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Anticancer activity of palladium and platinum metal ion complexes a review

Research Project

Submitted to the department of (Chemistry) in partial fulfillment of the requirements for the degree of B.Sc. of education in chemistry

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2023-2024

CERTIFICATE

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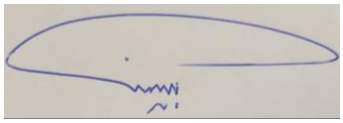
Signature  Name: **Beriwan Muhammad Hamad Ameen**

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Date: / / 2024

Dedication

To all my members and friends.

To all my teachers, especially my supervisor

To all who helped me to learn.

Acknowledgement

I'd like to express my heartfelt gratitude to my supervisor, Lec. Beriwan Muhamad for providing me with the opportunity to do this wonderful project on the subject **(Anticancer activity of palladium and platinum metal ion complexes a review)**, which also assisted me in doing a lot of research and allowing me to learn about a lot of new stuff. Second, I'd like to express my gratitude to my colleagues, who assisted me greatly in completing this project within the time constraints, allowing me to expand my knowledge and skills.

I am grateful to my supervisor, Asst Prof. Dler D. Kurda, for his support, direction, patience, trust, and advise during the course study and research project.

THANKS AGAIN TO ALL WHO SUPPORTED

Hozan Nafh Sabr

Abstract

This study's abstract demonstrated the potential of palladium and platinum complexes as anticancer medications. Our research is divided into three main sections. In the first portion, which is the most significant, we have discussed platinum and palladium independently. We have defined each of them, then the structure of each, and then the important role of palladium and platinum complexes Metal-based coordination compounds have been used throughout the history of human medicine to treat various diseases, including cancer. the second part included anticancer activity of palladium and platinum complexes, Since the discovery of cisplatin in 1965, a great number of metal coordination complexes, such as platinum, ruthenium, gold or copper have been designed, synthesized and tested in order to develop clinically effective and sate drugs. Finally, the third section is the review portion. After doing a search through a few of the scientific sources listed in this area, we eventually included the findings.

Keyword: Palladium, Platinum, anticancer.

List of Contents:

No.	Title	Page No.
1	Dedication	II
2	Acknowledgement	III
3	Abstract	IV
4	List of Contents	V
5	List of Figures	VI
6	1.Introduction	1
7	1.1 the chemistry of palladium	1
8	1.2 complexes of palladium	2
9	1.3 the chemistry of platinum	3
10	1.4 Complexes of platinum	3-4
11	1.5 anticancer activity of palladium and platinum complex	5-6
12	2.Literature review	7
13	2.1 Literature Review about anticancer activity of Pd(II) and Pt(II) complexes	7-14
12	3. Conclusion	15
13	4. Reference	16-20

List of Figures

Fig. No	Title	Page No.
(1.1)	Chemical structures of clinically approved and marketed platinum anticancer	4
(1.2)	The anti-cancer platinum complex (1) cisplatin and its inactive isomer (2) transplatin Second generation anti-cancer platinum complexes (3) carboplatin (4) AMD-473 and (5) oxaliplatin.	6
(2.1)	the structure of ligand and ORTEP diagram for [Pd(NQTS)Cl]2 . 2DMSO	7
(2.2)	Antitumor activity of some Palladium (II) and platinum (II) complexes	8
(2.3)	Structures of some trans-palladium (II) complexes (1-6)	8
(2.4)	Anticancer activities of six complexes 1–6a	9
(2.5)	The complexes showed cyctotoxic effects against human breast cancer (MCF7)	10
(2.6)	Structures of currently approved platinum-based anticancer drugs	11
(2.7)	Chemical structures of some platinum prodrugs.	12
(2.8)	Anticancer activity of $[Pd(HDANT)_2 Cl_2]$ and $[Pt(HDANT)_2Cl_2]$	13
(2.9)	Metal-based complexes demonstrated significant anticancer effects	14

Chapter One

1. Introduction:

1.1 The chemistry of palladium

Palladium is shiny, silvery metal and has melting and boiling points 1552 and 3141 °C respectively, it was discovered in 1803 by Wollaston. Palladium was named after the asteroid Pallas, and discovered about the same time. It occurs associated with other platinum group metals and the extraction processes depend on the particular ore used. It is the second most abundant platinum group metal with an abundance of about 0.015 ppm in the Earth's crust and its major sources are located in South Africa and Russia. It appears in group 10 of the periodic table with nickel and platinum in the region that bridges transition metals and main group metals, and has atomic number 46. Palladium complexes exist in four oxidation states: Pd(0), Pd(I), Pd(II), and Pd(IV); Pd(0) has the electronic configuration of $[Kr]5s^{2}4d^{8}$. The facile interconversion between these oxidation states is responsible for the broad utility of palladium in organic chemistry since each oxidation state exhibits different chemistry (Greenwood and Earnshaw 1997) (Cotton 1997) (Lide 2004). Palladium(II) complexes are extremely important in inorganic chemistry and organometallic chemistry. They are stable to air, thus, they are easily stored and handled. Palladium(II) is a class b or a soft metallic center. Accordingly, it forms numerous stable complexes with soft ligands. A vast palladium(II) coordination chemistry is found for S-, N-, P-, and As-donor ligands. Substitution reactions in palladium(II) complexes are a common preparative route to new types of derivatives. Halo-complexes are often employed as starting materials. These reactions are noticeably faster for palladium than for platinum and proceed through associative mechanisms whenever organometallic ligands are not present (Albéniz and Espinet 2006). Palladium-based anticancer drugs are a range of compounds containing the platinum group metal (PGM), palladium, in one of its various forms including metallic palladium (Pd(0)) and palladium ions in either the 2+ or 4+ oxidation states. In addition, radioactive 103Pd has also been used in cancer therapeutics. Examples include its use in fluoroscopy, a medical imaging technique which involves the real-time observation of internal organs, and in brachytherapy which uses medical implants of radioactive palladium-103 seeds.(Potrykowska, Strzelecki et al. 2014)

