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Review

Platinum coordination compounds with potent anticancer activity

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ABSTRACT

Many international researchers have strived to understand the mechanism of action or improve the efficacy of inorganic coordination compounds that have been identified to exhibit anticancer activity. The inherent challenges of chemotherapy demand that new strategies be developed utilising different mechanisms of action to interrupt the cellular machinery of cancer cells. In Australia, we have benefited from the research of colleagues who have influenced modern platinum chemistry by contributing to our understanding of platinum oxidation and reduction, the mechanism of action of cisplatin, and unique design strategies for new platinum complexes. The purpose of this review is to provide some background in the history and development of platinum(II) and platinum(IV) complexes.

Contents

1. Conventional platinum(II) complexes

In this review conventional platinum complexes satisfy the specific structural requirements as described by Cleare and Hoeschele [1–4]. In summary, these are neutrally charged with square-planar geometry and the general formula *cis*-[Pt(NH_2R)$_2$X$_2$]; where NH_2R is an ammine (such as NH_3); and X represents labile anionic leaving groups [2,3,5] to expedite binding to DNA.

2. First generation

The most well-known conventional platinum anticancer complex is cisplatin (*cis*-diamminedichloroplatinum, **Pt^{II}-1**, Fig. 1) which effectively treats testicular, ovarian, head, neck and small-cell lung cancer [6,7]. Vomiting (emetogenesis), hearing loss (ototoxicity), kidney damage (nephrotoxicity) and nervous system damage (neurotoxicity) are often the characteristic side effects of treatment [8,9]. Acquired resistance is frequently a consequence of sub-toxic accumulation inside the cell, due in part to reduced drug influx and increased drug efflux [10]. Resistance in cancer cells is enhanced by the repair/tolerance to DNA–cisplatin adducts,

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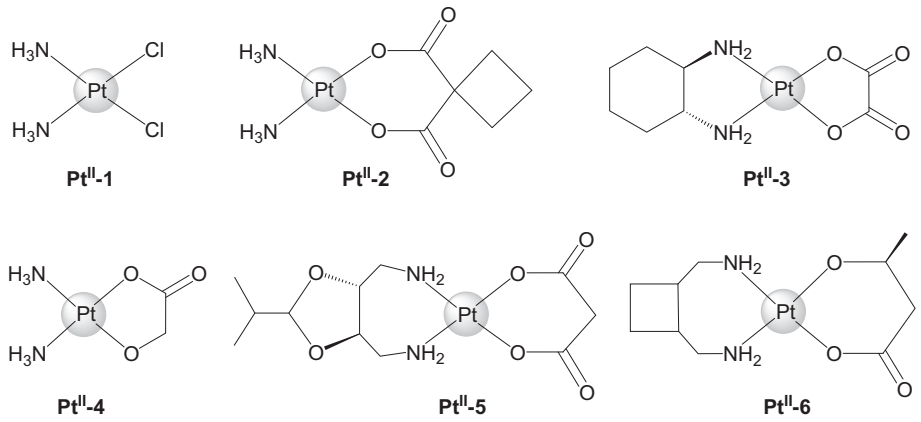

Fig. 1. Approved platinum chemotherapeutic drugs: cisplatin (**Pt^{II}-1**), carboplatin (**Pt^{II}-2**), oxaliplatin (**Pt^{II}-3**), nedaplatin (**Pt^{II}-4**), heptaplatin (**Pt^{II}-5**) and lobaplatin (**Pt^{II}-6**).

