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Ionic rhenocene derivatives with antitumor activity

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Summary. The antitumor activity of the three air-stable bis(cyclopentadienyl)rhenium derivatives $[(C_5H_5)_2ReCl_2]^+Cl^-$, $[(C_5H_5)_2ReCl_2]^+[AsF_6]^-$, and $[(C_5H_5)_2ReCl_2]^+[SbF_6]^-$ was tested against Ehrlich ascites tumor in female CF_1 mice. All three compounds contain the group-7 transition metal rhenium in the +5 oxidation state as their central metal atom. They are ionic, salt-like complexes that are composed of the cationic $[(C_5H_5)_2ReCl_2]^+$ moiety and one of the negatively charged counterions Cl^-, AsF_6^-, or SbF_6^-. Both the chloro and the hexafluoroarsenate complexes induced a maximal cure rate of 100% when given either in a dose range of 120–160 mg/kg (rhenocene trichloride) or at a single dose of 180 mg/kg (hexafluoroarsenate derivative). The hexafluoroantimonate complex effected a maximal cure rate of only 50% at 60 mg/kg. For the two former compounds, the values for the therapeutic index (TI) amounted to 1.7 and 2.1, respectively. No impairment of the general condition or pathologic symptoms in the viscera could be detected by observation of the animals during the days following treatment with therapeutic doses or by autopsy of the surviving animals on the key date (day 90). The rhenocene derivatives investigated in the present study represent a new class of antitumor metallocene compounds as well as the first rhenium(V) complexes exerting cytostatic activity.

Introduction

During the past two decades, strategies for the clinical chemotherapy of malignant tumors have been markedly changed by the introduction and the observed therapeutic success of *cis*-diamminedichloroplatinum(II) or cisplatin [16, 32–34]. This heavy-metal complex was the first inorganic antitumor agent to enter clinical studies during this century. Despite initial reservations regarding the therapeutic application of a heavy-metal compound, the clinical trials rapidly confirmed that cisplatin is one of the most effective antitumor agents that are capable of curing most patients suffering from testicular carcinomas [14] and of prolonging the survival of many patients suffering from ovarian, bladder, prostate, lung, and head and neck carcinomas [16, 32]. Worldwide, cisplatin is currently the most frequently applied cytostatic drug.

This clinical success stimulated a broad search for other metal-containing cytostatic agents in recent years. Numerous inorganic and organometallic compounds have been found to exhibit antitumor activity against diverse experimental animal tumors and against "stronger" models such as xenografted human tumors or autochthonous, chemically induced carcinomas [17, 19, 20]. These compounds include either platinum [16, 32] or platinum-group metals such as ruthenium [5, 19] and rhodium [2, 7] or other heavy metals such as gold [3]. Moreover, cytostatically active compounds of the main-group elements gallium [1], germanium [28, 30], tin [10, 11] and bismuth [21] have been developed. Of these, gallium trinitrate, Ge 132, and spirogermanium have entered clinical phase I and II trials. A third group of antitumor metal complexes comprises early-transition metal compounds; they are mainly represented by metallocene derivatives, i.e., bis(cyclopentadienyl)metal diacido complexes of the general formula $[(C_5H_5)_2MX_2]$ [24, 25]. These compounds are neutral complexes in which the position of the central metal atom M can be occupied by an atom of group 4 (Ti, Zr, Hf), group 5 (Nb, Ta), or group 6 (Mo, W) in the +4 oxidation state. Pronounced antitumor activity has thus far been confirmed for titanocene, vanadocene, niobocene, and molybdenocene complexes of the general formula $[(C_5H_5)_2MX_2]$, where M represents Ti, V, Nb, or Mo and whereby the acido ligands X could be widely varied without a loss of antitumor potency [22, 23].

In the present study, we addressed the question as to whether antitumor activity would also be characteristic for rhenocene derivatives that include as their central atom the group-7 element rhenium, a heavy-metal atom neighboring the platinum-group metals osmium and iridium.

