. Elemental analyses were performed on a Costech ECS 4010 instrument. Melting point of the ligand was determined by Stuart model SMT30 instrument. The mass spectra were obtained by using Waters SYNAPT G1 MS instrument. The exact mass analyses were made in positive mode (ES+) with HR-MS (Da 50-1000, ESI-TOF-MS). X-ray data of the HL were collected on a Bruker D8 Venture diffractometer using monochromated MoK_{α} radiation. The structure was solved and refined using the Bruker SHELXTL Software. The voltammetric measurements were made via BAS 100 W (Bioanalytical System, USA) electrochemical analyzer. The standard one-compartment three electrode cell of 10 mL capacity contained glassy carbon working electrode (BAS; Φ: 3 mm diameter), a Ag/AgCl reference electrode (BAS; 3 M KCl) and platinum wire counter electrode.

Computations

Computations were made by using G09 [11] program package. HOMO and LUMO orbitals of the ligands were computed as single point calculation using B97D/TZVP [12,13] level on the X-ray structure. DOS (density of state) spectrum was obtained using Gaussian [14] program package. The proposed [ML_2] complex structures were optimized using the same computational level. The optimized bond distances and angles were visualized by using CYLView[15] program package. Frequency calculations were also made to verify that optimized structures are stationary points (no imaginary frequency).

RESULTS and DISCUSSION

^{1}H-NMR

The ^{1}H-NMR spectra of the ligand there is a single peak at 8.37 ppm which corresponds to the N-H group. The aromatic C-H bonds are shown as multiple peaks at 7.28-7.14 ppm for HL. The N-H peaks, which are observed at 8.37 ppm, would not appear in the metal complexes. These data agree with the complexation reaction and structure of the metal complexes. The aromatic C-H protons are shown at 7.21-6.87 ppm for [NiL_2]. The

N-H protons are shown at 4.34 ppm for [NiL_2]. ^{1}H-NMR spectra of [CoL_2] and [CuL_2] complexes could not be obtained because of their paramagnetic properties.

X-Ray Crystallography

The single crystals suitable for X-ray diffraction analysis were grown from ethanol solutions. The structures were solved via direct methods and were refined on F^2 by full matrix least-squares using SHELXL 2013[16]. All non-hydrogen atoms were refined via anisotropic displacement parameters. The molecular structure plots were obtained by using Mercury CSD 2.4 software [17]. The crystal and instrumental parameters were summarized in the supporting information. Molecular structure with the atom-numbering scheme of the HL is given in Figure 2.

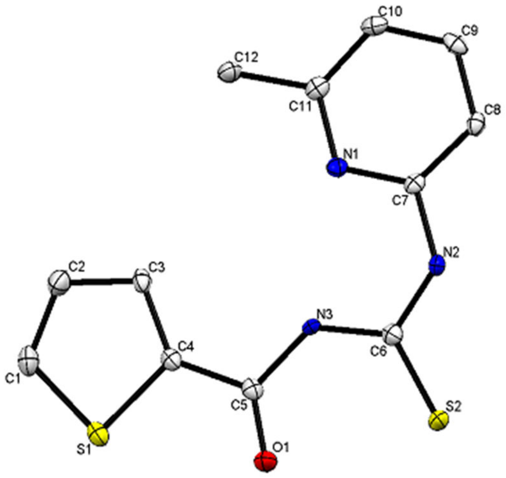


Figure 2 ORTEP view of the HL, thermal ellipsoids are shown at the 50% probability level.

Crystal data parameters of HL and some experimental parameters are given in the supplementary material file.

Packing scheme of the HL is given in Figure 3.

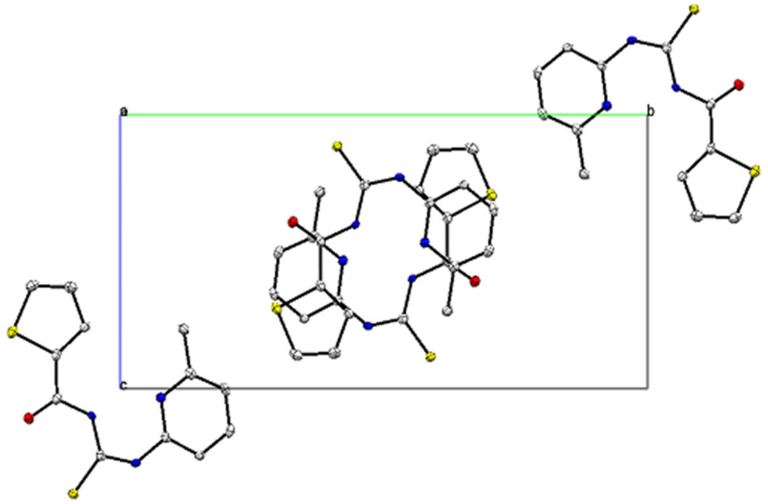


Figure 3 Crystal packing scheme of the HL in *P* 1 2_1/*c* 1.

