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Synthesis and Characterization of Novel Organic Ligands with Their Complexes of Platinum, Copper and Uranium

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SYNTHESIS AND CHARACTERIZATION OF NOVEL ORGANIC LIGANDS WITH THEIR COMPLEXES OF PLATINUM, COPPER AND URANIUM

by

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Transition metal complexes of symmetrical and asymmetrical Schiff bases have played a significant role in the field of coordination, inorganic, and bioinorganic chemistry as models for biological, analytical, industrial, and pharmaceutical applications. Over recent years a great deal of interest has developed in new transition metal complexes of Schiff base ligand. The preparation of novel organic ligands is the most important step in the development of metal complexes that exhibit unique properties and novel reactivity. To highlight the presentation of this dissertation and to provide more detailed investigations, the dissertation was separated into six chapters according to the sequence of the work.

The first chapter gives an overview of Schiff bases and the coordination chemistry of different metal complexes focusing on Pt (II), Pt (IV), Cu (II), U (IV), and U (VI) ions with ligands and their geometric preferences.

The second chapter presents the synthesis and characterization of five new platinum based anticancer drugs. They have been categorized under three different types. The first type, chelate agents, is done by having starting materials together in water. The platinum center will react with the organic compound and the solvent to work as a leaving group. Bidentate ligands have two donor atoms, allowing them to bind to a central metal atom. The second type consists of Pt (IV)-based complexes, where two additional ligands essentially keep the drugs inactive until they reach target DNA. Platinum (IV) complexes are the six-coordinate (octahedral coordination geometry),

and the two additional ligands allow for further tuning of the properties. The third type is π-bond binding, is a new and interesting field. The stability of the metal-olefin bond in platinum (II) complexes is related to the formal charge on the complex and has been the subject of studies in the past few years. The action occurs when the pi-acid alkene donates electron density to the platinum d-orbital from a π symmetry bonding orbital between the carbon atoms. Then, platinum donates electrons back from another filled d-orbital into the vacant π antibonding orbital.

The third chapter focuses on the synthesis and characterization of the novel Pt(II) and Pt(IV) complexes with derivatives of ciprofloxacin which is considered as an antibiotic that belongs to a class of drugs called fluoroquinolones. The novel design of these Pt-Cipro conjugates was based on the premise that attaching Cipro to cisplatin derivatives should result in simultaneous release inside the cell of two antiproliferative agents that act by different mechanisms on different cellular targets. Thus, the platinum conjugates could also serve to bring into the tumor cells, along with the free antitumor Pt(II) compound, also free Cipro in the amount that could make it possible to execute their biological function.

Chapter four presents the synthesis, characterization, and structural studies of different series of copper and uranium complexes of salicylaldehyde Schiff base derivatives with various organic diamine compounds. The Schiff bases act as neutral and bidentate ligands, which can attach to the metal through the azomethine nitrogen and furfural oxygens. These Schiff bases are prepared by reacting salicylaldehyde with organic diamines. In the case of most complexation reactions, highly colored precipitates were formed immediately. The complexes were found to have composition Cu (II)L and Cu (II)L$UO_2(NO_2)_2$, where L is the organic ligand. This implies “mono” structures one metal + one H_2L ligands, and “heterobimetallic” where the ligands hold two different metal atoms in close proximity.

Chapter five deals with another series of CuL complexes, UO_2L complexes and CuL-UO_2 heterobimetallic complexes of an hexadentate bicompartmental Schiff base ligand that their central coordination sites is composed of an imine-based N_2O_2 entity coordinating Cu (II) ions. The subsequent rearrangement of the ligand into a Ω-shape generates a second recognition site, O_2O_2, composed of four phenoxy groups, able to coordinate U(IV) ions. Our copper-based metalloligands (CuL), which act as interesting chelate ligands for the uptake of large cations, led us to explore their structural differences upon coordination to group 2 metal ions.

All ligands and the metal complexes were characterized by a combination of NMR spectroscopy, and mass spectrometry. Despite all our efforts, no crystals suitable for an X-ray crystallographic study, were obtained. The results of the spectroscopic studies revealed that the Schiff base ligands coordinated to metal ions through nitrogen atom in the platinum complexes as well as through the (>C=N) nitrogen and phenolic oxygen atoms in H_2L ligands and through N_2O_2 and O_2O_2 in H_4L ligands in copper and uranium complexes.

Finally, chapter six presents the future work and further investigation to support the results by studying the biological effects and using green chemistry to synthesize novel organic ligands which would be a unique method to stop using the organic solvents.

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CHAPTER 1

INTRODUCTION

1.1 Overview

The present dissertation embodies the results of reactions of phenanthroline, phendione, bipyridine, and salicylaldehyde Schiff base derivatives with platinum, copper, and/or uranium for the synthesis of mono- and heterobimetallic complexes and the characterization of the resulting complexes. The structural assessment of the complexes described in this dissertation is based on the data obtained from ^{1}H and ^{13}C NMR and mass spectrometry. Accordingly, the present chapter gives a brief account of the importance of the platinum, copper and uranium complexes followed by a literature survey on metal organic compounds, Schiff bases and platinum, copper, and uranium complexes.

As a result of extensive efforts on research over the last few decades, the objects of the fast progressing inter-disciplinary area of metal-organic chemistry or coordination chemistry has been emerging clearly. A greater understanding of the bonding and nature of these complexes has been developing especially with the advent of crystal field and ligand field theories which make the ability of utilizing a variety of Schiff bases and their complexes in diversified fields, like medicine, agriculture, environment, and industry.[1-6] The chemistry of metal organic compounds has been studied so. extensively that these compounds now include a significant part of organic chemistry and some area of biochemistry.[7] The concept of coordination chemistry has been associated with the complexation of metal cations (Lewis acids) by ligands (Lewis bases) that have one or more electron pairs, and the electron pairs can be donated to the central metal with the formation of a coordinate bond to the metal.[8] The coordination compounds have been concerned with the

transition metals, groups 3–12 in the periodic table, which are generally characterized by partially filled *d* subshells in the free elements or their cations. The transition metals exhibit significant horizontal similarities in chemistry in addition to their vertical similarities. [9]

Transition metal complexes are cationic, neutral, or anionic species in which a transition metal is coordinated by ligands.[10] The chemistry of metal-organic compounds has received considerable attention largely due to their potential biological activities such as antibacterial, antiviral, antifungal, antimalarial and anticancer activity. The metal ions are known to affect the activity of many drugs. The efficacy of many drugs is boosted when they are coordinated to a metal, and the combined synergistic effect is greater than the sum of the individual of the drug or metal alone.[8] Moreover, the metal ion compounds have played a crucial rule in the fields of medicine and bioinorganic chemistry and are used as a starting material for the synthesis of new catalysts and drugs.[6,11]

The metal complexes have been studied since 1798 and till nowadays significant progress has been made in the inorganic and organic chemistry concerning the synthesis, characterization, and application of this large group of metal complexes. The study of the structure of the metal complexes has considered those compounds which do not fit within the classical theory of valence, since the combination ratio of the elements exceeded their valences. This coordination theory developed by Alfred Werner indicated that the secondary valences of the elements are involved in the formation of the second-order combinations leading to the actual representation of the complexes formed by the first coordination sphere marked between brackets [central atom (ligand)] and the second coordination sphere (ionization sphere) coming outside of the brackets.[12]

1.2 Organic Ligands

In metal-organic chemistry, a ligand is an ion or molecule with a functional group that binds to a central metal atom to form a coordination complex. The ligands have lone pairs on one or more than one atom which make the ligands bind with metal ions through multiple sites. Monodentate ligands include virtually all anions and all simple Lewis bases. Thus, the halides and pseudo-halides are significantly important anionic ligands. Moreover, ammonia, carbon monoxide, and water are particularly common charge-neutral ligands. Simple organic compounds are also heavily used in coordination chemistry as ligands. All unsaturated molecules are also considered ligands which should be capable of forming the coordinate bond by utilizing their π-electrons, in forming the coordinate bond.[13]

The ligands that bind through two sites are classified as bidentate, and those with three sites as tridentate. A classic bidentate ligand is ethylenediamine, which is derived by the linking of two ammonia groups with an ethylene (-CH_2CH_2-) linker. Very versatile ligands used in complexation include monodentate (N-, P-, O-, S), bidentate (N,N-, O,O-, N,S-), and also multidentate examples.[14] Polydentate or chelating ligands bind via more than one atom. Chelating ligands are commonly formed by linking donor groups via organic linkers. EDTA is a common example of a hexadentate chelating agent which is able to bind through six sites, completely surrounding some metals. Polydentate ligands can be characterized by interacting with the central atoms. For example, trans-spanning ligands are bidentate ligands that can span coordination positions on opposite sides of a coordination complex.[15,16] The central metal ions can also attach to ambidentate ligands that are capable of binding metal-ion centers in more than one way through different donor-atom combinations to provide an efficient strategy in the construction of functional coordination assemblies.[14-18]

1.3 Schiff Base

Schiff bases and corresponding metal complexes have gained considerable attention because they are likely capable of forming stable complexes with metal ions, and they are simply prepared by the condensation aldehyde or ketone with imines both of which are easily available and relatively cheap.[19] Schiff bases are the most widely used organic compounds for industrial purposes.[20] Schiff bases provide interesting 3D exit vectors for substitution, with drug-like properties which are synthetically accessible because they have small and non-planar ring structures with robust conformations.[21] Schiff base compounds and their metal complexes are very important as catalysts in various biological systems, polymers, dyes and medicinal and pharmaceutical fields[22] and they have various therapeutically potent applications in the field of medicinal chemistry.[23,22]

Chelated Schiff bases are also utilized in quantitative analysis as analytical chemical reagents and/or separation reagent which have been also outlined and discussed[24], and in synthetic applications in the field of the organic and inorganic chemistry.[23] They have exhibited a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties.[20] It has been confirmed that some Schiff bases show increased bio-activity[25] and a number of metal chelates with anticancer activity have also been reported. The strong attraction for the bonding of Schiff bases to inner and non-inner transition metal ions is essential in metal complex synthesis.[26] These ligands coordinate to different metal atoms through the imine nitrogen and other groups such as hydroxyl, carbonyl oxygen, or amine.[27] They are beneficial chelating agents because of their structural varieties, ease of preparation, assorted densities, and electronic control and subtle steric on their frameworks.[28,29]

Schiff bases have played an influencing role in development of coordination chemistry and were involved as key points in the development of inorganic biochemistry and optical materials. Schiff bases are also used as catalysts, intermediates in organic synthesis, dyes, pigments, plant growth regulator and polymer stabilizers.[29] They also possess antimicrobial activities, antifungal activities, antiviral activities, antitumor and cytotoxic activities, and pharmaceutical properties.[30] Several model systems, including those with bidentate, tridentate, tetradentate, multidentate Schiff base ligands, and their coordination chemistry of copper attract much attention because of their biological relevance and their own interesting coordination chemistry such as variable geometries, flexible redox properties, and oxidation states.[31]

1.3.1 Synthesis of Schiff Base Ligands

Schiff bases are a class of compounds carrying imine or azomethine (–C=N–) functional group[32] which is a carbon-nitrogen double bond (>C=N-) as shown in figure (1). The nitrogen atom of azomethine is attached to an alkyl, aryl, cyclo-alkyl or heterocyclic group which may be variously substituted. They were first reported by Hugo Schiff in 1864.[33] These compounds are easily coordinated with metal ions through the imine nitrogen and other groups linked to the Schiff base.[34] Schiff base compounds are condensation products of primary amines and carbonyl compounds (aldehydes and ketones) and have the general structure (R_1R_2 C=NR) where R is a linear or cyclic alkyl and/or aryl group which gives the Schiff base its stability.[34] Schiff bases that are derived from aliphatic aldehydes are relatively unstable and readily polymerizable, while those of aromatic aldehydes have effective conjugation and stability.[35] In general, aldehydes react faster than ketones in Schiff base condensation reactions as the reaction center of aldehyde is sterically less hindered than that of ketone. Furthermore, the extra carbon of

ketone donates electron density and thus makes the ketone less electrophilic compared to aldehyde.[35]

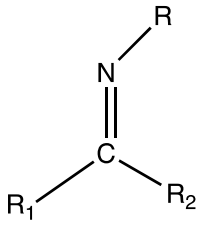


Figure 1. The Structure of a Schiff Base.

Chemists nowadays prepare well designed bridged Schiff bases which are represented as shown in figure (1-2). They are well known, versatile chelating agents with multiple donor atoms like O, N, S etc. A huge number of versatile metal complexes of multi-dentate Schiff base ligands with O, N, S donors have been reported with numerous applications.

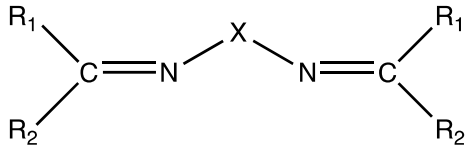
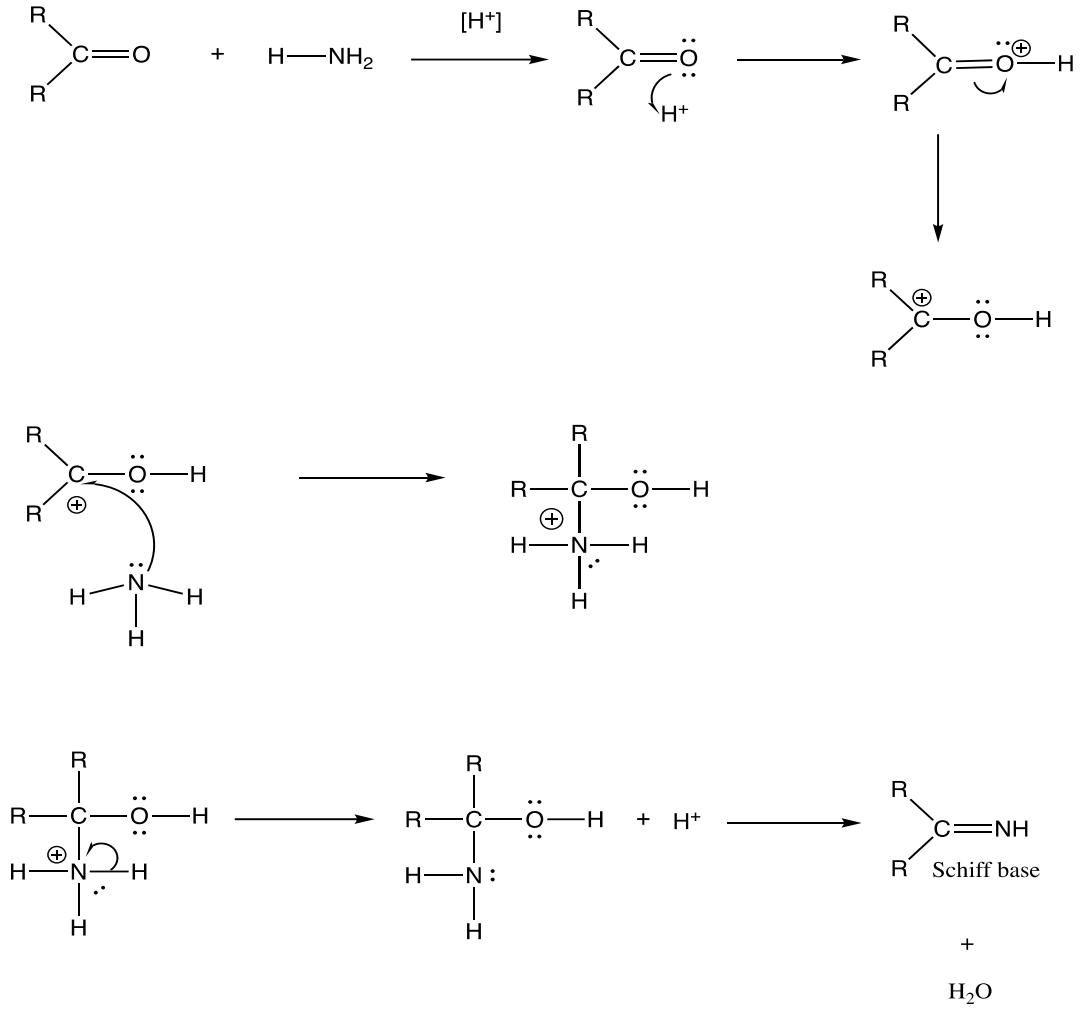


Figure 2. The Bridged Schiff Bases

Where R_1 = H or alkyl group, R_2 = phenyl or substituted phenyl group and X= an alkyl or phenyl group.[36]

1.3.2 Mechanism

The formation of a Schiff base from carbonyl compounds is a reversible reaction and generally goes under acid (or) base catalysis, or upon heating as shown in scheme (1).



Scheme 1. The Mechanism of Schiff Base Formation of Nucleophile Addition to The Carbonyl Group.

In scheme (1), the first step of the Schiff base mechanism, the amine reacts with the aldehyde or ketone to give an unstable addition compound called carbinolamine, which is obtained as an intermediate.[37] Water loss from the carbinolamine is by either acid or base catalyzed pathways, but the carbinolamine is considered an alcohol. Thus, it undergoes acid catalysis.

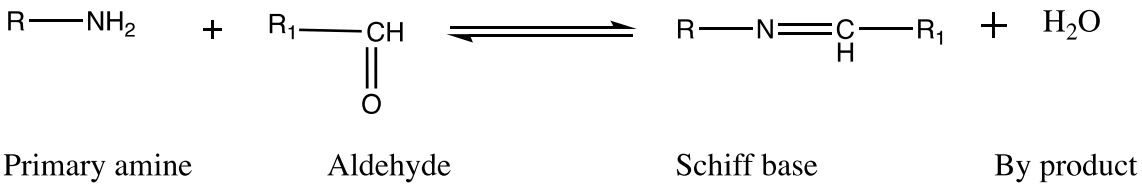
The dehydration of carbinolamine is considered as a rate-determining step in the formation of the Schiff Base process and that is why the reaction is catalyzed by acids or Lewis acid. But the concentration of acids present for the catalysis cannot be too high because amines are basic compounds. If the amine is deprotonated and becomes non-nucleophilic, equilibrium is pulled to the left and the carbinolamine will go back to aldehyde or ketone and primary amine, due to which this reaction is best carried out at a mildly acidic pH.[38]

Base catalysis is also used for the dehydration of carbinolamines. The reaction is somewhat similar to the E2 elimination of alkyl halides. The formation of Schiff bases can go in two steps through an anionic intermediate, i.e., addition followed by elimination. Several studies showed that the presence of a lone pair of electrons in a sp2 hybridized orbital of nitrogen atom of the azomethine group is of considerable chemical and biological importance.[39] The electron-donating groups, such as azomethines can trap metal ions which have large radii and high coordination numbers. In such a case, the two or more metal atoms are placed in one cavity so that they are in close proximity to each other and in turn can be characterized by unusual magnetic properties and catalytic activity.[40]

1.3.3 Potential Problem in Schiff Base Formation

The formation of the imine has a potential problem that the imine double bond could be hydrolyzed back to the starting materials. Although the formation of Schiff bases is reversible, due to the hydrolysis of the imine under certain conditions, it is still straightforward for the reaction to succeed. The Schiff bases are very sensitive to water and easily hydrolyze back to aldehyde. The successful completion is carried out by separating the Schiff base compound or removing side products, byproducts, or both. Most reactions of the Schiff base formation are generally conducted

smoothly in normal coordinated dry solvent such as MeOH or EtOH, it still has the potential problem in which the Schiff bases might be hydrolyzed.[41] The following three ways are focused on using some additional procedure to remove the side product, water, in the imine formation. (I) Schiff base formation involves drying agents such as anhydrous sodium sulphate or anhydrous magnesium sulphate in a dichloromethane (DCM) or chloroform solvent; (II) the method for water elimination was developed by using dehydrating solvents such as tetramethyl orthosilicate or trimethyl orthoformate;[42] (III) some reactants require forcing conditions such as heating to reflux in a high boiling solvent and may include the use of a Dean-Stark apparatus or molecular sieves or heating in a solvent that azeotropes away the water, e.g. ethanol.[43-45]



Scheme 2. The General Structure of Synthesis of Schiff Base.

The geometries adopted about the imine double bond are generally the trans orientation, which limits the steric interactions of the bulkier R group, with R being either aryl or alkyl substituents.[46] Furthermore, the reactivity of aldehydes is generally faster than that of the ketone in condensation reaction, that is less steric and more electrophilic than the ketone which has more electron density, and is relatively unstable, and freely polymerizable.[47] The Schiff base bonding ability depends on the nature of atoms that act as the coordination site, such as N, O, and S, the electronegativity and steric factors. Schiff bases act as active ligands due to the low electronegativity of nitrogen, N of the azomethine group (>C=N), the lone pair of electrons on the nitrogen atoms, and the electron donating character of the double bonds.[48] This brings about stability in metals with several oxidation states, regulating metal activities for a variety of useful

biological, catalytic conversions. Moreover, the lone pair of electrons on imine nitrogen can supply electrons which enable the formation of a proper donor bond to a metal ion for complexation to occur.[49] Many Schiff bases have a second functional group, normally OH and SH groups or another N atom, which are near the imine group. These functional groups can allow the formation of five or six member chelate rings when coordinated with different metal ions.

1.3.4 Salen Ligands

Salen ligands are condensation products of a diamine and two moles of salicylaldehyde or its derivatives, which possess tetradentate N_2O_2 donor sites as shown in figure 3.[50] The metal-salen complexes are readily available and have structural and chemical properties similar to porphyrins, which form stable complexes with most of metals due to the chelate effect. Therefore, the chemistry of metal complexes containing salen-type ligands has attracted much attention for a long time. Furthermore, great attention has been devoted to systems in which functionalized salen is used as a ligand and it was only in the mid-1980s that metal-salen complexes were tested for their catalytic activity. Since then, they have been successfully applied in various enantioselective reactions such as epoxidation,[51] aziridination,[52] cyclopropanation[53] the Diels-Alder,[54] and Strecker reactions[55] and in kinetic resolution of racemic epoxides.[56]

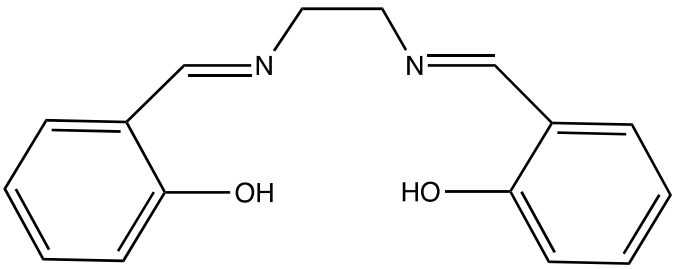


Figure 3: The Structure of The Salen Ligand

The salen complexes are conformationally flexible and adopt a variety of geometries such as square planar, tetrahedral, square pyramidal and octahedral as well, with additional ligand(s).[57,58] The 2-hydroxybenzaldehyde is a suitable building block due to the possible substitution patterns of the aromatic ring. Once the imine bond is formed from primary amine and aldehyde, the orientation of salen-type Schiff bases will form a more stable six-member ring when binding to metal ions. Moreover, two donor atoms, nitrogen and oxygen atoms of the chelated Schiff base have two opposite effects: that the phenolic oxygen is a hard donor and stabilizes the higher oxidation state, whereas the imine nitrogen is a border-line donor and stabilizes the lower oxidation state of the metal ion.[59] Therefore, salen can stabilize many different metals in various oxidation states and also can be used in a broad range of applications as homogeneous and heterogeneous catalysts in various organic transformation reactions. Although the salen ligands are sensitive towards hydrolysis which is catalyzed by acid, their metal complexes are quite stable and thus to avoid the hydrolysis of salen ligands during the applications, their metal-complexes are often used. Moreover, salen ligands have potential to stabilize metal ions in various oxidation states, making them good candidates as catalysts.[60]

Salen-type ligands with N and O donor atoms are important since their metal complexes find widespread applications as homogeneous and heterogeneous catalysts in various organic transformation reactions.[61] Interest in the synthesis of platinum (II), platinum (IV), copper (II) and uranium (VI) complexes is of crucial importance due to their applications in bioinorganic chemistry, pharmaceutical activity, magnetochemistry and homogeneous catalysis.[62] The main objective of the bioinorganic chemistry of these compounds is to understand the functional and structural properties. The focus of the current research is to synthesize the platinum, copper and

uranium complexes of Schiff base ligands and make further investigations of their applications and structural properties.

1.4 Platinum Anticancer Complexes

Platinum-based antitumor drugs are very effective anticancer agents which are used significantly in chemotherapy and play a crucial role in the treatment of various malignant tumors.[63] They are the backbone of many drugs which are clinically used for the treatment of different solid tumors such as genitourinary, colorectal, and non-small cell lung cancers.[64] The big challenges with this kind of anticancer agent are the toxic side effects, eventual inefficacy, and delivery systems. Thus, it is imperative to develop effective formulations that can address the above cited challenges and provide selective targeting of tumor sites without significant damage to the viability of healthy tissues. Although the efficacy and applicability of platinum drugs are heavily restricted, different strategies have been developed to alleviate or prevent the shortcomings of platinum-based chemotherapy.[65,66] The classical Pt (II)-drug complexes[67,68] are cisplatin (trade names Platinol and Platinol-AQ), carboplatin, oxaliplatin, nedaplatin, lobaplatin, and heptaplatin as shown in figure 4.

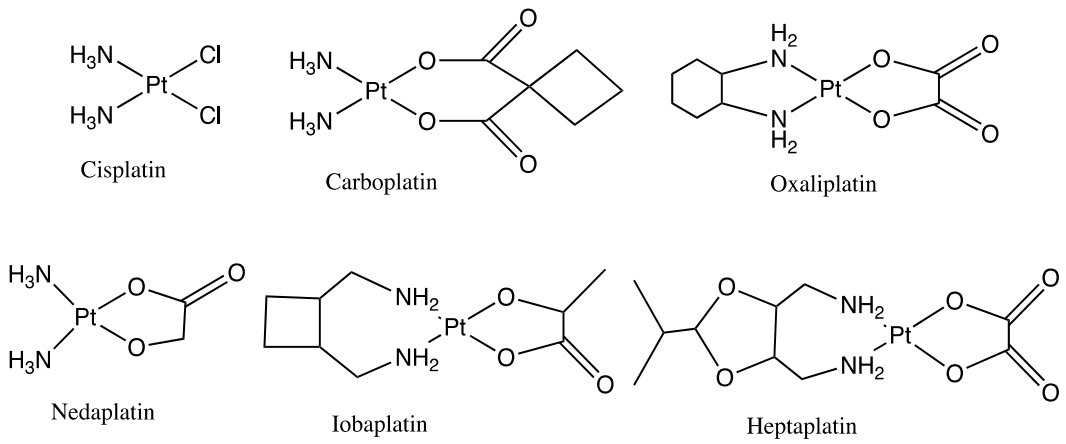


Figure 4. Approved Platinum-Based Anticancer Drugs

For the last four decades, thousands of platinum complexes have been prepared, designed, and developed in the hope of finding new drugs with a more tolerable toxicological profile and higher efficacy and for improving the efficiency of cisplatin itself.[69] The cisplatin drugs have become one of the more extensively used anticancer drugs with a high activity range against many tumors. Binding to DNA is the most accepted mode of action of cisplatin, and the failure of repair mechanisms to remove Pt-DNA adducts subsequently triggers apoptotic cellular suicide. Consequently, working in this field led to the development of cisplatin and improving the effectiveness of platinum-based drugs, extending the range of its medical application as well, such as reduced cellular drug uptake or increased drug efflux, enhanced repair mechanism in healthy cells, drug deactivation, or a combination of the above-mentioned mechanisms.[70-74]

Platinum-based anticancer chemotherapy has a major disadvantage which is a severe side effect because of poor specificity. For this reason, systemic toxicities for cisplatin like nephrotoxicity, neurotoxicity, ototoxicity, and metagenesis cause serious disorders or injuries in patients during treatment which may result in ending treatment.[75] In addition to systemic toxicities, the efficacy of cisplatin is often limited by the intrinsic and acquired resistance by various cancers.[76] Multiple mechanisms have been proposed to shed light on the cellular resistance to cisplatin and its analogues in preclinical models. The four representative mechanisms include: (i) decreased drug accumulation or increased drug efflux;[77] (ii) increased detoxification of the drug by sulfur-containing molecules within the cells;[78] (iii) enhanced repair and increased tolerance to DNA damage;[79] and (iv) changes in molecular pathways involved in the regulation of cell survival or cell death.[80]

The Italian chemist Michele Peyrone (1813–1883) was the first to synthesize cisplatin (cis-diamminedichloroplatinum (II)).[81] Over a century later came Rosenberg's discovery; he and his colleagues found that the cisplatin compound caused filamentation of bacteria cells and killed eukaryotic cells, including cancer cells.[82] Many more platinum compounds have been synthesized and evaluated as potential chemotherapeutic agents, although few of them have been used in the clinical treatment.[83] Worldwide annual sales of platinum-based anticancer drugs are currently around two billion U.S. dollars. Several other metal compounds have been found to show anticancer activity including a variety of complexes of ruthenium and gold, as well as metallocenes of Ti, Nb, Mo, and Re. Platinum(II) drugs, carboplatin and oxaliplatin have also found clinical use.[84,85] Cisplatin is responsible for the cure of over 90% of testicular cancer cases and it plays a vital role in the treatment of cancers such as ovarian, head and neck cancer, bladder cancer, cervical cancer, melanoma, and lymphomas, as well as several others.[86-87]

Barnett Rosenberg was a biophysicist at the University of Michigan who had decided to examine the electrical currents which played an important role in cellular division. This was prompted by Rosenberg's feeling that the mitotic spindles in a dividing cell appeared similar to the classic school science experiment, where magnetic field lines are formed by scattering iron filings on paper over a magnet.[87] In order to examine this, *Escherichia coli* (*E. coli*) cells growing in an ammonium chloride buffer had a current used on them through "inert" platinum electrodes immersed in the buffer. After a period of time, the *E. coli* cells began appearing long and filamentous, much like spaghetti, instead of their classical sausage shape. This effect was caused by inhibiting the cellular division but not the growth; after much investigation, it was determined that the phenomenon was not due to the electrical current, but that platinum hydrolysis products had formed.[80] A range of group 10 transition-metal compounds were tested and found to also result

in elongation of *E. coli* cells, and in fact, elongation of a range of gram negative bacilli is affected by the most effective platinum salt.[81] It was also reported by Rosenberg and co-workers that the cis form of the platinum(IV) complex was responsible for inhibition; the trans complexes were found to be ineffective and more toxic. The complexes demonstrated "potent" activity, shrinking large solid tumors in mice where the mice survived. Indeed, the cured mice did not show any signs of cancer. Based on these results, cisplatin entered clinical trials and it became the most used clinical drug for anticancer.[88]

Over 50 years ago, Cisplatin played an important role in Alfred Werner's theory of coordination chemistry that correctly proposed its square planar configuration and distinguished between the cis and trans isomers (cisplatin and transplatin).[90-93] Werner got the Nobel Prize for Chemistry for this work in 1913. In 1970 Dhara stated "A rapid method for the synthesis of cisplatin and the majority of subsequent cisplatin syntheses are based upon this method".[94]

Because of the trans effect, the procedure of preparation of cisplatin was acceptable. The concept of the trans effect is due to Chernyaev in 1926 who made the empirical observations that the rate of substitution of a ligand in a square planar or octahedral metal complex is mostly dependent on the group opposite (or trans) to it, much more so than groups in cis positions.[94] In 1965 Rosenberg et al. discovered that cisplatin was highly effective in inhibiting cellular division.[82] At present, cisplatin is one of the most widely employed drugs because it is more effective in the clinical treatment of 70–90% of testicular cancer, and especially when cisplatin is combined with other drugs, of brain, ovarian, bladder and breast cancer (Weiss and Christian, 1993). However, it exhibits several side-effects, such as nausea and vomiting, and particularly, high nephrotoxicity and ototoxicity. In addition, it may promote cross-resistance in the neoplastic

cells (Bloemink and Reedijk, 1996). To reduce the toxicity of platinum (II)-based drugs, sulfur-containing compounds (especially thiols or dithiocarbamates) have been administered as antidotes.[87] It is well established that glutathione (Hamers et al., 1993), which is substituted for amino ligands, and other thiolic compounds (Galbraith et al., 1987) reduced the nephrotoxic effects.[95,96] Recently, new Pd (II), Pt (II) and Pt (IV) complexes have been synthesized providing anticancer activity and lower toxic side effects (Von Nussbaum and Danishefsky, 2000).[97] Accordingly, thousands of platinum complexes have been tested in vitro and in vivo, and only a few of these showed chemotherapeutic properties and were suitable for clinical trials.

1.4.1 Side Effect of Platinum Based Drugs and Disadvantages

Unfortunately, cancer drugs are generally not selective, they will attack healthy cells as well as cancer cells. Long period of treatment, which could be more than five years of treatment have been a big reason to make some patients to give up these drugs.[98] Various side effects might occur such as nephrotoxicity, myelotoxicity, neurotoxicity, ototoxicity, nausea, and vomiting. The current studies are made in light of obtaining a safer drug delivery with lower toxicity and higher selectivity.

The disadvantages of cisplatin have provided us a good reason to improve the platinum-based anticancer drugs. Over the last 40 years, thousands of platinum complexes have been prepared with the aim of synthesizing new platinum drugs with a more tolerable toxicological profile and higher efficacy.[99] These attempts have helped bring five more drugs into clinical use, such us carboplatin, oxaliplatin, nedaplatin, lobaplatin, and heptaplatin, while about 10 others are currently under clinical trials. Each of the latecomers shows some qualities that are not shown by cisplatin.[69] For example, nedaplatin displays less nephrotoxicity and neurotoxicity than cisplatin

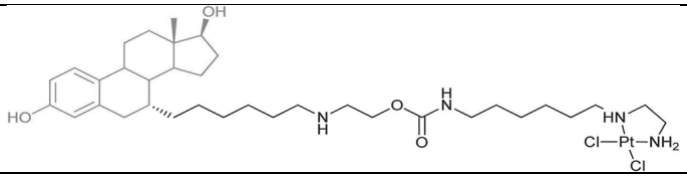
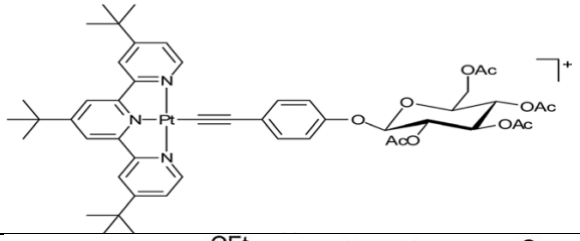
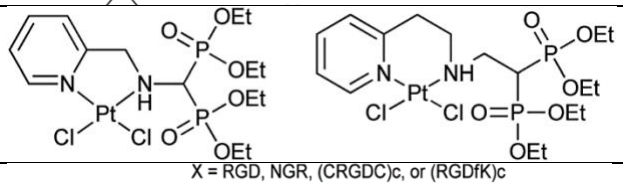
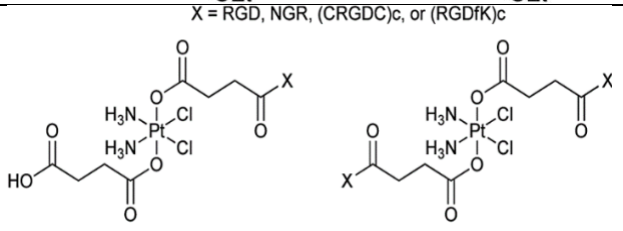
and carboplatin, and oxaliplatin demonstrates less toxicity and little or no cross resistance to cisplatin or carboplatin. However, since most of these drugs operate via a similar non-specific mechanism of action, some defects of cisplatin are consequently retained, albeit to a lesser extent. Thus, simple modification of the ligands seems unlikely to bring about a leap from an indiscriminative drug to a magic bullet. Systemic toxicity and drug resistance are the main concerns in the current development of platinum anticancer agents. Ideally, future platinum drugs should attack exclusively cancerous cells without affecting normal ones and enter the former more readily than the latter. However, this goal is virtually unattainable for such a complicated disease as cancer. Nonetheless, it is possible to approach the ideal situation by developing platinum-based prodrugs that are safe in the administered form but are cytotoxic within the cancer cells after being activated under certain conditions. Obviously, the realization of this ideal is determined by the tumor selectivity of platinum complexes.[100,101]

1.4.2 Targeting and Delivery of Platinum Based Anticancer Drugs

Drug targeting and delivery (DTD) represents a crucial field of research for drugs that can go deeper to their biological targets as ‘‘magic bullets’’.[102] If we compare cisplatin anticancer drugs with traditional chemotherapy, such targeted therapy for cancers will have two major advantages: avoidance of damage to normal tissues, and restraint of drug resistance. Recently, various DTD approaches have been developed in an endeavor to reduce the systemic toxicity and drug resistance of platinum-based anticancer drugs.[103] The ultimate goal of these endeavors is to create platinum drugs which are highly selective for tumor tissues and can be administered at lower doses with fewer side effects and an improved therapeutic index. DTD is based on the specific bio-molecular interactions between drugs and cell or tissue elements. This approach can be brought to tumors containing biochemical entities with big difference in quantity or functionality from normal

tissues. In a typical active DTD system, the targeting moiety is bound to the pharmacophore via a spacer and a linker; the specific functionality of the transporter-, antigen- or receptor-based conjugate drives the drug toward the tumor tissue by virtue of its specific binding affinity.[104] Bioactive substances, such as hormones, sugars, amino acids, proteins, and bisphosphonates, are commonly used to overcome the targeting function. Additionally, biodegradable molecules, such as polysaccharides, poly-amino acids, proteins, and water-soluble polyethylene glycol, are adopted to perform the delivery function. The addition of targeting functionality to the drug makes it possible to differentiate the cancerous cells or tissues form healthy ones, and thereby ensures the high efficacy and low side effects of the drug.[96,105]

Table 1. Shown Are The Several Carrier Drugs

No.	Carrier drugs	Structures	References
1	Estrogens as carriers		105
2	Carbohydrates as carriers		106
3	Bisphosphonates as carriers		107
4	Peptides and proteins as carriers		108

1.4.3 Synthetic Methods for The Preparation of Platinum Anticancer Complexes

In this part, we present an overview of known synthetic strategies for the synthesis of platinum anticancer complexes. The present reports provide chemists working with synthesis of inorganic materials with practical advice on the synthesis and purification of potential platinum anticancer agents. The coordination chemistry principles employed for the preparation of such compounds are emphasized and are useful to a wide audience of chemists. There are two major sections, for the synthesis of platinum(II) and platinum(IV) complexes. These sections are further divided based on the nature and stereochemistry of the target complexes. In each section, a short overview is provided of the anticancer properties of the target complexes. Multinuclear platinum complexes, some of which are excellent drug candidates, have been omitted from this review to maintain the focus on single-site reactivity.[109]

The reaction schemes do not display fully balanced chemical reactions, but instead illustrate only the major platinum-containing species. This choice stems from the complexity of many seemingly simple reactions of platinum compounds, the chemistry of which can be deceptively complicated. Two generic ligand types, L and X, are utilized (figure below), with ligands symbolized by "L" representing either an amine or *N*-heterocyclic unit. When "(L_2)" is used, the ligand is bidentate. Ligands designated with an "X" are monoanionic, like halides or carboxylates.

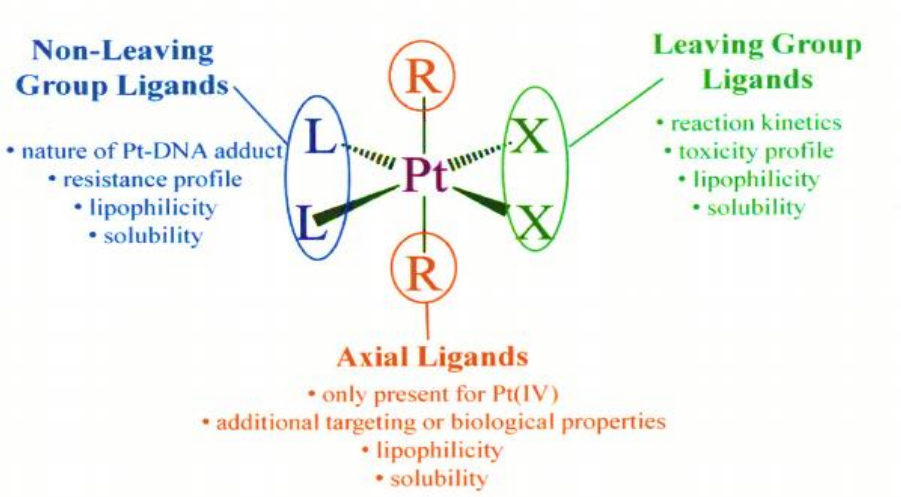


Figure 5. Different Components of Platinum Anticancer agents. Additional Factors That Can Be Varied Are The Stereochemistry and The Respective Number of Non-leaving and Leaving Group Ligands

1.4.3.1 Synthesis of Platinum (II) Complexes

All clinically used platinum drugs contain the element in the 2^+ oxidation state which have almost exclusively square-planar coordination geometries. The major reaction of the synthesis of platinum(II) and other square-planar d^8 complexes involves associative ligand substitution as shown in figures 6 and 7. Reactions proceed through five-coordinate trigonal-bipyramidal intermediates. The stereochemistry of the products is dictated by the relative trans effect of the ligands within the complex. An early review on the synthesis of monodentate amine complexes of platinum (II) is also available.[109,110]

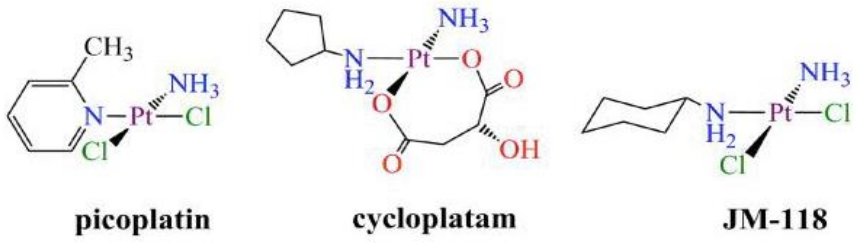


Figure 6. Cis-[PtLL'X_2], Complexes with Mixed Amine Ligands.[111]

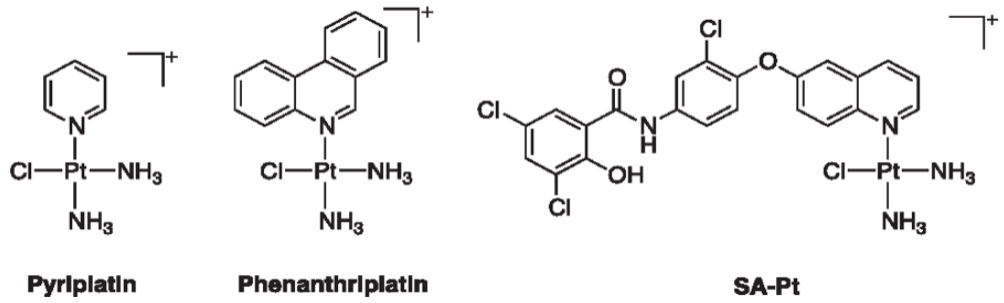
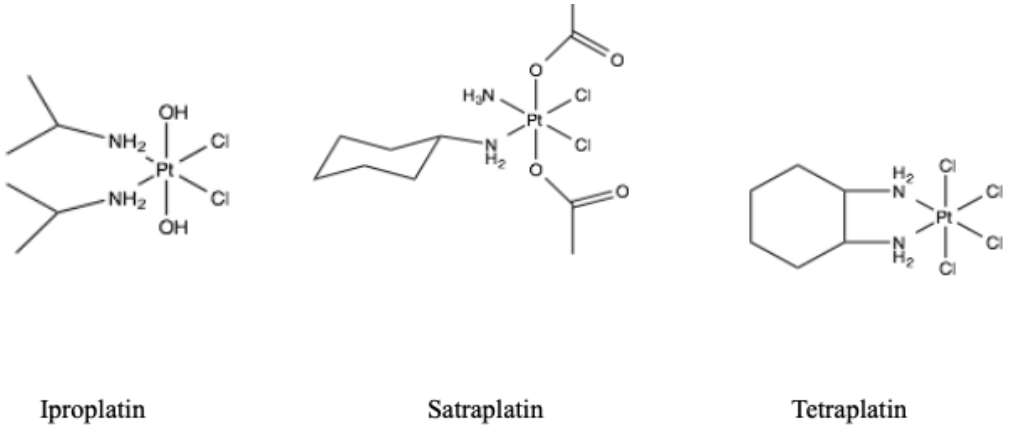


Figure 7. Monofunctional Platinum (II) Complexes.[112]

1.4.3.2 Synthesis of Platinum(IV) Anticancer Complexes

Platinum(IV) complexes have been subjected to clinical trials. Octahedral coordination geometry in platinum(IV) complexes gives an advantage over their platinum(II) analogs because two additional ligands allow for further tuning of the properties, as well as giving the ability to attach functional or targeting groups.[113] Moreover, being complexes of d^6 octahedral metal ions, platinum(IV) compounds are substantially more inert than those of platinum(II). Thus, undesirable side reactions with proteins or intracellular thiols can generally be avoided using platinum(IV) complexes.[114] The kinetic inertness of satraplatin is most likely due to the fact that platinum(IV) complexes in general are inert, and they usually undergo the reduction of platinum(II) before binding to their ultimate intracellular target, DNA.[115] Reduction of platinum(IV) occurs with loss of two ligands, giving a square-planar geometry for the platinum(II) product. It has generally been supposed that the two ligands lost upon reduction are located trans to each other and both derive from positions along the axis orthogonal to the original plane of four ligands. There are a number of reports in recent research that the composition of the reduced platinum(II) products is dependent on the nature of the reducing agent. Furthermore, the kinetics of intracellular platinum(IV) reduction depends on the type of cell, and the ligands define the coordination sphere of the complex.[116] The ability to rationally design new platinum(IV) anticancer drug candidates using

well-defined synthetic chemistry is critical for discovering new therapeutic agents and for further elucidating structure-activity relationships.[117] Different platinum(IV) complexes have been under clinical trials, but none has been approved by the Food and Drug Administration (FDA) for clinical use in the United States. These drugs are iproplatin, tetraplatin, and satraplatin figure 8.



Iproplatin Satraplatin Tetraplatin

Figure 8. Pt (IV) Based Complexes That Are Undergoing Clinical Trials

1.4.4 Mechanism of Action

Cisplatin produces anticancer activity by crosslinking and intercalating with DNA, causing cell death via "apoptosis".[118] After introduction into the bloodstream of a patient, cisplatin faces a high concentration of chloride in the blood plasma, which is around 100 mM, and the high concentration does not allow the replacement of its chloride ligands by water molecules; therefore, the process of aquation is prevented. Nonetheless, cisplatin is vulnerable to attack by proteins found in blood plasma, in particular those that have thiol groups, such as human serum (albumin) and the amino acid (cysteine). As a matter of fact, studies have shown that one day after cisplatin administration, more than 50% of the platinum in blood plasma is protein bound.[119] This protein is able to deactivate the drug[120] and produce some of the cisplatin treatment's severe side effects.[119]

In synthetic processes, this drug is formed together with the trans formation, which is not very cytotoxic, but is a strong systemic toxin and should be removed before treatment. The concentration, which is between 2 to 30 mM, of the chloride decreases inside cells, and after complete hydrolysis in the second step, the second chloride ligand is replaced by another water molecule forming $[Pt(NH_3)_2(H_2O)_2]^{2+}$ and Platinum binds to a second nucleotide, resulting in a rapid chelation reaction (see figure 9), forming 1,2 adducts. These aquated species readily react since H_2O is a better leaving group than Cl^-. The primary bifunctional adducts are of guanine-guanine or adenine-guanine which cause distortion of DNA proteins, signaling DNA repair or cell death. [121]

The vast difference in the reactivity of cisplatin and trans-platin is the result of the "trans effect." Trans-platin hydrolyses four times faster than cisplatin and reacts with ammonia approximately 30 times faster. The high reactivity of the trans isomer leads to side reactions and hence is not effective as an anti- cancer drug. The inability of trans isomer to form 1,2 adducts between adjacent purine bases can be attributed to steric effects. However, it has been discovered recently that trans complexes with bulky amine groups slow the rate of substitution reactions and are sources of potential drugs.[122]

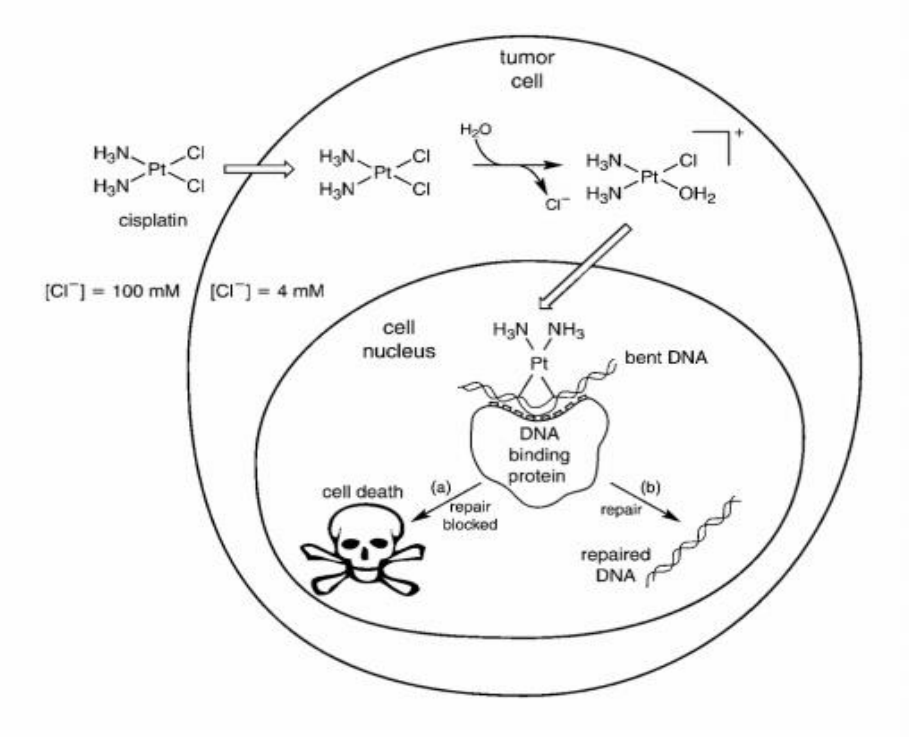


Figure 9. Mechanism of Action of Cisplatin "The Discovery and Development of Cisplatin[122]

1.5 Copper Complexes

Copper is a transition metal, which has an electron configuration of $[Ar]4s^1 4p^6 3d^{10}$ and other physical properties which are shown in table 2. Copper is found in three different oxidation states: Cu(I), Cu(II), and less commonly, Cu(III).[123] Cu(I) complexes configuration $[Ar]4p^6 3d^{10}$, is usually diamagnetic and colorless. If it is colored, the color is produced by a charge transfer band or an internal transition in a ligand.[124] Cu(II) with configuration $[Ar]4p^6 3d^9$, is the most common oxidation state of copper that exists in biological systems. Also, Cu(I) exists in biological systems and many important enzymes, and many proteins depend on the Cu(I)-Cu(II) interconversion. Due to its d^9 orbital configuration, Cu(II) provides a typical example of the Jahn-Teller effect which causes a splitting of e_g and t_{2g} orbitals.[125] The distortion is usually seen as axial elongation consistent with the lability and geometric flexibility of the complex. For that reason, typical Cu(II) complexes have square planar or square pyramidal geometries with weakly attached ligands in the

axial position(s), but some copper(II) complexes possess trigonal bipyramidal geometry and others exhibit distorted octahedral and tetrahedral symmetries since complexes easily undergo ligand rearrangement and/or solvent or counter anion coordination, giving more thermodynamically stable compounds with square pyramidal or trigonal bipyramidal structure.[126]

Much attention has been devoted to studying copper complexes because copper centers in the complexes have a variety of distortions,[127,128] and copper is considered hard and easily coordinates with N and O. Most Cu(II) complexes are observed in the electronic spectra of Cu(II) complexes as a single broad, poorly resolved band envelope. This envelope is typical of Cu (II) complexes in tetragonal complexes. These complexes are generally blue or green because of an absorption band in the 600-900 nm region of the spectrum.[124] A third oxidation state Cu (III) is relatively rare and difficult to attain without the use of strong π-donating ligands. These complexes usually adopt a square planar geometry due to the d^8 Cu (III) electron configuration.[129]

Table 2. Experimental Values for Selected Physical Properties of Copper

Property	**Cu**
Atomic number	29
Naturally occurring isotopes	2
Atomic weight	63.546
Electronegativity	1.9
metal radius / pm	128
ionic radius / pm. I	77
II	73
III	54
Ionization energy(eV) 1st	7.72
2nd	20.28
3rd	37.07

Copper is an essential trace element in all living organisms, important in the process of internal oxidation and reduction, employed as a structural and catalytic cofactor, and consequently it is involved in many biological pathways.[130] Focusing on this, much attention has been devoted to the mechanisms of absorption[131] distribution[132] metabolism, and excretion of copper,[133] as well as on its role in development of cancer and other diseases.[134,135] The copper concentration in the human body is tightly regulated at the levels of cells, organs, and body,[136] since copper free ions are potentially harmful. Once absorbed in the small intestine and stomach (adult human dietary recommendation is estimated at between 1.5 and 3.0 mg Cu/d),[137] the distribution of copper is regulated by the liver into the bloodstream through ceruloplasmin and albumin. Cu levels in serum and tissue have been demonstrated to be significantly greater in various human tumors, including breast, prostate, colon, lung and brain cancers.[136-139] Kuo *et al* reported that serum and tissue Cu levels in breast cancer patients were markedly higher than levels in the control group.[136] Moreover, abnormal accumulation of copper is associated with several human diseases, disorders and pathological states including oxidative-stress-related disorder, aceruloplasminemia, Alzheimer, Parkinson, Wilson's disease, Menkes disease , etc., rheumatoid arthritis, gastrointestinal ulcers, epilepsy, diabetes, and cancer.[140]

1.5.1 Biological Applications of Copper (II) Complexes

The complexes of copper (II) ion containing Schiff bases have attracted attention due to their remarkable properties as catalysts in various biological systems, polymers, dyes, antimicrobial activities, antifungal activities, antiviral activities, anti-inflammatory activities, antiradical activities, plant growth regulator, enzymatic activity, insecticides, antitumor and cytotoxic activities. They also possess wide applications in the analytical chemistry, agrochemical and pharmaceutical fields.[141] The crucial role of copper and the acceptance of its complexes as

important bioactive compounds in vitro and in vivo actuated an ever-increasing interest in these agents as potential drugs for therapeutic finding for various diseases.[142] The coordination chemistry of copper(II) has considerable attention due to its biological relevance and its own interesting coordination chemistry such as flexible geometry, redox property, and oxidation state.[143] Recently, coordination compounds have been known to be useful in constructing molecular information processing systems, particularly by biological self-organizing processes.[144] Especially for this purpose, synthesis of copper complexes has been directed towards mimics for metalloenzyme.[145]

The current research efforts have been devoted to the potential chemotherapeutic properties and antibacterial activities of copper complexes.[146] Therefore, several strategies have been developed for new anticancer therapeutics targeting the elevated tumor-specific copper level.[147] Actually, control of angiogenesis, tumor growth, and metastasis could be attained by chelating the excess of copper and small molecules with copper-binding ability that are easily synthesized and structurally manipulated has become an attractive tool.[148]

Somewhat reversing the anticancer strategy based on sequestration of copper to prevent establishment of the tumor blood supply, tumor cells may represent a suitable, selective target for a copper-based antitumor drug. For the success of copper-based anticancer strategies the chemical framework and ligand donor atom set is of crucial importance since it can modulate the hard/soft properties of the metal, the lipophilic/hydrophilic balance of the resulting complexes, and their solubility in extracellular fluids as well as the ability to permeate the bilayer lipidic membrane. Other important aspects that should be taken into account in the design of copper complexes include their stability toward trans chelation reactions with physiological molecules (individual amino acids, peculiar peptide sequencies, or whole proteins). These processes may sometimes

preclude the expected tumor targeting or, on the contrary, may sometimes facilitate the cellular internalization of the metal.[149] In addition, the study and development of Cu complexes could be helpful in the design and production of antiviral and antibacterial materials, the ability to deactivate HIV or H1N1 viruses[150] and antibiotic-resistant bacteria, respectively. Towards this aim, a method of producing copper-impregnated materials that possess broad-spectrum antimicrobial properties has been reported.[151] Cu (II) complexes of NSAIDs showing enhanced anti-inflammatory and antiulcerogenic activity, as well as reduced gastrointestinal toxicity compared to the uncomplexed drug, have been prepared and structurally characterized.[152]

1.5.2 Dinuclear Copper(II) Complexes

Interacting between two copper (II) ions leads to form a singlet and a triplet and separate the energy between them. This energy is called the isotropic exchange constant 2J as shown in figure 10. The signals arising only from the triplet states are observed. When there is an antiferromagnetic coupling between two copper ions, the intensity of the triplet spectrum is found to decrease with a decrease in temperature, since the triplet state is higher in energy, which is depopulated with a low temperature. A reverse effect is found in case of ferromagnetic coupling.[153] The sign and the magnitude of the isotopic exchange constant can be estimated by analyzing the temperature dependence of the triplet. For the triplet state total spin S=1, the allowed values for the spin angular momentum are –1, 0 and +1.[154]

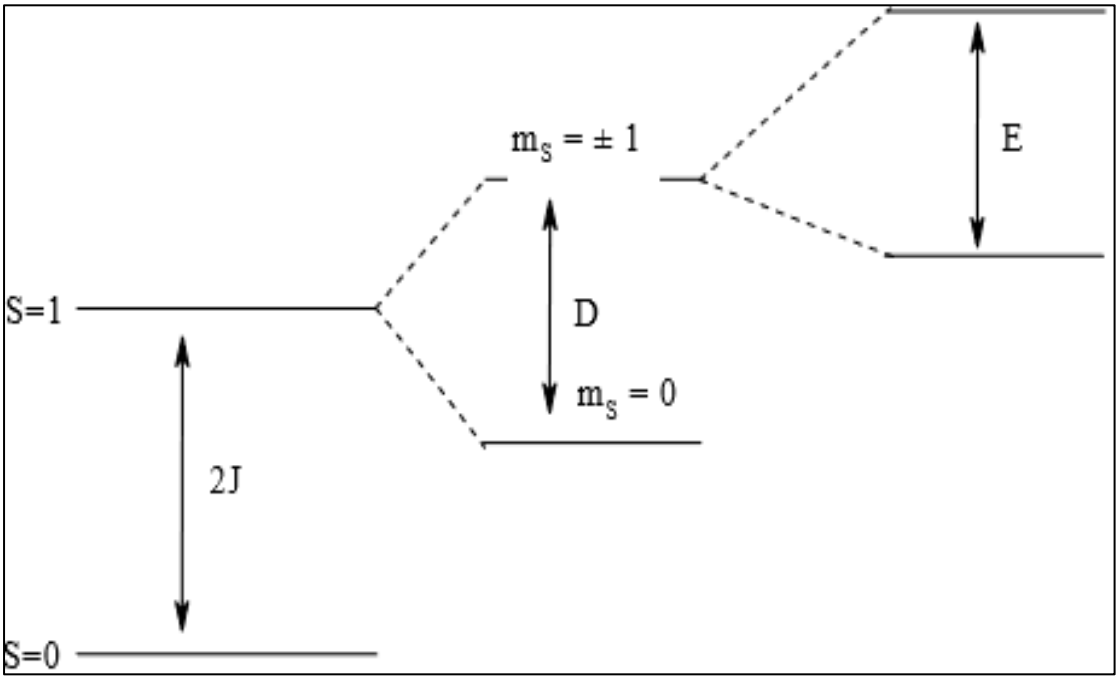


Figure 10. Schematic Representations of Energy Levels of Dinuclear Copper(II) Complexes in Presence of External Magnetic Field (E is proportional to magnetic field B). The Anisotropic Term D Can Arise from Ligand Asymmetry. J Measures Strength of Magnetic Coupling.