1.2 Complexes of palladium

Palladium(II) complexes are extremely important in inorganic chemistry and organometallic chemistry. They are stable to air, thus, they are easily stored and handled. Palladium(II) is a class b or a soft metallic center. Accordingly, it forms numerous stable complexes with soft ligands. A vast palladium(II) coordination chemistry is found for S-, N-, P-, and As-donor ligands. Substitution reactions in palladium(II) complexes are a common preparative route to new types of derivatives. Halo-complexes are often employed as starting materials. These reactions are noticeably faster for palladium than for platinum and proceed through associative mechanisms whenever organometallic ligands are not present (Albéniz and Espinet 2006). The four-coordinated square-planar geometry is energetically the most favorable. Indeed, it is by far the most frequently found geometry, and therefore the Pd(II) complexes are diamagnetic. However, there are exceptions to this behavior, depending on the ligands (Caminade, Ouali et al. 2015). Palladium(0) complexes are fairly nucleophilic, rather labile, and also easily oxidized, usually to the Pd(II) state. The most synthetically useful Pd(0) chemistry is based on the oxidative addition of aryl, vinylic, or allylic halides or triflates to Pd(0), Palladium(IV) is also a hard metal center and therefore it requires strong σ-donor ligands to give stable species that are six-coordinated and octahedral. Pd(IV) complexes are usually prepared by oxidation of the analogous Pd(II). Derivatives and halogens or nitric acid are generally used as oxidants (Zeni and Larock 2004).
Palladium complexes can be considered as substitute to platinum drugs for the treatment of different types of cancers owing to structural analogy However, their 105 times more reactivity than platinum complexes make them more susceptible to fast hydrolysis accompanied by isomerization (Amir, Khan et al. 2016).

1.3 The Chemistry of Platinum

Platinum was the first to be discovered among the platinum metals in 1748 (16). The chemistry of platinum has been studied for some 250 years. The metal has numerous uses in catalysis, jewelry and electrical application and the study of the complexes has been pivotal in the development of coordination chemistry. Complexes of platinum are commonly in oxidation state; 0, II or IV. Although all transition elements exhibit a range of oxidation states, platinum is one of the very few with three oxidation states differing by two electrons each. Since platinum is a third row transition element, the large values of the ligand field lead to low-spin, kinetically inert d^6 complexes of platinum (IV) with hexacoordinate structures, and low-spin kinetically inert d^8 complexes of platinum (II) having tetracoordinate planar geometry (Wilkinson G. et al.,1987). Platinum (II) is considered as a class b (soft) metal and form stable complexes with soft ligands such as phosphorous and sulfur (Hubbard and van Eldik 2010). Platinum-based compounds have been widely used in cancer chemotherapy. The primary compound that led to the development of this group is cisplatin. It was first synthesized in 1844 by an Italian chemist, Michele Peyrone, which is why it was originally called Peyrone's chloride. (Kapdi, A.R. 2014).

1.4 Complexes of Platinum

Platinum complexes have important applications in industry and medicine; a mixture of bis(diphenyphosphine)dichloroplatinum and several equivalents of tin(II) chloride generating the complex $[Pt(PPh_3)_2\ (SnCl_3)CI]$ which upon hydrogenation becomes $[Pt\ (PPh_3)_2\ (SnCl_3)H]$ which is a catalyst used for hydrogenation all but one double bond of soybean oil. When this catalyst is immobilized by attaching it to polystyrene, it is possible to hydrogenate one double bond of linolenic ester leaving two in the trans form (Carraher JR 1982). The catalytic activity of $[Pt(CN)_2(PPh_3)_2]$ in olefin hydrogenation has been tested (Wang, Chen et al. 2014). The successful use of inorganic complexes as chemotherapeutic agents is exemplified by cisplatin and its analogue carboplatin, which have been used clinically since 1971 and 1981 respectively (Sacht and Datt 2000).

Cisplatin **(Fig. 1.1)** is the most clinically successful DNA covalent binder, although it reacts with a diverse range of other biomolecules. For cisplatin, binding is dependent on the hydrolysis of its labile chloride ligands. This gives rise to the formation of the complex $[Pt(NH_3)_2Cl(H_2O)]^+$. The most nucleophilic sites of DNA are the N7 atoms of purine residues guanine and adenine, and these are preferentially platinated. 195Pt NMR spectroscopic monitoring experiments revealed that cisplatin first forms monofunctional adducts on DNA. The remaining chloride ligand is substituted for a second guanine base, forming a cross-link on the DNA. Such cross-links can occur between deoxyguanosines on the same strand or on different strands, giving rise to intrastrand and interstrand DNA crosslinks, respectively.(Lazarević, Rilak et al. 2017)

