A review on historical developments to current scenario of Pt complexes and their medicinal importance.

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Abstract

This review embraces the anticancer chemistry of platinum metal containing complexes, specifically with reference to Pt (IV). The impact of Pt (IV) complexes over Pt (II) complexes are discussed with suitable explanation. The roles of geometry triggering the medicinal importance of Pt complexes are also included with proper justification. The literature study includes earlier works on Pt (II) and (IV) complexes and their anticancer mechanism or activity. The literature studies on metal-ligand interaction at various interfaces have been summarized which includes the formation of anticancer agents through the coordination of Pt metal and nitrogen, oxygen, sulphur containing compounds as ligands. The interactions of Pt complexes with Biomolecules such as DNA are also explored with their probable mechanism. The nature, properties and anticancer activities of Pt complex as well as those of ligand have been deliberated to design new Pt chemotherapeutic complexes.

Keywords: Anticancer, Pt complexes, Metal-ligand interaction.

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Introduction

After serendipitous discovery of cisplatin (Figure 1), metal-based drugs have flared rapidly to give a variety of quite dissimilar and fruitful chemo-agents useful for the treatment of cancer. The anticancer mechanism of cisplatin made those complexes more interesting and reliable option for curing cancer.

Thus, many Pt based drugs have been commercially developed and undergone *in vitro* and *in vivo* analysis resulting in some of them reaching upto the clinical level [1] (Figure 2).

Almost, all the widely occurring tumors except those of solid tumors (breast and prostate) are treated with Pt drugs, often in combination of other chemotherapeutics having a cumulative number of other less frequent malignancies. Indeed, cancer patients to an extent of 50–70% are treated using Pt drugs [1].

Aim of article

This article aims to development of platinum drugs from cisplatin to currently available for procuring cancer disease from their *in vitro* studies to clinical trials.

Literature Review

Cancer and chemotherapy and concept of the pt complexes

Cancer is a fatal disease occurring in a biological system which is malignant neoplasm, caused by an uncontrolled growth of abnormal cell and turns into tumor in a specific part of the body. In a contrasting manner, the normal body cells complete their life cycle by growing, dividing and then dying while cancer cells are sufficiently different from normal cells those continue to grow and divide instead of dying, and proliferates new abnormal cells. Damaging of DNA is main cause of cancer cells which leads to all harmful activities and then the body becomes unable to repair those. Either environmental or habitual factors are attributed for causing cancers, such as those of consuming tobacco, diet and obesity, infections exposure to radiation which may be ionizing/non-ionizing, stress, lack of physical activity and pollutant [2,3]. Chemotherapy is a process in which a disease is treated by chemicals that have a specific toxicity towards the disease mediated via microorganisms (antibiotics) or they are able to selectively abolish cancerous tissue (anticancer therapy). For cancer therapy, mainly three conventional approaches have been developed such as surgery, radiotherapy and chemotherapy [2]. First successful treatment was developed for localized neoplasm by involving surgical removal of the tumor and nearby tissues. This procedure was of little assistance in case of a non-localized form (leukemia) and it resulted in spreading through blood or lymph to many parts of the body such as metastatic cancer. The next approach to treat cancer was developed using radiation therapy that produced a selective killing action against cancer cells. In the late 1940's when nitrogen mustard was involved in the treatment of leukemia, the dawn of chemotherapy had come [3,4]. Some years later, the field of cancer chemotherapy involves over thirty drugs encompassing the many classes of chemicals such as Pt coordination complexes, especially, amine ligands based Pt complexes [2].

Few bioinorganic complexes of platinum metal especially *cisplatin*, *carboplatin*, and *oxaliplatin* have been used in clinical treatment of cancer disease (Figure 3).

The *nedaplatin*, *lobaplatin*, and *heptaplatin* are approved for use in countries like Japan, China, and Korea, respectively (Table 1).

The Pt drug molecules have largely drawn researcher's attention for developing anticancer drugs especially square-planar induced Pt (II) complexes.

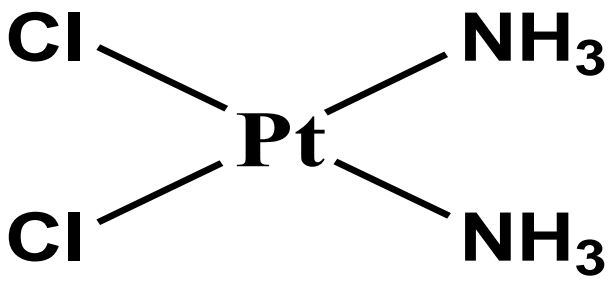

Figure 1. *Structure of Cisplatin: Anticancer Pt drug.*

Table 1. *Clinically approved platinum anti-cancer agents.*

Generic Name	Research Name	Trade Name	Approval Granted	Scope of Approval
Cisplatin	CDDP	Platinol	1978	Global
Carboplatin	JM8	Paraplatin	1989	Global
Oxaliplatin	I-OHP	Eloxatin	2002	Global
Nedaplatin	254-S	Aqupla	1995	Japan
Heptaplatin	SKI 2053R	Sunpla	1999	Korea
Lobaplatin	D-19466	----	2010	China

The electronic configurations $5d^8$ and $5d^6$ electronic configurations for Pt (II and IV) respectively make it highly suitable for coordination bonding, and it exhibits relatively slow ligand exchange rates that further impart it a covalent character as well as high crystal field stabilization energy. Secondly, the Pt which is a soft Lewis acid has a great and lower affinity toward soft and hard donor ligands respectively, especially, those of nitrogen, sulfur and oxygen. Pt complexes as anticancer drugs are exclusively employed as active entities among numerous chemotherapeutic agents. Cisplatin, a Pt (II) complex as illustrated in Figure 4, is the very first Pt based anticancer drug which was discovered in 1844, and it was also attributed for introducing the 'trans-effect' theory which was given by Werner [5-7]. Since platinum was thought to have no biological activity, Dr. Rosenberg and his colleagues put platinum electrodes into a solution containing the common laboratory bacteria E. coli and turned on the power. As soon as the current started, the bacterial cells stopped dividing, although they kept growing to up to 300 times their normal length. When the power was cut off, the bacterial cells began dividing again. It appeared that the electrical field was controlling cell division. Dr. Rosenberg later called this experiment the "accidental discovery that led eventually to cisplatin". However, Dr. Rosenberg and his colleagues did not yet know what they had discovered. They thought they might have found a way to control cell growth with electrical currents. They spent two years trying to discover why the electrical field had such a profound effect. Finally, they realized that electricity had nothing to do with it. Cell division was being blocked not by the electric field, but by a platinum compound released from the electrodes. After another two years, Dr. Rosenberg's team identified the compound that affected cell division so dramatically. It was later named cisplatin. Dr. Rosenberg then wondered whether cisplatin would also block cell division in tumors. Testing it in a sarcoma mouse model, he and his colleagues found that it did indeed attack tumors. While cisplatin was highly toxic—for example, causing kidney damage when used at a high dose—the mice were able to tolerate the drug in low doses. More importantly, the tumors responded to cisplatin and shrank. Six months later, the mice remained healthy and showed no return of the tumors. Thus, the discovery of cisplatin as anticancer Pt (II) drug opened a new window in the field of medicinal sciences by curing the fatal disease of cancer [8,9] with platinum complexes.

Anticancer chemistry of platinum complexes

The synthesis of Pt complexes was a great interest for scientists due to their anticancer activity which was typically proved by the presence of cisplatin. Along with the synthesis, the *in vitro* and *in vivo* studies of Pt complexes opened a new path in medicinal research, especially, in the treatment of cancer. With experiment of Barnet Rosenberg, both the cisplatin and transplatin were discovered but transplatin had not been considered upto clinical level due to its geometrical restriction for intra or interstrand DNA binding. The *cis* configuration makes cisplatin as a DNA binder to interfere in normal transcription or DNA replication mechanism that induces anticancer activity [10]. The cisplatin passes through bloodstream intravenously but to reach cell nucleus and binding with DNA, it has to pass through the cell membrane.

