Review Article

Exploring the DNA Binding Mechanisms of Platinum-Based Chemotherapeutic Agents: State of Art and Perspectives of the Candidates

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Abstract

Metallodrugs offer potential for exceptional instrument of medication activity dependent on the decision of the metal, its oxidation express, the sorts and number of organizing ligands and the coordination geometry. The ongoing advancement in the field of therapeutic bioinorganic science the same number of new ways to deal with the structure of imaginative metal-based anticancer medications is developing. The monometallic platinum complexes show multifunctional co-operations with DNA, RNA and proteins by means of platinum metal focuses and material as anticancer operators. A critical number of detailed platinum complexes display improved cytotoxicity just as tumor selectivity. Recent headway in the advancement of platinum-based complexes gives new headings to increasingly compelling medication improvement. This article represents an exhaustive survey of the improvement of platinum-based metal complexes including Pt(II) and Pt(IV) complexes, with therapeutic and biomedical applications. Instances of metal complexes and chelating agents currently in clinical use and preclinical advancements are featured.

Keywords: Cisplatin, oxaliplatin, heptaplatin, lobaplatin, Satraplatin, carboplatin, $[Pt(dpq)(dach)]^{2+}$ and $[Pt(phen)(dach)]^{2+}$

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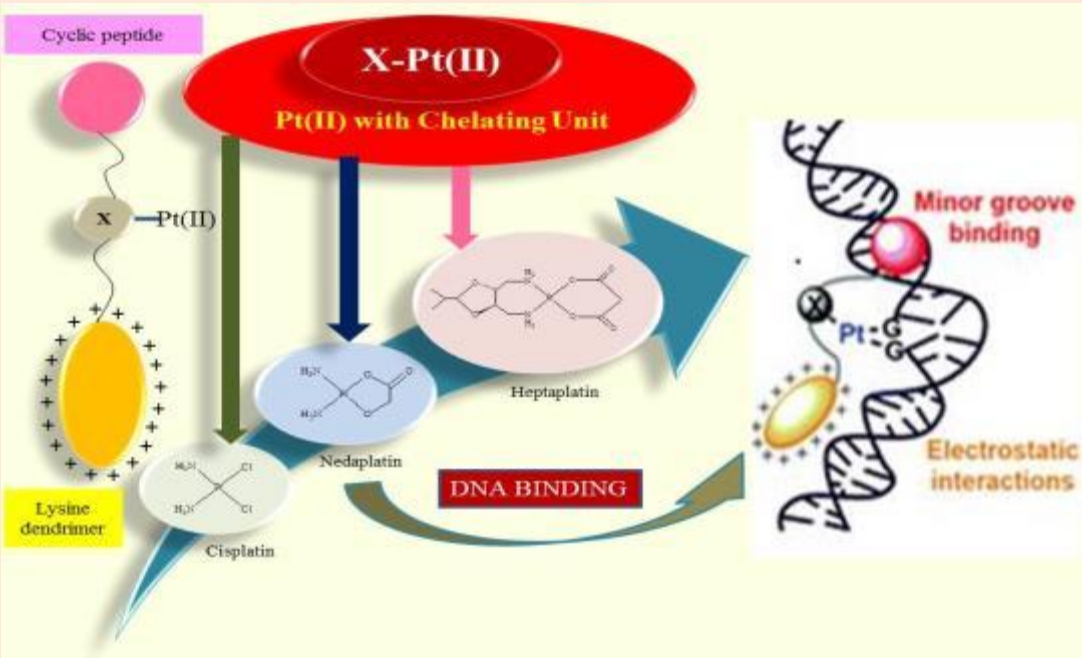

Introduction

Cancer, the second cause of worldwide mortality, can crudely be defined as a manifold of diseases where abnormal cells ensue, spread and proliferate uncontrollably. After the exposure of cisplatin, a large number of metal-based complexes with restorative applications have been examined. The quest for examining increasingly metal-based complexes proceeds for elective treatment techniques with improved adequacy and decreased side-effects. Platinum based complexes are generally utilized as chemotherapeutic specialists with a wide range of antagonistic to tumor exercises [1, 2]. To beat the reactions, tranquilize opposition of cisplatin, numerous new sterically hindered platinum

(II) and platinum (IV) complexes have been premeditated and tried throughout the years with a consciousness that their various nature of associations with DNA would upgrade hostile to tumor movement and constrict side-effects [3-6].

