# Organometallic compounds in oncology: implications of novel organotins as antitumor agents☆

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**Since the introduction of cisplatin in cancer therapy, metal complexes and organometallic compounds have been gaining growing importance in oncology.The impressive clinical effectiveness of cisplatin is limited by significant side effects and the emergence of drug resistance. Thus, novel classic and unconventional $Pt^{II}$ and $Pt^{IV}$ complexes have been introduced in therapy or are presently in advanced clinical trials.Moreover, innovative non-platinum metal-based antitumor agents, whose activity does not rely on direct DNA damage and may involve proteins and enzymes, have been developed.Gold and tin derivatives are enjoying an increasing interest and appear very promising as potential drug candidates.**

## Metal-based compounds in therapy

Metal-based compounds were largely present in old pharmacopoeias, side by side with raw drugs of natural (vegetal and animal) origin. Because of their limited selectivity and toxicity, metal derivatives were progressively neglected in favor of the more reliable organic compounds, either synthetic or isolated in pure form from natural sources. Thus, the number of metal-based drugs decreased steadily, even if novel forms and/or novel therapeutic indications for some of them have been introduced in the medical use. Nowadays some derivatives of three elements of group Va (As, Sb, Bi), as melarsaprol (for the late stages of African trypanosomiasis), sodium stibogluconate (for leishmaniasis and other protozoal infections), and bismuth citrate or subsalicylate (for traveler's diarrhea and *Helicobacter pylori* eradication) are worth of mention. To these, silver sulfadiazine and auranofin, containing metals of group Ib, should be added. The former still represents an agent of choice for the prevention of burn infections, while the latter, once highly valuable for the treatment of rheumatoid arthritis is being replaced by immunosuppressant and cytokine receptor antagonists. Finally, lithium carbonate or citrate, largely used in the past as a diuretic and (even if inappropriately) to solubilize urate deposits, is currently a mainstay for the treatment of mania and the prophylaxis of bipolar disorders.

The serendipitous discovery by Rosenberg in 1965 of the antiproliferative activity of a platinum complex [1], recognized as *cis*-diamminedichloroplatinum (cisplatin) and its subsequent successful introduction in the therapy of testicular cancer (1978), fostered a renewed and growing interest in metal-based drugs, particularly organometallic complexes, as antitumor agents. Indeed, a very impressively high cure-rate, was observed with cisplatin.

The *cis*-diamminedichloroplatinum was firstly prepared by Michele Peyrone [2], professor of chemistry at the University of Genoa. This compound, originally known as 'Peyrone's salt', was of fundamental interest in the development of the 'coordination theory' for which Alfred Werner earned the Nobel Prize in 1913.

Metal-based compounds enlarge the possibility of building up molecules better suited for binding to specific biological targets. Indeed, metal ions exhibit a wide range of coordination numbers and geometries, which allow to organize the most different anions and organic ligands (with their chemical and biological properties) in more appropriate spatial distributions, affording better modalities of attack to the target molecules.

Moreover, the redox potential of the metal can interact with the balanced cellular redox state, modifying cell viability either

☆ This review is dedicated to the memory of Michele Peyrone (1813–1883), Professor of Chemistry at the University of Genoa, who in 1844, prepared and studied the structure of *cis*-diamminedichloroplatinum (cisplatin), in recognition of his pioneering work on platinum complexes.

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directly or through the conversion of a rather inert compound in an activated one, thus tuning the inherent toxicity of the drug.

## Cisplatin and other platinum complexes in the therapy of cancer

Cisplatin is among the most active anticancer agents, producing DNA damage similar to alkylating agents. Its cytotoxic mechanism of action consists of activation through an aquation reaction involving the exchange of the two chloride leaving groups with water or hydroxyl ligands [3,4]. The water molecules then exchange with nitrogens and sulfurs of proteins and nucleic acids with a preference for the N-7 positions of adenine and guanine of DNA. Intrastrand coordination bond lesions, as well as other bifunctional lesions in DNA, are then formed. If the lesions occur on the same DNA strand and bases are adjacent, they are referred to as DNA adducts. If the sites are on different strands, the lesions are known as interstrand crosslinks. All of these injuries lead to inhibition of enzymes involved in RNA transcription, DNA replication and chain elongation of DNA polymerization.

The clinical effectiveness of cisplatin is, however, greatly limited by drug resistance and significant side effects that are the main factors responsible for recurrence and morbidity. Indeed, while some tumors exhibit intrinsic resistance to cisplatin, others develop acquired resistance after a few courses of treatment.

The development of less toxic, but equally effective, cisplatin analogs has been strongly pursued and a huge number of platinum compounds have been prepared and screened as potential antitumor agents over the past 30 years. Nearly 40 complexes have been investigated in clinical trials up to now; of these, only carboplatin and oxaliplatin have been approved for clinical use in 1989 and 2003, respectively [5].

At present, cisplatin, carboplatin, and oxaliplatin are the only metal-based anticancer agents soundly established in clinic and are found in a large number (>50%) of chemotherapeutic regimens (Figure 1).

