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PS6.15 — TU

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PLATINUM(II) AND PALLADIUM(II) HALIDE COMPLEXES WITH DITHIOCARBAMIC DERIVATIVES AND THEIR CYTOSTATIC ACTIVITY

The elevated toxicity is a severe dose-limiting factor in cisplatin antitumor therapy. Nephrotoxicity is one of the most important effects and it seems due to some metabolic pathways of the drug. It can be prevented by the contemporary administration of diuretics [1]. Protection by sulfur containing compounds could be an alternate mean of

preventing toxicity [2]. So far sodium diethyldithiocarbamate (DDTC) is the most promising one. Moreover DDTC exhibits a protective effect against chemical induced tumors. Its immunostimulating properties have been recently evidenced also [3]. The efficacy of cisplatin-DDTC combination is dose and time dependent in *in vivo* experiments.

Owing to the importance of DDTC metabolites and their possible interaction with cisplatin, we prepared and studied Pt(II) and Pd(II) complexes with dithiocarbamic esters. A number of them showed *in vitro* cytotoxicity (Table I), but the generally low solubility prevented to carry out a study in solution [4].

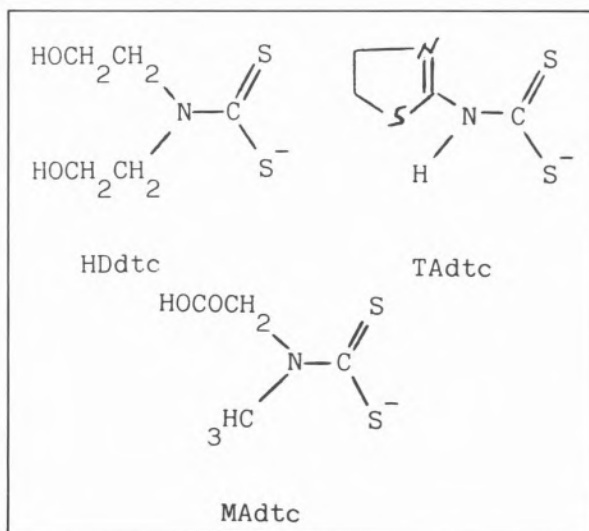
Table I
 "In vitro" Cytostatic Activity against KB cells

			Complexes	ID ₅₀ (μg/ml) *
$\begin{array}{c} \text{R} \quad \quad \text{S} \\ \quad \quad \diagup \quad \diagdown \\ \text{N}-\text{C} \\ \quad \quad \diagdown \quad \diagup \\ \text{R} \quad \quad \text{SR}' \end{array}$	R = R' = Me	TMDT	Pd(DMDTE)Cl ₂	**
	R = R' = Et	TEDT	Pd(DMDTE)Br ₂	3.6
	R = Me, R' = Et	DMDTE	Pd(TEDT)Cl ₂	0.17
	R = Et, R' = Me	DEDTM	Pd(TMDT) ₂ Cl ₂	1.02
			Pd(DMDTE) ₂ Br ₂	0.98
			Pt(TEDT) ₂ I ₂	3.8
			Pt(TMDT) ₂ Br ₂	2.8
			Pt(DMDTE) ₂ Br ₂	0.4

* The results of the cytostatic activity are expressed as dose at which the cells showed a 50% growth inhibition (ID₅₀). ID₅₀ value for cisplatin is 0.11 μg/ml.

** The complex is active but the value was not determined since dose-response relationship was not observed.

The following anions and some related esters have been synthesized:



Their reactions with platinum(II) and palladium(II) halides will be reported and discussed, together with the preliminary cytotoxicity data. Except for $M(\text{HDdte})_2$ and unlike the corresponding $M(\text{DEdte})_2$, where DEdte is the diethyldithiocarbamate anion, M is Pt or Pd, $M(\text{TAdtc})_2$ and $M(\text{MAdtc})_2$ are very soluble in several organic solvents, so that these compounds are promising for future biological studies.

ACKNOWLEDGEMENTS

L.T. was supported by a RECORDATI Industria Chimica e Farmaceutica S.p.A. grant.

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PS6.16 — TH

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THE ONCOGENE OF MURINE SARCOMA VIRUS V-Ki-ras MAY ARISE AS A RESULT OF CHEMICAL ACTION ON THE PROTOONCOGENE c-ras

The processes of nucleotide transition and transversion leading to point mutations in DNA play a certain role in the malignant transformation. The cause of such transformations may consist either

in bivalent transition metals, *e.g.* $G \cdot \text{Me}^{2+} \rightarrow A$ (where G is guanine and A is Adenine) as E.L. ANDRONIKASHVILI and N.G. ESIPOVA [1] have shown, or in the methylation processes considered in detail by G. KLOPMAN and A. RAY [2] from the view-point of quantum biochemistry. Thus, for instance, at CH_3 group binding with guanine 06 the electronic structure of this nucleotide becomes similar to that of adenine, whereas thymine alkylation in 04 transforms it into cytosine-like state.

On the other hand, as a result of the investigations carried out by R. WEINBERG [3], M. BARBACID [4] and their collaborators, it has become evident that the point mutation in coding GGC triplet occupying the 12th position in the normal cellular gene c-ras (which is also called protooncogene) is characteristic of human bladder carcinoma (of chemical origin). This mutation transforms GGC triplet into GTC triplet.

However, the same 12th triplet of protooncogene undergoing $\text{GGC} \rightarrow \text{AGC}$ mutation becomes a characteristic feature of Kirsten viral murine sarcoma. The respective oncogene is called V-Ki-ras. However, in order to cause $G \rightarrow A$ transition, as it has been shown in refs. [1] and [2], the interference of a certain chemical agent is sufficient. Such an agent may be both a bivalent transition metal ion and a methylic group CH_3 .

Thus, in order to cause the formation of oncogene typical of murine sarcoma virus from a normal cellular gene of c-ras type, it is sufficient that the first guanine of the 12th GGC triplet would trap a bivalent transition metal ion or that alkylguanine would arise instead of guanine.

The oncogene of virus causing malignant diseases formed as a result of chemical action will act subsequently in accordance with viro-genetic theory. It should be emphasized that other mutations of the GGC triplet under consideration, as well as those of coding triplets of other types, being characteristic of one or another neoplasia, may have no connection with viral transformation.

Clearly, at the present stage of carcinogenesis theory development, we have no reasons to make a sharp distinction between viro-genetic and chemical theories.