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SYNTHESIS AND ANTICANCER ACTIVITIES OF SOME METAL COMPLEXES INVOLVING N-HETEROCYCLIC CARBENE LIGANDS

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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ISRAA SAMI HADI ALKHUDHARI

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SYNTHESIS AND ANTICANCER ACTIVITIES OF SOME METAL COMPLEXES INVOLVING N-HETEROCYCLIC CARBENE LIGANDS

By Israa Sami Hadi ALKHUDHARI

February 2023

We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Master of Science

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ABSTRACT

SYNTHESIS AND ANTICANCER ACTIVITIES OF SOME METAL COMPLEXES INVOLVING *N*-HETEROCYCLIC CARBENE LIGANDS

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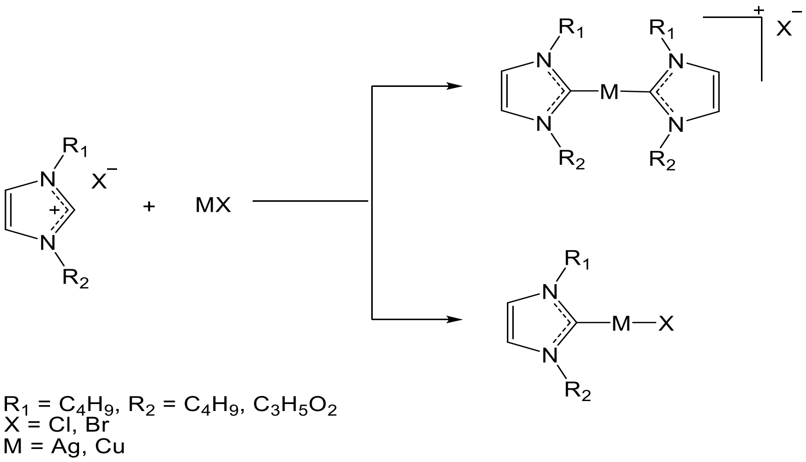
In this study, a series of novel copper(I)-NHC and silver(I)-NHC complexes were synthesized. Copper and silver-NHC complexes were synthesized by reacting metal sources with imidazolium salts in the presence of a mild base. The ligands and complexes were characterized by FTIR, ^{1}H NMR, and ^{13}C NMR spectroscopy. The Cu(I) and Ag(I)-NHC complexes were tested against breast cancer cells MCF7. The results showed that Cu(I) and Ag(I)-NHC complexes have promising effects as antiproliferative activity against breast cancer cells compared with normal cells.



$R_1 = C_4H_9$, $R_2 = C_4H_9$, $C_3H_5O_2$
X = Cl, Br
M = Ag, Cu

2023, 75 Pages

Keywords: N-heterocyclic carbene ligand, Metal complexes, Silver, Copper, Anticancer

ÖZET

N-HETEROSİKLİK KARBEN LİGANDLARINI İÇEREN BAZI METAL KOMPLEKSLERİN SENTEZİ VE ANTİKANSER FAALİYETLERİ

Israa Sami Hadi ALKHUDHARI
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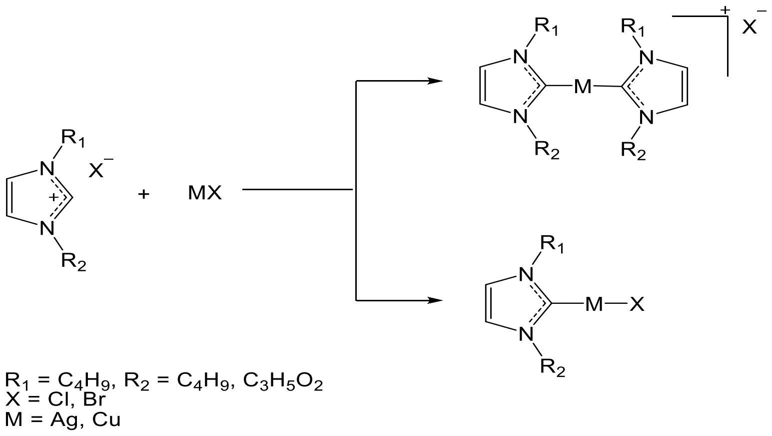
Bu çalışmada, bir dizi yeni bakır(I)-NHC ve gümüş(I)-NHC kompleksinin sentezlendi. Bakır ve gümüş-NHC kompleksleri, hafif bir baz varlığında metal kaynaklarının imidazolyum tuzları ile tepkimeye sokulmasıyla sentezlendi. Ligandlar ve kompleksler, FTIR, ^{1}H NMR ve ^{13}C NMR spektroskopisi ile karakterize edildi. Cu(I) ve Ag(I)-NHC kompleksleri, meme kanseri hücreleri MCF7'ye karşı test edildi. Sonuçlar, Cu(I) ve Ag(I)-NHC komplekslerinin, normal hücrelerle karşılaştırıldığında meme kanseri hücrelerine karşı antiproliferatif aktivite olarak ümit verici etkilere sahip olduğunu gösterdi.



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Keywords: N-heterosiklik karben ligandı, Metal kompleksleri, Gümüş, Bakır, Antikanser

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Israa Sami Hadi ALKHUDHARI
Çankırı-2023

CONTENTS

LIST OF SYMBOLS

%	Percent
cm^{-1}	Reciprocal length
G	Gram
mL	Milliliter
mmol	Millimole
ºC	Degree Celsius
µM	Micrometre

LIST OF ABBREVIATIONS

ATO	Arsenic trioxide
π	Bond referring to bonding between pi orbitals
Cu	Copper
^{13}CNMR	Carbon nuclear magnetic resonance
DMSO	Dimethyl sulfoxide
DMSO-d6	Deuterated dimethyl sulfoxide
DNA	Deoxyribonucleic acid
E.g.	Example
FBS	Fetal bovine serum
FT-IR	Fourier transformation infrared
NHC	N-heterocyclic carbine
^{1}HNMR	Proton nuclear magnetic resonance
PPM	Parts per million
Ag	Silver
THF	Tetrahydrofuran

LIST OF FIGURE

LIST OF TABLES

1. INTRODUCTION

Recently, organometallic compounds have been utilized in medical fields. The medicinal potential of gold compounds was well-known to ancient Egyptians (Nobili *et al.* 2010). Early in the development of modern pharmacology, gold compounds were frequently utilized to treat a variety of illnesses, particularly as anti-infective and anti-tubercular medicines. Gold compounds have only had limited medicinal applications and are currently exclusively utilized to treat severe rheumatoid arthritis, despite substantial clinical trials during that groundbreaking period (Messori and Marcon 2004). Due to the studied chemicals' low chemical stability and their significant systemic toxicity (such as nephrotoxicity), this is most likely the case. However, we think that the distinctive chemistry of the gold core is still underappreciated and has the potential to be employed for further, more pertinent pharmacological applications, particularly in the field of anticancer therapy (Nobili *et al.* 2010). Arsenic medications, such as arsenic trioxide (ATO), were once employed as antiseptics or to treat rheumatic illnesses, syphilis, and psoriasis in traditional Chinese medicine (Dilda and Hogg 2007, Tapio and Grosche 2006). Actually, ATO was among the first chemicals to be recommended for anticancer therapy, and it was the primary treatment for leukemia in the 18th and 19th centuries. The discovery of the platinum(II) complex cisplatin by Barnett Rosenberg in the 1960s marked the beginning of the modern era of metal-based anticancer drugs (Rosenberg *et al.* 1969).

Cisplatin, along with its descendants carboplatin and oxaliplatin, is now one of most often utilized chemotherapeutics in the treatment of many different types of cancers (Figure 1.1) (Kelland 2007). Following the success of cisplatin, a number of coordination compounds based on ruthenium, gold, titanium, copper, rhodium, vanadium, and cobalt were investigated for their anticancer efficacy, and other intriguing metal compounds are now being tested in clinical studies (Kostova 2009, Ott and Gust 2007).

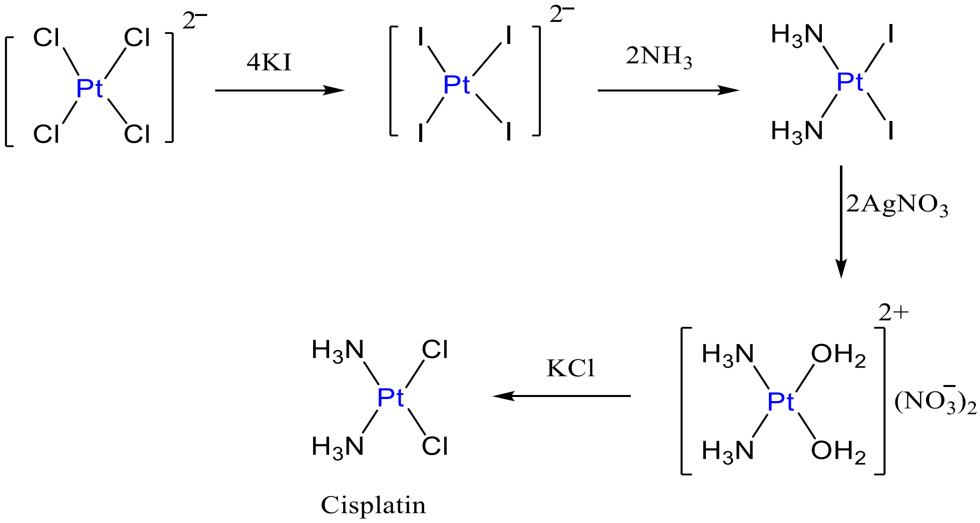


Figure 1.1 Synthesis of cisplatin

This prototype cisplatin anticancer medication is still one of the most efficient chemotherapeutic agents available at the moment (Jung and Lippard 2007). It is very effective against testicular cancer, with a near-100 percent cure rate when tumors are detected early. However, dose-limiting adverse effects such as neurotoxicity, hepatotoxicity, and nephrotoxicity severely restrict the practical use of cisplatin against this and other cancers (Jung and Lippard 2007). Furthermore, to the substantial systemic toxicity, platinum-based medicines are frequently linked with inherent or acquired resistance, which further restricts their clinical usage. To overcome these constraints, much work has been put into the creation of novel platinum medicines and the understanding of cellular reactions to them (Jung and Lippard 2007, van Zutphen and Reedijk 2005). Cis-platinum and its derivatives are used in around half of all cancer chemotherapy regimens (Kelland 2007). Despite cisplatin's shown effectiveness in the treatment of malignancies, Drug resistance and harmful side effects have reduced its efficacy (Wilson and Lippard 2014, Ghosh 2019). However, their shown antitumor effect spurs research into novel metal complexes as prospective cancer treatments (Akitsu 2018, Jia *et al.* 2017, Anthony *et al.* 2020).

Due to their unique characteristics, N-heterocyclic carbene (NHC) metal complexes have recently received a lot of interest: Highly stable metal complexes may be created by simply synthesizing NHC -metal complexes and then modifying the wingtip N-substituents to alter their physicochemical characteristics (Liu and Gust 2013). For the synthesis of novel bioactive metal NHC compounds, the ease of generating water-soluble NHC ligands is also a desirable characteristic (Schaper *et al.* 2013). Recent research has revealed that NHC- Ag, Au, Pt, Pd, Cu, Ir, Rh, and Ru complexes have an anti-proliferative effect, suggesting that they may be beneficial as anticancer medications (Patil *et al.* 2020, Tong *et al.* 2020). Some of them are capable of causing apoptosis and have cytotoxic effects equivalent to cisplatin. In vivo, various “Ag(I), Au(III), Pt(II), Pd(II), and Rh(I)” NHC complexes have been demonstrated to be effective as anti-cancer. (Tong *et al.* 2020, Guarra *et al.* 2021).

One of the deadliest illnesses, cancer takes the lives of millions of people every year, leaving them to suffer in agony all over the world. (Jia *et al.* 2017). Around 14. million new cases of cancer were diagnosed in 2012, and there were 8.2 million cancer-related deaths globally (Misra *et al*. 2010). Uncontrolled cell development is a typical symptom of many cancers. Cell division, apoptosis, and cell signaling all vary under the influence of a range of tumorigenic stimuli (Jia *et al*. 2017). First, cells in some tissues lost their normal growth control, giving them an edge over nearby cells in terms of survival and tumor formation (Shaili 2014). As a result of their unregulated growth and differentiation, the newly formed tumors become incurable after spreading to nearby tissues and organs. According to statistics, one out of every three people will develop cancer at some point in their lives. The greatest cause of mortality in both industrialized and developing nations is now cancer, surpassing cardiovascular diseases. Over one-fourth of all fatalities worldwide, including in the United States of America, are caused by cancer (Siegel *et al.* 2015).

Three major approaches are used to treat almost 200 different types of cancer: The first is surgical therapy: in the early stages of various cancers, surgical therapy prefers to perform an excision on the disease's source. Second, chemical treatment: anticancer drugs were utilized for chemical therapy to limit tumor proliferation after cancer cells were rapidly growing and dividing. Third, radiotherapy: this treatment is chosen to eliminate the cancer cell’s hereditary material, successfully controlling cancer cell proliferation. Although these treatments can be used to treat cancer patients, they must endure discomfort and severe side effects (Shaili 2014).

Metal complexes have attracted interest worldwide due to their intriguing potential in the treatment of various cancers. Metal complexes can have their thermodynamics, such as metal-ligand bond strengths, redox potential, etc., and kinetics, such as ligand exchange rates, changed by altering the central metal or its oxidation states (Romero-Canelon and Sadler 2013). Due to their exceptional photo physical and photochemical properties, metal complexes are also suitable scaffolding for a variety of biological applications (Weidmann *et al.* 2014).

2. LITERATURE REVIEW

2.1 Imidazole

Since it functions as both an acid and a base, imidazole is amphoteric. Imidazole has a pKa of 14.5 and is therefore more acidic than phenols, carboxylic acids, and imides while being somewhat less acidic than alcohols. On N-1, you may find the acidic proton. Imidazole is almost sixty times more basic than pyridine in terms of base pKa because the conjugated acid has a pKa of around 7. Resonance interactions, which increase the 3-nitrogen atom's basicity, account for these features. In (Figure 2.1), certain imidazole resonance structures are depicted (Siwach and Verma 2021).

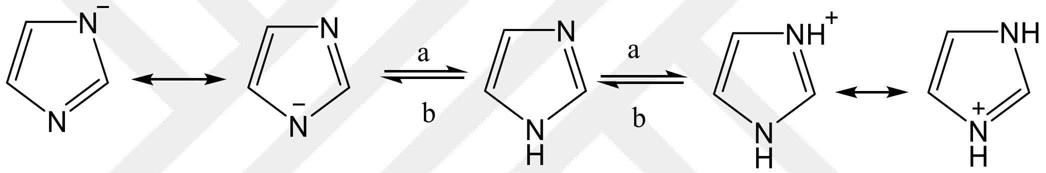


Figure 2.1 Structures of imidazole resonance and conditions for the reactions: (a) H^+, (b) $-H^+$

Imidazole is crucial in medicinal chemistry because some of its derivatives exhibit high levels of biological activity. The methods used to produce imidazole derivatives have shown biological activity as antibacterial, anti-inflammatory, analgesic, antifungal, anticancer, and antidepressants, in addition to within the biological functions of many treatment illnesses. There are several uses for imidazoles nowadays. They are crucial in fields like natural goods, pharmaceutical chemistry, materials science applications, and nonlinear optics (Brown 2012, Wang *et al*. 2002). Some imidazole compounds are employed in industrial settings as catalysts (Louie 2002, Duong *et al.* 2004). They have also been used to stop iron from corroding in acidic environments on a number of transitional metals, including silver and carbon steel (Abdallah *et al.* 2012, Gravogl *et al*. 2020, Antonijevic and Petrovic 2008, Bereket *et al*. 2002).

Imidazole is also present in a variety of substances that are employed in photography (Pandey *et al.* 2009), and the imidazole compounds are used as dopants for electronic or optoelectronic structural components, organic semiconductor matrix materials, and doping organic semiconductor materials.

2.2 Imidazolium Salts

Imidazolium salts, as opposed to their parent imidazoles, consist of a unique cation and anion pair and are frequently used as ionic liquids (Figure 2.2) (Riduan and Zhang 2013). There are several bio-applications for these imidazolium salts as well as utilization in biological systems, such as anticancer, antibacterial, antioxidant, and bioengineering applications, is a less well-known function of these salts. Due to the simplicity of structural variation, which allows for fine-tuning of features like amphiphilicity, lipophilicity, and solubility, imidazolium salts have a wide range of uses (Riduan and Zhang 2013).

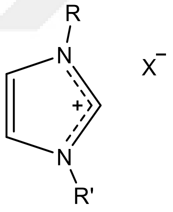


Figure 2.2 General representation of imidazolium salt

The cytotoxicity of imidazolium salts against cancer cells is either negligibly harmful or entirely nonexistent (Liu *et al.* 2021). However, it was demonstrated that a number of anticancer potentials exist for imidazole-based Ag(I), Au(I), and Pd(II)-NHC complexes (Figure 2.3).

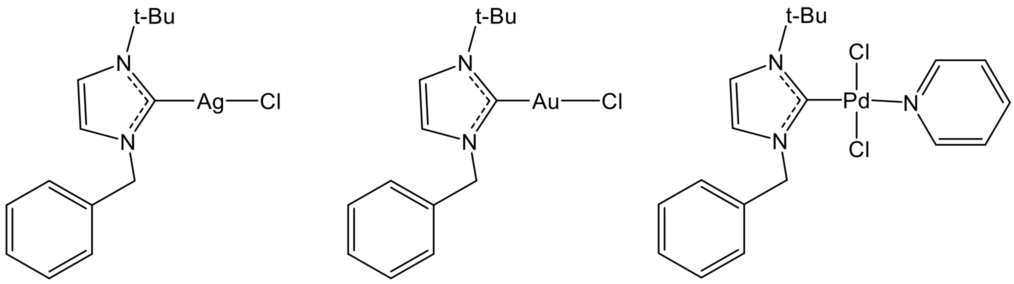


Figure 2.3 Examples of NHC complexes used as anticancer agents

N-substituted imidazolium salts have a wide range of biological uses, and one of them is the inhibition of many cytochrome enzymes involved in steroid and drug production in the liver. In particular, it has been observed that N-substituted imidazolium salts exhibit antithrombotic, herbicidal, and anthelmintic effects (McKellar and Scott 1990). These ligand precursors are increasingly becoming available in N-allyl substituted forms. However, only a few distinct mono- and bis-NHC designs exist. The effective application of both symmetric and asymmetric allyl/alkyl substituted ligands in the synthesis of biologically active compounds has facilitated the development of silver-based medicines with drastically reduced toxicity and associated side effects (Congiu *et al*. 2008).

2.3 Background of N-Heterocyclic Carbene

Divalent neutral carbon atoms with six electrons in their valance shell are called carbenes. Carbenes are thought to be significantly reactive to being separated. Chemistry has captivated with carbenes for the past 150 years, and attempts to isolate carbenes have been failed (Bertrand 2002). Typically, the carbenes are relatively reactive intermediates with a short life lifetime. However, the N-heterocyclic carbene, which has the carbene core attached to an N-heterocyclic ring, exhibits different properties. Wanzlick was the one who originally investigated it in the early 1960s (Benhamou *et al*. 2011). A short while later, in 1968, Wanzlick and Ofele reported the first use of NHC, in which they serve as a ligand to create complexes with metal (Wanzlick and Schönher 1968). Later, isolated and described the first crystalline NHC, which inspired a significant amount of research on the transition metal complexes with NHC ligands (Figure 2.4) (Hu *et al.* 2014).

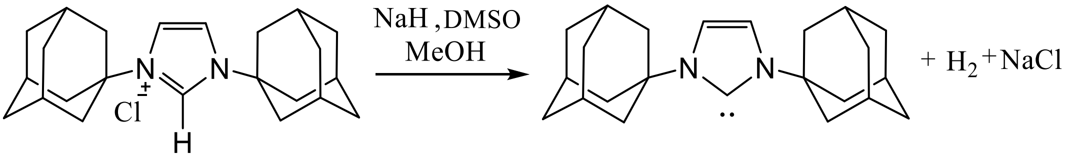


Figure 2.4 First isolation free carbine

There is a wide variety of NHCs that have alternative carbene rings, substitute nitrogen atoms, or include extra heteroatoms. As a result of steric shielding, NHCs have a longer lifespan because the carbon is stable. More broadly, it may be claimed that this property makes it an interesting ligand for coordination chemistry (Diez-Gonzalez *et al.* 2009). Additionally, NHCs serve as catalysts in chemical reactions without the usage of metals (Enders *et al*. 2007).

