Coordination Chemistry Reviews, 99 (1990) 253–296
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

METAL COMPOUNDS IN CANCER CHEMOTHERAPY

IONEL HAIDUC

Chemistry Department, Babeş-Bolyai University, R-3400 Cluj-Napoca (Romania)

CRISTIAN SILVESTRU

Institute of Chemical and Biochemical Energetics, Chemistry Department, Babeş-Bolyai University, R-3400 Cluj-Napoca (Romania)

(Received 28 June 1989)

CONTENTS

0010-8545/90/$15.40

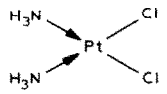
ABBREVIATIONS

ACNU	1-(4-amino-2-methylpyrimidin-5-yl)methyl-3-(2-chloroethyl)-3-nitrosourea
AMMN	acetoxymethyl-methylnitrosamine
bipy	2,2′-bipyridyl
Bu^n	*n*-butyl
Cy	cyclohexyl
DMSO	dimethyl sulfoxide
Et	ethyl
6-HMP	purine-6-thiol
HTG	thioguanine
ILS	increase in life span
i.m.	intramuscular
i.p.	intraperitoneal
Me	methyl
Ph	phenyl
phen	1,10-phenanthroline
Pr^i	isopropyl
Py	pyridine
s.c.	subcutaneous

A. INTRODUCTION

Chemotherapy is one of the main weapons in the fight against cancer. Until recently the majority of antitumor drugs were organic compounds or natural products including alkylating agents, antibiotics, alkaloids, enzymes and hormones. Inorganic compounds, especially metal-containing compounds, were not systematically investigated since most metals were considered to be potential carcinogens.

A crucial event happened in 1969 when Rosenberg et al. discovered that platinum complexes exhibit antitumor properties [1]. Following this discovery, an explosion of research occurred in this area. As a first major result, one of the earliest platinum complexes, *cis*-diamminedichloroplatinum(II), *cis*-$[Pt(NH_3)_2Cl_2]$ (**1**), later known as cisplatin, has passed all the screening



1

phases and is now used in the clinical treatment of several types of human cancer. This carbon-free coordination compound, first synthesized more

											B						
											Al	Si					
		Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As				
		Y	Zr	Nb	Mo		Ru	Rh	Pd	Ag	Cd	In	Sn	Sb				
		La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Ti	Pd	Bi	Te			

Fig. 1. Metals and metalloids whose compounds have been screened as antitumor agents.

Fig. 2. Metals and metalloids whose organometallic compounds have been screened as anticancer agents: (M), σ metal–C compounds; M, π complexes.

than a century ago by Peyrone [2], has become the first member of a new class of metal-based antitumor drugs.

The discovery of cisplatin prompted the search for novel potent antitumor agents among metallic compounds. Although platinum complexes have been the most intensively investigated, research has extended to practically all metals (Fig. 1). Purely inorganic compounds (those not containing organic fragments), coordination complexes and organometallic compounds (Fig. 2) are now extensively and systematically screened as antitumor agents.

Increasing interest in the antitumor properties of metal compounds is reflected by the large number of scientific papers and reviews published in specialized journals or collected in topical volumes [3–15].

B. INORGANIC AND COMPLEX COMPOUNDS

(i) Main group metal compounds

Unlike transition metals, few inorganic compounds of main group metals have been found to be highly active as anticancer agents.

(a) Aluminum, gallium, indium and thallium

Several salts of group 13 metals have been screened in vitro and in vivo towards a range of animal tumors [16–18]. The nitrates strongly inhibited the growth of i.p. transplanted Walker 256 carcinosarcoma but were only slightly active against leukemia cells (L1210, P388, K1964), Ehrlich

carcinoma or plasma cell YPC-1. Greater activity was found against s.c. transplanted solid tumors. The most efficient was gallium nitrate which was selected for further screening and even reached phase II of clinical trials, with promising results against refractory lymphoma [19].

(b) Boron

In contrast with these results, most inorganic compounds of boron (the first element of group 13) including boric acid esters, borazine derivatives, amine complexes of boron hydrides etc., showed no significant antitumor activity. However, some boron compounds containing alkylating groups inhibited the development of Walker 256 carcinosarcoma in rats, but were less active towards L1210 leukemia and sarcoma 180 in mice [20]. They were also too toxic. Other compounds, i.e. benzoxazaborines, have inhibitory properties against various tumors in mice and rats [21]. The boron hydride complexes of benzothiazepinole derivatives were found to inhibit P388 leukemia cells in mice [22].

(c) Silicon, germanium, tin and lead

Inorganic compounds of group 14 metalloids and metals seem to be of little interest as antitumor agents. However, silicic acid produces strand breakage of DNA [23], and some octahedral tin complexes, $SnCl_4 \cdot L$ (L = bipy or phen), have shown reproducible activity against P388 leukemia (ILS is 30% and 23% for complexes with L = bipy and L = phen respectively) [24]. The β-diketone tin(IV) dihalide complexes, $[PhC(O)CHC(O)Me]_2SnX_2$ (X = Cl or Br), are reported to increase significantly the life span of mice bearing sarcoma 180 tumor (ILS is 130% for X = Cl) [25].

The effects of tin compounds upon animals, mainly the influence of tin upon thymus gland activity, suggest that compounds of this element may play a role in preventing carcinogenesis and could also be useful for cancer treatment [26–29].

Although inorganic lead compounds have been used for the treatment of human cancers, the results were doubtful [30], and their high toxicity considerably reduces any potential antitumor value.

(d) Arsenic, antimony and bismuth

Inorganic arsenic compounds are generally considered to be carcinogenic agents, although their action has not been fully confirmed [31,32]. Some arsenic(III) derivatives, e.g. $KAsO_2$ and As_2O_3, and colloidal arsenic were used in the treatment of some types of cancer [33,34] in spite of their toxicity, but they never achieved any clinical value.

Antimony compounds have been largely used as emetics and in the treatment of tropical diseases. Some of them have also been screened as

antitumor agents and have been found active in vivo. Thus antimony(III) complexonates, e.g. ethylenediaminetetraacetate, propylenediaminetetraacetate and nitrilotriacetate, increase the life span of mice bearing Ehrlich ascites tumor and spindle cell sarcoma [35–37]. A tungstoantimoniate, namely $(NH_4)_{17}Na[NaW_{21}Sb_9O_{86}] \cdot 14H_2O$, has strong antiviral and antitumor activity [38,39].

Inorganic bismuth(III) compounds have been used less extensively in screening trials. However, significant activity was reported for bismuth complexes of 6-mercaptopurine (6-HMP) and thioguanine (HTG), i.e. $Na_2[BiO(6\text{-}MP)_3] \cdot 3H_2O$ and $[Bi(TG)_3(H_2O)] \cdot 3.5H_2O$, in mice bearing adenocarcinoma 755 and sarcoma 180, and in rats bearing Dunning ascitic leukemia [40,41].

(ii) Transition metal compounds

(a) Scandium, yttrium, lanthanides and actinides

Compounds of scandium and yttrium have scarcely been investigated as antitumor drugs. One of the first reports on this topic mentioned the inhibition of transplanted tumors in mice or rabbits produced by scandium inorganic derivatives [42]. Scandium trichloride, $ScCl_3$, was reported to inhibit strongly the growth of lymphatic leukemia BW5147, subcutaneously inoculated in mice, but its toxicity was also high [43].

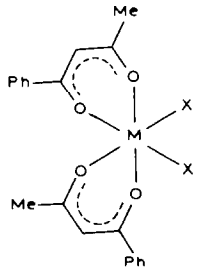
Although some lanthanides, e.g. lanthanum, cerium, praseodymium, neodymium etc., were proposed to have some carcinogenic effects in vitro and in vivo [44,45] studies on the antitumor properties of certain compounds of these metals were also performed. Inhibiting activity was found towards mice or rabbit transplanted tumors for cerium and ytterbium compounds [42] but negative results were reported for erbium, praseodymium and cerium nitrates against rat sarcoma 10 and Hyde rat carcinoma [46].

Lanthanum compounds have been more extensively studied. The antitumor properties of lanthanum trichloride, $LaCl_3$, or a lanthanum glycinato complex were demonstrated in mice bearing s.c. BW5147 leukemia or lymphosarcoma 6C3 HED [43]. Tumor growth inhibition was also observed against DS sarcoma, subcutaneously injected in mice, after treatment with $LaCl_3$ [47]. The mechanism of antitumor activity produced by lanthanum compounds seems to involve cation–cell membrane interaction [47,48].

Although thorium compounds were screened as early as 1913 [49], actinide inorganic compounds seem to have no therapeutic value as antitumor agents, since their carcinogenicity due to the radiation emitted by these elements cannot be ignored.

(b) Titanium, zirconium and hafnium

Titanium compounds are among the metal derivatives most investigated and the results are very promising in certain cases. Titanium β-diketonato complexes exhibited strong antitumor activity in mice and rats bearing various animal transplanted tumors and chemically-induced tumors [50–52]. Structure–activity studies focused attention towards bis(1-phenyl-1,3-butanedionato)titanium(IV) derivatives, **2** (M = Ti, X = Cl or OEt), and the diethoxy derivative **2** (X = OEt) was selected for more detailed investigation.



2

The antitumor properties of this compound have recently been reviewed [52,53]. Bis(1-phenyl-1,3-butanedionato)diethoxytitanium(IV), also known as budotitane, was active in vivo towards various animal tumors (Table 1) [53–56] and sometimes its effects were better than those obtained with cisplatin or 5-fluorouracil. The compound was also active against some human tumor xenografts in nude mice [57]. Preclinical investigations revealed that mild but reversible hepatotoxicity is the unique toxic side effect at

TABLE 1

Antitumor effects of budotitane against various in vivo animal tumors

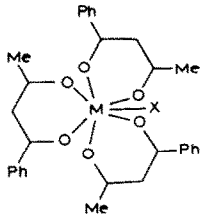
Tumor	Dose (mg kg^{-1})	Antitumor activity (%)		Ref.
		ILS	Growth inhibition	
L1210 leukemia [a]	92	28		54
P388 leukemia [a]	200	72		54
Sarcoma 180 (ascites) [a]	92	200		54
Sarcoma 180 (solid, s.c.) [a]	20		100	54
Sarcoma 180 (solid, i.m.) [a]	50		77	55
Colon ascitic adeno-carcinoma MAC 154 [a]	200	100		53, 55
Walker 256 carcinosarcoma [b]	300	117		54
AMMN-induced colorectal tumor [b]	10	46	81	56

[a] In mice. [b] In rats.

therapeutic doses (10–20 mg kg^{-1}, applied twice per week over several weeks) [52,53]. No myelotoxicity and mutagenicity were observed in this case [55], and nephrotoxicity and lung toxicity appeared only at a single high dose.

On the basis of the results obtained in animal screening, budotitane was used in phase I studies (started in 1986) on colorectal carcinoma patients, with at least acceptable results [58].

Analogous zirconium and hafnium complexes, e.g. the six-coordinate bis(1-phenyl-1,3-butanedionato)metal(IV) dihalides, **2** (M = Zr or Hf; X = halogen), or the seven-coordinate tris(1-phenyl-1,3-butanedionato)metal(IV) halides, **3** (M = Zr or Hf; X = halogen), were also found to be highly active



3

against the ascitic form of sarcoma 180 in mice, the best ILS value reaching 200% in some cases [59]. However, zirconium and hafnium derivatives were generally less active than the titanium analogs. Compound **2** (M = Zr; X = Cl) was inactive (9% inhibition) against chemically-induced autochthonous colorectal tumors in rats, while the hafnium complex was marginally active (37% inhibition) [56].

(c) Vanadium, niobium and tantalum

Metallic vanadium was inactive towards spontaneous mouse tumors, but vanadium(IV) salts decreased the incidence of spontaneous tumors in mice [60]. Some alkali and alkaline-earth metal vanadates were found to inhibit the in vitro growth of tumor cells [61,62]. In vivo, growth inhibition produced by $NaVO_3$ and sodium tartrato vanadate on Landschutz hyperploid subline of Ehrlich ascites tumor and Dba mouse leukemia in mice was observed, but the life span of mice was not affected [61]. However, ammonium vanadate did not affect the incidence of colon tumors induced by 1,2-dimethylhydrazine in mice [63]. Vanadyl sulfate, $VOSO_4$, was reported to inhibit the induction of murine mammary carcinogenesis produced by 1-methyl-1-nitrosourea in rats, and was suggested to be an efficient non-toxic drug for preventing breast cancer in these animals [64].

No significant antitumor activity was reported for inorganic niobium and tantalum compounds.

(d) Chromium, molybdenum and tungsten

Many reviews discuss the carcinogenic effects of chromium and its compounds [65–68] since occupational inhalation of chromium(VI) compounds is associated with lung cancer [65,66]. In view of these well-established toxic effects, only few chromium compounds have been screened as antitumor agents, and positive results have seldom been obtained.

By contrast, molybdenum and tungsten may exhibit strong antitumor properties. Thus Na_2MoO_4 (2–20 ppm in drinking water) significantly inhibits the incidence of esophagus and forestomach cancers induced by *N*-nitrososarcosine ethyl esters in Sprague–Dawley (SD) rats [69]. Molybdenum was demonstrated to exert an inhibiting effect on the mammary carcinogenesis in SD rats produced by intravenous injections with nitrosomethylurea [70]. Polymolybdates, e.g. $(NH_3Pr^i)_6[Mo_7O_{24}] \cdot 3H_2O$, exhibited antitumor properties in mice bearing chemically-induced sarcoma, HM 46 adenocarcinoma or MX-1 human breast carcinoma [71]. Surprisingly, the molybdenum complex of 1-phenyl-1,3-butanedione, **2** (M = Mo; X = Cl), was found to enhance the growth of autochthonous chemically-induced colorectal adenocarcinoma in SD rats, thus providing an effect opposite to that of titanium analogs [72].

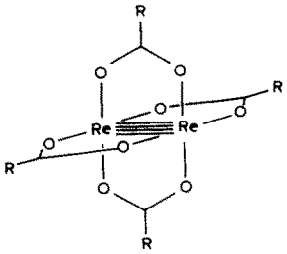
Many polytungstates and heteropolytungstates (containing boron, silicon, antimony etc. as the heteroatom) were demonstrated to exhibit antiviral and antitumor properties. One of the most extensively investigated compound was an ammonium tungstoantimoniate (coded HPA-23) with the composition $(NH_4)_{17}Na[NaSb_9W_{21}O_{86}] \cdot 14H_2O$ [73]. This compound was active against various virus-induced tumors, e.g. Friend leukemia virus or Moloney sarcoma virus [38,74]. It was, however, inactive towards L1210 leukemia in mice [38]. The antitumor effects may involve the action of HPA-23 on the viral polymerase and the NK activity stimulation [75].

(e) Manganese, technetium and rhenium

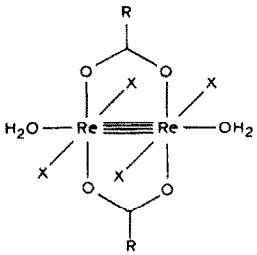
Many manganese complexes have been screened for antitumor activity but no significant effects have been obtained. However, manganese dust was shown to exhibit anticarcinogenic effects upon the tumorigenic action of nickel subsulfide, α-Ni_3S_2 [66,76], and manganese complexes of some thiosemicarbazones were found to be potent antileukemic agents [77,78].

The use of technetium compounds in cancer treatment is due to the radioactivity of this metal rather than to their chemotherapeutic properties. Indeed, ^{99}Tc compounds are frequently used in medical diagnostic imaging [79–83].

Rhenium compounds have not been extensively screened for antitumor properties. Alkali rhenates were active against Brown–Pierce tumor in rabbits or M-1 sarcoma in rats. Only two types of rhenium carboxylato



4



5

complexes, **4** and **5**, both containing metal–metal bonds, were tested against transplanted tumors in mice. The most active were the propionato derivatives [84,85].

