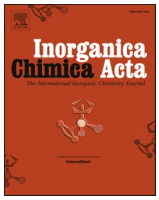
Inorganica Chimica Acta 548 (2023) 121388

Contents lists available at ScienceDirect

Inorganica Chimica Acta

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



An overview of recent advancements in anticancer Pt(IV) prodrugs: New smart drug combinations, activation and delivery strategies

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ARTICLE INFO

Keywords:
Platinum compounds
Platinum(IV) prodrugs
Anticancer agents
Cytotoxic compounds
Drug targeting

ABSTRACT

The discovery of the antineoplastic properties of cisplatin in 1965 by Rosenberg and co-workers, originated a renewed attraction for metal complexes for medicinal applications. Indeed, after its first outstanding clinical results, chemists involved in the metal complexes research field readily started to study safer and more effective alternatives to cisplatin itself. In this frame, after decades of intensive research mainly focused on classical Pt(II) compounds, also platinum(IV)-based compounds have been taken into account. The reason for this interest is that, despite the kinetic inertness of Pt(IV) compounds, they can undergo to "in-cell" reduction process which is able to activate the platinum centre through the generation of the more reactive Pt(II) counterpart. This kind of approach might offer some relevant advantages, such as the reduction of severe side effects associated with Pt(II) off-target reactions. Indeed, the lower redox potential of cancer cells with respect to the healthy ones is able to trigger the Pt(IV) reduction into the biologically active counterpart. In this review, we summarized the most recent goals achieved in the field of so-called Pt(IV) prodrugs.

1. Introduction

Since the serendipitous discovery of cisplatin in 1965 (Fig. 1) and its FDA approval for the treatment of testicular and ovarian cancer, the field of metal-based drugs gained increasing attention in the scientific community [1–3]. In particular, the unprecedented mechanism of action of cisplatin immediately spurred bioinorganic chemists to find new metal-based molecules capable to replicate its distinctive genomic binding properties [4]. Nowadays, cisplatin still represents a cornerstone of chemotherapy regimens, being employed in the treatment of many solid malignancies, such as testicular cancer, ovarian cancer, breast cancer, lung cancer and many others [5]. In this frame, the family of Pt(II) compounds was extensively investigated, with the aim of expanding the arsenal of metal-based compounds with anticancer properties. This labor-intensive research process was mainly justified by cisplatin's drawbacks that emerged over the years of clinical use [6]. However, during the last four decades only two other platinum-based drugs were approved worldwide (i.e., oxaliplatin and carboplatin, depicted in Fig. 1).

More in detail, oxaliplatin, which gained FDA approval in 2002, is nowadays employed as the first-line therapy in the treatment of colorectal cancer, usually in association with an antimetabolite drug such as the 5-fluorouracil [7,8]. On the other side, carboplatin, which received its approval by the FDA in 1989 with the commercial name Paraplatin®, was developed as an analogue of cisplatin with reduced nephrotoxicity and vomiting [9–11]. These drugs' commonly accepted mechanism of action involves their binding to purinic bases in the DNA, forming adducts that cause the distortion of the double-strand DNA, the DNA replication blockade and then the cellular apoptosis [12–18].

However, other interesting platinum derivatives were also approved in specific geographic areas. For example, compounds such as eptaplatin, lobaplatin and nedaplatin gained clinical approval in South Korea, China, and Japan respectively [18,19]. More in detail, eptaplatin (Fig. 2) has shown high antitumor activity against several cancer cell lines, including cisplatin-resistant ones [19]. Moreover, preliminary results suggested lower nephrotoxicity with respect to cisplatin [19–21]. Similarly, lobaplatin (Fig. 2) has a better toxicological profile, with a low incidence of vomiting and a 1-year survival percentage comparable with those of carboplatin [21]. Finally, nedaplatin (Fig. 2) showed lower systemic toxicity with respect to cisplatin, but it is only moderately successful in overcoming cisplatin resistance [19–21]. Other relevant platinum compounds are currently undergoing clinical trials. For

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https://doi.org/10.1016/j.ica.2023.121388
Received 1 December 2022; Received in revised form 9 January 2023; Accepted 11 January 2023
Available online 13 January 2023

example, picoplatin (Fig. 2) demonstrated activity in a variety of solid tumours, including lung, ovarian, colorectal, and hormone-refractory prostate cancer [18]. Despite its encouraging results in phase I and phase II clinical trials, picoplatin failed to hit its primary endpoint for advanced small-cell lung cancer in phase III clinical trials [22].