The synthesis of polynuclear metal complexes has attracted the attention of chemists for a long time,[155] because these provide invaluable opportunities for crossing boundaries both within and between the fields of metallobiochemistry,[156] materials science and theoretical chemistry.[157] Among a variety of polynuclear metal complexes, those containing oxygen-bridged copper(II) are of particular interest because they might represent valuable model compounds for the active site of a number of metalloenzymes and also for their interesting magnetic properties.[156] Dinuclear copper(II) complexes are known to be useful systems for the study of long-distance metal-metal interactions, since the metal ion has only one unpaired electron.[158]

The magnetic properties of bridged dinuclear copper(II) complexes have been extensively studied, since the copper(II) ions have an S = 1/2 spin, which makes them easier to deal with, from both the experimental and theoretical points of view.[159] Bleaney and Bowers, derived a theoretical

expression for the magnetic susceptibility of dinuclear copper(II) systems[160], making it possible to extract the exchange coupling constant (J) for each complex from the magnetic susceptibility curves. The wealth of available coupling constants allows the study of their relationship with structural parameters, in search for some trends that could lead to a rational design of new complexes with improved magnetic properties. For the related bis(hydroxo)[161] and bis(alkoxo)[162] bridged copper(II) complexes, linear relationships between the Cu–O–Cu bond angle and the J values obtained from a fitting of the experimental magnetic susceptibility data have been reported. For instance, in the case of hydroxo complexes, a transition from antiferromagnetism to ferromagnetism is observed for Cu–O–Cu angles smaller than 97°.[160]

This phenomenon is attributed to an "accidental orthogonality" of the orbitals bearing the unpaired electrons. Thus, to minimize electronic repulsions, the system adopts the high spin state that corresponds in this case to a triplet. From a molecular orbital point of view, Hoffmann[163] and Kahn[164] gave consistent explanations within the extended Hückel framework. More recently, the use of theoretical methods based on density functional theory (DFT) has made it possible to obtain remarkably good quantitative estimates of the J values for this kind of complexes, despite the small energy differences associated to these interactions. Ruiz et al.[165] earlier applied such an approach to the study of magnetostructural correlations in hydroxo- and alkoxobridged copper (II) complexes.[166] The results indicate that several structural parameters affect the J value, but the Cu–O–Cu angle (α), correlated with the phenyl out-of-plane shift angle (ι), plays a key role (see Figure 4). Among other structural parameters, a special mention of the bending of the Cu_2O_2 framework around the O· · ·O hinge, that can also play an important role if it is sufficiently large. All dinuclear bis(phenoxo) bridged CuII complexes belong to one of two general types, having two chelate

ligands spanning terminal and bridging positions, or with the phenoxo groups incorporated into a multidentate macrocyclic ligand.

The second family, known as Robson complexes, has been studied by Thompson et al.[167], who showed that the exchange coupling constant is correlated to the Cu–O–Cu bond angle. An important feature of the Robson-type macrocycles is that they are generally constrained to adopt a planar configuration. Thompson et al. also analyzed the effect of different electron withdrawing substituents on the value of the coupling constant. Theoretical studies of the different electronic effects of substituents on the magnetic exchange interaction between substituted dialkoxo Cu (II) systems and substituted carboxylate Cu(II) complexes were later published by Rodríguez-Fortea et al.[168] The effects reported in those two publications correspond to substituents only one or two bonds away from the bridging oxygen atoms.

1.6 A Brief History of Uranium

Uranium was discovered as an element in 1789 by Martin Heinrich Klaproth, a German apothecary and early analytical chemist, Klaproth had in fact produced only the oxide, not the pure element, and in 1841 the French chemist Eugène Péligot isolated the metal by reducing uranium tetrachloride with potassium metal.[169,170] Uranium remained a curiosity with no significant commercial use until the late 19th century, when the physicist Henri Becquerel discovered that uranium salts emitted invisible rays, now known to include gamma rays, which are at the high energy end of electromagnetic radiation which includes radio waves, microwaves, infrared, (visible) light, ultraviolet, X-rays, and gamma rays;[170] also emanated are alpha rays, now known to be helium nuclei and beta rays, no known to be electrons. In nature, its most common form is in uranyl $[O=U^{VI}=O]^{2+}$, which is trans-bis-oxo, including minerals such as schoepite, pitchblende, and uraninite, $U^{IV}O_2$, formed by exposure of uranium complexes to air or moisture. The most

common three isotopes are, ^{238}U (99.28%), ^{235}U (0.71%), and ^{234}U (0.005%)[170]: of these only the latter two can be used in nuclear fuels. Thus, UO_2 is oxidized to gaseous UF_6, which can be separated in ultracentrifuges to enrich the fissile isotopes. All isotopes are radioactive, with ^{238}U having the longest half-life of 4.468×10^9 years, decaying via α-particles emission; table 3 shows the decay data for uranium.

Table 3. Decay Data for Uranium

Isotope	Natural abundance	Half-life (billions of years)	Decay mode	Decay energy
^{234}U	0.0045%	0.000245	α	4.8 MeV
^{235}U	0.71%	0.704	α, γ	4.4, 0.21MeV
^{236}U	499.28%	4.468	α	4.2 MeV

Demand for uranium itself grew in 1939 when physicists announced that nuclear fission was theoretically possible, and that it could be used to produce a powerful weapon.[169] By the mid-1950s, many aspects of uranium metallurgy had been investigated, designed, piloted, and built into operating plants.[171] Most of the processes used today were developed and piloted in the 15-year period following World War II. The uranium industry today is considered a fully developed supply chain for the many nuclear power plants around the world. In the next process step, the respective halides or oxides can be reduced by alkali or earth alkali metals to give pure uranium metal.[171] The ^{238}U remaining after removal of the other isotopes, is called depleted uranium (DU), and its main applications are due to the fact that it is one of the highest metals, e.g. in armor piercing shells fired which can attain high momentum due to density. DU is nowadays also the main source for chemical transformations, while in the last century mainly uranyl containing minerals, different oxides, halides, or nitrates were used as starting materials for the development of uranium chemistry.[172]

Uranium compounds are difficult to reduce due to the strongly electropositive nature of the metal. Uranium metal is also highly reactive, being known to react with almost all the elements of the periodic table (with the exception of the noble gases). When exposed to oxygen or water, the metal reacts rapidly to form a black oxide layer at room temperature.[173]

As global energy consumption continues to rise, so do demands on the energy sector.[174] Nuclear power is a major contributor, and remains an integral asset, to carbon neutral energy production.[175] Even as nuclear power is integrated and essential to the energy market, there is a threat of environmental[176] contamination if radiation escapes, along with an increasing problem of nuclear waste storage. Interest in fundamental actinide research to better understand uranium and the other f-elements has been on the rise to elucidate their fundamental chemistry and pave the way for enhanced nuclear fuel remediation techniques.[177] Recently, depleted uranium, a by-product of enriching uranium, has been investigated for applications in catalysis to complete difficult chemical transformations.[178] Researchers have also sought to characterize the degree of actinide covalency both synthetically and computationally using ligands featuring nitrogen donors.[179] Sessler and co-workers have explored changes in ligand aromatic character when bound to an actinide.[180]

1.6.1 Coordination Chemistry of Uranium

The coordination chemistry of uranium is analogous to that of transition metals, but what distinguishes uranium from them is that its valence electrons reside in f orbitals.[181] Unlike the 4f and 5d orbitals of lanthanides, both 5f and 6d orbitals of uranium are actually less contracted and can have better overlap with ligand-based orbitals.[182] Another distinction is that the greater number of valence orbitals (seven f orbitals vs. five d orbitals for transition metals) allows uranium to support more types of coordination modes. Additionally, uranium can access a wide range of

oxidation states that are typically less accessible to transition metals. For example, uranium complexes are known for each oxidation state from +3 to +6, differentiating it from much of the f-block.[183,184] Despite relativistic effects, f orbitals are contracted by nature, and covalency in uranium-ligand bonding is more limited than in the d-block.[185] This dichotomy results in interesting reactivity and electronic structure observed nowhere else in the periodic table. All the characteristics described above lead to a unique behavior for uranium compounds, and its potential to catalyze a remarkable range of transformations has been revealed in the last couple of decades.[186]

The inspiration behind the synthesis and investigation of uranium–nitrogen complexes generally derives from four basic motives, namely a desire to: (i) explore the fundamental chemistry of 5f-elements' reactivity and coordination behavior; (ii) understand the bonding interactions between the metal center and ligand (ionic or covalent bonding); (iii) identify suitable trivalent actinide (An(III)) extractants for nuclear remediation and finally, (iv) explore possible applications of new complexes, such as in catalysis or as sensors. The first motive needs no further clarification: the rarity and radioactivity of the actinide elements has restricted them from widespread study, leaving them as one of the few unexplored areas of the periodic table. Moreover, the bonding behavior of the lanthanides and actinides has been a subject of debate for nearly 40 years[187], a fact that underlies the second motive for investigation. Since the report of uranocene [$U(COT)_2$] by Streitwieser and Müller-Westerhoff in 1968[188], many groups have tried to prove, or disprove, covalent interactions between the actinide cations and various ligands. For instance, metal-to-ligand-bonding has been observed in uranium–phosphorus complexes[189], and uranium–arene complexes,[190] leading to the suggestion that a covalent interaction is possible with uranium. A number of complexes have also been reported in which the presence of nitrogen back donation

with U(III) is proposed.[191] Evidence has also been put forth suggesting back bonding between amido groups and a U(II) center.[192]

Uranium, while not present in the trivalent coordination state in a significant amount in nuclear waste, is often chosen as a model for the minor actinides in extraction studies. Although not a perfect match in terms of electronic structure, U(III) salts often display reactivity that is similar to those of the minor actinides. This cation is also less radioactive than other actinide cations and available in readily usable quantities. Finally, a number of uranium-containing complexes have been shown to be useful in other applications, such as catalysis, anion and neutral molecule sensing and small molecule activation. These applications are providing a less specialized and easier-to-appreciate motivation for carrying out actinide-related chemical research.[193]

The most thoroughly investigated, best characterized and most stable oxometal cations are the dioxouranium (VI), dioxomolybdenum(VI) and oxovanadium(IV) ions. The strongly bound oxygens of these oxometal cations remain intact during chemical reactions and produce one or more additional absorption bands beyond those normally available in transition metal complexes. The formation of multiple covalent bonds to oxygen by uranium has been explained theoretically. The tendency of oxygen to delocalize its π electrons away from its highly compact valence shell by forming π bonds with π electron acceptor metals accounts for the formation of metal oxygen bond, at least qualitatively. Complexes of the uranyl ion, UO_2^{2+}, are of interest since they show seven-coordinate, pentagonal-bipyramidal geometry (Gatto *et al.*, 2004).[194] Due to the spectral properties (absorption and luminescence) and excited-state electron-transfer properties of the UO_2^{2+} ion, dioxouranium (VI) complexes have possible applications in solar energy conversion systems (Signorni and Dockal, 1996).[195]

The dioxouranium(VI) complexes with tetradentate Schiff bases have been the subject of many investigations, while the oxouranium complexes with bi- or tridentate Schiff bases seem to be fewer in the literature (Mandlik and Anwar, 2003).[196] The tridentate dibasic Schiff base ligands behave as an ONO-donor ((El-Tabl *et al.*, 2002)[197] and react with the uranyl salts to form two types of complexes, depending on the molar ratio of the reactions. The first liquid crystal (mesogen) complex containing U (the first uranomesogen), published in 2002[198], showed that a very heavy MW coordination complex could form liquid crystals (at that time not generally believed possible); the liquid crystal range was only over a short temperature range. Follow-up studies[199] showed that more U complexes form liquid crystals, and with much longer liquid crystal range. To build on this, it should be possible to make binuclear U complexes with liquid crystal properties with heavy substituents (e.g., halogens), demonstrating the possibility of much higher MW liquid crystals. The enabling chemistry for such new materials requires us to establish that suitable binuclear U chemistry is possible.

Only a few heterometallic 3d-5f complexes are reported. These 3d-5f complexes are derived mainly from uranium in different oxidation states by using various types of ligands, for example, phosphonates, hexadentate bicompartmental N_2O_4 Schiff base metalloligands, etc.[200] The compounds containing lower valence uranium ($U^{III/IV/V}$) have been synthesized mostly to explore their interesting magnetic properties.[201] On the other hand, the naturally occurring uranyl compounds which have been known for their interesting photophysical properties for centuries and have immense importance in terms of environmental, geological, or bioassay fields[202] are rarely explored to make photo responsive systems using interactions between transition metal complexes and uranyl ions.[203] The hexadentate bicompartmental ligands have been found to be very convenient to create heterometallic complexes including 3d-4f metal ions.[204] In recent years

the use of monocompartmental chelates derived from tetradentate salen type Schiff bases (salen = N,N′-bis(salicylidene)ethylenediamine) has also gained popularity.[205] The oxygen atoms of the neutral Cu(II) and Ni(II)-chelate of such ligands can coordinate to a second metal ion providing a facile way for the synthesis of bi-, tri-, tetra-, or polynuclear heterometallic complexes in which the second metal ion is a s-block, p-block, d-block, or 4f-block cation.[206] However, to date these chelates have not been used to synthesize heterometallic 3d-5f complexes. As actinyls are hard acids with a strong oxophilic character and prefer high coordination numbers (five, six or seven) around the equatorial plane, they are expected to be incorporated easily by these monocompartmental chelates.[207]

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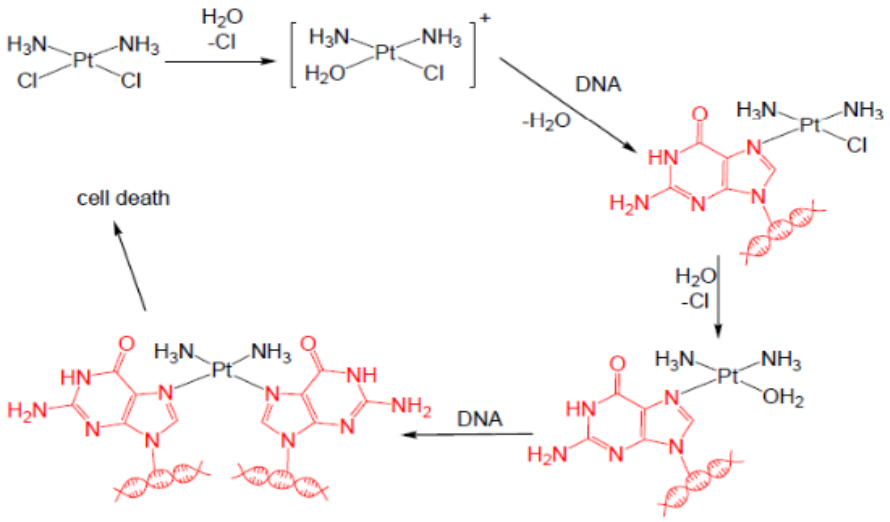
CHAPTER 2

SYNTHESIS AND CHARACTERIZATION OF PT-BASED ANTI-CANCER DRUGS

2.1 Introduction

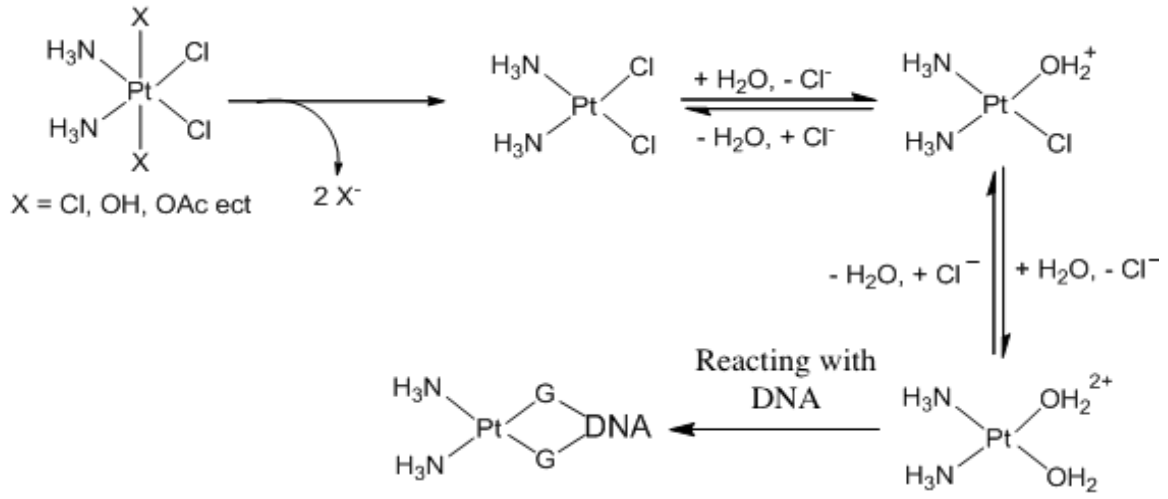
Cancer is an abnormal growth of cells. Over 100 types of cancer have been diagnosed, including breast cancer, skin cancer, lung cancer, colon cancer, prostate cancer, and lymphoma. Symptoms vary depending on the type. The fundamental reason for approximately 13% of all types of worldwide human deaths is cancer. Cancer treatment may include chemotherapy, radiotherapy, and/or surgery. Chemotherapy, commonly used to treat cancer cells, uses specific drugs to kill fast growing cells by stopping them from multiplying and spreading to other parts of the body. Even though remarkable processes have been studied, including chemotherapy, there is currently a significant increase in cancer diagnosis. The antitumor drug (cisplatin) discovered in the 1960s has become one of the most useful agents to treat different types of cancer.[1] Nowadays, it has been used in more than 50 percent of cancer treatments.[2] Over 100 drugs have been studied, tested, and used in chemotherapy. Anticancer drugs are used and relied on for specific kinds of cancer. Because of their cytotoxic activity, many Pt(II) and Pt(IV) complexes have been developed to improve the applicability on a broader spectrum of cancers, increase their therapeutic window and reduce the dose-limiting side effects. However, cisplatin has significant side effects that reduce its efficacy. These effects include nephrotoxicity, myelotoxicity, neurotoxicity, ototoxicity, nausea, vomiting, and harming healthy cells due to insufficient specificity in targeting tumor cells.[3] All those obstacles have been an incentive to scientists to overcome them with sophisticated solutions that will not affect healthy cells.

In this project, three different types of platinum-based anticancer drugs are considered. The first type, chelated agents, are produced by having starting materials together in water. The platinum center will react with the organic ligand compound and the solvent to work as a leaving group.[4] Bidentate ligands have two donor atoms, allowing them to bind to a central metal atom. Common examples of bidentate ligands are ethylenediamine, which can be used as a non-leaving group, and the oxalate ion can be used as an anionic leaving ligand.[3,4] It bonds via nitrogen or oxygen atoms on the adjacent edges of a planar Pt(II); each donor has two free electrons that can be used to bond to a central metal atom or ion. However, none of the approved drugs has organic bidentate ligands and monodentate anionic ligands, which is worth trying, as it can have a similar mechanism of action to that of cisplatin. If the leaving group is chloride, such as DPAPlatin, its loss is substantial before binding to target DNA. Another option to consider is having water molecules as leaving groups instead of chloride, such as the leaving group of PhenPlatin. In the present case, it is considered that the complex is very reactive and can interact with target DNA without any additional step. PhenPlatin can apply a second possibility, which is the second platinum's loss, leading to different drugs, which can work as two different drugs that can be administrated simultaneously.[4]



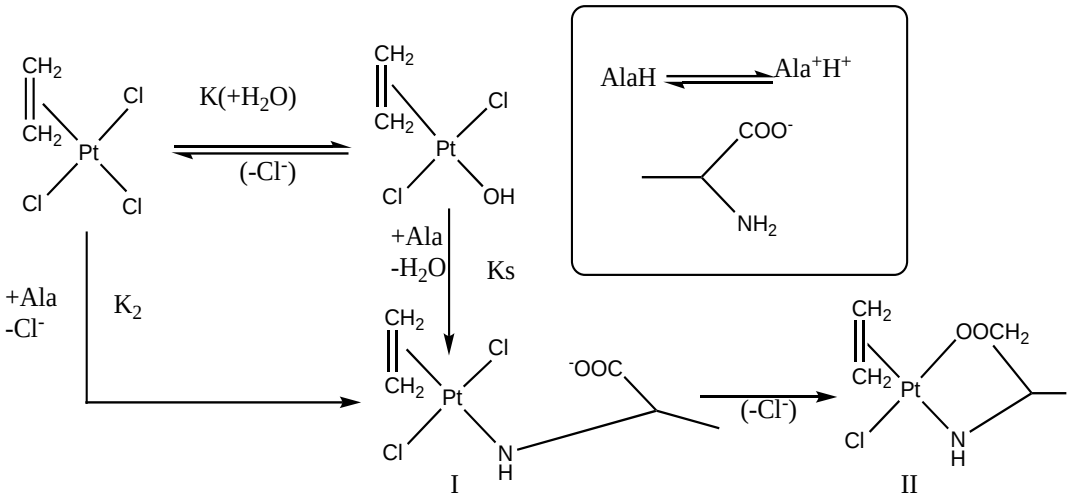
Scheme 3. Proposed Mechanism of Action of Chelated Agents

The second type is Pt(IV)-based complexes, which has two additional ligands that essentially keep the drugs inactive until they reach target DNA. Platinum(IV) complexes have six-coordinate octahedral coordination geometry, with two additional ligands, which allows for further tuning of the properties. Additionally, these complexes are more inert due to being d^6 octahedral metal ions. Therefore, the deactivation of the original platinum (II) drugs that can occur when they interact with thiol is prevented by using platinum (IV)-based anticancer drugs.[4] As platinum (IV)-based complexes are inert, the reduction to Pt (II) usually occurs before binding to the target, DNA.1 Reduction of Pt (IV) happens with the loss of two ligands, leading to the square planar geometry characteristic of Pt (II) complexes. It is believed that the (monodentate) ligands that are located trans to each other will be lost in the reduction step. Once the loss of two ligands occurs, the mechanism of action of the Pt (IV) prodrug will be reasonably similar to cisplatin, where it binds to the plasma protein, and then the loss of chloride will occur after substituting it with a water molecule, which is highly reactive towards the nucleus; then the formation of Pt-DNA will occur to prevent the cell from dividing and growing.[2]



Scheme 4. Proposed Mechanism of Action of Pt (IV) Based Complexes

The third type is π-bond binding, a new and interesting field. The stability of the metal-olefin bond in platinum (II) complexes related to the formal charge on the complex has been the subject of studies in the past few years.[5] The action occurs when pi-acid alkene donates electron density to the platinum d-orbital from a π symmetry bonding orbital between the carbon atoms. Then, the platinum donates electrons back from another filled d-orbital into the vacant π antibonding orbital. These two effects decrease the carbon-carbon bond order, resulting in an elongated C-C distance and a reduction of the vibrational frequency. One of the well-known examples is Zeise's salt $K[PtCl_3(C_2H_4)].H_2O$, which is believed to be the first known organometallic[3], and its C-C bond length increases from 133 picometer for ethylene to 134 picometres on bonding to the metal.[6] This action encourages the carbon atoms to have rehybridization to sp^3, which occurs by bending back the hydrogen atoms to ethylene from the metal.[7] The mechanism of action is quite similar to the mechanism of this action of chelate agents.



Scheme 5. The Proposed Mechanism of Action of Zeise's Salt

Scheme 5 involves bimolecular displacement of either chloride or water trans to ethylene by the amino group of the entering amino acid anion via parallel second-order routes, i.e., k_2 and ks, to the intermediate I. An overall second-order kinetic pattern results from the platinum substrate's solvolysis being faster than the subsequent reaction of the aqua species with the entering nucleophile. This is at variance customary behavior of platinum complexes toward nucleophilic displacements, where solvolysis is the rate-determining step for the solvent-assisted reaction pathway.[8] This may well be readily due to the extremely low concentration of the nucleophile (Ala) compared to water. The experimental rate constant related to the reactivity of Zeise's anion toward Ala, kz, is affected by a rather larger standard deviation than the ks term. To the extent that comparison is feasible, the aquo complex appears to react at a rate that is 30 times greater than that of Zeise's parent chloride, reflecting the higher lability of water as a leaving group.[9] Both ks and kz are greater than the second-order rate constant for a displacement of the chloride trans to ethylene in Zeise's anion by bipyridyl[7] (1.45 X 103 M"1 sec"1 at 25° in 95% aqueous methanol).

This is not unexpected since the nucleophilic ability of the primary amine group of alanine is greater than that of the tertiary nitrogen of bipyridyl.

2.2 Experimental

2.2.1 Materials and Methods

All chemicals used were of AnalaR grade and obtained from Sigma-Aldrich and Fluka. Metal salts were purchased from E. Merck and were used as received. Solvents were purified by standard methods and dried before use by conventional methods.

2.2.2 Synthesis of DPAPlatin

A suspension of dipicolylamine (0.2 mmol) in water (5 mL) was titrated with 0.1 M HCl by stirring until all the solids had dissolved, followed by the addition of a solution of K_2PtCl_4 (0.18 mmol) in water (3 mL). The precipitate of Pt-complex is formed after the above mixture has been refluxed at 70 ˚C for 2 h. The precipitate is collected and washed with 0.1 M HCl, water, and ethanol and then is dried at 50 ˚C under vacuum for 5 h.

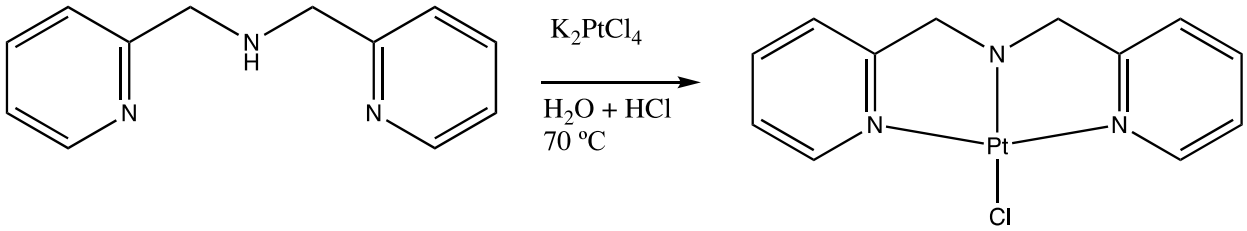


Figure 11. Synthesized of Drug DPAPlatin.

2.2.3 Synthesis of PhenPlatin

1,10-phenanthrolin-5-amine (0.2 mmol) in water (5 ml) was mixed with (2 ml) of MeOH and the solution was stirred until solid was dissolved, followed by the addition of a solution of

K_2PtCl_4 (0.18 mmol) in water (2 ml). The precipitate of Pt-complex is formed after the above mixture has been refluxed at 100 ˚C for 4 h. The precipitate is collected and washed with 0.1 M HCl, water and ethanol and then is dried at 50 ˚C under rotary evaporation for 8 hours.

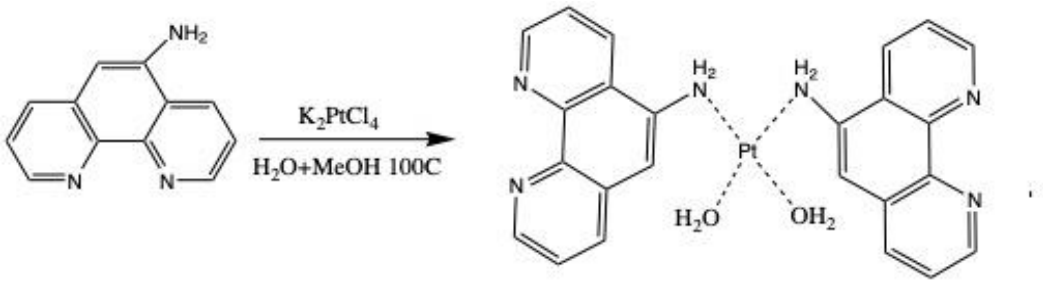


Figure 12. Synthesis of Drug PhenPlatin.

2.2.4 Synthesis of TriPicolyAminePlatin

125 mg of potassium tetrachloroplatinate (K_2PtCl_4) was added to 200 µl of water via a micro-syringe. The solution was heated while stirring in an oil bath to 70 ºC. To this a solution of 300 mg of KI in 500 µl of warm water was added. The mixture was heated to 80 ºC with continuous stirring. As soon as the temperature reached 80 ºC, the mixture was cooled down to room temperature. The solution was filtered using a Hirsch funnel to remove any solid impurities. Using a syringe, 0.4 mmol of the organic compound was added with HCl and water, after 45 min of stirring, another 0.4 mol of organic compound was added and stirred for another 45 min. An oily complex was obtained. The beaker was left to stand for an additional 20 min at room temperature.[10]

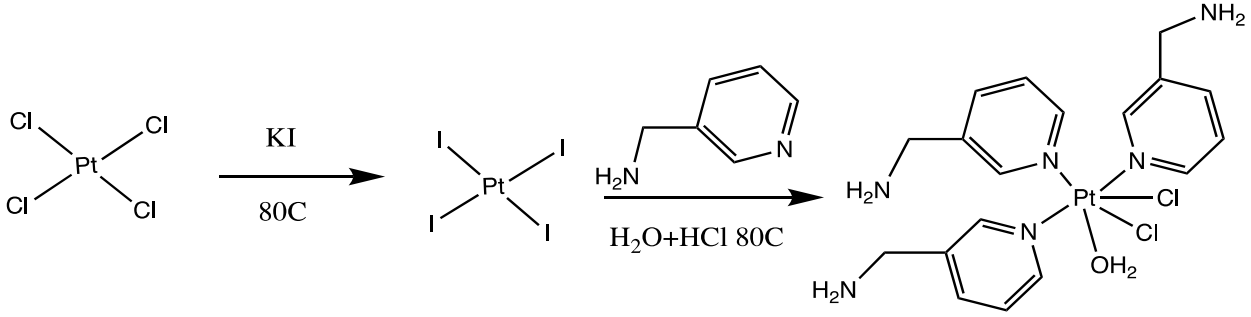


Figure 13. Synthesis of The Synthesized Drug TriPicolyAminePlatin.

2.2.5 Synthesis of DiPhenPlatin

125 mg of potassium tetrachloroplatinate (K_2PtCl_4) was added 200 µl of water via a micro-syringe. The solution was heated while stirring in an oil bath to 70 ºC. A solution of 300 mg of KI in 500 µl of warm water was added. The mixture was heated to 80 ºC with continuous stirring. As soon as the temperature reached 80 ºC, the mixture was cooled down to room temperature. Cl_2 gas was bubbled through the solution. This generated pale yellow solid products. After bubbling for another hour, the pale-yellow products were filtered using a Hirsch funnel to remove any solid impurities. Using a syringe, 0.4 mmol of the organic compound was added. As soon as the compound was added, fine red crystals of the complex precipitated. The beaker was allowed to stand for an additional 20 min at room temperature. The product was washed with 500 µl ice-cold ethanol, followed by 1 ml ether.[10]

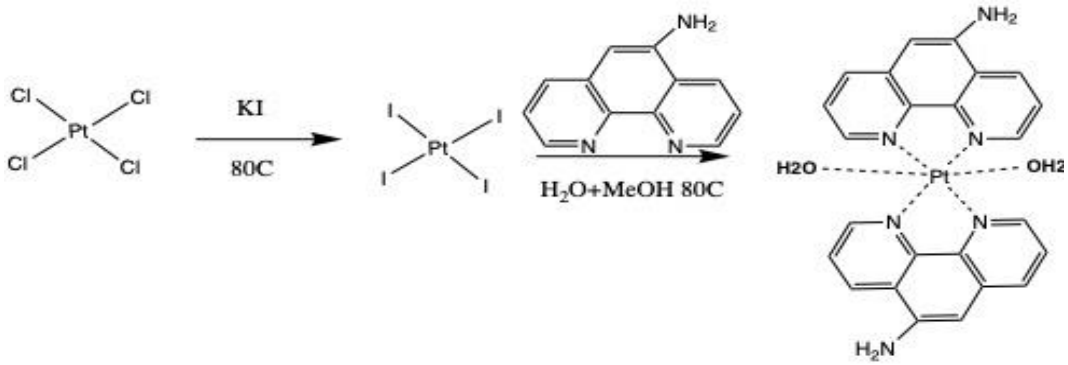


Figure 14. Synthesis of Drug DiPhenPlatin.

2.2.6 Synthesis of DCCPlatin

The hydrate is commonly prepared from K_2PtCl_4 and N,N'-dicyclohexylcarbodiimide in the presence of a catalytic amount of $SnCl_2$. The water of hydration can be removed in vacuo.[11]

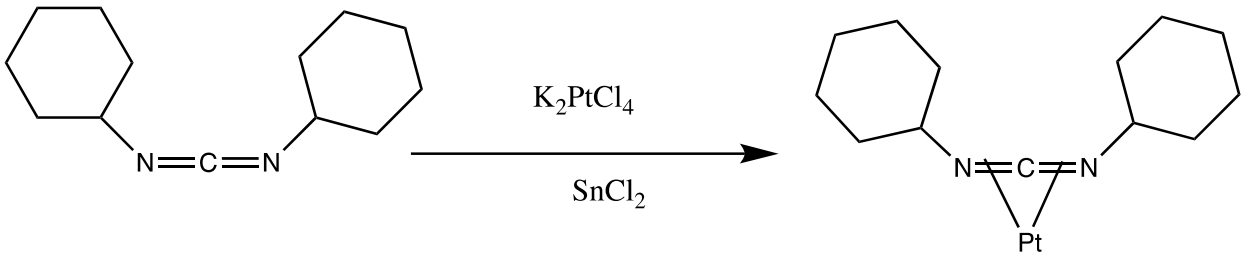


Figure 15: Synthesis of Drug DCCPlatin.

2.3 Results and Discussion

2.3.1 ^{1}H-NMR Spectra

We have recorded ^{1}H NMR spectra in DMSO-d6, because the solubility of the complexes in some other solvents ($CDCl_3$, CD_2Cl_2) was much smaller. The ^{1}H-NMR spectra of the complexes shown in figures (16-20), were recorded to confirm the structure of the mode of bonding in platinum complexes. ^{1}H NMR measurements, performed for complexes, in all cases exhibited the presence of distinct sets of sharp signals by coordinating between the free ligand molecules and the metal. The significant difference between the spectra of uncoordinated ligands and their platinum-bound complexes is deshielding of the peaks, which is expected to be higher for protons closer to the metal atom.[12,13] ^{1}H chemical shifts (δ ^{1}H; ppm) of all ligands and complexes, as well as the respective coordination shifts (Δ^{1}H coord = δ ^{1}H complex - δ ^{1}H ligand, ppm) are listed in Table 4.

The comparison of δ ^{1}H values of the DPAPlatin complex with a free ligand reveals the deshielding of H (4,6,1,5,7) atoms upon DPA replacement (yellow powder (95%) of the DPAplatin. ^{1}H NMR (DMSO-d6, 400 MHz,): δ/ppm = 8.95(m, 2H), 8.52 (m, 1H), 8.15 (m, 2H), 7.53 (m, 2H), 4.51 (d, 2H), respectively. The ^{1}H-NMR spectra of the Phenplatin complex show signals corresponding to protons were observed at 9.00 (dddd, 2H), 8.81 (m, 2H), 8.68 (m, 2H), 8.16 (m,2H), 7.85 (m, 2H), 7.51 (m, 2H). The ^{1}H-NMR spectra of TriPicolyAminePlatin shows

chemical shifts corresponding to protons were observed at 9.03 (s, 1H), 8.69 (m,3H), 7.76 (m, 1H) 7.55 (m,1H), 3.95 (dd,2H), 1.78 (dd, 2H). δ/ppm of DiPhenPlatin = 9.55 (d, 1H), 9.35 (d, 1H), 8.70 (d, 1H), 8.35 (m, 1H), 8.02 (m, 1H), 7.81 (d,1H), 7.55 (s,1H), 5.76 (s,2H) respectively. The ^{1}H-NMR spectra of DCCplatin complex shows signals corresponding to protons were observed at 3.47 (m, 1H), 2.039 (dddd, 2H), 1.80 (dddd, 2H), 1.58 (m,2H), 1.44 (m, 2H), 1.37 (m, 2H).

2.3.2 ^{13}C-NMR Spectra

^{13}C NMR measurements for all complexes have been performed in DMSO-d6. The significant difference between the spectra of uncoordinated ligands and their platinum-bound complexes is shielding of the peaks, which is expected to be higher for carbon atoms closer to the metal atom. ^{13}C chemical shifts (δ^{13}C; ppm) of complexes as shown in Figures (21-25): their chemical and coordination shifts (Δ^{13}C coord =δ^{13}C complex - δ^{13}C ligand; ppm) are listed in Table 5. The complexation of five complexes results in ^{13}C NMR high-frequency shifts. Surprisingly, they are mostly expressed for these carbons that are not directly adjacent to nitrogen, their Δ^{13}C coord parameters being ca 2–6 ppm. In contrast, Δ^{13}C coord values for carbon atoms neighboring to N are much smaller (up to ca. 2 ppm) or even negative (down to ca -2 ppm). Such an unusual pattern of coordination shifts suggests a competition of two opposite effects: general deshielding of all ^{13}C nuclei, and specific shielding of C atoms positioned in the nearest moiety of the coordination site. The relevant C atoms (adjacent to N (3) coordination site) were shielded by ca 2-10 ppm, in contrast to all other, slightly deshielded carbons.[14,15]

Table 4. Coordination Shifts (Δ^1H coord = δ ^{1}H Complex - δ ^{1}H ligand, ppm) of The Prepared Pt Complexes, in DMSO-d6

DPAPlatin and DPA	PhenPlatin and Phen	TriPicolyAminePlatin and PA.	DiPhenPlatin and Phen	DCCPlatin and DCC
H4 +0.838	H6 +0.19	H12 +0.45	H3 +0.66	H3 +0.32
H6 +1.01	H9 0.45	H8 +0.25	H13 +0.63	H2, H2 +0.49, +0.15
H1 +0.72	H16 +3.18	H10 +0.15	H5 +0.15	-
H5 +0.27	H5 +0.45	H9 +21	H11 +0.18	-
H8 +1.6	H12 +0.01	H24 +0	H12 +0.36	-
H7 +0.35	H13 +0.06	H23 +0	H4 +0.35	-

Table 5. Coordination shifts (Δ^{13}C coord = δ ^{13}C complex - δ ^{13}C ligand, ppm) of The Prepared Complexes, and Their Complexes (^{13}C coordination shifts, δ^{13}C coord, in parentheses), in DMSO-d6

DPAPlatin and DPA	PhenPlatin and Phen	TriPicolyAminePlatin and PA.	DiPhenPlatin and Phen	DCCPlatin and DCC
C2 (157.03) -8.03	C8(139) -8.02	C8(139.03) -10.02	C3(148) -2.21	C3(52) -5.02
C4(144) -15.1	C2(145.6) -2.09	C12(138.03) -10.1	C13(147) -3.02	C4(28) -7.12
C6(137) -3.19	C12(130.7) -2	C11(144) +8.01	C1(143) -5.03	C1(22) -3.01
C1(119) -2.43	C6(129) -2.12	C10(127) -11.05	C10(140) -5.5	C6(23) 0
C5(122) -2.55	C7(115.05) -3.11	C9(119) -6.03	C5(135) -8.01	C8(83) +3.023
C7(56) +4.22	C9(105) -5.04C8	C23(125) +2.01	C11(134) -7.011	-