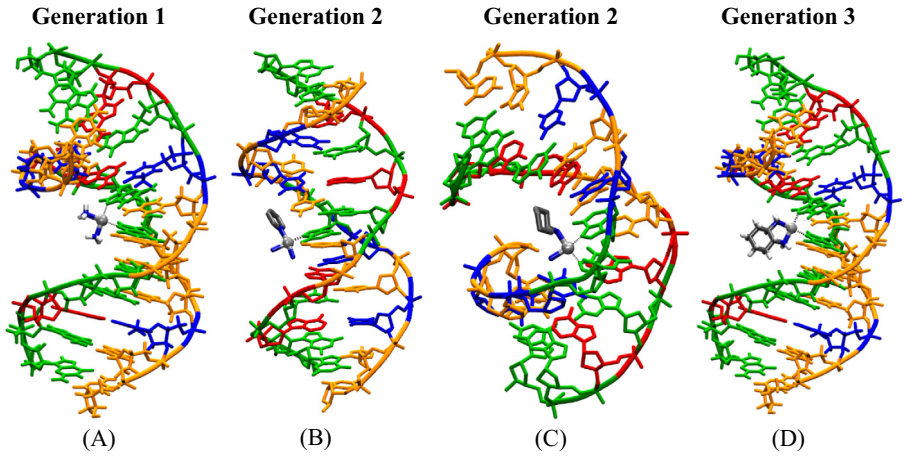

Fig. 2. PDB structures showing coordinative platinum binding to DNA. (A) Cisplatin (**Pt^{II}-1**) forming a 1,2-intra-strand DNA adduct (2NPW) [29]; (B) *cis*-diammine(pyridine) chloroplatinum(II), (**Pt^{II}-7**) forming a single strand DNA adduct (3CO3) [30]; (C) [platinum(ammine)$_2$(cyclohexylamine)]$^+$ (**Pt^{II}-8**) forming a 1,2-intra-strand DNA adduct (1LU5) [31]; and (D) oxaliplatin (**Pt^{II}-2**) forming a 1,2-intra-strand DNA adduct with (1PG9) [32]. G = green, C = orange, A = red, T = blue.

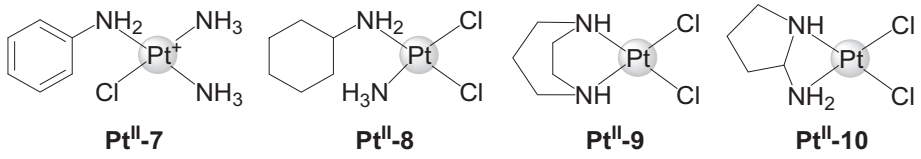

Fig. 3. Second generation platinum complexes: *cis*-Diammine(pyridine)chloroplatinum(II) (**Pt^{II}-7**), *cis*-ammine(cyclohexylamine)dichloro platinum(II) (**Pt^{II}-8**) *cis*-dichloro (1,4-diazacycloheptane)platinum(II) (**Pt^{II}-9**) and *cis*-dichloro(3-aminohexahydroazepine)platinum(II) (**Pt^{II}-10**).

modulation of the pathways that control regulated cell death, loss of function of upregulated sequence-specific binding factors such as proteins, and an increased concentration of glutathione and metallothioneins [11–13]. The clinical limitations of cisplatin have been the motivation for the creation of thousands of cisplatin analogues, resulting in complexes that employ the same mechanism of action where the platinum coordinately binds to DNA (Fig. 2).

Pioneering insights into platinum(II) complex synthesis and cisplatin hydrolysis was provided by employing ^{15}N, ^{195}Pt and ^{19}F NMR [14–25]. These experiments determined the rate of hydrolysis of ^{15}N labelled cisplatin to *cis*-[Pt(^{15}NH$_3$)$_2$(H$_2$O)$_2$]$^{2+}$, concluding that the nitrogen donor atoms of DNA were the primary targets and established that binding affinity towards 3′ purine bases within the GpG pair structures, led to a stereoselective mechanism stabilised by hydrogen bonding (Fig. 2) [26]. It was proposed that the adducts interfered with cell division or triggered intracellular mechanisms that caused irreparable damages to the cells [27]. These experiments were substantiated by monitoring the hydrolysis of cisplatin by HPLC [28].

3. Second generation

Structures that deviate from the cisplatin template are termed second generation; these still form coordinate bonds with DNA, but the ammine ligands are substituted by either mono- or bidentate ligands modulating the electronic, steric and basicity effects. Examples include: *cis*-diammine(pyridine)chloroplatinum (II), (**Pt^{II}-7**, Fig. 3), *cis*-dichloro(1,2-diaminobenzene)platinum(II), *cis*-ammine(cyclohexylamine)dichloro platinum(II) (**Pt^{II}-8**, Fig. 3) and *cis*-dichloro(1*R*,2*R*-diaminocyclohexane)platinum(II). The last two examples both exhibit cytotoxicity similar to cisplatin against

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