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Synthesis, characterization and biological activity study of some new palladium(II) complexes containing amine or azomethine groups

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ABSTRACT

This study reports the preparative methods of two types of palladium(II) complexes. The first method revealed two newly palladium (II) complexes derived from bidentate amine ligands, and the second one describes six newly palladium(II) complexes derived from bidentate Schiff base ligands. All the synthesized complexes have been characterized by elemental analysis, conductivity measurements, UV-Visible, FT-IR and ^{1}H NMR spectral data. *In vitro*, all the synthesized complexes have been tested for their growth inhibitory activity against Gram negative bacteria *Escherichia coli* and Gram positive *Staphylococcus aureus* as well as determining the minimum inhibitory concentration. In addition, the interactions between compounded complexes and human DNA were also studied.

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1. Introduction

Cancer may define as a disease or a group of diseases, which has the ability to metastasize into the body, destroy healthy tissues and endanger life. Therefore, it is the one of major causes of death in many countries across the world. About 20 million cancer cases are expected to occur in the next two decades, which render the quest for new antineoplastic agents [1]. Although many drug molecules are naturally organic, there are also metal elements, which offer different role in chemistry and have important therapeutic applications; such as platinum metal [1]. *cis*-Diamminedichloro platinum(II), *cis*-platin, is one of the most potent and effective antitumor agent that it was introduced to chemotherapeutic treatment in 1978 [2], its lack of selectivity through tumor tissues, however, many tumors have induced a resistance to this platinum complex [3]. To solve this problem though, modified versions of *cis*-platin leading to second and third generation platinum-based drugs have been synthesized over the past 30 years, and have got less toxic effect to their host tissue [4].

In recent years a great deal of effort has been devoted for developing transition metal as antitumor agents which have better therapeutic properties than prototype drug *cis*-platin [4,5]. Although the bulk of the work to date has involved investigations of platinum(II) complexes as potential anti-tumor agents [6-8], the significant similarity between the coordination chemistry of compounds has also advocated studies of palladium(II) complexes as anticancer drugs. A key factor that might explain why platinum is most useful comes from the ligand-exchange kinetics. The hydrolysis in palladium complexes is significantly rapid; about 10^5 times faster than their corresponding platinum analogues. The lability of palladium complexes for readily dissociating in solution lead to every reactive species enabling to reach their pharmacological targets [9].

One of the main challenges in the rational design of metal-containing chemotherapy agents is to enhance their cytostatic activity while simultaneously reducing toxicity [10,11]. For the most part, palladium complexes have shown little or no antitumor activity. This has been attributed to the higher lability and lack of stability comparatively to platinum(II) metal. Unfortunately, there are no antitumor activity for *cis*-palladium, *cis*-$[PdCl_2(NH_3)_2]$. It is well known that it undergoes into active *trans*-conformation and fast hydrolyze as consequently, they interact, *in vivo*, with a lot of molecules particularly proteins preventing them to reach the DNA as their pharmacological target [12]. Thus, whereas platinum compounds such as *cis*-platin maintain their structural integrity *in vivo* long enough to reach their cellular targets, analogous palladium compounds undergo hydrolysis and/or various substitution

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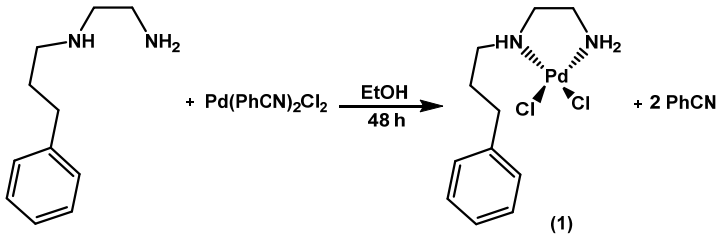


Scheme 1

reactions more quickly to be effective as antitumor agents. Higher activity of palladium complexes implies that if an antitumor palladium drug is to be developed, it must ideally be stabilized by a chelate or strongly coordinated with bulky monodentate nitrogen ligand and suitable leaving groups [8,13]. Due to the steric effect resulted from the bulk of donor atoms; these ligands could minimize any possible *cis*-trans isomerism [14]. In fact, carefully designed platinum and palladium complexes structurally different from *cis*-platin and its second-generation analogues are prone to display an altered spectrum of clinical activity and toxicity, due to differences in cellular biochemical pharmacology [15]. Therefore, parameters ruling their cytotoxicity may not follow the patterns applied to cisplatin-like agents. In fact to solve this problem, The Gill's approach was adopted by using the chelating ligands in order to stabilize the palladium complex [16].

On the other hand, amines are suitable chelating ligands for transition metal ions such as palladium, yielding stability and solubility of coordinated compounds. The linear aliphatic amines, in particular, are recognized to highly have a conformational freedom, and conveniently, they could be designed for displaying suitable flexibility and polydenticity features, which constitute an advantage for an efficient interaction with metal ions and biological receptors [17]. In fact, the high conformational freedom and the dual hydrophilic-lipophilic character of the amine or Schiff bases ligands, comprising both cationic amine and imine groups and variable length hydrophobic alkyl linkers allow these metal complexes to interact with DNA through a nonconventional way both covalently (through direct binding of the metal center to the purine bases) and non-covalently (via hydrophobic and hydrogen-bonding close contacts).