In the treatment of ovarian malignancy, the potential accommodating utilization of some platinum (IV) complexes had altogether higher cytotoxic impacts against human ovarian carcinoma cells than cisplatin [7]. The potential preferred position of platinum (IV) complexes over the mononuclear platinum (II) complexes is their low reactivity because of which the various cytotoxic side-effects diminish and the open door for the appearance to the unbiased cells increments. Some platinum (IV) complexes like $[PtCl_4(en)]$, more cytotoxic than cisplatin in vitro, yet it was very much endured in vivo with no observed side-effects.

Because of the counter tumor cytotoxicity, biocompatibility and potential for incitement of hostile to tumor immune response, some platinum (IV) complexes might be acceptable candidates in the field of biomedical science. This short review will x-ray the pattern in the quest for wide-spreadingbiological activity of platinum complexes and the desire for this interdisciplinary research region in medication.

Pt(II) complexes and applications

Cis-platin

There has been an immense enthusiasm for established researchers to create metal-based medicines/drugs after the exposure of cis-platin (**Figure 1**) having anticancer properties [8, 9]. Cisplatin restrains the replication of malignant cells by shaping covalent cross links with DNA, which alters its helical structure and anticipates restoration and replication, bringing about apoptosis [10]. Cisplatin covalently binds with DNA essentially through the N-7 atom of the guanine base attributable to its basicity and location on the exterior/surface of the significant groove [11, 12].

The X-ray crystallographic investigations of a cisplatin bound duplex DNA portion exposed that covalent binding of cisplatin to the nearby guanine causes the modification of the DNA double helix and a twist toward the significant groove [13]. The contortion brought about by cisplatin prompts the compression of the sugar phosphate spine, which at that point causes the sugar deposits on the 5' lateral of the platinum abrasion to pucker. These disfigurements prevent DNA replication and interpretation [11, 12, 14].

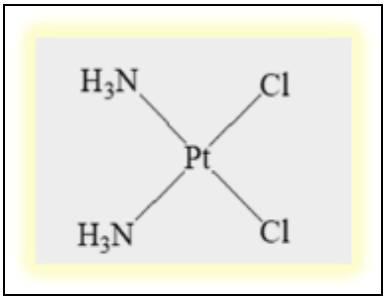

Figure 1 Cisplatin

For cisplatin, binding is reliant on the hydrolysis of its labile chloride ligands [15]. In the blood circulation system, high chloride ion concentration overwhelms this procedure, anyway once inside the cell, the lesser chloride ion concentration supports hydrolysis. Because of this hydrolysis, development of the complex $[Pt(NH_3)_2Cl(H_2O)]^+$ happens [15] (**Figure 2**).

The N-7 molecules of purine residues guanine and adenine are the most nucleophilic locales of DNA and these are especially platinated. Experiments exposed that cisplatin first formulate monofunctional adducts on DNA [16]. A cross connection on the DNA is molded by the rest of the chloride ligand which is relived for a subsequent guanine base. Such crosses links can emerge between deoxy-guanosines on a similar strand or on the different strands, offering ascend to intrastrand and interstrand DNA cross-links, individually.

Major operational changes in DNA can be brought about by the interstrand DNA cross-links. These progressions could be significant for cytotoxicity yet infrequently occur. The interstrand DNA cross-connect made by cisplatin unwinds DNA adjoining the platination site and twists the helix towards the minor groove where Pt is bound [17].

The assimilated obstruction and serious side-effects, for example, neurotoxicity and nephrotoxicity are the fundamental issues that limit the clinical utilization of cisplatin. Despite the fact that cisplatin is utilized to treat various malignancies, its utilization as an anti-cancer agent does have constraints. Cisplatin has symptoms including tumor obstruction, kidney toxicity, queasiness, retching, hearing loss, low white platelets, and bone marrow depressions [18-20].

