An-Najah National University

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SUCROSE BASED CISPLATIN ANALOGS: SYNTHESIS AND ANTICANCER ACTIVITY

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This Thesis was Defended Successfully on / / 2023 and approved by

Dedication

I dedicate my thesis to myself firstly, because I'm the champion of myself.

I also dedicate it to my supportive husband all the time, my great and lovely mother and father, as well as my sister and brothers, and my supportive second family, my husband's family.

I also dedicate it to my teachers who supply me to achieve my goals during studies and everyone who has helped or supported me even if with a word.

// Acknowledgment

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Lastly, it is an honor for me to express my sincere gratitude to everyone who helped complete this effort in some way.

Declaration

I, the undersigned, declare that I submitted the thesis entitled:

SUCROSE BASED CISPLATIN ANALOGS: SYNTHESIS AND ANTICANCER ACTIVITY

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name: ____

Signature: ____

Date: ____

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SUCROSE BASED CISPLATIN: SYNTHESIS AND ANTICANCER ACTIVITY

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Abstract

Sucrose chemistry has received a lot of attention since 1960s. Currently, over three hundred well identified sucrose derivatives have been reported in the literature as it is safe, abundant, and available at low cost. This work is planned on creating a drug for cancer with greater effectiveness and low toxicity based on sugar molecules.

The main goal of this study is to develop a unique, naturally derived cisplatin analogue. That can be used as a replacement for cisplatin and free of the side effect of the cisplatin.

To achieve the goal of the study two sucrose-based cisplatin complexes were synthesized from sugar. The synthesis was performed in a three-step process. The first step involved adding acetoacetate functionality to the sucrose, converting the acetoacetate functionality of Schiff base by reacting it with valine and 2,3-diaminopyrdien. The last step involved making the sucrose based cisplatin analog by complexing the potassium tetrachloro palatinate (K_2PtCl_4).

The structures of the prepared compound were identified by FT-IR and some by NMR spectroscopy. The cisplatin complexes showed a clear activity against Hela cancer cells. The inhibition reached about 67% and they showed mild effect on normal cells as the effect reached about 29%. The Schiff bases showed lower effect on Hella cancer cells.

The study concluded that sucrose based cis-platin analogues were successfully synthesized and their anticancer activity were evaluated. They showed promising results and Hela cancer cells. Still more work needs to done on structure elucidation and the activities of the cisplatin analogues against other cancer cells.

Keywords: Cancer, Schiff bases, Cisplatin analogues, Potassium tetrachloro platinate, Sucrose, Amino acids.

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Chapter One
Introduction

1.1 Background

1.1.1 Cancer Preview

Cancer is one of the most leading causes of death and one of the most widespread public health problems. World Health Organization (WHO) predicted an increase of about 70% in cancer cases by the next 20 years [1]. Cancer occurs when genetic mutilation to the cells prevents them from being receptive to normal tissue controls. The cancer spreads in the body when developed cancer cells multiply rapidly, forming a tumor [2-5].

There are two types of tumors: benign as well as malignant. It is important to understand the various differences between normal cells and malignant cells. When there are enough normal cells, they stop growing, while cancer cells continue to divide, causing a tumor to form [6].

Cancer cells do not respond to signals supplied by nearby healthy cells like normal cells do. Apoptosis happens in healthy cells but not in malignant cells. The body's normal cells do not spread to other areas, but cancer cells do because they lack adhesion molecules. Normal cells have an alkaline environment, but cancer cells have an acidic or slightly alkaline environment [6].

Benign tumors are typically localized, lack the potential to infect neighboring tissue and organs, and have the option of being removed even though they typically do not require removal. Cancerous tumors, also known as malignant tumors, grow quickly and infect neighboring human organs and tissues. As tumor cells enter the bloodstream or lymphatic system, they spread throughout the body (a process known as metastasis), which inevitably results in death.[7, 8]. However, the kind, location, and level of illness all have a major role in the therapy options.

Many types of cancer affect different populations differently; for example, breast cancer kills more women than males, but lung cancer kills more men than women overall [9, 10].

Studies show that prostate, lung, and liver malignancies are the most prevalent cancer forms in males, whereas breast and cervical cancer is the most frequently diagnosed neoplasm in women [9].

1.1.2 Cancer therapy and various forms of treatment

Chemotherapeutic, radiotherapy, surgery, hormone therapy, immunological therapy, and targeted therapy are all possible cancer treatments [9]. Surgery combined with chemotherapy or radiation is currently the most effective way to treat cancer [11].

Combination chemotherapy is the process of treating cancer with more than one medicine. Most modern cancer treatments for various cancer types combine two or more medications [12].

Chemotherapy medications have an impact on cancer cells at various stages of the cell cycle. The probability of destroying the majority of cancer cells improves with the usage of many medications [12].

Despite this, taking multiple medications has the drawback of increasing the number of probable chemical reactions that could result in it, making it impossible to distinguish which medicine was responsible [12].

In order to increase the potency of immunotherapy medications, chemotherapy has been used with some types of immune therapy. The advantages of combining immunotherapy and chemotherapy may exceed the usage of a medication combination. The immune system is assisted by immune system drugs in identifying and eliminating cancer cells. The immune system helps identify irregular cells after chemotherapy medications have eliminated cancer cells [13]. Reducing the probability that malignancies would resist therapy is one benefit of employing drug combinations over single drug treatments [14].

Chemotherapy is performed with medications that stop dividing cells. Four subcategories can be established from those drugs: antimetabolites, which block the metabolic processes required for DNA production. Antibiotics that prevent DNA from functioning result in DNA that is unable to carry out its genetic tasks. medicines made from plants that damage microtubules or inhibit topoisomerases [8].

Chemotherapy medications are broken down into two groups: the first affect the cell cycle (phase specific agents) and the second are classified based on their biochemical characteristics.

One of the first and most widely used anticancer medications is alkylating agent. In fact, alkylating varies in their therapeutic efficacy but share similar mechanisms of action. These substances directly interact with DNA, causing DNA crosslinking and strand breaks that result in irregular base pairing and prevent cell growth, consequently leading to cell death. Alkylating anticancer drugs are utilized to treat a variety of malignancies and are effective across the whole cell cycle. These substances mostly work better against slow-growing malignancies like solid leukemia and tumors [15].

Moreover, cisplatin is a type of an alkylating agent, a class of medications that chemically crosslink the DNA double helix to impede the function of the DNA [8].

Each sort of treatment has potential issues and drawbacks, and chemotherapy was no exception. Chemotherapy known to be the most effective option and widely used treatment in treatment of various types of malignancies. However, the side-effects result from the cancer chemotherapy such as fatigue, hair loss, nausea, vomiting, and even death in some cases, limit the use of chemotherapeutic treatment. Therefore, there is an ongoing research all over the world for the development of cancer treatment that is more effective and less harmful that can target cancer cells only, having little to no negative effects on healthy cells [16].

A chemotherapeutic agent (Anticancer drugs) is an example on therapies treatment that kills the rapidly dividing cancer cells, thus slowing and preventing the cancer from spreading in the body. Anticancer drugs have originated from a variety of sources such as plants, microbes, and fungi. Examples on these are shown in Table 1.1 [17].

Table 1.1

Examples on Natural based anticancer agent

Natural based anticancer agent	Structure
Genipin	
Penta-acetate geniposide	
Geniposide	
Geniposidic acid	

1.1.3 Metal ions with anticancer action

A subfield of chemistry is medicinal inorganic chemistry. Provide people the ability to create a variety of cutting-edge metal-based medicinal agents that are hard to find as organic chemicals. Metal ions distinctive features can be used in medicinal inorganic chemistry to create a variety of novel medication compounds [18]. Five thousand years have passed since metals were first used in medical applications [2].

The current push in the investigation for metal-based medicines was stimulated and led

by the discovery of cisplatin in 1965. The discovery of metal-based therapeutic agents with potential for different kinetics and mechanisms of action from those in conventional organic drugs as a result of cisplatin has started a new adventure [8].The osmotic balance, signal transmission, and the functions of different lipids, glycans, nucleic acids, and proteins all depend on metal ions. Methane oxidation, nitrogen fixation, and water splitting are just a few of the mysterious reactions that are catalyzed by metalloenzymes, which form around one-third of all the proteins in mammals [19].

The ability of metal ions to shed electrons from their elemental state and produce ions with a positive charge, which increase their solubility in biological fluids, is one of their most important characteristics. Metal becomes more reactive in biological reactions when it is changed into a cationic state. Because most biomolecules, including DNA and proteins, are electron-rich negatively charged rather than electron-deficient positively charged, the attraction between these opposing charges causes a general propensity for metal ions to attach to and interface with biomolecules [20].

Metal complexes are more likely to promote ligand substitution interactions with bio-molecular targets if ligands could be added to them. One approach is to bind to the selenium, nitrogen, or sulfur atoms of the protein's selenocysteine, histidine, or cysteine residues, which would have a hugely beneficial therapeutic effect [21].

1.1.3.1 Anticancer action of platinum

The metal platinum, which is characterized by its bright silver-white color, is malleable due to its ductility, does not dissolve in nitric acid and when treated with hot water forms chloroplatinic acid, resistant to high temperatures and has stable electrical properties and its oxidation state is +2 and +4 [22].

Because of its catalytic properties, its resistance to corrosion at high temperatures, its high melting point, great mechanical strength, and good ductility, it is used in glass, petroleum, electronic and electrical industries, in addition to playing an important role in medicine for the treatment of cancer and the preparation of dental fillings [22].

Platinum complexes have a great role in medicine, as there is a study that demonstrated the role of one of the platinum complexes in inhibiting the division of E. Coli cells, in

addition to the great activity of these complexes against cancer, as it is involved in the treatment of many tumors such as the ovaries, ovaries, bladder and others [22].

Platinum-based cancer drugs play an important role in chemotherapy, but cause side effects and drug resistance, and are considered an agent for destroying DNA, but it is characterized by poor selectivity, meaning that it does not target cancer cells only, but causes damage to normal cells [23].

Metal complexes such as cisplatin had, the mechanism action is suspected to be through binding directly to the DNA. Cisplatin is covalently complexed to DNA which form a complex structure that leads to different types of crosslinks between the cis-platin and the DNA causing a significant distortion of the helical structure of DNA. This causes inhibition and distortion in the replication of the DNA and transcription processes. Which finally causes cancer cell death through activating a suicide mechanism of the cell [24, 25].

1.1.3.2 Interaction of platinum with DNA

Platinum complexes capacity to travel and assemble within the cancer cell membrane as well as their activity against DNA, which they degrade due to their toxic characteristics, are key determinants of their capacity for killing cancer cells [26]. Platinum complexes containing halogens must through an aquation process in order to connect to DNA, which causes one or more of the halogens to be removed and the cancer cell's DNA to bind in their stead. Intrinsic affinity induces DNA distortion, which finally results in apoptosis, the cell death process [27].