Indeed, as a group, these complexes exhibit a broad antineoplastic spectrum and, in combination with other chemotherapeutic agents, can be highly effective in testicular, ovarian, colorectal, cervix, and lung cancers. Oxaliplatin is particularly active in combination with 5-FU in the treatment of advanced gastrointestinal tumors.

It is worth noting that carboplatin is better tolerated than cisplatin *in vivo* and, despite a rather poor activity in *in vitro* assays, is a valid alternative drug for different malignancies in patients unable to tolerate cisplatin. This observation calls for more careful evaluation criteria of novel drugs, in order to avoid prematurely discarding potentially useful compounds with only modest activity *in vitro* [6].

Cell resistance to cisplatin and its analogs is associated with upregulation of DNA repair, but also with the capture and inactivation of the complex by macromolecular blood components and/or thiol-containing reductants that might modulate the sensitivity of cells to the drug [7]. In an attempt to overcome this issue, novel $Pt^{II}$ (as thioplatin [8] and picoplatin [9,10]) and $Pt^{IV}$ (as satraplatin [10,11] and ethacraplatin [12]) complexes have been developed. The sterically hindered $Pt^{II}$ complex, picoplatin, which is under active clinical investigation against non-small cell lung cancer [9,10], exhibits reduced reactivity toward biomolecules and lower susceptibility to inactivation that allow this drug to be administered orally. Similarly, reduced reactivity and oral bioavailability is observed in the octahedrally coordinated $Pt^{IV}$ complexes, which need to be reduced to planar $Pt^{II}$ complexes to exert cytotoxicity. Satraplatin seems to offer several advantages over the standard *i.v.* platinum drugs, especially in hormone refractory prostate cancer [10,11].

Furthermore, the development of agents forming radically different adducts to DNA as the all-*trans* trinuclear platinum complexes BBR3464 [13] and triplatinNC [14] may help overcome resistance to cisplatin (Figure 1). These compounds strongly associate with DNA, either by long-range crosslinks or by binding to oxygen atoms of the phosphate. The former was up to 100-fold more potent than cisplatin against some resistant cell lines, but in clinical trials exhibited disappointing results [6]. TriplatinNC showed enhanced cellular uptake, despite the high positive charge (8+), and could play an interesting role as a carrier device capable of delivering drugs to DNA [14].

Finally, it is worth mentioning a UVA-photoactivated trans $Pt^{IV}$ complex that, differing from classic porphyrin photosensitizers, does not require oxygen to kill cancer cells (Figure 1). Therefore, its application in photodynamic therapy of hypoxic malignant tumors appears to be a reasonable hypothesis [15].

## Non-platinum metal compounds as antitumor drugs

Though the cisplatin molecular motif has led to the discovery of such successful drugs as carboplatin and oxaliplatin, further significant improvement in metal-based cancer therapy might be achieved from the study of platinum complexes of unconventional structures, such as those mentioned above, and from non-platinum metal compounds.

Indeed, Bell described the systemic use of colloidal lead to treat cancer in humans in 1924 and later, in 1929, Collier presented results on organolead and organotin compounds in experimental mouse cancer [16].

Following the Second World War, the chemistry of coordination compounds and the availability of stable organo-metals prompted the investigation of a growing number of metal compounds with potential cytotoxicity.

Several thousand compounds, derived from about thirty metals, have been prepared and tested and some of them are now in phase II and III clinical trials.

In particular, those elements belonging to group VIIIb of the periodic table, to which platinum belongs, have been preferentially studied. As information on such compounds increased, attention became mainly focused on ruthenium, iron, and cobalt (Figure 2).

### *Ruthenium*

Ruthenium complexes appear particularly promising [17]; despite exhibiting lower cytotoxicity compared to cisplatin, they are better tolerated *in vivo*. $Ru^{III}$ complexes maintain the metal oxidation state until they reach the tumor, where the low oxygen level permits their activation by reduction to $Ru^{II}$. The antitumor activity of ruthenium complexes involves binding to DNA, but additional mechanisms are also possible. The strong binding capacity for albumin and transferrin markedly influences the biodistribution of these complexes. Of great interest is their characteristic inhibition of angiogenesis and matrix metalloproteinases and, hence, metastasis *in vivo*.