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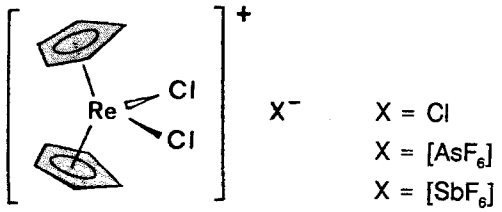

Fig. 1. Structure of the ionic rhenocene complexes investigated

Materials and methods

Three air-stable bis(cyclopentadienyl)rhenium(V) ("rhenocene") complexes of the general formula $[(C_5H_5)_2ReCl_2]^+X^-$ (Fig. 1) were tested for antitumor activity against Ehrlich ascites tumor in mice.

Substances. The compounds $[(C_5H_5)_2ReCl_2]^+Cl^-$, $[(C_5H_5)_2\ ReCl_2]^+[AsF_6]^-$, and $[(C_5H_5)_2ReCl_2]^+[SbF_6]^-$ were synthesized by methods described in the literature [9, 15]. They are typical metallocene derivatives, i.e., bis(cyclopentadienyl)metal complexes that contain the group-7 element rhenium in the +5 oxidation state as their central metal atom. All are ionic compounds and are composed of the cationic moiety $[(C_5H_5)_2ReCl_2]^+$, whereby the central metal is surrounded by four ligands, two organic cyclopentadienyl rings, and two chlorine atoms arranged in the configuration of a distorted tetrahedron, and one of the monoanions Cl^-,$[AsF_6]^-$, or $[SbF_6]^-$, which are necessary for electrostatic neutralization of the complexes. The complexes were chemically characterized by ^1H and ^{19}F nuclear magnetic resonance (NMR) and infrared (IR) spectroscopy. No impurities could be detected by these methods. The elemental analyses (C, H, Cl) revealed deviations that amounted to <0.8% of the calculated values.

For antitumor testing, the three rhenocene compounds were injected intraperitoneally at doses ranging from 20 to 260 mg/kg in increments of 20 mg/kg. For administration of the lower doses, the drugs were dissolved in pure saline, whereas for doses of >180 mg/kg, a portion of 10% dimethylsulfoxide (DMSO) was added to the injection solution. At present, no information is available as to whether the rhenocene complexes are stable in aqueous solutions. Thus, the substances were injected immediately after dissolution, their concentrations being selected such that each animal received a total volume of 0.4–0.5 ml (0.02 ml/g body weight).

Animals. Female CF_1 mice purchased from Winkelmann (Paderborn, FRG) were kept under standard specific pathogen-free (SPF) conditions. They received food (Altromin) and tap water ad libitum. At the beginning of the experiments, they were about 8–10 weeks of age and weighed 20–25 g.

Antitumor bioassay. The antitumor activity of the three rhenocene complexes was investigated in the present pilot study against Ehrlich ascites tumor growing as a fluid tumor in the peritoneal cavity of mice. This model is intermediate between in vitro systems and solid animal tumors since it is an in vivo system but is based on local intraperitoneal injection of substances. Although it is considered in the literature to be only moderately sensitive to antitumor agents [6], it proved to be very sensitive to metallocene complexes and other organometallic compounds; moreover, it is suitable for application as a primary screening system, as it provides preliminary indications of the antitumor properties of these compounds, which must subsequently be confirmed by the use of stronger and more expensive experimental models. Most metallocene complexes that have thus far been found to be active against Ehrlich ascites tumor were confirmed as being inhibitors of the growth of solid animal and xenografted human tumors [23].

Details of the propagation and transplantation of the Ehrlich ascites tumor have been described elsewhere [25, 26]. On day 0 of the experiments, the animals were inoculated intraperitoneally with 6×10^6 Ehrlich ascites tumor cells. At 24 h thereafter, they received a single intraperitoneal injection of the substances dissolved as described above. Each dose group consisted of 8 mice; another 30 animals (3 groups of 10 mice) served as untreated tumor-bearing controls which received 0.4–0.5 ml of the drug-free DMSO-saline mixture (1:9, v:v).