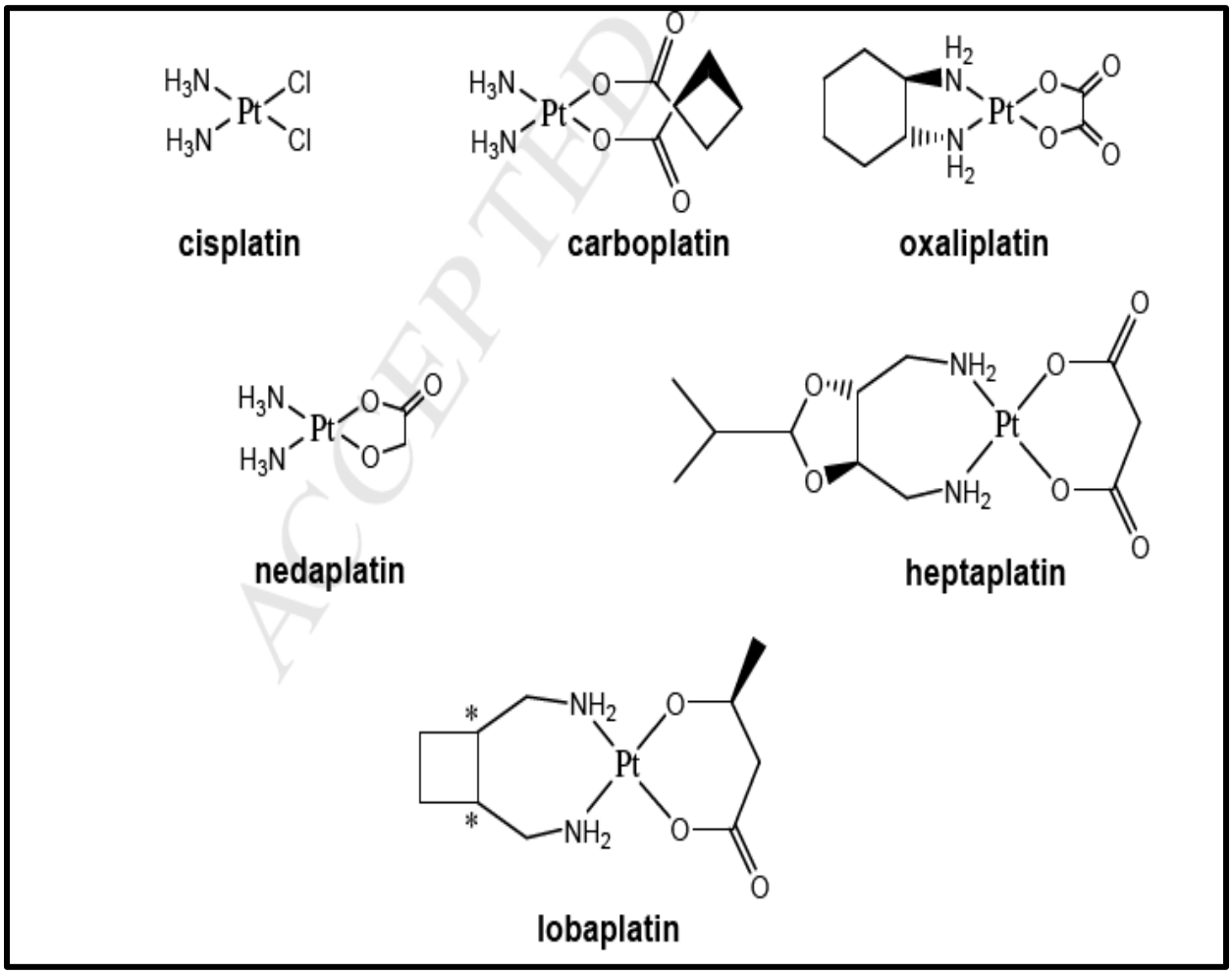

Fig. (1.1): Chemical structures of clinically approved and marketed platinum anticancer drugs

1.5 Anticancer activity of Palladium and Platinum complex

Cis-platin and its derivatives are undoubtedly the most famous coordination compounds used in anti-cancer chemotherapies. However, the use of metallodrugs is not limited to anticancer therapies, but it has also very interesting biological activities as antimalarial, antibacterial, or neuro-protector agents, against arthritis, etc. As dendrimers nowadays play a crucial role in biology (Kapdi and Fairlamb 2014), Palladium (Pd) based compounds have been proposed as substitute molecules, where cisplatin treatment is not effective due to the intrinsic or acquired resistance of cancer cells and against the untoward actions of the Pt drugs (Kacar, Cevatemre et al. 2017). Two novel metal based agents, palladium(II) saccharinate complexes with terpyridine (Pd(II) complexes, with anticancer properties. The anticancer activity was tested in vitro in a wide range of cancer cell lines, including breast, lung, glioblastoma, cervix, prostate and leukemia cells. Based on published literature, while different genetic backgrounds of the cells had an impact on how the cells were affected it can be concluded that Pd(II) complexes are more powerful than cisplatin in breast, lung, leukemia and in some prostate cell lines. Furthermore, the compounds are more effective *in vivo* for the reduction of tumor size compared to cisplatin and were less toxic in mice (Ray, Mohan et al. 2007).

A prospective basis for anticancer medicines is transition metals. Palladium-containing complexes are closely linked to their platinum analogs because the chemical and physical characteristics of both platinum and palladium are similar. The anticancer structures comprise palladium, like platinum, in metallic or ionic form (Pd^{2+} or Pd^{4+}). Radiotherapy can also make use of the metal itself, such as 103Pd. Platinum and palladium have comparable chemical and physical characteristics, indicating that they can be utilized interchangeably in equivalent anticancer chemicals (Al-Allaf and Rashan 2001).

Palladium compounds are 10 times less harmful than platinum-based compounds, according to toxicological experiments done on rats. The inability of the sulfhydryl groups to stand in for the firmly bound chelate ligands of Pd(II) when the molecule interacts with proteins inside the cells may help to explain the lower toxicity of palladium complexes to normal tissues(Gao, Liu et al. 2009) . Today, platinum-based cytostatic are much more common, but they have low solubility in water, significant toxicity, and studies have documented the development of cancer cell resistance. The problematic nature of platinum-based drugs has stimulated the search for alternatives, which may be palladium compounds. Because of the complexity of the issue, we have attempted to organize the existing data.(Abu-Surrah and Kettunen 2006)

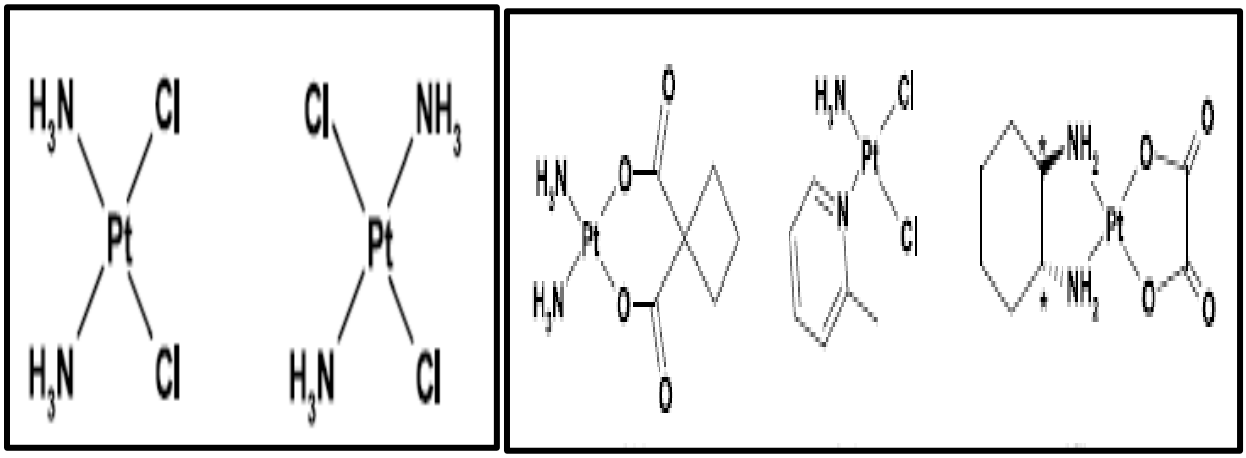

Fig (1.2): The anti-cancer platinum complex (1) cisplatin and its inactive isomer (2) transplatin. Second generation anti-cancer platinum complexes (3) carboplatin (4) AMD-473 and (5) oxaliplatin