Studies of palladium complexes with biologically active carriers are yielding promising results in the field of anticancer chemistry. Many reports have been demonstrated some complexes which contain Schiff base or ferrocenyl derivatives are highly active against several diseases including cancer [18-20].

2. Experimental

2.1. Instrumentation

Elemental analyses were performed by University of AL al-Bayt, Al-Mafraq, Jordan using a Euro vector EA 3000A Elemental Analysis (Italy). Infrared (IR) spectra were recorded for KBr pellets on a FT-IR spectrophotometer Shimadzu model 8400S in range 4000-400 cm^{-1} at Department of Chemistry, College of Education for Pure Science, University of Basrah. UV-Vis spectra for the synthesized complexes were recorded at Department of Chemistry, College of Science, University of Basrah by using Scan 80D (England) at range 200-800 nm using chloroform as a solvents and 1 cm^3 pathway quartz cells. ^1H nuclear magnetic resonance (NMR) spectra were recorded at Al al-Bayt University, Jordan, by using a Bruker 300 MHz (Germany). Chemical shift of all ^1H NMR spectra were recorded in δ (ppm) unit downfield from the internal reference tetramethylsilane (TMS), using dimethylsulfoxide DMSO-d_6 solvent. Conductivity measurements were measured in 1×10^{-3} M solutions of dimethyl sulfoxide (DMSO) solvent at room temperature using a Konduktoskop model 365B using standard conductivity cell with constant equal to 0.81 cm^{-1}.

2.2. Synthesis

N-(3-Phenylpropyl)ethane-1,2-diamine, *N*,*N*'-*bis*(3-phenyl propyl)ethane-1,2-diamine, *N*-2-furan methyledinebenzene-1,2-diamine, *N*,*N*'-*bis*(2-furanmethyledine)benzene-1,2-diamine, *N*-ferrocenmethyledinebenzene-1,2-diamine, *N*,*N*'-*bis*(ferrocenmethyledine) benzene-1,2-diamine, *N*-1-ferrocenethyli denebenzene-1,2-diamin, *N*,*N*'-*bis*(ferrocenethylidene) benzene-1,2-diamine were prepared in our previously paper [21]. Dichloro-*bis*(benzonitrile)palladium(II) was prepared by the literature method [22].

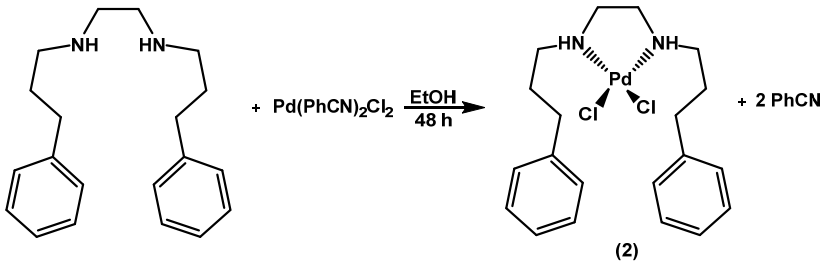
2.2.1. Synthesis of complexes

2.2.1.1. Synthesis of dichloro[N-(3-phenylpropyl)ethane-1,2-diamine]palladium(II) (1)

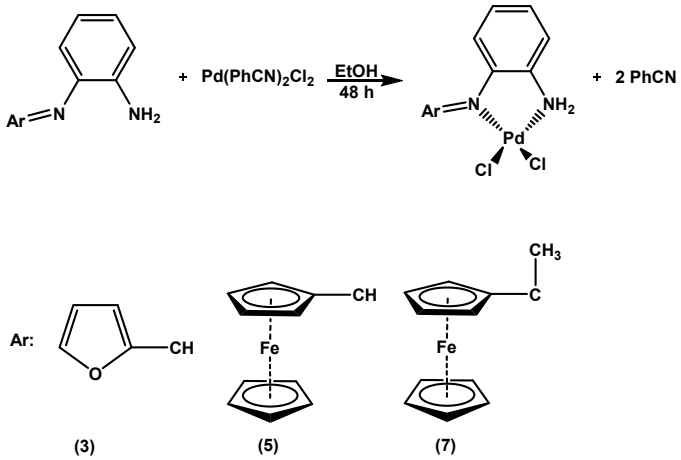
To dibenzonitriledichloro palladium(II), $PdCl_2(PhCN)_2$, (0.383 g; 1 mmol) (15 mL), *N*-(3-phenylpropyl)ethane-1,2-diamine (0.355 g, 1 mmol) dissolved in absolute ethanol (15 mL) was slowly added. After stirring 48 h at room temperature, the product was isolated by filtration. Then, the solid product was washed with water, ethanol, and finally, dried in vacuum (Scheme 1). Color: Pale yellow. Yield: 62%. M.p.: 75-77 °C. FT-IR (KBr, ν, cm^{-1}): 3346 , 3066, 2929, 2861, 1494, 1454, 1239, 752, 686, 666. ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.14 (t, 2H, CH_2Ph), 1.80 (q, 2H, $CH_2CH_2CH_2$), 2.60 (t, 2H, $CH_2CH_2CH_2NH$), 3.79 (t, 2H, $CH_2CH_2NH_2$), 4.46 (t, 2H, $CH_2CH_2NH_2$), 5.80 (s, 1H, NH), 5.90 (s, 2H, NH_2), 7.19-7.35 (m, 5H, Ar-H). Anal. calcd. for $C_{11}H_{18}Cl_2N_2Pd$: C, 37.15; H, 5.10; N, 7.88. Found: C, 37.17; H, 5.19; N, 7.91%. Λ_m ($ohm^{-1}.cm^2.mol^{-1}$): 7.91.

