Annals of Pharmacy Practice and Pharmacotherapy
ISSN: 3062-4436
2023, Volume 3, Page No: 103-113
Copyright CC BY-NC-SA 4.0
Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Impact of Chemical Structure and Hydrolysis Mechanisms on the Pharmacological Effects and Toxicity Profiles of Licensed Platinum-Based Drugs

Kim Ji-Hoon[1], Park Soo-Yun[1]*, Choi Min-Jae[1]

[1]College of Pharmacy, Sungkyunkwan University, Suwon, South Korea.

***E-mail** ✉ park.soo.yun@gmail.com

Received: 01 February 2023; **Revised:** 18 May 2023; **Accepted:** 23 May 2023

ABSTRACT

Resistance and toxicity remain major challenges in platinum-based anticancer therapies. This study aims to compare how the chemical structure and hydrolysis mechanisms influence the pharmacological activity and toxicological profiles of approved platinum drugs: Cisplatin, Carboplatin, Oxaliplatin, Nedaplatin, Lobaplatin, Heptaplatin, and Satraplatin. Carboplatin and Nedaplatin undergo hydrolysis via a two-step hydration process, ultimately generating the same active species as Cisplatin, namely diaquadiamine-platinum. In contrast, Oxaliplatin, Lobaplatin, Heptaplatin, and Satraplatin share a hydrolysis mechanism in which the first step involves ring-opening and addition of a water molecule, followed by ligand loss and formation of the di-aquated product through a second water addition. Regarding toxicity, Cisplatin, Carboplatin, and Oxaliplatin exhibit nephrotoxic effects, while Cisplatin and Heptaplatin are particularly nephrotoxic. Myelosuppression represents the primary dose-limiting toxicity for Carboplatin, Oxaliplatin, Nedaplatin, Lobaplatin, and Satraplatin.

Keywords: Cisplatin, Toxicology, Approved derivatives, Pharmacology, Hydrolysis

How to Cite This Article: Ji-Hoon K, Soo-Yun P, Min-Jae C. Impact of Chemical Structure and Hydrolysis Mechanisms on the Pharmacological Effects and Toxicity Profiles of Licensed Platinum-Based Drugs. Ann Pharm Pract Pharmacother. 2023;3:103-13. https://doi.org/10.51847/SQSRbv0oT9

Introduction

Carcinogenesis involves a series of stages through which normal cells gradually become tumor cells, including initiation, promotion, malignant transformation, and progression. Recent trends indicate an increase in breast cancer among women and lung, prostate, and colon cancers among men [1]. Platinum-based compounds are recognized as key agents in cancer therapy [2]. Data from the 2009 U.S. Centers for Disease Control and Prevention outpatient database show that platinum drugs rank among the most commonly used chemotherapeutics, with usage only exceeded by Methotrexate, Medroxyprogesterone, Leuprolide, Raloxifene, and Tamoxifen. Cytotoxic activity is observed in Pt(IV) derivatives after reduction to their active Pt(II) form, while certain Pt(III) compounds, such as hematoporphyrin derivatives [3] and monomeric Pt(III) complexes [4, 5], also display cytotoxic properties.

Cisplatin

Cisplatin (cis-dichlorodiammineplatinum II) **(Figure 1)** represents the first platinum coordination complex developed for clinical cancer therapy.

© 2023 Annals of Pharmacy Practice and Pharmacotherapy

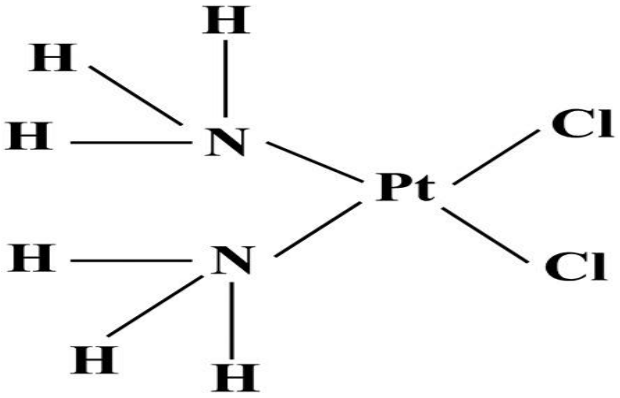

Figure 1. Chemical structure of Cisplatin.

In December 1978, the U.S. Food and Drug Administration authorized Cisplatin for managing testicular and ovarian cancers, with its first commercial availability occurring in Canada and the United States [6, 7].

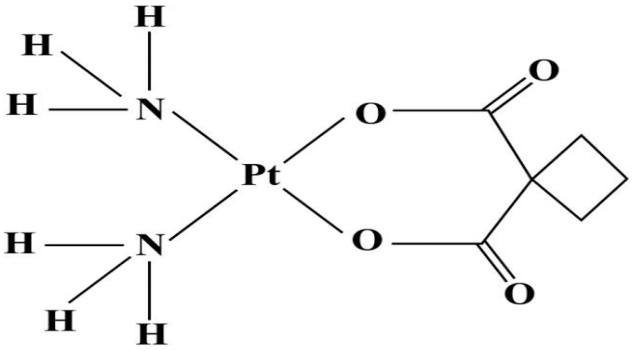

Figure 2. Chemical structure of Carboplatin.

Carboplatin's anticancer activity is mediated through DNA damage and the creation of cytotoxic DNA adducts [8]. Cisplatin is utilized in the treatment of ovarian carcinoma, testicular teratoma [9], and medulloblastoma [10]. Its toxicity profile includes kidney and nervous system damage, temporary blindness, seizures [11], and encephalopathy [12], while auditory effects appear as tinnitus [13] and partial hearing loss [14].

