

## **Antibacterial activity, synthesis and characterization of a new Ag(I) and Pd(II) complexes with N-heterocyclic carbene**

**Mohammad Kadhum Talib<sup>1</sup>, Mohammed Z. Ghadhyeb<sup>1</sup>**

<sup>1</sup>Department of Chemistry, Faculty of Science, University of Kufa, Najaf, Iraq.

Email: mohammed.alhallaqi@uokufa.edu.iq

### **Abstract**

Preparation of new complexes of silver(I) and palladium(II)-NHC using imidazolium salts were derived through methylimidazole with 2-chloro-N-(4-chlorophenyl) acetamide under certain conditions of temperature and certain solvents, to be synthesized silver complex from the reaction of substituted imidazolium salts with Ag<sub>2</sub>O using in situ deprotonation technique giving derived structures in good yield. To synthesis Pd(II)-NHC complexes using the transmetallation technique were used Ag(I)-NHC complexes as transfer reagents to prepare their respective. The free ligands and their complexes were characterized based on (FT-IR, Melting point, TLC, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, high-resolution mass spectra and UV). The biological activity studies show , the antibacterial activity of **(5)** is the highest and showed good inhibition against the tested bacteria even more than the azithromycin. A moderate activity for the complex **(3)**, low activity for the ligand **(2)** have been shown.

**Keywords:** Ag(I)-NHC, Antibacterial activity, Carbene, Heterocyclic, Imidazolium salts, Pd(II)-NHC,

### **Introduction**

NHCs have been widely used in inorganic and organometallic chemistry because of their potent metal coordinating properties. Numerous methods have been used to examine the creation of NHC metal complexes.<sup>1,2,3</sup> Metal complexes of N-Heterocyclic Carbenes can be made using a number of different techniques. The following is a list of the three most popular routes.<sup>4,5</sup> Imidazole is the organic compound where imidazole denotes a group of heterocycles with a similar cyclic structure but different substituents<sup>1</sup>. Imidazolium salts result from substitutions on each of the nitrogen atoms in the imidazole ring.<sup>2,3</sup> N-substituted azolium salts are the first of two methods that can be used to make N-heterocyclic carbene complexes. There are two common routes to synthetics:<sup>4</sup> Nucleophilic substitution starting at the imidazole heterocycle and Multi-component reaction, building up the heterocycle with the appropriate substituents in one step. Carbenes are unbounding compounds with a coordinate carbon atom and two valence shell electrons. Wanzlick and Feel reported the first two metal complexes of N-heterocyclic carbenes in 1968, a long time before Arduengo reported the existence of a stable free carbene.<sup>6,7</sup> Metal NHC complexes have been used as catalysts for a long time.<sup>8,9</sup> Later research showed that the NHC

derivatives of silver(I) and gold(I) can be employed for a variety of chemical changes in medicine. This paper will focus on the synthesis and use of silver(I) and gold(I) NHC derivatives in medicinal applications.<sup>10,11,12</sup> Most of the time, the N-heterocyclic carbenes are attached to the metal by giving it a carbene lone pair, which has little acceptor property. The specific metal and carbene under consideration determine the extent of the metal's -back donation. It was decided to use structure **(a)** to represent the N-heterocyclic carbene metal complexes in this thesis. This is done to stress that the Carbon carbene is proton-free. In the literature, representations **(a)** and **(b)** are both present.<sup>13,14,15</sup> NHCs have been widely used in inorganic and organometallic chemistry because of their potent metal coordinating properties. Numerous methods have been used to examine the creation of NHC metal complexes.<sup>16,17,18</sup> Metal complexes of N-Heterocyclic Carbenes can be made using a number of different techniques. The following is a list of the three most popular routes. The transmetallation processes can occur with air and moisture present, and they are also resistant to a variety of solvents, including water with various counter ions, this technique has been employed effectively with a range of metals, including Rh, Ir, Pd, Pt, Ru, Cu, and Au. The geometry of the ligands, reaction conditions, and solvent type all affect how the product is formed. palladium-NHC complexes are a family of organic palladium compounds in which palladium forms a coordination complex with N-heterocyclic carbenes (NHCs). They have been investigated for applications in homogeneous catalysis, particularly cross-coupling reactions<sup>19</sup>. Herein we report the Antibacterial activity, synthesis and characterization of a new Ag(I) and Pd(II) complexes with N-heterocyclic carbene. The ligand and their complexes were characterized based on (FT-IR, Melting point, TLC, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, high-resolution mass spectra and UV). The biological activity has been studied.

