# SYNTHESIS AND CHARACTERIZATION OF SOME PLATINUM (II) COMPLEXES WITH SELONE LIGANDS AND THEIR ANTICANCER ACTIVITY


BY

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# Dedication

*This work is dedicated to my wife, my lovely daughters Lammar and Mayar, my parents, my brothers and sisters for their love, encouragement and unceasing prayers that made me believe that all things are possible.*

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All the praise and glory to Almighty Allah, who gave me enough ability and strength to successfully complete this program.

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CDD : *Cis*-diamminedichloridoplatinum(II) complex

Cisplatin : *Cis*-diamminedichloridoplatinum(II) complex

DNA : DeoxyriboNucleic Acid

NMR : Nuclear magnetic resonance

GS-Se-SG : Selenodiglutathione

EA : Elemental Analyzer

XRD : Single Crystal X-ray

FTIR : Fourier transforms infra-red

FDA : Food and drug administration

GSH : Glutathione

DFT : Density functional theory

BER : Base-excision repair

NER : Nucleotide-excision repair

MMR : Mismatch repair

CTR1 : Copper transporter

HIV : Human immunodeficiency virus

| | | |
|---|---|---|
| HeLa | : | Human cervix epitheloid carcinoma |
| MCF-7 | : | Human breast adenocarcinoma |
| DMEM | : | Dulbecco's modified Eagle's medium |
| FBS | : | Fetal Bovine Serum |
| MTT | : | (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) |
| $IC_{50}$ | : | Drug concentration needed to inhibit cell growth by 50% Against a single cell line |
| TMS | : | Tetramethylsilane |

# ABSTRACT

Full Name : ALI OSMAN SAEED ALTOUM

Thesis Title : Synthesis and characterization of some platinum(II) complexes with selone ligands and their anticancer activity

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Despite the wide application of cisplatin as a chemotherapeutic agent, cisplatin exhibits severe side effects which limit the possibilities for gaining therapeutic benefits from dose intensification. Therefore, there is a need for new Pt(II) compounds that would have able enhance clinical effectiveness and eliminate the toxicity. In this study, two series of platinum complexes with some selone ligands have been synthesized and characterized by elemental analysis, infrared spectroscopy FTIR mid and far, nuclear magnetic resonance NMR ($^{1}H$,$^{13}C$,$^{77}Se$ and $^{195}Pt$ solution NMR) as well as $^{13}C$ solid state NMR and single crystal X-ray crystallography. The general formulas for these complexes are *trans*-$[Pt(selone)_2Cl_2]$ and ionic species which is $[Pt(selone)_4]Cl_2$. The spectroscopic methods confirm that the Pt(II) ion coordinate to selone ligands through selenium donor atoms not via nitrogen atoms. The X-ray structures for complexes $[Pt(EtImSe)_4]Cl_2$ (**B5**) and $[Pt(iso\text{-}prImSe)_4]Cl_2$ (**B7**), were showed that the platinum atom is bounded to four selenium atoms; each atom belonging to selone ligand in a distorted square planar geometry. The synthesized complexes **(A1-A7)** were screened for anticancer activity, and the results showed that the new compounds exhibit significant activities against HeLa (human cervical cancer) and MCF7 (human breast cancer) cell lines.

# ملخص الرسالة

**الاسم الكامل**: علي عثمان سعيد التوم

**عنوان الرسالة:** تخليق و توصيف معقدات البلاتين(II) مع بعض مترابطات السيلون ونشاطيتها كمضادات للسرطان.

**التخصص: كيمياء**

**تاريخ الدرجة العلمية**: مايو 2016

علي الرغم من التطبيقات الواسعه للسيسبلاتين كعامل علاج كيميائي،سيسبلاتين يظهر اثار جانبية حادة تحد من امكانية الحصول علي الفوائد العلاجية من تكثيف الجرعة لذلك هنالك حوجة ماسة لمركبات البلاتين (II) جديدة لديها قدرة عالية لتعزيز الفعالية السريرة و ازالة السمية. في هذه الدراسة، تم تخليق سلسلة من معقدات البلاتين مع بعض مترابطات السيلون و وصفت باستخدام التحليل العنصري، مطيافية الاشعة تحت الحمراء المتوسطة و البعيدة، الرنين النووي المغنطيسي، فضلا عن الرنين المغناطيسي النووي للحالة الصلبة و الاشعة السينية للبلورات. الصيغ العامة لهذه المعقدات هي trans- $[Pt(selone)_2Cl)_2]$ *والانواع الايونيه هي* $[Pt(selone)_4]Cl_2$ .

الطرق الطيفية اكدت ان ايون البلاتين ارتبط بمترابطات السيلون عبرذرة السلينيوم المانحة لا عن طريق النتروجين. هياكل الاشعة السينية لمعقدات اظهرت ان ذرة البلاتين محاطة باربعة ذرات سلينيوم كل ذرة منتمية لمترابط السيلون الحر في شكل رباعي السطوح المشوه. وضحت الاشعة السينية ان ذرة البلاتين للمعقدات (B5) $[Pt(EtImSe)_4]Cl_2$ و (B7 ) $[Pt(iso\text{-}prImSe)_4]Cl_2$ مرتبطة باربع ذرات سلينيوم وكل ذرة منتميه لمترابطات السيلون في شكل رباعي سطوح مشوه. المعقدات المخلقة من A1 الي A7 تم فحص نشاطيتها كمضادات للسرطان، وضحت النتائج ان المركبات الجديدة اظهرت نشاطية عالية ضد سرطاني الرحم (HeLa) و الثدي(MCF-7) .

# CHAPTER 1

# Introduction

## 1.1 Historical background

Cisplatin *c*is-[$PtCl_2(NH_3)_2$], (CDD) is one of the widely used anticancer agent, it has been investigated for the last 40 years, nevertheless it is known for approximately 150 years ago [1- 2]. The biological activity of cisplatin was unnoticed until the 1960 [2]. This discovery started from unrelated electromagnetic cell division experiments carried out by Barnett Rosenberg. He observed that platinum chloride complexes were unintentionally generated *in situ* from platinum electrodes and resulted in filamentous growth of E.coli cultures [3-5]. The clinical trials of cisplatin began in 1971 [6]. The trials showed that cisplatin was extremely effective in the treatment of solid tumors of genitourinary and gynecologic regions [7-10], in addition to the head, neck and lungs tumors [11]. Further clinical trials have shown cisplatin to be extremely effective in the treatment of advanced testicular and ovarian cancer [12-14]. In the past 15 years, the use of cisplatin has expanded rapidly and now it considered as one of the most widely used as anticancer drugs [12]. Previously, the long term cure rate for testicular cancer was only less than 10%. But now cisplatin drug has raised the long term survival rate to more than 80% [15]. However, its clinical use diminished by severe side effects such as nephrotoxicity [16], neurotoxicity, ototoxicity, nausea, vomiting and gastrointestinal effects [17]. Moreover, it's also diminished by inherent and acquired tumor resistance to the drug [15].

These limitations led to the preparation of new platinum(II) complexes such as carboplatin and oxaliplatin. It has been found that all platinum(II) complexes share one common structure which is the coordination of two amino groups (bearing at least NH) and two leaving groups such as chloride, citrate or oxalate [18-19], they connect to the DNA via N7 of two adjacent (G) Guanine atoms with Pt(II) center atom through intrastrand cross-link [20].

## 1.2 Statement of the problem

The anticancer activity of cisplatin is attributed to the interaction between (CDD) and the genomic DNA; this binding may suppress the DNA reproduction mechanism and lead to the death of tumor cell. Unfortunately, once cisplatin administered intravenously to the patient body, there are many possibilities for binding with the biomolecules in form of proteins, enzymes and peptides such as selenodiglutathione (GS-Se-SG) and selenoproteins (Figure 1) [21]. The interaction between Pt(II) complexes and these types of biomolecules will lead to form selenols [16, 22], and this prompting inactivation of an incredible measure of cisplatin compounds which are directly responsible about the toxicity occurrence, Moreover, binding of cisplatin to these molecules is responsible of the severe side effects of pharmacological properties that include some toxicity and resistance development [23].

On the other hand, it can be said that the great effectiveness of the Pt(II) complexes as anticancer agent is referred to the binding of the Pt metal with nitrogen containing biomolecules such as amino acid or nitrogen donor in DNA.

Many platinum complexes with thione ligands have been already synthesized, and most of them show higher cytotoxicity relative to cisplatin [24-26]. This success of thione

platinum(II) complexes in cancer treatment was encouraged us to synthesized a series of analogue selones platinum(II) complexes. So it is expected that these complexes have good anticancer activities.

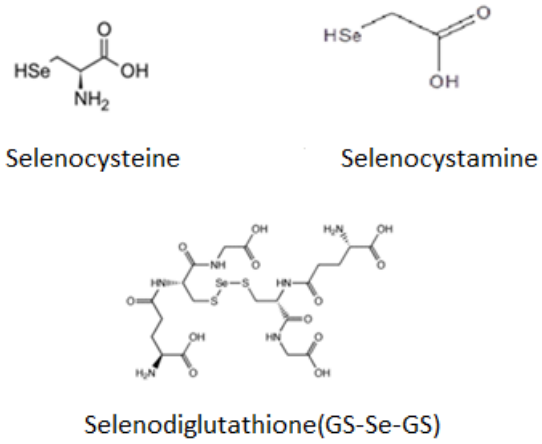



Figure 1: Chemical structues of Selenocysteine, Selenocystamine and Selenodiglutathione(GS-Se-SG).

## 1.3 Aims of the study

Selenium complexes suppress tumor growth [21]. The selenium complexes are develop gradually as anticancer agent (chemotherapeutic agents) through cancer cell selectivity and many targets response, which are lead to improve in inhibiting development of resistant of the cancer drugs. In addition to that, any ligands containing selenium such as selones and selenolates are attend to produce stable complexes form with metal ions class B (soft) [27], which attributed to selenium is considered to be a soft Lewis base. Moreover, the binding between them in the body will lead to reduce the toxicity of the selones and platinum metal [28-29]. The reactions of selone ligands with transition metals have been well studied. Complexes of Ag(I) [30-31], Au(I) [32-33], Cd(II) [34]

and Hg(II) [35], have synthesized in recent years in finding simple model compounds for metalloproteins. It is surprising that analogous Pt(II) with selones complexes have not got much consideration. So in this work, some new Pt(II) complexes have been prepared with general formula $[PtCl_2L_2]$ in case of 1:2 M: L ratio or $[PtL_4]Cl_2$ in case of 1:4 M: L ratio where M is Pt(II) central ion and L represents selone ligands as shown in Figure 2. Synthesized compounds were successfully characterized using various physical methods such as multinuclear NMR ($^{1}H$, $^{13}C$ and $^{77}Se$), Elemental analyzer (EA), Infrared spectroscopy (Mid and Far IR) as well as single crystal (XRD). The anticancer activity of synthesized complexes has been evaluated using model cancer cell lines.

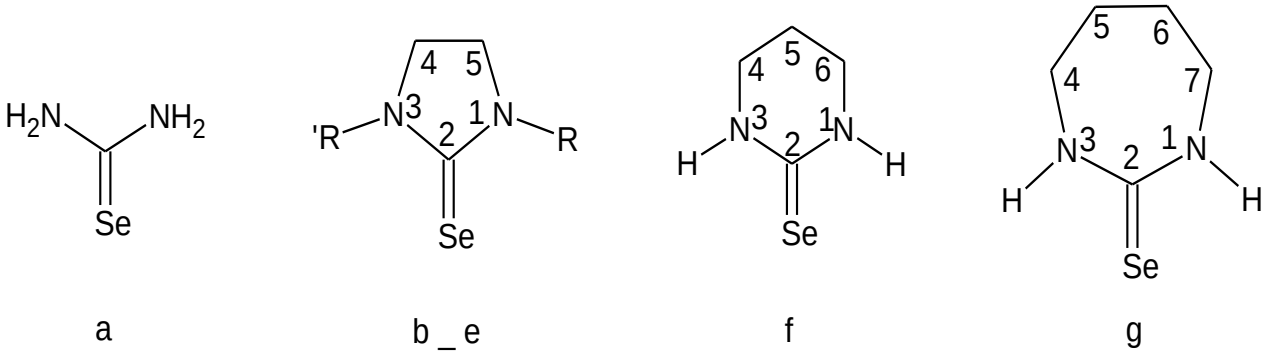



Figure 2: Structures of selone ligands

a) (SeU), Selenourea($CH_4N_2Se$)

b) "(ImSe), R = R/ = H; Imidazolidine-2-selone.

c) (EtImSe), R= $C_2H_5$, R/ = H; N-ethylimidazolidine-2- selone.

d) (N-PrIMSe), R= $C_3H_7$, R/ = H; N-propylimidazolidine-2- selone.

e) (i-PrImSe), R= i-$C_3H_7$, R/ = H; N-(i-propyl)imidazolidine-2- selone.

f) (DiazSe), 1,3-Diazinane-2- selone.

g) (DiapSe), 1,3-Diazipane-2- selone."

## 1.4 Objectives

The main objectives are:

1. Study the reaction of $K_2PtCl_4$ with a series of Selenium containing ligands (L) in 1:2 ratio to synthesize complexes with general formula $[PtL_2Cl_2]$.
2. Study the reaction of $K_2PtCl_4$ with a series of Selenium containing ligands (L) in 1:4 ratio to synthesize complexes with general formula $[PtL_4]Cl_2$.
3. Characterize the above synthesized complexes by some techniques such as: elemental analysis, FT-IR spectroscopy, $^{1}H$ NMR, $^{13}C$ and $^{77}Se$ NMR solution, $^{13}C$ solid state NMR and single crystal X-Ray crystallography.
4. Examine the biological efficiency of these new complexes *in vitro* against some human cancer cell lines compared to parent complex cisplatin and carboplatin as controls.

# CHAPTER 2

# Literature review

## 2.1 Applications of Metals in Medicine

The application of inorganic metals in medicinal field has been known for thousands years ago [36]. As a one of the famous metals, mercury was used for the treatment of syphilis during the European epidemic in the 15th and 16th centuries [36]. In addition, in 1909, Erich was introduced the arsenic compound Salvarsan, as a cure for syphilis too [37]. By the middle of the last century, great expansion in the application of metals in medicine was made hence the technetium and the platinum metals were introduced to this field. C. Perrier and E. Serge discovered technetium in 1937, by neutron capture in molybdenum ores. Within the end of the past century, technetium attracts much interest because of its important contribution to the diagnostic medicine. The platinum metal as well known in medicine as an anticancer drug, this fact started at the time of the great discovery made by Barnett Rosenberg, he was trying to find whether there is a contribution of magnetic or electronic dipole fields on cell division by applying electromagnetic radiation on mammalian and bacterial cells [3]. Recently, cisplatin is the widest compounds used as anticancer drugs [4]. This is due to its activity against cervical, bladder, ovarian, neck and head, lung and testicular cell cancers [15]. Despite the above mentioned fact, cisplatin is not effective in other forms of cancers for examples, renal, leukemia and gastrointestinal cancers [38].

## 2.2 Cancer Disease and Cancer Therapy

Cancer is a worldwide well-known disease caused by body cells, which become abnormal, and divides without control and can attack other normal tissues. Cancer cells could spread through the blood stream and lymph systems to other parts of the body. Inevitably, the tumor burden will bring the death, frequently by physically blocking or packing veins or organs, for example, the brain [38]. Cancers are of two types- malignant tumors and benign tumors. Malignant tumors are different from benign tumors as they show uncontrollable growth, invade locally, and metastasize to distant body parts, they named according to the type of cell or organ in which they start such as breast cancer, lung cancer, colon cancer. Benign tumors grow in one place and lack the ability to metastasize [39-40].

Cancer is brought by both, internal factors like hormones, inherited immune conditions and mutations or acquired/environmental factors such as radiation, diet, tobacco and infectious organisms [41].

Many methods was introduced for cancer treatment, it can be used alone or in combination including surgery, biological therapy, hormone therapy, immunotherapy, radiation, gene therapy and chemotherapy. Unfortunately, these treatments dose not totally help the patients, they may not give good treatment at all, or just increase the time of survival [36]. The chemotherapeutic drugs aim to kill malignant tumor cells through inhibiting their cellular division, but there are just a small number of subgroups that can benefit from the effective targeted therapies, which have been noted that the development of cancer chemotherapy is a very difficult task to achieve [42]. The most difficult problems found in cancer chemotherapy are the nonspecific toxicity due to the spread out

of the drug throughout the body, which requires large dose of the pharmaceuticals to achieve high concentrations at a local tumor [43]. Another problem in cancer chemotherapy is raised from drug resistance, which could be defined as the ability of cancer cells to resist different drugs [44]. There are different ways by which cancer cells can evade the chemotherapy. This resistance exists against all kinds of drugs, even the newly applied ones. Therefore, it is necessary to circumvent drug resistance to improve the chemotherapy [45]. The major problem that facing the development of a new anticancer chemotherapy is the big gap between the promising findings in preclinical *in vivo* and *in vitro* models and the real clinical results obtained in the complex therapeutic situation of cancer in patients [42].

## 2.3 Platinum based drugs for cancer therapy

The most well-known platinum compounds cisplatin is successfully used in chemotherapeutic indicated considerable activity toward some of the cancer cell lines, it was synthesized in 1844 by Michel Peyrone and named as Peyrone chloride [46], and in 1893 Alfred Warrner deduced the structure of cisplatin. Its biological activity was discovered by accident in 1960 by biophysicist Barnett Rosenberg at University of Michigan, United States [46].

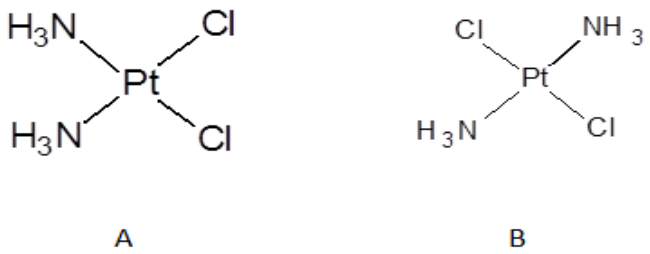



Figure 3: Isomeric structure of diammine dichlorido platinum(II) complex, A is Cisplatin and B is Transplatin.

Initially, he designed to study whether magnetic or electric dipole fields contribute to cell division, by applying electromagnetic radiation on mammalian and bacterial cells. Without intention, a group of platinum electrodes which is known not latent was included in the development load of Escherichia coli in $NH_4Cl$ buffer [47]. After the electromagnetic field turned on, the filamenation occurs which is a strange growth of the bacteria length; reached up to 300 times of the normal length. This phenomenon could not be attributed to the effect of the applied field. Investigations found that the observation is due to the presence of platinum(II) and platinum(IV) ammine chlorido complexes formed *in situ* originating from electrolysis at the platinum electrodes. Further investigations showed that specifically, *cis*-diammine dichlorido platinum(II) is the causing molecule of these biological effects [48].