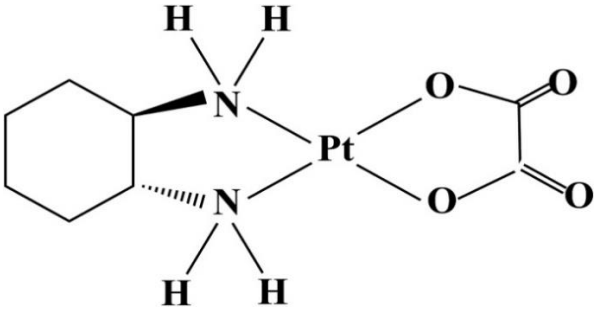

Figure 3. Chemical structure of Oxaliplatin.

Currently, several platinum-based drugs are in clinical use worldwide: Cisplatin and its second-generation analog Carboplatin (approved 1993); the third-generation derivative Oxaliplatin (approved 2002 in France); the second-generation Carboplatin analog Nedaplatin in Japan; third-generation Oxaliplatin derivatives Lobaplatin in China and Heptaplatin in North Korea; and the oral platinum compound Satraplatin [15]. Despite these developments, no Cisplatin analog has yet been created that surpasses it in both therapeutic efficacy and range of activity [6].

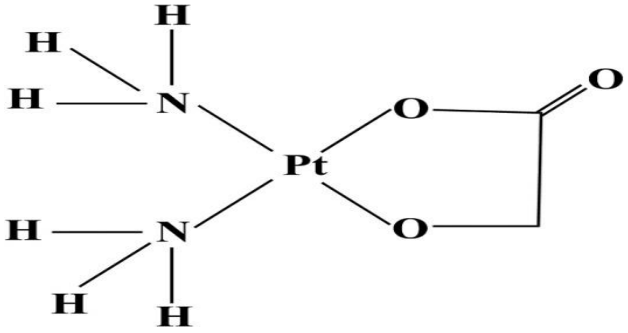

Figure 4. Chemical structure of Nedaplatin.

Cisplatin derivatives: carboplatin and oxaliplatin

Carboplatin

Bristol-Myers Squibb received approval for Carboplatin use in March 1989, making it the most clinically successful second-generation platinum complex, widely employed in the treatment of ovarian, head and neck, lung, and breast cancers [7].

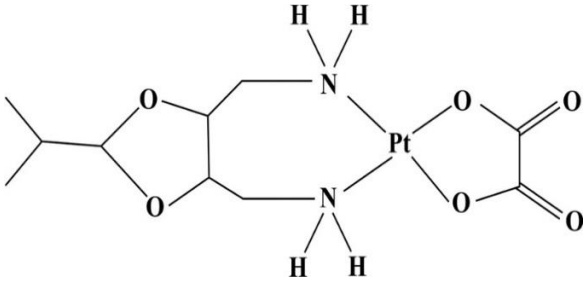

Figure 5. Chemical structure of Heptaplatin.

Carboplatin's major limitation lies in its blood-related toxicity, particularly causing myelosuppression [16, 17], whereas ear toxicity is infrequent, reported in only around 1.1% of patients [18].

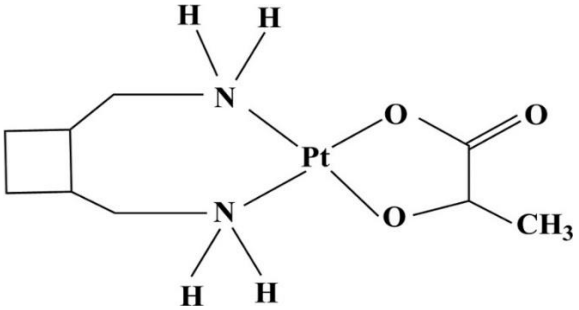

Figure 6. Chemical structure of Lobaplatin.

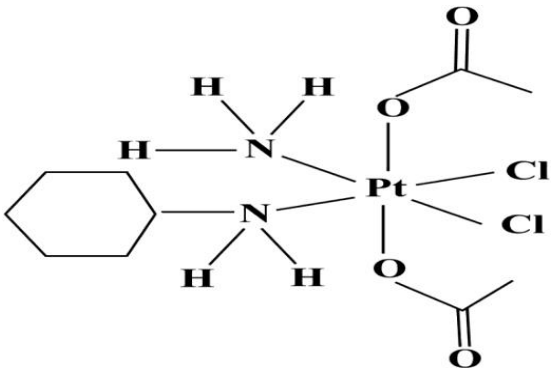

Figure 7. Chemical structure of Satraplatin.

Oxaliplatin

Oxaliplatin is utilized for treating non-small cell lung cancer, as well as head, neck, ovarian, and breast cancers [15]. In combination with folic acid and 5-fluorouracil, it is also effective against colorectal cancer [19]. Treatment is often halted due to neurotoxic effects and renal tubular damage [20, 21], with neurological complications—acute or chronic sensory peripheral neuropathy—being the primary dose-limiting concern [18].

Carboplatin derivatives: nedaplatin

In Japan, Nedaplatin is approved for cancers of the head, neck, esophagus, non-small cell lung, cervix, testis, and prostate [22]. Compared to Cisplatin, Nedaplatin shows reduced toxicity to the kidneys, nervous system, ears, gastrointestinal tract, and causes less leukopenia, while its main dose-limiting adverse effect is myelosuppression, including thrombocytopenia, neutropenia, and anemia [23].

Third-generation oxaliplatin derivatives: heptaplatin and lobaplatin

Heptaplatin

Heptaplatin received approval from the Korean FDA in 1999 for treating gastric cancer [6], with nephrotoxicity being its principal dose-limiting side effect [24].

Lobaplatin

Lobaplatin has been introduced in China for use against chronic myelocytic leukemia, hypopharyngeal carcinoma, esophageal squamous cell carcinoma [25], small-cell lung cancer [26], and gastric cancer [27]. The main toxicities are reductions in platelets and white blood cells, including neutrophils and granulocytes [23].