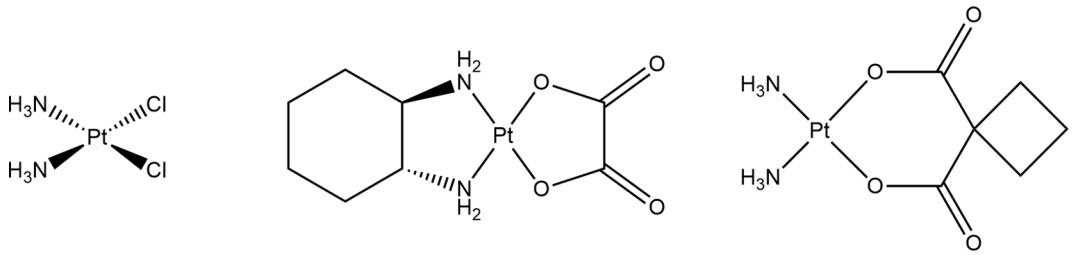
Despite their drawbacks, Pt-based compounds are still present in about 80% of the clinical protocols. Nonetheless, their use is often responsible for the insurgence of several undesired side effects [12,23] due to a lack of selectivity toward cancer cells [24–27]. Among the most common side effects there are, for example, ototoxicity and nephrotoxicity [28,29]. Moreover, cancer cells can develop resistance to these drugs [30,31]. A decreased cellular uptake of the drug, an increased drug efflux, the development of DNA repairing systems, detoxification systems or resistance to apoptosis are some of the mechanisms that cancer cells have developed to acquire resistance to these drugs [16–18,24–27,32–36]. In order to overcome these limitations, researchers have focused their attention on studying Pt(IV) complexes. This new class of Pt-based drugs possesses several advantages over their Pt(II) counterparts [33]. For instance, being more resistant to hydrolysis by gastric juices, they can be orally administrated, thus improving the patient's compliance and making treatment with these drugs much easier [17,37–39]. Furthermore, because of their improved chemical inertness, they show slower ligand substitution and thus, upon administration, they undergo fewer off-target reactions with biomolecules outside cancer cells, which increase the amount of active drug that can reach the target [17,33,38,40–46]. This behavior has been thought to be a useful characteristic for mitigating the unwanted side effects often associated with platinum(II) drugs [17,33,38,39,47–50]. The Pt(IV)-based complexes, indeed, remain substantially unreactive towards biomolecules until they are internalized inside the cancer cell, where they find the right environmental conditions able to trigger their reduction to the respective Pt(II) counterpart (which binds to the DNA), thus restoring the original reactivity [17,33,41,43–46,49–55]. In addition, during this reduction process, the octahedral platinum(IV) complex releases its axial ligands which, in turn, may exert additional pharmacological actions (Scheme 1) [17,33,41,43–46,49–55]. This mechanism is possible because the levels of cellular reductants (e.g. glutathione or thioredoxin) are enhanced in tumor cells to cope with the increased oxidative stress caused by the reactive oxygen species (ROS) overproduction, thus creating a reducing environment [56]. It is widely accepted that glutathione (γ-glutamylcysteinylglycine, GSH) and ascorbic acid are the main bio-reductants responsible for the activation of the Pt(IV) prodrugs to their corresponding Pt(II) analogue [51,55,57–60]. However, there are also other cellular reducing agents, such as cytochrome *c* and the thiol groups of proteins and, in addition, some Pt(IV) prodrugs specifically designed for this purpose can also be activated through photoexcitation [17,45,61–68]. Regarding the structure, the equatorial ligands of the Pt(IV) complexes are mainly responsible for the activity of the derived Pt(II) drugs, while the axial ligands are mostly accountable for the lipophilicity, stability and redox properties of the complex [42,49,69–71]. These properties are very important for the activity of these drugs, as the lipophilicity determines the amount of compound that will enter the tumor cells by passive diffusion, whereas the redox features influence the ease of reduction in the hypoxic tumor environment [70,71].

Several Pt(IV) complexes have been synthesized over the years but, so far, ormaplatin (or tetraplatin), LA-12, iproplatin and satraplatin (Fig. 3) are the only Pt(IV) complexes that have entered into clinical trials.

Among these, satraplatin, which showed a better pharmacological profile with respect to cisplatin, was the most promising one and it progressed to the third phase of the clinical studies, where it was tested against metastatic prostate cancer [18,33,40,41,54,72]. More precisely, it offers a toxicity profile without nephrotoxicity, neurotoxicity, or ototoxicity issues [73]. However, it also possesses some downsides, such as its lack of tumor specificity, due to its premature activation (through reduction) in the red blood cells [62,74]. Moreover, it doesn't significantly improve the overall survival rate compared to traditional platinum compounds [48,75,76].

As already said, redox features are of particular importance when designing Pt(IV) complexes, as the reduction step is fundamental for these complexes to exert their anticancer activity. However, the ease of reduction does not always enhance their activity. For instance, as in the case of satraplatin, the low reduction potential of tetraplatin causes its reduction in the blood prior to cell uptake, thus decreasing its effectiveness as prodrug [49,77]. At the same time, a difficult reduction does not necessarily hamper biological activity either. As a matter of fact, although iproplatin is mostly excreted unchanged through urine, the detection of some of its Pt(II) metabolites proves that its reduction can still occur [42,49,78]. The understanding of the above-mentioned Pt(IV) reductive activation process opened the way to a wide choice of biologically-active axial ligands. Indeed, as mentioned above, after the intracellular reduction step these ligands can be released in the cytosol acting, at least in principle, as a additional drug molecules with the possibility of synergistic effects with the Pt(II) complex. This concept is nowadays exploited in the design of new Pt(IV)-based "combo drug" candidates [79]. For example, interesting results have been obtained with the conjugation of approved platinum compound skeletons with valproic acid, being this latter an extensively studied drug for its histone deacetylase inhibitory activity [80–82]. Anyway, when Pt(IV) derivatives are conjugated with large organic moieties, a relevant water solubility reduction can be observed. In these cases, hydrophilic nanoformulations could be used as biologically-compatible drug carriers, improving both the solubility and biodistribution of the active molecule [83,84]. Interestingly, the nanoparticle's external surface can be further decorated with peptidic sequences or monoclonal antibodies able to selectively target specific cancer cells and, thus, become a very powerful tool for anticancer targeting strategy in personalised medicine [85].

This review summarized the most recent progress made in the field of Pt(IV) complexes. In general, having six ligands around the Pt core, many Pt(IV) prodrugs with different substituents can be synthesized. Moreover, over the years several strategies have been developed for the functionalization of the axial positions of Pt(IV) complexes. Numerous compounds bearing either a carboxylic, an amine or a hydroxy moiety

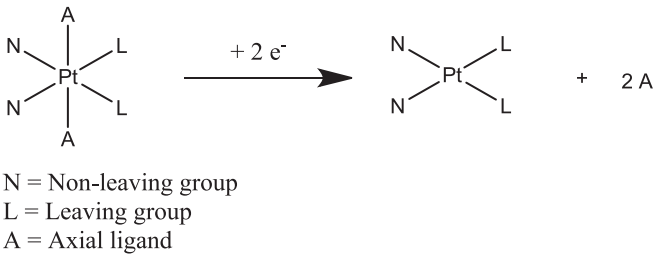


cisplatin oxaliplatin carboplatin

Fig. 1. Molecular structures of cisplatin, oxaliplatin and carboplatin, respectively.

have been tethered to the Pt center. However, other groups, such as thiols, have also been linked to the axial position thanks to coupling reagents such as N,N'-disuccinimidyl carbonate (DSC) [17,86]. For this reason, a high number of these complexes is reported in the literature. In this frame, we have decided to consider only those with high activity and that we consider particularly promising. In detail, we will discuss the categories of compounds described below (Fig. 4).

