Kurdistan Regional Government- Iraq
Ministry Of Higher Education &Scientific Research
Salahadin University- Erbil (SUE)
College Of Science
Department Of Chemistry

Review of palladium and platinum complexes as anti-cancer

A project submitted to the scientific committee in the chemistry department in partial fulfilment of the requirement for the degree of bacterial science in chemistry

Prepared By
Maryama Noori Hassan

Supervised By
Mr. Muhammed Haji

April 2023 Newroz 2722 Ramadan 1444

Acknowledgement

In our acknowledgments of this research, we would like to thank our dear parents who have helped us during our education and development and paved the way for our success

And then we would like to thank our teachers and supervisors who always helped us very much during our university years

We would also like to thank the Dean of our university who has always been the first and the best university thanks to him.

Table of Contents

Abstract

The abstract of this study showed that palladium and platinum complexes can be used as anticancer drugs. Our study consists of four main parts

In the second part, which is the most important part of our research, we have discussed palladium and platinum separately. 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. 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.

Then there is the review section, which is the third section. We searched some of the scientific sources available in this section and finally we put the results.

Chapter one

Introduction

Cancer represents one of the major causes of death in humans worldwide, only overcome by cardiovascular diseases, and represents a huge burden on society (both sociologically and economically). About 20 million cancer cases are expected to occur in the next two decades, which renders the quest for new and improved antineoplastic agents an urgent issue in the field of Biomedicine and Human Health. Over the past decade, efforts have been made in the way of understanding the carcinogenesis process, which is recognized to consist in a progressive disorganization at both the cellular and tissue levels. This knowledge is essential to develop new chemotherapeutic strategies, in order to control the incidence of the most recurrent cancer types. (Wojciechowska U,2016)

While many drug molecules are “organic” in nature, other elements in the periodic table, particularly metals, offer a much more diverse chemistry and have important therapeutic applications. The use of metal-based compounds as therapeutic drugs dates back to over 5000 years. In modern days, the study of organometallic pharmaceuticals started with the pioneering work of Köpf and Köpf-Maier (in the late 1970’s), who investigated the antitumor activity of early transition metal cyclopentadienyl complexes. Since the introduction of cisplatin (*cis*-dichlorodiammine platinum (II), *cis*-$Pt(Cl_2(NH_3)_2)$ to oncology, in the 1970’s, organometallic compounds have gained a progressively increasing interest in medicinal chemistry. Particularly in the treatment of malignant formations, inorganic compounds have had an enormous impact, their activity relying mostly on specific interactions with DNA, leading to damage and ultimately to cell death. The development of inorganic anticancer agents is widening rapidly beyond platinum

chemistry, encompassing a large variety of metal ions and ligands, and many diverse designs tailored according to the specific receptor or biological target. (Jahromi, E.Z., 2016)

One of the leading agents in clinical use with a high cytotoxic effect upon a variety of tumour types, in particular against testicular, ovarian, head and neck, and bladder carcinomas, as well as lymphoma. The therapeutic target of platinum complexes is DNA, *via* binding to the purine bases through 1,2-intrastrand cross-links, yielding one or more 1,2-d(GpG) and 1,2-d(ApG) bifunctional adducts in which the two chlorine atoms of the cisplatin molecules are replaced (upon hydrolysis) by N_7 atoms of adjacent purines. These adducts activate several cellular processes that mediate cytotoxicity, namely, bending and unwinding of the double helix leading to the disruption of DNA duplication and inducing cell death by apoptosis. (Didkowska J,2019)

.

Chapter 2
Literature review

Definition of palladium

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. (Strzelecki Z,2014)

What is platinum

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).The antitumor potential of cisplatin was found by accident and reported by Rosenberg in 1965. Rosenberg used platinum electrodes when studying the effects of low-voltage alternating currents on the growth of *Escherichia coli* bacteria. Inhibition of cell proliferation without a corresponding inhibition of bacterial growth was observed due to the reaction of platinum from the electrodes with NH_4Cl, resulting in the formation of cisplatin, which was the cause of these changes. Rosenberg and his partners began experimenting on mice with leukemia and sarcoma, which led to the start of clinical trials in 1971. This resulted in the official introduction of cisplatin for the treatment of testicular and ovarian cancer in 1978, a milestone in chemotherapy. Nowadays, cisplatin is used in various kinds of tumor diseases. Clinical guides mainly talk about treating testicular,

ovarian, bladder, head and neck, lung, and cervical cancer. Cisplatin, despite its undeniable benefits, has a dark side, i.e., its adverse effects. For drugs commonly used in platinum-based chemotherapy, many specific side effects may occur in the treated patient, such as cardiotoxicity, nephrotoxicity, ototoxicity, hematological toxicity, hepatotoxicity, gastrointestinal toxicity, and neurotoxicity. Unfortunately, tumor cells also develop resistance; thus, we are seeing a decline in efficacy and an associated reduction in patient survival, even though there is a good initial response to treatment. (Wiszniewska M, 2017)