## Synthesis part

### 2-chloro-N-(4-chlorophenyl) acetamide (1)

2-chloro acetyl chloride (1.5mL) was added after 4-chloroaniline (3g,0.021mol) was dissolved in Toluene (10mL). After 20 minutes of stirring, the chloroacetyl chloride (1.6 mL, 0.014 mole) was added drop by drop. At room temperature, the mixture was stirred for 30 minutes. The mixture is filtered and rinsed thoroughly with distilled water after completion of the reaction, and then recrystallized with ethanol to yield (83 % yield) as a fine white powder (m.p =130-133°C). <sup>1</sup>H NMR (500 MHz, Chloroform-*d*) δ 9.77 (s, 1H), 7.66 – 7.60 (m, 2H), 7.35 – 7.29 (m, 2H), 4.20 (s, 2H). <sup>13</sup>C NMR (125 MHz, Common NMR Solvents) δ 168.91, 136.85, 129.02, 127.95, 121.21, 42.59.

### 1-(2-((4-Chlorophenyl) amino)2-oxoethyl)-1methyl-1H-imidazol-3-ium (2)

(0.01 mol, 0.8 g) methylimidazole in a (50 mL) round bottom flask, (10 mL) acetonitrile was mixed with compound **(1)** (2 g, 0.0099 mol) was added to the mixture. For 24 hours, the mixture was refluxed at 90°C. The solvent was evaporated once the reaction was completed and then recrystallized with methanol. (2.1g, 75% yield) as a white powder (m. p= 125-127 °C).

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.62 (s, 1H), 9.25 (s, 1H), 7.80 (d, J = 1.8 Hz, 1H), 7.76 – 7.73 (m, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 5.33 (s, 2H), 3.90 (s, 3H).

$^{13}\text{C}$  NMR (126 MHz, DMSO- $d_6$ )  $\delta$  164.47, 138.36, 138.04, 129.18, 127.70, 124.31, 123.51, 121.13, 51.73, 36.30.

**Bis(1-(2-((4-chlorophenyl) amino)-2-oxoethyl)-3-methyl 2,3-dihidro-1H-imidazol-2-yl) silver (3)**

In 20 mL methanol, silver oxide (0.5 g, 0.0021 mol) was added to a solution of compound (2) (2.5g, 0.0043mol). In glassware, the mixture was swirled for 10 hours while being covered with aluminum foil. The solvent was removed under vacuum after the dark suspension was filtered through celite to remove the excess  $\text{Ag}_2\text{O}$ , leaving the result as a white solid 2.25g (75 % yield) (m.p = 173-180 °C).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  9.97 (ds, 1H), 7.71 – 7.66 (dm, 2H), 7.35 – 7.30 (dm, 2H), 6.46 (dd,  $J$  = 1.4 Hz, 2H), 4.04 (ds, 2H), 2.82 (dd,  $J$  = 1.5, 0.7 Hz, 3H).  $^{13}\text{C}$  NMR (125 MHz, Common NMR Solvents)  $\delta$  169.08, 169.05, 138.40, 138.35, 128.99, 128.97, 128.96, 128.62, 128.56, 121.69, 121.66, 121.64, 120.13, 120.07, 118.77, 118.72, 80.43, 80.38, 51.24, 51.18, 37.70, 37.67.

**Preparation of  $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$  (4)**

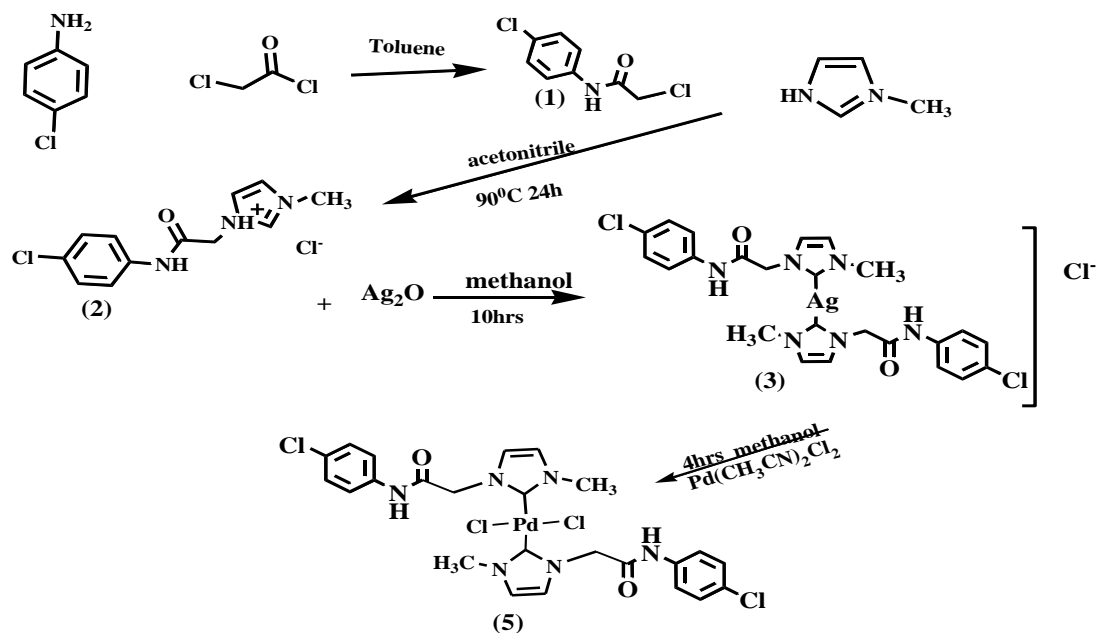
Palladium Chloride (0.5 g, 0.0028 mol) was dissolved in Acetonitrile (50 mL) and heated under reflux for 1 hr. The mixture was allowed to cool down and the solvent was evaporated slowly at ambient temperature to give complex (4) as an orange-reddish (0.45 g, 61 % yield) (m.p = 142-144 °C).