For this purpose a high intercellular chloride concentration, nearly about 100 mM suppresses the exchange of the chloride leaving groups for water molecules (an aquation reaction). Thus, cisplatin reaches to cancer or normal cells, and through trans-membrane-diffusion mechanism its cellular uptake takes place [11]. With this approach the chloride concentration becomes much lower inside the cell, as a result of ionization takes place whereby chlorine atoms are replaced by aqua ligand in a stepwise manner and aqua-complex is formed [3]. Now cisplatin undergoes DNA binding with inter or 1, 2 intrastrand cross-links base pairs that cause DNA structural distortion and inhibit the DNA replication process which demonstrates the anticancer activity of cisplatin [3,10] Due to a possibility of interaction between cisplatin and mitochondrial DNA of normal cells, the cellular toxicity is induced [10]. Many experimental results have proven that decreasing the reactivity and designing of Pt complexes having a different transport mechanism could lead to decreased toxic side-effects [10]. It could also lead to DNA interaction with structurally different nature from cisplatin and increase the efficacy of drug to circumvent certain resistance mechanisms related to DNA repair/tolerance [10]. For nuclear DNA interaction which is primary target of anticancer drug, possesses of Pt complex through cell membrane as well as nuclear membrane, is the most critical point that depends on hydrophobicity against lipid as a passive diffusion strategy [12]. It also depends on the non-polar nature of axial ligands where diminishing the cytotoxicity is enhanced by accumulation of Pt in the cell, especially, in the form of Pt (IV) complexes [13]. Many studies have revealed that sterically hindered ligands in Pt complexes like oxaliplatin, as depicted in Figure 5, protrude into the DNA helix and show better binding action as well as lower toxicity in comparison to non-sterically hindered ligands like cisplatin, and infers a role of ligand in the inhibition of replication and transcription of DNA [14,15].

For example, the cisplatin-DNA adduct is fused with the proteins of MRP and causes toxicity whereas the oxaliplatin, in which sterically hindered group is attached with Pt as dach ligand does not allow oxaliplatin-DNA adduct to bind with MRP in certain cell lines those are deficient in MMR [16-

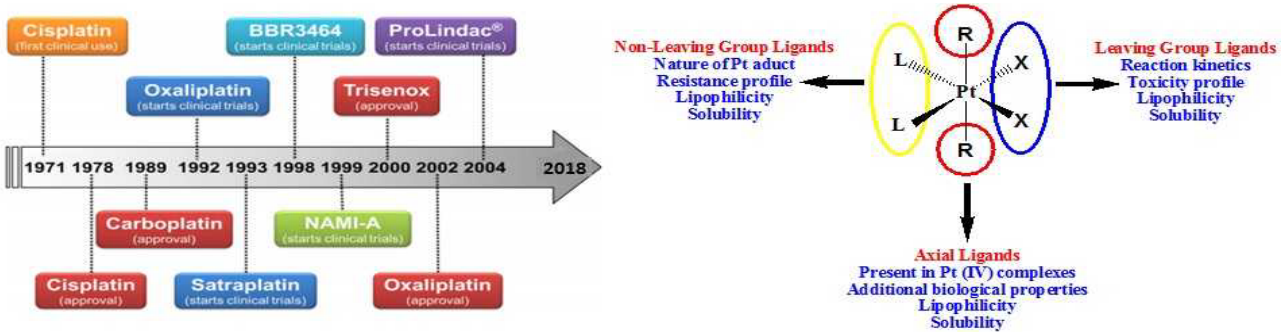

Figure 2. *Historical overview of the cytotoxic metal and metalloid complexes that have been approved or entered the clinical practice.*

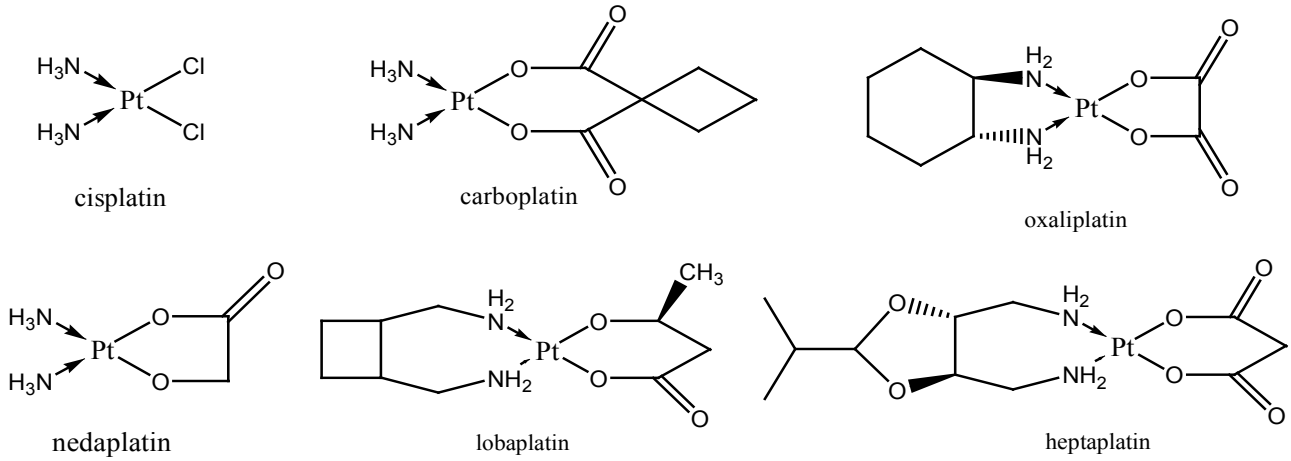

Figure 3. *The top three complexes, cisplatin, carboplatin, and oxaliplatin, are approved for use worldwide. The bottom three complexes, nedaplatin, lobaplatin, and heptaplatin, are approved for use in Japan, China, and Korea, respectively.*

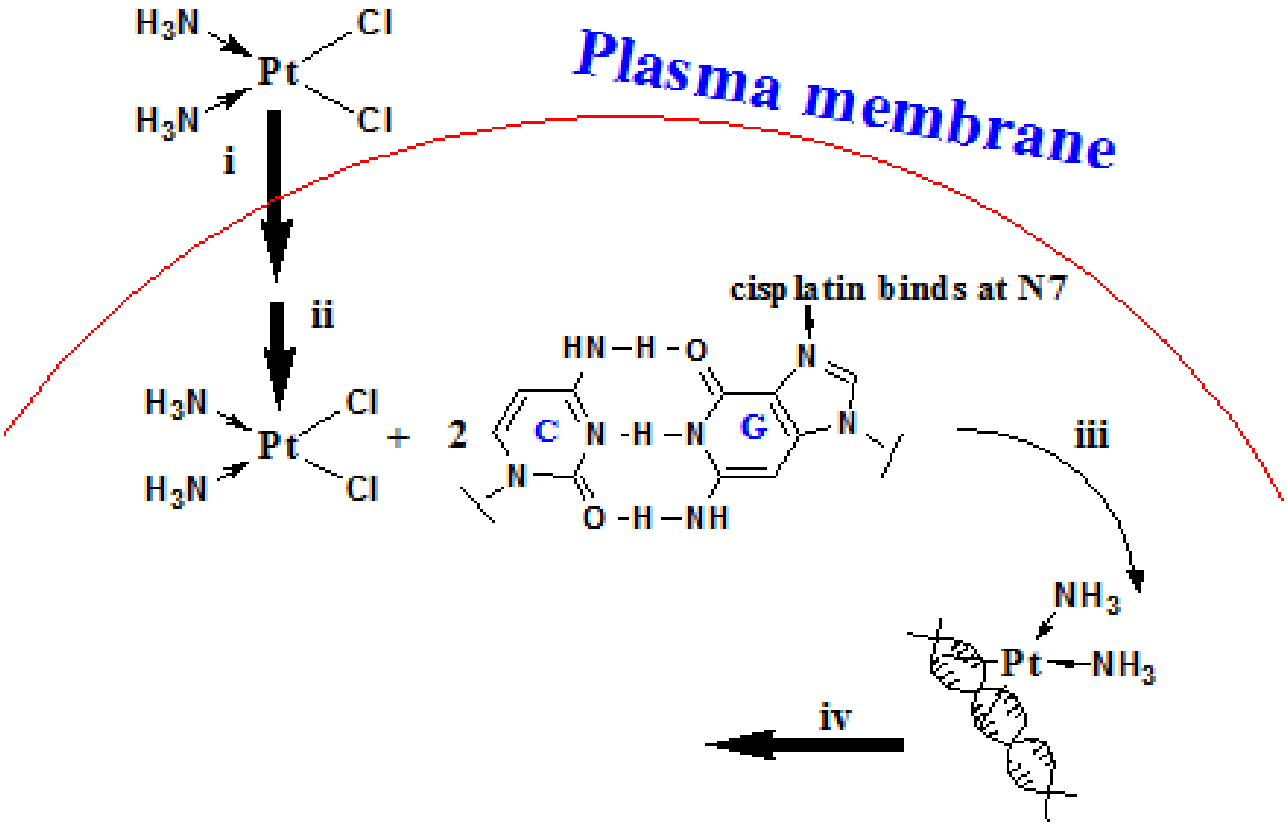

Figure 4. *Four steps of the mechanism of cisplatin and, by extension, related platinum anticancer drugs. (i) Cellular uptake, (ii) aquation/ activation, (iii) DNA binding, and (iv) cellular processing of DNA lesions leading to apoptosis.*