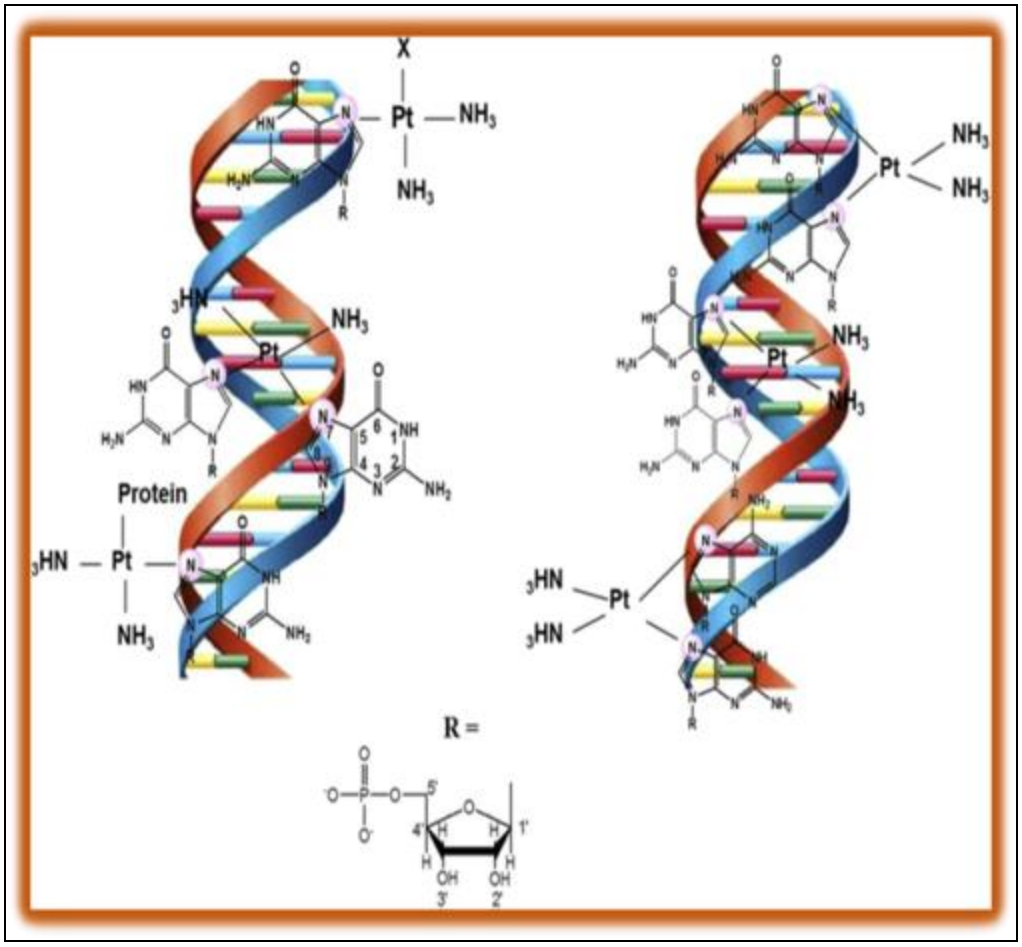

Figure 2: The different possibilities of coordination of cisplatin to DNA.

Carboplatin

Carboplatin is also a platinum(II) complex and has been certified by the US Food and Drug Administration as anticancer medicine [21-23]. Carboplatin (**Figure 3**) is a Pt(II) exasperate that varies from cisplatin by the presence of a bidentate dicarboxylate ligand as its leaving group as opposed to the more labile cis-platin's chlorides [24]. The second-generation platinum sedate carboplatin has in a general sense a similar system as the action to cisplatin towards tumor cells. It demonstrates lower systematic toxicity than that of cisplatin with respect to nephrotoxicity while looking after viability [25].