2.2.1.2. Synthesis of dichloro[N,N'-bis(3-phenylpropyl) ethane-1,2-diamine]palladium(II) (2)

To a stirring solution of dibenzonitriledichloropalladium (II), $PdCl_2(PhCN)_2$, (0.383 g, 1 mmol) in absolute ethanol (15 mL) with *N*,*N*'-*bis*(3-phenylpropyl)ethane-1,2-diamine (0.489 g, 1 mmol) in 25 mL of absolute ethanol were stirring for 48 h at room temperature , and a brown precipitate had formed. The crude solid was filtered, washed with water, ethanol, and dried *in vacuum* to afford the complex **2** (Scheme 2). Color: Orange solid. Yield: 71%. M.p.: 90-92 °C (dec.). FT-IR (KBr, ν, cm^{-1}): 3390, 3022, 2924, 2854, 1496, 1452, 1266, 750, 698, 617. ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.23 (t, 4H, $2CH_2Ph$), 1.79 (qu, 4H, 2 $CH_2CH_2CH_2$), 2.60 (t, 4H, 2 $CH_2CH_2CH_2NH$), 3.01 (t, 4H, 2 CH_2NH), 5.95 (s, 2H, 2NH), 7.10-7.40 (m, 10H, Ar-H). Λ_m ($ohm^{-1}.cm^2.mol^{-1}$): 5.10.



Scheme 2



Scheme 3

Anal. calcd. for $C_{20}H_{28}Cl_2N_2Pd$: C, 50.70; H, 5.96; N, 5.91. Found: C, 50.65; H, 5.87; N, 5.88%.

2.2.1.3. Synthesis of dichloro[N-(2-furanmethyledine) benzene-1,2-diamine]palladium(II) (3)

To a freshly prepared absolute ethanol (15 mL) solution of $PdCl_2(PhCN)_2$ (0.383 g, 1 mmol) was added *N*-(2-furfuraly dine)benzene-1,2-diamine (0.377 g, 1 mmol). The mixture was stirred at room temperature for 48 h. A dark brown participate was formed and was collected by filtration. The solid product was recrystallized by chloroform to afford the complex **3** (Scheme 3). Color: Dark brown. Yield: 60 %. M.p.: 129-131 °C (dec.). FT-IR (KBr, ν, cm^{-1}): 3359, 3068, 2926, 2852, 1656, 1500, 1454, 1234, 746, 673, 602. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.38-7.78 (m, 7H, Ar-H), 8.45 (s, 1H, CH=N), 8.81 (s, 2H, NH_2). Anal. calcd. for $C_{11}H_{10}Cl_2N_2OPd$: C, 36.34, H, 2.77; N, 7.71. Found: C, 36.34; H, 2.50; N, 7.73%. Λ_m ($ohm^{-1}.cm^2.mol^{-1}$): 5.40.

2.2.1.4. Synthesis of dichloro[N,N'-bis(2-furanmethyledine) benzene-1,2-diamine]palladium (II) (4)

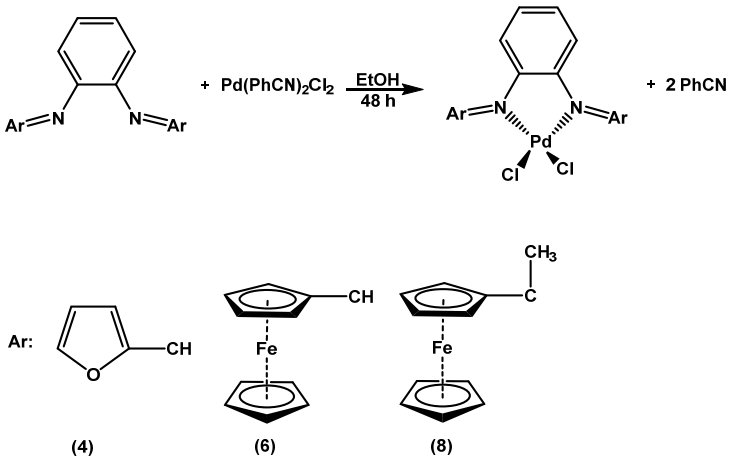
To an absolute ethanol solution of $PdCl_2(PhCN)_2$ (0.383 g, 1 mmol) was *N*, *N*'-*bis*(2-furfuralydine)benzene-1, 2-diamine (0.455 g, 1 mmol). The mixture was stirred at room temperature for 48 h. A brown participate was formed and was collected by filtration. The solid was then recrystallized from chloroform to afford complex **4** (Scheme 4). Color: Brown solid. Yield: 69 %. M.p.: 168-179 °C (dec.). FT-IR (KBr, ν, cm^{-1}): 3022, 2926, 2862, 1610, 1510, 1462, 1226, 748, 666, 602. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.38-8.02 (m, 10H, Ar-H), 8.66 (s, 2H, 2CH=N). Anal. calcd. for $C_{16}H_{12}Cl_2N_2O_2Pd$: C, 43.52; H, 2.74; N, 6.34. Found: C, 43.53; H, 2.78; N, 6.49%. Λ_m ($ohm^{-1}.cm^2.mol^{-1}$): 5.00.

