Research Article

Cyclopalladation of {$C_6H_5CH=CH-CH=N-C_6H_4-4$-I} Synthesis, Characterization and Biological Properties

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Abstract

Treatment of novel Schiff base ligand ($C_6H_5CH=CH-CH=N-C_6H_4-4$-I) (**L**) with $Pd(OAC)_2$ resulted in the formation of dimeric acetato bridged cyclopalladated complex (**1**) with folded open book shape structure. Metathetical reaction of complex **1** with NaCl, NaBr and NaI produced the corresponding cyclopalladated halido bridged complexes (**2**), (**3**) **and (4**), respectively with unfolded planar structure. Bridge splitting reaction of complex **1** with pyridine gave the monomeric complex **(5)**. The newly synthesized compounds is characterized via micro analytical data, spectral tools (IR, electronic, Mass and ^{1}HNMR) spectroscopy .The thermal stability of some complexes is evaluated by thermal gravimetric analysis (TGA). The ligand and the complexes are tested as antimicrobial agents and showed variable activities as antibacterial and antifungal agents. Also, the ligand and its complexes were tested in vitro for their antitumor activity against MCF-7 tumor cell lines**.**

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Keywords: Cyclopalladation , Spectroscopy, Antimicrobial studies, Antitumor MCF-7 cell lines activity.

1. Introduction

Cyclopalladated complexes containing C,N chelating ligands have attracted more interest because of their applications in several fields as organic and inorganic synthesis **[1],**insertion **[2],**optical resolution **[3],**biological active compounds **[4,5]** and catalytic materials **[6,7].**It is worth noticing that in most cases cyclopalladation of Schiff base ligands to produce µ-acetato bridged cyclometallated Pd (II) complexes. Schiff-base palladacycles where metallation is directly produced at an aliphatic sp^2-carbon atom are Scarce, and to the best of our knowledge the examples that are known are derived from insertion reactions of a previously metallated aromatic carbon atom **[8, 9]**. Pd (II) complexes of various donor atom ligands posses anti-tumor and anti-viral, -malarial, -fungal and -microbial activities **[10].**

Breast cancer, as the second most lethal cancer in women worldwide, is a quite important public health problem **[11].** More importantly, the incidence of breast cancer is dramatically rising in recent years and an estimated 1.7 million women with breast cancer will be found in 2020 from the current levels **[12].** Invention of improved drugs become more and more urgent in breast cancer treatment, due to the fact that breast cancer cells can subsequently survive and gain resistance after initially effective chemotherapy **[13].** The estrogen receptor-positive MCF-7 cell, derived from a patient with metastatic breast cancer, was a prominent model system used to study breast cancer as it relates to the susceptibility of the cells to apoptosis **[14]**.The role of metal-based complexes in diagnosis, medicine, and chemotherapy has attracted considerable attention in the past decades **[15].**From this point of view, the present paper deals with the synthesis, characterization and biological evaluation of cyclopalladated complexes derived from new Schiff base ($C_6H_5CH=CH-CH=N-C_6H_4-4$-I).

2. Experimental

2.1 Materials and Reagents

Analytical reagent grade, Cinnamaldehyde , p-Iodo aniline, $Pd(OAC)_2$, NaCl, NaBr, NaI and Pyridine were used (from Merck and Aldrich). Organic solvents used (toluene, methylene chloride and acetone) were HPLC or extra-pure grade, and used without further purification.

2.2 Instruments

Percentage of C, H and N were determined in the Organic Microanalysis Section, National Research Center, Giza. Percentage of Palladium determined using Back Titration with EDTA. IR spectra were recorded using KBr pellets on a Perkin-Elmer 1430 Spectrometer for the region (200 – 4000 cm^{-1}) at the Faculty of Science, Tanta University. Electronic spectra were measured in UV−Vis range (195 – 1100 nm) using a Perkin-Elmer lambda 35 UV-Vis Spectrometer at the Faculty of Science, Al−Azhar University. The NMR spectra were record on GEMINI-200"NMR" Spectrometer at the Microanalysis Laboratory, Cairo University, Giza. The mass spectra were recorded on GC−MSA−QP 5050 A Shimadzu at the Microanalysis Laboratory,Cairo University, Giza. The thermo gravimetric analyses (TGA) were recorded on "TGA-50H" at the Microanalysis Laboratory, Cairo University, Giza. Antitumor activity experiments were carrid out at Center of the fungus and its applications, Al-Azhar University, Cairo, Egypt.

2.3 *Synthesis of Schiff base Ligand L*

The Schiff base **L** was prepared by addition of p-Iodo aniline(2.19 g, 0.01 mole) in 25ml toluene to magnetically stirred solution of cinnamaldehyde (1.32 ml, 0.01 mol) in 25ml toluene. The reaction mixture was refluxed with continuous stirring .The yellow solid obtained after 1h was filtered and washed for several times with toluene, acetone and diethyl ether, then air dried. The precipitate was recrystallized by petroleum ether. The purity of **L** was tested using TLC, showed one spot under UV254. M.p. 105 ^oC; M.Wt. 333; anal.calc. for $C_{15}H_{12}N$ I: C,54.05 ; H,3,60 ; N,4.20 %, Found: C, 54.12; H, 3.55; N, 4.33 %, main IR Peaks (KBr,cm^{-1}): ν(C=N)1618.