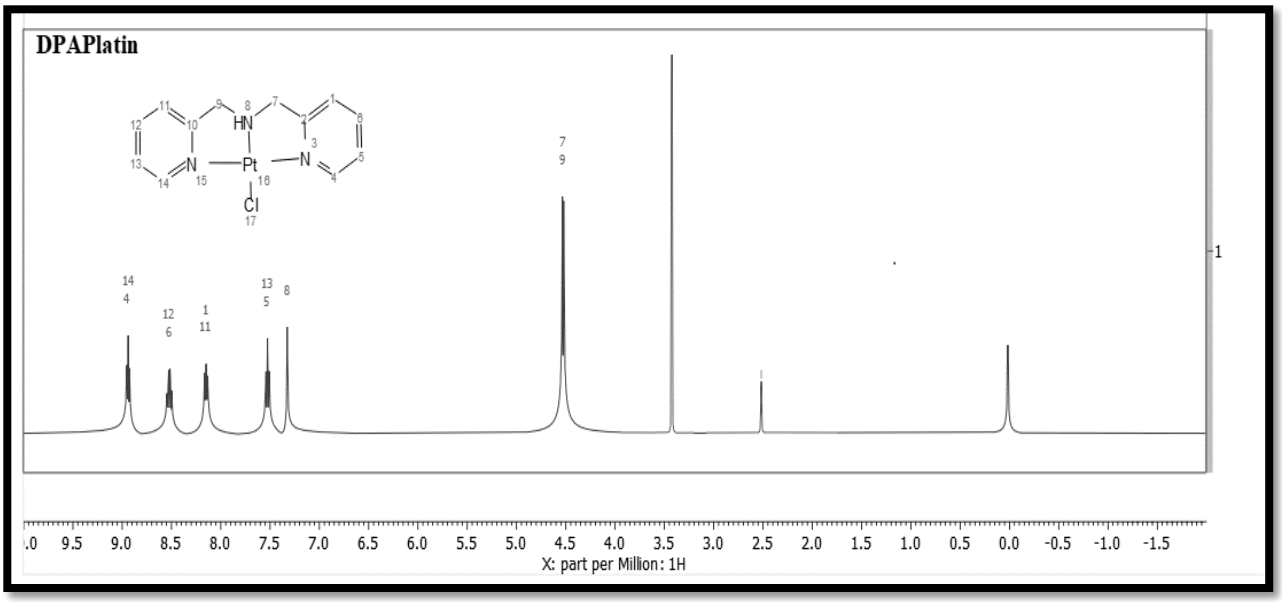


Figure 16. ^{1}H-NMR for DPAPlatin

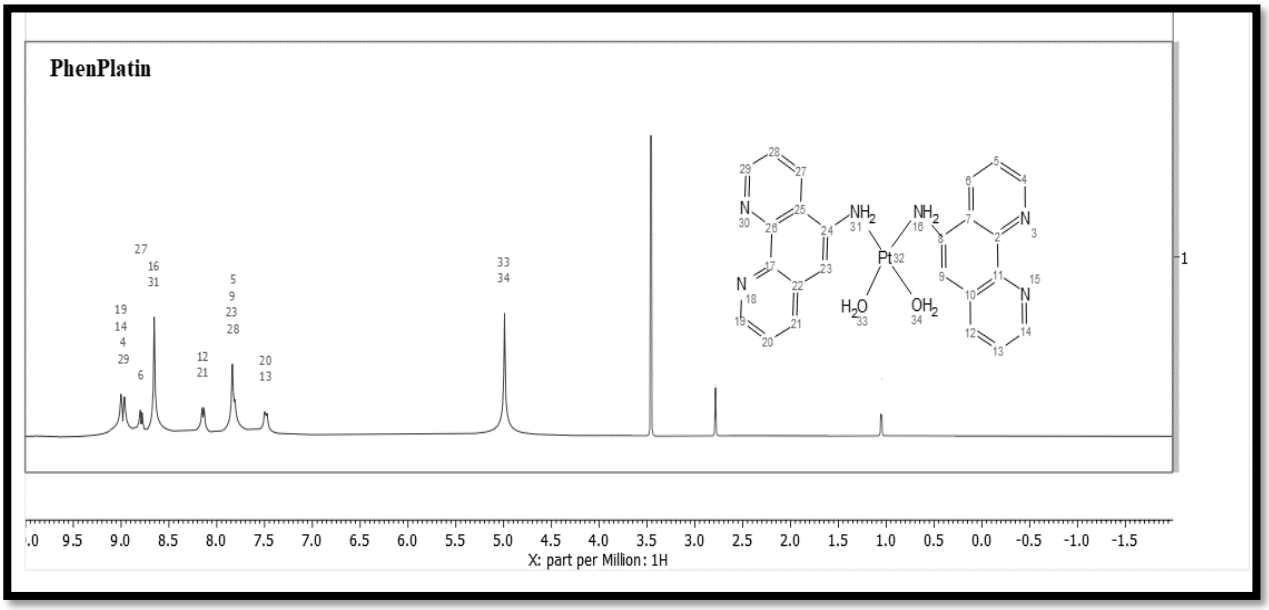


Figure 17. ^{1}H-NMR for PhenPlatin

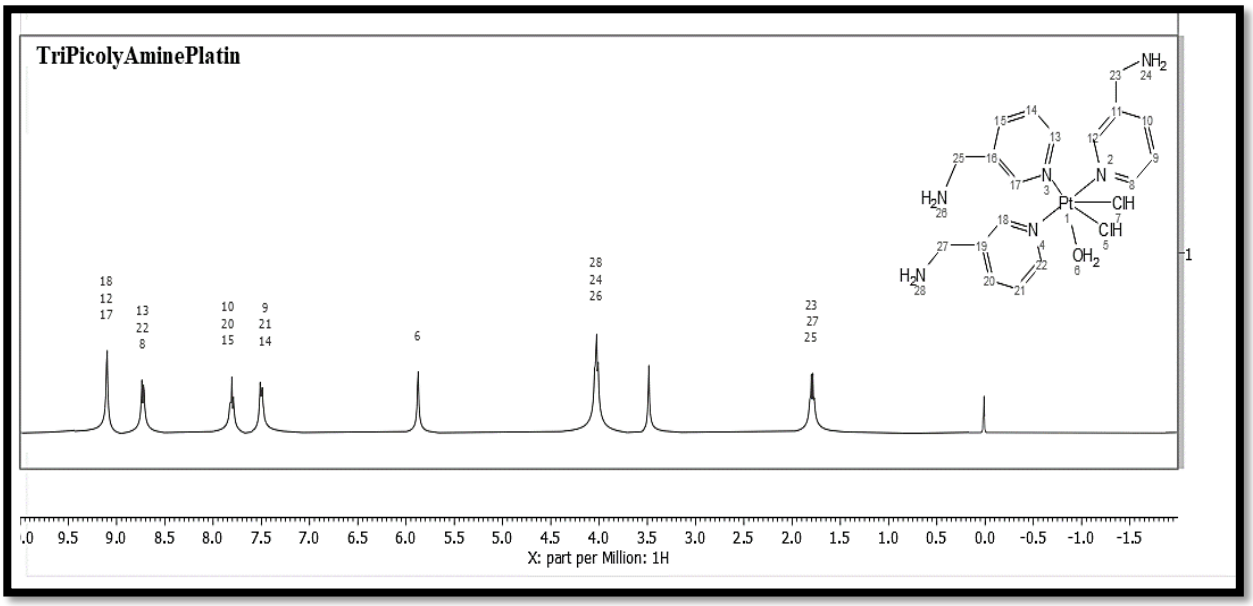


Figure 18. ^{1}H-NMR for TriPicolyAminePlatin

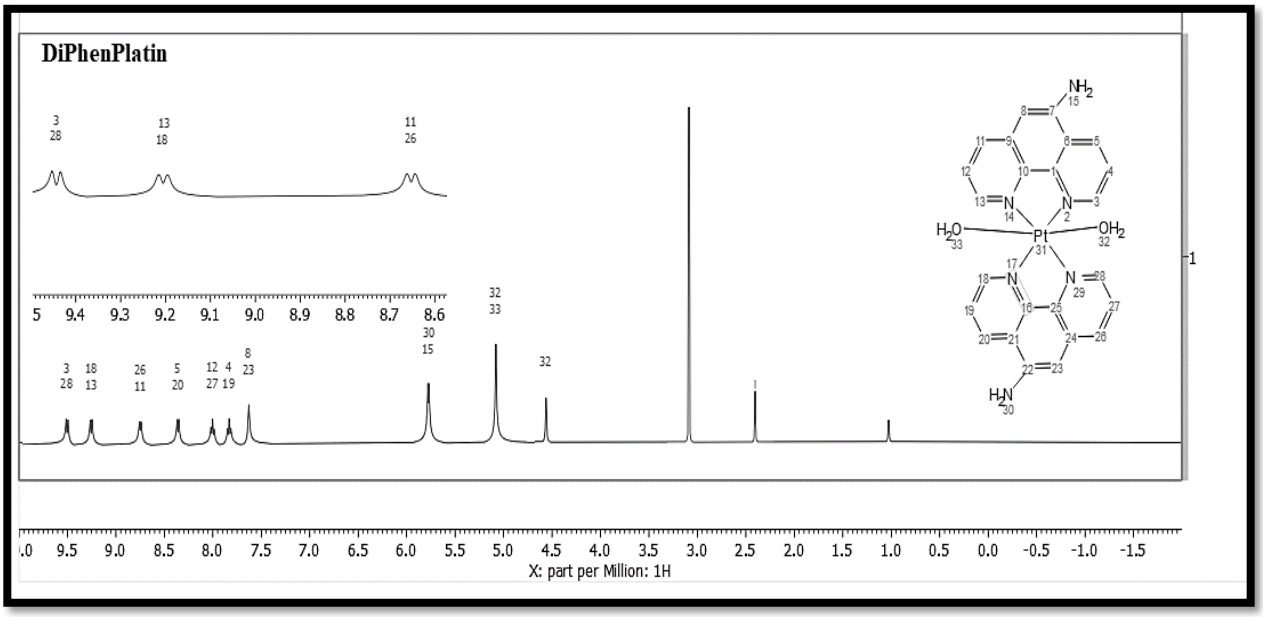


Figure 19. ^{1}H-NMR for DiPhenPlatin

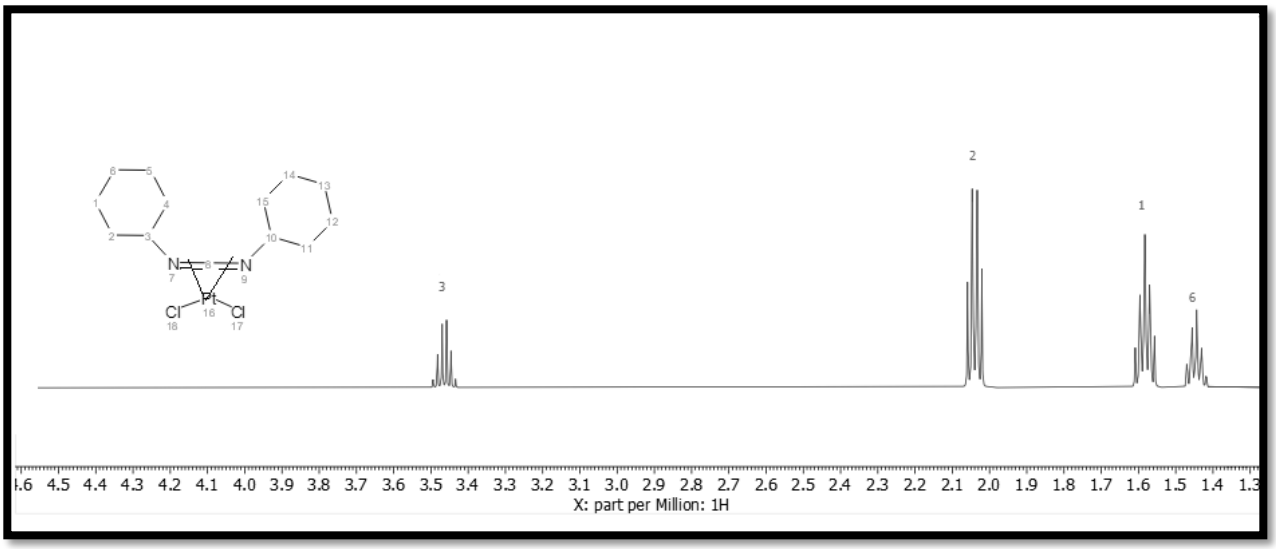


Figure 20. ^{1}H-NMR for DCCPlatin

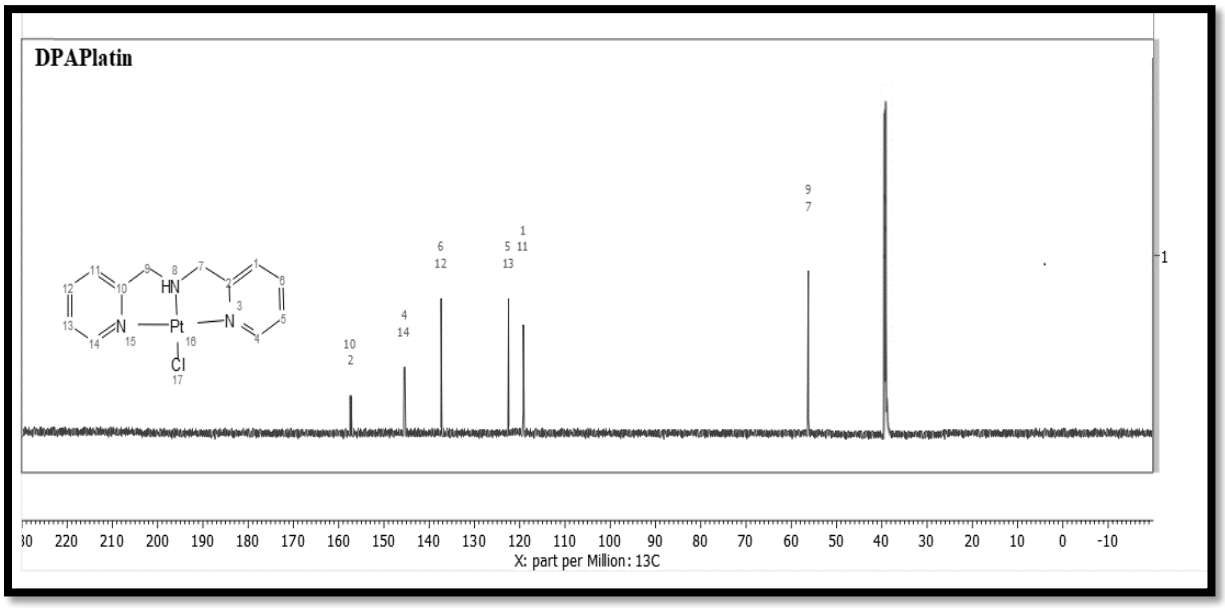


Figure 21: ^{13}C-NMR for DPAPlatin

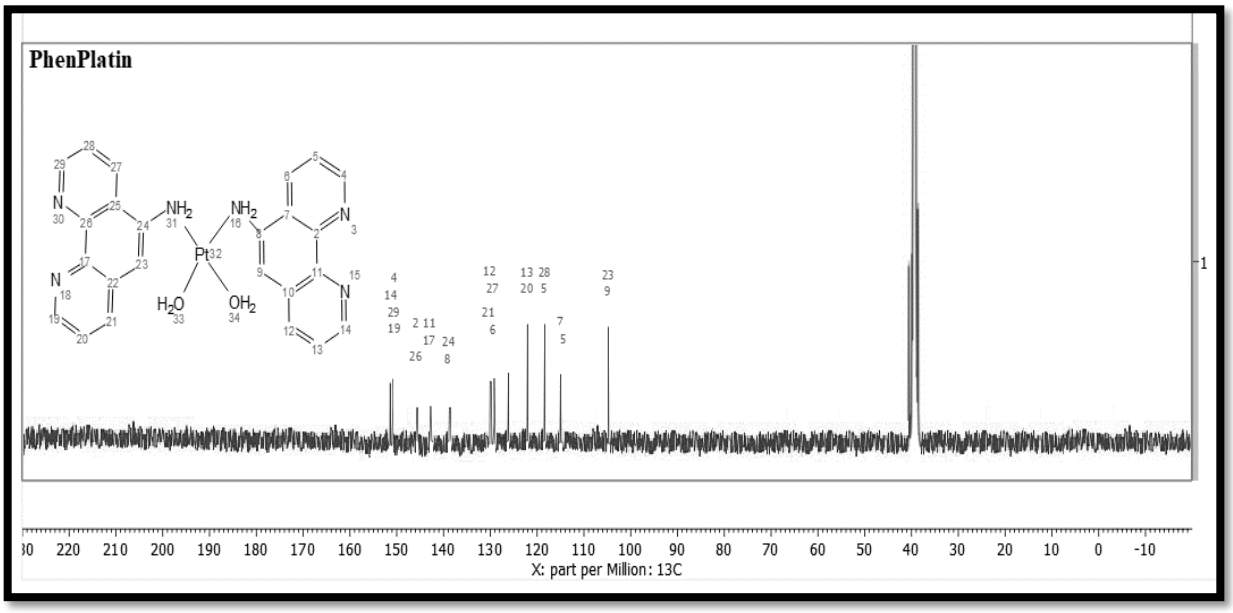


Figure 22. ^{13}C-NMR for PhenPlatin

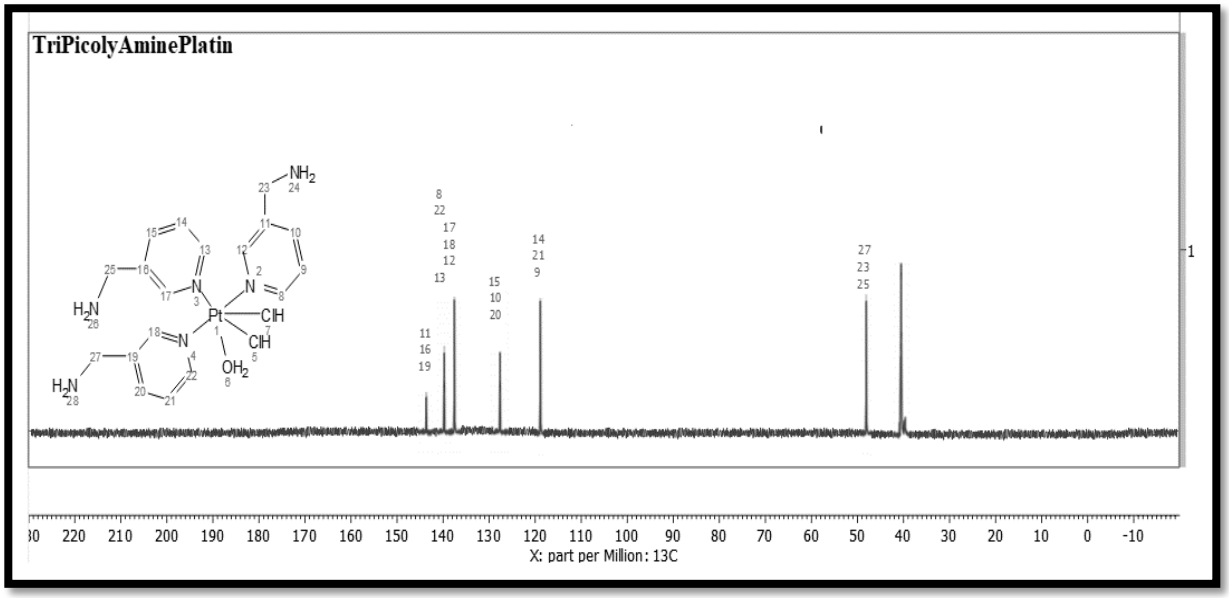


Figure 23. ^{13}C-NMR for TriPicolyAminePlatin

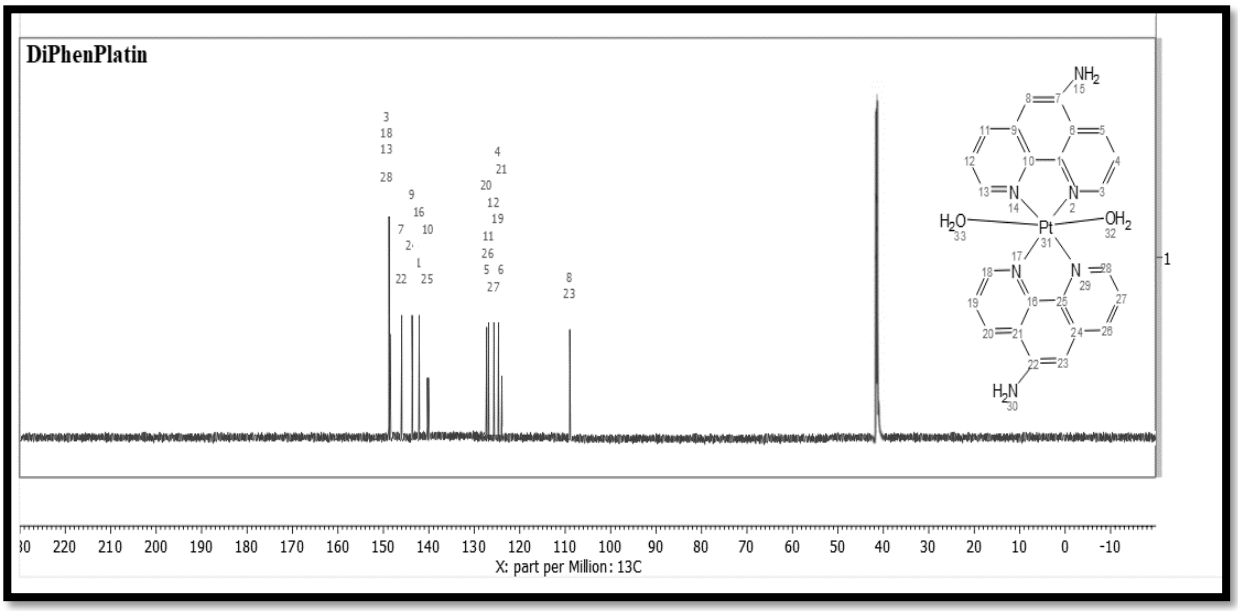


Figure 24. ^{13}C-NMR for DiPhenPlatin

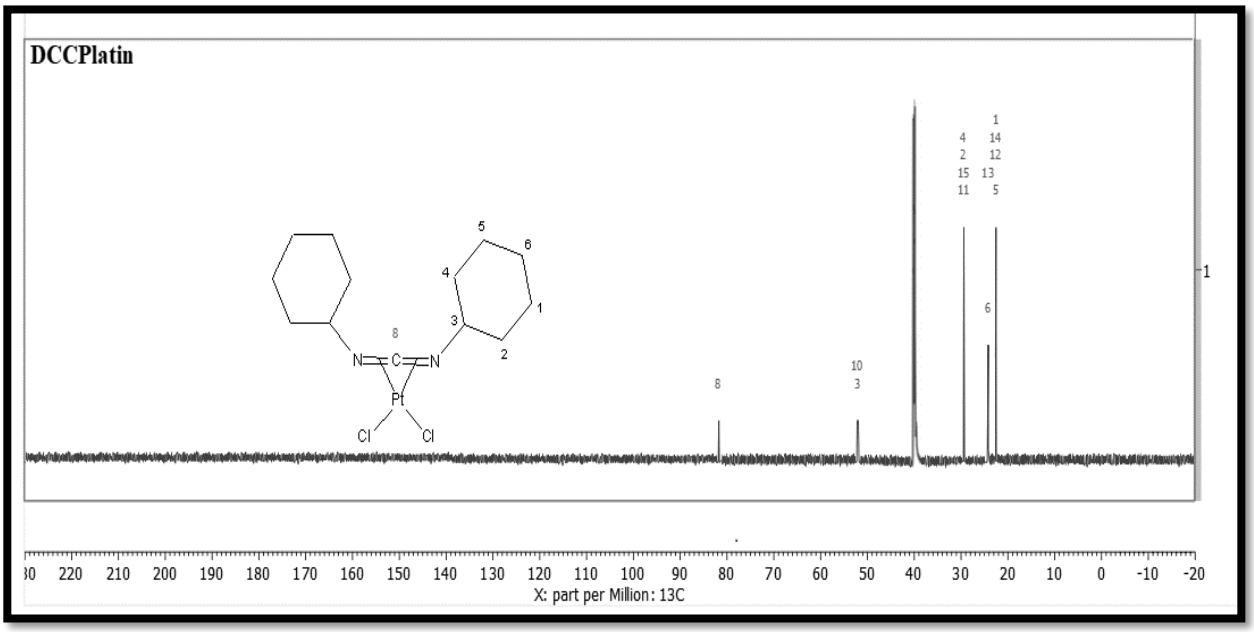


Figure 25. ^{13}C-NMR for DCCPlatin

2.3.3 Mass Spectroscopy and Mass Spectrometer

As one of the most important traditional spectroscopy analytical techniques, MS has been widely used to analyze the chemical structures of organic compounds and small biological molecules. Moreover, MS can provide information on the molecular mass of a sample. Since Thomson discovered isotopes of Ne by mass spectrometry in 1912, the MS technique has been developed rapidly in physics, chemistry, biology, and environmental and material sciences. The modern MS techniques allow more precise determination of atomic masses and analysis of compound structures. More importantly, with the discoveries of two soft ionization techniques, i.e., electrospray and matrix-assisted laser desorption/ionization in the late 1980s, MS can be successfully applied to analyze the mass of high molecular weight compounds, such as polymers, proteins, nucleic acids (DNA and RNA), etc. [16–18]

For the mass spectrometry measurement, samples must be ionized first by a beam of high energy electrons or other ionization techniques to generate (positively or negatively) charged molecular ions and possible fragmentations. After ionization, the charged molecular ions are then separated by acceleration under an electronic or electromagnetic field according to their mass-to-charge ratios (m/z). The separated ions and fragments are detected and analyzed. The output signals are finally transmitted to the data system, producing a mass spectrum.[33] A mass spectrum is usually presented as a plot of ion abundance versus mass-to-charge ratio. The relative amount of the ionized molecules and fragments is reflected from the height of each peak corresponding to the m/z values. In a mass spectrum, the strongest peak is called the base peak and assigned the relative abundance of 100%. The abundance of all the other peaks is given their proportionate values, as a percentage of the base peak. A mass spectrometer works based on the ionized molecules which should provide information concerning the nature and structure of the

corresponding precursor molecule. Therefore, in the spectrum of a pure compound, the highest value of m/z should correspond to the molecular ion, and the mass of the compound can be derived from the peaks. To avoid the collisions with other air molecules during the travel of molecular ions to the detector, is maintained under high vacuum (low pressure). In fact, possible collisions would make the molecular ions deviate from the original trajectory, and the ions would lose their charge against the walls of the instrument. On the other hand, collisions could produce unwanted species and hence increase the complexity of the spectrum and mass analysis. To date, various ionization techniques have been developed for mass spectrometry, including electron ionization (EI), chemical ionization (CI), field ionization (FI), fast atom bombardment (FAB), electrospray ionization (ESI), plasma desorption (PD), matrix-assisted laser desorption ionization (MALDI), laser desorption (LD), thermospray ionization (TI), atmosphere pressure chemical ionization (APCI). Each ionization method has its own advantages and disadvantages, so they can be used selectively on the basis of the type of analyzed sample and the mass spectrometer. For example, FD can only be used to analyze the molecules with low-mass ions (m/z ∼5000), while MALDI mass spectrometers have been successfully applied to the analysis of high-mass molecules, such as proteins, polymers, large organometallic compounds, and metallic clusters up to approximately m/z of 500 000. It should be noted that some ionization techniques are very energetic and lead to the formation of extensive fragmentations. Other techniques, however, are softer and produce predominantly the molecular ions, such as FAB, ESI, and MALDI. Due to the fine fragmentation, one of the advantages of the soft ionization methods is that the mass spectra are relatively easy to analyze and interpret. Sector, quadrupole, ion trap (IT), time-of-flight (TOF), and Fourier transform ion cyclotron resonance (FTICR) are the main types of mass analyzers used currently in mass spectrometers. The ion energy of the fragments with different mass-to-charge ratios is then

converted into electrical signals by the detector. The mass spectra were finally produced and analyzed with the data system. For more details about the principles of mass spectrometry and the structure of mass spectrometers, please refer to the comprehensive reference books. [19-23]

The ESI mass spectrometric analysis of DPAplatin, Phenplatin, Tripicolylamineplatin, Diphenplatin, and DCCplatin complexes leads to the mass spectrum reported in Figures (26, 27, 28, 29, and 30). The protonated molecular ions $[M + H]^+$ are easily detected at *m*/*z* values centered at 430.052, 622.153. 608.127, 622.153 and 473.0887 respectively. The mass spectrum for Phenplatin shows 656.134 and the mass spectrum for Tripicolylamineplatin shows one peak at one peak at 698.126 due to impurities or biproducts. The isotopic metal is in agreement with the theoretical isotope patterns. This feature indicates the formation of the complexes. The comparison between the theoretical and experimental masses of synthesized complexes has been collected in Table 6.

Table 6. Nominal and Exact Masses of The Most Intense Peak of $[M+H]^+$ of The Pt(II) Complexes

Complex	Theoretical	Experimental
DPAPlatin	429.0446	430.052
PhenPlatin	621.1450	622.153
TriPicolyAminePlatin	607.1199	608.127
DiPhenPlatin	621.1450	622.153
DCCPlatin	471.08807	473.086

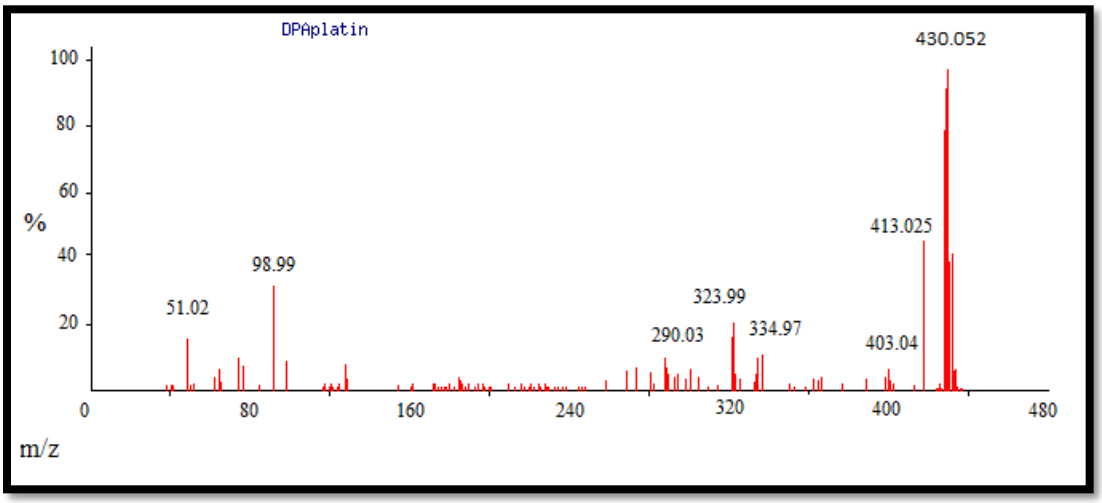


Figure 26. Mass Spectrum for DPAPlatin

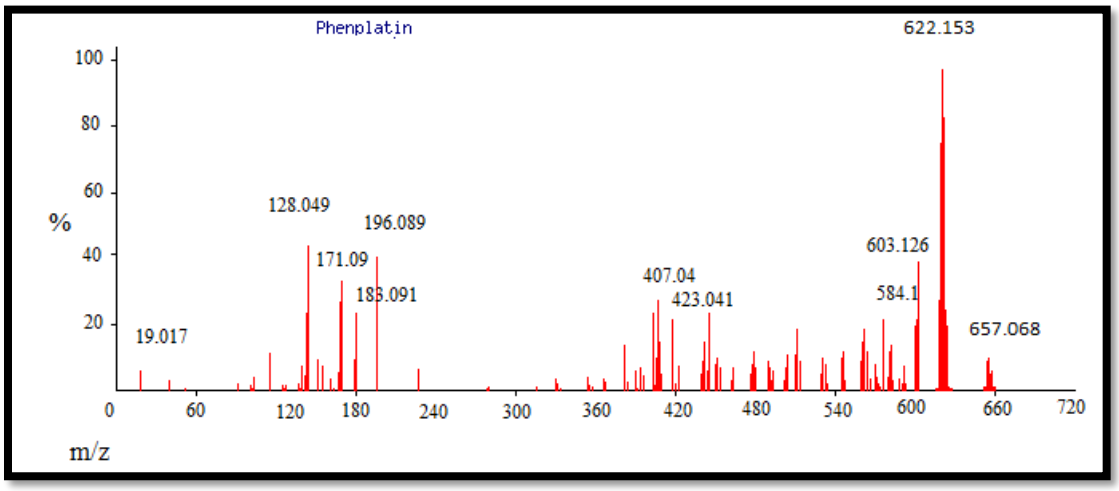


Figure 27. Mass Spectrum for PhenPlatin

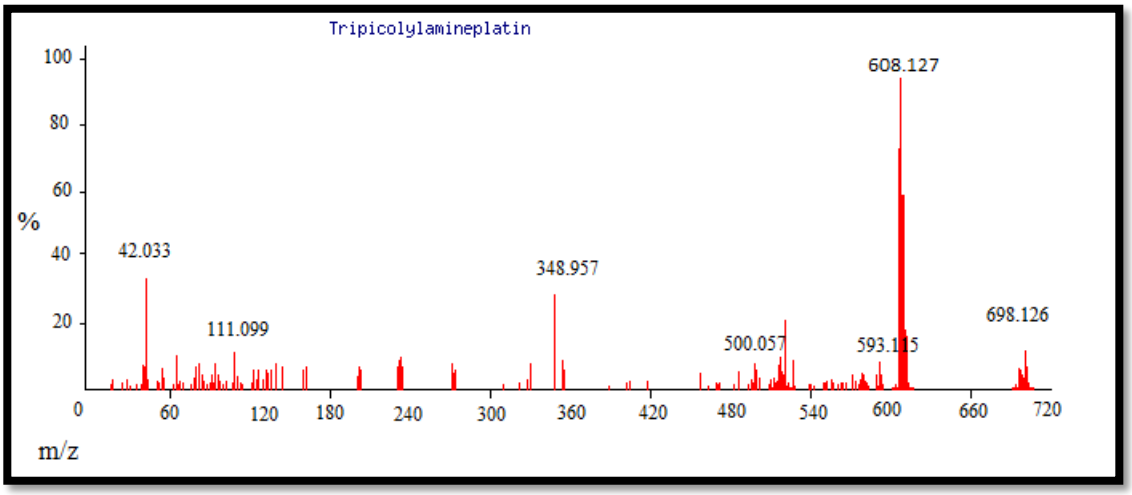


Figure 28. Mass Spectrum for TriPicolyAminePlatin

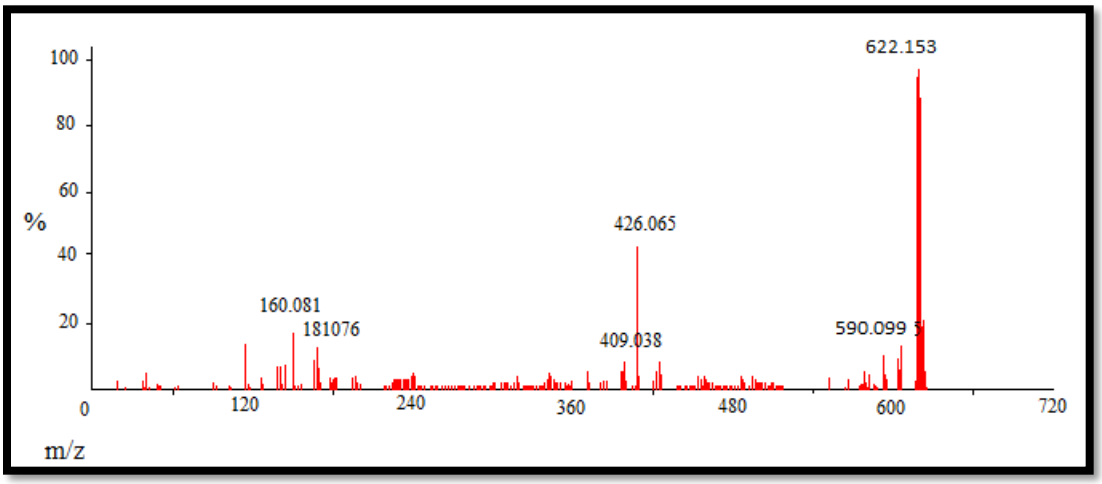


Figure 29. Mass Spectrum for DiPhenPlatin

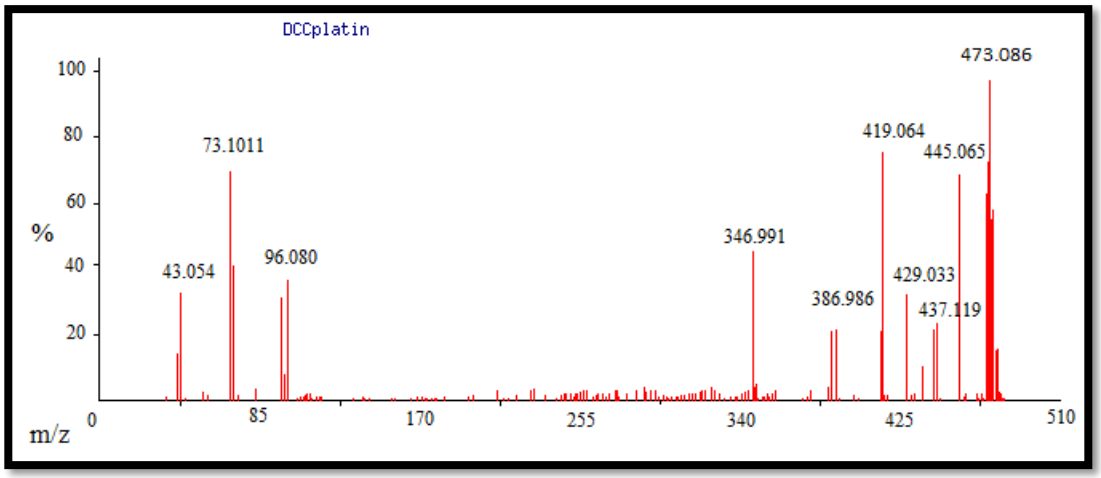


Figure 30. Mass Spectrum for DCCPlatin

2.4 Conclusion

Due to the severe systemic toxicity and side effects of these drugs, alternative platinum-based anticancer drugs are needed in order to obtain a drug that has lower or no side effects. For the last four decades, thousands of platinum-based anticancer drugs have been synthesized for hope in finding a new drug that can be administrated with a lower dose and higher efficacy. Five new platinum based anticancer drugs have been synthesized and categorized under three different types; Chelate agents provide the ability to have cis-configuration complexes which is the desired configuration for platinum-based anticancer drugs. Pt (IV)-based complex is a highly active field

with motivating results such as inertness before reaching the target cells. Platinum-π backbonding complex is a new field with a unique property where platinum metal is attached to the π bond of organic compounds. Due to the less solubility, it was not possible to purify these complexes that leads to show the peaks have masses bigger than the desired compounds. Although none of the complexes has yet been obtained in the crystalline state, the experimental results suggest that the coordination of the ligands show well-defined structure as suggested by the mass and NMR spectra.

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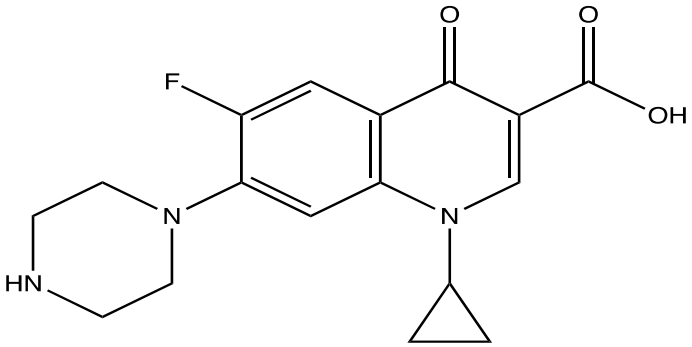
CHAPTER 3

SYNTHESIS AND CHARACTERIZATION OF NOVEL PLATINUM COMPLEXES CONTAINING CIPROFLOXACIN AS ANTI-CANCER DRUGS

3.1 Introduction



Chemical Structure of Ciprofloxacin

Ciprofloxacin (Cipro) is an antibiotic drug that belongs to a class of drugs called fluoroquinolones, and their first use in the medical practice was in 1987. It is relatively nontoxic, with broad-spectrum activity against Gram-negative aerobic bacilli but also against Gram-positive bacterial cells. Its bactericidal action is based on the inhibition of the bacterial DNA topoisomerase I. The highest concentrations of Cipro (several times higher than in serum) can be obtained in the lung, prostate, and urine.[1] Ciprofloxacin also inhibits topoisomerase II in eukaryotic cells, including mammalian cells. Cipro is frequently used in oncology patients with chemotherapy-induced neutropenia and antimicrobial fever prophylaxis in prostate biopsy and other infectious complications usually found in cancer patients.[2-4] Bacterial infections are a major cause of complications and death in cancer patients who suffer from granulocytopenia because of intensive myelosuppressive chemotherapy.[5,6] In addition, infections are recognized as major obstacles impeding patients' successful management of malignant diseases. The most common organisms

causing these infections include Pseudomonas aeruginosa and Staphylococcus aureus.[7] There are hopes of finding a much-needed antibiotic that may exert both antimicrobial and antitumor activity, to be used for prophylaxis and treatment of bacterial superinfections in cancer patients while also being effective in preventing the growth of cancer cells.

Moreover, Cipro showed anticancer properties like inducing cell cycle arrest and apoptosis and creating double-strand breaks in nucleic acid. In 1989, Cipro exerted dose-dependent inhibition of colony formation of hematopoietic progenitor cells and leukemic cell lines.[8] The concentration required for this inhibition was between 25 and 50 micrograms/ml. Therefore, Cipro is attractive to chemists for its anticancer effects. In 1990, two possible mechanisms for this inhibition were described:[9] 1) Uncoupling of oxidative phosphorylation with reduced intracellular energy (decrease of ATP) achieved with 200 microM[10]; this is preceded by selective loss of mitochondrial DNA content. 2) Inhibition of topoisomerase II.[11-13] This mechanism of action is probably the main effect in the order of an antiproliferative activity. Pessina et al. developed a leukemia cell line with specific resistance to Cipro.[14] The resistance was characterized by a decreased capacity of Cipro to produce cleavage of DNA, and they propose a decreased affinity of Cipro for the topoisomerase II-DNA complex in these cells. Recently other possible mechanisms were added: 3) Inhibition of Mcm2-7 replicative helicase[15] (minichromosome maintenance protein 2-7) preventing the proliferation of human cells. 4) In lymphoblastoid cells, a growth arrest pathway was described that does not include double-strand DNA breaks, including topoisomerase II mediated DNA changes without a double-strand break but with ATM activation that triggers the G2 M check point and G2 arrest.[16] 5) Lysosomal membrane permeabilization inducing apoptosis through the mitochondrial membrane permeabilization.[17]

Fluoroquinolones are lysosomotropic agents, which means that they are lipophilic bases that accumulate inside the lysosome, producing a detergent-like effect on lysosomal membranes. Cipro is a lysosomotropic agent and can induce apoptosis through the permeabilization of the lysosomal membrane.[18,19] Cipro also showed synergistic activity with interferon alpha-2a against leukemia cells[20] and activity against a murine bladder carcinoma cell line[21], synergistic effects with cisplatin on head and neck squamous carcinoma cells[22] and inhibition of proliferation of human transitional cell carcinoma lines,[23-26] human osteosarcoma cells[27], canine osteosarcoma cells[28], hamster ovarian cancer cells[29], and Jurkat cells[30]. They also found a decrease in mitochondrial calcium with altered mitochondrial permeability due to depolarization, which led to apoptosis.[31] Urothelial cancer cell lines seem particularly sensitive to Cipro, particularly when associated with chemotherapeutic drugs like epirubicin.[32] Chondrosarcoma cells treated with Cipro do not proliferate, and apoptosis is induced. Cipro produces abnormal lysosomes with degeneration products at the ultrastructural level and dilation of the endoplasmic reticulum.[33] It also enhances cisplatin's apoptotic effect via ERK activation.[34] Colorectal carcinoma cells also show susceptibility to anti-proliferative effects of Cipro, as shown by Herol et al., but the concentrations used in this research were high (200-500 micrograms/ml; the concentrations clinically achievable are between 50 and 400 micrograms/ml).[35] There is evidence that Cipro may enhance cancer cell death due to radiation therapy while protecting normal cells.[36] A Cipro derivative, piperonal ciprofloxacin hydrazine inhibited the proliferation of human hepatocarcinoma cells in a dose-dependent manner and induced apoptosis via inhibition of topoisomerase II.[37] Another Cipro derivative, trovafloxacin, showed growth inhibition of P388 murine leukemia cells and prolonged survival of experimental animals.[38] Kloskowski et al. tested Cipro in vitro against five different cancer cell lines: human non-small cell lung cancer, human

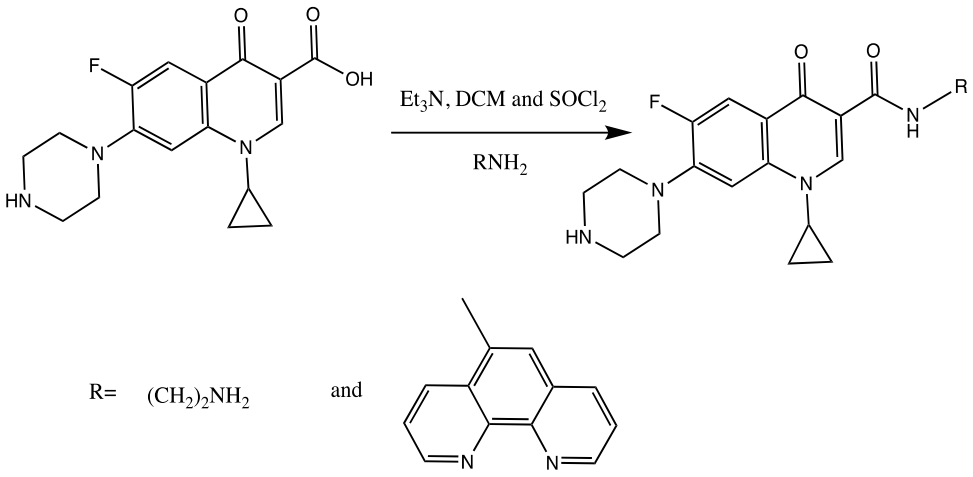
and mouse melanoma, hepatocellular carcinoma, and rat glioblastoma. An important reduction in cell viability was observed in human non-small cell lung cancer, while rat glioblastoma was insensitive to Cipro.[39] The other 3 lines showed partial sensitivity. They worked with concentrations between 10 and 1000 micrograms/ml. In a comparative study of apoptosis induction among four different fluoroquinolones used on a human non-small cell lung carcinoma cell line in culture, all of them caused growth inhibition. The most effective was enoxacin, followed by norfloxacin, Cipro, and levofloxacin.[40]

The design of these Pt-Cipro conjugates was based on the premise that attaching Cipro to cisplatin derivatives should result in simultaneous release inside the cell of two antiproliferative agents that act by different mechanisms on different cellular targets. Thus, the platinum conjugates could also improve targeting in the tumor cells, along with the free antitumor Pt (II) compound, also free Cipro in the amount that could make it possible to execute their biological function.

3.2 General Procedures for The Preparation of Cipro Derivatives and Their Pt (II), Pt (IV) Complexes

3.2.1 Synthesis of Cipro-en and Cipro-phen (L1 and L2)

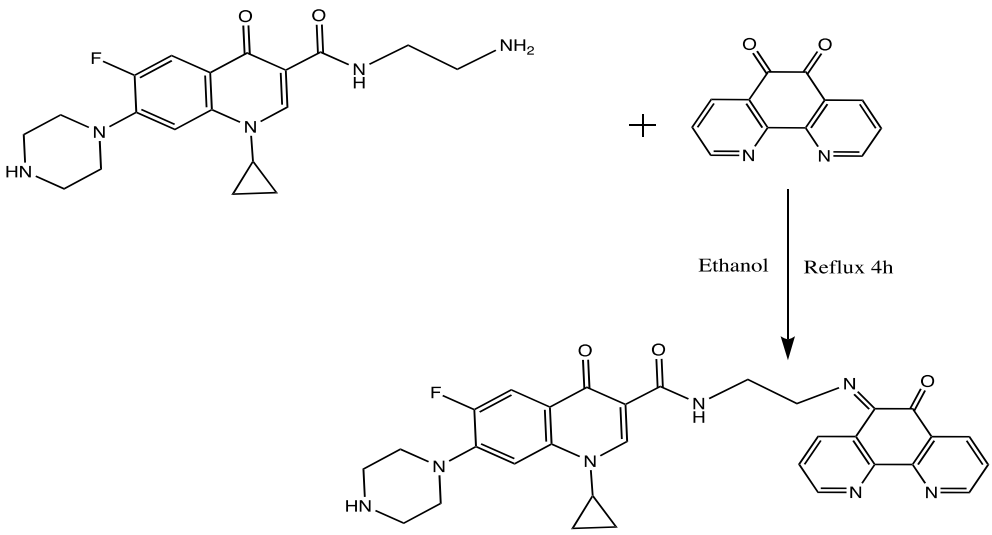
1 mmol of Ciprofloxacin was added to 1 mmol of amine (ethylene diamine and 1,10-phenanthroline-5-amine), and 3 mmol of triethylamine (Et_3N) in dichloromethane (DCM), then 1 mmol of $SOCl_2$ was added at room temperature. The mixture was stirred for 6 hours at room temperature. The recovery of the reaction product was performed by evaporating the solvent under reduced pressure (Scheme 6). The resulting residue was taken up in dichloromethane and washed first with 1 N HCl and then with 1 N NaOH. The organic phase was dried with anhydrous Na_2SO_4 and evaporated to dryness to afford the corresponding carboxylic amide.[41]



Scheme 6. Synthesis Procedure of Cipro-en and Cipro-phen

3.2.2 Synthesis of Cipro-en-phendione (L3)

For synthesis of (Cipro-en-phendione) (*E*)-1-cyclopropyl-6-fluoro-4-oxo-*N*-(2-((6-oxo-1,10-phenanthrolin-5(6*H*)-ylidene)amino)ethyl)-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamide (L2), 1,10-phenanthroline-5,6-dione (100 mg, 0.48 mmol) and *N*-(2-aminoethyl)-1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamide (0.114 g, 0.48 mmol) were taken in ethanol (50 ml) and refluxed for 4 h. After solvent evaporation at room temperature, a yellow powder appeared (Scheme 7). This product was future purified by column chromatography using alumina as the column support and chloroform–methanol (6:10, v/v) as the eluent.[42]

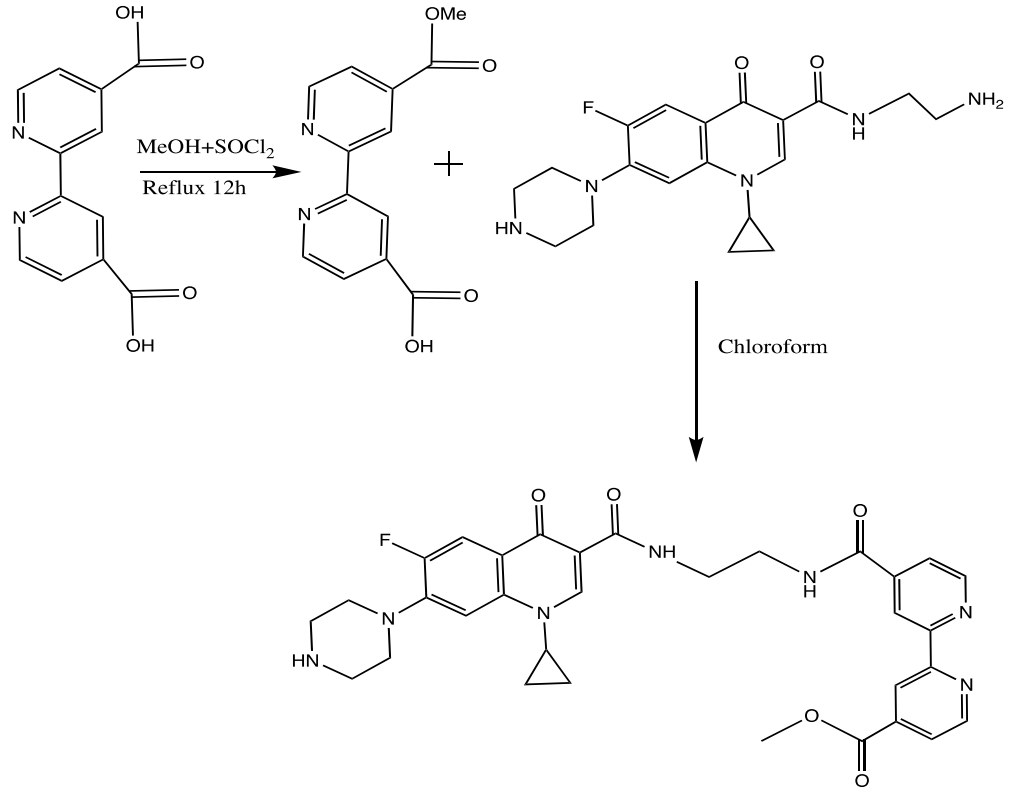


Scheme 7. Synthesis Procedure of Cipro-en-Phendione

3.2.3 Synthesis of Cipro-en-bipy (L4)

A monoester of 2,2′-bipyridyl-4,4′- dicarboxylic acid was prepared by a reported protocol.[43] For this purpose, thionyl chloride (4 equiv) was added dropwise in the suspension of 2,2′-bipyridyl-4,4′-dicarboxylic acid (1 equiv) in MeOH. The mixture was stirred under reflux conditions for 12 h. The solvent was removed, and the residue was partitioned between DCM and water. The organic part was washed thoroughly with saturated $NaHCO_3$ (aq) 3 times and kept over hot Na_2SO_4 for drying. The solvent was evaporated by using a rotovap to get solid dimethyl 2,2′-bipyridine-4,4′- dicarboxylate. This diester was further subjected to hydrolysis with NaOH to obtain the monoester (4′-(methoxycarbonyl)-2,2′-bipyridine-4-carboxylic acid). To a diester solution in MeOH/THF (1:1 v/v mL) was mixed aqueous NaOH (1 equiv in 2 mL of water). The reaction mixture was kept stirring overnight. The solvent was then evaporated, and the white solid was dissolved in water, followed by washing with EtOAc twice. The aqueous layer was acidified by adding HCl to pH=2. The white precipitation was collected and dried in a vacuum pump to

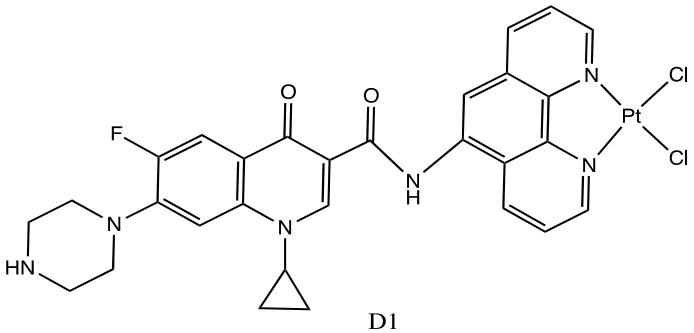
obtain the pure 4′-(methoxycarbonyl)-2,2′-bipyridine-4-carboxylic acid. The addition of Ciprofloxacin-en to a chloroform solution of the monoester (4′-(methoxycarbonyl)-2,2′-bipyridine-4-carboxylic acid) at room temperature affords Cipro-en-bipy in good yield (shown in Scheme 8). The use of chloroform avoids the formation of the cyclic lactone as a byproduct.



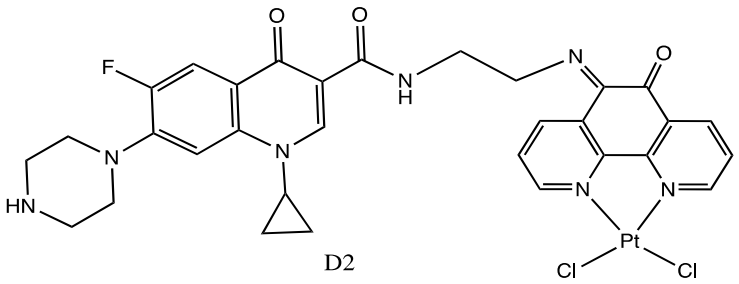
Scheme 8. Synthesis Procedure of Cipro-en-bipy

3.2.4 Synthesis of Pt (II) Based Drugs

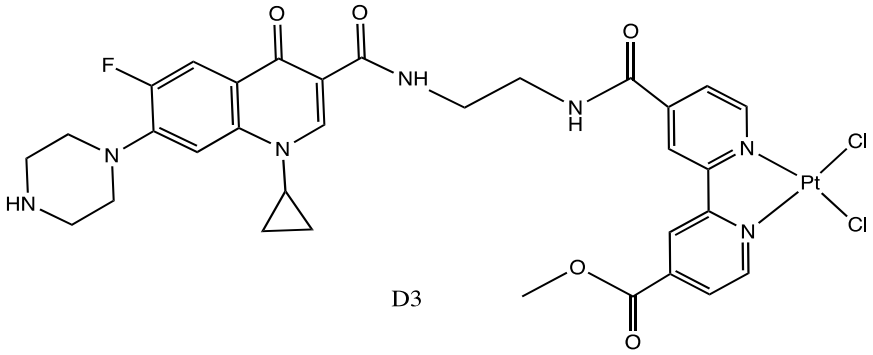
L1, L3 and L4 (0.2 mmol) in water (5 ml) with (2 ml) of MeOH and solution was stirred until solid was dissolved, followed by the addition of a solution of K_2PtCl_4 (0.18 mmol) in water (2 ml). The precipitate of Pt-complex was formed after refluxing the above mixture at 100 ˚C for 4 h. The precipitate was collected and washed with 0.1 M HCl, water and ethanol and then is dried at 50 ˚C under rotary evaporation for 8 hours.[44]



D1



D2



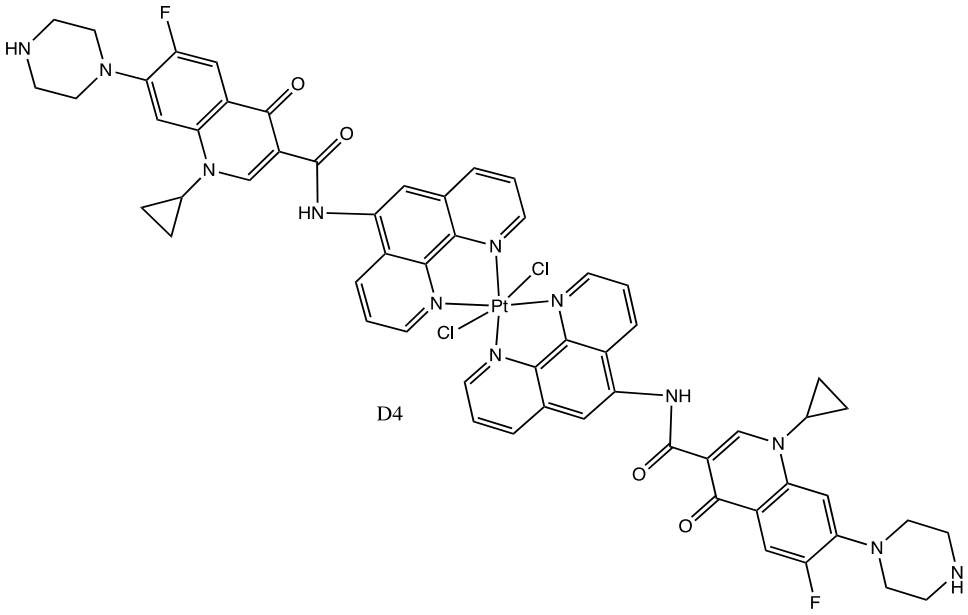
D3

Figure 31: Chemical structure of (Cis-[$PtCl_2$(Cipro-en)] D1, Cis-[$PtCl_2$(Cipro-en-phendione)] D2, and Cis-[$PtCl_2$(Cipro-en-bipy)] D3)

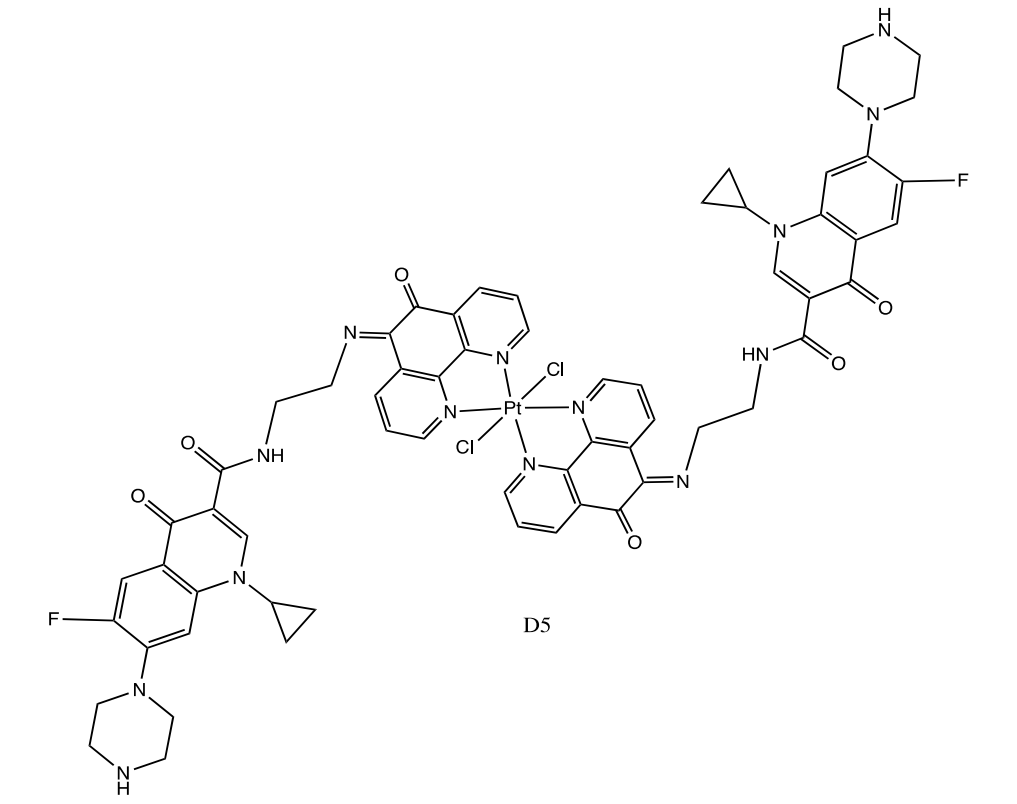
3.2.5 Synthesis of Pt (IV) Based Drugs

125 mg of potassium tetrachloroplatinate (K_2PtCl_4) was added to 200 µl of water via a micro-syringe. The solution was heated while stirring in an oil bath to 70 ºC. A solution of 300 mg of KI in 500 µl of warm water was added. The mixture was heated to 80 ºC with continuous stirring. As soon as the temperature reached 80ºC, the mixture was cooled down to room temperature. The solution was filtered using a Hirsch funnel to separate any solid impurities. Using

a syringe, 0.4 mmol of the organic compound was added. As soon as the compound was added, fine red product of the complex precipitated. The beaker was left to stand for an additional 20 min at room temperature. The product was washed with 500 µl ice-cold ethanol, followed by 1 ml ether.[45]



D4



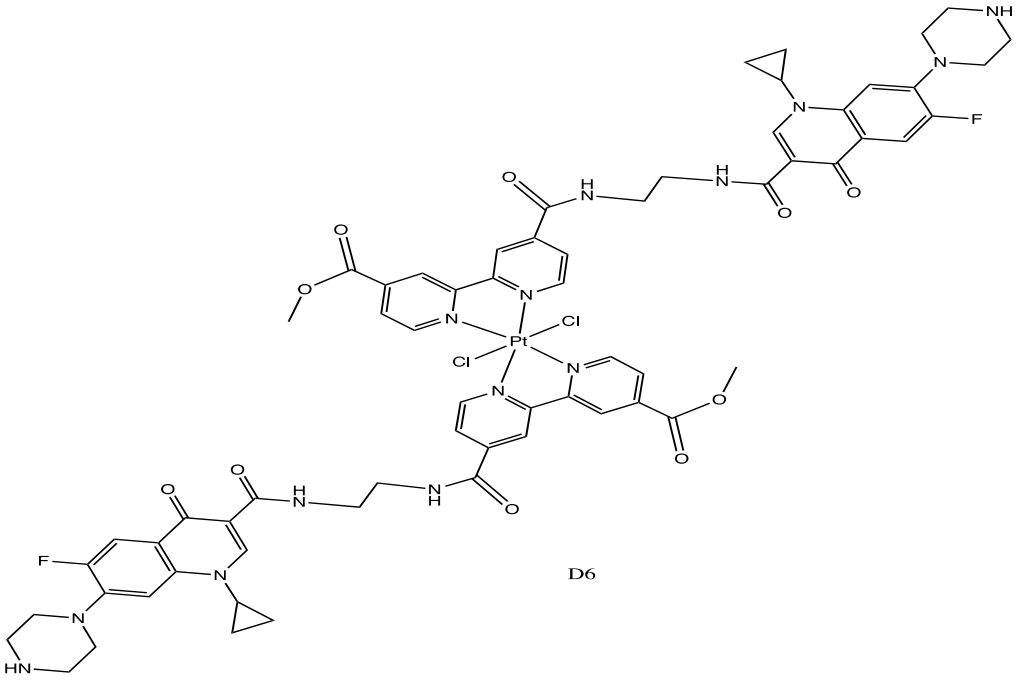


Figure 32: Chemical Structures of **(**[Pt(Cipro-en)$_2$(H$_2$O)(MeO)] D4, [Pt(Cipro-en-phendione)$_2$(H$_2$O)(MeO)] D5, and [Pt(Cipro-en-bipy)$_2$(H$_2$O)(MeO) D6)

3.3 Result and Discussion

3.3.1 ^{1}HNMR and ^{13}CNMR Spectra

^{1}H–^{13}C spectra of the ligands and complexes were measured in saturated $CDCl_3$ or DMSO-d6 solutions. Due to the low solubility of some complexes in other solvents, we have recorded ^{1}H and ^{13}CNMR spectra in DMSO-d6 only. After complexation, all proton signals are noticeably high-frequency shifted (by ca 0.15–0.7 ppm). The prepared complex + ligand mixtures (1:1 and 1:2; in DMSO-d6) have revealed distinct ^{1}H peaks for coordinated and uncoordinated species, which excludes a fast exchange of substituted ligands between the platinide coordination sphere and the solution. Indeed, the signals are most affected by coordination. These protons are also the most sensitive probes respect to the nature of metal core. ^{1}H chemical shifts (δ^{1H}; ppm) of all ligands and complexes, as well as the respective coordination shifts ($\Delta^{1H}coord = \delta^{1H}complex - \delta^{1H}ligand$, ppm) are presented in Table 6. Analogous deshielding of protons directly adjacent to nitrogens coordinated to a metal center ion was already described in a number of Au(III) chloride complexes with unsubstituted bpy or phen ($[Au(bpy)Cl_2][AuCl_4]$,[46,47] $[Au(bpy)Cl_2]PF_6$,[48] $[Au(bpy)Cl_2]ClO_4$,[49] $[Au(phen)Cl_2]Cl$,[50] $[Au(phen)Cl_2][AuCl_4]$,[46] $[Au(phen)Cl_2]PF_6$, [51] $[Au(phen)Cl_2]\ ClO_4$)[49]. Similar ^{1}H high-frequency shifts were also observed for H(6) in $[Au(dmbpy)Cl_2]ClO_4$ (δ H(6)= 9.34 ppm, in CD_3OD)[49] and H(2) in $[Pt(dpphen)Cl_4]$ (δ H(2) = 9.80 ppm, in DMSO-d6),[52] whereas in case of $[Au(dpphen)Cl_2]Cl$ the latter signal was surprisingly low-frequency shifted (δ H(2)= 8.31 ppm, in CD_3CN)[49]. Such an anomaly, unusual among square-planar coordination compounds, suggests that this compound had, in fact, another $[Au(dpphen)Cl_3]$ formula, with geometry intermediate between trigonal bipyramid and tetragonal pyramid (by analogy to the Au(III) chloride complex containing another bulky bidentate ligand, i.e. 2,2'-biquinoline – [Au(bquin)Cl3] (AUBQNL)).[53] The ^{1}H-NMR spectra of the Cipro-en,

Ciprophen, Cipro-enbipy, and Cipro-en-phendione as shown in figures (28-31) were recorded to confirm the structure of the ligands. The presence of amide, amine, and methyl protons of Cipro-en were confirmed by observing one proton triplet at 9.36 ppm, two multiplet at 3.39 ppm, and four protons multiplet at 3.05-3.31 ppm. One singlet corresponding to one proton assigned to O=C-NH of amide group of Cipro-phen was observed at 10.18 ppm. The ^{1}H-NMR spectra of Cipro-en-bipy shows two triplet signals at 9.58 and 8.58 ppm integrating for one proton each, assigned to O=C-NH(Cipro) and O=C-NH (bipy) respectively. The presence of amide protons of Cipro-en-phendione were confirmed by observing one proton triplet at 9.25 ppm. Signals due to aromatic protons were observed at 7.58–9.01 ppm.[54] The ^{1}H-NMR spectra of the Pt(Cipro-phen)Cl_2, Pt(Cipro-phen)$_2Cl_2$, Pt(Cipro-en-bipy)Cl_2, Pt(Cipro-en-bipy)$_2Cl_2$, Pt(Cipro-en-phendione)Cl_2, and Pt(Cipro-en-phendione)$_2Cl_2$ as shown in figures (32-37) were recorded to confirm the structure of the Pt(II) complexes and the Pt(IV) complexes. The observed ^{1}H high-frequency coordination shifts are mostly expressed for protons directly adjacent to nitrogens H(2,3,4,7,8,9) for Cipro-phen/Cipro-en-phendione and H(3,5,6,3',5',6') for Cipro-en-bipy, being always deshielded in case of Pt(II) and Pt(IV) complexes: $\Delta^{1H(2,9)}$coord = +0.11, +0.14, +0.11, +0.24 ppm for [Pt(Cipro-phen)Cl_2]/ [Pt(Cipro-phen)$_2Cl_2$], and $\Delta^{1H(2,9)}$coord= +0.45, +0.2, +0.39, +0.23 ppm for [Pt(Cipro-en-phendione)Cl_2]/ [Pt(Cipro-en-phendione)$_2Cl_2$] respectively, as well as $\Delta^{1H(6,6')}$coord = +0.3, +0.31, +0.28, +0.1 ppm for [Pt(Cipro-en-bipy)Cl_2]/[Pt(Cipro-en bipy)$_2Cl_2$]respectively. Some of the 1H NMR spectra show asymmetric peaks due to the calibration of the instrument or impurities coming from platinum salt, starting materials or biproducts. A purification of platinum complexes is not performed due to their less solubility in the organic solvents.