The structures were solved and refined using the Bruker SHELXTL Software Package. Selected bond lengths and angles of the HL are presented in supplementary material file. The bond lengths and angles in the HL are typical for thiourea derivatives; C6-S2 and C5-O1 bonds show a typical double-bond character with 1,672(18) and 1,212(2) Å, respectively. The bond lengths of the N2-C6, N3-C6, N3-C5, and N2-C7 were determined as 1,359(2), 1.368(2), 1.400(2) and 1,409(2) Å respectively. These results show that the bonds have partial double bond character. The carbonyl and thiocarbonyl part bound angles are N2-C6-S2, 119.3(14); N3-C6-S2, 125.7(14); N3-C5-O1, 124.4(17) and O1-C5-C4, 122.1(17)°[14,18-22]. The crystal packing is determined by intermolecular N-H…S hydrogen bonds [23,24]. Orbital diagrams of the HL were given in Figure 4. For HL molecule, HOMO are dominantly made up of π orbital of sulfur atom. On the other hand, LUMO are mainly delocalized over amide and thioamide moiety and thiophene ring of the HL molecule.

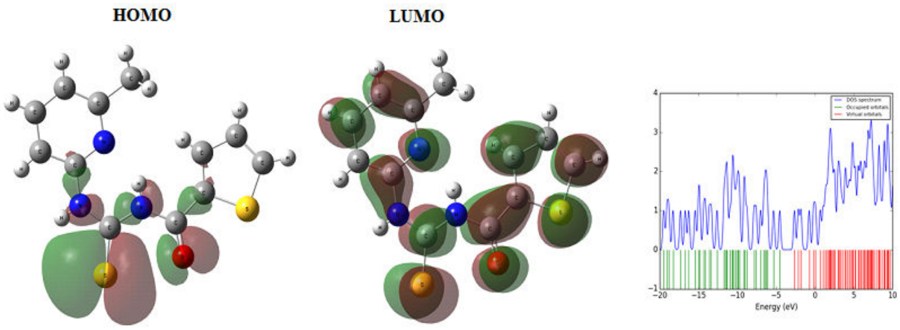


Figure 4 Orbital diagrams of the HL computed using B97D/TZVP level on the X-ray structure.

Complex Structure

The [ML$_2$] (M: Ni, Co, Cu) structures were proposed based on the reported cis-bis(*N,N*-dimethyl-*N*'-2-chlorobenzoylthioureato)Ni(II) crystal structure[25] and were optimized by using B97D/TZVP computational level. Figure 5 show optimized bond distances and O-M-S bond angles of the [ML$_2$] structures, respectively.

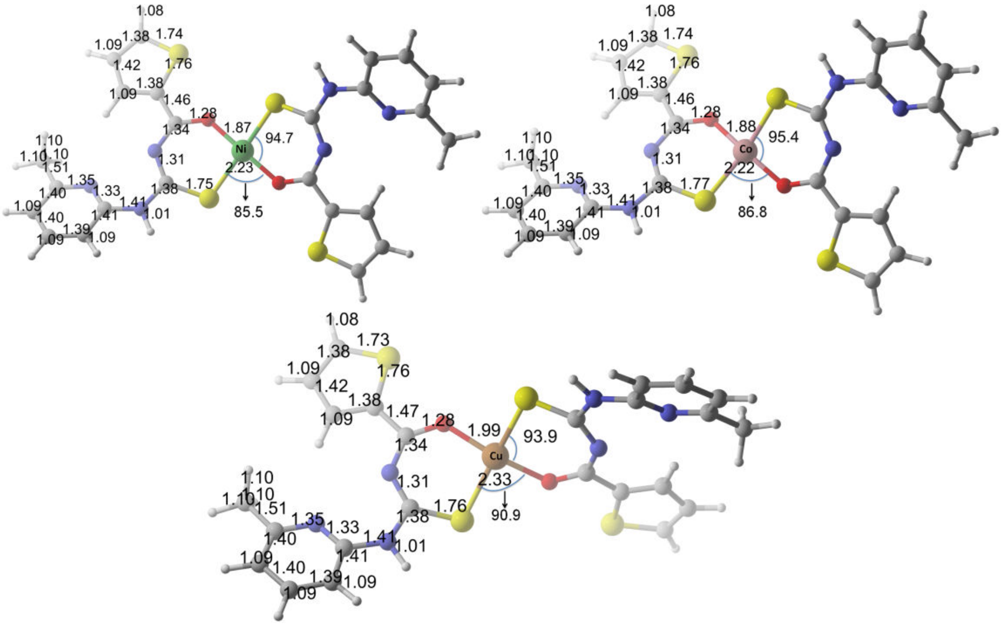


Figure 5 Optimized the [ML$_2$] structure using B97D/TZVP level.

