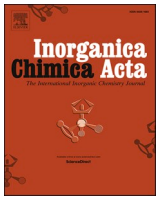
Inorganica Chimica Acta 574 (2025) 122396

Contents lists available at ScienceDirect

Inorganica Chimica Acta

journal homepage: www.elsevier.com/locate/ica



Review article

Platinum(II) triphenylphosphane and triphenylarsane complexes help overcome resistance against cisplatinum resistant cancer cell lines

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ARTICLE INFO

Keywords:
platinum(II) complexes
Triphenylphosphane
Synthesis
Anticancer properties
Resistance phenomena

ABSTRACT

In the field of anticancer metal complexes many efforts are continuously devoted to overcome resistance phenomena. Within thousands of new complexes proposed each year as potential metallodrugs, compounds showing modes of action other than that of cisplatin appear promising. This minireview reports about the class of triphenylphosphane complexes of platinum(II), describing their synthesis, antiproliferative properties and modes of action, with a special focus on the possibility of overcoming resistance phenomena.

1. Introduction

Platinum-based chemotherapeutics have revolutionized cancer treatment, with cisplatin being a cornerstone in various regimens.[1–7] However, the emergence of resistance and adverse side effects necessitate the exploration of novel platinum complexes.[8–16] Besides the first structural analogues of cisplatin, appearing among the metal based chemotherapeutics few years after the discovery of the parent drug, [3,17,18] a growing interest has been devoted to "non conventional" platinum complexes, characterized by a chemical backbone significantly different from that of cisplatin. As a matter of fact, a different chemical structure often means a different mode of action, leading to potential drugs showing interesting effectiveness also towards cancer cells unaffected by cisplatin treatment. Among these, platinum(II) phosphane complexes have emerged as promising candidates. Phosphane based ligands coordinate easily to platinum(II), affording robust complexes by relatively simple synthetic procedures, which have been consolidated in the course of years.[19] Moreover, studies on model lipid bilayers suggested that the lipophilic nature of phosphane ligands may significantly influence the cellular internalization of platinum phosphane complexes in cancer cells, affecting pharmacokinetics and therapeutic parameters by a different permeability mechanism with respect to cisplatin.[20–22] In addition, the presence of phosphane ligands has been sometimes connected to the impairment of mitochondrial functionality in cancer cells, leading to apoptosis.[23] In fact, the disruption of mitochondrial functions, caused by mitochondrial membrane depolarization, electron transport chain impairment and/or increased production of reactive oxygen species (ROS) was demonstrated in tumor cells by a number of metal phosphane complexes. [24–30].

This minireview provides an overview of recent advancements in the development and utilization of platinum triphenylphosphane complexes as possible anticancer agents. From their synthesis to their interactions with cellular targets, we delve into their potential to overcome existing limitations in cancer chemotherapy, opening avenues for more efficacious and safer treatments.

2. Synthesis of triphenylphosphane Pt(II) complexes

The most convenient synthetic approach to prepare $[PtX_2(PPh_3)(L)]$ complexes (L = neutral ligand) is based on the use of triphenylphosphane containing dinuclear precursors *trans*-$[Pt(\mu\text{-}X)X(PPh_3)]_2$. The dinuclear species have been known for a long time [31,32], but recently their preparations were optimized under solvothermal conditions starting from the readily available $[PtX_2(NCMe)_2]$ and triphenylphosphane.[33,34] They can be desymmetrized by a ring-opening reaction by neutral ligands L (Scheme 1). The reaction is oriented by the strong *trans* effect exerted by the triphenylphosphane ligand, thus *trans*-$[PtX_2(PPh_3)(L)]$ is the kinetic product, usually observed after a short time in the reaction mixtures. According to the nature of L, it is possible that a *cis,trans* isomerization takes place in solution. This process, that can be accelerated in the presence of excess L ligand, can be easily followed by ^{31}P NMR spectroscopy. Indeed, triphenylphosphane

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https://doi.org/10.1016/j.ica.2024.122396
Received 26 June 2024; Received in revised form 25 September 2024; Accepted 25 September 2024
Available online 5 October 2024

complexes of platinum afford simple ^{31}P NMR spectra, where the presence of one or two signals with satellites immediately reveals the presence of a single isomer or a mixture of the two of them.

Several compounds were prepared by this approach, varying the nature of L and X. For dichloro derivatives, the use of *N*-alkylamines and *N,N*-dialkylamines afforded *trans* products, stable in chlorinated solution up to weeks. The coordination geometry around the metal was confirmed by single crystal X-ray diffractometry in the case of L = *N*-isopropylamine [35], *N,N*-diethylamine [36], morpholine [37], while in the other cases it was assigned on the basis of the comparison of ^{31}P NMR signals and $^{1}J_{P\text{-}Pt}$ coupling constants with those of structurally characterized samples. On the other hand, the use of neutral, π-acidic ligands (CO [33], DMSO [37], RNC [38], *N*-acyclic carbenes [38]) afforded *cis* derivatives with a nearly complete stereoselectivity. The preparation of *trans*-[$PtCl_2(PPh_3)(NHRR')$] can be also obtained starting from *cis*-[$PtCl_2(PPh_3)(NCMe)$] and *N,N*-dialkylamines [37,39,40]. *Cis*-[$PtCl_2(PPh_3)(NCMe)$] is an intermediate in the synthesis of *trans*-[Pt(μ-Cl)Cl$(PPh_3)]_2$ and can be considered its synthetic equivalent when reacted with nucleophiles in refluxing acetonitrile: in these conditions an isomerization equilibrium takes place to *trans*-[$PtCl_2(PPh_3)(NCMe)$], which quickly reacts affording the substitution product, even when protic nucleophiles are used (Scheme 2) [36]. When the reaction is carried out at low temperature, the product arising from the addition of protic nucleophiles to coordinated acetonitrile is obtained (Scheme 2). [36].

