Chiral Discrimination in Platinum Anticancer Drugs

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In this article we review the biological activity of analogs of the antitumor drug cisplatin that contain chiral amine ligands. Interaction with DNA and formation of cross-links with adjacent purine bases are considered to be the crucial steps in the antitumor activity of this class of complexes. Because double-helical DNA has a chiral structure, interaction with enantiomeric complexes of platinum should lead to diastereomeric adducts. It has been demonstrated that DNA cross-links of platinum complexes with enantiomeric amine ligands not only can exhibit different conformational features but also can be processed differently by the cellular machinery as a consequence of these conformational differences. These results expand the general knowledge of how the stereochemistry of the platinum–DNA adduct can influence the cell response and contribute to understanding the processes that are crucial for antitumor activity. The steric requirements of the chiral ligands, in terms of configuration and flexibility, are also elucidated. ***Key words:*** **cross-link, DNA conformation, enantiomeric *cis*-dichloro-2,3-diaminebutane platinum(II), platinum anticancer drugs, repair.** ***Environ Health Perspect*** **110(suppl 5):779–782 (2002).**
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Cisplatin is an effective anticancer drug widely used in the treatment of several human carcinomas (*1–4*). The mechanism of anticancer activity involves formation of platinum–DNA adducts that are capable of inhibiting DNA and RNA synthesis (*5–16*) and inducing programmed cell death (*17,18*). Cisplatin binds preferentially to the N7 position of purine residues. The monofunctional adduct subsequently closes to a bifunctional adduct by linking a second purine that can be either of the same strand or of the opposite strand (*19*). There is general consensus that the antitumor efficacy of cisplatin is associated with the formation of DNA 1,2-intrastrand d(GpG) or d(ApG) cross-links (*5–16*). The 1,2-intrastrand cross-links locally unwind and bend double-stranded DNA toward the major groove (*14,20,21*), and the disturbance of DNA secondary structure seems to be the ultimate reason for inhibition of DNA replication and/or transcription and for triggering apoptotic cell death (*22,23*).

While the anionic-leaving ligands are likely to play a role in determining the transport of the complex throughout the living organism, the nonexchangeable aminic ligands play an important role in the drug–DNA adduct formation and stereochemistry. Thus, it is of great interest to see how different configurations of these nonleaving ligands can influence the DNA-binding properties and consequently the biological activity of platinum complexes.

In this review we focus on platinum complexes with enantiomeric amine ligands. Because double-helical DNA has a chiral structure, complexes with enantiomeric ancillary ligands should form diastereomeric adducts with DNA.

Platinum Complexes with Chiral Monoamines

The activity of *cis*-PtA_2X_2 compounds (A = aminic ligand, X = anionic ligand) decreases in the order A = NH_3 > RNH_2 > R_2NH (*24*). Therefore, most investigations were restricted to platinum complexes with chiral primary amines. Platinum complexes with monodentate enantiomeric primary amines do not show significant differences in their biological activity (*25*). One compound of this class, the platinum complex with phenethylamine, is shown in Figure 1.

A possible explanation for this result is that the free rotations of the chiral substituent around the carbon–nitrogen (C—N) bond and of the amine around the platinum–nitrogen (Pt—N) bond average the steric effect due to the ligand asymmetry and offset any stereospecificity in the interaction with biological substrates.

Platinum Complexes with Chiral N-Substituted Ethylenediamines

The degree of rotational freedom in a complex of the type described in the previous section can be reduced by bridging together the two nitrogens of the *cis* amines. A ligand that fulfills these requisites is ethambutol. This molecule was already used in medicine as an anti-tuberculosis, and very interestingly, only the *S,S* isomer was found very active; the *R,R* enantiomer was completely inactive (*26,27*). Starting with an isomerically pure ligand, coordination to platinum leads to formation of different isomers. The reason for this is that, upon coordination to platinum, the nitrogens also become stable chiral centers and can have either *R* or *S* configuration. The two enantiomers shown in Figure 2 were isolated in the pure form, with biological activities that could be compared.

It is interesting to note that the bridging of the two nitrogens with the ethylene chain not only blocks the rotation around the Pt—N bonds but also hinders, to some extent, the rotation of the asymmetric 1-butanol-2-yl radical with respect to the C—N bond. This was revealed by the ^1H nuclear magnetic resonance showing a remarkable diastereotopic splitting of the methylene protons of the CH_2Me groups adjacent to the asymmetric carbons. Therefore, the average orientation of the 1-butanol-2-yl radicals is such that the ethyl residues are hindered in their rotation around the carbon–ethyl bond (*28*).