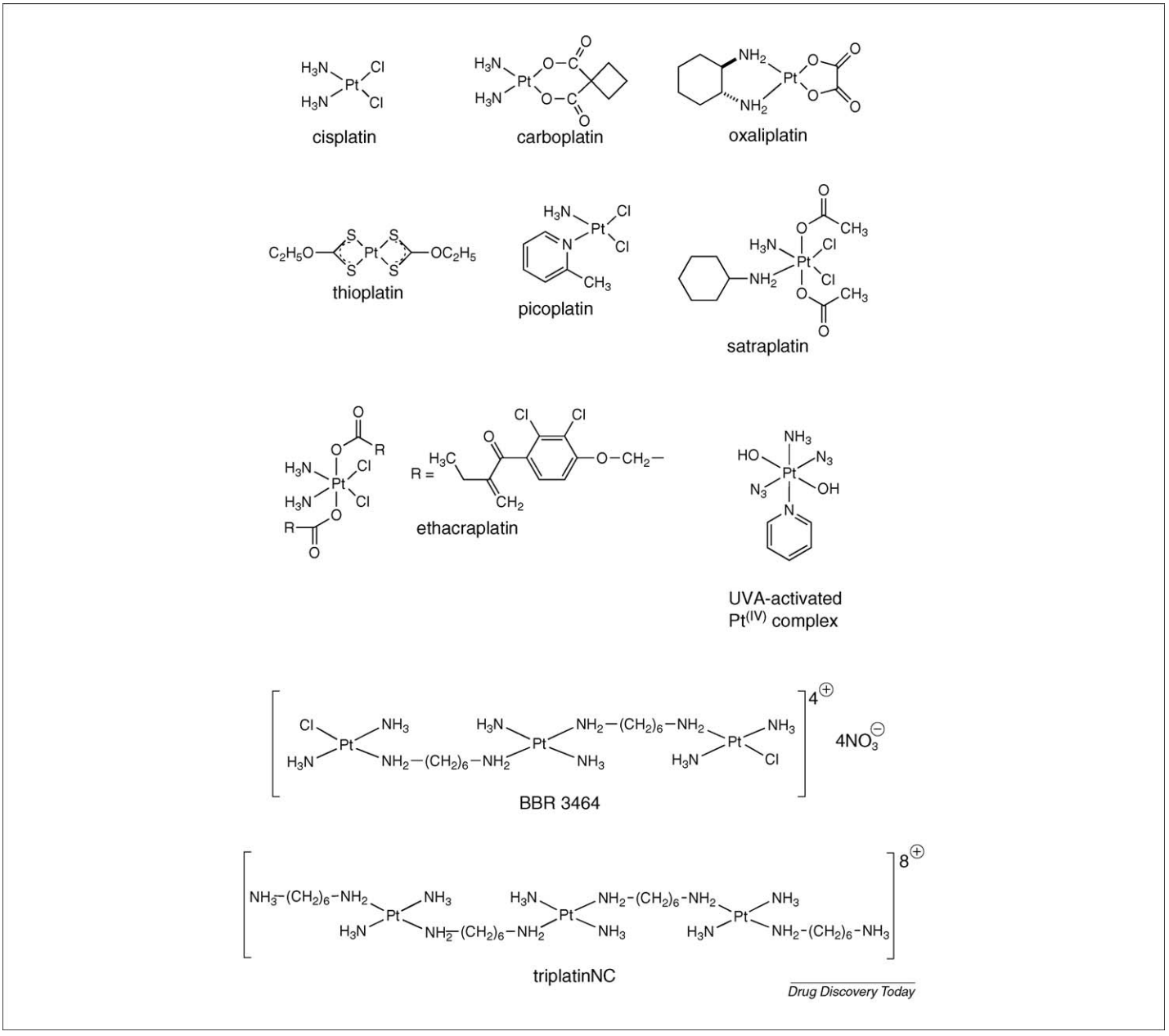


**FIGURE 1**

Chemical structures of platinum(II) and (IV) complexes.

The most interesting $Ru^{III}$ complexes are KP418, KP1019, and NAMI-A (Figure 2); the last two are presently under clinical evaluation. After *i.v.* administration of KP1019, five over eight patients with solid tumors experienced disease stabilization for almost 10 weeks [18]. The infusion of NAMI-A (300 mg/$m^2$/day; five days every three weeks) was proven safe in 24 patients with progressive non-small cell lung cancer and one patient had stable disease for 21 weeks [19].

### *Iron*

Simple ferricenium salts were the first iron complexes exhibiting some antitumor activity [20].

Recently, ferrocene derivatives of tamoxifen, a selective estrogen receptor modulator, have been described as antiproliferative compounds. In ferrocifen [21,22], a ferrocene moiety replaces the unsubstituted phenyl residue of the active metabolite of tamoxifen. This molecule is able to act on both estrogen receptor expressing (ER+) and non-expressing (ER−) human breast cancer cell lines. The activity of ferrocifen arises from the peculiar redox properties of the $Fe^{II}$ complex that initiates the chain of reactions leading to the formation of a quinone methide susceptible to nucleophilic attack from biomolecules.

Another aspect of the impact of iron on cancer therapy is the formation of active species from the union of the iron ion with chemotherapeutic agents, such as bleomycin, to produce activated species of oxygen responsible for DNA breakdown [23].

Moreover, the administration of iron chelators, such as desferrioxamine, together with cisplatin, etoposide, or doxorubicin has a synergistic effect, either through the formation of cytotoxic complexes or by the deprivation of iron to the cell itself.