Pt(IV) cisplatin derivatives: third generation satraplatin

Satraplatin is indicated for lung, prostate, and ovarian cancers [7], with hematological toxicity being the primary factor limiting its dose [28].

Hydrolysis mechanism of cisplatin derivatives

Cisplatin consists of a platinum(II) center bound to two ammonia molecules and two chloride ions in cis configuration. Once inside the cell, water molecules replace the chloride ligands, producing highly reactive mono- and diaqua species capable of binding DNA **(Figure 8)**. This activation is favored by the low intracellular chloride concentration, typically below 100 mmol/L [29].

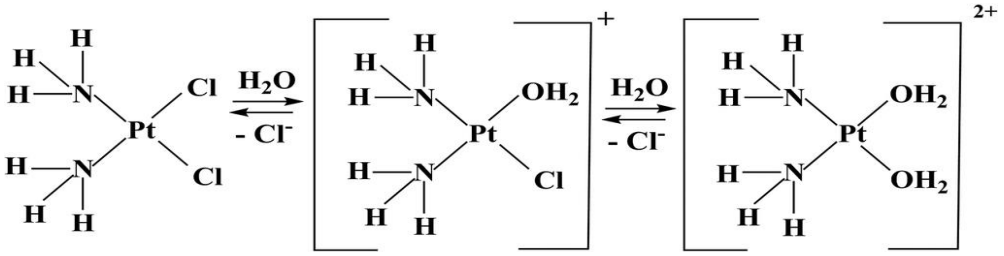

Figure 8. Hydrolysis mechanism of Cisplatin forming cytotoxic mono- and diaqua complexes

The aqua complexes generated from Cisplatin are highly electrophilic, allowing them to form covalent bonds with nucleophilic nitrogen atoms in DNA purine bases, creating DNA adducts that can be monofunctional (involving one leaving group) or bifunctional (involving two leaving groups). The presence of two labile ligands as leaving groups enables the formation of intra-strand crosslinks, and less commonly, inter-strand crosslinks within DNA. Cisplatin predominantly targets the N7 atom of guanine's imidazole ring, but can also bind to N3 and 4-NH2 of cytosine and N1 and 6-NH2 of adenine. Most Pt-DNA adducts form on a single DNA strand, with internal adducts being GpG (65%) and ApG (25%), while crosslinks between guanines on opposite strands occur less frequently (5%).

These adducts disrupt DNA structure, inhibiting replication and transcription, prolonging the G2 phase of the cell cycle, and ultimately triggering apoptosis. DNA-protein adducts can also form, and bifunctional adducts that generate intra- or inter-helix crosslinks induce significant local DNA distortion. In DNA-protein crosslinks, these bonds block replication and are key triggers for apoptosis [29].

In Carboplatin, the two chloride ligands are substituted with a bidentate cyclobutane-dicarboxylate group. The drug undergoes slow hydrolysis through double hydration, producing the same diaquadiamine-platinum species as Cisplatin. Its decomposition in water follows a biphasic mechanism: initially, ring-opening and aquation occur, followed by the loss of the malonato ligand and a second aquation step **(Figure 9)** [30].

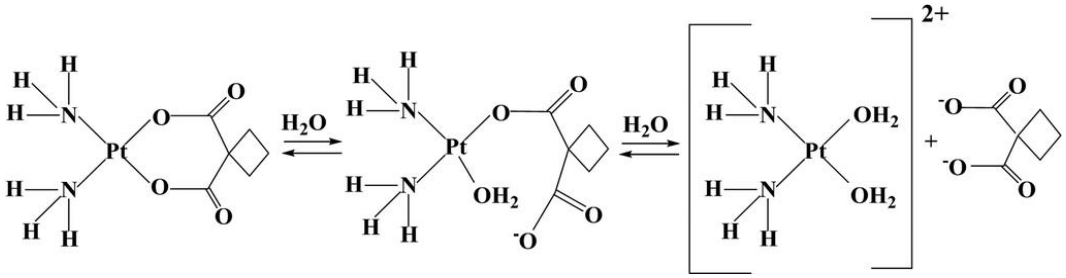

Figure 9. Hydrolysis mechanism of Carboplatin [30]

Carboplatin exhibits slower DNA binding because its carboxylate ligand is more stable, resulting in a slower hydrolysis rate. The resulting aqua complexes can interact with DNA, proteins, or other macromolecules.
For Oxaliplatin, hydrolysis involves ring-opening, water addition, and loss of the monodentate oxalato ligand, with the ring-opening step being the rate-limiting stage for neutral hydrolysis **(Figure 10)**. Its stable oxalate ligands slow DNA binding, and the formed aqua complexes also react with DNA and proteins. Although Oxaliplatin may generate fewer DNA adducts compared to Cisplatin, it exhibits greater cytotoxicity [31].

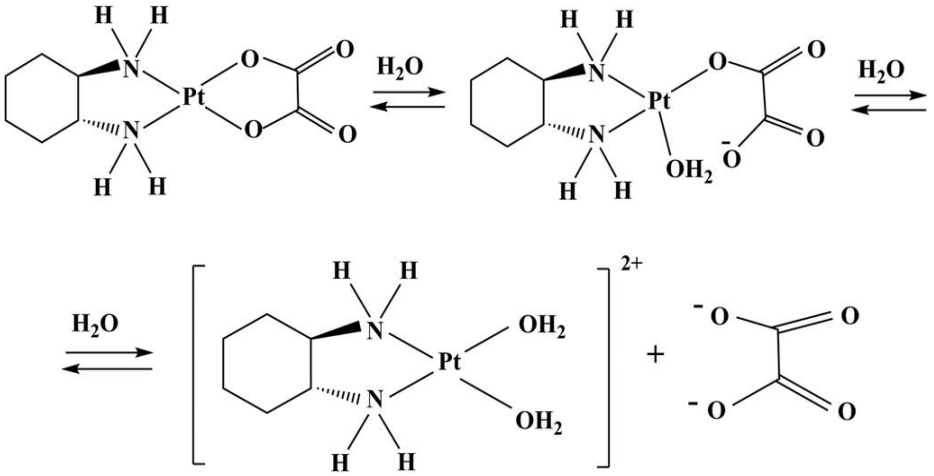

Figure 10. Hydrolysis mechanism of Oxaliplatin [31]

Nedaplatin is approximately ten times more soluble in water than Cisplatin and undergoes hydrolysis through double hydration, producing the same active diaquadiamine-platinum metabolite as Cisplatin. The hydrolysis process is depicted in **Figure 11**.