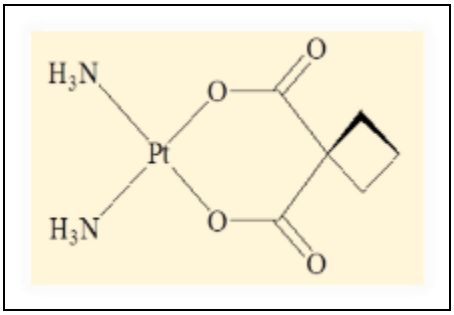

Figure 3 Carboplatin

The lower lethality of carboplatin has been certified to the slower hydrolysis of the cyclobutene-dicarboxylato ligand in contrast with the cis-chlorides of the cisplatin [25]. Blend of carboplatin with paclitaxel is utilized worldwide for the treatment of ovarian malignant growth [26]. Carboplatin has likewise discovered use in treating retinobastomas, neuroblastomas, nephroblastomas, and brain tumors, just as malignant growths of the head and neck, endometrium, cervix, testicles, breast, lung, bladder. Carboplatin doesn't show any extra action against cis-platin resistant cell lines and, as cisplatin, it experiences tumor resistance, which restrains the kind of malignant growths that can be dealt with [27].

Oxaliplatin

The third-generation platinum tranquilizer, oxaliplatin, was planned to diminish the reactions and the side effects caused by cisplatin and carboplatin. Oxaliplatin as appeared in **Figure 4**, is a Pt (II) complex which contains a bidentate 1,2-diaminocyclohexane (DACH) stable ligand and an oxalate as leaving gathering. The extended latent take-up of oxaliplatin diverged from cisplatin and carboplatin is a result of the higher lipophilicity of the DACH ligand. Oxaliplatin, as cisplatin, structures interstrand and intrastrand cross-joins with guanine base or some place in the scope of guanine and adenine bases, yet prompts unmistakable conformational turning on DNA due to the massiveness of DACH ligand [28].

Oxaliplatin is dynamic in mix with 5-fluorouracil and leucovorin for the treatment of colorectal cancerous growth of cells [29, 30], a disease where cisplatin and carboplatin have no elementary clinical activity [31]. The symptoms shown by the side-effects of oxaliplatin consolidate, neurotoxicity, hematological poisonous quality and gastrointestinal tract lethality [22, 32]. Neurotoxicity is the dose limiting toxic nature of oxaliplatin as it may cause various side-effects when larger amounts of anticancer drug can be taken.

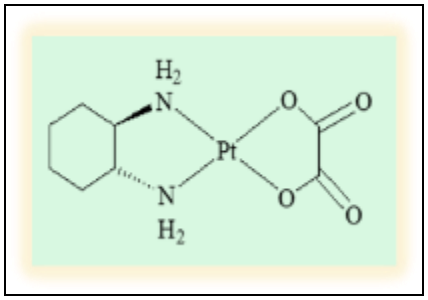

Figure 4 Oxaliplatin

Nedaplatin

Nedaplatin **(Figure 5)** is fundamentally like carboplatin. Because of resemblance in structure with cisplatin and carboplatin, it is normal that nedaplatin forms same sort of adducts as cisplatin and carboplatin. Diseases of head, neck and throat just as small cell lung malignant growth and non-small cell lung carcinoma can be treated by nedaplatin [33].

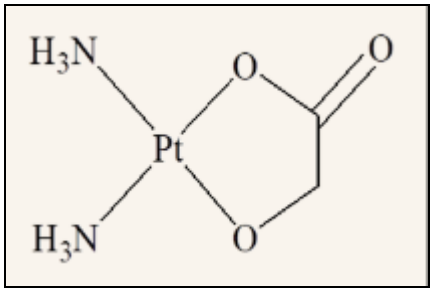

Figure 5 Nedaplatin

It has been discovered that nedaplatin is cross-resistant with cis-platin, yet less harmful [34]. No manifest benefit is showed up by nedaplatin over cisplatin in target response and for the overall survival. The nuclear segment data of antitumor effects of nedaplatin that this medicine reacts with guanine residues, yet it requires a reaction time around numerous times longer than that required by cisplatin.

Heptaplatin

Heptaplatin is a cisplatin subordinate. Heptaplatin, as shown in **Figure 6**, is a third-generation anticancer platinum complex having malonate as a chelating leaving group ligand, and also a chelating 2-(1-methylethyl)- 1,3-dioxolane-4,5-dimethanamine. A seven membered chelate ring is framed by the non-leaving ligand, giving the medication its conventional name. Heptaplatin has a more extensive range of anticancer action, inconsequential nephrotoxicity at the ideal/optimal dose and reasonable physicochemical properties, for example, high solubility [35]. In vitro investigations have exposed that Heptaplatin has high antitumor activity against different malignancy cell lines [35-37].