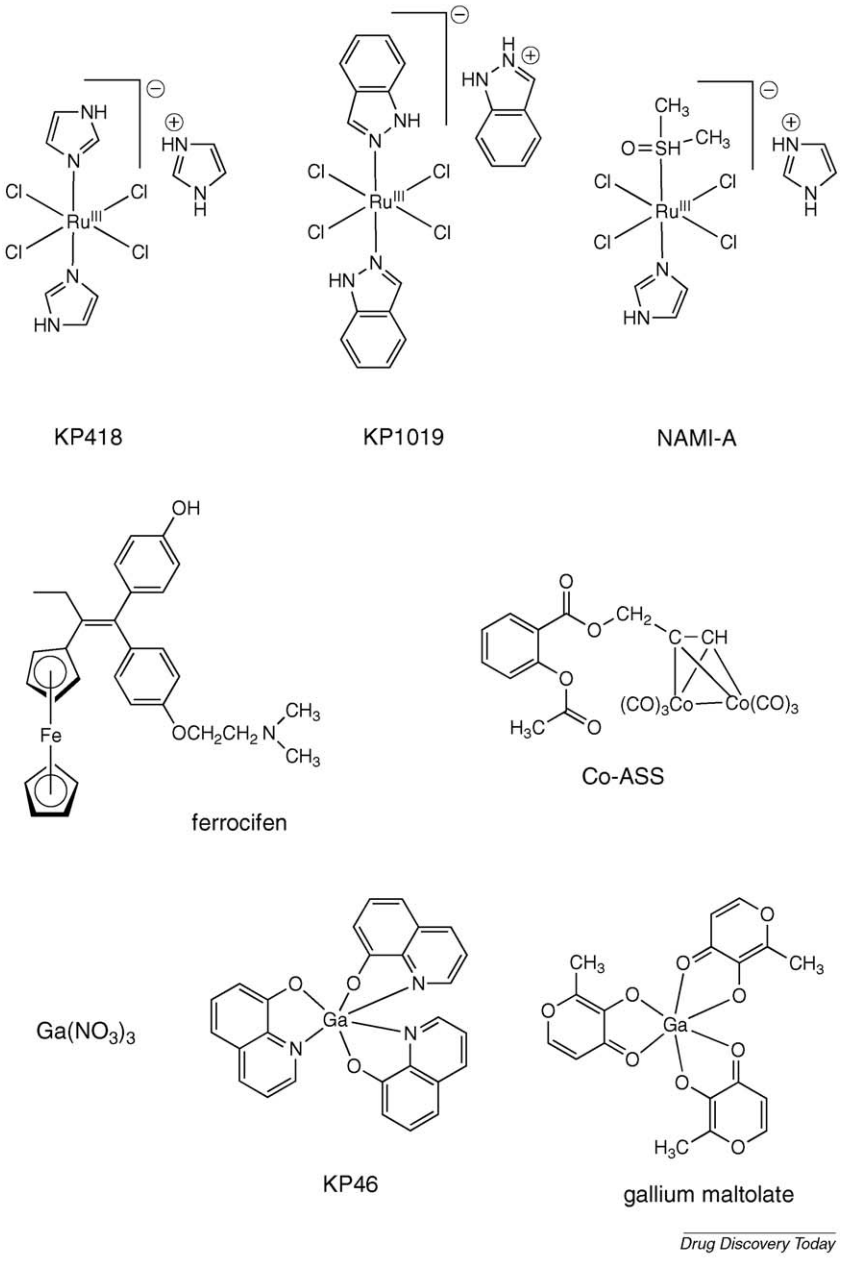


**FIGURE 2**

Chemical structures of ruthenium, iron, cobalt, and gallium complexes.

### *Cobalt*

Hexacarbonyl dicobalt and alkynes form peculiar complexes where the triple bond character is lost. They exhibit antiproliferative activity against several human cancer cell lines (particularly breast). The activity is most remarkable when the alkyne is the propargylic ester of aspirin (CoASS) [24]. Indeed, it has been shown that CoASS itself inhibits COX-1 and COX-2 more strongly than aspirin. Since cyclooxygenase inhibition retards the growth of established tumors and enhances their response to conventional therapies [25], it is likely that Co-ASS may exert its antiproliferative activity through a dual mechanism.

### *Gallium*

Of the elements of the main groups of the periodic table, gallium occupies an important position [6,26]. Gallium (III) exhibits coordination characteristics similar to $Fe^{3+}$, but differs from the latter being redox-inactive in cellular environments.

At present, two complexes, gallium 8-quinolinolate (KP46) and gallium maltolate (Figure 2), administered via the oral route, are under evaluation in the clinical setting [27]. In a phase I study, preliminary evidence of KP46 activity in renal cell carcinoma has been reported; partial response was noted in one patient and two patients exhibited disease stabilizations for up to 11 months, [28].

Furthermore, phase I/II studies have shown that gallium nitrate showed a 43% response rate in patients with relapsed or refractory non-Hodgkin's lymphoma (NHL) when administered as a continuous *i.v.* infusion [29].

The mechanism of action of gallium is mainly related to the inhibition of ribonucleotide reductase (RR), which catalyses the conversion of ribonucleotides to desoxyribonucleotides. The association of gallium derivatives with different inhibitors of RR (as, for instance, 1-formylisoquinoline thiosemicarbazone) produces highly potent antiproliferative complexes [30].