Several medicinal trials of cisplatin as a drug commenced soon thereafter, and it was used to treat first patient in 1971 [49]. Cisplatin was granted approval against several human cancers in 1978 by (FDA) United States for food and drug administration [49]. Recently, cisplatin is considered to be the first compound widely used as anticancer agents [23, 50].

This is due to its activity against a lot of cancer cells like cervical, bladder, neck and head, ovarian, testicular and lung cancers cells.

In spite of the mentioned advantages, the first platinum generation compounds (cisplatin) is not effective as drug for treating of some others tumors such as renal, leukemia and gastrointestinal cancers [51].

In general, it was believed that the relationship between structure and activity of platinum drugs to possess cis geometry, platinum atom should bind via amine ligands (bidentate ligands) or through the two amines and the two good leaving groups with an intermediate binding strength such as chloride, sulfate, Oxalate and citrate until Farrel and his group reported that platinum complexes with trans configuration also showed antitumor activity. Examples of such biologically active trans platinum compounds include *trans*-[$PtCl_2$(iminoether)$_2$] and *trans*-[$PtCl_2${$NH_2CH(CH_3)_2$}{NH-$(CH_3)_2$}] [52].

### 2.3.1 Cisplatin mechanism of Action

It has been noted that cisplatin becomes activated inside the cellular system before it reach its target of DNA through the equation mechanism (one of the chlorides is replaced by water) (Figure 4). Followed by formation of DNA adducts (Figure 5). Several studies conducted *in vitro* indicated platinum coordinating to DNA through N7 of the purine bases of guanine (G), and to a lesser degree, adenine (A) to produce different type of platinum- DNA adducts, such as GpG 1,2 intrastrand (60–65 percent of the total adducts) through binding of platinum complex to two adjacent guanine (G) of the same DNA strand, or ApG 1,2 intrastrand (20–25% of all adducts) through binding of platinum to two adjacent nucleobases; adenine (A) and guanine (G) of same DNA strand. There are also less frequent adducts which arise through binding to different DNA strands [53].

These adducts are the key to the success of the drug in programmed cell death (apoptosis) [50, 54].

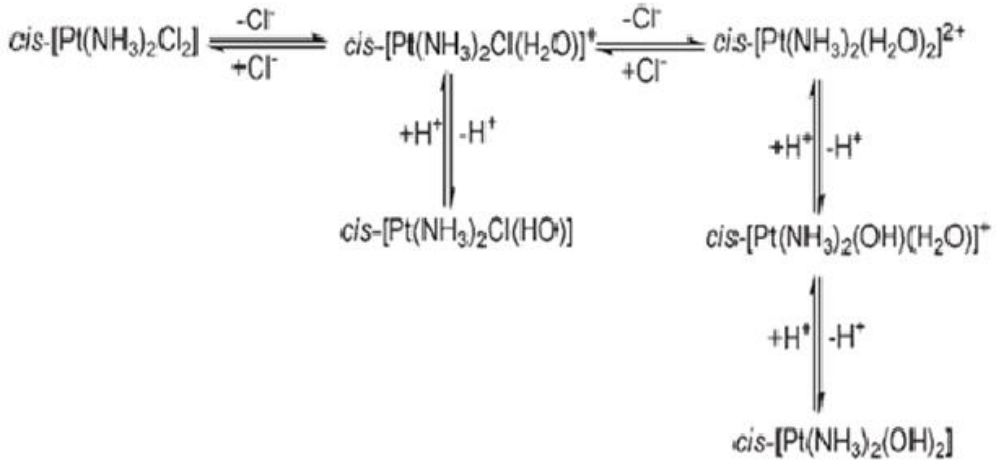



Figure 4: Cisplatin undergoes spontaneous hydrolysis in aqueous solutions

It's believed that the N7 position of the imidazole rings in the DNA purine bases guanine and adenine is most nucleophic and accessible site, which can be a major target to interact with cisplatin, mainly through [1,2-d(ApG) or 1, 2-d(GpG) intrastrand cross-links]. it was found that N7 of guanine thermodynamically and kinetically favorable site for binding that leads to resolve of DNA [52].

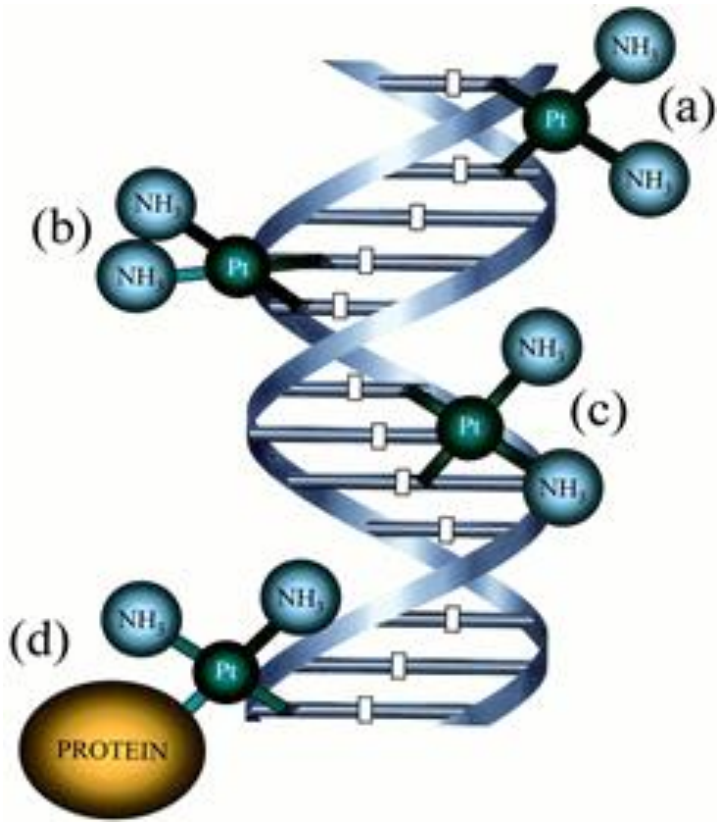



Figure 5: The main products produced from the cisplatin and DNA interaction.

a) is [1, 2-d(GpG) interstrand cross-link], b) is [1, 2-d(GpG) intrastrand cross-link], c) is [1, 3-d(GpG) intrastrand cross-link], d) is [protein-DNA adduct].


Figure 6: Guanine and Adenine structure, A. guanine, B. Adenine.

When the platinum binding to the nucleophilic site in the two structures form, the amine ligands ($NH_3$) act as donor hydrogen-bonding, while C6 position in (amino group) of adenine ring and (oxo group) of guanine ring, known to be hydrogen-bond acceptors.

Hydrogen bond between the N-H….O=C6 in case of guanine is much better than the hydrogen bond forms between the N-H….$NH_2$-C6 in case of adenine. In addition, strong interaction is identified for guanine compared to adenine using MO analysis [55].

To insure that the N7 for guanine is preferable site for platination over adenine, Lippard and his group used density functional theory (DFT) to study the interaction of [Pt $(NH_3)_2]^{2+}$ complexes with guanine and adenine. Thermodynamics and kinetics factors of the complexes were taken into account, verifying that of guanine is more reactive 20 times than adenine toward platination [56].

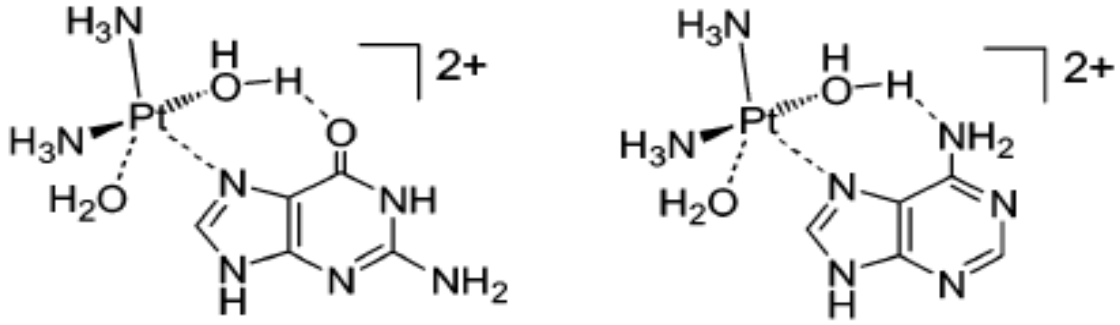



Figure 7: Hydrogen bonding in case of guanine and adenine after platination.

### 2.3.2 DNA-Repair

DNA-repair formed by four major pathways including (NER) nucleotide-excision repair, (MMR) mismatch repair, double-strand-break repair, and (BER) base-excision repair, but NER considered as the major pathway used to eliminate cisplatin lesions from DNA [16].

### 2.3.3 Resistance of Tumors to Cisplatin

The resistance of tumors to cisplatin attracted the attention of scientists to study how tumor resistance was made amid courses of chemotherapy with these anticancer

medications, and why a portion of alternate tumors were safe. Conventionally, some studies were keen on the explanation for the excessive touchiness of testicular tumor to cisplatin. These investigations concluded that, there might be two reasons for the above mentioned tumor resistance: initial, a disappointment of an adequate amount of cisplatin to reach the DNA target or an inability to accomplish cell death after platination process occurs [57].

### 2.3.4 Resistance through Insufficient DNA Binding

For many years, it has been reported that, in many cells' tumor resistance acquired through the course of cisplatin administration that is a reduction of platinum concentration accumulated in the cells in comparison to that of the parental cells [50]. However, until present, the exact molecular mechanism by which the anticancer drug enters the cells remained unclear. The uptake of cisplatin is affected by several factors [58], like pH, sodium and potassium ion concentrations, and the presence of reducing agents; and the way that it transports by transporters or through gated channels hypothesized in addition to passive diffusion (Figure 9). The major plasma-membrane transporter, copper transporter-1 (CTR1), which has an essential role in copper homeostasis, was found to be involved in cisplatin influx, the loss of CTR1 has led to increase in drug resistance even high in concentrations of cisplatin [59]. Besides, there is many of evidences that the high concentration of sulfur containing species, such as metallothioneins [60], and glutathione [61], which are rich in the sulfur-containing amino acids, methionine and cysteine, will lead to detoxification and there for resistance to cisplatin because platinum prefer to bind to sulfur insatiably [59].

### 2.3.5 Resistance mediated after DNA binding

The acquired resistance to cisplatin could also occur after the formation of platinum–DNA adducts, through cellular survival by either removal or tolerance of DNA damage [62]. The enhance sensitivity of testicular cancer to cisplatin was found to be a result from DNA-repair deficiency. On the other hand, there are many types of cisplatin-resistant cell lines have been shown to have tumor drug resistance because of the increase in the DNA-repair capacity [63].

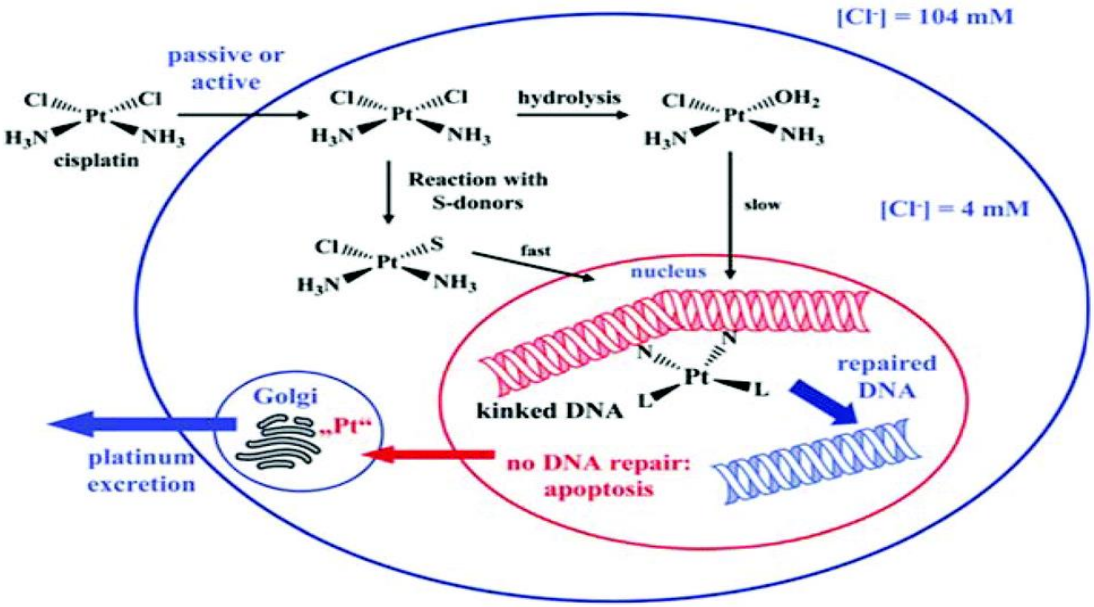



Figure 8: The interaction of activated cisplatin with biomolecules before reaching DNA of the cells.

### 2.3.6 The Side Effects of Cisplatin

Cisplatin as an anticancer agent is commonly used in solid tumors treatment, but it lacks the selectivity for tumor cells, which induce severe side effects such as gastrointestinal toxicity, bone-marrow suppression, ototoxicity, neuropathy, and nephrotoxicity. The

latest one is the main effect that hampers the use of cisplatin in the therapeutic process [64-65]. Several studies found that 25% of patients might develop reversible azotemia after receiving a single dose of cisplatin [66]. Besides, irreversible kidney failure also may occur at large doses, or with frequent cycles of treatment [67]. Nephrotoxicity induced by a complex process involves severe cytotoxic effects on tubular epithelial cells that reduce the tubular epithelial cells via apoptosis, and necrosis, followed by fibro proliferative changes and inflammatory cell infiltration [68].

Cisplatin partially inhibits the protein synthesis in the tubular epithelial cells, and disrupts the cellular antioxidant defense system (i.e., glutathione, GSH), resulting in DNA damage and lipid peroxidation. Glutathione, (GSH) could be administered to alter the nephrotoxicity induced by cisplatin [69], without affecting its antitumor activities [70].

## 2.4 Carboplatin

Carboplatin has been known as a second generation of cis-diammine(cyclobutane-1,1-dicarboxylato) platinum(II), that differs from cisplatin by the presence of a bidentate dicarboxylate ligand as leaving group instead of the more labile cisplatin's chlorides. It was discovered in the early 1970s by Rosenberg and his group to improve the performance of the first generation cisplatin and to expand the range of useful anticancer activity [71]. By 1989, carboplatin was approved as drug under the brand name paraplatin. Carboplatin has slower substitution rate compared to cisplatin, this feature makes it much less chemically reactive (ototoxic, neurotoxic, and nephrotoxic) in contrast with cisplatin and can be administrate in a higher measurement than cisplatin, this brief scientists to concentrate on instruments by which the compound can be initiated *in vivo*. When it going through the blood, carboplatin shows to enter the cell through

inactive dissemination, in spite of the fact that it may enter by means of dynamic transport or through particle channels. Osella and collaborators recommends that carboplatin enter the cell through an aloof dispersion mechanism [72].

The lower toxicity of carboplatin has been the point of preference that empowered it to get overall endorsement for clinical use. Shockingly, it's still just dynamic in the same scope of tumors as cisplatin is still managed intravenously [73] and possess similar structure as cisplatin that can bind form DNA adducts as cisplatin and can't be overcome. Therefore, the researchers focused for seeking on a new platinum compounds with improved tolerability profiles that may overcome the side effect of the first generation.

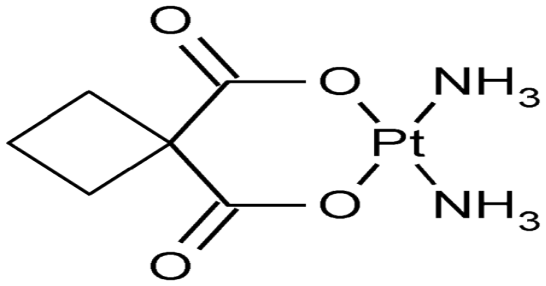



Figure 9: Chemical structure of [cis-diammine(cyclobutane-1,1-dicarboxylato) platinum(II)] (Carboplatin).

## 2.5 Oxaliplatin

The third generation of platinum(II) complex (([(1R,2R)-cyclohexane-1,2-diamine]-(ethanedioato-O,O′)platinum(II), is called oxaliplatin, which contain a rigid bidentate 1,2-diaminocyclohexane as stable ligand (instead of the monodentate of $NH_3$ ligands) and an oxalate leaving group, it was approved in 2002, under the name Eloxatin. Inclusion of

the rigid moiety diaminocyclohexane was intended to contribute to a larger cytotoxicity when compared to the first and second generation (more damaging Pt-DNA adducts), as well as to overcome cross resistance with those widely used drugs, the particularly high activity of this third-generation agent, even in cisplatin-resistant tumor models, coupled to its decreased toxicity, prompted further studies on its use as a treatment option after the failure of the cisplatin or carboplatin therapy [58].

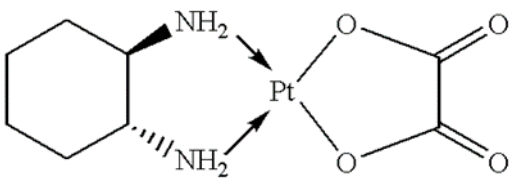



Figure 10: Oxaliplatin, [(1R, 2R)-cyclohexane-1,2-diamine]- (ethanedioato-O,O′)platinum(II).

## 2.6 The importance of selenium

The effect of selenium compounds on biological systems has been a great interest to researchers. Although selenium is toxic if taken in high doses, it is an essential trace element and natural ingredient of diets, is claimed to have the capability to become anti-carcinogenic, a claim supported by considerable evidence. In addition, the positive results of the recently conducted clinical experiments [74–77] prompt this outcome, especially when accompanied with similar evidence of studies from epidemiology, mechanistic research, and experimental animal. It suggests that Se can tackle cancer threat in two different ways: the first as a main source for many selenium enzymes with functions of antioxidant and redox-regulatory, and the second as a supplier of antitumorigenic selenium metabolites [78–80]. The first way could be seen much more relevant to cancer

prevention from beginning, while the other to cancer suppression. But it could be also that supra-nutritional amount of selenium, through modifying tissue level selenium shortages, could stop transformed cells through a group of effects, including selenium metabolites' anticancer activities and selenium protein activities as well [76].