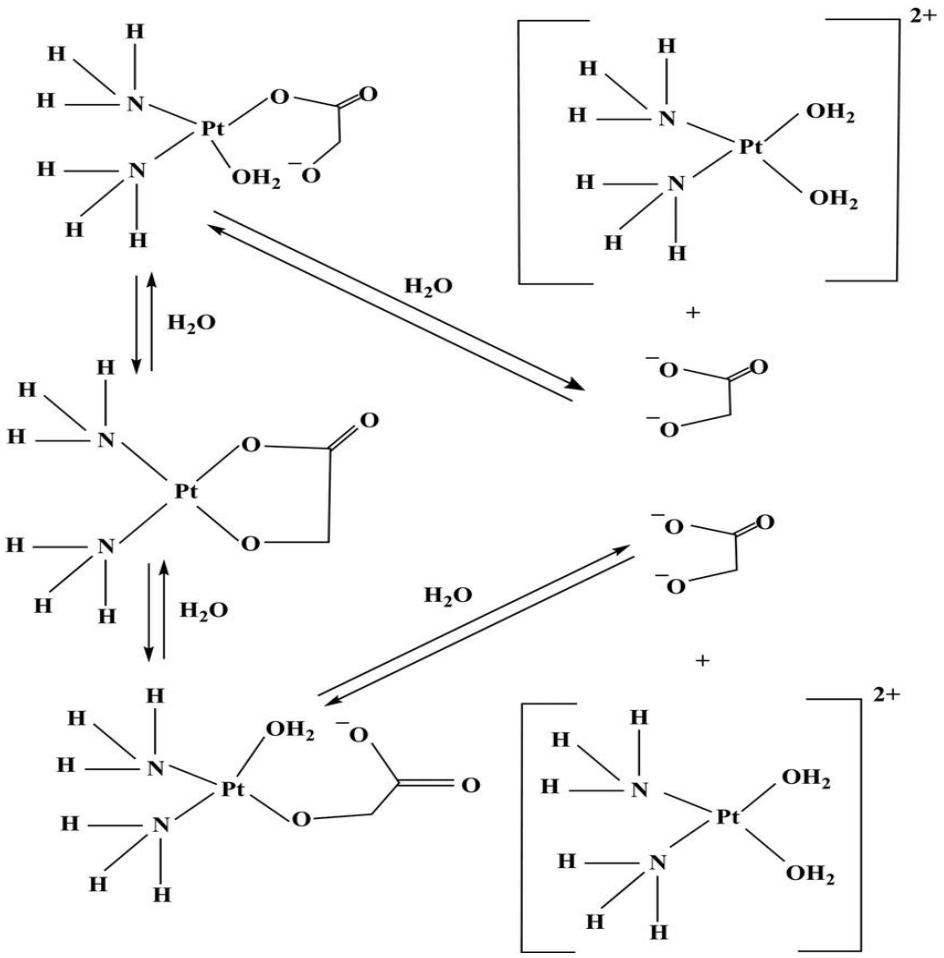

Figure 11. Hydrolysis mechanism of Nedaplatin [32]

The hydrolysis of Nedaplatin begins with ring opening and the first hydration step, followed by a second phase involving ligand loss and a second hydration. Under acidic conditions, the second hydrolysis step is rate-limiting, whereas in neutral conditions, the initial hydrolysis step limits the reaction [32].

Nedaplatin primarily binds to guanine in DNA. When the mismatch repair protein complex attempts to remove platinum cross-links, single-strand breaks are generated, and if repair fails, apoptosis is induced. Additionally, when combined with radiation therapy, Nedaplatin enhances radiosensitivity by promoting lethal double-strand breaks [22].

Heptaplatin bio-transformation **(Figure 12)**

Heptaplatin is converted into mono- and di-aquated species during hydrolysis. Similar to Oxaliplatin, the initial step involves ring opening and addition of the first water molecule, followed by ligand loss and formation of the di-aquated product via a second hydration. These hydrolysis products preferentially bind to guanine and adenine in DNA, forming DNA adducts, with guanine being favored due to more favorable hydrogen-bond interactions [33].