Chapter Two

2. Literature Review

2.1 Literature Review about anticancer activity of Pd(II) and Pt(II) complexes

In 2003, Afrasiabi.Z. et all synthesized Copper(II), nickel(II), palladium(II) and platinum(II) complexes of *ortho*-naphthaquinone thiosemicarbazone were characterized by spectroscopic studies. In both solution (NMR) and solid state (IR, single-crystal X-ray diffraction determination) the free ligand NQTS exists as the thione form. The Pd complex (X-ray) crystallizes as the H-bonded dimer [Pd(NQTS)Cl]2.2DMSO, where palladium(II) coordinates in a square planar configuration to the monodeprotonated, tridentate thiosemicarbazone ligand **Fig. (2.1)**. In vitro anticancer studies on MCF7 human breast cancer cells reveal that adding a thiosemicarbazone pharmacophore to the parent quinone carbonyl considerably enhances its antiproliferative activity. Among the metal complexes, the nickel compound exhibits the lowest IC50 value (2.25 lM) suggesting a different mechanism of action involving inhibition of topoisomerase II activity (Afrasiabi, Sinn et al. 2004).

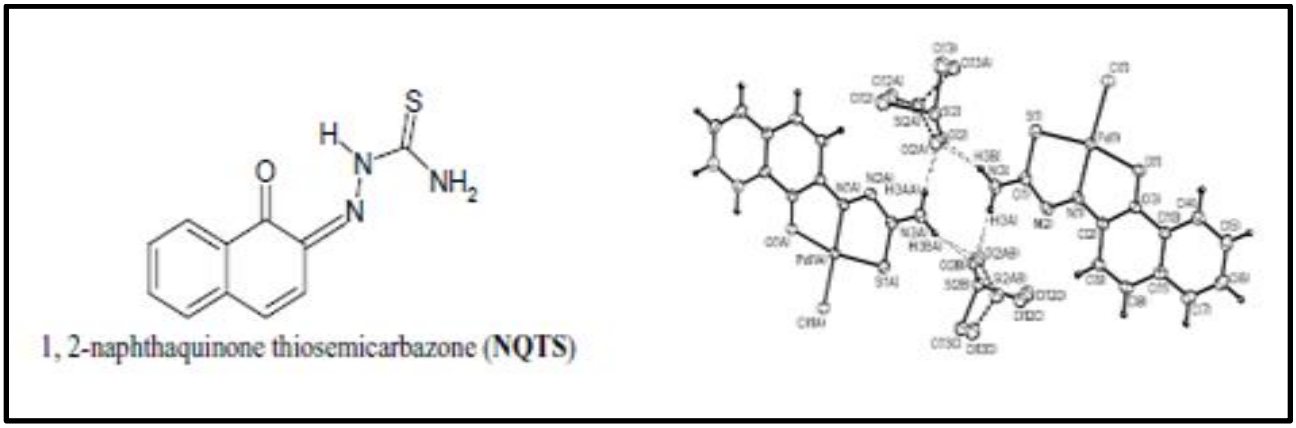

Fig. (2.1): the structure of ligand and ORTEP diagram for [Pd(NQTS)Cl]2 . 2DMSO

In 2007 Abu-Surrah.S.A et all synthesized Chemical pharmacological and clinical-research on anticancer coordination complexes has yielded remarkable anticancer agents such as cisplatin, carboplatin, and oxaliplatin. Since the discovery of cisplatin, the development of analogue complexes has been an empirical task. Studies have shown that the range of platinum complexes with antitumor activity is not restricted to the structural analogues of cisplatin **Fig. (2.2) (2.3)**. The foremost target of most research groups was to find a convenient anticancer drug that can be used efficiently for the treatment of human tumors. (Abu-Surrah, Al-Sa'doni et al. 2008)

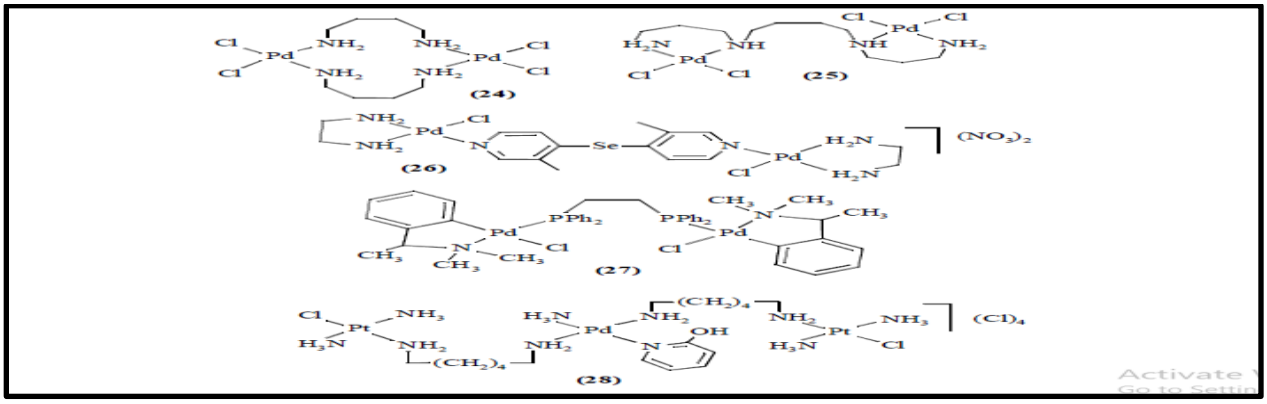

Fig. (2.2): Antitumor activity of some Palladium (II) and platinum (II) complexes