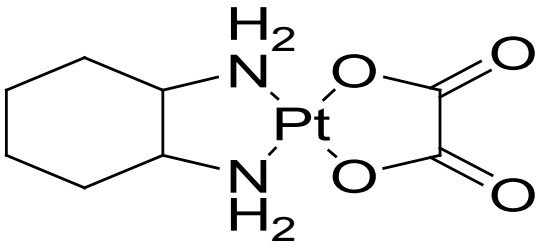

Figure 5. *Oxaliplatin: Pt complex with sterically hindered ligand.*

18]. Thus, steric hindrance which is caused by ligands is a critical point in understanding the reactivity and activity of a Pt complex against cancer cell which suggests that diminished stereochemical crowding can also produce diminishing in anticancer activity [19,20]. The reaction kinetics of the Pt based drug which depends on the ligand exchange rate in Pt complexes, reflect the efficacy of drug. In the body, there are many proteins or enzymes such asmetallothionein, methionine or glutathione which may be bound with Pt drug due to fast ligand exchange rate [21]. By this binding, the drug becomes detoxified due to its no longer availability to bind with DNA. Similarly, the slow ligand exchange rate is responsible for poor DNA binding but no so effective, which also gives inertness to the drug [21,22]. Along with nature of ligand, the oxidation state of central metal Pt is also important, and plays a critical role in regulating the anticancer mechanism of Pt (IV) complexes [13]. The +4 oxidation state of Pt in Pt (IV) complexes makes them much more inert than their +2 state counterparts, due to a higher effective nuclear charge and greater crystal field stabilization energy [13]. With this background several scientist worked in field of anticancer chemistry of Pt for both its II and IV complexes. Thus, the SAR to understand the anti-tumor mechanism of related *cis* oriented complexes assumed great significance and was carried out by *Cleare and Hoeschele* with leaving and non-leaving groups of ammines regulating their anti-tumor activity [23,24]. Many *trans* oriented Pt complexes with planar ligands like iminoether and aliphatic amine have also been reported to possess promising antitumor activity [25]. Therefore, by observing anticancer activity of *trans* oriented complexes, their mechanism became an interesting point. In this context, many studies reveal that in comparison of *cis*-platin, the *trans*-platin undergoes aquation four times faster due to quicker ionization that makes it more susceptible for reaction with cellular constituents, and cause toxicity or diminish cancerous activity [26]. Apart from antitumor Pt (II) complexes, the bis (acetato)amminedichloro (cyclohexylamine)-Pt (IV), commonly known as satraplatin was the first platinum (IV) complex to be used as an anticancer agent [27], as shown in Figure 6. Satraplatin resists therapeutic deactivation kinetically in the acidic medium of the stomach and could thus be taken orally [27]. For further investigation on anticancer mechanism of Pt (IV) complexes, several analogous complexes were designed on basis of *cis* configuration and tested against cancer *in vitro* and *in vivo* both. Many experimental studies have also been revealed that the Pt (IV) compounds are kinetically more inert than Pt (II) which is a cause of enhanced their anticancer potentiality [27].

It was believed that during DNA binding, the Pt (IV) was getting reduced into Pt (II) species, active for binding, and by amending lipophilicity at axial ligand sites of satraplatin, the toxicity could be reduced this brought an increasing interest in development of Pt (IV) complexes [27]. With these aspects, several Pt (IV) complexes containing iminoether and branched amines as ligands were synthesized, and their anticancer studies inferred them greater efficient lower toxic than cisplatin [26,28,29-32]. The Pt (IV) complexes show greater antitumor activity due to inertness when compared to Pt (II) complexes which is explained by ligand substitution mechanism, and with this reason Kelland et al. developed many platinum (IV) complexes and tested against tumor cell lines [33-35]. Thus, the cisplatin and satraplatin were established as potential anti-tumor agents to fight cancer in the form of Pt (II) and (IV) complexes respectively as anti-tumor agents. Above mentioned all aspects make Pt (II) and (IV) complexes clinically active, and thus, thousands of Pt complexes have been synthesized during the last decade but unfortunately many of them have not arrived in clinical trials [35,36].

Platinum (II and IV) complexes as antineoplastic drugs

Studies with *cis*-platin revealed the mechanism of action of Pt drugs, where *cis* configuration was found to be responsible for their anticancer potentiality, because, the cis-isomers of both Pt (II) and (IV) such as $[PtCl_2 (NH_3)_2]$ and $[PtCl_4 (NH_3)_2]$ respectively, interfered with the cell division while corresponding trans isomers were ineffective for the same [37]. Soon after, the activity of trans isomers were also reported by *Cleare and Hoeschele* for a large number of Pt (II) complexes but these were not so effective [38,39]. It was suggested that two good leaving groups in *cis* position were necessary for antitumor-activity. Therefore, some groups of Pt complexes were synthesized having resistance to tumor cells, such as that of Pt (II) trans- $[PtCl_2 (L) (L)]$, where L=pyridine-like ligands, and Pt (IV) complexes having formula cis- $[PtCl_2X_2 (L) (L)]$ where X=hydroxide or carboxylate ligands, L=ammine, and L=amine, trans- $[PtCl_2 (L) (L)]$ with L=alkyl-substituted amine and L= isopropylamine and trans- $[PtCl_2 (L) (L)]$ where L=iminoether ligand [40-55]. Alongside the discovery of cisplatin as a chemotherapeutic agent, its many properties such as that of poor solubility and narrow spectrum of activity emerged as numerous drawbacks resulting nephrotoxicity, neurotoxicity, emetogenesis and others [10]. Drawbacks of the cisplatin proved to be solid reasons for the exploration of other anticancer Pt complexes with improved pharmacological properties. On the basis of orientations either *cis* or *trans* similar to that of *cis*-platin or *trans*-platin, several anticancer square planar Pt (II) complexes were synthesized [45-48]. Due to the inactivity of transplatin, the derivatives with a *cis* configuration were mainly focused having either one bidentate or two monodendate non-leaving groups (usually consisting of a simple amine or ammonia) and one bidentate or two monodendate leaving groups. Consequently, thousands of Pt complexes with *cis* configuration were screened for their anticancer activity [24]. Also, the cis oriented complexes drew significant attention due to their strong activity against cancer with examples including those of *cis*-platin and *cis*-diammine (1, 1-cyclobutanedicarboxylato) Pt (II), routinely known as carboplatin (Figure 7). After the success of *cis*-platin at the clinical level, the carboplatin was used as the first follow-up agent of Pt (II) to enter worldwide clinical use, which contained bidentate dicarboxylate instead of two chloride leaving groups [52].

Results and Discussion

The anticancer mechanism of carboplatin was found to be analogous with that of cisplatin, and its DNA adducts were also found similar to the *cis*-platin. With less severe side effects, it was effectively found fit for treating ovarian cancer but ineffective against testicular, head and neck cancers. With an urgent need to minimize the side effects of Pt drug, alongside that of *cis*-platin and carboplatin; three other clinically approved drugs developed in that duration namely nedaplatin, heptaplatin and lobaplatin as illustrated in Figure 8.