2.4 *Synthesis of cyclopalladated complexes*

2.4.1 *Synthesis of Complex 1*

Complex **1** was prepared by drop wise addition of a methylene chloride solution of $Pd(OAC)_2$ (0.2246 g, 0.001 mol) to a methylene chloride solution of the ligand **L** (0.333 g , 0.001 mole). The reaction mixture allowed to continuous stirring for 2h at 25^0C .The obtained precipitate was filtered and washed by methylene chloride and diethyl ether then recrystallized from Chloroform . Complex **1** is orange solid, soluble in most organic solvents, M.p. 190 ^oC; M.Wt. 995; anal.calc. for $C_{34}H_{28}Pd_2N_2O_4I_2$: C,41.00 ; H,2.81 ; N,2.81 ; Pd,21.38 %, Found: C, 41.11; H, 2.90; N, 2.87 ; Pd,21.23 % ; main IR Peaks (KBr,cm-1):, ν(C=N)1583.

2.4.2 *Synthesis of Complexes 2, 3 and 4*

These complexes were prepared by drop wise addition of aqueous solutions of NaCl, NaBr and NaI to a solution of complex **1** in acetone. The precipitates were immediately formed for complexes **2, 3** and **4**, respectively. The precipitates washed with hot water, acetone and diethyl ether then air dried.

Complex 2

Greenish-yellow solid, not soluble in most organic solvents and sparingly soluble in DMSO and DMF M.p. >300 ^oC; M.Wt. 965.8; anal.calc. for $C_{30}H_{24}N_2Pd_2I_2Cl_2O$: C, 37.23; H, 3.19; N, 3.57; Pd, 27.10 %, Found: C, 46.50 ; H, 3.00 ; N, 3.20 ; Pd,28.9 % ; main IR Peaks (KBr,cm^{-1}): ν(C=N)1588.

Complex 3

Gray solid, not soluble in most organic solvents and sparingly soluble in DMSO and DMF M.p. >300 ^{o}C; M.Wt. 1072.6; anal.calc. For $C_{30}H_{26}N_2Pd_2I_2Br_2O_2$: C, 33.85; H, 2.05; N, 2.61; Pd, 19.77 %, Found: C, 33.90; H, 2.10; N, 2.76; Pd, 19.66 %; main IR Peaks (KBr,cm^{-1}): ν(C=N)1584.

Complex 4

Black solid, soluble in most organic solvents M.p. > 300 ^{o}C; M.Wt. 1148; anal.calc. for $C_{30}H_{24}N_2Pd_2I_4O$: C, 31.35 ; H, 1.91 ; N,2.43 ; Pd,18.46 % ,Found: C,31.24 ; H,1.95 ; N,2.50 ; Pd,18.45 %, ; main IR Peaks (KBr,cm^{-1}): ν(C=N)1572.

2.4.3 ***Synthesis of Complex 5***

The solid complex was prepared by drop wise addition of a solution of pyridine in $CHCl_3$ to a solution of complex **1** in acetone, the precipitate immediately formed for complex **5**. The precipitate washed with hot water, acetone and diethyl ether then air dried. Complex **5** is brown solid, M.p. 160 ^{o}C; M.Wt. 473.9; anal.calc. for $C_{22}H_{21}N_2Pd\ Cl\ O_3$: C,55.70 ; H,4.43 ; N,5.90 ; Pd,22.45 %, Found: C, 54.50; H, 4.01 ; N,5.20 ; Pd,21.90 % ; main IR Peaks (KBr,cm^{-1}): ν(C=N)1594.

2.5 Antimicrobial activity

All the newly synthesized compounds were tested for their antibacterial and antifungal activity. The method used to evaluate the antimicrobial activity was diffusion method **[16]**, the diffusion method requires filter paper disk, the medium used is Muller – Hinton agar with 2% of glucose and diameter of inhibition zone is visually read at 24 hours after incubation at 37 ^{o}C. The compounds are added on the filter paper containing this medium. The antimicrobial activity was estimated on the seeded agar plates. Miphinicol was used as standard. DMSO was used as solvent control. The zones of inhibition based upon zone size around the discs were measured.

2.6 Antitumor assay

Human breast cancer cell lines (MCF7) cell lines were used for *in vitro* screening experiments. The cancer cells were obtained frozen from VACSERA Tissue Culture Unit, Cairo, Egypt and the experiments were carried out in Center of the fungus and its applications, Al-Azhar University. The cells were propagated in Dulbecco's modified Eagles medium (DMEM) supplemented with 10 % heat-inactivated fetal bovine serum, 1% L-glutamine, HEPES buffer and 50% µg/ml gentamycin. All cells were maintained at 37^{0} C in humidified atmosphere with 5% CO_2 and sub cultured two times a week .Cells were seeded in 96-well plates at a cell concentration of 1x10^{4} cell/well in 100 µl of growth medium. Fresh medium containing different concentrations of the test sample was added after 24h of seeding. Serial two-fold dilutions of the tested compounds were added to confluent cell monolayers dispensed into 96-well, flat-bottomd microtiter plates (Falcon,NJ,USA) using a multichannel pipette. The micro titer plates were incubated at 37^{0}C in a humidified incubator with 5% CO_2 for a period of 48h .Three wells were used for each concentration of the tested sample.Control cells were incubated without test sample and with or without DMSO. The little percentage of DMSO present in the wells (maximal 0.1%) was found not to affect the experiment. After incubation of the cells for 24h at 37^{0}, various concentrations of sample (50, 25, 12.5, 6, 25, 3.125&1.56 µg) were added, and the incubation was continued for 48h and viable cells yield was determined by colorimetric method, Growth inhibition of cells was calculated spectrophotometrically using a standard method with crystal violet solution (1%) **[17]**.The optical density (OD) of each well was measured at 490 nm with an ELIZA, plate reader. Cisplatin (Sigma) was employed as the standard antitumor drug.The percentage of cell survival was calculated as follows:

