Volume 3, Issue 1, January- 2025 **ISSN (E):** 2938-3811

NOVEL AG (II), PD (II), AND PT (II) N-HETEROCYCLIC CARBENE COMPLEXES: SYNTHESIS AND STUDYING ANTICANCER PROPERTIES

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Abstract
Imidazolium salts were produced through different substitutions, including aliphatic chains and phenyl acetamide, resulting in symmetrically substituted salts. The Silver(I)-NHC complex was synthesized by reacting symmetrically substituted imidazolium salts with Ag2O, employing an in-situ the depr0tonation technique to obtain the desired structures with high yield. The Silver(I)-NHC complex was then utilized as a transfer reagent through the transmetallation technique to generate respective palladium (II)-NHC complexes. The platinum (II)-NHC complex synthesis was set under an atmosphere of nitrogen, using anhydrous toluene. The recently developed compounds were assessed for efficacy against three human cancer cell lines —gastric adenocarcinoma (AGS), and colon carcinoma (HT29), with the normal cell line (MCF-12A) serving as a control, using the MTT method. The characterization of the complexes involved various spectroscopic techniques, including 1HNMR, 13CNMR, Mass, UV-Vis, FT-IR, and determination of melting point.

Keywords: N-heterocyclic carbene, Imidazolium salts, silver(I)-NHC complex palldium (II)-NHC complex, platinum (II)-NHC complex, MTT assay, AGS, HT29,
anticancer activity.

Introduction

Imidazole-derived N-heterocyclic carbenes (NHCs) have held a significant place in organometallic chemistry for several decades, with imidazole-based derivatives possibly being among the earliest NHC ligands utilized by organometallic chemists.[1] Transition metal derivatives of NHC ligands, including those based on imidazole, have proven highly versatile and find extensive applications in metal-based drugs.[2,3] The historical significance of transition metal derivatives of imidazole-NHCs extends to catalysis and pharmacology studies, with noteworthy contributions dating back to the seminal work of Enders and Herrmann. Imidazole derivatives have been explored in organometallic chemistry,[4] particularly for biological applications. In the realm of organic chemistry, various organic derivatives of imidazole have exhibited promising therapeutic activities, including applications in cancer treatment.[5] The resemblance in structure between imidazole derivatives and naturally occurring nucleotides allows them to engage with the biopolymers present in living systems, highlighting their biological importance.[6]

Experimental

All chemicals, catalysts, and solvents were obtained in their highest analytical quality and sourced directly from companies. The remaining starting materials were synthesized following the procedures outlined in the literature method7. NMR spectroscopy measurements were conducted using a Bruker spectrometer model (300 MHz for 1HNMR and 75 MHz for 13C NMR) with DMSO-d6 as the solvent. High-resolution mass spectra were obtained, and infrared spectra were recorded using an FT-IR spectrophotometer (FTIR-Alpha-Bruker). UV–Visible spectrometry with double-beam configuration was carried out using a Biochrom instrument, serving as the standard for anticancer studies.

Synthesis Derivative of the amine

Synthesis compound (1)

The synthesis of first compound (1) involved dissolving o-toluidine (3.75g, 17.6 mmol) in dichloromethane (DCM) (20 mL), then followed by the addition organic base of trimethylamine (1.5 mL). The mixture was stirred for 20 minutes before dropwise addition of chloroacetyl chloride (1:2) (4g, 35.2 mmol) at room temperature, and the resulting reaction mixture was stirred for an additional 30 minutes. After finishing the reaction, the mixture was filtered., extensively washing with distilled water, and subsequently recrystallized using ethanol.

(1) the end product is a fine white powder (85 % yield, 5.5 g) (m.p = 280-283 ℃).**FT-IR cm^{-1}**: 3259 (N-H), 3019 (CH-Ar), 2917 (C-H_{aliph}), 1661 (C=O), 1251 (C-N).**^{1}HNMR** δ, ppm: 10.13 (s, 2H, Ar-NH), 7.55-7.40 (m, 4H,Ar-H), 4.25 (s, 4H,CO-CH_2), 2.45 (s, 6H, Ar -CH_3). **^{13}CNMR** δ, ppm: 166.87 (C=O), 135.19, 134.73, 129.46, 128.41,124.91,119.89(Ar-C), 42.98(carbonyl-CH_2), 20.19(Ar- CH_3)

Synthesis *N*-substituted imidazole

Synthesis *N*-decyl imidazole (2)

In a procedure involving Imidazole (1.54g, 22.6 mmol) dissolved in 20 mL of DMSO, NaOH (0.9 g, 22.5 mmol) was added after grinding. The resulting mixture was stirred for 2 hours at 90℃. Subsequently, the temperature was lowered to 30°C, and 1-bromodecane (5g, 22.6 mmol) was added dropwise, followed by raising the temperature to 40℃ for 1 hour. The resulting product was poured into 10 mL of distilled ice water and subjected to extraction with Petroleum ether (3 × 10 mL). After filtration, the Petroleum ether was removed to yield compound (2).

(2) It was prepared as a pale yellow liquid (80 % yield, 3.8 g). **FT-IR cm^{-1}**: 3104 (C-H_{Ar}), 2922 (C-H_{aliph}), 1655 (C=N) , 1568 (C=C) , 1228 (C-N). **^{1}H NMR** δ, ppm: 9.68 (s, 1H,NCHN), 7.96 (s, 1H,imH), 7.85 (s, 1H,imH), 4.26 (t, 2H,N-CH_2), 1.80 (p, *J* = 6.5 Hz, 2H,CH_2), 1.36 – 1.23 (m, 14H,CH_2), 0.85 (t, 3H,CH_3).**^{13}C NMR** δ, ppm: 136.34 (NCHN), 125.64, 123.52(im-CH), 46.27(N-CH_2-), 31.72, 29.38, 29.33, 29.07, 28.95, 28.55, 26.31, 22.66(-CH_2), 14.34(-CH_3).