Anti- cancer

Anticancer drug, also called antineoplastic drug, any drug that is effective in the treatment of malignant, or cancerous, disease. There are several major classes of anticancer drugs; these include alkylating agents, antimetabolites, natural products, and hormones. In addition, there ar e a number of drugs that do not fall within those classes but that demonstrate anticancer activity and thus are used in the treatment of malignant disease. The term chemotherapy frequently is equated with the use of anticancer drugs, although it more accurately refers to the use of chemical compounds to treat disease generally. (Moreno-Smith M,2010)

One of the first drugs that was used clinically in modern medicine for the treatment of cancer was the alkylating agent mechlorethamine, a nitrogen mustard that in the 1940s was found to be effective in treating lymphomas. In 1956 the antimetabolite methotrexate became the first drug to cure a solid tumour, and the following year 5-fluorouracil was introduced as the first of a new class of tumour-fighting compounds known as pyrimidine analogs. Since then many anticancer drugs have been developed and used with much success.the decision to use a certain anticancer drug depends on many factors, including

the type and location of the cancer, its severity, whether surgery or radiation therapy can or should be used, and the side effects associated with the drug. Most anticancer drugs are administered intravenously; however, some can be taken orally, and others can be injected intramuscularly or intrathecally (within the spinal cord).(Soung N, Kim B.2014)

Palladium And Platinum Complexes As Anti-Cancer

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 (Pd2+ or Pd4+). 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. On the periodic table, both metals are classified as platinum-group elements (PGE), and the lengths of the bonds they form are comparable. For example, the M-Cl bond length (M = Pt or Pd) in the compound $K_2[MCl_4]$ is 2.316 Å and 2.318 Å for platinum and palladium, respectively .For instance, the length of the M-Cl bond in the combination K2[MCl4] (where M is either platinum or palladium) is 2.316 and 2.318, respectively. (Al-Allaf, 2001) The kinetics of the palladium compounds are 105 times quicker despite their apparent resemblance. Because of its increased reactivity, the palladium ion must be stabilized by utilizing certain chelating ligands. Quantum chemistry is where the differences in this two transition metals' reactivity should be found. Palladium's electron configuration [Kr]4d10 and platinum's [Xe]4f145d96s1 have an effect on these metals' characteristics. The 5d orbital in platinum has a larger ionization potential than the 4d orbital in palladium because it is further away from the positively charged nucleus. The

6s orbital has a lower energy. The bonds produced in platinum compounds are stronger and the nucleus makes it simpler to "detach" an electron. Also, because the electrons in the 5d orbital may form bonds more readily than those in the 6s orbital, the modest difference in energy between the two orbitals is connected to the higher stability of platinum compounds. (Dai S, Mo Y, Wang Y, et al.2018)

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, E., 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 AS, Kettunen M (2006)

Palladium-Based Compounds

Palladium compounds can be divided into two groups. The first has one palladium atom in its core. This type of compound also contains ligands with proven biological activity. These ligands can be pyridine, quinoline, or their analogs. The second group of palladium derivatives with anticancer properties are molecules containing two palladium atoms in the core. As in the previous group, ligands are selected based on their potentially beneficial properties. (Pranczk, J., Jacewicz,2014). Cytostatics, containing transition metals in their core, interact with the DNA of cancer cells. This occurs by producing both

covalent and non-covalent bonds. In contrast to cisplatin, palladium derivatives bind to the oligonucleotide $[d(CGCGAATTCGCG)]_2$, which results in blocking the replication of DNA. Both groups of derivatives show high selectivity to other oligonucleotide end regions. Due to bypassing the resistance of cancer cells, it has been found that they can also enter into non-covalent, electrostatic, and hydrogen bonds with DNA. It is advantageous to introduce a monoethylphosphine or diethylphosphine group, which allows for increased solubility of the resulting complexes. (Ashiq M., Mohsin M.,2013)