2.2.1.5. Synthesis of dichloro[N-(ferrocenmethyledine) benzene-1,2-diamine]palladium(II) (5)

A filtered *N*-(ferrocenylidene)benzene-1,2-diamine (0.524 g, 1 mmol) dissolved into absolute ethanol (20 mL) was continuously added to a dissolved-$PdCl_2(PhCN)_2$ (0.383 g, 1 mmol) in absolute ethanol (15 mL) in stirring condition. After 48 h stirring at room temperature, a brown solid was formed. The solid product was purified by extraction with diethyl ether (5×4 mL), and then dried *in vacuum* (Scheme 3). Color: Orange. Yield: 67 %. M.p.: 115-117 °C (dec.). FT-IR (KBr, ν, cm^{-1}): 3350, 3030, 2930, 2853, 1656, 1566, 1462, 1274, 746, 666, 613. Anal. calcd. for $C_{17}H_{16}Cl_2N_2FePd$: C, 42.41; H, 3.35; N, 5.82. Found: C, 42.41; H, 3.39; N, 5.89%. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.20 (s, 5H, C_5H_5), 4.28 (d, 2H, H_2 and H_5), 4.35 (d, 2H, H_3 and H_4), 6.15-7.96 (m, 4H, Ar-H), 8.45 (s, 1H, CH=N), 9.09 (s, 2H, NH_2). Λ_m ($ohm^{-1}.cm^2.mol^{-1}$): 7.45

2.2.1.6. Synthesis of dichloro[N,N'-bis(ferrocenmethyledine) benzene-1,2-diamine]palladium(II) (6)

A filtered *N*, *N*'-*bis*(ferrocenmethyledine)benzene-1, 2-diamine (0.749 g, 1 mmol) dissolved in absolute ethanol (20 mL) was continuously added to $PdCl_2(PhCN)_2$ (0.383 g, 1 mmol) in absolute ethanol (15 mL) in stirring condition during 48 h at room temperature. As result, the orange solid was formed. The solid product was purified by extraction with diethyl ether (5×4 mL), and then dried *in vacuum* (Scheme 4). Color: Orange. Yield: 72 %. M.p.: 117-119 °C (dec.). FT-IR (KBr, ν, cm^{-1}): 3066, 2924, 2852, 1653, 1493, 1466, 1266, 772, 746, 666.



Scheme 4

^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.16 (s, 10H, 2×C_5H_5), 4.35 (d, 4H, 2H_2 and 2H_5), 4.85 (d, 4H, 2H_3 and 2H_4), 6.20-7.91 (m, 4H, Ar-H), 8.60 (s, 2H, 2×CH=N). Anal. calcd. for $C_{28}H_{24}Cl_2N_2Fe_2Pd$: C, 49.64; H, 3.57; N, 4.13. Found: C, 49.79; H, 3.68; N, 4.33%. Λ_m (ohm^{-1}.cm^2.mol^{-1}): 6.30.

2.2.1.7. Synthesis of dichloro[N-(1-ferrocenylethylidine) benzene-1,2-diamine]palladium(II) (7)

A mixture of *N*-(1-ferrocenylethylidine)benzene-1, 2-diamine (0.537 g, 1 mmol) and $PdCl_2(PhCN)_2$ (0.383 g, 1 mmol) in 30 mL of absolute ethanol was stirred at room temperature for 48 h. A brown precipitate was formed and then purified by extraction with diethyl ether (10 × 4 mL), and then dried *in vacuum* (Scheme 3). Color: Reddish brown. Yield: 64%. M.p.: 129-131 °C (dec.). FT-IR (KBr, ν, cm^{-1}): 3333, 3066, 2933, 2856, 1653, 1513, 1466, 1226, 759, 746, 666. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.50 (s, 3H, CH_3), 4.40 (s, 5H, C_5H_5), 4.71 (s, 2H, H_2 and H_5), 4.90 (s, 2H, H_3 and H_4), 6.55-7.68 (m, 4H, Ar-H), 9.54 (s, 2H, NH_2). Anal. calcd. for $C_{18}H_{18}Cl_2N_2FePd$: C, 43.63; H, 3.66; N, 5.65. Found: C, 43.79; H, 2.65; N, 4.90%. Λ_m (ohm^{-1}.cm^2.mol^{-1}): 8.50.