Synthesis of 3,3'dimethyl-1, 1'-phenylene bis(1- decyl-3-acetamide imidazole) (3)

Compound (1) (0.88g, 2.4 mmol) was dissolved in 10 mL of dioxane, and then compound (2) (1g, 4.8 mmol) was added dropwise to the mixture in a 1:2 molar ratio. The solution was refluxed at 90°C for 24 hours. After the reaction was complete, the solvent was evaporated under low pressure. The crude product was then subjected to purification to obtain compound (3).

(3) It was prepared as a white semi-powder (yield 86 % ,1.56g) (m.p = 180-1183 °C). **FT-IR cm-1:** 3268 (N-H), 3071 (CH-Ar), 2947 (C-Haliph), 1666 (C=O), 1264 (C-N).**^{1}HNMR δ, ppm**: 10.03(s, 2H, NH amide), 9.8(s, 2H, NCHN),7.57-7.49(m, 6H,Ar-H), 7.05(s, 2H, CHN im), 6.75(s, 2H, CHN im), 4.38(s,4H,carbonyl-CH_2-N),3.67-3.63(t,4H,N-CH_2),2.41 (t, 6H, Ar -CH_3),1.63-1.53(m,4H,CH_2) , 1.33-1.20(m,28H,CH_2), 0.91-0.87 (t, 6H,CH_3) . **^{13}CNMR δ,ppm** : 166.55(C=O), 162.25(Ar-C-N),141.56 (NCHN) ,125.99,124.43(Ar-C),124.34,122.98 (CHim),57.27 (carbonyl-CH_2-N) ,53.98 (N-CH_2), 20.20(Ar-CH_3), 31.82, 29.39, 29.35, 29.13,28.43, 27.41, 25.88, 22.63(-CH_2),14.13(-CH_3) .

Synthese of Silver(I)−*N*HC Complex

The silver complex (**4**) was developed based on the Ag_2O *in-situ* response procedure developed by Wang and Lin with the appropriate imidazolium salts except light [8] Scheme 1.

Synthesis of 3,3'dimethyl-1,1'-phenylene bis(1-decyl-3-acetamide imidazole) silver chloride (4)

To a solution of compound (3) (1g, 1.28 mmol) in 20 mL of acetonitrile, silver oxide (0.59g, 2.56 mmol) was added in a 2:1 molar ratio. The mixture was stirred for 8-10 hours in glassware covered with aluminum foil. Subsequently, the black suspension was filtered through celite to eliminate excess Ag_2O, and the solvent was removed using a rotary evaporator, yielding compound (4).

(4) It was prepared as a white solid of the product (70 % yield , 0.88 g) (m.p = 244-247 °C).**FT-IR cm^{-1}**: 3266 (N-H), 3119 (CH-Ar), 2922 (C-H_{aliph}), 1673 (C=O), 1249 (C-N).

^{1}HNMR δ, ppm: 10.05(s, 2H, NH amide), 7.37-7.21(m, 6H,Ar-H), 7.06(s, 2H, CHN im), 6.91(s, 2H, CHN im), 4.51(s,4H,carbonyl-CH_2-N),3.71-3.68(t,4H,N-CH_2),2.51 (t, 6H, Ar -CH_3),1.93-1.82(m,4H,CH_2) , 1.35-1.18(m,28H,CH_2), 0.92-0.88 (t, 6H,CH_3) . **^{13}CNMR δ, ppm :** 187.08(Ag-C),166.89(C=O), 164.05 (Ar-C-N), 132.11, 129.76, 127.78,123.74,122.90 (Ar-C),124.89, 123.51(im-CH), 58.21(carbonyl-CH_2-N),57.07(N-CH_2-),31.67, 31.19, 30.76, 29.98, 29.67, 28.98, 28.67, 25.67 (-CH_2), 23.23(Ar-CH_3), 13.12(-CH_3).

Synthesis of palldium (II)− NHC Complex

The pd-NHC complex **(5)** was prepared by transmetallation of corresponding silver complex **4** respectively. The treatment of complex with $Pd(CH3CN)_2Cl_2$ complex in refluxed methanol[9].

Synthesis of 3,3'dimethyl-1,1'-phenylene bis(1-decyl-3-acetamide imidazole) Bis(acetonitrile)Palladium chloride (5)

Palladium complex Pd(CH3CN)2Cl2 (0.04 g, 0.00015 mol) was dissolved in 7.5 mL of methanol, while silver complex (4) (0.15g, 0.00015 mol) was also dissolved in 7.5 mL of methanol. The solution of complex (4) was then added slowly to the solution mixture of

Pd(CH3CN)2Cl2 complex. The new mixture was stirred at room temperature for 4 hours. The product was filtered using celite, and the remaining solution was reduced to 1 mL. To precipitate the compound, 10 mL of petroleum ether was added, and the solution was left to dry, yielding compound (5).

(5) It was prepared as a white solid of the product (84 % yield , 0.145 g) (m.p = 288-291 ℃)**.FT-IR cm^{-1}**: 3267 (N-H), 3120 (CH-Ar), 2925 (C-H_{aliph}), 1675 (C=O), 1249 (C-N). **^{1}HNMR δ, ppm**: 10.02(s, 2H, NH amide), 7.38-7.18(m, 6H,Ar-H), 7.04(s, 2H, CHN im), 6.87(s, 2H, CHN im), 4.55(s,4H,carbonyl-CH_2-N),3.75-3.71(t,4H,N-CH_2),2.51 (t, 6H, Ar -CH_3),1.96-1.82(m,4H,CH_2) , 1.38-1.20(m,28H,CH_2), 0.94-0.90 (t, 6H,CH_3).**^{13}C NMR δ,ppm** : 186.98(C-pd) ,167.59(C=O), 162.78(Ar-C-N), 134.09, 127.45,127.09,124.43,122.89(Ar-C),126.08,124.33(im-CH),58.04(carbonyl-CH2-N), 55.21(N-CH2-),40.34, 40.31, 40.05, 39.67,39.45, 39.09,34.45, 32.09, 31.40, 30.76, 29.89, 29.56, 29.34, 28.98, 28.41, 25.96, 23.78,21.99(-CH2), 21.89(Ar-CH3), 13.39(-CH3)