Unfortunately, no dramatic clinical benefits were observed for these drugs over *cis*-platin. Further a Pt drug, oxaliplatin as illustrated in Figure 5, was synthesized whose clinical advantage showed a different spectrum of activities where it was effective against colorectal cancer, a disease not treatable using *cis*-platin or carboplatin [52,53].

The predominant DNA adducts of oxaliplatin were found to be analogous to *cis*-platin as 1, 2 intrastrand adducts. The nedaplatin, heptaplatin and lobaplatin were synthesized by considering oxaliplatin activity but these were not found to be much effective. Nowadays, at least seven further Pt drugs are currently in the phase of commercial development [54] such as those of satraplatin, miriplatin, prolindac, BP-C1, cisplatin lipid complex (Transave), aroplatin, iproplatin (Figure 9) and picoplatin, however, amongst them satraplatin and aroplatin are Pt (IV) species. Most of these agents were aimed at addressing the issues of administering a cisplatin-like or oxaliplatin-like effect but closest to the market appeared to be satraplatin (Figure 6), which is a Pt (IV) agent, and can be taken orally [54]. Similarly, oxaliplatin (Figure 5) formed DNA adducts like those of *cis*-platin due to the loss of acetate ligands, so, it was found to be more effective than others. This was used as prednisone (an anti-immune/anti-inflammatory agent) against hormone refractory prostate cancer [54]. Similarly, picoplatin, as shown in Figure 10, was developed and found to be active against some cisplatin-resistant cancers [55]. Activity of these drugs confirmed that modifying ligands on Pt can be retained in the DNA adducts.

Further, the basis of aroplatin and miriplatin synthesis was their liposomal delivery which increased a drug's bioavailability and, in some cases, liposomes were also found to be accumulating at the tumor sites by enhancing the vascular permeability and subsequent retention [52-56]. The nanoparticles of liposome-cisplatin (lipoplatin) and others were also explored to localize their delivery to the lungs for the site-specific treatment of lung cancer with a similar rationale [57]. All above mentioned drugs are in the clinical phase of development, like those of "classical" Pt-drug structures containing a square-planar Pt (II) centered two cis-amines, and two leaving groups. While, in case of satraplatin (Pt IV), was converted into classical Pt agent in the body during activation [52]. Not only the cis configurator complexes showed anticancer activity but also trans complexes of Pt (II) showed anticancer activity which could be enhanced using sterically hindered ligands that reduce the rate of replacement of the chloro ligands; it was an argument of Farrell [58]. In this context, the greater cellular uptake was found for pyridine containing complexes than that of the ammine complexes which come to be known through studies on L1210 cell lines (leukemia cells), and it was also supported by their DNA binding study [59]. It was due to, sterically hindered activity of the planar pyridine ligands to the axial positions of the platinum center. This steric feature enhances the reactivity of the Pt not only towards DNA but also towards glutathione (L-glutamyl-L-cysteinylglycine, GSH) and other sulphur-containing biomolecules [60]. However, the presence of pyridine ligands significantly slowed down the reaction but trans configurator complexes were found to be more effective than that of their cis configurator counterpart [61]. Thus, the several series of trans Pt complexes containing ligands such as pyridine, N-methyl imidazole or thiazole and quinolone were developed by Kauffman and Cowan [58,62,63]. Many antitumor trans Pt (II) complexes having pyridine, quinoline, thiozole, bypridine ligands were synthesized and investigated for their *in vitro* cytotoxicity. Also, some of them were modest but showed significant *in vivo* activity [64-66]. Many trans active complexes with iminoether ligands were investigated by *Coluccia* which were found to be more active than their cis analogues [67-69]. To confront cancer, several charged complexes were also investigated, for instance, meso-l,2-bis (2,6-dichloro-4-hydroxyphenyl)-ethylenediamine] diaqua-Pt (II) sulfate was designed [70] (Figure 8) on the basis of its ability to combine the cytotoxic cisplatin with an estrogen receptor (ER)-binding ligand for targeting to ER+ mammary tumor cells. This Pt complex selectively inhibited the growth of ER mammary tumors in rodents [70].

Many charged complexes were also developed and studied via *in vitro* and *in vivo* analysis such as [PPh_3Me] [$PtCI_3$ (caffeine)], [Pt (NH_3)CI_3]$^-$, [Pt (NH_3 (4-Br-pyridine)CI^+, but they were less active than non-charged molecules [71]. Alongside, complexes with non-amine neutral ligands were synthesized, and found to be active in their *in vitro* and *in vivo* trials [71]. For example, a series of pyridyl- and quiuoline-amines or imines have been investigated for their *in vitro* activities which showed an activity comparable with that of cisplatin [71]. Deacon and colleagues described an even more unusual series of complexes those were active against Pt resistant and human tumor cell lines [72]. A continuing interest in the development of new Pt complexes that were supposedly less toxic and had a broader spectrum of activity, slowly gathered upon. It comes to be known that variations in the nature of the amine/ammine can have a significant effect on the activity and toxicity of these complexes [72]. Several Pt complexes with N-heterocyclic ligands, such as those of imidazole, thiazole, benzimidazole, benzoxazole and benzothiazole have been reported for their significant anticancer activity [73-82]. On the same line, numerous Pt (II) complexes bearing 5 (6)-H or –CH -2-phenyl or - (29-pyridyl) or -mercaptomethylbenzimidazole ligands were synthesized and screened against HeLa (Human epithelial carcinoma cell line), MCF-7 (Human breast cancer cell line) and RD cell line (Tumor of the muscles) where they showed potent antitumor activities [83-90]. A special class of complexes was formed and named as "Pt Blue", which were formed upon the reaction of *cis*-diaquoplatinum (II) complexes with amides, such as those of acetamide, uracil or thymine [91]. Initial studies indicate that these complexes were very active antitumor agents but clinical trials could not confirm this [92]. The structures of these compounds remained highly mysterious for a long time, but recently the structure of a blue Pt complex formed