According to copper transporter 1, the chemical cisplatin is believed to enter cells both passively through diffusion and actively through active transport. After moving its two chlorides inside the cell, it binds to purines in the genomic DNA. When platinum binds to the double-stranded molecule, it prevents DNA replication and transcription, and the subsequent DNA damage reaction results in apoptosis [28].

It was proposed that some of the multifactorial cellular changes that result in cisplatin resistance include decreased cellular accumulation of platinum, platinum detoxification by substances containing thiols, and enhanced levels of DNA damage repair [29, 30].

All of these factors work together to reduce the amount of Pt-induced DNA lesions in the genomic DNA, which encourages the survival of cancer cells [29].

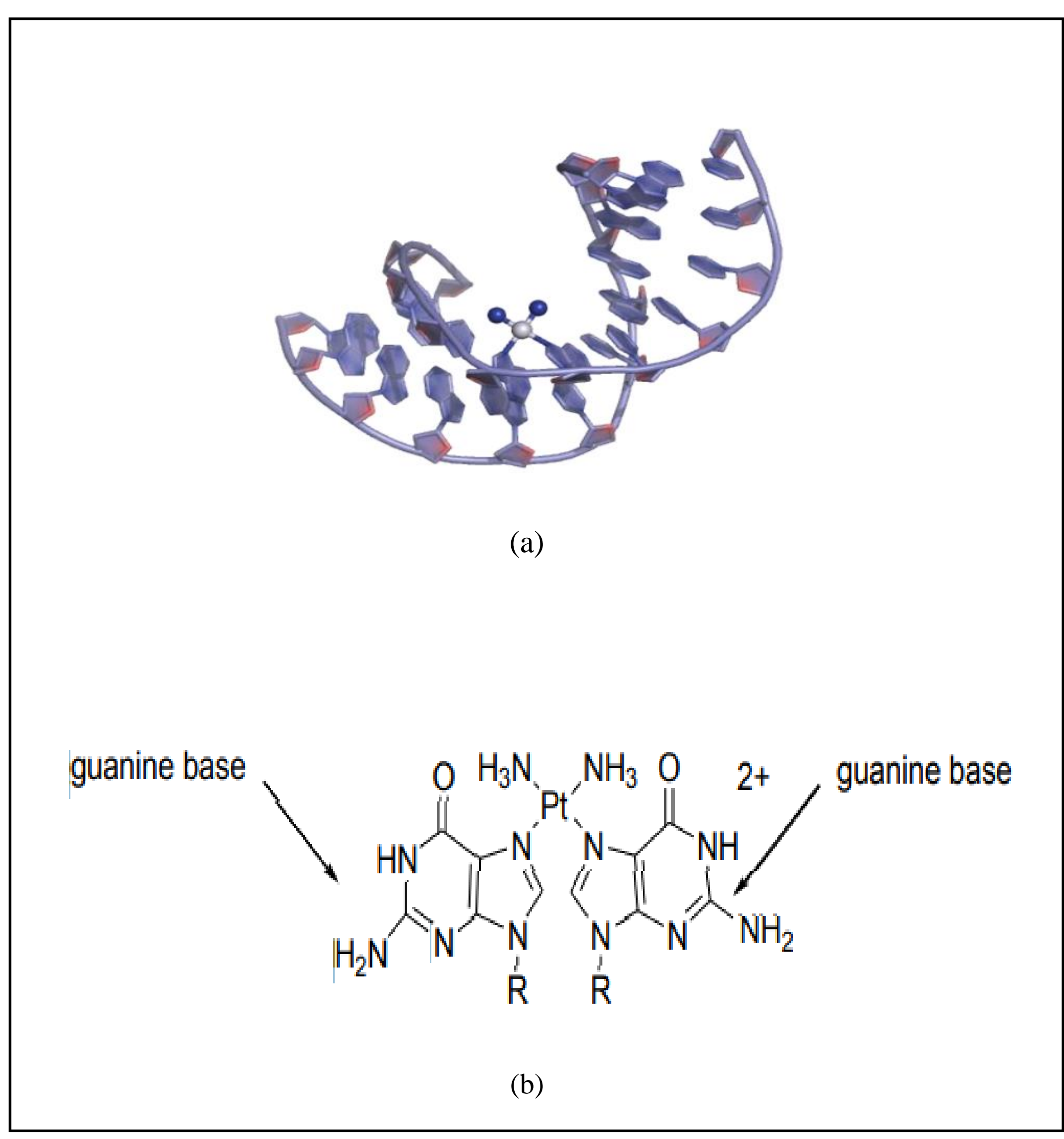
1.1.4 Cisplatin and analogs

As known, DNA is a genetic material that plays a key role in the cell division and replication. If DNA structure is changed or destroyed it cannot be fixed, then it will stop the dividing and the replicating process and will end up destroying itself by a process known as apoptosis.

The anticancer drugs such as cisplatin and analogues attack the DNA of the cancer cells. If the DNA of a cancer cell can be altered permanently, then it can be destroyed. Cis-Platinum (II) complexes and analogs are a key drug in anticancer treatment. They are able to cross-link with the DNA by covalently bonding to the DNA strand and prevent it from combining with another DNA strand and causing it to kink as shown in Figure 1.1 (a) [31, 32].

Figure 1.1

Covalently bonding of DNA with cisplatin



Note: (a) 3-D structure of the cisplatin- DNA complex, (b) Bonding of Cis-Platinum with DNA guanine bases

Figure 1.1 (b) shows the product from combining DNA with cisplatin [33, 34]. In Table 1.2 a summary of some recent platinum (II) complexes used in cancer treatment are shown (in the appendices) [35, 36].

Table 1.2

Some of platinum (II) analogs

Platinum (II) analogs	Structure
Cisplatin	
Carboplatin	
Nedaplatin	
Lobaplatin	
Oxaliplatin	
Picoplatin	
Miboplatin	
Enloplatin	
Spiroplatin	
Iproplatin	

Cisplatin complex is currently one of drugs used to treat cancer cells. As mentioned above it causes changes in the DNA structure. It has been shown that several binding sites of the DNA bind to cisplatin the major binding occurs with N7, it is bidentate binding between purine (Guanine) within the DNA strand (Figure 1.2 in the appendices) [27, 37].

There is some of cis-platin analogue mentioned in Figure 1.3 , at first is Carboplatin, its structure is shown in Figure 1.3 (a), it is considered the second-generation of Pt(II) anticancer medicine [38, 39] .

This complex is less nephrotoxic than the original cisplatin and is effective against the same cancer cell types as cisplatin drug [39, 40].

Figure 1.3

Chemical structure of cidplatin analogs

2

Carboplatin

(a)

(b)

(c)

(d)

(e)

(f)

Note. (a) Chemical structures of cis-platin and carboplatin, (b) Chemical structure of nedaplatin, (c) Chemical structure of Oxaliplatin, (d) Examples on carbonic anhydrase antitumor, (e) Examples on Structures on platinum (IV) with dihydro-2-quinoloneligand and oxaliplatin and bi DHQLO oxaliplatin, (f) Chemical structure of platinum (II) complex with folic acid.

Carboplatin has two carboxylate group chelate ring. Compared to cisplatin carboplatin is less reactive since it is difficult to displace the carboxylate group chelate ring while in cis-platin the chloride is the leaving group [41] .

The low reactivity of carboplatin toward substitution makes has lower toxicity compared to cisplatin and less effective as a cancer drug. The kinetics of carboplatin binding to DNA was defined experimentally [40]. It acts in a similar fashion to cis-platin as shown in Scheme 1.1 [42], it forms kind of Pt/DNA diadduct.

Scheme 1.1

Mechanism of carboplatin binding to the DNA

The other platinum complex nedaplatin shown in Figure 1.3 (b) is considered the second-generation cis-platin analogs. It is effective against various cancer cells, such as lung, cervical cancer, testicular and head and neck cancer cells [43-45] .

The structure of nedaplatin contains a glycolate ring that is bonding to Pt(II) , the structure makes it reactive to nucleophilic in the DNA structure and crosslink with it [46] . It has lower toxicity than cisplatin since the leaving groups is less toxic [43-45].

Oxaliplatin shown in Figure 1.3 (c) is another novel platinum analog that is effective against colorectal carcinoma [47] . It showed different bonding mechanism with DNA [47, 48].

Oxaliplatin a long with 5-fluorouracil and leucovorin exhibits activity against metastatic colorectal cancer [48].

One of the major concerns in this type of medicine is the polarity which makes them not transport into the cancer cell. One approach is to change the chemical structures of the Pt(II) complexes to something that imitate a nucleoside so it can access the cell as

shown in Figure 1.4 (in the appendices) [32].

Recent antitumor medicine carbonic anhydrase is shown in Figure 1.3 (d), they are proven to be more potent against breast cancer than cisplatin or oxaliplatin. They showed high selectivity but the cytotoxicity of these drugs on cancer cells are observed[49].

Examples on new Pt (IV) complexes with dihydro-2-quinolone ligand shown in Figure 1.3 (e) they are found to have higher efficiency than binary Pt (II) complexes. They showed better selectivity, and high activity against cells that have resistant against cisplatin, also it was shown to display mitochondria-damaging activity and, thus, can activate tumor cell apoptosis [50].

A new novel platinum complex with folic acid was also prepared (Figure 1.3(f)), it was used to treat breast cancer cells, its improvement in cytotoxicity and induced apoptosis more potently compared to cisplatin. Molecular docking showed that this complex is stable with folate receptors [50].

1.1.5 Applications of Carbohydrates derivatives drugs for cancer

Carbohydrates are one of the most abundant biomolecules, they play crucial roles in several cellular interactions, like for instance signaling between cellular molecules and cell surface receptors [51].

Many Carbohydrates are made from monosaccharide and oligosaccharide that are connected by glycosidic linkages (to form glycoconjugates known as glycan), also the biosynthesis of those Carbohydrates are controlled by number of enzymes, that make them important for disease progression [52] . For this reason, carbohydrates able to induce glycan-kind of interactions, are targeted as drugs therapeutic agents aimed at treating several diseases.

List of sugar based anticancer drugs are summarized in Table 1.3. Glufosfamide was the first sugar based drug to be synthesized by trying to decrease molecular toxicity and enhance the cancer selectivity of a DNA alkylating aglycon ifosfamide mustard [53].

The Glufosfamide drug showed 4.5-fold lower toxicity than aglycon ifosfamide in rats [53]. Human clinical trial, with twenty patients, was initiated in Europe in 1997 by Briasoulis group 1997 promising results were obtained [54].

Then several anticancer drugs, such as busulfan, chlorambucil, paclitaxel, and docetaxel, were conjugated with various monosaccharides using various linkers, such as amide, esters, ureas, and succinic acids.

