Antitumor Activity and Metal Complexes, a Comparison

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Recently we have studied the inhibition effect of cell proliferation for half hundred coordination compounds with respect to L 1210 leukemia and Ehrlich ascites carsinoma cells *in vitro* [1] and *in vivo* [2] to find new metal complexes possessing antitumor activity. Among the compounds studied *trans*-bis-(salicylaldoximato)copper(II) and *trans*-bis-(resorcylaldoximato)copper(II) appeared to have most promising properties in this respect.

In addition to this we have undertaken comparative experiments with L 1210 cells and *cis*-platin [3] *in vitro* in the same way as previously described [1] to investigate the proliferation inhibition effectiveness of the copper(II) complexes. These results are presented in Table I, and compared with earlier results [1] in Fig. 1.

The curves (Fig. 1) show the copper(II) complexes to have a 50% inhibition effect at about 5 ppm; a 100% inhibition is achieved at the 6.5–7.5 ppm concentration level. The results are practically identical after one or two days. For *cis*-platin the 50 and 100% inhibition effects are reached at around the 0.5 and 5–7 ppm concentration levels, respectively, but there is a greater difference between the results after one and two days. Approximately 100% inhibition is achieved after one day only by using a much higher concentration level. Therefore the inhibition effect of *cis*-platin appears to be more time dependent than that of the copper(II) complexes.

The difference in the curves for the *cis*-platin and the copper(II) complexes suggests that the mechanism of the inhibition effect of tumor cell proliferation by the copper(II) complexes is different from that of *cis*-platin [3, 4]. Furthermore, experiments

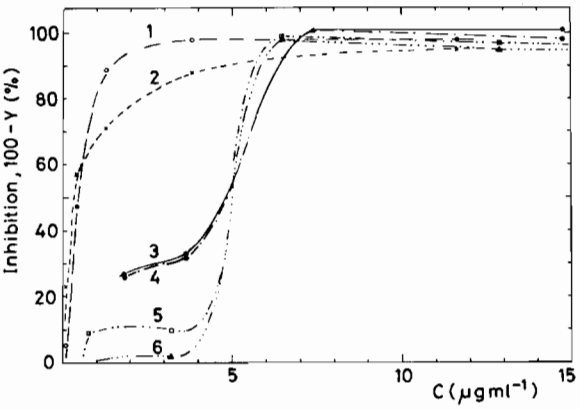

Fig. 1. Comparison of proliferation inhibition of L 1210 cells *in vitro*. Curves: 1 and 2, *cis*-$Pt(NH_3)_2Cl_2$; 3 and 4, *trans*-bis(resorcylaldoximato)copper(II); 5 and 6, *trans*-bis(salicylaldoximato)copper(II). Curves 2, 3 and 6 after 1 day; curves 1, 4 and 5 after 2 days.

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TABLE I. Cell Culture of L 1210 and Effect of *Cis*-diamminedichloroplatinum(II)[a].

	$Pt(NH_3)_2CL_2$ ($\mu g\ ml^{-1}$)	Initial cell density (10^6 cell ml^{-1})	Cell density (10^6 cell ml^{-1})		Y (%)	
			1 day	2 day	1 day	2 day
		B	C, A	C, A		
Control	–	0.28	0.801	1.859		
Control	–	0.28	0.779	1.885		
DMSO-contr.	–	0.28	0.784	1.989	100	100
DMSO-contr.	–	0.28	0.738	1.552	100	100
Complex	11.65	0.28	0.303	0.304	5	2
	3.85	0.28	0.340	0.311	12	2
	1.30	0.28	0.418	0.443	29	11
	0.43	0.28	0.428	1.075	43	53
	0.15	0.28	0.648	1.700	77	95

[a]The culture method and equipment used were the same as previously described [1]. 2.33 mg of *cis*-$Pt(NH_3)_2Cl_2$ (Aldrich, 99.99%) was dissolved in dimethylsulphoxide (Merck, zur Synthese) just before adding to the cell culture. 25 μl of this solution was added to 5 ml of the cell culture. Y (%) = ((A – B)/(C – B)) × 100, where A = the cell density of the sample tube, B = the initial cell density, and C = the mean cell density of the solvent controls.

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in vivo [2] showed that nasal swelling and severe weight loss in mice, typical symptoms of vitamin B_6 deficiency, disappeared a few days after administration of *trans*-bis(salicylaldoximato)copper(II). When comparing the molecular formulas of salicylaldoxime and pyridoxal (Fig. 2), it appears that the former or its copper(II) complex deactivates pyridoxal kinase by replacing the latter, and thus hinders the homogeneously catalyzed transamination and decarboxylation processes based on pyridoxal [5] in cells and blocks protein synthesis, DNA replication and cell division. In addition, the experiments *in vivo* [2] suggest that *trans*-bis(salicylaldoximato)copper(II) may concentrate especially in the tumor cells. Thus the proliferation of tumor cells is slowed and the natural defensive mechanism of the body is more able to destroy the tumor cells and enhance recovery. The experiments *in vivo* [2] also showed that some immunity against the cancer can be achieved. Consideration of the magnetic susceptibility and the number of unpaired 3d electrons [1, 6] of *trans*-bis(salicylaldoximato)copper(II) implies that electron transfer may be involved in the proliferation inhibition process.

Therefore, this provokes the idea that as far as the different varieties of tumor cells and their common and special enzymatic processes are recognized, it could be possible to find metal complexes or general compounds which impede one or several of these enzymatic processes and thus act as general or special cancer drugs [7].

Acknowledgements

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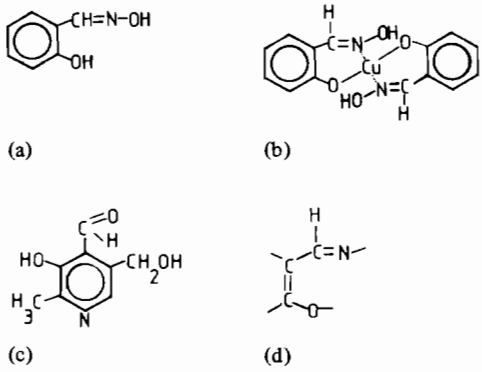

Fig. 2. Comparison of the molecular formulas: (a) salicylaldoxime, (b) *trans*-bis(salicylaldoximato)copper(II), (c) pyridoxal, (d) the essential organic skeletal part which may render it possible for aldoxime type compounds to displace pyridoxal and so to inhibit its phosphorylation and binding to its apoenzymes [5].

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