(f) Iron, ruthenium and osmium

Many iron inorganic and coordination compounds have been screened in vitro and in vivo, and several, including some thiosemicarbazonates [78,86–89], ascorbates and dehydroascorbates [90,91] exhibited antitumor properties towards animal tumors. The iron complexes were even used with some beneficial effects in the treatment of human cancer [92]. Certain studies reported the influence of iron on the antitumor properties of some clinically used anticancer drugs, e.g. 6-mercaptopurine [93], anthracycline drugs (adriamycin and daunomycin) [94–97] and bleomycin [95,98–102]. It seems that this metal plays an important role in the mechanism of action of bleomycin.

The implications of ruthenium complexes in cancer treatment have been reviewed [103–105]. "Ruthenium red", a mixed-valence ruthenium(III,IV) trinuclear complex, $[(NH_3)_5Ru–O–Ru(NH_3)_4–O–Ru(NH_3)_5]^{6+}$, is an active antitumor agent, e.g. it inhibits the growth of s.c. transplanted Lewis lung carcinoma in mice (72% inhibition and best ILS is 41%) [106,107]. Many ruthenium(II) and ruthenium(III) complexes with ammonia and organic amines as ligands were tested, but generally they were less active than platinum analogs [103,108–110]. The doses at which most ruthenium (III) complexes displayed antitumor activity are close to the toxic doses, thus leading to a low therapeutic index. The current available data suggest that such ruthenium(III) complexes play a role as prodrugs, the in vivo reduction to more sensitive ruthenium(II) complexes being necessary for exhibiting antitumor activity [103,108].

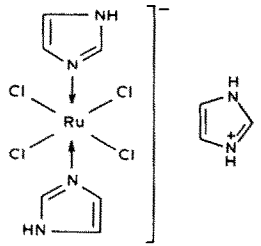
The antitumor properties of a new class of ruthenium(III) complexes containing imidazole or other heterocyclic derivatives as ligands were studied recently [111–115]. These are generally anionic water-soluble complexes such as **6** and **7** and display antitumor effects against a broad spectrum of animal tumors (Table 2).

TABLE 2

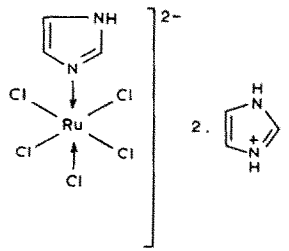
Antitumor effects of ruthenium compounds **6** and **8** towards various animal tumors (in mice)

Tumor	Dose (mg kg^{-1})	Antitumor activity (%)		Ref.
		ILS	Growth inhibition	
Compound 6				
B16 melanoma	8		87	111
AMMN-induced colorectal carcinoma [a]	14–28		80	112
P388 leukemia	71	94		115
Walker 256 carcinosarcoma	50	130		115
Sarcoma 180	81		55	115
Compound 8				
Lewis lung carcinoma (s.c.)	610		68 [b]	400
Lewis lung carcinoma (i.m.)	610	25	40 [b]	400
B16 melanoma (i.m.)	610	26	69 [b,c]	400
MCA mammary carcinoma (i.m.)	610	30	43 [b,c]	400
L1210 leukemia	565	25		393
Ehrlich ascites tumor	400	— [d]		393

[a] In rats. [b] Expressed as decrease in primary tumor weight. [c] After surgical amputation of primary tumor. [d] 100% cure rate.



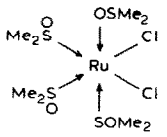
6



7

A water-soluble ruthenium(II) complex which has been subjected to numerous antitumor studies is *cis*-dichlorotetrakis(dimethyl sulfoxide)ruthenium(II) (structure **8**, with DMSO molecules bonded to the metal atom both through the oxygen and the sulfur atom) [116,117]. This complex exhibited significant tumor growth inhibition of Ehrlich ascites tumor, Lewis lung carcinoma, B16 melanoma and MCA mammary carcinoma in mice, but was less active in mice bearing L1210 leukemia.

Osmium compounds seem to have no practical value as anticancer agents, since none of the complexes tested exhibited more than marginal activity [118–121].

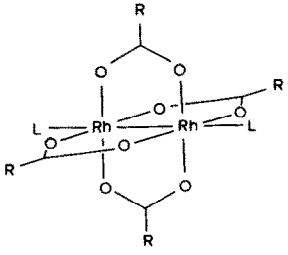


8

(g) Cobalt, rhodium and iridium

Many cobalt complexes with various ligands, e.g. amino-acids [122], phenanthroline derivatives [123,124], thiosemicarbazones [125,126], salicylaldoximes [127,128], bis(diphenylphosphino)ethane [129] etc. were tested as anticancer agents, but the degree of tumor inhibition was not spectacular. Cobalt(II) complexes of Schiff bases also exhibited only marginal effects in animals (mice or rats) bearing various tumors [130–133]. However, inorganic cobalt complexes containing porphyrinic ligands, i.e. protoporphyrin, were found to be powerful inhibitors of sarcoma 180 (solid or ascitic forms), Ehrlich ascites tumor (solid form) in mice and Yoshida sarcoma in rats [134]. In human patients, the protoporphyrin complex of cobalt clearly has an inhibiting effect [135].

Among rhodium(III) complexes with ammonia and organic amines as ligands, *mer*-$[Rh(NH_3)_3Cl_3]$, with leaving groups in the *cis* position as in cisplatin, was the most active in animal tumor systems [4,136]. Tetrakis(carboxylato)dirhodium(II) complexes, **9**, represent a class of com-



9

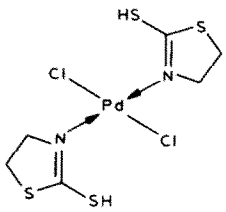
pounds with promising activity [136–138]. Their effectiveness towards animal tumors increases with increasing lipophilicity, although a charged mixed-valence rhodium(II,III) complex, $[Rh_2(O_2CCH_2CH_3)_4]^+$, which is water soluble was more active than the corresponding neutral complex [139,140]. The observed inhibition of DNA synthesis may be due to the blocking of some thiolic enzyme involved in DNA synthesis, since the rhodium(II) carboxylates do not bind to double-stranded DNA [141,142].

Iridium compounds have generally been little studied as antitumor agents; iridium(III) complexes with amine ligands are practically inactive towards sarcoma 180 and ADJ/PC6A leukemia in mice [4,136]. However, antitumor properties have been observed for hexachloroiridate(IV) salts [143–145].

(h) Nickel, palladium and platinum

In group 10, there is a striking difference between the behavior of the first element, nickel, and the following two, palladium and platinum. In spite of the fact that nickel compounds are generally considered as potentially carcinogenic, several nickel complexes were tested for antitumor properties; they were found inactive, or the results were not encouraging [40,127–129, 136,146–148]. Only bis(diethyldithiophosphato)nickel(II) was reported to be more active than the corresponding platinum or palladium derivatives against Walker 256 carcinosarcoma [149].

Various palladium(II) complexes were tested in animals bearing transplanted tumors, but generally their activity was lower than that of platinum analogs with similar structures [136,150,151]. In spite of this, many palladium(II) and palladium(IV) neutral complexes were found to exhibit antitumor activity [151,152]. Even some complexes with *trans* structures were active, e.g. *trans*-$[Pd(NH_3)_2Cl_2]$ towards sarcoma 180 and Landschutz ascites in mice [151], and compound **10** against hepatoma cells in vitro [153].

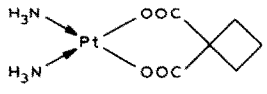


10

This behavior contradicts the usual generalization that the *cis* structure is a prerequisite for the antitumor activity of platinum complexes. Ionic palladium(II) and palladium(IV) derivatives were also found to be antitumor active, in spite of the expectation that such compounds would be rapidly eliminated from the body. These results suggested that useful anticancer drugs might be found among palladium complexes and that a more detailed investigation of the structure–activity relationship is necessary for these metal compounds [154]. As a result, following preliminary antitumor screenings, some palladium complexes are now in stage II of clinical testing [155].

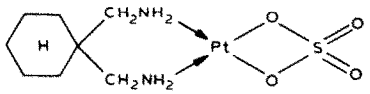
Since the antitumor properties and the mechanism of action of platinum(II) and platinum(IV) complexes have been the subjects of many detailed reviews and books [8–12,156–166], we only briefly mention here a

series of second-generation platinum antitumor agents, **11–14**, which together with cisplatin are now in clinical use. The last two complexes are platinum(IV) derivatives, thus suggesting that the oxidation state II is not a general condition for platinum complexes to exhibit very powerful antitumor activity.



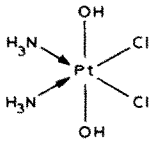
Carboplatin (CBDCA, JM 8)

11



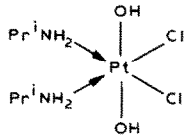
Spiroplatin (TNO 6)

12



Oxoplatin

13



Ipropiatin (CHIP, JM 9)

14

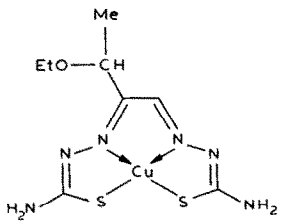
(i) Copper, silver and gold

Inorganic copper compounds and coordination complexes have been the subjects of numerous antitumor studies and many of them have been found to be active as anticancer or anticarcinogenic agents in animal systems [167–169]. Such complexes include bisthiosemicarbazonates and monothiosemicarbazonates [87,89,170–174], oximes, imines and hydrazones [175–179], salicylates [180–184], aminocarboxylates [40,185–187] and other complexes with various N-donor ligands [168,188,189]. Compounds **15–18** represent some of the most active copper complexes.

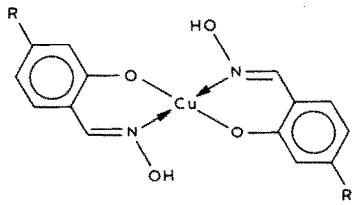
The interaction of copper ions with antibiotic compounds, e.g. bleomycin [95,99,100,102,190–192] and anthracycline drugs [193–195], was also extensively investigated, and it seems that metal ions are essential in the mechanism of action of such antitumor drugs.

Silver compounds have been investigated less extensively and none of them showed any promising antitumor activity [168,196].

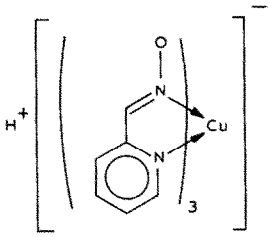
Many gold compounds were recently found to be strong antitumor agents. Thus auranofin (2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranosato-S)(triethylphosphino)gold(I), a known anti-inflammatory drug, was screened in vitro and in vivo towards various types of animal cancer. Although it has a broad spectrum of cytotoxicity in vitro, this compound displayed in vivo antitumor activity only against P388 leukemia in mice [197–200]. Much more promising were the binuclear gold(I) complexes of 1,2-bis(diphenylphosphino)ethane, $Ph_2PCH_2CH_2PPh_2$ [129,201–203]. Thus the chloro de-



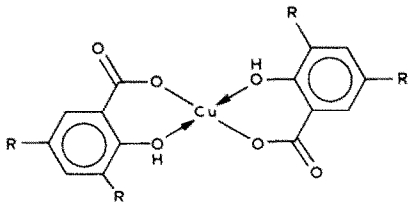
15



16

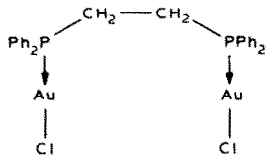


17



18

rivative **19** was eight times more potent in vitro against B16 melanoma than the free ligand, and was active towards P388 and L1210 leukemias. The gold complexes of this class were also active against other mouse tumors (M5076 reticulum cell sarcoma, mammary adenocarcinoma 16/c, ADJ/PC6 plasmocytoma) (Table 3), thus exhibiting a broader spectrum of action than auranofin [204]. Generally, gold(III) complexes were less active than the gold(I) analogs.



19

(j) Zinc, cadmium and mercury

The implications of zinc in tumor growth inhibition have been extensively studied [167,205,206], and many zinc inorganic and complex compounds have been screened as antitumor agents, e.g. bisthiosemicarbazonates and monothiosemicarbazonates [87,89,125,206,207], amino-acids [40,208] antibiotics [95,102,192,209] and other complexes with various amine ligands [40,123,127,189]. However, no spectacular results were obtained with any of them.

Cadmium and mercury are considered to be major pollutants of the environment and may have definite carcinogenic properties. For some

TABLE 3

Antitumor effects of $Au(Ph_2PCH_2CH_2PPh_2)_2Cl$ against mice tumors [201]

Tumor	Dose (mg kg^{-1})	Antitumor activity (%)	
		ILS	Growth inhibition
P388 leukemia (i.p.)	29.8	87	
P388 leukemia (cisplatin resistant) (i.p.)	3	77	
M5076 reticulum cell sarcoma (i.p.)	1.95	59	
B16 melanoma (i.p.)		39	
Mammary adenocarcinoma 16c (s.c.)			84

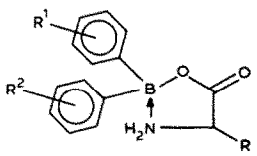
compounds of cadmium, e.g. 3-ethoxy-2-oxobutyraldehyde bis(N^4,N^4-dimethylthiosemicarbazonato)cadmium(II) [210], and the cadmium chloride complex of poly(vinylimidazole)–poly(vinylpyrrolidone) copolymer [211], antitumor properties were established, while inorganic mercury compounds were generally found to be too toxic for living organisms.

C. ORGANOMETALLIC COMPOUNDS

(i) Main group metal compounds

(a) Boron, aluminum, gallium, indium and thallium

The implication of organoboron compounds in cancer treatment was mainly related to their use as neutron capture agents [212–214]. The direct antitumor activity of organoboron compounds has been less investigated, but some exhibited significant antineoplastic behavior. Thus mixed anhydrides of diarylborinic acids with α-amino-acids, **20**, inhibited HeLa and L-16 cells in vitro and sarcoma 180 and Ehrlich ascites tumor in mice [215–217]. Boron analogs of α-amino-acids, especially aminocyanoborane, **21**, and aminocarboxyborane, **22**, were found to be active against Ehrlich



20

$R_3N \cdot H_2B—CN$ $R_3N \cdot H_2B—COOH$

21 22

ascites tumor in mice and many of them inhibited the development of this tumor system [218–222] by more than 90%. Some other compounds, $Me_3N \cdot H_2B–CN$ and $Me_3N \cdot H_2B–C(O)NHEt$, also exhibited antitumor activity towards Walker 256 carcinosarcoma, B16 melanoma and Lewis lung carcinoma, but were inactive or marginally active against P388 leukemia in mice [218,220]. The mechanism of action of this type of compound seems to be related to their action upon the enzymes required for rapid proliferation of cancerous cells [221].

No organometallic derivatives of the other elements of group 13, i.e. aluminum, gallium, indium and thallium, were screened for antitumor activity since such compounds are very sensitive to moisture and the atmosphere.

(b) Silicon, germanium, tin and lead

In contrast with inorganic compounds, organosilicon, organogermanium and organotin derivatives have been extensively investigated from the point of view of their antitumor activities [24,223,224].

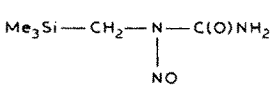
The antitumor-active organosilicon compounds can be divided into three classes: (a) silylated derivatives of organic compounds of known antitumor activity; (b) silicon analogs of organic compounds of known biological activity (one or more carbon atoms replaced by silicon atoms); (c) organosilicon compounds without organic analogs.

Lukevics et al. [225,226] reported anticancer properties for several quinoline derivatives bearing a trialkylsilyl group towards a panel of animal tumor systems including Ehrlich ascites tumor, L5178 leukemia and Lewis lung carcinoma. Purely organic compounds containing the quinolyl nucleus are known as potent antitumor agents.

