Antitumor Activity of some Organometallic Bismuth(III)thiolates

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Abstract

The neutral organobismuth(III)bis(thiolates) $CH_3Bi(SCH_3)_2$ and $CH_3Bi(p\text{-}SC_6H_4NH_2)_2$ and the ionic mercaptoanilinium derivative $[CH_3Bi(p\text{-}SC_6H_4NH_2CH_3)_2]^{2+}2I^-$ were tested for antitumor properties in the fluid Ehrlich ascites tumor system of mice. They all effected an optimum cure rate of 100% and were characterized by values of the therapeutic index ranging between 3.2 and 5.0.

Introduction

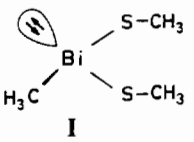
Main-group V compounds have an old tradition as chemotherapeutic agents. Already Paracelsus, "the true father of modern metallotherapy" [1], administered mixtures of diverse heavy metals including As against various diseases. The first communication in the literature concerning the use of an arsen compound (Liq. arsenic Fowler) against human malignancies dates to 1865 and reports upon the treatment of two patients suffering from leukemia [2]. The most famous example of an arsen compound used in clinical therapy is the arsen(III) compound arsphenamin (Salvarsan^R) exhibiting pronounced antimicrobial activity and which was approved as drug against syphilis before the era of antibiotics [3]. Tryparsamid and melarsenoxid are applied still nowadays against advanced stages of the African sleeping disease [4] caused by the protozoa trypanosomes.

Inorganic and organic compounds of arsen are burdened by severe toxicologic side effects limiting the medical use of arsen compounds [5, 6]. On the other hand, it is known that some organometallic compounds of bismuth, a heavier homologue of arsen, are also characterized by antimicrobial activity. This was shown for triphenylbismuth [7, 8] and recently for organobismuth(III)bis(thiolates) [9]. The latter are able to inhibit the growth of some enterobacteriaceae at low concentrations and to induce bacterial elongation *in vitro* [10]. In the present study, we investigated the antitumor effect of some organometallic chalcogeno bismuth(III) compounds including the mentioned thiolate derivatives and report upon the results observed with fluid Ehrlich ascites tumor in mice.

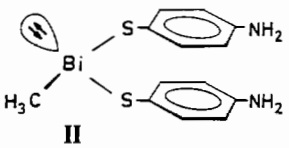
Experimental

Substances

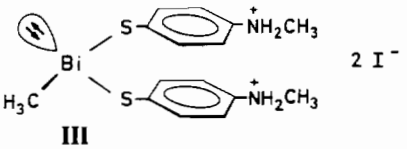
The methylbismuth(III)bis(thiolates) $CH_3Bi(SCH_3)_2$ **(I)**, $CH_3Bi(p\text{-}SC_6H_4NH_2)_2$ **(II)** and $[CH_3Bi(p\text{-}SC_6H_4NH_2CH_3)_2]^{2+}2I^-$ **(III)** were synthesized as described recently before [9] and characterized by elemental analysis (C, H, N), IR, ^1H NMR and mass spectra [9]. No impurities were detectable by these methods.



I



II



III

For testing purposes, the compounds were applied in doses ranging between 2.5 and 160 mg/kg. They are listed in Table I. As the compounds, especially **I** and **II**, were soluble in water to an only limited extent, the compounds were dissolved in

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TABLE I. Pharmacological Data of Organobismuth(III)bis(thiolates) against fluid Ehrlich Ascites Tumor

Compound	Applied doses (mg/kg)	Optimum doses (mg/kg)	Optimum cure rate (%)	LD_{50} (mg/kg)	LD_{100} (mg/kg)	T.I.[a]
I	2.5, 5, 10, 15, 20, 30, 40, 60, 80, 100	15–20	100	32	80	3.2
II	5, 10, 20; 40, 60, 80, ...; 160	40	100	85	140	4.3
III	5, 10, 20; 40, 60, 80, ..., 160	60–80	100	100	160	5.0

[a]T.I. = therapeutic index, determined by calculation LD_{50}/ED_{75}.