The number of deaths were registered daily. Deaths occurring within 7 days of substance administration were related to drug toxicity, and those noted later than day 8 after tumor transplantation were defined as tumor deaths. After day 8, all animals showed macroscopic signs of massive tumor development within the peritoneal cavity. The key date for determining the number of surviving mice was day 90, at which time all surviving animals were free of any recognizable signs of tumor and were considered to be cured. They were killed and examined macroscopically by autopsy.

Results

All control animals that had been treated with the DMSO-containing vehicle alone died between day 16 and day 23 after tumor transplantation and showed macroscopic symptoms of bulky tumor disease. The mean survival amounted to 19.8 ± 1.9, 21.1 ± 2.2, and 20.5 ± 2.2 days, respectively, in the three control groups. When tumor-bearing mice were treated on day 1 after transplantation with one of the three ionic rhenocene complexes given in a single dose ranging from 20 to 260 mg/kg, optimal cure rates of 50% and 100% were achieved. The main pharmacologic and toxicologic data characterizing the compounds are summarized in Table 1.

Table 1. Pharmacologic and toxicologic data on the activity of the ionic rhenocene complexes $[(C_5H_5)_2ReCl_2]^+X^-$ against Ehrlich ascites tumor as compared with the neutral titanocene complex $[(C_5H_5)_2TiCl_2]$ and the platinum complex $[cis\text{-}(NH_3)_2PtCl_2]$

	$[(C_5H_5)_2ReCl_2]^+X^-$			$[(C_5H_5)_2TiCl_2]$	$[cis\text{-}(NH_3)_2PtCl_2]$
	X = Cl	X = AsF_6	X = SbF_6		
Experimental dose range (mg/kg)	20–260	20–260	20–260	10–180	1–30
Optimal dose range[a] (mg/kg)	60–160	80–180	60	30– 70	6–12
Maximal cure rate (%)	100	100	50	100	100
Increase in life span at optimal dose (%)	355	327	167	380	371
LD_{50} (mg/kg)	240	250	170	100	25
LD_{100} (mg/kg)	>260	>260	200	140	ND
TI[b]	1.7	2.1	–	3.3	4.1

[a] Defined as the dose range achieving cure rates of ≥50%

[b] Therapeutic index, defined as LD_{50}/ED_{90}; TI values can be given only when the maximal cure rate is ≥90%

ND, Not determined

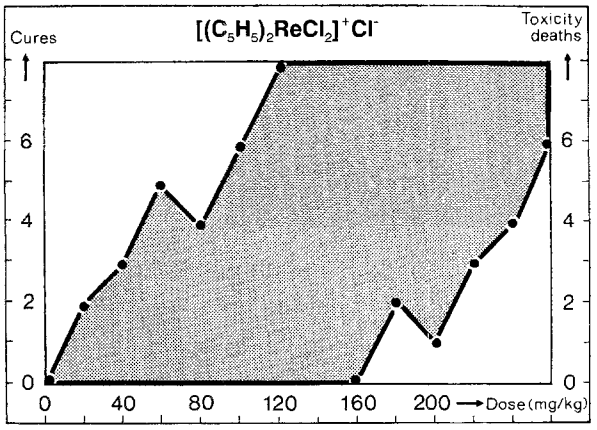

Fig. 2. Dose-activity (*left*) and dose-lethality (*right*) relationships of $[(C_5H_5)_2ReCl_2]^+Cl^-$ against Ehrlich ascites tumor. The *shaded area* indicates the range of surviving, cured animals