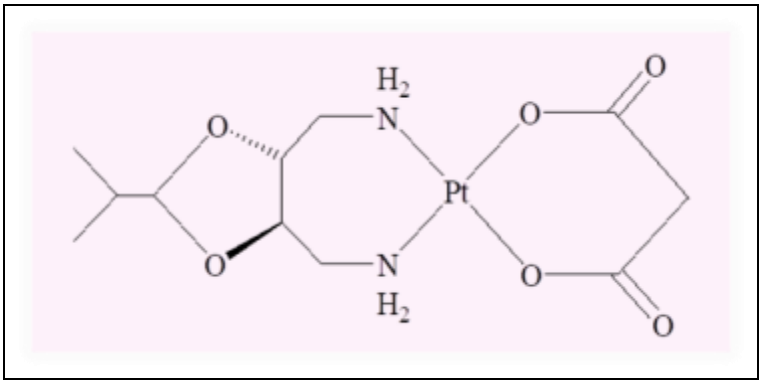

Figure 6 Heptaplatin

Lobaplatin

Lobaplatin **(Figure 7**) can be viewed as a subordinate of Heptaplatin in which a cyclobutane ring is stuck to the seven-membered chelate ring rather than a functionalized dioxolane. Lobaplatin is a diastereomeric blend of platinum (II) complexes containing a 1,2-bis(aminomethyl)cyclobutane stable ligand and lactic acid as the leaving group. The statement of the c-myc gene, is impacted by lobaplatin, which is engaged with oncogenesis, apoptosis and cell multiplication/proliferation.Lobaplatin is avowed mainly for the treatment of relentless/interminable myelogenous leukemia, and yet is used in patients encountering small cell lung carcinoma and metastatic bosom malignant cells [38].

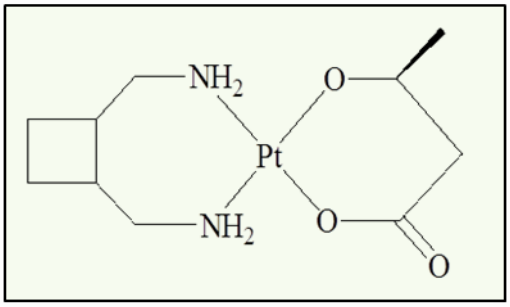

Figure 7 Lobaplatin

Lobaplatin is wrapping up as another platinum sedate, which beats a couple of sorts of cisplatin opposition in preclinical tumor models and turned out to be more helpful than cisplatin. Different potential clinical applications remain unexplored, for instance, its use in fell away from the faith testicular tumor and in blend with other toxic chemotherapeutic experts and ionizing radiation.

Some other Pt(II) complexes

Platinum complexes that interpolate with DNA commonly display anticancer activity. A prominent series of vigorous complexes are of the sort $[Pt(X_L)(Y_L)]^{2+}$, where X_L is a presenting ligand and Y_L is an auxiliary ligand. The positive charge of these building blocks thinks about improved dissolvability, explicit cell take-up through unique transference and high DNA proclivity [39]. It has been accounted for that independent fluctuations to I_L and A_L can change both biological activity and DNA affinity, and that practical gathering type and position have an impact [40]. For instance, Pt (II) structures $[Pt(dpq)(dach)]^{2+}$ (dpq = dipyrido(3,2-f:2',3'- h)quinoxaline, dach =1,2-diaminocyclohexane) (**Figure 8(a)**) had fundamentally higher confining proclivity than $[Pt(phen)(dach)]^{2+}$ (phen = 1,10-phenanthroline) (Figure 8(b)).

This was improved by the bigger sweet-smelling surface zone of dipyridoquinoxaline bringing about stronger stacking cooperation between the ligand and the DNA base pairs. Then again, the side-effects of cytotoxicity were resolved in the L1210 murine leukemia cell line and it has shown that all complexes with dipyridoquinoxaline subsidiaries are less active than those containing phen ligand [41, 42].