Cis-[$PtCl_2(PPh_3)(NCMe)$] was also a very useful precursor in the preparation of ionic complexes. In this case, a monodehalogenation reaction was carried out by $AgBF_4$ in a polar coordinating solvent at room temperature. In these conditions, the chloride ligand *trans* to PPh_3 was removed selectively, and the following substitution reaction by a suitable neutral ligand afforded the corresponding ionic complexes [41].

The ring-opening reaction of *trans*-[Pt(μ-Cl)Cl$(PPh_3)]_2$ was not always completely stereoselective, affording mixtures of geometric isomers. The composition of the equilibrium solutions varied according to the nature of L. While the reaction was completely stereoselective towards the *trans* isomer when quinolines [42] and toluidines [42] were used, a mixture with comparable amounts of both isomers was obtained with pyridine [43]. Occasionally, the equilibrium was displaced towards one or the other geometric isomer by steric requirements or by solubility, with *cis* isomers being generally less soluble in chlorinated solvents than the corresponding *trans* derivatives. As an example, when *trans*-[Pt(μ-Cl)Cl$(PPh_3)]_2$ was reacted with benzothiazole in $CDCl_3$, a clear solution was obtained after a few hours, containing the expected *trans* kinetic intermediate, which could be completely characterized in solution. Nevertheless, soon after its formation, a slow isomerization process to the scarcely soluble *cis* isomer took place, accompanied by its precipitation, which was complete in 48 h [42]. Finally, pure *cis*-[$PtCl_2(PPh_3)$(benzothiazole)] was recovered in high yield and structurally characterized.

A substantially identical reactivity was observed when a brominated dinuclear precursor was reacted with neutral ligands (Scheme 1, X = Br), with some differences in the composition of the product mixtures, arising from the steric requirements of the larger bromine atoms. [34,44].

Analogously, it was possible to prepare with the same approach some triphenylarsane amino derivatives, starting from *trans*-[Pt(μ-Cl)Cl$(AsPh_3)$]. In this case only *trans* complexes were obtained.[45].

When a series of arylaldoximes were used in the ring-opening reaction of *trans*-[Pt(μ-Cl)Cl$(PPh_3)]_2$ [46], mixtures were obtained, containing up to four possible products, since in this case *E/Z* isomerization around the oxime double C═N bond is also possible (Scheme 3).

The reaction was found anyway completely regioselective as for the coordination site, since only *N*-coordinated derivatives were observed. The composition of the observed equilibria (Scheme 3) was easily determined with the aid of ^{31}P NMR spectroscopy and was found strongly dependent on the steric hindrance of the aromatic residue [46]. As an example, in the case of 9′-anthracenyl derivative, only *trans* isomers were observed.

When 2́-hydroxyaryloximes were used in the ring-opening of *trans*-[Pt(μ-Cl)Cl$(PPh_3)]_2$ the formation of the expected kinetic Z-product was followed by HCl slow elimination, and the corresponding chelated complexes were obtained (Scheme 4). The reaction was optimized in the presence of silver acetate, aiding the dehalogenation step and leading quickly to the chelate oxime derivatives (Scheme 4).[47,48].

Interestingly, the oxime OH functional group is not involved in the formation of the complex and its typical reactivity can be exploited to furtherly functionalize the metal complexes. As an example, under phase transfer catalysis conditions, O-alkylation of the oxime hydroxyl group could be carried out (Scheme 5). [47].

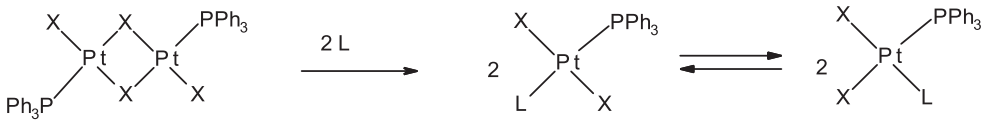
This mild synthetic procedure well tolerates the presence of other functional groups on the alkylating residue, opening thus the way to the introduction of specific building blocks on the platinum oxime scaffold.

Triphenylphosphane complexes prepared by the described synthetic approaches are generally characterized by a high degree of lipophilicity, which can help their cellular uptake, but makes them practically insoluble in water and/or ethanol. This feature makes the use of dimethylsulfoxide unavoidable to carry out suitable *in vitro* cytotoxicity tests. For all the described derivatives, thus, a preliminary stability test in this highly coordinating solvent was imperative, in order to select only stable compounds for the biological studies. The stability was generally checked by ^{31}P NMR analyses of solutions of the complexes in DMSO. Only derivatives found unaltered in DMSO solution for at least 24 h were chosen for the biological studies and are reported in the Scheme 6.

Biological activity.

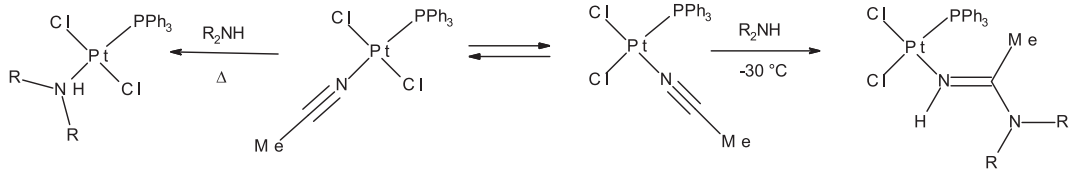
A significant number of Pt(II) complexes containing phosphanes showed promising antiproliferative properties [35,49–55] and in some cases the phosphane ligand in *trans* to a secondary amine allowed to obtain *trans*-dichloroplatinum complexes endowed with interesting biological properties, such as cytotoxic activity in both cisplatin sensitive and resistant cell lines.[35,51,52].