The O-Ni-S bond angles in the [NiL$_2$] and [CoL$_2$] structures are very similar but in the [CuL$_2$] they slightly differ from those of Ni and Co complexes. The M-O distance for complexes follows the order; Cu-O (1.99 Å) >Co-O (1.88 Å) >Ni-O (1.87 Å). The M-O distance values for complexes agree with literature values which are 1.94 Å, 1.92 Å and 1.86 Å, respectively [26-28]. The M-S distance order for complexes is Co-S < Ni-S < Cu-S. It can be said that the bond lengths for the rest of the bond types (the C-H, C-C, C-N, C-S and C-O bonds) are almost the same in all complex structures since the largest difference is only 0.02 Å. The C6-S2 bond distance elongates from 1.672 Å in the HL structure to 1.75 – 1.77 Å in the [ML$_2$] structure. Similarly, the C5-O1 bond length also stretches from 1.212 Å to 1.28 Å for the [ML$_2$]. Due to leaving proton from N3 atom, C6-N3 and C5-N3 bond lengths changed to 1.31 and 1.34 Å in the [ML$_2$], respectively.

Antioxidant and Antitumor Activity of the Complexes

In vitro antioxidant and antitumor properties of all complexes were studied in cell culture systems. The antioxidant activity of metal complexes was studied by using the DPPH and ABTS assays. The anticancer activity of complex was studied via MTT assay in MCF-7 breast cancer cells. MTT assay is fast, easy and with high accuracy**.** The amount of living cells will be determined depending on the amount of binding via spectrophotometric analysis. The DPPH, ABTS, Reduction power and IC_{50} values are presented in supplementary material file. Natural or synthetic antioxidants are important in the management of severe oxidative stress conditions. Synthetic antioxidants are currently being developed as therapeutic agents against oxidative stress. The antioxidant activity is related to DPPH, ABTS and reduction power values. The [CoL_2] shows good antioxidant properties. These results show that antioxidant properties of [CoL_2] is better than those of propyl gallate and worse than those of vitamin E. Both propyl gallate and vitamin E are important antioxidant materials [29]. The [CuL_2] complex shows good antitumor activity. The IC_{50} value of the [CuL_2] complex is comparable with that of Fluorouracil (5-FU) which is widely used in cancer treatment. Other compounds (IC_{50} values, >40 ppm) were less active against the tumor cells [30]. Similarly, the researchers examined the antitumor properties of the Cu complex. They observed that the Cu complexes show good antitumor properties [31,32].

Electrochemical Behavior of the [CuL_2]

The cyclic voltammetric (CV) studies were carried out to understand the electrochemical behavior of the [CuL_2]. In cyclic voltammogram of the [CuL_2], there are two peaks. One of these peaks is at about +0.52 V, which is an oxidation peak, and the other one is at about -1.40 V which is a reduction peak. By the help of the pH measurements, optimum pH of the medium was found to be pH=2, where the sharpest and best results were obtained. To understand whether the process was under control of diffusion or absorption, scanning rate studies were carried out between 25 mV/s and 750 mV/s. Studies were carried out in Britton-Robinson buffer solution at pH=2, where the best oxidation and reduction results were obtained. The characteristic scan rate curves of the [CuL_2] are given in Figure 6.

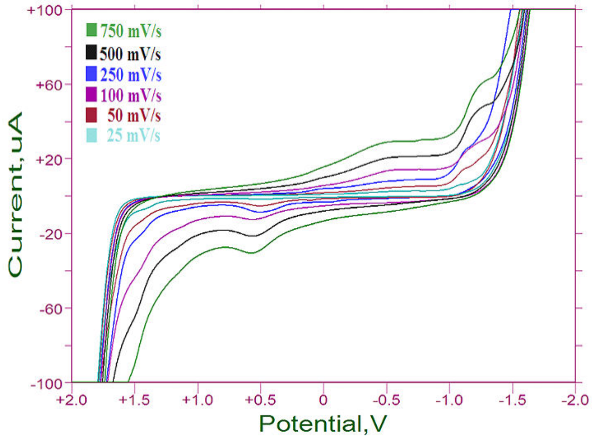


Figure 6 Cyclic Voltammograms of [CuL_2] compound with different scan rates.