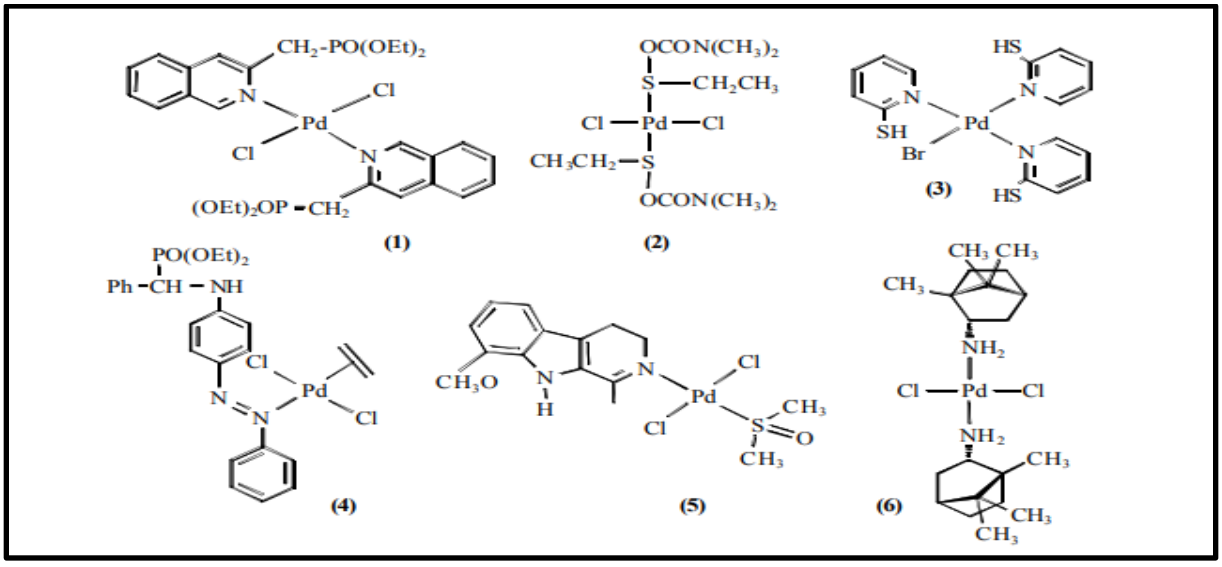

Fig. (2.3): Structures of some trans-palladium (II) complexes (1-6)

In 2008 Keter.F.K prepared A series of pyrazolyl palladium(II), platinum(II) and gold(III) complexes, [PdCl2(3,5-R2bpza)] {R = H (1), R = Me (2), bpza = bis-pyrazolyl acetic acid}, [PtCl2(3,5-R2bpza)] {R = H (3a), R = Me (4)}, [AuCl2(3,5-R2bpza)]Cl {R = H (5a), R = Me (6a)} and [PdCl2(3,5-R2bpzate)] {R = Me (7)} have been synthesised and structurally characterized **Fig.(2.4).** Single crystal X-ray crystallography showed that the pyrazolyl ligands exhibit N^N-coordination with the metals. Anticancer activities of six complexes 1–6a were investigated against CHO cells and were found to have low activities. Substitution reactions of selected complexes 1, 2, 3a and 5a with L-cysteine show that the low anticancer activities compounds and that the rate of substitution with sulfur-containing compounds is not the cause of the low anticancer activities (Keter, Ojwach et al. 2009).

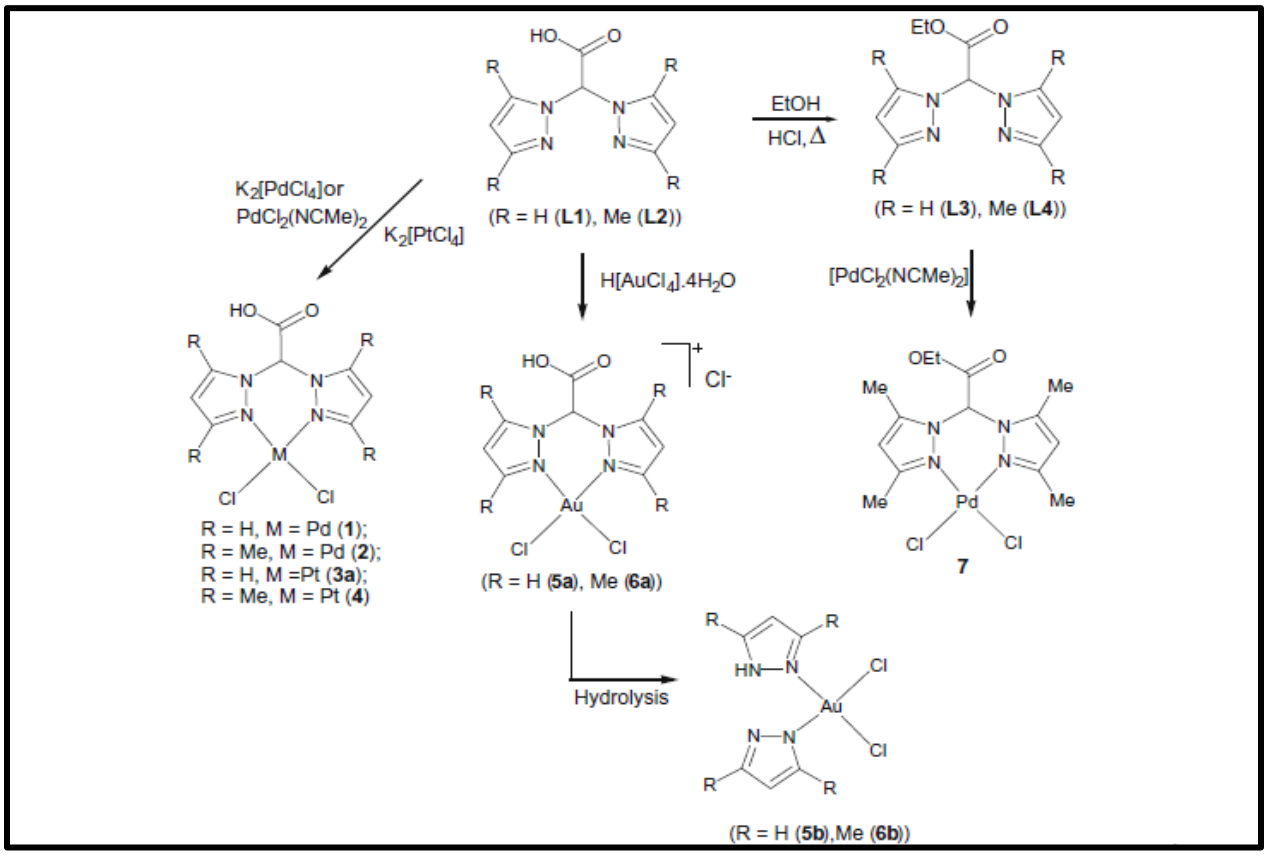

Fig. (2.4): Anticancer activities of six complexes 1–6a

In 2011 Nour.T prepaered [$MLCl_2$] (L = (1H-benzimidazol-2-ylmethyl)-N-(4-bromo-phenyl)-amine; M = Pd , Pt) and [$PdL(OH_2)_2$] ·2X·zH2O (X= Br, I, z =2; X = SCN, z = 1; X= NO3, z =0) complexes have been synthesized as potential anticancer compounds and their structures were elucidated using elemental analysis, spectral, thermal analysis and X-ray powder diffraction. FT-IR and ^{1}H NMR studies revealed that the ligand L is coordinated to the metal ion via the pyridine-type nitrogen (Npy) of the benzimidazole ring and secondary amino group (NHsec). The complexes showed cyctotoxic effects against human breast cancer (MCF7), hepatocarcinoma (HepG2) and colon carcinoma cells (HCT). The platinum complex (6) exhibited a moderate antitumor activity against MCF7 with IC50 =10.2 mM comparing to that reported for cis-platin 9.91 mM **Fig. (2.5)** (Ghani and Mansour 2012).