2.2.1.8. Synthesis of dichloro[N,N'-bis(1-ferrocenyl ethylidine)benzene-1,2-diamine]palladium(II) (8)

A mixture of *N*,*N*'-*bis*(1-ferrocenylethylidine)benzene-1,2-diamine (0.775 g, 1 mmol) and $PdCl_2(PhCN)_2$ (0.383 g, 1 mmol) in 30 mL of absolute ethanol was stirred for 48 h at room temperature. A brown solid was obtained and purified by extraction with diethyl ether (10×4 mL) and then dried *in vacuum* (Scheme 4). Color: Brown solid. Yield: 60%. M.p.: 91-93 °C (dec.). FT-IR (KBr, ν, cm^{-1}): 3092, 2933, 2853, 1653, 1458, 1375, 1280, 693, 666, 626. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.98 (s, 6H, 2CH_3), 4.40 (s, 10H, 2×C_5H_5), 4.71 (s, 4H, 2H_2 and 2H_5), 4.92 (s, 4H, 2H_3 and 2H_4), 6.60-7.49 (m, 4H, Ar-H). Anal. calcd. for $C_{30}H_{28}Cl_2N_2Fe_2Pd$: C, 51.07; H, 4.00; N, 3.97. Found: C, 51.06; H, 4.19; N, 4.00%. Λ_m (ohm^{-1}.cm^2.mol^{-1}): 8.40.

2.3. Antimicrobial activity

For all biological experiments, stock solution of compounds **1-8** (1000 µg/mL) were prepared as follow: For Pd(II) complexes, DMSO was used as a solvent to prepare their stock solutions (the final concentration of the solvent should be 1 %). *In vitro* antibacterial screening is generally performed by the agar diffusion method for testing antibacterial activity of the prepared palladium(II) complexes (Table 1). This method includes agar well diffusion assay and disc assay. In this test, the antimicrobial compound is applied to an agar plate on a paper disc or in a well. The compound diffuses into agar resulting in a concentration gradient that is inversely proportional to the distance from the disc or well. The diameter of the inhibition zone around the disc or well is a measure of the degree of degree of inhibition. The resulting of the tests are mostly qualitative [23]. For antimicrobial activity, compound stock solutions (1000 µg/mL) from which, serial dilutions of work concentrations were diluted sufficiently for this assay with sterilized water to avoid solvent interferences. The solvent was used as a negative control in each separated assay. The primary screening of antibacterial activity of the palladium(II) complexes compared to *cis*-platin were determined at concentration of 250 µg/disc against to Gram-positive (*Staphylococcus aureus* (ATCC 25923)), and Gram-negative (*Eschericha coli* (ATCC25922)) bacteria as described by the disc diffusion method [23]. Whatman no.4 filter paper was used for the preparation of diffusion disc (7 mm in diameter) and the discs were saturated with Pd(II) complexes and other standard complexes at a concentration of 250 µg/mL. The medium used in this respect was nutrient agar, the plates were inoculated with tested bacteria, and the complexes-impregnated disc was a specially placed on the agar surface, and the plates were incubated for 24 hrs, zone diameter were measured, and the results were compared with *cis*-platin.

2.3.1. In vitro antimicrobial activity

1-2 mL of nutrient broth was inoculated with the test organisms and incubated at 37 °C for 24 hr. Sterile nutrient agar plates were also prepared and holes of 5 mm diameter were cut. The test organisms after 24 hr of incubation were spread onto separate agar plates. The compounds which dissolved in DMSO were poured into labeled holes. The plates of each bacterial strain were prepared. The plates were incubated aerobically at 37 °C for 24 hr. The antimicrobial activity was determined by measuring the diameter of the zone (mm) showing a complete inhibition with respect to control (DMSO).

2.4. DNA concentration

DNA concentration per nucleotides was determined by electronic absorption spectroscopy at λ_{max} = 260 nm in human blood, and each 1 absorption unit (AU) = 50 µg DNA/mL at 258 nm.

2.4.1. Study of palladium (II) complexes-human DNA interaction

The binding of the prepared palladium(II) complexes **1**-**8** with DNA were studied by following of the change of their absorbance (concentrations) over time with U.V.-Visible spectroscopy technique as following: (i) Absorbance of DMSO solutions (80 µM) of complexes **1**-**8** were measured at 200-800 nm. (ii) Absorbance of mixture (0.1 mL of human DNA and 3 mL of 80 µM of the prepared complexes **1**-**8**, respectively) were measured at 200-800 nm range at different period of time (*i.e.* at time = 0, 1, 2, and 24 h) (Table 2) [24].