with 2-pyridone has been resolved by single-crystal X-ray diffraction [93]. There have been many Pt (II) complexes such as purine and pyrimidine complexes, nucleoside complexes, (poly) nucleotide complexes that were synthesized in the last few decades for their anticancer studies [94-97]. Many Pt (II) complexes were synthesized and screened against solid tumor cell lines under standard pH screening conditions as well as in the acidified cell culture medium [98]. In this context, *Markus* Galanski et al. synthesized a Pt (II) complex namely bis (2-aminoethanolato-N,O), its binding behavior to 50-GMP as well as cytotoxicity against cisplatin were investigated *via* both *in vitro* and *in vivo* routes, where these complexes revealed cytotoxicity [98]. Recently, it was reported that pyrazoles and substituted pyrazoles Pt complexes exhibited lower toxicity than cisplatin [99,100]. Therefore, *Tebogo* Segapelo et al. used pyrazolyl–pyridine ligands to prepare new Pt (II) complexes and investigated their anticancer activity against HeLa cells, where some of them showed positive activity [101]. The Pt (II) complexes with chloroquine were also described which were shown to display anticancer activities as well as a protective effect [102-110], and these were reported as antitumor agents against MCF-7 and SKBR-3 (Breast cancer cell line). The Pt (II) complexes with Josiphos ligands like (R)-1- [(S)-rocenyl] ethyldicyclohexylphosphine and Walphos ligands like (R)-1 [(R)-2- (20-diphenylphosphinyl) ferrocenyl] ethyldo (bis-3,5 trifluoromethylphenyl)phosphine) were also reported as care of cancers where these were tested against HeLa cell, and showed better cytotoxicity in compare to cisplatin [111]. Recently, Yanyan Sun et al. investigated the cytotoxic effect of alkyl groups as hindrance for synthesizing some Pt (II) complexes of N-monoalkyl-1R, 2R-diaminocyclohexane derivatives where *in vitro* biological evaluation of these complexes revealed their antitumor activity to be in a close relationship with the shape of alkyl groups [112]. A series of Pt (II) complexes with thiosemicarbazones ligands were synthesized and *in vitro* studied, where some of them exhibited best cytostatic activities against human cervix carcinoma cell line [113]. In order to improve the pharmacological profile, several new acridine based tethered (ethane-1,2-diamine) Pt (II) complexes were synthesized which were connected by a polymethylene chain [114]. Their *in vitro* cytotoxicity was assessed in human colon carcinoma cancer cells lines such as those of HCT 116, SW480 and HT-29, where higher cytotoxic effect was displayed according to the size of the polymethylene linker [114]. The Pt (II) complexes with 2,9-disubstituted-6-benzylaminopurines were developed by Michal Malon and coworkers [115]. These were screened for their *invitro* cytotoxicity against G-361 (human malignant melanoma), HOS (human osteogenic sarcoma), K-562 (human chronic myelogenous leukemia) and MCF-7 cell lines, all the complexes were significantly active in comparison of cisplatin and oxaplatin [115]. In order to improve the medicinal benefit, the mix of ammine/cyclohexylamine Pt (II) complexes with 1- (substituted benzyl) azetidine-3, 3-dicarboxylates as leaving groups were synthesized and screened against HepG-2 (Liver hepatocellular cells), MCF-7, A549, HCT-116 cancer cell lines, where they showed potent cytotoxicity [116]. The Pt (II) complexes with chelating dinitrogen ligand such as 4,7-dimethyl-1,10-phenanthroline were synthesized and their DNA binding study revealed that they were anticancerous in nature [117]. A new mononuclear Pt (II) complex containing 4,4-dimethyl-2,2-bipyridine and 4,7-diphenyl-1,10-phenantroline has been recently synthesized, where their DNA binding study demonstrated them as anticancer agents [118]. An alternative of the existing anticancer Pt (II) complexes was needed due to their toxicity, which was accomplished with the development of Pt (IV) complexes. To evaluate a variety of preclinical tumors, along with Pt (II) complexes many analogues of cisplatin containing Pt (1V) were synthesized [119-124]. Pt (IV) complex has an octahedral geometry and undergoes slow ligand substitution reaction as compared to that of Pt (II) analogues. To be suitable for antitumor activities, the Pt (IV) complexes undergo a reaction with reducing agents present in body liquids which make them kinetically more labile, and therefore, they are designated as pro-drugs [125,126]. There are many evidences showing that Pt (1V) species can enter in cells and react with isolated DNA directly, and also these drugs bind to simple or monomeric nucleic acids without the addition of any reducing agent [127,128]. Several Pt (1V) molecules could reach intracellular DNA without their reduction and modify it in a specific way which causes an antitumor effect [129]. However, Pt (IV) complexes are more effective when compared to *cis*-platin but these have lower reaction rates in contrast to *cis*-platin which is a drawback [127-129]. The *cis*-platin binds to DNA within 48 hours at 37° C while Pt (IV) compound such as oxoplatin (Figure 12), binds to DNA after 12 days under identical conditions [130].

Zak et al. developed another Pt (IV) drug, (LA-12, Figure 13), and tested it against cisplatin resistant tumor lines, then found that LA-12 demonstrated lower IC_{50}'s as compared to that of cisplatin [131]. Further, tetraplatin as illustrated in Figure 14, another Pt (IV) analogue, entered phase-I clinical trials for toxicity assessment and was tested to determine a maximum tolerated dose. Nausea, vomiting and myelosuppression were moderate, but neurotoxicity was symptomatic in all the patients which caused significant functional impairment in some patients, thus, ending further clinical trials [132].

Several nitro-platinum (IV) complexes were also synthesized to confront the risk of systemic toxicity and ensured increased anti-tumor activities as analogous to cisplatin [133]. A trans Pt (IV) complex containing quinoline ligand was synthesized which had a better *in vivo* anticancer activity than that of cisplatin [134]. Kelland et al. investigated several Pt (IV) complexes like trans [Pt (NH_3) (RNH_2)Cl_2] and [Pt (NH_3) (RNH_2) (OH)Cl_2] where R = cyclohexyl group, and these were found to be highly active *in vitro* and *in vivo* [135]. The early report of Harder and Rosenberg on the inhibition of DNA synthesis of cells treated *in vitro* with the Pt complexes also included cis- and trans-Pt (NH_3)Cl_4 [136]. Several carboplatin derivatives Pt (IV) complexes such as carboplatin succinate, hydroxyl carboplatin, carboplatin monosuccinato, carboplatin monoacetato and carboplatin amino succinato were developed and tested for their cytotoxicities [137]. A series of estrogen tethered Pt (IV) complexes were synthesized to reduce the cytotoxicity to carboplatin like cis, cis,trans-diamminecyclobutanedicarboxila tebis-(17- (N-carbonylmethylsuccinate) estradiol-3-benzoate) Pt (IV). These complexes were screened against MCF-7 cell lines, and some of them showed positive response [137]. Many research groups exploited the cytotoxic property of folic acid,

therefore, several folic acids conjugated Pt (IV) complexes were developed such as Pt (IV) carboplatin monofolate, and tested against HeLa cell, but they did not show expected results [137]. The Pt (IV) complexes were also conjugated with cancer targeting peptide chlorotoxin for a promising strategy to selectively target cancer tissue [138], as illustrated in Figure 15, which was reported by *Graf* et al. These were tested *in vitro* on HeLa, MCF-7 and lung (A549) cancer cells, where these were found to be effective [138] (Figure 11).

More recently, N,N′-methylene modified cyclohexyl ethylenediamine-N,N′-diacetate type ligands containing Pt (IV) complexes have been reported and tested *in vitro* on human melanoma A375, human glioblastoma U251, human prostate cancer PC3, HCT116, mouse melanoma B16 and mouse colon cancer CT26 and CL25 cells [139]. These complexes revealed stronger antitumor potential with preserved efficacy against cisplatin resistant lines and less toxicity towards their nonmalignant counterparts [139]. A series of bis (carboxylato) dichloride (ethane-1,2-diamine) platinum (IV) complexes were investigated with respect to their lipophilicity, cellular accumulation in cancer cells *in vitro* such as CH_1, HeLa, SW480 and SK-OV-3 cells and they possessed cytotoxicity [140].

DNA binding activity (DBA)

In cellular processes such as DNA and ribonucleic acid have vital importance in regulating cellular processes, because they are fundamental entity of biological systems [141]. There are 46 chromosomes in human cells each of which consists a single DNA duplex. DNA molecule is a polymer of nucleotides units which consists of a phosphate group, a 2-deoxyribose sugar and a heterocyclic amine base, as has been illustrated in Figure 16.

Through a sugar moiety, the deoxyribose sugar and phosphodiester repeating units are attached to the adenine and guanine or cytosine and thymine which have been illustrated in Figure 17. In a helix conformation, the sequence of nucleotides is arranged specifically, so that it matches with the complementary