**Mono(bis(1-(2-chlorophanyl) amin-2-oxoethyl-1H-imidazol-3-ium-2-yl) palladium (IV)) dichloride (5)**

Palladium complex  $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$  (4), (0.04 g, 0.00015 mol) was dissolved in methanol (7.5 ml) and then the solution (4) was add drop wise to silver complex (3) (0.2 g, 0.00033 mol) that dissolved in methanol (7.5 ml). The mixture was stirred for 4 hrs at room temperature. The product was filtered by using celite and then left it to remains(1ml), Petroleum ether was adding (10ml) to precipitate, left the solution to dry to obtain 0.17 g (70 % yield) as Pale-Brown solids (m.p = 115-117 °C).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.67 – 7.61 (m, 2H), 7.38 – 7.32 (m, 2H), 6.46 (d,  $J$  = 10.9 Hz, 1H), 6.40 (dq,  $J$  = 11.0, 1.1 Hz, 1H), 4.15 (s, 2H), 3.08 (s,  $J$  = 1.2 Hz, 3H).  $^{13}\text{C}$  NMR (125 MHz, Common NMR Solvents)  $\delta$  169.28, 169.25, 138.34, 138.29, 129.00, 128.99, 128.98, 128.10, 128.04, 123.11, 123.04, 123.00, 122.93, 122.29, 122.24, 121.79, 121.77, 121.74, 52.41, 52.35, 38.02, 37.98.

**Result and discussion**

The compound 2-chloro-N-(4-chlorophenyl) acetamide (1) was used to prepare imidazolium salt (2) by reaction with methyl imidazole (1:1 mol) in acetonitrile and the mixture was refluxed with stirring at 90°C for 24hrs (scheme 1). The imidazolium salt (2) were treated with silver oxide in methanol at reflux for 10 hrs in glassware wrapped with aluminum foil at 50°C, to obtain the product as white solid with suitable yield of corresponding Ag-NHC complexes (3), (scheme 1). The pd(II)-N heterocyclic carbene complex (5) were prepared by transmetallation of corresponding silver complex (3). The treatment of Ag(I)-NHC complexes with  $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$  in methanol and stirred for 4 hrs at room temperature, the new products precipitated as pale yellow solid complexes with acceptable yield (scheme 1).



Scheme 1 Centered and representation of the synthesis of ligand, Ag(I) and Pd(II)-NHC

FTIR spectrum of compound (2) showed the characteristic peaks include but not limited to the following: the absorption at  $2936\text{ cm}^{-1}$  is attributed to the stretching vibration of (C-H<sub>aliph</sub>), and the band at  $1558\text{ cm}^{-1}$  is assigned for stretching vibration of the (C=N) bond while the band at  $1252\text{ cm}^{-1}$  could be refer to the stretching vibration of (C-N) bond figure (1).