Scan rates were investigated between the 25-750 mV/s and at 1 x 10^{-5} M concentration. The linear dependence of peak current Ip (µ) on the square root of the scan rate $v^{1/2}$ (mVs^{-1}) was found by GCE, demonstrating diffusional behavior. The equations about scan rate studies for the $[Cu(L)_2]$ is noted via the equation below (1);

$$\text{Log } I_p\,(\mu A) = 0,\,2607\,\sqrt{v}\,(mVs^{-1}) - 0,\,5439\;(r^2 = 0,\,9501) \qquad (1)$$

The linear relationship between Log I_p and Log v was also investigated and the equations about these relationships are given via the equation below (2);

$$\text{Log } I_p\,(\mu A) = 0,\,4455\,\text{Log } v\,(mVs^{-1}) - 0,\,3970\;(r^2 = 0,\,9940) \qquad (2)$$

The slope of the relationships fit with the theoretically expected values for an ideal diffusion controlled reaction (0.5) [33]. The Cu(II) complexes could be studied because they are stable in this pH range.

CONCLUSIONS

N-((6-methylpyridin-2-yl)carbamothioyl)thiophene-2-carboxamide, $C_{12}H_{11}N_3OS_2$ (HL), and its Co(II), Ni(II) and Cu(II) complexes have been synthesized. Characterization of the compounds were made by elemental analysis, FT-IR, ^{1}H-NMR and HR-MS methods. In addition, HL was characterized by single crystal X-ray diffraction method. The HL crystallizes in the monoclinic crystal system with $P1\ 2_1/c\ 1$ space group, Z=4, a=7.2326(8) Å, b=18.3492(16) Å, c=9.7724(9) Å. Molecular orbitals of both HL calculated and the $[ML_2]$ structures were optimized by B97D/TZVP level. The anticancer and antioxidant activities of the complexes were also investigated. Antioxidant activities of the complexes were determined by using DPPH and ABTS assays. The $[CoL_2]$ shows good antioxidant properties. Anticancer activity of the complex was investigated via MTT assay in MCF-7 breast cancer cells. The IC_{50} values of complexes are 111, 79 and 31 ppm for $[CoL_2]$, $[NiL_2]$ and $[CuL_2]$, respectively. The $[CuL_2]$ complexes were found to have better antitumor activities. Cyclic voltammograms of the complexes show oxidation and reduction peaks at +0.52 V and -1.40 V for the $[CuL_2]$.

Appendix A. Supplementary material

Crystallographic data for the HL structure have been deposited at the Cambridge Crystallographic Data Centre (CCDC), CCDC 1055243 (HL). This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Cartesian coordinates of optimized geometries are also available. The tables in the text were also combined in the Supplementary Material.

ACKNOWLEDGEMENTS

This work was supported by Kahramanmaraş Sütçü İmam University Research Fund (BAP-project no:2013/4-28M). We also thank TUBITAK ULAKBIM, High Performance and Grid Computing Center (TR-Grid e-Infrastructure) for the calculations.

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Türkçe Öz ve Anahtar Kelimeler

N-((6-metilpiridin-2-il)karbamotioil)tiyofen-2-karboksamid ve Co(II) Ni(II) ve Cu(II) komplekslerinin sentezi ve karakterizasyonu: Molekül Orbitallerin Hesaplanması, Antioksidan ve Antitümör Aktiviteleri

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Öz: N-((6-metilpiridin-2-il)karbamotioiltiyofen-2-karboksamid, $C_{12}H_{11}N_3OS_2$ (HL) ve Co(II), Ni(II) ve Cu(II) kompleksleri (ML_2 türü) sentezlenmiş ve elementel analiz, FT-IR, ^{1}H-NMR HR-MS yöntemleriyle karakterize edilmiştir. Bunun dışında, HL tek kristal X-ışını saçılması yöntemi ile karakterize edilmiştir. HL monoklinik kristal sisteminde P 1 21/c 1 uzay grubunda kristallenir ve Z = 4 a=7.2326(8) Å, b=18.3492(16) Å, c=9.7724(9) Å.olarak bulunmuştur. [ML_2] kompleks yapıları B97D/TZVP seviyesinde optimize edilmiştir. HL ligandının moleküler orbitalleri de aynı seviyede hesaplanmıştır. Komplekslerin antioksidan aktiviteleri DPPH ve ABTS deneyleri ile belirlenmiştir. Kompleksin antikanser aktivitesi MTT deneyi ile MCF-7 meme kanser hücrelerinde çalışılmıştır.

Anahtar kelimeler: Tiyoüre; tiyofen; antikanser aktivitesi, kristal yapısı; moleküler orbital.

Sunulma: June 27, 2016. **Kabul:** July 9, 2016.