2.4.2. Extraction of Human DNA

Human DNA was extracted from human blood by Sambrook method [25]: To special test tube containing 1.0 mL of human blood, 0.6 mL of RBC buffer was added, and then the result mixture was centrifuged at 5000 cycle/min for 15 min repeatedly. Several times and then the white precipitate were obtained. To the formed precipitate though, a mixture of 0.6 mL of sodium dodecyl sulfate and 0.03 mL of proteinase K and 0.03 mL of NLB was added, then after that it was occupied in water bath at 65 °C for 2h. After the incubating time was ended up, 0.1 mL of 5 M NaCl solution was added and re-incubated in water bath at 65 °C for 10 min. After that, 0.75 mL of chloroform-isopropyl alcohol (24:1) was added for every sample, and then it was centrifuged at 12000 cycle/min for 8 min. Therefore, three layers were obtained, the upper layer was selected and then 0.55 ml of cold absolute ethanol was added and was kept deep freezer at -20 °C.

3. Results and discussion

Eight complexes of palladium(II) were synthesized by reacting of dibenzonitrile dichloropalladium(II) with *N*-(3-phenyl propyl)ethane-1, 2-diamine, *N*, *N*'-*bis*(3-phenylpropyl) ethane-1, 2-diamine, *N*-2-furan methyledinebenzene-1, 2-diamine, *N*, *N*'-*bis*(2-furanmethyledine)benzene-1, 2-diamine, *N*-ferrocen methyledinebenzene-1,2-diamine, *N*, *N*'-*bis*(ferrocene methyledine)benzene-1, 2-diamine, *N*-1-ferrocenethylidene benzene-1, 2-diamin, *N*,*N*'-*bis*(ferrocenethylidene) benzene-1,2-diamine, respectively, in absolute ethanol at room temperature for 48 h, Scheme 1-4.

In general, all the prepared palladium(II) complexes **v1**-**8** are pale yellow to orange solids with moderate melting points (Dec.) ranged at 75-168 °C, and they are soluble in common organic solvents like carbon tetrachloride, chloroform, dichloromethane, dimethylformamide and dimethylsulfoxide which indicate that these complexes are neutral.

The carbon, hydrogen, and nitrogen analyses for palladium(II) complexes **1**-**8** agreed well with the calculated values. Elemental analysis of these complexes showed that all the palladium(II) ion to the ligand ratio in the dichloro complexes is 1:1. Due to geometrical reasons and the nature of ligands which are bidentate, we believe that all the synthesized complexes adapted to *cis*-form.

The molar conductivities were measured for the complexes **1**-**8** in 1×10^{-3} M solutions of DMSO solvents at room temperature. The molar conductance of complexes **1**-**8** were found at range 5.00-8.50 $ohm^{-1}.cm^2.mol^{-1}$. This indicates that these complexes behave as non-electrolytes which are in agree well with previous literatures [26].

The IR spectra of all new synthesized complexes **1**-**8** display common feature in certain region and characteristic bands in the fingerprint and other regions. The IR spectra of complexes **1**, **2**, **3**, **5** and **7** show a broad band at 3333-3390 cm^{-1} range which attributed to N-H stretching [27,28]. The shift was observed toward low frequency for amino groups than the free ligands [21] at range 8-58 cm^{-1} due to the coordination of the palladium(II) ion with the amino groups. The IR spectra of complexes **3**-**8** indicate a strong band at 1610-1656 cm^{-1} attributed to CH=N stretching [27,28]. This band shifted to higher frequency at range 9-45 cm^{-1} compared with the corresponding ligands could be considered as coordinated azomethine groups in these ligands with palladium ion [27,28]. These shift can be attributed to the π-back donation between empty π* of CH=N and *d*-orbitals of palladium(II) ion. Two strong bands appeared at the range1458-1566 and 1375-1466 cm^{-1} which reveal that they attributed to asymmetrical and symmetrical stretching of aromatic C=C, respectively [27,28]. The IR spectra of complexes **1**-**8** show a weak band in the range 3022-3092 cm^{-1} due to aromatic C-H stretching [28,29]. Two weak bands were appeared at 2924-2933 and 2853-2862 cm^{-1} due to asymmetrical and symmetrical stretching of aliphatic C-H bands, respectively [28,29]. Furthermore, three variable bands between 695-772 cm^{-1} range can be assigned to aromatic C-H bending while the band at 1226-1280 cm^{-1} due to aliphatic C-H bending [27,28]. Two well defined bands were appeared at range 628- 620 cm^{-1} can be assigned to ν(Pd-N) which are confirm that palladium ion coordinate to the corresponding ligand through nitrogen atoms of amine and imine groups and in cis geometry [30,31].

The UV-visible spectra of all palladium(II) complexes **1**-**8** were recorded at 1×10^{-4} M solution of DMSO solvent at range 200- 800 nm by using quartz cells. The UV-Vis. spectra for complexes **1** and **2** showed one absorption region at 300 nm with molar extinction ranged (ε = 1050-1820 $M^{-1}.cm^{-1}$) which may be attributed to π-π* transition of phenyl group [32,33]. The UV-Vis. spectra for palladium(II) complexes **3**-**8** showed three electronic transitions, the first band appeared at range 300-312 nm with molar extinction ranged 2280-6100 $M^{-1}.cm^{-1}$ might be attributed to π-π* transition of phenylene group [32,33]. The second band was observed at range 322-390 nm with molar extinction 2670-4011 $M^{-1}.cm^{-1}$ which is due to π-π* transition of the aromatic rings (for instance likely furan ring for complexes **3** and **4**; ferrocenyl groups for complexes **5**-**8**) [32-35]. The third band was observed between 450 and 460 nm (ε = 2409-4041 $M^{-1}.cm^{-1}$) which is attributed to π-π* of the azomethine (CH=N) groups [32-34]. The azomethine band were observed to be red shifted at range 14-30 nm comparatively to complexes **3**-**8** with the corresponding ligands which can be attributed to coordinate this groups with palladium(II) ion. No *d*-*d* transitions were observed for all complexes **1**-**8**, this may be due to their overlap with π-π* transition of the phenylene group which lead to masked it.