There is potential for a few coordination metal complexes to intercalate with DNA in more than one way. Platinum complexes bearing conjugated heterocyclic ligands, for example, terpyridine and its subordinates establish a broad class of potential anticancer operators tried as of late. There are a few instances of Pt terpyridine buildings that have been depicted as effective DNA intercalating units and dynamic antitumor operators. Three nitrogen giver atoms

are well-appointed by the terpyridine ligand and the fourth coordination position is quiet variable factor in such type of frameworks [43-45]. Binding investigations of the complex $[Pt(tpy)Cl]^+$ (tpy = 2,2':6',2''- terpyridine) (**Figure 9(a)**) have uncovered that this mind boggling will basically intercalate with DNA, and along these lines structure covalent bonds to base combines after the loss of the labile chloride ligand [46, 47]. A wide range of complexes of this type have been produced experimentally (Figure 9(b, c)), and some have uncovered higher cytotoxicity than carboplatin in human ovarian malignant growth cell lines.

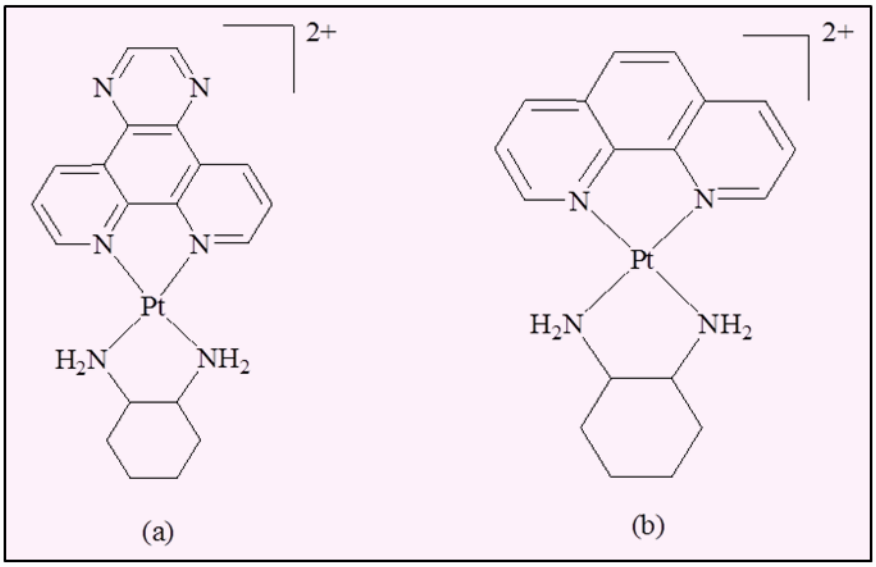

Figure 8: (a) $[Pt(dpq)(dach)]^{2+}$ and (b) $[Pt(phen)(dach)]^{2+}$

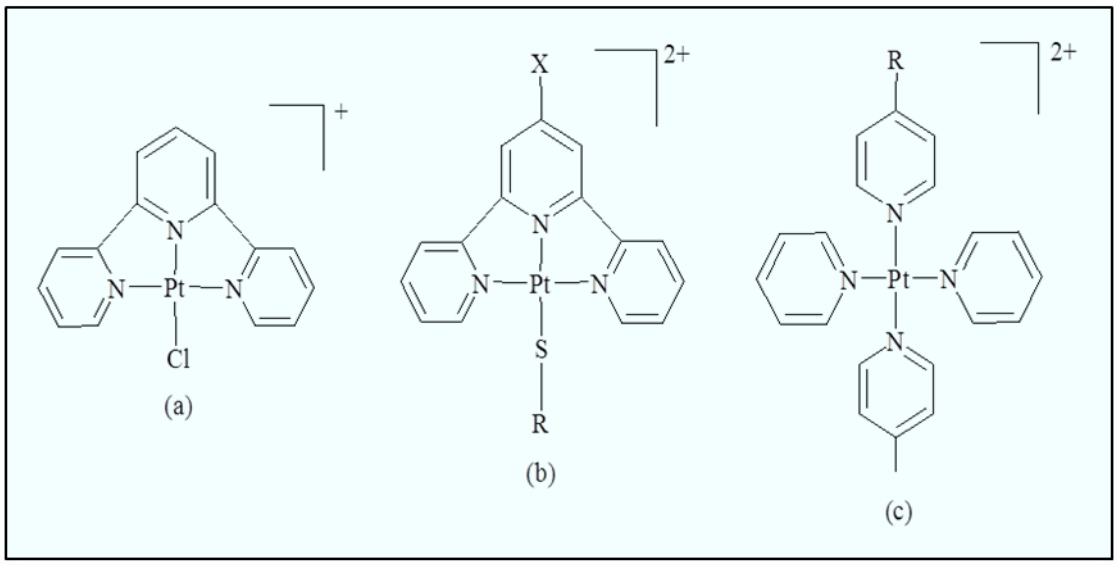

Figure 9 (a) $[Pt(tpy)Cl]^+$ and some other Pt(II) complexes (b) & (c)

Pt (IV) Complexes and its applications

As of recent advancements, Pt (IV) prodrugs are another class of particles that may recover the pharmacological properties of the Pt(II) anticancer operators. The relative kinetic inertness of these Pt(IV) building blocks makes them reasonable for oral organization by diminishing both (a) the side products by the reactions in the circulation system and (b) the unfortunate reactions. They can possibly be utilized as prodrugs dependent on an initiation by decrease component of the reduction mechanism gave that the comparing square planar Pt(II) self-motivated complex. The most probable reducing agents are glutathione and ascorbate, yet significant decrease by cell proteins was additionally revealed [48].

Satraplatin (**Figure 10**) was the principal orally directed platinum based antineoplastic specialist that is under scrutiny as one treatment of patients with cutting edge prostate malignant growth who have failed chemotherapy. It has not yet gotten understanding from the U. S. Nourishment and Drug Administration [33].