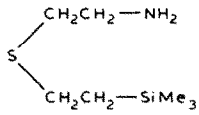
Japanese investigators studied a large number of organic compounds with a trialkylsilyl (largely trimethylsilyl) group attached to a carbon atom [227–233]. Such compounds included derivatives of known antitumor drugs, e.g. *N*-trimethylsilylmethyl-*N*-nitrosourea, **23** [232], 2-trimethylsilylethylthioethylamine, **24** [229,231], and the 5-fluorouracil derivative **25** [233,234].

Compound **24** inhibited the growth of cancer cells in vitro and was highly active in vivo [229,231]. Thus the effect of this compound against Ehrlich ascites tumor and sarcoma 180 in mice was 1.74 times better than that obtained with 5-fluorouracil, and the effect towards B16 melanoma and Lewis lung carcinoma was also comparable to that of this known antitumor drug. It exhibited an antimetastatic effect against Lewis lung carcinoma. However, the development of L1210 and P388 leukemias in mice was not affected after treatment with compound **24**.

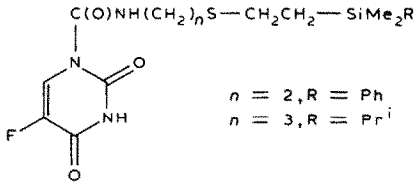
Compound **25** ($n = 2$; R = Ph) was effective against leukemias (P388 and L1210) and solid tumors (B16 melanoma and Lewis lung carcinoma). The



23



24

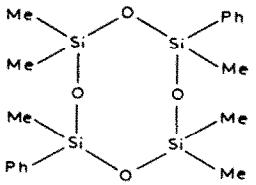


25

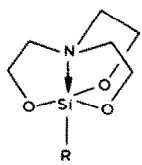
life span of mice bearing MM46 carcinoma (ILS, 321%) was remarkably increased [233].

Compound **25** ($n = 3$; R = Pr^i) was twice as active against L1210 leukemia in mice as 1-hexylcarbamoyl-5-fluorouracil and was also markedly effective (by oral administration) against B16 melanoma, Lewis lung carcinoma, colon 38 adenocarcinoma and MM46 carcinoma [234].

Interesting antitumor properties were found for some organosilicon compounds without organic analogs. Thus cyclotetrasiloxane derivatives, e.g. *cis*-1,1,3,5,5,7-hexamethyl-3,7-diphenylcyclotetrasiloxane, **26**, have been used



26



27

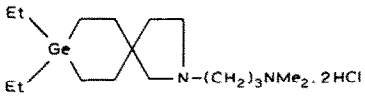
as palliatives in the treatment of prostatic cancer [235,236]. Bis(trimethylsilylmethyloxy)phosphite, $(Me_3SiCH_2O)_2POH$, was found to be more active than 5-fluorouracil and is comparable with ACNU (two established cytostatics) in the inhibition of sarcoma 180 and B16 melanoma tumors [227].

Silatrane derivatives, **27**, containing an unusual five-coordinate geometry at the silicon atom [237], exhibit strong antitumor properties in several animal tumor systems [223,224,238–242]. One of the most active silatranes was the methoxy derivative (**27**, R = MeO). This compound strongly inhibited the growth of Walker 256 carcinosarcoma (59–79% inhibition) and Pliss lymphosarcoma (67–76% inhibition). The ethoxy derivative (**27**, R = EtO), also known as migugen, exhibits 50% inhibition of Walker 256 carcinosarcoma [224]. The structure–activity relationship in this class of

compound was investigated; it was observed that the introduction of substituents at the carbon sites of the heterocycle in alkylsilatranes produces a decrease in the antitumor activity or a change in the spectrum of action [239]. Thus 3,7,10-trimethyl-1-chloropropylsilatrane exhibited antitumor properties against several tumors, but no dose–activity relationship could be established [224].

Generally, organosilicon compounds seem to owe their antitumor properties to the stimulation of the immuno-defensive system of the organism [227–229,240].

Organogermanium compounds have been thoroughly investigated as antitumor drugs [19,224,243,244] in the last ten years, and promising results have been obtained with some. The most investigated organogermanium compound is spirogermanium, a heterocyclic compound of structure **28**. This



28

compound inhibited the development of a broad spectrum of cancer cells in vitro in a manner depending upon the dose, time, temperature and degree of evolution of tumor cells. The results obtained in vitro [245–247] and in vivo [248–251] screening have suggested that spirogermanium might be useful in the treatment of human cancers. Passing through toxicological studies, spirogermanium has entered in clinical trials on human subjects bearing cancerous tumors [19,252,253]. There are now many reports on its antitumor effectiveness on a large number of human tumor types, e.g. ovarian carcinoma [254–257], cervix carcinoma [258], breast carcinoma [259–262], renal cell carcinoma [263,264], melanoma [265,266], non-Hodgkin lymphoma [267–269], non-small-cell lung cancer [270], central nervous system tumors (glioblastomas) [271], colorectal carcinoma [272], metastatic prostate cancer [273,274] etc. The best results were obtained against non-Hodgkin lymphoma [267,269,275], ovarian cancer [254] and breast cancer [260], but since the majority of the trials were on patients who were previously treated (chemotherapy, radiotherapy, surgical methods) and were resistant to further conventional therapy or were in an advanced stage of the disease, the use of spirogermanium in combination with other antitumor drugs, in an early stage of the disease and as a first line of chemotherapy, might lead to much better results.

Another organogermanium compound which has received much attention in the last few years is carboxyethylgermanium sesquioxide, $(HOOCCH_2CH_2GeO_{1.5})_n$, also named Ge-132. It has a layer structure consisting of large

TABLE 4

Antitumor effects of Ge-132 against various tumors in mice

Tumor	Dose [a] (mg kg^{-1})	Antitumor activity (%)		Ref.
		ILS	Growth inhibition	
Walker 256 carcinosarcoma [b]	512 [c]	193		277
Walker 256 carcinosarcoma	10		25	280
Adenocarcinoma 755	108	15	33	280
Sarcoma 37	300	28		280
Sarcoma 180	28	42		280
Lewis lung carcinoma	100 [c]		63	284
B16 melanoma	300		40	280
Sarcoma MN-2 (induced by methylcholanthrene)	2.2		18	280
Sarcoma MN-18 (induced by methylcholanthrene)	6.0		18	280
Meth A sarcoma (induced by methylcholanthrene)	100	9		283
Ehrlich ascites tumor	100	84		283
RL 1 leukemia	100	63		283
EL-4 leukemia	200	7		283

[a] Oral administration. [b] In rats. [c] i.p. administration.

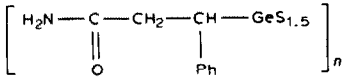
Ge_6O_6 rings similar to "crown ethers", with pendant $-CH_2CH_2COOH$ groups forming interlayer hydrogen bonds [276]. This compound was investigated in detail especially by Japanese researchers and was found to be active in a range of animal tumors [277–284]. It increased the survival time of animals bearing ascites hepatomas, syngeneic bladder cancer, Walker 256 carcinosarcoma, Ehrlich ascites tumor, sarcoma 180, Lewis lung carcinoma, L1210 leukemia, methylcholanthrene-induced sarcoma etc. (Table 4). Only two human clinical trials of Ge-132 are known to us at the time of writing. In one of them, Ge-132 was administered alone or in combination with other antitumor drugs, and decreases in the tumor size were obtained in the case of prostate and uterus carcinomas and myeloma [285]. In another trial, a placebo-controlled Ge-132 study on unresectable lung tumor was performed, and survival advantages were reported in some cases [286].

The mechanism of action of Ge-132 involves the stimulation of γ-interferon production by T-lymphocytes and activation of macrophages by γ-interferon [283,287–290].

A large number of other organogermanium sesquioxides have been mentioned as having antitumor properties, sometimes even better than those of Ge-132 [280,291,292]. These derivatives were obtained by substitution of the CH_2 group or by modification of the carboxylic groups (carbamoyl, esters,

nitriles etc.), e.g. $(XCH_2CH_2GeO_{1.5})_n$ or $(XCH_2CHRGeO_{1.5})_n$, with X = COOH, COOMe, $CONH_2$, COCl etc. and R = Me or Ph.

Analogous sesquisulfides also exhibited antitumor activity in animal tumor systems. Thus compound **29** was more active than Ge-132 against IMC carcinoma in mice, although it lacked in vitro activity towards this tumor and L1210 and L5178Y leukemias [291].

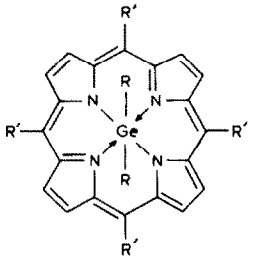


29

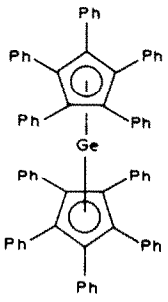
Several other organogermanium compounds containing four, three, two or one Ge–C bonds were screened for antitumor activity and many of them exhibited inhibitory effects. Thus diorganogermanium compounds **30** (R = Me or Et; R′ = 3,5-di-*tert*-butylphenyl), containing a substituted porphyrin nucleus, were active against carcinomas in mice [293]. The dimethyl derivative **30** (R = Me) was cytotoxic in vitro towards HeLa cells, inhibited the solid form of B16 melanoma and IMC carcinoma (33% and 39% inhibition respectively) and produced a complete remission of tumors in 50% of rats bearing Walker 256 carcinosarcoma [293].

Some germatranes have also been screened and seem to possess antitumor properties similar to those of the silicon analog [280].

Recently, monomeric air-stable decaphenylgermanocene, **31**, containing π Ge–C bonds, was reported to produce 40–80% cure rates in mice bearing fluid Ehrlich ascites tumor [294].



30



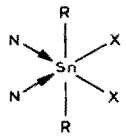
31

The biological properties of organotin compounds have been extensively investigated. Such compounds are now largely used in agriculture as pesticides [295–297]. In recent years, much attention has been focused on their antitumor properties, and in the 1980–1982 period alone, more than 1200 organotin compounds were screened at the National Cancer Institute in

U.S.A. [298]. The best results were obtained with complexed and uncomplexed diorganotin derivatives: 50% and 40% respectively of the tested compounds were active towards P388 leukemia in mice [299,300]. Tetraorganotin derivatives, SnR_4, triorganotin derivatives, R_3SnX, and monoorganotin derivatives, $RSnX_3$ were, however, significantly less active [299,300]. The increasing interest in the anticancer properties of tin compounds and their implications in antioncogenesis led to the organization of four international symposia on this subject. The antitumor activity of organotin compounds has been reviewed [24,301].

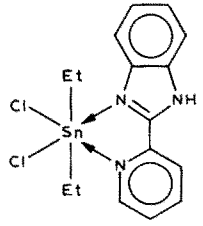
Many diorganotin dihalides and pseudohalides exhibited marginal antitumor activity against P388 leukemia in mice [302]. Dibutyltin dichloride was also found to be active in vivo towards other animal tumors, e.g. adenocarcinoma 755 [303], chemically-induced pancreatic adenocarcinoma [304,305], Ehrlich ascites tumor and IMC carcinoma [306].

A large number of octahedral diorganotin dihalide complexes with N-donor ligands, **32**, were reported to prolong the survival of mice bearing

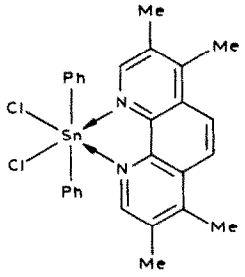


32

P388 leukemia, but generally the antitumor properties of such compounds were limited to this tumor system [302,307–311]. Thus complexes **33** and **34** were tested on a panel of tumors, i.e. B16 melanoma, L1210 leukemia, Lewis lung carcinoma and colon 38 carcinoma, but were inactive [224]. However, both complexes were highly active towards renal adenocarcinoma (the best ILS is 118% for compound **33** and 73% for compound **34**) [224,312].



33

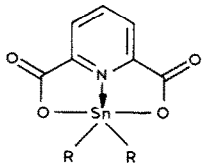


34

Structure–activity correlations suggested that, in contrast with cisplatin and metallocene dichlorides, in which the value of the Cl–M–Cl angle is discriminatory between active and inactive agents [313], with octahedral

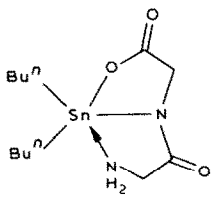
diorganotin dihalides other factors seem to be involved in the formation of intrastrand links in nucleic acids via the organotin moiety; thus Sn–N bond lengths higher than 2.39 Å are required for exhibiting antitumor properties [302,308,309].

A series of organotin derivatives with increased water solubility has been synthesized [300,314,315] but this property has not led to the expected increase in antitumor activity. Although such complexes, e.g. diorganotin(IV) derivatives of 2,6-pyridine dicarboxylic acid, **35**, display very high activity in vitro against leukemia cells (P388, L1210, P815), the in vivo results were disappointing [314,315].

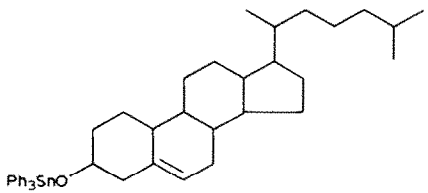


35

Organotin complexes with biological ligands, e.g. amino-acids, dipeptides and tripeptides, purine bases (adenine, 6-mercaptopurine) [316–319], carbohydrates [320] and steroids [321–324], also exhibit antitumor properties in animal systems. Di-*n*-butyltin glycylglycinate, **36**, significantly increased the life span of mice bearing P388 leukemia (ILS, 50%) and exhibited marginal activity against Lewis lung carcinoma (ILS, 27%), mammary tumor $CD8F_1$ (50% inhibition) and MX-1 tumor (53% inhibition) [318]. Monoorganotin, diorganotin and triorganotin derivatives of steroids (cholic acid, cholesterol, testosterone, deoxycholic acid etc.) were recently screened for antitumor properties and best results were obtained with a triphenyltin cholesteryl ether, **37** [322,323].



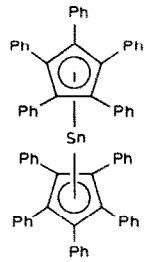
36



37

The binding of 5-fluorouracil to $Et_2SnCl_2 \cdot$ phen improves the antitumor activity compared with that of the complex alone [325].

Recently a π-bonded organotin compound, $(Ph_5C_5)_2Sn$, **38**, was found to produce 40–90% cure rates in mice with fluid Ehrlich ascites tumor, thus suggesting that air-stable π complexes of main group metals might also exhibit favorable antitumor effects [294].



38

In contrast with the organometallic derivatives of silicon, germanium and tin, organolead compounds seem to have no practical value as antitumor agents because of their high toxicity.

(c) Arsenic, antimony and bismuth

The chemotherapeutic use of organoarsenic(III) and arsenic(V) compounds enjoyed considerable popularity after Ehrlich discovered Salvarsan in 1907 and introduced it in the current treatment of syphillis [326,327]. Other organoarsenicals were also used in the treatment of various other diseases. However, after the discovery of penicillin, this class of therapeutic agent was removed from medical usage [328]. A number of arsenic(III) and arsenic(V) compounds containing metal–C bonds were screened for antitumor activity in animal tumor systems, but none were subjected to further clinical tests. In recent years, many diorganoarsino derivatives of sugars, amino-acids, dipeptides and tripeptides, 6-mercaptopurine, steroids and nucleosides etc. were found to be active against P388 leukemia in mice [329–334]. Some produced a significant increase in the life span of tumor-bearing animals, thus suggesting that further investigations may lead to the discovery of more powerful antitumor agents.

In contrast with organoarsenic compounds, organoantimony derivatives have not been investigated extensively as antitumor agents and the majority were inactive. However, organoantimony(V) polyamines were found to exhibit inhibitory activity in vitro against HeLa, BHK-21 and L929 tumor cells [335], while diphenylantimony(III) diorganodithiophosphinates and dithiophosphates were the first examples of organoantimony(III) compounds to be found active in vivo against Ehrlich ascites tumor in mice [336].