The platinum complexes of general formula *trans*-[$PtCl_2(L)(L')$] (L = PPh_3, PMe_2Ph; and L'= NH_3, isopropylamine, dimethylamine, and 1-aminoindane, Scheme 7), are more potent than cisplatin in SKOV3 cells, an ovarian carcinoma cell line intrinsically resistant to cisplatin, and have resistance factor (RF) values (ratio of the IC_{50} on resistant cells/IC_{50} on wild type cells) between 0.6–1.1 in the ovarian carcinoma CH1 and CH1cisR pairs, much lower than 2.8, obtained for cisplatin. A mechanism of action independent of checkpoints activation was assumed because apoptosis occurred without G_2/M or G_1 cell accumulation. In particular, the steric hindrance, along with the lipophilic

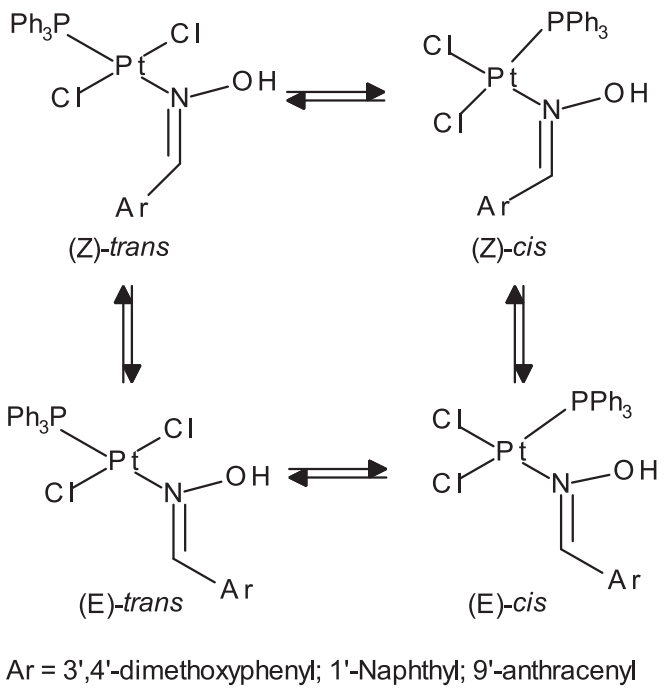


L = neutral ligand
X = Cl, Br

Scheme 1. Synthesis of [$PtX_2(PPh_3)(L)$] complexes from *trans*-[Pt(μ-X)X$(PPh_3)]_2$.



Scheme 2. Stereochemistry driven outcome of the reaction between *cis*-[$PtCl_2(PPh_3)(NCMe)$] and protic nucleophiles as a function of temperature.



Scheme 3. *Cis/trans*, *E/Z* isomerization equilibria in [$PtCl_2(PPh_3)(N(OH)CHAr$] complexes.

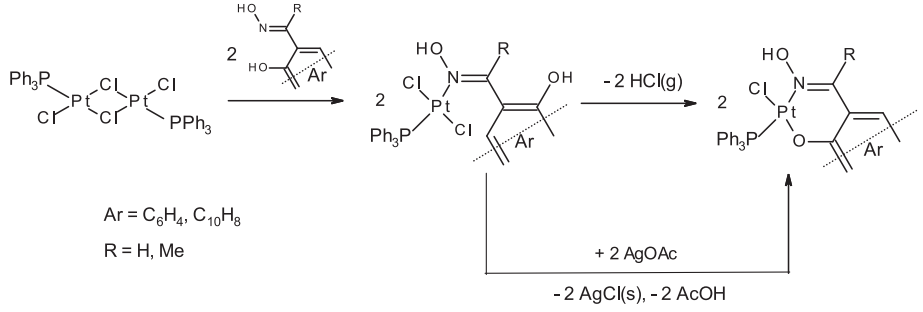
contribution of the bulky hydrophobic PPh_3, were hypothesized to produce a great DNA damage and an increased cell uptake, respectively, both concurring to the relevant cytotoxic activity.[35].

Later, *trans* platinum complexes in the phosphane series where the phosphane ligand is PPh_3 and the aliphatic amine is either racemic or (S)-2-methylbutanamine ((S)–$NH_2CH_2CH(CH_3)CH_2CH_3$), demonstrated an interesting antiproliferative activity on murine adenocarcinoma cells. [51].

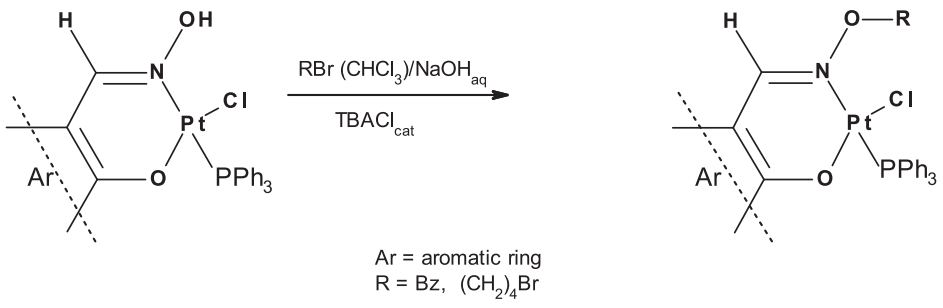
The synthesis of [Pt(O2,O3-DHA)$(PPh_3)_2$] (DHA = dehydroascorbic acid, Scheme 8) by Bergamini et al.,[52] where DHA is used as carrier with the aim to allow the crossing of blood–brain barrier, led to a complex with interesting antiproliferative effect.

The IC_{50} values on cisplatin sensitive T2 human cell line (a hybrid cell obtained by the fusion of the human lymphoblastoid line 174 with the CEM human leukemia cancer line), were similar for the complex and cisplatin, whereas on cisplatin-resistant SKOV3, values of resistance factor of 5.75 for the complex and 71.8 for cisplatin, were found, supporting the hypothesis of a different mechanism of action for the two Pt (II) complexes.[52].