- Pt(IV) complexes functionalized with drugs commonly used in clinical practice (e.g., non-steroidal anti-inflammatory drugs, NSAIDs) (paragraph 2). This will not only provide insights into some of the most commonly employed synthetic strategies for the synthesis of Pt (IV) drugs, but it will also provide an overview of some of the most well-known complexes already synthesized in literature.
- Pt(IV) complexes functionalized with molecules with high anticancer activity (e.g., tubulin polymerization inhibitors) (paragraph 3). This will provide some examples of Pt(IV) complexes bearing other anticancer drugs. Indeed, this strategy has been exploited for obtaining new complexes with improved anticancer activity. Moreover, with respect to the previously described drugs, these complexes target both DNA and tubulin.
- Pt(IV) complexes functionalized with analogues of micronutrients normally present in the human body (e.g., α-tocopherol succinate, α-TOS) (paragraph 4). These complexes represent another example of dual-targeting compounds, which exert their anticancer action by targeting both DNA and mitochondria. Moreover, these complexes might push to take into account other classes of molecules when designing new Pt(IV) complexes.
- Delivery strategies for Pt(IV) complexes (paragraph 5). This will provide some examples of different approaches through which Pt(IV) complexes can exert their anticancer action. Indeed, drugs with improved tumor-targeting abilities benefit not only from an enhancement of their anticancer activity, but also from a reduction of their side effects.
- Photoactivatable Pt(IV) complexes will also be discussed (paragraph 6), thus providing an example of a different mechanism of activation for these prodrugs, besides the ones already discussed in this paragraph. This strategy is particularly interesting because it focuses not only on improving the activity of Pt drugs, but also on reducing their side effects through a selective activation at the tumour site.



Scheme 1. Representation of Pt(IV) intracellular reduction mechanism.

2. Pt(IV) complexes functionalized with NSAIDs in the axial position

2.1. A brief overview of the first NSAID to be linked in a Pt(IV) complex (Aspirin)

One of the hallmarks of cancer is inflammation which, when chronic, can promote tumor development [87]. Cyclooxygenase (COX) (which includes two isoforms, COX-1 and COX-2) is an important enzyme involved in the generation of inflammation [88]. COX-1 is normally expressed in most tissues, whereas COX-2 levels are usually very low [89,90]. However, the level of this second isoform is enhanced in inflamed sites and also in tumor tissues [91]. Moreover, COX-1 and COX-2 promote tumorigenesis and tumor cell resistance against platinum-based drugs [92–94].

NSAIDs, such as Aspirin, ibuprofen and indomethacin, are a class of drugs capable of inhibiting COX-2 [92–94] and it has been reported that colorectal cancer can be prevented by the inhibition of COX enzymes by Aspirin and other NSAIDs [91]. Moreover, it has been confirmed that some NSAIDs are able to decrease the side effects of cisplatin and increase its chemotherapeutic efficacy [95–100]. For all these reasons, NSAIDs have been proposed as anticancer agents and tested as axial substituents in some Pt(IV) complexes [101–103].

In this frame, many Pt(IV) complexes bearing NSAIDs have been synthesized over the years, the first one being asplatin (or platin-A), a prodrug of cisplatin bearing one molecule of acetylsalicylic acid in the axial position (complex **I**, Fig. 5) [104,105]. It is synthesized by acylating oxoplatin with the corresponding anhydride of Aspirin (Scheme 2) [104].

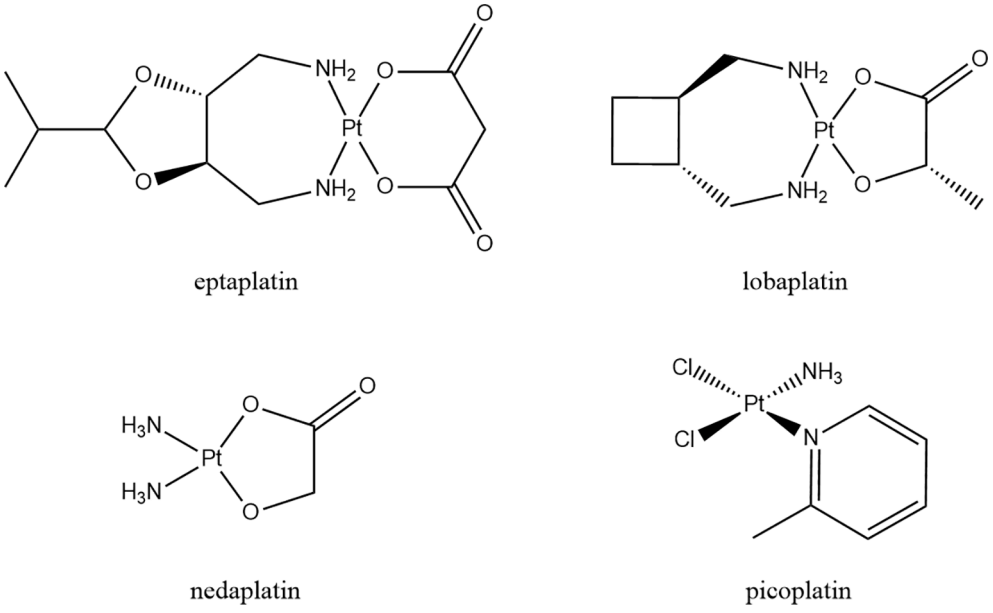


Fig. 2. Structures of eptaplatin, lobaplatin, nedaplatin, and picoplatin respectively.