## Gold and tin compounds

Of the non-platinum metal compounds with antitumor activity, particular interest has been focused on gold and tin derivatives, which have a common activity on mitochondria and a strong affinity to thiol groups of proteins and enzymes [30-32].

### *Gold*

Gold thiolates have been used for a long time in the therapy of rheumatoid arthritis [33,34]; interestingly, treated patients exhibited a lower rate of malignancy than the age-matched and sex-matched general population. Indeed auranofin (but not sodium aurothiomalate) exhibited potent *in vitro* cytotoxicity against a number of tumor cell lines (Figure 3).

The importance of the presence of a phosphine ligand was soon recognized and other gold(I) complexes with triethylphosphine, triphenylphosphine, 1,2-bis(diphenylphosphine)ethane (dppe), and so on, were prepared and found to be active in *in vitro* and *in vivo* assays [31,33,35].

The tetrahedral complex, $[Au(dppe)_2]Cl$, demonstrated particular efficacy in several cancer models (Figure 3) but exhibited cardiotoxicity in rabbits and severe hepatotoxicity in dogs [31].

Studies with chloro(triethylphosphine)gold(I), $[Au(dppe)_2]Cl$, and auranofin showed that mitochondria are the targets of gold complexes [31]. Indeed, gold displays a high electrophilic affinity for thiols and inhibition of mitochondrial human glutathione reductase (hGR) and thioredoxin reductase (hTrxR) has been demonstrated [36,37]. The thioredoxin system provides the reducing equivalents for ribonucleotide reductase to form desoxyribonucleotides and is, therefore, involved in the process of cell division. Mammalian ThxRs are selenoenzymes, incorporating selenocysteine as the penultimate aminoacid. Micromolar concentrations of gold are required to inhibit GR, while even nanomolar concentrations are capable of affecting TrxR.

Phosphol-containing gold complexes (Figure 3) have been shown to inhibit both hGR and hTrxR at 0.8–7 nM concentrations but display antiproliferative activity in glioblastoma cell lines with $IC_{50}/ID_{50}$ (drug concentration or dose reducing survival by 50% vs. control) in the range 5.4–15.2 μM [38].

The thioredoxin system is involved in the formation and regeneration of methylselenol, which is responsible for detoxifying the reactive oxygen species that initiate cancer formation. On the contrary, increased expression of Trx is often associated with aggressive tumor growth and resistance to traditional treatment modalities [37].

In order to improve the selectivity of $[Au(dppe)_2]Cl$ complex for cancer cells over normal cells, molecular lipophilicity was lowered by exchanging phenyl residues for pyridines (that can be protonated and are, therefore, more hydrophilic) or introducing carboxylic groups on the ethylene chains [31].

The 2-pyridylphosphine analog, which is endowed with moderate lipophilicity and cation character, was very active against murine subcutaneous colon 38 tumors, whereas the second type of analogs, whose anionic character prevented their access to the negatively charged matrix of tumor cell mitochondria, were inactive [31,39].

Very promising compounds, with novel lipophilic cationic characteristics, have been obtained by replacing the phosphine ligands with N-heterocyclic carbene ligands, obtained from dialkylimidazolinium salts [31].

To balance the lipophilic–hydrophilic character of phosphine-gold(I) complexes, the metal valence was also saturated with aminothiolate anions, whose lipophilicity may be enhanced by increasing the number of carbon atoms, while hydrophilicity is conferred by the protonable nitrogen.

Available data concerning eight compounds, derived from diethylaminoethanethiol, 1-methylpiperazine-4-ethanethiol and from the bulky bicyclic, highly lipophilic, and strongly basic lupinylthiol [(1*R*,9a*R*)-octahydro-2*H*-quinolizine-1-methanethiol], seemed to confirm this assumption. The compounds containing triphenylphosphine or 1,2-bis(dimethylphosphine)ethane as ligands were moderately or poorly active, while the others exhibited good activity against human ovarian cancer cell lines compared to cisplatin [40].

Several gold (III) complexes have also been studied and proved to be extremely active when containing appropriate ligands to stabilize the oxidation state. Despite being isoelectronic and isostructural to square planar $Pt^{II}$ complexes, they weakly interact with DNA but inhibit thioredoxin reductase [41].

### *Organotin*

Early studies, in 1929, on the cytotoxic activity of organotin(IV) derivatives produced contradictory results [16]. Later, in 1972, it was shown that triphenyltin acetate (but not the corresponding chloride) retarded tumor growth in mice [42]. Since then, a huge number of organotin derivatives have been prepared and tested *in vitro* and *in vivo*, firstly, against murine leukemia cell lines and, after that, against different panels of human cancer cell lines [42-44].

Many organotin compounds are widely available, since they have found a variety of industrial and agricultural applications and are suitable as starting materials for the synthesis of novel derivatives. Moreover, organotins have been extensively studied as environmental toxicants since they are well known for their potent biocidal action.