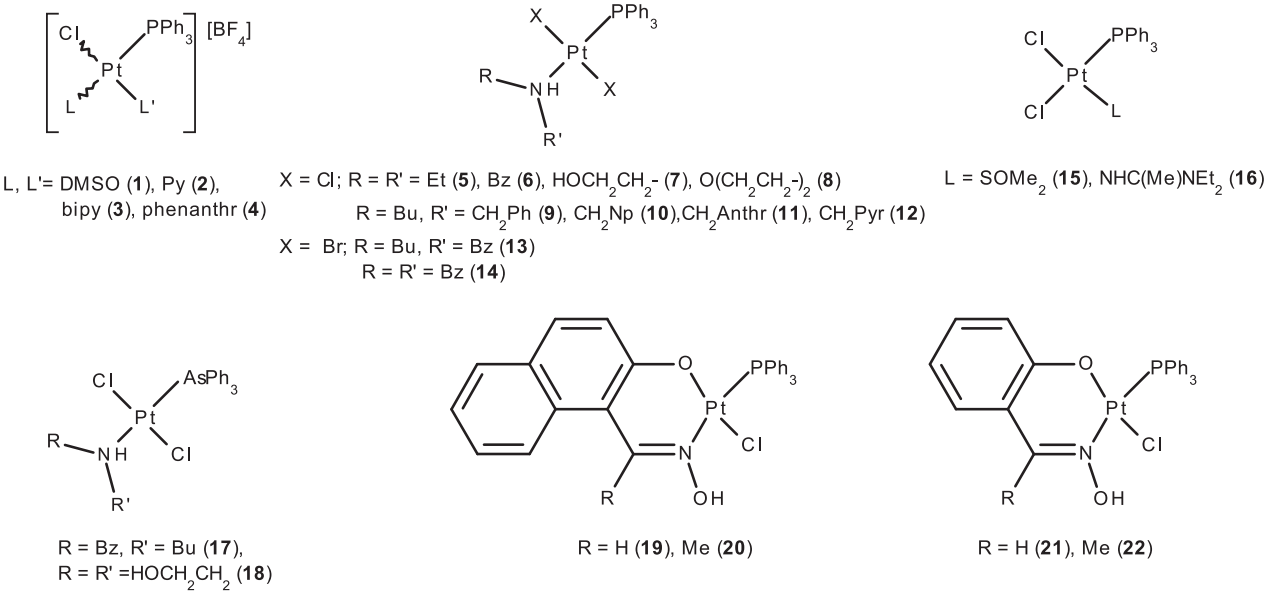
Actually, the mechanism of action for the Pt(II) complexes containing phosphane ligands is characterized by distinct features with respect to the drug. Indeed, the crucial role of phosphane in determining the biological profile appears relevant also in Au(I) complexes. The cationic tetra-coordinate Au(I) [$Au(dppe)_2$]Cl complex, containing two chelated 1,2-bis(diphenylphosphane)ethane ligands (Scheme 9), showed significant *in vivo* antitumor activity in murine tumor models. The investigation on the mechanism of action suggested alterations in mitochondria of isolated rat hepatocytes. In fact, after cell uptake, increased oxygen consumption and morphological changes in the intracellular organelles



Scheme 4. Synthesis of chelating arylaldoxime derivatives.



Scheme 5. Functionalization of platinum(II) chelating oxime complexes.



Scheme 6. Structures of complexes tested as antiproliferative agents.

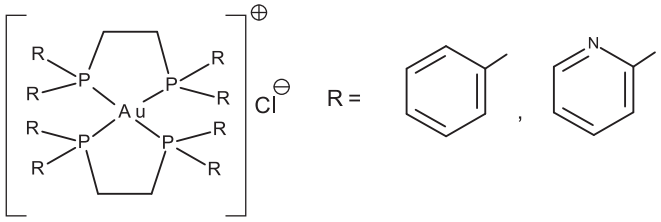
Scheme 7. Structure of *trans*-[$PtCl_2(L)(L')$] complexes.

were detected.

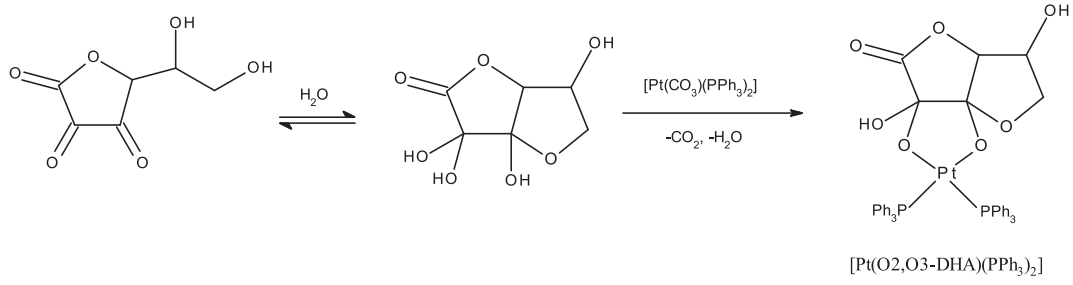
Furthermore, in isolated rat hepatocyte mitochondria a rapid dissipation of the inner membrane potential, calcium efflux, mitochondrial swelling and increased permeability of inner membrane were observed. Uncoupling of oxidative phosphorylation appeared due to an effective uptake of the complex into the organelles, related to the cationic-lipophilic nature of the complex.[24] The high lipophilicity and accumulation inside mitochondria led to a general membrane permeabilization retained responsible for the severe hepatoxicity observed in dogs. Such drawbacks halted a possible clinical development.[56,57] Otherwise, mono-functional ionic Pt(II) complexes containing triphenylphosphane, a chloride and *N,N*- chelating or non-chelating ligands (Scheme 6, 1-4) showed a very weak cytotoxicity on human tumor cell lines, suggesting that monofunctional ionic features have detrimental properties for the development of antitumor agents (Table 1). [41].