Recently, organobismuth(III) compounds, i.e. thiolates, were mentioned as potent anticancer agents, producing a cure rate of 100% and a therapeutic index of 3.2–5.0 in mice bearing fluid Ehrlich ascites tumor [337].

Anticarcinogenic effects of diaryltellurium(IV) derivatives and of some amino-acids containing organotellurium(II) groups have also been reported [338,339].

(ii) Transition metal σ-M–C compounds

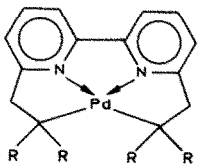
Transition metal complexes containing σ metal–C bonds are generally less stable than those with π metal–C bonds and such compounds have only sporadically been subjected to antitumor screening. Only cobalamin derivatives and organomercury compounds have received some atention, but the results were not encouraging.

Vitamin B_{12} (cyanocobalamin) is an important biological compound containing a σ Co–C bond (Co–CN). Its implication in cancerous disease has been reviewed [340], and the available data suggest that it has a stimulating effect upon the growth of animal tumors, in a dose-dependent manner. A similar effect was observed with methylcobalamin, a derivative which contains a Co–CH_3 bond instead of a Co–CN bond [341–344]. However, other cobalamin derivatives, i.e. 5,6-dimethylbenzimidazolylcobalt-5′-deoxyadenosylcobamide, chlorodifluoromethylcobalamin, methylcobalamin trichloropalladate complex and the hydroxycobalamin, were found to have an opposite effect on animal tumors [343–352]. Methylcobalamin itself was reported to be useful in the treatment of cancer [353,354]. These contradictory data suggest that the antitumor properties of various cobalamin derivatives strongly depend on the organic group attached to cobalt and deserve further investigation.

Many monoorganomercury(II) or diorganomercury(II) compounds were screened for antitumor activity. Although some of them were found to be active [355–357], they do not seem to be useful for treating cancer in humans, since the toxicity of this element is well established.

A ruthenium(II) complex, [Ru(II)(1,3-dimethylxanthine)$(NH_3)_5$]Cl_2, with a σ Ru–C bond between the metal atom and the C(8) carbon atom of the xanthine ligand, failed to exhibit in vivo activity against L1210 leukemia, but inhibited in vitro DNA synthesis in KB cell cultures [103,358].

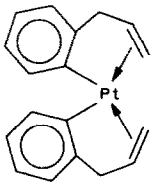
Recently, σ-bonded Pd–C complexes such as **39** were mentioned as potent anticancer agents, since they were found to interact with DNA in a dose-dependent relation [359–361].



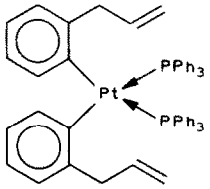
R = COOEt

39

Some platinum complexes containing both σ and π metal–C bonds or only σ metal–C bonds, for example **40** and **41** respectively, were shown to



40



41

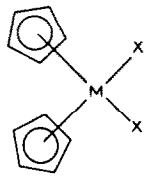
produce filamentation or to inhibit the growth of *Escherichia coli*, and to interact with DNA, but in vivo antitumor screening has not yet been performed [362–364]. Water-soluble platinum ascorbate complexes with *cis*-diaminocyclohexane, which may contain σ metal–C bonds, depending on the procedure used for obtaining them, were also shown to increase significantly the life span of mice bearing the ascitic form of sarcoma 180 [365,366].

Some gold(I) and gold(III) compounds containing σ Au–C bonds, e.g. $[Me_2AuCl_2]AsPh_4$ and $[Me_2AuSCN]_2$, were evaluated in vitro and in vivo, but only marginal effects have been observed [168].

(iii) Transition metal π-complexes

(a) Titanium, zirconium and hafnium; vanadium, niobium and tantalum

Transition metal π-complexes are very common. In recent years some have been extensively studied as potential antitumor agents. Among these, bis(η^5-cyclopentadienyl)metal dihalides (metallocene dihalides), **42**, are remarkable [7,313,367–377]. One of the most thoroughly investigated compounds is titanocene dichloride, **42** (M = Ti; X = Cl), which exhibits anti-



M = Ti, Zr, Hf, V, Nb, Ta, Mo, W.

42

tumor properties against a broad spectrum of solid and ascitic tumors (Table 5). Other titanocene derivatives, including water-soluble compounds, e.g. **42** (X = $-O(O)C-CH=CH-C(O)OH$, $-O(O)C-CCl_3$ or $-S-C_6H_4-NH_3^+Cl^-$-*p*), were also potent antitumor agents against animal tumors.

Titanocene dichloride is less toxic than cisplatin and at least as active as this clinically used drug. Cytologic investigations suggested that intracellular DNA is the primary target of titanocene dichloride attack, and immunologi-

TABLE 5

Antitumor effects of titanocene dichloride against various in vivo animal tumors (in mice)

Tumor	Dose (mg kg^{-1})	Antitumor activity (%)		Ref.
		ILS	Growth inhibition	
Ehrlich ascites tumor	60	958	–	371
Ehrlich ascites tumor (solid)	30	–	86	372
L1210 leukemia	80	26	–	372
P388 leukemia	60	30	–	372
Lewis lung carcinoma	40–60	–	65–71	7
Sarcoma 180 (ascites)	50	184	–	373
Sarcoma 180 (solid)	50	–	77	373
B16 melanoma (ascites)	–	109	–	313
B16 melanoma (solid)	30	–	80	374
Colon 38 carcinoma	30	–	81	374
Human colon carcinoma	30	–	77	375
Human colon carcinoma (C-Stg-2)		–	87	7
Human rectum adenocarcinoma	30	–	55	376
Human lung adenocarcinoma L261	15	–	73	313
Human cell lung carcinoma L182	20	–	73	313
Human breast carcinoma	–	–	77	376

cal processes also seem to be stimulated in vivo.

In addition to titanocene dichloride, the vanadium analog, **42** (M = V; X = Cl), has also been extensively investigated and seems to be very promising as an antitumor agent. Its activity against various animal tumors (Table 6) is similar to that of titanocene dichloride, although its in vitro inhibitory effect against Ehrlich ascites tumor is stronger [7,313,367–370,377].

Other metallocene dichlorides were inactive (zirconocene and hafnocene dichlorides) or significantly less active (niobocene, tantalocene, molybdo-

TABLE 6

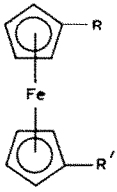
Antitumor effects of vanadocene dichloride against various animal tumors (in mice)

Tumor	Dose (mg kg^{-1})	Antitumor activity (%)		Ref.
		ILS	Growth inhibition	
Ehrlich ascites tumor	80–90	1084		367
Ehrlich ascites tumor (solid)	50		31	372
L1210 leukemia	60	29		372
P388 leukemia	40	24		372

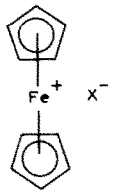
cene and tungstenocene dichlorides) against Ehrlich ascites tumor in vitro or in vivo [7,313,367–370]. Zirconocene and hafnocene derivatives were also inactive against Lewis lung carcinoma and P388, L1210 and L615 leukemias in mice [378]. This behavior may be explained in some cases by the lability of the compounds, e.g. **42** (M = Zr, Mo; X = Cl) in aqueous media [379,380].

(b) Iron and ruthenium

Another type of cyclopentadienyl compound, i.e. ferrocene derivatives of the "sandwich" structure, **43**, has also been investigated [381–384]. None of these neutral compounds bearing alkylating or other organic groups exhibited strong antitumor properties. On the contrary, ferricenium complexes **44** (X = CH_3COO^-, $1/2[Cl_3FeOFeCl_3]^{2-}$, $[FeCl_4]^-$, 2,4,6-$(O_2N)_3C_6H_2O^-$)



43



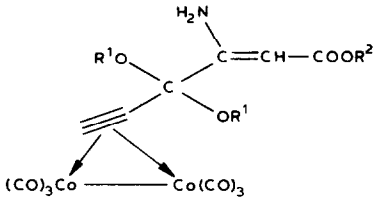
44

were strong antitumor agents, stopping the cellular proliferation of Ehrlich ascites tumor cells in vitro [385] and increasing the survival time of animals bearing the same tumor (ascitic form) [386]. Some ferricenium complexes were also found to be effective against other tumors in mice, e.g. the solid form of Ehrlich tumor, B16 melanoma, L1210 and P388 leukemias, although the tumor-inhibiting activity was less pronounced than that of titanocene dichloride [385]. Good results were obtained in the case of some tumor xenografts transplanted to nude mice, i.e. rectum adenocarcinoma, lung adenocarcinoma and lung small-cell carcinoma [313,376].

Some related neutral ruthenocene derivatives were screened, but the antitumoral effects were not very encouraging [387–389]. Complexes of ruthenium(II) chloride with cyclooctadiene or norbornadiene were active towards solid Friend leukemia, but inactive against L1210 leukemia and sarcoma 180 in mice [390].

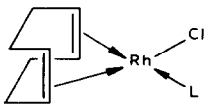
(c) Cobalt, rhodium and iridium

Cobalt complexes containing π metal–C bonds have only occasionally been tested for antitumor activity. Such unusual complexes, which also contain metal–carbonyl and metal–metal bonds, **45**, were mentioned as neoplasm inhibitors in a patent [391]. For R^1 = Et, R^2 = Bu^n, the compound **45** was strongly active in vitro against P388 leukemia cells.

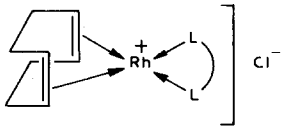


45

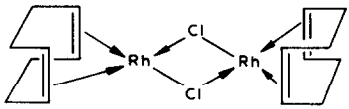
Monomeric neutral (**46**), ionic (**47**) and dimeric (**48**) complexes of rhodium(I) with cyclooctadiene and other dienic systems (norbornadiene, hexadiene) were screened as antitumor agents, and many of them were



46

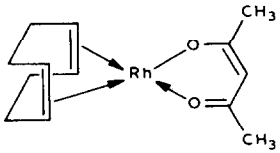


47



48

found to be active in vivo. Thus compound **47** (L–L = bipy) was active against L1210 leukemia in mice (ILS, 28%), while complexes **46** (L = NH_3 or piperidine) were active in the sarcoma 180 tumor system [392]. Most of the complexes tested were active against fluid Ehrlich ascites tumor in mice, producing tumor regression [393,394]. The acetylacetonato derivative **49** at



49

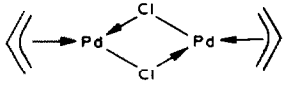
sublethal doses produced 100% cures of mice bearing this tumor, its activity being similar to that of cisplatin [393]. The norbornadiene analog was also highly effective against Ehrlich ascites tumor [395]. The complex **49** was able to inhibit both the growth of the primary tumor and the development of spontaneous and artificial lung metastases, produced by Lewis lung carcinoma in mice [394]. Similar effects were also noted for ionic complexes

47 (L–L = 2-Py–C=N–R; R = Me, Et or Pr^i) against Lewis lung carcinoma subcutaneously inoculated in mice [396]. It seems that the mechanism of action of rhodium(I) organometallic complexes differs from that of cisplatin and rhodium(II) carboxylates, since they lack any effect upon DNA synthesis in Ehrlich ascites tumor cells in vitro.

When the central rhodium atom was replaced by iridium in this class of π complexes, the antitumoral effects of the resulting complexes were similar to those of the rhodium(I) analogs. Thus the *cis,cis*-cycloocta-1,5-diene iridium(I) acetylacetonate produces 100% cures in mice bearing Ehrlich ascites tumor [395] and is also effective in inhibiting the growth of the primary tumor produced by s.c. inoculation of mice with Lewis lung carcinoma. However, it fails to exhibit antimetastatic effects in this tumor system [394] probably because of rapid oxidation in the lung tissue to a chemically inert iridium(III) complex.

(d) Palladium, platinum and gold

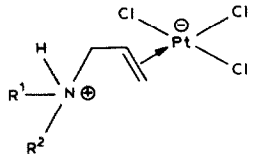
Very few π complexes of palladium and gold have been screened for antitumor activity. η^3-Allylpalladium chloride, **50**, inhibits the development



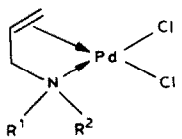
50

of sarcoma 180 and Landschutz ascites in mice but is also very toxic [152]. The gold(I) complex of cyclooctene was found to be of low cytotoxicity in a clonogenic assay with B16 melanoma cells ($IC_{50} = 120\ \mu M$) [397] but exhibited a moderate increase in the survival time of mice bearing P388 leukemia (ILS, 41%) [397].

Some platinum π-complexes were included in the screening trials. Complexes of types **51** and **52** were active in vitro towards L1210 leukemia cells [398]. Only complexes **51** of protonated primary and secondary amines exhibited some cytotoxicity, but always smaller than that of cisplatin. However, complexes **51** ($R^1 = R^2 = H$ or $R^1 = H$, R^2 = Et, Cy) were active



51



52

towards L1210 cell subline resistant to cisplatin. Complexes **51** of tertiary amines were always inactive, while the cytotoxicity of neutral complexes **52** was generally lower than that of protonated amine complexes. These complexes were inactive in vivo towards the same tumor [398].

Organoplatinum complexes containing cyclooctadiene were found to inhibit effectively the growth of Friend virus, leukemia cells HL-60 and HeLa cells [399].

D. CONCLUSIONS

The conclusion that coordination and organometallic compounds of all metals and metalloids may exhibit antitumor properties seems to emerge from this review. In addition to platinum compounds, the coordination compounds of gallium, titanium, iron, ruthenium, rhodium, palladium, copper and gold, and the organometallic compounds of silicon, germanium, tin, titanium, vanadium, iron and rhodium seem to be the most promising. Moreover, four compounds, i.e. two organometallic derivatives of germanium (spirogermanium and Ge-132), gallium nitrate and budotitane, have already been used clinically in the treatment of human patients with cancer diseases.

The phase I and phase II clinical trial results were encouraging; since most of the trials were on patients with advanced stages of tumor development, who had already undergone surgery, radiotherapy or chemotherapy with traditional (organic) cytostatics, it is certainly possible that the use of metal-containing antitumor drugs could give much better results in earlier stages of the disease. Before approval of such clinical tests on humans, a detailed investigation of the toxicity and side effects of a new drug must be carefully examined, and this explains why the process is so slow. Platinum antitumor drugs have been in clinical use for only about 15 years and in this short time a remarkable amount of work has been done on other metal compounds [15]. The examples cited in this review suggest that no air-stable organometallic or coordination compound should be regarded as too exotic for antitumor use and the screening of any new class of such compounds is strongly recommended.

REFERENCES

1 B. Rosenberg, L. van Camp, J.E. Trosko and V.H. Mansour, Nature (London), 222 (1969) 385.
2 M. Peyrone, Justus Liebigs Ann. Chem., 51 (1844) 1.
3 R.D. Williams, Chem. Rev., 72 (1972) 203.
4 M.J. Cleare, Coord. Chem. Rev., 12 (1974) 349.
5 A.I. Stetsenko, M.A. Presnov and A.L. Konovalova, Usp. Khim., 50 (1981) 665; Chem. Abstr., 95 (1981) 46.