Most of the compounds tested early on, exhibited interesting activity in specific cancer models, but they often lacked activity against a broad spectrum of experimental tumors. Nevertheless, the large possibility for variation of the organic moieties and donor ligands linked to the metal has resulted in several diorganotin and triorganotin(IV) compounds with high antiproliferative activity *in vitro* against a variety of solid and hematologic cancers [44,45].

In solution, triorganotin compounds may undergo spontaneous disproportionation into the corresponding diorganotin and tetraorganotin derivatives [46] while, *in vivo*, the loss of one

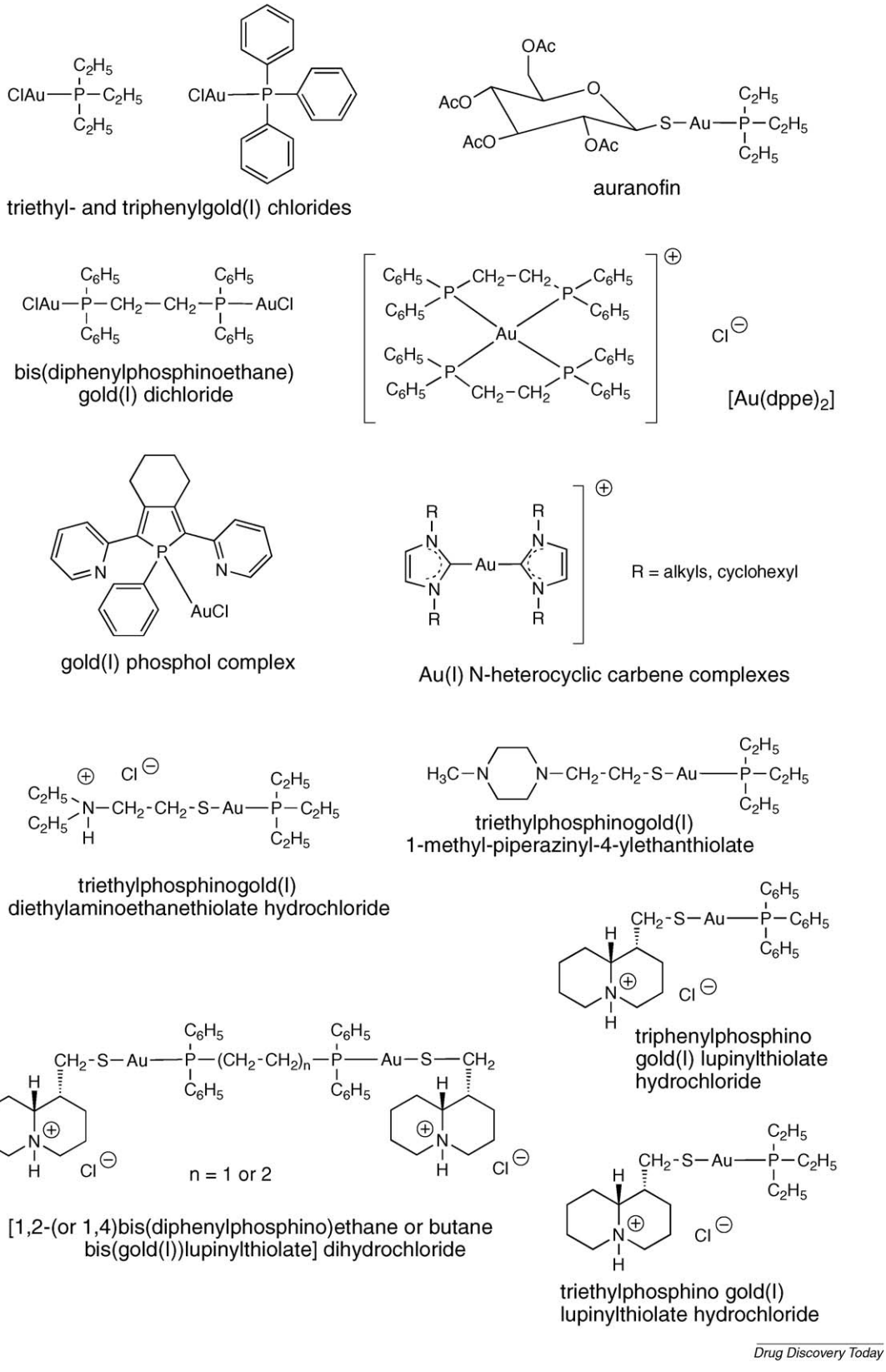


**FIGURE 3**

Chemical structures of gold complexes.