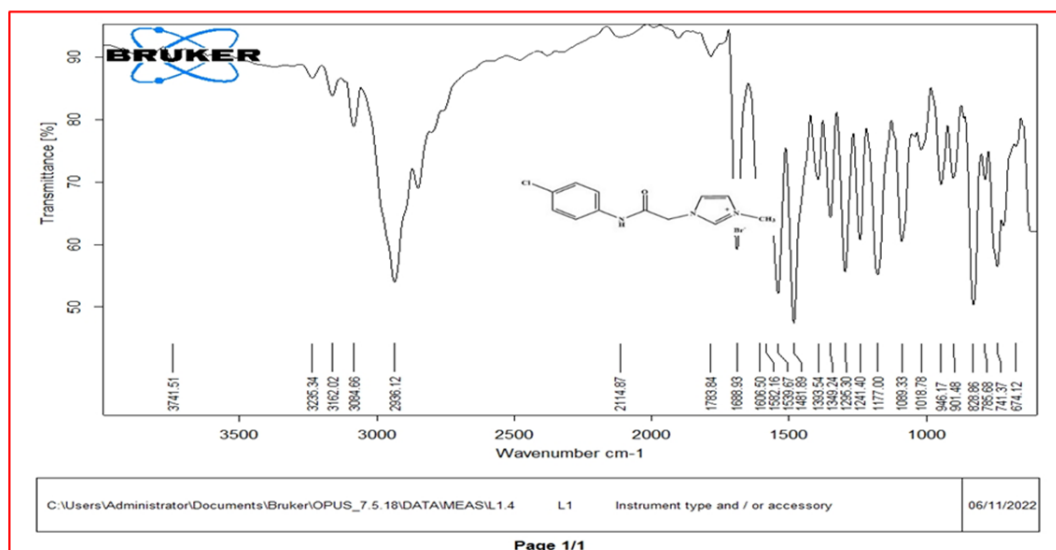


Figure (1) FTIR spectrum to the ligand (3)

The <sup>1</sup>HNMR spectrum of ligand (2) showed the characteristic peaks which is confirm the structure of desired product. The singlet at 3.67 ppm is assigned to the methyl group that attached directly to the nitrogen of imidazole, while the singlet at 5.3 ppm is referred to the

methylene group that connected between the nitrogen of imidazole and the carbonyl group. In addition, the two doublets at 7.87 and 7.82 ppm could be assigned to the para substituted benzene ring four protons figure (2).

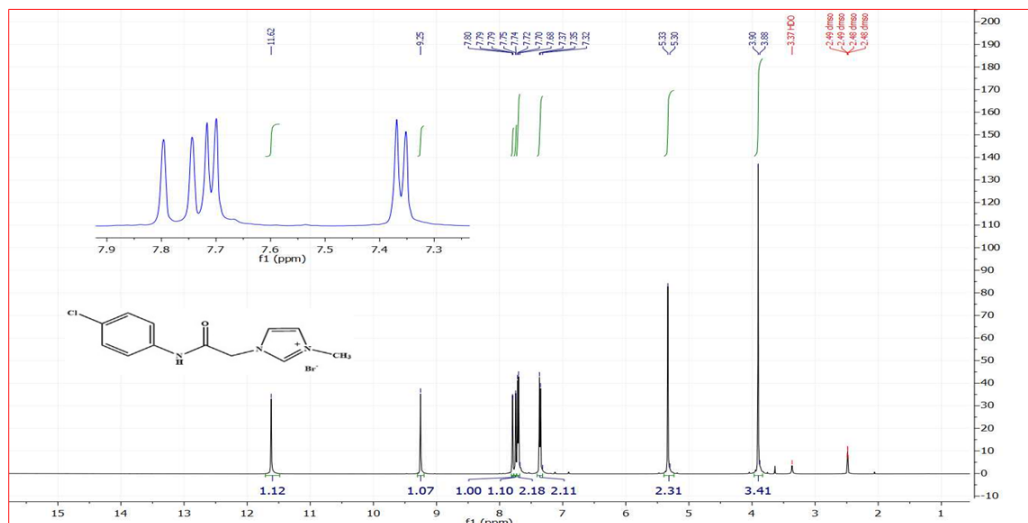


Figure (2)  $^1\text{H}$ NMR full spectrum of ligand (2)

Moreover, the two singlets at 7.75 and 7.81 ppm are assigned to the protons of imidazole at 4 and 5 positions of imidazole ring. Indeed, these two singlets expected to be doublets instead of singlets, however, this observation can be explained due to the position of the neighboring protons can split each other in small J-value approximately 1 Hz. This is caused the peaks to be more broad as shown in expansion of spectrum. Furthermore, the singlet at 9.30 ppm is assigned to the carbine proton on 2 position. Finally, the singlet at 11.61 ppm is referred to the amide proton figure (2). The  $^{13}\text{C}$ NMR spectrum showed the characteristic peaks which confirm the structure of desired product. The signal at 36.30 ppm is assigned to the carbon of methyl group that attached directly to the nitrogen of imidazole, while the signal at 51.73 ppm is referred to the carbon of methylene group that connected between the nitrogen of imidazole and the carbonyl group. In addition, the two signals at 124.31 and 123.51 ppm are assigned to the carbon of imidazole at 4 and 5 positions of imidazole ring. Moreover, the four signals at 138.04, 129.18, 127.70 and 7121.13 ppm could be assigned to the carbon of benzene ring. Furthermore, the signal at 138.36 ppm is assigned to the carbine carbon NCHN. Finally, the signal at 164.47 ppm is referred to the carbonyl group figure (3). The FTIR spectrum of the complex (3) was showed the characterized peaks of major bands which interpret by major functional groups. The band at  $1694.27\text{ cm}^{-1}$  is assigned to the stretching vibration of (C=O) group, in the same manner the bands at  $3117.53 - 3261.16\text{ cm}^{-1}$  is referred to the stretching vibration of (C-H<sub>aliph</sub>) in alkane, while the band at  $1613.2\text{ cm}^{-1}$  could be assigned to (C=N) group. In addition, the two bands at  $1372.9$  and  $1554.59\text{ cm}^{-1}$  is assigned for the (C-N) and (C=C) groups respectively figure (4).