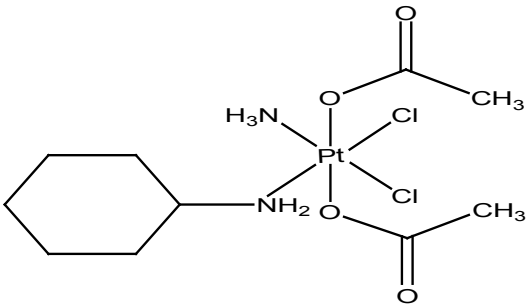

Figure 6. *Satraplatin: Anticancer Pt (IV) complex.*

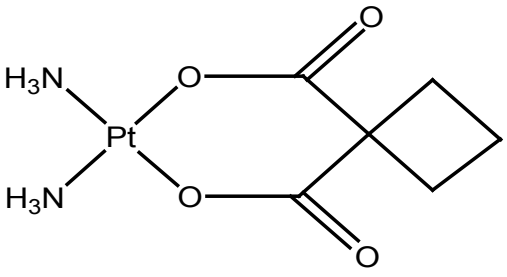

Figure 7. *Structure of Carboplatin.*

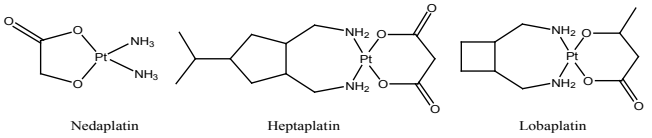

Figure 8. *Structures of Nedaplatin, Heptaplatin and Lobaplatin.*

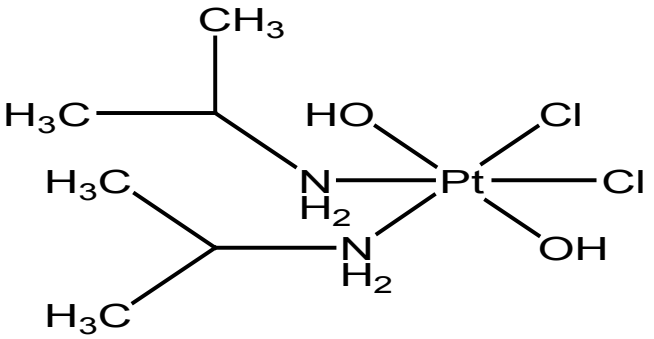

Figure 9. *Structure of Iproplatin: Pt (IV) complex.*

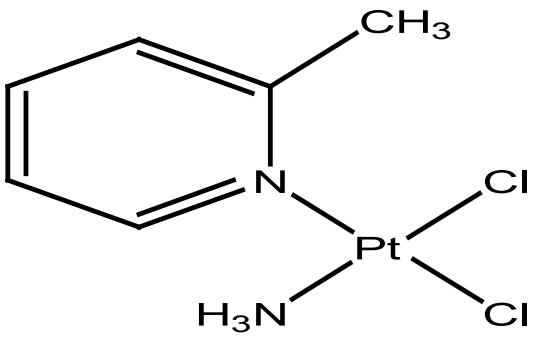

Figure 10. *Structure of Picoplatin.*

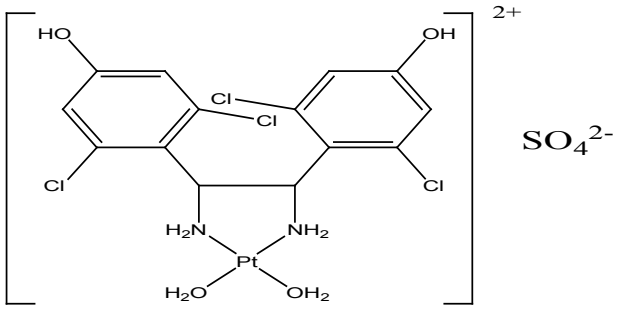

Figure 11. *Charged Pt complex: meso-l,2-bis (2,6-dichloro-4-hydroxyphenyl)ethylenediamine] diaqua-Pt (II) sulfate (meso-6-$PtSO_4$).*

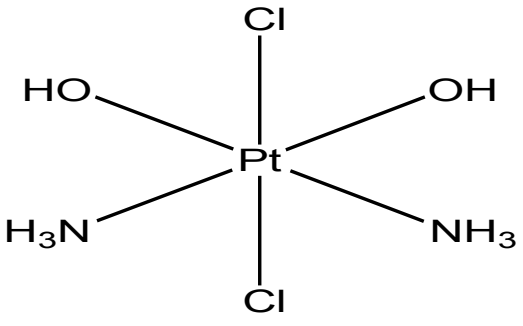

Figure 12. *Structure of Oxoplatin: Pt (IV) complex.*

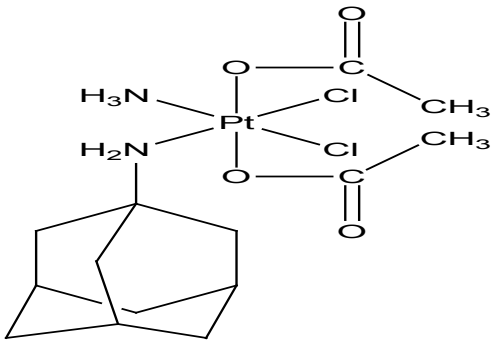

Figure 13. *Structure of LA 12 Pt (IV) complex.*

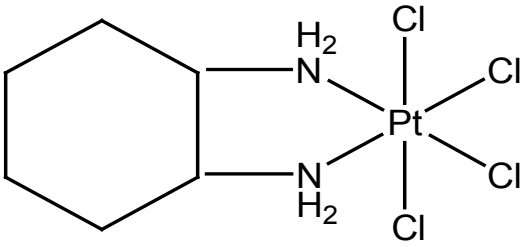

Figure 14. *Structure of Tetraplatin.*

one to form a double-helix. The bases pointing towards the center of the double-helix are held together by hydrogen bonds and base stacking while the phosphates are located on the more solvent accessible surface of the helix. The sequence of bases such as adenine-thymine and guanine-cytosine of purines and pyrimidine respectively, determines the genetic coding [142].

The genetic information of the cell is held by DNA as genome which is surrounded by the chromosomes. Major cellular processes such as replication and transcription of the DNA occur inside the nucleus. These processes require the genomic information, and therefore, if the DNA of cancer cells could be targeted, then there is a possibility to stop cell division, and hence kill the cancer. Thus, medicinal trials such as *in vitro* and *in vivo* studies of Pt complexes have been performed since last few decades and highlight that a substantial activation energy barrier in required to identify their anticancer activity and shepherding their trial to clinical levels [143]. Along with *in vitro* and *in vivo* studies, some excellent metallo-drug biomolecule interaction models have been developed to understand that how metallo-drugs are involved in curbing cancer that indicate a new role of metallo-drug interaction in developing therapeutic strategies [144]. For binding with DNA, the Pt complex may undergo intercalation or covalent or coordinate binding with the DNA structural units.

Intrastrand and interstrand binding mechanism

Discovery of the anticancer *cis*-Platin stimulated the need to investigate the action mode of Pt complexes. The biological target of Pt complexes was one of the fundamental issues that needed to be understood. Intentionally, the nature of Pt drug binding to the DNA has been focused as a target for inhibition of cancer cell growth [145]. In this context, numerous research efforts have been evolving over the past several years for a fairly detailed understanding of Pt complexes binding to DNA, which causes DNA to be modified [146]. The physical nature of DNA importantly reflects the metal DNA interactions mechanism, where, low pKa value of the phosphate groups makes it highly charged molecule. That is why; it has high charge density on itself which is liable to attract oppositely charged ions such as positively charged metal complex and repel negatively charged ones such as chloride ions. In this respect, nucleobases act as ligands or reactive species and coordinately or covalently bind to the positively charged metal species [147]. On the basis of cis and trans configuration of Pt complexes, the mode of DNA binding is specifically influenced. Both the complexes are neutral, thermodynamically stable, and known to retain their co-ordination environment in blood plasma [148]. With an example of cisplatin, a DNA binding mechanism has been shown in Figure 16. Many studies reveal that cisplatin and its isomers penetrate cell membrane through passive diffusion or active transport mechanism [149]. Cisplatin encounters a relatively high concentration of chloride ions (100 mM) in the blood stream which suppresses hydrolysis and maintains the compound in a neutral state. Thus, the chloride ion concentration drops to near about 4 mM in the cytoplasm Figure 18. The implication is that drug (cisplatin) undergoes hydrolysis when it passes through the cell membrane into the cytoplasm. In this process a range of aquated and non-aquated products are formed [150] in which the positively charged Pt hydrolysis product is electrostatically attracted by the negatively charged DNA macromolecule.

