Inorganica Chimica Acta, *137* (1987) 123–124

A Doxorubicin–Pt(II) Complex. Chemistry and Antitumor Activity*

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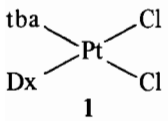
Abstract

Compound **1**, *cis*-[$PtCl_2$(Dx)(tba)], where Dx is *N*-coordinated doxorubicin and tba is *tert*-butylamine, is active against murine P388 and murine L1210 leukemias, including cisplatin- and doxorubicin-resistant sublines, but against a Dx-resistant solid tumor its activity resembles that of doxorubicin. Preliminary results, based on circular dichroism spectroscopy, suggest that **1** interacts with DNA mainly by intercalation of the Dx moiety, rather than by covalent binding of Pt.

Introduction

Synergism between cytotoxic agents is well documented and is the basis for combination chemotherapy [1]. More recently antitumor agents carrying more than one cytotoxic moiety in the same molecule (multifunctional antitumor agents) have been proposed as a possible approach to improve the effectiveness of a drug [2]. This has been done also in the case of cisplatin [3], and we report here one such case, *i.e.* compound **1**, in which tba is *tert*-butylamine and Dx is doxorubicin.



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Results and Discussion

The compound was prepared as follows:

$$[PtCl]_4^{2-} + \text{tba} \xrightarrow{\text{DMF}} \underset{\mathbf{2}}{[PtCl_3(\text{tba})]^-} \xrightarrow{\text{Dx·HCl}} \underset{\mathbf{1}}{cis\text{-}[PtCl_2(\text{Dx})(\text{tba})]} + \text{HCl}$$

*Paper presented at the Symposium on Cisplatin and Inorganic Anticancer Drugs, Bari, Italy, November 6–7, 1986.

The infrared spectrum of **1** shows two ν(Pt–Cl) (320 and 330 cm^{-1}, polyethylene disks). The bands of Dx, in particular those of the hydroxyanthraquinone moiety, are unaffected. Electronic and circular dichroism (CD) spectra of **1** are also superimposable on those of Dx·HCl. Moreover one equivalent of HCl is liberated during the formation of **1**. We therefore believe that Dx is coordinated to Pt via the 3′-amino group and *cis* to tba.

By reaction, in aqueous solution, of **1** with guanosine (guo) *cis*(?)-[Pt(dx)(tba)(guo)$_2$]Cl_2, **3** has been obtained. The CD spectrum of **3** is very similar to that of **1** and does not show any sign of the doublet centered at about 260 nm which has been observed when two guo molecules are bound to Pt in the *cis*-position [4]. Therefore, either the doublet is buried under the strong bands of Dx, or isomerization has occurred. In the FAB mass spectrum of **3** we could observe peaks due to species containing Pt, guo and tba, but no species with Dx.

Compound **1** has been reacted with DNA (at Pt/G ratios 1 and 0.5). The CD spectra of the resulting solutions show a rise in intensity of the positive band at 275 nm of DNA, superimposable on the spectra of the Dx–DNA adducts obtained under the same conditions. This behavior has been interpreted as typical of intercalation into the DNA, with concomitant unwinding of the helix [5]. No sign of the spectral behavior reported for the interaction of cisplatin and its analogs with DNA [6] has been detected. We therefore believe that, at least *in vitro*, **1** interacts with DNA mainly through intercalation, in contrast with what was found for other cisplatin analogs bound to intercalating drugs, which show cooperative effects in the unwinding of DNA [7].

FAB mass spectra of compound **3** suggest that the Dx–Pt bond can be broken. The spectral features observed in the interaction of **1** with DNA may therefore be due only to intercalation of Dx, followed by dissociation of a Pt-containing species; a separate experiment has in fact shown that the interaction of **2** with DNA does not give rise to relevant change of the CD spectrum.