N-Heterocyclic carbenes are a challenging technique to add functional groups to. NHCs are very reactive while being stable, and strong bases are needed to prepare them since they have the propensity to protonate rapidly. NHCs can refer as “Bronsted bases” as they take protons. Bronsted bases can once more be considered as nucleophiles that can interact with electrophiles. NHCs are therefore also Lewis bases, i.e. σ-donor. The reactions shown in Figure 2.5 unequivocally demonstrate that NHCs are σ-donors. The potential number of functional groups that can be added is constrained by the fact that this reactivity is not just restricted to electrophiles but also to Lewis acidic transition metals (Kühl 2007).

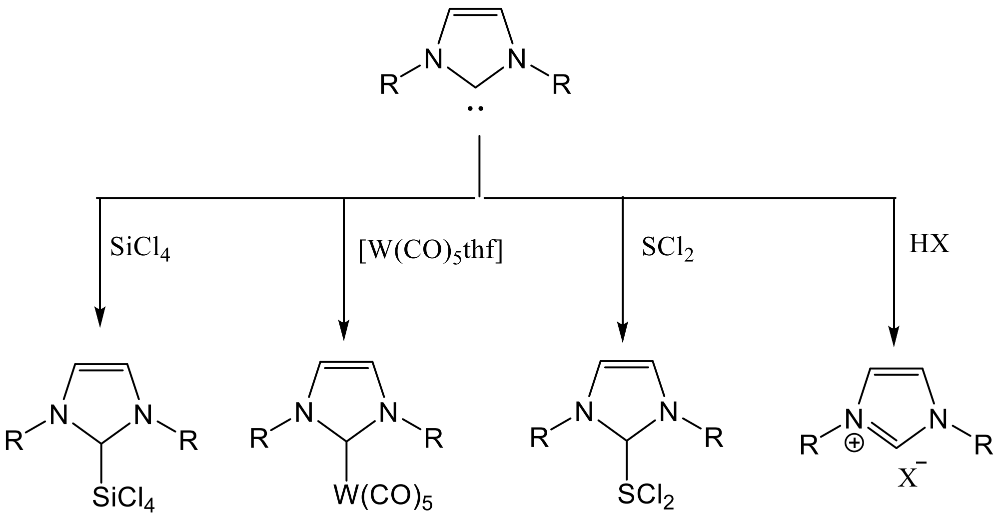
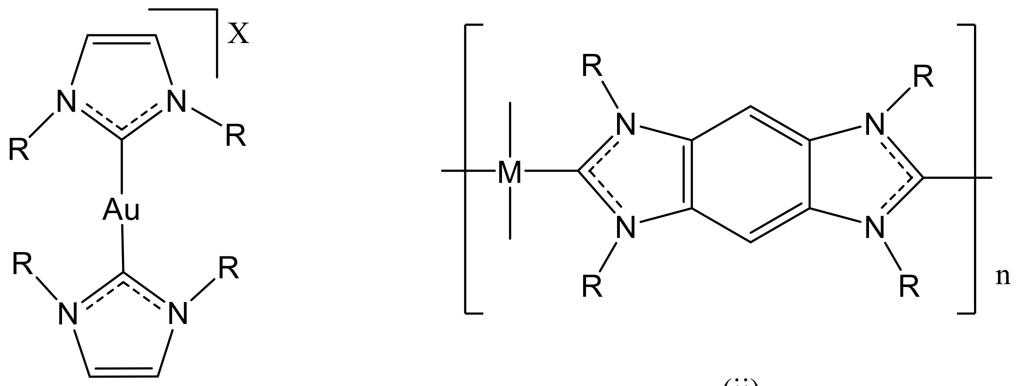


Figure 2.5 NHCs as σ-donor ligands

Prior to the development of N-heterocyclic carbenes, phosphines were the most widely used ligands in the field of organometallic chemistry. NHCs are comparable to phosphines in that they have strong σ-donor and weak π acceptor features; as a result, NHCs were first employed to imitate the related transition metal-phosphine complexes (Crabtree 2005). These two categories of ligands do differ in some ways, though. In general, NHCs have larger bond-dissociation energies than phosphines because they donate more electrons, resulting in reduced bond lengths between the metal and ligand and stronger metal-ligand connections. Additionally, NHC complexes exhibit strong catalytic activity and are more air and moisture-stable (Hopkinson *et al.* 2014), As a result, NHCs are now on par with phosphines in the field of organometallics. Currently, f-block metals (Arnold and Casely 2009), alkali earths (Kuhn and Al-Sheikh 2005), and in various oxidation states, N-heterocyclic carbene complexes provide access to all transition metals. Uses of N-heterocyclic carbenes that require coordination to transition metals are the bulk of them. Catalysis is the field in which NHC metal complexes are used most often. Herrmann and coworkers reported the first catalytic use of NHC utilizing the imidazole-2-ylidene Pd-NHC complex in the Mizoroki-Heck reaction (Herrmann *et al*. 1995). NHCs are now accessible with a variety of transition metals and are used as catalysts in both academic and commercial domains (Herrmann 2002, Diez-Gonzalez *et al*. 2009).

In hydrogenation and hydrogen transfer processes, ruthenium and iridium NHC complexes are frequently used (Normand and Cavell 2008). The field of -bond activation makes considerable use of the gold NHC complexes (Marion and Nolan 2008). Hydrosilylation processes work exceptionally well with rhodium and platinum with NHCs (Marciniec 2009). Using a cross-coupling (NHC complexes of palladium and other transition metals) (Kantchev *et al.* 2007, Valente *et al.* 2012), and ruthenium-NHC catalyzed olefin metathesis process are the two catalytic reactions that have been the subject of the most studied (Vougioukalakis and Grubbs 2010). NHCs are now used in the fields of materials and medicine notwithstanding catalysis. Silver(I) and gold(I) NHC complexes have outstanding anti-cancer and antibacterial properties. Numerous silver complexes of imidazoline-2- and imidazole-2-ylidene have antibacterial activity against both gram-positive and gram-negative bacteria (Hindi *et al.* 2009). Frequently seen in human cancers, selenizyme thioredoxin reductase, is selectively inhibited by the cationic complex of Au(I) in Figure 2.6 (i) (Hickey *et al.* 2008, Barthes *et al. 2020).* However, because of their thermal stability and capacity to alter their electronic and steric properties, NHC-transition metal complexes are ideal for the creation of organometallic materials (Mercs and Albrecht 2010). The main or side chains of polymers frequently include NHC-metal complexes. The self-healing properties of the platinum(II) and palladium(II) organometallic polymer in Figure 2.6 (ii) and its potential as an electrical conductor are also noteworthy (Boydston *et al.* 2005, Visbal and Gimeno 2014).



(i)

R=Propyl, ethyl
X=Cl, Br

(ii)

R= butyl, benzyl
M= pt, pd
X= Cl, Br

Figure 2.6 NHC complexes used in materials science and medicine

The stability of NHCs, according to several research groups utilizing NHC, should be improved by a certain substitution pattern of the substituted alkyl or aryl groups (Figure 2.7) (Wanzlick 1962).

Figure 2.7 Examples of phenyl and mesityl substituted NHCs

Imidazole-based derivatives have been utilized as the very first NHC ligands in their experiments decades ago, although imidazole-derived NHCs have been well-known for many years. With regard to a range of metal-based medications, transition metal derivatives of NHC ligands, such as imidazole, exhibit tremendous value (Rubbiani *et al.* 2010).

2.4 Synthesis of N-Heterocyclic Carbenes

By taking a proton out of related azolium salts, N-heterocyclic carbenes may be made most easily, such as “imidazolium, pyrazolium, triazolium, tetrazolium, benzimidazolium, oxazolium, or thiazolium salts” with the right bases. There are two methods for creating imidazolium salts. The first technique involves alkylating existing imidazoles using the proper electrophiles. In contrast, condensation processes are used in other techniques to create the imidazolium ring. The procedures associated to its production have been developed on a regular basis as interest in the synthesis of NHCs and imidazolium salts has grown fast (Bharti *et al*. 2022). There are methods to synthesize N-heterocyclic carbenes:

1. Numerous heterocyclic carbenes, including saturated, unsaturated, and benzannulated ones, can be produced when N-heterocyclic thiones are reduced to sulfur. Potassium in THF has been used to reduce imidazole-2-thione to carbene (Figure 2.8). Within three weeks, toluene and Na/K alloy cause a decrease in benzimidazole-2-thiones at the same time (Glorius *et al.* 2002, Hahn *et al.* 2005).

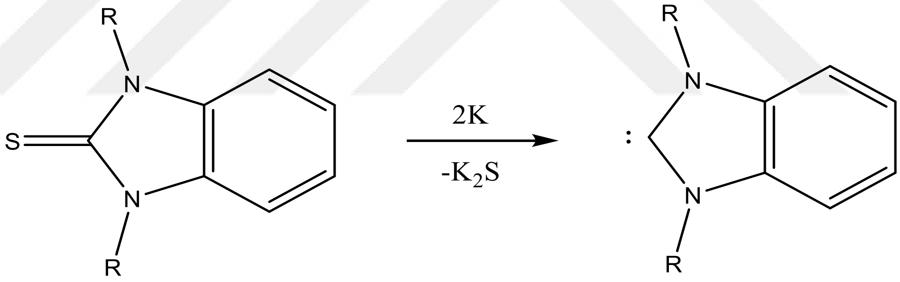


Figure 2.8 Desulfurization of thiones

2. Dehalogenation or α-elimination: Derivatives of imidazolium salts (A) with bulky N, N′-substituents go through an elimination process to produce NHCs (B) under the influence of heat induction (Figure 2.9(1)) (Bharti *et al.* 2022). Grubbs developed the equivalent alcohol elimination from 2-alkoxyimidazolidines (C) to produce imidazolin-2-ylidenes of type (D) (Figure 2.9(2)) after Wanzlick and Kleiner’s initial failed attempts. Additionally, 2-(fluorophenyl) imidazolines (E) were accessible by α-elimination of fluorinated aryls to provide imidazoline-2-ylidenes (D) (Figure 29.9(3)) (Blum *et al.* 2007). Additionally reported (Figure 2.9(4)) is the α-elimination of acetonitrile from (G) to produce benzimidazole-2-

ylidene (H) (Korotkikh *et al.* 2006). Bertrand described the dechlorination reaction between bis (trimethylsilyl)mercury and tetrahydro pyridinium chloride (I) that produced NHC (J) (Figure 2.9(5)).

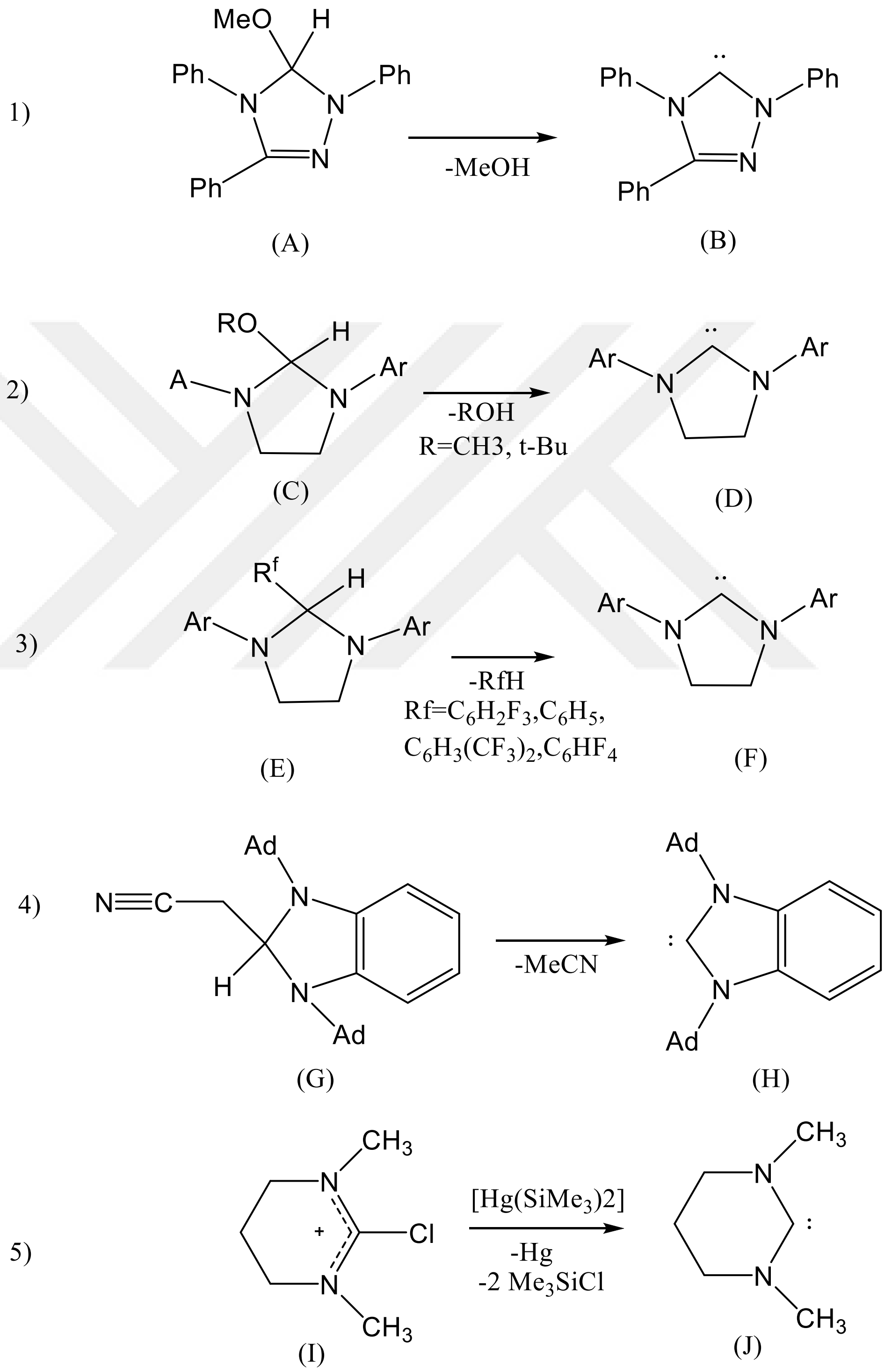
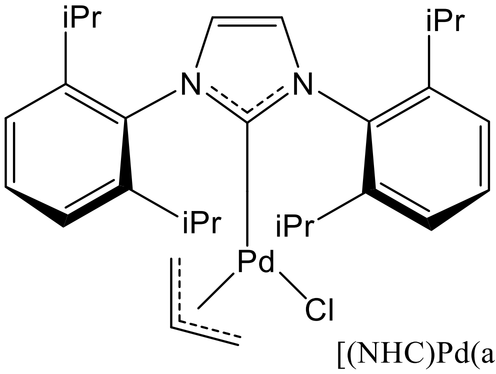


Figure 2.9 Synthesis of NHCs by α-elimination or dehalogenation

2.5 N-Heterocyclic Carbene Metal Complexes

Recently, organic transformations and metal-based pharmaceuticals have employed organometallic compounds having N-heterocyclic carbene (NHC) ligands (Liu and Gust 2016, Zou *et al*. 2015). The selection of useful ligands is likely to affect how well organometallic compounds work in medicinal applications, which is in turn influenced by the trace metal binding forms (Fricker 2007). NHCs showed potent antibacterial and anticancer properties (Asif *et al.* 2016, Napoli *et al.* 2013). NHCs are a well-known class of weakly accepting and strongly donating organometallic ligands. Non-covalent interactions between metal-NHC complexes (metal: “silver, gold, palladium, rhodium, ruthenium, iridium and platinum”) and deoxyribonucleic acid (DNA) has been observed, this is believed to largely explain their capacity to shatter DNA strands and their anti-proliferative impact (Muenzner *et al.* 2015). Metal-NHC complexes (metal: “silver, gold, palladium, rhodium, ruthenium, iridium and platinum”) have been extensively studied due to their significant applications in catalysis, in addition to their antimicrobial and anticancer properties. In comparison to other transition metals, silver is less harmful (Youn and Yoo 2017).

N-Heterocyclic carbenes (NHCs) are generated from stable divalent carbon molecules known as persistent carbenes. NHCs are excellent σ-donors because they are well stabilized by σ-donating substituents. σ-bonding with the metal, on the other hand, is ineffective. The catalytic abilities of metal-NHC complexes are well-known (Figure 2.10). The complexes are also interesting candidates for medication development due to its remarkable stability and derivatives' simplicity (Raubenheimer and Cronje 2008, Teyssot *et al.* 2009).



[(NHC)Pd(allyl)Cl] complex

Figure 2.10 Organometallic compounds are employed in medical chemistry in many different ways (Gasser *et al.* 2011)

There is an urgent need for substitutes for the widely used medication cisplatin and its derivatives, which are still utilized in more than half of all cancer treatment regimens (Jakupec *et al.* 2008, Dyson and Sava 2006). Despite their huge success, platinum compounds have two significant drawbacks: they are useless against platinum-resistant cancers and have harmful side effects such nephrotoxicity. The latter disadvantage arises as a result of the fact that these medications' ultimate aim is universal: Pt antitumor medicines are thought to work by targeting DNA, which is found in every cell (Wang and Lippard 2005). Additionally, due of its distinct chemical structure, cisplatin in particular has little room for logical advancement in terms of tumor selectivity, which leads to unfavorable side effects.

In 2017, Miguel-Coello *et al.* (2018) synthesized the NHC-metal complexes by reacting the triphenylene-imidazolium salt and metal source (Figure 2.11).

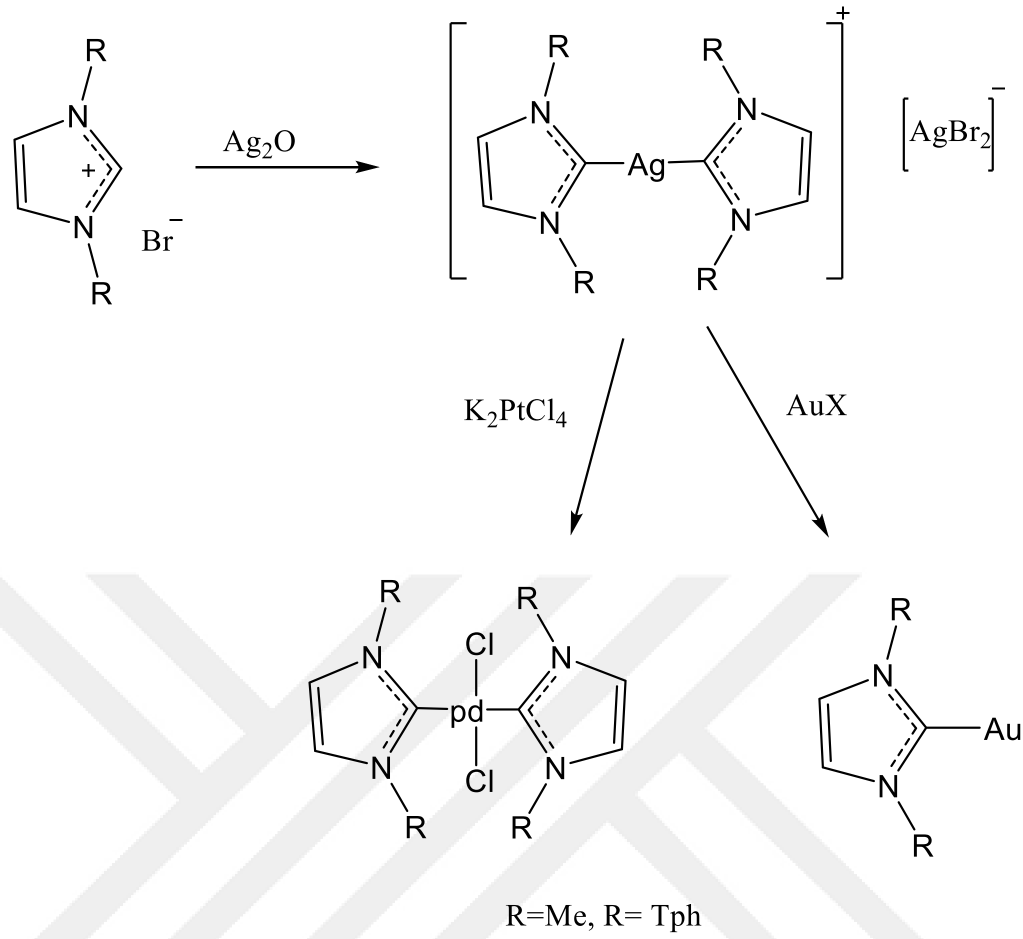


Figure 2.11 Metal complexes’ synthesis

Although Wanzlick and Schönherr recognized that a carbene carbon sandwiched between two nitrogen atoms may be stabilized by an electron-rich imidazole framework, no free carbenes were ever isolated in this early work (Wanzlick 1962). However, by reacting 1,3-diphenylimidazolium perchlorate with $Hg(OAc)_2$ (Figure 2.12), they managed to create the first mercury-carbene complex. A straightforward method for making metal-carbene complexes is the reaction of a metal acetate with an imidazolium salt, and many research teams have employed this method (Magill *et al*. 2001).