Survival fraction = OD (treated cells) / OD (control cells)

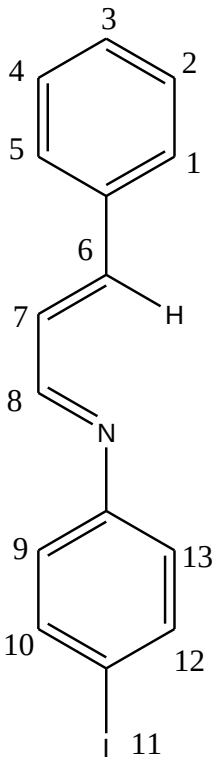
The IC_{50} value is the concentration required to productive 50% inhibition of cell growth. The results are compared with a similar run of *cis*-platin as an antitumor compound.

3. Results and Discussion

Condensation of cinnamaldehyde with *p*-iodo aniline in toluene afforded new Schiff base ligand **L**, **(Figure 1**) in high yield .The reaction of **L** with $Pd(OAc)_2$ in methylene chloride resulted in the formation of acetato bridged cyclopalladated complex **1** after activation of olefinic carbon (C6), **(Figure 2**)

Complex **1** shows a cis dimeric structure with folded open book shape structure. The ligand molecule acts as bidentate ligand through olefinic carbon atom (C6) and azomethine nitrogen atom. Metathetical reaction of complex **1** in acetone with aqueous solutions of NaCl, NaBr and NaI gave the corresponding chloro bridged **2**, bromo bridged **3** and iodo bridged **4** complexes with unfolded planar structure. Monomerization of complex **1** by the reaction with pyridine undergoes scission of the Pd_2X_2 unite to give mononuclear cyclopalladate **5**, (**Scheme.1**)

The level of the purity of the ligand and the complexes has been checked by running TLC on a silica gel coated plate using EtOAc–EtOH (6:4, v/v) as the eluent. The elemental analysis data of the Schiff base and its cyclopalladated complexes are agree well with the proposed structures.



(4-Iodo-phenyl)-(3-phenyl-allylidene)-amine

Figure 1 Structure of Schiff base ligand **L**

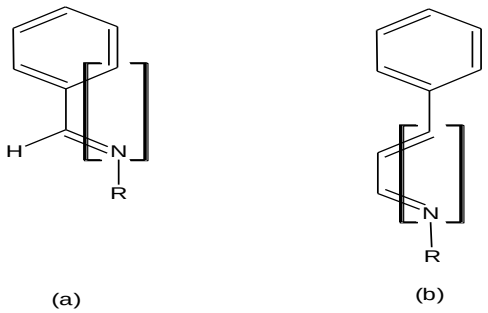
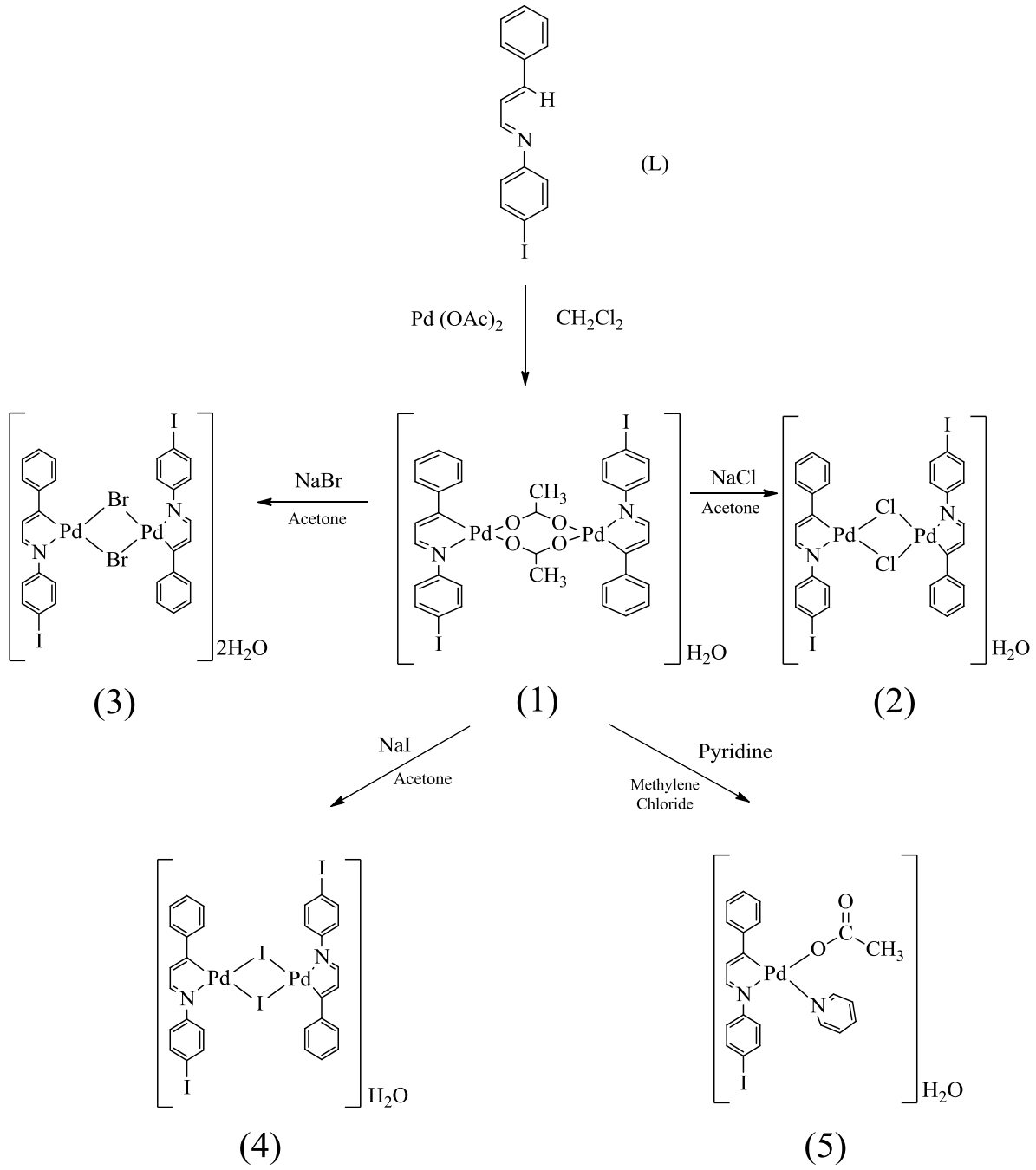