Later, in an attempt to modulate the lipophilic-hydrophilic balance, the phenyl substituents were replaced by pyridyl groups obtaining a bis-chelate Au(I) complex of 1,3-bis(di-2-pyridylphosphane)propane (Scheme 9), selectively toxic in breast cancer cells. The investigation of the cell targets showed the ability of the complex to be accumulated into mitochondria thanks to the transmembrane electric potential, negative inside, and to affect the Trx/TrxR system.[25] For the platinum (II) complex [$PtCl(\eta^1\text{-}C_9H_7)L_2$] (where L_2 = 1,2-bis(diphenylphosphane) ethane, Scheme 10) we also demonstrated the ability to induce cytotoxicity by affecting mitochondrial functions rather than DNA, that is the crucial target for cisplatin.

Indeed, the phosphane complex tested on isolated rat liver mitochondria, induced mitochondrial swelling, release of the proapoptotic factors cytochrome *C* and AIF and oxidation of mitochondrial glutathione and thiol groups. The protective effect of cyclosporine A on cell growth inhibition, mitochondrial swelling and proapoptotic factors release suggested the ability of the complex to induce the phenomenon of mitochondrial permeability transition (MPT), and supported the



Scheme 9. Structure of some cationic tetracoordinate Au(I) complexes. [2425].

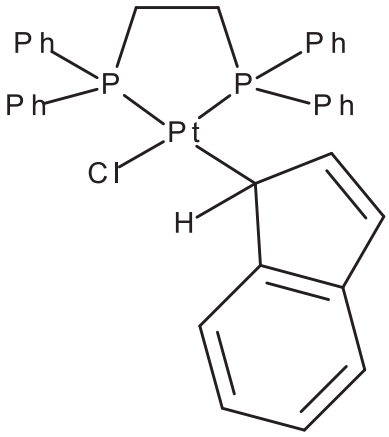


Scheme 8. Synthesis of [$Pt(O2,O3\text{-}DHA)(PPh_3)_2$] [52].

Table 1
Antiproliferative effects of platinum(II) triphenylphosphane complexes on human cervix adenocarcinoma cells (HeLa).

Complex	GI_{50} (μM) HeLa
1[a]	>20
2[a]	>20
3[a]	>20
4[a]	>20
5[b]	5.1 ± 1.5
6[b]	3.3 ± 1.7
7[b]	0.42 ± 0.06
8[b]	9.7 ± 0.7
15[b]	5.7 ± 1.6
16[b]	7.0 ± 1.2
cisplatin[b]	1.5 ± 0.6

[a] calculated from ref.[41].
[b] taken from ref.[37].



Scheme 10. Structure of a bis(phosphane) platinum(II) complex affecting mitochondrial functions.[58].

hypothesis that cell apoptosis occurred through mitochondrial pathway.[58].

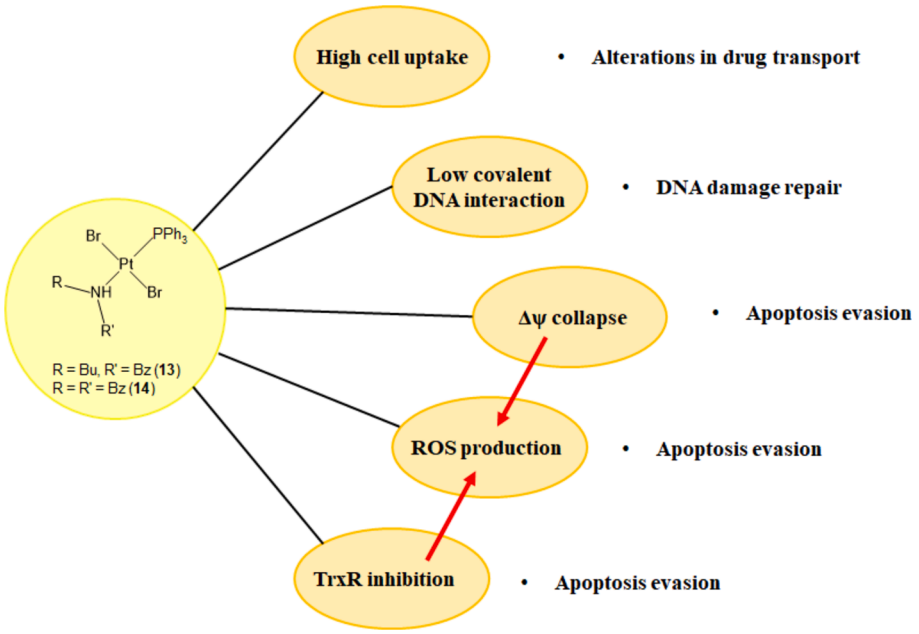
The role of mitochondria appeared crucial also in the investigation of the mechanism of action responsible for the antiproliferative effect of a series of Pt(II) complexes bearing triphenylphosphane of general formula $[PtCl_2L(PPh_3)]$ (Scheme 6, L = Et_2NH (**5**), Bz_2NH (**6**), $(HOCH_2CH_2)_2NH$ (**7**), *N*-morpholine (**8**), $SOMe_2$ (**15**), $Et_2NC(Me)NH$ (**16**)), tested on three human tumor cell lines.[37,39] A significant inhibition of cell growth is induced by the complex characterized by a *trans* configuration and carrying a bis(2-hydroxyethyl)amine ligand coordinated to platinum (complex **7**, Table 1). Some structure–activity analyses allowed us to affirm that all the most biologically active complexes contain the *trans* isomer and a dialkylamine coordinated to the Pt (II) preferably presenting available hydroxyl groups (Table 1). The study of the mechanism responsible of cell death caused by the treatment with the most effective complex, suggested the occurrence of two different dose-dependent death pathways, the first occurring at 10–20 μM concentration and the second at higher concentration (30 μM). At lower concentration the complex acts as mitochondrial permeability transition inducer \\promoting collapse of mitochondrial transmembrane potential and swelling and, in part, as a protonophore inducing an alteration of the mitochondria membrane. At higher concentration the main effect is an aspecific membrane damage due to the formation of leaks that appeared dependent on thiols oxidation. This aspecific membrane permeabilization, independent from the mitochondrial permeability transition phenomenon could be ascribed to the high hydrophobic phosphine ligand.[39].