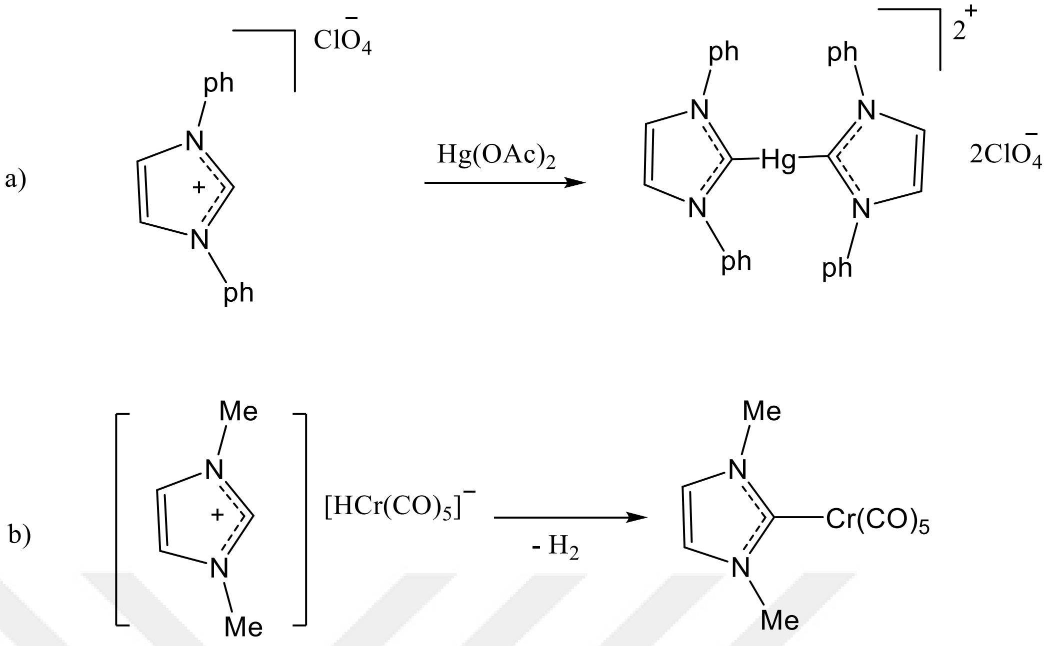


Figure 2.12 In-situ deprotonation technique for making metal-NHC complexes

The direct reaction of a pre-formed imidazol-2-ylidene with a metal source (Figure 2.13) may also be used to synthesize metal-carbene complexes (Herrmann *et al.* 1997). This technique has the advantage that a wide variety of metal sources can be used to form metal-carbene complexes. However, the production of free carbenes is not always practical because they are very sensitive and difficult to study (Bildstein *et al.* 1999).

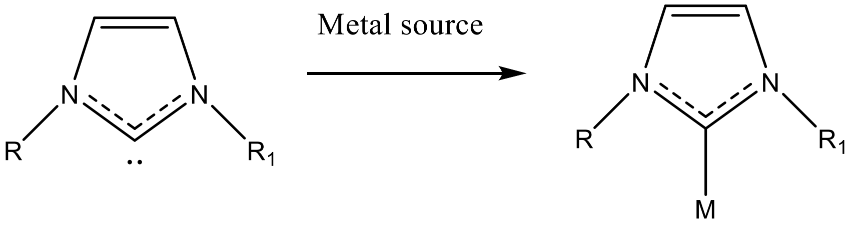


Figure 2.13 Synthesis metal-carbene complexes by the direct reaction with a metal source

Silver-carbene complexes are transition metal carbene complexes used as transfer reagents (Nielsen *et al.* 2002). Imidazolium salts reacting with Ag_2O readily produce silver-carbene complexes. Other metal species, such as $PdCl_2(CH_3CN)_2$ or

$PdClCH_3(COD)$, that have weakly coordinating ligands can accept the carbene unit from Ag (Wang and Lin 1998).

2.6 N-Heterocyclic Carbene Copper (I) Complexes

In 1993, Arduengo and coworkers made the initial discovery of the N-heterocyclic carbene (NHC) copper complex (Arduengo III *et al.* 1993) (Figure 2.14), its applications in homogeneous catalysis have shown considerable interest (Zhang and Hou 2012, Zhang and Hou 2013), particularly for the hydrosilylation of carbonyl compounds to produce the corresponding silyl compounds (Kaur *et al.* 2004), carbene transfer reactions to produce the three-membered ring (Trost and Dong 2006), the cycloaddition of azides and alkynes to enable new triazole ring reactions (Figure 2.15) (Collinson *et al.* 2013), and other reactions to produce the γ-selective allylic (Brown *et al.* 2007). New catalytic uses for NHC-Cu(I) complexes are developing recently in a number of CO_2 transformations, including the carboxylation of a variety of substrates (Zhang *et al.* 2012) as well as the conversion of CO_2 into CO or formic acid (Kleeberg *et al.* 2011).

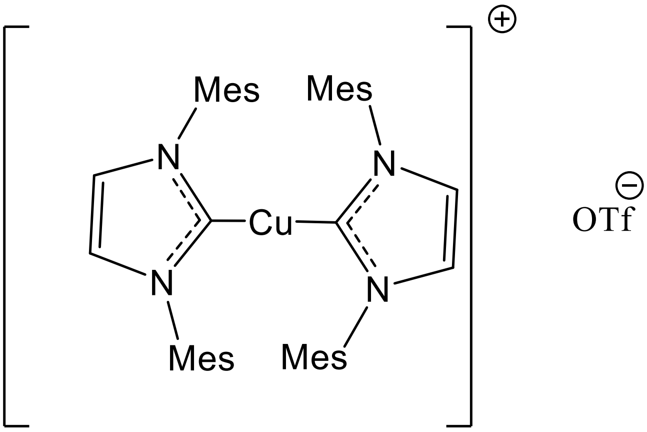


Figure 2.14 First NHC-copper(I) complex

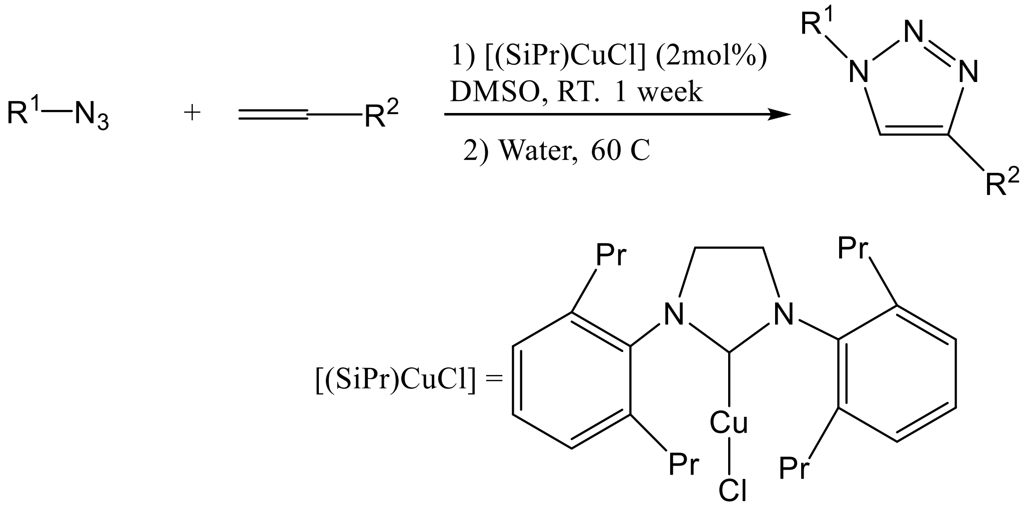


Figure 2.15 Cycloaddition of azides and alkynes

Despite the fact that copper has a lengthy history in chemistry (Evano *et al.* 2008), *N*-heterocyclic carbene (NHC) supportive ligands for transition metals were just recently found. This opened up new possibilities for copper reactivity and catalysis research (Arduengo III *et al*. 1993). Raubenheimer and coworker published a study of a neutral copper carbene complexes (Raubenheimer *et al.* 1995). The field, however, was abandoned for over 10 years. Early in the new millennium, additional discoveries were made. Danopoulos originally detailed the creation of NHC-copper using Cu_2O, and Woodward then reported the catalyst's initial application (Tulloch 2001). The subsequent work by Buchwald and Sadighi provided extensive descriptions of the first catalysis employing a well characterized complex (Jurkauskas *et al.* 2003).

Because of their steric and electrical characteristics, NHCs have received a lot of interest as ligands (Clavier and Nolan 2010, Gaillard *et al.* 2012). For some, it became clear and fruitful to combine copper with the NHC ligand family (Gaillard *et al.* 2012).

2.7 Synthesis of N-Heterocyclic Carbene Copper (I) Complexes

Several systems have only recently (10 years) been developed. Neutral mono-NHC derivatives and cationic bis-NHC derivatives, including [Cu(X)(NHC), are the two main classes of NHC-copper(I) complexes. When combined with [Cu(NHC)(L)[Y], (X = halide, acetate, hydroxide, hydride, etc.). Y = PF6, BF4, and L = NHC or PR3 (Lazreg *et al.* 2012) (Figure 2.16). The synthesis of NHC-copper complexes was needed for the copper sources with imidazolium salts. NHC-copper complexes are usually synthesized using one of two methods, according to the literature: First, imidazolium salts are treated with a suitable base and then sequentially reacted with copper sources (Diez-Gonzalez *et al.* 2008). Second, the formation of the NHC-silver complex involves the reaction of silver oxide (Ag_2O) with imidazolium salts, As opposed to the NHC-copper complexes, which are formed by replacing the silver moieties with copper sources, (Figure 2.17)(Arnold *et al.* 2004).

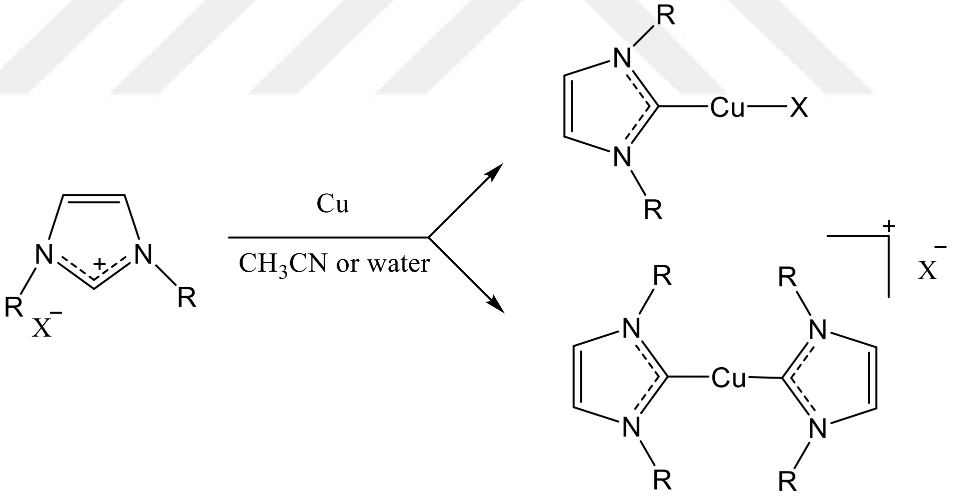


Figure 2.16 Complexes of [(NHC)$_2$Cu]PF6 and [(NHC) CuX], which are N-heterocyclic carbene copper (I) complexes

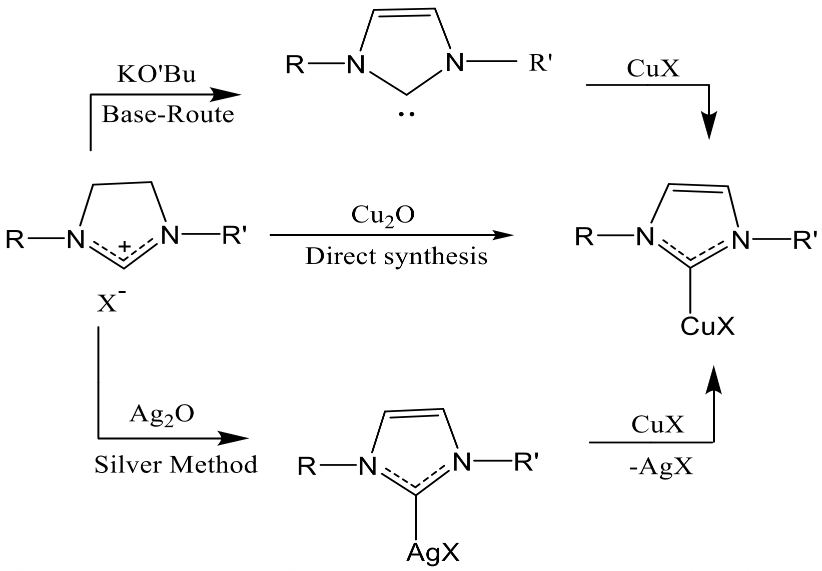


Figure 2.17 The synthesis of NHC-copper(I) complex

2.8 N-Heterocyclic Carbene Silver(I) Complexes

In the 1960s, research on silver-based antimicrobials had a resurgence due to the identification of resistance mechanisms. Today, silver-based compounds can be helpful in the fight against infections. The low toxicity and efficacy of this metal are key factors in its success. Numerous investigations show that Ag(I) is a bioactive species, despite the fact that the exact action mechanism is still unclear (Lansdown 2002). Due to their biological traits, including their effects against germs, cancer, and microbes, silver-NHC complexes, one of the many established anticancer medicines made of organometallic compounds, have garnered a lot of interest (Iacopetta *et al.* 2017). Ag-NHC complexes have been suggested as water purifiers, antiseptics, and antimicrobials to prevent infections (Da Silva *et al.* 2016). Until the invention of antibiotics, gonorrhea was treated with metallic silver, and silver nitrate was widely employed as an antibacterial agent before penicillin was discovered in antiquity (Mirsattari *et al.* 2004).

2.9 Synthesis of N-Heterocyclic Carbene Silver(I) Complexes

A free carbene was utilized to produce the first silver-NHC complex (Arduengo III *et al.* 1993). However, due to the difficulty in producing the majority of free carbenes, which are delicate to air, moisture, and heat, only a small number of silver-NHC complexes have been created using this technique (Garrison and Youngs 2005, Chung 2002).

The most popular approach for producing NHC-silver complexes is in situ deprotonation of imidazolium salts with fundamental silver precursors. As alternatives to silver(I) oxide, silver(I) acetate and silver(I) carbonate are also employed, this base is most usually used. Bertrand and colleagues' reaction of thiazolium salt with silver acetate was the first instance of this technique (Guerret *et al.* 2000). Lin and a colleague invented the process of combining silver oxide with 1,3-diethylbenzimidazole-2-ylidine to produce silver complexes (Figure 2.18) (Wang and Lin 1998). More recently, silver-NHC complexes were reported to be produced by deprotonating imidazolium salts with silver carbonate, according to Danopoulos and colleagues (Tulloch *et al.* 2000).

Synthesis of NHC silver complexes are significantly simpler because of the usage of silver oxide (Lee *et al*. 2005). The reactions may be carried out in a variety of solvents, including water, under ambient conditions with a minimal amount of setup effort (Quezada *et al*. 2004). Due to the fact that free NHCs are sensitive to water, the formation of silver complexes in water suggests that coordination with the metal center and deprotonation of the imidazolium salt are coordinated processes (Garrison and Youngs 2005). Silver-NHC complexes can take on a wide range of forms in the solid state depending on the ratio of silver to imidazolium salts employed in the synthesis, the kind of NHC ligand, and the silver sources. Structure may also depend on the presence of counter anions, the solvent, and the temperature (Melaiye 2005).

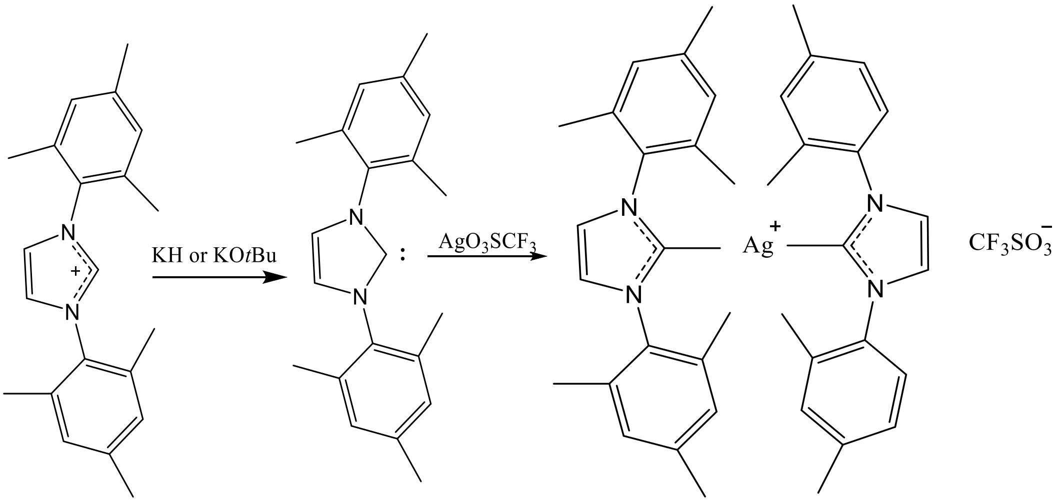


Figure 2.18 Ag(I) NHC complex synthesis (Kascatan-Nebioglu *et al.* 2007)

Imidazolium salts and Ag_2O, Ag_2CO_3, or AgOAc are combined to form Ag-NHC complexes, which have rather strong silver-carbon bonds, Figure 2.19. They are able to circumvent issues with traditional silver antibiotics such rapid activity loss and pathogen sulfonamide resistance thanks to their enhanced stability (Hindi *et al.* 2009). It is anticipated that Ag-NHC complexes would operate as antibacterial agents since the release of silver ions is delayed compared to that of ionic silver complexes like $AgNO_3$.

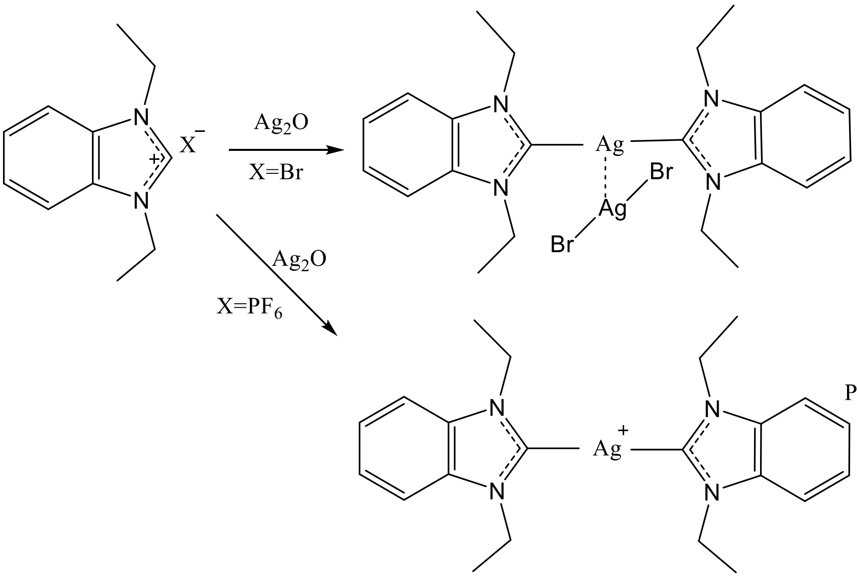


Figure 2.19 Ag_2O deprotonation produces Ag(I) NHC complexes (Kascatan-Nebioglu *et al*. 2007)

Additional in vivo research with intraperitoneal injection of [4,5-dichloro-1,3-dimethy imidazol-2-ylidene-] silver(I) acetate demonstrated activity against ovarian cancer in mice (Figure 2.20). According to these findings, depending on the kind of cancer, Ag-NHC complexes may be helpful in chemotherapy (Medvetz *et al.* 2008).