Figure 2 Metallation ligand atoms with C (sp^2) aromatic (a) and C (sp^2) olefinic (b) carbons.



Scheme 1 Cyclopalladation reactions of Schiff base (**L**)

3.1. Characterization of the ligand

The infrared spectrum of ligand **L**, exhibits absorption bands due to νC−H aromatic, νC−H olephinic, ν C=N and observed at 3071, 2859 and 1586 cm^{-1}, respectively. The ^{1}HNMR spectral study exhibits ABX Pattern for H_6−H_8 protons which appeared as doublet−triplet−doublet AB part (H6, doublet at б = 7.41,7.46 and H7, triplet at б =

7.15,7.19 and 7.23 ppm).while X−part (H8, doublet at ϭ = 8.43,8.48 ppm).The aromatic protons (H_1-H_5) show multiplet signals at ϭ = 7.26 – 7.35 ppm and (H_9−H_{12}) show $AA^{-}BB^{-}$ system at(AA^{-} 7.47 and 7,52 ppm)and (BB- 7.71 and 7,75ppm) (**Figure 3).**The electronic spectrum of **L** recorded in DMF solution shows absorption band at 413 nm which arises from a spin allowed n−Π* transitions. The bands below 300 nm are attributed to Π−Π* transitions of olefinic and aromatic systems. The mass spectrum of **L** shows the molecular ion peak at m/z= 333 which agrees with the molecular formula given.