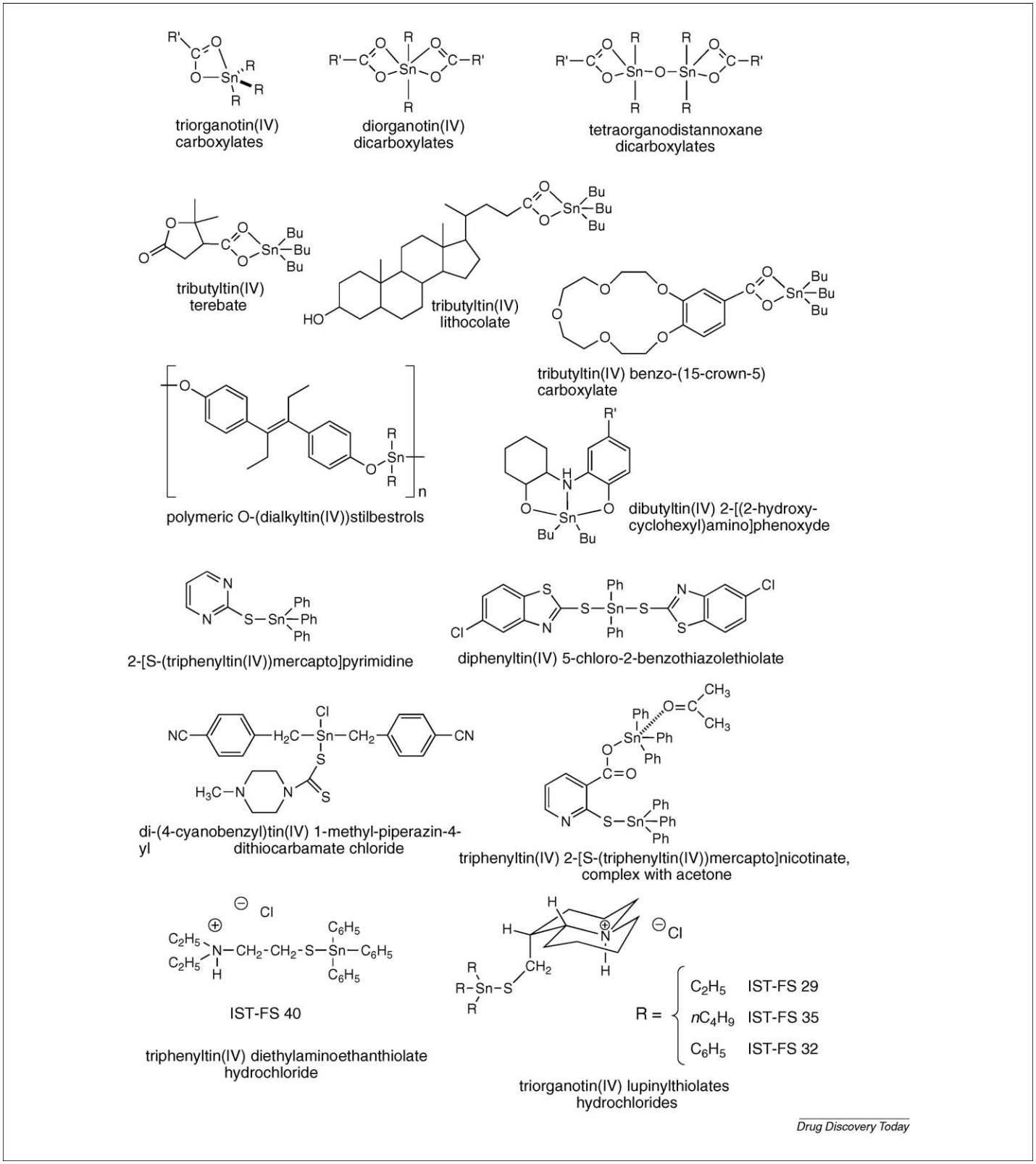


**FIGURE 4**

Chemical structures of diorganotin and triorganotin derivatives.

alkyl or aryl group may occur through the intervention of enzymes such as aromatase [47].

On the basis of the above consideration, diorganotin compounds might be considered to be the ultimate cytotoxic agents and the frequently observed higher activity of triorganotins may be related to pharmacokinetic considerations.

Inhibition of macromolecular synthesis, mitochondrial energy metabolism, and reduction of DNA synthesis, as well as direct

interaction with the cell membrane (increase in cytosolic $Ca^{2+}$ concentration), have been implicated in organotin-induced cytotoxicity [48,49]. In addition, promotion of oxidative and DNA damage *in vivo* has been detected [50]. Both oxidative damage and increased concentration of intracellular calcium ions seem to be the major factors contributing to triorganotin-induced apoptosis in many cell lines.

Increased histone acetyltransferase activity [51] and activation of retinoid X receptor and PPARγ [52] may play additional roles in the antiproliferative activity of organotins.

Besides halides ($Cl^-$, $Br^-$) or pseudohalides ($SCN^-$), most organotin compounds contain carboxylic acid residues as exchangeable groups (Figure 4). Triorganotin carboxylates may exist in monomeric or polymeric forms, while diorganotin derivatives may exist as true dicarboxylates or as distannooxane salts [$(R_2SnOCOR')_2O$] and may further aggregate in a number of ways that influence both solubility and bioavailability.