6 C. Silvestru and I. Haiduc, Rev. Chim. (Bucharest), 33 (1983) 81.
7 P. Köpf-Maier and H. Köpf, Chem. Rev., 87 (1987) 1137.
8 T.A. Connors and J.J. Roberts (Eds.), Platinum Coordination Complexes in Cancer Chemotherapy, Springer-Verlag, Berlin, 1974.
9 A.W. Prestayko, S.T. Crooke and S.K. Carter (Eds.), Cisplatin: Current Status and New Developments, Academic Press, New York, 1980.
10 S.J. Lippard (Ed.), Platinum, Gold and Other Metal Chemotherapeutic Agents: Chemistry and Biochemistry, ACS Symposium Series, No. 209, American Chemical Society, Washington, DC, 1983.
11 M.P. Hacker, E.B. Douple and I.M. Krakoff (Eds.), Platinum Coordination Complexes in Cancer Chemotherapy, Developments in Oncology Series, Vol. 17, Martinus Nijhoff, Boston, MA, 1984.
12 M. Nicolini (Ed.), Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy, Martinus Nijhoff, Boston, MA, 1988.
13 H. Sigel (Ed.), Metal Ions in Biological Systems, Vol. 11, Metal Complexes as Anticancer Agents, Marcel Dekker, New York, 1980.
14 M. Gielen (Ed.), Metal-based Antitumor Drugs, Freund, London and Tel Aviv, 1988.
15 I. Haiduc and C. Silvestru, Organometallics in Cancer Chemotherapy, CRC Press, Boca Raton, FL, 1989.
16 M.M. Hart and R.H. Adamson, Proc. Natl. Acad. Sci. U.S.A., 68 (1971) 1623.
17 M.M. Hart, C.F. Smith, S.T. Yancey and R.H. Adamson, J. Natl. Cancer Inst., 47 (1971) 1121.
18 R.H. Adamson, G.P. Canellos and S.M. Sieber, Cancer Chemother. Rep., 59 (1975) 599.
19 S.G. Ward and R.C. Taylor, in M. Gielen (Ed.), Metal-based Antitumor Drugs, Freund, London and Tel Aviv, 1988, p. 1.
20 Y.F. Shealy and R.F. Struck, J. Med. Chem., 12 (1969) 907.
21 L.S. Povarov and O.D. Ryazanova, Zh. Obshch. Khim., 42 (1972) 1010.
22 Hamari Yakuhin Kogyo Co. Ltd., Jpn. Kokai Tokkyo Koho, JP 59 101, 498, 1984; Chem. Abstr., 101 (1984) 171292.
23 S.G. Khan, R.Y. Rizvi, S.M. Hadi and Q. Rahman, Mutat. Res., 208 (1988) 27.
24 A.J. Crowe, Drugs of the Future, 12 (1987) 255.
25 H.J. Keller, B.K. Keppler, U. Kruger and R. Linder, Eur. Pat. Appl., 0 049,486, 1982; Chem. Abstr., 97 (1982) 150723.
26 N.F. Cardarelli (Ed.), Tin as a Vital Nutrient; Implications in Cancer Prophylaxis and Other Physiological Processes, CRC Press, Boca Raton, FL, 1986.
27 N.F. Cardarelli, Rev. Silicon,Germanium, Tin Lead Compds., 9 (1986) 307.
28 L.R. Sherman, Rev. Silicon, Germanium, Tin Lead Compds., 9 (1986) 323.
29 N.F. Cardarelli and F. Fazely, Thymus, 11 (1988) 123.
30 W.B. Bell, Br. Med. J., (1929) 431.
31 J.M. Peters, D. Thomas, H. Falk, G. Oberdörster and T.J. Smith, Environ. Health Perspect., 70 (1986) 71.
32 A. Yamamato, A. Hisanaga and N. Ishinishi, Int. J. Cancer, 40 (1987) 220.
33 A.C. Hendrick and E.F. Burton, Can. Med. Assoc. J., 33 (1935) 421.
34 S. Shimotsura, Shika Gakuho, 86 (1986) 1237; Chem. Abstr., 106 (1987) 125225.
35 C.H. Chou, P. Hsu, T.Y. Wang, M.C. Liu and S.T. Chen, Yao Hsueh Hsueh Pao, 7 (1959) 259; Chem. Abstr., 54 (1960) 10127.
36 P. Hsu, C.H. Chou, J.T. Chen and M.L. Shen, Acta Unio Intern. Contra Cancrum, 20 (1964) 245; Chem. Abstr., 61 (1964) 8777.
37 P. Hsu, J.S. Kao, J.S. Tsai, C.H. Chou, M.C. Liu, M.L. Shen, T.Y. Meng, Y.F. Yen, P.C. Pan and S.W. Li, Sci. Sinica (Peking), 13 (1964) 789; Chem. Abstr., 61 (1964) 7570.

38 C. Jasmin, J.C. Cherman, G. Herve, A. Teze, P. Souchay, C. Boy-Loustau, N. Raybaud, F. Sinoussi and M. Raynaud, J. Natl. Cancer Inst., 53 (1974) 469.
39 R. Lidereau, C. Bouchet, F. Sinoussi, R. Saracino and J.C. Cherman, in W. Siegenthaler and R. Luethy (Eds.), Current Chemotherapy, Proc. 10th Int. Congr. Chemother., 1977, American Society of Microbiology, Washington, DC, 1978, Vol. 2, p. 1323.
40 S. Kirschner, Y.K. Wei, D. Francis and J.G. Bergmen, J. Med. Chem., 9 (1966) 369.
41 S.M. Skinner, J.M. Swatzell and R.W. Lewis, Res. Commun. Chem. Pathol. Pharmacol., 19 (1978) 165.
42 F. Ishiwara, Gann, 21 (1927) 1.
43 L.J. Anghileri, Arzneim.-Forsch. (Drug Res.), 25 (1975) 793.
44 K. Hisada, Gan no Rinsho, 18 (1972) 831; Chem. Abstr., 80 (1974) 56143.
45 H.J. Palmer, J.L. Butenhoff and J.E. Stevens, Environ. Res., 43 (1987) 142.
46 L.C. Maxwell and F. Bischoff, J. Pharmacol., 43 (1931) 61.
47 L.J. Anghileri, Eur. J. Cancer, 15 (1979) 1459.
48 L.J. Anghileri, M.C. Crone-Escanye and J. Robert, Anticancer Res., 7 (1987) 1205.
49 A. Caan, Munchen med. Wochenschr., 60 (1913) 1078; Chem. Abstr., 7 (1913) 2620.
50 H.J. Keller, B. Keppler and D. Schmähl, Arzneim.-Forsch. (Drug Res.), 32 (1982) 806.
51 H.J. Keller, B.K. Keppler and D. Schmähl, J. Cancer Res. Clin. Oncol., 105 (1983) 109.
52 B.K. Keppler and M.E. Heim, Drugs of the Future, in press.
53 B.K. Keppler, N. Bischoff, M.R. Berger, M.E. Heim, G. Reznik and D. Schmähl, in M. Nicolini (Ed.), Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy, Martinus Nijhoff, Boston, MA, 1988.
54 B.K. Keppler and D. Schmähl, Arzneim.-Forsch. (Drug Res.), 36 (1986) 1822.
55 B.K. Keppler, M.E. Heim, H. Flechtner, F. Wingen and B.L. Pool, J. Cancer Res. Clin. Oncol., 1988, in press.
56 H. Bischoff, M.R. Berger, B.K. Keppler and D. Schmähl, J. Cancer Res. Clin. Oncol., 113 (1987) 446.
57 J. Mattern, B.K. Keppler and M. Volm, Arzneim.-Forsch. (Drug Res.), 34 (1984) 1289.
58 M.E. Heim and B.K. Keppler, J. Cancer Res. Clin. Oncol., 113 (Suppl.) (1987) S-46, Abstr. No. D-THER 09.
59 B.K. Keppler and K. Michels, Arzneim.-Forsch. (Drug Res.), 35 (1985) 1837.
60 M. Kanisawa and H.A. Schroeder, Cancer Res., 27 (1967) 1192.
61 J. Kieler, A. Gromek and N.J. Nissen, Acta Chir. Scand. Suppl., 343 (1965) 154.
62 U. Hanauske, A.H. Hanauske, M.H. Marshall, V.A. Muggia and D.D. Von Hoff, Int. J. Cell Cloning, 5 (1987) 170.
63 A.N. Kingsnorth, G.M. La Muraglia, J.S. Ross and R.A. Malt, Brit. J. Cancer, 53 (1986) 683.
64 H.J. Thompson, N.D. Chasteen and L.D. Meeker, Carcinogenesis (London), 5 (1984) 849.
65 Committee on Biologic Effects of Atmospheric Pollutants, Chromium, Medical and Biologic Effects of Environmental Pollutants, National Academy of Sciences, Washington, DC, 1974, pp. 1–82.
66 F.W. Sunderman, Jr., in P. Emmelot and E. Krick (Eds.), Environmental Carcinogenesis, Elsevier/North-Holland Biomedical Press, Amsterdam, 1979, p. 165.
67 T. Norseth, EHP Environ. Health Perspect., 40 (1981) 121.
68 H.J. Raithel, K.H. Schaller, A. Reith, K.B. Svenes and H. Valentin, Int. Arch. Occup. Environ. Health, 60 (1988) 55.
69 X.M. Luo, H.J. Wei and S.P. Yang, J. Natl. Cancer Inst., 71 (1983) 75.
70 H. Wei, X. Luo and X. Yang, Zhonghua Zhongliu Zazhi, 9 (1987) 204; Chem. Abstr., 108 (1988) 1995.

71 T. Yamase, H. Fijita and K. Fukushima, Inorg. Chim. Acta, 151 (1988) 15.
72 F.T. Garzon, M.R. Berger, B.K. Keppler and D. Schmähl, Cancer Lett., 34 (1987) 325.
73 J. Fisher, L. Ricard and R. Weiss, J. Am. Chem. Soc., 98 (1976) 3050.
74 C. Jasmin, J.C. Chermann, M. Raynaud, G. Werner, N. Raybaud, F.Sinoussi and C. Boy-Loustau, in G.K. Daikos (Ed.), Progress in Chemotherapy (Antibacterial, Antiviral, Antineoplastic), Proc. 8th Int. Congr. Chemother., 1973, Hellenic Society of Chemotherapy, Athens, 1974, Vol. 2, p. 956.
75 D. Dormont, R. Lidereau, M. Beuzelin, F. Herodin, J.C. Chermann, F. Gourmelon and R. Saracino, in Current Chemotherapy and Immunotherapy, Proc. 12th Int. Congr. Chemother., Florence, 1981, p. 1194.
76 R.J. Smialowicz, R.R. Rogers, M.M. Riddle, R.W. Luebne, L.D. Fogelson and D.G. Row, J. Toxicol. Environ. Health, 20 (1987) 67.
77 M. Mohan, P. Sharma, M. Kumar and N.K. Jha, Inorg. Chim. Acta, 125 (1986) 9.
78 J.D. Scovill, D.L. Klayman and C.F. Franchino, U.S. Pat., 4,657,903, 1987; Chem. Abstr., 107 (1987) 134205.
79 H.G. Seiler, in H. Sigel (Ed.), Metal Ions in Biological Systems, Marcel Dekker, New York, 1983, Vol. 16, p. 317.
80 E. Deutsch, K. Libson, S. Jurisson and L.F. Lindoy, in S.J. Lippard (Ed.), Progress in Inorganic Chemistry, Wiley, New York, 1983, Vol. 30, p. 75.
81 S.K. Shukla, G.B. Manni and C. Cipriani, Inorg. Chim. Acta, 92 (1984) 83.
82 D.R. Elmaleh, P.C. Zamecnik, F.P. Castronovo, Jr., H.W. Strauss and E. Rapaport, Proc. Natl. Acad. Sci. U.S.A., 81 (1984) 918.
83 M.J. Clarke and L. Podbielski, Coord. Chem. Rev., 78 (1987) 253.
84 N.V. Dimitrov and G.W. Eastland, in W. Siegenthaler and R. Luethy (Eds.), Current Chemotherapy, Proc. 10th Int. Congr. Chemother., 1977, American Society of Microbiology, Washington, DC, 1978, Vol. 2, p. 1319.
85 G.W. Eastland, G. Yang and T. Thompson, Methods Find. Exp. Clin. Pharmacol., 5 (1983) 435.
86 G.J. van Giessen and H.G. Petering, J. Med. Chem., 11 (1968) 695.
87 D.H. Petering and H.G. Petering, in A.C. Sartorelli and D.G. Johns (Eds.), Handbook of Experimental Pharmacology, Springer-Verlag, Berlin, 1975, p. 841.
88 J.P. Scovill, D.L. Klayman and C.F. Franchino, J. Med. Chem., 25 (1982) 1261.
89 D.H. Petering, W.E. Antholine and L.A. Saryan, in R.M. Ottenbrite and G.B. Butler (Eds.), Anticancer and Interferon Agents, Synthesis and Properties, Marcel Dekker, New York, 1984, p. 203.
90 F. Arloing, A. Morel and A. Josseraud, C. R. Soc. Biol., 118 (1935) 551.
91 A. Morel, F. Arloing, A. Josseraud and L. Perrot, C. R. Soc. Biol., 137 (1943) 117.
92 F. Arloing, A. Morel and A. Josseraud, C. R. Soc. Biol., 118 (1935) 1435.
93 W.D. Yang, Q. LeMe and S.Q. Peng, Inorg. Chim. Acta, 106 (1985) 65.
94 M. Gosalvez, M.F. Blanco, C. Vivero and F. Valles, Eur. J. Cancer, 14 (1978) 1185.
95 J.C. Dabrowiak, in H. Sigel (Ed.), Metal Ions in Biological Systems, Marcel Dekker, New York, 1980, Vol. 11, p. 305.
96 H. Beraldo, A. Garnier-Suillerot, L. Tosi and F. Lavelle, Biochemistry, 24 (1985) 284.
97 C. Myers, L. Gianni, J. Zweier, J. Muindi, B.K. Sinha and H. Eliot, Fed. Proc., 45 (1986) 2792.
98 J.C. Dabrowiak, F.T. Greenaway, F.S. Santillo and S.T. Crooke, Biochem. Biophys. Res. Commun., 91 (1979) 721.
99 J.C. Dabrowiak, F.T. Greenaway and F.S. Santillo, in S. Hecht (Ed.), Bleomycin: Chemical, Biochemical and Biological Aspects, Springer Verlag, New York, 1979, p. 137.
100 J.C. Dabrowiak, J. Inorg. Biochem., 13 (1980) 317.