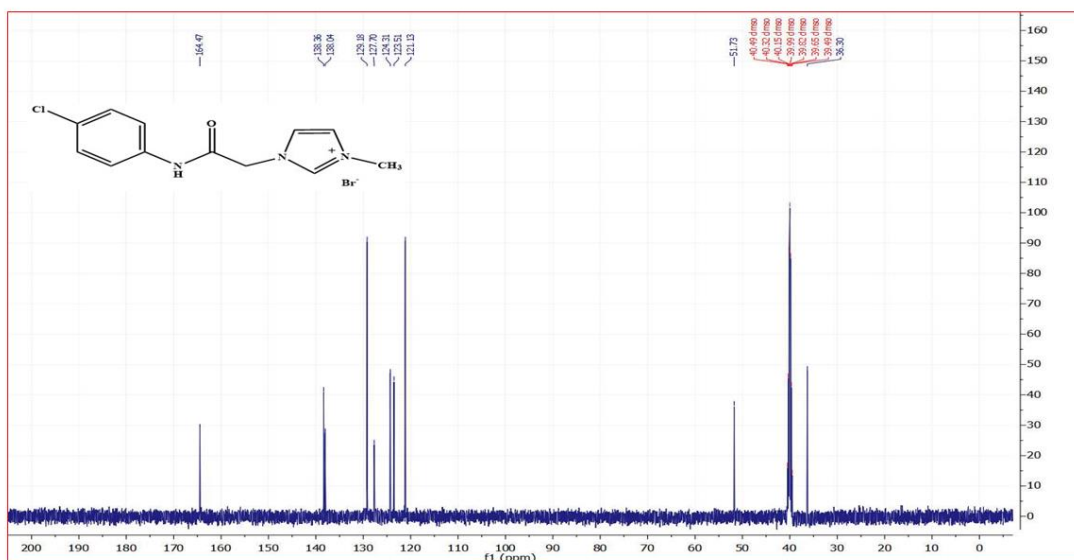
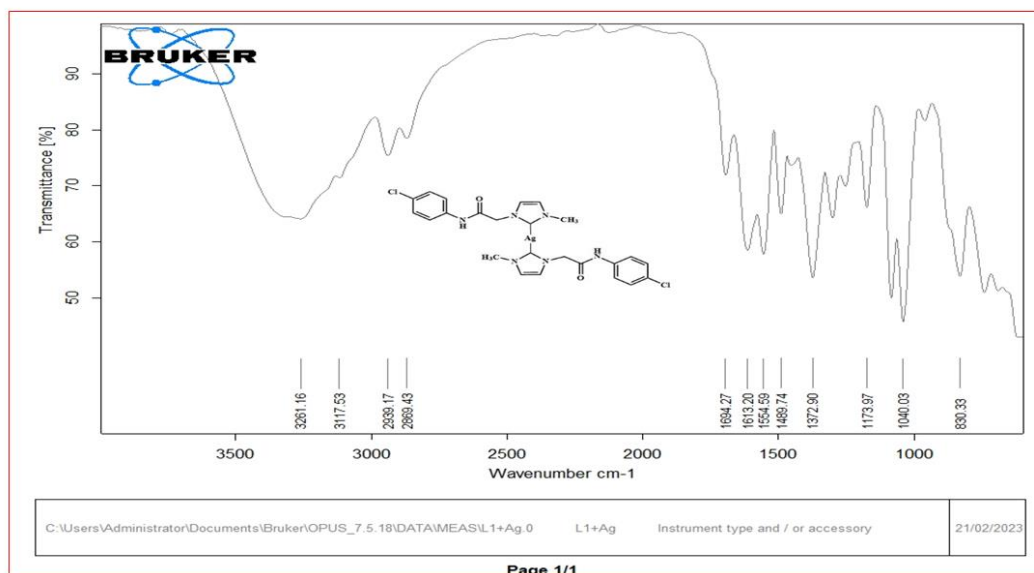
Figure (3)  $^{13}\text{C}$ NMR spectrum of ligand (2).