Table 1.3

Examples on sugar-based drugs with anticancer activity

Sugar-based drugs with anticancer activity	Structure
Glufosfamide	
Glucose-conjugated methane sulfonate	
Glucose-conjugated cadalene	
Glucose-conjugated azomycin	
2-D- Glucose-conjugated paclitaxil	
Glucose-conjugated quinolnyl	
Glucose-conjugated clioquinol	

Natural iminosugars have noted to show anticancer activity with the ability to target the *N*-glycan biosynthesis pathway. These amino sugars are considered carbohydrate analogs, where the oxygen is replaced by a more basic nitrogen atom. The most common Natural iminosugars are summarized in Table 1.4. Biological evaluations of these sugars showed glycosidase and glycosyltransferase inhibition properties [55].

Recently, these natural iminosugars gained importance in the development of potent anticancer drugs.

1.1.5.1 Sugar based derivatives with anticancer activities

Sucrose is the most abundant carbohydrate, it is available in all plant tissues [56]. It is a disaccharide, bio-renewable, biodegradable and variable at low cost. Several scientist showed it can be used in the production of compounds with biological activity [57].

It is composed of D-glucopyranose and D-fructofuranose connected to each other via anomeric position. It is a non-reducing sugar because the anomeric hydroxyl groups is blocked [58]. The sources of sucrose is mainly plants [59].

The main source of it is sugar beets and sugar can [47, 48]. The main use of sucrose is in food, it can also be used in the production of detergent, epoxy emulsifying agent, artificial sweeteners [59], surfactant and polymers. Sucrose is very polar and has high solubility in water, it showed moderate solubility in polar solvents, and it is insoluble in organic solvents, stable in alkaline but undergoes hydrolysis in acidic medium [58].

Glucose almost have similar properties to sucrose, recently several routs for the synthesis of glucose esters with antic caner activities have been reported [60]. Examples on these are shown in Scheme 1.2. This type of drugs showed activity against prostate cancer cells and human melanoma.

Scheme 1.2

Glucose based fatty esters with anticancer activities

Some of the application of sucrose in cancer treatment are summarized. Biodegradable nanogel of hyaluronic acid and its polymeric were prepared with sucrose using the crosslinking agent glycerol diglycidyl ether (GDE). The produced nanogel was used in a long term delivery (over 2 days) of cancer drugs with hydrophobic properties [61].

The naturally occurring phenyl propanoid sucrose ester extracted and isolated from various plants are widely used in folk medicine, it possess various biological activities such as antibacterial, antitumor, , antiviral, antioxidant and anti-inflammatory [62].

Another example the naturally occurring caffeic acid phenethyl easter (CAPE) showed anti-carcinogenic activity, its solubility in water is low, the sucrose fatty acid easter (SFAE) performed as used to nano capsulate in hydrated propylene glycol (PG), so it improved the cytotoxicity of the CAPE against breast cancer colon cancer [63].

The chemical and physical properties of sucrose fatty acid easter makes it useful for use in many chemical industries such as surfactants in addition to having an anticancer activity against. Many simple esters are made by esterifying the appropriate acid and alcohol under Fischer-type conditions, but sucrose esters are difficult to make this way .This is due to the fact that sucrose exhibits glycosidic bond cleavage at the required

variables (namely, at pH 2-3 and 70–80 ºC), resulting in a mixture of glucose and fructose [59].

Transesterification of fatty acid esters with sucrose typically occurs in the industrial synthesis of sucrose esters, eliminating the need for highly acidic conditions. Given that the source carbohydrate of sucrose contains eight different hydroxyl groups, chemical production of sucrose fatty acid esters is exceptionally difficult. By esterifying any given acid with sucrose, there are 255 different esters that can result, including 8 mono-esters, 28 di-esters, 56 tri-esters, and others. Due to their typically better Hydrophilic-lipophilic Balance (HLB) values, the mono-esters of sucrose are the most preferred as emulsifiers [59].

Sucrose dieaster of aryldihydronaphthaline known as echiumins, extracted and isolated from butanol fraction of echium angustifolium Mill. showed good activity against HepG2 and MCF7 cancer cell [64].

1.1.5.2 Sucrose

Sucrose (known as sugar) has been widely used as a sweetener for more than 4000 years. It is extracted from sugarcane and sugar beet (Beta vulgaris). Its total world production exceeds 116 million tons annually [65].

Sucrose chemistry received a lot of attention since 1960s. Currently, over three hundred well identified sucrose derivatives have been reported in the literature [66]. Sucrose chemical structure is shown in the following figure (Figure 1.5).

Sucrose exists in two crystalline structures: a structure A- crystallized from H_2O and has melting point of 184.0–185 ◦C. Structure B recrystallized from CH_3OH with melting point of 169.0 –170 ºC [66, 67]. It is considered a nonreducing sugar with eight OH groups, five of them secondary and 3 are primary.

The configurations at the glycosidic linkage was determined by enzymic hydrolysis process [68] , x-ray [69, 70] and neutron diffraction analysis [71, 72].Sucrose derivatives include sucrose ether, sucrose ester, sucrose phosphate and sulfate, sucrose epoxy [73-75].

Figure 1.5

chemical structure of sucrose

In this work we decide to make a use of the safe chemical sucrose and its availability at low cost and create for it a cis platin analogue.

A novel sucrose β-ketoester derivative was prepared and converted to metal ligand by reacting it with various amino acid compounds. The new ligand was complexed with Pt (II) to create a new cis-plating analogues with anticancer activity.

1.1.6 The aim of the study

The aim of this study is to develop a novel cisplatin analogue with a natural basis that is efficient against cancer cells. The study has three main goals as follows:

1. Create a new class of sucrose-based platinum complexes and synthesize them.
2. Analyze the structure and the physical properties of the prepared complexes by infrared spectroscopic.
3. Evaluate the anticancer activity and an in vitro cytotoxicity of the prepared compounds against several tumor cell lines

Chapter Two
Experimental

2.1 Materials

All of the chemicals used in this research were bought from the Aldrich Company and utilized exactly as received, the chemicals needed to accomplish this work are sucrose, dimethyl acetamide (DMAc), t-butyl acetoacetate (t-BAA), ethyl acetate, tetrahydrofuran (THF), acetic acid, ether, methanol, 2,3-diamino pyridine, valine amino acid, potassium tetrachloropalatinate (K_2PtCl_4).

2.2 Instrumentation

The prepared complexes were characterized by various spectroscopic techniques including ^{1}H Nuclear Magnetic Resonance ^{1}H NMR and IR.

The obtained spectra were captured using a 300 MHz Varian Gemini 2000. Dimethyl sulfoxide (DMSO)-d_6 was used in the NMR analysis. The chemical shifts (δ) of the NMR peaks were recorded in parts per million (ppm) downfield from TMS (tetramethyl silane).

All ^{13}C NMR spectra were also reported in ppm relative to DMSO-d_6 chemical shift 39.52 ppm. A Shimadzu 820 PC FT-IR spectrometer Nicolet iS5, iD3 ATR (Thermo-scientific) was used in the IR analysis The reactions completion was detected by TLC plates pre-coated with Merck Kieselgel 60 F254, and produced spots were visualization using a UV lamp.

The spots elution was performed using hexane: ethyl acetate (6: 4) mixture. All melting points were determined using Cole-Parmer® MP-200 (Antylia Scientific Ltd. United Kingdom). Samples purifications was performed using (100-200 mesh) silica gel in either flash chromatography or crystallization.

2.3 Complexes synthesis

2.3.1 Preparation of sucrose-acetoacetate (1)

A sample of Sucrose (5.0 g, 14.6 mmol) was placed in a two necked round bottom flask equipped with a condenser, a magnetic stir bar and a nitrogen gas inlet and outlet. To a sucrose sample a 100.0 ml DMAc was added. The mixture was stirred until a clear result was attained then t-Butyl acetoacetate (12.0 ml, 11.5 g, 73 mmol, 4 Eq/sucrose) was added dropwise (10 min) to the sucrose mixture under the N_2 shield of protection.

The produced solution was heated at 120 ^oC for 3 hours, then stirred overnight at room temperature. The reaction mixture was transferred to a separatory funnel mixed with water (500 mL) and extracted with ethyl acetate (3 x 100 mL). The ethyl acetate layers were collected, dried over anhydrous calcium chloride and the solvent was evaporated using a rotary evaporator to produce an oily material. The oily product was purified by flash chromatography using ethyl acetate: hexane (4:6) TLC employing the eluting solvent hexane ethyl acetate to produce about 5.0 g of yellow oily material with 87% yield that was analyzed by FT-IR spectroscopy V_{cm}^{-1}: 1449 cm^{-1} (C=O, ester), 1632 cm^{-1} (C=O, ketone), 2980 cm^{-1} (C-H) 1050 cm^{-1} to 1150 cm^{-1} (C-O). degree of substitution was determined by proton NMR to be about 2.0.

2.3.2 Sucrose with β-amino ester functionality

2.3.2.1 Reaction of sucrose acetoacetate with 2,3-diaminopyridine (2)

A sample of sucrose acetoacetate (1.0 g, 1.96 mmol) was dissolved in ethanol (50.0 ml) after being placed in a round bottom flask. To the solution was added 2,3-diaminopyridine (0.6 g, 4.0 mmol).

The produced solution was treated with acetic acid (1.0 mL) as catalyst and refluxed for 3 hr.

The reaction was monitored by TLC using Hexane: ethyl acetate (6:4) as an elution solvent. Solvent was evaporated under vacuum and residue was washed several times with diethyl ether. And recrystallized from EtOH water to produce about 1.5 g of black solid and 80% yield.

FT-IR V_{cm-1}: 3320 cm^{-1} (N-H), 1716 cm^{-1} (C=O of the ester group), 1630 cm^{-1} (C=C-NH and C=N), 1590 cm^{-1} (C=C of pyridine ring).

2.3.2.2 Reaction of sucrose acetoacetate with Valine (3)

A sample of sucrose acetoacetate (1.0 g, 1.96 mmol) was dissolved in acetic acid (20.0 mL) after placed in a round bottom flask. Then was added valine (0.6 g, 4.0 mmol) to the solution.

The reaction solution was refluxed for 3 hr. Solvent was evaporated under vacuum and residue was washed several times with diethyl ether and recrystallized form EtOH water 1.6 g of dark brown solid with 85% yield. FT-IR (neat) V_{cm-1} 3300 cm^{-1} to 2800 cm^{-1} (OH of the carboxyl group) 1717 cm^{-1} (C=O of ester), 1614 cm^{-1} (C=N) imine.

2.3.3 Preparation of Pt-sucrose complex (4)

A sample of K_2PtCl_4 (0.21 g, 0.50 mmol) was dissolved in a 3 mL of distilled water, the mixture was stirred to obtain a clear solution. The amino sugar **2** (0.3 g) was dissolved in 4 mL distilled water then added it to the platinum (II) solution. The produced solution was stirred at room temperature for 30 minutes then heated at 80 ºC for 2 hours. The reaction mixture was placed in the refrigerator for 24 hours and the produced solid was on a filter paper and analyzed it by FT-IR. The product is dark brown solid. Milting point was about 254 ^{o}C and the mass of the product was about 0.6 g and yield 80%.