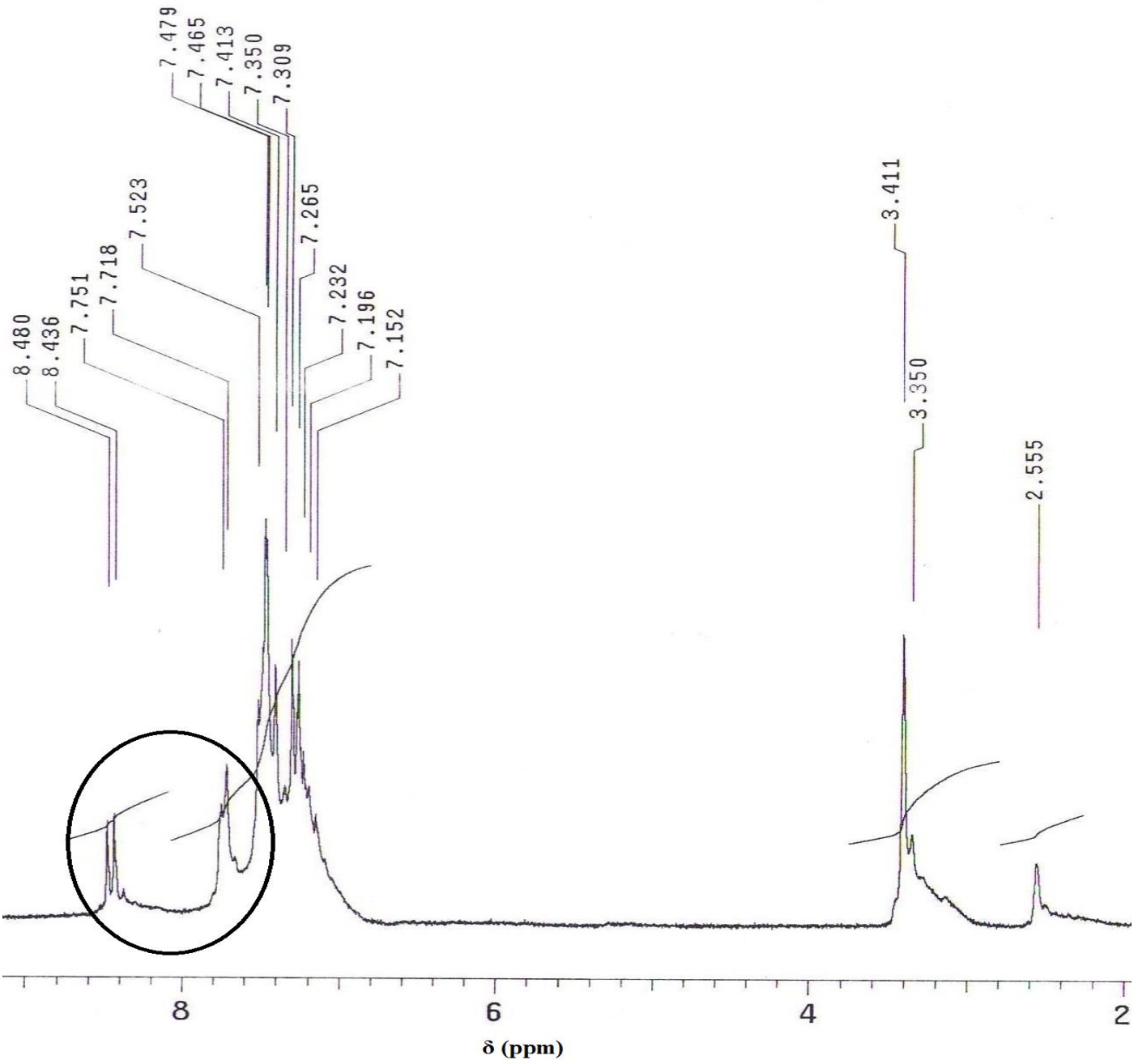


Figure 3 [1]HNMR spectrum of **L**

3.2. Characterization of cyclopalladated complexes

The cyclopalladated complexes display weak multiple bands in the range 3054−2840 cm^{-1} due to aromatic and aliphatic C−H stretches. All the cyclopalladated species display strong band in the range (1572−1594) cm^{-1}. This band is due to the azomethine fragment (−C=N) of the Schiff base. The shift of the C=N stretch to lower wave number as compared to that of the free ligand (1586) cm^{-1} is expected due to N coordination of the azomethine in all complexes **[18]**. The infrared spectrum of complex **1** exhibits the typical asymmetric and symmetric stretching modes of the acetato groups with strong absorption at 1583 and 1413 cm^{-1}. Δν of acetato bands indicate the presence of bridging mode **[19]**. The infrared spectrum of complex **2** shows two asymmetric ν Pd−Cl stretching absorptions at 339 and 308 cm^{-1} which give good evidence to the presence of chloro bridges. The ν Pd−Br (bridging) shows stretching absorption at 330 and 306 cm^{-1} in complex **3** and ν Pd−I (bridging) shows absorption at 321 and 300 cm^{-1} in complex **4**. The far infrared region of all complexes shows a medium intensity band in the range (533−585) cm^{-1}. This band is attributed to ν M−N, This band is observed as broad in the spectrum of complex **5** due to the vibrational coupling of two M−N bonds in this complex **[20]**. All complexes show strong band in the range 585−637 cm^{-1} due to ν Pd−C **[21]**. The ^{1}HNMR spectrum of complex **1** (**Figure 4)** shows the presence of a broadened signals in the aromatic region which can explain the folded open-book shape structure of this complex, the folded structure of the acetate bridged complexes caused the aromatic ring protons signals to be broadened , probably it is attributed to the anisotropic effect of the ring currents.

