Macedonian Journal of Chemistry and Chemical Engineering, Vol. **41**, No. 2, pp. xx–xx (2022)

MJCCA9 –

ISSN 1857-5552
e-ISSN 1857-5625

Received: May 20, 2022
Accepted: July 18, 2022

DOI: 10.20450/mjcce.2022.2526
Original scientific paper

THE Pd(II) COMPLEX INVOLVING A NEW PYROLE-BASED LIGAND: SYNTHESIS, SPECTRAL ANALYSIS, AND ANTIMICROBIAL ACTIVITY

Mesut Boz, Övül Tetik, Özlen Altun*

Trakya University, Department of Chemistry, 22030 Edirne, Turkey
*mesutboz@trakya.edu.tr, ovultetik@gmail.com, *ozlenaltun@yahoo.com*

In the current study, firstly, a new pyrrole-based ligand (3,4-(ethylenedimercaptodiacetoxy)-*N*-(benzyl)-diethyl-2,5-pyrroledicarboxylate (L) was synthesized in the presence of diethyl-*N*-benzyl-3,4-dihydroxy-1*H*-pyrrole-2,5-dicarboxylate and 2,2'-(ethane-1,2-diylbis(sulfanediyl))diacetylchloride. Then, the palladium(II) complex of the synthesized ligand was obtained, and its structural features were examined by spectral (HRMS, ESI-MS, UV-Visible, FTIR, ^{1}H NMR, ^{13}C NMR, XRD-POWDER, SEM, EDX) and thermogravimetric (TG-DTA) techniques. The spectral and thermal measurements of the ligand and its Pd(II) complex show that the ligand is coordinated to the Pd^{2+} ion. Antimicrobial activities of both the ligand and its palladium complex were examined. It was determined that whereas the ligand indicated modest antimicrobial activity against *Staphylococcus aureus* and *Candida albicans* at a concentration of 6.25 μg/ml, the palladium complex was significantly effective against *C. albicans* at a concentration of 6.25 μg/ml.

Keywords: heterocyclic compounds; palladium(II); spectral characterization; biological activity

КОМПЛЕКС НА Pd(II) СО НОВ ЛИГАНД НА ОСНОВА НА ПИРОЛ: СИНТЕЗА, СПЕКТРАЛНА АНАЛИЗА И АНТИМИКРОБНА АКТИВНОСТ

Во ова истражување најпрвин беше синтетизиран лиганд на основа на пирол (3,4-(етилендимеркаптодиацетокси)-*N*-(бензил)-диетил-2,5-пиролдикарбоксилат (L) во присуство на диетил-*N*-бензил-3,4-дихидрокси-1*H*-пирол-2,5-дикарбоксилат и 2,2'-(етан-1,2-диилбис(сулфандиил))диацетилхлорид. Беше добиен паладиум(II) комплекс со наведениот лиганд и неговите структурни карактеристики беа испитани со спектрални (HRMS, ESI-MS, UV-Vis, FTIR, ^{1}H NMR, ^{13}C NMR, XRD-POWDER, SEM, EDX) и термогравиметриски (TG-DTA) техники. Спектралните и термичките мерења на лигандот и на комплексот на Pd(II) укажуваат дека лигандот е координиран со јонот на Pd^{2+}. Беше испитана и антимикорбната активност и на лигандот и на неговиот паладиумски комплекс. Беше утврдено дека, иако лигандот покажува скромна антимикорбна активност спрема *Staphylococcus aureus* и *Candida albicans* во концентрации од 6,25 μg/ml, комплексот на паладиумот е значајно поефикасен спрема *C. albicans* при истата концентрација.

Клучни зборови: хетероциклични соединенија; паладиум (II); спектрална карактеризација; биолошка активност

1. INTRODUCTION

Pyrroles are a significant class of heterocyclic aromatic compounds and have different biological activities. Today, derivatives of the heterocycle pyrrole and their metal complexes take part in numerous biochemical and physiological fields, such as photosynthesis, amino acids, DNA bases, vitamins, and endogenous neurotransmitters.[1, 2] In the Paal-Knorr method, which is the best known method for pyrrole synthesis, a 1,4-dicarbonyl compound is condensed with an excess of

primary amine or ammonia under neutral or weakly acidic conditions. Pyrrole synthesis has been successfully carried out in many modified forms of this reaction.[3] N-substituted pyrroles can be synthesized by the condensation of 2,5-dialkoxytetrahydrofurans with primary aromatic and aliphatic amines. This method is known as the Clauson-Kaas Pyrrole synthesis.[4]

Pd(II) complexes have an important place in organic synthesis. For example, Pd-catalyzed coupling reactions are used as an effective method for the formation of C–C and C–heteroatom bonds.[5, 6] Pd-catalysts facilitate unique transformations that are not easily achieved by classical methods. Many studies investigating the biological properties of Pd-based pyrrole compounds have been reported in the literature.[7–9] However, there have been no references in the literature on the synthesis and investigation of the biological activity of our ligand (L) and its Pd(II) complex. For these reasons, in this study, diethyl 1-benzyl-3,4-dihydroxy-1*H*-pyrrole-2,5-dicarboxylate starting from diethyl *N*-benzyl iminodiacetate was synthesized and derivatized with 2,2'-(ethane-1,2-diylbis(sulfandiyl))diacetylchloride. Then, the Pd(II) complex of the resulting compound 3,4-(ethylenedimercaptodiacetoxy)-*N*-(benzyl)-diethyl-2,5-pyrroledicarboxylate (L) was prepared. Structural features and antimicrobial activities were investigated.