2.3.4 Preparation of Pt-sucrose complex (5)

Dissolved the K_2PtCl_4 (0.21 g, 0.50 mmol) in 3 mL of distilled water, the mixture was stirred to produce a clear solution. The amino sugar **3** (0.3 g) was dissolved in 4 mL distilled water then added it to platinum solution. The produced solution was stirred at room temperature for 30 minutes then heated at 80 ºC for 2 hours. The solution was placed in the refrigerator overnight and finally collect by suction filtration using a glass sintered funnel and analyzed it by FT-IR. The product mass is 0.5 g and it is black solid with milting point 235ºC and yield 85%.

2.4 Biological

2.4.1 Serial solutions

Solutions of Sucrose-acetoacetate **1**, Sucrose with β-amino ester functionality using 2,3-diaminopyridine **2**, Sucrose with β-amino ester functionality using valine **3**, Pt complex

with sugar amine (2,3-diaminopyridine) **4**, Pt complex with sugar amine (valine) **5** were prepared at concentration of 500 µg/mL of phosphate buffer solution (Pbs) solvent [15].

Diluted solutions with various concentrations were prepared form the stock solution using serial dilution method (1, 0.5, 0.25, 0.125, 0.0625 µg/mL) [15].

2.4.2 Cell culture

Culture of normal muscle cells (L6 cells from mortal cadaverous muscle) and cervix cancer cells (HeLa cells from a cervical melanoma) were obtained from American Type Culture Collection (ATCC) [15].

HeLa and L6 cells were both grown in Roswell Park Memorial Institute Medium (RPMI) medium with the addition of 10% fetal shin serum, 1% nonessential amino acid, 1% penicillin streptomycin, 1% l-glutamine, and 1% amphotericin B. Both cell lines were cultured at a temperature of 37 °C in a humidified environment containing 95% air and 5% CO_2, with at least twice-weekly medium changes [15].

Except for the amphotericin B and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) reagent from SIGMA Corporation, all of the chemicals used were purchased from Biological Diligence. Cell lines were handed by Dr. Ashraf Sawafta.

For the first test which is called screening test, the cells were cultured in 30-well plates and grown in 950 µl of RPMI medium that including 2×10^4 cells/well and 5% Fetal bovine serum (FBS).

Then 50 µL of different concentrations (1.0, 0.5, 0.25, 0125, and 0.0625 µg/mL) of Sucrose-acetoacetonate **1**, Sucrose with β-amino ester functionality using 2,3-diaminopyridine **2**, Sucrose with β-amino ester functionality using valine **3**, Pt complex with sugar amine (2,3-diaminopyridine) **4**, Pt complex with sugar amine (valine) **5** were applied to the prepared 30-well plates, and the plates were incubated for 24 hours at 37 °C, 5% CO_2, 95% air, and 100% relative humidity [15].

Using an inverted microscope (Labomed, USA), the morphological variations of the cells were observed [15].

2.4.3 Cytotoxic assay

By eliminating the culture medium and adding 0.05% of Ethylenediaminetetraacetic acid trypsin-(EDTA), cells in culture with convergences of more than 70–80% were separated from the culture flask [15].

A suspension of 100 µL (2.5×10^4 cells/well) of viable cells were planted in a 30-well plate, also tested with different concentrations (1.0, 0.5, 0.25, 0125, and 0.0625 µg/ mL) of the Sucrose-acetoacetonate **1**, Sucrose with β-amino ester functionality using 2,3-diaminopyridine **2**, Sucrose with β-amino ester functionality using valine **3**, Pt complex with sugar amine (2,3-diaminopyridine) **4**, Pt complex with sugar amine (valine) **5** followed by a 24-hour incubation period at 37°C for the MTT assay [15].

2.4.4 MTT assay

The anticancer activity of Sucrose-acetoacetonate **1**, Sucrose with β-amino ester functionality using 2,3-diaminopyridine **2**, Sucrose with β-amino ester functionality using valine **3**, Pt complex with sugar amine (2,3-diaminopyridine) **4**, Pt complex with sugar amine (valine) **5** were tested by the 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) assay [15].

The samples were cultivated for 24 hours at 37 °C in 5% CO_2, 95% air with different concentrations of the compounds (1, 0.5, 0.25, 0.125, and 0.0625 g/mL) [15].

MTT (5 mg/ mL) solution was applied in a quantity equivalent to 10% of the culture volume, or 20 µL. The 30-well plates were then incubated for 4 hours [15, 76].

The culture solution was removed after 4 hours, then MTT detergent was applied to the 30-well plate. The gyratory shaker used to gentle moving [15].

Less than an hour after applying MTT detergent, the absorbance of the MTT formazan was determined using an enzyme-linked immunosorbent assay (ELISA) at 600 nm wavelength [76].

The results of viable cells were compared with its control cells [15].

Chapter Three

Result and Discussion

3.1 Synthesis of sucrose-based Schiff bases

A set of sucrose-based cisplatin analogues were synthesized and evaluated as anticancer agents. The synthesis of these analogs required several steps, in the first step a transesterification process was performed by adding acetylacetonate (β-ketoester) functionality to sucrose molecule. This was carried out by reacting sucrose with tert-butyl acetoacetate (t-BAA) as shown in Scheme 3.1. The reaction was carried out in DMSO at about 120 ^{o}C. During the reaction course primary hydroxyl (OH) of sucrose make a nucleophilic attack on ester carbonyl and displaces the bulky t-butyl which acts as a good leaving group. As a result of the reaction, compound **1** was formed, and t-butyl alcohol formed as a byproduct.

Scheme 3.1

Synthesis of sucrose with β-ketoester functionality

DMAc, 120 ^{o}C

6 hr

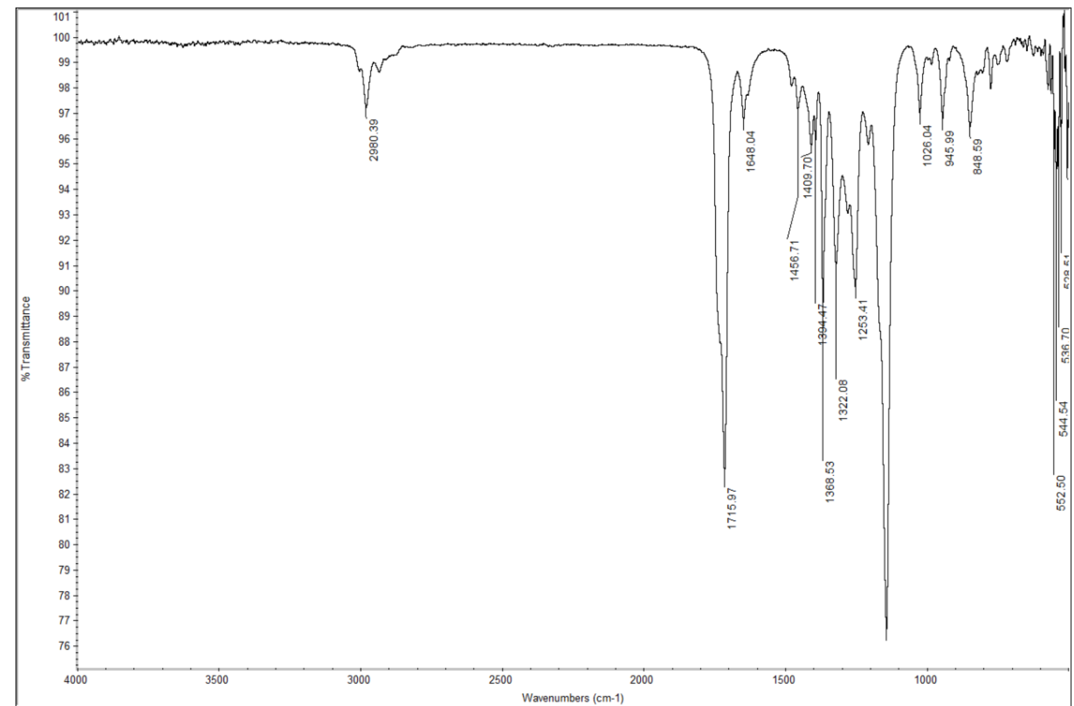
Sucrose

1

FT-IR spectrum of the starting material t-butyl acetoacetate is displayed in Figure 3.1. It has a strong peak at about 1715 cm^{-1} and weak band at 1650 cm^{-1} corresponding to C=O stretching of ester and ketone respectively. The band at 2980 cm^{-1} represents the stretching vibration of the C-H bond. The C-O stretching band appears at 1120 cm $^{-1}$.