101 J.C. Dabrowiak, F.T. Greenaway, F.S. Santillo, S.T. Crooke and J.M. Essery, in A.E. Martell (Ed.), Inorganic Chemistry in Biology and Medicine, ACS Symposium Series, No. 140, American Chemical Society, Washington, DC, 1980, p. 237.
102 E.A. Rao, L.A. Saryan, W.E. Antholine and D.H. Petering, J. Med. Chem., 23 (1980) 1310.
103 M.J. Clarke, in H. Sigel (Ed.), Metal Ions in Biological Systems, Marcel Dekker, New York, 1980, Vol. 11, p. 231.
104 M.J. Clarke, in S.J. Lippard (Ed.), Platinum, Gold and Other Metal Chemotherapeutic Agents. Chemistry and Biochemistry, ACS Symposium Series, No. 209, American Chemical Society, Washington, DC, 1983, p. 335.
105 M.J. Clarke, in E.D. Zysk and J.A. Bonucci (Eds.), Precious Met. Proc. 9th Int. Precious Met. Inst. Conf., 1985, International Precious Metals Institute, Allentown, PA, 1986, p. 369.
106 L.J. Anghileri, Z. Krebsforsch., 83 (1975) 213.
107 T. Tsuruo and H. Iida, Gann, 71 (1980) 151.
108 M.J. Clarke, in A.E. Martell (Ed.), Inorganic Chemistry in Biology and Medicine, ACS Symposium Series, No. 140, American Chemical Society, Washington, DC, 1980, p. 157.
109 R.E. Yasbin, C.R. Matthews and M.J. Clarke, Chem. Biol. Interact., 31 (1980) 355.
110 F.P. Dwyer, E. Mayhew, E.M.F. Roe and A. Shulman, Br. J. Cancer, 19 (1965) 195.
111 B.K. Keppler and W. Rupp, J. Cancer Res. Clin. Oncol., 111 (1986) 166.
112 F.T. Garzon, M.R. Berger, B.K. Keppler and D. Schmähl, Cancer Chemother. Pharmacol., 19 (1987) 347.
113 B.K. Keppler, D. Wehe, H. Endres and W. Rupp, Inorg. Chem., 26 (1987) 844.
114 B.K. Keppler, W. Belzer and V. Seifried, Arzneim.-Forsch. (Drug Res.), 37 (1987) 770.
115 B.K. Keppler, W. Rupp, U.M. Juhl, H. Endres, R. Niebl and W. Balzer, Inorg. Chem., 12 (1987) 4366.
116 G. Mestroni, G. Zassinovich, E. Alessio and A. Bontempi, Inorg. Chim. Acta, 137 (1987) 63.
117 G. Sava, S. Zorzet, L. Perissin, G. Mestroni, G. Zassinovich and A. Bontempi, Inorg. Chim. Acta, 137 (1987) 69.
118 A. Doadrio, D. Crăciunescu and C. Ghirvu, An. Quim., 73 (1977) 1042; Chem. Abstr., 88 (1978) 145351.
119 D. Crăciunescu, An. R. Acad. Farm., 43 (1977) 265; Chem. Abstr., 88 (1978) 32017.
120 A. Doadrio, D. Crăciunescu, C. Ghirvu and J.C. Nuno, An. Quim., 73 (1977) 1220; Chem. Abstr., 89 (1978) 173626.
121 A. Doadrio, D. Crăciunescu and C. Ghirvu, An. R. Acad. Farm., 46 (1980) 153; Chem. Abstr., 94 (1981) 10880.
122 C. Drăgulescu, M. Jitaru, I. Havlik, A. Maurer, S. Policec, V. Topciu and N. Csaki, Farmacia (Bucharest), 29 (1981) 215; Chem. Abstr., 97 (1982) 381.
123 A. Shulman, G.M. Laycock and T.R. Bradley, Chem. Biol. Interact., 16 (1977) 89.
124 J.K. Barton, PCT Int. Appl., W0 86 04, 358 (1986); Chem. Abstr., 106 (1987) 61217.
125 G.J. van Giessen, J.A. Crim, D.H. Petering and H.G. Petering, J. Natl. Cancer Inst., 51 (1973) 139.
126 Y.S. Chough, H.S. Yoo and M. Bae, Seoul Natl. Univ. Fac. Pap., Sci. Technol. Ser., 4 (1975) 45; Chem. Abstr., 85 (1976) 87232.
127 P. Lumme, H. Elo and J. Janne, Inorg. Chim. Acta, 92 (1984) 241.
128 H. Elo, Inorg. Chim. Acta, 136 (1987) L33.
129 R.M. Snyder, C.K. Mirabelli, R.K. Johnson, C.M. Sung, L.F. Faucette, F.L. McCabe, J.P. Zimmerman, M. Whitman, J.C. Hempel and S.T. Crooke, Cancer Res., 46 (1986) 5054.

130 E.M. Hodnett, C.H. Moore and F.A. French, J. Med. Chem., 14 (1971) 1121.
131 E.M. Hodnett and W.J. Dunn, J. Med. Chem., 15 (1972) 339.
132 Z. Liu, F. Zheng, X. Gao and X. Zhang, Huazhong Shiyuan Xuebao, Ziran Kexuebao, 3 (1983) 68; Chem. Abstr., 101 (1984) 203963.
133 Z. Wu, Z. Yan, J. Liu, Y. Zhou, Z. Liu, F. Zheng, X. Gao and X. Zhang, Wuji Huaxue, 2 (1986) 108; Chem. Abstr., 107 (1987) 50768.
134 E. Sako, Juzen Igakkai Zasshi, 67 (1961) 384, 390 and 395; Chem. Abstr., 61 (1964) 8792.
135 H. Fujimori, in Proc. 3rd Int. Congr. Chemother., Stuttgart, 1963, 2 (1964) 1061; Chem. Abstr., 65 (1966) 9568.
136 M.J. Cleare and H.C. Hydes, in H. Sigel (Ed.), Metal Ions in Biological Systems, Marcel Dekker, New York, 1980, Vol. 11, p. 1.
137 E.B. Boyar and S.D. Robinson, Platinum Met. Rev., 26 (1982) 65.
138 J.L. Bear, in E.D. Zysk and J.A. Bonucci (Eds.), Precious Met., Proc. 9th Int. Precious Met. Inst. Conf., 1985, International Precious Metals Institute, Allentown, PA, 1986, p. 337.
139 J.L. Bear, R.A. Howard and A.M. Dennis, in W. Siegenthaler and Luethy (Eds.), Current Chemotherapy, Proc. 10th Int. Congr. Chemother., 1977, American Society of Microbiology, Washington, DC, 1978, Vol. 2, p. 1321.
140 K. Das, R. Howard, A. Dennis and J.L. Bear, Bioelectrochem. Bioenerg., 5 (1978) 741.
141 J.L. Bear, H.B. Gray, L. Rainen, I.M. Chang, R. Howard, G. Serio and A.P. Kimball, Cancer Chemother. Rep., Part 1, 59 (1975) 611.
142 P.N. Rao, M.L. Smith, S. Pathak, R.A. Howard and J.L. Bear, J. Natl. Cancer Inst., 64 (1980) 905.
143 G.R. Gale, E.M. Walker, Jr., A.B. Smith and A.E. Stone, Proc. Soc. Exp. Biol. Med., 136 (1971) 1197.
144 G.M. Kolodny, Report 1983, DOE/EV/10327-2; Order No. DE 84,005,770; Energy Res. Abstr., 9 (1984) Abstr. No. 12757; Chem. Abstr., 101 (1984) 83659.
145 G.M. Kolodny and C. Rose, Cancer Res., 43 (1983) 3101.
146 M. Das and S.E. Livingstone, Br. J. Cancer, 37 (1978) 466.
147 A.A. Chachoyan and B.T. Garibdzhanyan, Biol. Zh. Arm., 39 (1986) 260; Chem. Abstr., 105 (1986) 218414.
148 M. Mohan, N.S. Gupta, L. Chandra and N.K. Jha, J. Inorg. Biochem., 31 (1987) 7.
149 S.E. Livingstone and A.E. Mihkelson, Inorg. Chem., 9 (1970) 2545.
150 M.J. Cleare and J.D. Hoeschele, Bioinorg. Chem., 2 (1973) 187.
151 M.J. Cleare, Recent Results Cancer Res., 48 (1974) 12.
152 R.D. Graham and D.R. Williams, J. Inorg. Nucl. Chem., 41 (1979) 1245.
153 J. Dehand, J. Jordanov and J.P. Beck, Chem. Biol. Interact., 11 (1975) 605.
154 D. Gill, in M.P. Hacker, E.B. Douple and I.M. Krakoff (Eds.), Platinum Compounds in Cancer Chemotherapy (Developments in Oncology Series, Vol. 17), Martinus Nijhoff, Boston, MA, 1984, p. 267.
155 M. Grandi and V. Santoro, in 14th Int. Cancer Congr., Budapest, 2–7 August, 1986, Karger and Akademiai Kiado, Budapest, 1986, Vol. 2, p. 671.
156 D.C.H. McBrien and T.F. Slater (Eds.), Biochemical Mechanisms of Platinum Antitumor Drugs, IRL Press, Oxford, 1986.
157 D.D. Bradock, T.A. Connors, H. Jones, A.R. Khokhar, D.H. Melzeck and M.L. Tobe, Chem. Biol. Interact., 11 (1975) 145.
158 B. Rosenberg, Cancer, 55 (1985) 2303.
159 P. Köpf-Maier and H. Köpf, Naturwissenschaften, 73 (1986) 239.
160 J.J. Roberts and M.P. Pera, Jr., Top. Mol. Struct. Biol., 3 (1983) 183.

161 C.F.J. Barnard, M.J. Cleare and P.C. Hydes, Chem. Br., 22 (1986) 1001.
162 J. Reedijk, Pure Appl. Chem., 59 (1987) 181.
163 J.C. Dabrowiak and W.T. Bradner, Prog. Med. Chem., 24 (1987) 129.
164 J. Reedijk, A.M.J. Fichtinger-Schepman, A.T. Van Oosteron and P. Van de Putte, Struct. Bonding (Berlin), 67 (1987) 53.
165 P.C. Hydes and M.J.H. Russell, Cancer Metast. Res., 7 (1988) 67.
166 J.J. Roberts and M.F. Pera, Jr., in S.J. Lippard (Ed.), Platinum, Gold and Other Metal Chemotherapeutic Agents: Chemistry and Biochemistry (ACS Symposium Series, No. 209), American Chemical Society, Washington, DC, 1983, p. 3.
167 M.M. Jacobs and A.C. Griffin, in M.S. Zedeck and M. Lipkin (Eds.), Inhibition of Tumor Induction and Developments, Plenum, New York, 1981, p. 169.
168 P.J. Sadler, M. Nasr and V.L. Narayanan, in M.P. Hacker, E.G. Douple and I.H. Krakoff (Eds.), Platinum Coordination Complexes in Cancer Chemotherapy (Developments in Oncology Series, Vol. 17), Martinus Nijhoff, Boston, MA, 1984, p. 290.
169 W.M. Willingham and J.R.J. Sorenson, Trace Elem. Med., 3 (1986) 139.
170 F.A. French and E.J. Blanz, Jr., Cancer Res., 25 (1965) 1454.
171 D.H. Petering, Adv. Exp. Med. Biol., 91 (Inorg. Nutr. Aspects Cancer) (1978) 179.
172 D.H. Petering, in H. Sigel (Ed.), Metal Ions in Biological Systems, Marcel Dekker, New York, 1980, Vol. 11, p. 197.
173 D.L. Klayman, J.P. Scovill, C.J. Mason, J.F. Bartosevich, J. Bruce and A.J. Lin, Arzneim.-Forsch. (Drug Res.), 33 (1983) 909.
174 M. Mohan, P. Sharma and N.K. Jha, Inorg. Chim. Acta, 107 (1985) 91.
175 K. Takamiya, Gann, 50 (1959) 277 and 291.
176 Z. Wu, Z. Yen, Y. Zhou, M. Yang, X. Gao and Z. Liu, Huazhong Shifan Daxue Xuebao, Ziran Kexueban, 20 (1986) 179; Chem. Abstr., 106 (1987) 11884.
177 H. Elo and P. Lumme, Inorg. Chim. Acta, 136 (1987) 149.
178 H. Elo, I. Sunila and P. Lumme, Inorg. Chim. Acta, 136 (1987) 61.
179 H. Elo, Cancer Lett., 36 (1987) 333.
180 S.W.C. Leuthauser, L.W. Oberley, T.D. Oberley, J.R.J. Sorenson and K. Ramakrishna, J. Natl. Cancer Inst., 66 (1981) 1077.
181 J.R.J. Sorenson, L.W. Oberley, R.K. Crouch, T.W. Kensler, V. Kishore, S.W.C. Leuthauser, T.D. Oberley and A. Pezeshk, Biol. Trace Elem. Res., 5 (1983) 257.
182 R.K. Crouch, T.W. Kensler, L.W. Oberley and J.R.J. Sorenson, in K.D. Karlin and J. Zubieta (Eds.), Biological and Inorganic Copper Chemistry, Adenine Press, Guilderland, NY, 1986.
183 J.J. Reiners, Jr., and A.B. Colby, Carcinogenesis (London), 9 (1988) 629.
184 C.G. Crispens, Jr., and J.R.J. Sorenson, Anticancer Res., 8 (1988) 77.
185 C. Drâgulescu, M. Mracec, Z. Simon, A. Maurer, S. Policec, V. Topciu and N. Csaki, Sci. Tech. Bull. Polit. Inst. "Traian Vuia" (Timisoara), 24 (1979) 71.
186 E.M. Treshchalina, A.L. Konovalova, M.A. Presnov, L.F. Chapurina, N.I. Belichuk and I.A. D'yakon, Dokl. Akad. Nauk SSSR, 248 (1979) 1273.
187 E.M. Treshchalina, A.L. Konovalova and M.A. Presnov, Vestn. Akad. Med. Nauk SSSR, 1986 (5) 51.
188 L. Cohen and S. Schwartz, Cancer Res., 26 (1966) 1769.
189 S. Policec, R. Vasiliev, A. Maurer, M. Mracec, I. Havlik, O. Costisor, M. Jitaru, V. Topciu and N. Csaki, Timisoara Med., 26(3) (1981) 29; Chem. Abstr., 97 (1982) 66073.
190 S.M. Hecht (Ed.), Bleomycin: Chemical, Biochemical and Biological Aspects, Springer-Verlag, New York, 1979.
191 D. Solaiman, E.A. Rao, W.E. Antholine and D.H. Petering, J. Inorg. Biochem., 12 (1980) 201.

192 S. Lyman, B. Ujjani, K. Renner, W.E. Antholine, D.H. Petering, J.W. Whetstone and J.M. Knight, Cancer Res., 46 (1986) 4470.
193 M. Spinelli and J.C. Dabrowiak, Biochemistry, 21 (1982) 5862.
194 F.T. Greenaway and J.C. Dabrowiak, J. Inorg. Biochem., 16 (1982) 91.
195 V. Malatesta, A. Gervasini and F. Morazzoni, Inorg. Chim. Acta, 136 (1987) 81.
196 M.D. Joesten, in H. Sigel (Ed.), Metal Ions in Biological Systems, Marcel Dekker, New York, 1980, Vol. 11, p. 285.
197 T.M. Simon, D.H. Kunishima, G.J. Vibert and A. Lorber, Cancer, 44 (1979) 1965.
198 T.M. Simon, D.H. Kunishima, G.J. Vibert and A. Lorber, Cancer Res., 41 (1981) 94.
199 S.T. Crooke and C.K. Mirabelli, Am. J. Med., 75(6A) (1983) 109.
200 C.K. Mirabelli, R.K. Johnson, C.M. Sung, L. Faucette, K. Muirhead and S.T. Crooke, Cancer Res., 45 (1985) 22.
201 S.J. Berners-Price, C.K. Mirabelli, R.K. Johnson, M.R. Mattern, F.L. McCabe, L.F. Faucette, C.M. Sung, S.M. Mong, P.J. Sadler and S.T. Crooke, Cancer Res., 46 (1986) 5486.
202 C.K. Mirabelli, B.D. Jensen, M.R. Mattern, C.M. Sung, S.M. Mong, D.T. Hill, S.W. Dean, P.S. Schein, R.K. Johnson and S.T. Crooke, Anticancer Drug Design, 1 (1986) 223.
203 C.F. Shaw, A. Berry and G.E. Stocco, Inorg. Chim. Acta, 123 (1986) 213.
204 R.K. Johnson, C.K. Mirabelli, L.F. Faucette, F.L. McCabe, D.M. Sutton, D.L. Bryan, G.R. Girard and D.T. Hill, Proc. Am. Assoc. Cancer Res., 26 (1985) 254; Abstr. 1001.
205 A.M. van Rij and W.J. Pories, in H. Sigel (Ed.), Metal Ions in Biological Systems, Marcel Dekker, New York, 1980, Vol. 10, Chapter 7.
206 D.H. Barch and P.M. Iannaccone, Adv. Exp. Med. Biol., 206 (Essent. Nutr. Carcinog.) (1986) 517.
207 G. Atassi, P. Dumont and J.C.E. Harteel, Eur. J. Cancer, 15 (1979) 451.
208 C. Drăgulescu, I. Havlik, A. Maurer, S. Policec, V. Topciu and N. Csaki, Farmacia (Bucharest), 28 (1980) 139; Chem. Abstr., 94 (1981) 185514.
209 J. Haidu and E.C. Armstrong, J. Am. Chem. Soc., 103 (1981) 232.
210 D. Solaiman, L.A. Saryan and D.H. Petering, J. Inorg. Biochem., 10 (1979) 135.
211 G.C. Skvortsova, A.I. Skushnikova, E.S. Domnina, I.G. Veksler, K.P. Balitskii and M.G. Voronkov, Khim.-Farm. Zh., 18 (1984) 679.
212 A.H. Soloway, in H. Steinberg and A.L. McCloskey (Eds.), Progress in Boron Chemistry, Pergamon, Oxford, 1964, Vol. 1, p. 203.
213 W. Kliegel, Pharm. Unserer Zeit, 2 (1973) 21.
214 R. Larsson, in Proc. 1st Int. Symp. Neutron Capture Therapy, Cambridge, MA, 1983, p. 34.
215 S.H. Tung, K.M. Chang, S.L. Tah, C.C. Liu and S.L. Chang, K'o Hsueh T'ung Pao, 17 (1966) 414; Chem. Abstr., 66 (1967) 37990.
216 G. Zhang, S. Dong, H. Zhu and H. Liu, Wuhan Daxue Xuebao, Ziran Xexueban, (1981) 43; Chem. Abstr., 98 (1983) 17023.
217 K. Lin, G. Zhang and N. Fu, Youji Huaxue, (1985) 228; Chem. Abstr., 104 (1986) 207334.
218 I.H. Hall, C.O. Starnes, B.F. Spielvogel, P. Wisian-Neilson, M.K. Das and L. Wojnowich, J. Pharm. Sci., 68 (1979) 685.
219 B.F. Spielvogel, M.K. Das, A.T. McPhail, K.D. Onan and I.H. Hall, J. Am. Chem. Soc., 102 (1980) 6343.
220 B.F. Spielvogel, in R.W. Parry and G. Kodama (Eds.), Boron Chemistry, Pergamon, Oxford, 1980, p. 119.