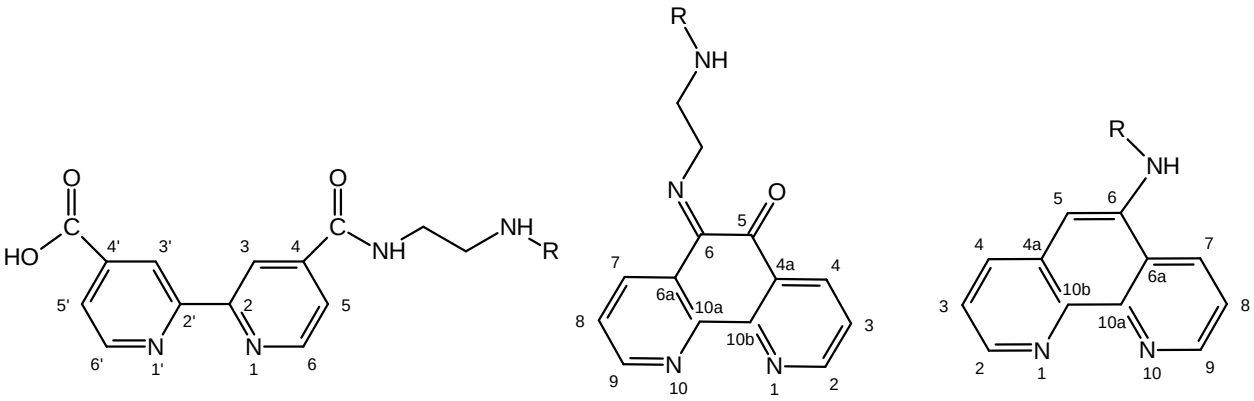


Table 7. ^{1}H NMR Chemical Shifts (δ^{1H}, ppm) of Bipy, Phendione, Phen and Their Pt (II) or Pt (IV) Chloride Complexes (^{1}H coordination shifts, Δ^{1H}coord, in parentheses), in DMSO-d6

Compound	**H (2)**	**H (3)**	**H (4)**	**H (7)**	**H (8)**	**H (9)**
Cipro-phen	**9.107**	**7.600**	**8.271**	**8.422**	**7.83**	**9.030**
Pt(Cipro-phen)Cl_2	9.222 [+0.11]	7.759 [+0.16]	8.465 [+0.19]	8.931 [+0.51]	7.91 [+0.08]	9.142 [+0.11]
Pt(Cipro-phen)$_2Cl_2$	9.25 [+0.14]	8.07 [+0.47]	8.51 [+0.28]	9.01 [+0.53]	7.92 [+0.09]	9.27 [+0.24]
Cipro-en-phendione	**8.79**	**7.58**	**7.93**	**8.21**	**7.55**	**8.84**
Pt(Cipro-en-phendione)Cl_2	9.24 [+0.45]	8.30 [+0.72]	8.59 [+0.66]	9.11 [+0.9]	8.30 [+0.75]	9.23 [+0.39]
Pt(Cipro-en-phendione)$_2Cl_2$	8.99 [+0.2]	8.37 [+0.79]	8.12 [+0.19]	8.31 [+0.1]	8.42 [+0.87]	9.07 [+0.23]
Compound	**H (6)**	**H (5)**	**H (3)**	**H (6')**	**H (5')**	**H (3')**
Cipro-en-bipy	**8.83**	**7.68**	**8.46**	**8.71**	**7.76**	**8.71**
Pt(Cipro-en-bipy)Cl_2	9.10 [+0.3]	7.89 [+0.21]	8.60 [+0.14]	8.99 [+0.28]	7.89 [+0.13]	8.57 [-0.14]
Pt(Cipro-en-bipy)$_2Cl_2$	9.11 [+0.31]	7.75 [+0.07]	8.56 [+0.1]	8.81 [+0.1]	7.94 [+0.18]	8.60 [-0.11]

The ^{13}C-NMR spectra of the Cipro-en, the Ciprophen, the Cipro-enbipy, and the Cipro-en-phendione as shown in figure (38-40) were recorded to confirm the structure of the ligands. The presence of all signals of Cipro-phen were confirmed by observing $\delta^{C2,9}$ =150.39 ppm, 150.13 ppm, $\delta^{C3,8}$ = 123.63 ppm, 120.79 ppm, $\delta^{C4,7}$ = 133.55 ppm, 130.42 ppm, and $\delta^{C10a,10b}$ = 146.37 ppm, 143.24 ppm. The ^{13}C-NMR spectra of Cipro-en-bipy shows observing $\delta^{C6,6'}$ =149.84 ppm, 152.23

ppm, $\delta^{C5,5'}$ = 122.66 ppm, 125.69 ppm, $\delta^{C4,4'}$ = 140.13 ppm, 147.42 ppm, $\delta^{C3,3'}$ = 120.57 ppm, 123.90 ppm, and $\delta^{C2,2'}$ = 150.70 ppm, 156.64 ppm. The presence of signals of Cipro-en-phendione were confirmed by observing observing $\delta^{C2,9}$ =156.26 ppm, 151.38 ppm, $\delta^{C3,8}$ = 125.91 ppm, 126.19 ppm, $\delta^{C4,7}$ = 136.80 ppm, 133.74 ppm, and $\delta^{C10a,10b}$ = 149.62 ppm, 152.38 ppm.[54]

^{13}C chemical shifts (δ^{13C}; ppm) of all ligands and complexes, as well as the respective coordination shifts (Δ^{13C}coord = δ^{13C}complex - δ^{13C}ligand, ppm) are presented in Table 7. The ^{13}C-NMR spectra of the Pt(Cipro-phen)Cl_2, Pt(Cipro-phen)$_2Cl_2$, Pt(Cipro-en-bipy)Cl_2, Pt(Cipro-en-bipy)$_2Cl_2$, Pt(Cipro-en-phendione)Cl_2, and Pt(Cipro-en-phendione)$_2Cl_2$ as shown in figure (41-43) were recorded to confirm the structure of the Pt(II) complexes and Pt(IV) complexes. the observed ^{13}C high-frequency coordination shifts are mostly expressed for carbons directly adjacent to nitrogens C(2, 3, 4, 7, 8, 9) for Cipro-phen/Cipro-en-phendione and C(2, 3, 5, 6, 2', 3', 5', 6') for Cipro-en-bipy, being shielded in case of Pt(II) and Pt(IV) complexes: $\Delta^{13C(2,9)}$coord = -17.3/-9.51, -15.49/-10.86 ppm, and $\Delta^{13C(10a,10b)}$coord = -10.14/-10.41, -14.53/-4.62 ppm for [Pt(Cipro-phen)Cl_2]/[Pt(Cipro-phen)$_2Cl_2$], and $\Delta^{13C(2,9)}$coord = -16.53/-12.31, -15.14/-8.98 ppm, $\Delta^{13C(10a,10b)}$coord= -8.75/-7.1,-7.21/-6.03 ppm for [Pt(Cipro-en-phendione)Cl_2]/[Pt(Cipro-en-phendione)$_2Cl_2$] respectively, and $\Delta^{13C(6,6')}$coord= -12.08/-7.61, -14.65/-10.26 ppm and $\Delta^{13C(2,2')}$coord = -11.81/-8.02, -16.82/-14.67 ppm for [Pt(Cipro-en-bipy)Cl_2]/[Pt(Cipro-en-bipy)$_2Cl_2$ respectively.

Table 8. ^{13}C NMR Chemical Shifts (δ^{13C}, ppm) of Bipy, Phendione, Phen and Their Pt (II) or Pt (IV) Chloride Complexes (^{13}C coordination shifts, Δ^{13C}coord, in parentheses), in DMSO-d6

Compound	C(2)	C(3)	C(4)	C(10b)	C(9)	C(8)	C(7)	C(10a)
Cipro-phen	**150.39**	**123.63**	**133.55**	**143.24**	**150.13**	**121.79**	**130.42**	**146.37**
Pt(Cipro-phen)Cl_2	133.07 [-17.3]	121.01 [-2.62]	125.64 [-7.91]	128.71 [-14.53]	134.64 [-15.49]	120.50 [-0.29]	125.95 [-4.47]	136.23 [-10.14]
Pt(Cipro-phen)$_2Cl_2$	140.88 [-9.51]	125.74 [+2.11]	126.84 [-6.71]	138.62 [-4.62]	139.27 [-10.86]	125.86 [+4.07]	126.66 [-3.76]	135.96 [-10.41]
Cipro-en-phendione	**156.26**	**125.91**	**136.80**	**152.38**	**151.38**	**126.19**	**133.74**	**149.62**
Pt(Cipro-en-phendione)Cl_2	139.74 [-16.53]	124.23 [-1.68]	130.45 [-6.35]	145.17 [-7.21]	136.24 [-15.14]	124.23 [-1.96]	128.54 [-5.2]	140.87 [-8.75]
Pt(Cipro-en-phendione)$_2Cl_2$	143.95 [-12.31]	129.88 [+3.97]	131.45 [-5.35]	146.35 [-6.03]	142.40 [-8.98]	129.12 [+2.93]	129.11 [-4.63]	142.52 [-7.1]
Compound	**C(6)**	**C(5)**	**C(3)**	**C(2)**	**C(6')**	**C(5')**	**C(3')**	**C(2')**
Cipro-en-bipy	**149.84**	**122.66**	**120.57**	**155.70**	**152.23**	**125.69**	**123.90**	**156.64**
Pt(Cipro-en-bipy)Cl_2	137.76 [- 12.08]	127.72 [+5.06]	123.49 [+2.95]	140.42 [-11.81]	137.58 [-14.65]	128.22 [+2.53]	125.65 [+1.75]	139.82 [-16.82]
Pt(Cipro-en-bipy)$_2Cl_2$	142.23 [-7.61]	128.71 [+6.05]	124.32 [+3.75]	147.68 [-8.02]	141.97 [-10.26]	129.31 [+3.62]	129.31 [+5.41]	141.97 [-14.67]

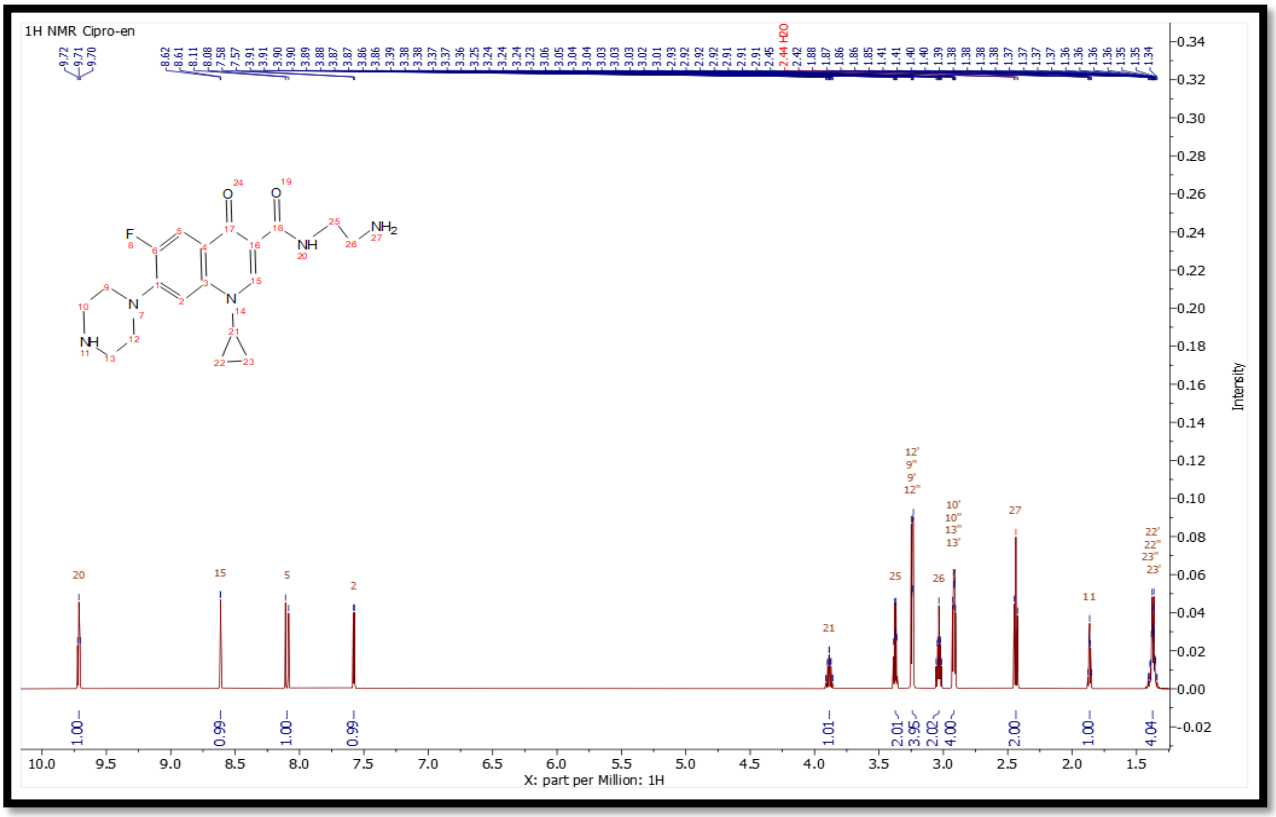


Figure 33. ^{1}H-NMR for Cipro-en

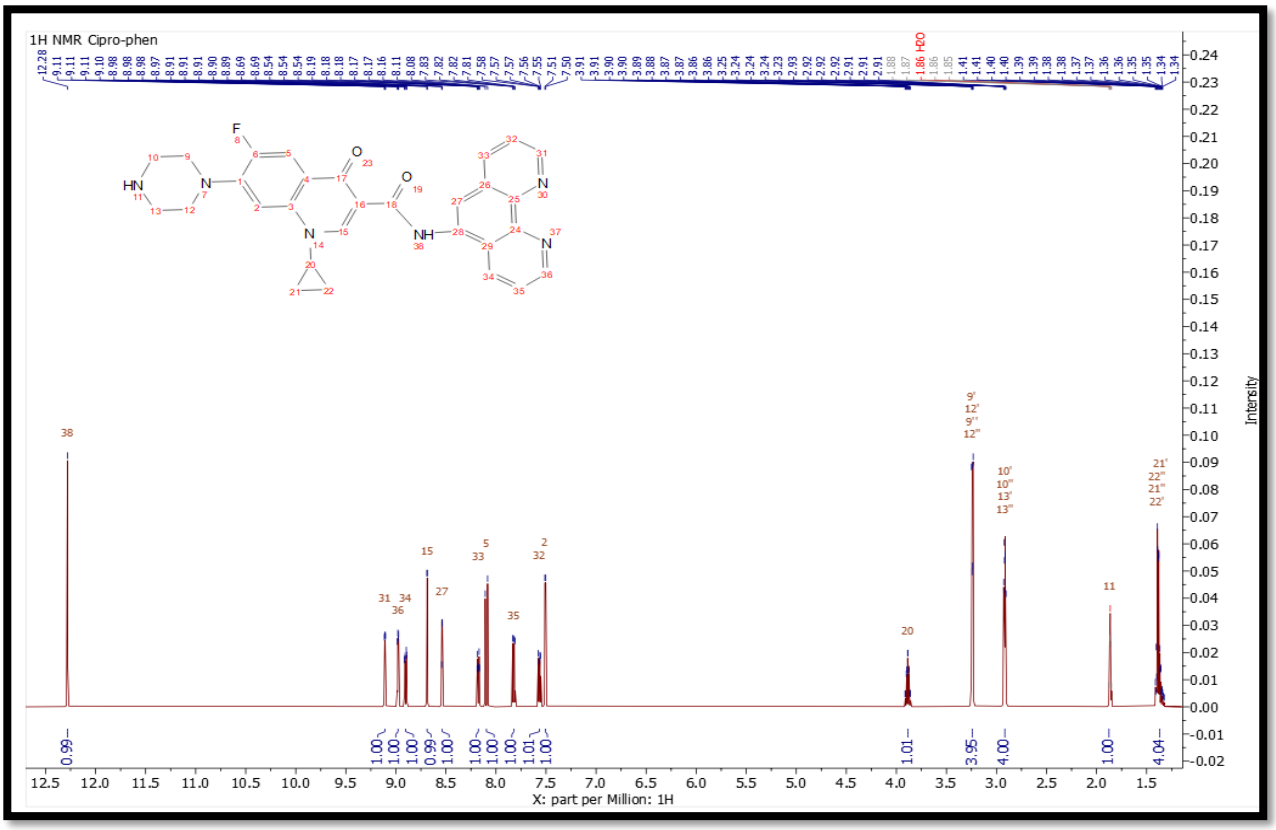


Figure 34. ^{1}H-NMR for Cipro-phen

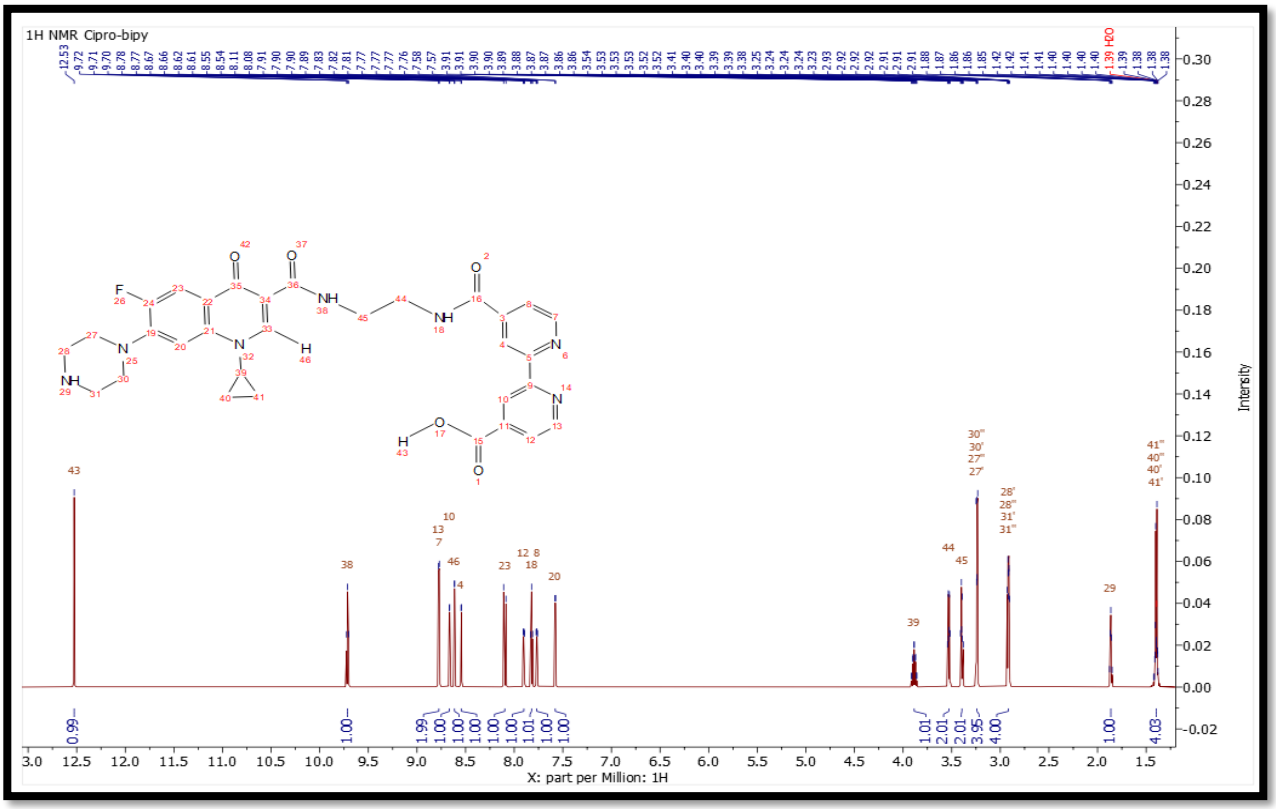


Figure 35. ^{1}H-NMR for Cipro-en-bipy

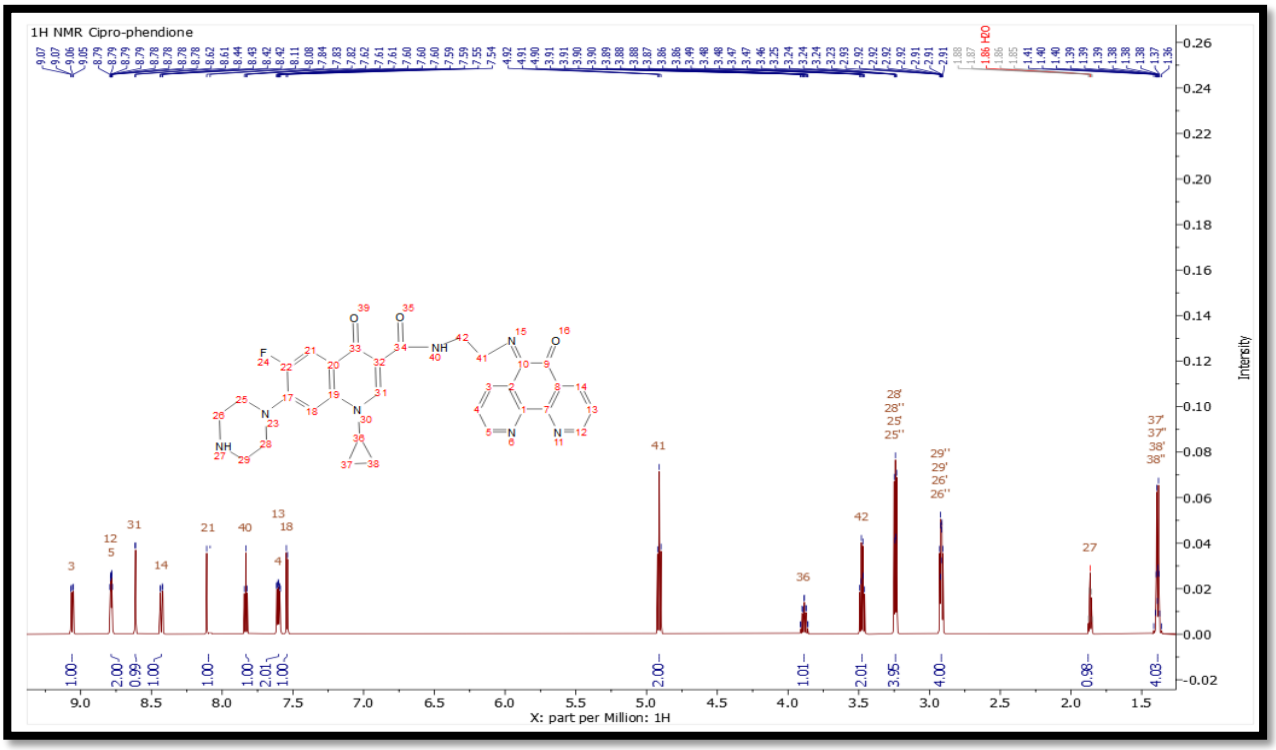


Figure 36. ^{1}H-NMR for Cipro-en-phendione

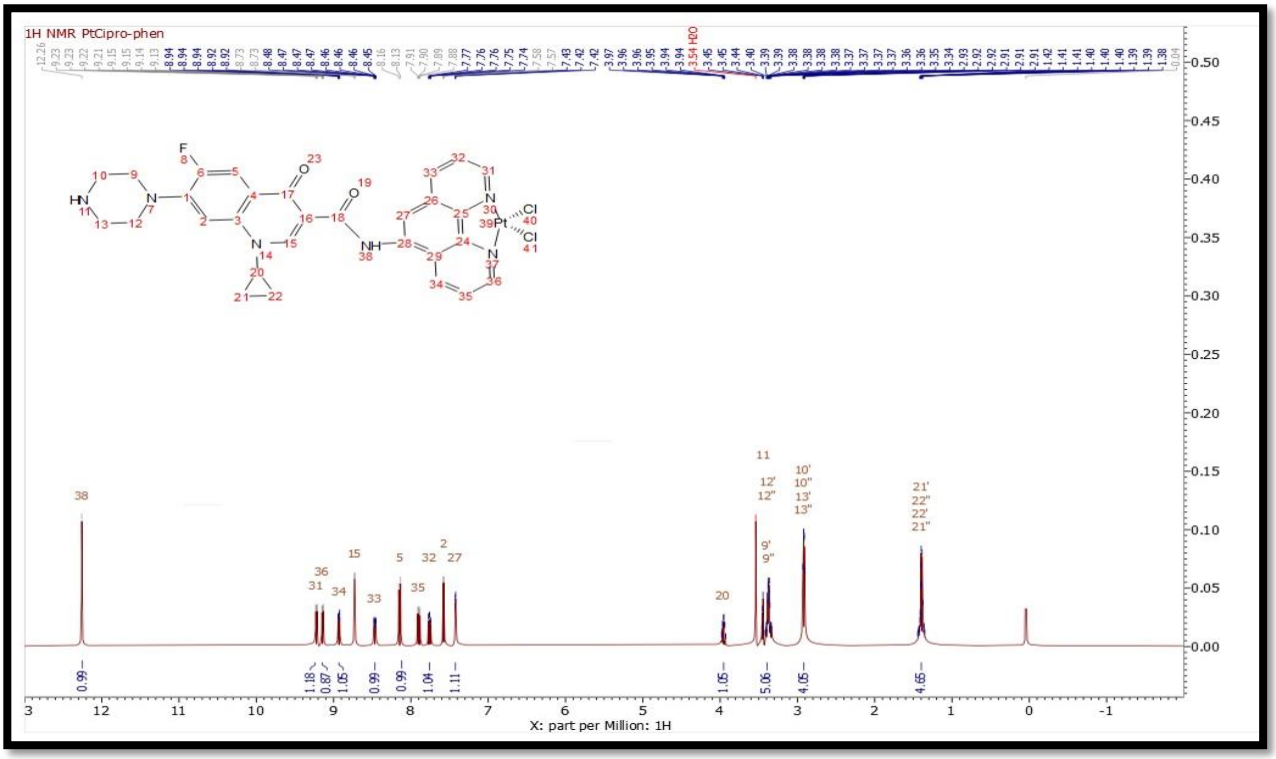


Figure 37. ^{1}H-NMR for [Pt(Cipro-phen)Cl_2]

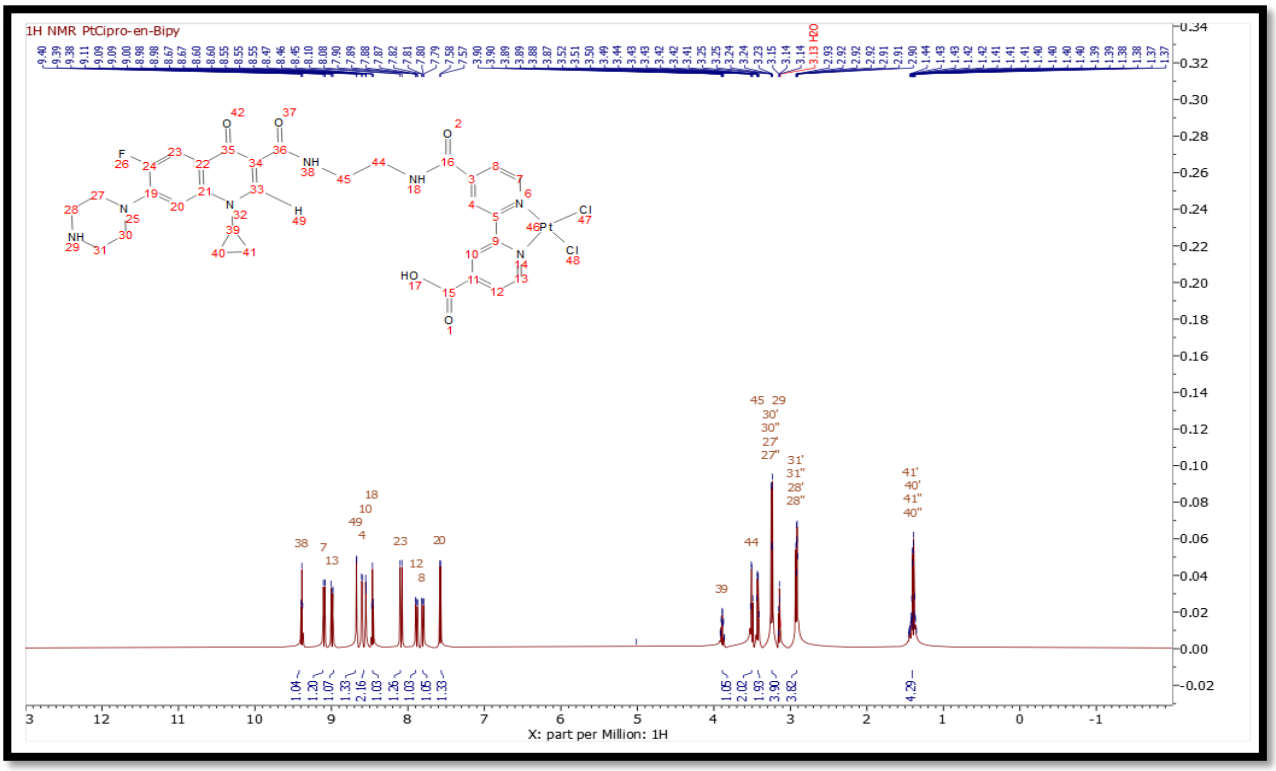


Figure 38. ^{1}H-NMR for [Pt(Cipro-en-bipy)Cl$_2$]

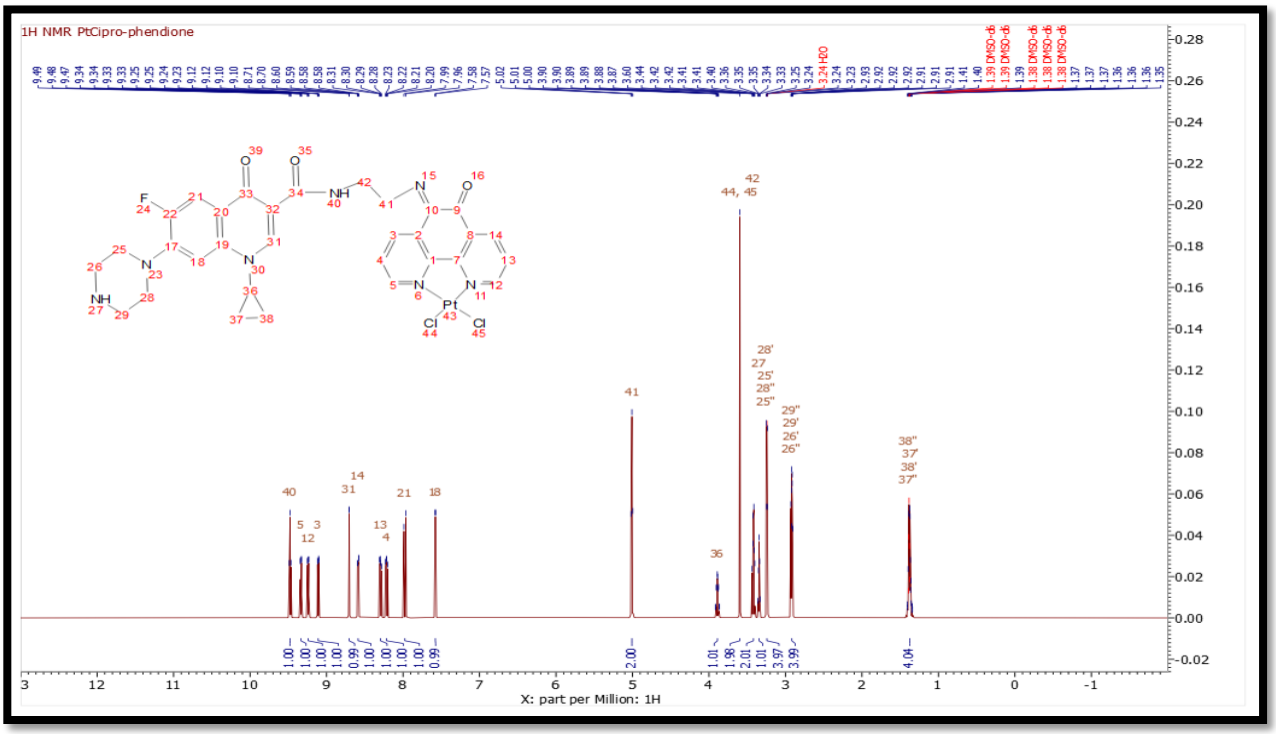


Figure 39. ^{1}H-NMR for [Pt(Cipro-en-phendione)Cl$_2$]

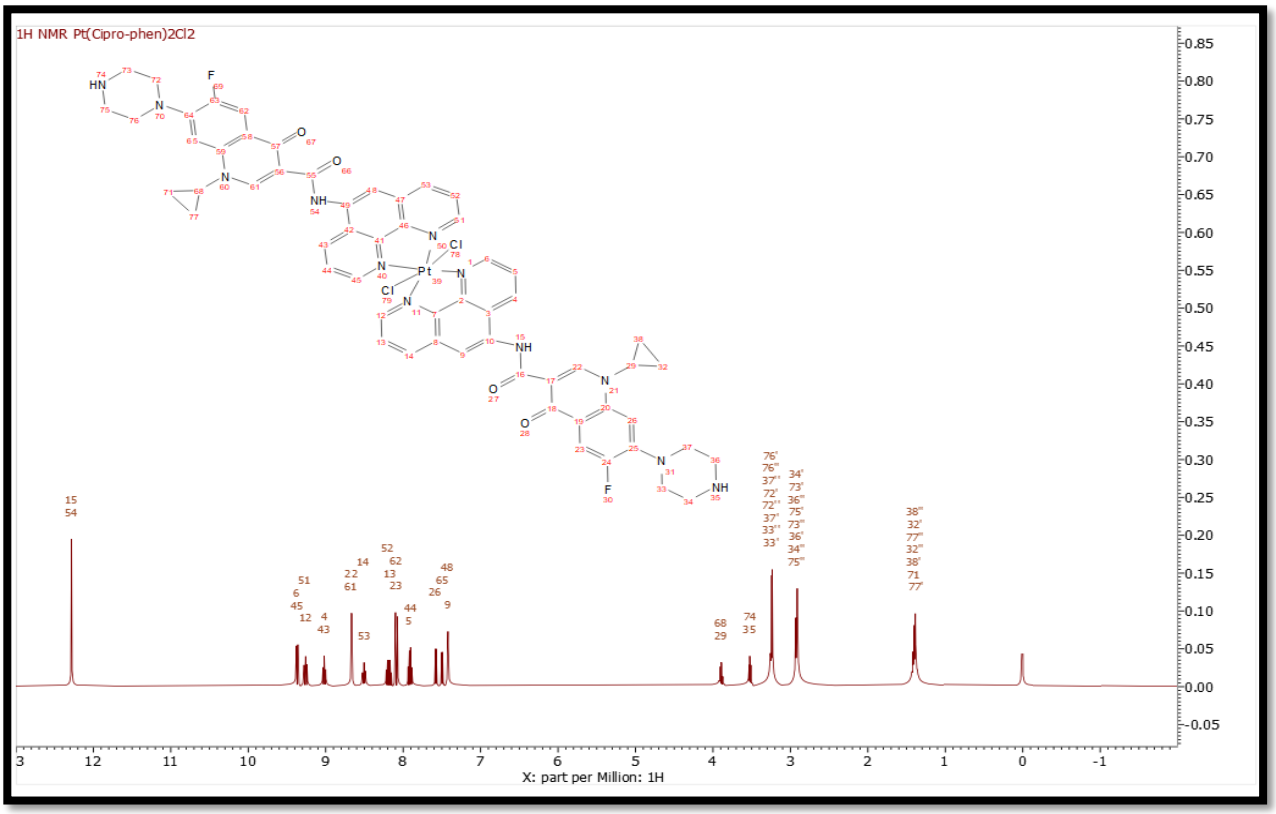


Figure 40. ^{1}H-NMR for [Pt(Cipro-phen)$_2$Cl$_2$]

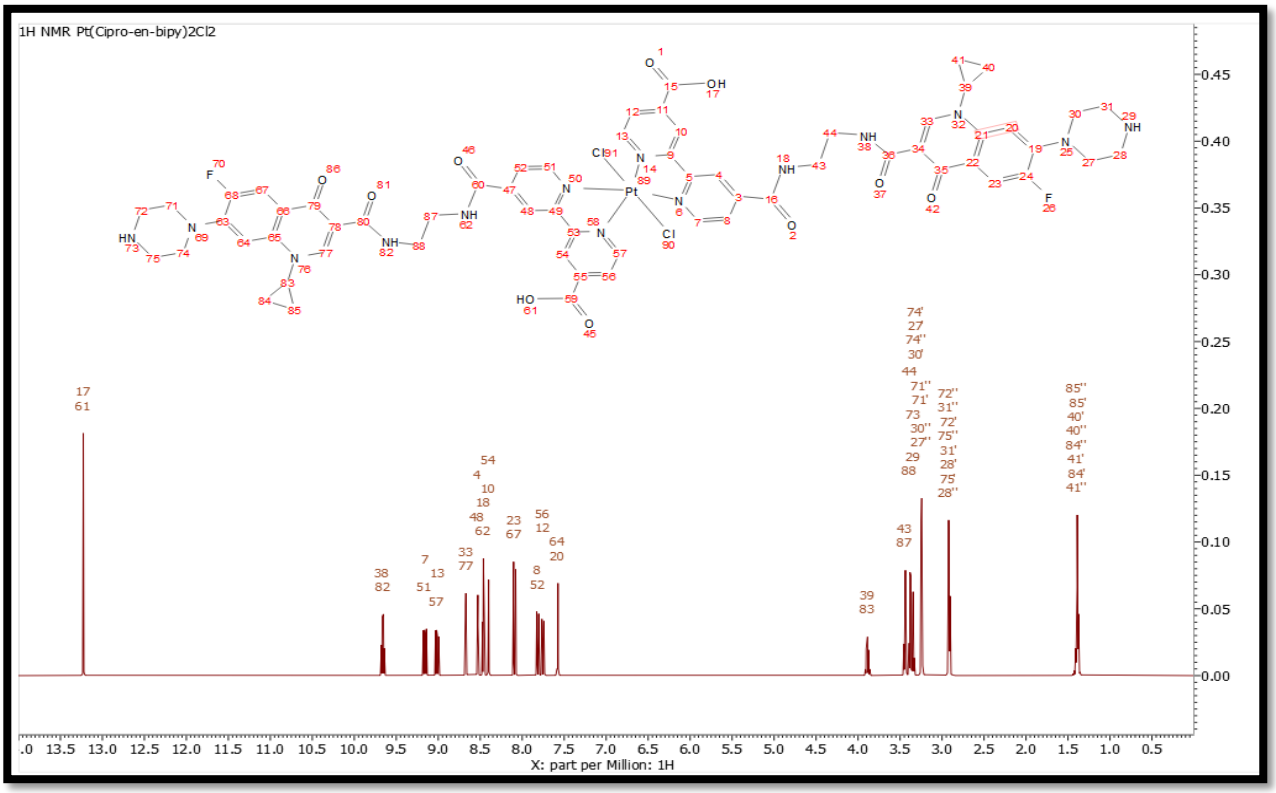


Figure 41. ^{1}H-NMR for [Pt(Cipro-en-bipy)$_2$Cl$_2$]

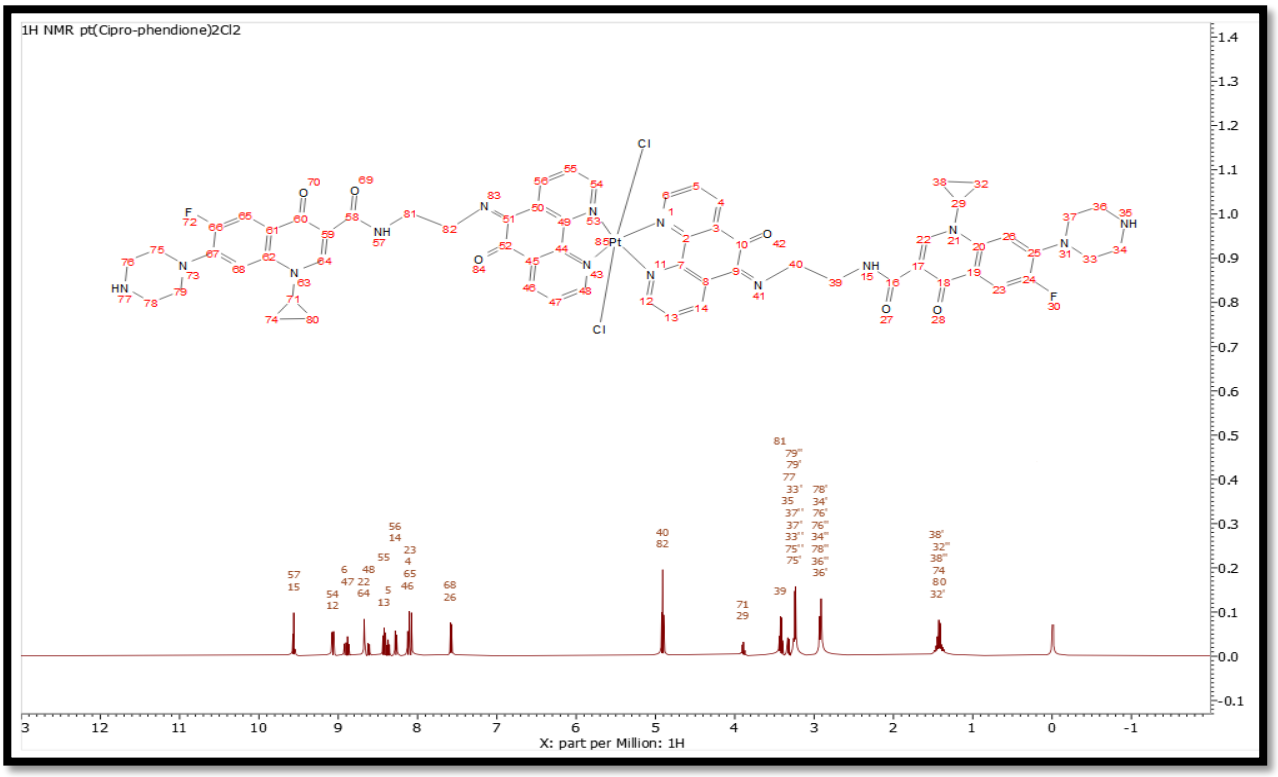


Figure 42: ^{1}H-NMR for [Pt(Cipro-en-phendione)$_2$Cl$_2$]

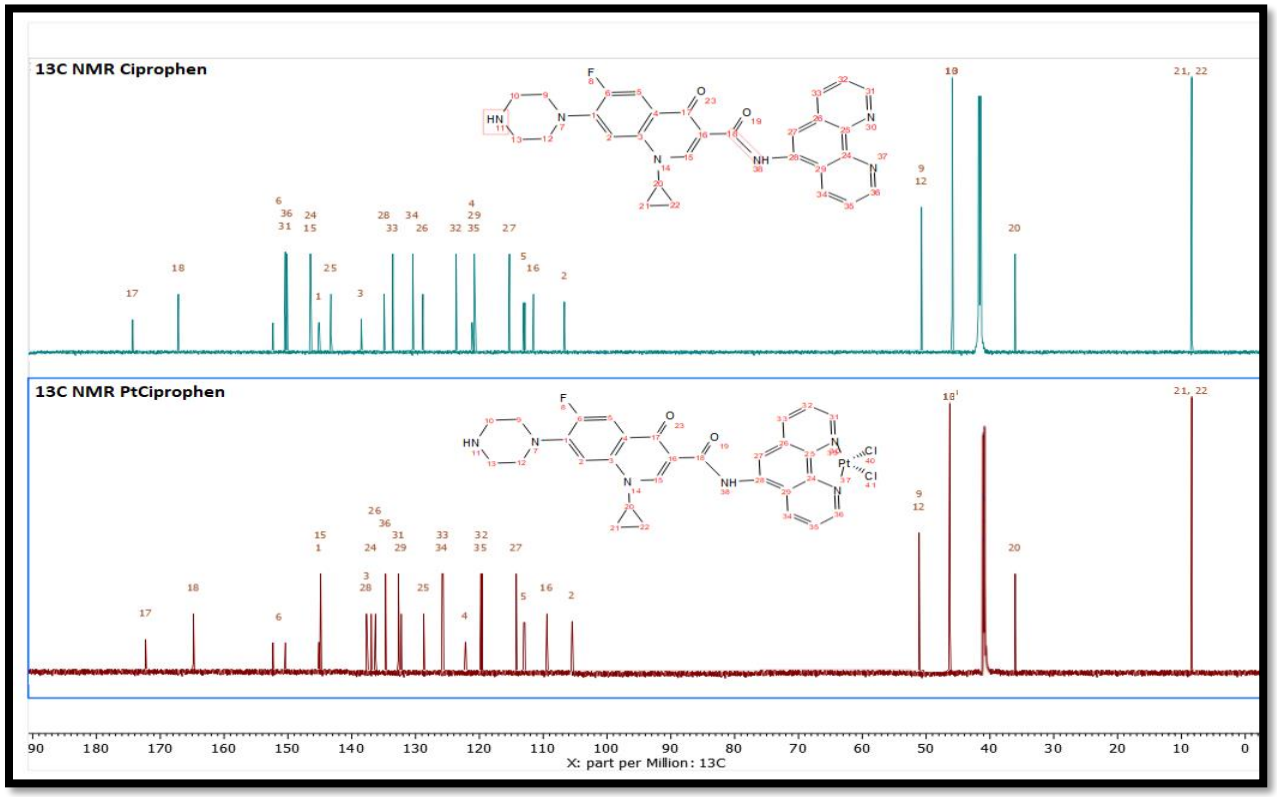


Figure 43. ^{13}C-NMR for Cipro-phen and [Pt(Cipro-phen)Cl$_2$]

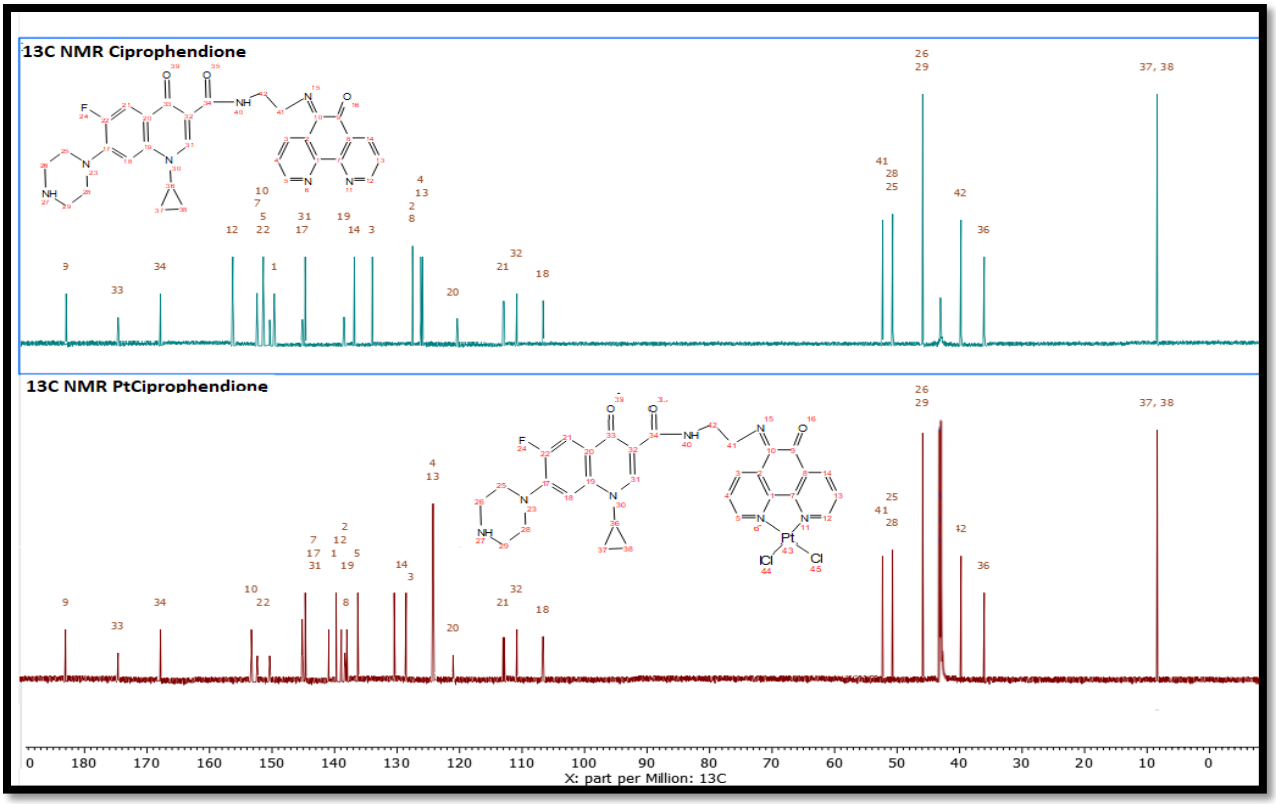


Figure 44. ^{13}C-NMR for Cipro-en-phendione and [Pt(Cipro-en-phendione)Cl_2]

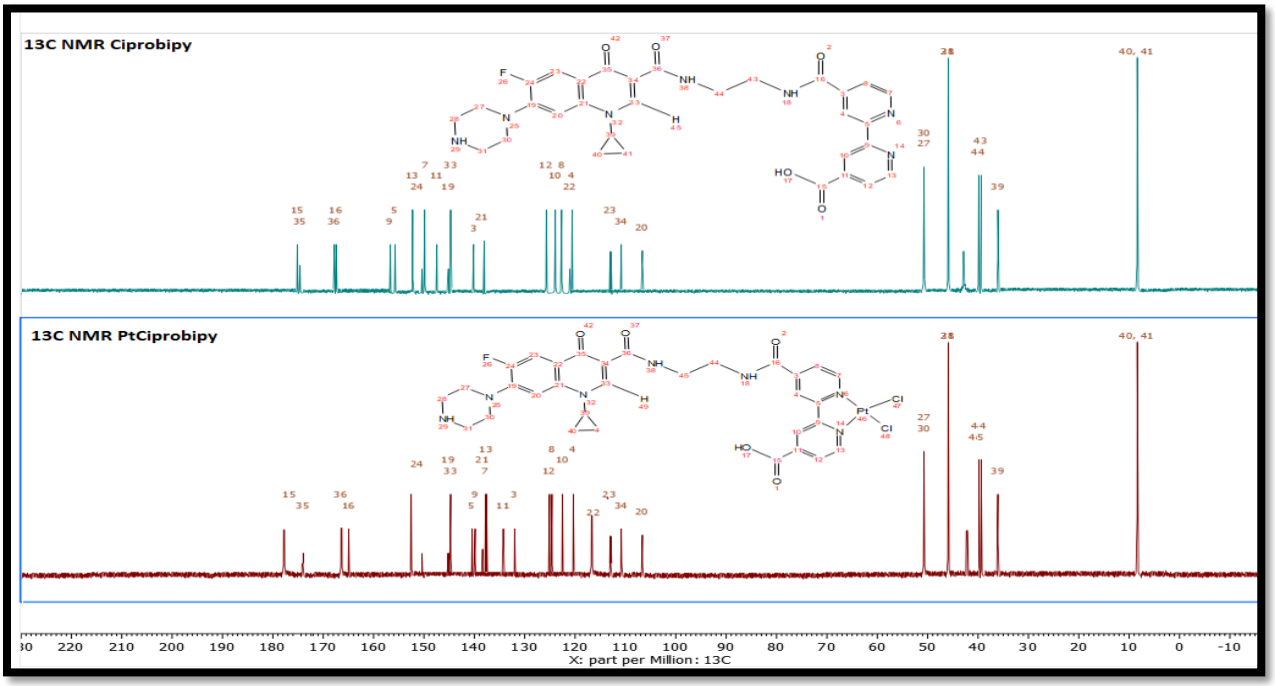


Figure 45. ^{13}C-NMR for Cipro-en-bipy and [Pt(Cipro-en-bipy)Cl_2]

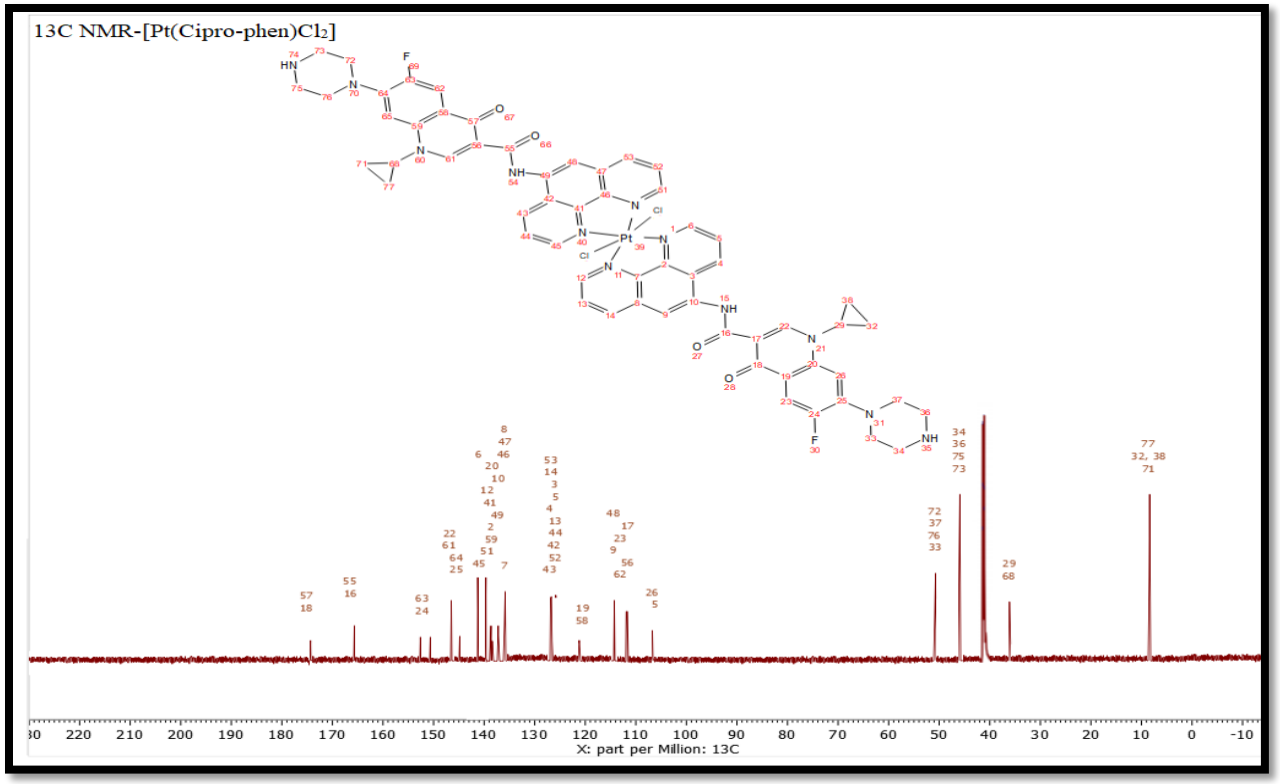


Figure 46. ^{13}C-NMR for [Pt(Cipro-phen)$_2$Cl$_2$]

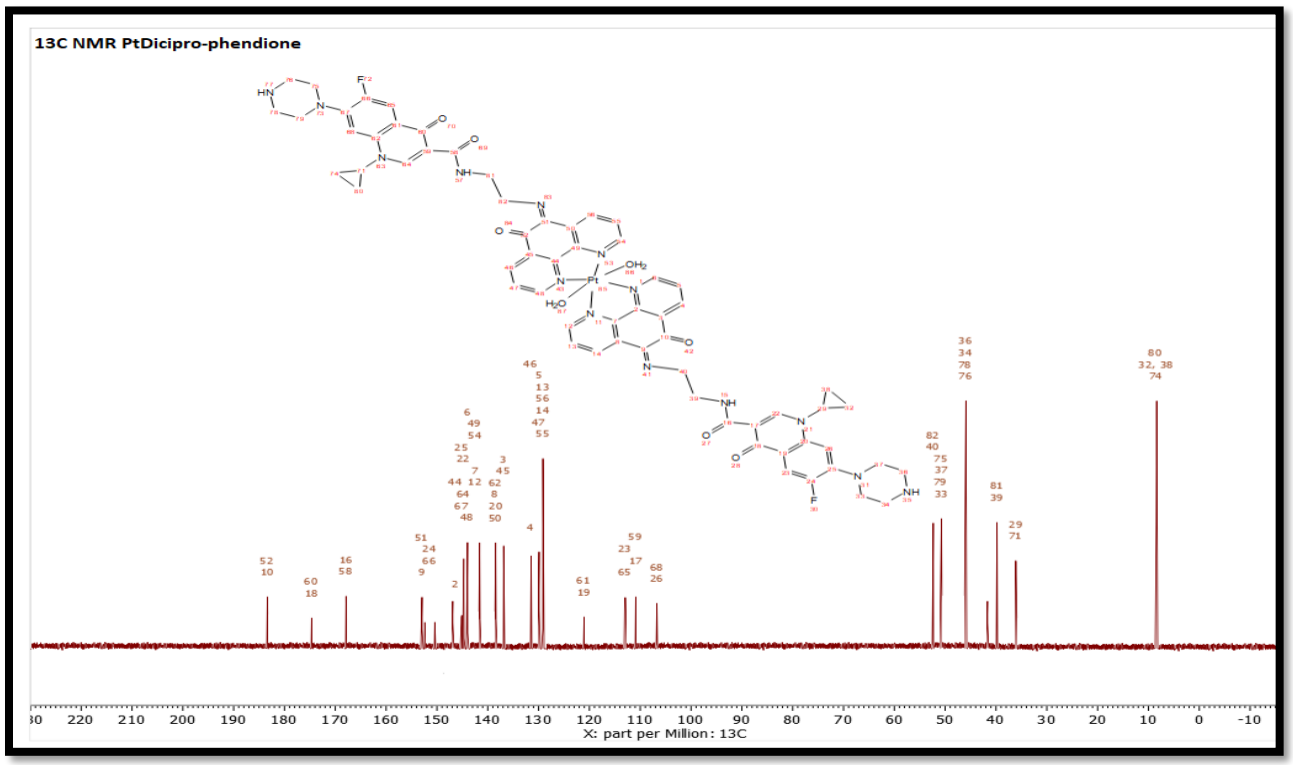


Figure 47. ^{13}C-NMR for [Pt(Cipro-en-phendione)$_2$Cl$_2$]

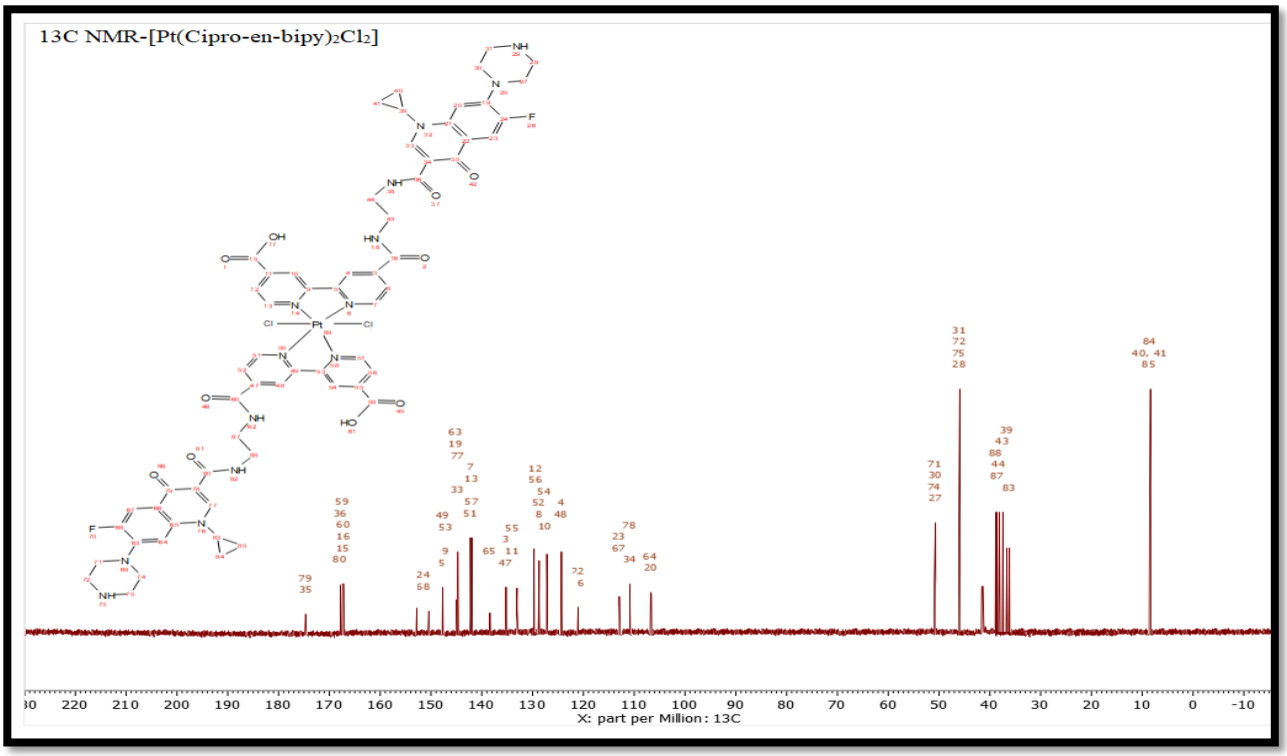


Figure 48. ^{13}C-NMR for [Pt(Cipro-en-bipy)$_2$Cl$_2$]

3.3.2 Mass Spectroscopy and Mass Spectrometer

The ESI mass spectrometry is considered one of the most powerful analytical techniques in the field of organometallic compounds.[55] For this reason, all the studied compounds were analyzed by such a technique. In the case of Pt(II) complexes, the ESI mass spectra, reported in Figures (49, 50, and 51) has been obtained operating in positive ion mode. The molecular ions are detected the base peaks of the spectra at *m*/*z* 774,112 831.134, and 865.139 respectively for three Pt(II) complexes. These correspond to the protonated molecular ion $[M+H]^+$ and they can be generated by the ionization conditions or by ion-molecule reactions inside the ion trap analyzer. The ESI mass spectra for complexes of Pt(IV) are shown in Fig (52, 53, and 54). The protonated molecular ions $[M + H]^+$ are detected at *m*/*z* values centered at 1282.314, 1396.350, and 1464.368 respectively: the isotopic cluster is in agreement with the theoretical one. This feature indicates the

formation of the complexes. The comparison between the theoretical and experimental masses of synthesized complexes has been collected in Table 9.