Figure 3.1

FT-IR for tert-butyl acetoacetate

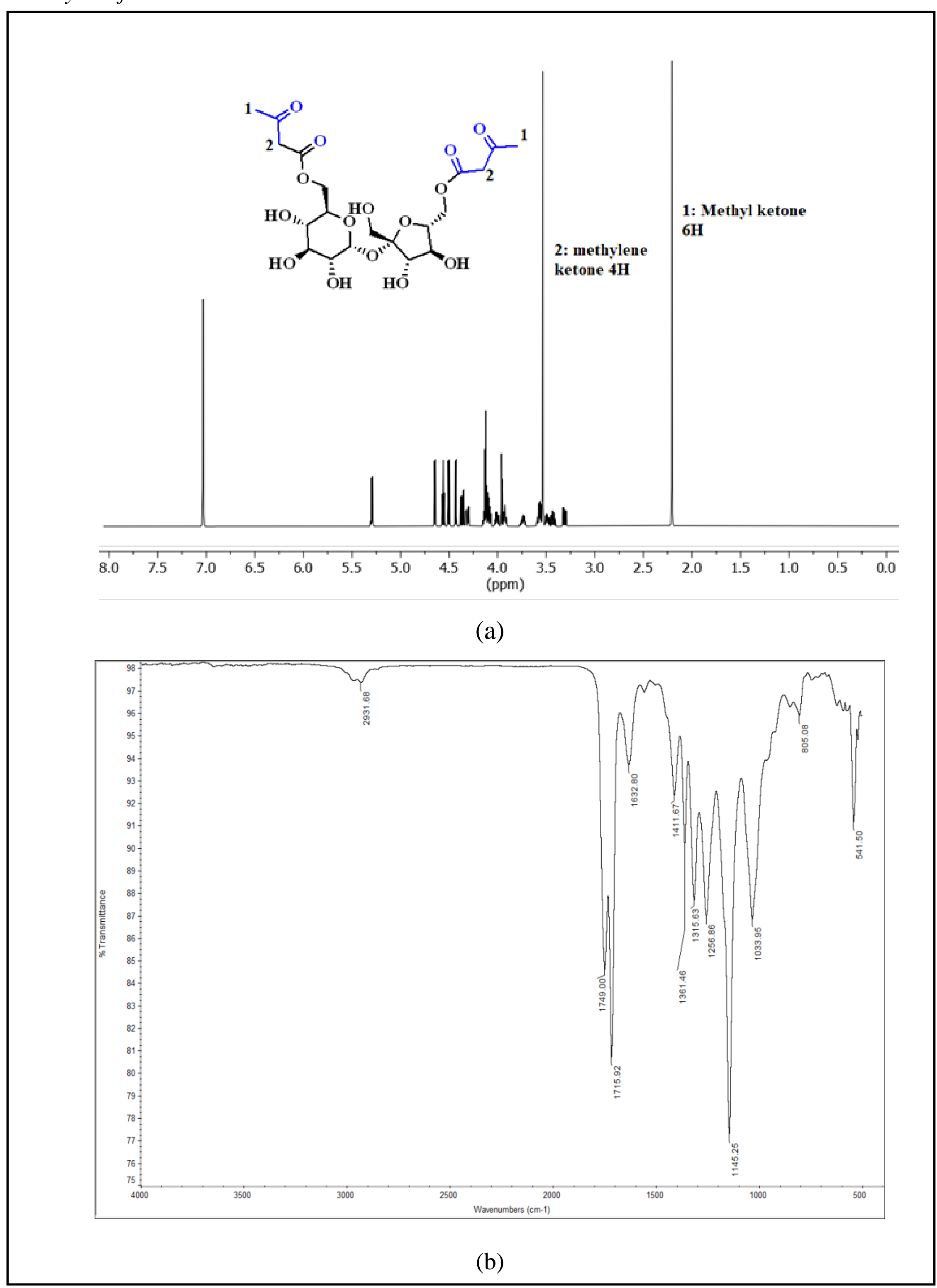


Sucrose acetylacetonate was analyzed by ^{1}H NMR spectroscopy (Figure 3.2 (a)). The spectrum clearly shows the methyl and methylene groups in addition to the sucrose hydrogens.

The integration shows the presence of 6 methyl protons and 4 methylene protons. The results indicate that the degree of substitution is 2 as shown in Figure 3.2 (a).

Figure 3.2

Analysis of sucrose acetoacetate



Note. (a) 1H NMR of sucrose acetoacetate, (b) FT-IR for sucrose-acetoacetate

The IR of the sugar ester compound **1** is represented in Figure 3.2 (b). The IR clearly shows the following peaks that indicate the formation of the product. As shown in Figure 3.2(b) the new C=O band appears on 1749 cm^{-1} that represents the formation of the new ester group. The C=O stretching of the ketone band show a minor shift to a lower frequency it appears at 1632 cm^{-1}, the band at 2980 cm^{-1} represents the stretching vibration of the C-H bond. More than band appear in the range of 1050 cm^{-1} to 1150 cm^{1}, which could be attributed to the glycosidic linkage in sucrose and C-O bonds.

The second step in the synthesis involved reacting sucrose β-acetylacetonate **(1)** with 2,3-diaminopyridine and formation of sucrose with β-amino acetate (Schiff base **2**) as shown in Scheme 3.2.

The reaction is a condensation reaction that involved a nucleophilic addition of amine on the acetyl carbonyl then a self-protonation using H+ as a catalyst to form oxonium ion and then dehydration by loss of H_2O molecule and formation of an imine which tautomerizes to enamine 2.

Scheme 3.2

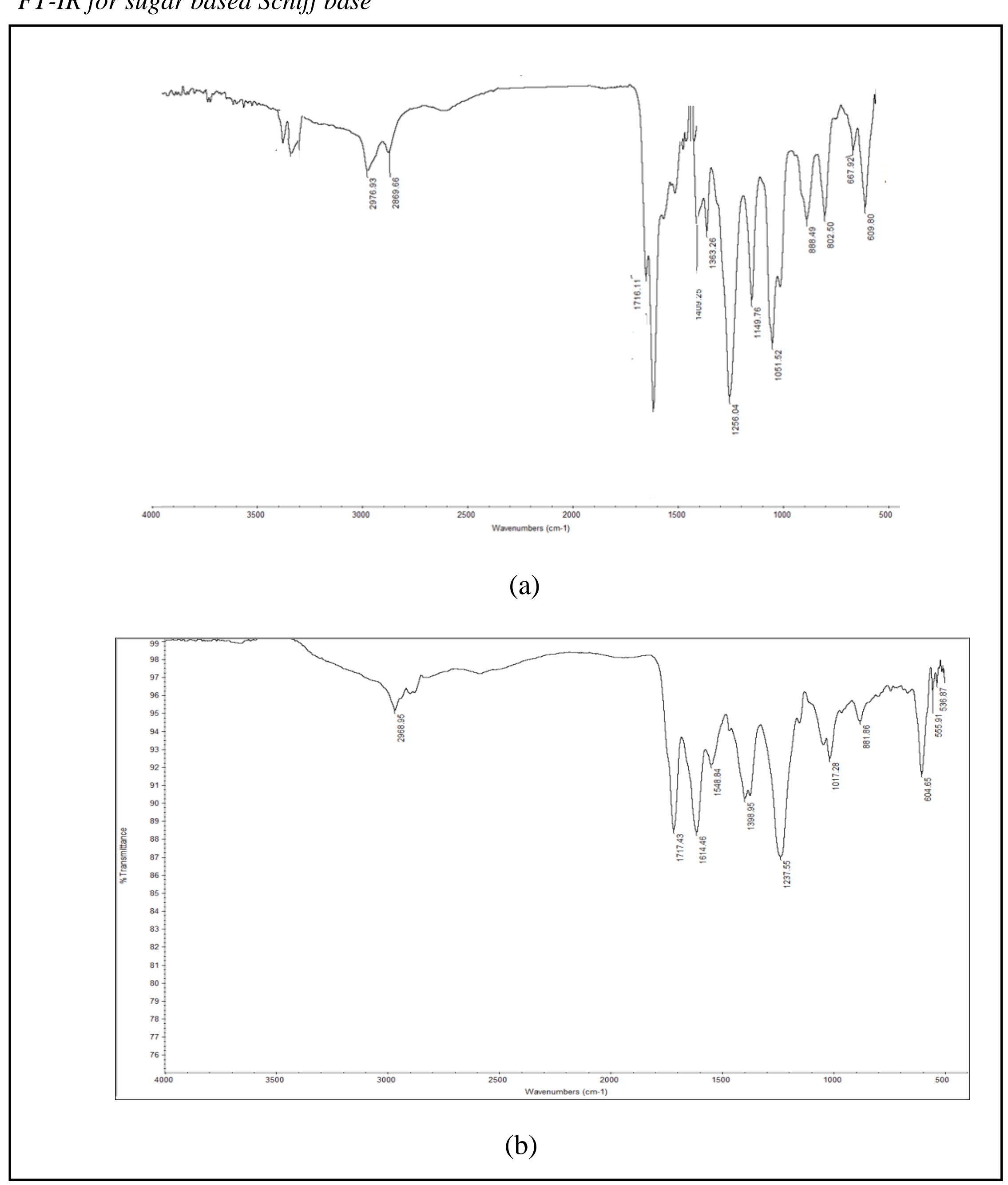
Formation of sucrose with Schiff base functional group

The IR spectrum for compound 2 is represented in Figure 3.3 (a), it shows a peak at 3320 cm^{-1} which could be attributed to the amine (N-H).

The peak at 1716 cm^{-1} could be related to C=O of the ester group and the peak at 1630 cm^{-1} could be related to C=C-NH and C=N. The small peak at 1590 cm^{-1} could be related to the C=C of pyridine ring.

Figure 3.3

FT-IR for sugar based Schiff base



Note. (a) FT-IR for sugar-based Schiff base 2, (b) FT-IR sugar-based Schiff base 3

Sucrose acetoacetate (1) was converted to Schiff base 3 by reacting it with the amino acid valine. Due to the insolubility of valine in methanol, the reaction was carried out in acetic acid, which acted as a solvent and catalyst. The reaction is summarized in Scheme 3.3.

The reaction mechanism is a condensation reaction similar to the reaction of sucrose acetoacetate and the aminopyridine compound.

Scheme 3.3

Synthesis of sucrose with amino acid functionality

Valine

1

3

The FT-IR spectrum of compound 3 is displayed in Figure 3.3 (b). The spectrum shown the OH of the carboxyl group that extends from 3300 cm^{-1} to 2800 cm^{-1}. It also shows two bands at 1717 cm^{-1} and 1614 cm^{-1} corresponding to C=O of ester and imine groups, respectively.

3.2 Preparation of platinum Complexes

The novel Pt-sucrose complexes were prepared by reacting the sucrose-based Schiff bases 2 and 3 with Potassium tetrachloroplatinate (K_2PtCl_4) as shown in Scheme 3.4 and 3.6, respectively. The reaction was carried out in water at about 80 ^oC. Two of the four Cl on Pd were replaced by the Schiff base ligands.

That complexed with Pt(II) from the two sites (acted as a bidentate ligand) the C=O and the N-H. Amine is known to have high affinity for Pt(II). The other possibilities are Pt complexed with the two amino groups or with the amine of the Schiff base and the N of the pyridine ring as shown in Scheme 3.5. The most probable complex is complex 7, since the amine as mentioned above has much higher affinity for Pt than the weak

ligand carbonyl group. Complex 6 has some strain which cusses instability to the complex. The only way to determine the correct structure is by running analysis using x-ray crystallography.

Scheme 3.4

Synthesis of sucrose-based platinum complex form compound 2

K_2PtCl_4

2

4

Scheme 3.5

Structures of possible Pt complexes with Schiff base 2

6

7

The second complex was prepared from reacting the sucrose-based Schiff base 3 and potassium tetrachloroplatinate as shown in scheme 3.6. In this case only one possible complex. The other possibility which is coordination of Pt with OH of carboxyl and the amine group, but the OH of carboxyl is a very week complexing ligand.

