Synthesis and Evaluation of Biological Activity of Binuclear Cisplatin Analogues with Polyoxypropylene-α,ω-diamines as the Bridging Groups

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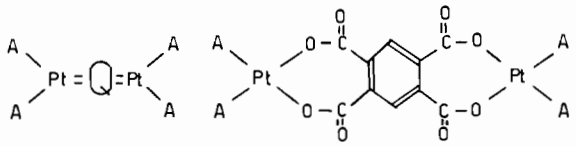
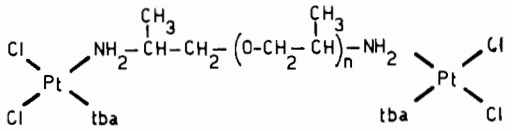
The search for analogues of the antitumour agent cisplatin (*cis*-diamminodichloroplatinum(II)) with improved therapeutic indices has led to the synthesis of a very high number of compounds designed on the basis of a variety of rational approaches [1–4]. One such approach has been the synthesis of binuclear complexes of the type **1a** [1, 5–9]. Most reported complexes consist of two A_2Pt units (A = amine or 1/2 diamine) linked by a quadrifunctional moiety (Q) acting as the common leaving group. An example is **1b** in which Q is benzene tetracarboxylic acid [7–9].



1a **1b**

Since some derivatives of the binuclear complexes **1b** possess promising biological properties, it was thought interesting to examine binuclear cisplatin analogues derived by the alternative approach of binding two $PtCl_2$ moieties to a common non-leaving group. In molecules **2a** and **2b** (tba = t-butylamine) the two Pt atoms are linked by a diamine sufficiently long to avoid chelate formation. The diamines used were the polyoxypropylene-α,ω-diamines jeffamine D230 (**2a**) and D400 (**2b**), which were kindly supplied by Texaco. This choice was dictated by their easy availability and by the consideration that the polyether chain beside conferring water and liposolubility to the complexes, could act as a carrier increasing cytotoxicity [10–12]. As for the choice of t-butylamine, see ref. 13.



2a, n = 2.6; **2b**, *n* = 5.6; tba = t-butylamine.

Experimental

The compounds were prepared by reaction of 2 moles of $K[PtCl_3tba]$ (see ref. 14) with 1 mole of jeffamine in methanol at 40 °C for 4 h. After addition of chloroform KCl was filtered off and the solution was evaporated to dryness. Compound **2a** was obtained as yellow crystals by addition of ether; **2b** was a yellow oil.

Compound **2a**: *Anal.* Found: C, 25.1; H, 5.4; N, 6.3. Calc. for *n* = 2.6: C, 25.0; H, 5.3; N, 6.3%. ν(Pt–Cl) 315sh, 330 cm^{-1} (polyethylene disks).

Compound **2b**: *Anal.* Found: C, 30.6; H, 5.9; N, 5.4. Calc. for *n* = 5.6: C, 31.0; H, 6.1; N, 5.2%. ν(Pt–Cl): 320, 330 cm^{-1} (KBr disks).

Further proof for the *cis*-dichloro structure was obtained by the Kurnakov test: both compounds gave deep yellow solutions by reaction with aqueous thiourea [15].

The compounds are soluble in water and in the common organic solvents.

Exponentially growing cells were exposed to the drugs for 72 h. Cytotoxic activity was determined by growth inhibition tests [16]. L1210 leukemia models and evaluation of antitumour activities have already been described [17]. The drugs were administered intraperitoneally (i.p.) as a single dose on day one after tumour transplantation.

Results and Discussion

Compound **2a** was found to be poorly cytotoxic towards L1210 leukemia cells *in vitro*: ID_{50} = 1.6 nmol/ml (corresponding to 3.2 nmoles of Pt/ml); for cisplatin, ID_{50} = 0.49 nmol/ml in the same experiment. Compound **2b** was not cytotoxic up to 2 nmol/ml towards the same cell line. Moreover, **2a** was inactive towards i.p.-transplanted L1210 leukemia in mice up to a dose of 50 mg/kg, corresponding to 0.1 mmoles of Pt/kg (cisplatin gave a *T/C%* value of 175 at 0.02 mmol/kg in the same experiment). However, no toxicity was observed at this dose.

The pharmacological and cytotoxic potencies were too low, thus these compounds are considered to be unsuitable for future development as anticancer drugs and no further experiments are planned.

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The inactivity of compounds **2** must be compared with the reported high activity of some binuclear Pt complexes with a common leaving group (**1**). Such a difference may arise from unfavourable pharmacokinetics at the cellular level, or from the different chemical properties of structures **1** and **2**. For instance, if aquation is a key step of the mode of action of cisplatin analogues [18, 19], hydrolysis of compounds such as **1** will release the pharmacologically active *monomeric* species A_2PtS_2 ($S = H_2O$, OH). On the contrary, the *dimeric* species $S_2Pt{-}{-}{-}PtS_2$ may form with difficulty (the wholly aquated species would have a +4 charge), or be inert towards the target macromolecules.

Since these differences are important in designing new binuclear (and perhaps polynuclear) cisplatin analogues, work is being planned to clarify the biological and chemical properties of molecules such as **1** and **2**.

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Note Added in Proof

After the submission of this paper we became aware of binuclear Pt complexes based on a similar approach: N. P. Farrel, S. G. De Almeida and K. A. Skov, *J. Am. Chem. Soc., 110* (1988) 5018.