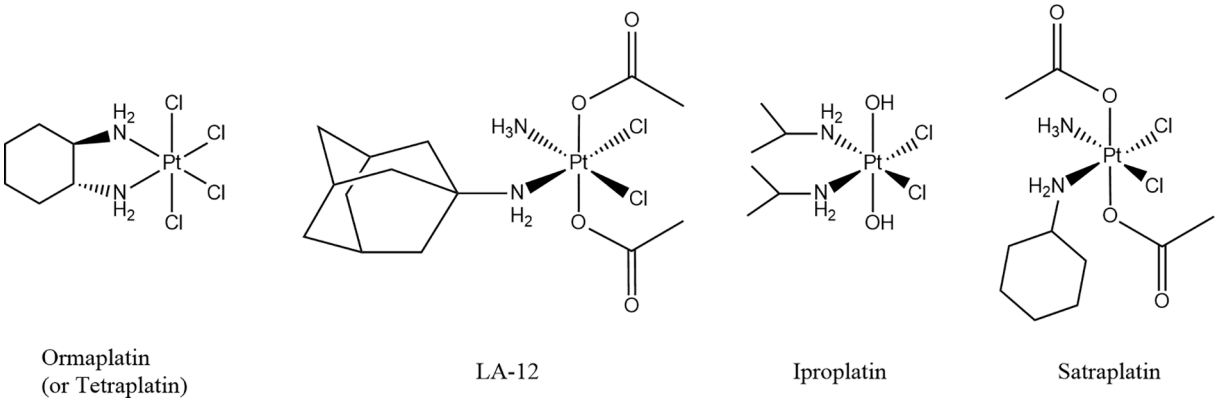


Fig. 3. Pt(IV) complexes that have entered clinical trials.

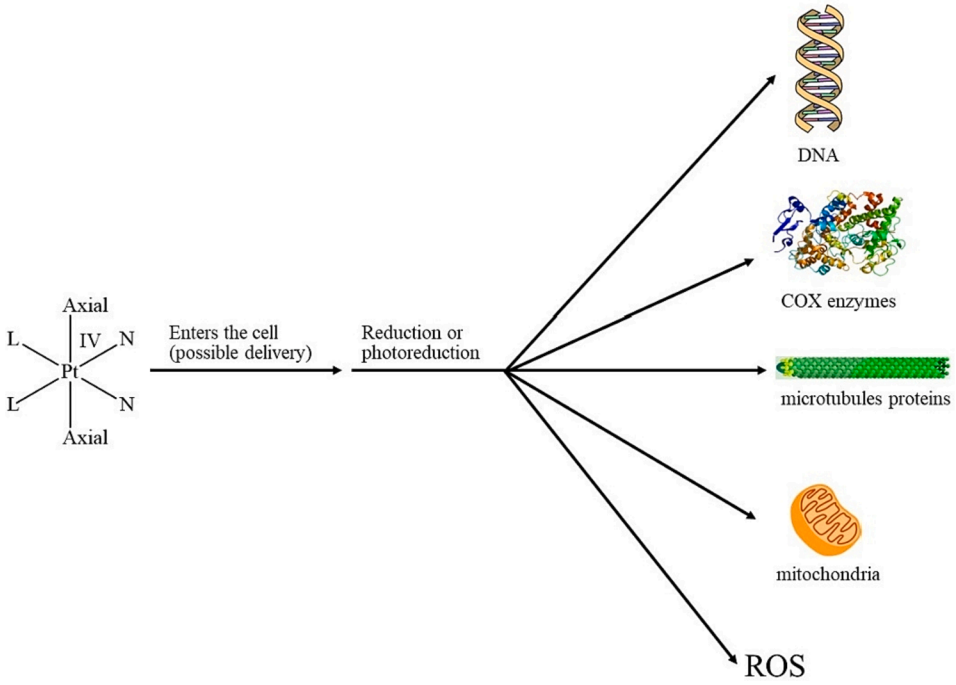


Fig. 4. Some of the strategies examined in this review.

Its cytotoxicity is superior to that of cisplatin in A549 (human lung carcinoma), MCF-7 (human breast carcinoma), Hep G2 (human liver carcinoma) cell lines, and in the cisplatin-resistant A549R cancer cell line [105]. This increased cytotoxicity has been explained as a result of a synergistic effect between the Pt(II) drug and the axial ligand. Moreover, Aspirin seems to be able to sensitize cancer cells to cisplatin and its ligation enhances the lipophilicity of the complex with regard to the corresponding Pt(II) drug, which grants higher uptake levels from cancer cells [104,105].

2.2. A report about recently synthesized Pt(IV) complexes with NSAIDs as axial ligands

After Aspirin, also ibuprofen and indomethacin have been linked to the axial positions of both cisplatin and oxaliplatin (complexes **II**, **III**, **IV**, and **V**, Fig. 5) [106,107].

These complexes were tested for their activity against HCT-116 (human colon carcinoma; no expression of COX enzymes) and MDA-MB-231 (human breast adenocarcinoma; high expression of COX enzymes) cancer cell lines. Results showed that the indomethacin derivatives (**II** and **IV**) are less cytotoxic than the ibuprofen ones (**III** and **V**) against these cell lines. Being indomethacin a stronger COX inhibitor, the authors concluded that there is no correlation between the ability of the axial ligands to inhibit COX-2 and the cytotoxicity of these resulting complexes. In contrast, it was suggested that their higher cytotoxicity could derive from their enhanced cellular accumulation, which is a consequence of their improved lipophilicity, with regard to the corresponding Pt(II) drug [107]. Noteworthy, prodrugs **II** and **III** are also more cytotoxic than cisplatin on HCT-116, OVCAR3 (human ovary adenocarcinoma), MDA-MB-231 and 1483 HNSCC (head and neck squamous cell carcinoma cell line) cell lines [106].