Following the interesting results observed in [39] and with the aim to expand the knowledge about structure–activity relationships, four complexes characterized by the maintenance of the *trans* dichloro(triphenylphosphane)platinum(II) scaffold and containing an aromatic residue on the secondary amines were prepared. The complexes showed the general structure *trans*-$[PtCl_2(PPh_3)\{NH(Bu)CH_2Ar\}]$ (Scheme 6, 9-12), where the dimension of the aromatic residue on the secondary amines varied as follows: Ar = Phenyl (**9**), 1-Naphthyl (**10**), 9-Anthracenyl (**11**), 2-Pyrenyl (**12**).[40] The investigation of the antiproliferative activity highlighted an interesting and comparable antiproliferative effect on human tumor cell lines, and on resistant cells. The GI_{50} values obtained for A2780 (ovarian cancer cells) and the counterpart A2780cis, resistant to cisplatin, are similar and, notably, for one complex the GI_{50} value in resistant cells is about halved with respect to that of cisplatin (Table 2).

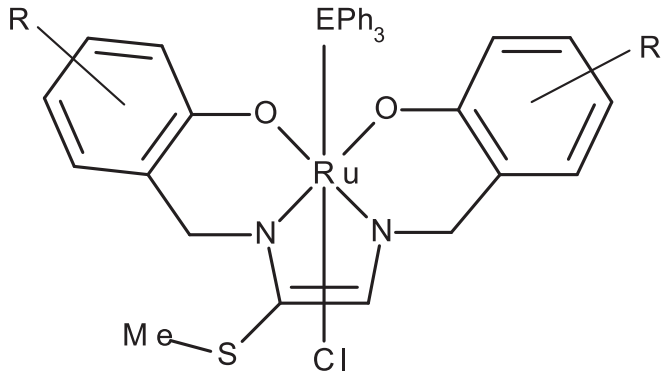
Flow cytometry analysis demonstrated in A2780cis the occurrence of the apoptotic process, and quantitative evaluation performed by ICP-AES technique indicated a binding capacity to DNA lower than cisplatin. The inhibition of the relaxation activity catalyzed by topoisomerase II, a nuclear enzyme involved in replication, transcription and chromosome segregation, suggested the enzyme as a further intracellular target. The role played by topoisomerase II on cisplatin resistance phenomenon [59–63] allowed to hypothesize that the inhibitory effect exerted by the complexes on the enzyme could be related to their ability to overcome resistance in A2780cis.[40].

The opportunity to overcome the plethora of complex events concurring to drug resistance encouraged the synthesis and the study of the biological properties of two new *trans*- triphenylphosphanedialkylamino Pt(II) complexes, strictly related to the most interesting complex described in [40], and characterized by the replacement of the chloride with bromide groups.[44] In this more recent paper the panorama of the possible targets of the Pt(II) complexes containing triphenylphosphane is further broadened. Interestingly, the cytotoxicity induced by both *trans*-$[PtBr_2(NHRR')(PPh_3)]$ complexes (Scheme 6, R = Bu, R'=Bz (**13**); R = R'=Bz (**14**)) on a panel of human tumor cell lines is comparable, like the effect on the resistant cell line, A2780cis, thus indicating a similar role for both substituents in the coordinated amine. Interestingly, the effect on resistant ovarian carcinoma cells, A2780cis, is comparable to that on the parent line A2780 and then a RF of about 1 was calculated for both **13** and **14**, while for cisplatin a value of about 7 was obtained (Table 2). The comparison with cisplatin demonstrated for **13** an IC_{50} value on the resistant cells about 3 times lower and a time-dependent and greater accumulation that after 3 h reaches a value about three times higher to that detected for cisplatin.

Otherwise, the reference drug appears able to bind to salmon testes DNA with greater efficiency, because an amount of Pt about ten times higher (about 800 ppb) with respect to that of **13** (about 80 ppb) is determined after 48 h of incubation. For the new complexes also a stronger dose-dependent mitochondrial membrane depolarization and increase in intracellular ROS production in resistant cells was observed. The overall redox imbalance appears related also to the intracellular thiol antioxidant system. In fact, in resistant cells a considerable decrease of total thiols was observed, along with a good inhibitory effect on thioredoxin reductase, one of the key enzymes participating to the modulation of the cellular antioxidant response. In comparison with cisplatin both **13** and **14** exhibited a remarkably higher inhibitory activity on both cytosolic and mitochondrial mammalian isoforms, especially evident on the cytosolic isoform, for which IC_{50} values in the low nanomolar range were obtained (2.27 nM and 2.59 nM for **13** and **14**, respectively), and one order of magnitude lower with respect to that calculated for cisplatin (22.5 nM). Interestingly, the absence of any effect on the enzyme from *Escherichia coli*, lacking the second active site containing the selenocysteine, pointed to the amino acid a suitable candidate for the site of inhibition. By considering the overall results obtained from the investigations on the mechanism of action of the two *trans*-dibromide-triphenylphosphanedialkylamino Pt(II) complexes, it is



Scheme 11. Features of *trans*-[$PtBr_2$(NHRR')(PPh_3)] complexes (Scheme 6, R = Bu, R'=Bz (**13**); R = R'=Bz (**14**)) and possible mechanisms of resistance overcome.