## 2.7 Selenium antitumorigenesis Mechanisms

Based on this, it could be expected for selenium's anticarcinogenic effects to change with the amount and way of its delivery, and with the recipient's selenium condition. Therefore, people with selenium shortage might appear to take the advantages of additional selenium dependent glutathione peroxidases and thioredoxin reductases, which work against cancer inception through protecting against reactive oxygen species.

Meanwhile, people who are selenium sufficient, on the other hand, might be taking the advantages of its supra-nutritional does that increasingly produce selenium metabolites, which in turn have the capabilities to improve the observation of the immune system, change carcinogen metabolism, prevent proliferation of cells, boost apoptosis and inhibit tumor neo-angiogenesis [81]. As indicated by evidence, some specific selenium metabolites could tackle these anticarcinogenic effects, such as hydrogen selenide [82–84], methylselenol [85–90] and selenodiglutathione in people who are exposed to selenate or selenite [91–96]. In animal model, these effects have been constantly linked to selenium intakes equivalent to a minimum of tenfold the amount needed to prevent clinical symptoms of selenium shortage. On a basis of unit body weight (around 100 μg/kg rodents body weight), they are much larger than what most people around the world are exposed to, which is going to be below 100 μg/day. Since the selenium proteins

seem to be exciting in its highest level in animal tissues at dietary levels not exceeding 0.5 μg Se/Kg, there has been a current conception that the anticarcinogenic effects caused by such levels of selenium are probably not associated with selenium protein [91].

## 2.8 Selenourea and its derivatives (selones)

Thione compounds have shown many pharmacological benefits [97]. Thiourea, 1,3-imidazolidine-2-thiones and their derivatives are an interesting class of ligands, they possess ambidentate nature. They have been used for a long time as antifungal agents, protecting agent against side effects of kidney during administration of cisplatin, and as anti-HIV. The reactions of thione ligands with transition metals have been well studied in order to find simple model compounds for metalloproteins [98]. However, the analogous complexes containing selone ligands doesn't receive any attention, may give a better result if they coordinated with platinum(II) ion. Although, Devillanova and his team have reported the preparation of the (ImSe) with Cd(II), Hg(II) and Zn(II) complexes. And also Saeed Ahmed and his team workers have investigated these ligands with Ag(I), Au(I) and Cd(II) [34,35 and 40].

Selone ligands can bind to platinum ion via selenium or nitrogen atoms. These complexes may exist in a selenol ‑ selone equilibrium see Figure 12. However, it has been established that the selenone form dominates in the solid state of these complexes [99].

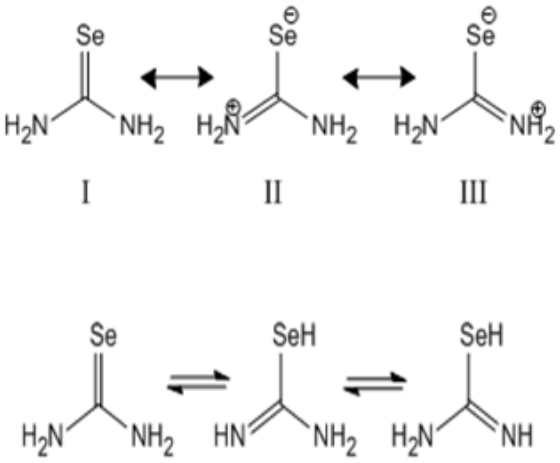



Figure 11: Resonance and tautomerism structure of selenourea (selenol – selone equilibrium).

# CHAPTER 3

# Experimental work

## 3.1 Chemical Materials

Potassium tetrachloroplatinate(II) was obtained from "Strem Chemicals,In. All the Selone ligands (Figure 2) are prepared according to the procedure that described in the literature [100-101]. The NMR solvents were purchased from Sigma-Aldrich Chemical Co. While the other solvents were collected from Fluka Chemical Co." and these materials handled without any further purification.

## 3.2 Instrumentations

### 3.2.1 Elemental Analysis

Elemental analysis of carbon, hydrogen and nitrogen of the synthesized complexes has been done using CHNs Elemental Analyzer (EA).

### 3.2.2 Melting Points

Melting points of the synthesized complexes were made on Electro thermal apparatus and are uncorrected.

### 3.2.3 Infrared Spectroscopy Measurements

The all FT- IR data of the synthesized Platinum(II) compounds and their original selone ligands were carried out on 180 spectrophotometer (Perkin–Elmer Fourier transform infrared spectroscopy) using solid KBr pellets in the window from 400 to 4000 $cm^{-1}$.

### 3.2.4 $^{1}$H NMR Measurements

The $^{1}$H NMR spectra were conducted on a (Jeol JNM-LA 500) NMR spectrophotometer at room temperature, at a frequency of 500 MHz under conditions 32 K data points, 1.50 s pulse dely, and 45° pulse angle.

### 3.2.5 $^{13}$C NMR Measurements

The spectra of $^{13}$C nuclear magnetic resonance have been performed at 500 MHz under conditions 32 K data points with $^{1}$H broadband decoupling at 297 K. And 0.963 acquisition time, 3.2 s pulse delay and a 5.75μs pulse width for $^{1}$H NMR and 2.5 s pulse delay and a 5.12μs pulse width for $^{13}$C NMR. All the $^{13}$C NMR data were measured relative to external reference Tetramethylsilane (TMS).

### 3.2.6 $^{13}$C Solids NMR Measurements

$^{13}$C solid state NMR spectra have been done on a "JEOL LAMBDA 500 spectrometer at 125.65 MHz (11.74 T)" operating frequency, at room temperature. Our synthesized complexes were pressed into 6mm of rotors of zirconium oxide tubs. High power decoupling and solid state cross polarization were applied. Using contact time of 5.0 ms and pulse delay of 7.0 s in the CPMAS experiments. Using magic angle spinning range between 2000 Hz to 4000 Hz.

### 3.2.7 $^{77}$Se NMR Measurements

$^{77}$Se NMR spectra for the selone ligands and their relative Pt(II) species were recorded using ($NaHSeO_3$ in $D_2O$) as external reference at 1308.00 ppm, using 95.35 MHz, 0.311 s acquisition time and using a 2.00 s as pulse delay.

## 3.3 Synthesis of Compounds

### 3.3.1 Synthesis of Selone Ligands

Selenourea was prepared from Thiourea by converting it to S-methylthiouronium iodide using methyl iodid and then an aqueous NaHSe solution was added to S-methylthiouronium iodide.The desired product was obtained and recrystallized from ethanol [100-101].

### 3.3.2 Synthesis of $[PtL_2Cl_2]$ complexes

Due to the easy decomposition of the free selones ligand in air, these complexes were synthesized by dissolved (1mmol) of selone ligands in methanol solvent added to (0.5mmol) of Potassium tetracholoropaltinate(II) which dissolved in a hot acetonitrile. Then the mixture solutions were stirred for 1hour under nitrogen in a dry box using anhydrous deairated solvents, colored precipitate were formed after filtration process were sufficiently stable to be handled in the air (yield 70 - 91%). Elemental analysis data and melting points were carried out, their results are summarized in Table 1.

### 3.3.3 Synthesis of $[PtL_4Cl_2]$ complexes

As mentioned above for selone ligands instability in air $[PtL_4]Cl_2$ complexes were prepared by same method earlier with varying the ratio by dissolved (1mmol) of selone ligands in methanol solvent added to (0.25mmol) of Potassium tetracholoropaltinate(II) which dissolved in a hot acetonitrile. Then the mixture solutions were stirred for 1hour under nitrogen in a dry box using anhydrous deairated solvents, colored solution were observed. Then solutions were filtered and the solvents were evaporated and the products were obtained and finally they were recrystallized with methanol and the desired compounds were obtained by yields from 60–90%. All the analytical data and melting points of these complexes were summarized in Table 2.

Table 1: Elemental analyses and melting points (°C) of $[PtL_2Cl_2]$ complexes.

| | Complex | Found **(Calcd.)** (%) | | | Melting point (°C) | Color | Yield % |
|---|---|---|---|---|---|---|---|
| | | **C** | **H** | **N** | | | |
| **A1** | $(DiazSe)_2PtCl_2$ | 16.22 **(15.96)** | 2.72 **(2.58)** | 9.46 **(9.04)** | 183-186 | Orange | 76.45 |
| **A2** | $(DiapSe)_2PtCl_2$ | 19.36 **(20.18)** | 3.25 **(3.43)** | 9.03 **(8.78)** | 215-218 | Brown | 85.56 |
| **A3** | $(PrIMSe)_2PtCl_2$ | 22.23 **(22.75)** | 3.73 **(3.87)** | 8.64 **(8.98)** | 161-163 | Brown | 78.87 |
| **A4** | $(SeU)_2PtCl_2$ | 4.69 **(4.72)** | 1.57 **(1.39)** | 10.94 **(10.56)** | 191-192 | Black | 69.74 |
| **A5** | $(EtIMSe)_2PtCl_2$ | 19.36 **(19.85)** | 3.25 **(3.38)** | 9.03 **(9.20)** | 195-198 | Yellow | 81.98 |
| **A6** | $(IMSe)_2PtCl_2$ | 12.77 **(12.89)** | 2.14 **(2.27)** | 9.93 **(10.19)** | 226-229 | Yellow | 91.28 |
| **A7** | $(i\text{-}PrIMSe)_2PtCl_2$ | 22.23 **(22.05)** | 3.73 **(3.54)** | 8.64 **(8.73)** | 178 | Brown | 66.81 |

Table 2: Elemental analysis and melting points (°C) of $[PtL_4]Cl_2$ complexes.

| | Complex | Found **(Calcd.)** (%) | | | Melting point (°C) | Color | Yield % |
|---|---|---|---|---|---|---|---|
| | | **C** | **H** | **N** | | | |
| **B1** | $(DiazSe)_4PtCl_2$ | 20.92 **(20.76)** | 3.51 **(3.58)** | 12.20 **(12.14)** | 250 | Orange | 65.68 |
| **B2** | $(DiapSe)_4PtCl_2$ | 24.65 **(23.78)** | 4.13 **(4.02)** | 11.49 **(10.97)** | 301-304 | Green | 76.5 |
| **B3** | $(PrIMSe)_4PtCl_2$ | 27.97 **(25.90)** | 4.69 **(4.42)** | 10.87 **(10.02)** | 119-122 | Golden Yellow | 83.16 |
| **B4** | $(SeU)_4PtCl_2$ | 6.33 **(5.98)** | 2.12 **(2.07)** | 14.78 **(13.98)** | 195-197 | Yellow | 64.65 |
| **B5** | $(EtIMSe)_4PtCl_2$ | 24.65 **(23.97)** | 4.13 **(4.08)** | 11.49 **(11.23)** | 215 | Yellowish Green | 90.82 |
| **B6** | $(IMSe)_4PtCl_2$ | 16.71 **(16.87)** | 2.80 **(2.86)** | 12.99 **(12.68)** | 219-221 | Yellow | 85.81 |
| **B7** | $(i\text{-}PrIMSe)_4PtCl_2$ | 27.97 **(27.05)** | 4.69 **(4.57)** | 10.87 **(10.33)** | 173-176 | Orange | 81.16 |

## 3.4 Single crystal X-ray crystallography

X- Ray measurements of ***B5*** and ***B7*** were obtained as yellow plates by methanol. The data were performed at 203K (-70°C) and 293(20°C) respectively on a Stoe Mark II-Image Plate Diffraction System [102] equipped by goniometer of two-circle and using monochromated radiation ( $\lambda$ = 0.71073 Å) MoK $\alpha$ graphite. Molecular structures were obtained using SHELXS-2014 [103]. The all calculations and refinement were achieved usingSHELXL-2014 [104].

The C-bound H-atoms and NH were calculated and treated as riding atoms: C-H = 0.97 - 0.98 Å with $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl H atoms and = $1.2U_{eq}(C)$ for other H-atoms. While the non-H atoms were refined anisotropically using full-matrix least-squares on

$F^2$. A semi-empirical absorption correction was applied using the MULABS routine in PLATON [105]. The figures were drawn using the program Mercury [106].

The whole molecules of the **B5** and **B7** compounds are generated by inversion symmetry, with the Pt(II) ion located at inversion center of the complex.

Table 3: Summary of crystallographic data for complexes for **B5**.

| | |
|---|---|
| Crystal data | |
| Chemical formula | $C_{20}H_{38}N_8PtSe_4 \cdot 2(Cl)$ |
| Molecular weight | 974.43 |
| Crystal system, space group | Triclinic, P-1 |
| Temperature (K) | 203 |
| *a*, *b*, *c* (Å) | 9.2384 (9), 9.6001 (10), 10.7454 (12) |
| α, β, γ (°) | 116.430 (8), 96.169 (9), 109.714 (8) |
| *V* (Å$^3$) | 764.95 (15) |
| *Z* | 1 |
| Radiation type | Mo *K*α |
| μ (mm$^{-1}$) | 9.54 |
| Crystal size (mm) | 0.40 × 0.24 × 0.03 |
| Data collection | |
| Diffractometer | STOE *IPDS* 2 diffractometer |
| Absorption correction | Multi-scan (*MULABS*; Spek, 2009) |
| $T_{min}$, $T_{max}$ | 0.598, 1.000 |
| No. of measured, independent and observed [$I > 2\sigma(I)$] reflections | 11226, 3088, 2360 |
| $R_{int}$ | 0.105 |
| $(\sin \theta/\lambda)_{max}$ (Å$^{-1}$) | 0.622 |
| Refinement | |
| $R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S* | 0.042, 0.058, 1.16 |
| No. of reflections | 3088 |
| No. of parameters | 168 |
| No. of restraints | 2 |
| H-atom treatment | H-atom parameters constrained |
| $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å$^{-3}$) | 1.35, - 2.19 |

Computer programs: *X-AREA* (Stoe & Cie, 2009), *X-RED32* (Stoe & Cie, 2009), *SHELXS2014*/6 (Sheldrick, 2008), *PLATON* (Spek, 2009) and *Mercury* (Macrae *et al.*, 2008.

Table 4: Summary of crystallographic data for complexes for **B7**.

| | |
|---|---|
| Crystal data | |
| Chemical formula | $C_{24}H_{48}Cl_2N_8PtSe_4$ |
| Molecular weight | 1030.53 |
| Crystal system, space group | Monoclinic, P $2_1/c$ |
| Temperature (K) | 293K |
| *a*, *b*, *c* (Å) | 11.6644 (6), 25.9727 (17), 13.5261 (8) |
| α, β, γ (°) | 90, 98.711 (5), 90 |
| *Volume* (Å$^3$) | 4050.5 (4) |
| *Z* | 4 |
| Radiation type | Mo *K*α |
| μ (mm$^{-1}$) | 7.22 |
| No. of measured, independent and observed [$I > 2\sigma(I)$] reflections | 18644, 9348, 6857 |
| $R_{int}$ | 0.045 |
| $(\sin \theta/\lambda)_{max}$ (Å$^{-1}$) | 0.685 |
| | |
| Refinement | |
| $R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S* | 0.067, 0.231, 1.34 |
| No. of reflections | 9348 |
| No. of parameters | 361 |
| H-atom treatment | H atoms treated by a mixture of independent and constrained refinement |
| $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å$^{-3}$) | 4.31, - 1.74 |

Computer programs: *SHELXS97* (Sheldrick, 1990), *SHELXL97* (Sheldrick, 1997).

## 3.5 *In vitro* cytotoxic activity against HeLa and MCF7 human cancer cell lines

### 3.5.1 Cell cultures

Human Cervical cancer HeLa and Brest cancer cell lines MCF-7 were grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% Fetal Bovine Serum (FBS), and 1% penicillin (10,000 units), streptomycin (10 mg), in 74 cm2 flask and incubated until 80% confluences obtained in humidified environment of, 5% $CO_2$, 95% air, 37 °C.

### 3.5.2 MTT assays for anticancer activity of $[PtL_2Cl_2]$ complexes

All $[PtL_2Cl_2]$ complexes and cisplatin (positive control) at 0.195 µM, 0.39µM, 0.781µM, 1.56µM, 3.125 µM, 6.25 µM, 12.5 µM, 25 µM, and 50 µM concentrations were prepared in DMEM. Cancer cells were seeded and maintained in quadruplicate in a 96-well tissue culture plate at 5 X 104 cells per well in 200 µl of same medium. The cancer cells were incubated 24 hours before the treatment. All compounds were dissolved in 50% DMSO. Therefore, DMSO was used as a negative control. The final DMSO concentration, in each well, was less than 0.1%. The cancer cells were treated with the synthesized compounds along with the cisplatin and the resultant cultures were incubated for 24 h. The medium of wells was discarded and 100 µL DMEM containing MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) (5 mg/mL) was added to the wells and incubated in a $CO_2$ incubator at 37 °C in the dark for 4 hrs. After incubation, a purple colored formazan (artificial chromogenic dye, a product of the reduction of water insoluble tetrazolium salts e.g., MTT by dehydrogenases and reductases) in the cells is

produced and appeared as dark crystals in the bottom of the wells. The medium of culture was discarded from each well carefully to avoid disruption of the monolayer. Around 100 µL of isopropanol has been added in each well. To dissolve the formazan crystals the solution was mixed in the wells which gave a purple solution. Using Mithras2LB943 against reagent blank, the absorbance of the 96-well plate was taken at 570 nm. All data presented are mean ± standard deviation.

# CHAPTER 4
# RESULTS AND DISCUSSIONS

## 4.1 Synthesis of the compounds

The interaction of platinum(II) with selone ligands gave two types of compounds with a general formula of $[PtCl_2(L)_2]$ and ionic species of $[Pt(L)_4]Cl_2$ in a good yields with different melting points see Table 1 and 2.

The two types of complexes were synthesized by direct addition of a solution of potassium tetracchloroplatinate(II) $K_2PtCl_4$ to aqueous solution of the selenium containing ligands. The first series of these complexes have been synthesized in molar ratio 1:2 (0.500 mmol) of $K_2PtCl_4$ with (1.00 mmol) of selone ligands resulted in a clear colored solutions,colored precipitate complexes were obtained directly after sterring. These compounds are expected to have *trans*-configurations based on stereochemical aspects.

The elemental analyses data of the $[PtCl_2(L)_2]$ complexes were summarized in Table 1.