Besides intercalation into DNA, other targets of the molecular mechanism of palladium(II) complex activities have been described. One of them is the induction of apoptosis proceeding through both extrinsic (death receptors-mediated) and intrinsic (mitochondrial) pathways. It was observed that these compounds caused upregulation of Bax protein and downregulation of Bcl-2 protein, which resulted in decreased mitochondrial potential and a release of cytochrome c, activating the caspase cascade, proving that apoptosis occurs via the mitochondrial pathway. Meanwhile, in the death receptor-mediated pathway, it was reported that Pd(II) complexes caused an increase in the expression of cell death receptor genes DR4 and DR5. Apart from defects in mitochondria, existing damage of the endoplasmic reticulum (ER) was also reported and was caused by oxidative stress. Excessive generation of reactive oxygen species (ROS) was the result of Pd(II) reacting with thiol groups of proteins, including antioxidant system proteins (glutathione-S-transferase (GST), glutathione peroxidases (GPxs), catalase (CAT), and glutathione (GSH)), and a decrease in their levels in the cell. (Caires, A.C., 2007) In addition, cell arrest in the G2/M phase of the cell cycle was also noted. Despite the many similarities between palladium(II)-based complexes and their platinum analogs, both in terms of chemistry and mechanism of action, there are some minor differences between them. First, as mentioned earlier, their complexes have different stabilities. Secondary, their mechanisms of molecular action are slightly different.

Platinum analogs, the same as Pd(II) complexes, also intercalate into DNA, cause oxidative stress, and induce apoptosis via the extrinsic and intrinsic pathways. The difference between them is likely only in the phase of the cell cycle in which the cells are arrested. There are reports that, besides arresting cells in the G_2/M phase, platinum analogs can also arrest them in the G_1 and S phase of the cell cycle. (Oun R., Moussa,2017)

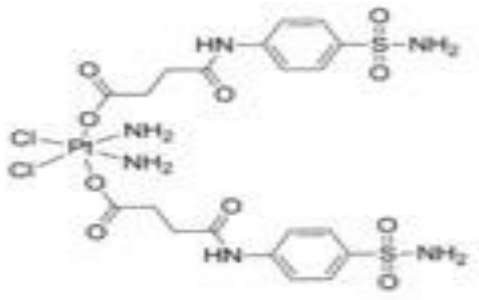
Platinum-Based Compounds

Modern antitumor drugs are substances that (and have a strong affinity for) carbonic anhydrase inhibition. The targeting is caused by an acidic environment and hypoxia in the tumor cells. Due to this, these substances suppress tumor metabolic pathways, which results in increased therapeutic effects proven on MDA-MB-231 breast cancer cells in comparison to cisplatin and oxaliplatin. With the modification, significantly higher selectivity and cytotoxicity of the new drugs on cancer cells under hypoxia are observed.

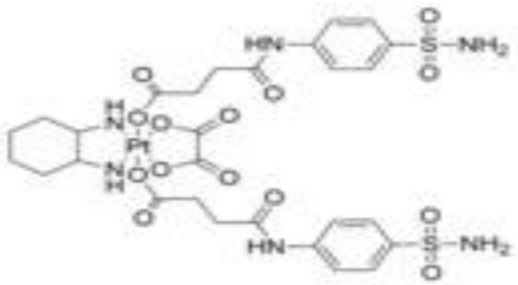
New complexes of Pt(IV) with dihydro-2-quinolone, namely DHQLO, are also being investigated. The alkyl chain connecting the platinum core and DHQLO was also shown to have a significant effect on the results. The use of a butyryl linker causes a similar effect as cisplatin or oxaliplatin, but demonstrates better selectivity, and is active against cells resistant to cisplatin. In addition to binding to the DNA of tumor cells, DHQLO derivatives display mitochondria-damaging activity and, thus, can activate tumor cell apoptosis. Investigations into new drugs are directed towards specific ways of binding DNA, mainly basing themselves on giving the molecule alkylating abilities. This is achieved by selecting appropriate ligands for platinum complexes, such as those based on terpyridine with mustard substituents, or derivatives obtained by hydroxylation. The designed compounds had potent antiproliferative effects on four cancer cell lines—

human colorectal (HCT116), non-small cell lung (NCI-H460), cervical (SiHa), and colon (SW480) cancer, with compound 13 exhibiting higher efficacy. The acceptable stability of the complex was proven, which provides hope for the discovery of another way to transition metal-based drugs. (Marth C., Landoni F.,2014)