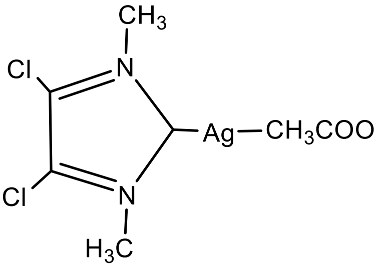
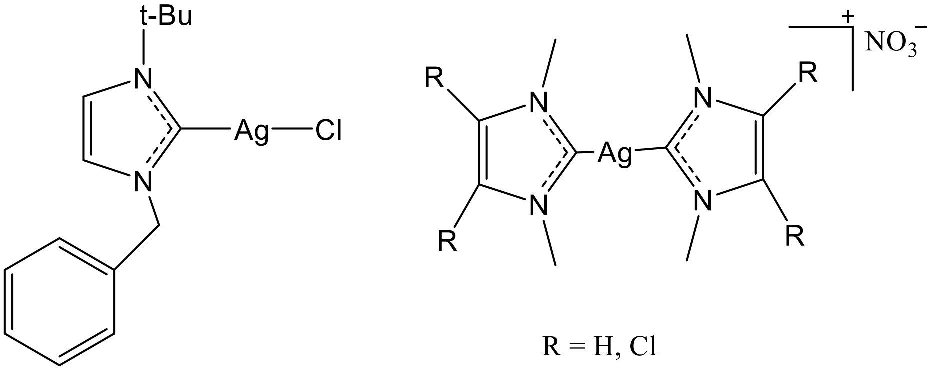


Figure 2.20 Imidazol-2-ylidene silver(I) acetate

The study was mainly done by Mercs and Albrecht (2010) and Kascatan-Nebioglu *et al.* (2007) encouraged by the results from other groups regarding the anti-tumor activity of silver complexes. Ag–NHC complex (Figure 2.21(A)) with low cytotoxic effects on HeLa cells (3% proliferation inhibition at a 10 µm concentration) was reported by (Ray *et al.* 2007). Later, the same group created two Ag-bis (NHC) complexes: "bis [1,3-dimethylimidazol-2-ylidene] silver (I) nitrate and bis [4,5-dichloro-1,3-dimethylimidazol-2-ylidene] silver (I) nitrate" (Figure 2.21(B)) both of which exhibited comparable anticancer effectiveness against H460 lung cancer cells. The primary factor here is likely the pace at which silver salt is released, and it appears to affect the stability of the complex. The maximum concentration evaluated for these substances was 100 M, and the imidazolium salts, AgBr, and $AgPF_6$ used as comparisons all have IC50 values above this level. The cytotoxicity of silver NHCs is therefore clearly influenced by the synergistic interaction between the silver core and the NHC ligand (Panzner *et al.* 2009).



(A) (B)

Figure 2.21 Depending on the kind of cancer, Ag-NHC complexes can be effective in chemotherapy

2.10 Biological Activity

In both therapeutic and diagnostic medicine, medicinal inorganic chemistry plays a crucial role. Because it takes a lot of work to obtain a compound of interest, designing metal complexes as medications is not a simple undertaking. Despite all of its limitations and negative side effects, transition metal complexes remain the most often used chemotherapeutic medicines and significantly contribute to medical therapy (Zou *et al.* 2018). The use of NHC ligands as metal carrier molecules in biological applications, however, has only lately become widespread. In catalytic chemistry, metal-NHC complexes have long been used. Copper is one of the several transition metals that have been employed with NHCs (Charra *et al.* 2017). Copper and other biometals are gaining popularity because they are less poisonous and biocompatible than non-endogenous heavy metals. Cu is a fascinating candidate for the treatment of cancers due to its bioavailability and the finding that cancer tissues have higher Cu levels (two to three times larger than in normal tissues) (Santini *et al.* 2014).

Researchers have recently looked into imidazole-based Ag(I) and Au(I) based NHC as outstanding biological agents. Their diverse biological uses, which have few adverse effects, are increasingly gaining attention on a global scale in the form of complexes. The prevention of the metal complex from disintegrating before reaching the target, it is also crucial to establish a solid metal-ligand link. Another crucial aspect of medication design is the creation of harmless breakdown products. These problems can be managed because to the unique properties of NHCs, this can be utilized to create medications made of stable, selective metals with manageable adverse effects. Ag(I) and Au(I)-NHC complexes, NHC derivatives have demonstrated exceptional anticancer activity. A survey of the literature revealed that the imidazole derivative-based Ag(I), Au(I), and Pd(II)-NHC complexes displayed very potent action against the human cancer cell line (Roland *et al.* 2011, Prencipe *et al.* 2021).

The aim of this study is to synthesize and characterize a series of new copper(I)-NHC and silver(I)-NHC complexes, and to investigate their antiproliferative activities. In this context, this study was conducted according to the following flow stage:

1. Synthesis of N-heterocyclic carbene (NHC) ligands. A diverse range of N-heterocyclic carbene (NHC) ligands are synthesized by alkylation of imidazole by nucleophilic substitution at nitrogen with halogenated compounds.
2. Synthesis of N-heterocyclic carbene copper(I) complexes by reacting NHC ligand with a copper resource.
3. Investigation of anti-cancer activities of the synthesized NHC-copper and silver complexes.

3. MATERIALS AND METHODS

3.1 General Procedures

Unless otherwise stated, nuclear magnetic resonance spectra were captured at room temperature using a Bruker ARX400 (400.13 MHz for 1H) spectrometer. Referencing solvent residual signal (DMSO-d6: ^{1}H 2.50 ppm; ^{13}C 39.52 ppm), ^{1}H and ^{13}C NMR chemical shifts were calculated. With an FT-IR spectrophotometer, the infrared spectra were captured (FTIR- Alpha-Broker).

3.2 Chemicals and Materials

The finest analytical quality of chemicals, reagents, and solvents were employed, and they were all procured from businesses and commercial sources. Imidazole (Aldrich), Sodium hydroxide (Unilab, AR), Dimethyl sulfoxide (Aldrich),1-Bromobutane (Aldrich), dichloroethane (Fluka), methyl chloroacetate (Aldrich), Diethyl Ether (Aldrich), Silver oxide (Fluka), Ag_2O, K_2CO_3, Acetone

3.3 Synthesis of Ligands

3.3.1 Synthesis of Ligand A

First step: Imidazole solution (1.36g, 20 mmol) in DMSO (10 mL) was mixed with sodium hydroxide (1.19g, 30 mmol), then the reaction was allowed to rest for 30 minutes at room temperature. After the reaction was cooled to 0 ºC and the mixture was given two hours to reheat to room temperature, 1-Bromo butane (1.9 mL, 20 mmol) was added dropwise over the course of ten minutes. To dilute the mixture, 100 cc of water was used, and DCM was used to extract the product (5 x 10 mL). After combining the organic extracts and removing the solvent under vacuum, a colorless product (1.7g, 78.5%) was obtained (Figure 3.1).

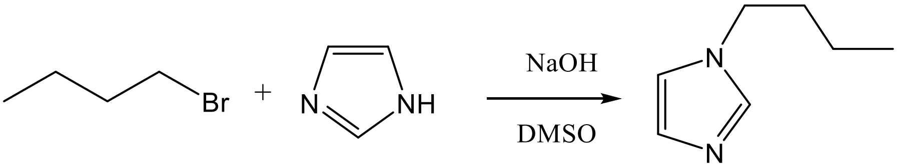


Figure 3.1 Synthesis of ligand A (first step)

Second step: 1-butyl imidazole (1.3g, 11 mmol) was added to 1-Bromo Butane (2.74g, 20 mmol), then heated the mixture for three hours at 45 ºC, the material was precipitated, filtered, and then 25 mL of diethyl ether was used as a wash to get the resulting ligand A (Figure 3.2).

^{1}H NMR DMSO-d_6: δ 9.32 1H$_{\text{Carbene}}$, 7.84 (2H, H4/H5); 4.1 (4H, H6); 1.80 (4H, H7); 1.26(4H, H8); 0.9 (6H, CH_3).

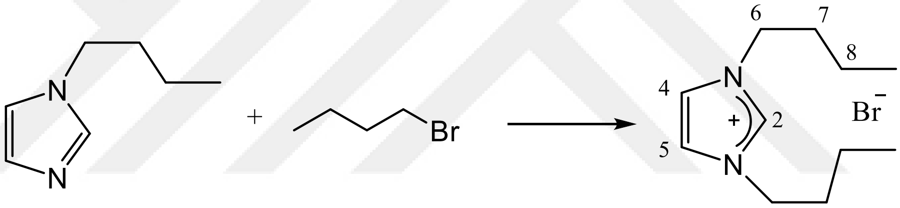


Figure 3.2 Synthesis of ligand A (second step)

3.3.2 Synthesis of ligand (B)

Methyl chloroacetate (2.30 mL, 24.6 mmol) and 1-butyl imidazole (1.32 g, 12 mmol) were mixed together and then refluxed for an extended period of time. The result was filtered out, washed with ET2O (3 x 10 mL), dried under vacuum, and left as a white crystalline solid when the mixture was cooled to room temperature (2.54 g, 91%) (Figure 3.3).

^{1}H NMR DMSO-d_6: δ 9.32 1H$_{\text{Carbene}}$, 7.83-7.76(2H, H4/H5); 5.02 (2H, CH_2-C=O); 4.10(2H, CH_2); 2.54(3H, OCH_3); 1.72(2H, CH_2); 1.22(2H, CH_2); 0.9(3H, CH_3).

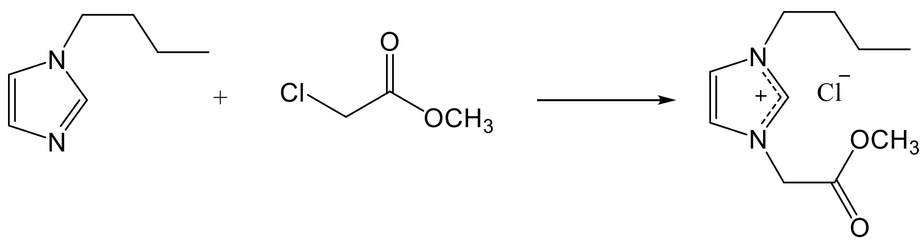


Figure 3.3 Synthesis of ligand B

3.4 Synthesis of Metal−NHC Complexes

3.4.1 Synthesis of (1,3-dibutyl-2,3-dihydro-1H-imidazol-2-yl) silver(II) bromide (1)

Silver(I) oxide (0.15 g, 0.65 mmol) was immediately added to a solution as a solid of ligand A (0.012g, 0.1 mmol) in 5 mL of dichloromethane. The reaction container was covered with aluminum foil and kept at room temperature for a day while it stirred. To get rid of any insoluble gray particles, the reaction liquid was run through a glass pipette equipped with a pad of celite-alop filter paper. A surplus of diethyl ether 5 mL was then added to the amber-colored filtrate after it had been reduced under vacuum to 1 mL, causing it to precipitate an off-white solid. The solid was suspended in 2 mL of diethyl ether and the supernatant was decanted. A white solid was produced when the solid was fully dried under vacuum (Figure 3.4).

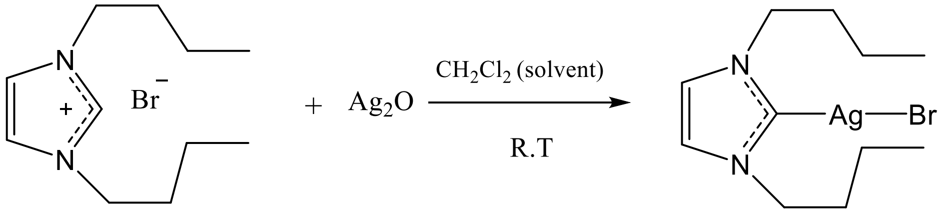


Figure 3.4 Silver complex (1)

3.4.2 Synthesis of bis (1,3-dibutyl-2,3-dihydro-1H-imidazol-2-yl) silver (I) bromide (2)

Silver(I) oxide (0.23g, 0.1 mmol) was immediately added to a solution as a solid of ligand A (0.24g, 0.2 mmol) in 10 mL of dichloromethane. The reaction container was covered with aluminum foil and kept at room temperature for a day while it stirred. To get rid of any insoluble gray particles, the reaction liquid was run through a glass pipette equipped with a pad of celite-alop filter paper. A surplus of diethyl ether (5 mL) was then added to the amber-colored filtrate after it had been reduced under vacuum to 1 mL, causing it to precipitate an off-white solid. The solid was suspended in 2 mL of diethyl ether and the supernatant was decanted. A white solid was produced when the solid was fully dried under vacuum (Figure 3.5).

^{1}H NMR DMSO-d_6: δ 7.49(4H, H4/H5); 4.10 (4H, CH_2); 1.70 (4H, CH_2); 1.20 (4H, CH_2); 0.87 (6H, CH_3).

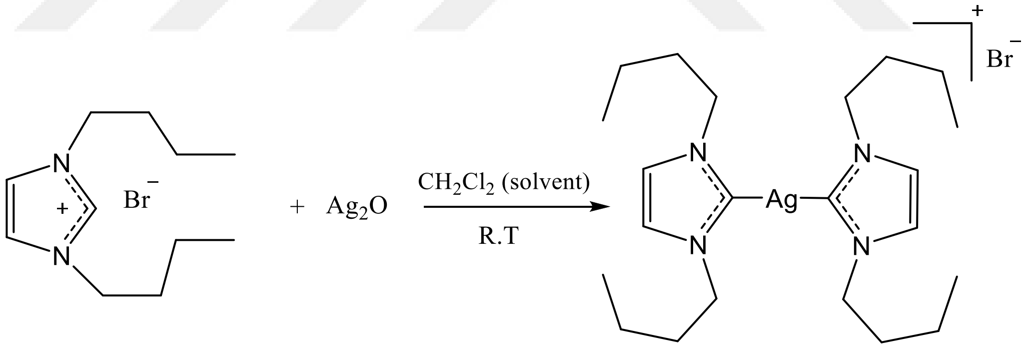


Figure 3.5 Silver complex (2)

3.4.3 Synthesis of (1-butyl-3-(2-methoxy-2-oxoethyl)-2,3-dihydro-1H-imidazol-2-yl) silver(I) chloride (3)

Silver(I) oxide (0.15g, 0.65 mmol) was immediately added to a solution as a solid of ligand B (0.021g, 0.1 mmol) in 15 mL of dichloromethane. The reaction container was covered with aluminum foil and kept at room temperature for a day while it stirred. To get rid of any insoluble gray particles, the reaction liquid was run through a glass pipette equipped with a pad of celite-alop filter paper. A surplus of diethyl ether 5 mL was then added to the amber-colored filtrate after it had been reduced under vacuum to 1 mL, causing it to precipitate an off-white solid. The solid was suspended in 2 mL of diethyl ether and the supernatant was decanted. A white solid was produced when the solid was fully dried under vacuum (Figure 3.6).

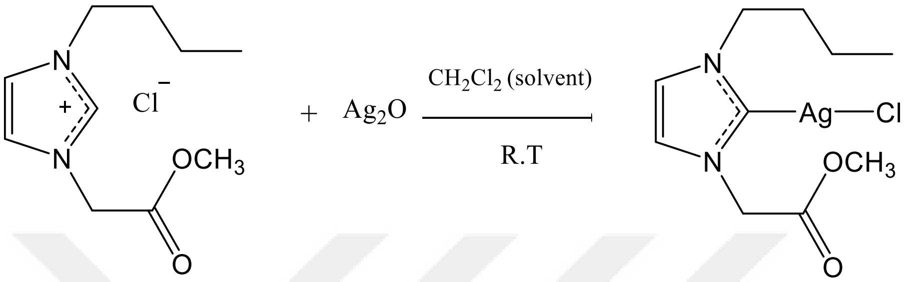


Figure 3.6 Silver complex (3)

3.4.4 Synthesis of bis(1-butyl-3-(2-methoxy-2-oxoethyl)-2,3-dihydro-1H-imidazol-2-yl) silver(I) chloride (4)

Silver(I) oxide (0.023g, 0.01 mmol) was immediately added to a solution as a solid of ligand B (0.043g, 0.2 mmol) in 25 mL of dichloromethane. The reaction container was covered with aluminum foil and kept at room temperature for a day while it stirred. To get rid of any insoluble gray particles, the reaction liquid was run through a glass pipette equipped with a pad of celite-alop filter paper. A surplus of diethyl ether 5 mL was then added to the amber-colored filtrate after it had been reduced under vacuum to 1 mL, causing it to precipitate an off-white solid. The solid was suspended in 2 mL of diethyl ether and the supernatant was decanted. A white solid was produced when the solid was fully dried under vacuum (Figure 3.7).

^{1}H NMR DMSO-*d*$_6$: δ 7.71-7.64 (4H, H4/H5); 2.6(3H, OCH_3); 4.19(2H, CH_2); 1.77(2H, CH_2); 1.23(2H, CH_2);0.88(3H, CH_3).

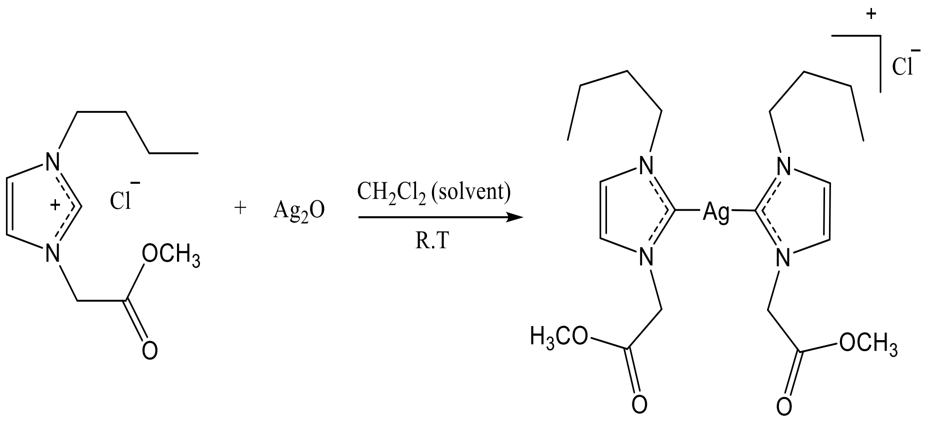


Figure 3.7 Silver complex (4)

3.4.5 Synthesis of (1,3-dibutyl-2,3-dihydro-1H-imidazol-2-yl) copper(II) bromide (5)

CuCl (0.065g, 0.65 mmol) was added to a solution of ligand A (0.012g, 0.1 mmol) and K_2CO_3 (0.027g, 0.2 mmol). The mixture was then agitated for 24 hours at 60 ºC while being suspended in 10 mL of acetone. After that, silica was used to filter the mixture. Dichloromethene was used to clean the silica pad (3 x 1 mL). Pentane (3 mL) was added to a concentrated solvent to get the required result, which was then washed with further amounts of pentane (3 x 1 mL) and dried under vacuum (Figure 3.8).

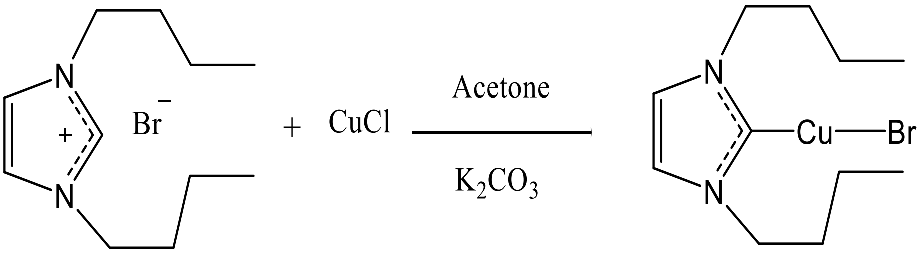


Figure 3.8 Copper complex (5)

3.4.6 Synthesis of bis(1,3-dibutyl-2,3-dihydro-1H-imidazol-2-yl) copper bromide (6)

CuCl (0.09g, 0.1 mmol) was added to a solution of Ligand A (0.24g, 0.2 mmol) and K_2CO_3 (0.055g, 0.4 mmol). The mixture was then agitated for 24 hours at 60 ºC while being suspended in 10 mL of acetone. After that, silica was used to filter the mixture. Dichloromethene was used to clean the silica pad (3 x 1 mL). Pentane (3 mL) was added to a concentrated solvent to get the required result, which was then washed with further amounts of pentane (3 x 1 mL) and dried under vacuum (Figure 3.9).