Scheme 3.6

Synthesis of sucrose-based platinum complexes

K_2PtCl_4

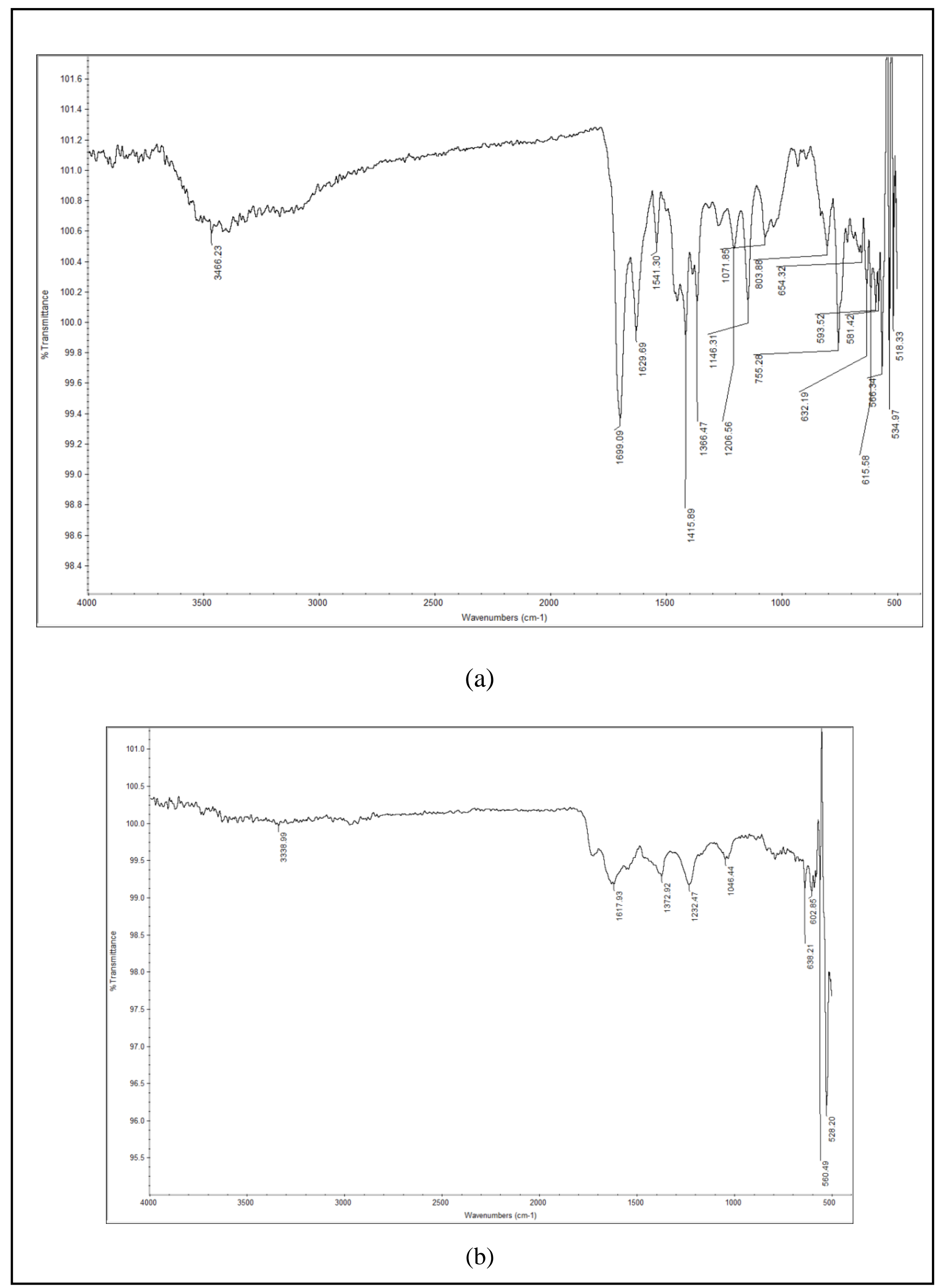
3

5

The FT-IR of complex 4 is represented in Figure 3.4 (a). the spectrum shows a C=O peak at 1700 cm^{-1} and another peak at 1629 cm^{-1} corresponding to C=C-NH and 1540 cm^{-1} could be attributed to aromatic ring (pyridine) C=C. Comparing this spectrum to the one shown for the ligand shown in Figure 3.3 (a). There is clear shift in the peaks frequency it could be explained by the coordination to Pt(II).

Figure 3.4

FIT-IR for prepared complexes



Note. (a) FT-IR of Pt-complex 4, (b) FT-IR for Pt complex 5.

The FT-IR of complex 5 is presented in Figure 3.4 (b). the spectrum shows sever band broadening and shift in peak frequency when compared to that of the ligand shown in Figure 3.3 (b). The result could be related to the strong complexation with Pt(II).

3.3 Anticancer activity

Sucrose and its derivatives have been known to have a wide variety of therapeutic effects, ranging from anti-inflammatory, chemo-preventive, anti-proliferative, and anti-metastatic.

In this work a novel set of sucrose-based cisplatin complexes were screened for their cytotoxic effect against HeLa cells and L6 normal cells.

The *in vitro* cytotoxic effect of the prepared Sucrose with β-amino ester functionality using 2,3-diaminopyridine **2**, Sucrose with β-amino ester functionality using valine **3**, Pt complex with sugar amine (2,3-diaminopyridine) **4**, Pt complex with sugar amine (valine) **5** were evaluated using MTT test.

3.3.1 HeLa cells cytotoxicity caused by the prepared compounds.

A new set of starting materials in vitro anticancer effects against the HeLa cancer cell were studied. The results show that the produced sucrose-acetoacetate, sucrose with β-amino ester functionality using 2,3-diaminopyridine and sucrose with β-amino ester functionality with valine showed different cytotoxic effects on the HeLa cells at varying concentrations.

Within the tested concentration range (1.0, 0.5, 0.25, 0.125 and 0.0625 μg/mL), HeLa cell viability decreased by 28.5% to 41.7%, as represented in Table 3.1 and Figure 3.5 (a).

Table 3.1

Effects of starting materials (compounds 1,2 and 3) on the viability of HeLa cells at various concentrations (μg/mL)

Compounds	Cell viability (% of inhibition)					
Concentration (μg/mL).	0	1	0.5	0.25	0.125	0.0625
1	100%	35.9%	35.2%	32.4%	29.4%	28.5%
2	100%	39.7%	38.5%	35.9%	34.5%	34.2%
3	100%	41.7%	39.9%	37.9%	37.3%	36.7%

Note. 1: Sucrose-acetoacetate, 2: Sucrose with β-amino ester functionality using 2,3-diaminopyridine, 3: Sucrose with β-amino ester functionality using valine.

In comparison to the other studied compounds **1** and **2**, compound **3** showed greater potency on HeLa cancer cells. Compound **3** treatment decreased the viability (increased the inhibition) of HeLa cells by between 36.7% and 41.7%.

It decreased the viability of the studied HeLa cells to 41.7% at a concentration of 1 μg/mL to 36.7% at a concentration of 0.0625 μg/mL. The viability of the studied HeLa cells was decreased by prepared compound **2** between the ranges of 34.2% at 0.0625 μg/mL concentration and 39.7% at 1 μg/mL concentration, and by prepared compound **1** between the ranges of 28.5% at 0.0625 μg/mL concentration and 35.9% at 1 μg/mL concentration as shown in Table 3.1.

Figure 3.5 (a) represented the Effects of starting materials at various concentrations on HeLa cells (μg/mL).

As shown when the concentration increased the percentage of inhibition increased and cell growth decreased.

Concentration 0 μg/mL represented to a control which is used as a reference for comparison with other cells.

By comparing the different concentrations of compounds **1**, **2** and **3** with each other, it was found that the compound **3** had the higher effect on HeLa cancer cells than compounds **1** and **2** and higher concentration 1 μg/mL had the greatest % of inhibition (lowest viability).

3.3.2 L6 cell cytotoxicity caused by the sucrose-based compounds

The new set of sucrose-based compounds were evaluated in vitro anticancer properties against the L6 cancer cell. According to the results, the synthesized sucrose-acetoacetate, sucrose with β-amino ester functionality using 2,3-diaminopyridine and sucrose with β-amino ester functionality using valine all show variable degrees of cytotoxicity on L6 cells.

During the tested concentration range, the viability of L6 cells has decreased by 26.2-45.1%, as represented in Table 3.2 and Figure 3.5 (b).

Table 3.2

Effects of starting materials on the viability of L6 cells at various concentration (µg/mL)

Compounds	Cell viability (% of inhibition)					
Concentration (µg/mL)	0	1	0.5	0.25	0.125	0.0625
1	0%	33.3%	32.5%	29.2%	26.4%	26.2%
2	0%	45.1%	36.7%	35.9%	33.9%	32.9%
3	0%	36.3%	34.1%	32.7%	31.2%	30.3%

Note. 1: Sucrose-acetoacetate, 2: Sucrose with β-amino ester functionality using 2,3-diaminopyridine, 3: Sucrose with β-amino ester functionality using valine.

Compared to the other studied compounds, compound **2** demonstrated greater efficacy on L6 normal cells.

Compound **2** decreased the viability of L6 normal cells by between 32.9% and 45.1%. The evaluated L6 cells' viability was decreased by between 32.9% at 0.0625 µg/mL concentration and 45.1% at 1 µg/mL concentration.

The viability of the evaluated L6 cells was decreased by compound **3** within the ranges of 30.3% at 0.0625 µg/mL concentration and 36.3% at 1 µg/mL concentration, and by prepared compound **1** between the ranges of 26.2% for 0.0625 µg/mL concentration and 33.3% for 1 µg/mL concentration. as represented in Table 3.2.

Figure 3.5 (b) represented the Effects of starting materials at various concentrations on L6 normal cells (µg/mL).

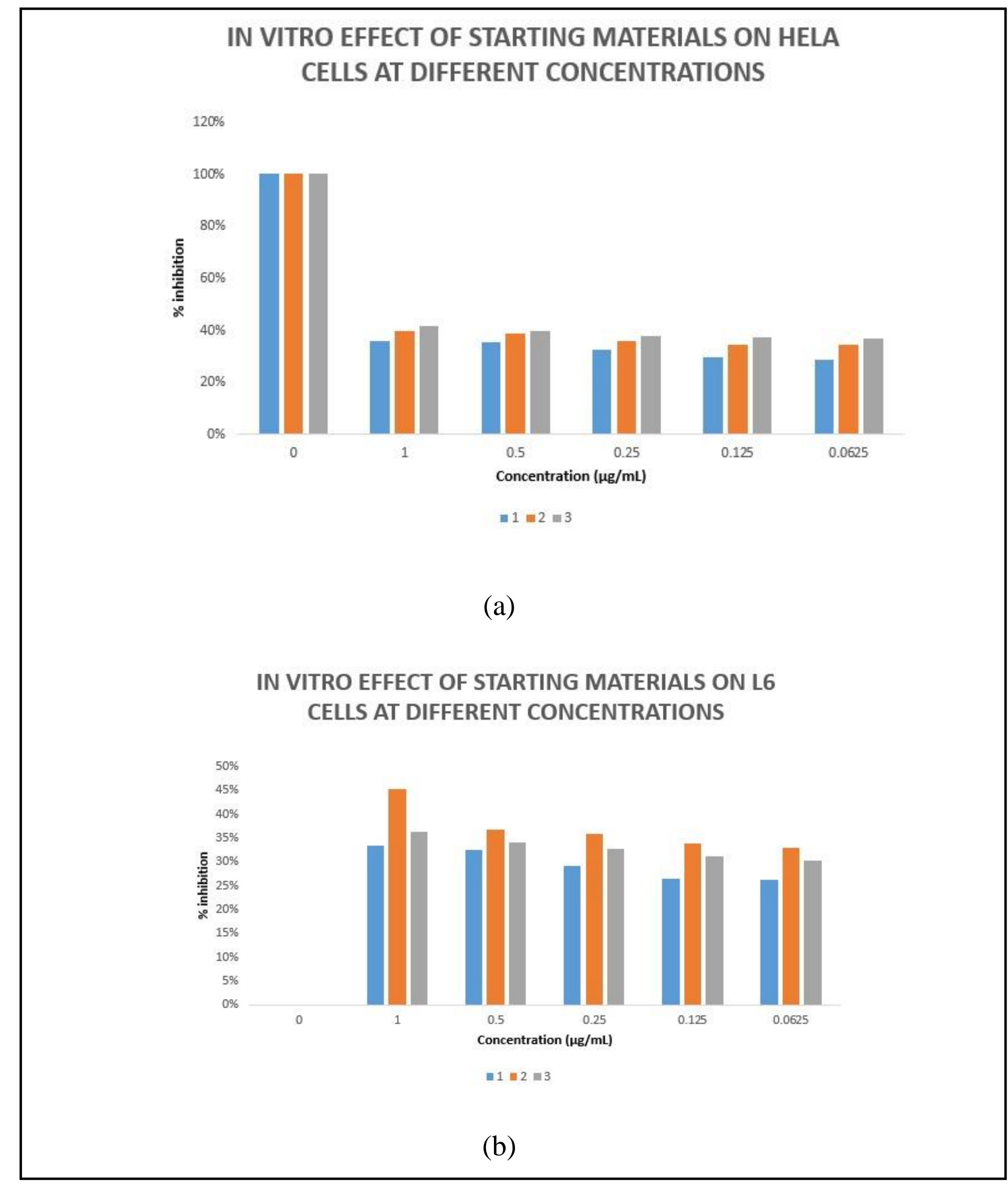
As shown in figure 3.5 (b) when the concentration increased the percentage of inhibition increased and cell growth decreased.