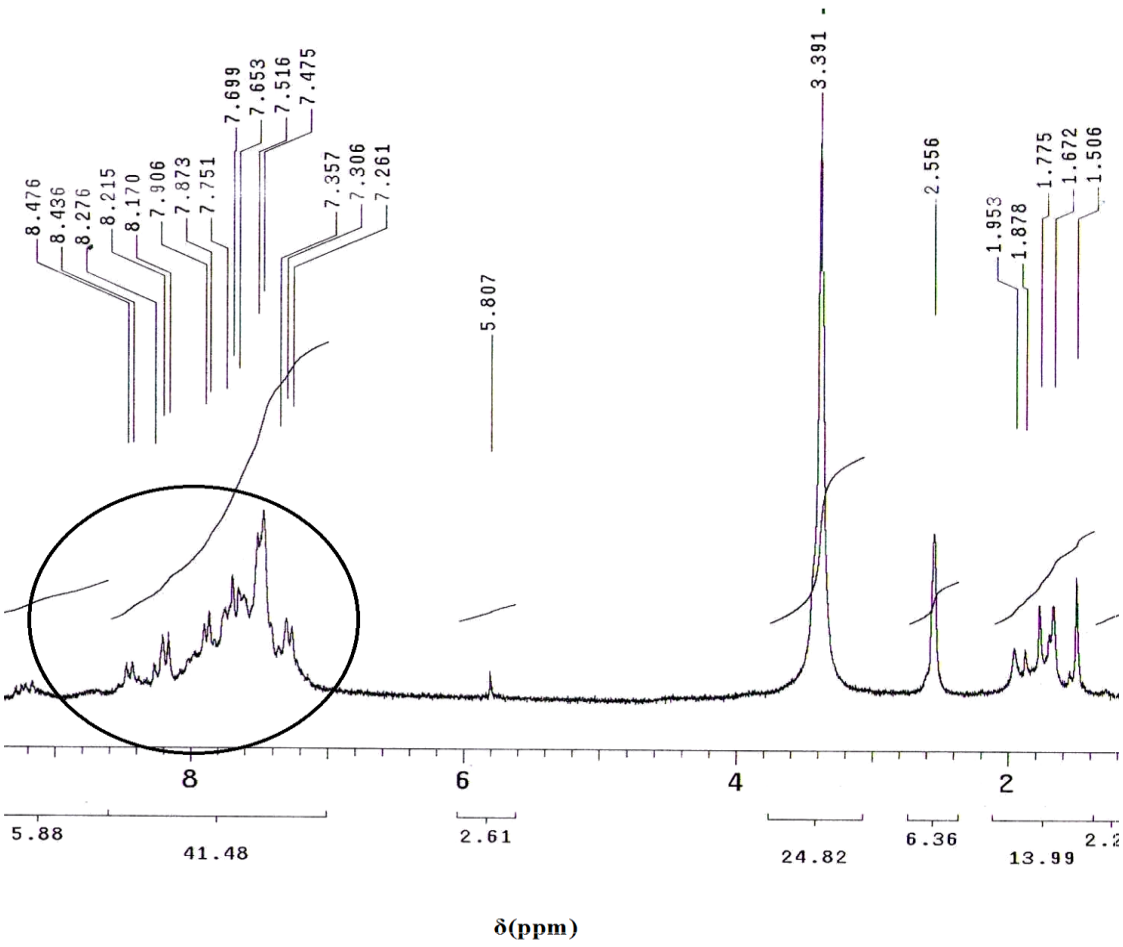


Figure 4 The ^{1}HNMR spectrum of complex **1**

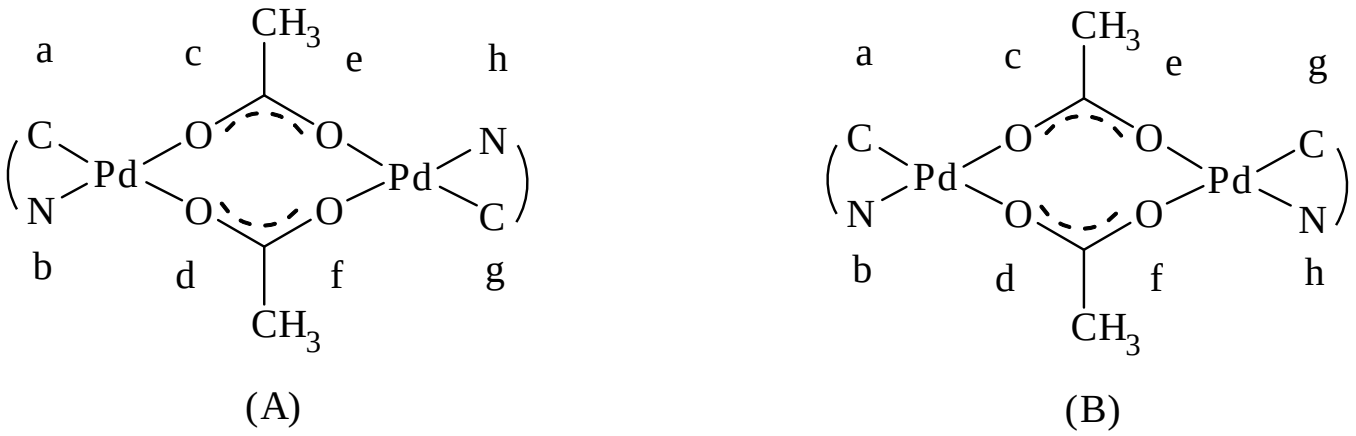


Figure 5 The geometrical isomers of complex **1**

There are two possible structures for the arrangement of the ligands in the acetates **[22]**, ab−hg type which the methyl protons are magnetically equivalent (**Figure 5.A)** and non-equivalent methyl protons in an ab − gh type (**Figure 5.B**). In case of ab-hg type, the magnetically equivalent methyl protons appear as sharp singlet in the range 1.8−2.2 ppm, but in case of ab-gh type, the nonequivalent methyl protons appear as two resonances at 1.12−2.2 ppm. The ^{1}HNMR spectrum of complex **1** shows cis arrangement of the ligand in the acetates, infreed from the acetate bridged methyl protons appearing as two signals at б=1.2 ppm and б=1.9 ppm, ascribable to ab-gh structural isomer. Metallation of ligand **L** through aliphatic carbon at C6 after deprotonation of H6 was observed from studying the ^{1}HNMR spectra of the ligand and its complexes. The absence of doublet – triplet – doublet due to the ABX system of the aliphatic chain AB part ,H6, doublet at б = 7.41,7.46 ppm and H7, triplet at б = 7.15,7.19 and 7.23 ppm. while X−part,H8,doublet at б = 8.43,8.48 ppm) which substituted by AB part, doublet of doublet (quartet) (H7,doublet at б=8.21 and 8.27 ppm) and (H8,doublet at б=8.43 and 8.47 ppm) the absence of signals at б=7.41,7.46 ppm due to (H6) which replaced with Pd.

The ^{1}HNMR spectra of the cyclopalladate species show down field shift of H7 to lower field in comparison with that in the free ligand which may be due to the flow of charge from the electron rich (d^8) metal bonding to the aromatic ring (π−back bonding). The electronic spectra of the cyclopalladate complexes were recorded in 800 – 200 nm in DMF and assigned on the basis of literature data **[23]**. The broad band in the visible region in 420 – 480 nm may be assigned to the charge from dπ (Pd) → metallated carbon **[24]**. Absorbtion below 400 nm are due to d−d spin allowed transition from the three lower lying'd' levels to the empty dx^2-y^2 orbital. The bands are attributed to $^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$, and $^1A_{1g} \rightarrow {}^1E_g$, transitions **[25]**. The electronic spectra as well as the diamagnetic behavior of the cyclopalladated complexes suggest the square planar arrangement of ligands around the palladium atoms.