Scheme 12. Structure of Ru(III) isothiosemicarbazone complexes [RuCl(Eph_3)L^{1-4}] (E = P, As; H_2L^{1-4} = Bis(salicylaldehyde) S-methylisothiosemicarbazone (H_2L^1); Bis(5-chloro-salicylaldehyde) S-methylisothiosemicarbazone (H_2L^2); Bis (o-vanilin) S-methylisothiosemicarbazone (H_2L^3); Bis(2-hydroxynapthaldehyde) S-methylisothiosemicarbazone (H_2L^4)).[68].

assumed that the interesting effect, observed on resistant cells, could come from an enhanced intracellular accumulation, the low covalent interaction with DNA and from the involvement of multiple intracellular targets, that are, mitochondria and thioredoxin reductase [44], all having a significant impact on some recently defined hallmarks of cisplatin resistance (Scheme 11).[64].

In detail, the high cell uptake suggests the ability to overcome the mechanisms of resistance due to alterations in drug transport, like reduced uptake or increased efflux. The low covalent DNA interaction can allow the evasion of the mechanism of resistance involving increased DNA damage repair and can also ensure lower genotoxicity. The induced collapse of transmembrane mitochondrial potential (ΔΨ) could allow to overcome the mechanism of resistance involving evasion of apoptosis due to the stabilization of the outer mitochondrial membrane (like through the overexpression of Bcl-2 antiapoptotic proteins); moreover, it could promote mitochondrial ROS production. Finally, the inhibitory effect on thioredoxine reductase (TrxR) could induce a decrease in thioredoxin reduced form (Trx-SH) with a consequent release of the propapoptotic ASK1 kinase. [65] It is to note that the impairment in thioredoxine system can also contribute to the increase

Table 2
Antiproliferative effects of platinum(II) triphenylphosphane and triphenylarsane complexes on human ovarian carcinoma cell lines sensitive (A2780) and resistant to cisplatin (A2780cis).

Complex	GI_{50}/IC_{50} (μM) A2780	A2780cis
9[a]	3.55 ± 0.26	3.63 ± 0.21
10[a]	6.41 ± 0.65	5.91 ± 1.14
11[a]	7.97 ± 0.45	12.6 ± 1.1
12[a]	4.90 ± 0.75	6.95 ± 1.45
13[b]	2.19 ± 0.06	2.15 ± 0.19
14[b]	2.99 ± 0.19	3.45 ± 0.34
17[c]	0.49 ± 0.18	1.85 ± 0.16
18[c]	3.66 ± 1.36	6.62 ± 1.50
19[d]	0.94 ± 0.28	1.40 ± 0.06
20[d]	0.62 ± 0.12	2.73 ± 0.21
21[e]	0.31 ± 0.03	1.08 ± 0.41
22[e]	0.62 ± 0.16	1.43 ± 0.36
cisplatin[a]	0.91 ± 0.13	6.61 ± 0.61

GI_{50}/IC_{50} (μM) concentration of complex (μM) required for 50% inhibition of cell growth with respect to the control culture.
[a] taken from ref.[40].
[b] taken from ref.[44].
[c] taken from ref [45].
[d] taken from ref [47].
[e] taken from ref [48].

the intracellular ROS production, and high doses of ROS in cell have been linked to the activation of intracellular components of the apoptotic pathway. [66].

Bearing in mind the most interesting *trans*-triphenylphosphane Pt(II) complexes reported in [39] and [40], the design and the synthesis of two Pt(II) complexes characterized by the same coordination sphere of the metal, chloride ligands and dialkylamino residues, but the triphenylarsane as ligand, were performed (Scheme 6, 17 and 18).[45].

Previous data on the antiproliferative effect on tumor cells induced by metallodrugs containing a triphenylarsane ligand were quite scarce and the reports were mainly devoted to the role of other residues coordinated to the metal. [67–71] Ruthenium (II)/(III) complexes bearing 4-hydroxy-pyridine-2,6-dicarboxylic acid and PPh_3/$AsPh_3$ were synthesized and tested for DNA binding properties, antioxidant and antiproliferative effects. The cytotoxicity assayed on a panel of human

tumor cells highlighted Ru(II) complexes more effective on tumor cells than on healthy ones and Ru(III) endowed with remarkable radical scavenging activity. Regarding the role of triphenylphosphane and triphenylarsane ligands, almost comparable antioxidant activity was observed for both Ru(II) and Ru(III) complexes with similar structures, whilst the presence of the triphenylarsane appeared detrimental for the *in vitro* antiproliferative activity. [67] A similar effect was observed by comparing the cell growth inhibition of ruthenium complexes [Ru(HL)$(CH_3CN)(CO)(PPh_3)_2$] and [Ru(HL)$(CH_3CN)(CO)(AsPh_3)_2$], with (HL = 4-oxo-4*H*-pyran-2,6-dicarboxylic acid). Again, the phosphane analogue appeared more interesting from a biological point of view because, apart from a comparable intense interaction with DNA and antioxidant activities, the complex was clearly more potent than the corresponding arsane compound in inducing cell membrane damaging and cell death on human lung cancer cell line, A549. [68] Otherwise, a series of Ru(III) isothiosemicarbazone complexes [$RuCl(Eph_3)L^{1-4}$] (Scheme 12, E = P or As; H_2L^{1-4} = Bis(salicylaldehyde) S-methylisothiosemicarbazone (H_2L^1); Bis(5-chloro-salicylaldehyde) S-methylisothiosemicarbazone (H_2L^2); Bis(o-vanilin) S-methylisothiosemicarbazone (H_2L^3); Bis(2-hydroxynapthaldehyde) S-methylisothiosemicarbazone (H_2L^4)), obtained from the reactions between [$RuCl_3(Eph_3)_3$] and (H_2L^{1-4}) ligands, demonstrated an opposite behavior.