And the second series of complexes have been synthesized in molar ratio 1:4 when an aqueous solutions of $K_2PtCl_4$ (0.25 mmol) was treated with selenium containing ligands (selone ligands) (1.00 mmol) such as isopropyl-IMSe **(B7)** and ethyl-IMSe **(B5)** resulted in the form of a yellow clear solution. After the mixture was left at ambient temperature, the resultant yellow crystals appropriate for X-ray structure determination were recovered after solvent mixtures were evaporated. While the other selone ligands gave powder products when they are treated with $K_2PtCl_4$, the observed elemental analytical data

(CHNS) % of ionic species of $[Pt(L)_4]Cl_2$ compounds is consistent with their compositions as given in Table 2.

## 4.2 Spectral measurements

### 4.2.1 Infrared Spectroscopy

The ambidentate selenium containing ligands (selones) are potentially capable to interact through the selenium or the nitrogen atoms. There are three major infrared bands that are generally diagnose the particular binding mode of selones to platinum(II) ions. These include ν(>C=Se), ν(C- N) and ν(N–H) [40]. All the selected infrared spectroscopic absorption frequencies of the selenium containing ligands (selones) and their related platinum(II) species are listed in Table 5. The assignment of selenocarbonyl(>C=Se) frequencies for the all of the platinum(II) compounds with selone ligands is difficult in the infrared spectra, this is attributed to the strongest coupling between selenocarbonyl(>C=Se) band with various absorptions signal in the region of fingerprint in FTIR spectrum. However, the characteristic band in the range from (500-650 $cm^{-1}$) directly assigned for (>C=Se) vibrations [107]. A shift in ν(>C=Se) mode of all free selone ligands towards lower frequencies is observed on its complexation with platinum(II). This shifting of bands towards lower wave number in most platinum(II) complexes, is in agreement with our suggestion that selenium atom is bonded to platinum center and the double bond character has been reduced,and this confirms that the selone ligand coordinate to the platinum(II) ion through selenium of selenocarbonyl group [107].

The strong and broad band in the range of 1400-1600 $cm^{-1}$ was observed for all free selones and their corresponding compounds. According to the literature, this band

assigned for (C- N) stretching vibrations. Upon the coordination this signal shifted to higher frequency (wave number), this is indicating to an increase in the number of # electron density of C-N bond because of the connection via selenium [107-108].

The characteristic band in the spectrum of the free selone near 3200 $cm^{-1}$ was observed and assigned directly to N–H stretching vibrations. This band is shifted to a higher frequency in all the synthesized platinum (II) compounds as a result of increase in the double bond character of C-N and this confirms that the selone ligand coordinate to the platinum(II) ion through selenium of selencarbonyl group not via nitrogen atom [109].

The existence of (N–H) vibration mode in the compounds after the complexation confirms the presence of solid state selone ligands in our new complexes [110].

The far-infrared spectra in the frequency region below 400 $cm^{-1}$ has been done to investigate v(M-Se) and v(M-Cl) stretching frequencies, which lie in the range of about 300 $cm^{-1}$ for the transition-metal complexes according to literature [111]. In all complexes a sharp peak around 270 $cm^{-1}$ was observed and assigned to platinum-seleinum bond. In case of the first series another peak around 300 $cm^{-1}$ were observed and assigned for Pt-Cl bond [111].

Table 5: Selected mid and far infrared absorption ($cm^{-1}$) of the selones and their corresponding complexes.

| Code | Species | Mid and Far-IR frequencies ($cm^{-1}$) | | | | |
|---|---|---|---|---|---|---|
| | | ν(C=Se) | ν(C-N) | ν(N–H) | ν(Pt–Se) | ν(Pt-Cl) |
| - | DiazSe | 601 | 1430 | 3200 | - | - |
| **A1** | $(DiazSe)_2PtCl_2$ | 561 | 1469 | 3267 | 262 | 326 |
| **B1** | $(DiazSe)_4PtCl_2$ | 587 | 1473 | 3285 | 268 | - |
| - | DiapSe | 615 | 1453 | 3224 | - | - |
| **A2** | $(DaipSe)_2PtCl_2$ | 510 | 1459 | 3350 | 265 | 331 |
| **B2** | $(DaipSe)_4PtCl_2$ | 606 | 1549 | 3386 | 274 | - |
| - | PrImSe | 513 | 1460 | 3210 | - | - |
| **A3** | $(PrImSe)_2PtCl_2$ | 492 | 1497 | 3343 | 275 | 321 |
| **B3** | $(PrImSe)_4PtCl_2$ | 501 | 1510 | 3390 | 281 | - |
| - | SeU | 736 | 1520 | 3265 | - | - |
| **A4** | $(SeU)_2PtCl_2$ | 560 | 1565 | 3267 | 263 | 328 |
| **B4** | $(SeU)_4PtCl_2$ | 586 | 1609 | 3310 | 271 | - |
| - | EtIMSe | 514 | 1465 | 3198 | - | - |
| **A5** | $(Et\text{-}ImSe)_2PtCl_2$ | 479 | 1479 | 3265 | 273 | 332 |
| **B5** | $(Et\text{-}ImSe)_4PtCl_2$ | 574 | 1505 | 3106 | 287 | - |
| - | ImSe | 561 | 1463 | 3250 | - | - |
| **A6** | $(ImSe)_2PtCl_2$ | 513 | 1499 | 3325 | 268 | 327 |
| **B6** | $(ImSe)_4PtCl_2$ | 566 | 1520 | 3369 | 272 | - |
| - | *i*-PrImSe | 601 | 1453 | 3210 | - | - |
| **A7** | $(i\text{-}PrImSe)_2PtCl_2$ | 556 | 1486 | 3267 | 273 | 334 |
| **B7** | $(i\text{-}PrImSe)_4PtCl_2$ | 598 | 1532 | 3304 | 281 | - |

### 4.2.2 $^1$H NMR

All the $^1$H NMR spectra of the two types of synthesized complexes of general formula of $[PtCl_2(L)_2]$ and ionic species of $[Pt(L)_4]Cl_2$ have been measured in DMSO $d_6$ solution,

and all of the synthesized compounds shows the expected signals and all the signal assigned to the free selenium containing ligands(selones) observed In the $^{1}$H NMR spectra were also observed in the synthesized complexes spectra.

$^{1}$H NMR data for the synthesized compounds and their original free ligands are listed in Table 6 (numbering of ligands in Figure 2). The N-H resonance shift of selone ligands, are observed after coordination to Pt(II) ion. However, this signal upon coordination to platinum metal becomes less intensity and shifted slightly downfield toward higher frequency by the range from 0.86 ppm at **A5** complex to 1.6 ppm at **B7** compound from their positions in the free ligands. These shifts are due to the move of the electron density from the group of selenocarbonyl to the neighboring N-C bond [108]. This increasing of electron density shift for the double bond character of C-N single bond while reducing, the double bond character of the >C=Se, resulting in a downfield shift for the N-H resonance [110,112]. This downfield shift is characteristic of the free selones bounded to Pt(II) ion via the selenium atoms not through atoms of nitrogen [113-114]. These NMR shifts upon coordination are consistent with platinum binding stabilizing, the resonance structure formula that describes the places of the positive charge into the heterocyclic ring which are schemed in Figure 12.

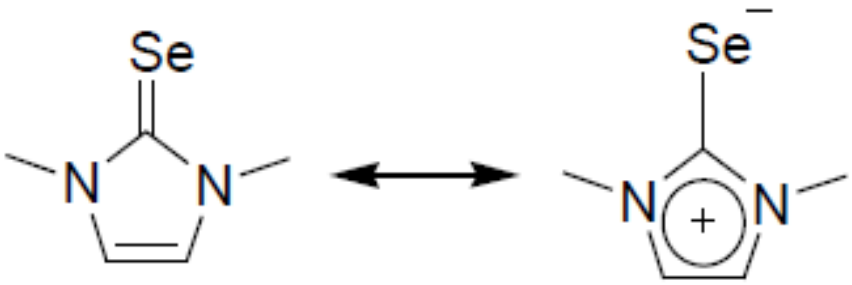



**Figure 12: Resonances structures for the selone ligands.**

### 4.2.3 $^{13}$C NMR

All the $^{13}$C {$^{1}$H} NMR chemical shifts for free selone ligand and their corresponding platinum complexes are summarized in Table 6.

$^{13}$C {$^{1}$H}NMR spectroscopy of Pt(II) with selone ligands compounds. For all of the platinum compounds, the $^{13}$C {$^{1}$H} NMR resonances for the selenocarbonyl(>C=Se) of the platinum bound selenium containing ligands (selones) are shifted upfield relative to uncoordinated ligands, and this shows a good consistent with that reported by the literature [111].

This upfield shift is assigned for the C-2 resonance corresponding to selenocarbonyl >C=Se resonance observed in lower frequency regions by the range from 2.75 ppm at **B5** to 13.97 ppm at **A6** specie as compared to the free selone ligands.

These shifts are due to the decreasing in the double bond character of the >C=Se and formation of partial double bond character in the C-N bond. This confirms the suggestion that selones ligands are coordinated to the Pt(II) ion via selenium of selenocarbonyl not through nitrogen atom [ 112 ,115].

The increased of # electron density for the C-N bond upon coordination to platinum metal results in negligible increases in deshielding effects on C-4 and C-5, as supported by observed downfield shifts of the C-4 and C-5 resonances directly [116].

Table 6:$^{1}$H and $^{13}$C{$^{1}$H} NMR chemical shifts in ppm for the Pt(II) compounds with selones in DMSO $d_6$.

| Code | Species | N-H | C-2 | C-4 | C-5 | C-6 | C-7 | N-C1 | N-C2 | CH3 |
|---|---|---|---|---|---|---|---|---|---|---|
| | DiazSe | 8.07 | 169.07 | 40.36 | 18.88 | 40.36 | - | - | - | - |
| A1 | $(DiazSe)_2PtCl_2$ | 9.30 | 160.48 | 40.26 | 18.46 | 40.26 | - | - | - | - |
| | Δ | 1.23 | -8.59 | -0.10 | -0.42 | -0.10 | - | - | - | - |
| B1 | $(DiazSe)_4PtCl_2$ | 9.08 | 162.13 | 40.15 | 18.86 | 40.15 | - | - | - | - |
| | Δ | 1.01 | -6.94 | -0.21 | -0.02 | -0.21 | - | - | - | - |
| | DiapSe | 8.07 | 180.83 | 45.5 | 26.86 | 26.86 | 45.5 | - | - | - |
| A2 | $(DaipSe)_2PtCl_2$ | 9.16 | 171.71 | 46.78 | 26.4 | 26.4 | 46.78 | - | - | - |
| | Δ | 1.09 | -9.12 | 1.28 | -0.46 | -0.46 | 1.28 | - | - | - |
| B2 | $(DaipSe)_4PtCl_2$ | 9.19 | 171.88 | 46.64 | 26.25 | 26.25 | 46.64 | - | - | - |
| | Δ | 1.12 | -8.95 | 1.14 | -0.61 | -0.61 | 1.14 | - | - | - |
| | PrImSe | 8.81[b] | 179.55[a] | 50.19 | 48.62 | - | - | 42.60 | 20.37 | 10.99 |
| A3 | $(PrImSe)_2PtCl_2$ | 9.85 | 176.65 | 52.21 | 49.85 | - | - | 43.27 | 21.32 | 11.21 |
| | Δ | 1.04 | -2.90 | 2.02 | 1.23 | - | - | 0.67 | 0.95 | 0.22 |
| B3 | $(PrImSe)_4PtCl_2$ | 9.66 | 170.42 | 49.82 | 49.59 | - | - | 43.82 | 20.76 | 11.1 |
| | Δ | 0.85 | -9.13 | -0.37 | 0.97 | - | - | 1.22 | 0.39 | 0.11 |
| | SeU | 7.59 | 178.83 | - | - | - | - | - | - | - |
| A4 | $(SeU)_2PtCl_2$ | 8.59 | 168.02 | - | - | - | - | - | - | - |
| | Δ | 1.00 | -10.83 | - | - | - | - | - | - | - |
| B4 | $(SeU)_4PtCl_2$ | 8.55 | 171.19 | - | - | - | - | - | - | - |
| | Δ | 0.96 | -7.64 | - | - | - | - | - | - | - |
| | Et-ImSe | 8.32 | 178.66 | 43.33 | 47.91 | - | - | 42.51 | - | 12.09 |
| A5 | $(Et\text{-}ImSe)_2PtCl_2$ | 9.15 | 174.59 | 43 | 48.38 | - | - | 42.9 | - | 12.19 |
| | Δ | 0.83 | -4.07 | -0.33 | 0.47 | - | - | 0.39 | - | 0.10 |
| B5 | $(Et\text{-}ImSe)_4PtCl_2$ | 9.67 | 175.91 | 43.18 | 48.96 | - | - | 43.18 | - | 12.23 |
| | Δ | 1.35 | -2.75 | -0.15 | 1.05 | - | - | 0.67 | - | 0.14 |
| | ImSe | 8.32 | 177.05 | 45.26 | 45.26 | - | - | - | - | - |
| A6 | $(ImSe)_2PtCl_2$ | 9.47 | 163.08 | 45.64 | 45.64 | - | - | - | - | - |
| | Δ | 1.15 | -13.97 | 0.38 | 0.38 | - | - | - | - | - |
| B6 | $(ImSe)_4PtCl_2$ | 9.59 | 167.93 | 45.34 | 45.34 | - | - | - | - | - |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Δ | 1.27 | -9.12 | 0.08 | 0.08 | - | - | - | - | - |
| | *i* -PrImSe | 8.26 | 177.71 | 42.65 | 42.69 | - | - | 48.21 | - | 19.45 |
| A7 | (*i*-PrImSe)$_2$PtCl$_2$ | 9.44 | 167.47 | 44.00 | 43.58 | - | - | 48.35 | - | 19.65 |
| | Δ | 1.18 | -10.24 | 1.35 | 0.89 | - | - | 0.14 | - | 0.20 |
| B7 | (*i*-PrImSe)$_4$PtCl$_2$ | 9.86 | 167.3 | 43.13 | 43.69 | - | - | 48.92 | - | 19.41 |
| | Δ | 1.60 | -10.41 | 0.48 | 1.00 | - | - | 0.71 | - | -0.04 |

[a] Dissolved in $D_2O$. [b] Dissolved in $CDCl_3$. Δ = Change in chemical shifts.

### 4.2.4 $^{13}$C solid state NMR

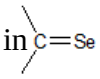
Table 7, lists all the significant $^{13}$C solid state NMR signals of the selones and their relevant platinum(II) compounds. In solid state $^{13}$C NMR, no significant change in the chemical shifts of the selones ligand after coordination were observed other than C-2 signals see Table 7. Upfield shifts of 5.70 to 14.88 ppm in  resonance indicates that in all compounds, platinum(II) ion is coordinated to selenium containing ligands (selones) via selenium not through nitrogen atom [115-116].

Table 7: Shows the solid state $^{13}C$ NMR chemical shifts of Pt(II) complexes with selones.

| Code | Species | C-2 | C-4 | C-5 | C-6 | C-7 | N-C1 | $-CH_3$ |
|---|---|---|---|---|---|---|---|---|
| | DiazSe | 171.07 | 40.36 | 19.55 | 40.36 | - | - | - |
| A1 | $(DiazSe)_2PtCl_2$ | 162.25 | 40.26 | 18.98 | 40.26 | - | - | - |
| B1 | $(DiazSe)_4PtCl_2$ | 166.54 | 40.15 | 19.25 | 40.15 | - | - | - |
| | DaipSe | 183.08 | 48.62 | 27.21 | 27.21 | 48.62 | - | - |
| A2 | $(DaipSe)_2PtCl_2$ | 168.2 | 45.75 | 27.8 | 27.8 | 45.75 | - | - |
| B2 | $(DaipSe)_4PtCl_2$ | 174.79 | 48.47 | 28.38 | 28.38 | 48.47 | - | - |
| | SeU | 178.21 | - | - | - | - | - | - |
| A4 | $(SeU)_2PtCl_2$ | 167.91 | - | - | - | - | - | - |
| B4 | $(SeU)_4PtCl_2$ | 172.51 | - | - | - | - | - | - |
| | Et-ImSe | 177.02 | 43.33 | 47.91 | - | 42.51 | - | 12.09 |
| A5 | $(Et\text{-}ImSe)_2PtCl_2$ | 166.23 | 43.11 | 48.38 | - | 42.92 | - | 12.19 |
| B5 | $(Et\text{-}ImSe)_4PtCl_2$ | 168.11 | 43.18 | 48.96 | - | 43.18 | - | 12.23 |
| | ImSe | 176.38 | 45.91 | 45.91 | - | - | - | - |
| A6 | $(ImSe)_2PtCl_2$ | 166.41 | 41.29 | 19.23 | - | - | - | - |
| B6 | $(ImSe)_4PtCl_2$ | 168.38 | 42.39 | 20.96 | - | - | - | - |

### 4.2.5 $^{77}Se\{^1H\}$ NMR

$^{77}Se$ NMR measurements were reported relative to ($NaHSeO_3$ in $D_2O$) as external reference at 1308.00 ppm, using 95.35 MHz, 2.00 s pulse delay and using 0.311 s acquisition time.

The $^{77}Se\{^1H\}$ solution NMR spectra for all of the synthesized platinum(II) complexes with selone ligands have been carried out in DMSO-$d_6$ as they are given in Table 8.

In all Pt(II) complexes, the >C=Se signal shifted upfield in the range between (δ -4.38 for complex B7 to -76.25 at complex **A2**) upon the selenium containg ligands(selones) coordinated to platinum central atom relative to their free selone ligands.

This upfield shift due to the binding of selenium atom to electron-rich site of Platinum ion. However, there is no correlation exists between the lengths of (Pt-Se bond) and $^{77}Se$ NMR shifts. Also this shift related to an increasing in π e density in of N-C bond after coordination took place [117]. This very large shielding provides a clear evidence for selenium binding to platinum (II) ion not to nitrogen atom [115,117].

### 4.2.6 $^{195}$Pt NMR

All our synthesized platinum(II) complexes containing selone ligands and their precursor potassium tetracholoplatinate ($K_2PtCl_4$ with **δ = -1620 ppm** in $D_2O$) have been tested using $^{195}Pt$ NMR solution in $CD_3OD$ as NMR solvent and all of them their platinum signals shifted to upfield after the complexation due to highest shielding occurred by the movement of the electrons from the selenium atom of the selone ligands to the central platinum atom of these complexes through covenant bond, these upfield shifts confirmed the suggestion that the Pt(II) ion connected to the free selone ligands through the selenium atom only [118-119]. And all their data listed in Table 8.

