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Metal-based anticancer chemotherapeutic agents

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Since the discovery of the cisplatin antitumor activity, great efforts have focused on the rational design of metal-based anticancer agents that can be potentially used in cancer chemotherapy. Over the last four decades, a large number of metal complexes have been extensively investigated and evaluated *in vitro* and *in vivo*, and some of them were at different stages of clinical studies. Amongst these complexes, platinum (Pt^{II} and Pt^{IV}), ruthenium (Ru^{II} and Ru^{III}), gold (Au^{I} and Au^{III}) and titanium (Ti^{IV}) complexes are the most studied metals. We describe here some most recent progresses on Pt^{IV} prodrugs which can be activated once enter tumor cells, polynuclear Pt^{II} complexes which have unique DNA binding ability and mode, anti-metastatic Ru^{II}/Ru^{III} complexes, and Au^{I}/Au^{III} and Ti^{IV} antitumor active complexes. The key focuses of these studies lie in finding novel metal complexes which could potentially overcome the hurdles of current clinical drugs including toxicity, resistance and other pharmacological deficiencies.

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Introduction

The modern use of transition metal complexes as chemotherapeutic agents dates back to the serendipitous discovery of cisplatin by Rosenberg *et al.* in 1965 [1]. Such a discovery opened the gate of unexplored world of metal-based chemotherapeutic agents which have different kinetics and mechanism of action from those of conventional organic drugs [2]. Cisplatin, carboplatin and oxaliplatin are FDA approved platinum anticancer drugs that are used in clinic world-wide for the treatment of various cancers, while nedaplatin, lobaplatin, and heptaplatin are approved for clinical use respectively in Japan, China and Korea (Figure 1).

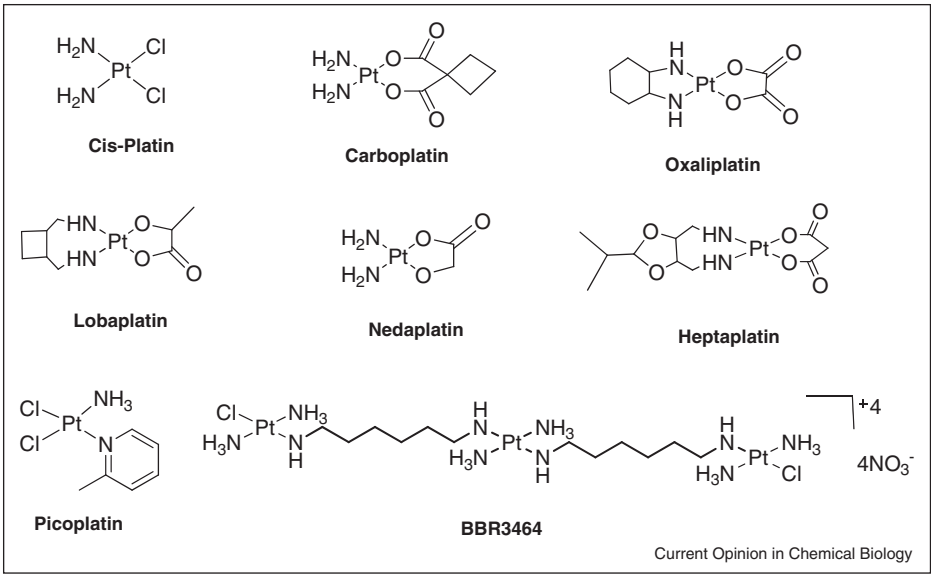
However, side effects, toxicity and drug resistance are the major obstacles for wider clinical application of these drugs [3]. Bioinorganic and medicinal chemists are exploring different strategies to overcome the problems, which includes targeted delivery of clinical drugs [4,5] and design of novel platinum and non-platinum metal complexes which have different structural features and reactivities [6•]. Because of the excellent review coverage on the chemistry, biology and medicine of Pt^{II}-based anticancer drugs, in this short review we concentrate on some most recent advances on Pt^{IV} prodrugs, polynuclear Pt^{II} complexes, and $Ru^{II/III}$, $Au^{I/III}$ and Ti^{IV}-based anticancer complexes.