The ^{1}H NMR spectra of all the synthesized complexes **1**- **8** were taken in DMSO-d_6 solvent. In general, ^{1}H NMR spectra of the recorded complexes show the expected signals in proper intensity ratio. The ^{1}H NMR spectra of palladium(II) complexes **1** and **2** display singlet signal in the range between δ 5.80 and 5.95 ppm due to protons of N-H [36]. These protons shifted toward higher chemical shift (downfield) compared to their free ligands [21] at range δ 1.05-1.34 ppm, which are confirm the coordination between palladium(II) ion with corresponding ligands through nitrogen atoms of amine groups. Due to phenyl group, the protons were found in their expected regions as multiple signals at δ 7.10-7.40 ppm [35,36]. Also, ^{1}H NMR spectra of complexes **1** and **2** show several signals at range δ 1.14 - 3.41 ppm due to different methylene groups CH_2. On the other hand, the ^{1}H NMR spectra of complexes **3**-**6** showed a singlet signal in the range between δ 8.45 and 8.66 ppm which-may be attributed to the imines protons CH=N [35-37]. These signals also shifted toward higher chemical shift (downfield) than their free ligands signals at the range δ 0.10-0.44 ppm which indicate an evidence of coordinated palladium(II) ion with the corresponding ligand via nitrogen atom of azomethine groups. ^{1}H NMR spectra of complexes **3**, **5** and **7** showed a singlet signals at δ 8.81, 9.09, 9.54 ppm, respectively, which were pointed out by protons of terminal amine group NH_2 [35].

Table 1. *In vitro* antibacterial activity and minimum inhibitory concentration (MIC) values of the palladium(II) complexes and *cis*-platin against *Staphylococcus aureus* and *Escherichia coli bacteria*.

Complex	Concentration (µg/mL)								MIC
	250	200	150	100	50	25	10	1	
Staphylococcus aureus									
1	28	24	17	13	7	NI	NI	NI*	50
2	27	23	15	12	5	NI	NI	NI	50
3	34	30	21	15	11	7	NI	NI	25
4	32	30	19	14	9	5	NI	NI	25
5	50	43	34	28	20	13	9	7	1
6	38	28	20	17	13	10	5	NI	10
7	48	40	34	28	19	11	6	NI	10
8	47	36	28	20	11	8	NI	NI	25
Escherichia coli									
1	12	8	NI	NI	NI	NI	NI	NI	200
2	8	5	NI	NI	NI	NI	NI	NI	200
3	17	14	11	8	NI	NI	NI	NI	100
4	14	12	10	8	NI	NI	NI	NI	100
5	40	32	26	18	13	9	6	NI	10
6	21	17	14	10	7	NI	NI	NI	50
7	35	26	17	12	8	6	NI	NI	25
8	18	15	13	9	6	NI	NI	NI	50
cis-Platin	28	21	18	13	9	7	NI	NI	25

* NI: No inhibition.

Table 2. Molar absorptivity of complexes **1**-**8** with human DNA at different times.

Complex	Absorbance				
	T = 0	T = 1 min	T = 1 h	T = 2 h	T = 1 week
1	1.561	1.307	1.180	1.090	1.000
2	1.742	1.509	1.400	1.302	1.211
3	1.900	1.633	1.500	1.400	1.300
	1.730	1.550	1.459	1.360	1.270
4	1.716	1.455	1.350	1.263	1.140
	1.520	1.377	1.277	1.200	1.120
5	1.888	1.525	1.420	1.310	1.219
	1.639	1.500	1.400	1.302	1.223
	1.750	1.537	1.426	1.343	1.240
6	1.747	1.500	1.400	1.300	1.215
	1.600	1.450	1.345	1.271	1.205
	1.650	1.510	1.411	1.318	1.241
7	1.833	1.527	1.430	1.311	1.221
	1.690	1.424	1.300	1.300	1.155
	1.740	1.534	1.430	1.333	1.237
8	1.880	1.530	1.430	1.330	1.240
	1.700	1.500	1.400	1.300	1.210
	1.727	1.521	1.432	1.349	1.255