Table 8: $^{77}Se\{^{1}H\}$ and $^{195}Pt$ NMR data in ppm for the platinum(II) compounds with selones in DMSO $d_6$ .

| Code | Species | δ $^{77}$Se in ppm [a] | δ $^{195}$Pt in ppm [b] |
|---|---|---|---|
| | DiazSe | 199.93 | - |
| **A1** | $(DiazSe)_2PtCl_2$ | 126.35 | - 3950 |
| | Δ | -73.58 | 2330 |
| **B1** | $(DiazSe)_4PtCl_2$ | 176.69 | - 4220 |
| | Δ | -23.24 | - 2600 |
| | DaipSe | 292.00 | - |
| **A2** | $(DaipSe)_2PtCl_2$ | 215.75 | - 3934 |
| | Δ | -76.25 | 2314 |
| **B2** | $(DaipSe)_4PtCl_2$ | 273.78 | - 4318 |
| | Δ | -18.22 | 2698 |
| | N-PrImSe | 57.93 | - |
| **A3** | $(N\text{-}PrImSe)_2PtCl_2$ | 26.91 | - 3875 |
| | Δ | -31.02 | 2255 |
| **B3** | $(N\text{-}PrImSe)_4PtCl_2$ | 43.70 | -4327 |
| | Δ | -14.23 | 2707 |
| | (SeU) | 200.70 | - |
| **A4** | $(SeU)_2PtCl_2$ | 149.60 | N/A |
| | Δ | -51.12 | - |
| **B4** | $(SeU)_4PtCl_2$ | 172.84 | N/A |
| | Δ | -27.88 | - |
| | EtImse | 64.85 | - |
| **A5** | $(EtImse)_2PtCl_2$ | 47.35 | - 3975 |
| | Δ | -17.50 | 2355 |
| **B5** | $(EtImse)_4PtCl_2$ | 57.23 | -4315 |
| | Δ | -7.62 | 2695 |
| | ImSe | 73.53 | - |
| **A6** | $(ImSe)_2PtCl_2$ | 48.52 | N/A |
| | Δ | -25.01 | - |
| **B6** | $(ImSe)_4PtCl_2$ | 60.61 | N/A |
| | Δ | -12.92 | - |
| | *i*-PrImSe | 69.29 | - |
| **A7** | $(i\text{-}PrImSe)_2PtCl_2$ | 29.50 | - 3810 |
| | Δ | -39.79 | 2190 |
| **B7** | $(i\text{-}PrImSe)_4PtCl_2$ | 64.91 | - 4317 |
| | Δ | -4.38 | 2697 |

[a] in DMSO and [b] in $CD_3OD$

## 4.3 Structural analysis of tetrakis-platinum(II) selone complexes

### 4.3.1 Crystal structure of complex B5 and B7

The X-ray structure of compounds **B5** and **B7** are shown in Figures 13 and 15 respectively. The geometrical parameters are given in Table 9. The $Pt^{2+}$ ion in both **B5** and **B7** is coordinated to four selenium atoms, each belonging to an *N*-alkylimidazolidine-2-selenone ligand. The Pt–Se bond lengths of 2.4200(11)–2.4389(7) Å are similar to the related compounds [46, 67] such as, tetrakis(selenourea)platinum(II) chloride [61]. In **B5**, the *cis* Se–Pt–Se angles are 86.98(3) and 93.02(3)°, while the *trans* angles are 180°. In **B7**, the *cis* angles around Pt are nearly 90°, whereas the *trans* angles are 165.64(4)° and 173.49(4)° (Table 9). These values reflect that the geometry at platinum is somewhat distorted square planar. The SeCN2 moieties of the ligand molecules are essentially planar. The smaller N–C(Se) bond lengths compared to the otherN–C bond distances are in agreement with a marked double bond character in the N–C(Se) bond. In **B5**, the N–H groups (N1-H1 and N3–H3) of two *cis* selenone ligands are engaged in hydrogen bonding with a common chloride ion giving a hydrogen bonding bridge [N–H···Cl···H–N] as shown in Figure 14. A closer look to hydrogen bonding interactions in **B7** reveals that all the selenone ligands are engaged in hydrogen bonding interactions with one chloride counter ion resulting in an umbrella like structure as shown in Figure 16. This H-bonding scheme gives two decametallacycles [PtSeCNH···Cl···HNCS] in which all the selenium atoms are pushed out of the [PtSe4] mean plane. The details of hydrogen-bond geometry (Å, °) in **B5** and **B7** are given in Tables 10 and 11 respectively.

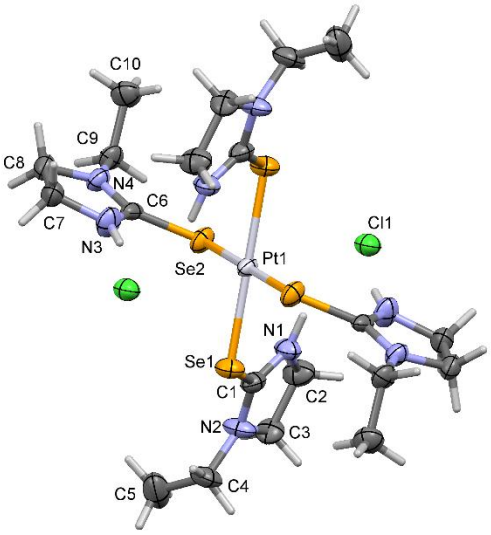



Figure 13: A view of the molecular structure of **B5**, with atom labelling. The displacement ellipsoids are drawn at the 50% probability level. The unlabeled atoms are related to the labelled atoms by symmetry code: -x + 1, -y + 1, -z + 1.

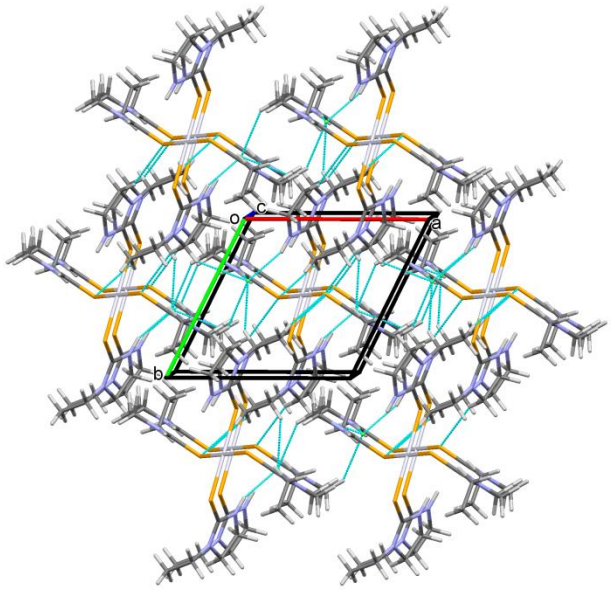



Figure 14: The packing of the crystal **B5**, observed along the (a) axis. The N-H…Cl, C-H…Cl and C-H…Se hydrogen bonds (dashed lines) lead to the formation of a three-dimensional supramolecular structure.

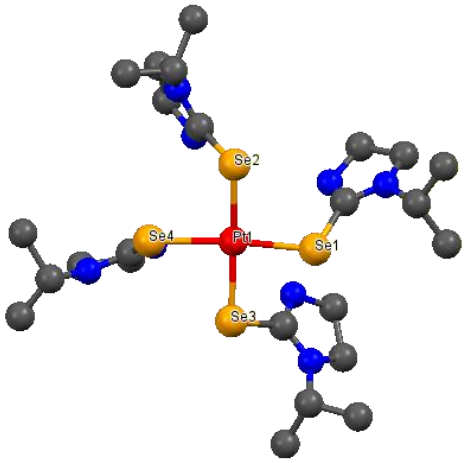



Figure 15: A view of the molecular structure of **B7**, with atom labelling. The displacement ellipsoids are drawn at the 50% probability level. The unlabeled atoms are related to the labelled atoms by symmetry code: -x + 1, -y + 1, -z + 1.

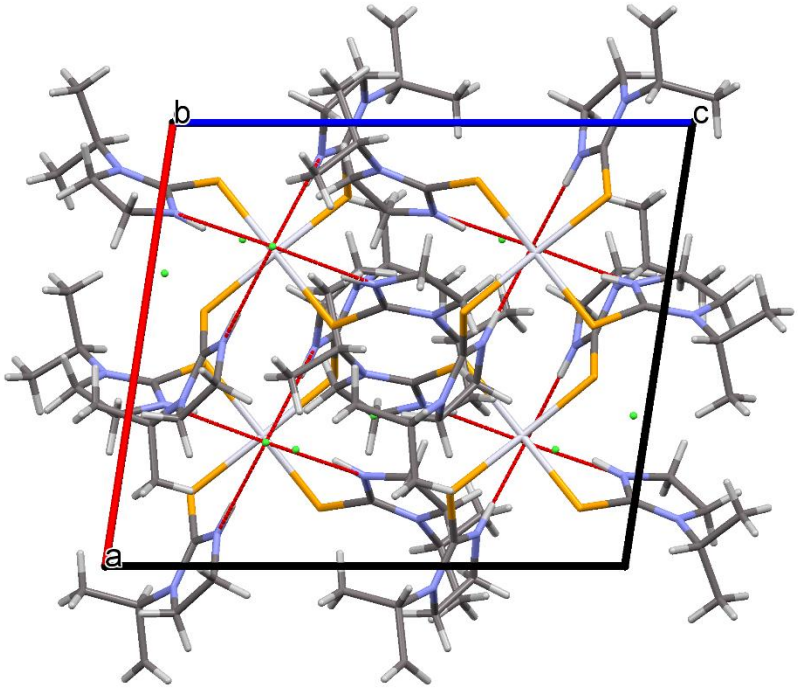



Figure 16: The packing of the crystal B7, observed along the (a) axis. The N-H…Cl and C-H…Cl hydrogen bonds (dashed lines).

Table 9: Selected bond distances (Å) and bond angles (˚) for compound **B5** and **B7**.

| | | | |
|---|---|---|---|
| **B5** | | | |
| Pt1-Se1 | 2.4320(7) | Se1-Pt1-Se2 | 93.02(3) |
| Pt1-Se2 | 2.4389(7) | Se1a-Pt1-Se2a | 93.02(3) |
| Se1-C1 | | Se1-Pt1-Se2a | 86.98(3) |
| N1-C1 | | Se1a-Pt1-Se2 | 86.98(3) |
| N1-C2 | | Se1-Pt1-Se1a | 180.00 |
| | | Se2-Pt1-Se2a | 180.00) |
| **B7** | | | |
| Pt1-Se1 | 2.4278(11) | Se1-Pt1-Se2 | 89.48(4) |
| Pt1-Se2 | 2.4216(11) | Se1-Pt1-Se3 | 89.64(4) |
| Pt1-Se1 | 2.4200(11) | Se1-Pt1-Se4 | 165.64(4) |
| Pt1-Se1 | 2.4305(11) | Se2-Pt1-Se3 | 173.49(4) |
| | | Se2-Pt1-Se4 | 90.05(4) |
| | | Se3-Pt1-Se4 | 89.20(4) |

Symmetry code for **1**, a = 1-x,1-y,1-z

Table 10: Hydrogen-bond geometry (Å, °) for **B5**.

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| N1—H1N···Cl1 | 0.88 (2) | 2.28 (3) | 3.122 (6) | 159 (6) |
| N3—H3N···Cl1$^{i}$ | 0.87 (2) | 2.33 (3) | 3.174 (7) | 165 (6) |
| C2—H2A···Cl1$^{ii}$ | 0.98 | 2.99 | 3.715 (7) | 132 |
| C3—H3A···Se2$^{iii}$ | 0.98 | 3.04 | 3.958 (8) | 157 |
| C3—H3B···Cl1$^{ii}$ | 0.98 | 2.86 | 3.625 (8) | 135 |
| C5—H5B···Se2$^{iv}$ | 0.97 | 3.08 | 4.045 (8) | 171 |
| C8—H8A···Se1$^{v}$ | 0.98 | 3.14 | 3.865 (7) | 132 |
| C8—H8A···Cl1$^{vi}$ | 0.98 | 2.88 | 3.707 (7) | 143 |

Symmetry codes: (i) -*x*+1, -*y*+1, -*z*+1; (ii) -*x*+2, -*y*+2, -*z*+2; (iii) -*x*+1, -*y*+2, -*z*+2; (iv) *x*, *y*+1, *z*; (v) -*x*, -*y*+1, -*z*+1; (vi) *x*- 1, *y*, *z*.

Table 11: Hydrogen-bond geometry (Å, °) for **B7**

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| N8—HN8···Cl1$^{i}$ | 0.86 | 2.46 | 3.266 (9) | 155.8 |
| N6—HN6···Cl1$^{i}$ | 0.86 | 2.43 | 3.262 (10) | 163.5 |
| N2—HN2···Cl1$^{i}$ | 0.86 | 2.45 | 3.244 (10) | 154.6 |
| N4—H4A···Cl1$^{i}$ | 0.86 | 2.5 | 3.284 (11) | 152.3 |
| C20—H20A···Cl2A | 0.97 | 2.95 | 3.616 (16) | 126.7 |
| C23—H23C···Cl2B | 0.96 | 2.92 | 3.882 (18) | 177 |
| C23—H23A···Se4$^{ii}$ | 0.96 | 3.19 | 3.810 (14) | 123.7 |
| C21—H21A···Cl2B$^{i}$ | 0.97 | 2.76 | 3.541 (18) | 137.6 |
| C16—H16···Se3 | 0.98 | 2.79 | 3.287 (11) | 111.8 |
| C16—H16···Se3$^{iii}$ | 0.98 | 3.17 | 3.819 (12) | 125.4 |
| C10—H10···Se2 | 0.98 | 2.72 | 3.279 (11) | 116.9 |
| C10—H10···Se2 | 0.98 | 2.72 | 3.279 (11) | 116.9 |
| C16—H16···Se3 | 0.98 | 2.79 | 3.287 (11) | 111.8 |
| C16—H16···Se3$^{iii}$ | 0.98 | 3.17 | 3.819 (12) | 125.4 |
| C20—H20A···Cl2A | 0.97 | 2.95 | 3.616 (16) | 126.7 |
| C21—H21A···Cl2B$^{i}$ | 0.97 | 2.76 | 3.541 (18) | 137.6 |

| | | | | |
|---|---|---|---|---|
| C23—H23C···Cl2B | 0.96 | 2.92 | 3.882 (18) | 177 |
| N2—HN2···Cl1$^{i}$ | 0.86 | 2.45 | 3.244 (10) | 154.6 |
| N4—H4A···Cl1$^{i}$ | 0.86 | 2.5 | 3.284 (11) | 152.3 |
| N6—HN6···Cl1$^{i}$ | 0.86 | 2.43 | 3.262 (10) | 163.5 |
| N8—HN8···Cl1$^{i}$ | 0.86 | 2.46 | 3.266 (9) | 155.8 |
| Symmetry codes: (i) *x*, −*y*+1/2, *z*+1/2; (ii) −*x*+1, −*y*, −*z*+1; (iii) −*x*+1, −*y*, −*z*+2. | | | | |

## 4.4 *In vitro* cytotoxicity of $[PtL_2Cl_2]$ complexes

The cytotoxicity of synthesized complexes **A1, A2, A3, A4, A5, A6, A7** and cisplatin were assessed against two human cancers cell lines such as MCF7 (human breast cancer) and HeLa (human cervical cancer) cell lines. The cells were brooded with the studied compounds for 24 h and the feasibility was evaluated by a conventional MTT test. The $IC_{50}$ values of the synthesized compounds and cisplatin for MCF7 and HeLa human cancer cell lines were collected from the curves of the cell percentage viability and the concentration of the compound [120]. Furthermore, the impact of $PtL_2Cl_2$ complexes in μM on the percentage feasibility % of HeLa and MCF7 human cancer cells has been indicated graphically in figures 16 and 17 respectively. The $IC_{50}$ values of synthesized compounds run between 8.30 – 25.74 μM as given in Table 14.

Table 14, showed the effect of the **A1, A2, A3, A4, A5, A6** and **A7** complexes on HeLa (human cervical cancer) cell line, the $IC_{50}$ values for these compounds ranged from 11.33 to 25.74 μM indicates that the synthesized complexes are better *in vitro* cytotoxic agents than that of cisplatin, except compound **A6** was recognized to be less cytotoxic than cisplatin with $IC_{50}$ value of 25.74 μM, while the $IC_{50}$ value of cisplatin is of is 21.40 μM.

On the other hand, the result showed the complexes A1-A6 are two times higher cytotoxicity than cisplatin.

The synthesized complexes were also examined against (human breast cancer) MCF7 cell line; the compounds **A5, A6** and **A7** were showed more cytotoxic than cisplatin. However, the *in vitro* cytotoxicity of compounds **A1-A4** against MCF7cell lines was found to be less than cisplatin.

On the other hand, the observed results of these synthesized compounds **A1-A7** have consistent with a significant discerning cytotoxicity against specific human cancer cell lines and these complexes have high ability to interact with biomolecules such as proteins and DNA through ligand exchange.

Table 12: The potential cytotoxicity of the synthesized complexes **A1–A7** and cisplatin given as $IC_{50}$ ± S.D. in μM.

| Code | Complexes | $IC_{50}$ ± SEM[a] | |
|---|---|---|---|
| | | HeLa | MCF7 |
| - | **Cisplatin** | **21.40 ± 0.73** | **8.98 ± 0.07** |
| **A1** | **$(DiazSe)_2PtCl_2$** | **11.33 ± 0.20** | **12.27 ± 0.01** |
| **A2** | **$(DaipSe)_2PtCl_2$** | **11.50 ± 0.22** | **16.68 ± 0.02** |
| **A3** | **$(N\text{-}PrImSe)_2PtCl_2$** | **12.89 ± 0.16** | **18.64 ± 0.03** |
| **A4** | **$(SeU)_2PtCl_2$** | **19.78 ± 0.13** | **11.11 ± 0.05** |
| **A5** | **$(EtImse)_2PtCl_2$** | **17.73 ± 0.14** | **8.59 ± 0.07** |
| **A6** | **$(ImSe)_2PtCl_2$** | **25.74 ± 0.19** | **8.11 ± 0.06** |
| **A7** | **$(i\text{-}PrImSe)_2PtCl_2$** | **14.03 ± 0.16** | **8.30 ± 0.06** |

[a] Limit of errors is given in SEM as standard deviations determined from at least three independent experiments.