The much less rotational freedom of the asymmetric substituents in these complexes leads to a different biological activity for the two enantiomers. Indeed, enantiomer *a* is less mutagenic and less toxic than enantiomer *b* but, in contrast, exhibits good antitumor activity toward P388 sarcoma and Lewis lung carcinoma (*29*). Evidently, *a* can couple reduced mutagenic activity with good antitumor activity, and this appears to be a rather noteworthy result.

In the compound just described, the configuration at the nitrogen atoms was stable at neutral pH for days at room temperature; however, at higher temperatures and/or more basic pH, isomerization can take place. This phenomenon has prevented further studies on complexes of this class.

Platinum Complexes with Chiral C-Substituted Ethylenediamines

The complication arising from isomerization at the nitrogen atoms could be avoided by using chiral diamines in which the chiral carbon(s) are inserted in the organic chain bridging the two nitrogens. In this way the steric

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rigidity of the nonleaving ligands is further increased because the chiral groups are no longer free to rotate around the C—N bonds, as is the case of the compound considered in the preceding section.

Kidani and co-workers have reported that platinum complexes with l,2-diaminocyclohexane, having different configurations at the two chiral carbons bridging the two nitrogens, had biological activities dependent on the chirality of the diamine ligand (*30–33*). Although the isomers with *R,R* and *S,S* configurations at the asymmetric carbons produce the same type of intra- and interstrand cross-links (*34*), the biological activity of the two enantiomers is different, and the *R,R* enantiomer exhibits higher antitumor activity and lower mutagenicity than the *S,S* isomer (*35*). Chiral diamines other than 1,2-diaminocyclohexane have also been investigated (*36–40*).

A comparative study of three strictly related platinum complexes with chiral diamines [$PtCl_2$(N—N), where N—N = 1,2-diaminopropane (1,2-DAP), 2,3-diaminobutane (2,3-DAB), or 1,2-diaminocyclohexane (1,2-DACH)] has been also carried out by some of us (Figure 3). The biological tests, *in vitro*, have revealed a marked difference among isomers. For instance, the mutagenic activity, which is strictly related to the interaction of the drug with DNA, is even 10 times greater in one isomer relative to the corresponding enantiomer. In all cases examined the *S,S* isomer was by far the most mutagenic, indicating that the different isomers give adducts with DNA that can be discriminated by the enzymatic systems involved in mutagenesis (*41*).

The conclusions based on mutagenic data concerning the relevance of the configuration of nonleaving ligands in platinated DNA have been confirmed by the studies of inhibition of restriction enzyme activity. The extent of inhibition of the enzymes cutting at guanine (G)-rich sites is significantly different for the different isomers, the *R,R* form being more active than the others.

As a result of the markedly different behavior of the two enantiomeric forms, only the *R,R* enantiomer of [Pt(DACH)(oxalato)] (oxaliplatin) has been approved for clinical use (*42*). Hence, studies have mainly focused on DNA modifications and biological properties of enantiomeric DACH and closely related DAB complexes (*43–47*).

In the next section we concentrate mainly on a deeper insight into the biological behavior of the latter two types of complexes. However, before concluding this section, we consider nonleaving ligands of the type just described but having also an alkyl substituent on each coordinated nitrogen [e.g., *N,N′*-Me_2DAB and bipiperidine; Figure 4). Although these compounds are less effective as antitumor drugs because the coordinated nitrogens are no longer primary amine groups (*24*), they are able to exert steric control on the coordination of nucleotides with platinum. This phenomenon has allowed us to unravel details of the dynamics and conformations of the 1,2-intrastrand cross-links that, as already pointed out, are the major lesions formed by cisplatin-type complexes on DNA (*48–52*).

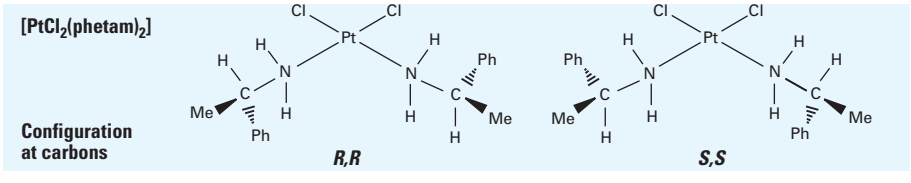

Figure 1. Example of the platinum complex with monodentate enantiomeric primary amines. Ph, phenyl; phetam, phenylamine.