Tween 80 (Serva, Heidelberg) and then suspended in saline. The volume ratio Tween:saline always amounted to 1:9. The substance concentrations were selected in such a way that each mouse received a total volume of 0.4–0.5 ml (0.02 ml/g body weight). The preparations were administered intraperitoneally within 30 min after dissolution.

Animals

Female CF1 mice (Winkelmann, Paderborn) weighing 20–25 g were kept under standard conditions. They received feeding (Altromin^{R}) and tap water ad libitum.

Antitumor Bioassay

The antitumor activity of the substances was tested against Ehrlich ascites tumor growing as fluid tumor in the peritoneal cavity of mice. For tumor transplantation, the ascites of donor mice bearing Ehrlich ascites tumor for 8 days was diluted with saline 1:7 (*v*:*v*). About 6×10^6 cells were transplanted intraperitonelly into each animal on day 0 of the experiment. The intraperitoneal administration of the substances applied as single doses was performed 24 h later. Every dose group consisted of 8 animals. Another 16 mice served as untreated tumor-bearing control animals. They obtained 0.5 ml of the Tween-saline mixture (1:9, *v*:*v*) without drug addition.

The number of deaths was recorded daily. Deaths within 7 days after substance application were defined as toxic deaths, those occurring later, as tumor deaths. All animals dying after day 8 showed macroscopic signs of tumor development. The control animals died between day 16 and 23, the mean value of survival time amounting to 19.4 ± 2.3 days. The key-date for determining the survival rate was day 60 after tumor transplantation. All animals, being still alive on key-date, had no recognizable signs of tumor. They were considered as cured.

Results

All three organometallic methylbismuth(III)thiolates **I**–**III**, investigated in the present study, were characterized by antiproliferative activity against Ehrlich ascites tumor (Figs. 1–3). They effected an optimum cure rate of 100% (Table I), *i.e.* all animals

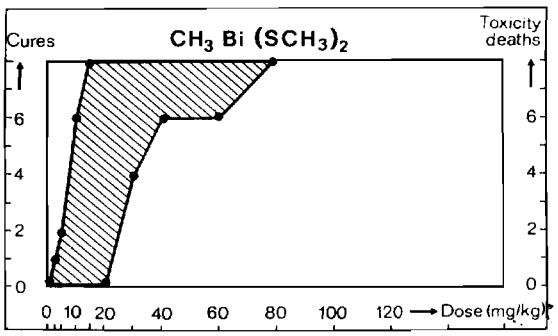


Fig. 1. Dose-activity (left) and dose-lethality (right) curves obtained by treatment of mice bearing fluid Ehrlich ascites tumor with $CH_3Bi(SCH_3)_2$ (**I**). The shaded area indicates the range of surviving animals.

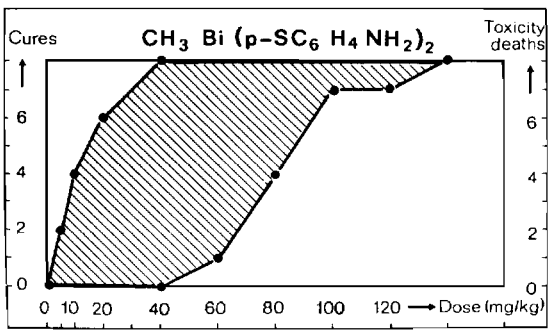


Fig. 2. Dose-activity and dose-lethality curves after treatment with $CH_3Bi(p\text{-}SC_6H_4NH_2)_2$ (**II**). For further details *cf.* legend to Fig. 1.

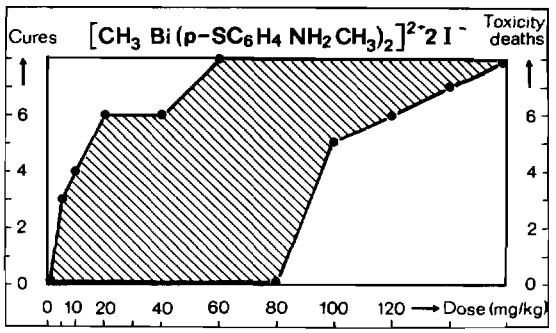


Fig. 3. Dose-activity and dose-lethality curves after treatment with $[CH_3Bi(p\text{-}SC_6H_4NH_2CH_3)_2]^{2+}2I^-$ (III). For further details *cf.* legend to Fig. 1.