Synthesis of platinum (II)− NHC Complex

Synthesis of 3,3'dimethyl-1,1'-phenylene bis(1-decyl-3-acetamide imidazole) 4-bromopyridine platinum dichloride (6)

The synthesis of the platinum(II)−NHC complex was conducted in a nitrogen atmosphere, employing anhydrous toluene as the medium11. In toluene, a mixture of 1.05 equivalents of imidazolium salts (2), 1 equivalent of platinum dichloride salt, and 1.05 equivalents of 4-bromopyridine was stirred for one day at 100 °C. Subsequently, the excess organic the solvent was eliminated by employing a rotatory evaporator. The remaining solids were dissolved in CH2Cl2 under an air atmosphere, followed by filtration through a Celite plug. The resulting solution was concentrated to yield a solid, which underwent further purification through chromatography (SiO2, DMC/hexane), resulting in the desired NHC platinum(II) dichloride complex that was analytically pure, giving compound (6).

(6) It was prepared as a white solid of the product (81 % yield , 0.132 g) (m.p = 291-294 ℃)**.FT-IR cm^{-1}**: 3268 (N-H), 3118 (CH-Ar), 2924 (C-H_{aliph}), 1674 (C=O), 1250 (C-N).

^{1}H NMR δ, ppm: 10.06 (s, 2H, Ar-NH), 8.96-7.86 (m, 8H, Ar-H_{pyr}), 7.50-6.89 (m, 6H, Ar-H), 7.05(s, 2H, CHN im), 6.89(s, 2H, CHN im), 4.53 (s, 4H, carbonyl-CH_2-N), 3.89(t, 4H, N-CH_2), 2.54 (t, 6H, Ar -CH_3), 1.91-1.74(m,4H, CH_2), 1.48–1.24 (m, 28H, CH_2), 0.96-0.93 (t, 6H,CH_3).
^{13}C NMR δ, ppm: 178.44 (C-Pt),164.23(C=O), 144.75 (2C_{O-pyr}), 137.41 (1C_{p-pyr}),134.65 (2C_{m-pyr}), 163.76(Ar-C-N), 132.78, 129.05, 127.80, 123.82, 122.94 (Ar-C), 124.60, 123.32(im-CH), 55.96 (carbonyl-CH_2-N), 54.73(N-CH_2-),41.10, 40.07, 39.98,39.41,39.18,33.63, 31.77, 31.34, 29.72, 29.50,29.42,29.38, 28.91, 28.45, 27.41, 27.19, 24.75, 23.59 (-CH_2),12.44(-CH_3).