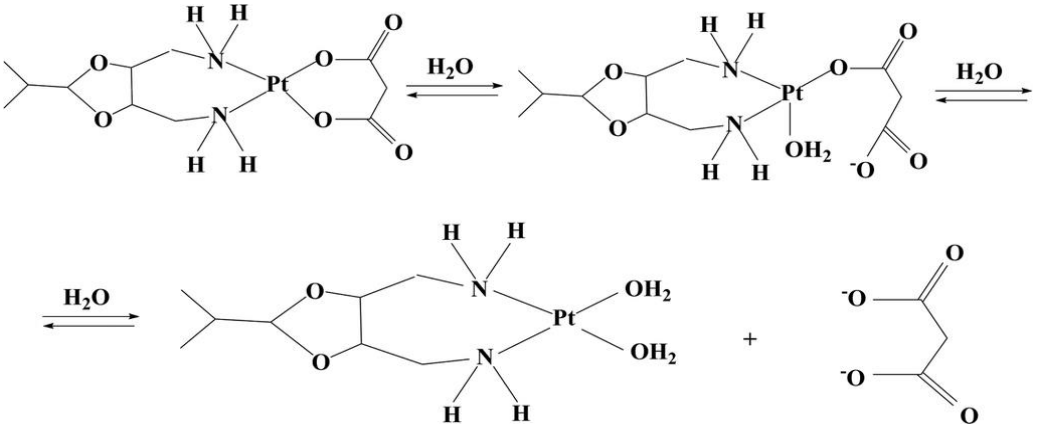

Figure 12. Hydrolysis mechanism of Heptaplatin [33]

For Lobaplatin, under neutral aqueous conditions, the ring-opening step is the slowest and thus rate-limiting stage of hydrolysis. Once fully hydrolyzed, the complex interacts with DNA purine bases. In acidic environments, ligand dissociation becomes the rate-limiting step, and the resulting monohydrated species binds to DNA. The hydrolysis process of Lobaplatin is illustrated in **Figure 13** [34].

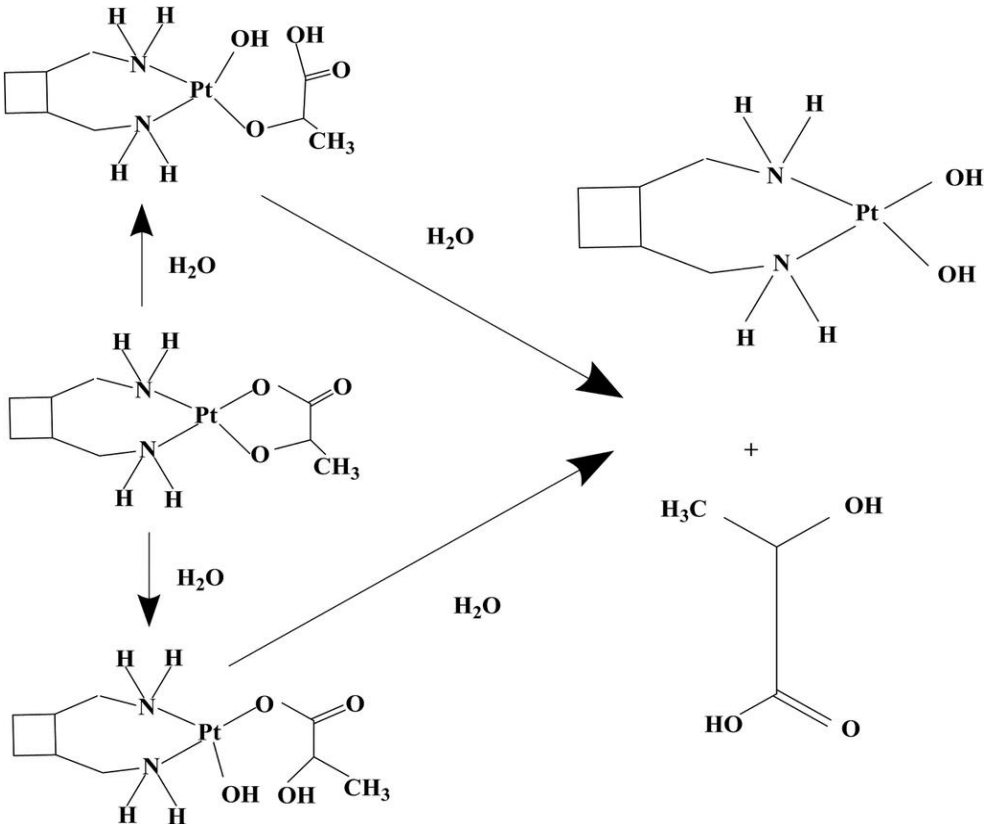

Figure 13. Hydrolysis mechanism of Lobaplatin [34]

Pt(IV) complexes exist in an "inactive" state, predominantly interacting with proteins in the bloodstream, and accumulate in cells via passive diffusion. Their activation requires reduction to Pt(II), which occurs alongside the release of axial ligands. This reduction is essential for antitumor activity because six-coordinate octahedral Pt(IV) compounds are more kinetically stable, less reactive, and resistant to ligand substitution compared to four-coordinate Pt(II) complexes, minimizing undesired interactions with biomolecules. Depending on ligand composition, some Pt(IV) complexes can bind DNA and induce structural deformation. Cytotoxicity studies indicate that Pt(IV) complexes, like Pt(II) compounds, localize in the cell nucleus, forming DNA adducts similar to those produced by Cisplatin, and in vitro data suggest higher efficacy than their Pt(II) counterparts.

Due to their kinetic inertness, Pt(IV) complexes can overcome limitations of intravenous administration; for example, Satraplatin is the first orally available platinum-based anticancer drug. Its enhanced bioavailability is attributed to two polar acetate groups, and its hydrolysis is illustrated in **Figure 12** [35]. Once inside the cell, Pt(IV) is activated via two metabolic pathways: (1) reduction by bioreductants such as glutathione and ascorbic acid to the Pt(II)-like active metabolite JM118, and (2) direct antitumor activity of the active Pt(IV) species JM383. JM216 can also form Pt-DNA adducts resembling those of Cisplatin and Oxaliplatin, though in smaller quantities [35].

Resistance to Cisplatin and its derivatives mainly arises from the mammalian nucleotide excision repair pathway, which corrects DNA damage. Satraplatin, due to its unique cyclohexamine adducts, evades recognition by DNA repair proteins, leaving DNA damaged and replication blocked. By binding to guanine residues, Satraplatin inhibits DNA replication and transcription, ultimately triggering apoptosis [35].