Pt(IV) prodrugs: a strategy to reduced toxicity and drug resistance

Pt^{IV} complexes came into the medicinal stage soon after the toxicity of cisplatin became a major clinical issue for cancer treatment. It is believed that octahedral Pt^{IV} complexes are kinetically more inert in blood stream but can be activated once enters into the cells by reducing agents to give cytotoxic Pt^{II} species, offering potential advantage over Pt^{II} compounds regarding oral availability, reduced drug resistance and toxicity. Following the early efforts of Rosenberg and co-workers on Pt^{IV} analogues of cisplatin [7], thousands of Pt^{IV} complexes have been synthesized and evaluated in the context of prodrugs. The rationales behind the design of Pt^{IV} complexes are the fine tuning of their redox potential, kinetic stability, hydrophilicity/lipophilicity to achieve desired reactivity and activity through selection of axial and equatorial ligands. Two best known examples are satraplatin (**1**) (formally known as JM216) and LA-12 (**2**) [8]. Satraplatin **1** was once in the advanced stage of clinical trials for prostate, lung and ovarian cancers. It can be orally active, unlike other Pt^{II} drugs which have to be given intravenously. As a prodrug, **1** is activated by reduction in the presence of intracellular reducing agents such as glutathione, ascorbic acid, among others [9], and demonstrates little nephrotoxicity, neurotoxicity and ototoxicity. Complex **2** is an analogue of **1** and contains a bulky hydrophobic ligand, adamantylamine which could potentially increase the uptake of **2** by the cancer cells. Complex **2** was significantly more efficient than cisplatin against cisplatin resistant ovarian carcinoma A2780cisR cells, causing the increase of p53 level and cell cycle perturbations [10].

Wilson *et al.* synthesized a series of Pt^{IV} carbamate complexes (**3**–**5**) by reacting various alkyl and aryl isocyanates with Pt^{IV} hydroxy complex $[Pt(NH_3)_2Cl_2(OH)_2]$ [11••]. Slightly higher reduction potentials were found for the aryl carbamate complexes than for the alkyl carbamate complexes, which can be correlated with computed adiabatic electron affinities. All these complexes show equivalent or higher cytotoxicity than cisplatin against human

Figure 1



Clinically approved Pt^{II} drugs and complexes evaluated in clinical trials.

lung carcinoma A549 cells. In addition, compounds **4** and **5** that contain tert-butyl and cyclopentyl based carbamate ligands showed higher cytotoxicity than other complexes of this series. It is worth to mention that these complexes show higher cytotoxicity against cancer cells than normal cells such as normal lung MRC-5 cells.

Medrano *et al.* [12] have synthesized two *trans*-Pt^{IV} phosphane complexes **6** and **7** to take advantage of the lipophilicity of phosphane group. Both complexes contain aliphatic amines *trans* to phosphane ligands, which enhances the stability of Pt^{IV} complexes. Both **6** and **7** are stable in solution and have IC_{50} values similar to that of cisplatin against carcinoma cell lines NCI-H460 and metastatic melanoma A375. Interestingly, both complexes were shown to be more selective and cytotoxic than that of cisplatin against HCT116 cells absent of wild-type p53 (HCT116−/− cells).

By tethering lipophilic carboxylate ligands in the axial position, Varbanov *et al.* have prepared a series tetracarboxylate Pt^{IV} complexes which demonstrate potent cytotoxicity against a variety of cancer cell lines (**8**, Figure 2e) [13•]. It was concluded that both the reduction potential and the rate of reduction has major influences on the cytotoxic properties of these complexes and their amide/ester derivatives. Another series of dicarboxylated Pt^{IV} complexes **10–12**, which were developed by Ravera *et al.* [14], were based on picoplatin (Figure 1), an active Pt^{II} antitumor agent able to circumvent acquired Pt-chemotherapy resistance. The presence of a sterically demanding 2-methylpyridine in picoplatin hinders the axial approach of GSH to the platinum center without detriment of the level of DNA platination. These complexes demonstrated potent activity against several different tumor cell lines sensitive and resistant to cisplatin. Interestingly, the cytotoxicity and selectivity of these complexes against resistant cell lines increases with the elongation of the axial chain.

Pichler *et al.* [15••] have recently synthesized a series of symmetrically and unsymmetrically substituted Pt^{IV} complexes containing various bulky groups at the equatorial position (e.g. **13–15**). These bulky groups were found to play a major role in determining the stability and reaction patterns of the Pt^{IV} complexes. All these complexes show strong inhibitory effect against different tumor cell lines sensitive and resistant to cisplatin. An interesting correlation between the cytotoxicity and the lipophilicity of the complexes was proposed, although it is neither strong nor strictly linear, and has some exceptions.

Selective photoactivation of Pt^{IV} complexes in cancer cells might avoid toxic side effects and extend their application to cisplatin resistant cells. Farrer *et al.* [16] reported a *trans* di-pyridine complex **16** which can be phototoxic against a number of human carcinoma cells when irradiated with UVA and visible light. This diazido complex is stable in solution and particularly inert toward GSH. The pyridine ligands appear to remain strongly bound to platinum, even after photoactivation. It seems clear that the molecular pharmacology of the photoactivatable excited state Pt^{IV} complex **16** is quite distinct from that of ground-state Pt^{IV} complexes.