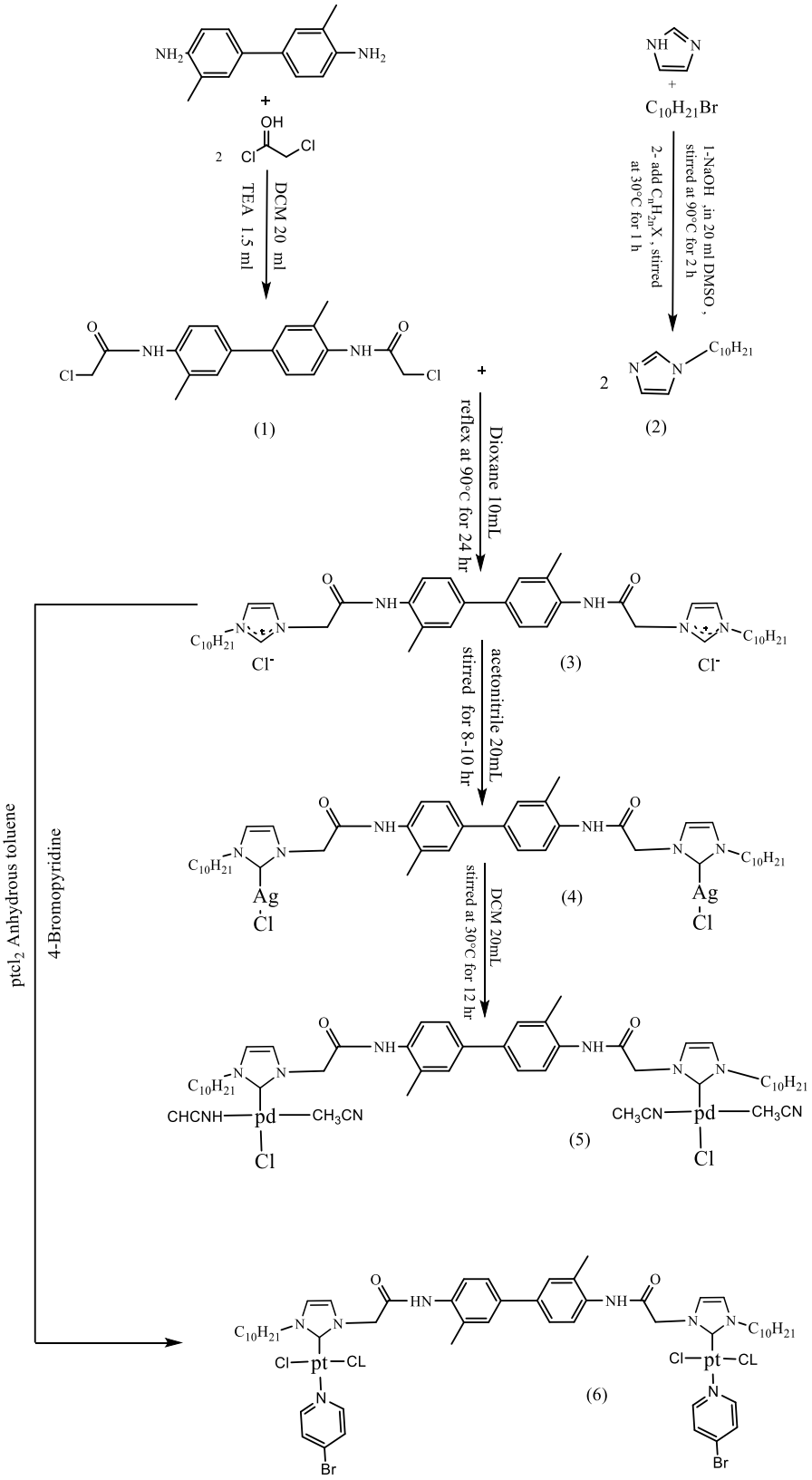
Results and Discussion

NHC proligand and complexes

In the beginning was prepared derivative of the amine *N*,*N'*-(3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl) bis (2-chloroacetamide) (**1**) as a starting materials[12]. The reaction of aromatic amine with chloroacetyl chloride in presence TEA as catalyst and DCM as solvent to produce aromatic

amine derivative (**1**).The compound **(1)** characterized by FT-IR spectrum showed new band at 3259 due to (N-H) and 1661(C=O). The ^{1}HNMR spectrum of compound(1) showed there is a new singlet signal at 4.25 ppm for acetyl group (carbonyl-C**H**$_2$) , while the exchangeable proton at 10.13 ppm for the proton of amide group.The ^{13}CNMR of compound **(1)** showed there is a new signal at 166.87 ppm for the carbon of carbonyl group , while the signal at 42.98 ppm for the carbon of amide group (carbonyl-**C**H$_2$). The *N*-substituted imidazole derivative **(2)** were prepared by reaction of imidazole with alkyl halide ($C_{10}H_{21}Br$) in presence NaOH and DMSO as solvent.[13] The FTIR spectrum of prepared compound **(2)** showed new band at the range 2922-2920 due to (C-H$_{asy\text{-}aliph}$), whereas new band at the range 2856-2852 cm^{-1} due to (C-H$_{sy\text{-}aliph}$),and stretching vibration at the range 1568-1559 cm^{-1} assigned to(C=C). On the other hand showed new band at the range 1237-1228 cm^{-1} assigned to (C-N). The ^{1}HNMR spectrum of compound (**2)** showed there is a new triplet signal at 4.26 ppm for the proton (N-C**H**$_2$), while the multiple signal for the aliphatic chain at 1.35-1.17 ppm and triplet signal at 0.85 for the protons of methyl group . The ^{13}CNMR of compound (**2)** showed there is a new signal at 46.27 ppm for the carbon of (N-**C**H$_2$), while the signal at the range 31.72-22.66 ppm for the carbon aliphatic chain and signal at the 14.34 ppm for the carbon of methyl group (CH$_3$)[14]. The ^{1}HNMR spectrum of compound (**3)** showed there is a new singlet signal at the 10.03 ppm for the proton of amide group(NH amide), while the singlet signal at the 9.8 ppm for the proton carbon carbene (NCHN) and multiple signal at the range 7.57-7.49 ppm for aromatic ring protons (Ar-H) and the two signals at (7.05 and 6.75 ppm) were assigned to the imidazole ring protons(CH-im)and the singlet signal at the 4.38 ppm for the proton of (N-**C**H$_2$). The ^{13}CNMR of compound (**3)** showed that there is a new signal at the 166.55ppm for the carbon of carbonyl group (C=O), while the signal at the 162.25 ppm for the carbon aromatic ring that connected amide group and signal at the 141.56 ppm for the carbon of carbene(NCHN)and the signal at the range 125.99-124.43 ppm for the carbon aromatic ring (Ar-C) and the two signals at (124.34 and 122.98 ppm) were attributed to the carbon imidazole ring (CH-im) and signal at the 57.27ppm for the carbon of (carbonyl-**C**H$_2$-N). The FTIR spectrum of silver complex **(4)** showed band at the range 3266 cm^{-1} due to (N-H), and new band at the range 1673-1660 cm^{-1} due to (C=O).The ^{1}HNMR spectrum of complex (**4)** showed that there is a singlet signal at the 10.05 ppm for the proton of amide group(NH amide), while multiple signal at the range 7.37-7.21 ppm for aromatic ring protons (Ar-H) and the two signals at (7.06 and 6.91 ppm) were due to the imidazole ring protons(CH-im)and the singlet signal at the 4.51ppm for the proton of (N-**C**H$_2$). The effective bonding of carbon carbene to the silver (I) complex through the de-protonation of (NCHN) is the absence of characteristic singlet proton crest in the average (9.8ppm) compared with ligand**(3)** spectra.[15,16] . The ^{13}CNMR spectra of the complex (**4)** showed the new signals within 187.08 of metal-NHC (Ag–C), whereas carbon carbene (NCHN) in the ligands(**3)** appeared at 141.56 ppm this is good evidence to occur complexation between metal-NHC. Additional carbon signals were observed in the anticipated regions, showing no significant changes in frequency. [17,18]. The ^{1}HNMR spectrum of complex (**5)** showed that there is a singlet signal at the 10.02 ppm for the proton of amide group(NH amide), while multiple signal at the range 7.38-7.18 ppm for aromatic ring protons (Ar-H) and