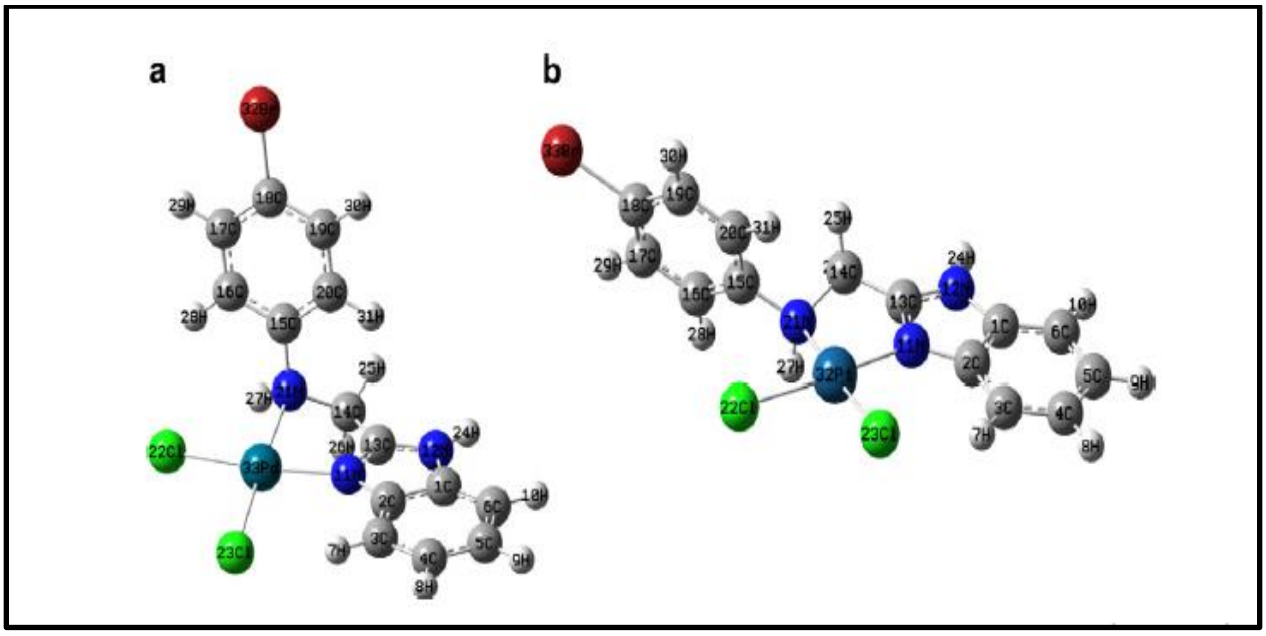

Fig (2.5): The complexes showed cyctotoxic effects against human breast cancer (MCF7)

Muhammad K. A.in 2016 prepared Although it is well known that *cisplatin* and its analogues are effective anticancer agents, but their clinical use is restricted by some serious side effects. Palladium complexes are emerged as alternative metalloanticancer drugs merited by their structural similarity to platinum(II) complexes, more labile nature, minimal chemo resistance and often water solubility **Fig.(2.6).** However, due to exceptional high reactivity of palladium complexes than their platinum counterparts, they are not only obstructed by the sulfur containing molecules to reach their pharmacological targets but also significantly enhance their affinity to convert into inactive *trans* isomers (Amir, Khan et al. 2016).