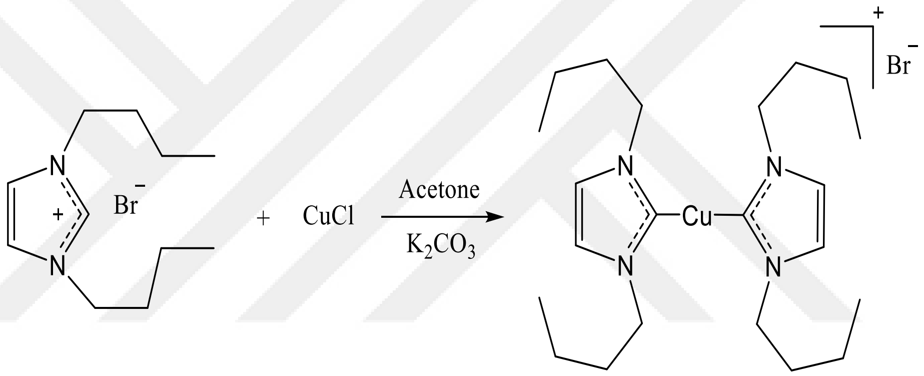


Figure 3.9 Copper complex (6)

3.4.7 Synthesis of (1-butyl-3-(2-methoxy-2-oxoethyl)-2,3-dihydro-1H-imidazol-2-yl) copper(II) chloride (7)

CuCl (0.06g, 0.65 mmol) was added to a solution of ligand B (0.021g, 0.1 mmol) and K_2CO_3 (0.027g, 0.2 mmol). The mixture was then agitated for 24 hours at 60 ºC while being suspended in 10 mL of acetone. After that, silica was used to filter the mixture. Dichloromethene was used to clean the silica pad (3 x 1 mL). Pentane (3 mL) was added to a concentrated solvent to get the required result, which was then washed with further amounts of pentane (3 x 1 mL) and dried under vacuum (Figure 3.10).

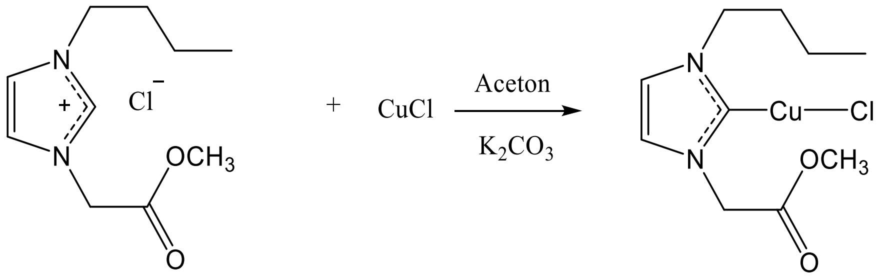


Figure 3.10 Copper complex (7)

3.4.8 Synthesis of bis(1-butyl-3-(2-methoxy-2-oxoethyl)-2,3-dihydro-1H-imidazol-2-yl) copper chloride (8)

CuCl (0.099g, 0.1 mmol) was added to a solution of Ligand B (0.043g, 0.2 mmol) and K_2CO_3 (0.055g, 0.4 mmol). The mixture was then agitated for 24 hours at 60 ºC while being suspended in 10 mL of acetone. After that, silica was used to filter the mixture. Dichloromethene was used to clean the silica pad (3 x 1 mL). Pentane (3 mL) was added to a concentrated solvent to get the required result, which was then washed with further amounts of pentane (3 x 1 mL) and dried under vacuum (Figure 3.11).

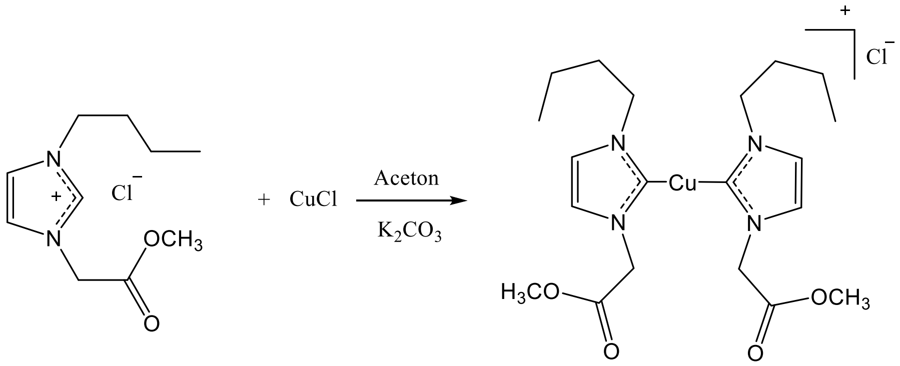


Figure 3.11 Copper complex (8)

3.5 The MTT Assay

3.5.1 Preparation of test solution

Serial two-fold dilutions from 100 µg to 6.25 µg were processed for cytotoxicity experiments and utilized as the treatment.

3.5.2 Procedure

The monolayer cell culture was trypsinized and expanded to 1.0 x 105 cells/mL using an appropriate medium containing 10% FBS. The diluted cell solution containing 50,000 cells was added to each well of the 96-well microtiter plates. Upon the development of a sectional monolayer after 24 hours, the supernatant was collected and washed with the medium. Adding 100 µl of samples at various test concentrations on top of the layer on microtiter plates. Following that, the plates were incubated for 24 hours at 37°C and 5% CO_2. The plates were then incubated for 24 hours at 37 °C with 5% CO_2. Following the incubation period, the test solutions in the wells were withdrawn, and 100 µl of MTT (5 mg/10 mL of MTT in PBS) was added to each well. The plates were damaged. 100 µl of DMSO was added following the removal of the supernatant. To dissolve the produced formazan, the plates were gently shaken. A microplate reader operating at a 590nm wavelength was used to measure the absorbance. The method below was used to compute the percentage growth inhibition, and the data for the dose-response curves for each cell line were used to obtain the test drug's 50% inhibitory concentration (IC_{50}).

3.5.3 Calculating inhibition

Inhibition % = 100-(OD of sample/ OD of control) x 100

4. RESULTS AND DISCUSSION

4.1 Synthesis of Ag(I)- And Cu(I)-NHC Complexes

By reacting imidazole with alkyl halides and using DMSO and NaOH as solvents, it was possible to create N-substituted imidazole. By reacting N-substituted imidazole with alkyl halides to create ligands, imidazolium salts were created (A and B). Direct complexation of silver(I) oxide with ligands (A and B) in dichloromethane has been described as a method for creating Ag(I)-NHC complexes (Figure 4.1). In a similar manner, CuCl was added to a solution of the ligands (A and B) in the presence of K_2CO_3 to create Cu(I)-NHC complexes (Figure 4.2).

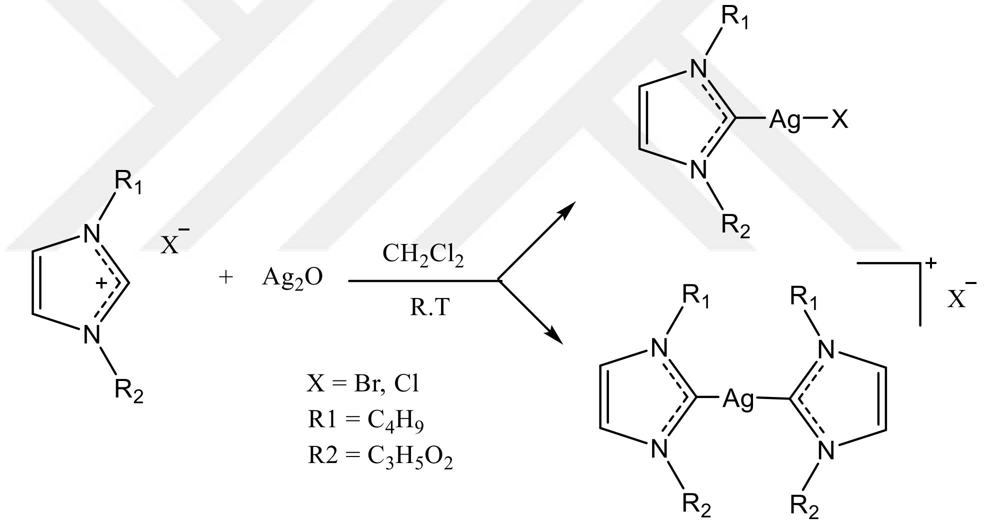


Figure 4.1 Synthesis of Ag(I)−NHC complexes

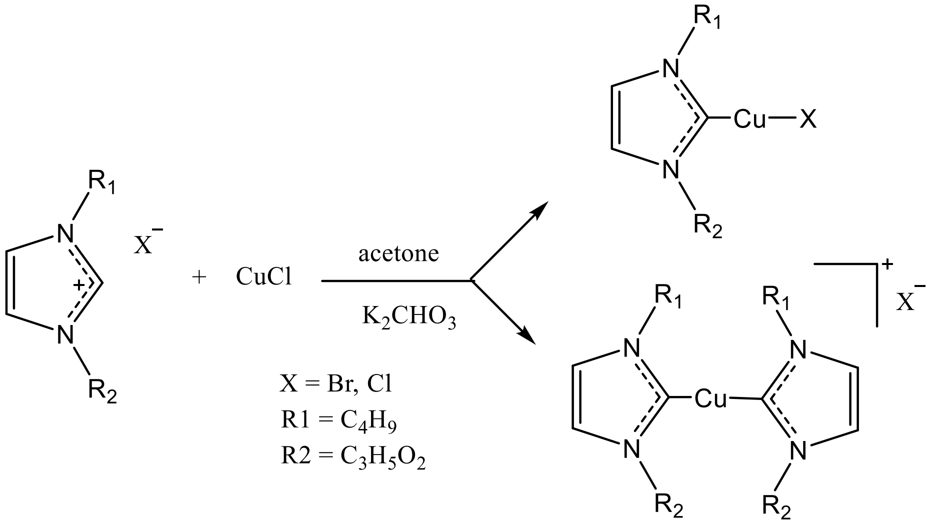


Figure 4.2 Synthesis of Cu(I)−NHC complexes

4.2 Identification Infrared of Imidazole

The FTIR spectrum of imidazole was shown in Figure 4.3. In the spectrum, the band appeared at 3398 cm^{-1} refers to (N-H) and the frequency at 3116 cm^{-1} due to (C-H), and bands at 1670 and 1670 cm^{-1} refer to (C=N) and (C=C) respectively. The band of (C-N) appears at 1321 cm^{-1}.

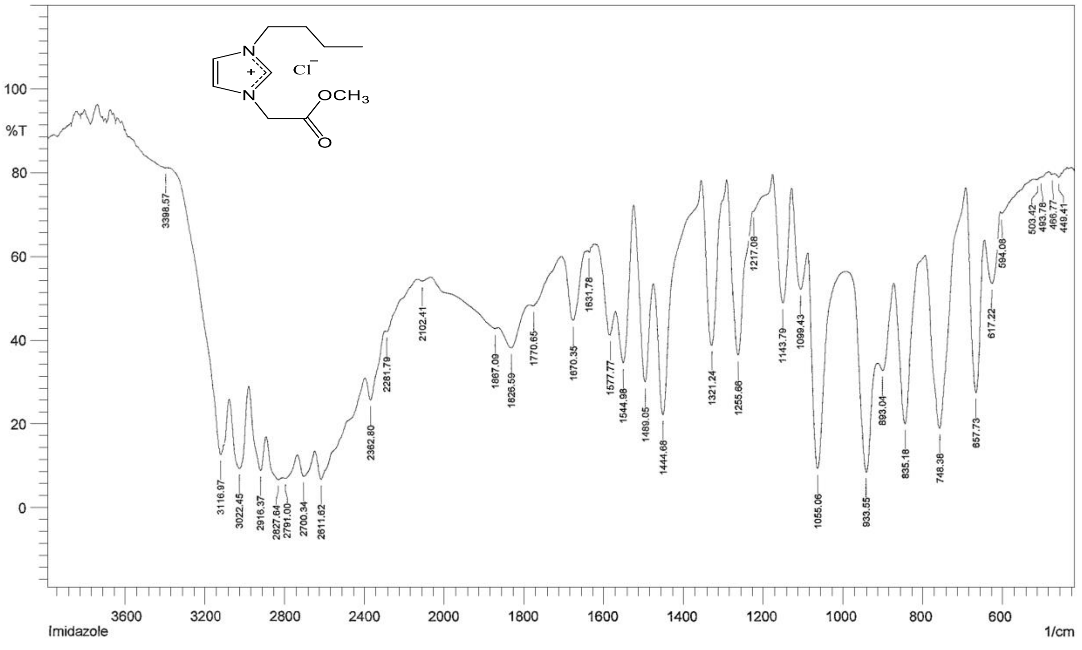


Figure 4.3 FTIR spectrum of imidazole

4.3 Identification Infrared of Ligand A

Figure 4.4 shows the FTIR spectrum of ligand A. The spectrum shows disappearance of a frequency (N-H), which indicates the formation of the compound, and frequency at 3128 cm^{-1} due to (C-H) aromatic, and (C-H) aliphatic at 2954, and bands at 1564 and 1624 cm^{-1} refer to (C=C). The bands of (C-N) appear at 1624 cm^{-1}. There is broad band appears at 3430 cm^{-1}, which refers to the remaining moisture H_2O in the compound.

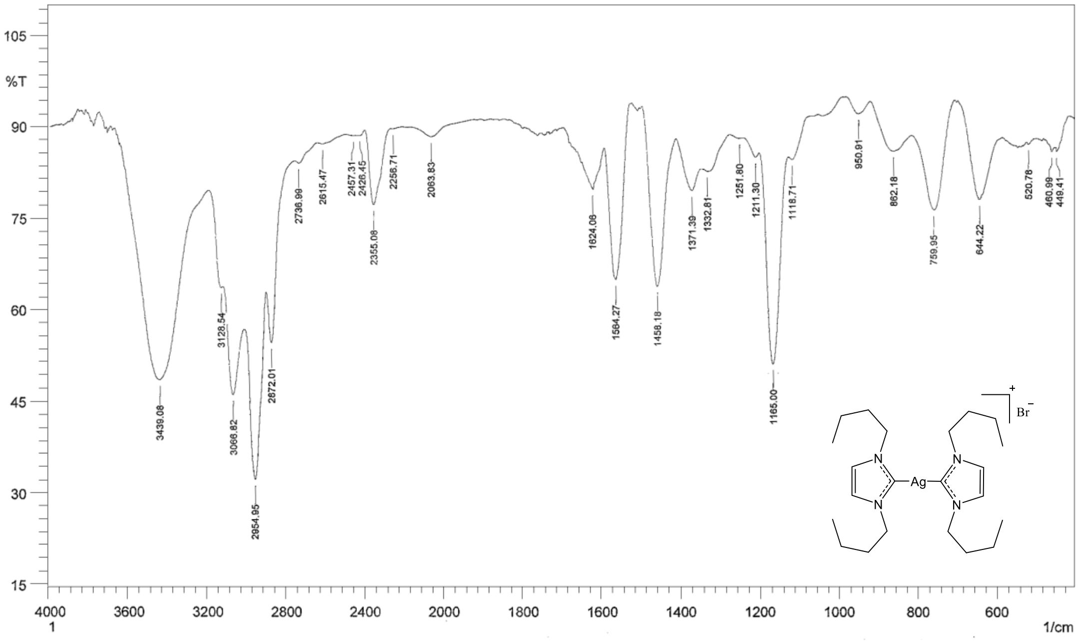


Figure 4.4 FTIR spectrum of ligand (A)

4.4 Identification Via ^{1}HNMR of Ligand A

In the ^{1}H NMR spectra of ligand A in DMSO-d_6 solution at room temperature (Figure 4.5) shows doublet signals that appear with a chemical shift of δ (7.83-7.83) ppm belong to the protons of the H4/H5 of imidazolium salt, as well as a triple signal at a chemical shift δ (4.16-4.19) ppm belonging to the (CH_2) group linked to the imidazolium salt. When multiple signals at a chemical shift δ (1.79) ppm refer to the hydrogen of the (CH_2) group of carbon number 7, as well as multiple signals when a chemical shift δ (1.27) ppm returns to the hydrogen of the (CH_2) group of carbon atom number 8, as well as a triple signal at a chemical shift of δ (0.89) ppm belonging to the hydrogen of the (CH$_3$). The ^{13}C NMR of ligand A showed at 49.02 ppm for the carbon of carbon of (N-CH$_2$). The single signal at 136.44 ppm refers to C2 of the imidazolium salt, while the signals at 122.93 ppm refer to C4/C5 of the imidazolium salt. The signals at 31.75 and 19.26 ppm for the carbon of CH$_2$CH$_2$ group, while the single at 13.76 ppm refers to CH$_3$ group (Figure 4.6).

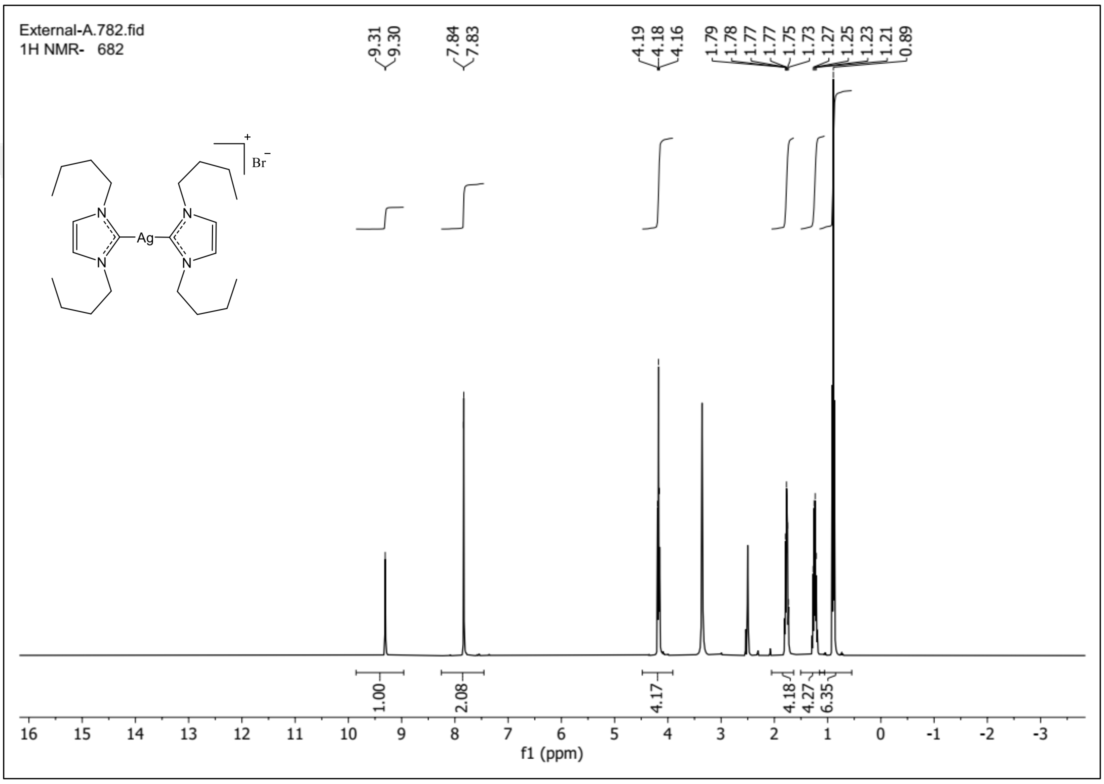


Figure 4.5 ^{1}HNMR spectrum of ligand A

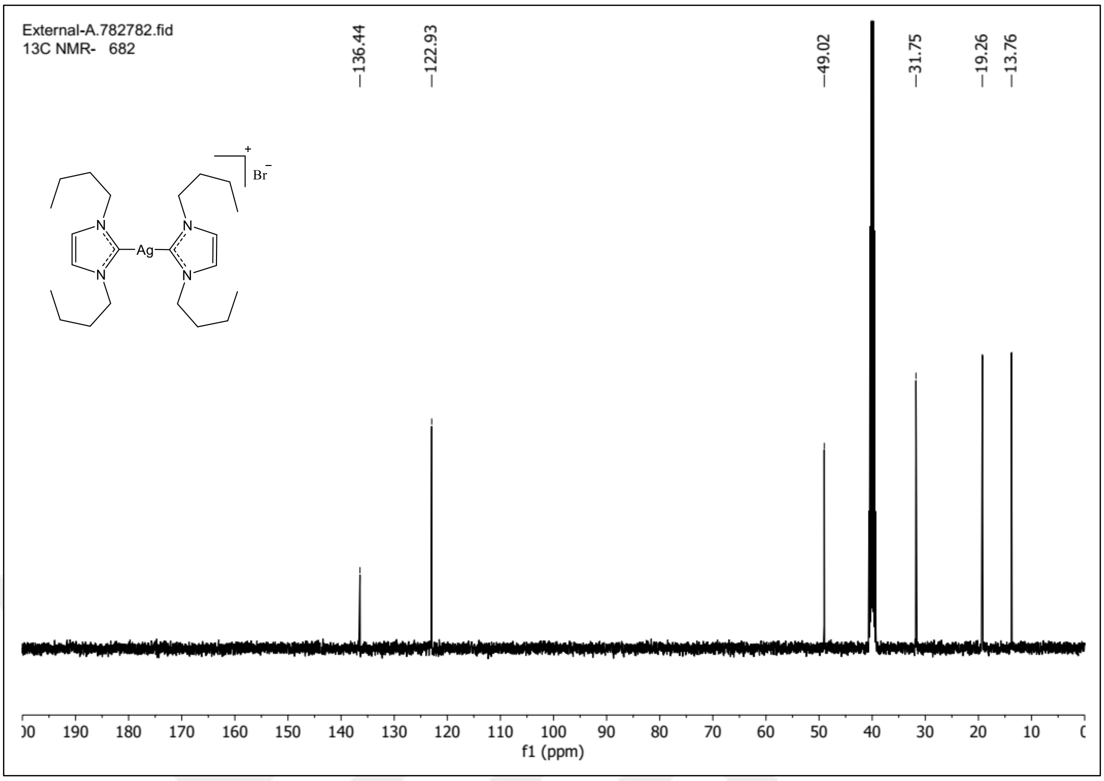


Figure 4.6 ^{13}CNMR spectrum of ligand A

4.5 Identification Infrared of Methyl Chloroacetate

The FTIR spectrum of methyl chloroacetate was shown in Figure 4.7. The spectrum shows the band at 1261 cm^{-1} refer to (C-O), and the frequency at 3985 cm^{-1} due to (C-H). The spectrum also appears the bands at the 1741 cm^{-1} refer to (C=O), and at 569 cm^{-1} refer to (C-Cl).