2. EXPERIMENTAL SECTION

2.1. *Materials and measurements*

All chemical reagents and solvents were purchased from commercial companies such as Sigma-Aldrich and Merck and used without purification. The molar conductivity of the complex was measured in DMSO with an Inolab Thermal 740P. High Resolution Mass Spectra (HRMS) were acquired on an AB-SCIEX Triple TOF 4600 System for L, and an Agilent 6400 Series Triple Quadrupole was used for Electrospray Ionization Mass Spectra (ESI-MS) of the palladium complex. Electronic spectra were recorded by a Shimadzu UV-1700 Pharma spectrophotometer in the 200–800 nm range. Fourier Transform Infrared Spectra (FTIR) were acquired by using a Perkin-Elmer Frontier FTIR spectrophotometer in the frequency range of 450–4000 cm^{-1}. NMR spectra were obtained in $CDCl_3$ with a Varian Mercury Plus 300 MHz spectrometer. An EVO LS 10 analyser was used for Energy Dispersive Spectroscopy (EDX) analysis. SEM analysis was performed with a Scanning Electron Microscope (SEM), model ZEIS LEVO LS 10. X-Ray Diffraction (XRD) analysis was performed on a Shimadzu XRD-6000 analyser. A Seiko Exstar TG/DTA 6200 thermal analyser was used to obtain Thermogravimetric/ Differential Thermal Analysis (TG/DTA) curves.

2.2. *Synthesis of diethyl N-benzyl iminodiacetate* (**1**)

The starting compound diethyl *N*-benzyl iminodiacetate (**1**) was prepared from ethyl chloroacetate and benzylamine.[10] Benzylamine (6.25 ml, 57.5 mmol) was added to an acetonitrile solution (50 ml) containing potassium carbonate (31.74 g, 230 mmol) under a nitrogen atmosphere and stirred. After stirring for 10 min, ethyl chloroacetate (12.30 ml, 115 mmol) was added dropwise, stirred while refluxing for 48 h, quenched by distilled water (50 ml), and extracted with EtOAc (3 × 50 ml). Then, the organic layers were combined and dried over magnesium sulphate. After filtration and removal of EtOAc, column chromatography involving silica gel as the stationary phase and a hexane:ethyl acetate solvent system (5:1) as the mobile phase was used to purify the resulting residue and obtain diethyl *N*-benzyl iminodiacetate (**1**) (9.46 g colorless oil, 59 % yield). **Analysis.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46–7.23 (m, 5H), 4.17 (q, *J* = 7.1 Hz, 4H), 3.92 (s, 2H), 3.55 (s, 4H), 1.27 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.45, 138.41, 129.30, 128.61, 127.60, 60.68, 58.05, 54.43, 14.50.

2.3. *Synthesis of diethyl 1-benzyl-3,4-dihydroxy-1H-pyrrole-2,5-dicarboxylate* (**2**)

Condensation of diethyl *N*-benzyl iminodiacetate (**1**) with diethyloxalate in basic media gave diethyl 1-benzyl-3,4-dihydroxy-1*H*-pyrrole-2,5-dicarboxylate (**2**).[10] Metallic Na (0.69 g, 30 mmol) was slowly added to magnetically stirred absolute ethanol (20 ml) under a reflux condenser under a nitrogen atmosphere and stirred for about 2 h until dissolution was completed to give sodium ethoxide. To this mixture, a solution of diethyl *N*-benzyl iminodiacetate (3.1 g, 11 mmol) and diethyl oxalate (1.51 ml, 11 mmol) in 10 ml ethanol was added dropwise, refluxed for 18 h, and cooled to 25 °C. It was then poured into 100 ml of ice-water and pH = 5 was made with glacial acetic acid. It was then kept in the cold for 1 day to complete the precipitation. The product was recrystallized from acetone to obtain diethyl 1-benzyl-3,4-dihydroxy-1*H*-pyrrole-2,5-dicarboxylate (**2**) (0.77 g white solid, 21 % yield). **Analysis.** ^{1}H NMR (300 MHz,

$CDCl_3$): δ 7.81 (s, 2H), 7.35–7.15 (m, 3H), 6.91 (m, 2H), 5.77 (s, 2H), 4.32 (q, *J* = 7.1 Hz, 4H), 1.26 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.82, 139.83, 139.38, 128.66, 127.17, 125.75, 111.24, 61.50, 49.55, 14.43.

2.4. *Synthesis of 2,2'-(ethane-1,2-diylbis(sulfanediyl))diacetyl chloride* (**3**)

Compound **3** was synthesized from the chlorination of 2,2′-(ethylenedithio)diacetic acid with thionyl chloride.[11] A solution of thionyl chloride (12.2 ml, 167 mmol) was added to 2,2'-(ethylenedithio)diacetic acid (1.68 g, 8 mmol) and magnetically stirred. It was then refluxed for 3 h under a N_2 atmosphere. A dark oily residue was obtained by removing excess thionyl chloride under reduced pressure (9.46 g, 92 % yield). From the ^{1}H and ^{13}C NMR spectra, it was found that this residue was quiet pure. **Analysis.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85–3.72 (m, 4H), 3.00–2.85 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.60, 45.25, 32.03.

2.5. *Synthesis of 3,4-ethylenedimercaptodiacetoxy-N-benzyl-diethyl-2,5-pyrroledicarboxylate (L)* (**4**)

Compound **2** was treated with 2,2′-(ethane-1,2-diylbis(sulfandiyl))diacetylchloride (**3**) under basic reaction conditions to give **4** (L) with a 14 % yield.[11] A solution of 2,2'-(ethane-1,2-diylbis(sulfanediyl))diacetyl chloride (1.557 g, 6.3 mmol) in dry CH_2Cl_2 (5 ml) was added dropwise to a solution of diethyl 1-benzyl-3,4-dihydroxy-1*H*-pyrrole-2,5-dicarboxylate (2.01 g, 6 mmol) and triethylamine (1.79 ml, 12.6 mmol) in dry CH_2Cl_2 (8.1 ml) at 0 °C and magnetically stirred for 4 h under a N_2 atmosphere. The temperature was then increased to 25 °C with stirring. The reaction was monitored by Thin Layer Chromatography (TLC) (hexane: ethylacetate; 3:1). After 18 h, the solution was poured into water and extracted with CH_2Cl_2 (3 × 20 ml). The organic layers were combined and washed with saturated $NaHCO_3$ solution (2 × 30 ml) and 30 ml brine and dried over magnesium sulphate. The solvent was removed under reduced pressure, the remaining product was purified by column chromatography on silica gel, and L (**4**) was obtained as white crystals (0.43 g, 14 % yield). **Analysis.** FTIR (cm^{-1}): 2987.9, 2924.0, 1773.7, 1752.7, 1717.8, 1701.4, 1605.0, 1432.6, 1362.8, 1267.3, 1092.0, 1019.7. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.16 (m, 3H), 7.01 (m, 2H), 6.15 (s, 2H), 4.21 (q, *J* = 7.1 Hz, 4H), 3.47 (s, 4H), 3.05 (s, 4H), 1.23 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.03, 159.15, 138.14, 132.30, 128.80, 127.35, 126.13, 117.06, 61.31, 49.75, 33.55, 32.48, 14.32. HRMS (*m/z*): $[M + NH_4]^+$ calcd for $C_{23}H_{29}O_8S_2N_2^+$, 525.136537; found, 525.1402.