the two signals at (7.04 and 6.87 ppm) were due to the imidazole ring protons(CH-im)and the singlet signal at the 4.55 ppm for the proton of (N-**C**H_2). The peaks of methyl, acetamide, aliphatic chain, aromatic ring and imidazole aromatic protons nuclei were almost the same, as the proton resonance in the spectra of the corresponding silver complex [19,20] and the carbene carbon resonace was found 0.5 ppm and 0.6 ppm upfild to that of the corresponding silver complexes indicating the formation of the carbene complexes [21] .The ^{13}CNMR spectra of the complex (**5)** showed the new signals within 186.98 ppm of metal-NHC (Au–C). Additional carbons were observed in the anticipated regions, displaying no notable frequency shifts. By comparing silver (I) and palldium (II) complexes via the ^{13}CNMR spectra technique, were seen a slight shift in the signal peak obtained by transmetallation between complex (Ag–C) and (pd–C) , where silver (I) complex **(4)** show signal at the range 187.08 ppm for (Ag–C) while the palldium (II) complex appear signal at the range 186.98 ppm [22]. The FTIR spectrum of silver complex **(6)** showed band at the range 3266 cm^{-1} due to (N-H), and new band at the range 1674 cm^{-1} due to (C=O).The ^{1}HNMR spectrum of complex **(6)** showed that there is a singlet signal at the 10.06 ppm for the proton of amide group(NH amide), while multiple signal at the range 7.50-6.89 ppm for aromatic ring protons (Ar-H) and the two signals at (7.05 and 6.89 ppm) were due to the imidazole ring protons(CH-im)and the singlet signal at the 4.53ppm for the proton of (N-**C**H_2). The effective coordination of carbon carbene to the platinum(II) complex, achieved through the de-protonation of (NCHN), is evident in the absence of the distinctive singlet proton peak around the average (9.8 ppm) when compared to the ligand (3) spectra. The ^{13}CNMR spectra of the complex **(6)** showed the new signals within 178.44 of metal-NHC (pt–C), whereas carbon carbene (NCHN) in the ligands(**3)** was appearance at 141.56 ppm this is good evidence to occur complexation between metal-NHC. Additional carbons were observed in the anticipated regions, displaying no notable frequency shifts.



Scheme 1: Synthesis of *N*-heterocyclic dicarbene complexes

Cytotoxic Studies of Silver Complex

The MTT assay results of effects of silver complex **4** in different concentrations (1,2 and 4 mg/mL) on AGS and HT29 cell lines. These complexes have shown anti-cancer high activity to different extents, depending on the type and concentration of the complex. In the case of **HT29**, complex **4** has shown high cell toxicity in 2 and 4 mg/mL concentrations in comparison to the non-treated group (control) (***p<0.001***p<0.001, ****p<0.0001, respectively). The result showed that IC_{50} values of complex **4** on the **HT29** cell line were 8.8 % mg/mL, and the percentage of survival **HT29** cells was (15-25) %, as demonstrated in fig. (1 and 3).

In the case of **AGS**, complex **4** has shown high cell toxicity in 1,2 and 4 mg/mL concentrations in comparison to non-treated group (control) ((*p<0.01, ***p<0.001and****p<0.0001, respectively). The result showed that IC_{50} values of complex **4** on the **AGS** cell line were 10.9% mg/mL, and the percentage of survival **AGS** cells was (11-20) %, as demonstrated in fig. (2 and 4). IC_{50} value shows with non-tumorigenic cells (**MCF-12A**) about (56.61) %.

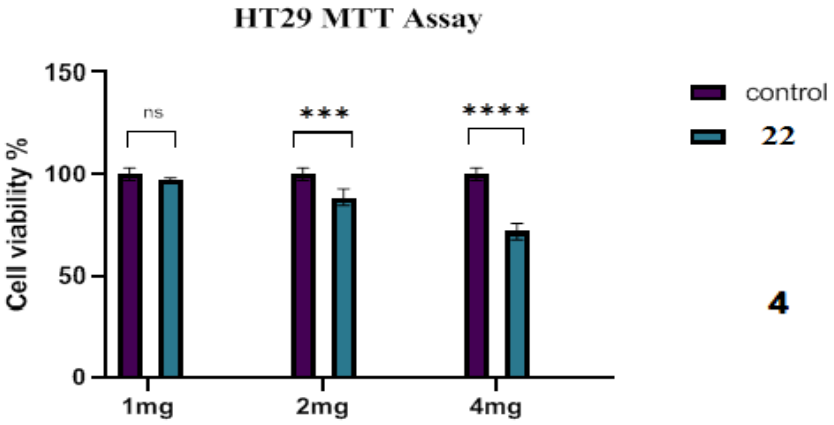
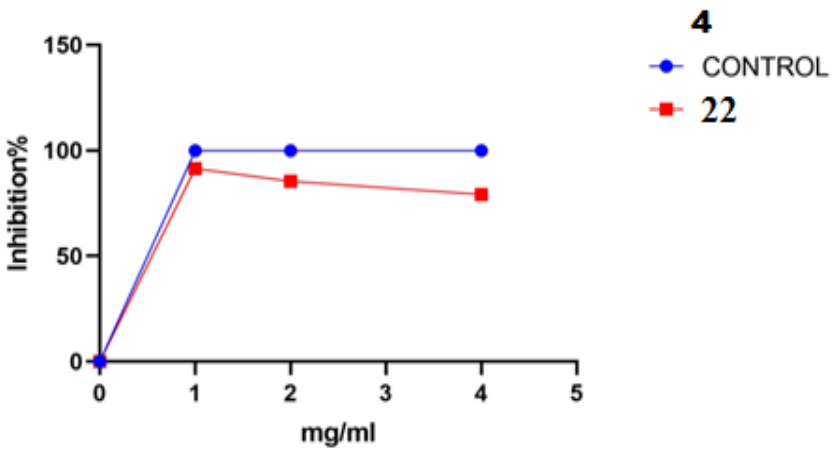