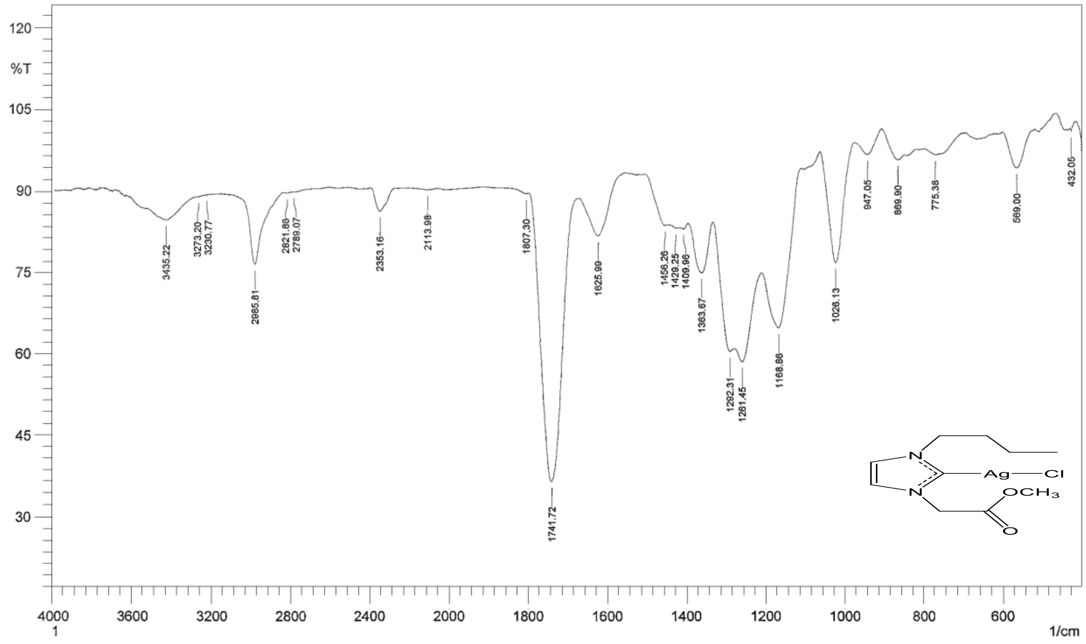


Figure 4.7 FTIR spectrum of methyl chloroacetate

4.6 Identification Infrared of Ligand B

The FTIR spectrum of ligand B was shown in Figure 4.8. The spectrum shows frequency at 3134 cm^{-1} due to (C-H) rink, and (C-H) aliphatic at 2962, and bands at the 1728 and 1629 cm^{-1} refer to (C=O) and (C=C) respectively. The bands of (C-N) appear at 1381 cm^{-1}. There is broad band appears at 3425 cm^{-1}, which refers to the remaining moisture H_2O in the compound. The frequency at 1458 refers to bending (C-H).

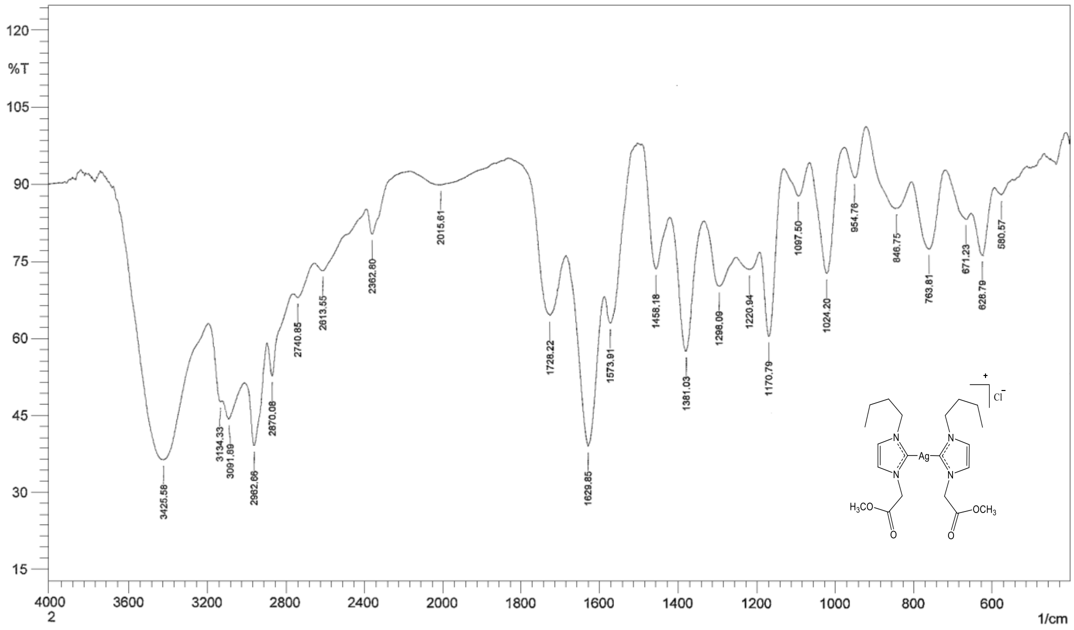


Figure 4.8 FTIR spectrum of ligand B

4.7 Identification Via ^{1}HNMR of Ligand B

In the ^{1}H NMR spectra of ligand B in DMSO-d6 solution at room temperature (Figure 4.9) shows a single belonging to the (CH) group attached to the imidazole ring at a chemical shift of δ (2.3-2.2) ppm, while the several signals associated with a chemical shift of δ (7.83–7.76) ppm are the protons of the H4/H5 of the imidazolium salt., and it was characterized by the appearance of a signal at a shift of δ (5.02 ppm) belonging to the (CH_2) group linked to the carbonyl group and an imidazolium salt ring, in addition a triple signal at a chemical shift δ (4.1) ppm belonging to the (CH_2) group linked to the (imidazolium salt). When a chemical shift δ (2.54) ppm belongs to the (OCH_3) group, a several signals at a chemical shift δ (1.73) ppm refers to the hydrogen of the (CH_2) group of carbon number 7, in addition a multiple signal for the hydrogen of the (CH_2) group in carbon atom number 8 is present at a chemical shift of δ (1.21) ppm, in addition a triple signal at a chemical shift of δ (0.87) ppm belonging to the hydrogen of the (CH_3) group of carbon atom number 9. The ^{13}C NMR of ligand B showed there is a new signal at 168.61 ppm for the carbon of carbonyl group. The single signal at 137.90 ppm refers to C2 of the imidazolium salt, while, the signals at 124 -122 ppm refer to C4/C5 of the imidazolium salt. The signals in the range of 48.91- 40.80 ppm for the carbon of butyl group, while (carbonyl-CH_2) appears at 50.89 ppm (Figure 4.10).

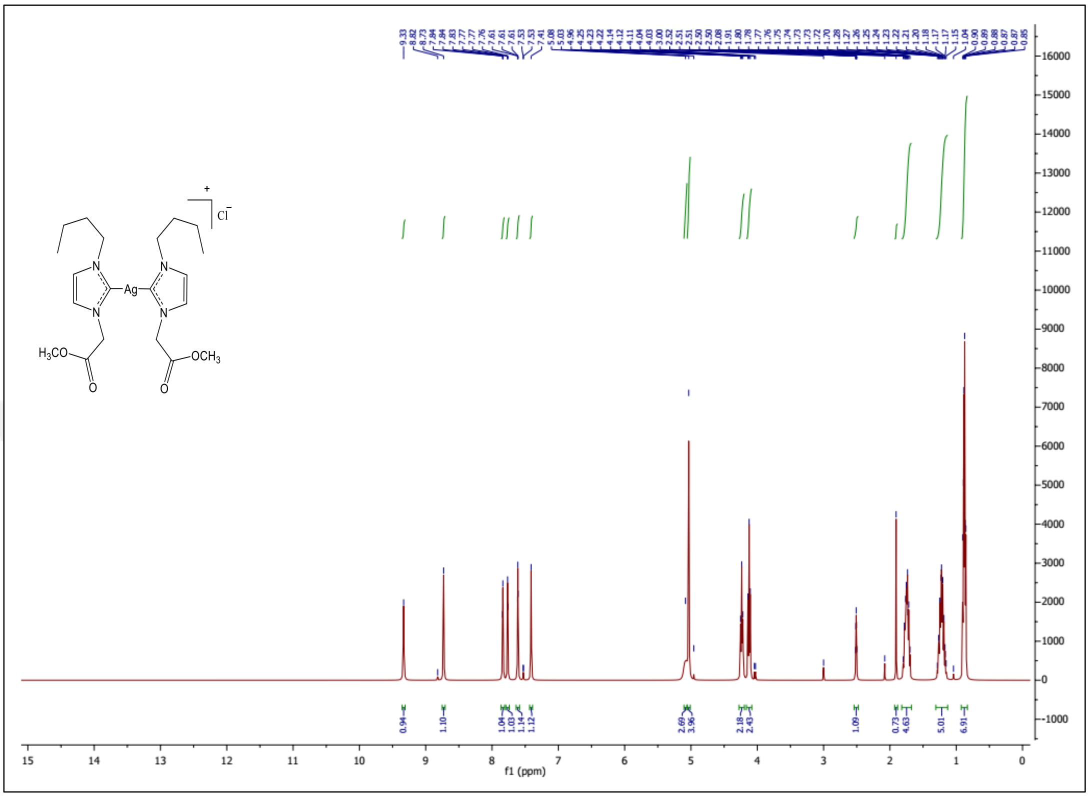


Figure 4.9 ^{1}HNMR spectrum of ligand B

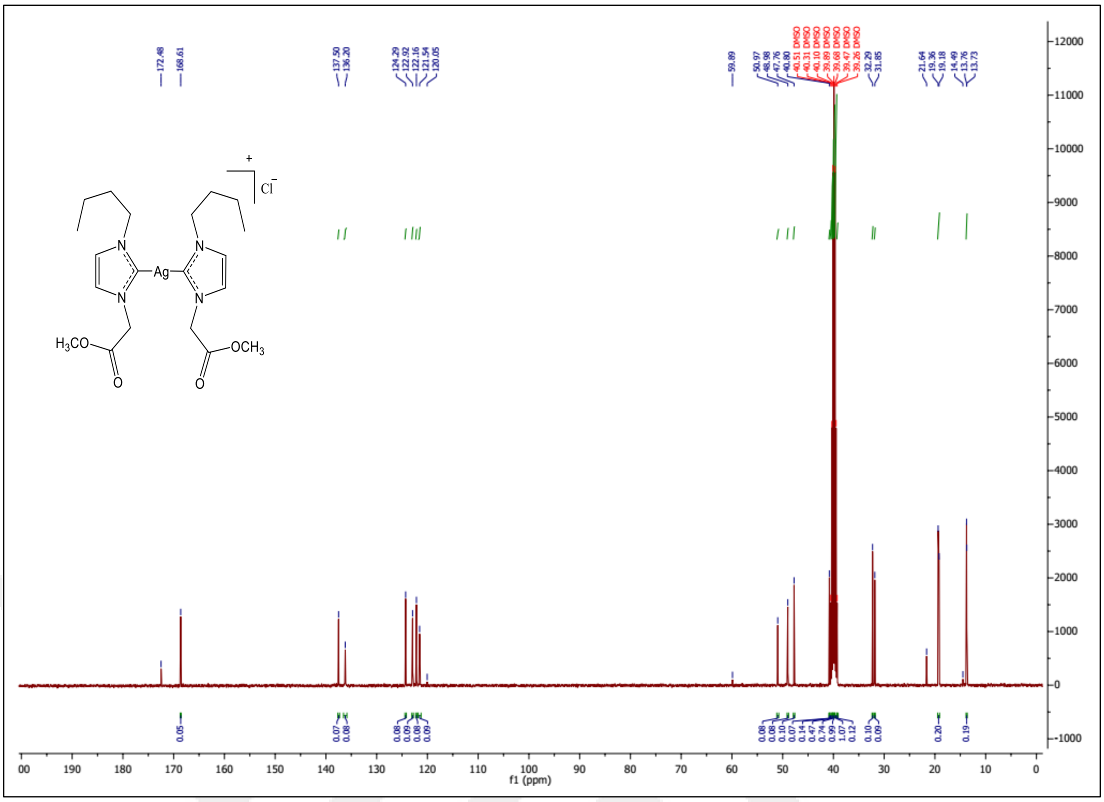


Figure 4.10 ^{13}CNMR spectrum of ligand B

4.8 Identification Infrared of Ag(I)-NHC Complex (1)

The FTIR spectrum of silver complex (1) was shown in Figure 4.11. The spectrum shows the band at 3128 cm^{-1} due to (C-H) ring, and (C-H) aliphatic at 2954, and bands at the 1566 cm^{-1} refer to (C=C). The bands of (C-N) appear at 1620 cm^{-1}, and at 664 cm^{-1} refer to (Ag-Br). There is broad band appeared at 3448 cm^{-1}, which refers to the remaining moisture H_2O in the compound.

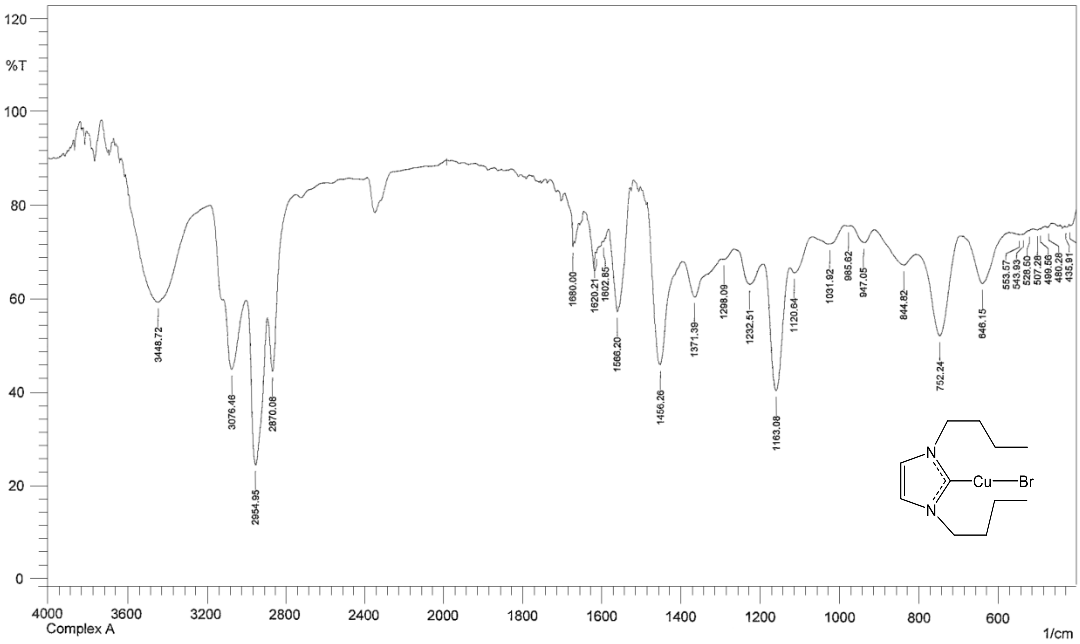


Figure 4.11 FTIR spectrum of silver complex (1)

4.9 Identification Infrared of Ag(I)-NHC Complex (2)

The FTIR spectrum of silver complex (2) was shown in Figure 4.12. The spectrum shows the band at 3128 cm^{-1} due to (C-H) ring, and (C-H) aliphatic at 2955 cm^{-1}, and the bands of (C-N) appear at 1625 cm^{-1}, and at the 1566 cm^{-1} refer to (C=C). There is broad band appearing at 3446 cm^{-1}, which refers to the remaining moisture H_2O in the compound. (C-C) band appears at 1163 cm^{-1}, and the band at 646 cm^{-1} refer to (C-Br).

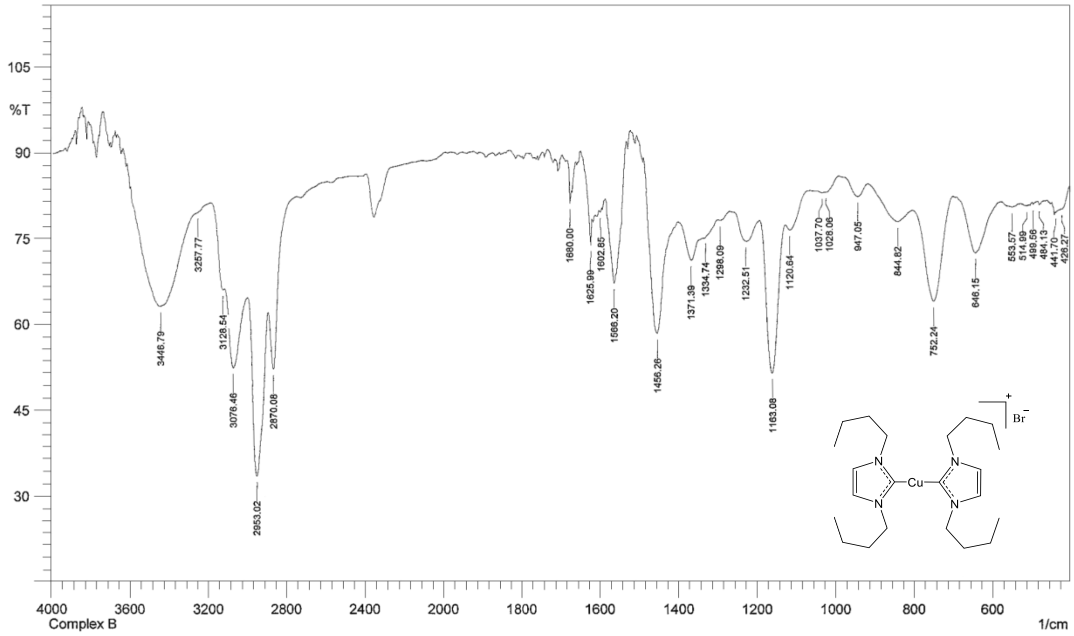


Figure 4.12 FTIR spectrum of silver complex (2)

4.10 Identification Via 1HNMR of Ag(I)-NHC Complex (2)

The ^{1}H NMR spectra of silver complex (2) DMSO-d_6 solution at room temperature shows two single signals with a chemical shift of δ (7.49-7.86) ppm, which belong to the protons of the H4/H5 of imidazolium salt (Figure 4.13). The spectrum exhibits multiple signals at a chemical shift δ (4.10) ppm belonging to the (CH_2) group linked to the imidazolium salt. Multiple signals at a chemical shift δ (1.79) ppm refer to the hydrogen of the (CH_2) group of carbon number 7. Multiple signals at chemical shift δ (1.26) ppm return to the hydrogen of the (CH_2) group of carbon atom number 8. A triple signal at the chemical shift of δ (0.87) ppm belongs to the hydrogen of the (CH_3). The ^{13}C NMR of silver complex (2) showed at (50.95) ppm for the carbon of (N-CH_2). The single signal at δ (180.02) ppm refers to $C_{carbene}$ of the imidazolium salt while the signals at δ (122.91-122.06) ppm refer to C4/C5 of the imidazolium salt. The signals at 33.55, 19.56 and 16.98 ppm are due to presence of the carbon of alkyl group (Figure 4.14). In both spectrum ^{1}H and ^{13}C NMR of complex 2, there are signals which appear regarding to corresponding ligand since the complex 2 decomposed. The complex 2 was stable in solution until the end of the 40th day.