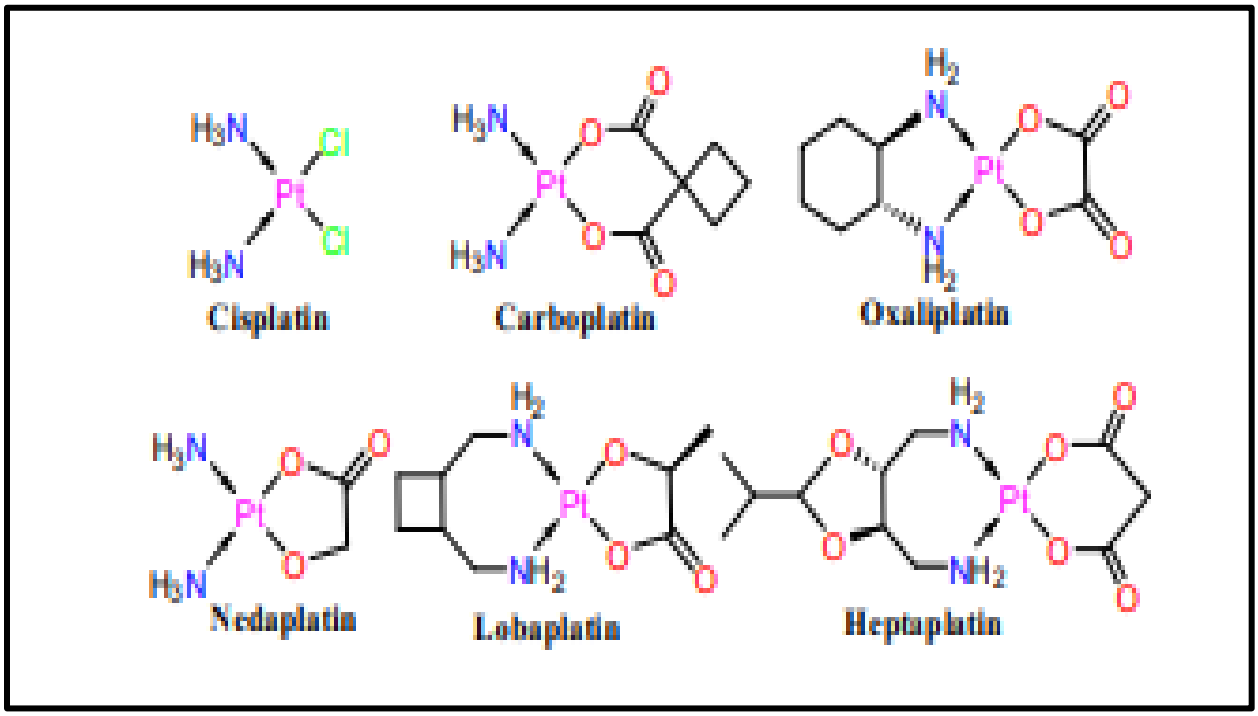

Fig (2.6): Structures of currently approved platinum-based anticancer drugs

In 2017 Lazarević,T et all prepared Metallodrugs offer potential for unique mechanism of drug action based on the choice of the metal, its oxidation state, the types and number of coordinated ligands and the coordination geometry. This review illustrates notable recent progress in the field of medicinal bioinorganic chemistry as many new approaches to the design of innovative metal-based anticancer drugs are emerging. Current research addressing the problems associated with platinum drugs has focused on other metal-based therapeutics that have different modes of action and on prodrug and targeting strategies in an effort to diminish the side-effects of cisplatin chemotherapy (Lazarević, Rilak et al. 2017)

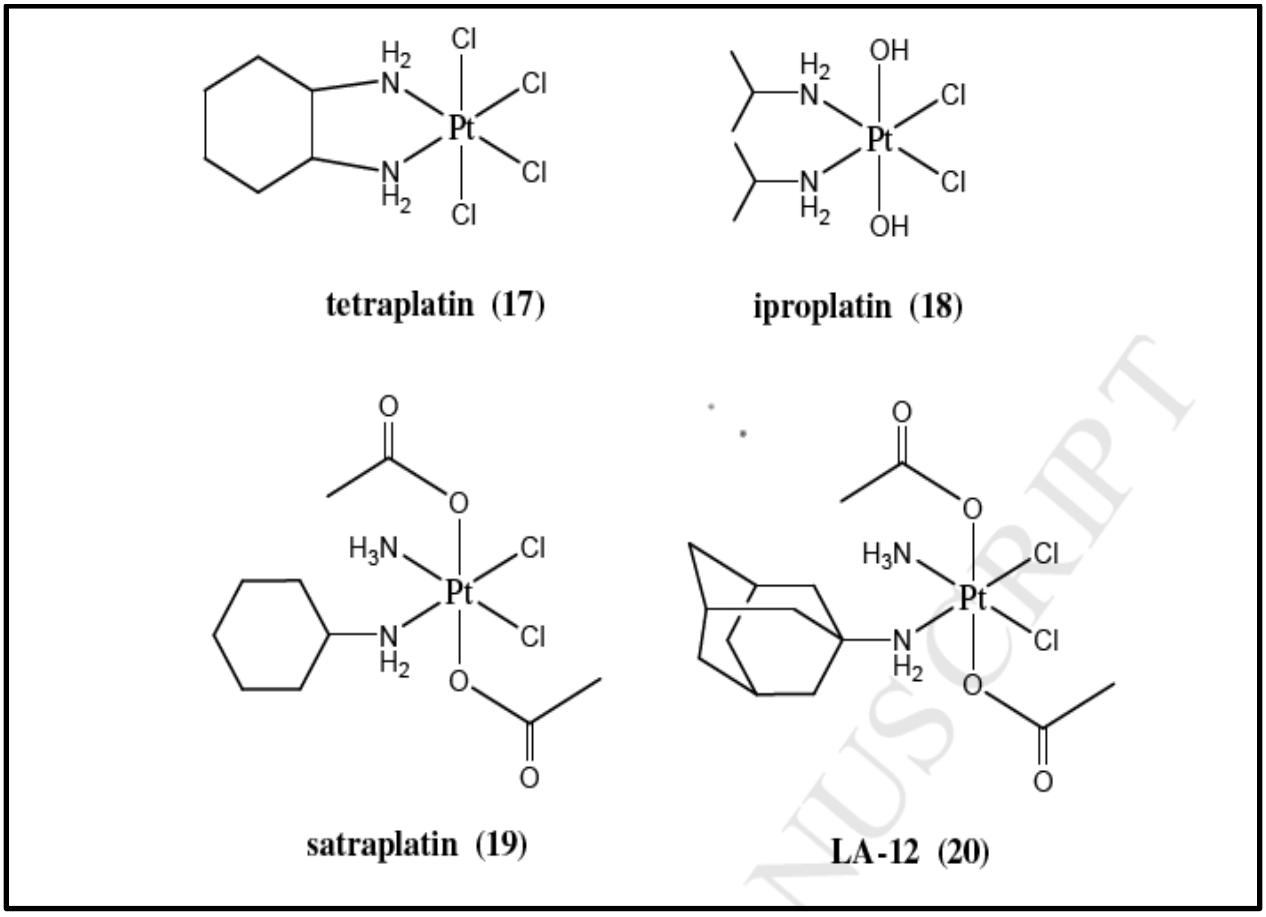

Fig (2.7): Chemical structures of some platinum prodrugs.

In 2021 Ahmed S. Faihan et all Treatment of two molar equivalents of 1,8-diaminonaphthalene-2-thione with one molar equivalent of the metal's(II) salt (Pd, Pt, Hg, Cd, Zn) afforded both neutral thione complexes and thionate derived complexes. On the other hand, Complexes (**1**) and (**2**) were tested against MCF-7 (breast) and LoVo (colon) cancer cells using MTT assay **Fig. (2.8)**. It was found that the palladium complex showed a promising antiproliferative activity against colon (LoVo) and breast (MCF-7) cancer cells with IC 50 values 21.13 and 22.25 μM respectively. In addition the anti-bacterial activity was study against two different pathogenic bacteria, and the Pd(II) complex displayed highest activity compared with other complexes (Faihan, Hatshan et al. 2022)