Further studies elucidated that complexes **III** and **V** are not able to inhibit neither COX-1 nor COX-2, whereas complexes **II** and **IV** are potent COX inhibitors, despite having different selectivity for the two enzymes. In particular, complex **II** has high selectivity for COX-2, whereas complex **IV** is able to bind only to COX-1, showing no activity against COX-2. The incapability of complex **IV** to bind to COX-2 was explained to be due to the bulky oxaliplatin equatorial ligands, which prevented it from entering the active site of the enzyme. On the contrary, complex **II** is COX-2 selective thanks to the additional interactions of the

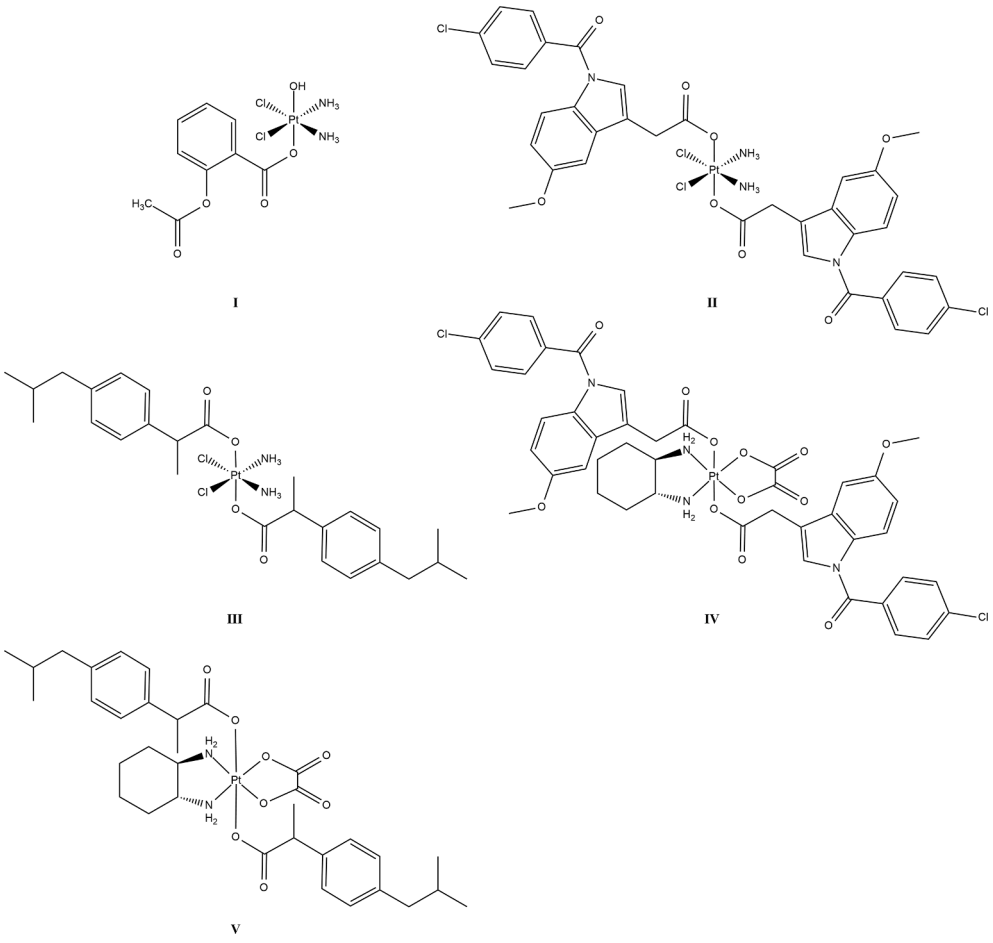
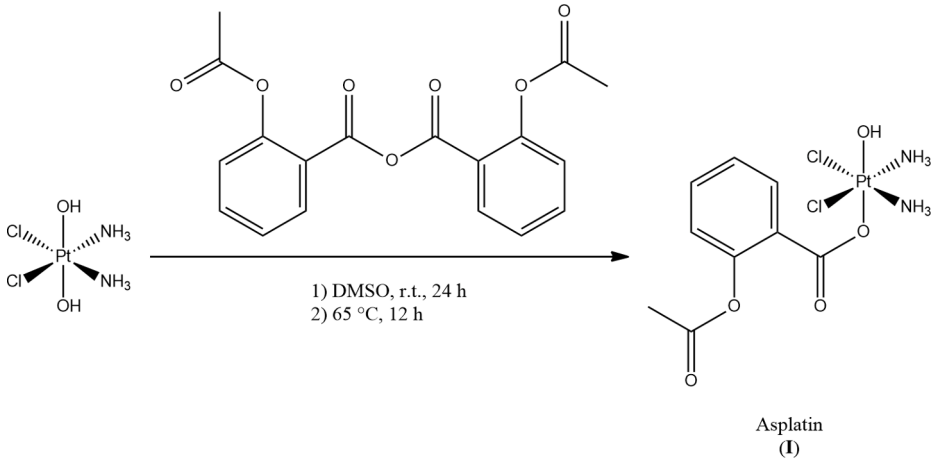


Fig. 5. Molecular structures of complexes **I**-**V**.



Scheme 2. Synthesis of asplatin (complex **I**) [104].

second indomethacin with the enzyme [106,107].

Another NSAID that was exploited in this field is ibuprofen, which was linked to the axial position of kiteplatin (complex **VI**, Fig. 6).