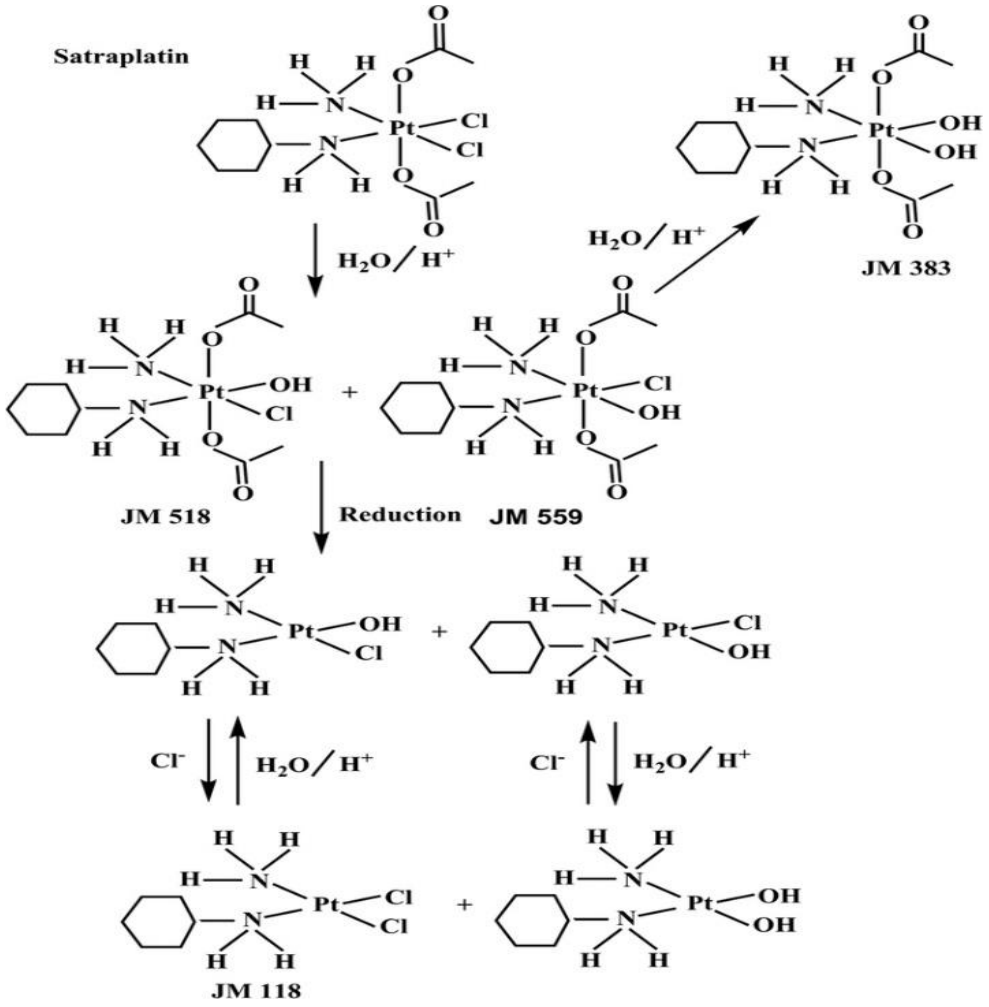

Figure 14. Hydrolysis mechanism of Satraplatin [35]

Impact of Chemical Structure on Pharmacological Activity and Toxicity of Platinum Complexes

The classical structural features required for antitumor activity, derived from Cisplatin, include:

1. A square planar Pt(II) geometry;
2. Cis-orientation of the two “leaving” ligands;
3. Amino or imino groups at the remaining coordination sites;
4. Presence of NH functional groups, which enhance adduct stability through hydrogen bonding.

Development of new platinum complexes focuses on introducing diverse ligands—amines, alkylamines, purines, pyrimidines, hydantoins, carbonyl groups—to achieve selective cytotoxicity or activity against resistant tumors. Altering leaving groups (labile, hydrolyzable, or exchangeable ligands) influences cytotoxic potency, activity spectrum, and toxicological profile. The leaving group affects the cytostatic range, with the order of effectiveness

being Cl^- > oxalato$^-$ > cyclobutanedicarboxylato$^-$, reducing cross-resistance in Cisplatin-resistant tumors. For example, in Carboplatin, platinum is bound to cyclobutanedicarboxylic acid, while in hydroxycarboxylic acid-based complexes (e.g., lactic or glycolic acid), platinum is bidentately coordinated to carboxyl and hydroxyl oxygens. Specific leaving groups include: cyclobutanedicarboxylate in Carboplatin, glycolate anion in Nedaplatin, bidentate lactate in Lobaplatin, and bidentate oxalate in Oxaliplatin. Conversion to active diaquacomplexes occurs mainly intracellularly; their greater stability compared to chloride ligands requires higher concentrations for cytotoxicity but reduces nephrotoxicity by limiting direct interaction with nucleophilic thiol groups in the kidney. Carboplatin and Nedaplatin are considered Cisplatin precursors because their metabolism yields dichloro-diamine platinum intermediates. DNA adducts formed by Carboplatin are identical to those of Cisplatin, but require 20–40 times higher drug concentrations and form approximately ten times slower [7].