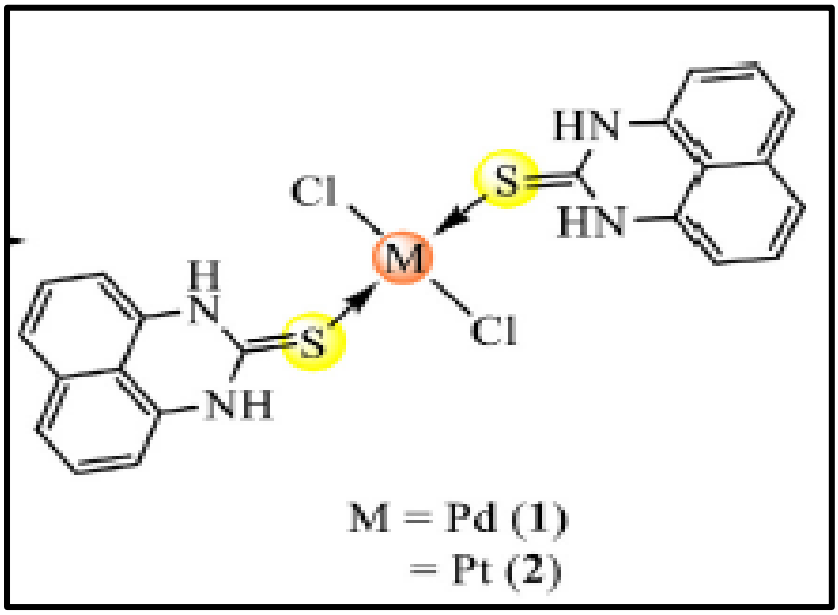

Fig. (2.8): Anticancer activity of [Pd(HDANT)$_2$ Cl $_2$] and [Pt(HDANT) $_2$Cl $_2$]

In 2024 Abdolmaleki.S.P showed Metal-based complexes which have demonstrated significant anticancer effects and have emerged as candidates with great potential for cancer therapy. These agents are effective in a variety of cancers, including those resistant to conventional chemotherapeutic agents. The use of some metal-based agents in cancer therapy is based on their ability to interact with DNA and other biomolecules, resulting in cell death. In this review, several important metal complexes such as platinum, ruthenium, gold, copper and iron are explained as promising anticancer agents, and an overview of their multiple functions, such as DNA binding and damage, inhibition of enzymes and proteins, generation of ROS, as well as their mechanisms of action is given. Targeted cancer therapy using metal complexes is offered as a favorable strategy to improve the efficacy and selectivity of cancer treatment (Abdolmaleki, Aliabadi et al. 2024).

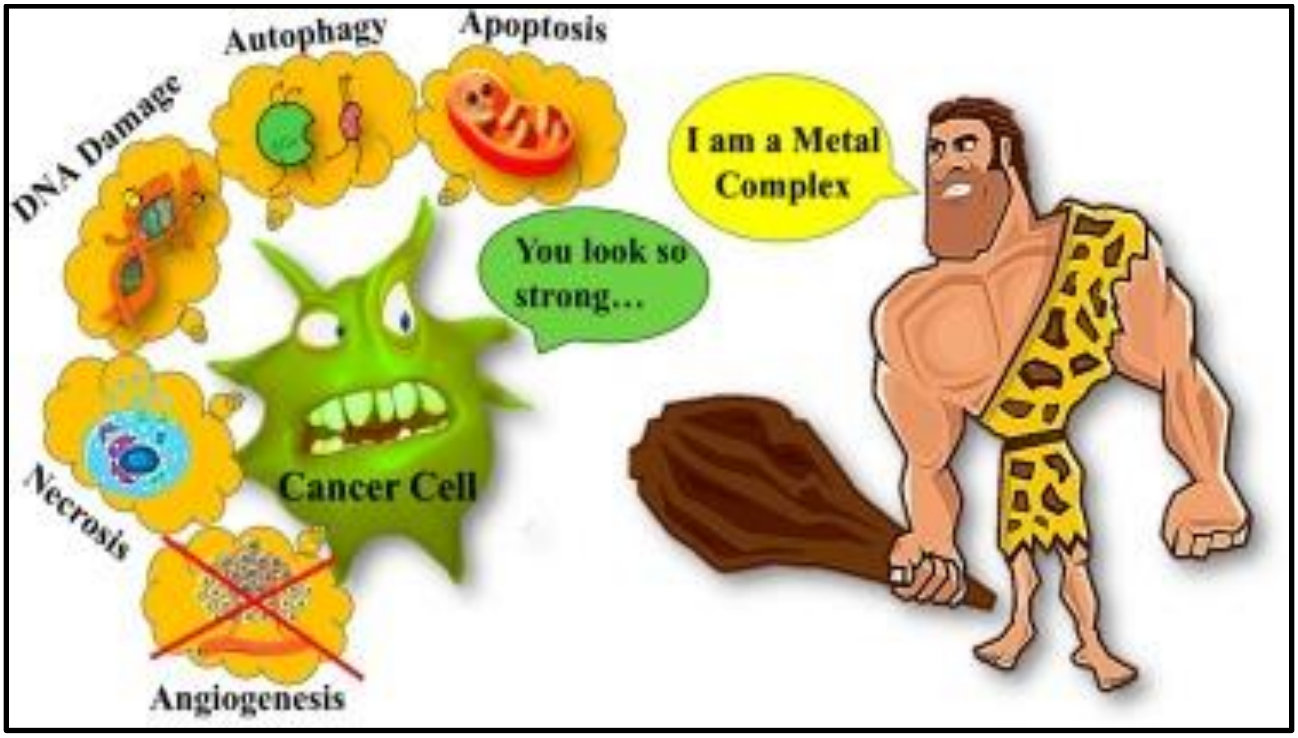

Fig (2.9): Metal-based complexes demonstrated significant anticancer effects

Chapter Three

3. Conclusion

A great deal of research has been done to explore the suitability of platinum complexes as anticancer medicines as a result of this study. Other alternative metal-based anticancer medications have been developed in response to the severe adverse effects caused by platinum's covalent interaction with DNA. Palladium complexes, which include dimeric, tetrameric, monomeric, cyclopalladated, palladacyclic, and heterobimetallic complexes, have been described. Palladacycles and cyclopalladated complexes in particular have demonstrated encouraging activity. The area is still nascent and requires further studies to be carried out, particular on the mode of action of the multitude of complexes that have now been tested against simple cancer cell lines (as very few studies are reported). It could be noted that the solubility of palladium complexes is better compared to platinum-based complexes as is also evident from the water-soluble nature of some of the Pd complexes.

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