The complex was synthesized by making ibuprofen acyl chloride react with *cis,trans,cis*-[$PtCl_2(OH)_2$(*cis*-1,4-DACH)] in acetone in the presence of pyridine in the dark at 75 °C for 48 h (Scheme 3) [108].

The reduction potential of complex **VI** was reported to be suitable to ensure its stability during its circulation in the body and to enable its reduction, and consequent release of the bioactive molecules, in cancer cells [108]. Prodrug **VI** is more potent than both kiteplatin and cisplatin on HCT-116 and HCT-15 (human colon adenocarcinoma) cancer cell lines, probably because of its improved lipophilicity (bestowed by the ibuprofen ligands), which could ultimately result in an enhancement of its cellular uptake and accumulation in cancer cells [108].

Another NSAIDs that was exploited in this field is flurbiprofen, which was linked to cisplatin (complex **VII**, Fig. 6) by Tan et al. [103]. The cytotoxicity of this complex is superior in all tested cancer cell lines (even in the cisplatin-resistant ones) with regard to the corresponding Pt

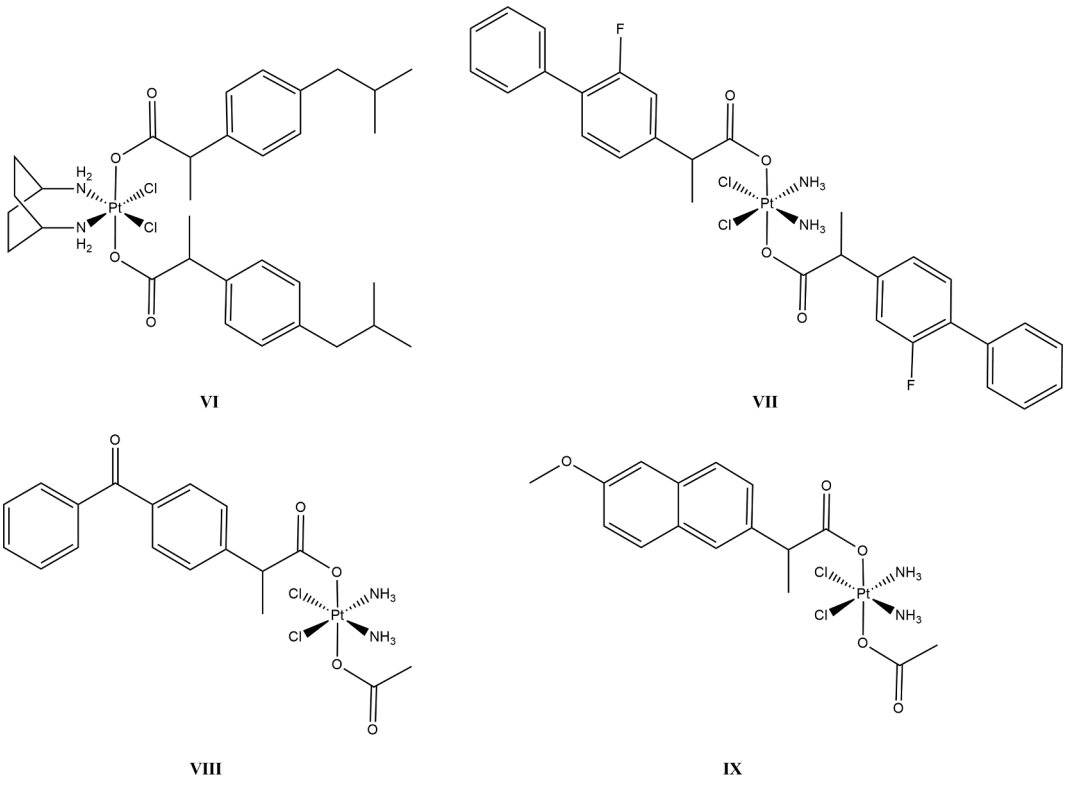
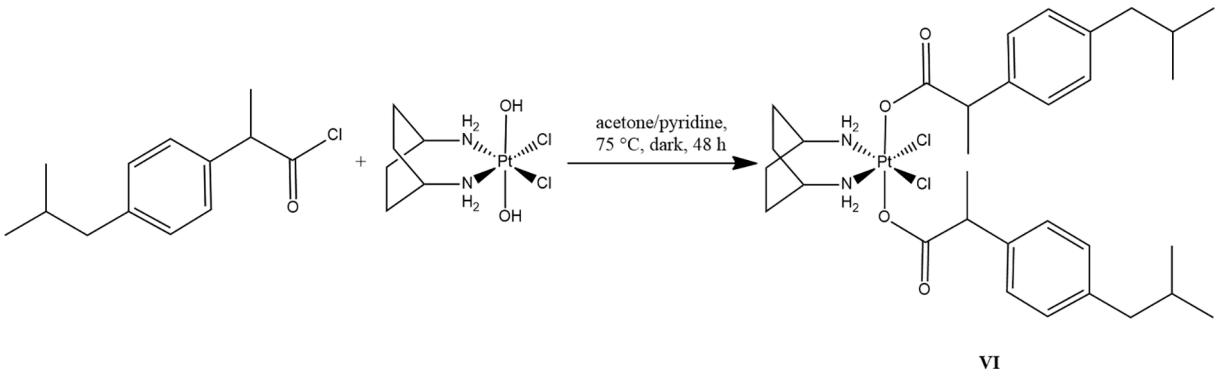


Fig. 6. Molecular structures of complexes **VI-IX**.



Scheme 3. Synthetic route for complex **VI** [108].

(II) drug and a mixture of cisplatin and flurbiprofen (Table 1) [103].