The carrier ligands (ammonia in Cisplatin, Carboplatin, Nedaplatin) are tightly bound and do not react with water or nucleophilic DNA bases; altering them significantly changes antitumor activity, action spectrum, and toxicity profile. Partial or full replacement of ammonia with mono- or bidentate nitrogen ligands—including aliphatic, alicyclic, aromatic mono- and diamines, or heterocycles—modifies activity. Examples include the 1,2-diaminocyclohexane (DACH) ligand in Oxaliplatin and the seven-membered Pt-1,2-bis-(methylamino)cyclobutane chelate in Lobaplatin. Expanding the heterocyclic ring (4 to 6 atoms) enhances efficacy against Cisplatin-resistant tumors. DACH-containing complexes are active in resistant tumors, but their neurotoxicity limits use. Oxaliplatin exhibits higher cytotoxicity than Cisplatin by inhibiting nucleic acid polymerases and inducing apoptosis, aided by its hydrophobicity, which enhances uptake through transport proteins overexpressed in tumor cells. Chemotherapy challenges include drug resistance and toxicity, as cytostatics affect normal rapidly dividing cells, such as bone marrow and gastrointestinal epithelium. Myelosuppression increases infection risk and is typical of alkylating agents and antimetabolites. Toxicity can be mitigated via combination therapy, polynuclear platinum agents, Pt(IV) prodrugs, and targeted nanocarriers (e.g., polymers, liposomes) [6].

Dose-Limiting Toxicities of Approved Platinum Complexes:

1. Cisplatin – nephrotoxicity, ototoxicity [21], neuropathy [36];
2. Carboplatin – neurotoxicity, myelosuppression [17];
3. Oxaliplatin – neurotoxicity [20], hematological and gastrointestinal toxicity [21];
4. Nedaplatin – myelosuppression [23];
5. Heptaplatin – nephrotoxicity [24];
6. Lobaplatin – myelosuppression [23];
7. Satraplatin – myelosuppression [28].

Conclusion

A major challenge in anticancer therapy is drug toxicity. Cisplatin, Carboplatin, and Oxaliplatin primarily exhibit nephrotoxicity, while Cisplatin and Heptaplatin are also nephrotoxic. Myelosuppression represents the common dose-limiting toxicity for Carboplatin, Oxaliplatin, Nedaplatin, Lobaplatin, and Satraplatin [21]. Structural modifications of platinum complexes can markedly alter their antitumor efficacy, activity spectrum, and toxicological profile. Current strategies in designing new platinum-based anticancer agents focus on enhancing antitumor potency, expanding their therapeutic range, reducing toxicity, and developing targeted cytostatics. Nanocarrier systems, including polymers and liposomes, play a key role in overcoming resistance and minimizing side effects of Cisplatin derivatives by improving targeted delivery, increasing cellular uptake, promoting selective tumor accumulation, and enhancing overall therapeutic outcomes.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. O'Brien RM, Cannon A, Reynolds JV, Lysaght J, Lynam-Lennon N. Complement in tumourigenesis and the response to cancer therapy. Cancers. 2021;13(6):1209. doi:10.3390/cancers13061209
2. Kostova I. Platinum complexes as anticancer agents. Recent Pat Anticancer Drug Discov. 2006;1(1):1-22. doi:10.2174/157489206775246458
3. Momekov G, Karaivanova M, Ugrinova I, Pasheva E, Gencheva G, Tsekova D, et al. In vitro pharmacological study of monomeric platinum(III) hematoporphyrin IX complexes. Invest New Drugs. 2011;29(5):742-51. doi:10.1007/s10637-010-9412-8
4. Momekov G, Bakalova A, Karaivanova M. Novel approaches towards development of non-classical platinum-based antineoplastic agents: design of platinum complexes characterized by an alternative DNA-binding pattern and/or tumor-targeted cytotoxicity. Curr Med Chem. 2005;12(19):2177-91. doi:10.2174/0929867054864877
5. Momekov G, Momekova D. Recent developments in antitumour platinum coordination compounds. Expert Opin Ther Pat. 2006;16(10):1383-403.
6. Johnstone TC, Suntharalingam K, Lippard SJ. The next generation of platinum drugs: targeted pt(ii) agents, nanoparticle delivery, and pt(iv) prodrugs. Chem Rev. 2016;116(5):3436-86. doi:10.1021/acs.chemrev.5b00597
7. Zhou J, Kang Y, Chen L, Wang H, Liu J, Zeng S, et al. The drug-resistance mechanisms of five platinum-based antitumor agents. Front Pharmacol. 2020;11:343. doi:10.3389/fphar.2020.00343
8. Hu J, Lieb JD, Sancar A, Adar S. Cisplatin DNA damage and repair maps of the human genome at single-nucleotide resolution. Proc Natl Acad Sci U S A. 2016;113(41):11507-12. doi:10.1073/pnas.1614430113
9. Matysiak W, Gustaw-Rothenberg K. Pharmacological profi le and clinical features of cisplatin. J Pre-Clin Clin Res. 2009;3(1):20-3.
10. Packer RJ, Sutton LN, Elterman R, Lange B, Goldwein J, Nicholson HS, et al. Outcome for children with medulloblastoma treated with radiation and cisplatin, CCNU, and vincristine chemotherapy. J Neurosurg. 1994;81(5):690-8. doi:10.3171/jns.1994.81.5.0690
11. Cattaneo MT, Filipazzi V, Piazza E, Damiani E, Mancarella G. Transient blindness and seizure associated with cisplatin therapy. J Cancer Res Clin Oncol. 1988;114(5):528-30. doi:10.1007/BF00391507
12. Brück W, Heise E, Friede RL. Leukoencephalopathy after cisplatin therapy. Clin Neuropathol. 1989;8(6):263-5.
13. Kaltenbach JA, Rachel JD, Mathog TA, Zhang J, Falzarano PR, Lewandowski M. Cisplatin-induced hyperactivity in the dorsal cochlear nucleus and its relation to outer hair cell loss: relevance to tinnitus. J Neurophysiol. 2002;88(2):699-714. doi:10.1152/jn.2002.88.2.699
14. Knight K. Hearing loss in pediatric cancer survivors treated with cisplatin. Oncology (Williston Park). 2008;22(4):35-7.
15. Ndagi U, Mhlongo N, Soliman ME. Metal complexes in cancer therapy - an update from drug design perspective. Drug Des Devel Ther. 2017;11:599-616. doi:10.2147/DDDT.S119488. PMID: 28424538
16. Cheng YJ, Wu R, Cheng ML, Du J, Hu XW, Yu L, et al. Carboplatin-induced hematotoxicity among patients with non-small cell lung cancer: Analysis on clinical adverse events and drug-gene interactions. Oncotarget. 2017;8(19):32228-36. doi:10.18632/oncotarget.12951
17. Schmitt A, Gladieff L, Laffont CM, Evrard A, Boyer JC, Lansiaux A, et al. Factors for hematopoietic toxicity of carboplatin: refining the targeting of carboplatin systemic exposure. J Clin Oncol. 2010;28(30):4568-74. doi:10.1200/JCO.2010.29.3597
18. Amptoulach S, Tsavaris N. Neurotoxicity caused by the treatment with platinum analogues. Chemother Res Pract. 2011;2011(1):843019. doi:10.1155/2011/843019
19. Kweekel DM, Gelderblom H, Guchelaar HJ. Pharmacology of oxaliplatin and the use of pharmacogenomics to individualize therapy. Cancer Treat Rev. 2005;31(2):90-105. doi:10.1016/j.ctrv.2004.12.006
20. Gamelin E, Gamelin L, Bossi L, Quasthoff S. Clinical aspects and molecular basis of oxaliplatin neurotoxicity: current management and development of preventive measures. Semin Oncol. 2002;29(5):21-33. doi:10.1053/sonc.2002.35525
21. Oun R , Moussa YE , Wheate NJ . The side effects of platinum-based chemotherapy drugs: a review for chemists. Dalton Trans. 2018;47(19):6645-53. doi:10.1039/c8dt00838h