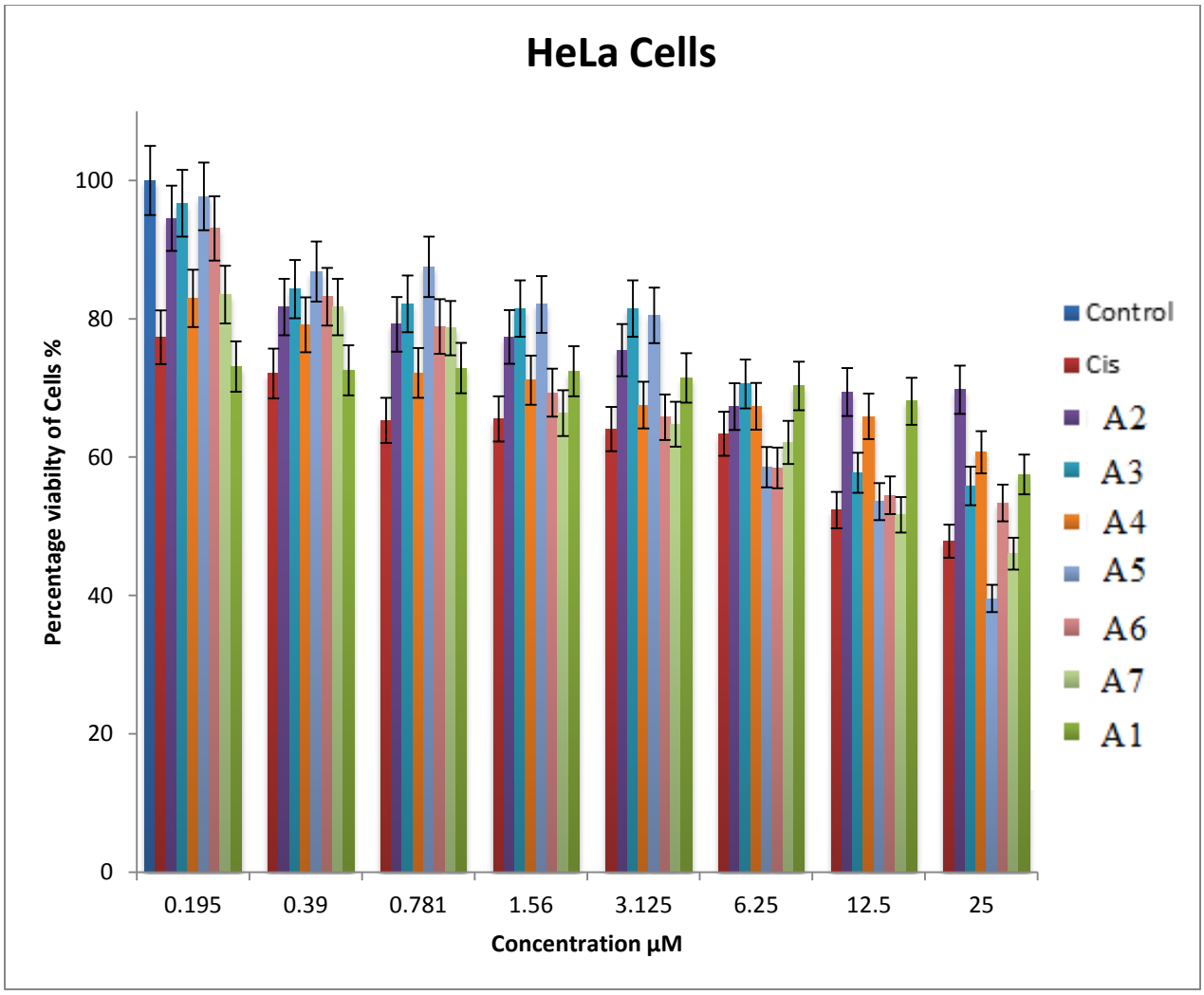



Figure 17: Effect of concentration in µM of $[PtL_2Cl_2]$ complexes and cisplatin on the percentage of cell viability of HeLa.

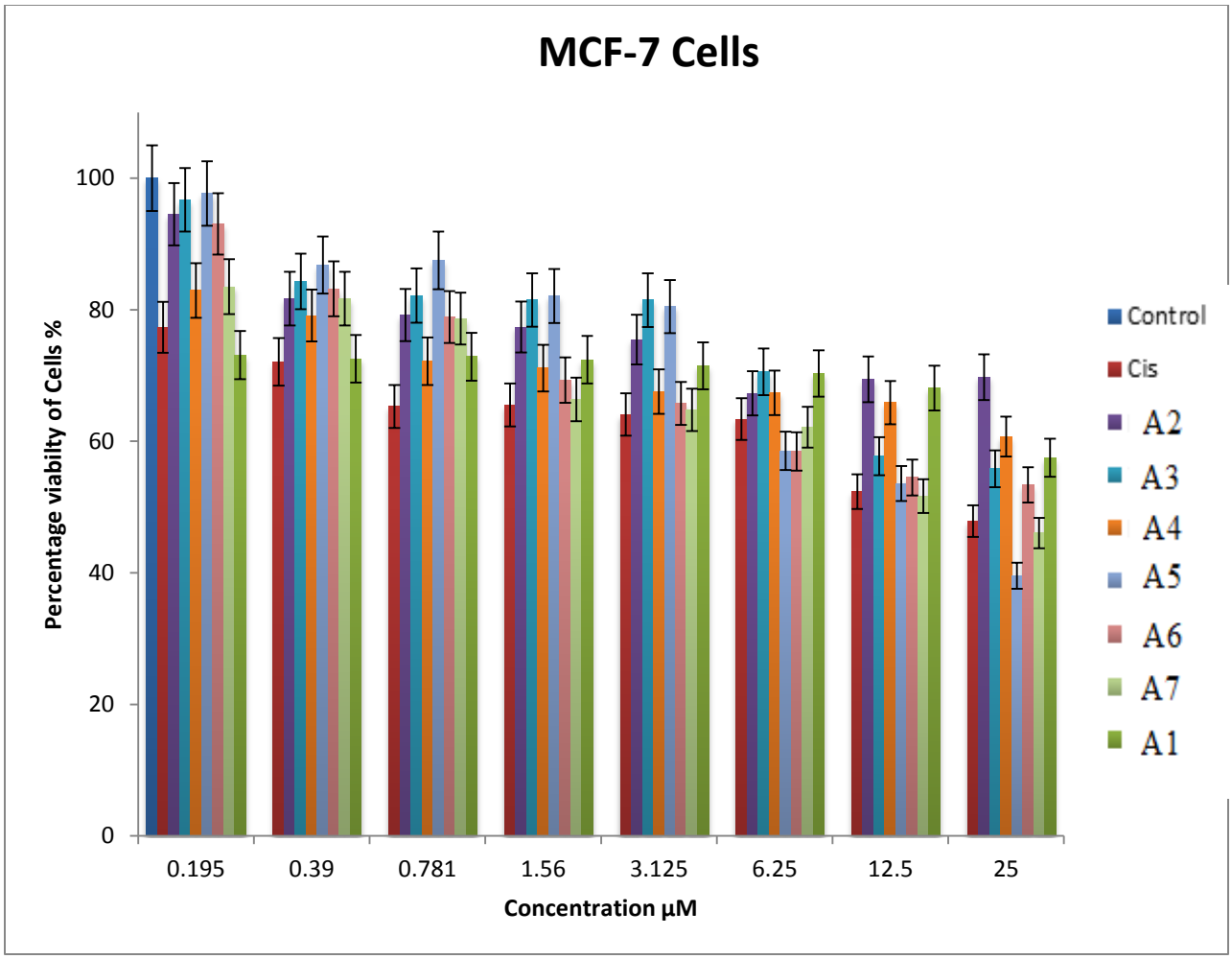



Figure 18: Effect of concentration in µM of $[PtL_2Cl_2]$ complexes and cisplatin on the percentage of cell viability of MCF7.

# CHAPTER 5
# CONCLUSION AND RECOMMENDATIONS

## 5.1 Conclusion

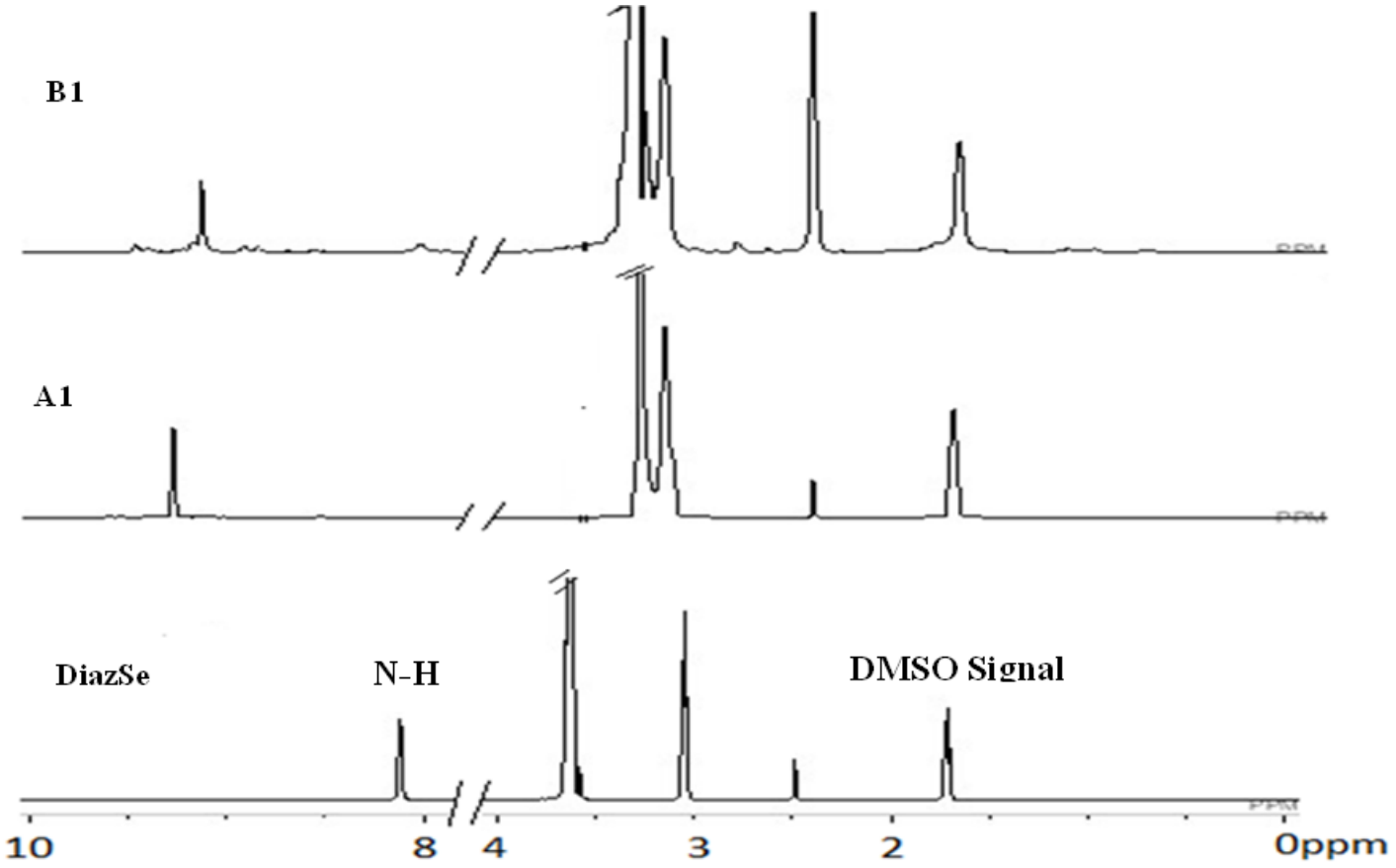
Biologically active $Pt^{2+}$ selone complexes have been synthesized and characterized using both spectroscopic and analytical techniques and their anticancer activity has been studied and compared to cisplatin. The X-ray measurements for compounds $[Pt(etimse)_4][Cl_2]$ (**B5**) and $[Pt(isoprimse)_4][Cl_2]$ (**B7**) have been determined. The data indicated that the platinum(II) ions were surrounded by the selone ligands via their selenium atoms and not via nitrogen atoms and the four-coordinate selone complexes of **B5** and **B7** adopt distorted square planar geometry.

The anticancer potential of the synthesized complexes was evaluated against HeLa and MCF7 human cancer cell lines. Most of the synthesized complexes showed higher cytotoxicity than cisplatin, and as it is clear in Table 14, **A1** complex have shown the highest cytotoxicity in HeLa cancer cell more than two fold better than cisplatin and the **A6** complex is best one in the treatment of the breast cancer. These finding could be the subject of further pharmacological investigations.

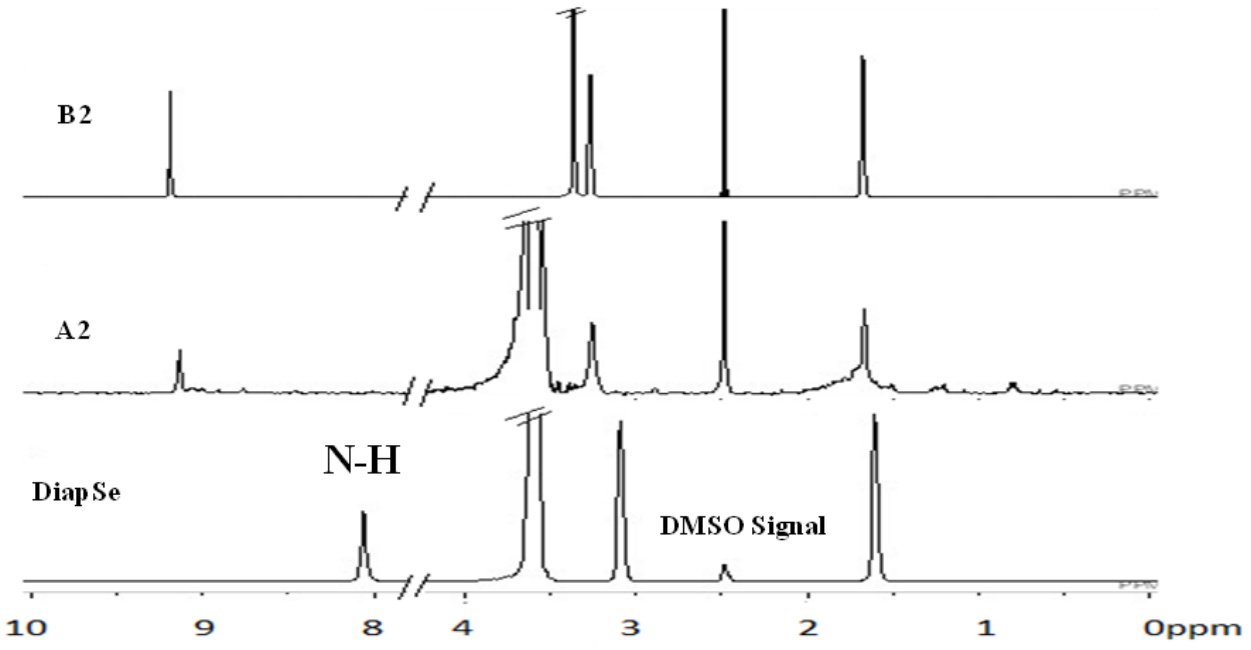
## 5.2 Recommendations

For future work, we highly recommend to study the interaction of the synthesized complexes with DNA, to explore the electronic effect of the ligands as well as to investigate the *in vivo* cytotoxicity of these complexes.