treated with optimum doses of **I**, **II**, or **III** survived without any signs of developing tumor disease. The values of the therapeutic index (T.I. = LD_{50}/ED_{90}), expressing numerically the distance between the dose-lethality and dose-activity curves, ranged between 3.2 and 5.0 (Table I) whereby the ionic mercaptoanilinium derivative **III** exhibited best antitumor activity, the T.I. value amounting to 5.0. An only slightly smaller width of the therapeutic range and a T.I. value of 4.3 was found for the neutral aminothiophenolate derivative **II**, whereas the neutral compound **I**, containing three CH_3 groups, was characterized by low toxic threshold values and, in consequence, by the comparably small T.I. value of 3.2.

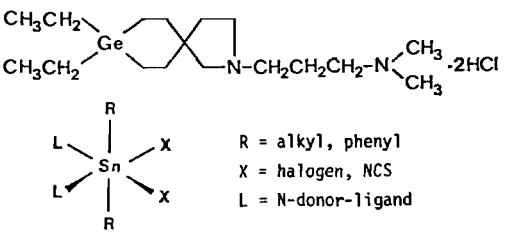
Another important parameter for the biological application of chemicals is their solubility in polar solvents, especially in water. With this respect, **III** surpasses **II** and **I** because of its salt-like, ionic character, though the water solubility of **III** is not high enough to be administered in pure saline without addition of a solubilizer.

Discussion

A previous study on the biological activity of organobismuth(III) compounds revealed antimicrobial properties of the chalcogeno bismuth(III) compounds **II** and **III** and showed inhibition of the growth of *Escherichia coli, Streptococcus faecalis, Bacillus subtilis* and *Lactobacillus plantarum* at concentration levels as low as 5×10^{-6} g/g [9]. Under this treatment, the bacterial shape became elongated and filamentous, whereby signs of cellular division were absent. In this connection it is worth mentioning that a similar finding of filamentous growth of *Escherichia coli* was the first hint to the biological activity of inorganic platinum complexes of the type of *cis*-diamminedichloroplatinum(II) (cisplatin) [11–13], leading later on to the detection of pronounced antitumor effectivity against animal and human tumors [14, 15].

The present study confirms antitumor activity for organobismuth(III) compounds and, thus, enlarges the spectrum of non-platinum-group metal antitumor agents by main-group V compounds. Cytostatic non-platinum-group metal compounds yet known are represented by transition metal complexes of Ti, V, Fe, Cu or Au as well as by main-group compounds such as inorganic salts of group III elements, especially $Ga^{3+}(NO_3^-)_3$, and organometallic group IV compounds of the type of organogermanium(IV) compounds and di(organo)tin(IV) complexes [16, 17]:

$[(Ge\,CH_2\,CH_2\,COOH)_2\,O_3]_n$



The detection of tumor-inhibiting compounds of main-group V compounds continues an old tradition and joins the first trials of chemotherapy of human malignancies performed with an arsen compound during the last century [2]. In comparison with arsen, bismuth certainly exhibits advantages because of less severe toxic properties. The pattern of toxicity induced by bismuth and its compounds shows similarity to that of mercury being characterized by typical symptoms of heavy-metal toxicity like nephrotoxicity and gastrointestinal irritation, but lacking phenomena due to lesions of capillaries and other blood vessels which are characteristic for the acute arsen intoxication [5]. Nevertheless, the finding of antitumor activity of organobismuth compounds is remarkable, as it is known that toxic phenomena which are typically induced by certain elements can be modified and masked by suitable changes of the molecular structures. Toxicologic studies are necessary to evaluate the actual pattern of organ toxicity induced by the organobismuth(III) compounds considered in the present study.

On the other hand, further investigations are inevitable to confirm the antitumor activity of organobismuth compounds against other, especially against solid tumor models, and to find active species with enhanced water solubility. The synthesis of ionic derivatives similar to **III** seems to be a promising way.

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