In cellular uptake experiments performed on BEL7404 (human liver cancer cell line), BEL7404-CP20 (the analogue cisplatin-resistant cell line), and SW480 (human colon cancer cell line) cancer cell lines, complex **VII** exhibited a higher cellular uptake than both cisplatin and a mixture of cisplatin and flurbiprofen. Moreover, the amount of platinum coordinated with the DNA was found to be higher in the case of complex **VII** than for cisplatin and a mixture of cisplatin and flurbiprofen [103].

The improved cellular uptake, cytotoxicity and ability to induce apoptosis of complex **VII** have been explained by the ability of this

Table 1
IC_{50} values (μM) of complex **VII** on different cancer cell lines in comparison with cisplatin, flurbiprofen and their mixture (data retrieved from [103]).

Compound	IC_{50}						
	SW480	PC-3	PANC-1	A549	A549-DDP	BEL7404	BEL7404-CP20
cisplatin	49.2 ± 1.1	21.2 ± 1.1	14.4 ± 1.1	7.4 ± 1.0	20.3 ± 1.1	14.7 ± 1.1	>50
Mixture of cisplatin and flurbiprofen	29.6 ± 1.0	22.4 ± 1.1	11.1 ± 1.1	7.1 ± 1.0	21.1 ± 1.2	18.1 ± 1.0	>50
VII	0.6 ± 1.1	3.4 ± 1.0	3.4 ± 1.1	2.7 ± 1.1	2.5 ± 1.1	1.4 ± 1.1	3.1 ± 1.1
flurbiprofen	48.8 ± 1.1	>50	>50	>50	>50	>50	>50

complex to auto-assemble in carrier-free nanoparticles in aqueous solution. These nanoparticles form spontaneously and make account for the enhanced level of platinum in cells treated with this prodrug compared to cells treated with cisplatin and the mixture of cisplatin/flurbiprofen. Moreover, this prodrug was reported to have a suitable reduction potential to allow its reduction in the cellular environment, releasing the flurbiprofen and cisplatin molecules. In light of this, the authors' proposed mechanism of action for this prodrug is illustrated in Scheme 4 [103].

Two other NSAIDs, namely ketoprofen and naproxen, have also been tethered to cisplatin, thus forming complexes **VIII** and **IX** (Fig. 6) [94,109,110]. These complexes were tested for their activity on A-549, HT-29 (human colon adenocarcinoma), HCT-116, SW480, A2780 (human ovarian endometrioid adenocarcinoma), and MSTO-211H (human lung biphasic mesothelioma, a highly chemo-resistant tumor) cancer cell lines [109]. Complex **IX** is more cytotoxic than complex **VIII** in almost all the tested cell lines, but both of them are more active than cisplatin, oxaliplatin and complex **I** in all cell lines ranging from 2 to 24 times. Interestingly, the activity of complexes **VIII** and **IX** don't correspond to the expression of COX-2 in the cell lines. For instance, HCT-116 and SW480 cancer cell lines, although being characterized by a lower expression of COX-2 with regard to HT-29, are more sensitive to the treatment with prodrugs **VIII** and **IX**. Given these findings, the authors concluded that the antiproliferative activity of these prodrugs is more likely related to their lipophilicity (which affects their cellular accumulation) rather than to the expression of COX-2 in the cell lines. Indeed, complex **IX**, the most lipophilic compound tested, is the most cytotoxic, while cisplatin, the least lipophilic in the panel, is the least active in almost all the cell lines (Table 2) [109,111].

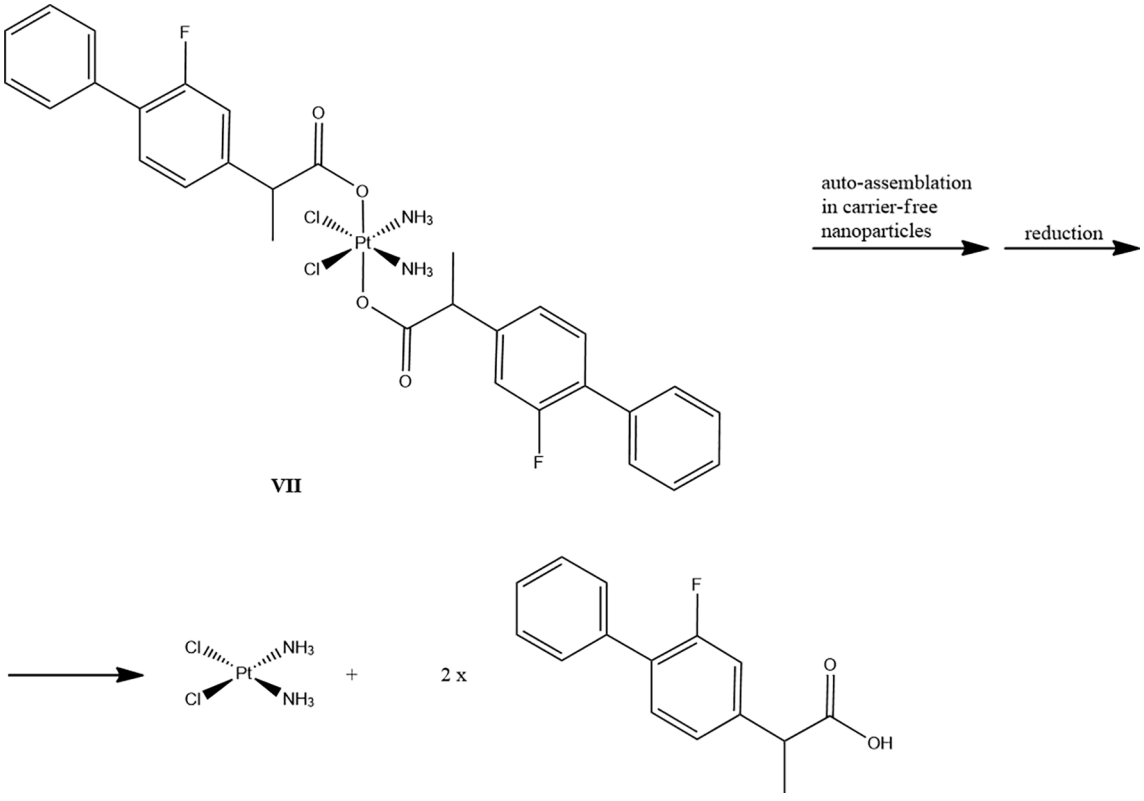
Given that no relationship was found between the activity of prodrugs **VIII** and **IX** and COX-2 expression in the cancer cells, the authors suggested that their mechanism of action is independent from this enzyme and, instead, they proposed it to consist in the activation of NAG-1 (NSAID activated gene) [109]. NAG-1 is a protein with antitumorigenic and pro-apoptotic activity which was recently proved to be involved in the antiproliferative activity of NSAIDs [112–115]. Indeed, NSAIDs induce NAG-1 expression both in COX-expressing and non-COX-expressing cells [116–119]. In particular, the authors suggested that cisplatin, released after the reduction of these complexes, is the main responsible for the anticancer activity of prodrugs **VIII** and **IX.** However, to the cytotoxicity also concurs the activation of NAG-1 due to the released NSAIDs. This was proved by the finding that complexes **VIII** and **IX**, as well as free ketoprofen and naproxen (although more slightly), enhance the expression of NAG-1 on A-549 and HCT-116 cell lines. However, a part of this enhancement was also due to cisplatin [109].