2.6. *Synthesis of the palladium(II) complex of L* (**5**)

The synthesized L (**4**) (0.51 g, 1 mmol) was dissolved in ethanol (5 ml). $PdCl_2$ (0.18 g, 1 mmol) was added to this solution and magnetically stirred at room temperature for 3 days. The obtained yellow solid was recrystallized from an ethanol:water mixture, filtered, and dried to give the Pd complex of L (0.59 g yellow crystals, 85 % yield). The complex was soluble only in organic solvents. **Analysis.** Yield: 85 %. m.p.: 235.3 °C. Conduct. (Ω^{-1} cm^2 mol^{-1}): 145.00. FTIR (cm^{-1}): 2988.9, 2905.1, 1769.3, 1733.0, 1710.6, 1606.2, 1429.9, 1366.4, 1286.3, 1155.2, 1026.0, 954.0, 755.5. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.29 (m, 3H), 7.07–6.99 (m, 2H), 6.17 (s, 2H), 4.57–4.50 (m, 1H), 4.22 (q, *J* = 7.2 Hz, 4H), 3.62–3.34 (m, 6H), 3.06 (s, 1H), 1.24 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.01, 159.15, 138.13, 132.29, 128.71, 127,34, 126.05, 117.05, 61.29, 49.74, 33.54, 32.47, 14.30. ESI-MS (*m/z*): $[M]^+$ calcd for $PdC_{23}H_{25}O_8S_2NCl_2^+$, 682.943344; found, 682.9500.

2.7. *Antimicrobial activity*

For the antimicrobial activities, Gram (–) *Escherichia coli* ATCC 25922, *Salmonella thyphimirium* ATCC 14028, *Listeria monocytogenes* ATCC19115, Gram (+) *Staphylococcus aureus* ATCC 25923, *Bacillus cereus* ATTCC 11778, and fungal *Candida albicans* ATCC 1023 were used. Ampicillin was used as the antibiotic in both bacterial and fungal cultures. Minimal inhibitory concentration values (MIC) were determined by Clinical and Laboratory Standards Institute (CLSI) standards and the micro broth dilution method.[12–15] The microorganisms were prepared in the concentration range of 6.25–200 μg/ml, transferred on a sterile 96-well microplate, and incubated for 24 h at 37 °C. The absorbance was measured at 600 nm with a Thermo Multiscan GO Microplate Reader Spectrophotometer. For positive, any color change from purple to pink was visually determined. The MIC value was considered the lowest concentration with a color change. Experiments were made in duplicate.

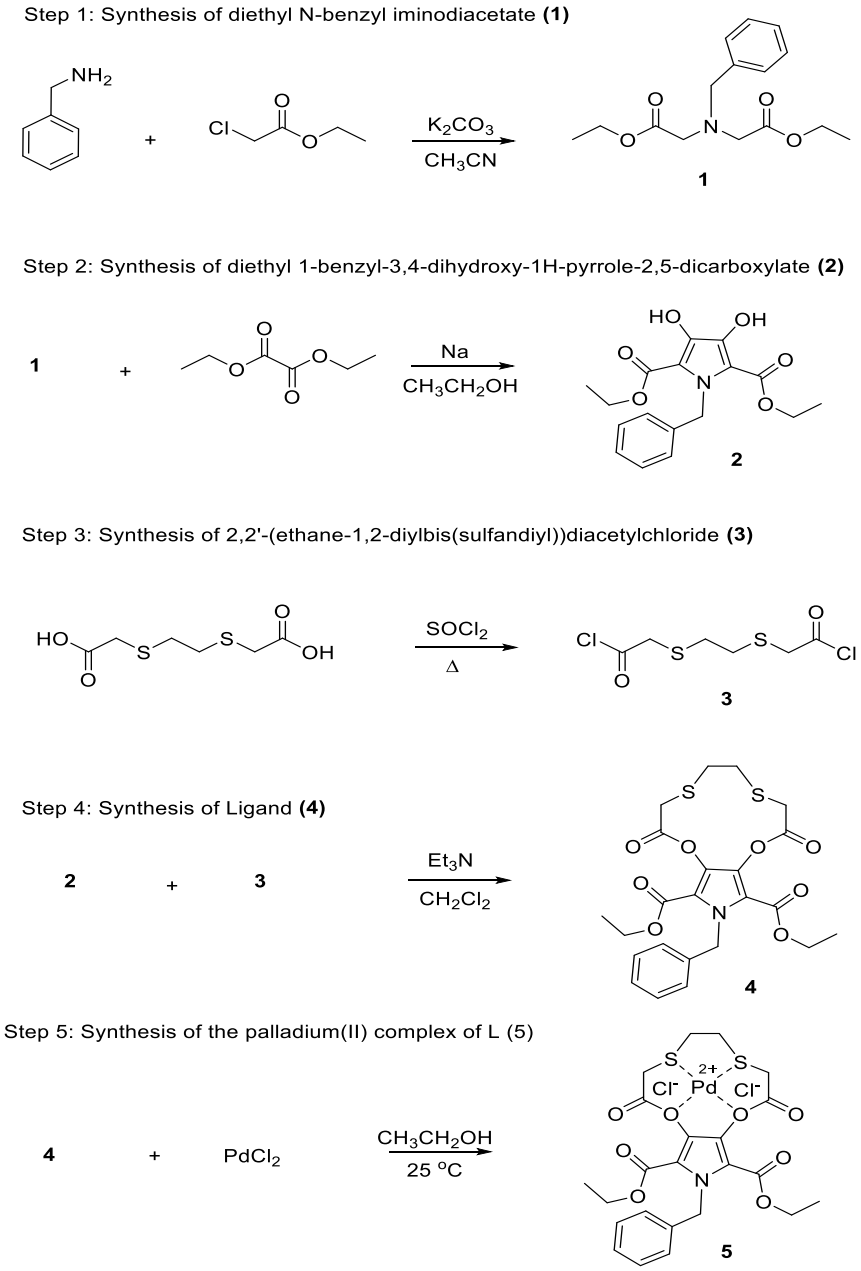
3. RESULTS AND DISCUSSION

The synthesis of the palladium(II) complex of 3,4 ethylenedimercaptodiacetoxy-*N*-benzyl-diethyl-2,5-pyrroledicarboxylate (L) was constructed by a five-step synthesis procedure (Scheme 1). In the first