At a concentration of 0 µg/mL which represents the control and used as a reference for comparison with other cells.

By comparing the effect of compounds **1**, **2** and **3** based on concentrations, it was found that compound **2** had the highest effect on L6 normal cells than compounds **1** and **3** and higher concentration 1 µg/mL had the greatest % of inhibition (lowest viability).

Figure 3.5

Effect of starting materials at various concentations of hela and L6 cells



Note. (a) Effects of starting materials at various concentrations on HeLa cells (μg/mL), (b) Effects of starting materials at various concentration on L6 cells (μg/mL)

Table 3.3 represented to some pictures under microscope shown the effect of starting material compounds (1,2 and 3) with various concentration on HeLa cells and L6 normal cells.

The shape of the Hela cells caner is represented in picture A. in this photo no anticancer agents are present.

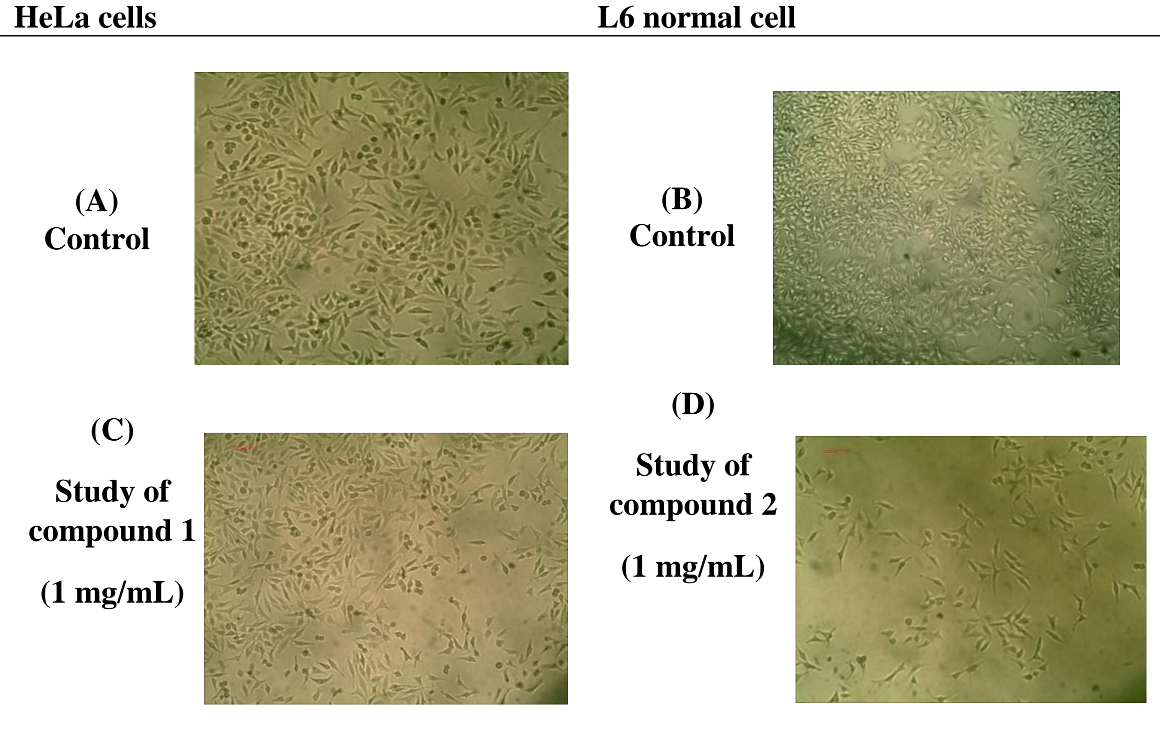
Picture C appeared the effect of compound **1** with concentration 1.0 µg/mL on HeLa cells . The effect is clear by no of cells was dropped by about 35.9% compared to the control, as represented in Table 3.1.

The shape of the L6 normal cells caner is represented in picture B. It has a concentration of 0 µg/mL which represents the control and used as a reference for comparison with other cells.

Picture D shows the effect of compound **2** with concentration (1.0 µg/mL) on L6 cells. The effect is clearly reduced by 45.1% compared to the control, as represented in Table 3.2.

Table 3.3

Effect of starting material compounds with various concentration on HeLa cells and L6 normal cells



3.1.1 HeLa cells cytotoxicity caused by the sucrose-based cisplatin complexes.

A novel class of sucrose-based cisplatin complexes **4** and **5** were tested for their in vitro anticancer effects on the HeLa cancer cell.

According to the results, different concentrations (1, 0.5, 0.25, 0.125 and 0.0625 μg/mL) of the produced platinum complexes **4** and **5** had varying degrees of cytotoxicity on HeLa cells.

Within the examined concentration range (1, 0.5, 0.25, 0.125 and 0.0625 μg/mL), HeLa cell viability dropped by 46.8 to 67.2%, as represented in Table 3.4.

In general, cell development slowed down as the concentration of produced platinum complexes rose as displayed in Figure 3.6 (a).

Table 3.4

Effects of various concentrations (µg/mL) of sucrose-based cisplatin complexes in vitro on the viability of HeLa cells

Sucrose Derivatives	Cell viability (% of inhibition)					
Concentration (µg/mL).	0	1	0.5	0.25	0.125	0.0625
4	100	67.2%	65.9%	64.6%	60.6%	56.4%
5	100	55.2%	53.9%	51.2%	47.3%	46.8%

Note. 4 : Pt complex with sugar amine 2 (2,3-diaminopyridine) , 5 : Pt complex with sugar amine 3 (valine) .

In comparison to the other studied complex **5**, the sucrose-based cisplatin complex **4** demonstrated greater potency on HeLa cancer cells.

Sucrose-based cisplatin complex **4** decreased the viability of HeLa cells by between 54.4% and 67.2%.

The evaluated HeLa cells' viability was decreased from 56.4% at 0.0625 µg/mL concentration to 67.2% at 1.0 µg/mL concentration. It decreased the viability of the studied HeLa cells in the range of 46.8% for 0.0625 µg/mL concentration to 55.2% for 1 µg/mL concentration in the generated Sucrose-based cisplatin complex **5** as represented in Table 3.4.

Figure 3.6 (a) represented the Effects of various concentrations of sucrose-based cisplatin complexes **4** and **5** on HeLa cells (µg/mL).

As shown when the concentration increased the percentage of inhibition increased and cell growth decreased. Concentration 0 µg/mL represented to the control.

By comparing the concentrations of complexes **4** and **5** with each other, it was found that the compound **4** had the higher effect on HeLa cancer cells than compound **5** and higher concentration 1.0 µg/mL had the greatest % of inhibition (lowest viability).

3.3.3 L6 cell cytotoxicity caused by the sucrose-based cisplatin complexes.

A novel collection of sucrose-based cisplatin complexes **4** and **5** were tested against the L6 normal cell for their in vitro anticancer properties.

The results show that different concentrations (1, 0.5, 0.25, 0.125 and 0.0625 μg/mL) of the produced platinum complexes **4** and **5** exhibit varying degrees of cytotoxicity toward L6 cells.

Within the investigated concentration range (1, 0.5, 0.25, 0.125 and 0.0625 μg/mL), the viability of L6 cells decreased by between 25.5% and 44.6%. as shown in Table 3.5 and Figure 3.6 (b).

Table 3.5

Effects of various concentration of sucrose-based cisplatin complexes in vitro on the viability of L6 normal cells (μg/mL)

Sucrose Derivatives		**Cell viability (% of inhibition)**				
Concentration (μg/mL)	0	1	0.5	0.25	0.125	0.0625
4	0%	29.8%	29.7%	29.5%	26.98%	25.5%
5	0%	44.6%	44.3%	40.4%	37.92%	33.8%

Note. 4 : Pt complex with sugar amine 2 (2,3-diaminopyridine) , 5 : Pt complex with sugar amine 3 (valine) .

Compared to the other studied compound **4**, the sucrose-based cisplatin complex **5** shown greater efficacy on L6 normal cells. Sucrose-based cisplatin complex **5** reduced the viability of L6 cells by between 44.6% and 33.8%.

The measured L6 cells' viability was decreased by the generated Sucrose-based cisplatin complex **5** between 33.8 at 0.0625 **μ**g/mL concentration and 44.6% at 1 **μ**g/mL concentration.

The viability of the tested L6 cells was decreased by the generated Sucrose-based cisplatin complex **4** in the range of 25.5% for 0.0625 **µ**g/mL concentration to 29.8% for 1 **µ**g/ml concentration. as represented in Table 3.5.