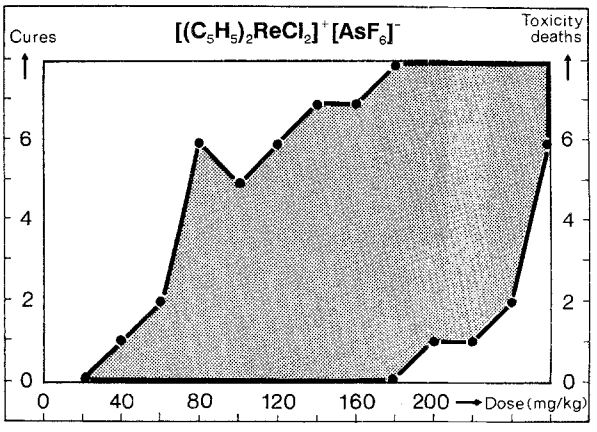

Fig. 3. Dose-activity (*left*) and dose-lethality (*right*) relationships of $[(C_5H_5)_2ReCl_2]^+[AsF_6]^-$ against Ehrlich ascites tumor (cf. legend to Fig. 2)

All animals that had been treated with rhenocene trichloride at doses ranging from 120 to 160 mg/kg survived until the key date (Fig. 2). This corresponds to an optimal cure rate of 100% and an increase in life span of 355% as compared with untreated control values. Lethality occurred dose-dependently, and the values of the toxic thresholds for 10%, 50%, and 100% of the mice (LD_{10}, LD_{50}, and LD_{100}) amounted to 180, 240, >260 mg/kg, respectively. The therapeutic index (TI) as calculated by relating the LD_{50} value to the effective dose for 90% of the animals (ED_{90}) came to 1.7 for the rhenocene chloride complex; this value was smaller than that obtained for either the neutral complex titanocene dichloride or the heavy-metal cytostatic drug cisplatin under the same experimental conditions (Table 1). The animals that had received therapeutic doses of rhenocene trichloride failed to show either behavior abnormalities following application of the compound or noteworthy symptoms that were detectable by autopsy on the key date, i.e., on day 90 after tumor transplantation.

For the $[(C_5H_5)_2ReCl_2]^+[AsF_6]^-$ complex, in which hexafluoroarsenate functions as a counterion to the positively charged rhenocene moiety, a maximal cure rate of 100% was attained after treatment with 180 mg/kg (Fig. 3). This corresponded to an increase in life span of 327% in relation to the control value as determined on day 90. Below the optimal dose of 180 mg/kg, cure rates of between 50% and 90% were observed in the rather broad dose range of 80–160 mg/kg. Lethality was clearly dose-dependent, the LD_{10} value being 200 mg/kg and the LD_{50} value, 250 mg/kg. The LD_{100} value was obviously >260 mg/kg. Although the dose range over which 100% of the treated animals were cured and survived until the key date was much lower than that for rhenocene trichloride, the TI value indicating the therapeutic width amounted to 2.1 for the hexafluoroarsenate derivative; this value slightly exceeded that found for rhenocene trichloride but failed to reach that obtained for either titanocene dichloride or cisplatin (Table 1). Similar to the case of rhenocene trichloride, the animals that had been treated with therapeutic doses of the rhenocene hexafluoroarsenate derivative showed neither abnormal behavior during the days following treatment nor conspicuous pathologic symptoms in the inner organs that were detectable by autopsy on the key date. After the administration of toxic doses, however, the livers were remarkably pale and blunt-edged.

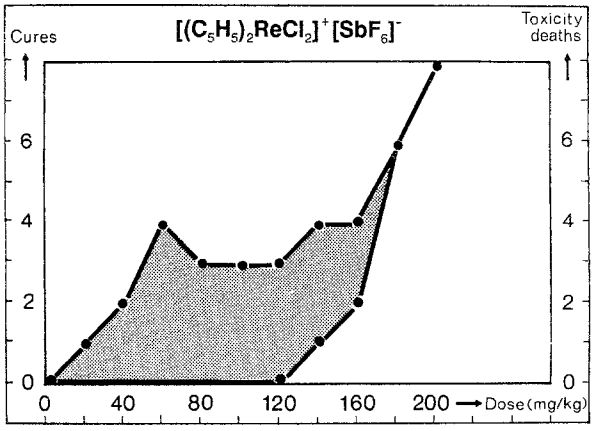

Fig. 4. Dose activity (*left*) and dose-lethality (*right*) relationships of $[(C_5H_5)_2ReCl_2]^+[SbF_6]^-$ against Ehrlich ascites tumor (cf. legend to Fig. 2)