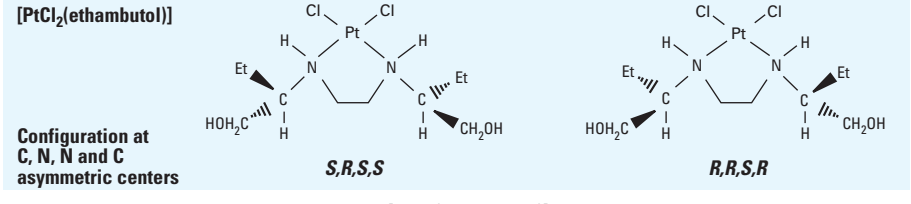

Figure 2. Structures of enantiomeric forms of [$PtCl_2$(ethambutol)]. Et, ethyl.

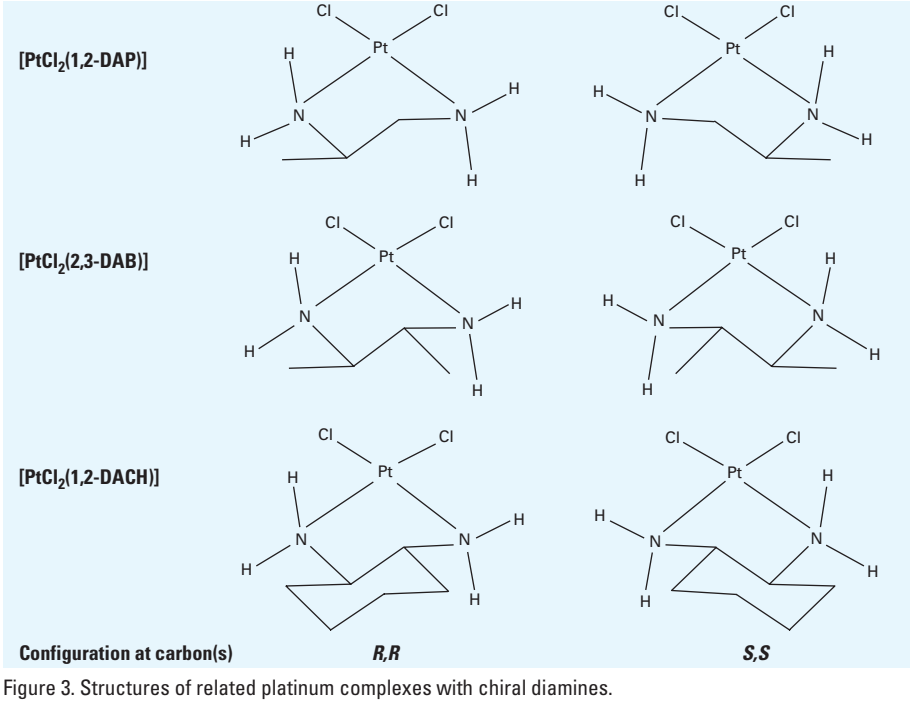

Figure 3. Structures of related platinum complexes with chiral diamines.

Biochemistry of Platinum Complexes with Enantiomeric DACH and DAB Ligands

The recently reported crystal structure of 1,2-GG intrastrand cross-link formed by oxaliplatin on a DNA dodecanucleotide duplex has shown that the overall geometry is similar to that of cisplatin. However, a novel feature of this structure is the presence of a hydrogen bond between the pseudoequatorial N—H hydrogen atom of the *R,R*-DACH ligand and the O6 atom of the cross-linked G in 3′ position (*43,44*). This finding has confirmed the importance of chirality in mediating the interaction between cisplatin analogs containing enantiomeric amine ligands and double-helical DNA.

We have shown in a recent work (*46*) that 1,2-GG intrastrand cross-links of *R,R*- and *S,S*-DAB platinum complexes (Figure 3) not only destabilize DNA differently but also bend and unwind DNA to a different extent.

DNA containing platinum adducts that induce stable directional bending and unwinding attracts various damaged-DNA–binding proteins such as those containing the high-mobility group (HMG) domain (*53–56*). A recent report (*45*) has demonstrated that HMGB1 and TATA binding proteins recognize 1,2-GG intrastrand cross-links formed by

R,R-DACH–platinum(II) species. The affinity of these proteins to 1,2-GG intrastrand cross-links of cisplatin depends on several factors, and the efficiency with which the adducts thermodynamically destabilize DNA is among the most important. The binding of these proteins has been postulated to mediate the antitumor properties of the platinum drugs (*55,56*). In addition, several reports (*57–59*) have demonstrated that intrastrand cross-links of cisplatin and its direct analogs are removed from DNA during nucleotide excision repair (NER) reactions and that NER is also an important mechanism contributing to cisplatin resistance.