221 I.H. Hall, C.J. Gilbert, A.T. McPhail, K.W. Morse, K. Hassett and B.F. Spielvogel, J. Pharm. Sci., 74 (1985) 755.
222 B.F. Spielvogel, L. Wojnowich, N.K. Das, A.T. McPhail and K.D. Hargrave, J. Am. Chem. Soc., 98 (1976) 5702.
223 M.A. Ignatenko, Khim.-Farm. Zh., 21 (1987) 402.
224 G. Atassi, Rev. Silicon, Germanium, Tin Lead Compds., 8 (1985) 219.
225 E. Lukevics, A. Zidermane, A. Dauvarte, T.V. Lapina, L.N. Khokhlova and I.D. Segal, Khim.-Farm. Zh., 12 (1978) 62.
226 E. Lukevics, T.V. Lapina, N.M. Sukhova, A. Zidermane, A. Dauvarte and V.A. Voronova, Khim.-Farm. Zh., 15 (1981) 53.
227 S. Toyoshima, K. Fukushima, H. Fujita, T. Sakurai, Y. Sugimoto, N. Yagi, H. Tomioka, M. Fukuma and Y. Seto, Gan to Kagaku Ryoho (Jpn. J. Cancer Chemother.), 7 (1980) 1942; Chem. Abstr., 94 (1981) 114438.
228 S. Toyoshima, K. Fukushima, Y. Seto, T. Sakurai, Y. Sugimoto, Y. Yagi, N. Shinohara, Y. Yamamoto and K. Ito, Gan to Kagaku Ryoho (Jpn. J. Cancer Chemother.), 8 (1981) 579; Chem. Abstr., 96 (1982) 62661.
229 S. Toyoshima, K. Fukushima, T. Sakurai, Y. Sugimoto, Y. Ohbayashi, Y. Seto, N. Shinohara, Y. Yamamoto and K. Ito, Gan to Kagaku Ryoho (Jpn. J. Cancer Chemother.), 8 (1981) 1130; Chem. Abstr., 96 (1982) 79531.
230 S. Toyoshima, K. Fukushima, T. Sakurai, Y. Sugimoto, H. Sato and H. Taguchi, Gan to Kagaku Ryoho (Jpn. J. Cancer Chemother.), 9 (1982) 225; Chem. Abstr., 96 (1982) 210528.
231 T. Sakurai,, K. Fukushima, H. Fujita and S. Toyoshima, in Proc. 13th Int. Congr. Chemother., 16 (1983) 284/135–284/140; Chem. Abstr., 103 (1985) 205748.
232 A. Hakura, K. Kohda and Y. Kawazoe, Mutat. Res., 157 (1985) 87.
233 K. Fukushima, H. Fujita, T. Sakurai, Y. Yamaki, Y. Seto and S. Toyoshima, in 14th Int. Cancer Congr., Budapest 2–7 August, 1986, Karger and Akademiai Kiado, Budapest, 1986, Vol. 2, p. 667.
234 S. Toyoshima, H. Fujita, K. Fukushima, T. Sakurai, M. Koketsu and Y. Seto, in J. Ishigani (Ed.), Recent Adv. Chemother., Proc. 14th Congr. Chemother., 1985, Anticancer Section 2, University of Tokyo Press, Tokyo, p. 945; Chem. Abstr., 106 (1987) 311.
235 D.R. Bennett and B. Aberg, Acta Toxicol. Pharmacol., Suppl. 3, 36 (1975) 5.
236 A. Pilbrant and B. Strinberg, Acta Toxicol. Pharmacol., Suppl. 3, 36 (1975) 139.
237 P. Hencsei and L. Párkányi, Rev. Silicon, Germanium, Tin Lead Compds., 8 (1985) 191.
238 M.G. Voronkov, Chem. Br., 9 (1973) 411.
239 G. Zelchan, A. Lapkina, I.I. Soldmennikova, A. Dauvarte, A. Zidermane and E. Lukevics, Biol. Akt. Soedin. Elem. IVB Gruppy, (1977) 28; Chem. Abstr., 89 (1978) 109694.
240 M.G. Voronkov, in G. Benz and I. Lindquist (Eds.), Biochemistry of Silicon and Related Problems, Plenum, New York, 1978, p. 395.
241 M.G. Voronkov and V.M. Dyakov, Silatrany (Silatranes), Nauka, Novosibirsk, 1978.
242 A. Grna, N. Ledinko, F. Fazely, S. Darling and J. Hogan, Anticancer Res., 8 (1988) 249.
243 J.S. Thayer, Appl. Organomet. Chem., 1 (1987) 227.
244 M. Bai, L. Geng and L. Sun, Huaxue Tongbao, 11 (1988) 23; Chem. Abstr., 109 (1986) 22989.
245 B.T. Hill, S.A. Whatley, A.S. Bellamy, L.Y. Jenkins and R.D.H. Whelan, Cancer Res., 42 (1982) 2852.
246 S.J. Yang and S. Rafla, Am. J. Clin. Oncol., 5 (1983) 331.
247 B.T. Hill and R.D. Whelan, Invest. New Drugs, 4 (1986) 359.

248 L.M. Rice, J.W. Wheller and C.F. Geschickter, J. Heterocycl. Chem., 11 (1974) 1041.
249 L.M. Rice, M. Slavik and P. Schein, Clinical Brochure Spirogermanium (NSC 192965), prepared by the National Cancer Institute, Bethesda, MD, 1977.
250 Screening Data Summaries, Drug Research and Development Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD, 1977.
251 B.F. Kimler, D.F. Martin, R.G. Evans, R.A. Morantz and T.S. Vats, N.C.I. Monographs, 1988 (6) 115.
252 M. Slavik, L. Elias, J. Mrema and J.H. Saiers, Drugs Exp. Clin. Res., 8 (1982) 379.
253 M. Slavik, O. Blanc and J. Davis, Invest. New Drugs, 1 (1983) 225.
254 C. Trope, W. Mattsson, I. Gynning, J.E. Johnson, K. Sigurdsson and B. Orbert, Cancer Treat. Rep., 65 (1981) 119.
255 L. Weiselberg, D.R. Budman, D. Schulman, V. Vinciguerra, T.J. Degman and M. Pasmantier, Cancer Treat. Rep., 66 (1982) 1675.
256 D.E. Brenner, H.W. Jones, N.B. Rosenshein, A. Forastiere, M. Dillon, F. Grubine, S. Tipping, L. Burnett, F.A. Greco and P. Wiernick, Cancer Treat. Rep., 67 (1983) 193.
257 J.J. Kavanagh, P.B. Saul, L.J. Copeland, D.M. Gershenson and I.H. Krakoff, Cancer Treat. Rep., 69 (1985) 139.
258 D.E. Brenner, N.B. Rosenshein, M. Dillon, H.W. Jones, A. Forastiere, S. Tipping, L.S. Burnett, F.A. Greco and P.H. Wiernik, Cancer Treat. Rep., 69 (1985) 457.
259 D.R. Budman, S. Ginsberg, M. Perry, V. Weinberg, P. Schein, J. Hanson, M. Coleman and W. Wood, Cancer Treat. Rep., 66 (1982) 1667.
260 G. Falkson and H.C. Falkson, Cancer Treat. Rep., 67 (1983) 189.
261 J.P. Kuebler, D.C. Tormey, G.R. Harper, Y.C. Chang, J.D. Khandekar and G. Falkson, Cancer Treat. Rep., 68 (1984) 1515.
262 K. Pinnamaneni, H.Y. Yap, S.S. Legha, G.R. Blumenschein and G.P. Bodey, Cancer Treat. Rep., 68 (1984) 1197.
263 P. Schulman, R.B. Davis, S. Rafla, M. Green and E. Henderson, Cancer Treat. Rep., 68 (1984) 1305.
264 J.M. Salera, M. Slavik, R.L. Stephens and E.D. Crawford, Cancer Treat. Rep., 71 (1987) 207.
265 E. Eisenhauer, I. Kerr, A. Bodurtha, N. Iscoe, P. McCulloch, K. Pritchard and I. Quin, Invest. New Drugs, 3 (1985) 303.
266 J.W. Goodwin, K. Kopecky, M.Slavik, B.L. Tranum, S.P. Balcerzak, W.S. Fletcher and J.J. Costanzi, Cancer Treat. Rep., 71 (1987) 985.
267 E.Eisenhauer, I. Quirt, J.M. Connors, J. Maroun and J. Skillings, Invest. New Drugs, 3 (1985) 307.
268 L. Boros, A.A. Tsiatis, R.S. Neiman, R.B. Mann and J.H. Glick, Cancer Treat. Rep., 70 (1986) 917.
269 R. Espana, R. Kaplan, K. Robichaud, P. Gustafson, P. Wiernik, F. Smith, P. Wooley and P. Schein, Proc. Am. Soc. Clin. Oncol., 1 (1982) 166.
270 H.M. Dhingra, T. Umsawasdi, D.F. Chiuten, W.K. Murphy, P.Y. Holoye, G. Spitzer and M. Valdivieso, Cancer Treat. Rep., 70 (1986) 673.
271 J.M. Goodwin, J. Crowley, B. Tranum, R. Vance, M. Slavik, S. Balcerzak and D. Hacker, Cancer Treat. Rep., 71 (1987) 99.
272 J.A. Ajani, J.S. Faintuch, R.K. McClure, B. Levin, B.M. Boman and J.H. Krakoff, Invest. New Drugs, 4 (1986) 383.
273 F. Dexeus, C. Logothetis, M.L. Samuels and B. Hossan, Cancer Treat. Rep., 70 (1986) 1129.
274 N.M. Bui, J. Chauvergne, R. Brunet, P. Richaud, B. Hoerni, C. Lagarde and M. Le Guillou, Bull. Cancer (Paris), 73 (1986) 65.

275 P.J. Byrne, P.S. Schein, P. Maguire, D. Hoth, F. Smith, J. Brown and P.V. Wooley, Proc. Am. Soc. Clin. Oncol., (1980) 351 (Abstr. C-129).
276 M. Tsutsui, N. Kakimoto, D.D. Axtell, H. Oikawa and K. Asai, J. Am. Chem. Soc., 98 (1976) 8287.
277 N. Kumano, Y. Nakai, T. Ishikawa, S. Koinumaru, S. Suzuki and K. Konno, Sci. Rep. Res. Inst., Tohoku Univ., Ser. C, 25(3/4) (1978) 89.
278 H. Sato and T. Iwaguki, Gan to Kagaku Ryoho (Jpn. J. Cancer Chemother.), 6 (1979) 79; Chem. Abstr., 90 (1979) 180106.
279 H. Aso, T. Yamaguchi, K. Nakata, T. Ebina and N. Ishida, Proc. Jpn. Cancer Assoc., 39 (1980) 87.
280 E. Lukevics, S.K. Germane, A.A. Zidermane, A.Z. Dauvarte, I.M. Kravchenko, M.A. Trushule, V.F. Mironov, T.K. Gar, N.Yu. Khromova, N.A. Viktorov and V.I. Shiryaev, Khim.-Farm. Zh., 18 (1984) 154.
281 H. Aso, E. Shibuya, F. Suzuki, T. Nakamura, H. Inoue, T. Ebina and N. Ishida, Gan to Kagaku Ryoho (Jpn. J. Cancer Chemother.), 12 (1985) 2345.
282 F. Suzuki, Gan to Kagaku Ryoho (Jpn. J. Cancer Chemother.), 12 (1985) 1445.
283 F. Suzuki, R.R. Brutkiewicz and R.B. Pollard, Anticancer Res., 5 (1985) 479.
284 N. Kumano, T. Ishikawa, S. Koinumaru, T. Kikumoto, S. Suzuki, Y. Nakai and K. Konno, Tohoku J. Exp. Med., 146 (1985) 97.
285 S. Arimori, K. Watanabe, M. Yoshida and T. Nagao, in Proc. Int. Symp. Immunomodul. Microbial Products Rel. Synth. Compds., Osaka, 1981, Excerpta Medica, Int. Congress Ser., 563 (1982) 498.
286 Y. Nakai, S. Suzuki, N. Kumano and N. Konno, in 14th Int. Cancer Congr., Budapest, 2–7 August, 1986, Karger and Akademiai Kiado, Budapest, 1986, Vol. 1, p. 215.
287 F. Suzuki, R.R. Brutkiewicz and R.B. Pollard, Int. J. Immunother., 2 (1986) 239.
288 T. Munakata, S. Arai, K. Kuwano, M. Furukawa and Y. Tomita, J. Interferon Res., 7 (1987) 69.
289 F. Suzuki, Gan to Kagaku Ryoho (Jpn. J. Cancer Chemother.), 14 (1987) 127.
290 R.R. Brutkiewicz and F. Suzuki, In Vivo, 1 (1987) 189.
291 I. Sato, B.D. Yuan, T. Nishimura and N. Tanaka, J. Biol. Response Modif., 4 (1985) 159.
292 N. Kakimoto, M. Akiba and T. Tanaka, Heterocycles, 21 (1984) 753.
293 T.K. Miyamoto, N. Sugita, Y. Matsumoto, Y. Sasaki and M. Konno, Chem. Lett., (1983) 1695.
294 P. Köpf-Maier, C. Janiak and H. Schumann, Inorg. Chim. Acta, 152 (1988) 75.
295 C.J. Evans and S. Karpel, Organotin Compounds in Modern Toxicology, Elsevier, Amsterdam, 1985.
296 W.N. Aldrige, in N.F. Cardarelli (Ed.), Tin as a Vital Nutrient: Implications in Cancer Prophylaxis and Other Physiological Processes, CRC Press, Boca Raton, FL, 1986, p. 245.
297 A.K. Saxena, Appl. Organomet. Chem., 1 (1987) 39.
298 P.J. Sadler, Chem. Br., 18 (1982) 182.
299 V.L. Narayanan, in D.N. Reinhoudt, T.A. Connors, H.M. Pinedo and K.W. van de Poll (Eds.), Structure–Activity Relationships of Anti-Tumour Agents (Developments in Pharmacology, Vol. 3), Martinus Nijhoff, The Hague, 1983, p. 5.
300 M. Gielen, in N.F. Cardarelli (Ed.), Tin as a Vital Nutrient: Implications in Cancer Prophylaxis and Other Physiological Processes, CRC Press, Boca Raton, FL, 1986, p. 169.
301 A.J. Crowe, in M. Gielen (Ed.), Metal-Based Antitumor Drugs, Freund, London and Tel Aviv, 1988, p. 103.
302 A.J. Crowe, P.J. Smith and G. Atassi, Inorg. Chim. Acta, 93 (1984) 179.