step, diethyl *N*-benzyl iminodiacetate (**1**) was synthesized from ethyl chloroacetate and benzylamine in the presence of acetonitrile and potassium carbonate. Then, diethyl 1-benzyl-3,4-dihydroxy-1*H*-pyrrole-2,5-dicarboxylate (**2**) was obtained by condensing compound **1** with diethyloxalate in a basic medium. In the third step, 2,2′-(ethane-1,2-diylbis(sulfandiyl)) diacetylchloride (**3**) was prepared from the chlorination of 2,2′-(ethylenedithio)diacetic acid with thionyl chloride. 3,4-ethylenedimercaptodiacetoxy-*N*-benzyl-diethyl-2,5-pyrroledicarboxylate (L) (**4**) was synthesized from the reaction of compound **2** with compound **3** under basic reaction conditions in the fourth step. Finally, the treatment of compound **4** with $PdCl_2$ gave the targeted Pd(II) complex (**5**).

The molar conductivity of the palladium complex was determined in 10^{-3} mol/l DMSO solvent at 30 °C, and the molar conductivity value was determined to be 137 ohm^{-1} cm^2 mol^{-1}. According to this value, the complex is an electrolyte with two ionizable chloride ions outside of the coordination sphere.[16, 17] It is predicted that the formula of the palladium complex is $[Pd(L)]Cl_2$.

The value observed at *m/z*: 525.1402 in the HRMS spectra of the L refers to the molecular ion peak of the L. In the ESI-MS spectra of the palladium complex, a maximum intensity at *m/z*: 682.9500 is consistent with the calculated molecular weight of the palladium complex.



Scheme 1. The synthetic protocol of the compounds

3.1. *Electronic spectra*

In the electronic spectra of the free L and palladium complex (Fig. 1), the free L has two absorption bands assigned to a π-π* transition at 228 (ε = 251 L mol^{-1} cm^{-1}) and an n-π* transition at 353 nm (ε = 834 L mol^{-1} cm^{-1}).

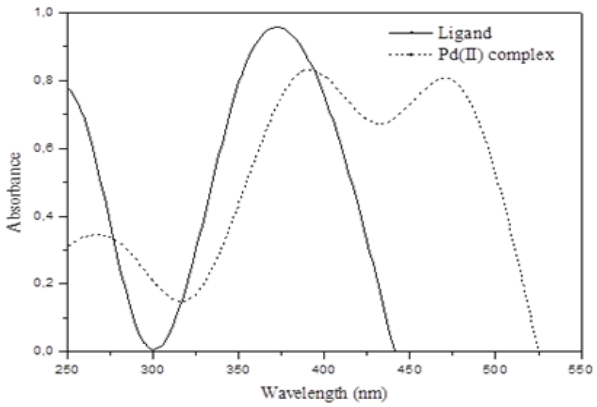


Fig. 1. Electronic spectra of the L and palladium complex

The electronic spectra of the palladium complex indicates three absorption bands in the range 478 (ε = 789 L mol^{-1} cm^{-1}), 387 (ε = 827 L mol^{-1} cm^{-1}), and 282 nm (ε = 315 L mol^{-1} cm^{-1}), which are assigned to $^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$, and $^1A_{1g} \rightarrow {}^1E_g$ transitions, respectively. The absorbance observed at 282 nm represents the transition charge transfer from the L to the palladium(II) ion. According to the electronic spectra results, the synthesized palladium complex has a square-planar geometry with the coordination of the central Pd^{2+} ion by the L.[18–21]

3.2. *FTIR spectra*

The FTIR spectra of the L and its palladium complex are presented in Table 1. The FTIR spectra of the ligand demonstrates bands at 2987.9 (C–H stretching), 2924.0 (C–H stretching), 1773.7 (C=O stretching), 1752.7 (C=O stretching), 1717.8 (C=O stretching), 1701.4 (C=O stretching), 1432.6 (CH_2 bending), 1362.8 (C–N stretching), 1267.3–1092.0 (C–O stretching), and 1019.7 cm^{-1} (C–S stretching).[22–24] The FTIR spectra of the complex demonstrates bands at 2988.9 (C–H stretching), 2905.1 (C–H stretching), 1769.3 (C=O stretching), 1733.0 (C=O stretching), 1710.6 (C=O stretching), 1429.9 (CH_2 bending), 1366.4 (C–N stretching), 1286.3–1155.2 (C–O stretching), and 1026.0 cm^{-1} (C–S stretching).