To shed light on how chirality at the carbon atoms of the carrier ligand in cisplatin analogs can affect processing its major adducts in cells, the studies have been performed to demonstrate how HMGB1 box proteins and the NER differentiate between major DNA adducts of cisplatin analogs having enantiomeric nonleaving ligands during *in vitro* reactions (*47*). For these studies the *R,R*- and *S,S*-DAB derivatives were chosen because the effect of chirality at the carbon atoms on the biological activity of these compounds was most pronounced (*41*). Electrophoretic mobility shift assays have shown that domains A and B of HMGB1 protein bind to the cross-links generated by *R,R*-DAB–platinum(II) with a higher affinity than to those generated by the *S,S*-DAB–platinum(II) enantiomer (Figure 5). The cross-links of both enantiomers are removed by NER with a similar efficiency; however, HMGB1 protein significantly inhibits removal of *R,R*-DAB–platinum(II) adducts, but not those of the *S,S*-DAB–platinum(II) enantiomer (Figure 6). Therefore, HMG domain proteins discriminate among different conformations of the 1,2-GG intrastrand cross-links of the two enantiomeric analogs of cisplatin, which results in different NER of these cross-links.

The results obtained with DAB–platinum(II) complexes apply also to the DACH–platinum(II) species (*60*). They imply that the higher affinity of HMGB1 proteins to an *R,R*-DACH–platinum(II) cross-link than to an *S,S*-DACH–platinum(II) cross-link coupled with a greater error-prone NER repair of the *S,S*-DACH–platinum(II) cross-links could explain both the better antitumor activity of the *R,R* form of oxaliplatin and the greater mutagenic activity of the *S,S*-enantiomer.

Conclusions

Platinum complexes containing enantiomeric ligands pose an interesting theme to investigate structure–pharmacological activity relationship of platinum compounds. The pharmacologically relevant target of platinum compounds is DNA. The major adducts are the 1,2-GG and 1,2-AG intrastrand cross-links. Recognition and repair of these lesions by DNA binding proteins are crucial steps in the cellular response to the drug treatment. The bulk of the results demonstrate that the different stereochemistry of these cross-links is responsible for their different affinities for HMG box proteins and, consequently, for the different NER of these lesions. It is possible to conclude that DNA cross-links of platinum complexes with enantiomeric carrier ligands not only can exhibit different conformational features but also can be processed differently by the cellular machinery as a consequence of these conformational differences. However, the conformational freedom of the enantiomeric platinum compounds has to be limited, so a relevant chiral discrimination might play a role in the biological activity. This was the case for chiral centers inserted in the chelating chain of a diamine.

The results reviewed in this article expand the general knowledge of how the stereochemistry of the carrier amine ligands of antitumor platinum compounds can influence some crucial processes underlying their toxicity toward

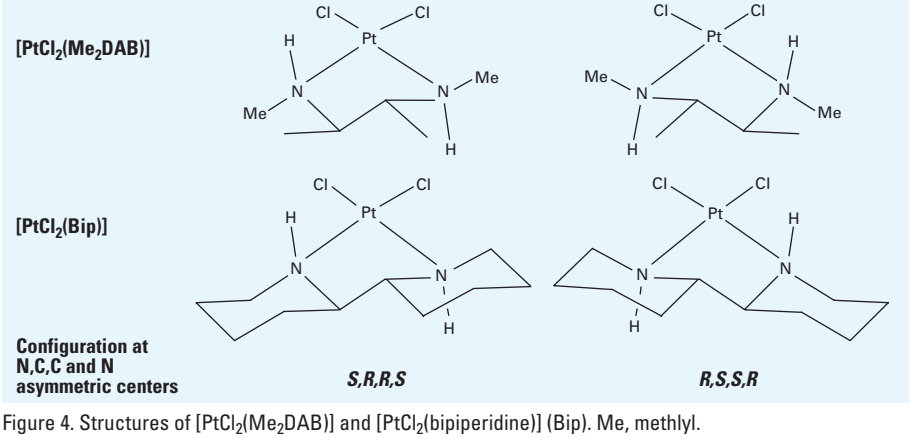

Figure 4. Structures of [$PtCl_2(Me_2DAB)$] and [$PtCl_2$(bipiperidine)] (Bip). Me, methlyl.