Efforts are being made to decrease the negative effects of known antitumor agents. One example of a modification aimed at establishing this state is via the synthesis of new platinum complexes, with glycine derivatives as ligands, with the pattern [Pt(R-amine)2(R-gly)]NO3. The R-amine position contains propylamine, start-Pentylamine, or isopentyl amine, and the R-gly position contains propyl glycine, tert-pentyl glycine, or isopentyl glycine. The MTT assay was used to evaluate cytotoxicity on the MCF-7 human breast cancer cell line. In this investigation, cisplatin was used as a reference compound. Based on the nucleophilicity predictions of the new complexes and the LADME (liberation, absorption, distribution, metabolism, and excretion) results, the anticancer properties of the new complexes should be equal or superior to the reference. The propyl derivative exhibited the best activity. The research revealed the interaction between the new complex and DNA. Circular dichroism (CD) spectrum confirmed the bonding of the positively charged complex through electrostatic interactions, which are less effective than hydrogen interactions, from which we can conclude that the side effects of glycine derivatives can be significantly reduced compared to cisplatin. (Shakil, M.S.; Parveen,2021)



9



10

Important role the platinum and palladium to complex anti- cancer

Metal-based complexes contribute a vital part to the available arsenal of cytotoxic agents today. Platinum(II) complexes, specifically targeting genomic DNA (e.g., cisplatin, carboplatin, and oxaliplatin), are widely used in the clinic to treat various cancers. Nearly 50% of cancer patients, who undergo chemotherapy, receive a platinum drug either alone or in combination therapy. Despite their central role in cancer chemotherapy, platinum drugs suffer serious drawbacks such as the limited spectrum of antitumor activities, systemic dose-related toxicity, and the frequent induction of drug resistance, often leading to treatment failure. These observations have prompted a strong interest in the investigation of nonplatinum metal-based drugs as an effective alternative. Several other platinum and nonplatinum metal complexes (e.g., Ti, Pd, Ru, Au) have shown potent cytotoxic and antitumor effects. Unlike platinum drugs, these often rely on DNA-independent biochemical mechanisms such as targeting tumor-associated proteins and induction of immunogenic antitumor properties for their therapeutic effects. Notably, a few of these drugs are already in clinical trials, and several are at advance stage of preclinical development. In this context, the “Metal-Based Complexes in Cancer Treatment” Special Issue was edited, focusing on the design and development of targeted metal-based anticancer agents, understanding their mechanisms of action, and innovative drug delivery approaches. This Editorial briefly summarizes the findings and highlights of the nine published papers (six original research and three reviews). Among the six original articles, the first published study was by Shakil and colleagues. With the aim of synthesizing novel metal drugs, the authors explored the potential anticancer activity of new hydroxypyridones (HPs) and

hydroxy(thio)pyridones (thio-HPs) derivates and their respective ruthenium (Ru) complexes in several human cancer cell lines (colorectal, non-small cell lung, cervical and colon cancer cell lines). (Dorovskikh, S.I.; Vikulova, E.S.;2021)They demonstrated the higher antiproliferative activity of the thio-HPs derivates, while the HPs and Ru complexes of both compound types were less potent, despite still showing IC50 values in the μM range. The most potent thio-HPs derivates were further tested on other cancer cell lines revealing higher cytotoxicity towards lung cancer cells in comparison to breast cancer cells and human prostate epithelial cells. The biological analysis pointed out the ability of these compounds to trigger apoptotic cell death without affecting cell cycle progression. In the second published original article by Dorovskikh and colleagues, the noble metals were used to modify the surface of implant materials with the aim of improving their biological properties such as chemical inertia, high biological compatibility, corrosion resistance, and reduced risk of developing toxic or allergic reactions as well as bacterial infections. The authors developed a new approach to modify the surface of implant materials obtaining the most promising results with silver, gold, and platinum coatings. The study published by Gorini, and colleagues dealt with the attempt to improve the knowledge of gold metal-based compounds as anticancer agents. In detail, they deeply investigated the anticancer properties of two dinuclear oxo-bridged gold(III) compounds (Au2phen and Auoxo6) against A2780 human ovarian cancer cells.