Table 9. The Theoretical and Experimental Masses of The Most Intense Peak of [M+H] of the Pt (II) and Pt (IV) complexes

Complex	Theoretical	Experimental
$Pt(Cipro\text{-}phen)Cl_2$	773.1048	774.112
$Pt(Cipro\text{-}phendione)Cl_2$	830.1263	831.134
$Pt(Cipro\text{-}bipy)Cl_2$	864.1317	865.139
$Pt(Cipro\text{-}phen)_2Cl_2$	1281.3071	1282.314
$Pt(Cipro\text{-}phendione)_2Cl_2$	1395.3500	1396.350
$Pt(Cipro\text{-}bipy)_2Cl_2$	1463.3610	1464.368

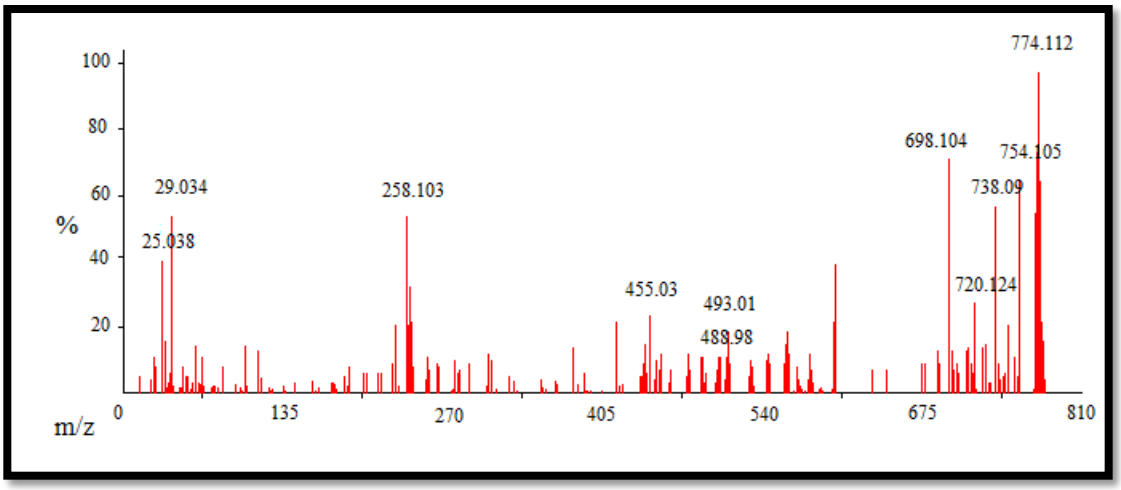


Figure 49. Mass Spectrum for $[Pt(Cipro\text{-}phen)Cl_2]$

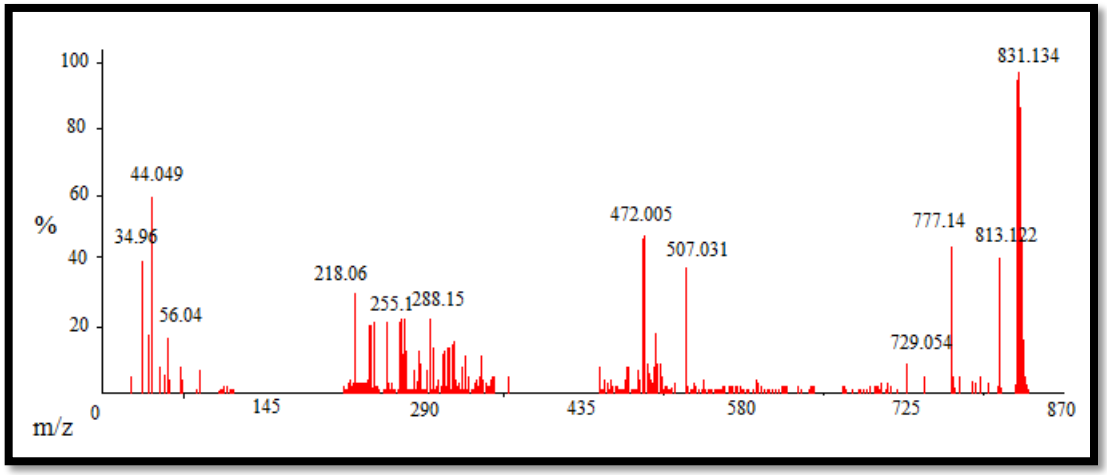


Figure 50. Mass Spectrum for $[Pt(Cipro\text{-}en\text{-}phendione)Cl_2]$

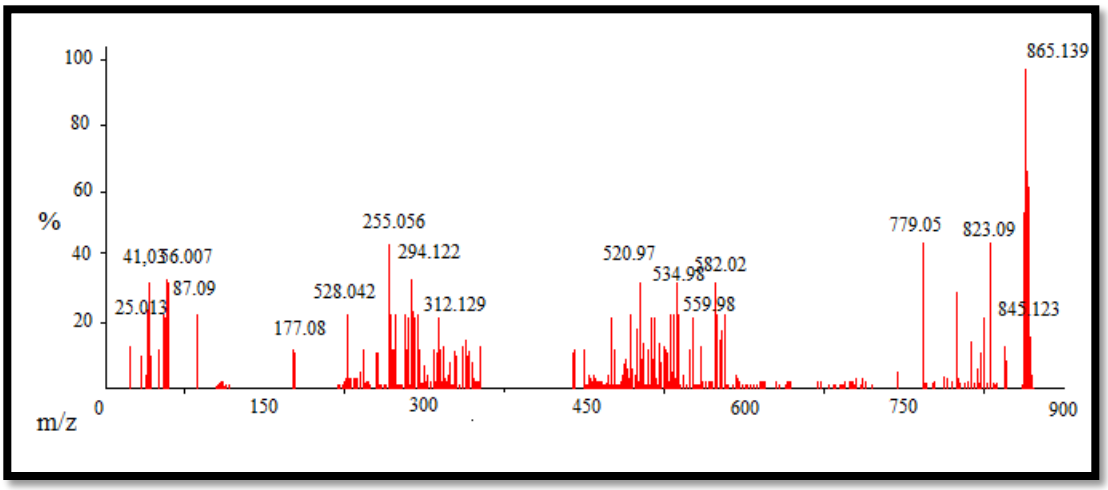


Figure 51. Mass Spectrum for [Pt(Cipro-en-bipy)Cl_2]

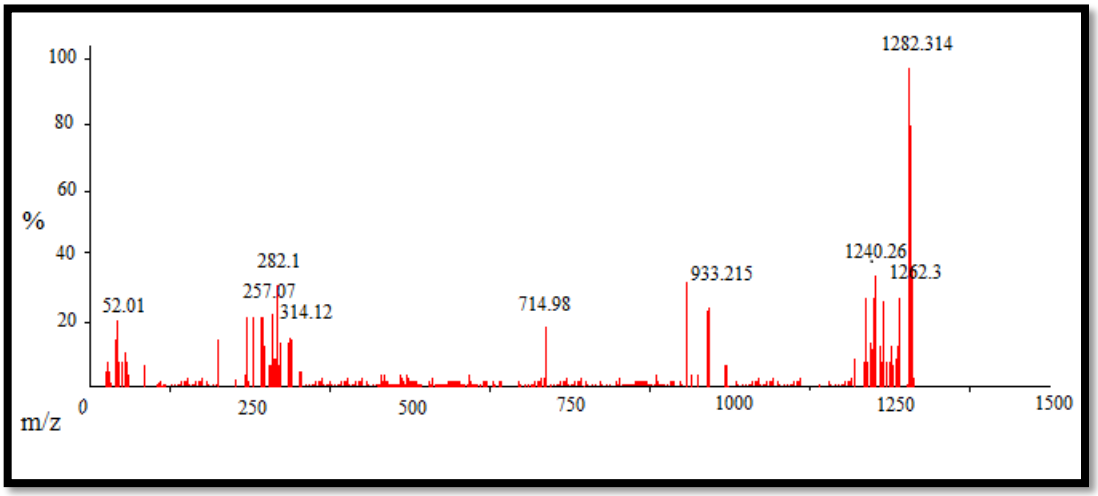


Figure 52. Mass Spectrum for [Pt(Cipro-phen)$_2Cl_2$]

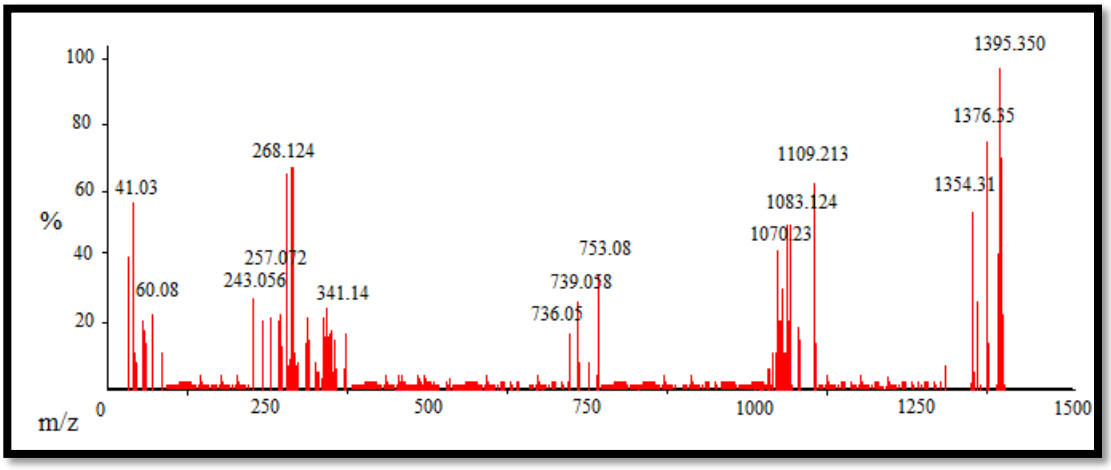


Figure 53. Mass Spectrum for [Pt(Cipro-en-phendione)$_2Cl_2$]

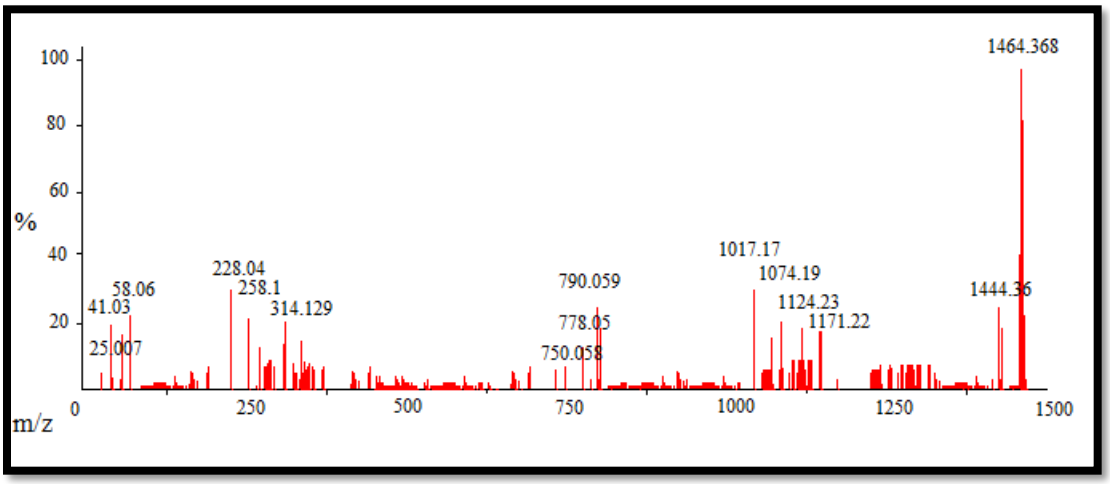


Figure 54. Mass Spectrum for [Pt(Cipro-en-bipy)$_2$Cl$_2$]

3.4 Conclusion

Six complexes of Pt(II) and Pt(IV) have been prepared and characterized by spectroscopic methods. The complexes described above represent a development of the class of organometallic Pt(II) derivatives with two nitrogen-donor ligands bound to the same metallic center. Platinide(II) and (IV) chloride coordination of bpy and phen ligands results in the deshielding of all ^{1}H NMR signals. This effect is mostly pronounced for protons directly adjacent to nitrogens, i.e., H (6) in bipy and H(2) in phen. For all studied complexes, usually observed ^{13}C NMR high-frequency shifts are noticeably larger for carbons far distanced from nitrogen than for those directly adjacent to the N atom (the latter ^{13}C signals can be even low frequency shifted). Most likely, such a pattern results from a general deshielding effect appearing for all carbon nuclei, in combination with a specific shielding of C atoms in the nearest moiety of the coordination site. Although none of the complexes has been obtained in the crystalline state, the experimental results suggest that the coordination of the ligands show well-defined structure as suggested by the mass spectra.

3.5 References

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CHAPTER 4

SYNTHESIS, CHARACTERICATION OF METALLOLIGANDS AND USE THEM IN FORMATION OF HETEROBIMETALLIC COPPER(II)-URANYL COMPLEXES

4.1 Introduction

Transition metal complexes of multidentate ligands especially tetradentate Schiff bases have important applications in catalysis and material chemistry.[1-5] The coordination and organometallic chemistry of actinides, especially uranium, have been explored extensively over last two decades.[6-12] These studies have great applications not only in the extraction of actinides,[13-15] nuclear fuel processing,[16] environmental remediation,[17] and nuclear forensics[18] but also in the fields of magnetism,[19,20] optics,[21,22] catalysis,[23,24] and electrochemistry.[25-27] Tetradentate Schiff bases N,O-donor ligands set atoms provide suitable coordination environments for a wide variety of metal ions.[28] Metal complexes which involve derivatives of salicylaldehyde and diamine act as potential catalysts for the insertion of oxygen into an organic substrate.[29-32] Moreover, metal complexes of Schiff bases derived from salicylaldehyde and diamine can increase their dimensionality and can form supramolecular architectures through O–H…N and N–H…O type of hydrogen bonds. One of the recent trends in coordination chemistry is to explore new types of molecular architectures using relatively less common metal ions.

The f-block metals have shown potential toward multifunctional materials in terms of magnetic and optical properties.[33] In contrast to recently developed copious novel multifunctional heteronuclear 3d-4f molecular compounds and co-ordination polymers, only a few heterometallic 3d-5f complexes are reported. These 3d-5f complexes are derived mainly from uranium in different oxidation states by using various types of ligands, for example, phosphonates, hexadentate bicompartmental N_2O_4 Schiff base metalloligands, etc.[34] The compounds containing

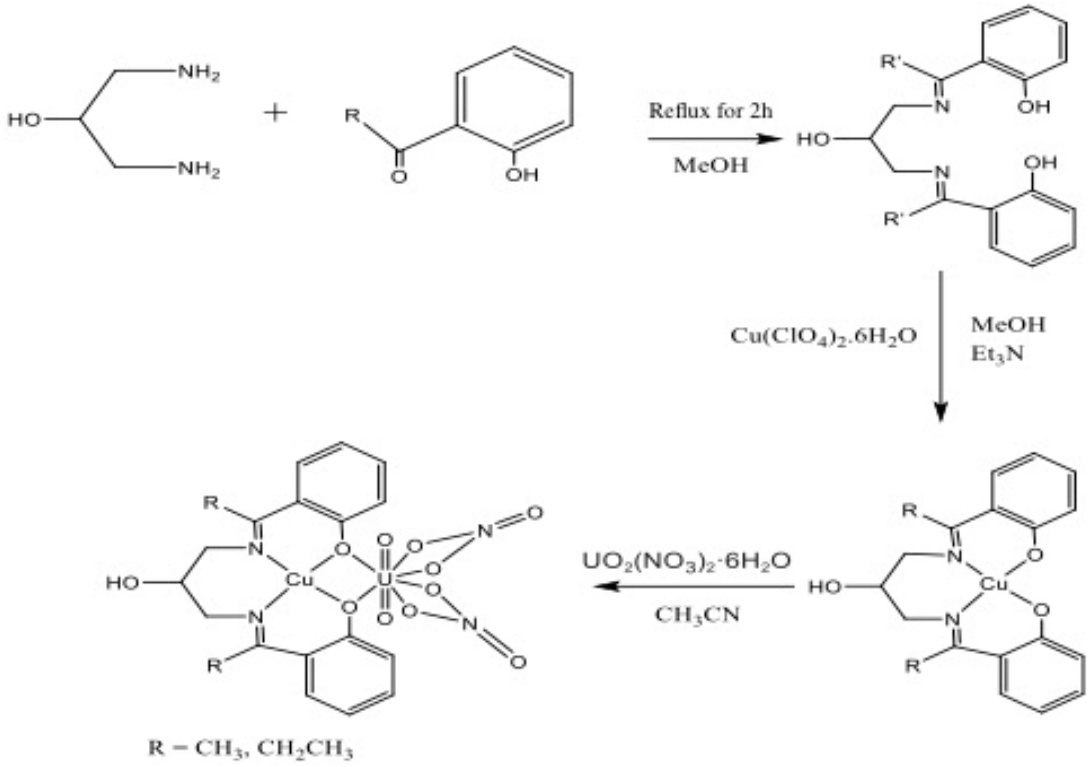
lower valence uranium (UIII/IV/V) have been synthesized mostly to explore their interesting magnetic properties.[35] On the other hand, the naturally occurring uranyl compounds which are known for their interesting photophysical properties for centuries and have immense importance in terms of environmental, geological, or bioassay fields[36] are rarely explored to make photo-responsive systems using interactions between transition metal complexes and uranyl ions.[37]

As actinyls are hard acids with a strong oxophilic character and prefer high coordination numbers (five, six or seven) around the equatorial plane, they are expected to be incorporated easily by these monocompartmental chelates.[38] On the other hand, N,O-donor ligands have been used widely for the synthesis of heterometallic complexes in past few decades. The relatively softer N-donor sites of such ligands bind the soft metal ions (e.g., transition metal), and harder O-donor groups select the hard cations (e.g., alkali and alkaline earth, Ln^{3+}. etc.).[39-42] One such notable group of ligands is N_2O_4-donor bicompartmental Schiff bases, which form stable neutral chelates incorporating divalent transitions metal ions within their inner N_2O_2 core. These chelates quite successfully accommodate another guest metal ion inside the outer $O_2O'_2$ compartment to produce the desired heterometallic complexes.[43] These ligands were originally designed to accommodate 4f metal ions in the outer compartment, but it was later found that most of the other metal ions could also be housed there.[44,45] However, when such ligands were used to synthesize 3d–5f complexes with $UO_2(NO_3)_2$, in some cases U entered into the outer compartment to form the desired complexes while in some other cases it stayed outside of its $O_2O'_2$ compartment and resulted in solid co-crystallized products.[46-48] However, the N,O-donor monocompartmental ligands, which usually form less stable heterometallic complexes than the bicompartmental ligands with other metal ions, produced the desired 3d–U coordination complexes in all reported

instances.[49,50] To date, these apparently inconsistent phenomena have not been rationalized by any theoretical calculations or systematic experimental observations.

Nuclear fuel is of potential concern in terms of economic and environmental issues, such as recycling and radioactive waste handling.[51-54] During the nuclear fission process, a number of radioactive fission products, e.g., cesium, strontium, barium, lanthanides, etc., are formed and need to be separated from the spent nuclear fuel in a timely manner.[55] One of the convenient ways to separate these metal ions is to use a ligand that can selectively bind either uranium or these metal ions.[56-58] The selectivity of such a ligand exploits the key differences of size and chemistry between the linear triatomic uranyl cation, which allows the coordination of the ligand only to the equatorial plane from these metal ions with no coordination site preference. Moreover, if the ligand is stereochemically rigid, then it often shows unusual coordination behavior toward metal ions with a coordination preference due to the mismatch in cavity size and denticity of ligand vs the size and available coordination site of the guest, which is crucial for selectivity.[59]

In the present work, Cu(II) complexes of N_2O_2 Schiff base ligands, [CuL] were reacted with uranyl nitrate to investigate their ability to form coordination $[(CuL)UO_2(NO_3)_2]$ complexes with it. All the complexes were characterized by several analytical techniques.



Scheme 9. Synthetic Route of Cu(II) Complexes (5-8) and [(CuL)$UO_2(NO_3)_2$] Complexes (9-12)

4.2 Experimental

All chemicals used were of AnalaR grade and obtained from Sigma-Aldrich and Fluka. Metal salts were purchased from E. Merck and were used as received. Uranyl nitrate is a water-soluble yellow salt with the formula $UO_2(NO_3)_2).6(H_2O)$. The compound is mainly of interest because it is an intermediate in the preparation of nuclear fuels.

4.2.1 Synthesis of The Ligands (H_2L) 1-4

Tetradentate Schiff-base ligands, H_2L (1-4) were prepared by standard methods.[60] Briefly, 5 mmol of 1,3-diaminopropanol was mixed with 10 mmol of the required carbonyl compound (2'-hydroxyacetophenone (1.2 mL) or 2`-hydroxypropiophenone (1.5 mL) , 3-hydroxy-2-naphthaldehyde (1.72 g) and 4-(diethylamino)-2-hydroxybenzaldehyde (1.932 g) respectively) in

methanol (20 mL). The resulting solutions were refluxed for about 2 h and allowed to cool. The yellow colored methanolic solutions were used directly for complex formation.[61,62]

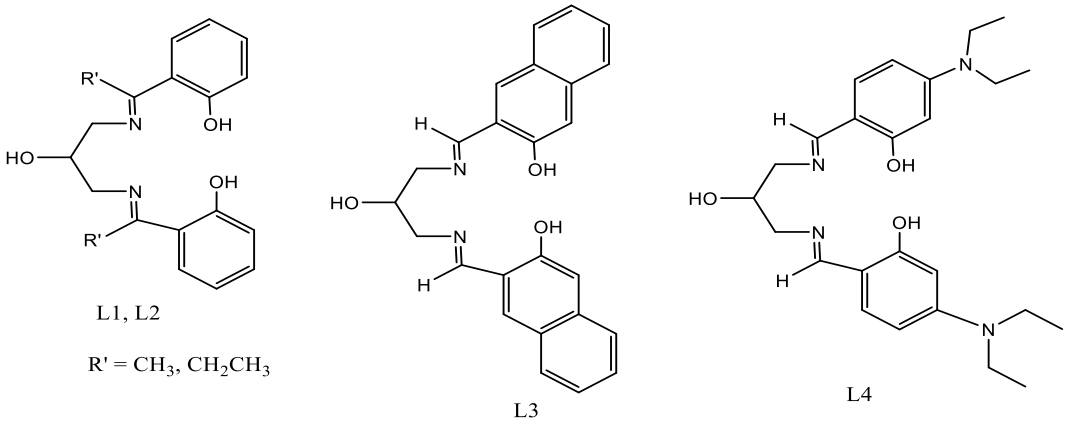


Figure 55: Chemical Structures of Synthesized Ligands

4.2.2 Synthesis of The Copper Complexes (Cu-L) 5-8

A methanolic solution (20 mL) of Cu(ClO4)2·6H2O (1.852 g, 5 mmol), a methanolic solution of H_2L(1-4) (5 mmol, 10 mL) and triethyl amine (1.4 mL, 10 mmol) were added to prepare the respective precursor "metalloligands" [CuL5-8], as reported earlier.[60,61]

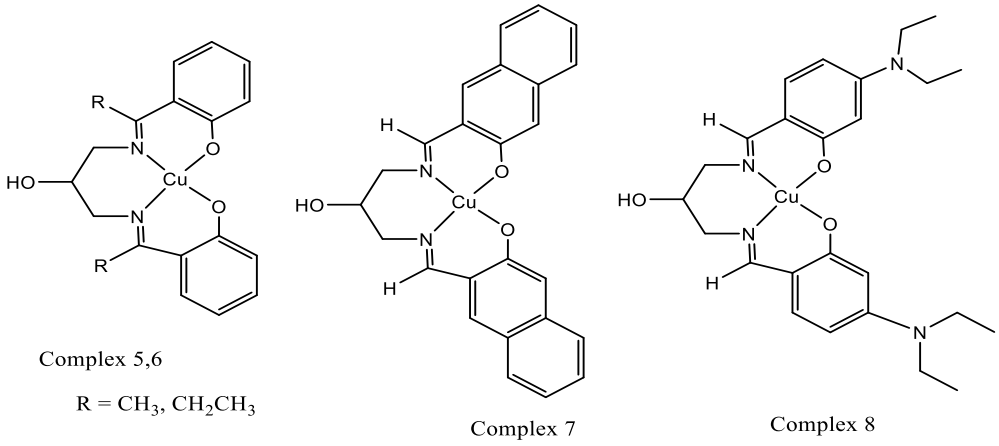


Figure 56. Chemical Structures of Cu(II) Complexes

4.2.3 Synthesis of The Heterobimetallic Complexes [(CuL)$UO_2(NO_3)_2$] (9-12)

Caution: Uranium is a radioactive and toxic element, uranium-containing samples must be handled with suitable care and protection, together with a plan for safe waste disposal.

The metalloligand [CuL] (5-8) (0.04 mmol) was dissolved in acetonitrile (5 mL) and added to solution of $UO_2(NO_3)\cdot 6H_2O$ (20.0 mg, 0.04 mmol in 5 mL of acetonitrile), the mixed solution was stirred for 5 min and then left to stand overnight at room temperature when reddish product deposited at the bottom of the vessel. These compounds were isolated by filtration and redissolved in 5 mL of acetone by warming, and the solution was kept in a long tube for slow evaporation.[62]

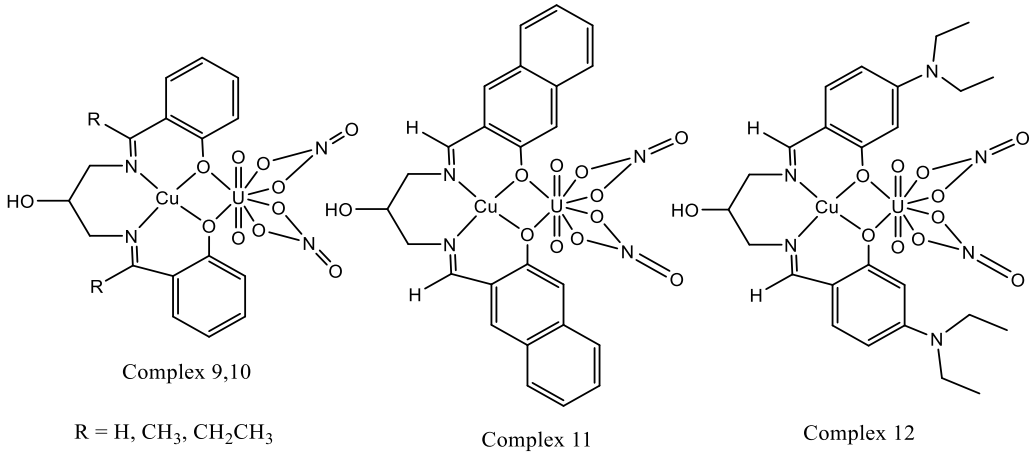


Figure 57. Chemical Structures of [(CuL)$UO_2(NO_3)_2$] Complexes

4.3 Results and Discussion

4.3.1 ^{1}H-NMR Spectra

The ^{1}H NMR spectra of the Schiff base ligands and complexes were recorded in DMSO-d_6 or chloroform-d in Table (10). In the ^{1}HNMR spectra of Schiff base ligand, peaks appeared at 13.85, 12.5, 11.55 and 11.66 ppm were assigned to the protons of phenolic group in ligands respectively. In the ^{1}H NMR spectra of ligands exhibit sharp multiple signals between 6.24 to 8.22 ppm due to Ar-H.

The NMR spectra of the copper(II) complexes shown in Figures (62, 63, 64, and 65). The phenolic OH signals observed in the spectrum of the ligands are not seen in the spectrum of the Cu(II) complexes indicating the participation of the phenolic OH group in chelation with proton displacement. The signal due to the azomethine proton gets shifted upon complexation, which is probably due to the donation of the lone pair of electrons by the nitrogen to the central metal atom, resulting in the formation of a coordinate linkage (M-N). The azomethine proton signal shifts downfield upon complexation, confirming that the azomethine nitrogen as the second coordination site. The coordination of the azomethine nitrogen is inferred by the downfield shifting of the -CH=N- proton signal from 8.22 and 8.5 ppm in the ligand 3 and 4 respectively to 8.4 and 8.6 ppm in the Cu(II) complexes. The downfield shifting of the -CH-OH protons is observed at 4.1, 4.1, 4.39 and 3.76 ppm for (H3) in the ligands to 4.34, 4,52, 4,52 and 3.97 ppm in the complexes respectively. The chemical shifts for (H12) in the ligands are 4.78, 4,75, 4.62 and 3.84 ppm are shifts downfield to 4.8, 4.87, 4.87 and 4.10 ppm in spectrum of the Cu(II) complexes respectively.[63]

In the spectra of $[(CuL)UO_2(NO_3)_2]$ complexes the protons of the Ar-H, the azomethine group and the -CH-OH are shifted downfield compared to that of the free ligand and Cu(II)

complexes as a result of chelation of azomethine group and phenolic group to copper and uranium ions, indicating that the chelation of the ligand with the metal ions involves the nitrogen atom of the ligands.[64] Furthermore, the number of protons calculated from the integration curves, and those obtained from the values of the mass spectra match.

Table 10. ^{1}H NMR Chemical Shifts (δ^{1H}, ppm) of Ligands to, Cu (II) Complexes and Cu (II)-U(VI) Complexes

Compound	-OH	-CH=N-	Ar-H	H (4,4')	H (12)	H (3)
L1	13.85	-	7.00-7.23	3.09 & 3.48	4.69	4.18
CuL1	-	-	7.04-7.43	3.42 & 3.59	4.79	4.33
$[(CuL1)UO_2(NO_3)_2]$	-	-	6.29-7.28	3.82 & 4.00	4.83	4.73
L2	12.5	-	7.00-7.55	3.23 & 3.52	4.72	4.09
CuL2	-	-	7.07-7.68	3.77 & 4.07	4.87	4.52
$[(CuL2)UO_2(NO_3)_2]$	-	-	7.04-7.29	3.71 & 4.07	4.87	4.39
L3	11.43	8.52	7.42-8.17	3.41 & 3.65	4.62	4.34
CuL3	-	8.58	7.44-8.21	3.65 & 3.94	4.87	4.50
$[(CuL3)UO_2(NO_3)_2]$	-	8.62	7.50-8.23	3.54 & 4.01	4.89	4.24
L4	11.6	8.18	6.24-7.48	3.67 & 3.93	3.91	3.84
CuL4	-	8.27	6.00-7.55	3.69 & 3.95	4.42	3.96
$[(CuL4)UO_2(NO_3)_2]$	-	8.35	6.52-7.70	3.81 & 4.02	4.29	4.02

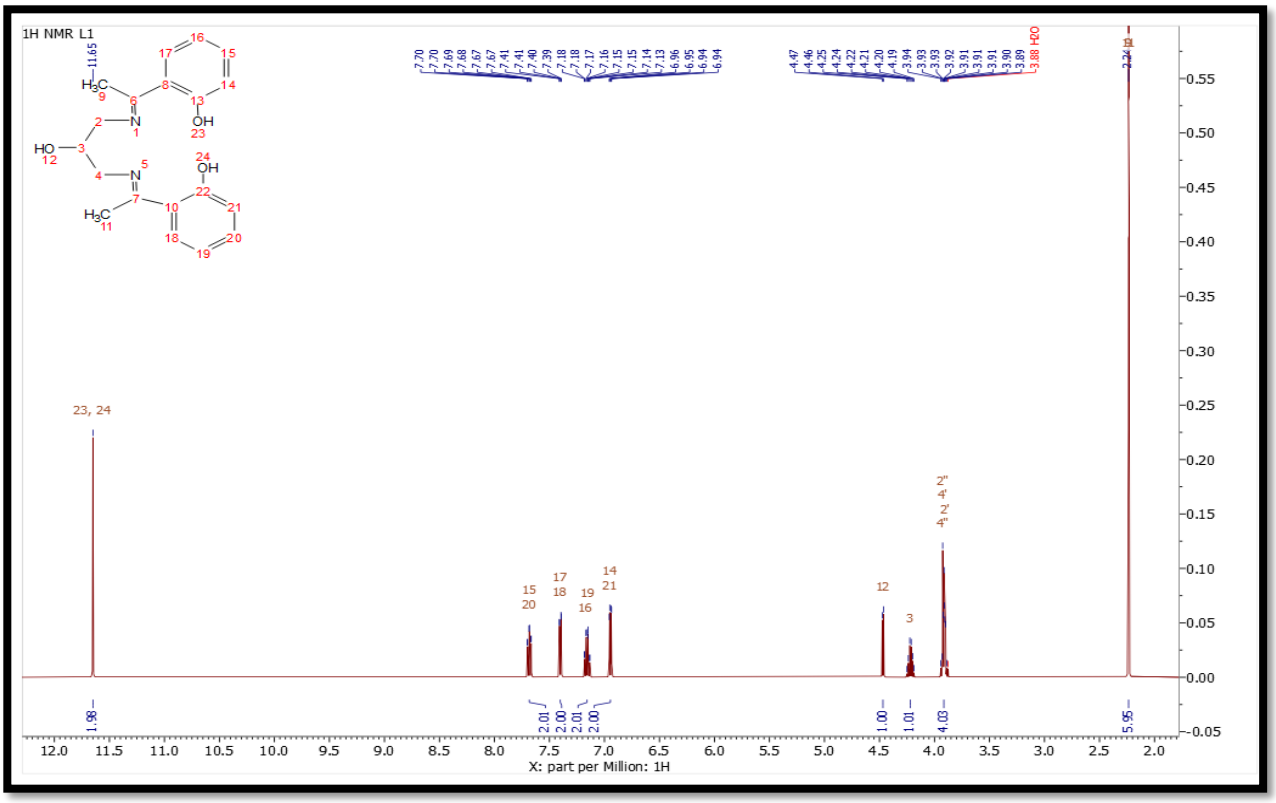


Figure 58. ^{1}H-NMR for L1

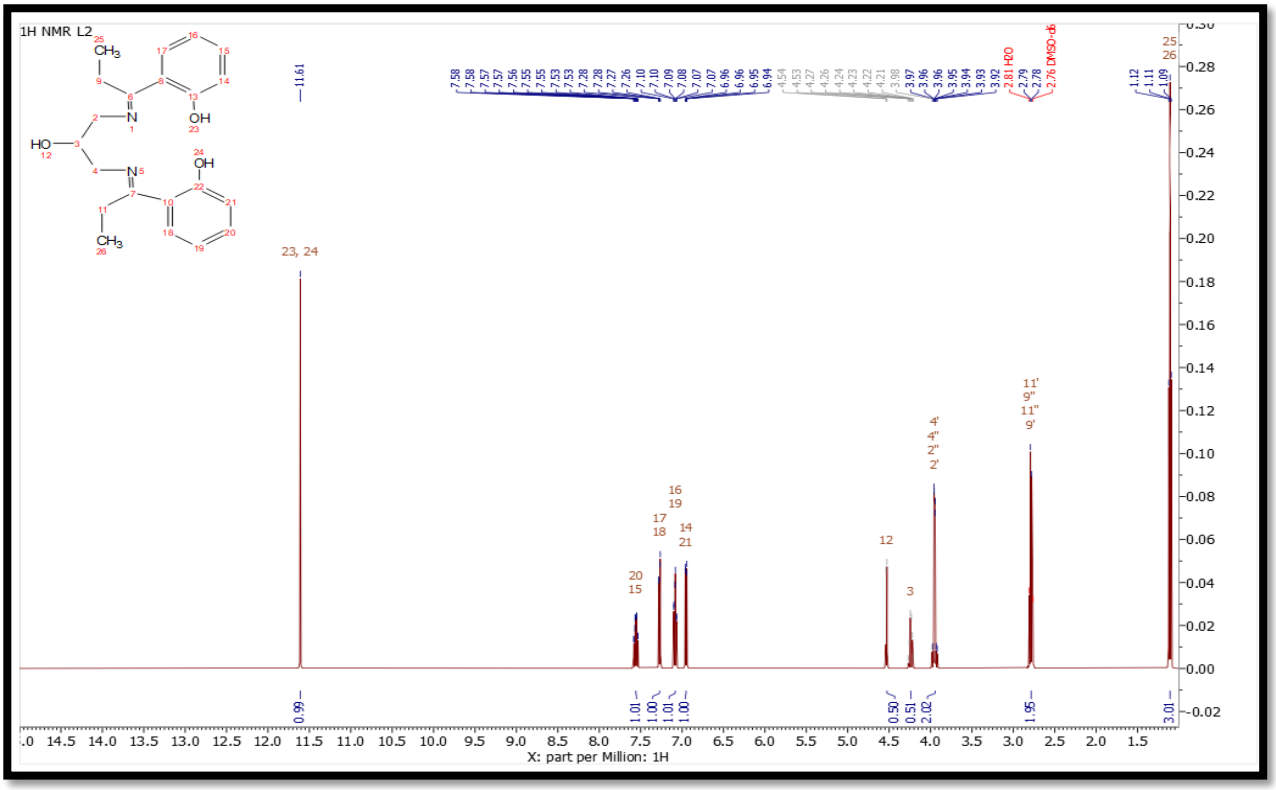


Figure 59. ^{1}H-NMR for L2

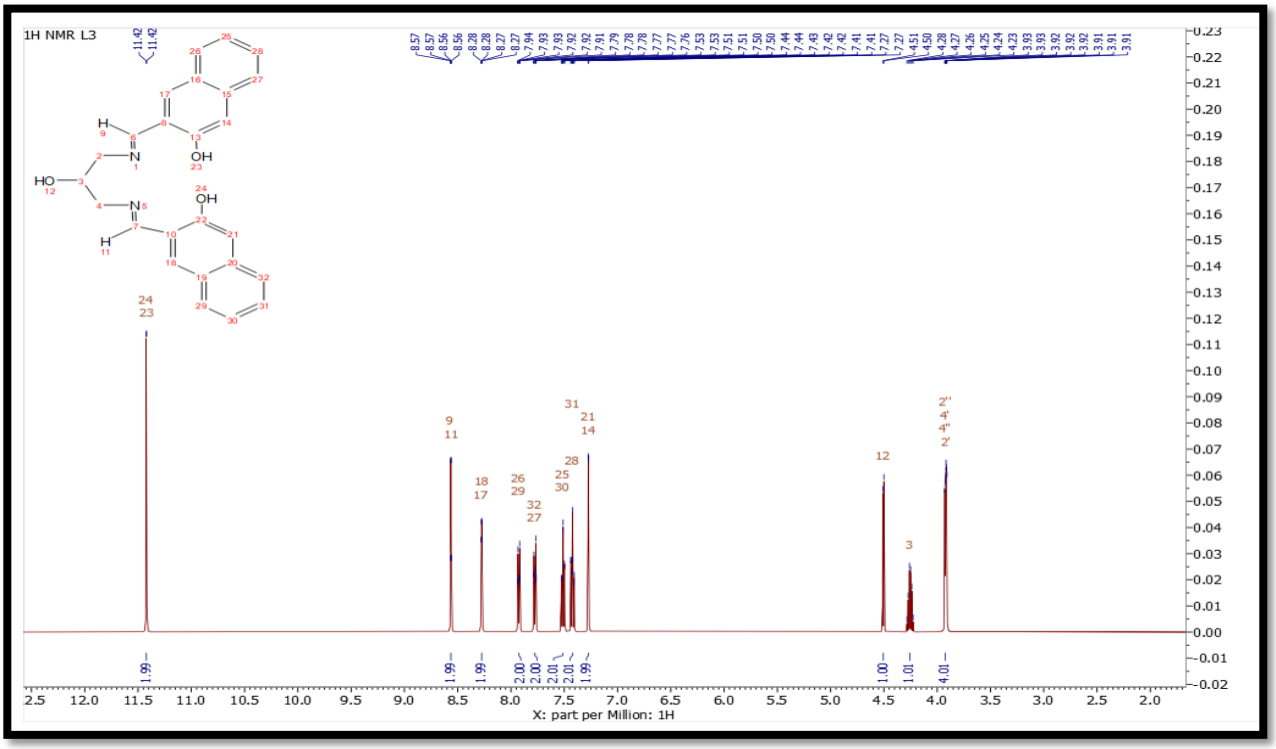


Figure 60. ^{1}H-NMR for L3

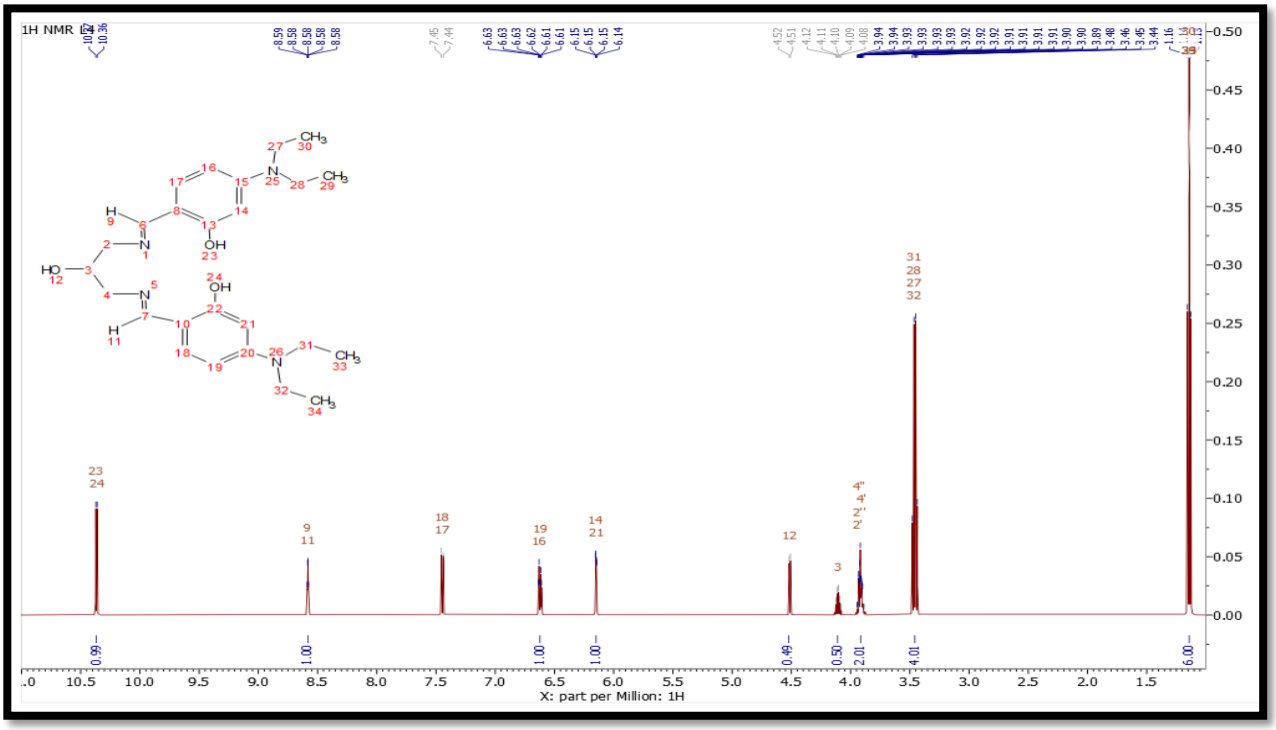


Figure 61. ^{1}H-NMR for L4

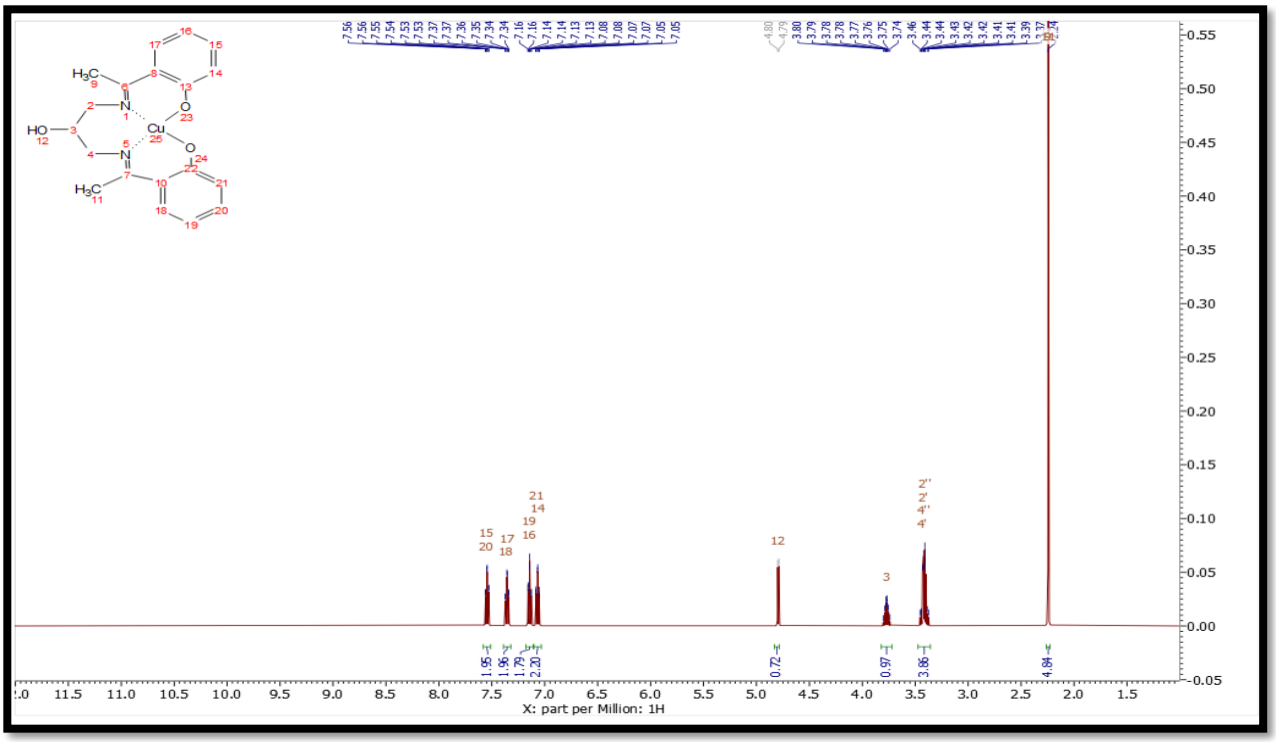


Figure 62. ^{1}H-NMR for complex 1 (CuL1)

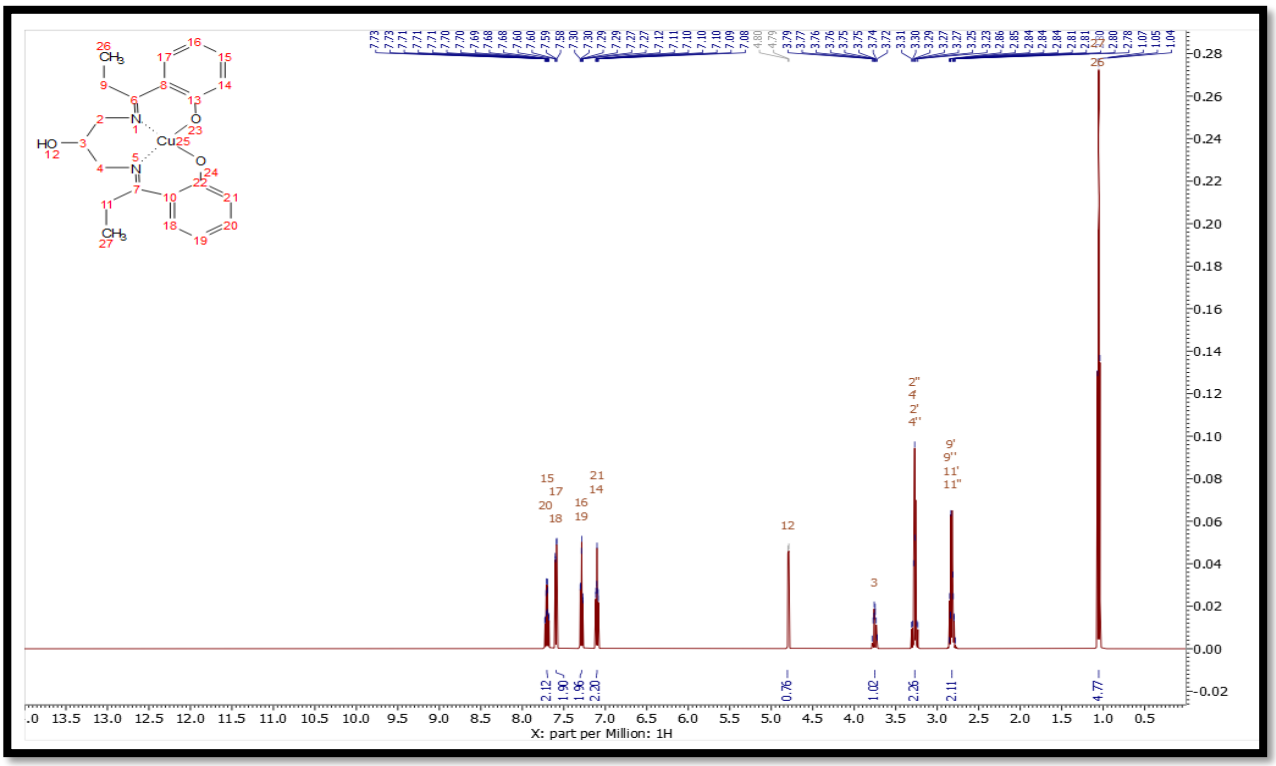


Figure 63. ^{1}H-NMR for complex 2 (CuL2)

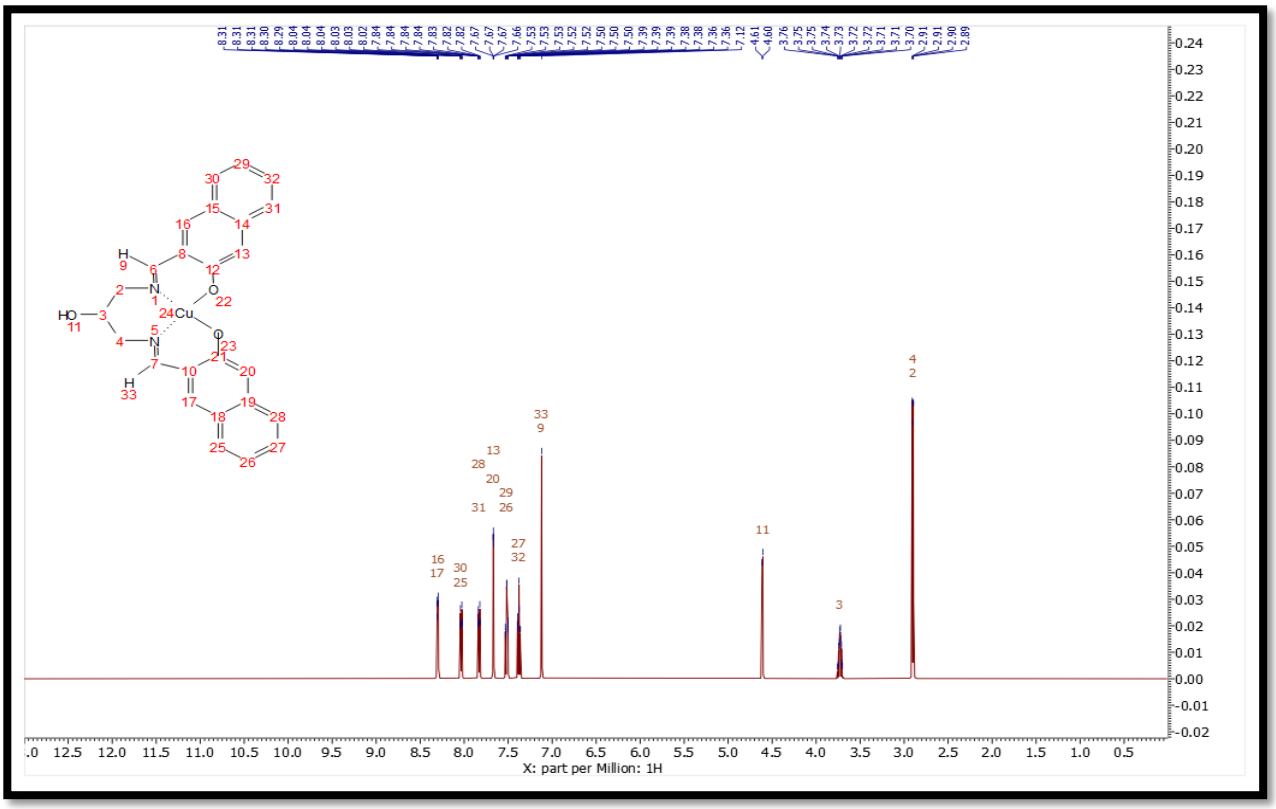


Figure 64. ^{1}H-NMR for complex 3 (CuL3)

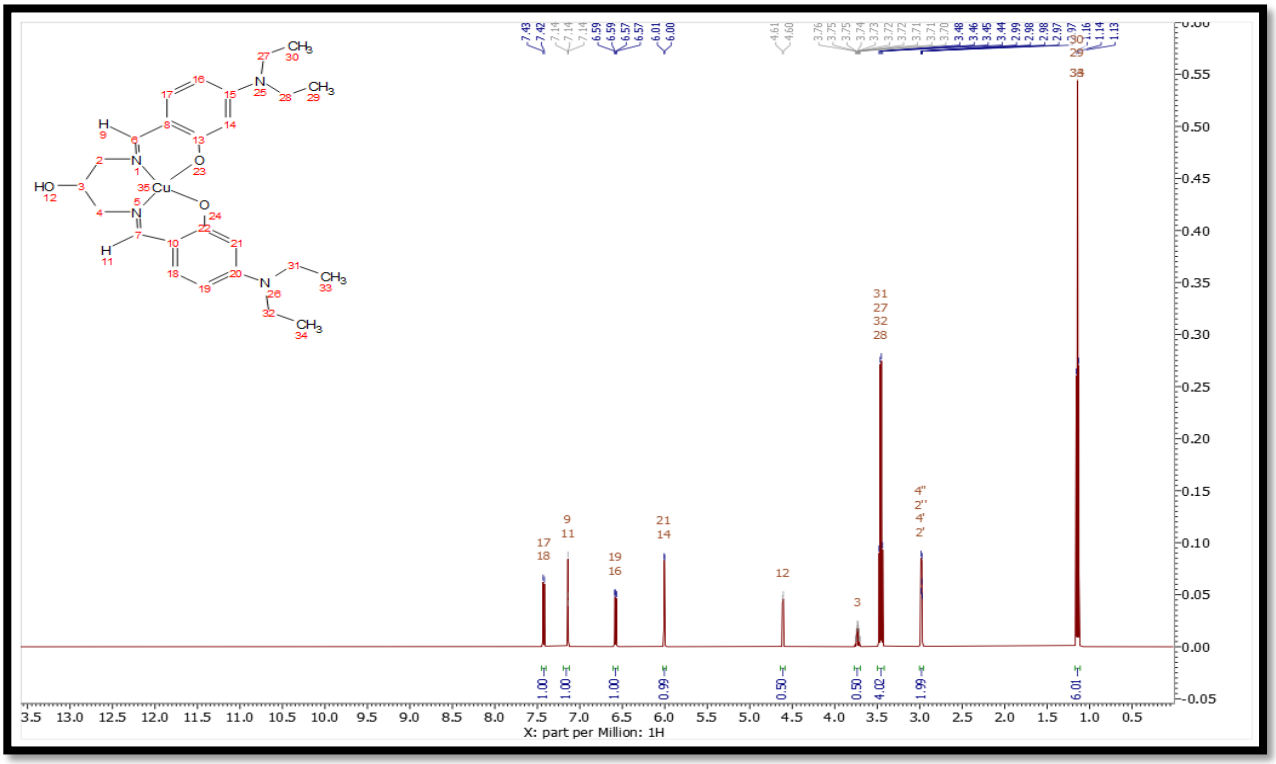


Figure 65: ^{1}H-NMR for complex 4 (CuL4)