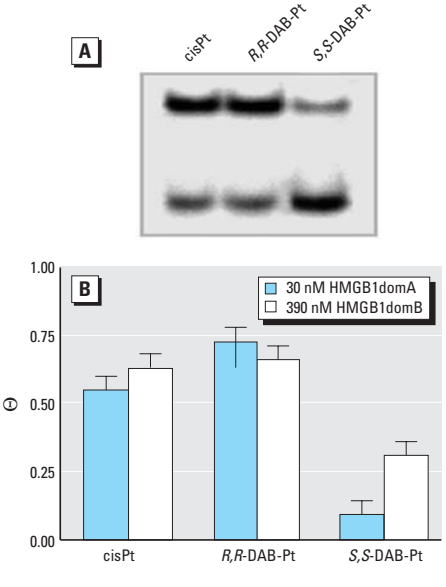

Figure 5. Gel mobility shift assay analysis of the titration of the 20-bp DNA duplex with central sequence TGGT/ACCA containing the single 1,2-GG intrastrand cross-link of cisplatin, *R,R*-DAB–platinum complex, or *S,S*-DAB–platinum complex with HMGB1a and HMGB1b. (*A*) Autoradiogram of the gel mobility assay of the reaction with HMGB1a (30 nM). The concentration of the DNA duplex was 10 nM. (*B*) Bar graph illustrating the fraction of bound DNA (Θ) for oligonucleotide duplex containing the single 1,2-intrastrand cross-link of cisplatin, *R,R*-DAB–platinum complex, or *S,S*-DAB–platinum complex at 30 nM HMGB1a and 390 nM HMGB1b. Values are averages of three independent experiments.

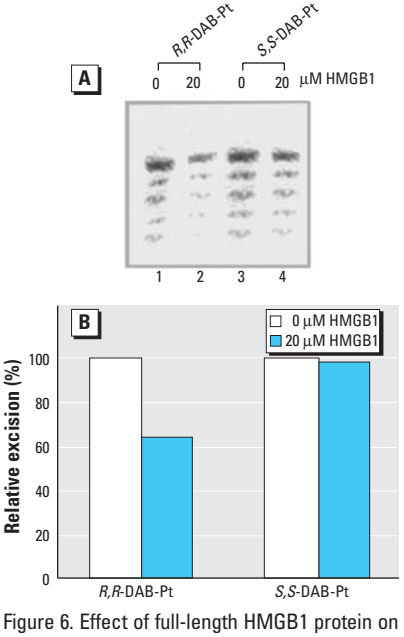

Figure 6. Effect of full-length HMGB1 protein on NER of the 1,2-GG intrastrand cross-link of *R,R*-DAB–platinum complex or *S,S*-DAB–platinum complex by rodent excinuclease. (*A*) The excision product region of an autoradiogram of the denaturing 10% polyacrylamide gel showing inhibition of excision of the 1,2-intrastrand cross-link of *R,R*-DAB–platinum complex (lanes 1, 2) and *S,S*-DAB–platinum complex (lanes 3, 4). The 148-bp substrates containing the single and central cross-link were incubated with the 20 μM HMGB1 for 1 hr before the addition of the rodent cell–free extract and further incubation for 40 min. (*B*) Bar graph illustrating the relative excision of 148-bp substrates without HMGB1 (gray bars) or after preincubation with the 20 μM HMGB1 (black bars). Values are averages of three independent experiments.

cancer cells and can provide a rational basis for the design of new platinum antitumor drugs.