Multiple signals were observed at ^{1}H NMR spectra of complexes **3**-**8** between the range of δ 6.20 and 8.02 ppm designed by aromatic protons [35-37]. On the other hand, the complexes which contain ferrocenyl moiety (*i.e.* complexes **5**-**8**) showed all the expected proton signals which are in a good agreement with the previously literatures [35-38]. These spectra showed a singlet signal in the range δ 4.16-4.40 ppm attributed by protons of unsubstituted cyclo-pentadienyl ring because all these protons are magnetically equivalent. The substituted cyclopentadienyl ring appeared two singlet singles at the ranges δ 4.28-4.71 ppm due to (H2 and H5); while the second signal at the range δ 4.35-4.92 ppm due to H3 and H4. These protons shifted downfield because increasing the resonance due to the coordination between the corresponding ligands and the palladium ion. Furthermore, ^{1}H NMR spectra of complexes **7** and **8** showed a singlet signal at δ 2.50 and 2.98 ppm, respectively attributed to methyl group with only a minor shift for this signal could be observed compared with the corresponding free ligands [21].

In vitro, antibacterial screening was performed by the disc diffusion method against two types of bacteria: Gram positive *Staphylococcus aureus* (ATCC 25923) and Gram negative *Escherichia coli* (ATCC 25922) bacteria for the primary selection of the complexes as a therapeutic agents and compared with commercial drug, *cis*-platin. The results of antibacterial activity of Pd(II) complexes were at 250 µg/mL and minimum inhibitory concentration (MIC) define as the lowest concentration of the compound in a medium without visible growth of the test organisms in concentration ranging from 1-250 µg/mL are shown in Table 1.

In fact, the results of this study indicate that all palladium(II) complexes have variable antibacterial activity against both *Staphylococcus aureus* and *Escherichia coli* bacteria. In comparison with the ligands [21], the palladium(II) complexes were found to be more antimicrobial activity. In general, the results of screening show that most of palladium(II) complexes which contain imino groups complexes **3**-**8** are more antibacterial active than those which contain amine groups complexes **1** and **2**. On the other hand, the antibacterial activity of palladium(II) complexes which contain ferrocenyl moiety, and have a better activity against both *Staphylococcus aureus* and *Escherichia coli bacteria*, in particular the complex **5** showed a maximum activity against tested bacterial strains, whereas complex **4** which contain furan moiety has worst against them. Finally, based on antibacterial activity study, the palladium(II) complexes were actively ordered against both *Staphylococcus aureus and Escherichia coli bacteria* this way: **5** > **7** > **6** > **8** > **3** > **4** >**1** > **2**.

It is well known that the complexes containing Schiff base ligands tend to powerfully act as potent bactericidal agents to kill microorganisms. This is due the fact that the metal has partially positive charge coordinate with the donor atom of ligand as well as there is π-electron delocalize over the whole chelate ring. As a result, this increases the lipophilic character of the metal chelate, which favors its permeation through the lipoid layers of the microorganism membranes. In addition, other factors such as solubility conductivity and dipole

moment may also be the possible reasons of increasing activity.

The interaction between the prepared complexes **1**-**8** and human DNA was studied by using UV.-visible spectroscopy. The change complexes' concentrations (2 mL of 80 µM) with the time (0, 1, 2, 24 h and 1 week) were followed by adding the human DNA (2 mL of 80 µg). These data confirm the interaction between the complexes **1**-**8** and human DNA by decreasing the band absorbance, Table 2, Figure 1 (as an example).

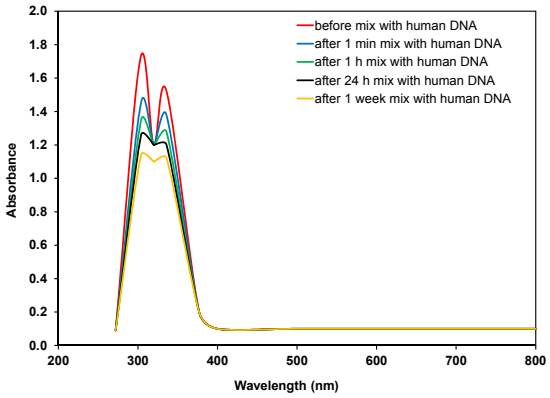


Figure 1. UV-Visible spectrum of complex **1** with human DNA at different times.

4. Conclusions

In summary, we have prepared eight of bidentate amine and Schiff base palladium(II) complexes. The resulting complexes assume a neutral square planar configuration in *cis*-form. We are examining the biological activity for antibacterial activity of all the prepared complexes **1**-**8** beside their interaction with human DNA. The antibacterial activity of compounds **1**-**8** against two types of bacterial: the first negative towards Gram stain (*Escherichia coli*) and against positive towards Gram stain (*Staphylococcus aureus*) was tested. These data proved that all palladium(II) complexes show a significant antibacterial activity for growth inhibition of *Staphylococcus aureus* and *Escherichia coli* bacteria. Antibacterial activity of all palladium(II) complexes show slightly active against Gram negative bacteria and has a better activity against Gram positive bacteria which complex **5** showed a maximum activity against both tested bacteria strains 40 and 50 mm, respectively. On the other hand, DNA interaction study of complexes **1**-**8** with human DNA showed that all these complexes are binding with DNA which is enhances the probability of using these complexes as drug.

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