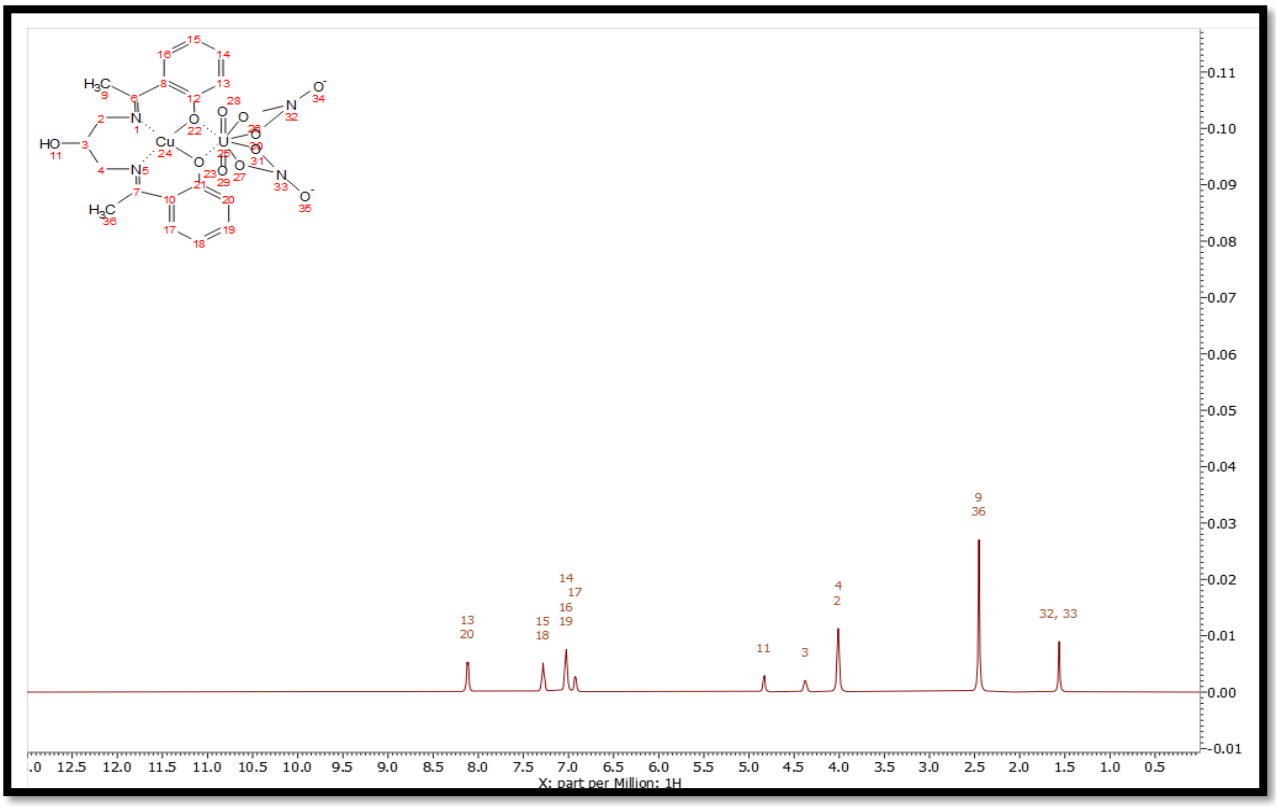


Figure 66. ^{1}H-NMR for Complex 5 [(CuL1)$UO_2(NO_3)_2$]

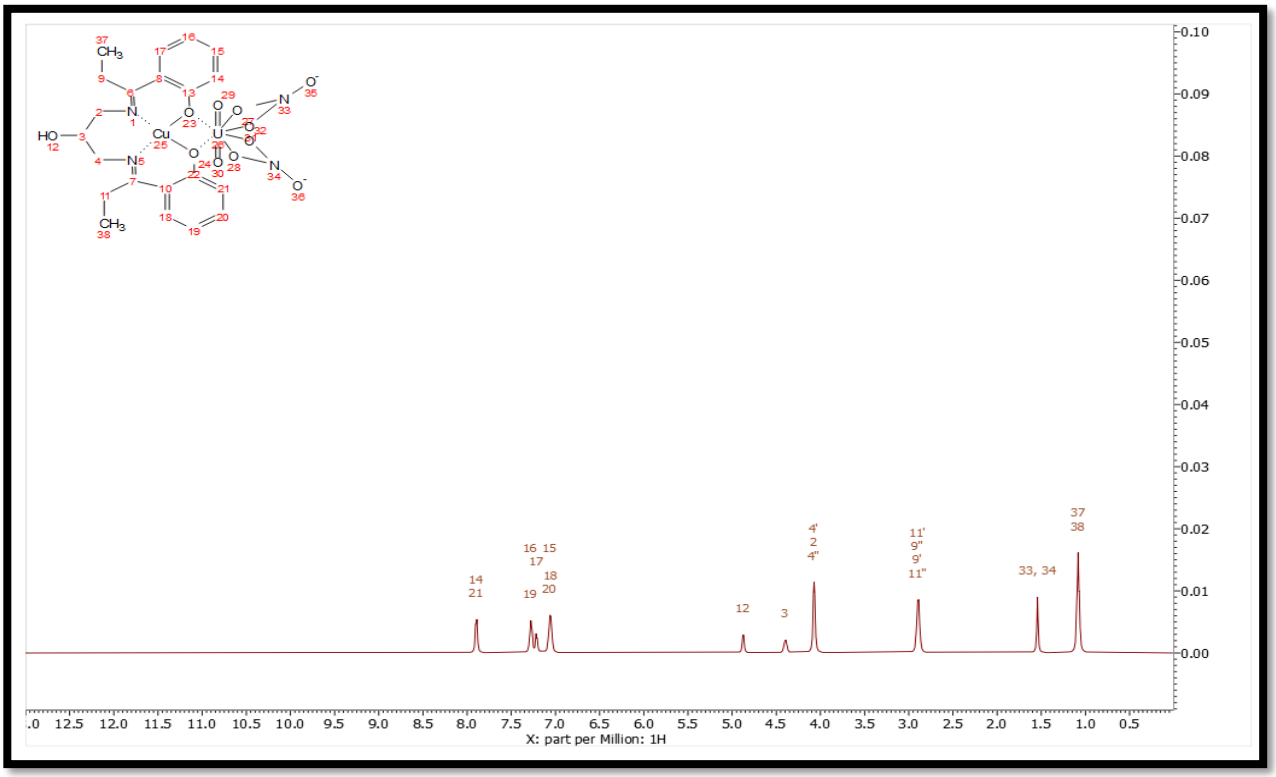


Figure 67. ^{1}H-NMR for Complex 6 [(CuL2)$UO_2(NO_3)_2$]

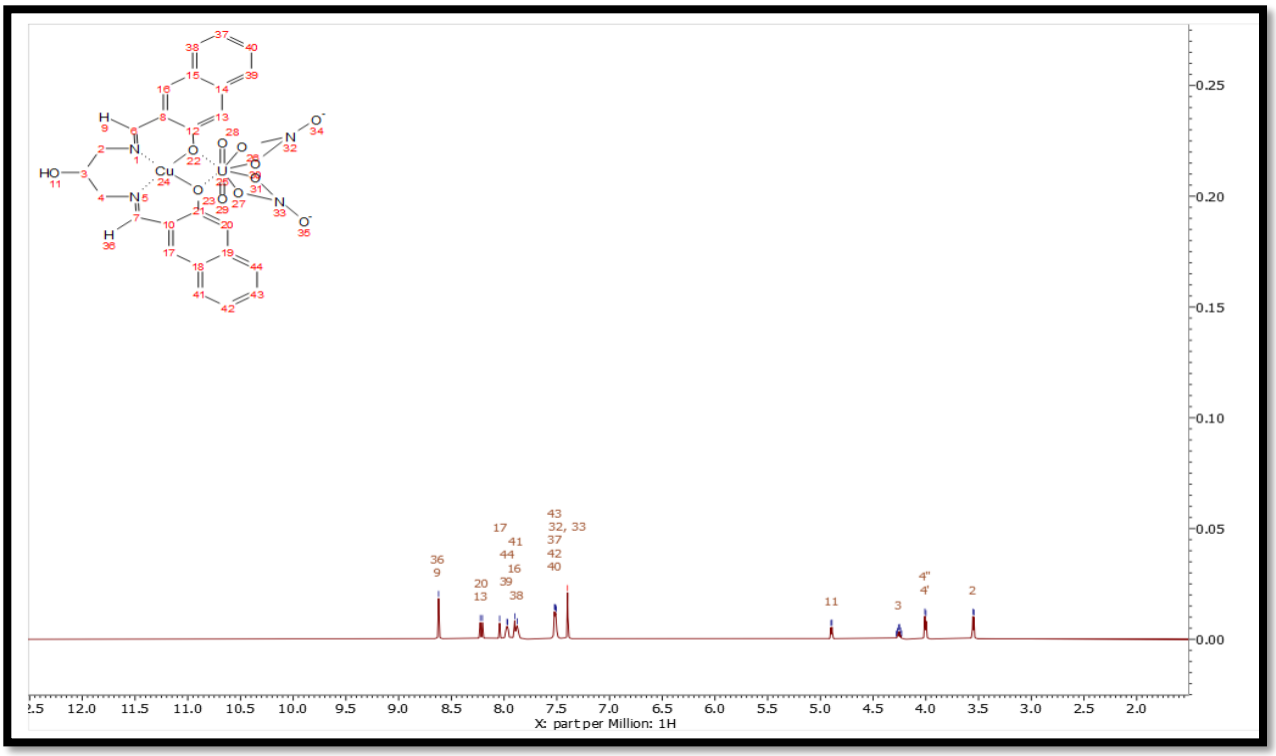


Figure 68. ^{1}H-NMR for Complex 7 [(CuL3)$UO_2(NO_3)_2$]

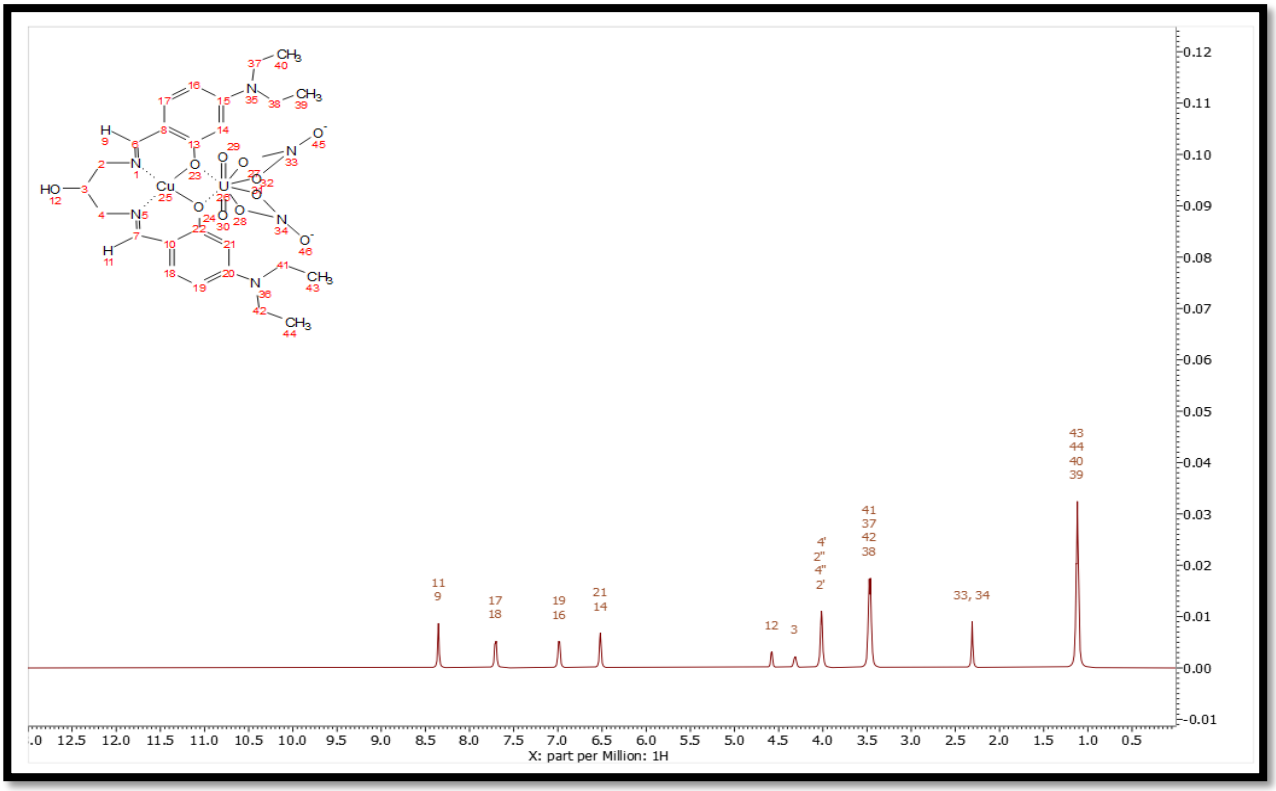


Figure 69. ^{1}H-NMR for complex 8 [(CuL4)$UO_2(NO_3)_2$

4.3.2 Mass Spectroscopy and Mass Spectrometer

The mass spectra of the copper complexes and heterobimetallic of Cu-U were recorded and compared for their stoichiometric composition. The mass spectral data of copper complexes [Cu-L] reported in figures (70,71,72, and 73) were obtained operating in positive ion mode. The mass spectra of the metal complexes showed molecular ion peaks, which were in good agreement with the expected values. The molecular ions are detected the base and the main peaks of the spectra at *m*/*z* 388.084, 416.116, 460.084 and 502.200 respectively for the four Cu(II) complexes. These correspond to the protonated molecular ion $[M+H]^+$ and they can be generated either by the ionization conditions or by ion-molecule reactions inside the ion trap analyzer. Moreover, the mass spectra for complexes Cu-U were shown in Figures (74, 75, 76 and 77). The protonated molecular ions $[M1\text{-}M2 + H]^+$ were detected at *m*/*z* values centered at 782.1005, 810.138, 854.1005 and 896.216 respectively: the isotopic cluster is in agreement with the theoretical one for the complexes 5 and 8. The fragmentation pattern of [Cu-U] complexes also displayed important peaks at m/z 388.08, 414.09, 442.07 and 502.19 respectively, because of loss of $[H_3N_2O_8U]^+$ from the parent complex at m/z 397.039. This feature further confirms the formation of the complexes: the comparisons between the main peaks of synthesized complexes have been collected in table 11.

The results of mass spectrometry are consistent with the proposed formulas for these compounds as the peaks observed in these spectra correspond to fragments resulting from the expected fragmentations of the compounds.

Table 11. Main MS Peaks of The Synthesized Mono and Heterobimetallic Complexes

Ligands	$[CuL+H]^+$	$[(CuL)UO_2(NO_3)+H]^+$	$[H_3N_2O_8U]$	Theoretical
L1	388.084	782.101	397.039	$[C_{19}H_{20}CuN_2O_3]^+$ (387.077)
L2	416.116	810.132	397.039	$[C_{21}H_{23}CuN_2O_3]^+$ (415.1083)
L3	460.084	854.101	397.039	$[C_{25}H_{19}CuN_2O_2]^+$ (459.077)
L4	502.200	896.216	397.039	$[C_{25}H_{35}CuN_4O_3]^+$ (501.1927)

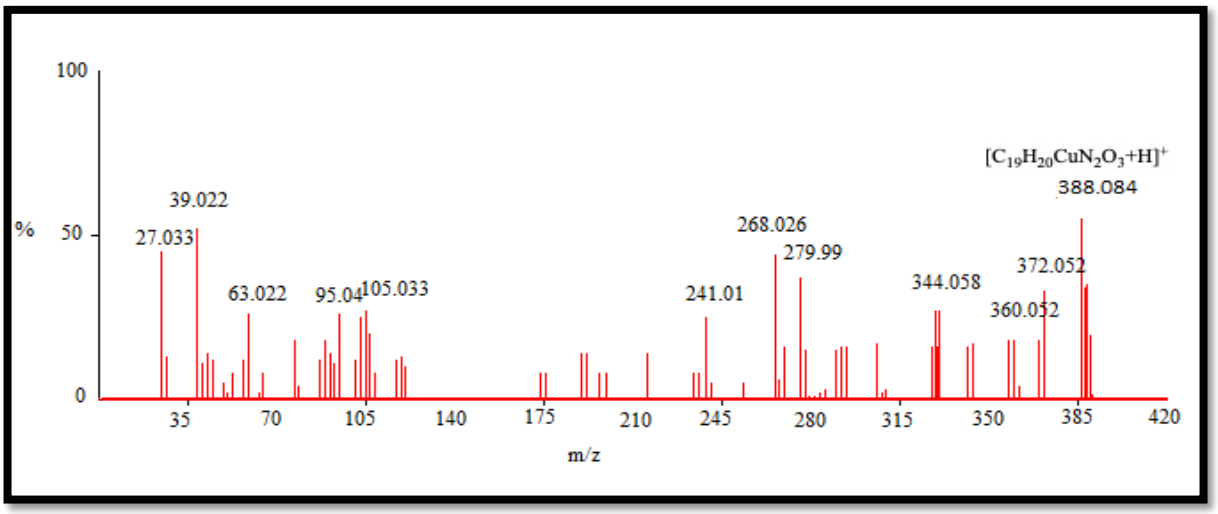


Figure 70. Mass Spectrum for Complex 1 (CuL1)

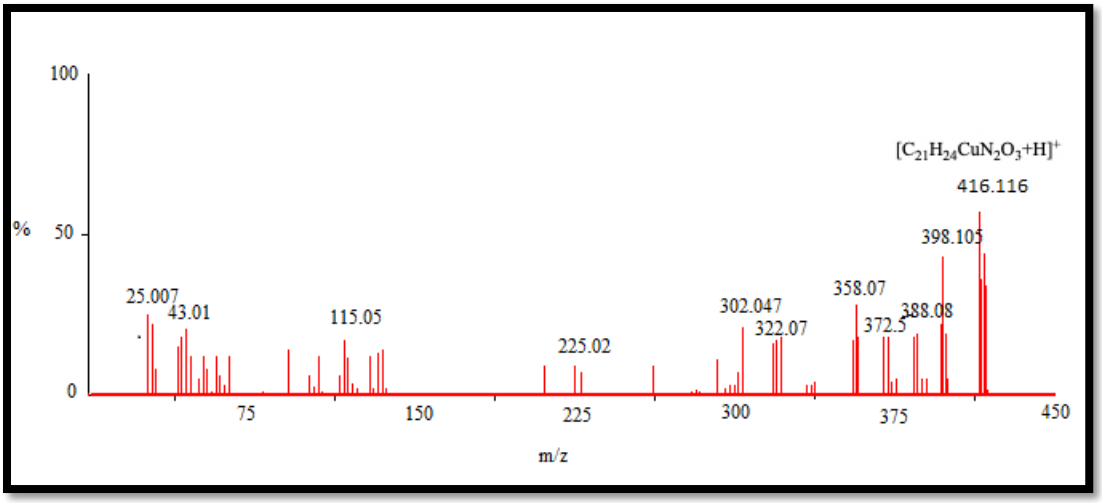


Figure 71. Mass Spectrum for Complex 2 (CuL2)

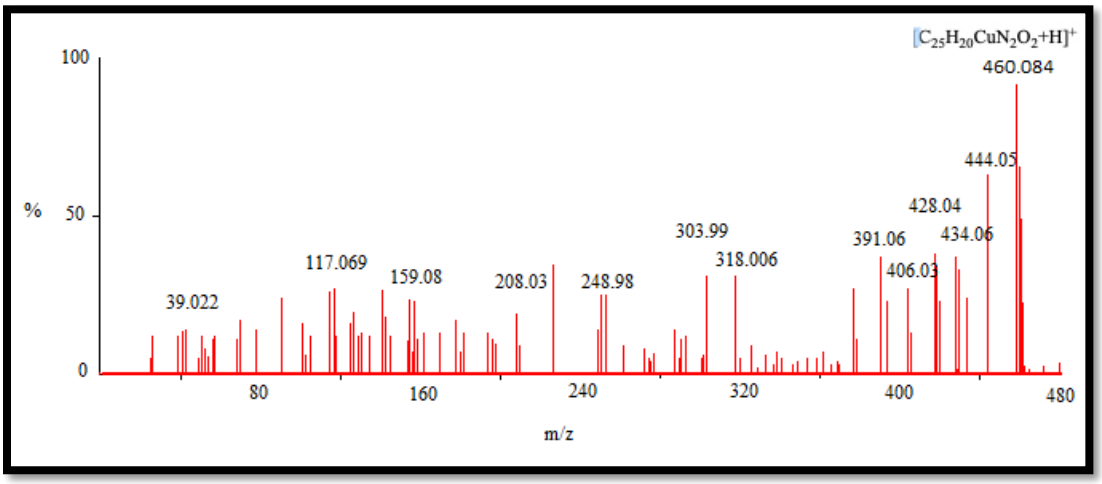


Figure 72. Mass Spectrum for Complex 3 (CuL3)

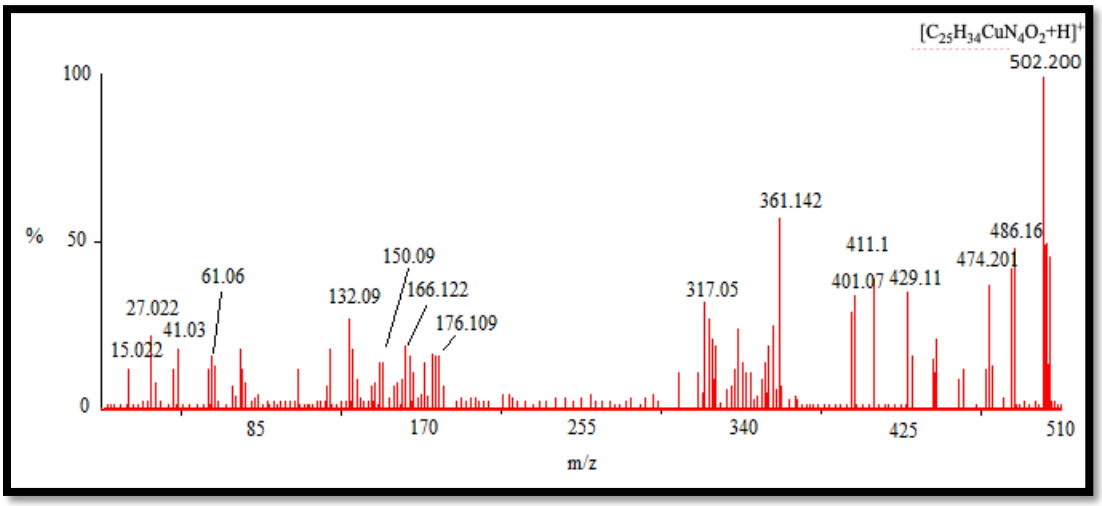


Figure 73. Mass Spectrum for Complex 4 (CuL4)

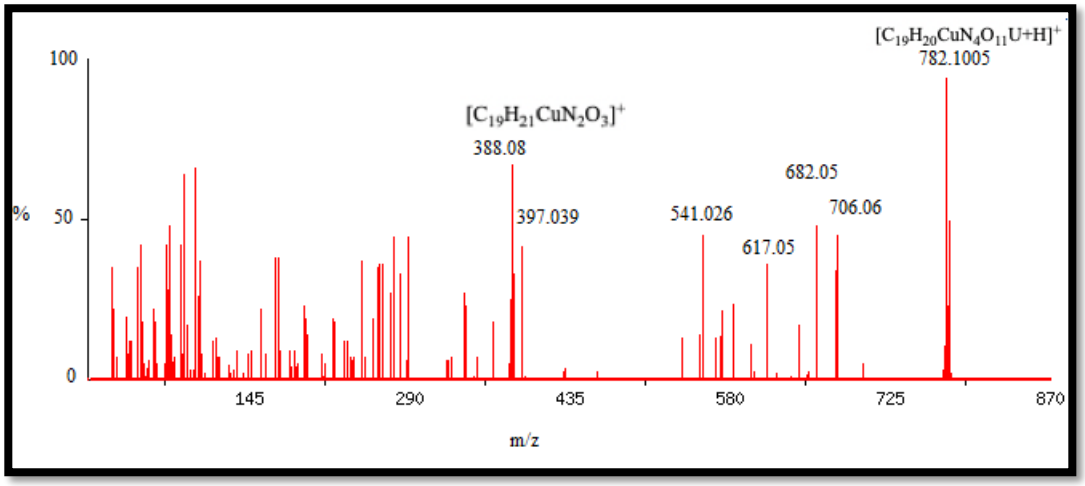


Figure 74. Mass Spectrum for Complex 5 [(CuL1)$UO_2(NO_3)_2$]

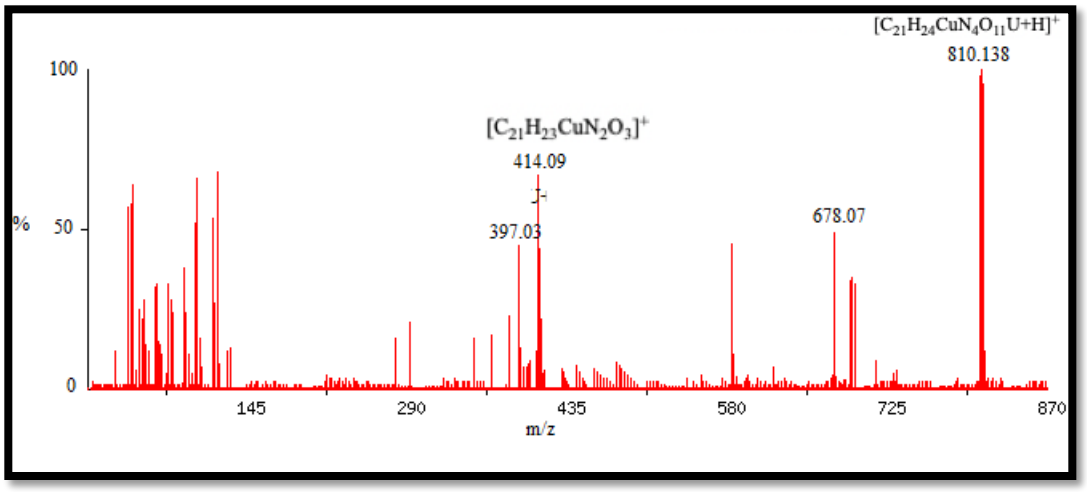


Figure 75. Mass Spectrum for Complex 6 [(CuL2)$UO_2(NO_3)_2$]

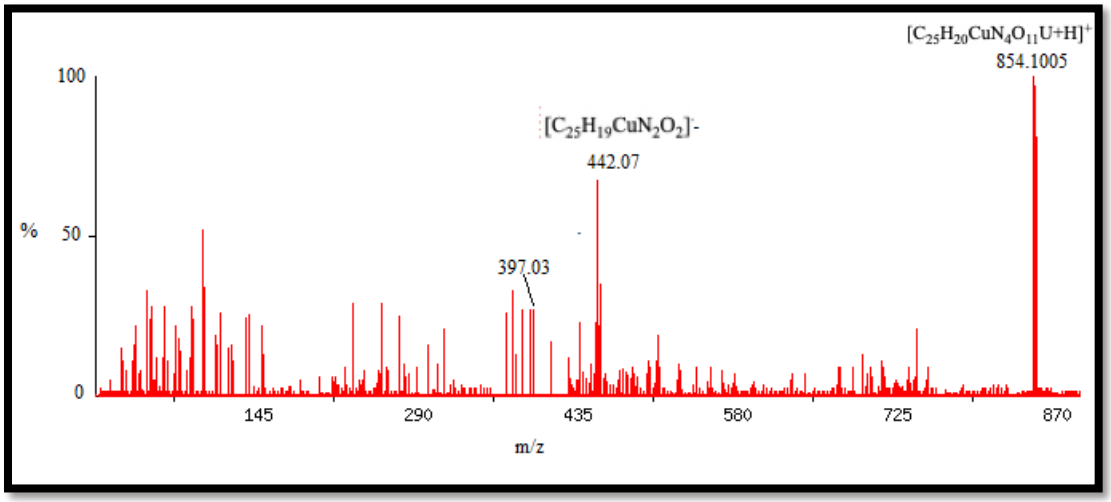


Figure 76. Mass Spectrum for Complex 7 [(CuL3)$UO_2(NO_3)_2$]

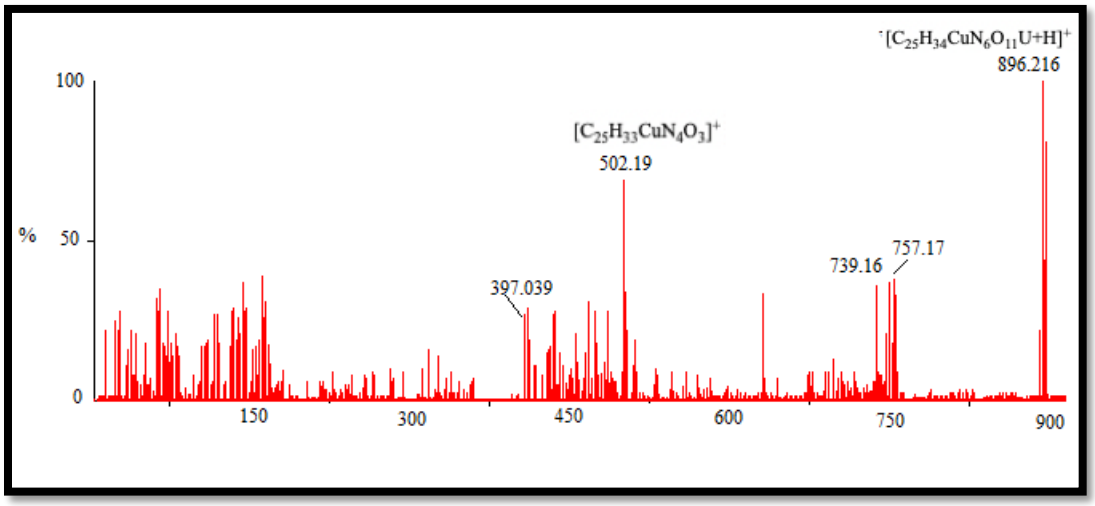


Figure 77. Mass Spectrum for Complex 8 [(CuL4)$UO_2(NO_3)_2$

4.4 Conclusion

The four different N_2O_2 functionalized, potentially tetradentate ligands (H_2L1 to H_2L4) showed variation in their coordination properties when binding to metal ion Copper. Structures of 1to 4 confirm that the denticity of the Schiff bases are four in the respective complexes. Four heterobimetallic copper(II)−uranium(VI) complexes have been synthesized by reacting Cu (II)-derived metalloligands with $UO_2(NO_3)_2 \cdot 6H_2O$ in 1:1 ratio. In this research, we report the synthesis and the structural characterization of new mixed metal complexes corresponding to the coordination of the uranium by (CuL). According to the phenolic OH signals observed in the spectrum of the ligands are not seen in the spectrum of the Cu(II) complexes indicating the participation of the phenolic OH group in chelation with proton displacement. The Mass spec discussed above, it was deduced that the uranium ions in the copper-uranium heterobimetallic complexes bind to the outer oxygen sites of the nitrate ion ligands and are coordinated to the oxygen atoms of both the phenolic groups. The column purification of the ligands and complexes is not performed due to the formation of a Schiff base from carbonyl compounds is a reversible reaction and Silica gel is consisting of oxygen atoms which caused to hydrolyze back to starting materials.

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CHAPTER 5

SYNTHESIS AND CHARACTERIZATION OF HEXADENDATE SCHIFF BASE LIGANDS AND THEIR NOVEL CU(II)-U(IV) DERIVATIVES

5.1 Introduction

A great interest has been dedicated to the formation of bonds between metal ions of the transition elements in the past few years. These compounds may be divided into several classes, depending on the interaction between the metal atoms which may be direct, or indirect involving interaction via other atoms. Compounds with the direct interaction show a weak interaction or strong covalent bonding, depending upon the metal chosen, the oxidation state, and the attached ligands. Bonds between dissimilar transition metal atoms are less common than those between similar metal atoms, but this appears to be due to lack of purposeful effort to obtain such derivatives until recently.[1]

Although it was considered at one stage to be a relatively rare type of bonding, it has now been claimed in some valency state for every element of the transition block. For elements of the later transition elements, this type of interaction is mainly confined to the low oxidation states, as typified by carbonyl and substituted carbonyl compounds, but with the earlier elements it occurs in the higher oxidation states when many oxide and simple halide systems have been shown to exhibit this kind of interaction. For the latter categories of compounds, it has been more difficult to recognize the formation of this type of bond as one of the most readily applied criterion for detecting such an interaction, namely the magnetic properties of the complexes, is complicated because of the polymeric nature of these complexes. It is becoming more apparent, however, as more data are being obtained, that the chemistry of the compounds in this area of the periodic table likely tends to form metal-metal bonds and polymeric structures.[1-3]

The tendency to form metal-metal bonds appears to increase in the second and third rows of the transition series, and as stated above to be more common with the higher oxidation states to the left-hand side of the transition series, whereas it is more favored by lower oxidation states for the elements on the right-hand side of the transition series.[2,3] This may be correlated with the effective nuclear charge of the metal ion. Moving across the periodic table, the effective nuclear charge of the ions will increase, and the bonding orbitals will tend to be contracted in size. This will alter the overlap properties between orbitals of different atoms and may well reduce the effective overlap to negligible proportions. Within a given series the orbital size will increase on descending a group and hence this will affect the probability of metal-metal bonding. For a given element a reduction in oxidation state will be accompanied by an increase in the size of the orbital as the effective nuclear charge will be reduced by the screening of the added electrons. There is obviously the possibility of a large variation in the size of the metal orbitals depending upon the position of the element in the periodic table and oxidation state of the metal. If it is assumed that favorable overlap occurs with the early transition elements for the higher oxidation states, the probability of favorable orbital overlap must decrease across the periodic table for the higher oxidation states, because of this orbital contraction.[4] The stability of the metal-metal bonds in the lower oxidation states for the later transition elements may then be related to the more favorable orbital overlap properties associated with the increase in orbital size. For the early transition elements, the lower oxidation states are not as well established, and this may be associated with the lower effective charge on the metal nucleus leading to ready loss of electrons from these systems with oxidation to higher oxidation states. There are obviously other factors involved in determining the stability of the metal-metal bonds in complexes, but there does often appear to be a critical balance between the charge on the atom and the stability of the metal-metal bond.

Heterometallic complexes are important in catalysis and small-molecule activation because of the multimetallic synergistic effects from different metals. However, multimetallic species that contain uranium–metal bonds remain very rare due to the difficulties in their synthesis.[4] A multidentate ligand platform is introduced that enables the isolation of both homo- and heterobimetallic complexes. Hexadentate Schiff bases possess two cavities and are widely used as ditopic ligands.[4] Ditopic ligands are capable of coordination at two separate sites and allow the creation of complexes containing different cations.[5] They are usually N-, P-, O-, and S-containing (or in their N, O-, N, S,- and N, P-combinations) organic molecules, and have been used in various applications such as monitoring guest exchange and the creation of metal organic frameworks.[5] However, these molecules are also able to bind more than two cations and act as metallic cluster assemblers because of the bridging ability of their oxygen atoms and their conformational flexibility. Due to the latter, which is enhanced in the case of the largest di-imino bridges, they may even be converted from convergent into divergent ligands.[4] The relatively softer N-donor sites of such ligands bind the soft metal ions (e.g., transition metal), and harder O-donor groups select the hard cations (e.g. alkali and alkaline earth, Ln^{3+}. etc.).[6-9] One such notable group of ligands is N_2O_4-donor bicompartmental Schiff bases, which form stable neutral chelates incorporating divalent transitions metal ions within their inner N_2O_2 core. These chelates quite successfully accommodate another guest metal ion inside the outer $O_2O'_2$ compartment to produce the desired heterometallic complexes.[10]

The interest of compartmental Schiff bases as ligands in the building of high-nuclearity metallic complexes has recently been demonstrated in the case of d transition metals[11] and of uranium(IV).[12] Compartmental systems have received a growing interest in the recent past owing to their ability to give rise to compounds with unusual, although preordered, properties.[13-17] The

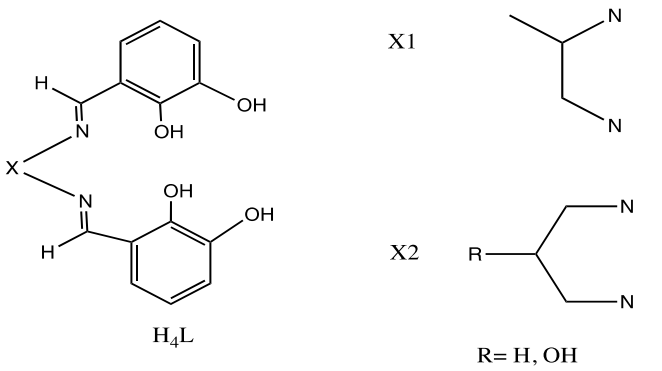
presence of two recognition sites in close proximity confers the capability to undergo two similar or dissimilar recognition processes, for instance the coordination of two identical or different metal ions in a well-defined stereochemistry and at an appropriate from distance each other.[18-20] This causes a mutual influence between the two metal ions giving rise to systems with new physico-chemical properties which have been used in the design of molecular magnetic or optical devices, molecular probes for the selective recognition of charged and neutral molecules or polynuclear catalytic systems. It was proved, in fact, that two metal ions, communicating with each other through suitable bridging groups, can give rise to antiferro- or ferromagnetic interactions, to electron-transfer processes or can produce asymmetric or symmetric activation of specific molecules and hence peculiar, highly selective and efficient catalytic processes.[21-24] Moreover, dinucleating systems containing a paramagnetic center fixed in one chamber (i.e., lanthanide(III), manganese(II), etc.) can considerably influence the properties of the second metal ion coordinated to the adjacent chamber (i.e., an alkali metal ion) and hence can serve as molecular devices for its recognition and qualitative detection in the solid state and in solution.[25] Synthesis of compartmentalized multimetallic compounds is also of particular interest as precursors for the production of mixed metal oxides[26–30] via the single-source precursor method.[31,32] Although diketonates[33-35] and ketoimines[36,37] are the typical ligands for binding alkaline-earth ions, a multitopic polyetherbased ligand with specific chelating sites has been designed, allowing the selective coordination of Cu(II) in one site and Ba(II) or Ca(II) in a second site.[38] The obtained heterometallic complexes were further thermally decomposed to stoichiometric mixed metal compounds. The choice of a versatile organic ligand with specific coordination sites is thus of crucial importance for the synthesis of such compounds.[39] During the past few years, several

research groups have carried out numerous studies on multi-metal-containing host−guest complexes based on salen-type ligands.[40-42]

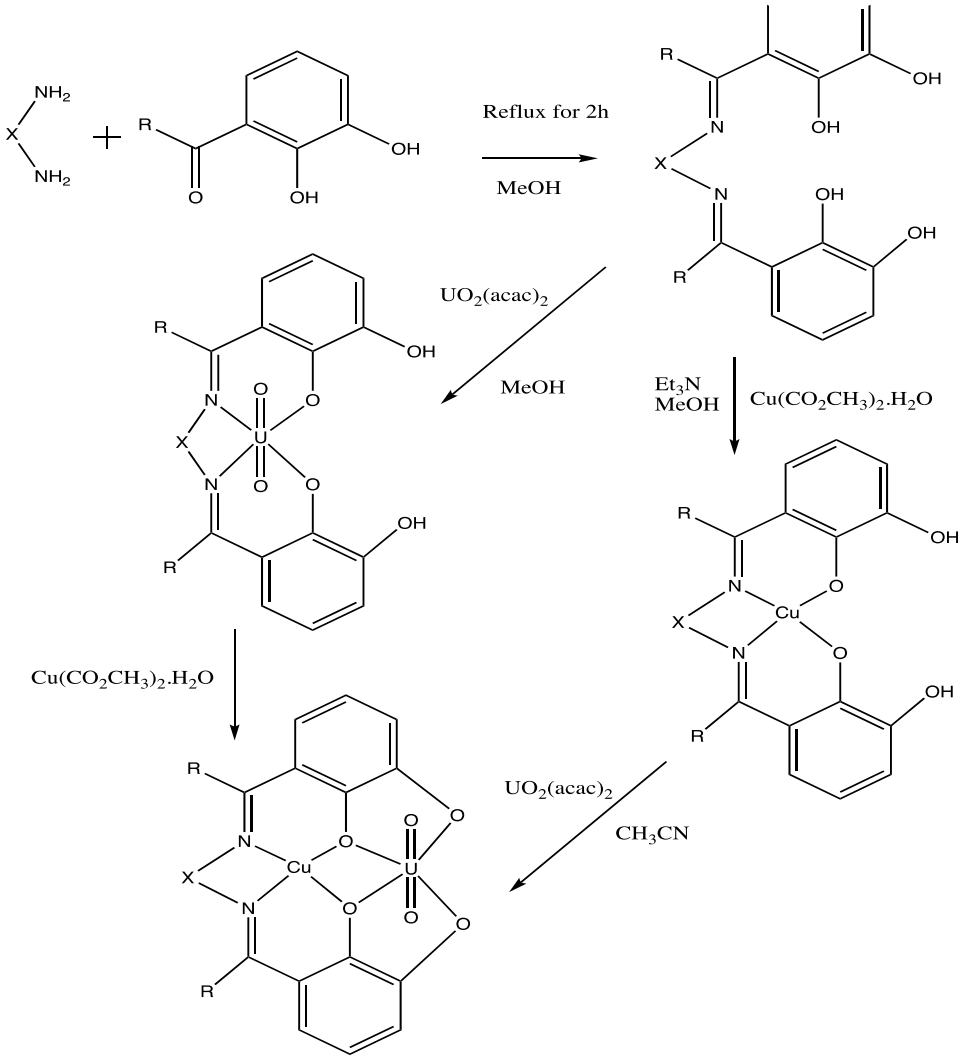
The design and synthesis of new mixed transition-metal complexes are of interest in many fields such as catalysis,[43,44] material science,[45,46] or biochemistry.[47,48] Moreover, since the discovery, in 1985, of ferromagnetic coupling in Cu_2Gd complexes,[49] many studies have been devoted to such compounds of the lanthanides (Ln) in order to understand the basics of the interaction of the 3d and 4f ions and to develop the molecular approach to magnetic materials with controlled and tunable properties.[50] In contrast, virtually nothing is known about the magnetic behavior of molecular compounds containing simultaneously 3d and 5f ions, even though interesting magnetic properties should be anticipated, since the f electrons for the actinide ions are less shielded than they are for the lanthanide ions. Magnetic properties of the most accessible uranium(IV) complexes (Th^{4+} is diamagnetic) are difficult to analyze because this $5f^2$ ion possesses a first-order orbital momentum, which prevents the use of a spin-only Hamiltonian for the description of the spectrum of the low-lying states;[51] the temperature dependence of $\chi_M T$ (χ_M being the molar magnetic susceptibility and T the temperature) is due to both the thermal population of the excited states and the exchange interaction. It is for the same reason, that is, the lack of a general theoretical model to describe the magnetic susceptibility χ_M of a Ln^{3+} ion in its ligand field, that the magnetic studies on 3d-4f complexes were at first essentially limited to the case of the lanthanide(III) ion. The isotropic gadolinium(III) has an $^8S_{7/2}$ single-ion ground state without first-order orbital momentum in these complexes. The 3d ion is usually Cu^{2+},[52-54] can also be Co^{2+}, Ni^{2+}, Fe^{3+}, and the vanadyl ion VO^{3+}.[55] Magnetic studies on Cu-Ln complexes other than those of Gd have been rather scarce.[56] However, the problem of the spin-orbit coupling of the 4f ions was overcome by the empirical approach, proposed in 1998, in which one compares the magnetic

properties of a 3d-4f complex with those of an isostructural derivative in which the paramagnetic ion (Cu^{2+}) has been replaced with a diamagnetic ion, and low-spin such as Ni^{2+} or Zn^{2+}.[57,58] Therefore, in the Zn-Ln compounds; the deviation of χ_M with respect to the Curie law reflects the sole thermal population of the f ion Stark levels, and by transferring this information to the magnetic properties of the former 3d-4f complex. In the Cu-Ln complexes, it is possible to determine the nature of the exchange interaction. This method was applied to two series of Cu-Ln [58] and Cu_3Ln_2 [57] compounds; it is clearly transposable to uranium complexes, as demonstrated in this project. The other reason for the lack of magnetic studies on molecular 3d-5f complexes that is obviously related to the first one, is the scarcity of such compounds, which is interesting from a magnetic point of view; most of these complexes are organometallics with the 3d ion diamagnetic.[59] Very recently, the Mn-U compound $[K_2Mn(C_2O_4)_4U].9H_2O$ was synthesized, but no magnetic coupling was detected in this three-dimensional network of paramagnetic units.[60] A large number of 3d-4f compounds have been synthesized with the aid of Schiff bases as dinucleating ligands, and we have considered this approach for the preparation of heteropolymetallic complexes containing both 3d and uranium ions, although U^{3+} and U^{4+} complexes with Schiff base ligands are quite uncommon.[61-63]

In this work, we have synthesized and characterized the heterometallic systems derived from 2,3-dihydroxybenzaldehyde-diamine and 2-hydroxy-3-methoxybenzaldehyde-diamine ligand (H_4L) containing two specific coordination sites. Three CuL, $UL(acac)_2$ and new mixed metal complexes correspond to the coordination of the uranium(IV) by Cu-L as shown in schemes 10 and 11. The results reveal that the Cu(II)–U(IV) interaction, is strongly dependent on structural and ligand effects. All the complexes were characterized by studying NMR and the Mass spectra for all monometallic complexes and heterobimetallic complexes.



Scheme 10. The H_4L Schiff bases.



Scheme 11. Synthetic Route of Cu(II) Complexes (9-11), $[UO_2L]$ (12-14), and $[(CuL)UO_2]$ Complexes (15-17)

5.2 Experimental

All chemicals employed for the synthesis were of analytical reagent grade and of highest purity available. 1,3-diaminopropane, 1,3-diamino-2-propanol, 1,2-diaminopropane, 2,3-dihydroxybenzaldehyde, and 2`,3`-dihydroxyacetophenone obtained from Sigma-Aldrich and Fluka. Copper acetate monohydrate $Cu(CO_2CH_3)_2.H_2O$ and uranyl acetylacetonate $[UO_2(acac)_2]$ were purchased from E. Merck and were used as received. Solvents were purified by standard methods and dried before use by conventional methods.

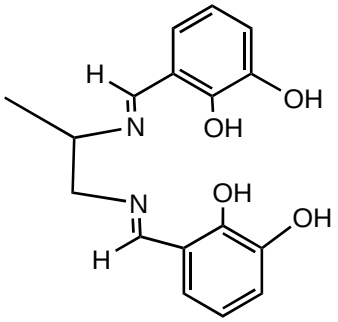
5.2.1 Synthesis of The Ligands (H_4L)

5.2.1.1 Synthesis of The Ligands (L5)

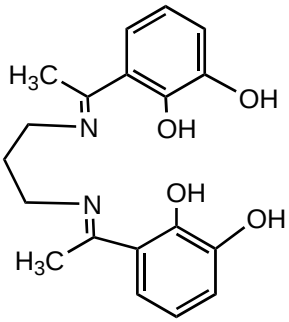
Hexadentate Schiff-base ligand, H_4L (L5) was prepared by standard methods.[60] Briefly, 5 mmol of propane-1,2-diamine was mixed with 10 mmol of the required carbonyl compound 2,3-dihydroxybenzaldehyde in methanol (20 mL). The resulting solution was refluxed for about 2 h and allowed to cool. The yellow colored methanolic solution was used directly for complex formation.[64,65]

5.2.1.2 Synthesis of The Ligands (L6 and L7)

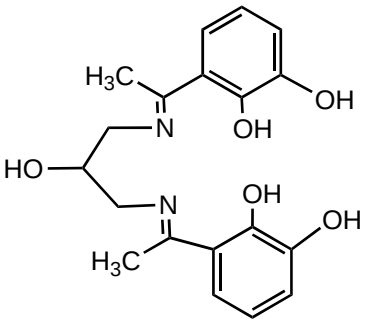
Two hexadentate Schiff-base ligands, H_4L (6 and 7) were prepared by standard methods.[60] Briefly, 5 mmol of 1,3-diaminopropan or 1,3-diaminopropan-2-ol was mixed with 10 mmol of the required carbonyl compound 2`,3`-dihydroxyacetophenone in methanol (20 mL). The resulting solutions were refluxed for about 2 h and allowed to cool. The yellow colored methanolic solutions were used directly for complex formation.[64,65]



L5



L6

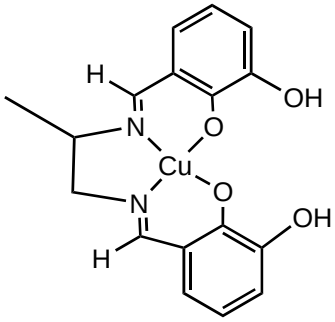


L7

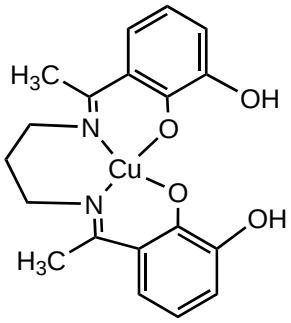
Figure 78. Chemical Structures of Synthesized Ligands H4L (5-7)

5.2.2 Synthesis of The Copper Complexes (Cu-L) (9-11)

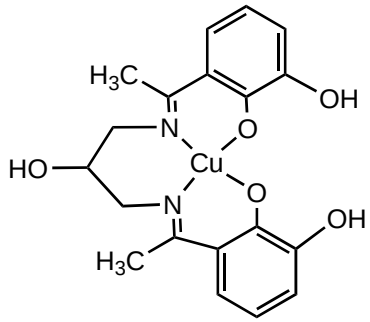
A methanolic solution (20 mL) of $Cu(acac)_2$ (5 mmol), a methanolic solution of $H_4L(5,7)$ (5 mmol, 10 mL) and triethyl amine (1.4 mL, 10 mmol) were mixed to prepare the respective precursor "metalloligands" [CuL] (9-11), as reported earlier.[64,65]



Complex 9 (CuL5)



Complex 10 (CuL6)



Complex 11 (CuL7)

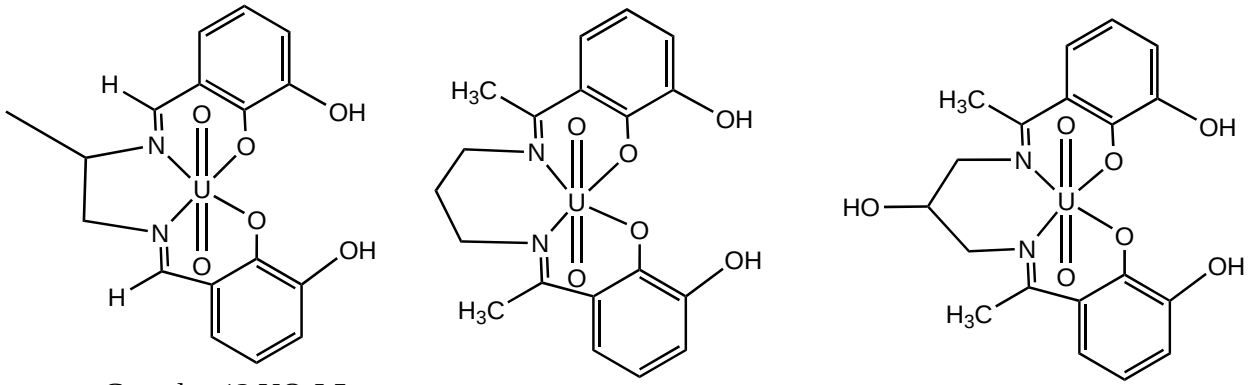
Figure 79. Chemical Structures of Cu(II) Complexes (9-11)

5.2.3 Synthesis of The Uranium Complexes [UO_2L] (12-14)

Caution: Uranium is a radioactive and toxic element, uranium-containing samples must be handled with suitable care and protection, together with a plan for safe waste disposal.

A Solution of UO_2L (5 mmol) in methanol (20 mL) was added dropwise to methanolic solution of H_4L (5,7) (5 mmol, 10 mL) with constant stirring. The solution reaction mixture was

stirred for 5h at RT and left for evaporation. After a few days, orange product of "metalloligands" [UO_2L] complexes (12-14) were seperated.[3]

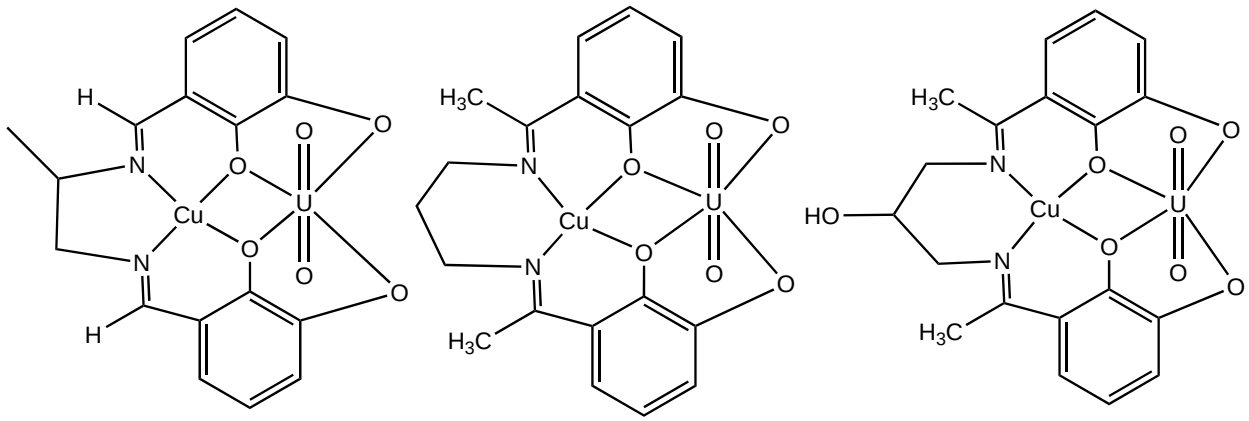


Complex 12 UO_2L5 Complex 13 UO_2L6 Complex 14 UO_2L7

Figure 80. Chemical Structures of [UO_2L] Complexes (12-14)

5.2.4 Synthesis of The Heterobimitallic Complexes [(CuL)UO_2] (15-17)

The metalloligands [CuL] (9-11) (0.04 mmol) were dissolved in acetonitrile (5 mL) and a solution of $UO_2(acac)_2$ (0.04 mmol in 5 mL of acetonitrile) was added, stirred for 5 min and then allowed to stand overnight at room temperature when complexes (15-17) deposited at the bottom of the vessel. These compounds were isolated by filtration and redissolved in 5 mL of acetone by warming, and the solution was kept in a long tube for slow evaporation.[66]



Complex 15 [CuL5UO_2] Complex16 [CuL6UO_2] Complex 17 [CuL7UO_2]

Figure 81. Chemical Structures of [(CuL)UO_2] Complexes

5.3 Results and Discussion

5.3.1 ^{1}H-NMR Spectra

The ^{1}H NMR chemical shifts of the organic ligands and their complexes shown in table (12) were recorded in DMSO-d_6 or Chloroform-d. In the ^{1}HNMR spectra of ligands, peaks appeared at (12.20,12.30), 10.61 and 10.55 ppm were assigned to the protons of phenolic group in ligands and (8.60,8,73), 9.04 and 9.02 ppm were assigned to the protons of the second phenolic group respectively. In the ^{1}H NMR spectra of ligands exhibit sharp multiple signals between 6.50 to 7.27 ppm due to Ar-H as shown in Figure (82-84)

The NMR spectra of the copper (II) complexes were recorded in Figures (85, 86, and 87). The phenolic OH signals observed in the spectrum of the ligands are not seen in the spectrum of the Cu (II) complexes indicating the participation of the phenolic OH group in chelation with proton displacement. However, the peaks appeared at (7.95-8.00), 8.04 and 6.51 ppm were assigned to the protons of the second phenolic group in ligands.

The NMR spectra of the uranium complexes were recorded in Figures (88, 89, and 90). The phenolic OH signals observed in the spectrum of the ligands are not seen in the spectrum of the uranium complexes indicating the participation of the phenolic OH group in chelation with proton displacement. However, the peaks appeared at (7.65,7.71), 7.78 and 7.62 ppm were assigned to the protons of the second phenolic group in ligands.

The NMR spectra of [(CuL)UO_2] complexes were recorded in Figures (91, 92, and 93) showed the absence of the signal assigned to the proton of the first and second phenolic group in the ligands which indicated that deprotonation of the phenolic group occurred on complexation and that the phenolic oxygens take part in the copper and uranium to form heterobimetallic complexes. In the spectra of [(CuL)UO_2] complexes the protons of the Ar-H, the -CH-OH are

shifted downfield compared to that of the free ligand and Cu (II) complexes as a result of chelation of azomethine group, the first and the second phenolic group to copper and uranium ions, indicate that, the coordination of the ligand with the metal ions involves the nitrogen atom of the ligands. Furthermore, the number of protons calculated from the integration curves, and those obtained from the values of the mass spectra.