References and Notes

1. O'Dwyer PJ, Stevenson JP, Johnson SW. Clinical status of cisplatin, carboplatin, and other platinum-based antitumor drugs. In: Cisplatin. Chemistry and Biochemistry of a Leading Anticancer Drug (Lippert B, ed). Zürich:VHCA, Wiley-VCH, 1999;31–72.
2. Rixe O, Ortuzar W, Alvarez M, Parker R, Reed E, Paull K, Fojo T. Oxaliplatin, tetraplatin, cisplatin, and carboplatin: spectrum of activity in drug-resistant cell lines and in the cell lines of the National Cancer Institute's Anticancer Drug Screen panel. Biochem Pharmacol 52:1855–1865 (1996).
3. Lippert B. Impact of cisplatin on the recent development of Pt coordination chemistry: a case study. Coord Chem Rev 182:263–295 (1999).
4. Pinedo J, Schornagel M, eds. Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy. New York:Plenum Press, 1996.
5. Johnson NP, Butour JL, Villani G, Wimmer FL, Defais MP, Pierson V, Brabec V. Metal antitumor compounds: the mechanism of action of platinum complexes. Prog Clin Biochem Med 10:1–24 (1989).
6. Lepre CA, Lippard SJ. Interaction of platinum antitumor compounds with DNA. Nucleic Acids Mol Biol 4:9–38 (1990).
7. Lemaire MA, Schwartz A, Rahmouni AR, Leng M. Interstrand cross-links are preferentially formed at the d(GC) sites in the reaction between *cis*-diamminedichloroplatinum(II) and DNA. Proc Acad Sci USA 88:1982–1985 (1991).
8. Schöllhorn H, Raudaschl-Sieber G, Müller G, Thewalt U, Lippert B. DNA-intrastrand guanine, guanine cross-linking by cisplatin: comparison of three model compounds with head-head orientation of the nucleobases. J Am Chem Soc 107:5932–5937 (1985).
9. Fichtinger-Shepman AMJ, van der Veer JL, den Artog JHJ, Lohman PHM, Reedijk J. Adducts of the antitumor drug cis-diamminedichloroplatinum(II) with DNA: formation, identification, and quantitation. Biochemistry 24:707–713 (1985).
10. Eastman A. Interstrand cross-links and sequence specificity in the reaction of cis-dichloro(ethylenediamine)platinum(II) with DNA. Biochemistry 24:5027–5032 (1985).
11. Lippert B, Raudaschl-Sieber G, Lock CJL, Pilon P. "Real" model compounds for intrastrand crosslinking of two guanine bases by cisplatin: crystal structures of cis-diammine-bis(9-ethylguanine-N7)platinum(II) dichloride trihydrate, $[Pt(NH_3)_2(C_7H_9N_5O)_2]Cl_2.3H_2O$, and cis-diamminebis(9-ethylguanine-N7)platinum(II) sesquichloride hemibicarbonate sesquihydrate $[Pt(NH_3)_2(C_7H_9N_5O)_2]Cl_{1.5}(HCO_3)_{0.5}.1.5H_2O$. Inorg Chim Acta 93:43–50 (1984).
12. Sherman SE, Gibson D, Wang AHJ, Lippard SJ. X-ray structure of the major adduct of the anticancer drug cisplatin with DNA: cis-$[Pt(NH_3)_2(d(pGpG))]$. Science 230:412–417 (1985).
13. Admiral G, van der Veer JL, de Graaff RAG, den Hartog JHJ, Reedijk J. Intrastrand bis(guanine) chelation of trinucleoside diphosphate d(CpGpG) to cis-platinum: an X-ray single-crystal structure analysis. J Am Chem Soc 109:592–594 (1987).
14. Takahara PM, Rosenzweig AC, Frederick CF, Lippard SJ. Crystal structure of double-stranded DNA containing the major adduct of the anticancer drug cisplatin. Nature 377:649–652 (1995).
15. Schröder G, Sabat M, Baxter I, Kozelka J, Lippert B. Cis-$[Pt(NH_3)_2$(9-MeA-N7)(9-EtGH-N7)$](PF_6)_2.1.5H_2O$ (9-MeA = 9-methyladenine; 9-EtGH = 9-ethylguanine): a right-handed helicoidal model compound for the intrastrand A,G cross-link in duplex DNA. Inorg Chem 36:490–493 (1997)
16. Schröder G, Kozelka J, Sabat M, Fouchet MH, Beyerle-Pfnür R, Lippert B. Model of the second most abundant cisplatin-DNA cross-link: X-ray crystal structure and conformational analysis of cis-$[(NH_3)_2Pt$(9-MeA-N7)(9-EtGH-N7)$]$ $(NO_3)_2.2H_2O$ (9-MeA = 9-methyladenine; 9-EtGH = 9-ethylguanine). Inorg Chem 35:1647–1652 (1996).
17. Barry MA, Behnke CA, Eastman A. Activation of programmed cell death (apoptosis) by cisplatin, other anticancer drugs, toxins and hyperthermia. Biochem Pharmacol 40:2353–2362 (1990).
18. Ormerod MG, O'Neill C, Robertson D, Kelland LR, Harrap KR. Cis-diamminedichloroplatinum(II)-induced cell death through apoptosis in sensitive and resistant human ovarian carcinoma cell lines. Cancer Chemother Pharmacol 37:463–467 (1996).