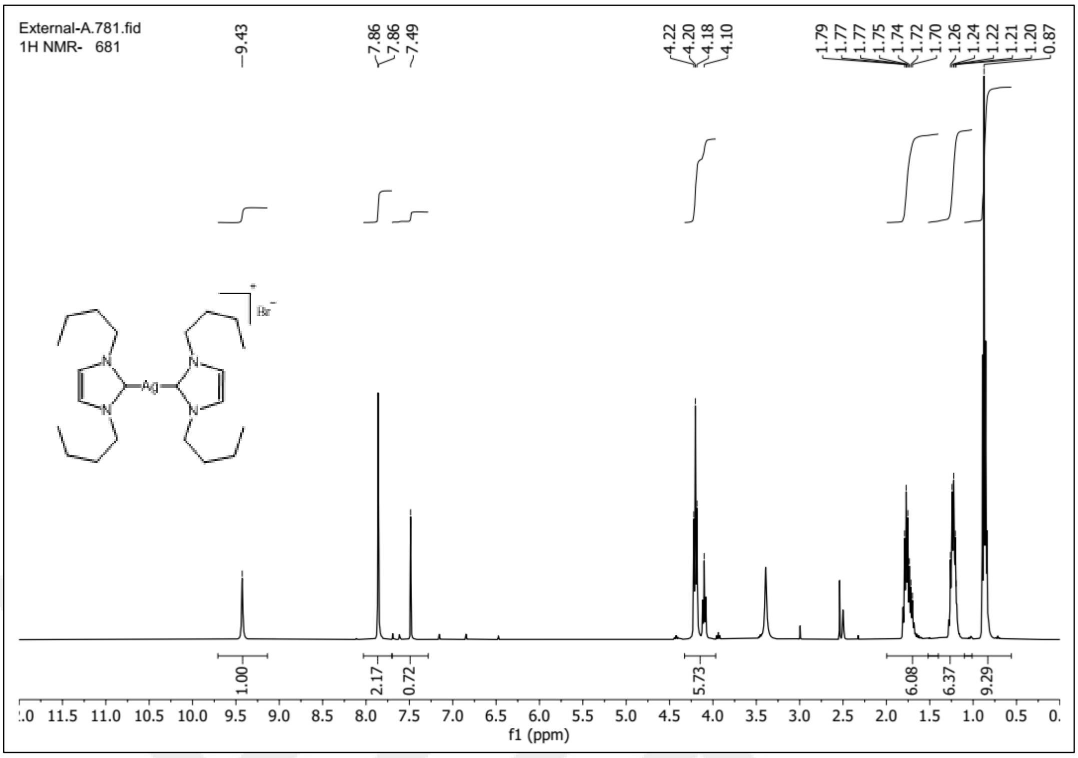


Figure 4.13 ^{1}HNMR spectrum of silver complex (2)

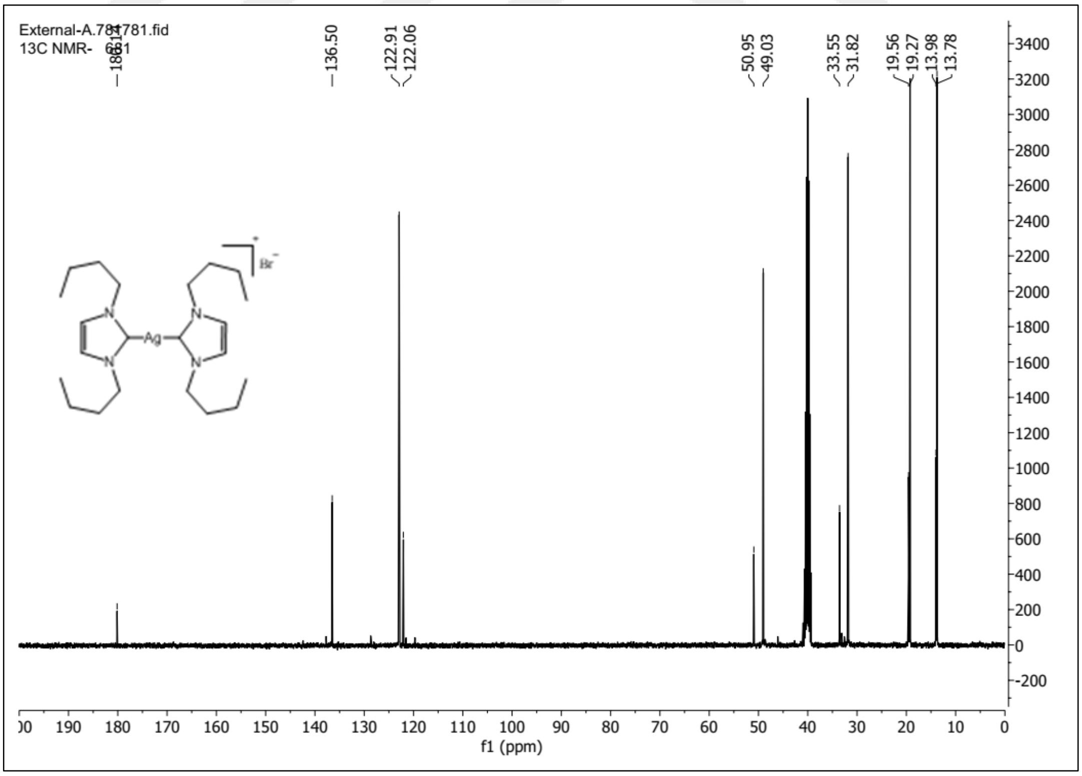


Figure 4.14 ^{13}CNMR spectrum of silver complex (2)

4.11 Identification Infrared of Ag(I)-NHC Complex (3)

The FTIR spectrum of silver complex (3) is shown in Figure 4.15. The spectrum shows the band at 3128 cm^{-1} related to (C-H) ring, and (C-H) aliphatic at 2953 cm^{-1}, and bands at the range 1680 - 1466 cm-1 refer to (C=O) and (C=C), respectively. The spectrum also shows the bands of (C-N) appearing at 1371 cm^{-1}, and the band of (C-O) appearing at 1232 cm^{-1} and the band at 748 cm^{-1} refers to (Ag-Cl). There is a broad band appearing at 3433 cm^{-1}, which refers to the remaining H_2O in the compound.

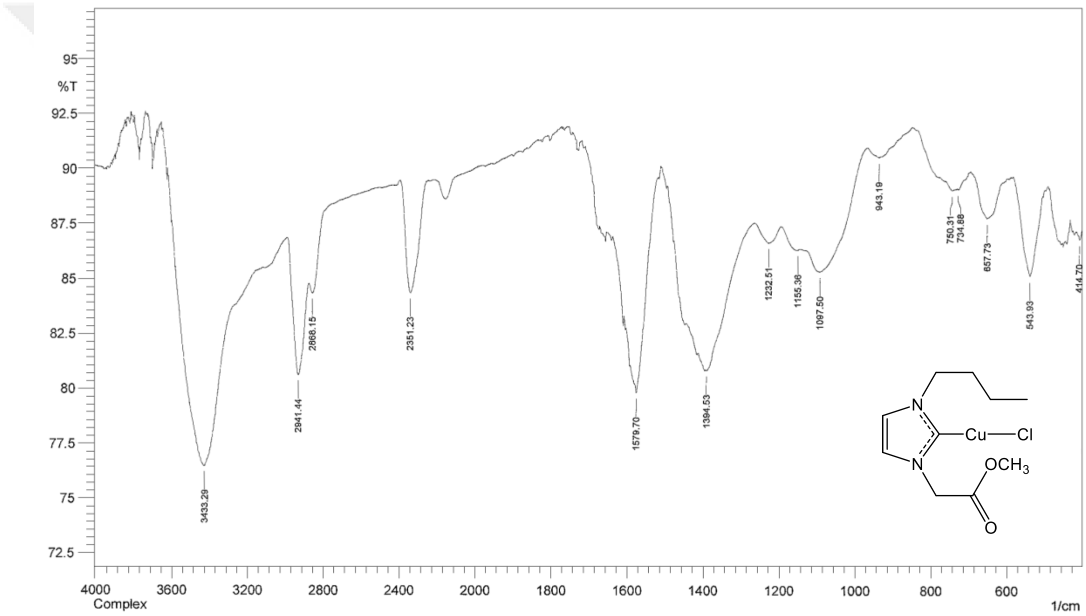


Figure 4.15 FTIR spectrum of silver complex (3)

4.12 Identification Infrared of Ag(I)-NHC Complex (4)

The FTIR spectrum of silver complex (4) is shown in Figure 4.16. The spectrum shows the band at 3091 cm^{-1} due to (C-H) ring, and (C-H) aliphatic at 2951 cm^{-1}, and band at the range 1720 cm^{-1} refers to (C=O), and band at the 1622 cm^{-1} refers to (C=C). The spectrum also shows the band of (C-O) appearing at 1218 cm^{-1}. There is a broad band appearing at 3441 cm^{-1}, which refers to the remaining moisture in the compound, the peak at 748 cm^{-1} refers to Ag-Cl.

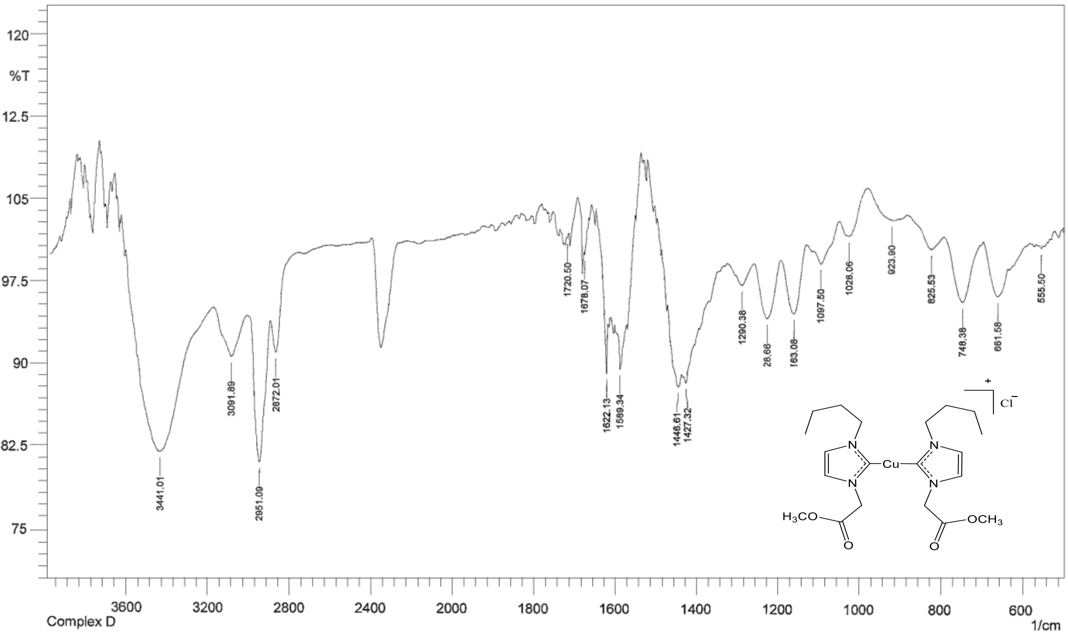


Figure 4.16 FTIR spectrum of silver complex (4)

4.13 Identification Via ^{1}HNMR of Ag(I)-NHC Complex (4)

The ^{1}H NMR spectra of silver complex (4) DMSO-d6 solution at room temperature shows two single signals with chemical shifts of δ (7.71-7.64) ppm which belong to the protons of the H4/H5 of imidazolium salt (Figure 4.17). The spectrum shows a single signal at δ (4.64) ppm belonging to the (CH_2) group linked to the carbonyl group and an imidazolium salt ring. It was characterized by the appearance of a signal belonging to the (OCH_3) group at a chemical shift of δ (2.5) ppm, which may have overlapped with signal of DMSO-d6. The spectrum shows a several signals at a chemical shift δ (4.19) ppm belonging to the (CH_2) group linked to the imidazolium salt. While multiple at a chemical shift of 1.78 and 1.25 ppm refer to the hydrogen of the CH_2CH_2 group. A triple signal at a chemical shift of δ (0.92) ppm belongs to the hydrogen of the (CH_3), while the multiple signals that appear with a chemical shift of δ (2.50) ppm belong to the DMSO-d6 solvent.

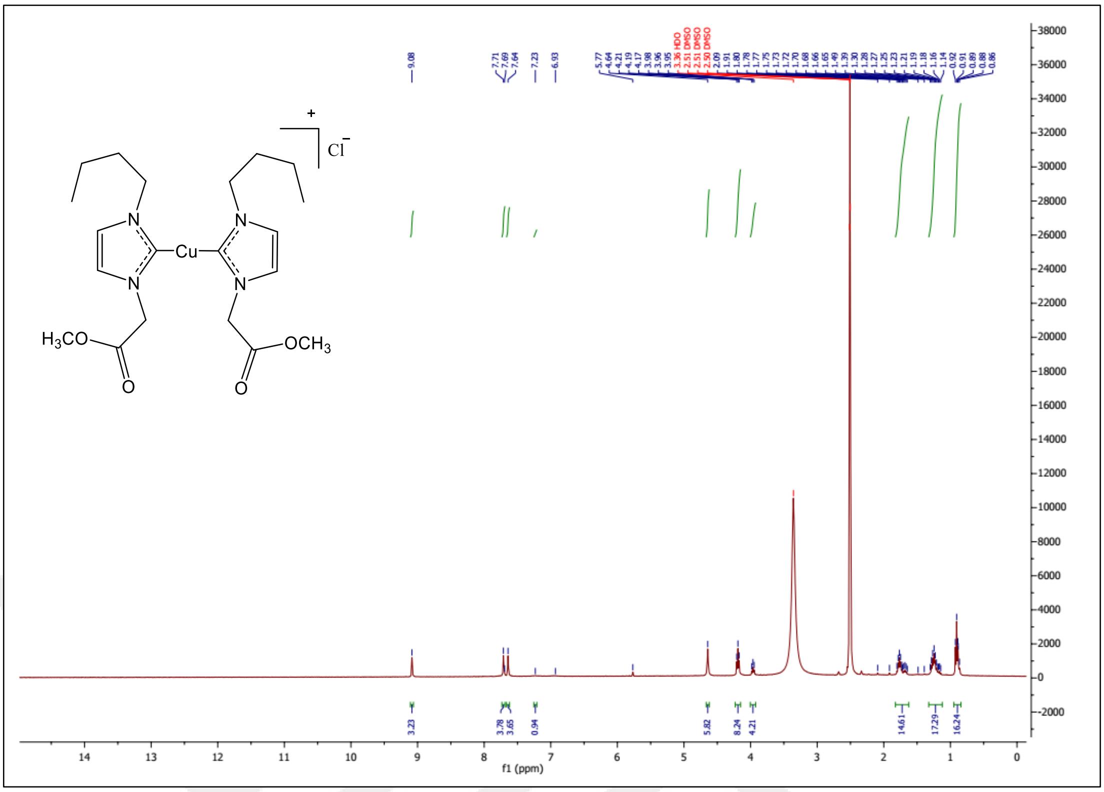


Figure 4.17 ^{1}HNMR spectrum of silver complex (4)

4.14 Identification Infrared of Cu(I)-NHC Complexes (5)

The FTIR spectrum of copper complex (5) is shown in Figure 4.18. The spectrum shows the band at 3107 cm^{-1} related to (C-H) aromatic, and (C-H) aliphatic at 2960, and the band at the 1674 cm^{-1} refers to (C-N). The bands of (C=C) appear at 1508 cm^{-1}, and the one at 665 cm^{-1} refer to (Cu-Br). There is a broad band appearing at 3414 cm^{-1}, which refers to the remaining H_2O in the compound.

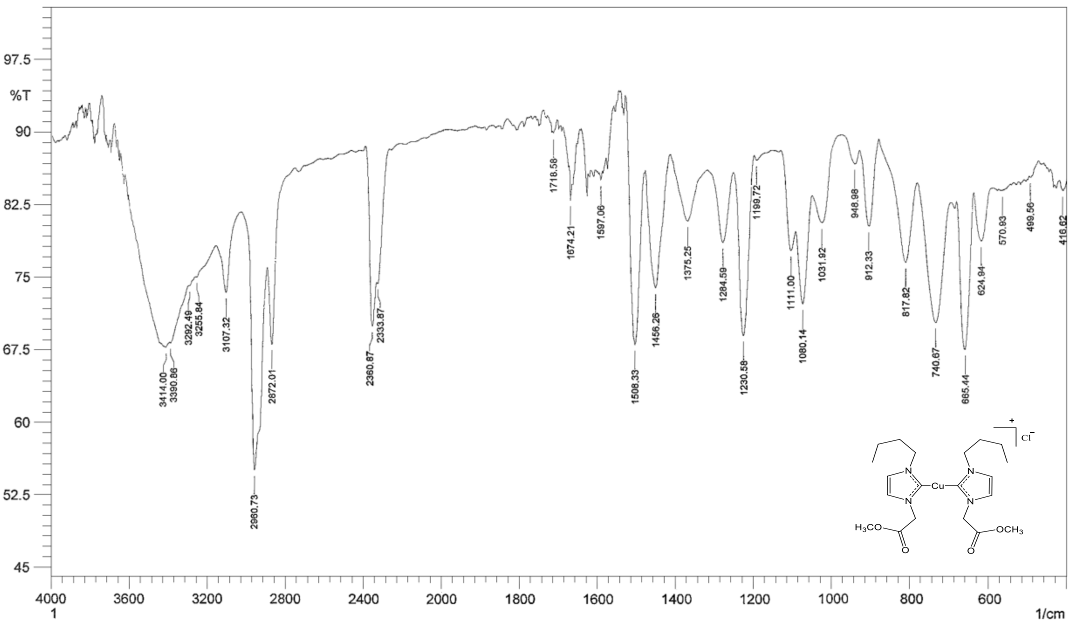


Figure 4.18 FTIR spectrum of cupper complex (5)

4.15 Identification Infrared of Cu(I)-NHC Complexes (6)

Figure 4.19 shows the FTIR spectrum of copper complex (6). The spectrum shows the band at 3082 cm^{-1} is due to (C-H) aromatic, and (C-H) aliphatic at 2951, and the band of (C-N) appears at 1672 cm^{-1}, and the peak at the 1570 cm^{-1} refers to (C=C). A broad band appearing at 3444 cm^{-1} is due to the moisture in the compound.