Table 12. ^{1}H NMR of The Schiff Base Ligands and Its Complexes

Compound	-OH	-OH	Ar-H	H(23,23`)	Other
L5	12.20,12.30	8.60,8.73	6.66-6.83	3.40,3.82	-CH=N- 8.10,8.30
CuL5	-	7.95,8.00	7.33-7.74	3.53,3.73	8.43,8.51
UO_2L5	-	7.65,7.71	6.79-7.07	2.77-2.94	8.54,8.62
[(CuL1)UO_2]	-	-	6.86-7.23	3.10,3.17	8.44,8.50
L6	10.61	9.04	6.82-7.08	3.43	H(25) 2.02
CuL6	-	8.04	6.84-6.98	3.11,3.16	1.91
UO_2L6	-	7.78	6.83-7.10	3.18,3.26	2.07
[(CuL2)UO_2]	-	-	7.01-7.73	4.02	2.3
L7	10.55	9.02	6.50-7.27	3.68,3.90	H(25) 3.93
CuL7	-	6.51	7.02-7.46	3.60,3.91	4.15
UO_2L7	-	7.62	7.10-7.37	3.23,3.43	4.07
[(CuL3)UO_2]	-	-	7.21-7.98	3.26,3.55	4.12

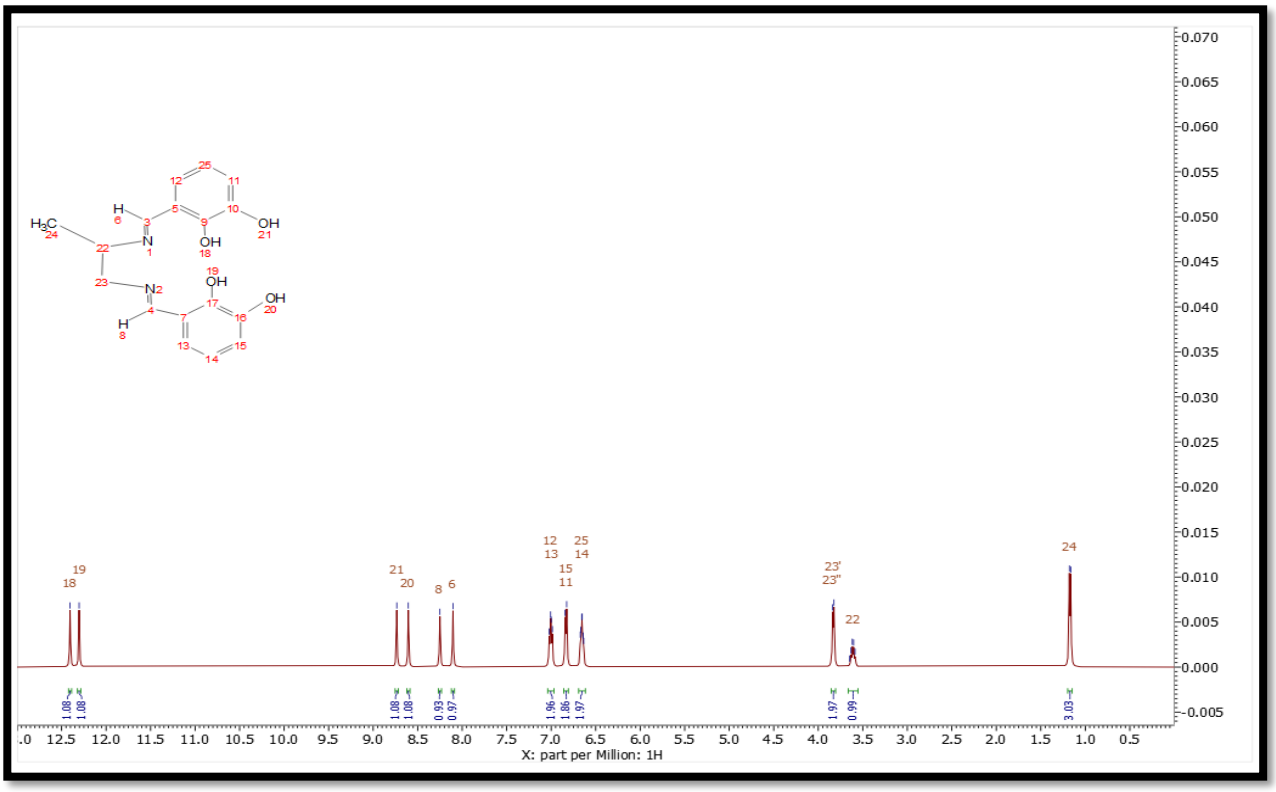


Figure 82. ^{1}H-NMR for L5

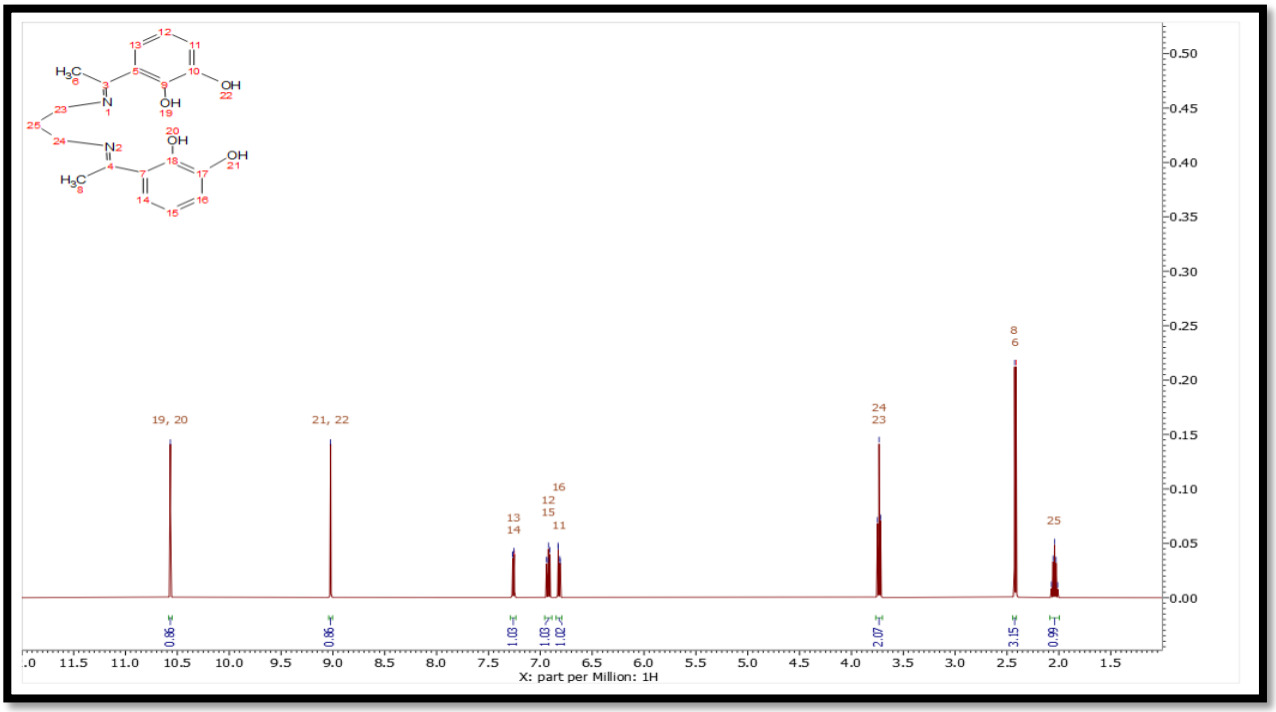


Figure 83. ^{1}H-NMR for L6

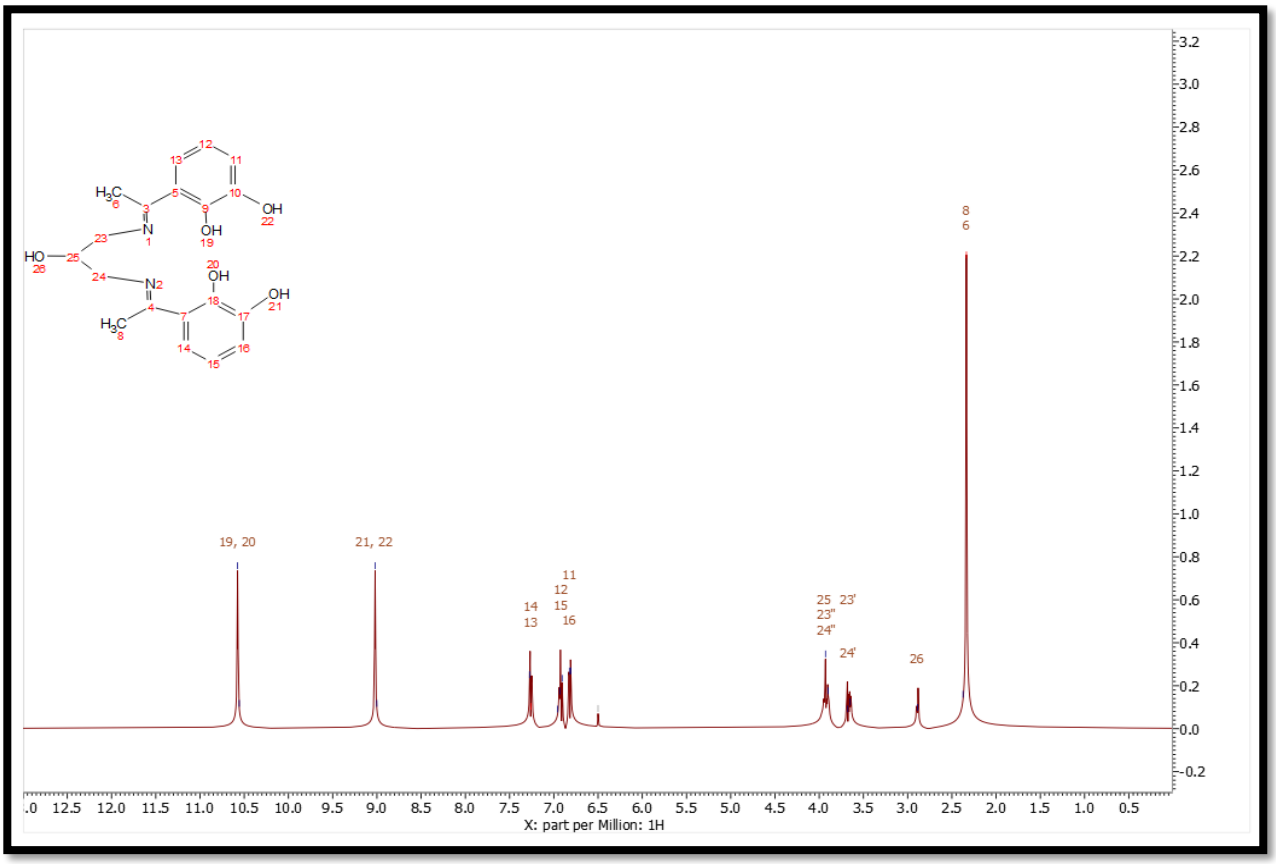


Figure 84. ^{1}H-NMR for L7

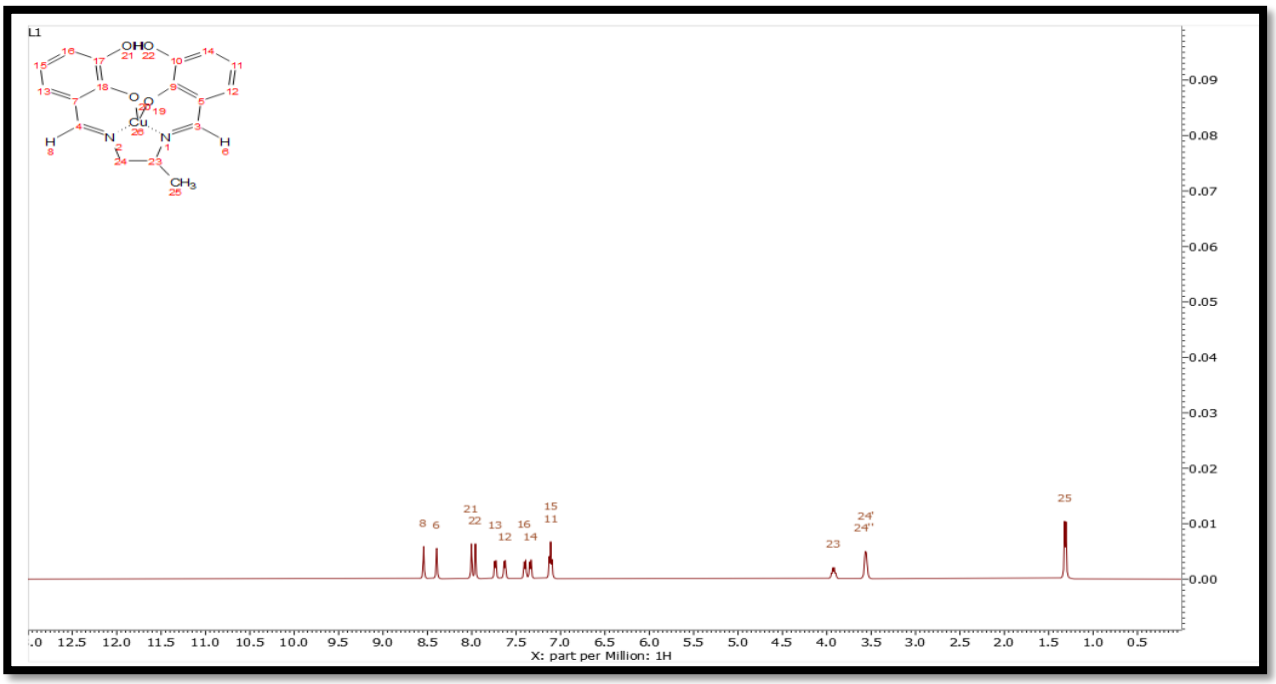


Figure 85. ^{1}H-NMR for Complex 9 (CuL5)

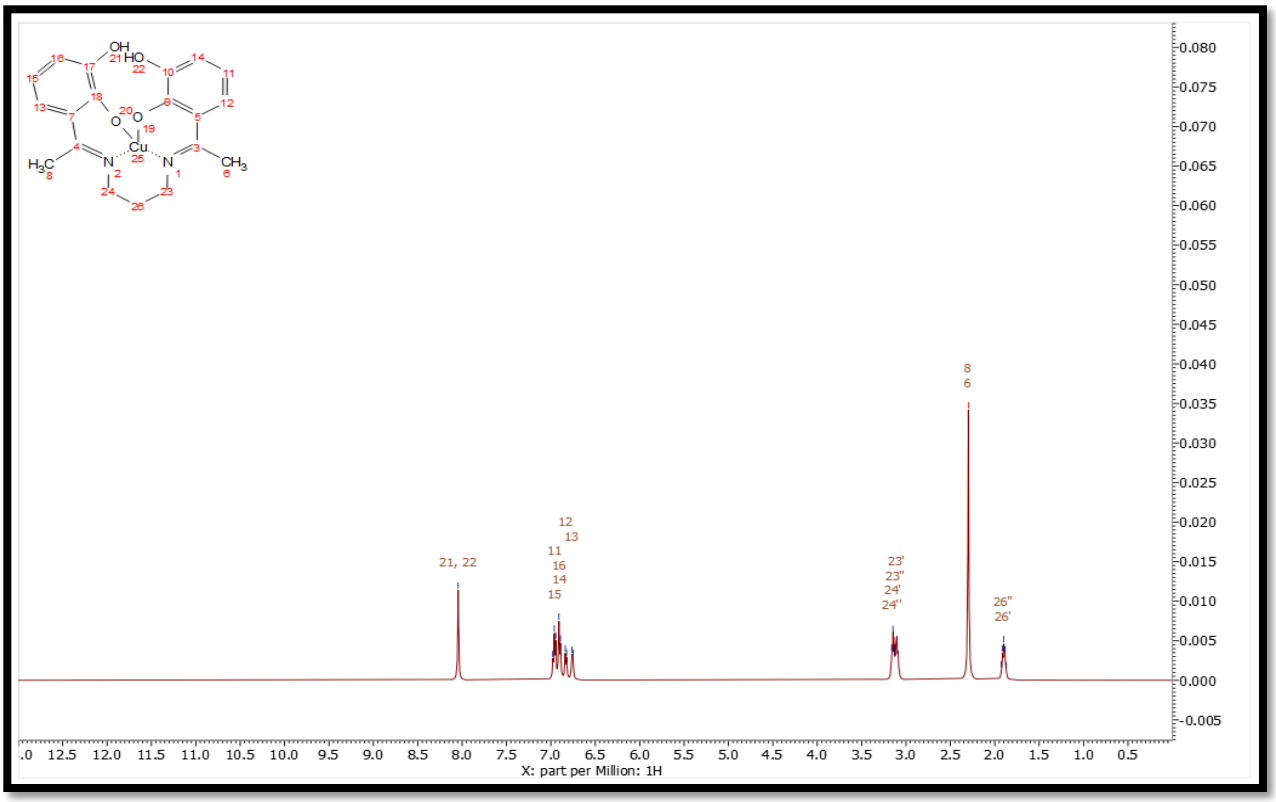


Figure 86. ^{1}H-NMR for Complex 10 (CuL6)

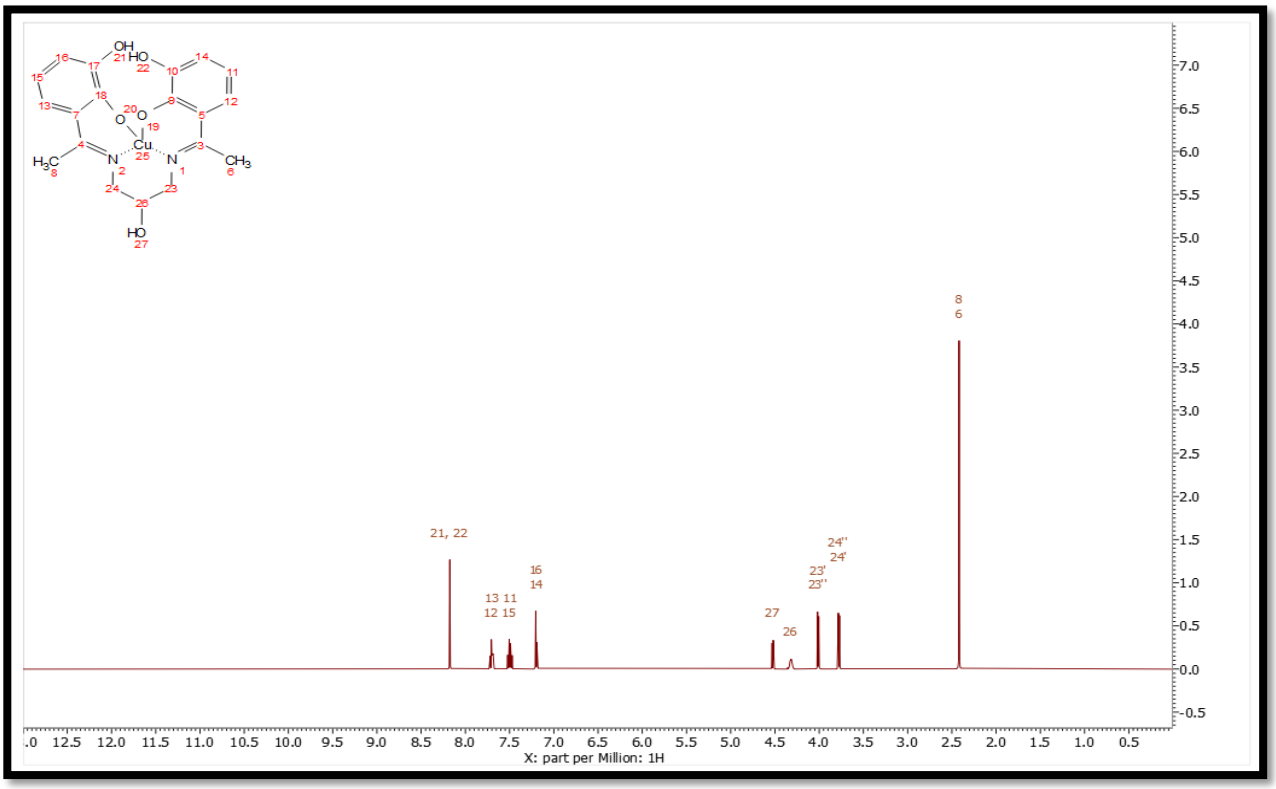


Figure 87. ^{1}H-NMR for Complex 11 (CuL7)

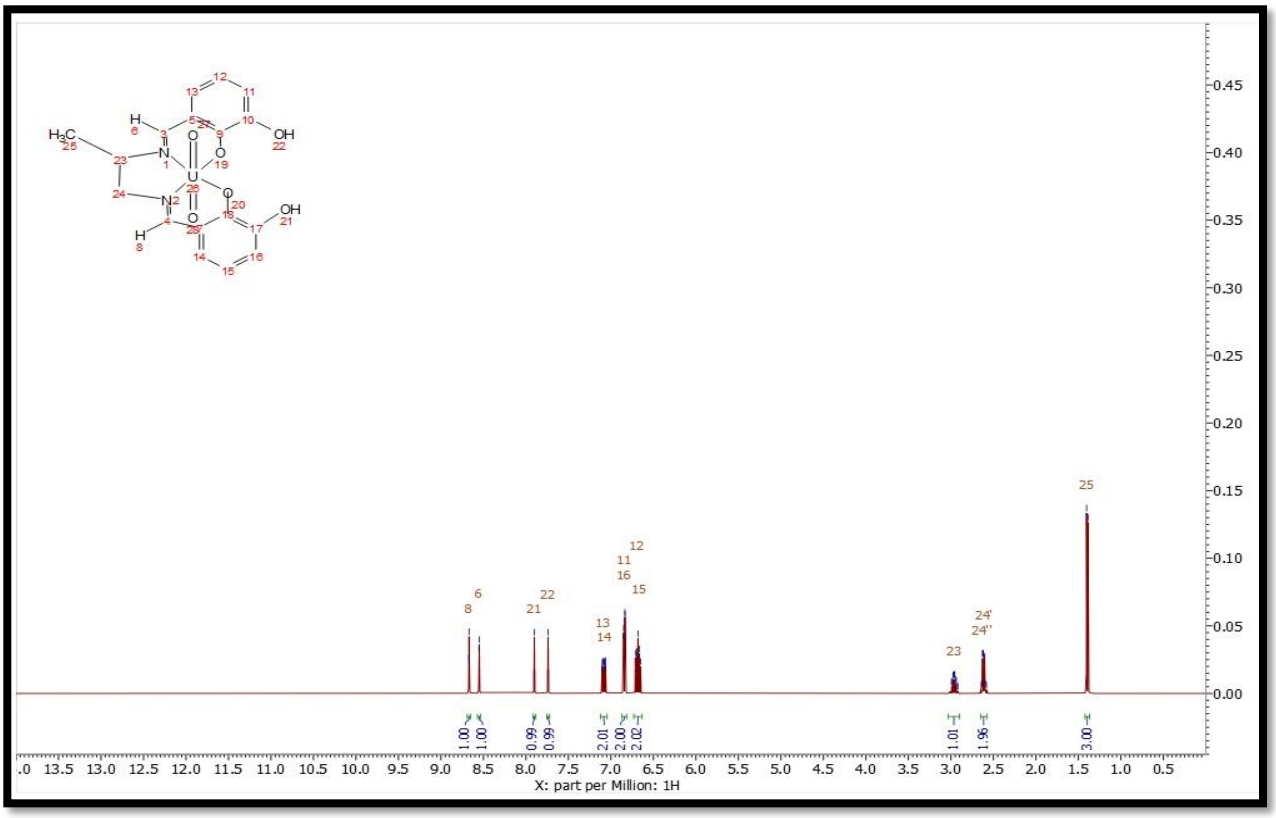


Figure 88. ^{1}H-NMR for Complex 12 [UO_2L5]

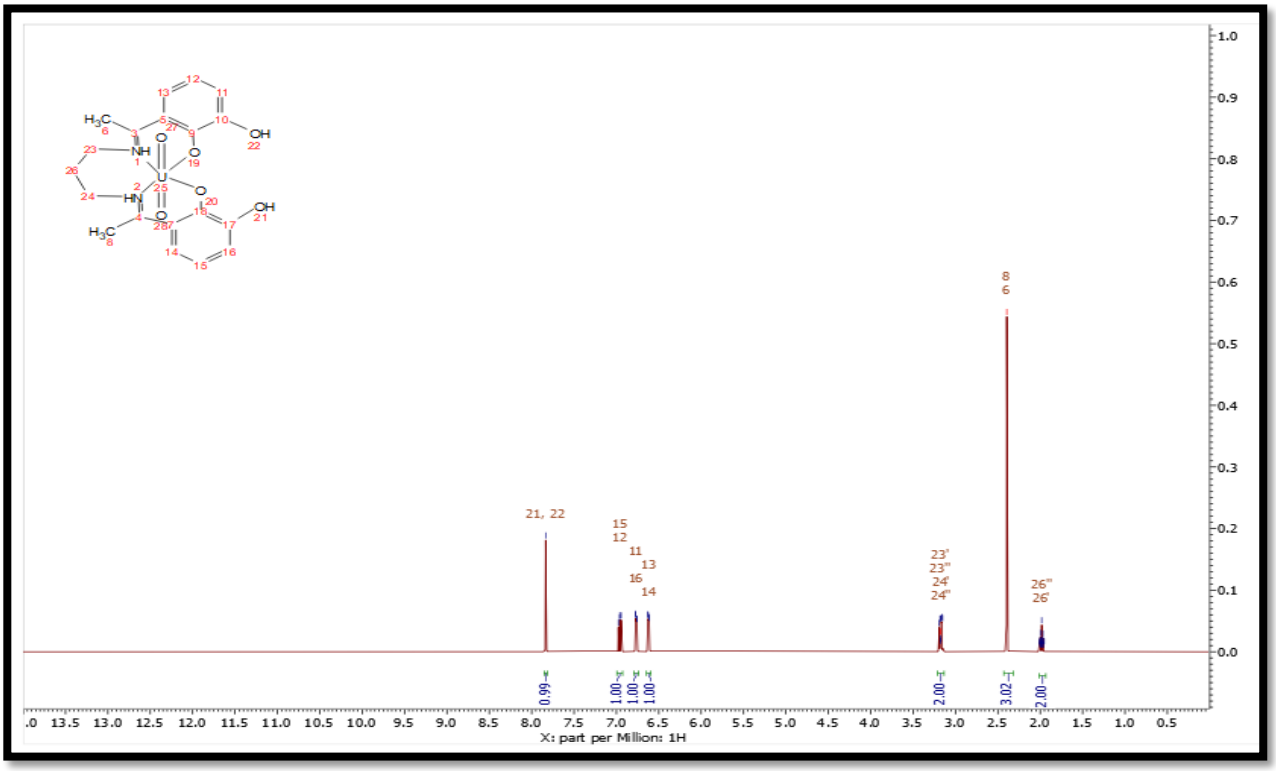


Figure 89. ^{1}H-NMR for Complex 13 [UO_2L6]

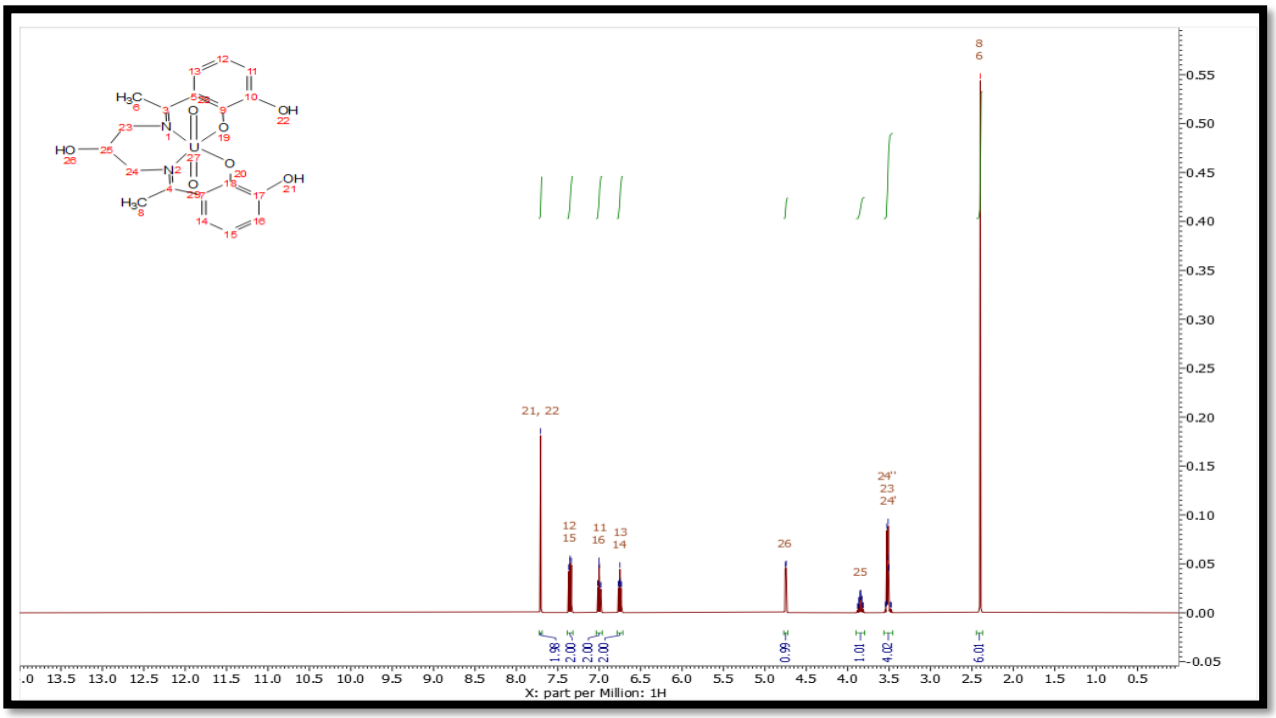


Figure 90. ^{1}H-NMR for Complex 14 [UO_2L7]

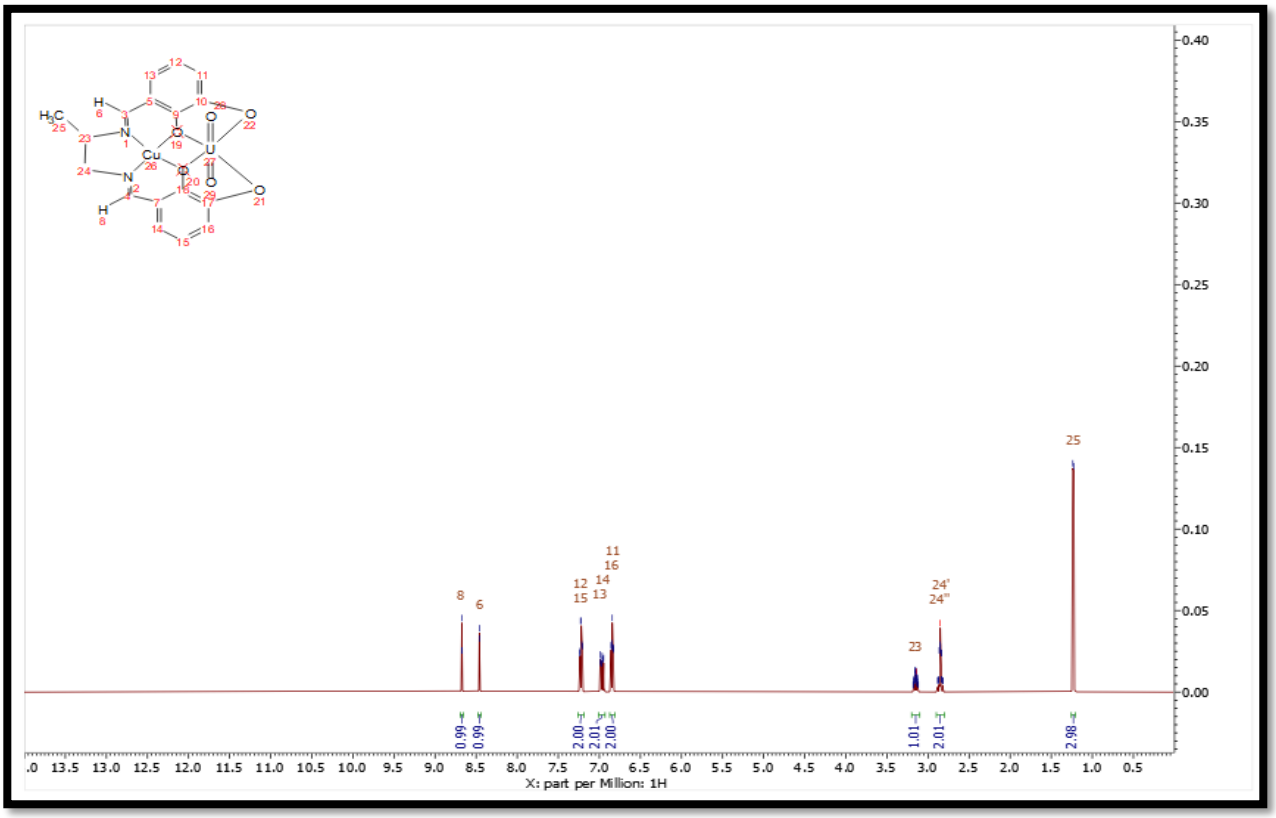


Figure 91. ^{1}H-NMR for Complex 15 [(CuL5)UO_2]

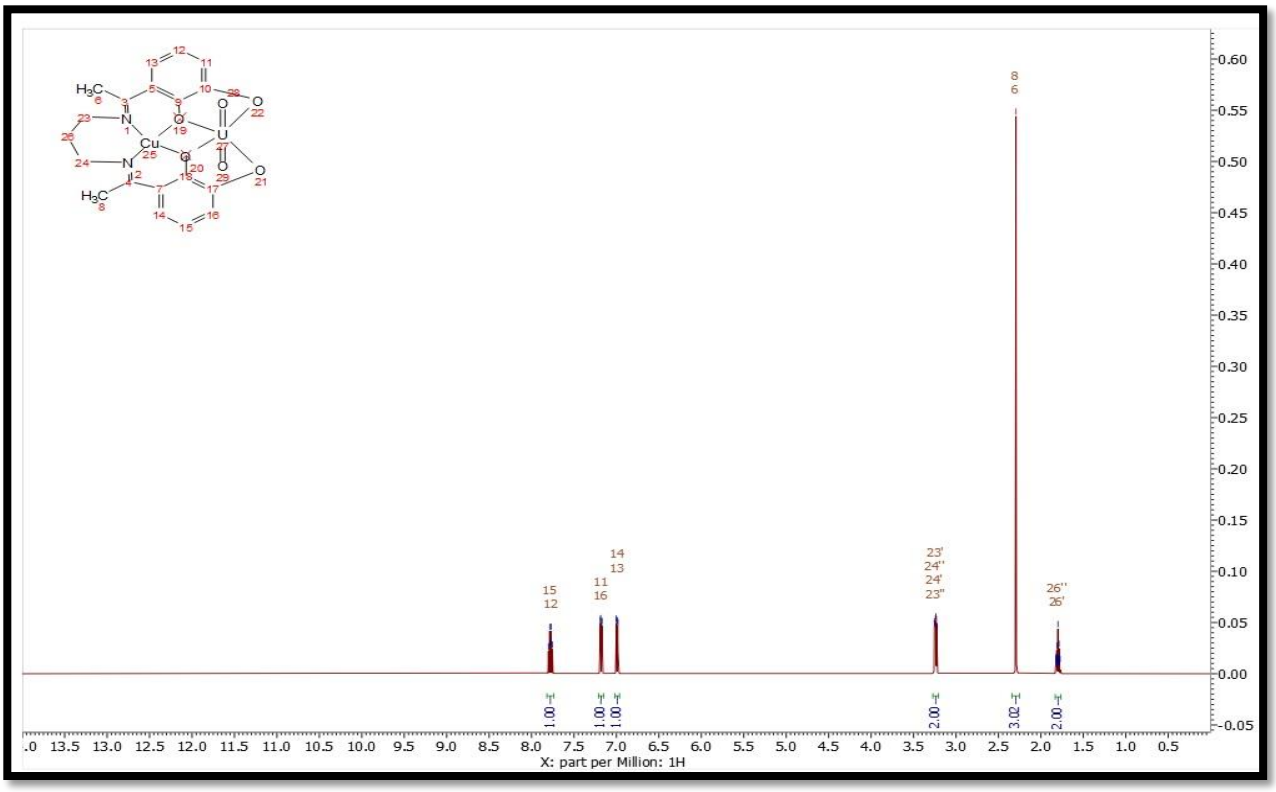


Figure 92. ^{1}H-NMR for Complex 16 [(CuL6)UO_2]

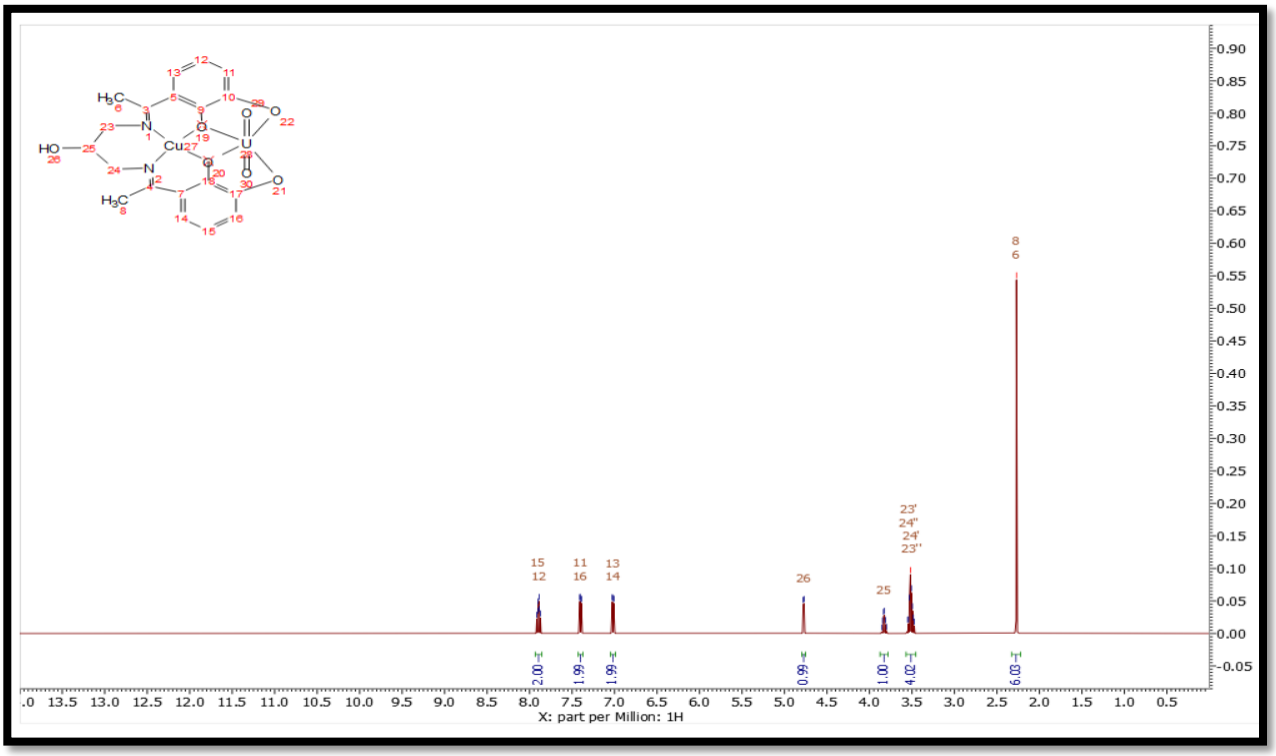


Figure 93. ^{1}H-NMR for Complex 17 [(CuL7)UO_2]

5.3.2 Mass Spectroscopy and Mass Spectrometer

The mass spectra of the copper complexes, uranium complexes and heterobimetallic of [(CuL)UO_2] complexes were recorded and compared for their stoichiometric composition. The mass spectra of mono-complexes in Figures (94-99) have been obtained operating in positive ion mode. The molecular ions were detected the base and main peaks of the spectra at *m*/*z* 376.048, 404.079 and 420.074 respectively for three Cu(II) complexes which correspond to the protonated molecular ion $[M+H]^+$ and they could be generated either by the ionization conditions or by ion-molecule reactions inside the ion trap analyzer. The mass spectra of the metal complexes showed molecular ion peaks, which were in good agreement with the expected values. The main peaks for the [UO_2L] complexes were detected, at 583.158, 611.184, and 627.185 (m/z) were ascribable to mono-uranium complexes. respectively for three uranium complexes, that correspond to the protonated molecular ion $[M+H]^+$.

Moreover, the mass spectra for complexes Cu-U were shown in Figures (99, 100, and 101). The protonated molecular ions $[M_1\text{-}M_2+H]^+$ were detected at *m*/*z* values centered at 644.066, 672.104 and 688.092 m/z respectively: the isotopic cluster is in agreement with the theoretical one. The fragmentation pattern of [Cu-U] complexes displayed important peaks at m/z 342.042, 368.058 and 386.068 m/z respectively, because of loss of $[H_3O_4U]^+$ from the parent complexes 15, 16, 17 respectively. This feature indicates the formation of the complexes and the comparison between the main peaks of synthesized complexes have been collected in Table 13.

The results of mass spectrometry are consistent with the proposed formulas for these compounds as the peaks observed in these spectra correspond to fragments resulting from the expected fragmentations of the compounds.

Table 13. The Main Peaks of The Synthesized Mono and Heterobimetallic Complexes

Ligands	$[CuL+H]^+$	$[UO_2L+H]^+$	$[(CuL)UO_2+H]^+$		
L5	376.048	583.158	$[C_{17}H_{14}CuN_2O_6U+H]^+$ 644.072	$[H_3O_4U]^+$ 305.053	$[C_{17}H_{15}CuN_2O_2]^+$ 342.042
L6	404.079	611.184	$[C_{19}H_{18}CuN_2O_6U+H]^+$ 672.104	$[H_3O_4U]^+$ 305.053	$[C_{19}H_{17}CuN_2O2]^+$ (368.058)
L7	420.074	627.185	$[C_{19}H_{18}CuN_2O_7U+H]^+$ 688.099	$[H_3O_4U]^+$ 305.053	$[C_{19}H_{19}CuN_2O3]^+$ (386.068)

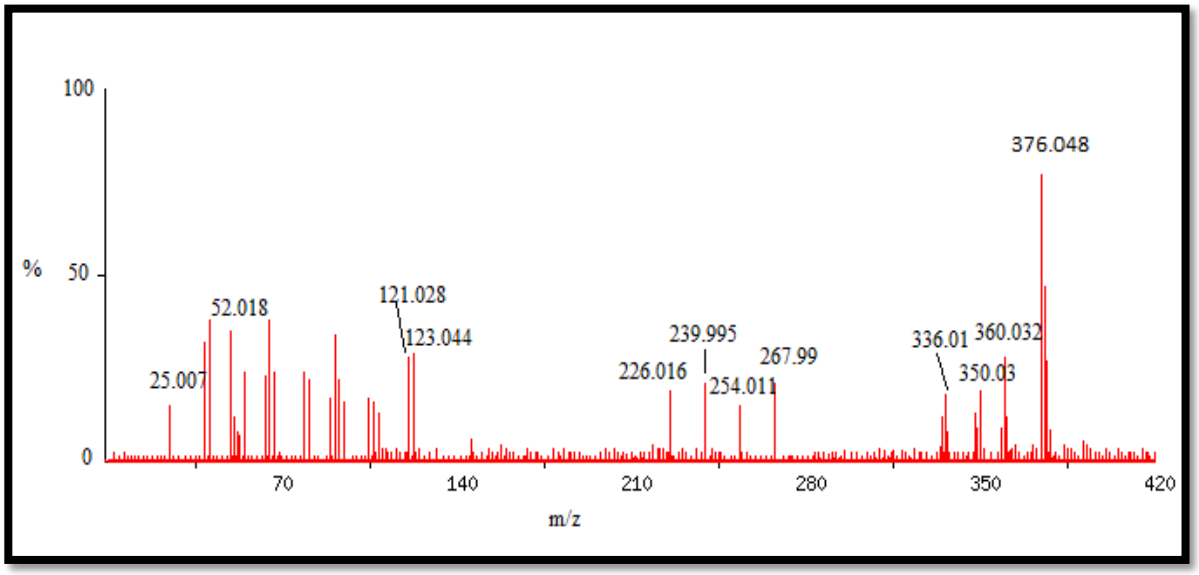


Figure 94. Mass Spectrum for Complex 9 (CuL5)

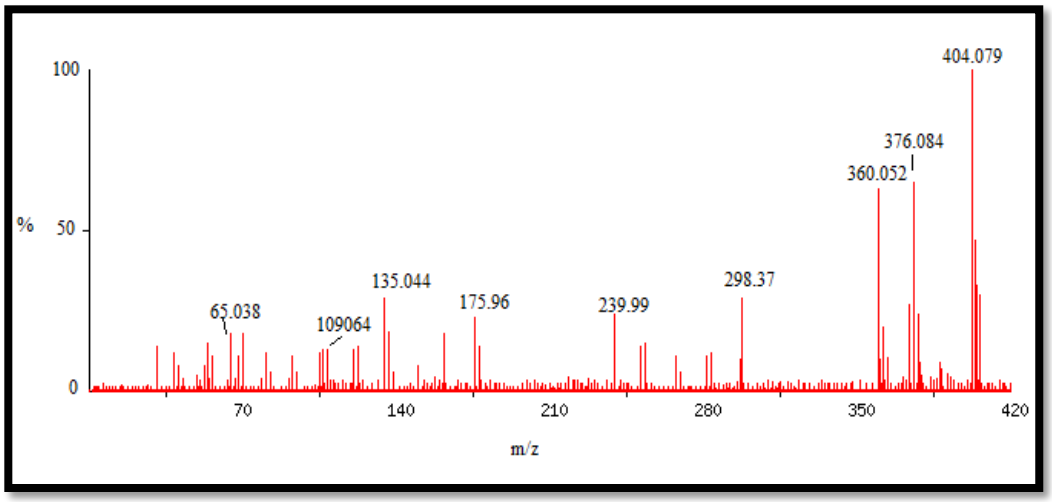


Figure 95. Mass Spectrum for Complex 10 (CuL6)

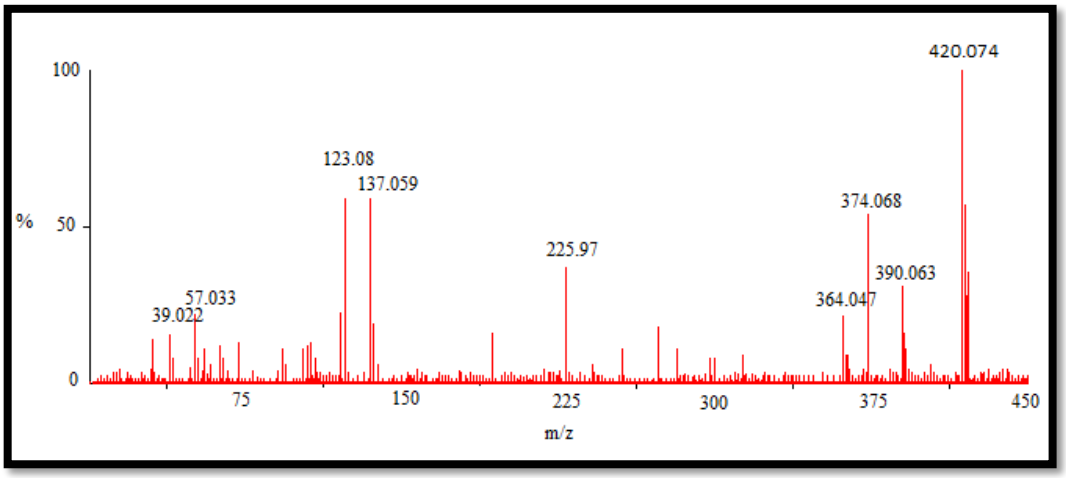


Figure 96. Mass Spectrum for Complex 11 (CuL7)

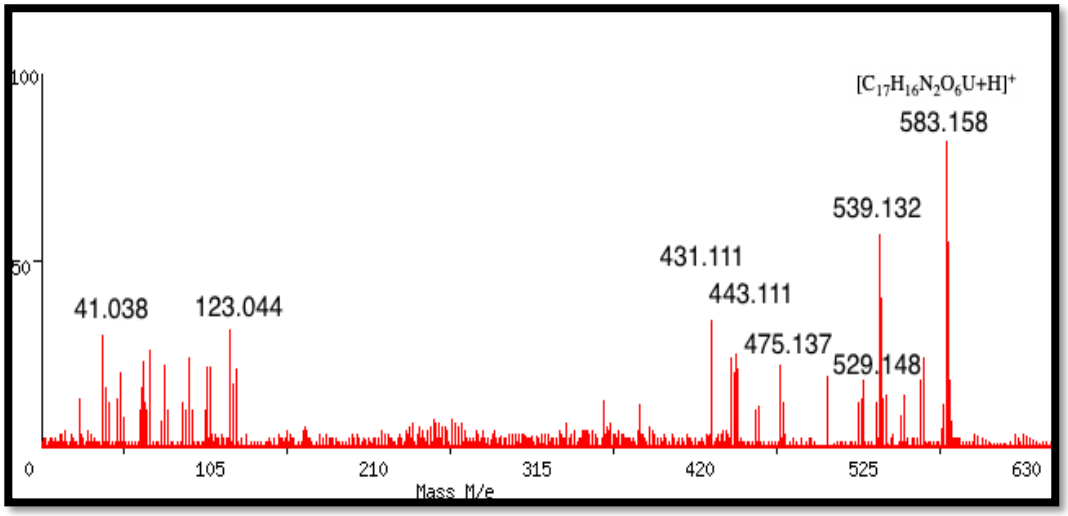


Figure 97. Mass Spectrum for Complex 12 [UO_2L5]

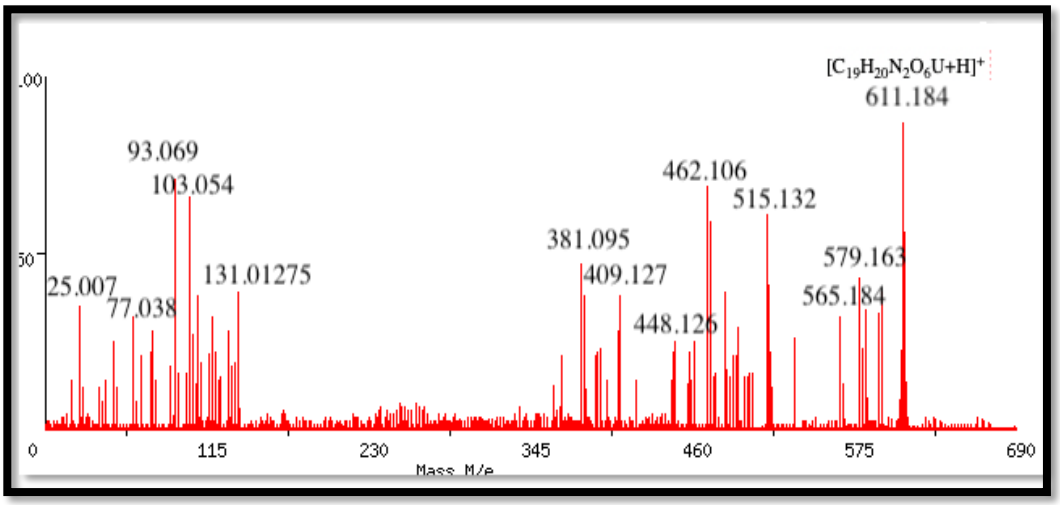


Figure 98. Mass Spectrum for Complex 13 [UO_2L6]

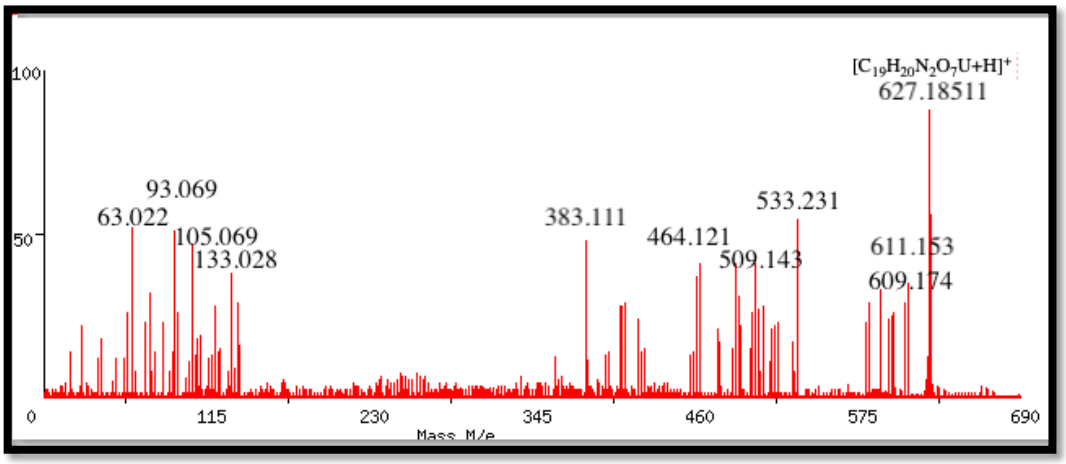


Figure 99. Mass Spectrum for Complex 14 [UO_2L7]

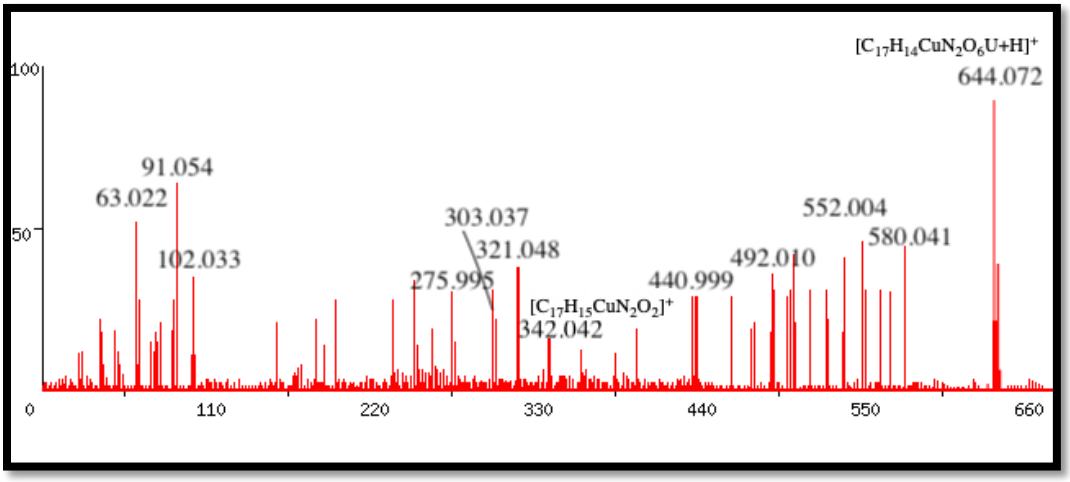


Figure 100. Mass Spectrum for Complex 15 [(CuL5)UO_2]

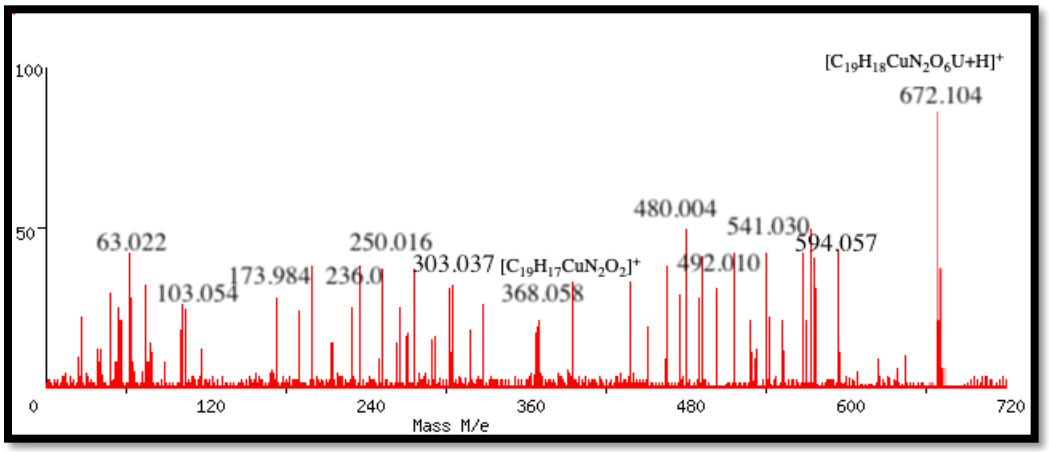


Figure 101. Mass Spectrum for Complex 16 [(CuL6)UO_2]

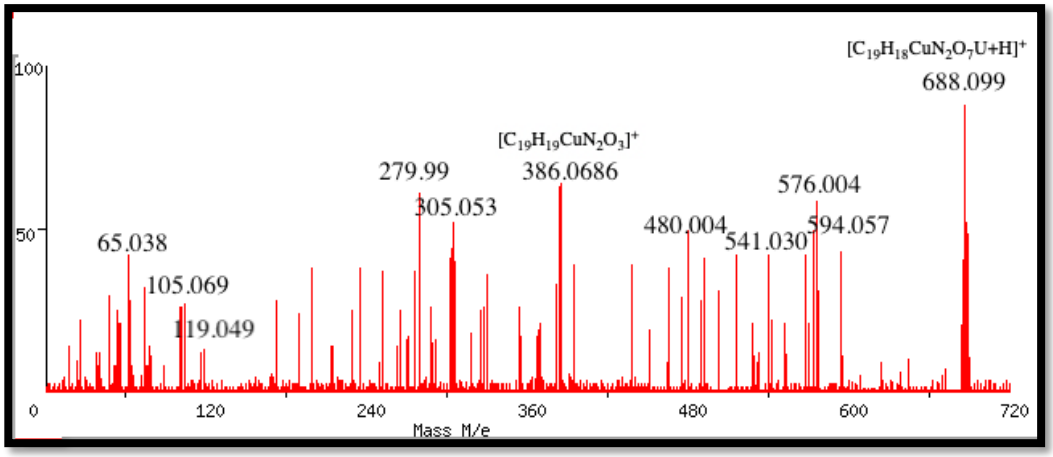


Figure 102. Mass Spectrum for Complex 17[(CuL7)UO_2]

5.4 Conclusion

The use of an hexadentate bicompartmental Schiff base ligand permitted the synthesis of the first complexes, in which a Uranium (IV) ion is located next to it. These are unique molecular compounds exhibiting a linear arrangement of an f element and d transition metals. Their central coordination sites were composed of an imine-based N_2O_2 entity coordinating Cu (II) ions. The subsequent prearrangement of the ligand into a Ω-shape generated a second recognition site, O_2O_2, composed of two phenoxy groups are able to coordinate to U(IV) ions. Our copper based metalloligands (CuL), which demonstrated interesting, chelated ligands for the uptake of large

cations, led us to explore their structural differences upon coordination to group 2 metal ions. In this research, we report the synthesis and the structural characterization of nine new mixed metal complexes corresponding to the coordination of the uranium by (CuL). According to the phenolic OH signals observed in the spectra of the ligands are not seen in the spectra of the Cu(II) and UO_2L complexes indicating the participation of the phenolic OH group in chelation with proton displacement. Moreover, ^1H NMR spectra of heterobimetallic complexes indicate to coordinate the metal center ions Cu(II) and U(IV) with hexadentate ligands due to the phenolic OH signals observed in the spectra of the ligands are not seen in the spectra of the Cu-UO_2L complexes indicating the participation of the phenolic OH group in coordination with proton displacement.

