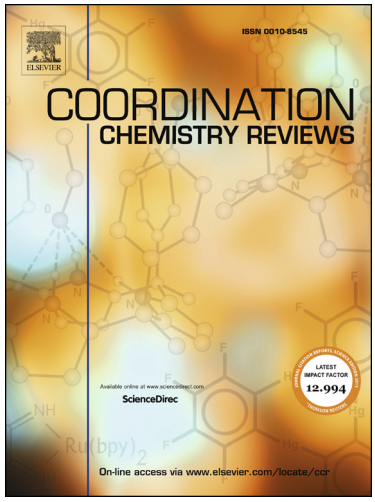

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Cytotoxic platinum coordination compounds. DNA binding agents

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ABSTRACT
Despite the widespread use of antineoplastic platinum drugs, a number of accompanying disadvantages exist. In connection with attempts to circumvent these problems new platinum compounds have been prepared and mechanisms underlying their biological activity have been extensively investigated. These mechanistic investigations involve research focused on understanding interactions of platinum agents with DNA since DNA binding and recognition of DNA modified by these metallodrugs are the important processes responsible for their anticancer properties. In this review, we discuss how various classes of platinum(II) complexes, which can interact with DNA by coordination, intercalation and other noncovalent modes of binding or by combination of these DNA binding modes, can alter the cellular response induced by conventional platinum drugs. We describe that these alterations can be achieved by changing: (i) the nature and structure of the DNA lesion induced; (ii) conformational alterations induced in DNA by these lesions; and (iii) various cellular signaling pathways initiated by platinum-DNA damage. We anticipate that summarization of the results on DNA binding of cytotoxic platinum compounds may help to shed light on their potency and will make it possible to create new strategies to design rationally new anticancer platinum compounds and/or combine platinum drugs with other cytotoxic agents.

Keywords:
Platinum
DNA binding
Cross-links
Photoactivation
Cytotoxicity

Abbreviations: 1,0,1/t,c,t, [{*trans*-$PtCl(NH_3)_2$}$_2$μ-*cis*-$Pt(NH_3)_2\{H_2N(CH_2)_6NH_2\}_2]^{4+}$; 1,0,1/t,t,t, *trans*-$PtCl(NH_3)_2$}$_2$μ-*trans*-$Pt(NH_3)_2\{H_2N(CH_2)_6NH_2\}_2]^{4+}$ (BBR3464); 1,1/c,c, [{*cis*-$PtCl(NH_3)_2$}$_2$μ-{$H_2N(CH_2)_6NH_2$}]$^{2+}$; 1,1/c,c-prz, [{*cis*-$Pt(NH_3)_2$}$_2$(μ-OH)(μ-pyrazolato)]$^{2+}$; 1,1/t,t, [{*trans*-$PtCl(NH_3)_2$}$_2$μ-{$H_2N(CH_2)_6NH_2$}]$^{2+}$; 1,1/t,t-dien, [{*trans*-PtCl(dien)}$_2$-μ-$(CH_2)_n]^{2+}$; 1,2/c,c, [{*cis*-$PtCl(NH_3)_2$}$H_2N(CH_2)_6NH_2${*cis*-$PtCl_2(NH_3)$}]$^+$; 1,2/t,c, [{*trans*-$PtCl(NH_3)_2$}$H_2N(CH_2)_6NH_2${*cis*-$PtCl_2(NH_3)$}]$^+$; 2,2/c,c, *cis*-[{$Pt(NH_3)Cl_2$}$_2$-μ-$H_2N(CH_2)_4NH_2$]; 2,2/t,t-pz, *trans,trans*-[{$Pt(NH_3)Cl_2$}$_2$(piperazine)]; 4-dpt = 2,4-diamino-6-(4-pyridyl)-1,3,5-triazine; ACRAMTU, 1-[2-(acridin-9-ylamino)ethyl]-1,3-dimethylthiourea; ACV, acyclovir; AO, acridine orange; BBR3464, *trans*-$PtCl(NH_3)_2$}$_2$μ-*trans*-$Pt(NH_3)_2\{H_2N(CH_2)_6NH_2\}_2]^{4+}$ (1,0,1/t,t,t,); BER, base excision repair; bpy, 2,2'-bipyridine; carboplatin, *cis*-diammine-[1,1-cyclobutanedicarboxylato]platinum(II); chrysi, 5,6-chrysenequinonediimine; cisplatin, *cis*-diamminedichloridoplatinum(II); CL. cross-link; DAB, 2,3-diaminobutane; DACH = diaminocyclohexane; dien, diethylenetriamine; dpa = bis-(2-pyridylmethyl)amine; DPE, 1,1-di(pyridin-2-yl)ethanol); dzpm, 4,4'-dipyrazolylmethane; DSC, differential scanning calorimetry; en, ethane-1,2-diamine; GSH, glutathione; hAAG, human 3-methyladenine DNA glycosylase; Han-acac, anthracenyl appended acetylacetone;