When the rhenocene derivative containing hexafluoroantimonate as an anion was injected under the same experimental conditions, the therapeutic effect was much less pronounced than that noted for the other two rhenocene complexes (Fig. 4). The maximal cure rate attained only 50% at a single dose of 60 mg/kg; beyond that, the cure rates ranged from 20% to 40% following doses of between 40 and 120 mg/kg. The life span of the animals that had received the optimal dose (60 mg/kg) of the hexafluoroantimonate complex increased by 167% in relation to the control value. After the application of 140 mg/kg, the first toxic deaths occurred, and the LD_{50} value for the hexafluoroantimonate complex amounted to 170 mg/kg. When a dose of 200 mg/kg was given, all treated animals died within 7 days. This means that, surprisingly, the rhenocene hexafluoroantimonate complex is obviously more toxic than the analogous hexafluoroarsenate and chloride derivatives.

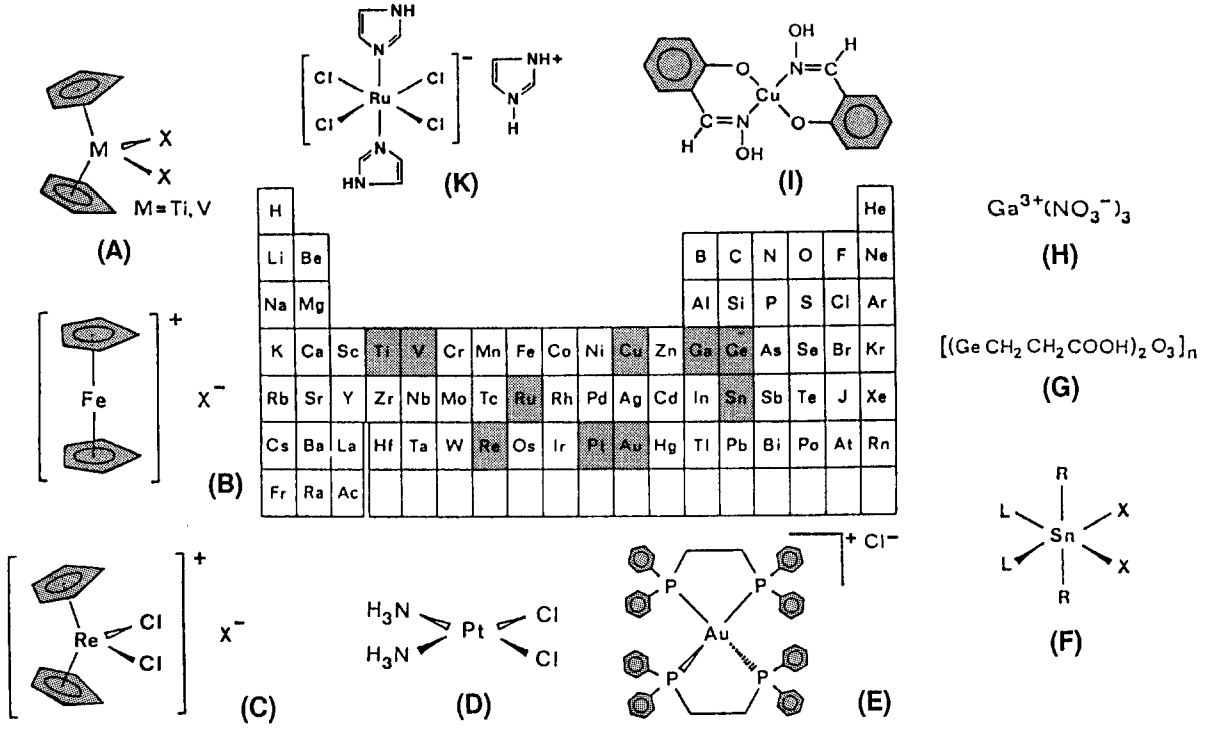

Fig. 5 A – K. Typical examples of platinum and non-platinum metal antitumor agents and the respective position of their central metal atoms in the Periodic Table. **A** bis(Cyclopentadienyl)diacido metal(IV) complexes. **B** bis(Cyclopentadienyl)iron(III) complex salts. **C** bis(Cyclopentadienyl)dichlororhenium(V) complex salts. **D** *cis*-Diammine-dichloroplatinum(II). **E** bis[1,2-bis(Diphenylphosphino)ethane]gold(I) chloride. **F** Diorganodihalotin(IV) complexes. **G** bis(Carboxyethylgermanium) trioxide (germanium sesquioxide). **H** Gallium(III) nitrate. **I** *trans*-bis(Salicylaldoximato)copper(II). **K** Imidazolium *trans*-bis(imidazole)tetrachlororuthenate(III)

Discussion

Rhenium compounds are not unknown in experimental medicine. Due to the close chemical relationship between Re and Tc, the latter being called "the working horse of nuclear medicine," and to the nearly optimal radiophysical properties of ^{186}Re and ^{188}Re, efforts are currently under way to develop rhenium complexes as therapeutic and diagnostic agents in nuclear medicine for local and embolyzing radiotherapy of human tumors and for binding to monoclonal antibodies raised against tumor-cell surface antigens [4]. Moreover, some rhenium(III) carboxylato complexes have been found to exhibit antitumor properties against certain animal tumors, e.g., B16 melanoma and sarcoma S180 [12, 