T a b l e 1

FTIR bands (cm^{-1}) of the L and palladium complex

Compound	L	Palladium complex
ν(Aliphatic C-H stretching)	2987.9	2988.9
ν(Aliphatic C-H stretching)	2924.0	2905.1
ν(ester C=O stretching)	1773.7	1769.3
ν(ester C=O stretching)	1752.7	–
ν(ester C=O stretching)	1717.8	1733.0
ν(ester C=O stretching)	1701.4	1710.6
ν(aromatic C=C stretching)	1605.0	1606.2
ν(CH2 bending)	1432.6	1429.9
ν(C-N stretching)	1362.8	1366.4
ν(Ester C-O stretching)	1267.3–1092.0	1286.3–1155.2
ν(C-S stretching)	1019.7	1026.0
ν(Pd-S)	–	954.0
ν(Pd-O)	–	755.5

Especially, four absorption bands of carbonyl stretching are seen in the FTIR spectrum of the ligand, whereas three carbonyl absorption bands are observed in the spectrum of the complex. The absorption bands of both of the two carbonyl groups on the cyclododecane ring and the two carbonyl groups bound to the pyrrole ring of the ligand were observed in the FTIR spectra as four different bands. This is due to the different conformations of the cyclododecane ring. In the complex, two carbonyl groups on the cyclododecane ring become identical due to the locking of the conformation by palladium, giving a single absorption band. The ester carbonyl groups were observed with two absorption bands in the complex as in the ligand. Additionally, it was observed that the C=O, C–O, and C–S stretching bands shift to higher frequencies in the complex. This is due to the fact that

sulfur and oxygen atoms use their lone pair electrons to bond with palladium. In this case, the corresponding atoms meet the electron need from the neighbouring carbon. For example, the carbonyl carbon uses the electrons of the double bond more equally with oxygen and absorbs at a higher frequency. The new bands at 954.0 and 755.5 cm^{-1} in the spectrum of the palladium complex may be related to ν(Pd–S) and ν(Pd–O), respectively.[25]

3.3. *^{1}H and ^{13}C NMR spectra*

The ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C spectra (75 MHz, $CDCl_3$) for the L and palladium complex were examined to confirm the binding of the L molecule to the Pd^{2+} ion. In the ^{1}H NMR spectra, L has signals at δ: 7.40–7.16 (m, 3H), 7.04–6.99 (m, 2H), 6.15 (s, 2H), 4.21 (q, *J* = 7.1 Hz, 4H), 3.47 (s, 4H), 3.05 (s, 4H), 1.23 (t, *J* = 7.1 Hz, 6H). The ^{13}C NMR spectra of the L show signals at δ: 168.03, 159.15, 138.14, 132.30, 128.80, 127.35, 126.13, 117.06, 61.31, 49.75, 33.55, 32.48, 14.32.

In the ^{1}H NMR spectra of the palladium complex, the complex has signals at δ: 7.38–7.29 (m, 3H), 7.07–6.99 (m, 2H), 6.17 (s, 2H), 4.57–4.50 (m, 1H), 4.22 (q, *J* = 7.2 Hz, 4H), 3.62–3.34 (m, 6H), 3.06 (s, 1H), 1.24 (t, *J* = 7.1 Hz, 6H). The signal of the CH_2 protons adjacent to the sulfur atom and carbonyl group in the palladium complex has shifted compared with that of the free L. These shifts of the CH_2 signals in the NMR result from the coordination of oxygen and especially sulfur atoms in the L with the Pd^{2+} ion. The signal of the CH_2 protons at about 3.0 ppm appears to shift downfield because the coordination with the palladium ion leads to the fact that CH_2 protons are more deshielded.[26] In the ^{13}C NMR spectra of the palladium complex, the complex has signals at δ: 168.01, 159.15, 138.13, 132.29, 128.71, 127,34, 126.05, 117.05, 61.29, 49.74, 33.54, 32.47, 14.30.

3.4. *XRD, SEM, and EDX analysis*

The XRD-powder values of the synthesized palladium complex were obtained over the 2θ = 5–80° range and are given in Figure 2. For the palladium complex, the three characteristic peaks at 2h = 38.29º, 44.43º, and 64.68º correspond to (111), (200), and (220), respectively, confirming that the sample was formed from crystalline palladium. The average crystallite size (D) of the palladium complex was found to be 27.4 nm using the Debye Scherrer equation.[27, 28] This result shows that the complex is in a nano-crystalline phase.

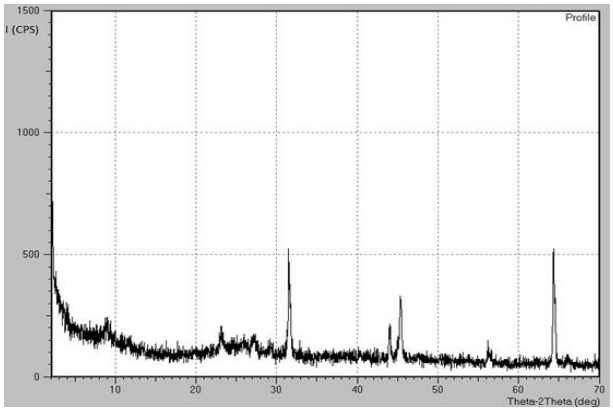
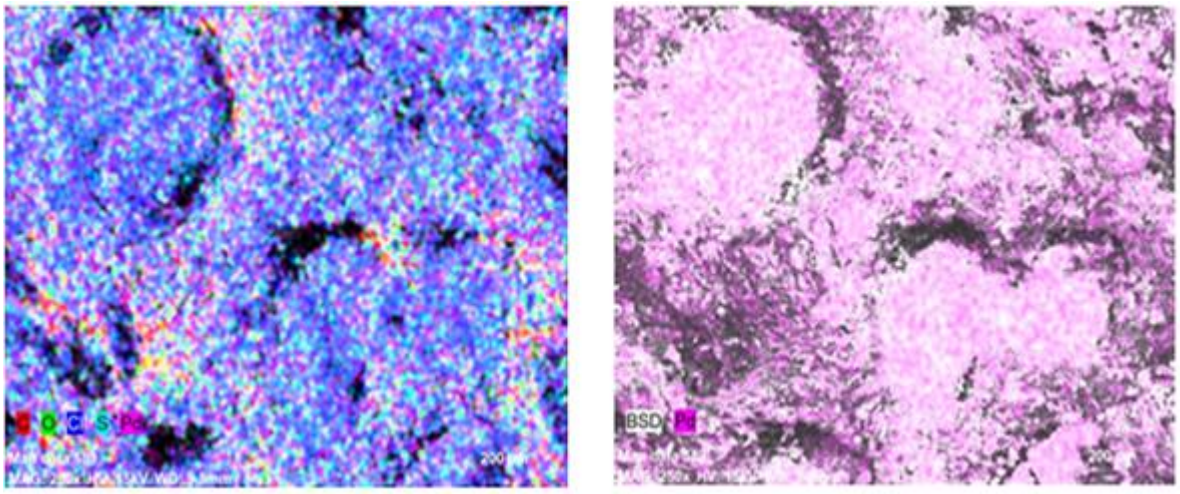


Fig. 2. XRD spectrum of the palladium complex

The surface image of the palladium complex determined by SEM[29–31] given in Figure 3 indicates that small palladium particles in the nanometer range that are spherical in shape are quite visible throughout the complex**.**



(a) (b)

Fig. 3. (a) and **(b)**: SEM pictures of the palladium complex

The EDX analysis,[29–31] which is used for elemental analysis of nanoparticles of different sizes, is given in Figure 4.