22. Shimada M, Itamochi H, Kigawa J. Nedaplatin: a cisplatin derivative in cancer chemotherapy. Cancer Manag Res. 2013;5:67-76. doi:10.2147/CMAR.S35785
23. Wu Q, Zhu C, Zhang S, Zhou Y, Zhong Y. Hematological toxicities of concurrent chemoradiotherapies in head and neck cancers: comparison among cisplatin, nedaplatin, lobaplatin, and nimotuzumab. Front Oncol. 2021;11:762366. doi:10.3389/fonc.2021.762366
24. Ahn JH, Kang YK, Kim TW, Bahng H, Chang HM, Kang WC, et al. Nephrotoxicity of heptaplatin: a randomized comparison with cisplatin in advanced gastric cancer. Cancer Chemother Pharmacol. 2002;50(2):104-10. doi:10.1007/s00280-002-0483-x
25. Du L, Fei Z, Song S, Wei N. Antitumor activity of lobaplatin against esophageal squamous cell carcinoma through caspase-dependent apoptosis and increasing the Bax/Bcl-2 ratio. Biomed Pharmacother. 2017;95:447-52. doi:10.1016/j.biopha.2017.08.119
26. Zhang H, Chen R, Yang S, Liu W, Li K, Zhang H, et al. Lobaplatin for the treatment of SK-MES-1 lung squamous cell line in vitro and in vivo. Onco Targets Ther. 2016;9:4215-24. doi:10.2147/OTT.S108032
27. Hua S, Kong X, Chen B, Zhuang W, Sun Q, Yang W, et al. Anticancer mechanism of lobaplatin as monotherapy and in combination with paclitaxel in human gastric cancer. Curr Mol Pharmacol. 2018;11(4):316-25. doi:10.2174/1874467211666180813095050
28. Bhargava A, Vaishampayan UN. Satraplatin: leading the new generation of oral platinum agents. Expert Opin Investig Drugs. 2009;18(11):1787-97. doi:10.1517/13543780903362437
29. Sawant A, Kothandapani A, Zhitkovich A, Sobol RW, Patrick SM. Role of mismatch repair proteins in the processing of cisplatin interstrand cross-links. DNA Repair (Amst). 2015;35:126-36. doi:10.1016/j.dnarep.2015.10.003
30. Pavelka M, Lucas MF, Russo N. On the hydrolysis mechanism of the second-generation anticancer drug carboplatin. Chemistry. 2007;13(36):10108-16. doi:10.1002/chem.200700887
31. Lucas MF, Pavelka M, Alberto ME, Russo N. Neutral and acidic hydrolysis reactions of the third generation anticancer drug oxaliplatin. J Phys Chem B. 2009;113(3):831-8. doi:10.1021/jp8086539
32. Alberto ME, Lucas MF, Pavelka M, Russo N. The second-generation anticancer drug Nedaplatin: a theoretical investigation on the hydrolysis mechanism. J Phys Chem B. 2009;113(43):14473-9. doi:10.1021/jp9056835
33. Mukherjee S, Mitra I, Moi SC. A theoretical investigation on bio-transformation of third generation anti-cancer drug heptaplatin and its interaction with DNA purine bases. Chemical Physics Letters. 2017;690:105-15.
34. Mukherjee S, Mitra I, Mahata S, Linert W, Moi SC. Hydrolysis mechanism of anticancer drug lobaplatin in aqueous medium under neutral and acidic conditions: a DFT study. Chemical Physics Letters. 2016;663:115-22.
35. Ritacco I, Al Assy M, Abd El-Rahman MK, Fahmy SA, Russo N, Shoeib T, et al. Hydrolysis in acidic environment and degradation of satraplatin: a joint experimental and theoretical investigation. Inorg Chem. 2017;56(10):6013-26.
36. Krarup-Hansen A, Helweg-Larsen S, Schmalbruch H, Rorth M, Krarup C. Neuronal involvement in cisplatin neuropathy: prospective clinical and neurophysiological studies. Brain. 2007;130(Pt 4):1076-88. doi:10.1093/brain/awl356