The presence of the triphenylarsane group induced the higher antioxidant activity and better activity in optimization binding studies, and for some of the complexes the anticancer activity on human breast cancer cell line MCF-7 revealed IC_{50} values notably lower than that calculated for cisplatin. [69] Moreover, the synthesis of palladium(II) complex [$Pd(AsPh_3)L$] containing 4-hydroxybenzoic acid (3-ethoxy-2-hydroxybenzylidene)hydrazide as ligand (H_2L), led to complexes exerting on HeLa and MCF-7 human tumor cells a cytotoxic effect significantly lower than cisplatin and, again, a biological profile inferior than the phosphane counterpart. [70] Similarly, ruthenium(III) thiosemicarbazone complexes of the type [$RuCl_2(Eph_3)L$] (where E = P/As; L = monobasic tridentate thiosemicarbazone ligand) resulted less effective than cisplatin on HeLa cells treated for 48 h. [71].

In this connection, the investigation on the biological properties of the two *trans*-dichloro(triphenylarsane)(*N,N*-dialkylamino)platinum(II) complexes reported in [45], opened a new scenario on the triphenylarsane complexes. The analogue carrying the *N*-butyl,*N*-benzylamino chains (Scheme 6, **17**) exerted on both sensitive and resistant ovarian carcinoma cell lines a notable antiproliferative effect, higher than cisplatin, with GI_{50} values about two and three times lower with respect to those obtained for the reference drug on A2780 and A2780cis, respectively (Table 2). The binding to salmon testes DNA is significantly lower than cisplatin, in detail, about 180 ppb of platinum after 48 h of incubation versus 800 ppb in the same experimental conditions. Otherwise, in cells incubated with **17**, it was observed an uptake significantly higher than that of cisplatin on both sensitive and resistant ovarian carcinoma cell lines. It was assumed that this ability resulted from the high lipophilicity of the complex. This property could enable a passive intake in the resistant cells, independent from any uptake mechanisms mediated by protein systems, whose impairment it is assumed may contribute to the occurrence of the resistance phenomenon. For **17** an inhibitory effect on topoisomerase II catalytic activity was also demonstrated and this ability is of particular interest given the upregulation of the enzyme in aggressive ovarian cancer and the correlation of the enzyme expression with tumor cell proliferation, migration and invasiveness. [72] Mitochondria seemed also a target for the antiproliferative effect induced by the triphenylarsane complex. Indeed, in resistant cells, a dose dependent increase in cell percentage showing mitochondria depolarization, paralleled by the increase of apoptotic cells, was demonstrated. [45] It is to note that cisplatin, even at a concentration 3 times higher than **17**, promotes a notably lower mitochondrial membrane depolarization, confirming that the intracellular organelles play a marginal role in the cytotoxicity induced by the drug. Overall, the differences in cell targets along with a significantly greater ability to enter in resistant ovarian carcinoma cells, underline the importance of complex **17** in view to obtain new chemical scaffolds able to overcome cisplatin resistance.

In an attempt to move towards nonconventional analogues of cisplatin, some interesting oxime-chelated Pt(II)-PPh_3 complexes, characterized by a naphthalene [$Pt(Cl)(PPh_3)\{(\kappa^2$-N,O)-(1{C(R) = N(OH)-2(O)$C_{10}H_6$})}] (Scheme 6, R = H (**19**), Me (**20**)) [47] or a benzene [$Pt(Cl)(PPh_3)\{(k^2$-N,O)-(1{C(R) = N(OH)-2(O)C_6H_4})}] (Scheme 6, R = H (**21**), Me (**22**)) [48] residue on the oxime ligand, were prepared and studied for the antiproliferative effect on both sensitive and resistant cell lines (Table 2). The two naphthyl containing analogues demonstrated a cytotoxicity comparable or slightly lower than cisplatin in sensitive cells and, interestingly, an antiproliferative effect significantly higher in resistant A2780cis cells.[47] A similar biological profile was observed when the naphthyl group was replaced by the smaller phenyl moiety. [48] The study of the mechanism of action of complex **21** revealed a scarce binding ability toward DNA, about five times lower than cisplatin, likely due to both the monohalogenated character of the complex and the presence of the bulky PPh_3 ligand. Otherwise, this lipophilic ligand may promote a large cell uptake in resistant cells, which results, after 3 h of incubation, in an amount (ppb) of Pt about 30 times higher than that measured in resistant cells treated with cisplatin. Moreover, **21** showed a more efficient compartmentalization in mitochondrion-enriched fraction than the reference drug, suggesting mitochondria as intracellular target. This hypothesis was supported by the strong dose-dependent mitochondria membrane depolarization induced by the oxime complex on resistant cells, significantly more pronounced than that induced by cisplatin.[48].

3. Conclusions

In the wide field of anticancer drugs, the metal-based complexes, cisplatin and related approved drugs, continued to play an undoubtable crucial role. Nevertheless, the side effects, in particular the occurrence of both acquired and intrinsic resistance, represent the more feared limiting factor to achieve success in anticancer treatments. The multifaced nature of resistance makes overcoming the phenomenon difficult, nevertheless, the development of non-conventional Pt-based drugs endowed with a different spectrum of biological targets, could represent an approach worth to be pursued. The platinum triphenylphosphane complexes reported in this minireview are accessible through a sound synthetic procedure which allowed, over the years, the building of a library of compounds containing different residues besides PPh_3. The antiproliferative properties shown by many of them and in particular, their biological effects on cisplatin resistant cells, would pave the way to devise novel therapeutic strategies aimed to face resistance phenomenon. In particular: *i)* incorporation of the most promising structures into suitable nanocarriers could enhance selectivity, aiding the complex to reach target tissues; *ii)* most promising complexes could be tested in combination with already assessed drugs to obtain synergistic effects; *iii)* the scaffold of most promising structures could be suitably modified to incorporate new coordination sites, to bind different metals. This modification would allow to synthesize new, dinuclear complexes containing two metal centers with complementary pharmacological properties.

Funding

This work was supported by Pisa University, Fondi di Ateneo 2022 and 2023 and by Padova University, Fondi di Ateneo 2022 and 2023.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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