19. Sherman SE, Lippard SJ. Structural aspects of platinum anticancer drug interaction with DNA. Chem Rev 87:1153–1181 (1987).
20. Takahara PM, Frederick CA, Lippard SJ. Crystal structure of the anticancer drug cisplatin bound to duplex DNA. J Am Chem Soc 118:12309–12321 (1996).
21. Rice JA, Crothers DM, Pinto AL, Lippard SJ. The major adduct of the antitumor drug cis-diamminedichloroplatinum(II) with DNA bends the duplex by 40° toward the major groove. Proc Natl Acad Sci USA 85:4158–4161 (1988).
22. Sorenson CM, Barri MA, Eastman A. Analysis of events associated with cell cycle arrest at G2 phase and cell death induced by cisplatin. J Natl Cancer Inst 82:749–755 (1990).
23. Barri MA, Behnke CA, Eastman A. Activation of programmed cell death (apoptosis) by cisplatin, other anticancer drugs, toxins and hyperthermia. Biochem Pharmacol 40:2353–2362 (1990).
24. Orbell JD, Taylor MR, Birch SL, Lawton SE, Vilkins LM, Keefe LJ. The crystal structures of four models for the binding to DNA of cisplatinum derivatives containing a bidentate tertiary diamine. Inorg Chim Acta 152:125–134 (1988).
25. Coluccia M, Correale M, Giordano D, Mariggiò MA, Moscelli S, Fanizzi FP, Natile G, Maresca L. Mutagenic activity of some platinum complexes with monodentate and bidentate amines. Inorg Chim Acta 123:225–229 (1986).
26. Wilkinson RG, Shepherd RG, Thomas JP, Baughn C. Stereospecificity in a new type of synthetic antituberculous agent. J Am Chem Soc 83:2212–2213 (1961).
27. Kritsyn AM, Likhoshertov AM, Protopopova TV, Skoldinov AP. Ethambutol and related compounds. Synthesis and stereochemical relationships. Dokl Akad Nauk SSSR 145:332–335 (1962).
28. Giannini G, Natile G. Steric constraints inside the metal-coordination sphere as revealed by diastereotopic splitting of methylene protons. Inorg Chem 30:2853–2855 (1991).
29. Coluccia M, Fanizzi FP, Giannini G, Giordano D, Intini FP, Lacidogna G, Loseto F, Mariggiò MA, Nassi A, Natile G. Synthesis, mutagenicity, binding to pBR322 DNA and antitumor activity of platinum(II) complexes with ethambutol. Anticancer Res 11:281–288 (1991).
30. Kidani Y, Inagaki K, Tsukagoshi S. Examination of antitumor activities of platinum complexes of 1,2-diamminocyclohexane isomers and their related complexes. Gann 67:921–922 (1976).
31. Kidani Y, Inagaki K, Saito R, Tsukagoshi S. Synthesis and antitumor activities of platinum(II) complexes of 1,2-diaminocyclohexane isomers and their related derivatives. J Clin Hematol Oncol 7:197–208 (1977).
32. Kidani Y, Inagaki K, Iigo M, Hoshi A, Kuretani K. Antitumor activity of 1,2-diamminocyclohexane-platinum complexes against sarcoma 180 ascites form. J Med Chem 21:1315–1318 (1978).
33. Kidani, Y, Noji M, Tashiro T. Antitumor activity of platinum(II) complexes of 1,2-diaminocyclohexane isomers. Gann 71:637–643 (1980).
34. Boudny V, Vrana O, Gaucheron F, Kleinwächter V, Leng M, Brabec V. Biophysical analysis of DNA modified by 1,2-diaminocyclohexane platinum(II) complexes. Nucleic Acids Res 20:267–272 (1992).
35. Noji M, Okamoto K, Kidani Y, Tashiro T. Relation of conformation to antitumor activity of platinum(II) complexes of 1,2-cyclohexanediamine and 2-(aminomethyl)cyclohexylamine isomers against leukemia P388. J Med Chem 24:508–514 (1981).
36. Okamoto K, Noji M, Tashiro T, Kidani Y. Preparation of platinum(II) complexes of diamine isomers [PtX(1,3-diamine)] (X = Cl_2, SO_4, $(NO_3)_2$, oxalato, D-glucuronato and D-gluconato) and determination of their antitumor activity against leukemia L1210. Chem Pharm Bull (Tokyo) 29:929–939 (1981).
37. Noji M, Motoyama S, Tashiro T, Kidani Y. Synthesis and antitumor activity of Pt(II) complexes containing 2,3-diaminopropanol isomers. Chem Pharm Bull (Tokyo) 31:1469–1473 (1983).
38. Noji M, Gohchi Y, Kidani Y. Preparation of antitumour platinum(II) complexes of 1,2-diphenylethylenediamine isomers and their interactions with DNA and its purine moieties. Chem Biol Interact 51:37–48 (1984).
39. Vickery K, Bonin AM, Fenton RR, O'Mara S, Russell PJ, Webster LK, Hambley TWJ. Preparation, characterization, cytotoxicity, and mutagenicity of a pair of enantiomeric platinum(II) complexes with the potential to bind enantioselectively to DNA. J Med Chem 36:3663–3668 (1993).