303 J. Leiter, B.J. Abbott, A.R. Bourke, S.A. Schepartz and I. Wodinsky, Cancer Res., Suppl., 23(6, Part 2) (1963) 1085.
304 M. Takahashi, F. Furukawa, T. Kokubo, Y. Kurata and Y. Hayashi, Cancer Lett., 20 (1983) 271.
305 J.J. Jang, M. Takahashi, F. Furukawa, K. Toyoda, R. Hasegawa, H. Sato and Y. Hayashi, Jpn. J. Cancer Res. (Gann), 77 (1986) 1091.
306 Y. Arakawa, in 3rd Int. Symp. on the Effect of Tin upon Malignant Cell Growth, September 5–6, 1986, University of Padua, Italy, Abstract C-1, p. 8.
307 A.J. Crowe and P.J. Smith, Chem. Ind. (London), (1980) 200.
308 A.J. Crowe, P.J. Smith and G. Atassi, Chem. Biol. Interact., 32 (1980) 171.
309 A.J. Crowe, P.J. Smith, C.J. Cardin, H.E. Parge and F.E. Smith, Cancer Lett., 24 (1984) 45.
310 B.N. Biddle, J.S. Gray and A.J. Crowe, Appl. Organomet. Chem., 1 (1987) 261.
311 L.R. Sherman and F. Huber, Appl. Organomet. Chem., 2 (1988) 65.
312 M. Vandendris, P. Dumont, R. Heimann and G. Atassi, Cancer Chemother. Pharmacol., 11 (1983) 182.
313 P. Köpf-Maier and H. Köpf, Drugs of the Future, 11 (1986) 297.
314 M. Gielen, R. Willem, T. Mancilla, J. Ramharter and E. Joosen, Rev. Silicon, Germanium, Tin Lead Compds., 9 (1986) 349.
315 M. Gielen, E. Joosen, T. Mancilla, K. Jurkschat, R. Willem, C. Roobol, J. Bernheim, G. Atassi, F. Huber, E. Hoffmann, H. Preut and B. Mahieu, Main Group Metal Chemistry, 10 (1987) 147.
316 R. Barbieri, L. Pellerito, G. Ruisi, M.T. LoGiudice, F. Huber and G. Atassi, Inorg. Chim. Acta Lett., 66 (1982) L39.
317 F. Huber, G. Roge, L. Carl, G. Atassi, F. Spreafico, S. Filippeschi, R. Barbieri, A. Silvestri, E. Rivarola, G. Ruisi, F. De Bianca and G. Alonzo, J. Chem. Soc., Dalton Trans., (1985) 523.
318 G. Ruisi, A. Silvestri, M.T. LoGiudice, R. Barbieri, L. Lamartina, G. Atassi, F. Huber and K. Gräatz, J. Inorg. Biochem., 25 (1985) 229.
319 F. Huber and R. Barbieri, in N.F. Cardarelli (Ed.), Tin as a Vital Nutrient: Implications in Cancer Prophylaxis and Other Physiological Processes, CRC Press, Boca Raton, FL, 1986, p. 175.
320 A.H. Penninks, M. Bol-Schoenmakers, J.L. Wardell and F. Caruso, in 4th Int. Symp. on the Effect of Tin on Malignant Cell Growth, Chapman Lake, July 31–August 3, 1988, University of Scranton, PA, Abstr. 5.
321 N.F. Cardarelli, in N.F. Cardarelli (Ed.), Tin as a Vital Nutrient: Implications in Cancer Prophylaxis and Other Physiological Processes, CRC Press, Boca Raton, FL, 1986, p. 133.
322 S.V. Kanakkanatt, in N.F. Cardarelli (Ed.), Tin as a Vital Nutrient: Implications in Cancer Prophylaxis and Other Physiological Processes, CRC Press, Boca Raton, FL, 1986, p. 189.
323 N.F. Cardarelli, in N.F. Cardarelli (Ed.), Tin as a Vital Nutrient: Implications in Cancer Prophylaxis and Other Physiological Processes, CRC Press, Boca Raton, FL, 1986, p. 199.
324 N.F. Cardarelli, in N.F. Cardarelli (Ed.), Tin as a Vital Nutrient: Implications in Cancer Prophylaxis and Other Physiological Processes, CRC Press, Boca Raton, FL, 1986, p. 263.
325 J. Wan, J. Huang, Z. Huang, D. Shi and S. Hu, Inorg. Chim. Acta, 152 (1988) 67.
326 P. Uhlenhuth, Sitzungsber. Heidelb. Akad. Wiss. Math. Naturwiss. Kl., (1948) 41; Chem. Abstr., 44 (1950) 2657.

327 W. Hermann and H. Hilmer, Angew. Chem., 66 (1954) 349.
328 A.J. Crowe, Chem. Ind. (London), 1983, 304.
329 R.A. Zingaro, Chem. Scr., 8A (1975) 51.
330 J.R. Daniel and R.A. Zingaro, Phosphorus Sulfur, 4 (1978) 179.
331 J.R. Daniel, R.L. Whistler and R.A. Zingaro, Phosphorus Sulfur, 7 (1979) 31.
332 C.H. Banks, J.R. Daniel and R.A. Zingaro, J. Med. Chem., 22 (1979) 572.
333 C.R. Mitchell, Diss. Abstr. Int. B, 41 (1980) 1363; Chem. Abstr., 94 (1981) 47700.
334 N.L.M. Dereu and R.A. Zingaro, Bull. Soc. Chim. Belg., 91 (1982) 685.
335 C.E. Carraher, Jr., M.D. Naas, D.J. Giron and D.R. Cerutis, J. Macromol. Sci. Chem., A19 (1983) 1101.
336 I. Haiduc, C. Socaciu, A. Bara and C. Silvestru, Anticancer Res., in press.
337 P. Köpf-Maier and T. Klapötke, Inorg. Chim. Acta, 152 (1988) 49.
338 H. Taniyama, F. Miyoshi and E. Sakakibara, Kyushu Yakugakkai Kaiho, 22 (1968) 57; Chem. Abstr., 71 (1969) 28990.
339 Ajimoto Co. Inc., Jpn. Kokai Tokkyo Koho, JP 59-216,868 (84-216,868) (1984); Chem. Abstr., 102 (1985) 185497.
340 S. Kanopkaite and G. Brazenas, in H. Sigel (Ed.), Metal Ions in Biological Systems, Marcel Dekker, New York, 1980, Vol. 10, p. 253.
341 V.R. Kal'nev, J. Rackus and S. Kanopkaite, Prikl. Biokhim. Mikrobiol., 13 (1977) 677.
342 F.G. Arsenyan, N.V. Myasishcheva, Z.P. Sof'ina, M.C. Raushenbakh, I.P. Rudakova, E.G. Chauser and A.M. Yurkevich, Khim.-Farm. Zh., 12 (1978) 49.
343 Z.P. Sof'ina, N.V. Myasishcheva, F.G. Arsenyan and A.M. Yurkevich, Vestn. Akad. Med. Nauk SSSR, 1979, No. 1, p. 72.
344 N.V. Myasishcheva, Z.P. Sof'ina, O.D. Golenko and F.G. Arsenyan, Eksp. Onkol., 4 (1982) 29.
345 N.V. Myasishcheva, O.D. Golenko, F.G. Arsenyan, G.K. Gerasimova and Yu.V. Vares, Vestn. Akad. Med. Nauk SSSR, 1981, No. 7, p. 24.
346 I.P. Rudakova, E.G. Chauser, T.A. Pospelova, E.M. Techkova, A.M. Yurkevich, F.G. Arsenyan, O.L. Golenko, N.V. Myasishcheva, N.P. Yavorskaya and Z.P. Sof'ina, Sint. Izuch. Nov. Otechestv. Protivoleikoznykh. Prep., Tesizy Konf., (1979) 31; Chem. Abstr., 92 (1980) 174359.
347 N.V. Myasishcheva, E.V. Quadros, Yu.V. Vares and J.C. Linnell, in B. Zagalek and W. Friedrich (Eds.), Vitamin B_{12}, Proc. 3rd Eur. Symp., 1979, Walter de Gruyter, Berlin, 1979, p. 1125.
348 M.E. Poydock, J.C. Fardon, D. Gallina and C. Herber, Exp. Cell. Biol., 47 (1979) 210.
349 M.E. Poydock, D. Reikert and J. Rice, Exp. Cell. Biol., 50 (1982) 88.
350 M.E. Poydock, L. Phillips and P. Schmidt, IRCS Med. Sci. Biochem., 12 (1984) 813.
351 M.E. Poydock, S. Harguindey, T. Hart, H. Takita and D. Kelly, Am. J. Clin. Oncol., 8 (1985) 266.
352 H.F. Pierson, J.M. Fisher and M. Rabinowitz, Cancer Res., 45 (1985) 4727.
353 Eisai Co., Ltd., Jpn. Kokai Tokkyo Koho, 80-113,721 (1980); Chem. Abstr., 94 (1981) 52951.
354 N. Shimizu, R. Hamazoe, H. Kanayama, M. Maeta and S. Koga, Oncology, 44 (1987) 169.
355 M. Abe, T. Kaku, D. Mizuno, K. Nishioka, T. Takeuchi, T. Ugai, M. Wakagi and T. Yamamoto, Yakugaku Zasshi (J. Pharm. Soc. Jpn.), 78 (1958) 804.
356 L. Goodman, L.O. Ross, M.O. Greene, J. Greenberg and B.R. Baker, J. Pharm. Med. Chem., 3 (1961) 65.
357 S. Osato, H. Mori and M. Morita, Tohoku J. Exp. Med., 75 (1961) 223.

358 A.D. Kelman, M.J. Clarke, S.D. Edmonds and H.J. Peresie, J. Clin. Hematol. Oncol. 7 (1977) 274.
359 G.R. Newkome, M. Onishi, W.E. Puckett and W.A. Deutsch, J. Am. Chem. Soc., 102 (1980) 4551.
360 G.R. Newkome, D.C. Panteleo, W.E. Puckett, P.L. Ziefle and W.A. Deutsch, J. Inorg. Nucl. Chem., 43 (1981) 1529.
361 G.R. Newkome, U.S. Pat., US 4,598,073, 1986; Chem. Abstr., 106 (1987) 50471.
362 M. Aresta, D. Giordano, A. Ingrosso, S. Riccardi and E. Sinigaglia, Chem. Biol. Interact., 28 (1979) 61.
363 M. Aresta, M. De Fazio, A. Ingrosso and D. Giordano, J. Inorg. Nucl. Chem., 43 (1981) 1415.
364 M. Aresta, M. Coluccia, M. Correale and D. Giordano, 16th Congr. Naz.Chim. Inorg. (Atti), 1983, p. 431; Chem. Abstr., 100 (1984) 132185.
365 L.S. Hollis, A.R. Amundsen and E.W. Stern, J. Am. Chem. Soc., 107 (1985) 274.
366 A.R. Amundsen, L.S. Hollis and E.W. Stern, Eur. Pat. Appl., EP 174,114, 1986; Chem. Abstr., 106 (1987) 50468.
367 H. Köpf and P. Köpf-Maier, in S.J. Lippard (Ed.), Platinum, Gold and Other Metal Chemotherapeutic Agents: Chemistry and Biochemistry, ACS Symposium Series, No. 209, American Chemical Society, Washington, DC, 1983, p. 315.
368 P. Köpf-Maier and H. Köpf, Anticancer Res., 6 (1986) 227.
369 K.E. Dombrowski, W. Baldwin and J.E. Sheats, J. Organomet. Chem., 302 (1986) 281.
370 P. Köpf-Maier, Naturwissenschaften, 74 (1987) 374.
371 P. Köpf-Maier, B. Hesse and H. Köpf, J. Cancer Res. Clin. Oncol., 96 (1980) 43.
372 P. Köpf-Maier, W. Wagner, B. Hesse and H. Köpf, Eur. J. Cancer, 17 (1981) 665.
373 P. Köpf-Maier, F. Preiss, T. Marx, T. Klapötke and H. Köpf, Anticancer Res., 6 (1986) 33.
374 P. Köpf-Maier and H. Köpf, Arzneim.-Forsch. (Drug Res.), 37 (1987) 532.
375 P. Köpf-Maier, A. Moormann and H. Köpf, Eur. J. Cancer Clin. Oncol., 21 (1985) 853.
376 P. Köpf-Maier, in Proc. Seminar on Human Tumor Xenografts in Anticancer Drug Development, Milano, 1986.
377 M.S. Murthy, L.N. Rao, L.Y. Kuo, J.H. Toney and T.J. Marks, Inorg. Chim. Acta, 152 (1988) 117.
378 S.I. Chang, T.P. Chu, F.L. Lu, C.C. Lu, P.C. Lu and W.H. Hsu, Yao Hsueh T'ung Pao, 16 (1981) 57; Chem. Abstr., 95 (1981) 108656.
379 J.H. Toney and T.J. Marks, J. Am. Chem. Soc., 107 (1985) 947.
380 L.Y. Kuo, M.G. Kanatzidis and T.J. Marks, J. Am. Chem. Soc., 109 (1987) 7207.
381 F.D. Popp, S. Roth and J. Kirby, J. Med. Chem., 6 (1963) 83.
382 G.N. Yashchenko, A.A. Shashmurina, G.M. Anoshina, L.A. Gorelova, N.G. Evstigneeva, L.V. Alekseeva and L.B. Radina, Khim.-Farm. Zh., 12 (1978) 68.
383 V.J. Fiorina, R.J. Dubois and S. Brynes, J. Med. Chem., 21 (1978) 393.
384 V.P. Krasnov, A.A. Shashmurina, L.V. Alekseeva, G.M. Anoshina and A.S. Barybin, Khim.-Farm. Zh., 14 (1980) 45.
385 P. Köpf-Maier, Z. Naturforsch., Teil C, 40 (1985) 843.
386 P. Köpf-Maier, H. Köpf and E.W. Neuse, J. Cancer Res. Clin. Oncol., 108 (1984) 336.
387 M. Wenzel, E. Nipper and W. Klose, J. Nucl. Med., 18 (1977) 367.
388 A. Taylor and M. Wenzel, Naturwissenschaften, 64 (1977) 273.
389 M. Wenzel, M. Schneider and E. Liss, Z. Naturforsch., Teil C, 34 (1979) 670.
390 S.A. Schepartz, B.J. Abbott and J. Leiter, Cancer Res., Suppl., 26 (8, Part 2) (1966) 950.
391 T. Hyama, K. Nishida, H. Saimoto, Y. Kusano, K. Sakai and K. Yamada, Jpn. Kokai Tokkyo Koho, JP 61-205,592 (1986); Chem. Abstr., 107 (1987) 229145.

392 C. Monti-Bragadin, T. Giraldi, M. Cantini, G. Zassinovich and G. Mestroni, FEBS Lett., 43 (1974) 13.
393 T. Giraldi, G. Sava, G. Bertoli, G. Mestroni and G. Zassinovich, Cancer Res., 37 (1977) 2662.
394 G. Sava, T. Giraldi, G. Mestroni and G. Zassinovich, Chem. Biol. Interact., 45 (1983) 1.
395 T. Giraldi, G. Sava, G. Mestroni, G. Zassinovich and D. Stolfa, Chem. Biol. Interact., 22 (1978) 231.
396 G. Sava, S. Zorzet, G. Mestroni and G. Zassinovich, Anticancer Res., 5 (1985) 249.
397 C.K. Mirabelli, R.K. Johnson, D.T. Hill, L.F. Faucette, G.R. Girard, G.Y. Kuo, C.M. Sung and S.T. Crooke, J. Med. Chem., 29 (1986) 218.
398 D.B. Brown, A.R. Khokhar, M.P. Hacker, J.J. McCormack and W.M. Stalick, Inorg. Chim. Acta, 67 (1982) 45.
399 M. Takesawa, H. Morioka, H. Shibai, J. Tsuji, M. Okutsu and T. Meguro, Jpn. Kokai Tokkyo Koho, JP 61-152,625 (1986); Chem. Abstr., 106 (1986) 43990.
400 G. Sava, S. Zorzet, T. Giraldi, G. Mestroni and G. Zassinovich, Eur. J. Cancer Clin. Oncol., 20 (1984) 841.