The Mass spectra discussed above, deduced that the uranium ions in the copper-uranium heterobimetallic complexes bind to the outer $O_2O`_2$ sites of the ligands and are coordinated to the oxygen atoms of both the phenolic groups. As previously reported, U(IV) ions prefer to bind to outer O_2O_2 coordinating sites of ligands which possess in addition inner N_2O_2 sites.

5.5 References

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CHAPTER 6

FUTURE WORK

In the present study of chapter 2 and 3, designing, synthesizing, and fully characterizing the Platinum complexes are addressed. Cisplatin, arguably the most famous transition metal anticancer drug, was first described in 1845, but it was not until 1965 that by happenstance the cell growth inhibitory properties were discovered. Even now, almost 40 years after its FDA approval, questions are still swirling around its utilization as a chemotherapeutic agent due to the rise of cisplatin-resistant cancers. Given the challenges faced with this famous and widely prescribed drug, it seems the real question remaining is: will we ever fully understand exactly what pathways in the interconnected signaling web are the most important to effect to obtain only our desired result? Looking forward from an evolutionary perspective, what can we as researchers learn from the evolution of cisplatin resistance, and how can we apply that knowledge to platinum-based chemotherapeutics? With near-infinite design possibilities of transition metal complexes and rapidly advancing scientific methods, we may never fully understand the complete mechanisms of many of the drugs, but that should not stop one from investigating in detail. As targeted therapies involving small interfering technology move towards clinical application, infinite opportunities to target specific genes may offer some complementary way forward on a patient-by-patient basis for these drugs. Considering the emergence of these new targeted treatment options, the days of serendipitous discoveries are behind us, but like all hypothesis-driven science, in some cases a bit of serendipity is always much appreciated.

For proper insight into the structure-activity relationship of the compounds to be gained, further studies into the metal-DNA interaction, cellular uptake potential, DNA binding properties,

oxidative cleavage studies should be carried out; in vitro and in vivo anticancer studies should be carried out on other carcinoma cell lines. The lipophilicity which describes the ability of compounds to permeate cells would also be investigated to establish the ability of these compounds to enter cells. The compounds would be tested against different cell lines such as breast cancer and ovarian cancer cell lines.

The possible side effects of synthesized complexes should be tested on normal living cells as well. In vitro activity of the compounds by the hydroxyl radical scavenging, NO, and reducing power methods should be examined. Efforts will be made to implement further work to establish additional experiments will evaluate other important drug properties, including the lipophilicity of the complexes and DNA interactions. Further attempts at growing crystals proved to be fruitless. The platinum(II) and (IV) complexes were obtained as very small crystals, but they were too small for X-ray crystallographic analysis. Using different solvent combinations as well as different growing techniques may prove more rewarding for complete structure determination of the water-soluble platinum complexes.

In this dissertation, chapters 4 and chapter 5 have addressed the synthesis and characterization of several copper complexes, uranium complexes, and Cu-U complexes. In the future, further work needs to be done to obtain single crystals of the Schiff bases and their metal complexes for structural studies. There is a need to obtain single crystals of the Schiff bases and their metal complexes for structural studies.

Metals contribute important roles in a biological system. It is recognized that metals are highly linked in cellular and subcellular functions. With the application of novel and experienced tools to study biological and biochemical systems, the true role of inorganic salts in the biological systems can be studied. Schiff base metal complexes show a broad range of biological activity.

The activity of Schiff base ligand is usually increased by complexation with the metal ion. The copper complexes of Schiff bases have striking properties such as antibacterial, antifungal, antiviral, anti-inflammatory, anti-tumor and cytotoxic activities, plant development controller, enzymatic activity, and applications in pharmaceutical fields. In future work, our main focus will be on research undertaken for biological activity study of Cu(II) metal complexes containing Schiff bases. Moreover, uranium-nitrogen multiple bonds have been synthesized in one ligand framework. The electronic structures of these compounds should be investigated using computational and experimental methods, and reactivity explored in some cases.

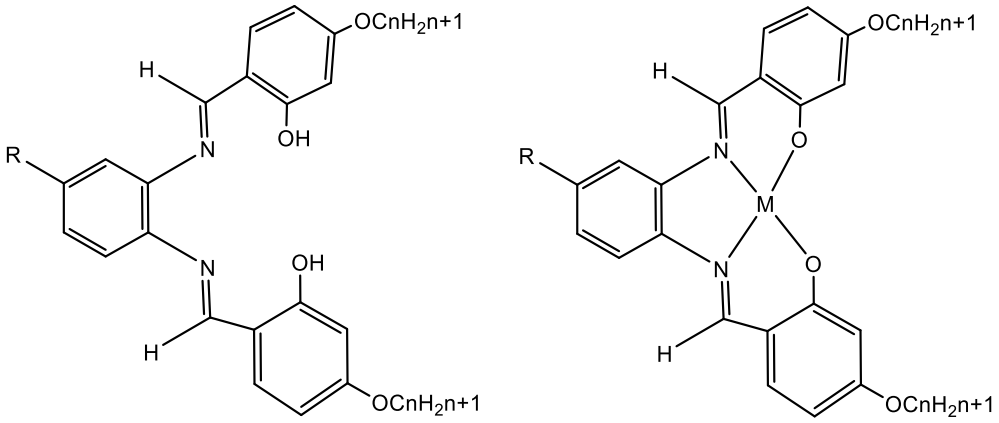
The present study describes the synthesis of tetradentate, and hexadentate Schiff base complexes with moderate to high yield products. Hence, the preparation methodology will be useful for the synthesis of additional Schiff bases with different substituents on the aromatic aldehydes and their metal complexes followed by various biological activities exploration. The outcomes from this research reveal that most of the complexes could lead for the development of novel antibacterial, antioxidant, and/ or cell antiproliferative agents.

Attempts to prepare heterobimetallic complexes in which binuclear of copper and uranium magnetic ions are associated with utilizing the Schiff bases H4L derived from 2,3-dihydroxysalicylaldehyde or 2-hydroxy-3-methoxysalycylaldehyde. The hexadentate Schiff base ligand (L) is useful for the synthesis of novel trinuclear complexes. These studies on the synthesis, structure, and magnetic behavior of these complexes of CuL-UO_2 should be undertaken in future work. Moreover, Absorption and fluorescence quenching experiments (steady-state and time-resolved) indicate the formation of 1:1 ground-state charge transfer copper(II)−uranium(VI) complexes in solution and should be studied.

Recently, there has been growing concern over the environmental impact of chemicals; thus, that cleaner green reaction conditions in synthetic processes have been advocated to maintain environmental awareness, requiring us to prevent the generation of waste, avoid the use of auxiliary substances (e.g., organic solvents, additional reagents), and minimize the energy requirement. The use of water as the reaction medium offers several advantages as (a) it is cheap, non-toxic, and safe to use[1,2], (b) its unique physical and chemical properties often increase the reactivity or selectivity, which sometimes is unattainable in organic solvents[3], and (c) it eliminates the additional efforts required to make the substrates/reagents dry before use and thus reduces/eliminates the consumption of drying agents, energy, and time. Schiff bases are typically formed by the condensation of a primary amine and an aldehyde which involves the use of organic solvents such as methanol, tetrahydrofuran (THF), and 1,2-dichloroethane (DCE) [4]. In future projects, microwave-assisted preparation of a series of Schiff bases without solvent [5] should be used instead of using the classic preparation method.

Interest in metallomesogens has steadily grown in the recent past owing to the immense possibility of combining optical, electronic, and magnetic characteristics of transition metal complexes with anisotropic fluids.[6–11] Salen-based metallomesogens are considered as one of the major thrust areas of liquid crystals.[12–16] The transition metal-salen complexes have been regarded as promising materials that have been extensively studied owing to their ability to catalyze an extremely broad range of chemical transformations.[17–19] The synthesis of liquid crystal (LC) based on metal coordination with suitably designed structure provides a useful route for obtaining new multifunctional soft material combining anisotropic fluidity with those properties imparted by the metal component, such as optical, electronic, and magnetic properties.[20] The coordination geometry of the complex determines the overall molecular shape and in turn the mesomorphic

behavior.[21,22] In future work, we are planning to synthesize several 'salen'-type N_2O_2 donor Schiff base ligands containing 4-substituted long alkoxy chains on the side aromatic rings as shown in figure 103. The free ligands are devoid of mesomorphism; however, on coordination with the metal center, induction of mesomorphic character occurs due to conformational change in the ligands.



R= Cl, CH_3 and OH
n= 12 and 15
M= Cu(II) and U(VI)

Figure 103. Chemical Structures of Ligands Containing 4-substitute Alkoxy Chain and Metal Complex

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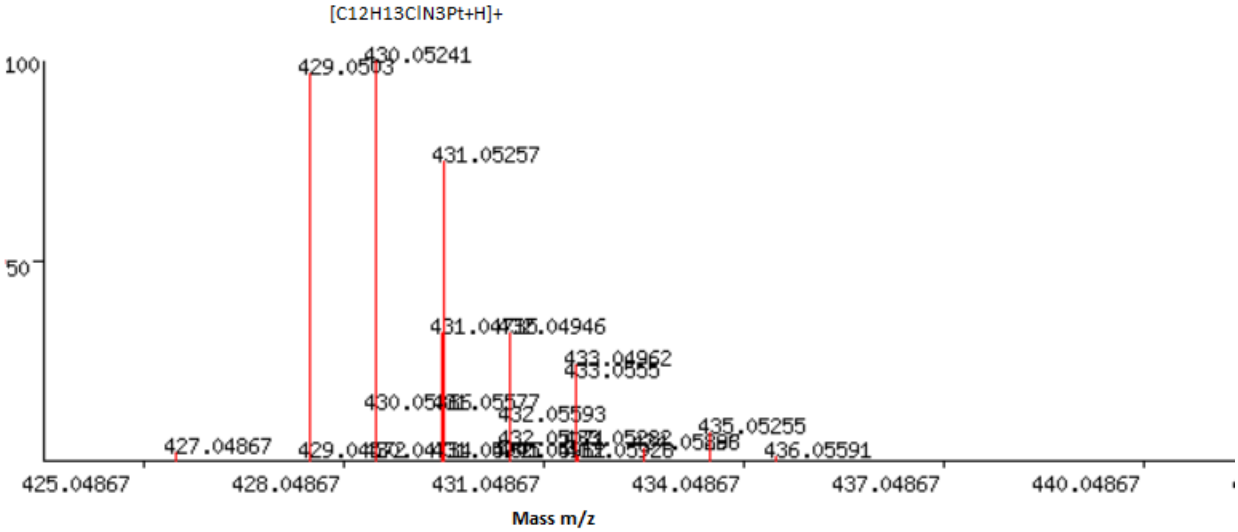
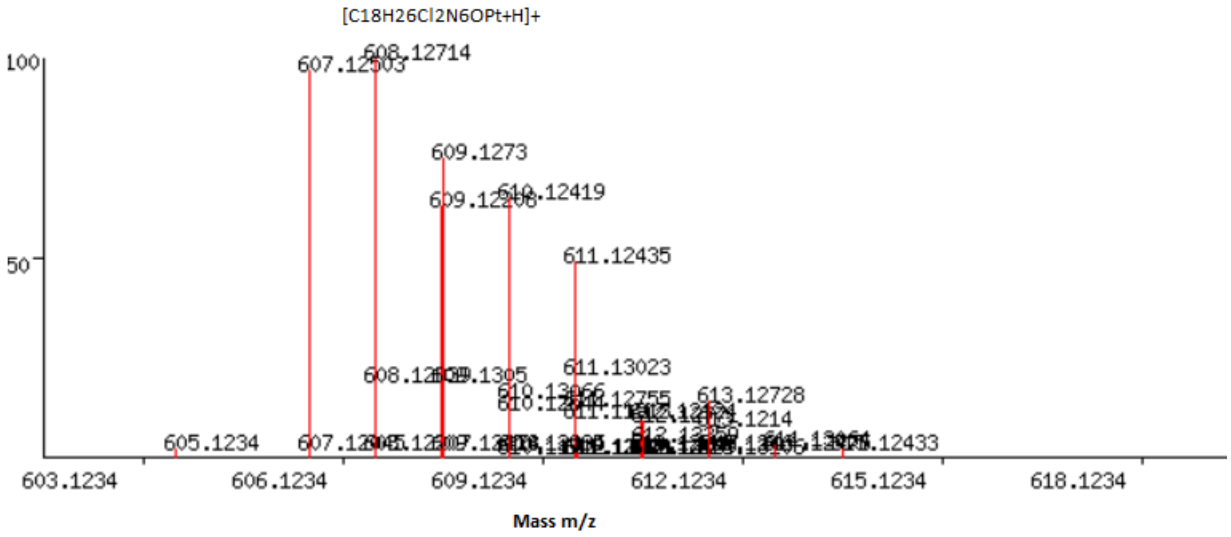
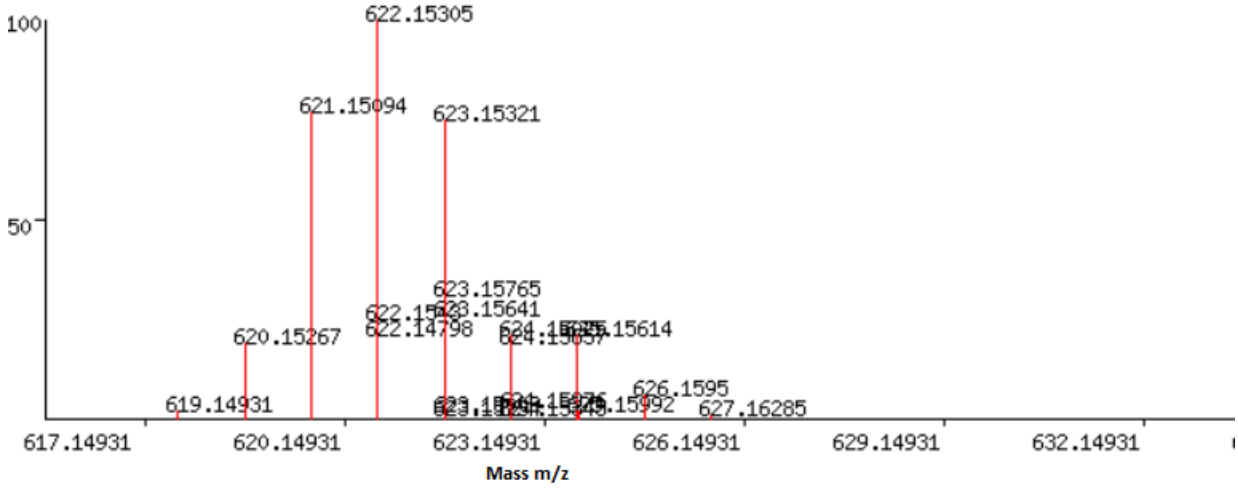
APPENDIX

A. Figures for Mass Spectrometry of Complexes and Theoretical Calculations

Chapter 2







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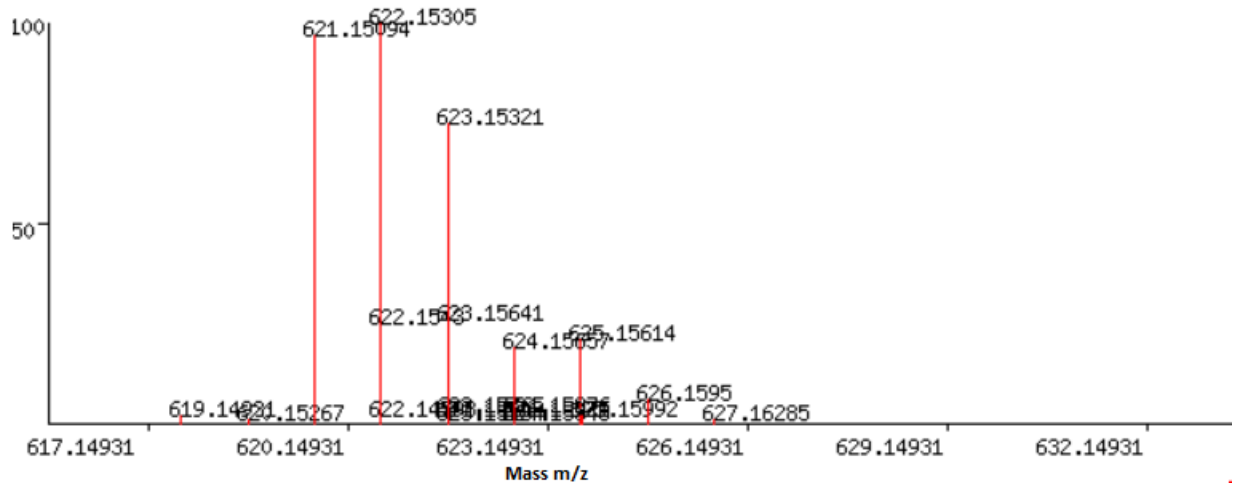

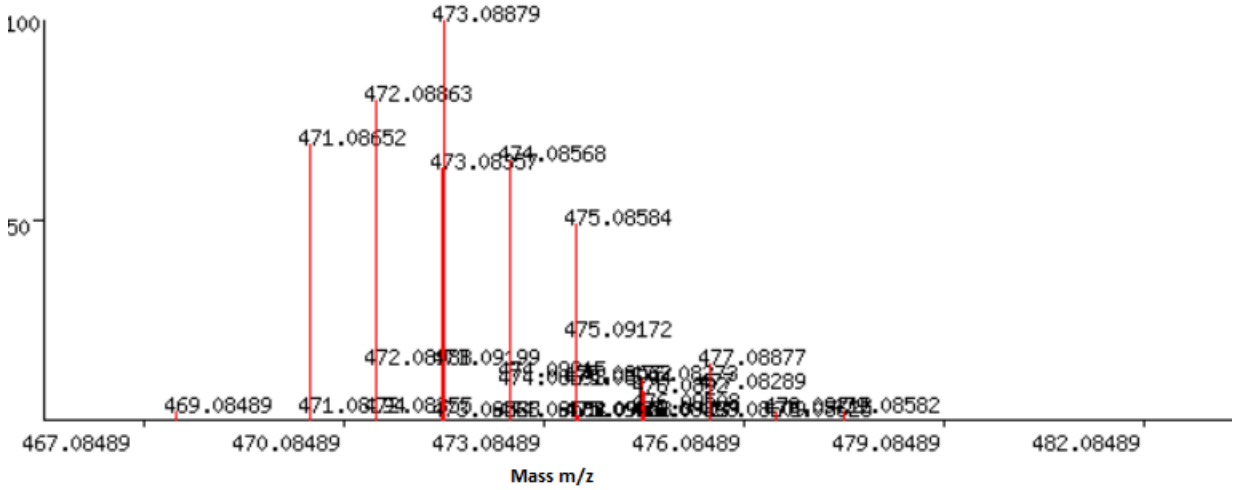

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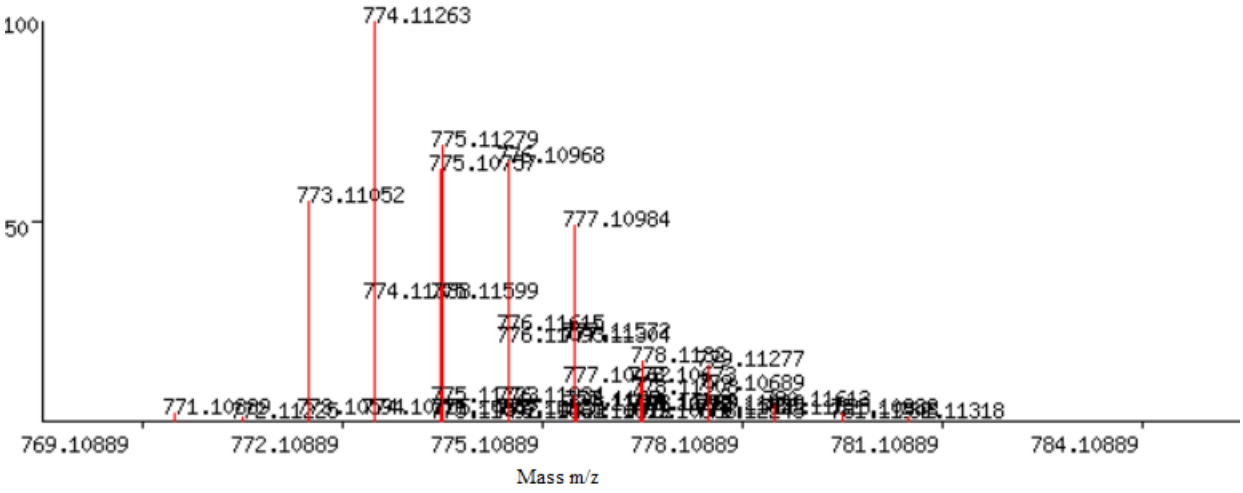
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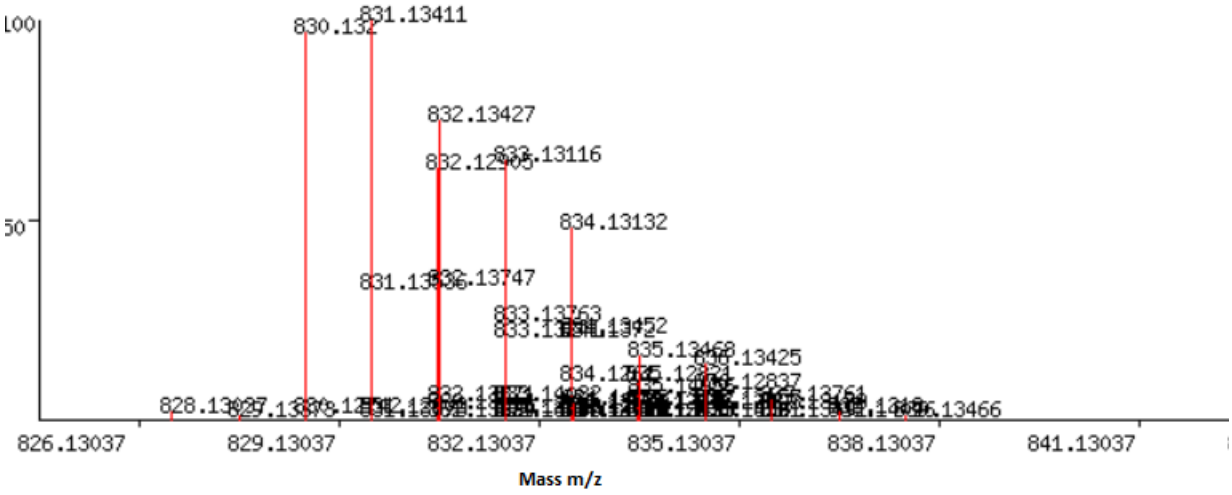
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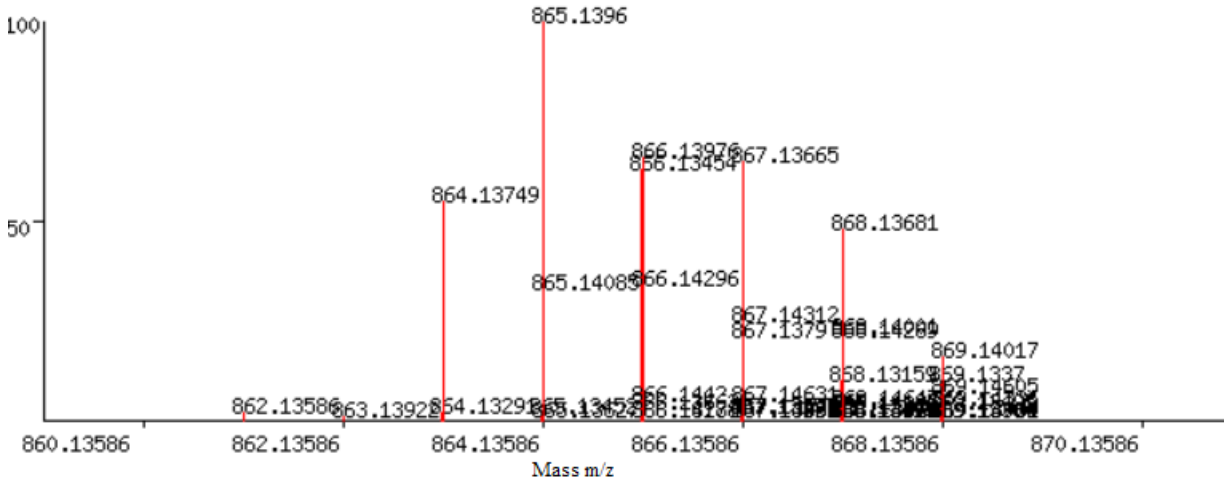
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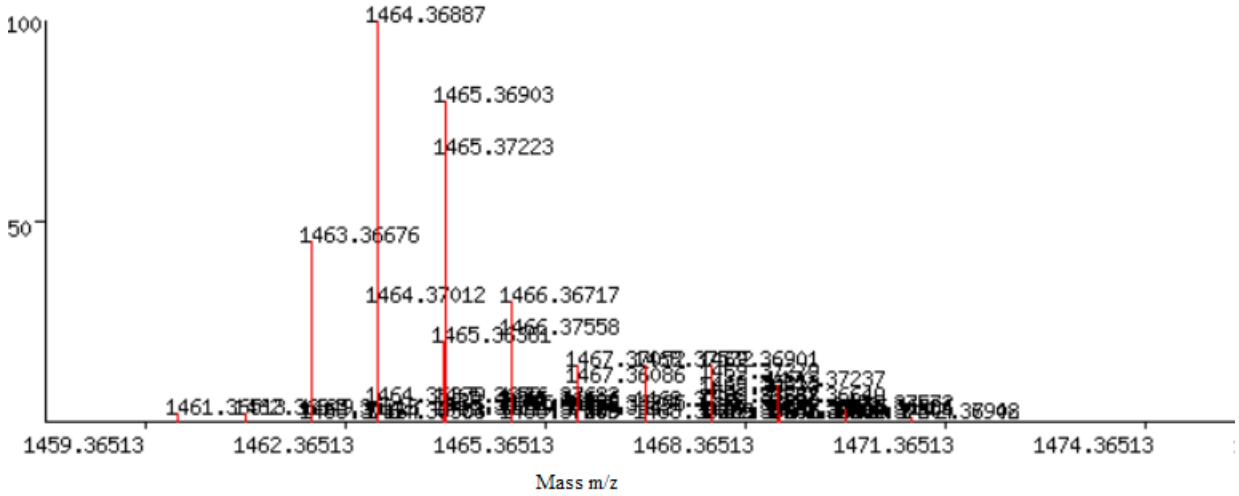
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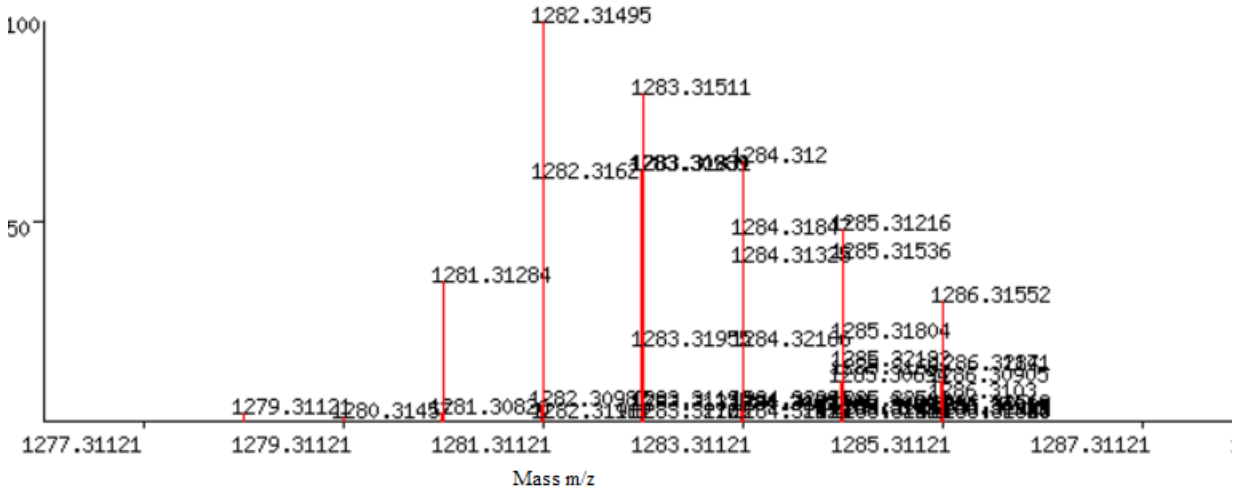
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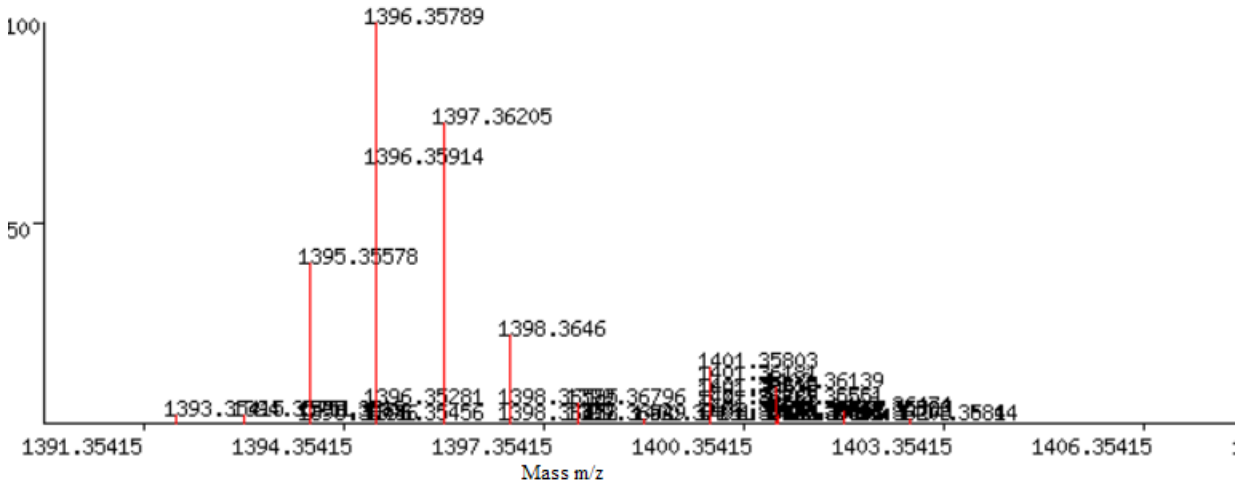
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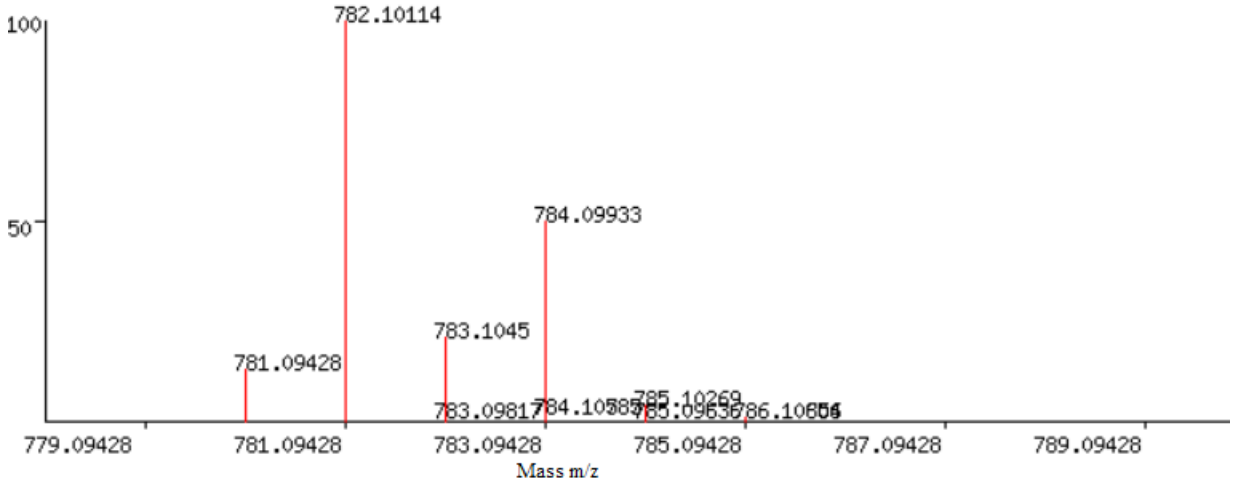
Chapter 4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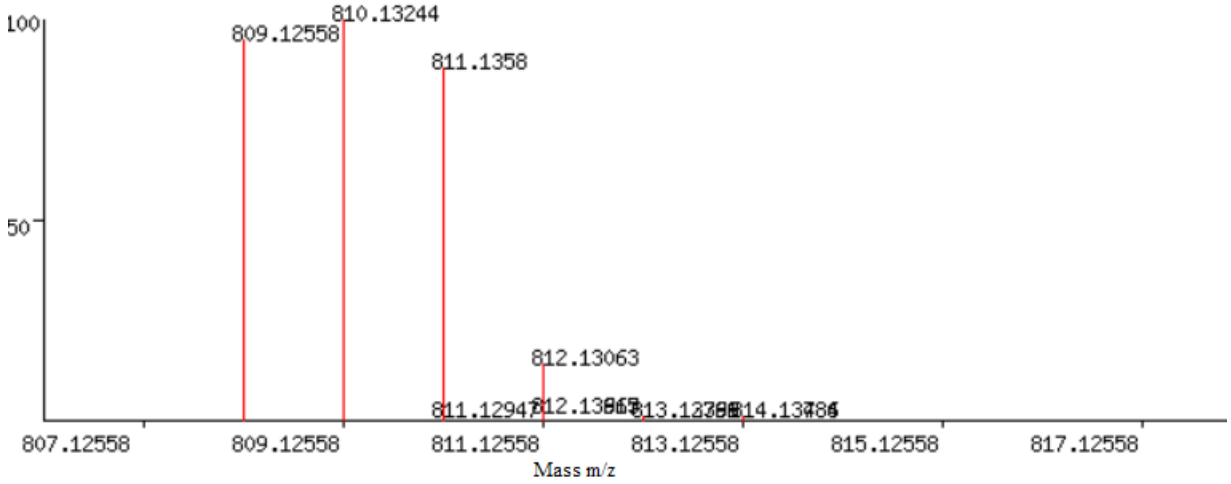
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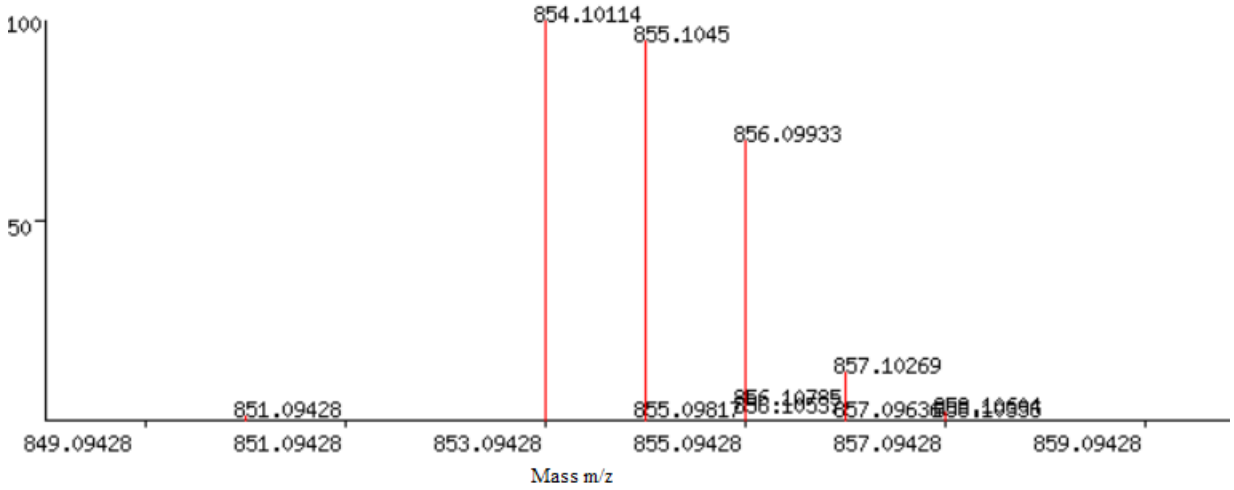
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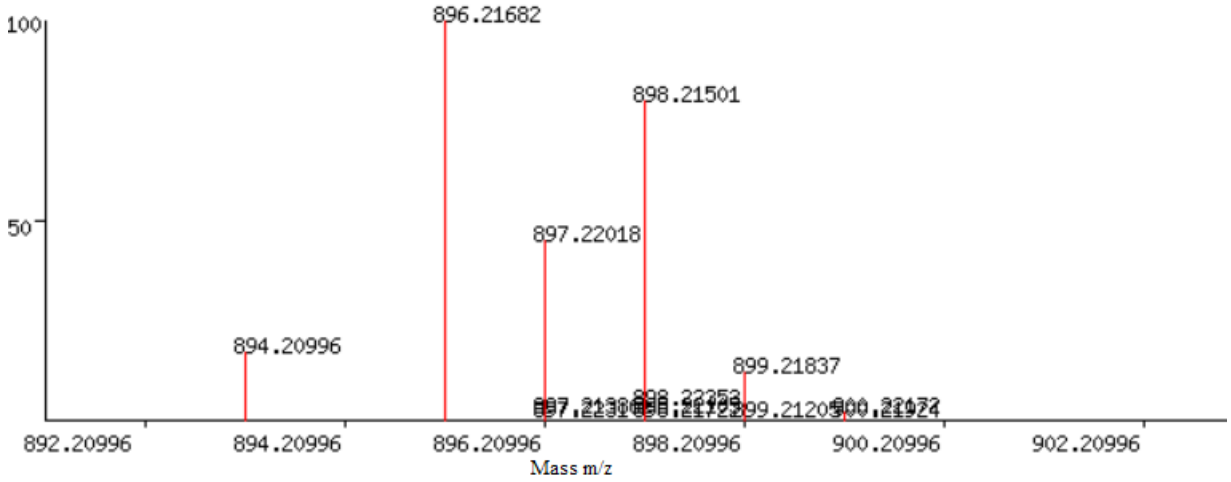
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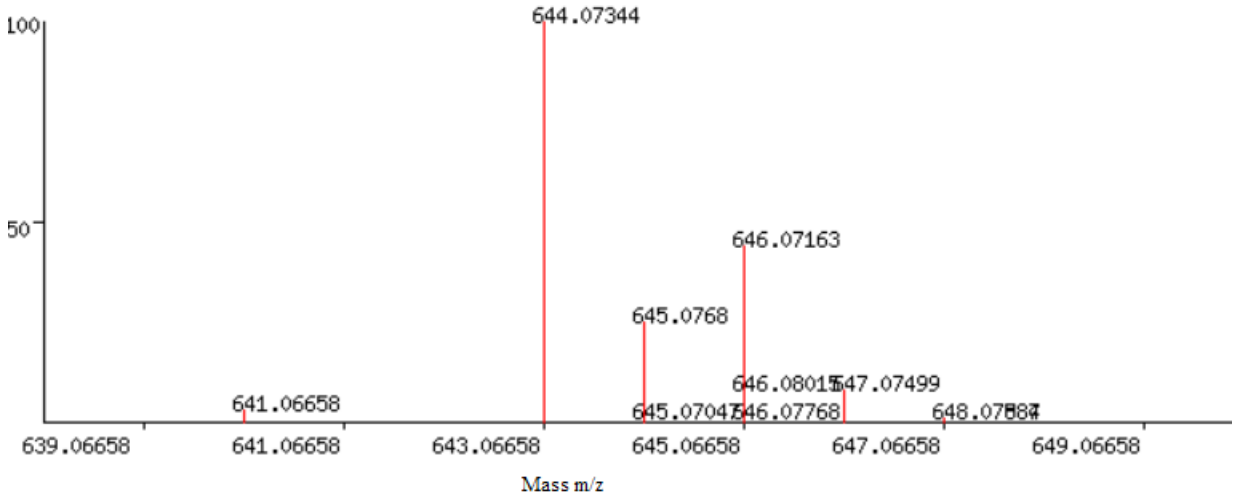
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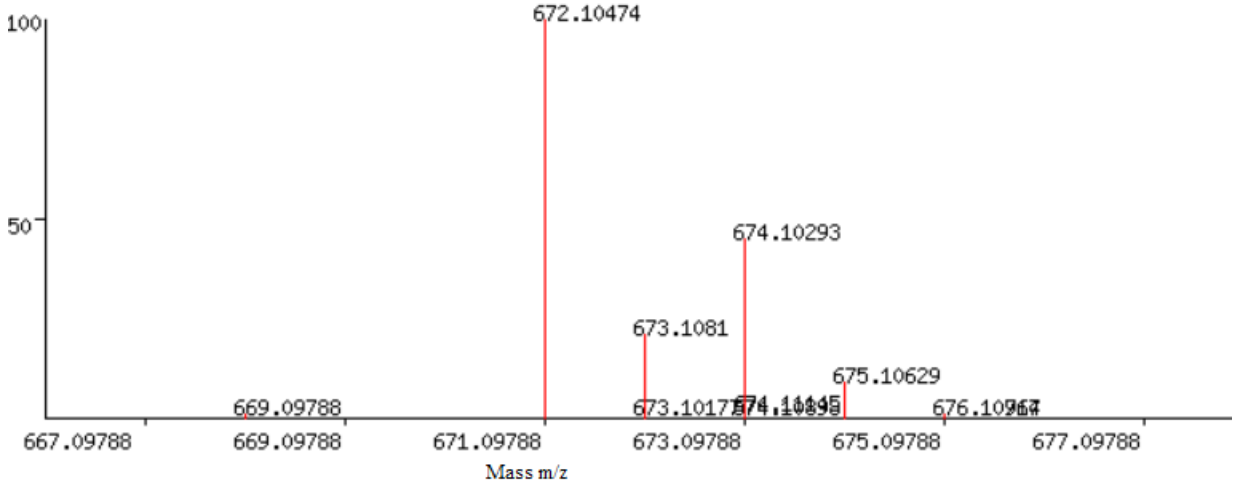
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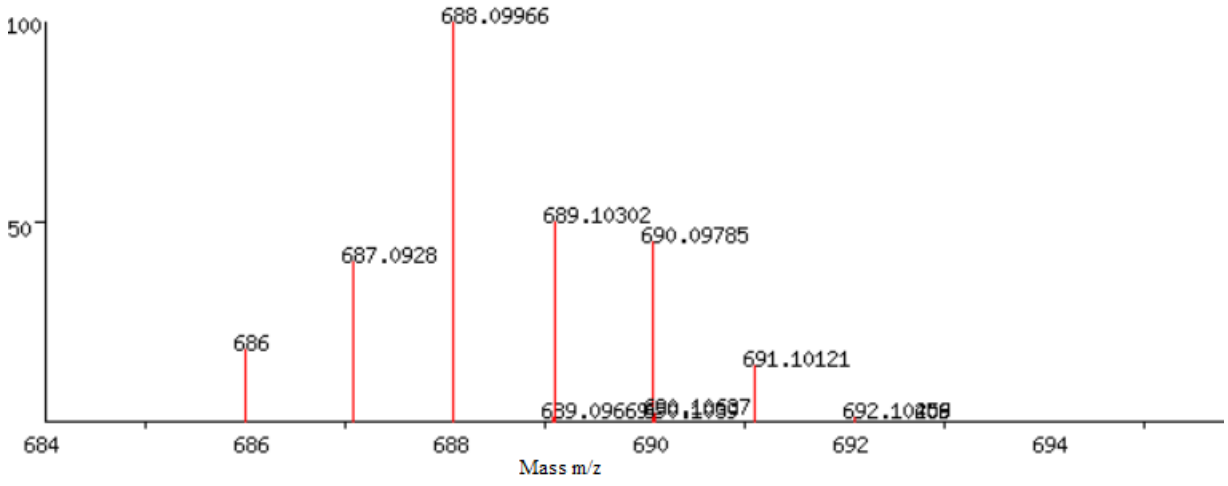
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Theoretical Calculations

Let's address one example to calculate isotope patterns theoretically:

(^{190}Pt negligible, ^{192}Pt small, 0.7%), so consider just the 4 main isotopes ^{194}Pt 33.0%, ^{195}Pt 33.8%, ^{196}Pt 25.2%, ^{198}Pt 7.2%, Weighted average MW = 195.08

H at 2 isotopes, 99.99% ^{1}H and 0.01% ^{2}H, so for illustrative purposes, ignore the trace of ^{2}H

N has 2 isotopes, 99.64% ^{14}N and 0.36% ^{15}N. So, for illustrative purposes, ignore the small amount of ^{15}N). Similarly ignore the small amounts of ^{17}O and ^{18}O

For $(C_{12}N_3H_9)_2(H_2O)_2Pt$ or $C_{24}N_6H_{22}O_2Pt$, expect approx. pattern for just the C_{24} (assuming ^{12}C – is 99% and mass 12 and ^{13}C is 1% and mass 13: About 1% chance any C atom is ^{13}C, so for 24 C atoms, about 24% of having one ^{13}C altogether. Of the remaining 23 atoms, again about 23% chance of an extra ^{13}C atom, ~ 5.5%, so peaks at M=288 ~ 76 height, M=289 ~ 24 height, M=230 ~ 5.5% height. Ignore M=231 < 2% height

Ignoring small trace isotope in O and N, we have the above peaks shifted by 22x1 (H) + 6x14 (N) + 2x16 (O) = 138 :

M=426 at ~ 76 height, M=427 at ~ 24 height, M= 428 at 5.5 height. Using M^+ not $(M+H)^+$

Add this spectrum to each Pt isotope; the abundance multiples the height

So, when we add the ^{194}Pt isotope: 33% x (M=620 at ~ 76; M=621 at ~ 24; M=622 at ~ 5.5)

When we add the ^{195}Pt isotope: 34% x (M=621 at ~ 76; M=622 at ~ 24; M=623 at ~ 5.5)

When we add the ^{196}Pt isotope: 25% x (M=622 at ~ 76; M=623 at ~ 24; M=624 at ~ 5.5)

When we add the ^{198}Pt isotope: 7% x (M=624 at ~ 76; M=625 at ~ 24; M=626 at ~ 5.5)

Peak M=620 has height 33x76 = 2541 ……...…….…75

Peak M=621 has height 33x24 + 34x76 = 792+2584 = 3376……....100

Peak M=622 has height 33x5.5 + 34x24 + 25x76 = 182 +816 + 1900 = 2898 ……..86

Peak M=623 has height 34x5.5 + 25x24 = 187 +600 = 787 ……...23

Peak M=624 has height 25x5.5 + 7x76 = 138 +532 = 670 ……..20

Peak M=625 has height 7x24 = 16…….…. 3

Peak M=626 has height 7x5.5 = 39…….….. 1

Agreement surprisingly good considering the approximations.

Approximations: Didn't do Carbon statistics exactly, ${}^{n}C_{m}$; used 1% for abundance of ^{13}C isotope, which is higher in actual; ignored small abundance of heavier isotopes of H, N, O; assumed 1, 14 and 15 for atomic masses of H, N, O; assumed 13 for atomic mass of ^{13}C. Also used only the first 3 peaks of the original C_{24} spectrum, ignoring the M=231 peak

Chapter 2

1- Chemical Formula: C12H13ClN3Pt

Exact Mass: 429.04

Molecular Weight: 429.79

m/z: 430.04 (100.0%), 429.04 (94.5%), 428.04 (91.8%), 431.04 (34.9%), 432.04 (26.5%), 432.05 (20.7%), 430.05 (13.0%), 429.05 (12.0%), 431.05 (10.0%), 434.04 (6.4%), 433.05 (5.8%), 426.04 (2.2%)

2- Chemical Formula: C24H22N6O2Pt

Exact Mass: 621.15

Molecular Weight: 621.56

m/z: 621.15 (100.0%), 622.15 (83.2%), 620.14 (77.6%), 624.15 (19.6%), 623.15 (19.4%), 625.15 (4.9%), 622.14 (2.2%), 618.14 (1.8%), 621.14 (1.7%), 623.14 (1.3%)

3- Chemical Formula: C18H26Cl2N6OPt

Exact Mass: 607.12

Molecular Weight: 608.43

m/z: 607.12 (100.0%), 608.12 (82.6%), 606.12 (81.5%), 609.12 (77.9%), 610.12 (69.7%), 608.11 (52.3%), 612.12 (14.3%), 611.11 (11.2%), 610.11 (9.8%), 611.12 (9.8%), 612.11 (6.6%), 613.12 (4.0%), 611.13 (3.6%), 614.12 (2.0%), 604.12 (1.9%), 607.11 (1.8%), 609.13 (1.8%), 610.13 (1.3%), 606.11 (1.2%), 609.11 (1.2%)

4- Chemical Formula: C24H22N6O2Pt

Exact Mass: 621.15

Molecular Weight: 621.56

m/z: 621.15 (100.0%), 622.15 (83.2%), 620.14 (77.6%), 624.15 (19.6%), 623.15 (19.4%), 625.15 (4.9%), 622.14 (2.2%), 618.14 (1.8%), 621.14 (1.7%), 623.14 (1.3%)

5- Chemical Formula: C13H22Cl2N2Pt

Exact Mass: 471.08

Molecular Weight: 472.32

m/z: 472.08 (100.0%), 471.08 (75.7%), 470.08 (64.2%), 473.08 (55.3%), 474.08 (51.9%), 476.08 (15.3%), 474.07 (6.9%), 475.07 (6.8%), 475.08 (6.2%), 477.08 (2.1%), 475.09 (2.0%), 468.08 (1.5%), 478.08 (1.5%), 470.07 (1.0%)

Chapter 3

1- Chemical Formula: C29H25Cl2FN6O2Pt

Exact Mass: 773.10

Molecular Weight: 774.54

m/z: 774.10 (100.0%), 773.10 (73.3%), 772.10 (70.6%), 775.10 (61.8%), 776.10 (42.7%), 776.11 (35.5%), 774.11 (26.3%), 773.11 (22.1%), 775.11 (21.8%), 777.11 (18.4%), 778.10

(18.2%), 777.10 (11.0%), 779.11 (3.7%), 778.11 (3.1%), 779.10 (2.1%), 770.10 (1.7%), 780.10 (1.6%)

2- Chemical Formula: C31H30Cl2FN7O5Pt

Exact Mass: 864.13

Molecular Weight: 865.61

m/z: 865.13 (100.0%), 864.13 (96.1%), 863.13 (70.1%), 867.13 (68.9%), 866.13 (62.4%), 865.14 (28.0%), 868.13 (23.4%), 866.14 (23.3%), 869.13 (18.6%), 868.14 (8.7%), 867.12 (7.1%), 867.14 (4.6%), 870.14 (3.8%), 869.14 (3.5%), 870.13 (2.8%), 871.13 (2.1%), 861.13 (1.6%), 866.12 (1.1%)

3- Chemical Formula: C31H28Cl2FN7O3Pt

Exact Mass: 830.13

Molecular Weight: 831.59

m/z: 830.13 (100.0%), 831.13 (86.2%), 829.12 (74.3%), 832.12 (66.5%), 831.12 (49.6%), 833.12 (45.0%), 833.13 (39.3%), 832.13 (25.2%), 834.13 (21.5%), 835.13 (13.2%), 834.12 (11.8%), 835.12 (9.4%), 836.13 (4.3%), 836.12 (2.5%), 830.12 (2.3%), 827.12 (1.8%), 837.12 (1.7%), 837.13 (1.1%), 835.14 (1.0%)

4- Chemical Formula: C58H50Cl2F2N12O4Pt

Exact Mass: 1281.31

Molecular Weight: 1283.10

m/z: 1281.31 (100.0%), 1282.31 (99.5%), 1283.31 (68.8%), 1280.30 (61.1%), 1284.31 (57.7%), 1283.30 (43.4%), 1282.30 (41.4%), 1284.30 (38.6%), 1285.31 (38.5%), 1286.31 (18.5%), 1285.30 (12.9%), 1286.30 (10.0%), 1287.31 (8.7%), 1287.30 (3.8%), 1288.31 (3.3%), 1286.32

(3.3%), 1281.30 (3.3%), 1284.32 (3.1%), 1283.32 (2.7%), 1285.32 (2.5%), 1288.30 (1.5%), 1278.30 (1.4%), 1289.31 (1.3%), 1287.32 (1.0%)

5- Chemical Formula: C62H60Cl2F2N14O10Pt

Exact Mass: 1463.36

Molecular Weight: 1465.23

m/z: 1464.36 (100.0%), 1463.36 (79.9%), 1465.36 (76.9%), 1466.36 (63.9%), 1462.36 (45.6%), 1467.36 (34.2%), 1468.36 (21.3%), 1465.37 (14.9%), 1466.37 (12.5%), 1467.37 (11.4%), 1464.37 (10.9%), 1469.36 (9.0%), 1468.37 (5.5%), 1466.35 (4.7%), 1469.37 (2.8%), 1470.36 (2.4%), 1470.37 (2.3%), 1465.35 (1.6%), 1460.36 (1.1%)

Chemical Formula: C62H56Cl2F2N14O6Pt

Exact Mass: 1395.35

Molecular Weight: 1397.20

m/z: 1396.35 (100.0%), 1395.35 (96.3%), 1397.35 (95.9%), 1398.35 (77.4%), 1394.35 (56.5%), 1396.34 (36.1%), 1399.35 (34.5%), 1400.35 (21.9%), 1397.36 (16.6%), 1398.36 (13.9%), 1399.36 (13.6%), 1401.35 (11.1%), 1398.34 (7.7%), 1399.34 (7.7%), 1400.36 (5.9%), 1400.34 (5.0%), 1402.35 (3.2%), 1395.34 (2.9%), 1401.36 (2.8%), 1402.36 (2.3%), 1397.34 (2.0%), 1392.35 (1.3%), 1403.35 (1.3%)

Chapter 4

1- Chemical Formula: C19H20CuN4O11U

Exact Mass: 781.09

Molecular Weight: 781.96

m/z: 781.09 (100.0%), 783.09 (44.9%), 782.10 (21.2%), 784.09 (9.8%), 783.10 (4.4%), 785.10 (2.0%), 782.09 (1.5%)

2- Chemical Formula: C21H24CuN4O11U

Exact Mass: 809.12

Molecular Weight: 810.01

m/z: 809.12 (100.0%), 811.12 (44.9%), 810.13 (23.4%), 812.13 (11.2%), 811.13 (4.9%), 813.13 (2.2%), 810.12 (1.5%)

3- Chemical Formula: C25H20CuN4O11U

Exact Mass: 853.09

Molecular Weight: 854.03

m/z: 853.09 (100.0%), 855.09 (44.9%), 854.10 (27.7%), 856.09 (12.7%), 855.10 (5.9%), 857.10 (2.8%), 854.09 (1.5%), 856.10 (1.3%)

4- Chemical Formula: C25H34CuN6O11U

Exact Mass: 895.21

Molecular Weight: 896.15

m/z: 895.21 (100.0%), 897.21 (47.4%), 896.21 (29.7%), 898.21 (12.5%), 897.22 (3.7%), 899.21 (2.9%), 898.20 (1.0%), 898.22 (1.0%)

Chapter 5

1- Chemical Formula: C17H14CuN2O6U

Exact Mass: 643.07

Molecular Weight: 643.88

m/z: 643.07 (100.0%), 645.06 (44.6%), 644.07 (18.8%), 646.07 (8.6%), 645.07 (3.0%), 647.07 (1.3%)

2- Chemical Formula: C19H18CuN2O6U

Exact Mass: 671.10

Molecular Weight: 671.94

m/z: 671.10 (100.0%), 673.10 (48.0%), 672.10 (21.0%), 674.10 (9.6%), 675.10 (1.6%)

3- Chemical Formula: C19H18CuN2O7U

Exact Mass: 687.09

Molecular Weight: 687.93

m/z: 687.09 (100.0%), 689.09 (44.7%), 688.10 (21.0%), 690.09 (9.6%), 689.10 (3.5%), 691.10 (1.0%)