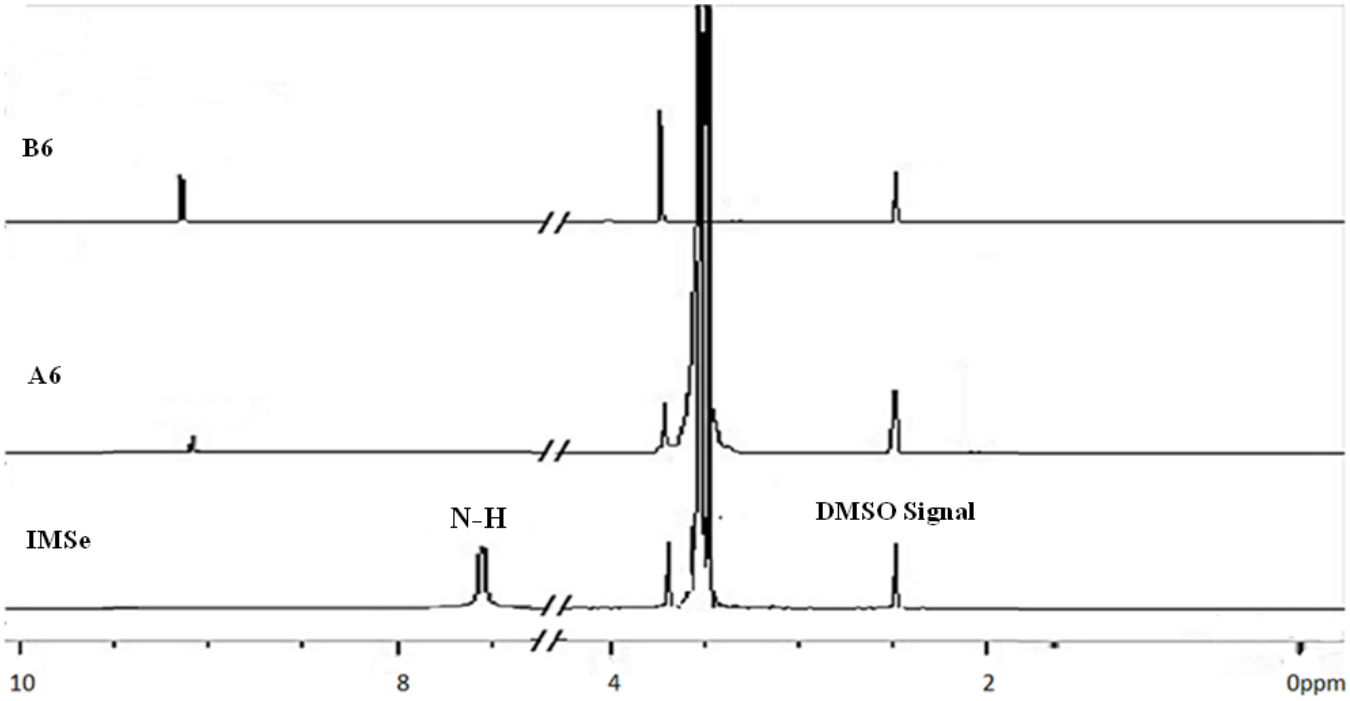
# Appendix A. $^{1}$H NMR




**$^{1}$H chemical shifts (ppm) of DiazSe and its Pt(II) complexes[A1 and B1] in DMSO-$d_6$**

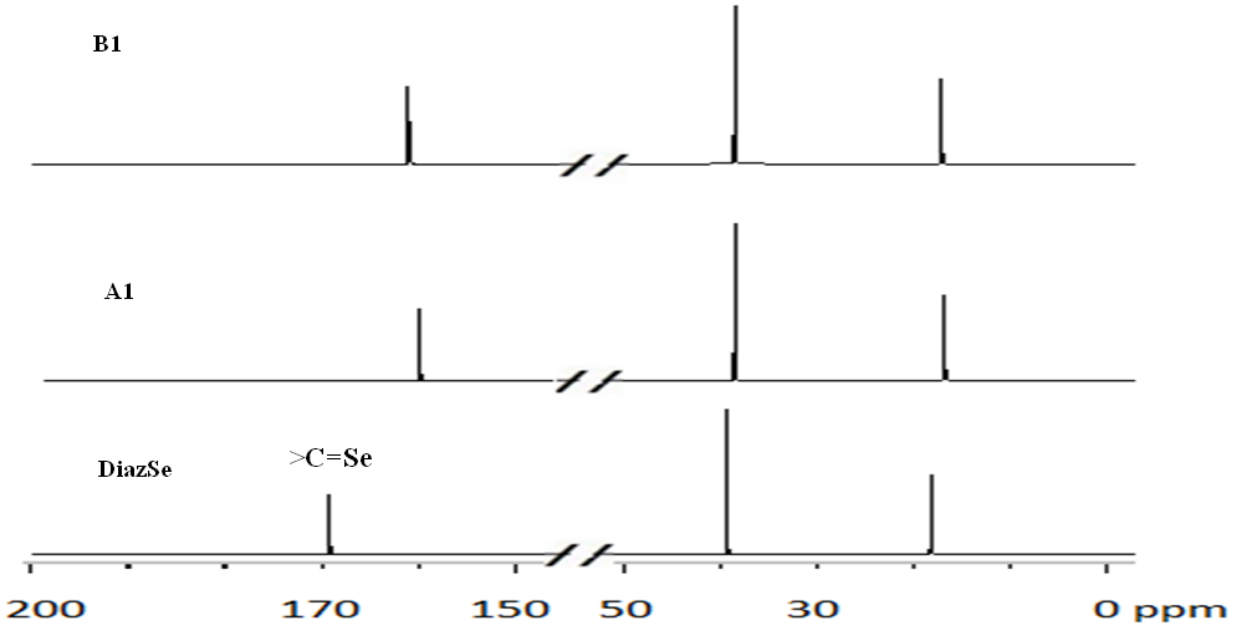



**$^{1}$H chemical shifts (ppm) of DiapSe and its Pt(II) complexes[A 2 and B2] in DMSO-$d_6$**

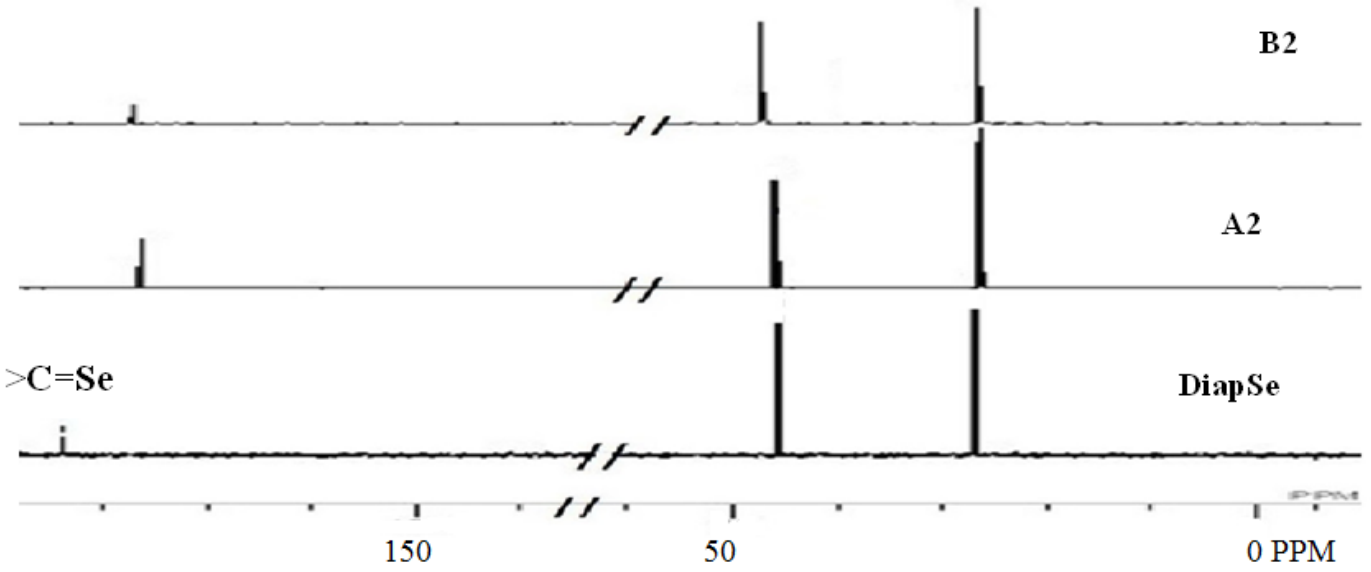



**$^{1}$H chemical shifts (ppm) of IMSe and its Pt(II) complexes[A6 and B6] in DMSO-$d_6$.**

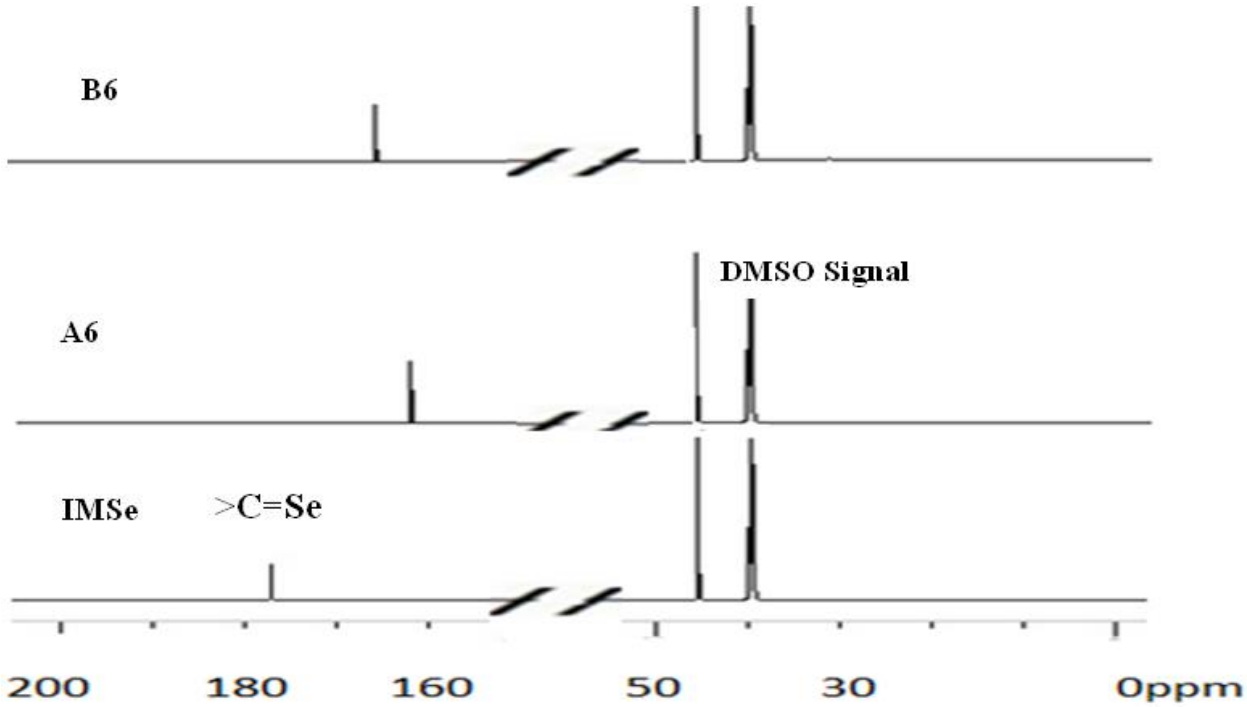
# Appendix B. $^{13}C$ NMR




**$^{13}C$ chemical shifts (ppm) of DiazSe and its Pt(II) complexes[A1 and B1] in $D_2O$.**

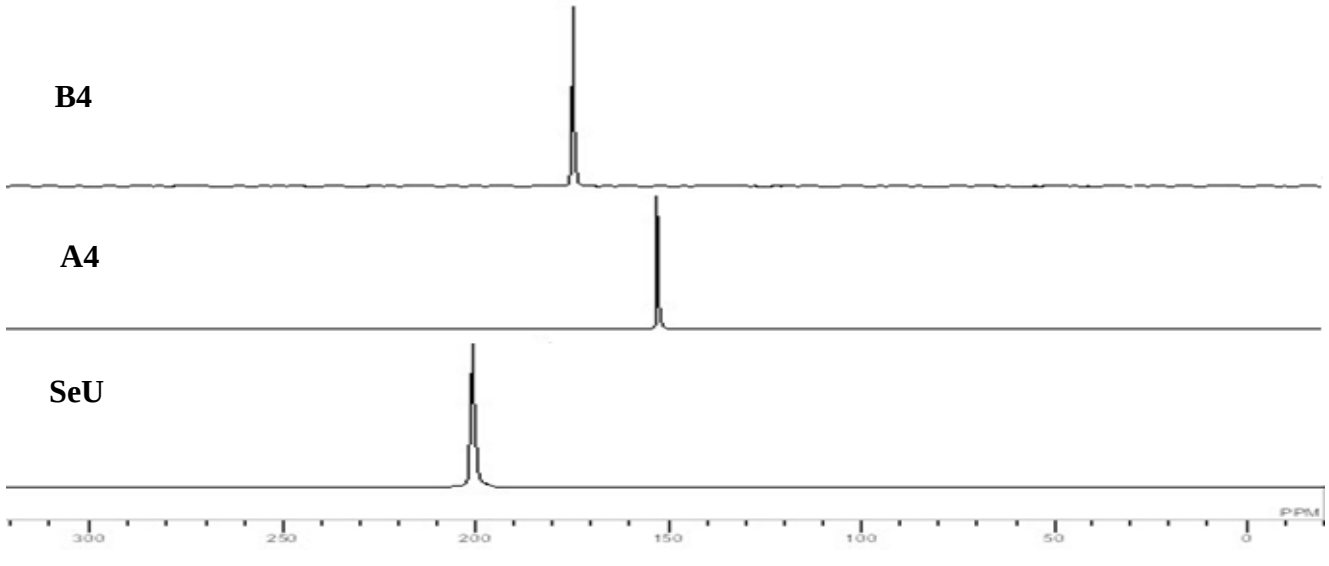



**$^{13}$C chemical shifts (ppm) of DiapSe and its Pt(II) complexes[A 2 and B2] in $D_2O$.**

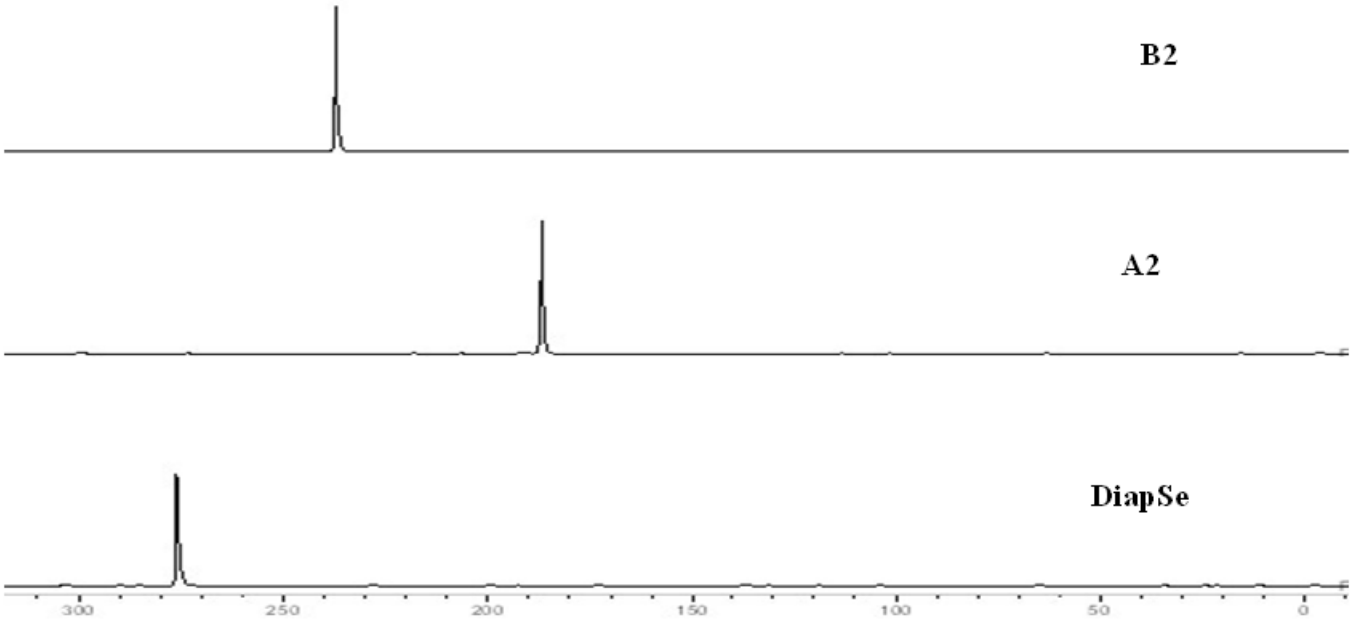



**$^{13}$C chemical shifts (ppm) of IMSe and its Pt(II) complexes[A6 and B6] in DMSO-$d_6$.**

# Appendix C. $^{77}$Se NMR

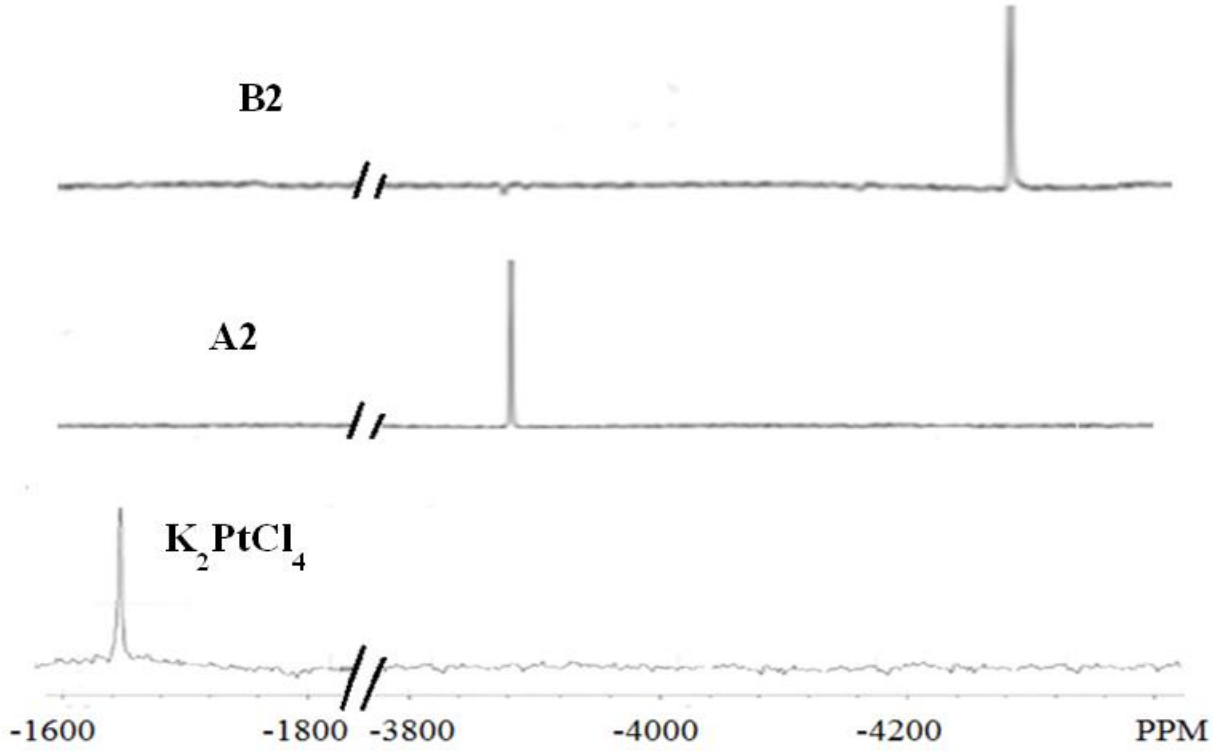



**$^{77}$Se chemical shifts (ppm) of SeU and its Pt(II) complexes[A4 and B4] in DMSO-$d_6$.**




**$^{77}$Se chemical shifts (ppm) of DiapSe and its Pt(II) complexes[A2 and B2] in DMSO-$d_6$.**

# Appendix D. $^{195}$Pt NMR




**$^{195}$Pt chemical shifts (ppm) of $K_2PtCl_4$ and its Pt(II) complexes[A2and B2] in DMSO-$d_6$.**

# References


[1] E. L. M. Lempers, J. Reedijk. *Adv. Inorg. Chem.* **1991**, 37, pp. 175-217.

[2] B. Lippert. *Inorg. Chem*. **1989**, 37, pp. 1-97.

[3] B. Rosenberg, L. Van Camp, T. Krigas. *Nature*.**1965**, 205, pp. 698-699.

[4] B. Rosenberg, E. Renshaw, L. Van Camp, J. Hartwick, J. J. Drobnik. *Bacteriol*. **1967**, 93, pp.7l6- 721.

[5] B. Rosenberg, L.Van Camp, E. B. Grimely, A. J. J. Thomson. *Biol. Chem.* **1967,**242, pp.1347-1352.

[6] D. J. Higby, H. J. Wallace, J. F. Holland. *Cancer Chemother. Rep.* **1973,** 57, pp.459-463.

[7] H. J. Wallace, D. J. Higby. *Recent Results Cancer Res.* **1974,** 48, pp. 167-177.

[8] J. M. Hill, E. Loeb, A. S. Maclellan, N. A. Hill, A. Kahn, J. Kogler. *Recent Results Cancer Res.* **1974,**48, pp.145-152.

[9] J. M. Hill, E. Loeb, A. S. Maclellan, N. O. Hill, A. Kahn, J. J. King.*Cancer Chemother. Rep.* **1975,** 59, pp.647- 648.