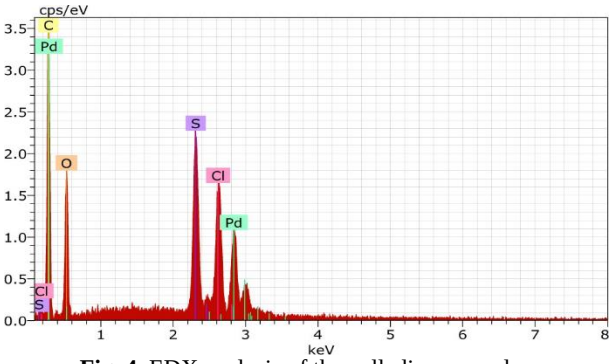


Fig. 4. EDX analysis of the palladium complex

Figure 4 shows that there are palladium, carbon, nitrogen, and oxygen peaks and a homogeneous distribution of each metal ion in the palladium complex.

3.5. *Thermogravimetric analysis*

The thermogravimetric analysis values of the palladium complex are presented in Table 2. According to the thermogravimetric analysis of the palladium complex, the 1st step between 25 and 200 °C is a 17.1 % weight loss due to removal of chloride ions. The 2nd step in the range of 200–500 °C shows the separation of the organic compound (55.1 %). The range of 500–900 °C is the formation of PdO (18.9 %), and the compound remaining over 900 °C was determined to be Pd (15.7 %). The thermogravimetric analysis results indicate that the molecular weight ratio of PdO and Pd is compatible with the proposed structure.[32]

T a b l e 2

Thermogravimetric analysis data of the palladium(II) complex

Compound	Steps	Tb-Tc (°C)	Weight loss (%)	Assignments
Pd(II) complex	1st	25–200	17.1	2Cl
	2nd	200–500	55.1	Organic component
	3rd	500–900	18.9	PdO
	4th	900–1000	15.7	Pd

3.6. *Antimicrobial activity results*

Previous studies involving the antimicrobial activities of various palladium(II) complexes have indicated a wide spectrum of antimicrobial activity.[33–37] It has been reported that the palladium complex is a very potent antimicrobial agent, especially against Gram (+) *S. aureus* and fungal *C. albicans*. In the current study, the antimicrobial activities of synthesized L and its palladium complex by CLSI standards and the micro broth dilution method were examined against antimicrobial strains that can provide resistance to antibiotics with various biochemical changes, and MIC values were recorded. The obtained results are given in Figure 5 and Table 3. As compared with previously reported literature data on antimicrobial activity, the Pd(II) complex in our study has especially significant activity against the *S. Aureus* bacterial strain. According to our antimicrobial activity data, the free L indicated modest antimicrobial activity against *Staphylococcus aureus* and *C. albicans* at a concentration of 6.25 µg/ml and the complex was significantly effective against *C. albicans* at a concentration of 6.25 µg/ml. These results indicate that the palladium complex is more effective against the fungal strain.

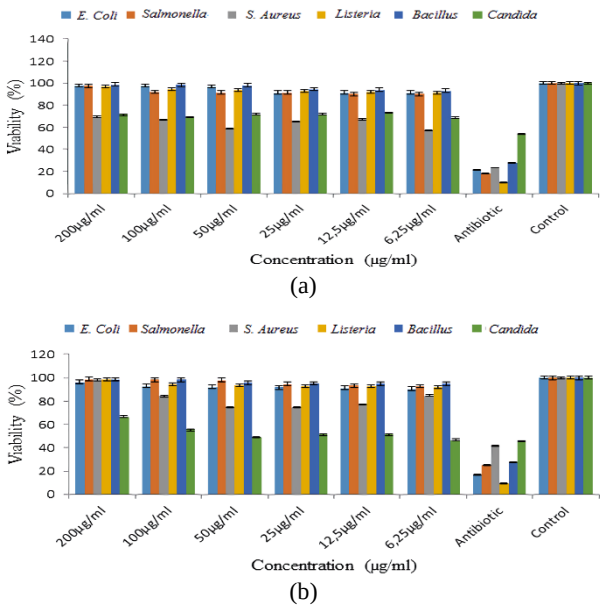


Fig. 5. The viability (%) values of the L (a) and palladium complex (b) at different concentrations (200–6.25 µg/ml) for *E. coli*, *S. typhimurium*, *S. aureus*, *L. monocytogenes*, *B. Cereus*, and *C. albicans* ($n = 2$) ± S. E.

Table 3

Antimicrobial activity data for the L and palladium complex

Name of fungus	İnhibition % Free L (Complex)	MIC (µg/ml) Free L (Complex)
S. aureus	42.9212±0.52 (25.6549±0.59)	6.25 (25)
C. albicans	31.2163±0.55 (53.2004±0.53)	6.25 (6.25)

* Ampicillin and amphotericin B

4. CONCLUSIONS

A pyrrole derivative ligand was synthesized starting from *N*-benzyliminodiacetate through a series of reactions in our laboratory, and its structure was analysed by electronic, FTIR, ^{1}H and ^{13}C NMR, HRMS, ESI-MS, and other techniques. The L formed a stable complex with $PdCl_2$, which was also confirmed by spectral and thermogravimetric techniques. The L and its palladium complex were examined for antimicrobial activity against bacterial and fungal strains. The antimicrobial activity analysis data show that the palladium complex has a higher value of antifungal activity, whereas the free L indicated modest antimicrobial activity against *S. aureus* and *C. albicans*. As a result, the synthesized L and its palladium complex in this study have the ability to kill microbes. Therefore, it can be suggested that these compounds can be used in the pharmaceutical industry in the future.