Satraplatin is an orally bioavailable platinum chemotherapeutic director a work in progress for a few sorts of tumors including hormone-refractory prostate carcinogenic advancement (HRPC). Satraplatin is being set up for the treatment of men with chemorefractory HRPC for a couple of reasons. Satraplatin has an incredible poisonous quality profile, and seems to have clinical activity against a grouping of malignancies, for instance, breast tumor cells, prostate disease and lung malignant growth.

Satraplatin has some side reactions as it causes anemia, diarrhea, clogging, queasiness, increment in risk of contamination. Satraplatin can influence female's capacity to become pregnant i.e., impact regenerative framework and may cause a male to become sterile.

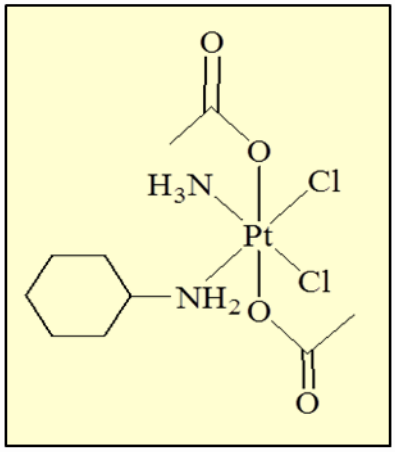

Figure 10 Satraplatin

Conclusion

Platinum-based medications are utilized as malignant growth therapeutics throughout the previous 40 years [1, 2]. In any case, tranquilize natural or acquired obstruction and nephrotoxicity are the significant confinements of the utilization of platinum-based complexes in cancer treatment [49-51]. Much endeavors have been placed into the improvement of new platinum-based anticancer complexes, yet none of them has arrived at overall clinical applications up until now. The component of activity of cisplatin depends on the cis-$Pt(NH_3)_2$ unit to cell DNA at two neighboring guanine bases [52] and the resulting acceptance of apoptosis. In any case, cisplatin, as other platinum (II) complexes, can non-specifically tie to macromolecules too, that outcomes with diminished bioavailability, diminished antitumor cytotoxicity and expanded lethal symptoms. The clinical utilization of platinum (II)- based cytostatic is restricted in light of their serious reactions (for instance, nephrotoxicity, hepatotoxicity, neurotoxicity, ototoxicity, myelosuppression, emesis and alopecia) [53-56]. Then again, potential advantage of Pt(IV) complexes contrasted with mononuclear platinum(II) complexes is their lower reactivity that diminishes the quantity of symptoms and expands the open door for their appearance to the target cells.

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