[10] E. Wiltshaw, B. Carr. *Cancer Res*. **1974**, 48, pp.178-182.

[11] I. H. Krakoff, A. J. Lippman. *Cancer Res*. **1974**, 48, pp. 183-193.

[12] C. F. J. Barnard. *Platinum Metals Rev*. **1989**, 33, pp.162-167.

[13] A. W. Prestayko, J. C. D. Aoust, B. F. Issel, S. T. Crooke. *Cancer Treatment Rev*. **1979**, 6, pp.17-39.

[14] M. Dentino, F. C. Luft, M. N.Yum, S. D. Williams, L. H. Einhorn. *Cancer*. **1978**,47, pp.1274-1281.

[15] R. Weiss, M. C. Christian . *Drugs.* **1993**, 46,pp.360–365.

[16] S. J. Fischer, L. M. Benson, A. Fauq, S. Naylor, and A. J. Windebank. *Neurotoxicology*. **2008**,29,pp. 444–452.

[17] M. Baik, R. A. Friesner, and S. J. Lippard . *J. Am. Chem. So.* **2003**, 140, pp. 82–92.

[18] M. Goren, R. Wright, and M. Horowitz. *Cancer Chemotherapy and Pharmacology*. **1986**, 18,pp. 69-73.

[19] L. Kelland. *Cancer Research*.**1993**, 53,pp. 2581-2586.

[20] E. T. Martins,H. Baruah, J. Kramarczyk, G. Saluta, C. S. Day, G. L. Kucera, and U. Bierbach. J. *Med. Chem*. **2001**,44, pp. 4492–4496.

[21] S. Misra, M. Boylan, A. Selvam, J. E. Spallholz, and M. Björnstedt. *Nutrients*. **2015**, 7, pp.3536-3556.

[22] J.M. Abrams, B. A. Murrer. *Science*. **1993**,261,pp 725–730.

[23] C. Marzano, A. Trevisan, L. Giovagnini, and D. Fregona. *Toxicoogyl in Vitro*.**2002**,16, pp. 413–419.

[24] A.Z.A. Mustafa, M. Altaf, M. Monim-ul-Mehboob, M. Fettouhi, M.I.M. Wazeer, A.A. Isab, V. Dhuna,G. Bhatia, K. Dhuna. *J. Inorg. Chem. Commun*.**2014**, 44, pp. 159-163.

[25] A.Z.A. Mustafa, , M. Monim-ul-Mehboob, M. Y. Jomaa,M. Altaf, M. Fettouhi, M.I.M. Wazeer, A.A. Isab, H. S. Evans, G. Bhatia, and V. Dhuna. *J. Coor. Chem*. **2015**, 68, pp. 3511–3524.

[26] J.M. Brow, C.R. Pleatman, U. Bierbach. *Bioorg. Med. Chem. Lett*.**2002**, 12, pp. 2953.

[27] R.B. Weiss, M.C. Christian. *Drugs*. **1993**, 46,pp. 360-377.

[28] D. Lebwohl, and R. Canetta. *Eur. J. can*. **1998**,34, pp. 1522-1534.

[29] J. Reedijk. *Chemical Reviews*. **1999**, 99, pp. 2499-2510.

[30] M.A. Fuertes, C. Alonso, J.M. Pérez. *Chem. Rev*. **2003**,103, pp. 645–662.

[31] A. B. Witte, K. Anestål, E. Jerremalm, H. Ehrsson, E.S.J. Arnér. *Free Radic. Biol. Med*. **2005**,39, pp. 696–703.

[32] C.J. Dillard, A.L. Tappel. *J. Inorg. Biochem*. **1986**,28, pp.13.

[33] C. Sasakura, K.T. Suzuki. *J. Inorg. Biochem*.**1998**,71, pp. 159.

[34] S. Ahmed, A. A. Isab, and A. P. Arnold . *J. Coord. Chem.* **2003**,56, pp.539-544.

[35] S. Ahmed, and A.A. Isab. *Inorg.Chem.Comm.***2002**,5, pp.355.

[36] C. J. Jones and J. Thornback. Textbook, Medicinal Applications of Coordination Chemistry. *Royal Society of Chemistry*.**2007**.

[37] S. Gibaud and G. Jaouen. *Med. Organometallic Chem*. **2010**,32, pp. 1-20.

[38] A. S. Abu-Surrah and M. Kettunen. *Curr. Med. Chem*. **2006**, 13, pp.1337-1357.

[39] D. J. Newman, G. M. Cragg and K. M. Snader. *Natural Products as Sources of New Drugs over the Period 1981 – 2002*. **2003**, 66, pp. 1022–1037.

[40] W. Ashraf, S. Ahmad, and A. A. Isab. *Transit. Met. Chem.* **2004**, 29, pp. 400–404.

[41] Cancer Facts and Figures. *http//www.cancer.gov/.* **2015**, pp. 1- 52.

[42] C. Lengauer, L. A. Diaz, S. Saha. *Nat Rev Drug Discov.* **2005**, 4, pp. 375-380.

[43] P. Nygren and R. Larsson. *J. Internal Med.* **2003**, 253, pp.46-75.

[44] V. P. Torchilin. European Journal of Pharmaceutical Sciences. **2000**, 11, Supplement 2, S81-S91.

[45] D. Jackman, W. Pao, G. J. Riely, J. A. Engelman, M. G. Kris, P. A. Jänne, T. Lynch, B. E. Johnson, V. A. Miller. *J. Clin. Oncology.* **201**0, 28, pp. 357-360.

[46] M. Domagała, R. Kontek, R. Osiecka, and J. Ochocki. *Biochem*. **2005**, 99, pp. 2024–2031.

[47] E. H. Thomas, B. Yu, and J. Reynisson. *J. Clin. Onco*. **2012**,3, pp. 1–6.

[48] R. A. Alderden, M. D. Hall and T. W. Hambley. *Chem. Edu*. **2006**, 83, pp. 728–734.

[49] J. R. Nilsson. *Cell. Sci.* **1987**, 90, pp. 707–716.

[50] L. Kelland. *Nature Reviews Cancer*. **2007**, 7, pp. 573–584.

[51] J. Lin, G. Lu, L. M. Daniels, X. Wei, J. B. Sapp, and Y. Deng. *Coord. Chem*. **2008**, 61, pp. 2457–2469.

[52] A. S. Abu-Surrah and M. Kettunen. *Current. Med. Chem*. **2006**, 13, pp. 1337–1357.

[53] S. Miranda, E. Vergara, F. Mohr, D. D. Vos, E. Cerrada, A. Mendía and M. Laguna. *Inorg. Chem.* **2008**, 47, pp. 5641–5648.

[54] L. R. Kelland. *Critical Reviews in Oncology/Hematology*. **1993**, 15, 191-219.

[55] Z. H. Siddik. *Oncogene*. **2003**, 22, pp.7265–7279.

[56] R. C. Todd, and S. J. Lippard. *Metallomics*. **2009**, 1, pp. 280–291.

[57] R. A. Holton, C. Somoza, H. B. Kim, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile, and J. H. Liu. *J. Am. Chem. Soc.* **1994**, 116, pp. 1597–1598.

[58] L. R. Kelland, P. Mistry, G. Abel, S. Y. Loh, C. F. O'Neill, B. A. Murrer, K. R. Harrap. Cancer Research. **1992**, 52, pp.3857-3864.

[59] D. P. Gately and S. B. Howell. *British journal of cancer*. **1993**, 67, pp.1171-1176.

[60] C. A. Larson, B. G. Blair, R. Safaei, S. B. Howell. *Molecular Pharmacology*. **2009**, 75, pp.324-330.

[61] J. Holford, P. J. Beale, F. E. Boxall, S. Y. Sharp, L. R. Kelland. *Eur. J. Can*. **2000**, 36, pp.1984-1990.

[62] L. R. Kelland, P. Mistry, G. Abel, S. Sidhar, K. R. Harrap. *British journal of cancer*. **1991**, 64, pp.215–220.

[63] S. W. Johnson, R. P. Perez, A. K. Godwin, A. T. Yeung, L. M. Handel, R. F. Ozols, T. C. Hamilton. *Biochemical Pharmacology*. **1994**, 47, pp.689-697.

[64] S. W. Johnson, P. A. Swiggard, L. M. Handel, J. M. Brennan, A. K. Godwin, R. F. Ozols, T. C. Hamilton. *Cancer Research*. **1994**, 54, pp.5911-5916.

[65] T. L. Cornelison and E. Reed. *Gynecologic Oncology*. **1993**, 50, pp. 147-158.

[66] H. H. Moon, K. W. Seo, K. Y. Yoon, Y. M. Shin, K. H. Choi, S. H. Lee. *World Journal of Gastroenterology*. **2005**, 148, pp.106-120.

[67] J. Kovach, C. Moertel, A. Schutt, R. Reitemeier, R. Hahn. *Cancer chemotherapy reports Part 1*. **1973**, 57, pp.357-359.

[68] D. Higby, H. Wallace Jr, J. Holland. *Can. chemother. reports Part 1*. **1973**, 57, pp.459-463.

[69] S. Groth, H. Nielsen, J. B. Sørensen, A. B. Christensen, A. G. Pedersen, M. Rørth. *Can. Chemother. Pharmacol.* **1986**, 17, pp.191-196.

[70] S. Oriana, F. Re, S. Bohm, G. Battista Spatti, F. Zunino. *Can.Chemother. Pharmacol*. **1990**, 25, pp. 355-360.

[71] J. Smyth, A. Bowman, T. Perren, P. Wilkinson, R. Prescott, K. Quinn, M. Tedeschi. *Annals of oncology*. **1997**, 8, pp. 569-573.

[72] D. Chen, V. Milacic, M. Frezza, and Q. P. Dou. *Curr. Pharm. Des.* **2009**, 15, pp. 777–791.

[73] M. Domagała, R. Kontek, R. Osiecka, and J. Ochocki. *Inorg. Biochem*. **2005**, 99, pp. 2024–2031.

[74] G. Marverti, M. Cusumano, A. Ligabue, M. L. D. Pietro, P. A. Vainiglia, A. Ferrari, M. Bergomi, M. S. Moruzzi, and C. Frassineti. *Inorg. Biochem.* 2008, 102, pp. 699–712.

[75] P.R. Taylor, J.Y. Li, ; B. Li, W.J. Blot, W. Guo, S. Dawsey, G.Q. Wang, C.S. Yang, S.F. Zheng, M. Gail, G.Y. Li, B. Liu,J. Tangrea, Y. Sun, F. Liu, F. Fraumeni Jr. and Y.H. Zhang. *J. Nati. Can.Insti*.**1993**, 85, pp.1492–1498.

[76] L.C. Clark, G.F. Combs Jr., B.W. Turnbull, E. Slate, D. Alberts, D. Abele, R. Allison, J. Bradshaw, D. Chalker, J. Chow,D. Curtis, J. Dalen, L. Davis, R. Deal, M. Dellasega, R. Glover, G. Graham, E. Gross, J. Hendrix, J. Herlong, F. Knight, A. Krongrad, J. Lesher, J. Moore, K. Park, J. Rice, A. Rogers, B. Sanders, B. Schurman, C. Smith, E. Smith, J. Taylor and J. Woodward. *J. Ameri. Med. Asso*. **1996**, 276, pp.1957–1963.

[77] L.C. Clark, B. Dalkin, A. Krongrad, G.F.Combs Jr., B.W. Turnbull, E.W. Slate, R. Witherington, J.H. Herlong, E. Janosko, D. Carpenter, C. Borosso, S. Falk and J. Rounder. *Briti. J. Urology*. **1998**, 81 , pp. 730–734.

[78] S.Y. Yu, Y.J. Zhu and W.G. Li. *Biologi. Trace Elem.Resea*. **1997**, 56 , pp 117–124.

[79] G.F. Combs Jr, and W.P. Gray. *Pharmacolo. and Therapeutics*. **1998**, 79 , pp.179–192.

[80] C. Ip. *J. Nutri.* **1998**, 128, pp.1845–1854.

[81] G.F. Combs Jr, L.C. Clark, D. Heber, G.L. Blackburn,V.L.W. Go. *Academic Press*. **1999**, pp. 215–222.

[82] H.E. Ganther. *Carcinogensis* . **1999**,20, pp.1657–1666.

[83] A.C. Wilson, H.J. Thompson and P.J. Schedin. *Biochem. Pharmacolo*. **1992**, 43, pp.1137–1141.

[84] M. Kaeck and C. Jiang. *Biochemical Pharmacology*. **1994**, 47, pp.1531–1534.

[85] M. Kaeck and C. Jiang. *Biochemical Pharmacology*. **1995**,252, pp.7392–7394.

[86] H.E Ganther and C. Ip. *Cancer Research*. **1990**, 50, pp.1206–1211.

[87] H.E Ganther and C. Ip. *Carcinogenesis.* **1991**, 12, pp. 365–372.

[88] H.E Ganther and C. Ip. *Carcinogenesis*. **1992**, 13, pp.1167–1170.

[89] H.E Ganther and C. Ip. *Journal of Inorganic Biochemistry*. **1992**, 46, pp.215–222.

[90] R.M. Budnick, C. Ip and C. Hayes. *Cancer Research.* **1991**, 51, pp.595–600.

[91] S. Vanhanavikit, C. Ip and H.E.Ganther. *Xenobiotica.* **1993**, 23, pp.731–745.

[92] J. Lanfear, J. Flemming and L. Wu. *Carcinogenesis*. **1994**, 15, pp.1387–1392.

[93] J. Lanfear, L. Wu, and P.R. Harrison. *Carcinogenesis*. **1995**, 16, pp.1579–1584.

[94] M. Bjornstedt, S. Kumar and L. Bjorkhem. *Biomed. and Environ. Scien*. **1997**, 10, pp.271–279.

[95] L.N. Vernie, C.J. Hamburg and W.S. Bont. *Cancer Letters*. **1981**, 14, pp.303–308.

[96] K.A.Poirer and J.A. Milner. *Journal of Nutrition*. **1983**,113, pp.2147–2154.

[97] A. Muscella, N. Calabriso, S. A. De Pascali, L. Urso, A. Ciccarese, F. P. Fanizzi, D. Migoni, and S. Marsigliante. *Biochem. Pharmacol.* **2007**, 74, pp. 28–40.

[98] S. A. Tirmizi, S. Nadeem, and A. Hameed, M. H. S. Wattoo, A. Anwar, Z. A. Ansari and S. Ahmed. *Spectroscopy.* **2009**, 23, pp. 299–306.

[99] A. A. Isab, M. I. M. Wazeer and A. El-rayyes. *Spectroscopy*. **2004**, 18, pp. 113–119.

[100] A. Francesco, Devillanova and G. Verani. *Transition Met. Chem*. **1977**, 2, pp. 9-11.

[101] M. I. M Wazeer, A. I. Isab and H. P. Perzanowski . *Magn. Reson. Chem*. **2003**,41, pp.1026–1029.

[102] Stoe & Cie. X-Area & X-RED32. Stoe & Cie GmbH, Darmstadt, Germany. **2009**.

[103] G. M. Sheldrick. *Acta Cryst.* **2008**, A64, pp.112-122.

[104] G. M. Sheldrick. *Acta Cryst*. **2015** , C71, pp. 3-8.

[105] A .L. Spek. *Acta Cryst*.**2009**, 65, pp.148-155.

[106] C. F. Macrae, I. J. Bruno, J. A. Chisholm, P. R. Edgington, P. McCabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. van de Streek , P. A. Wood. *J. Appl. Cryst.* **2008**, 41, pp.466-470.

[107] B. Swanson, D. F. Shriver, and J. A. Ibers. *J. Inorg. Chem.* **1969**, 8, pp. 2182-2189.

[108] D. J. Williams, T. A. Ly, J. W.Mudge, D. Vanderveer, and R. L. Jones. *J. Inorg. Chem. Acta.* **1994**, 218, pp. 133-138.

[109] D. L. Reger, and J. E. Collins. *Organometallics.***1996**, 15, pp. 2029-2032.

[110] X. Ribas, J. Dias, J. Morgado, K. Wurst, M. Almeida, J. Veciana, and C. Rovira. *Cryst. Eng. Comm.* **2002**, 4, pp.564-567.

[111] D. M. Adam, and J. B. Cornell. *Chem. Soc.* **1967**, 213, pp. 884 - 889.

[112] T. S. Lobana, and A. Castineiras. *Polyhedron.* **2002**, 21, pp.1603-1611.

[113] A. Beheshti, W. Clegg, V. Nobakht, M. P. Mehr, and L. Russo. *Dalton Trans*. **2008**, pp.6641-6646.

[114] U. Bierbach, T. W. Hambley, and N. Farrell. *J. Inorg. Chem.* **1998**, 37, pp.708-716.

[115] D. H. Lee, L. Y. Q. Hatcher, M. A. Vance, R. Sarangi, A. E. Milligan, A. A. N. Sarjeant, C. D. Incarvito, A. L. Rheingold, K. O. Hodgson, B. Hedman, E. I. Solomon, and K. D. Karlin. *J. Inorg. Chem.* **2007**, 46, pp.6056-6068.

[116] F. A. Devillanova, G. Verani, L. P. Battaglia, and B. A. Corradi. *Transition Met. Chem.* **1980**, 5,pp. 362-364.

[117] M. D. Spicer, and J. Reglinski. *Eur. J. Inorg. Chem.* **2009**,12, pp.1553-1574.

[118] J. D. Woollins, A.Woollins and B. Rosenberg. *Polyhedron*.**1983**,2,pp.175.

[119] L. B. Kumbhare. *Inorg. Chimi. Acta*. **2011**,374, pp.69.

[120] J. Arpalahti, and B. Lippert. *J. Inorg. Chem. Acta.* **1988**, 153, pp.5l-55.

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Papers.

1. **Ali O. S. Altoum**, Muhammad Altaf ,Mohammed I.M.Wazeer , Anvarhusein A. Isab* , Ján Vančo, Radka Křikavová, Zdeněk Trávníček and Zdeněk Dvořák. *Synthesis Structural Characterization and Antitumor Studies of Platinum(II) complexes of Selenones*. **(To be submitted).**
2. **Ali O. S. Altoum**, Muhammad Altaf , Mohammed I.M.Wazeer , Anvarhusein A. Isab*, Synthesis, characterization and in vitro cytotoxicity of *Trans* - dicholorobisselone-platinum(II) complexes**.(In progress).**

Patent.

1. **Ali O. S. Altoum**, Ali Alhoshani, Muhammad Altaf , and Anvarhusein A. Isab*. *Synthesis, characterization and in vitro cytotoxicity of platinum(II) complexes of selenones*.**(Submitted).**