Fig. 1: Cytotoxic activity of silver complex 4 vs HT29 Assay cell line



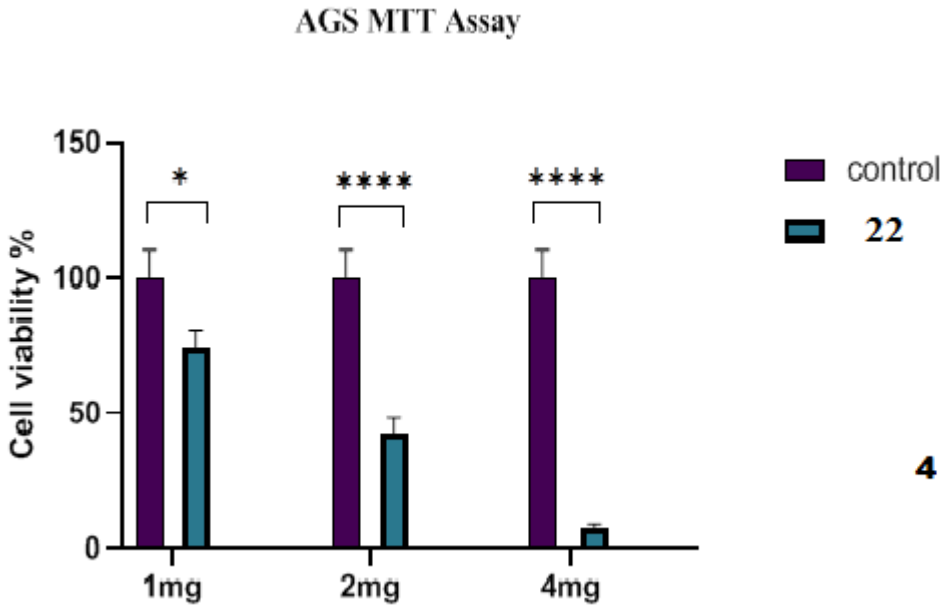


Fig. 3: Cytotoxic activity of silver complex 4 vs AGS Assay cell line

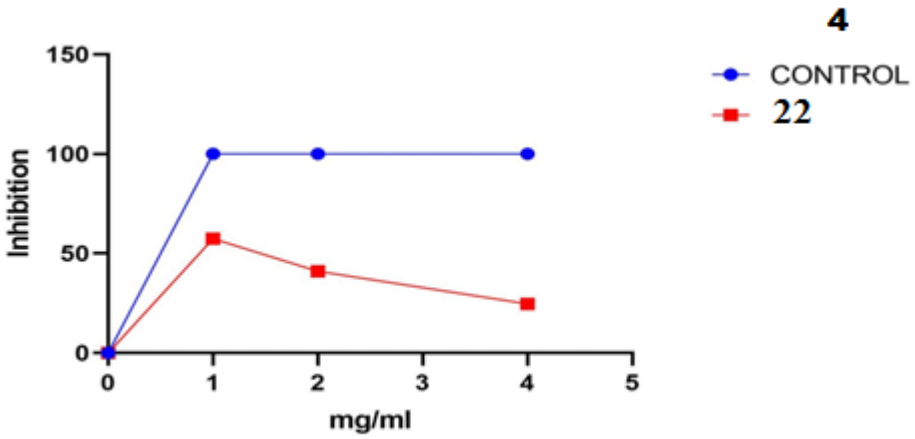


Fig. 4: IC_{50} of silver complex 4 vs AGS Assay cell line

Cytotoxic Studies of Palladium Complex

The MTT assay results of effects of Complex **5** in different concentrations (1,2 and 4 mg/mL) on **AGS** and **HT29** cell lines. These complexes have shown anti-cancer activity to different extents, depending on the type and concentration of the Complex. In the case of **HT29**. The result showed that IC_{50} values of Complex **5** on the **HT29** cell line was (52.2) % mg/mL, and the percentage of survival in **HT29** cells was (35-70) %, as demonstrated in fig. (5 and 6). In the case of **AGS**, Complex **5** has not shown any toxicity in 1,2 mg/mL concentrations but the Complex **5** had a cell toxicity in 4 mg/mL in comparison to control (**p<0.01). The result

showed that IC $_{50}$ values of ligand **5** on the **AGS** cell line were (38.2) % mg/mL, and the percentage of survival **AGS** cells was (15-45) %, as demonstrated in fig. (7 and 8). IC $_{50}$ value shows with non-tumorigenic cells (**MCF-12A**) about (42.61) %.