13]. The most effective representatives of this group of compounds were the ionic inorganic complex tetra-μ-propionatodirhenium(III) sulfate and the neutral compound bis(μ-propionato)diaquotetrabromodirhenium(III), both being dimer complexes that contain multiple metal-metal bonds. Remarkably, only a few minor side effects such as hair loss and, at high doses, lesions of the liver were observed following treatment with both of these compounds. This led to the statement of the authors that "rhenium seems to be one of the least toxic of the metallic elements" [12, 13]. To our knowledge, no other reports have been published on these antitumor rhenium(III) carboxylato complexes. They are structurally analogous to rhodium carboxylate dimers, which have been shown to effect similar antitumor activity against animal tumor systems by blocking some thiolic enzymes that are involved in DNA synthesis [2].

In the present study, we investigated the antitumor activity of three air-stable rhenocene derivatives, i.e., bis(cyclopentadienyl)rhenium compounds, in which rhenium(V) functions as the central metal atom and found remarkable antitumor properties for $[(C_5H_5)_2ReCl_2]^+Cl^-$ and $[(C_5H_5)_2ReCl_2]^+[AsF_6]^-$ in the Ehrlich ascites tumor system. This antitumor activity was reflected in an optimal cure rate of 100% over a dose range that was broader with respect to absolute dose values than those for either titanocene dichloride or cisplatin. However, in terms of TI values, which are defined as the quotient of LD_{50}/ED_{90} and which indicate the relationship between toxic and effective values, the rhenocene complexes proved to be less advantageous than either of the control compounds. This was mainly due to the higher doses of the rhenocene complexes that were required to effect similar antitumor activity as estimated by the cure rate. These doses are within the same order of magnitude as the therapeutic doses of the second-generation platinum complex carboplatin and are thus in principle not too high to be used in humans. In this connection, the comparably low toxicity, especially of the rhenocene hexafluoroarsenate complex, was remarkable insofar as arsenic is generally known in pharmacology and toxicology to be a highly toxic metalloid, the toxicity of which seems to be disguised in the AsF_6^- anion by the coordination of six fluorine atoms.