Chapter three

Methodology

In research (Ulukaya, 2011) Potential applications of palladium(II) compounds in pharmacology have been extensively studied in recent years. This is because there is a great interest for finding new metallodrugs capable of overcoming the issues of toxicity and intrinsic or acquired resistance produced by the coordination square-planar platinum(II) compounds *cisplatin*, *carboplatin* and *oxaliplatin* nowadays in clinical use worldwide for the treatment of different cancers in humans, and also because several palladium(II) compounds present *in vivo*, using mice as models, good profiles as anticancer, Most of the palladium(II) compounds with good pharmacological activities *in vivo* are mononuclear or dinuclear palladium(II) cyclometallated compounds, and in this latter case, bridging diphosphate acetate, complete the coordination sphere of the palladium(II) centres. In addition, a k^1-C_{ortho}-phenylpalladium(II) compound with a chelating diphosphane ligand and a terminal *N*-thiocyanato ligand, and a few ionic or neutral mononuclear palladium(II) coordination compounds containing k^3-*N*,*N*,*N* , k^2-*N*,*N* or k^2-*O*,*O* chelating ligands also present a good anticancer activity *in vivo*. In these latter compounds, the chelating ligands form very stable five- or six-membered metallacycles.

M. Shaharyar,(2010) Platinum complexes which are most studied metal complexes due to their importance as adjuvant therapy of cancers aiming to induce tumor-cell-death. Some of the platinum-based antitumor drugs like cisplatin, carboplatin and oxaliplatin, have several disadvantages including side effects, cisplatin-resistant tumors, limited solubility in aqueous media, and so on. Thus, to achieve lower undesirable toxicity, enhanced solubility, and tumor selectivity, significant amount of work have been devoted

to the preparation of modified platinum complexes. One of the ways to design the new anti-tumor agents related to cisplatin is to change the nature of central metal ion. Among the non-platinum metal complexes studied for cancer treatment, palladium(II) derivatives were readily chosen due to their structural analogy with those containing Pt(II) complexes. This review focuses on anti-tumor property of Pd(II) complexes and makes comparisons with similar property of cisplatin. Then, in the review, palladium(II) complexes have been classified according to their leaving ligands into palladium(II) complexes. In the last part, the most important factors affecting on the anti-tumor activity of the Pd(II) complexes were discussed. These factors are encouraging more researches in this field, for future applications

Chapter four

Conclusion

As a result of this study, A significant amount of work has been carried out in understanding the applicability of platinum complexes as anticancer agents. However, dramatic side effects arising from the covalent interaction of platinum with DNA has prompted the development of other alternative metal-based anticancer drugs. Palladium complexes (palladium complexes ranging from monomeric, cyclopalladated, palladacyclic, dimeric, tetrameric as well as heterobimetallic complexes have been described), particularly palladacycles or cyclopalladated have shown promising 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.

Reference

1. Abu-Surrah A., Al-Sa'doni H., Abdalla M. Palladium-based chemotherapeutic agents:Routes toward complexes with good antitumoractivity. Cancer Ther. 2008;6:1.

2. Ashiq M., Mohsin M., Bari S., Mukhtar F. Chemistry of Platinum and Palladium Metal Complexes in Homogeneous and Heterogeneous Catalysis: A Mini Review. Int. J. Sci. Basic Appl. Res. 2013;7:50–61.
3. Al-Allaf, T.A. and Rashan, L.J., 2001. Cis-and trans-platinum and palladium complexes: a comparative study review as antitumour agents. Bollettino Chimico Farmaceutico, 140(3), pp.205-210.
4. Abu-Surrah AS, Kettunen M (2006) Platinum Group Antitumor Chemistry: Design and development of New Anticancer Drugs Complementary to Cisplatin. Curr Med Chem 13:1337–1357
5. Chemistry (Formerly current medicinal chemistry-anti-cancer agents), 9(3), pp.356-368.
6. Wiszniewska M, Lipinska-Ojrzanowska A, Witkowska A, et al. Occupational cancers – Epidemiology and certification. Medycyna Pracy. 2017, doi: 10.13075/mp.5893.00620.
7. Caires, A.C., 2007. Recent advances involving palladium (II) complexes for the cancer therapy. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents), 7(5), pp.484-491.

8. Dorovskikh, S.I.; Vikulova, E.S.; Chepeleva, E.V.; Vasilieva, M.B.; Nasimov, D.A.; Maksimovskii, E.A.; Tsygankova, A.R.; Basova, T.V.; Sergeevichev, D.S.; Morozova, N.B. Noble Metals for Modern Implant Materials: MOCVD of Film Structures and Cytotoxical, Antibacterial, and Histological Studies. Biomedicines 2021, 9, 851.