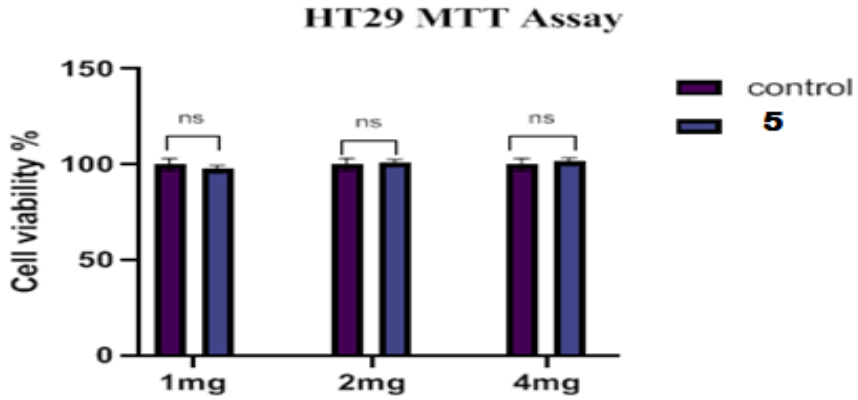


Fig. 5: Cytotoxic activity of complex 5 vs HT29 Assay cell line

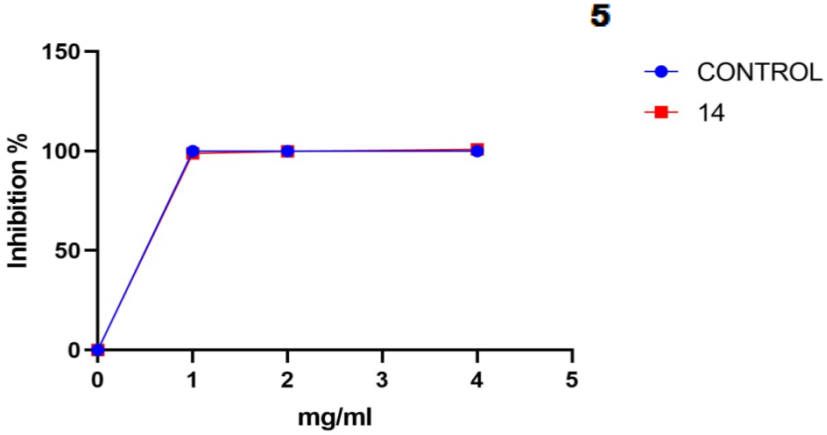


Fig. 6: IC$_{50}$ of complex 5 vs HT29 Assay cell line

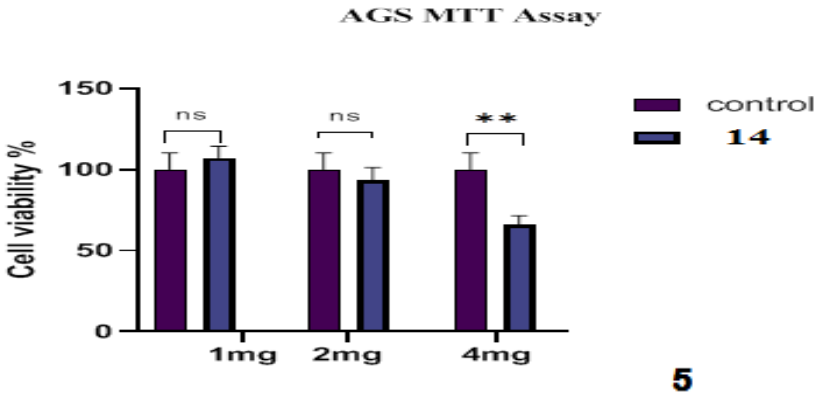


Fig. 7: Cytotoxic activity of complex 5 vs AGS Assay cell line

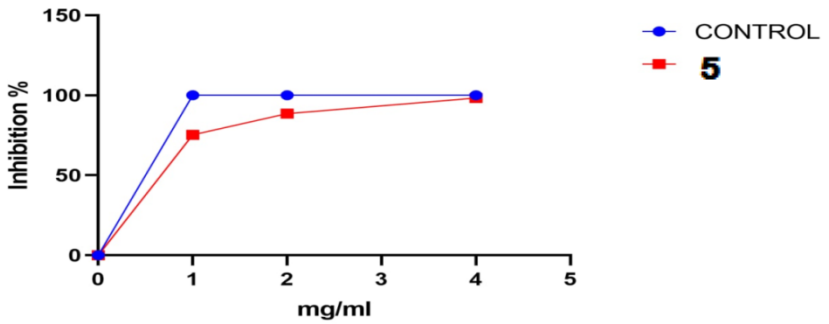


Fig. 8: IC_{50} of complex 5 vs AGS Assay cell line

Cytotoxic Studies of Platinum Complex

The MTT assay results of effects of gold complex **6** in different concentrations (1,2 and 4 mg/mL) on AGS and HT29 cell lines. These complexes have shown anti-cancer high activity to varying degrees, depending on the type and concentration of the complex. In the case of **HT29**, complex **6** has shown high cell toxicity in 4 mg/mL concentration in comparison to the non-treated group (control) (**p<0.01). The result showed that IC_{50} values of complex **6** on **HT29** cell line were 16.0 % mg/mL, and the percentage of survival **HT29** cells was (34-45)% , as demonstrated in fig. (9 and.10). In case of **AGS** , complex **6** have shown the high cell toxicity in 1and 2 mg/mL concentrations in comparison to non-treated group (control) (**p<0.01 and ***p<0.0001, respectively). The result showed that IC_{50} values of complex **30** on the **AGS** cell line were 14.1 % mg/mL, and the percentage of survival **AGS** cells was (12-23)%, as demonstrated in fig. (11 and.12). IC_{50} value shows with non-tumorigenic cells (**MCF-12A**) about (42.68) % .