It was observed that, a monofunctionally Pt- DNA adduct is formed at the N7 position of guanine or adenine through an intrastrand binding, which reacts further to form a bi-functional adduct through interstrand binding at the N7 position of the nearby guanine, and seldomly to the adenine base [15]. In an intrastrand crosslink, the nucleotide bases are on the same DNA strand as opposed to an interstrand cross-link, whereby the coordination occurs with the bases being on opposite DNA strands, as depicted in Figure 19. Both the binding modes have been evidently proved where the products are chromatographically identified and characterized with ^{1}H NMR spectra [151]. Thus, it is clear that transplatin analogue is stereo-chemically imperfect to get involve in intrastrand binding. It has not been unequivocally established as to which of the drug/DNA adduct is responsible for the cytotoxic activity. Conventionally, it is believed that the intrastrand or interstrand bifunctional adducts are responsible for anticancer activity of Pt complexes [152]. Earlier, the interstrand adducts were favored partly because they could be readily measured, and partly because it was easy to imagine how an adduct links the two strands of a DNA molecule during its replication [153]. The cytotoxic activity of cisplatin due to intrastrand adducts is further supported by the cytotoxic study on HMG proteins which is a DNA protein, confirmed *via* 1,2-intrastrand cross-links, and therefore can regulate the processing of the main cisplatin lesion by altering the cellular sensitivity to the drug [154]. The DNA damage is induced by cisplatin which is recognized by HMG proteins; however its trans analog does not exhibit the following activity due to its geometrical restriction [155]. A method for the screening the combinatorial mixtures of potential Pt antitumor drugs, based on the ability of Pt compounds to bind with HMG proteins has also been reported earlier [156]. In both covalent and coordinate bonding modes, the same mechanism is involved the only difference being that the bases of DNA act as electron

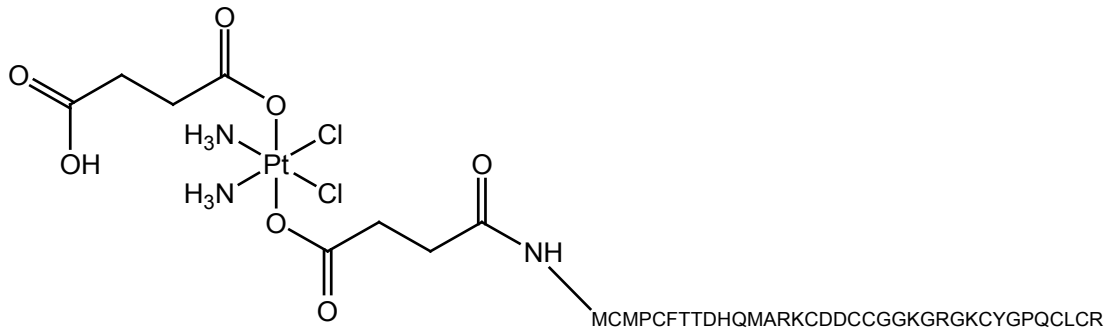

Figure 15. *Peptide chlorotoxin conjugated Pt (IV) complex.*

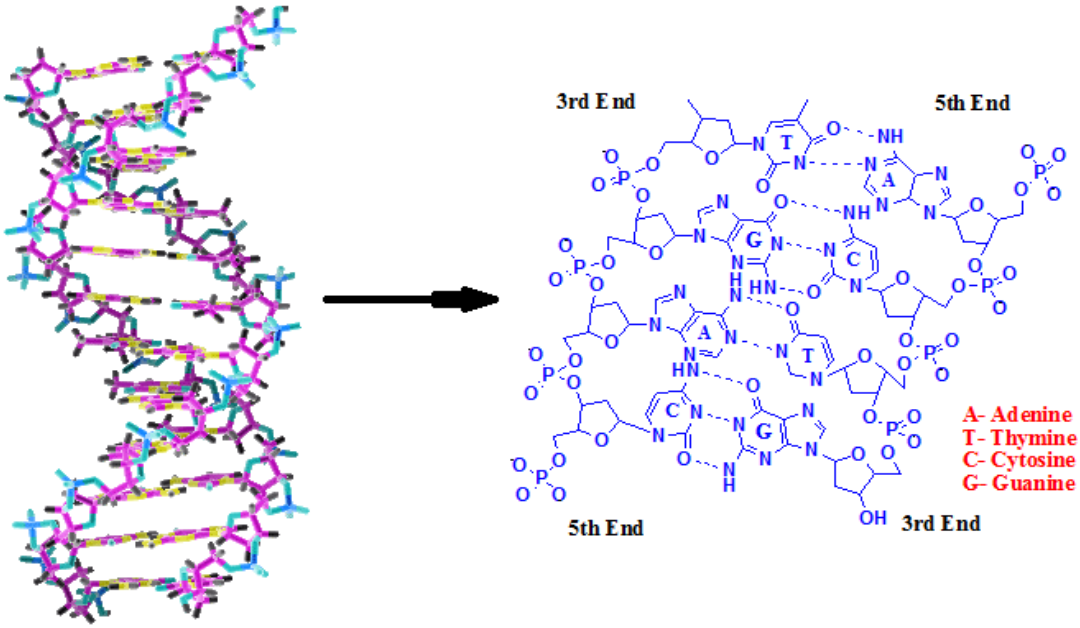

Figure 16. *General structure of DNA.*

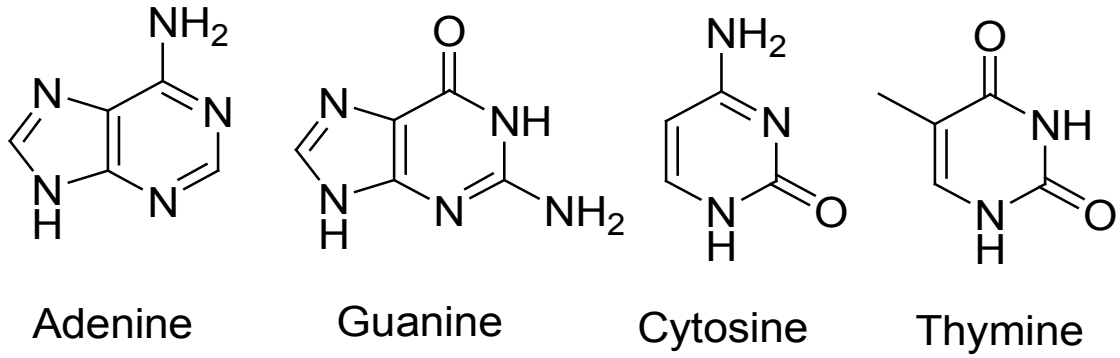

Figure 17. *Structures of nitrogen bases of DNA.*

pair donor molecules or reactive species which coordinate or covalent with Pt complex.

Intercalating mode

Metal complexes containing σ-bonded aromatic side armaments can act as dual-function complexes by binding DNA either by metal coordination or through intercalation [157]. The aromatic side arms introduce an intercalating mode for DNA binding that involves mutual interactions between aromatic arm and DNA helix. This has created much interest in the field of cancer chemotherapy to inhibit nucleic acid activity, and lead to the activity like those of mutagens, antibiotics, antibacterial, trypanocides, schistosomicides and antitumor agents [158]. Intercalation between DNA helix and aromatic organic intercalators such as ethidium bromide (Figure 20), acridine and benzopyrene etc. has been studied to prove intercalation through hydrogen bonding or electrostatic interaction [159].

Many bulky intercalators have also been reported which showed antitumor activity [160]. There are two major modes of intercalation investigated: classical and threading intercalation where classical intercalation involves binding to DNA duplexes