Figure (4) FTIR spectrum complex (3).

The  $^1\text{H}$ NMR spectrum of complex (3) showed the characteristic peaks which confirm the structure of desired product. The singlet at 3.1 ppm is assigned to the methyl group that is attached directly to the nitrogen of imidazole, while the singlet at 4.2 ppm is referred to the methylene group that connected between the nitrogen of imidazole and the carbonyl group.



In addition, the two doublets at 7.32 and 7.69 ppm could be assigned to the para substituted benzene ring four protons. Moreover, the two singlets at 6.71 and 7.09 ppm are assigned to the protons of imidazole at 4 and 5 positions of imidazole ring. Furthermore, the most powerful evidence about formation of complex is the disappearing of singlet at 9.30 ppm which is previously assigned for the carbene proton. On other words, the silver oxide is abstracting this proton due to its basic properties. Finally, the singlet at 9.14ppm is referred to the amide proton which is shifted up filed from its previous position on the free ligand at 11.2 ppm due to the new electronic environments when the silver is forming the complex and abstracting the carbene proton making the nitrogen proton more shielded as figure (5). The  $^{13}\text{C}$ NMR spectrum showed the characteristic peaks which confirm the structure of desired product. The signal at 35.8 ppm is assigned to the carbon of methyl group that attached directly to the nitrogen of imidazole, while the signal at 51.16 ppm is referred to the carbon of methylene group that connected between the nitrogen of imidazole and the carbonyl group. In addition, the two signals at 118.6 and 120.75 ppm are assigned to the carbon of imidazole at 4 and 5 positions of imidazole ring. Moreover, the four signals at 137.4,129.21,128.5 and 127.41 ppm could be assigned to the carbon of benzene ring. Furthermore, the signal at 163.93 ppm is assigned to the carbene carbon NCHN. Finally, the signal at 168.93 ppm is referred to the carbonyl group (7), figure (6).

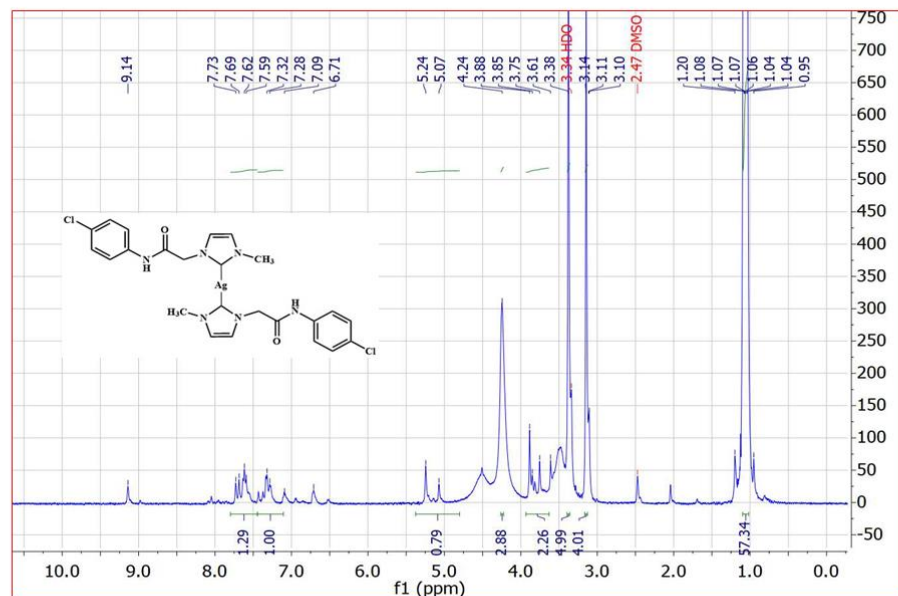


Figure (5)  $^1\text{H}$ NMR spectrum to the complex (3).