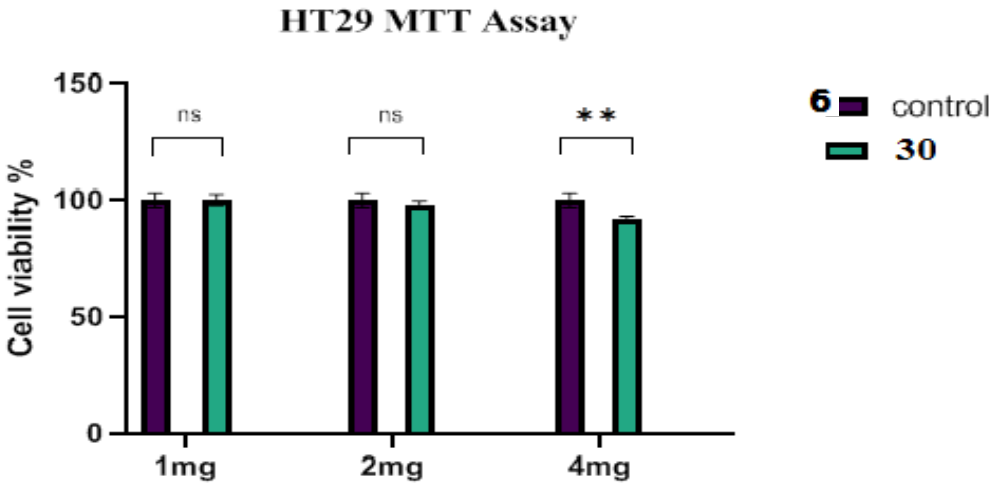


Fig. 9: Cytotoxic activity of complex 6 vs HT29 Assay cell line

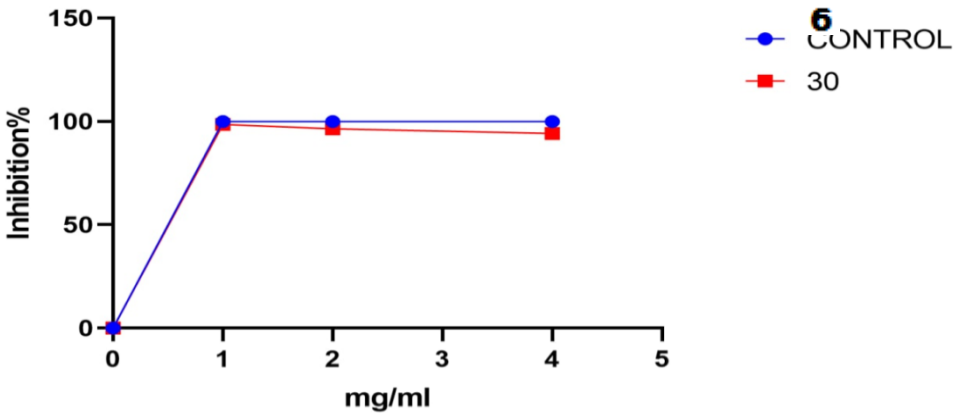


Fig. 10: IC_{50} of gold complex 6 vs HT29 Assay cell line

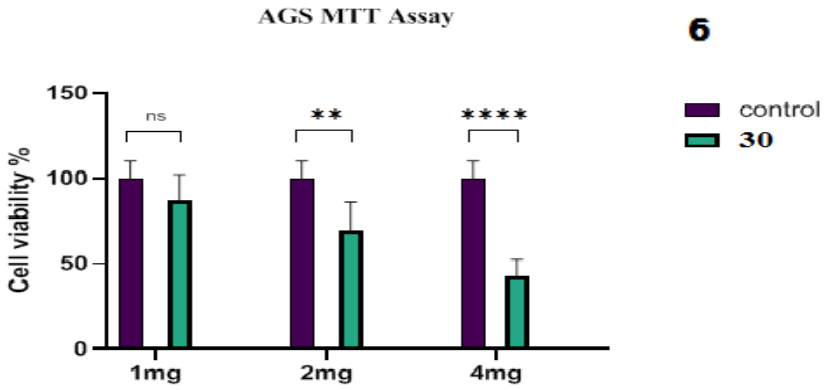


Fig. 11: Cytotoxic activity of complex 6 vs AGS Assay cell line

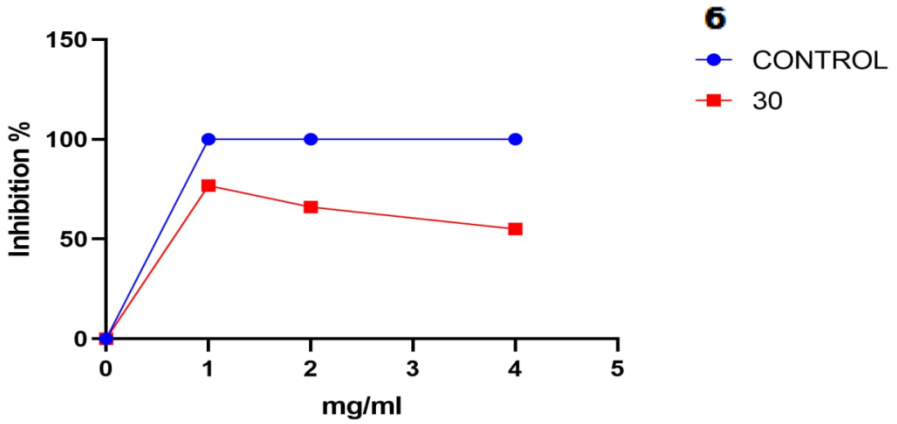


Fig. 12: IC_{50} of complex 6 vs AGS Assay cell line

The newly synthesized derivatives were evaluated for their anticancer potential towards gastric adenocarcinoma **(AGS)** ,colon carcinoma **(HT29)**, and normal cell line **(MCF-12A)** . Generally, all the derivatives synthesis compounded concentration -dependent effects on all cell lines (Table 1).

Table (1): IC_{50} value to four synthesized compounds

Com.No.	IC_{50} value at 24 hour (mg/moL)		
	Cancer cells		Normal cells
	HT29	AGS	MCF-12A
4	52.2	38.2	42.61
5	8.8	10.9	56.61
6	16.0	14.1	42.68

Conclusions

This work included three sections in order to the gradation of work. The first part is preparation of new symmetrically substituted imidazolium salts. The imidazole reacting with aliphatic and aromatic substituents at 90°C to formed imidazolium salts.

The ^{1}H NMR spectra of imidazolium salt showed three typical signals at (9.8 NHCH) , (7.05 and 6.75 Him) ppm due to imidazole ring protons of ligand (3).The second part of this study focused on the synthesis of new compounds of Ag(I) , pd(II) and pt(II)-NHC derivatives of imidazolium salts (**4,5 and 6**) and determination by using ^{1}H-NMR , ^{13}C-NMR spectroscopy, FT-IR spectrophotometer, high resolution mass spectra and melting point. The imidazole derivatives were synthesized by using *in-situ* method via the reaction of an NHC precursor imidazolium salt with Ag_2O in an appropriate organic solvent (acetonitrile) to afford Ag(I)-NHC complex. This approach yielded high quantities of the synthesized products. The Pd(I)-NHC complex (5) was obtained in a quantitative yield under mild conditions using the transmetallation technique. This involved employing the corresponding Ag(I)-NHC complex as a carbene transfer reagent and reacting it with Pd(CH3CN)2Cl2 in refluxed methanol at room temperature for 4 hours. The complex precipitated as a white solid powder with a reasonable yield. The synthesis of the platinum(II)-NHC complex was conducted under a nitrogen atmosphere, utilizing anhydrous toluene. Imidazolium salts (2) were reacted with platinum dichloride salt and 4-bromopyridine, stirred overnight at 100°C. The 1H NMR spectra of the silver(I), palladium(II), and platinum(II) complexes exhibited a loss of the imidazolium proton H2, confirming the formation of the Ag(I), Pd(II), and Pt(II)-NHC complexes. In the third part, the study explores the anticancer properties of the Ag(I), Pd(II), and Pt(II) complexes. The Ag(I), Pd(II), and Pt(II)-NHC complexes (4, 5, and 6) demonstrated significant cytotoxicity.

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