40. Fenton RR, Easdale WJ, Er HM, OMara SM, McKeage MJ, Russell PJ, Hambley TW. Preparation, DNA binding, and *in vitro* cytotoxicity of a pair of enantiomeric platinum(II) complexes, [(*R*)- and (*S*)-3-aminohexahydroazepine]dichloroplatinum(II). Crystal structure of the S enantiomer. J Med Chem 40:1090–1098 (1997).
41. Fanizzi FP, Intini FP, Maresca L, Natile G, Quaranata R, Coluccia M, Di Bari L, Giordano D, Mariggio MA. Biological activity of platinum complexes containing chiral centers on the nitrogen or carbon atoms of a chelate diamine ring. Inorg Chim Acta 137:45–51 (1987).
42. Misset JL. Oxaliplatin in practice. Br J Cancer 77(suppl 4):4–7 (1998).
43. Spingler B, Whittington DA, Lippard SJ. 1,2-d(GpG) intrastrand cross-link formed by oxaliplatin with duplex DNA: a crystallographic study. J Inorg Biochem 86:440–440 (2001).
44. Spingler B, Whittington DA, Lippard SJ. 2.4 A crystal structure of an oxaliplatin 1,2-d(GpG) intrastrand cross-link in a DNA dodecamer duplex. Inorg Chem 40:5596–5602 (2001).
45. Wei M, Cohen SM, Silverman AP, Lippard SJ. Effects of spectator ligands on the specific recognition of intrastrand platinum-DNA cross-links by high mobility group box and TATA-binding proteins. J Biol Chem 276:38774–38780 (2001).
46. Malina J, Hofr C, Maresca L, Natile G, Brabec V. DNA interactions of antitumor cisplatin analogs containing enantiomeric amine ligands. Biophys J 78:2008–2021 (2000).
47. Malina J, Kasparkova J, Natile G, Brabec V. Recognition of major DNA adducts of enantiomeric cisplatin analogs by HMG box proteins and nucleotide excision repair of these adducts. Chem Biol 9:629–638 (2002).
48. Xu Y, Natile G, Intini FP, Marzilli LG. Stereochemically controlled influence atropisomerization of Pt(II) nucleotide complexes. Evidence for head-to-tail and stable L head-to-tail atropisomers. J Am Chem Soc 112:8177–8179 (1990).
49. Ano SO, Intini FP, Natile G, Marzilli LG. Viewing early stages of guanine nucleotide attack on Pt(II) complexes designed with in-plane bulk to trap initial adducts. relevance to *cis*-type Pt(II) anticancer drugs. J Am Chem Soc 119:8570–8571 (1997).
50. Ano SO, Intini FP, Natile G, Marzilli LG. A novel head-to-head conformer of d(GpG) cross-linked by Pt: new light on the conformation of such cross-links formed by Pt anticancer drugs. J Am Chem Soc 120:12017–12022 (1998).
51. Marzilli LG, Ano SO, Intini FP, Natile G. New concepts relevant to cisplatin anticancer activity from unique spectral features providing evidence that adjacent guanines in d(GpG), intrastrand-cross-linked at N7 by a *cis*-platinum(II) moiety, can adopt a head-to-tail arrangement. J Am Chem Soc 121:9133–9142 (1999).
52. Ano SO, Intini FP, Natile G, Marzilli LG. Retro models of Pt anticancer drug DNA adducts: chirality-controlling chelate ligands restriction of guanine dynamic motion in (2,2′-bipiperidine)PtG_2 complexes (G = guanine derivative). Inorg Chem 38:2989–2999 (1999).
53. Kasparkova J, Brabec V. Recognition of DNA interstrand cross-links of cis-diamminedichloroplatinum(II) and its trans isomer by DNA- binding proteins. Biochemistry 34:12379–12387 (1995).
54. Zlatanova J, Yaneva J, Leuba SH. Proteins that specifically recognize cisplatin-damaged DNA: a clue to anticancer activity of cisplatin. FASEB J 12:791–799 (1998).
55. Ohndorf UM, Rould MA, He Q, Pabo CO, Lippard SJ. Basis for recognition of cisplatin-modified DNA by high-mobility-group proteins. Nature 399:708–712 (1999).
56. Zamble DB, Lippard SJ. The response of cellular proteins to cisplatin-damaged DNA. In Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug (Lippert B, ed). Zürich:VHCA, Wiley-VCH, 1999;73–110.
57. Zamble DB, Mu D, Reardon JT, Sancar A, Lippard SJ. Repair of cisplatin-DNA adducts by the mammalian excision nuclease. Biochemistry 35:10004–10013 (1996).
58. Reardon JT, Vaisman A, Chaney SG, Sancar A. Efficient nucleotide excision repair of cisplatin, oxaliplatin, and bis-aceto-ammine-dichloro-cyclohexylamine-platinum(IV) (JM216) platinum intrastrand DNA diadducts. Cancer Res 59:3968–3971 (1999).
59. Moggs JG, Szymkowski DE, Yamada M, Karran P, Wood RD. Differential human nucleotide excision repair of paired and mispaired cisplatin-DNA adducts. Nucleic