**Figure (6)  $^{13}\text{C}$ NMR spectrum to the complex (3).**

The characterization of complex (5) with FT-IR spectra which showed no match difference from the silver complexes analogues. This is not surprise as the region of the metal carbene bond vibration is appear according to the literatures between  $400\text{-}155\text{ cm}^{-1}$  figure (7). This is difficult to observe in the FT-IR spectrophotometer which is limited to  $400\text{ cm}^{-1}$  in addition to the rubbish peaks in the region of  $600\text{-}400\text{ cm}^{-1}$ . Moreover, the FT-IR based salt disk, i.e., potassium bromide disk is not suitable for this purpose as is limited to  $400\text{ cm}^{-1}$ . The only salt is fit this region is the cesium iodide which is unfortunately unavailable during the measurements of the spectra that can go up to  $200\text{ cm}^{-1}$ . The other technique used for the characterization of the palladium complexes (5) is the NMR. Indeed, the proton NMR is useless analogues (3). The peaks of the ligands of palladium complexes is shifted up field slightly compare to their Ag-complexes analogues; this is match the fact that there is no hydrogen left to show in the spectrum as the carbene proton is abstracted before when the Ag-complex is formed figure (8). The more interesting experiment that indicate the formation of palladium complexes is the  $^{13}\text{C}$  NMR spectra. In which the carbon in the center between the nitrogen in the imidazolium ring is linked directly to the metal. However, the shift of this carbon is gone to the downfield of the spectrum when the silver complexes formed as discussed previously. The palladium complexes showed downfield shifting as well but is less than the silver complexes due to the different electronic environments that surrounded the silver and palladium metals. The shift of the carbene carbon to the up filed in complex (5) to the  $165.39\text{ ppm}$  compared to its previous position in the silver analogue (3) at  $163.93\text{ ppm}$ . In addition, the signal at  $168.25\text{ ppm}$  refers to the carbonyl group as show in the Figure (9).

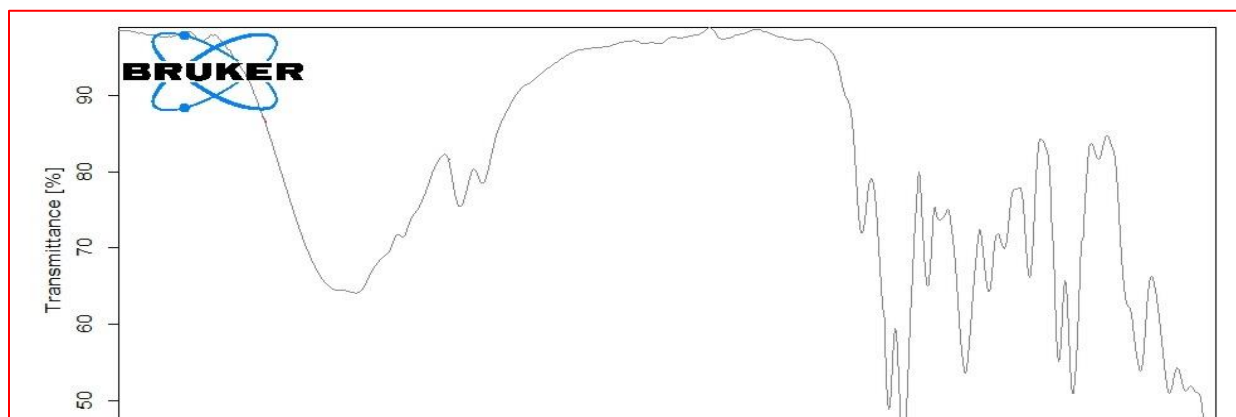
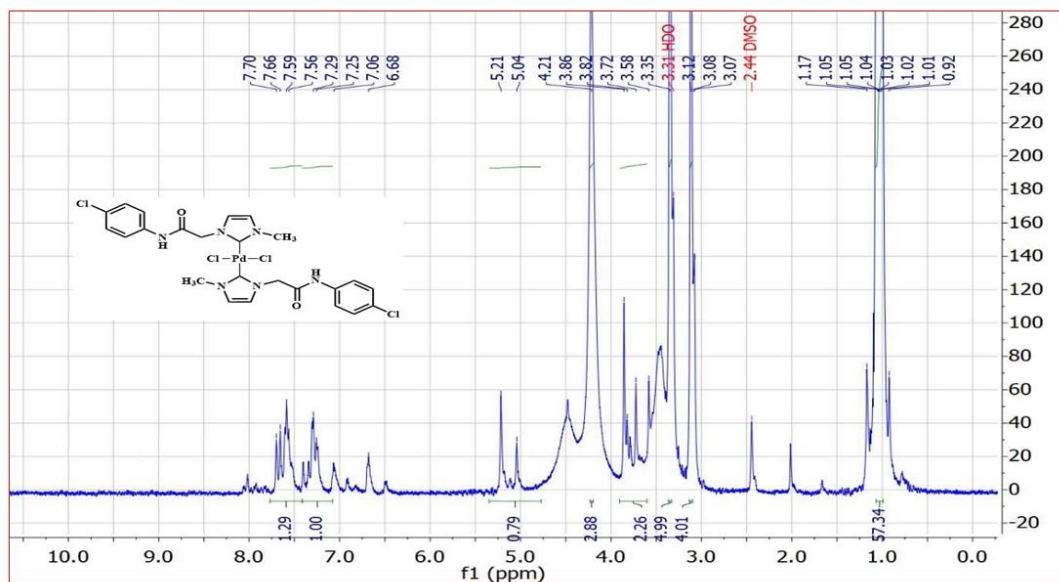




Figure (7) FTIR spectrum complex (5).