3.3 Thermal studies

The thermal behaviors of complex **1** were studied by thermo gravimetric analysis (TGA) at the atmosphere of nitrogen with heating rate 10^{o}C/min between room temperature and 1000^{o}C. The correlation between the different decomposition steps of the complex with the corresponding weight losses are discussed in terms of the proposed formula of the complex. The representative thermo gram of complex (**1**) is depicted in (**Figure 6**). The TGA profiles over the temperature range 25−250 ^{o}C are usually duo to loss of water molecules. The complex has first decomposition stage in the range 35−250 ^{o}C. This dehydration process probably is due to the loss of water molecules resulted from the hydrated H_2O of the ionizable sphear, above 250 ^{o}C, the complex decompose in a gradual manner, which may be due to fragmentation and thermal degradation of the organic moiety. The continuous loss of weight is

observed up to 706 ^{o}C. The final solid product of thermal decomposition is identified as 2PdO. (Found; 27.02 %, Calc.; 26.20 %).

From above thermo gravimetric analysis, the overall weight losses for complex **1**, agree well with the proposed formula obtained by elemental analysis, IR, ^{1}HNMR, electronic and magnetic susceptibility measurements.

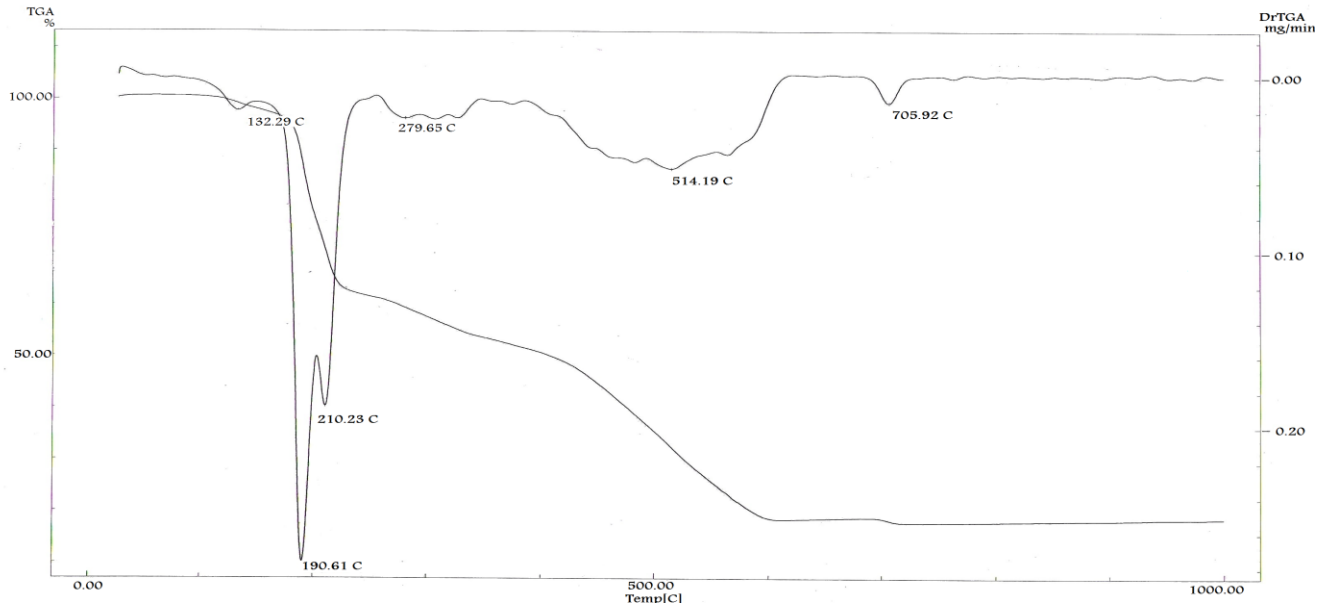


Figure 6 TG and DTG graph of complex **1**

4. Antimicrobial studies

The measured zone of inhibition against the growth of various microorganisms of the compounds is listed in **(Figure 7).** The results show a variable effect of the compounds on the microorganisms. The results showed that the ligand **L** exhibited the highest activity against all the tested fungi, Gram positive bacteria and (Salmonella typhimurium) as Gram negative bacteria. Complexes **5** and **1** showed activity against all the tested microorganisms. But, complex **5** shows higher inhibition zones against (Bacillus subtilis NCIB 3610), and (Salmonella typhimurium). While complex **2** showed more inhibition zone against (Staphylococcus aureus NCTC 7447) , (Candida albicans IMRU3669) and (Escherichia coli NCTC 10416). Complex **4** not only exhibits no activity against (Bacillus subtilis) and (Escherichia coli) but also it showed the lowest inhibition toward (Salmonella typhimurium), (Candida albicans) and (Aspergillus niger).

The variation in the activity of the compounds against the different microorganisms depends on the impermeability of the cell or differences in the ribosomes in the microbial cells **[26]**. The lipid membrane surrounding the cell favors the passage of any lipid soluble materials and it is known that lipophilicity is an important factor controlling antimicrobial activity **[27]**. The variation of the solubility of the compounds leads to the variation of lipophilicity of the compounds. Lipophilicity, which correlates well with the bioactivity of chemicals, is a very important molecular descriptor and different lipophilic behavior of compounds plays an important role in their biological activity mechanisms.

There are other factors which also increase the activity, which are solubility, conductivity and stability of the compounds. Stability depend on the bond length between the metal and the ligand, these factors may explain the

values resisted in the present case. It has also been proposed that concentration plays a vital role in increasing the degree of inhibition, as the concentration increases the activity increases **[28]**.

The high activity of the Schiff base ligand **L** may be due to the formation of a hydrogen bond through the azomethine nitrogene atom with the active centers of the cell constituents, resulting in interference with the normal cell process **[29]**, while in the complexes, the lone pair involved in complexation with metal ions. The high activity of complex **1** may be attributed to the delocalization of the π electrons of the ring of the acetate bridges and enhance the lipophilicity of the complex. This increased lipophilicity enhances the penetration of the complexes into lipid membrane and the blocks, the metal binding sites on enzymes of microorganisms **[30]**, and then it disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the organism **[31,32]**.