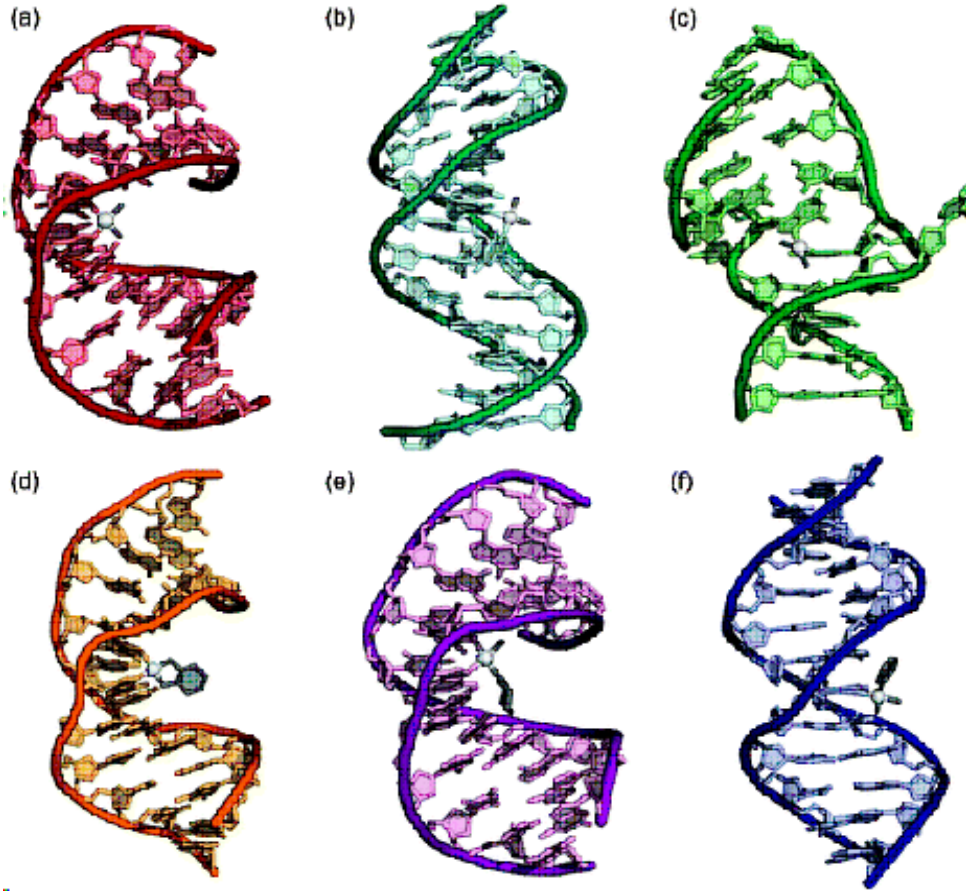

Figure 18. *Structures of double-stranded DNA adducts of different platinum anticancer agents as determined by X-ray crystallography or NMR spectroscopy. (a) Cisplatin 1,2-d(GpG) intrastrand cross-link (PDB 1AIO). (b) cis-platin 1,3-d(GpTpG) intrastrand cross-link (PDB 1DA4). (c) Cisplatin interstrand cross-link (PDB 1A2E). (d) Oxaliplatin 1,2-d(GpG) intrastrand cross-link (PDB 1PG9). (e) Satraplatin 1,2-d(GpG) intrastrand cross-link (PDB 1LU5). (f) cDPCP monofunctional adduct (PDB 3CO$_3$).*

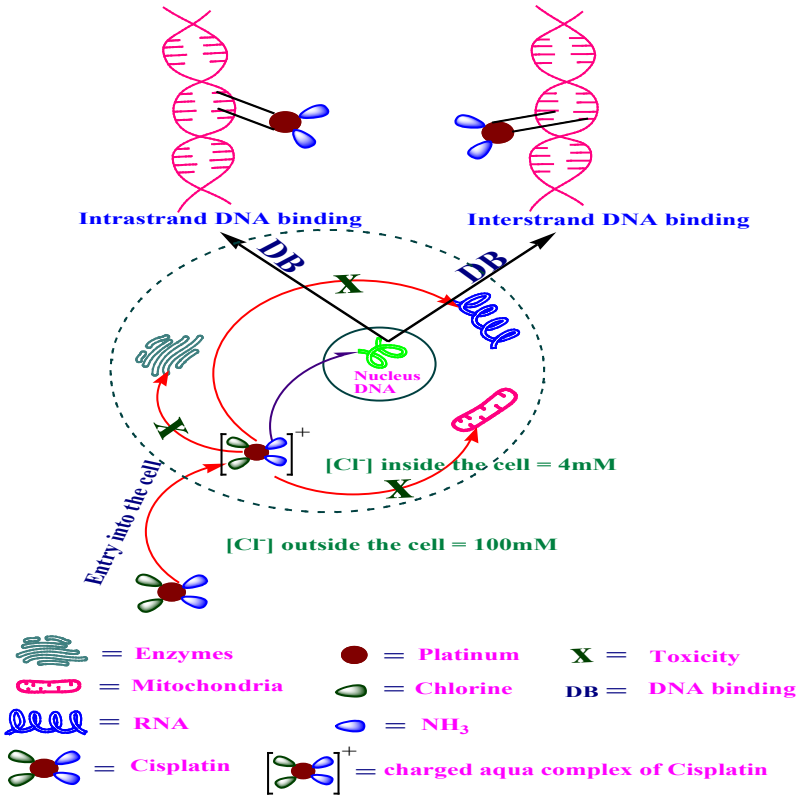

Figure 19. *Depiction of DNA binding mechanism of Pt complex.*

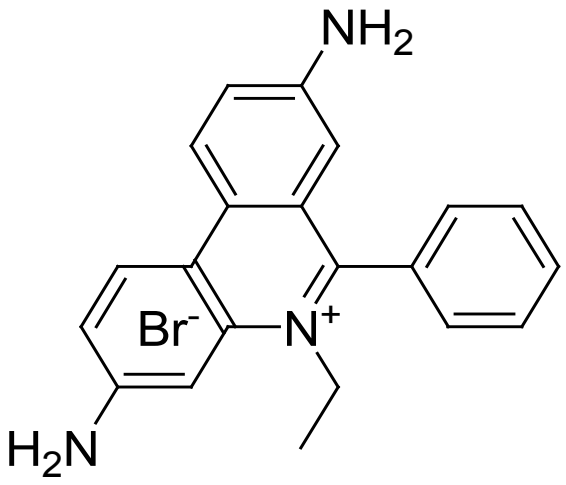

Figure 20. *Structure of Ethidium bromide: An organic intercalator.*

with aromatic system inserted between base pairs, and form intercalation site top to bottom [161]. On the other hand, a threading intercalator interacts strongly with both the minor and major grooves of DNA simultaneously giving distortion to the DNA structure [162]. Metal complexes such as square-planar Pt (II) and octahedral derivatives can have intercalative interactions with DNA by relatively inert coordinate bonds saturated with aromatic ligands or intercalation into DNA, which mainly involves the aromatic ligands [163]. Lippard et al. have shown that square-planar containing aromatic fragments bind to DNA by intercalation without coordination [164,165].

Brief on imaging of cancer

Diffusion-weighted MR imaging has evolved as a promising tool in the evaluation of the breast cancer. It is commonly used forthe differentiation of malignant tumors from benign masses, because breast cancer has lower ADCs compared to benign lesions and normal breast tissue [166]. It has been used for the characterization of breast cancer and the detection of tumor extension. Diffusion-weighted MR imaging is potentially useful forthe early assessment of response to treatment. In this regard Ahmed Abdel Khalek Abdel Razek et al. [167] have discussed about diffusion-weighted MR imaging playing a role in the differentiation breast cancer from benign lesions, the characterization of malignancy, and the detection of tumor extension. The apparent diffusion coefficient of breast cancer is correlated with tumor cellularity and some prognostic factors of breast cancer. That can be used for the differentiation of recurrent tumors from post treatment changes and monitoring of patients after chemotherapy. Diffusion-weighted MR imaging is used for the characterization of breast mass, diagnosis, and the grading and staging of breast cancer, as well as prediction of the responses of patients with breast cancer to chemotherapy. Sepahdari et al. [168] confirmed that benign and malignant orbital tumors have significant differences. Ahmed Abdel Khalek Abdel Razek [169] has also reported that MR imaging is essential for diagnosis of neoplastic and non-neoplastic lesions of the brain and the spine in patients with NF-1. This information is essential for treatment planning and monitoring patients with NF-1. Also the same author discussed diffusion MR imaging offers functional imaging of lung cancer due to its ability to probe the tumoral microstructure, which is complementary to routine anatomic MR imaging of the chest. The potential value of diffusion MR imaging is in its detection, characterization, grading and staging of lung cancer. In addition, it has been used for the diagnosis and characterization of mediastinal and pleural tumors. It can be obtained in a short time without injection of contrast medium. The gradual development and standardization of imaging sequences and widespread research will make diffusion MR imaging of the chest more suitable for clinical applications in the future [170].

Conclusion

This review concludes the historical importance of Pt metal complexes and provides brief information about the clinical trials conducted for different Pt metal complexes. Not only had the square planer complexes, the octahedral complexes changed the development scenario of anticancer agents. The importance of two extra ligands and higher oxidation states was the turning point in the research and development of Pt complexes. The role of toxicity of these complexes was considered as reason for the saturation of this field of research. But the binding ability potential of these complexes were well addressed and found very impressive and this is the reason for the current development of this field. Platinum complexes have been found effective activities against cancer since long time. Especially, the complexes have exhibited prominent anticancer activity against solid tumour cell lines which correlates with their DNA interaction analysis. Comparative studies of Pt (IV) and Pt (II) have suggested the stronger intercalating nature and anticancer activity for Pt (II) complexes.

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