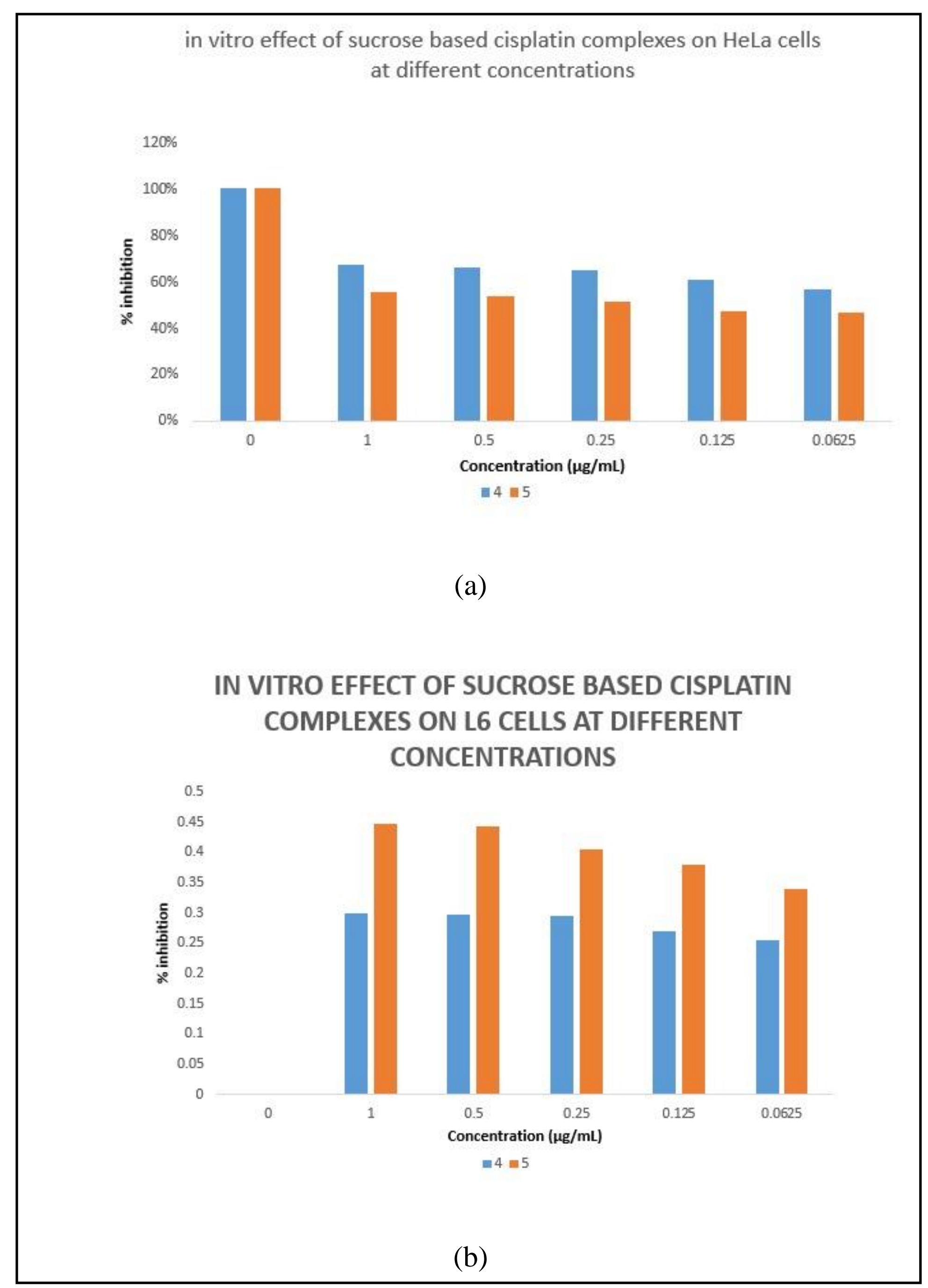
Figure 3.6 (b) represented the Effects of various concentrations of sucrose-based cisplatin complexes in vitro on L6 cells (µg/mL).

As shown when the concentration increased the percentage of inhibition increased and cell growth decreased.

By comparing the concentrations of complexes **4** and **5** with each other, it was found that the compound **5** had the higher effect on L6 normal cells than compound **4** and higher concentration 1 µg/mL had the greatest % of inhibition (lowest viability).

Figure 3.6

Effect of prepared complexes at various concentrations on hela and L6 cells



Note. (a) Effects of various concentrations of sucrose-based cisplatin complexes on HeLa cells (µg/mL), (b)Effects of various concentrations of sucrose-based cisplatin complexes in vitro on L6 cells (µg/mL).

Table 3.3 represented to some pictures under microscope shown the effect of prepared complexes (4 and 5) with various concentration on HeLa cells and L6 normal cells.

In picture A appeared the effect of compound **4** with concentration (1 μg/mL) on HeLa cells. The effect is clear by 67.2% compared to the control, as represented in Table 3.4.

Picture C appeared the effect of compound **4** with concentration (0.25 μg/mL) on HeLa cells. The effect is clear by 64.6% compared to the control, as represented in Table 3.4.

Picture E appeared the effect of compound **5** with concentration (0.5 μg/mL) on HeLa cells. The effect is clear by 53.9% compared to the control, as represented in Table 3.4.

Picture F shows the effect of compound **5** with concentration (0.25 μg/mL) on HeLa cells. The effect is clear by 51.5% compared to the control, as represented in Table 3.4.

Picture B appeared the effect of compound **5** with concentration (1 μg/mL) on L6 cells. The effect is clear by 44.6% compared to the control, as represented in Table 3.5.

Picture D appeared the effect of compound **5** with concentration (0.5 μg/mL) on L6 cells. The effect is clear by 44.3% compared to the control, as represented in Table 3.5.

3.4 Conclusion

New cis-platin analogues were created through synthesis. Sucrose and tert-butyl acetoacetate were reacted in a three-step method to complete the synthesis. In the subsequent step, 2,3-diaminopyridine and the amino acid valine were reacted with sucrose acetoacetate to create Schiff base. The final stage involved complexing the generated Schiff bases with Pt(II). A novel set of synthetic platinum complexes were tested for their in vitro anticancer properties against the HeLa cancer cell line and L6 normal muscle cells as a control. The results showed that, at various concentration, each of the complexes tested has a varied level of cytotoxicity on HeLa cells. The viability of HeLa cells was decreased in the range between 46.8% and 67.2% within the tested concentration. As the concentration of the prepared complexes increased, cell growth reduced.

The *in vitro* anticancer activities of that the prepared sucrose-acetoacetonate, sucrose with β-amino ester functionality using 2,3-diaminopyridine and sucrose with β-amino ester functionality using valine against L6 normal muscle cells and HeLa cancer cells were tested. According to the results, all of the examined compounds have different degrees of cytotoxicity toward HeLa cells at various concentrations. HeLa cells viability was decreased by between 28.5 and 41.7% at the concentration under evaluation. As the concentration of the prepared complexes rose, cell growth slowed down.

List Of Abbreviations

Abbreviation	Meaning
ATR	Average True Range
CAPE	Caffeic acid phenethyl easter
C9-Me	Nine carbons-methyl
DMAc	Dimethylacetamide
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic acid
ELSIA	Enzyme-linked immunosorbent assay
FBS	Fetal bovine serum
FT-IR	Fourier-Transform Infrared Spectrophotometer
GDE	Glycerol diglycidyl ether
HLB	Hydrophilic–lipophilic balance
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
NMR	Nuclear Magnetic Resonance Spectroscopy
Pbs	Phosphate-Buffered Saline
PG	Propylene Glycol
RPMI	Roswell Park Memorial Institute Medium
SFAE	Sucrose Fatty Acid Easter
t-BAA	T-Butyl Acetoacetate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetra Methyl Silane
WHO	World Health Organization

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Appendices

Appendix A

Figures

Figure 1.2

cis-platin and cisplatin crosslink with DNA Guanine

Figure 1.4

nucleoside structure

Appendix B

Tables

Table 1.4

Examples of Natural iminosugars

Iminosugars	Structure
Pyrrolidine	
Piperidine	
Pyrrolizidine	
Indolizine	
Nojirimycin	
1-Deoxynojirimycin	
Swainsonine	
Casuarine	
Calystegine B_2	

Calystegine A_3	
Castanospermine	
Australine	

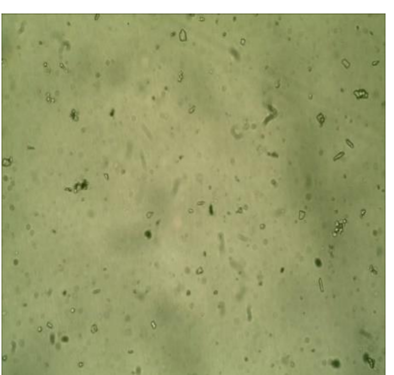
Table 3.6

Effect of prepared complexes with various concentration on HeLa cells and L6 normal cells

HeLa cells	L6 normal cells
(A) Study of compound 4 (1 µg/mL)	**(B) Study of compound 5 (1 µg/mL)**
(C) Study of compound 4 (0.25 µg/mL)	**(D) Study of compound 5 (0.5 µg/mL)**
(E) Study of compound 5 (0.5 µg/mL)	

(F) Study of compound 5

(0.25 μg/mL)



جـامعـــة النجاح الوطنية

كليــة الدراســـات العليـــا

السيسبلاتين القائم على السكروز: تحضيره ونشاطه المضاد للسرطان

إعداد

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إشراف

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قدمت هذه الرسالة استكمالا لمتطلبات الحصول على درجه الماجستير في الكيمياء، من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس– فلسطين.

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الملخص

تلقت كيمياء السكروز الكثير من الإهتمام منذ الستينيات، حالياً تم الإبلاغ عن أكثر من ثلاثمائة من مشتقات السكروز المحددة جيداً في الأدبيات لأنها آمنة ووفرة ومتاحة بتكلفة منخفضة. تم التخطيط لهذا العمل على ابتكار دواء للسرطان بفاعلية أكبر وسمية منخفضة يعتمد على جزيئات السكر .

الهدف الرئيسي من هذه الدراسة هو تطوير نظير سيسبلاتين فريد ومشتق بشكل طبيعي يمكن استخدامه كبديل للسيسبلاتين وخالي من الآثار الجانبية للسيسبلاتين .

تم تعديل مركبين بلاتينيين أساسهما السكروز بإضافة وظيفة أسيتيل أسيتونيت إلى السكروز عن طريق تفاعله مع ثلاثي–بيوتيل أسيتو أسيتات ثم تحويله الى قاعدة شيف عن طريق تفاعله مع الأحماض الأمينية ثم تفاعله مع رباعي كلورو البوتاسيوم لتحضير مجمعات البلاتين القائمة على السكروز .

أظهرت المركبات في هذه الدراسة نشاطاً واضحاً ضد خلايا هيلا السرطانية حيث قام المركب الأول بتثبيطها بنسبة 67% تقريباً و مع وجود تأثير خفيف على الخلايا الطبيعية بنسبة 29% ، وأظهرت خلايا شيف تأثيراً أقل على خلايا هيلا السرطانية.

تم تقييم النشاط المضاد للسرطان للمركبين المتطورين في المختبر باستخدام خلايا سرطانية مختلفة. أظهر المركبان نتائج واعدة على خلايا هيلا السرطانية من خلال قتلها ومنع تكاثرها بشكل واضح. ولا يزال هناك المزيد من العمل الذي يتعين القيام به بشأن توضيح البنية وأنشطة نظائرها ضد الخلايا السرطانية الأخرى.

الكلمات المفتاحية: السرطان، قواعد شيف، نظائر السيسبلاتين، معقدات البلاتين ، السكروز ، الأحماض الأمينية ، صفيحات رباعي كلورو البوتاسيوم .