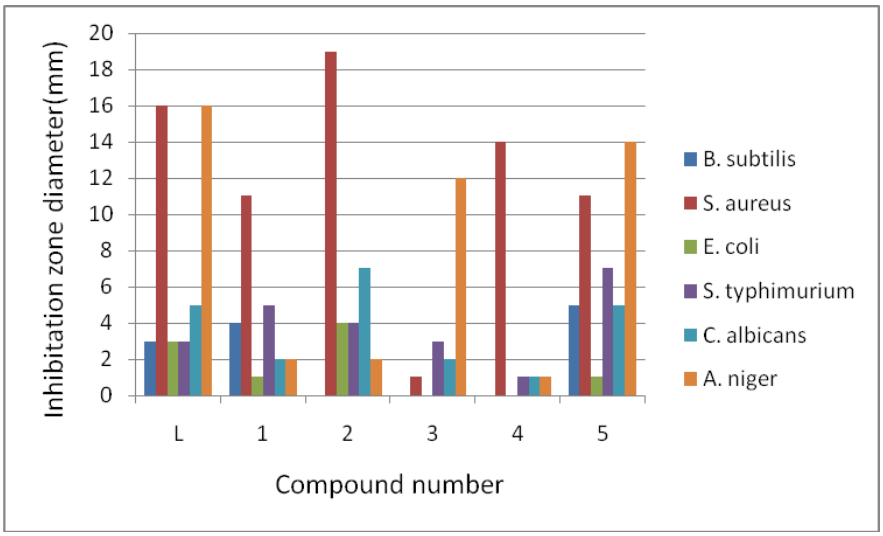


Figure 7 Chart of biological evaluation of ligand **L** and its complexes

5. Anticancer activity

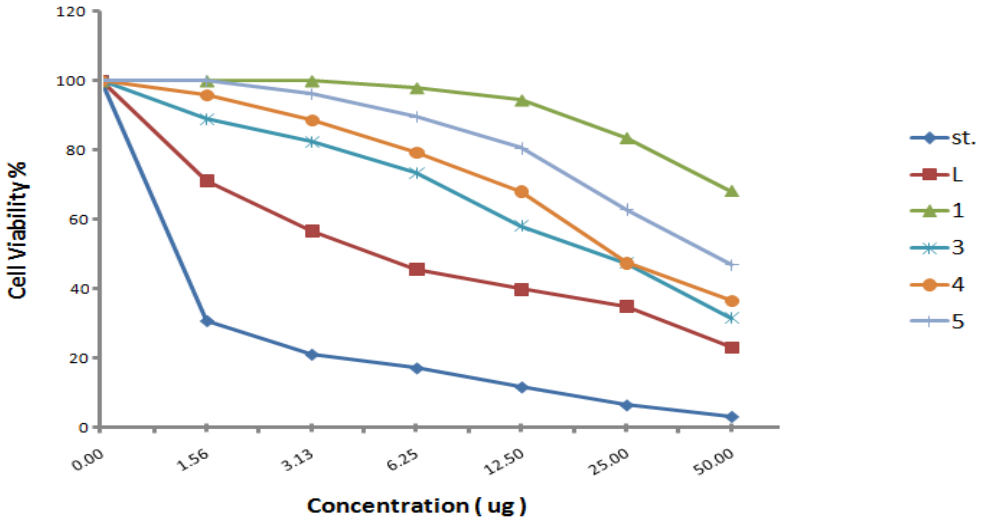


Figure 8 Chart of evaluation of cytotoxicity against MCF-7 cell line to ligand **L** and its complexes

Cyclopalladated compounds might have promising potential anticancer applications, since these planar metal complexes can lead to possible alternative modes of cytotoxic action, such as intercalative DNA lesion **[33,34]** ,square-planar metal complexes with aromatic ligands bind to DNA by intercalation **[35]**. The cytotoxicity activities of ligand **L** and its cyclopalladated complexes were tested against (MCF-7)human tumor cell lines. The reported results in terms of IC_{50} values are **5, 50, 21.9, 23.5 and 45.1** µg/ml for L**, 1, 3, 4** and **5**, respectively.(**Figure 8**). For comparison purposes, the cytotoxicity of cisplatin, as standard antitumor drug, was evaluated and produced IC_{50} value (6.7 µg/ml) under the same conditions.

Conclusions

Herein, the synthesis of five new cyclopalladated complexes by cyclopalladation , metathesis and bridge splitting reactions were reported. The aim was to prepare palladacycles by activation of a non-aromatic C-H bond, with displacement of hydrogen atom. For which purpose, the author chose Schiff-base ligand derived from cinnamaldehyde and *p*-chloro aniline. The evaluation of the antimicrobial activity of **L** and its cyclopalladated complexes showed variable activities as antibacterial and antifungal agents. The evaluation of the in vitro cytotoxic activity of **L** and its palladacycles revealed that they exhibit growth inhibitory activity against breast (MCF-7) human cancer cell lines.

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thiourea-Pt(II) complexes against cisplatin-sensitive and -resistant human ovarian cancer cells. *J. Inorg. Biochem.* **2008**, *102*, 699-712.

Publication History
Received 23rd Feb 2014
Revised 10th Mar 2014
Accepted 20th Mar 2014
Online 03rd Apr 2014