**Figure (9)  $^{13}\text{C}$ NMR spectrum to the complex (5).**

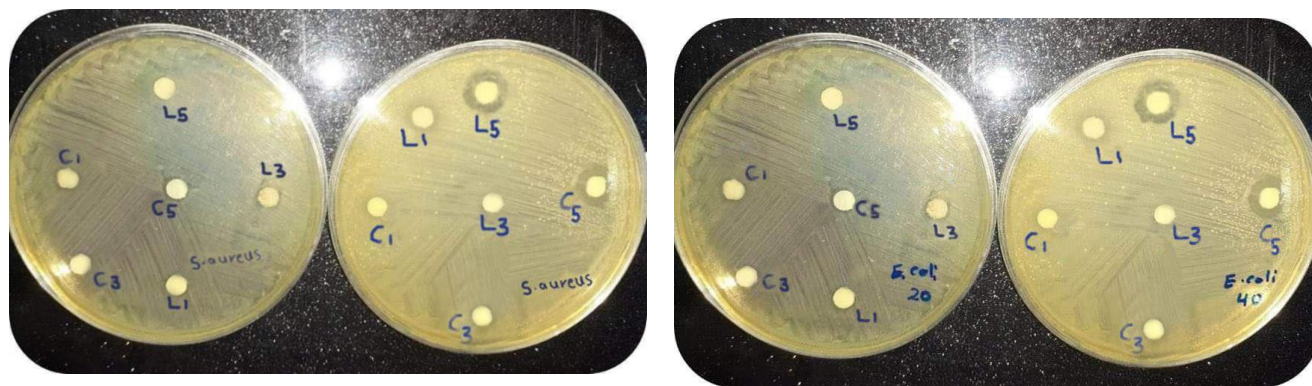
**Antibacterial activity:**

The search for new biological reagents is gaining popularity. This is consistent with the fact that new types of pharmaceutical products are discovered on one side and the resistance to most common drugs on the other. However, exploring novel agents of biological activity has grown exponentially in recent years. NHC-carbenes and their complexes are compounds that can bind to other molecules by hydrogen bonding, which makes them more soluble in aqueous media and enhances their interaction with biomolecules. The NHC-carbenes have been applied in medicine as therapeutic agents depend upon their variety of biological screening, which include but are not limited to, antimicrobial, antiviral, antifungal, and anticancer. For all of these, Using azithromycin as a standard, the antibacterial activity of substituted imidazolium salts and their N-heterocyclic carbene related Ag(I) and Pd(II) complexes was investigated against *E. coli* as a Gram-negative bacteria and *S. aureus* as some Gram-positive bacteria. The substituted ligand and their Ag(I) and Pd(II) complexes showed an effect against the investigated microorganisms when compared with azithromycin. The antibacterial activity of substituted imidazolium salts and their respective

Ag(I) and Pd(II) complexes was evaluated against the bacterial strains *E. coli* as representative gram-negative and *S. aureus* as gram-positive bacteria. All the substituted imidazolium salts and respective Ag(I) and Pd(II) complexes showed an activity against the tested bacteria. A representative picture of zone of inhibition is shown in figure (Table 1). According to the tabulated results, the antibacterial activity of (5) is the highest and showed good inhibition against the tested bacteria even more than the azithromycin. A moderate activity for the complex (3), low activity for the ligand (2) have been shown. However, *E. coli* depicted highest resistance against ligand (2). The sensitivity of the gram-negative bacteria increases as the volume of the complex suspensions increases. For the bacteria *S. aureus*, the results were almost similar to that of *E. coli* as depicted in Figure(1 and Table 1).The ligand (2) showed low antibacterial activity. Similarly, the sensitivity of the gram-positive bacteria increases as the volume of the complex suspensions increases. All other compound showed different values at the concentrations 100 and 200  $\mu\text{g mL}^{-1}$ .

**Table (1) Antibacterial activities of compounds 2, 4 and 5 against *E. coli*. and *S. aureus***

Compound	Concentration ( $\mu\text{g mL}^{-1}$ )			
	<i>E. coli</i> .		<i>S. aureus</i>	
	Inhibition zone (mm)		Inhibition zone (mm)	
	100 $\mu\text{g mL}^{-1}$	200 $\mu\text{g mL}^{-1}$	100 $\mu\text{g mL}^{-1}$	200 $\mu\text{g mL}^{-1}$
<b>2</b>	15	20	10	15
<b>3</b>	25	35	25	30
<b>5</b>	25	35	20	30
Azithromycin	20	25	20	25



**Figure 11** Effect of the ligand and its complexes towards *E. coli.* and *S. aureus*

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