AUTHOR INFORMATION
M. BOZ, ORCID: https://orcid.org/0000-0002-0668-2933
O.TETİK, ORCID: https://orcid.org/0000-0001-7405-5598
O. ALTUN, ORCID: https://orcid.org/0000-0002-2979-4460

Acknowledgement: This study was financially supported by Trakya University. Research Fund (TUBAP, project # 2017/07).

REFERENCES

(1) Li, J. J., *Heterocyclic Chemistry in Drug Discovery*. Wiley : New York, 2013. ISBN 978-1-118-14890-7.

(2) De Leon, C. Y; Ganem, B., A new approach to porphobilinogen and its analogs. *Tetrahedron* **1997,** *53* (23), 7731–7752. https://doi.org/10.1016/S0040-4020(97)00469-9

(3) Banik, B. K.; Samajdar, S.; Banik, I., Simple synthesis of substituted pyrroles. *J. Org. Chem.* **2004,** *69* (1), 213–216. https://doi.org/10.1021/jo035200i

(4) Clauson-Kaas, C.; Tyle, Z., Preparation of cis- and trans 2,5-dimethoxy-2-(acetamidomethyl)-2,5-dihydrofuran, of cis- and trans 2,5-dimethoxy-2-(acetamidomethyl)-tetrahydrofuran and of 1-phenyl-2-(acetamidomethyl)-pyrrole. *Acta Chem. Scand.* **1952,** *6*, 667–670. https://doi.org/10.3891/acta.chem.scand.06-0667

(5) Negishi, E.; Anastasia, L., Palladium-catalyzed alkynylation. *Chem. Rev.* **2003,** *103*, 1979–2017. https://doi.org/10.1021/cr020377i

(6) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko M. F., Regioselective palladium-catalyzed arylation of 3-carboalkoxy furan and thiophene. *Org. Lett.* **2003,** *5* (3), 301–304. https://doi.org/10.1021/ol027266q

(7) Han, F. B.; Zhang, Y. L.; Sun, X. L.; Li, B. G.; Guo, Y. H.; Tang İ. Y., Synthesis and characterization of pyrrole-imine [N⁻NP] nickel(II) and palladium(II) complexes and their applications to norbornene polymerization. *Organometallics* **2008,** *27*, 1924–1928. https://doi.org/10.1021/om701297k

(8) Paul, P.; Bhattacharya, S., Palladium complexes of pyrrole-2-aldehyde thiosemicarbazone: Synthesis, structure and spectral properties. *J. Chem. Sci.* **2014,** *126* (5), 1547–1555. https://doi.org/10.1007/s12039-014-0699-4

(9) Mbugua, S. N.; Sibuyi, N. R. S.; Njenga, L. W.; Odhiambo, R. A.; Wandiga, S. O.; Meyer, M.; Lalancette, R. A.; Onani, M. O., New palladium(II) and platinum(II) complexes based on pyrrole Schiff bases: synthesis, characterization, X-ray structure, and anticancer activity. *ACS OMEGA* **2020,** *5*, 14942–14954. https://doi.org/10.1021/acsomega.0c00360

(10) Merz, A.; Schropp, R.; Dotterl, E., 3,4-dialkoxypyrroles and 2,3,7,8,12,13,17,18-octaalkoxyporphyrins. *Synthesis* **1995,** *7*, 795–800. https://doi.org/10.1055/s-1995-3993

(11) Rajakumara, P.; Abdul Rasheed, A. M., Synthesis, characterization and ion transportation studies of some novel cyclophane amides. *Tetrahedron* **2005,** *61*, 5351–5362. https://doi.org/10.1016/j.tet.2005.03.064

(12) *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard*—Second Edition. NCCLS document M27-A2 (ISBN 1-56238-469-4). Clinical and Laboratory Standards Institute, Wayne : Pennsylvania, 2002.

(13) *Performance Standards for Antimicrobial Susceptibility Testing*, Twenty-Second Informational Supplement. CLSI Document M100-S22, Clinical and Laboratory Standards Institute, Wayne: Pennsylvania, 2012.

(14) Kaya, E.; Ozbilge, H., Determination of the effect of fluconazole against *Candida albicans* and *Candida glabrata* by using microbroth kinetic assay. *Turk. J. Med. Sci.*, **2012,** *42* (2), 325–328. https://doi.org/10.3906/sag-1010-1211

(15) Altun, Ö.; Koçer M. Ö., Spectral, kinetic and thermodynamic studies of Pd(II) with Schiff base derived from

L-asparagine and furfuraldehyde in the presence of 8-hydroxyquinoline. *J. Mol. Struc.* **2021,** *1224* (129242), 1–9. https://doi.org/10.1016/j.molstruc.2020.129242

(16) Geary, W. J., The use of conductivity measurements in organic solvents for the characterisations of coordination compounds. *Coord. Chem. Rev.* **1971,** *7* (1), 81–122. https://doi.org/10.1016/S0010-8545(00)80009-0

(17) Kettle, S. F. A., *Coordination Compounds*. Thomas Nelson and Sons : London,1975. ISBN: 10:0177710136 / ISBN 13: 9780177710131

(18) Dyer, J. R., *Application of Absorption Spectroscopy of Organic Compounds*; Prentice-Hall : New Jersey, 1965. ISBN-10: 0130388106; ISBN-13: 978-0130388100

(19) Lever, A. B. P., *Inorganic Electronic Spectroscopy*; Elsevier : New York, 1984. ISBN*:* 0444423893 9780444423894

(20) Kang, J. G.; Cho, D. H.; Park, C.; Kang, S. K.; Kim, I. T.; Lee, S. W.; Lee, H. H.; Lee, Y. N.; Lim, D. W.; Lee, S. J.; Kim, S. H.; Bae, Y. J., X-ray crystal structure and luminescence properties of Pd(II) and Pt(II) complexes with dithiopyrrole. *Bull. Korean Chem. Soc.* **2008,** *29* (3), 599–603. https://doi.org/10.5012/bkcs.2008.29.3.599