9. Dorovskikh, S.I.; Vikulova, E.S.; Chepeleva, E.V.; Vasilieva, M.B.; Nasimov, D.A.; Maksimovskii, E.A.; Tsygankova, A.R.; Basova, T.V.; Sergeevichev, D.S.; Morozova, N.B. Noble Metals for Modern Implant Materials: MOCVD of Film Structures and Cytotoxical, Antibacterial, and Histological Studies. Biomedicines 2021, 9, 851.

10. Gao, E., Liu, C., Zhu, M., Lin, H., Wu, Q. and Liu, L., 2009. Current development of Pd (II) complexes as potential antitumor agents. Anti-Cancer Agents in Medicinal Chemistry (Formerly current medicinal chemistry-anti-cancer agents), 9(3), pp.356-368.

11. Jahromi, E.Z., Divsalar, A., Saboury, A.A., Khaleghizadeh, S., Mansouri-Torshizi, H. and Kostova, I., 2016. Palladium complexes: new candidates for anti-cancer drugs. Journal of the Iranian Chemical Society, 13, pp.967-989.

12. Kapdi, A.R. and Fairlamb, I.J., 2014. Anti-cancer palladium complexes: a focus on PdX 2 L 2, palladacycles and related complexes. Chemical Society Reviews, 43(13), pp.4751-4777.

13. Didkowska J, Wojciechowska U, Czaderny K. Cancer in Poland in 2017. Polish National Cancer Registry Department of Epidemiology and Cancer Prevention. 2019 : 1–96.

14. Strzelecki Z. Prognozy rozwoju chorób nowotworowych w Polsce. In: Potrykowska A, Strzelecki Z, Szymborski J. et al. ed. Zachorowalność i umieralność na nowotwory a sytuacja demograficzna Polski. Zakład Wydawnictw Statystycznych, Warszawa 2014: 7–17.
15. Wiszniewska M, Lipinska-Ojrzanowska A, Witkowska A, et al. Occupational cancers – Epidemiology and certification. Medycyna Pracy. 2017, doi: 10.13075/mp.5893.00620.
16. Moreno-Smith M, Lutgendorf SK, Sood AK. Impact of stress on cancer metastasis. Future Oncol. 2010; 6(12): 1863–1881, doi: 10.2217/ fon.10.142, indexed in Pubmed: 21142861.
17. Pranczk, J., Jacewicz, D., Wyrzykowski, D. and Chmurzynski, L., 2014. Platinum (II) and palladium (II) complex compounds as anti-cancer drugs. Methods of cytotoxicity determination. Current Pharmaceutical Analysis, 10(1), pp.2-9.
18. Soung N, Kim B. Psychological stress and cancer. J Anal Sci Technol. 2015; 6(1), doi: 10.1186/s40543-015-0070-5.
19. Dai S, Mo Y, Wang Y, et al. Chronic Stress Promotes Cancer Development. Front Oncol. 2020; 10: 1492, doi: 10.3389/fonc.2020.01492, indexed in Pubmed: 32974180.
20. Marth C., Landoni F., Mahner S., McCormack M., Gonzalez-Martin A., Colombo N. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2017;28:iv72–iv83. doi: 10.1093/annonc/mdx220.
21. Oun R., Moussa Y.E., Wheate N.J. The side effects of platinum-based chemotherapy drugs: A review for chemists. Dalton Trans. 2018;47:6645–6653. doi: 10.1039/C8DT00838H.

22. Shakil, M.S.; Parveen, S.; Rana, Z.; Walsh, F.; Movassaghi, S.; Söhnel, T.; Azam, M.; Shaheen, M.A.; Jamieson, S.M.F.; Hanif, M.; et al. High Antiproliferative Activity of Hydroxythiopyridones over Hydroxypyridones and Their Organoruthenium Complexes. Biomedicines 2021, 9, 123

23. Wojciechowska U, Czaderny K, Ciuba A. Cancer in Poland in 2016. Polish National Cancer Registry Department of Epidemiology and Cancer Prevention. 2018: 1–98.

24. Ulukaya, E., Ari, F., Dimas, K., Ikitimur, E.I., Guney, E. and Yilmaz, V.T., 2011. Anti-cancer activity of a novel palladium (II) complex on human breast cancer cells in vitro and in vivo. European journal of medicinal chemistry, 46(10), pp.4957-4963.

25. M. Shaharyar, M.M. Abdullah, M.A. Bakht, J. Majeed, Pyrazoline bearing benzimidazoles: search for anticancer agent. Eur. J. Med. Chem. 45, 114 (2010)