Monomeric, Air-stable Metallocenes of Main-group Elements as Antitumor Agents

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Bis(cyclopentadienyl)metal diacido complexes containing early transition metals are known to exhibit antiproliferative properties against diverse animal and human tumors [1–4]. The most effective agents of this group of compounds are the metallocene dichlorides $(C_5H_5)_2TiCl_2$ and $(C_5H_5)_2VCl_2$ [1–5]. Other examples of non-platinum-group metal antitumor agents are some organometallic compounds of tin and germanium being mainly represented by the diorganotin dihalide complexes $R_2SnX_2L_2$ [6] and the germanium compounds 8,8-diethyl-2-[3-(*N*-dimethylamino)propyl]-2-aza-8-germaspiro[4,5]decane ('spirogermanium') [7] and bis[(carboxyethyl)germanium]trioxide ('germanium sesquioxide', Ge-132) [8].

In the present study, we investigated the antitumor properties of a hybrid of both types of compounds, represented by decaphenylstannocene and decaphenylgermanocene $[\eta^5\text{-}(C_6H_5)_5C_5]_2M^{II}$ with M = Sn (**I**) or G (**II**) (Fig. 1). They are the first air-stable cyclopentadienyl complexes of germanium(II) and tin(II).

Both complexes were synthesized as described recently [9, 10], dissolved or suspended in a mixture of Tween 80 and saline (1/9, *v/v*) and administered intraperitoneally to mice bearing fluid Ehrlich ascites tumor which is considered to be a tumor not very sensitive to cytostatic agents [11]. Details of the antitumor bioassay were described before [12, 13]. **I** was applied in doses of 20, 40, 60, ..., 600 mg/kg, **II** in doses ranging between 20 and 700 mg/kg. Every dose group consisted of 10 animals. Because of limited water solubility of **I** and **II**, no doses higher than 600 or 700 mg/kg, respectively, were administered.

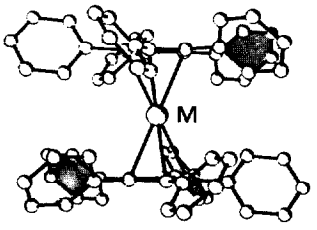

Fig. 1. Molecular structure of $[\eta^5\text{-}(C_6H_5)_5C_5]_2M^{II}$ (M = Sn, I; M = Ge, II).

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After treatment with both compounds, cure rates of 40–90% (**I**) or 40–80% (**II**) were provoked in dose ranges of 160–460 mg **I**/kg or 280–700 mg **II**/kg, respectively, (Figs. 2, 3). Obviously, there was no strong dependence between the doses applied and the cure rates effected, as it is usually observed after application of other cytostatic metal complexes [4]. In the case of **I**, toxic deaths were caused by doses exceeding 440 mg/kg, the LD_{50} amounting to a value even higher than 600 mg/kg. Toxic deaths did not occur after administration of **II** within the experimental dose range up to 700 mg/kg. Though the toxic threshold was not yet attained for **II**, higher doses were not applied because it was difficult to dissolve them sufficiently.

I and **II** are the first main-group metallocenes for which antiproliferative activity was found. Respecting the chemical features of other non-platinum-group metal antitumor agents, this result is quite surprising, because **I** and **II** do neither contain covalently bound

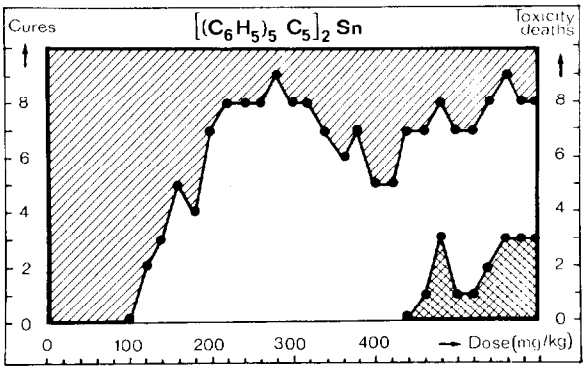

Fig. 2. Dose-activity (left graph) and dose-lethality (right graph) relationships of I against fluid Ehrlich ascites tumor in mice. ▨ Tumor deaths, ▩ deaths due to substance toxicity, □ surviving, cured animals.

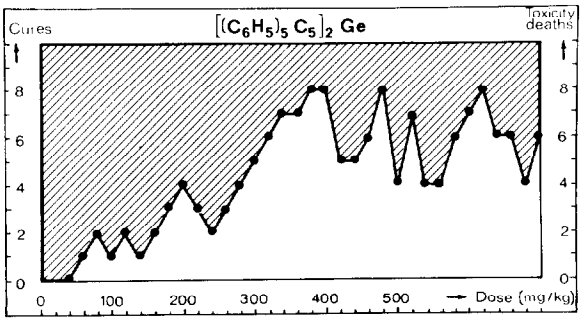

Fig. 3. Dose-activity relationships of II against fluid Ehrlich ascites tumor in mice. ▨ Tumor deaths, □ surviving animals.

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acido ligands, as it is known for other antitumor compounds such as *cis*-diamminedichloroplatinum(II), titanocene and vanadocene dihalides or the diorganotin dihalide complexes [4], nor comprise unsubstituted cyclopentadienyl groups, as it seems to be a prerequisite for strong antitumor potency of metallocene diacido complexes containing early transition metals [14]. Further investigations are necessary to clarify if the central atoms of **I** and **II** or the organic ligands are mainly responsible for the antiproliferative activity of decasubstituted stannocene and germanocene complexes.

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