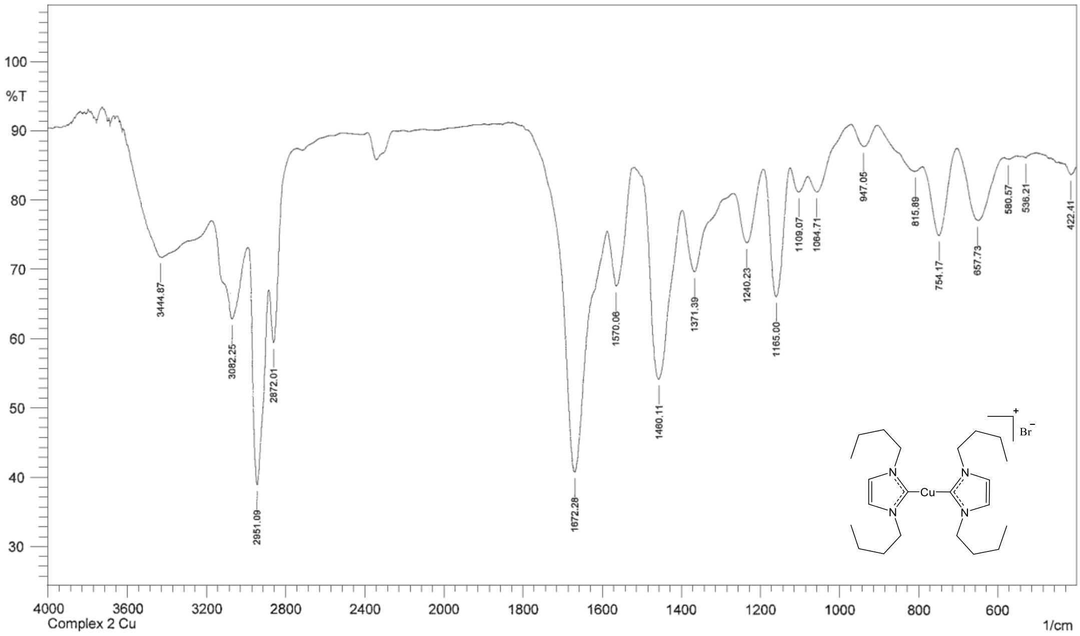


Figure 4.19 FTIR spectrum of cupper complex (6)

4.16 Identification Infrared of Cu(I)-NHC Complex (7)

The FTIR spectrum of copper complex (7) is shown in Figure 4.20. The spectrum shows the band at 3136 cm^{-1} related to (C-H) aromatic, and (C-H) aliphatic at 2949 cm^{-1}, and the bands in the range of 1641 - 1610 cm^{-1} refer to (C=O), and the band at (1452) cm^{-1} refers to (C=C). The spectrum also shows the bands of (C-N) appearing at 1369 cm^{-1}, and the band of (C-O) appears at 1240 cm^{-1} and the peak at 761 cm^{-1} refer to (Cu-Cl). Remaining moisture in the compound is observed as a broad band at 3402 cm^{-1}

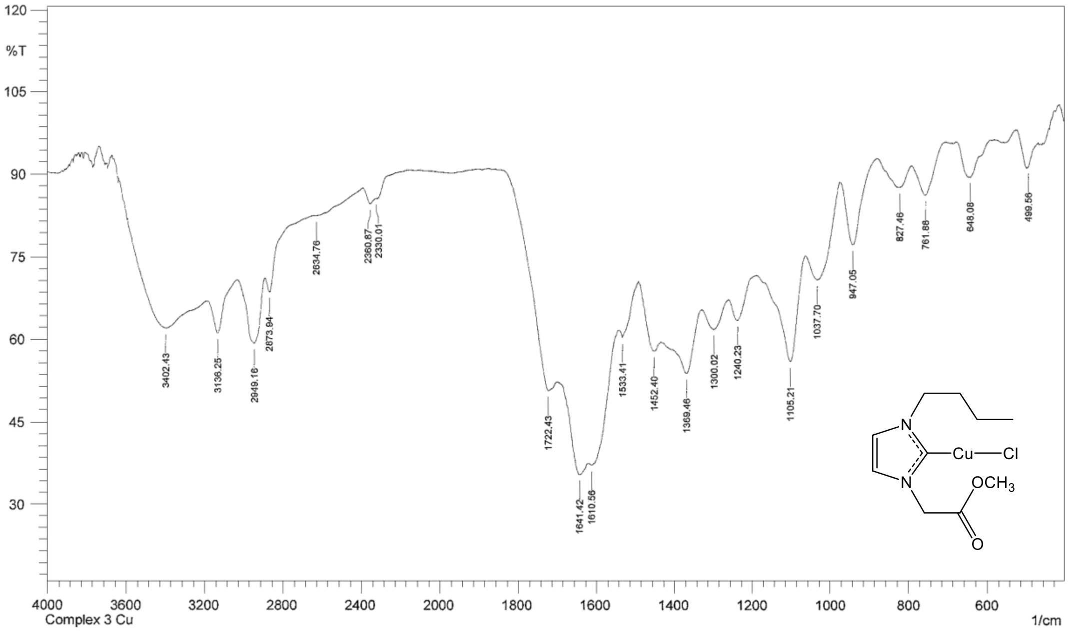


Figure 4.20 FTIR spectrum of cupper complex (7)

4.17 Identification Infrared of Cu(I)-NHC Complex (8)

The FTIR spectrum of copper complex (8) is shown in Figure 4.21. The spectrum shows the band at 3132 cm^{-1} corresponding to (C-H) aromatic, and (C-H) aliphatic at 2953 cm^{-1}, and the band at 1716 cm^{-1} refers to (C=O), and the band at 1622 cm^{-1} belongs to (C=C). In the spectrum, there is the band of (C-O) at 1240 cm^{-1}. A broad band observed at 3421 cm^{-1} refers to the remaining moisture in the compound.

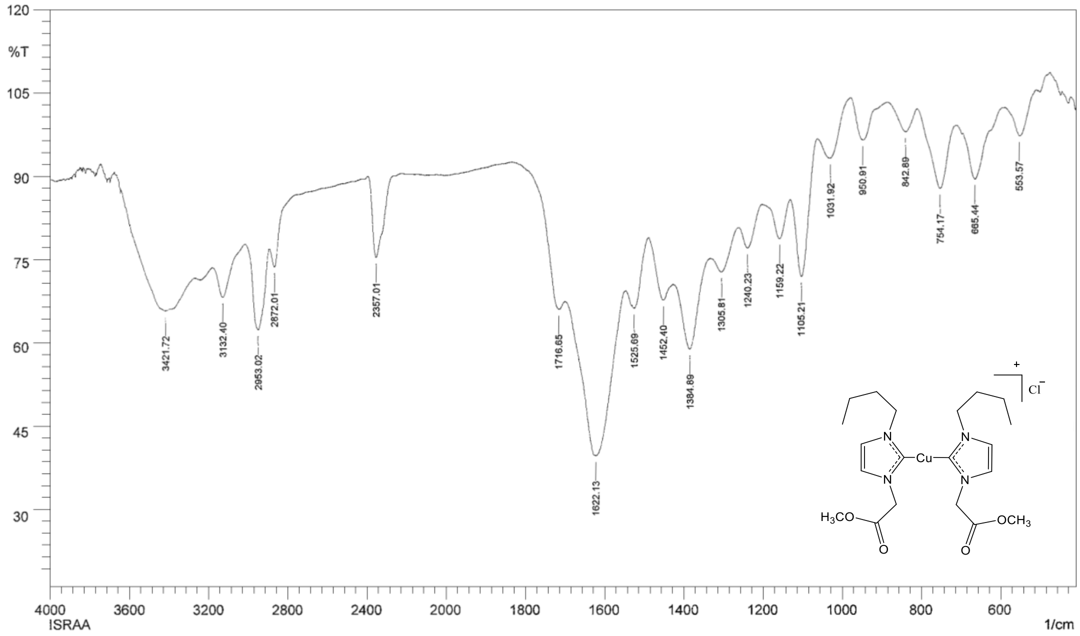


Figure 4.21 FTIR spectrum of cupper complex (8)

4.18 Identification Via NMR of Cu(I)-NHC Complexes

The Cu(I)-NHC complexes were characterized by ^{1}H and ^{13}C-NMR techniques. Surprisingly, there is no signal appeared in all NMR spectra, which shows that the all Cu(I)-NHC complexes were oxidized to Cu(II)-NHC complexes. Because the Cu(II)-NHC complexes are paramagnetic, therefore no signal belonging to the complexes appears (Figures 4.22 and 4.23).

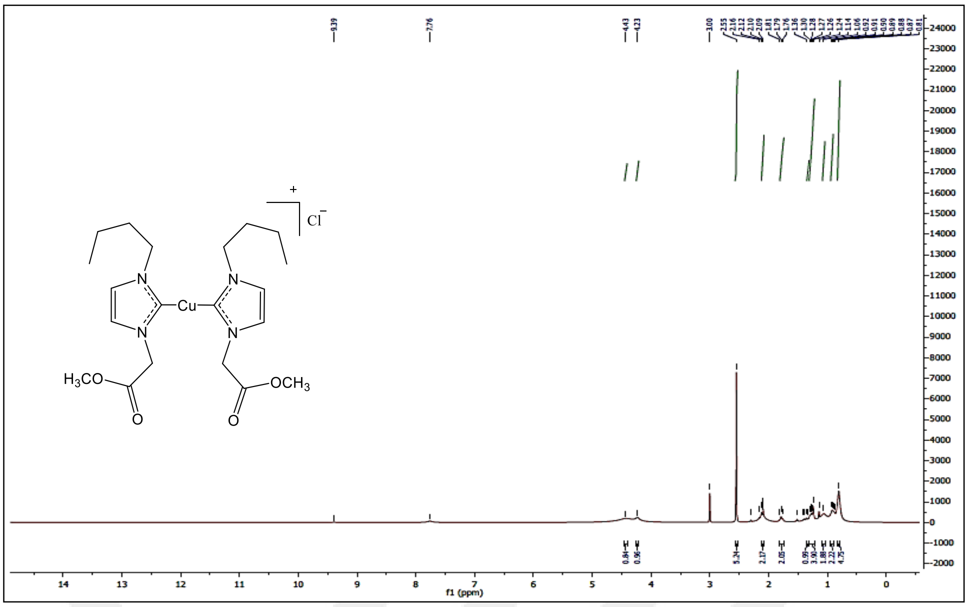


Figure 4.22 ^{1}HNMR spectrum of cupper complex (8)

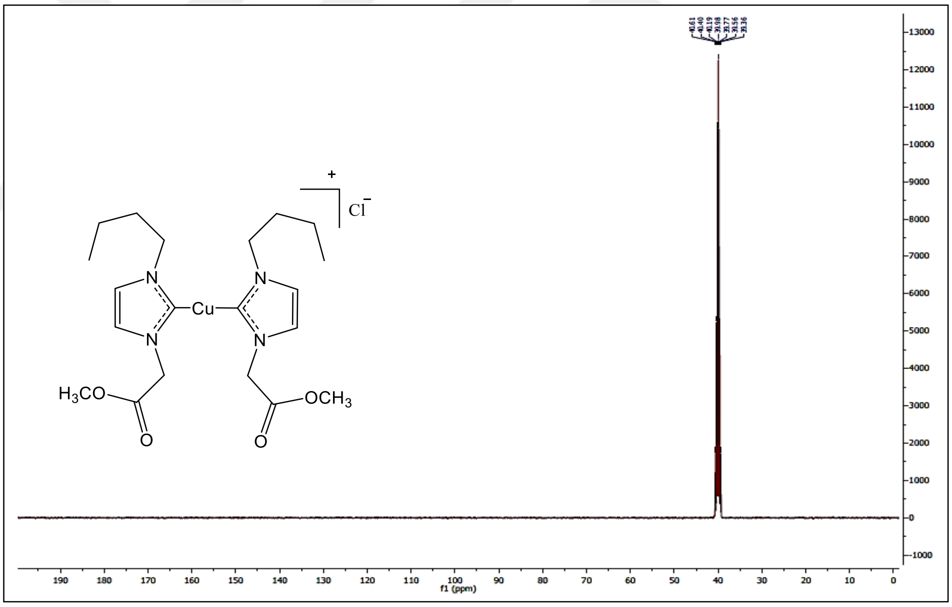
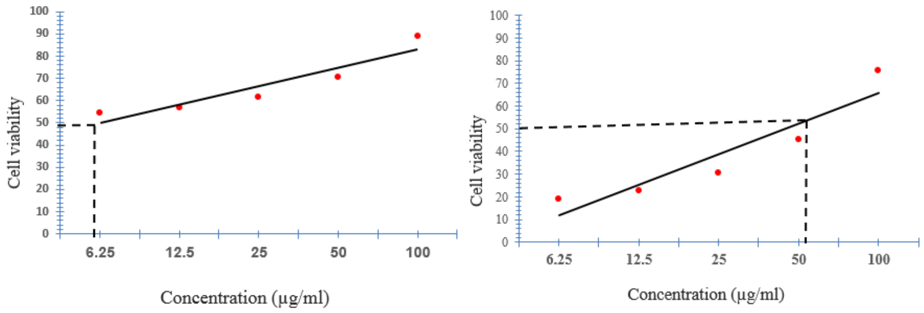


Figure 4.23 ^{13}CNMR spectrum of cupper complex (8)

4.19 Cytotoxic Study by Use Assay (MTT)

MTT is one of the most common techniques to assess cell viability. This approach uses a colorimeter (Mosmann 1983). In the absence of cells, Readings of background absorbance are hardly produced by the MTT reagent. In order to accurately detect changes in the rate of cell death or growth, the MTT test creates a linear relationship between metabolically active cells and the color produced (Van de Loosdrecht *et al.* 1994). MTT is frequently employed in the evaluation of medications to evaluate cytotoxicity and cell viability. In the MTT experiment, the cellular metabolic processes that lead to the reduction of MTT (yellow-colored) and other tetrazolium dyes are carried out by NAD(P)H-dependent cellular oxidoreductase enzymes (Berridge *et al*. 2005). Healthy, quickly-growing cells exhibit notable rates of MTT reduction to formazan as compared to dormant or inactive cells. The MTT reduction process results in the formation of formazan which can be readily dissolved in DMSO and has a purple hue. In the MTT test, viability is determined by measuring formazan at 540 nm, which is linearly associated with the enzyme activity and, indirectly, the number of living cells. Higher purple color intensity is associated with greater cell viability, while lower purple color intensity is associated with lesser cytotoxicity since there are fewer cells present.

The MTT assay results of the effects of ligand B on cytotoxic cells was 56.36 % at the concentration of 100 μg/mL. At the same time, the cell viability was 43.64 % at the concentration of 100 μg/mL. Dose and time dependent cytotoxic cell was observed in ligand B in the range of 6.25-100 μg/mL concentration. Anti-cancer activity is $P < 0.05$. The results showed that IC_{50} value of ligand B on the breast cancer cell line was 5.73 % mg/mL (Figure 4.24).



LigB IC_{50}= 5.73 Cu IC_{50}= 57.55

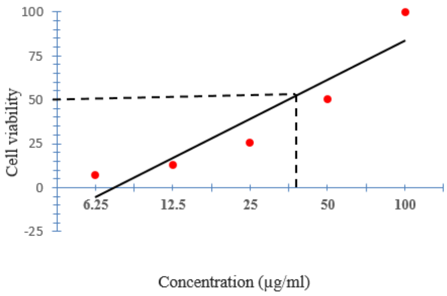


Figure 4.24 IC50 of ligand B and Ag(I)- And Cu(I)-NHC complexes vs breast cancer cell line

At a concentration of 100 µg/mL, the effects of the silver complex (4) on cytotoxic cells were measured by the MTT test at 42.42%. At 100 µg/mL of concentration, the cell viability was 57.58%. A range of 6.25 to 100 µg/mL of ligand B was shown to have dose- and time-dependent cytotoxic cell activity, which is highly anti-cancer active ($P < 0.000$). The analysis revealed that the silver complex has an IC 50 value of 49.62% mg/mL against the breast cancer cell line.

Akkoç *et al.* (2022) studied the cytotoxic and anticancer effects of Ag(I)-NHC complexes on the normal fibroblast cell line L929, the breast cancer cell line MCF-7, and the neuroblastoma cell line (SH-SY5Y). The complexes were more hazardous to SH-SY5Y and MCF-7 cell lines than L929 cell lines compared to cisplatin, and less toxic to L929 cell lines. considering that they are highly cytotoxic to cancer cells while being just somewhat harmful to normal fibroblast cell lines (Akkoç *et al.* 2022).

At a concentration of 100 µg/mL, the copper complex (8) had a 93.33% effect on cytotoxic cells according to the findings of the MTT experiment. At the same time, the cell viability was 6.67% at 100 µg/mL of the concentration. At concentrations of 6.25 to 100 µg/mL, ligand B showed dose- and time-dependent cytotoxicity. High anti-cancer activity is seen in this range ($P < 0.000$). The results revealed that the copper complex's inhibitory concentration (IC 50) on the breast cancer cell line was 57.55% mg/mL.

Our results for copper complexes are consistent with the results of Touj *et al*. (2020) In that study, the (NHC) Cu(I) complexes were tested against MCF7 and MDA-MB-231 cancer cells and showed significant activity against cancer cells. Copper nanoparticles are preferred to silver ones because copper is cheaper than silver, more stable physically and chemically, and is simpler to combine with polymers (Mallik *et al.* 2001). Although smaller nanoparticles are more active, they have the risk of clustering and losing key features (Tolaymat *et al.* 2010).

After exposure to various concentrations of the complexes, a cytotoxic reaction that was dependent on concentration was seen. In the 25–100 µg/mL range, Copper complex was determined to be the most cytotoxic, followed by Lig B and Ag complex. The detailed MTT assay results are given in Table 4.1.

Table 4.1 Cytotoxicity of breast cancer cell lines using MTT assay according to different doses of ligand B, Cu and Ag complex

Conc.	**100µg/mL**	**50µg/mL**	**25µg/mL**	**12.5µg/mL**	**6.25µg/mL**	**P value**
Lig B	56.36%	38.78%	37.37%	36.36%	32.12%	0.05*
Cu	93.33%	84.84%	38.78%	31.51%	16.36%	0.000**
Ag	42.42%	31.51%	21.21%	16.96%	14.54%	0.000**

* refer to significant difference between groups at ($P < 0.05$) according to Chi2 test.

** refer to high significant difference between groups at ($P < 0.01$) according to Chi2 test.

The analysis of half inhibitory concentration (IC50) of all samples concluded the action of (Cu complex) was showing as high as that of other samples. The order of activity for samples was found as Cu > Ag > Lig B. The inhibitory activity graphics are shown in Figure 4.25.

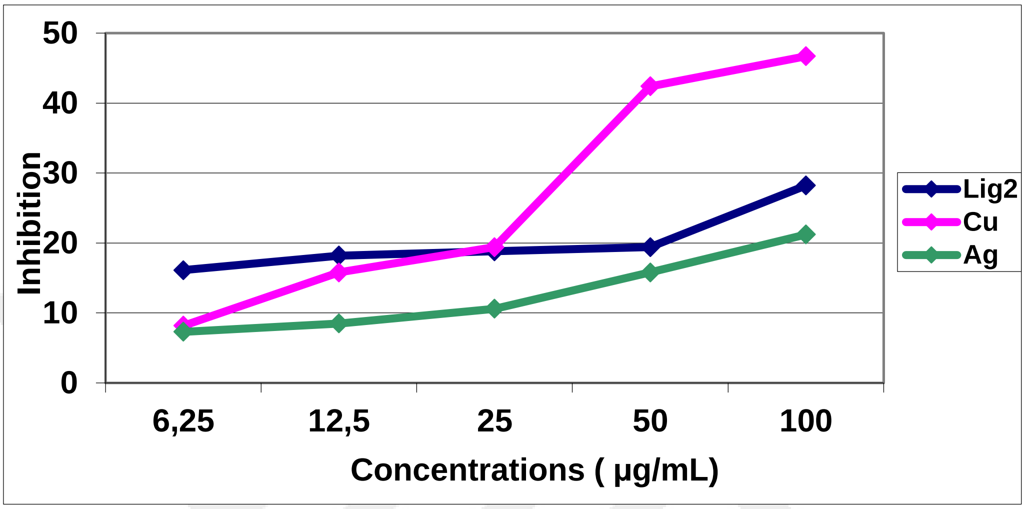


Figure 4.25 Cytotoxicity results for different doses of ligand B, Cu and Ag complex

5. CONCLUSION AND RECOMMENDATIONS

In this study, it was reported the synthesis and characterization of a series of new copper(I)-NHC and silver(I)-NHC complexes and their antiproliferative activities. The study consists of three stages. The first part is the preparation of new ligands. N-substituted imidazole was reacted with alkyl halides to form imidazolium salts. The ligands were characterized by FTIR and NMR spectroscopy. The ^{1}H NMR spectra of ligand (B) showed three main signals at (7.83–7.76 H4/H5), (6.7 and 7.09 CH_2) ppm linked to the carbonyl group and an imidazolium salt ring, and the single signal at (2.54 ppm) refers to OCH_3 group.

The creation of novel compounds, such as Ag(I)- and Cu(I)-NHC complexes (1–8), and their characterization using FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy made up the study's second phase. Using an in situ approach, complexes (1–4) were created by reacting Ag_2O with an imidazolium salt in a suitable solvent, such as dichloromethane. This process produced large yields. Cu(I)-NHC complexes (5–8) were produced in quantifiable quantities during a 24-hour period using acetone as the solvent under moderate conditions. The complexes precipitated in a respectable yield as a white solid.

The ^{1}H NMR spectra of Ag(I)-NHC complex (4) characterized by the appearance of a signal at a shift of δ (2.5 ppm) belonging to the (OCH_3) group may overlap with the signal of DMSO-d_6. On the other hand, The Cu(I)-NHC complex (4) was characterized by ^{1}H and ^{13}C-NMR spectra. Surprisingly, there are no signals appeared in all NMR spectra, which presumes that all Cu(I)-NHC complexes oxidized to Cu(II)-NHC complexes due to the Cu(II)-NHC complexes being paramagnetic, therefore there were no signals that appeared to belong to the complexes.

In the third phase, it has investigated the anticancer properties of the ligand (B), Ag(I), and Cu(I)-NHC complexes (4,8). Cu(I)-NHC complex (8), in an intriguing finding, shown strong activity against breast cancer cells.

Previous research on *N*-heterocyclic carbene complexes has concentrated on creating new compounds that are essential to enhancing our lives and so that we can survive.

Finding novel complexes to replace platinum compounds as anticancer medicines have received more attention in the scientific study during the last few decades. Ag(I) and Cu(I)-NHC complexes made from imidazole derivatives showed strong anticancer activity, according to the complexes synthesized for this thesis. To combat cancer cell lines, new transition metals such as Au and Ru complexes should be investigated in future studies.

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