The biological activity of **1** was evaluated in comparison with cisplatin and Dx, as reference

0020-1693/87/$3.50

compounds, in murine tumors (Tables I–III). Compound **2**, the synthetic precursor of **1**, was also included in these experiments. The activity of **1** was comparable to that of Dx against P388 and L1210 leukemias, which are also sensitive to cisplatin. However, when tested against two resistant sublines of leukemia (L1210/DDP, resistant to cisplatin, and P388/Dx, resistant to doxorubicin) **1** showed lack of cross-resistance in both models. Against the solid murine tumor colon carcinoma #26 (naturally resistant to Dx) the antitumor effects of **1** resemble that of Dx, being less active than cisplatin.

These results indicate that the activity of **1** more closely resembles that of Dx. Studies are in progress to elucidate the possible lack of cross-resistance of **1** with Dx.

TABLE I. Antitumor Activities of Cisplatin, Dx, **1**, and **2** towards Murine Leukemias[a] [8]

Drug	Dose (μmol/kg)	*T/C* (%)	LTS	Toxic deaths
P388 (10^6 cells, i.p.)				
cisplatin	23	246	0/10	1/10
2	40	211	0/10	0/10
Dx	17.3	305	7/19	0/19
	26	300	7/10	0/10
1	17.3	363	8/19	0/19
	26	388	5/10	0/10
L1210 (10^5 cells, i.p.)				
cisplatin	23	175	1/8	0/8
2	48.3	137	0/8	0/8
Dx	17.3	187	0/9	0/9
	24	200	1/9	1/9
1	17.3	187	0/9	0/9
	24	187	0/9	0/9
	33.8	225	0/9	1/9

[a]Single dose i.p.; LTS = long-term survivals (>60 days).

TABLE II. Antitumor Activities of Cisplatin, Dx, and **1** towards Murine Leukemia Sublines Resistant to Dx and Cisplatin[a] [8]

Drug	Dose (μmol/kg)	*T/C* (%)	LTS	Toxic deaths
P388/Dx (10^6 cells, i.p.)				
cisplatin	16.7–23	183 (175–191)	0/18	4/18
Dx	17.3	100	0/9	0/9
	26	100	0/9	0/9
1	17.3	230	0/9	0/9
	26	170	0/9	2/9
L1210/DDP (10^5 cells, i.p.)				
cisplatin	23	100	0/10	0/10
	33	100	0/10	1/10
Dx	17.3	145	2/10	0/10
	27	159	2/10	1/10
1	17.3	136	0/9	0/9
	24	145	0/10	0/10

[a]Single dose i.p.; LTS = long-term survivals (>60 days).

TABLE III. Antitumor Activity of Cisplatin, Dx, and **1** against Solid Murine Early Colon Carcinoma #26[a]

Compound	Dose (μmol/kg)	*T/C* (%)	TWI (%)	Toxic deaths
cisplatin	15	152	91	1/10
	20	101	96	7/10
Dx	10.4	132	23	1/10
	12.9	130	70	2/10
1	10.4	138	40	0/10
	13.3	94	70	2/10

[a]Tumor was transplanted s.c. Drugs were given i.v. q7dx3. TWI = tumor weight inhibition. On day 20 tumor weight in control mice was 900 mg.

Acknowledgement

We thank the CNR Rome for financial support.

References

1 V. T. De Vita, Jr., in V. T. De Vita, Jr., S. Hellman and S. A. Rosenberg (eds.), 'Cancer', Lippincott, Philadelphia, 1985, p. 257.
2 M. A. Khaled, R. D. Morin, F. Benington and J. P. Daugherty, *Cancer Chemother. Pharmacol., 13,* 73 (1984).
3 A. Pasini and F. Zunino, *Angew. Chem.*, in press.
4 M. Gullotti, G. Pacchioni, A. Pasini and R. Ugo, *Inorg. Chem., 21,* 2006 (1982).
5 For instance, F. Hudecz, J. Kajtar and M. S. Zekerk, *Nucleic Acids Res., 9,* 6959 (1981).
6 A. Pasini, A. Velcich and A. Mariani, *Chem.-Biol. Interact., 42,* 311 (1982) and references therein.
7 R. E. Bowler and S. J. Lippard, *Biochemistry, 25,* 3031 (1986).
8 F. Zunino, G. Savi and A. Pasini, *Cancer Chemother. Pharmacol., 18,* 180 (1986).