Similar to the case in the neutral metallocene compounds of the early-transition metals titanium(IV) or vanadium(IV), $[(C_5H_5)_2TiCl_2]$ and $[(C_5H_5)_2VCl_2]$, which are known to exhibit antitumor activity against diverse animal and human tumors [22, 23], the rhenium(V) atom in

the rhenocene derivatives tested is characterized by the same coordination number 4 and is similarly surrounded by two cyclopentadienyl rings and two chlorine atoms arranged in the shape of a distorted tetrahedron [9, 15]. Because of the incomplete compensation of the rhenium +5 oxidation state by only four uninegative ligands ($2 \times C_5H_5^-$, $2 \times Cl^-$), the $(C_5H_5)_2ReCl_2$ moiety is positively charged and must be electrostatically neutralized by appropriate counterions in a salt-like lattice. Thus, the rhenocene derivatives investigated in the present study differ fundamentally from the aforementioned early-transition metal metallocene complexes [22, 24, 25] in their charged, ionic character. Although electric neutrality has been postulated as being an essential prerequisite for the exertion of antitumor activity by metal complexes [8, 29], the ionic rhenocene compounds effected remarkable inhibition of the growth of Ehrlich ascites tumor, which is considered to be only moderately sensitive to antitumor agents [6]. This finding demonstrates that at least in the case of rhenium compounds and metallocene derivatives, electric neutrality cannot be imperative for the realization of pronounced antitumor properties. This can be similarly concluded from the findings that both the neutral bis(μ-propionato)diaquotetrabromodirhenium(III) complex and the ionic tetra-μ-propionatodirhenium(III) sulfate complex are active against the same animal tumors, particularly against B16 melanoma [12, 13]. Moreover, even in the case of bis(cyclopentadienyl)titanium compounds, ionic derivatives such as the *N*-methylaminothiophenolate compound $\{(C_5H_5)_2Ti[o\text{-}S(NHCH_3)C_6H_4]\}^+I^-$ and the acetonitrile complex $[(C_5H_5)_2TiCl(NCCH_3)]^+[FeCl_4]^-$ have been shown to exhibit antitumor activity against animal and human tumors that is similar in strength to that exerted by the parent neutral compound titanocene dichloride [27]. The advantage of all ionic compounds over neutral species is their improved solubility in water, which markedly facilitates their application in biological systems and organisms.

From a general point of view, the results of the present study provide further confirmation that numerous metal atoms can display antitumor properties, provided that they are in an appropriate molecular environment. These atoms comprise early-, medium-, and late-transition metals as well as main-group elements (Fig. 5). Some of the gallium and germanium compounds have entered clinical phase II trials. Others, such as titanium or ruthenium complexes, are currently being investigated in phase I studies. Because of the great number of inorganic and organometallic compounds that have been found to exhibit antitumor activity over the past 20 years, it can reasonably assumed that this development will continue such that numerous other antitumor compounds will be detected during the next few years. In this connection, it is noteworthy that amplification of the arsenal of metal-containing cytostatic agents from platinum, to non-platinum metal compounds seems to be beneficial, especially insofar as many of the non-platinum metal compounds are characterized by a different pattern of toxicity and lack the typical features of heavy-metal toxicity that are usually dominated by severe nephrotoxicity. This has been confirmed for budotitane, titanocene dichloride, and vanadocene dichloride as well as for organogermanium compounds [18, 23, 30, 31]. For rhenium carboxylate antitumor compounds, only minor side effects such as hair loss following doses in the therapeutic range and macroscopic liver lesions at toxic doses have been reported [13]. Studies examining the toxicologic properties of the rhenocene derivatives investigated in the present study will be undertaken in the near future to define the pattern of toxic symptoms induced by these ionic medium-transition metal complexes.

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