Among all, diorganotin and triorganotin terebates and lithocolates (Figure 4), tested against a panel of seven human cancer cell lines, were found to be highly active and more potent than cisplatin with $ID_{50}$ values in the range <3–134 ng/ml (<4.5–245 nM). In both cases, tributyl derivatives demonstrated higher efficacy than triphenyl and dibutyl derivatives. Nevertheless, although some *in vivo* activity of tributyltin terebate was observed, toxicity was also reported [53].

Impressive cytotoxicity against the same panel of cancer cells was exhibited by dibutyltin polyoxaalkanoates and benzo-(15-crown-5) carboxylates with $ID_{50}$s never higher than 3.3 ng/ml (5.5 nM) and often lower than 1 ng/ml (1.2 nM) [53].

Additional organotin derivatives containing oxygen donor ligands, other than carboxylates, were obtained from polyethyleneglycols [54], 4-acylpyrazolin-5-ones and from different kinds of phenolic compounds, as the polymeric derivatives of some O-(dialkyltin)stilbestrols [55] and the dibutyltin 2-[N-(hydroxyalkyl)amino]phenoxides [56]. Both types of compounds were tested against four (colon, breast, and prostate) and five (glioblastoma, prostate, chronic myelogenous leukemia, colon, and breast) human cancer cell lines, respectively, exhibiting, in the first case, cytotoxicity comparable to or, in the second one, slightly higher than that of cisplatin.

Earlier studies had already ascribed particular relevance to organotin(IV) complexes with sulfur donor ligands. Indeed, while the organotin moiety is crucial for cytotoxicity, the ligand plays a key role in transporting and addressing the molecule to the target, resisting untimely exchanges with biomolecules. Sulfur-containing ligands (which may represent widely differing chemical structures) appear particularly suitable to fulfil this task although, in some cases, the leaving group might be released too slowly for activity to be seen.

Triphenyltin(IV) pyrimidine thiolate and diphenyltin(IV) 5-chloro-2-benzothiazole thiolate were the most active among a number of analogs against rat sarcoma cells. Besides $IC_{50}$ values in the submicromolar range, an interesting correlation between cytotoxicity and inhibition of lipooxygenase-induced peroxidation of linoleic acid was also reported [57,58].

Within a set of ten di(4-cyanobenzyl)tin(IV) dithiocarbamates, very high activity against five human tumor cell lines was observed. The highest activity was shown by the complex $(4\text{-}NC\text{–}C_6H_4\text{–}CH_2)_2Sn(Cl)S_2C\text{–}N(CH_2CH_2)_2N\text{–}CH_3$ against MCF-7 and IGROV cells, with $IC_{50}$ values of 14 and 19.3 nM, respectively [45].

Furthermore, the complex triphenyltin 2-(triphenyltinmercapto)nicotinate exhibited an $IC_{50}$ as low as 0.005 μg/ml (5.5 nM) against leiomyosarcoma [45].

*tert*-Aminoalkylthiols have not received much attention as ligands to address the solubility issue so often encountered with organotin derivatives. Indeed, the link of triorganotin residues (R = methyl, ethyl, butyl, and phenyl) with diethylaminoethanethiol and lupinylthiol led to lipophilic compounds retaining reasonable water solubility after protonation.

While the trimethyltin derivatives were inactive, all the other triorganotin derivatives of the above two thiols exhibited good to high cytotoxicity against human ovarian cancer cell lines [40].

Because of their interesting activity and better stability, the triethyl and tributyltin(IV) lupinylthiolates, IST-FS 29 and IST-FS 35 (Figure 4), were studied more thoroughly against a number of human cancer cell lines exhibiting $IC_{50}$ values in the range 0.6–12.4 μM for IST-FS 29 and 0.16–1.8 μM for IST-FS 35 [59-63].

Moreover, while IST-FS 29 was very active *in vivo* in murine tumor models (P388 myelomonocytic leukemia, B16-F10 melanoma and 3LL Lewis lung carcinoma), after repeated oral administrations, IST-FS 35 was able to inhibit the tumor growth of implanted P388 and B16-F10 cells, by up to 96%, after a single *i.v.* injection. Since IST-FS 35 produced peritoneal irritation via the *i.p.* route and did not appear to be well absorbed orally, *i.v.* administration was considered as the treatment of choice [62,63].

No important signs of toxicity were observed with either compound, and autoptical and histological examinations confirmed their mild toxicity. Therefore, these compounds appear as potential drug candidates and deserve further development in *in vivo* preclinical setting in the perspective of their clinical application.

## Conclusions

Very important progress in medicinal organo-metallic chemistry has been seen in the past few years, allowing the rational design of novel, non-conventional, platinum compounds, as well as innovative non-platinum metal-based antitumor agents.

Ruthenium and gallium are drug candidates of high relevance, but gold and tin derivatives, which, in the 1990s were not considered serious candidates as antitumor drugs, are now enjoying resurgence and, indeed, appear very promising as potential drugs. As a consequence of their mechanism of action, targeting macromolecular synthesis, mitochondrial energy metabolism, and DNA, gold and tin derivatives may result in compounds that are particularly active against cisplatin-resistant cancers.

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