(21) Jambi, S. M. S.; Kandil, S. S., Synthesis and characterization of Ni(II), Pd(II), Pt(II) complexes of N-allyl-N'-(4-methylthiazol-2-yl)thiourea. *J. Mater. Environ. Sci.* **2012,** *3* (3), 591–604. ISSN: 2028–2508 CODEN: JMESCN

(22) *Organic Structural Analysis*. Lambert, J. B.; Shurwell, H. F.; Berbit, L.; Cooks, R. G.; Stout, G. H., Mac Millan : New York, 1976. ISBN-13: 978-0023672903, ISBN-10: 0023672900

(23) Nakamato, K., *Infrared and Raman Spectra of Inorganic and Coordination Compounds*; John Wiley and Sons : New York, 1997. ISBN: 978-0-471-74339-2

(24) Socrates, G., *Infrared Characterization Group Frequencies: Tables and Charts, 3rd Edition*; John Wiley and Sons : UK, 2004. ISBN: 978-0-470-09307-8

(25) Giovagnini, L.; Ronconi, L.; Aldinucci, D.; Lorenzon, D.; Sitran, S.; Fregona, D., Synthesis, characterization, and comparative in vitro cytotoxicity studies of platinum(II), palladium(II), and gold(III) methylsarcosinedithiocarbamate complexes. *J. Med. Chem.* **2005,** *48* (5), 1588–1595. https://doi.org/10.1021/jm049191x

(26) Jin, L.; Sakiyan, I.; Gonzales, N. S.; Lane, D.; Cherala, S., Synthesis, characterization and Cu^{2+} binding studies of l-histidine ester of 8-hydroxyquinoline. *Inorg. Chim. Acta* **2014,** *423*, 72–78. https://doi.org/10.1016/j.ica.2014.07.042

(27) Salem, M. A.; Bakr, E. A.; El-Attar, H. G., Pt@Ag and Pd@Ag core/shell nanoparticles for catalytic degradation of Congo red in aqueous solution. *Spectrochim. Acta, Part A* **2018,** *188*, 155–163. https://doi.org/10.1016/j.saa.2017.07.002

(28) Warren, B. E., *X-ray Diffraction*. Dover : New York, 1990. ISBN: 978-0-486-66317-3

(29) Velammal, S. P.; Devi, T. A.; Amaladhas, T. P., Antioxidant, antimicrobial and cytotoxic activities of silver and gold nanoparticles synthesized using Plumbago zeylanica bark, *J. Nanostructure Chem.* **2016,** *6* (3), 247–260. https://doi.org/10.1007/s40097-016-0198-x

(30) Atta, A. H.; El-Shenawy, A. I.; Refat, M. S.; Elsabawy, K. M., Preparation and characterization of some gold nanometric compounds with simple organic materials as precursor: Spectroscopic, biological and anti-cancer assessments. *J. Mol. Struct.* **2013,** *1039*, 51–60. https://doi.org/10.1016/j.molstruc.2013.01.029

(31) Barbosa, H. F. G. A.; Attjioui, M.; Ferreira, A. P. G.; Dockal, E. R.; Gueddari, N. E. E.; Moerschbacher, B. M.; Cavalheiro, E. T. G., Synthesis, characterization and biological activities of biopolymeric Schiff bases prepared with chitosan and salicylaldehydes and their Pd(II) and Pt(II) complexes. *Molecules* **2017,** *22* (11), 1–19. http://dx.doi.org/10.3390/molecules22111987

(32) Yılmaz, V. T.; Ertem, A.; Guney, E.; Buyukgungor, O., Palladium(II) and platinum(II) saccharinate complexes with 2-aminomethylpyridine and 2-aminoethylpyridine: synthesis, characterization, crystal structures, and thermal properties. *Z. Anorg. Allg. Chem*. **2010,** *636* (3–4), 610–615. https://doi.org/10.1002/zaac.200900325

(33) Al-Hamdani, A. A. S.; Balkhı, A. M.; Falah, A.; Shaker, S. A., New azo-Schiff base derived with Ni(II), Co(II), Cu(II), Pd(II) and Pt(II) complexes: preparation, spectroscopic investigation, structural studies and biological activity**.** *J. Chil. Chem. Soc.* **2015,** *60* (1), 2774–2785. http://dx.doi.org/10.4067/S0717-97072015000100003

(34) Pahontu, E.; Paraschivescu, C.; Ilies, D. C.; Poirier, D.; Oprean, C.; Paunescu, V.; Gulea, A.; Rosu, T.; Bratu, O., Synthesis and characterization of novel Cu(II), Pd(II) and Pt(II) complexes with 8-ethyl-2-hydroxytricyclo (7.3.1. 02,7)tridecan-13-onethiosemicarbazone: Antimicrobial and in vitro antiproliferative activity. *Molecules* **2016,** *21* (5), 1–18. https://doi.org/10.3390/molecules21050674

(35) Kavitha, K.; Reddy, L., Pd(II) complexes bearing chromone based Schiff bases: Synthesis, characterisation and biological activity studies. *Arab. J. Chem.* **2016,** *9* (5), 640–648. https://doi.org/10.1016/j.arabjc.2013.06.018

(36) Kumar, V. A.; Sarala, Y.; Siddikha, A.; Vanitha, S.; Babu, S.; Reddy, A. V., Synthesis, characterization, antimicrobial and antioxidant activities of 2,4-dihydroxybenzaldehyde-4-phenyl-3-thiosemicarbazone (DHBPTSC) and its Pd(II), Ni(II)dppm mixed ligand and Cu(II) complex having heterocyclic bases. *J. Appl. Pharm. Sci.* **2018,** *8* (04): 071–078. https://doi.org/10.7324/JAPS.2018.8410

(37) Mihalache, M.; Negreanu-Pirjol, T.; Dumitraşcu, F.; Draghici, C.; Calinescu, M., Synthesis, characterization and biological activity of new Ni(II), Pd(II) and Cr(III) complex compounds with chlorhexidine. *J. Serb. Chem. Soc.* **2018,** *83* (3), 271–284. https://doi.org/10.2298/JSC170911119M