3. Pt(IV) complexes functionalized with tubulin-targeting agents

3.1. The anticancer mechanism of tubulin-targeting agents

Polymerization of heterodimers of α- and β-tubulins generate microtubule proteins, which exert important functions in cell replication, intracellular transport and migration [120–122]. Their disruption can induce cell cycle arrest in the G2/M phase and the development of anomalous mitotic spindles. Given the high importance of microtubules in mitosis and cell division, they became an interesting target for chemotherapy [123–126]. Indeed, several natural compounds exert their activity by targeting tubulin, thus causing the aforementioned cell cycle arrest and formation of abnormal mitotic spindles [126]. Based on their mechanism of action, these drugs are divided into two classes: (a) microtubule destabilizing agents, such as vinca alkaloids (e. g. vinblastine, vincristine and similar molecules), *cis*-stilbene combretastatin A4 (CA4), and colchicine; (b) microtubule stabilizing agents such as the taxanes (e. g. paclitaxel and docetaxel) [127–129].

Nowadays inhibitors of tubulin polymerization are employed in clinic as anti-mitotic agents [130,131], however, their toxicity has



Scheme 4. Mechanism of action of complex **VII**, as proposed by the authors [103].

Table 2
Lipophilicity (log k') and IC_{50} (μM) values of complexes **VIII** and **IX** on different cancer cell lines in comparison with cisplatin, oxaliplatin, aspirin, ketoprofen, naproxen and asplatin (complex **I**). Numbers in parentheses represent the ratios between the IC_{50} of cisplatin and the IC_{50} of the corresponding Pt(IV) complex (data retrieved from [109]).

Compound	log k'	IC_{50}					
		A-549	**HT-29**	**HCT 116**	**MST0-211H**	**SW480**	**A2780**
cisplatin	−0.50	3.60 ± 0.90	2.72 ± 0.39	3.05 ± 0.28	1.33 ± 0.35	2.27 ± 0.12	0.460 ± 0.110
oxaliplatin	−0.28	0.74 ± 0.25	0.92 ± 0.08	1.16 ± 0.09	1.01 ± 0.55	0.48 ± 0.02	0.171 ± 0.008
aspirin	−0.08	1672 ± 152	2835 ± 885	2578 ± 772	639 ± 374	1607 ± 386	1597 ± 455
ketoprofen	0.40	725 ± 69	828 ± 229	984 ± 179	518 ± 296	830 ± 173	676 ± 36
naproxen	0.50	701 ± 28	764 ± 158	640 ± 91	427 ± 159	927 ± 257	353 ± 64
asplatin (I)	−0.32	6.4 ± 2.7	4.42 ± 0.21	1.50 ± 0.083	1.74 ± 0.21	0.217 ± 0.07	0.552 ± 0.123
		(0.56)	(0.62)	(2.0)	(0.75)	(1.1)	(0.83)
III	0.14	0.825 ± 0.388	0.486 ± 0.235	0.184 ± 0.088	0.198 ± 0.035	0.0948 ± 0.023	0.063 ± 0.033
		(4.4)	(5.6)	(17)	(6.7)	(24)	(7.3)
IX	0.18	0.486 ± 0.075	0.313 ± 0.186	0.149 ± 0.076	0.161 ± 0.040	0.0844 ± 0.0287	0.045 ± 0.016
		(7.4)	(8.7)	(20)	(8.3)	(27)	(10)

restricted their clinical application [132]. In order to improve the therapeutic efficacy of these drugs, researchers have combined these molecules with platinum agents [132]. Indeed, the resulting bioconjugates could potentially target both DNA and tubulin, overcoming the drawbacks and the side effects of both single drugs [132,133].

3.2. New Pt(IV) complexes bearing tubulin polymerization inhibitors in the axial position

In this frame, among the inhibitors of tubulin polymerization, there is CA4 (Fig. 7), an antimitotic, antiproliferative and antiangiogenic agent [134–139]. Indeed, by binding to the β-subunit of tubulin, CA4 prevents the cell's production of microtubules, which are crucial for cytoskeleton formation [140,141]. Its potency has been evaluated on A2780 (ovarian cancer), A2780R (the cisplatin-resistant variant), A375 (human skin malignant melanoma), PC9 (human lung adenocarcinoma), HT-29, MCF-7, MDA-MB-231, and SK-HEP-1 (human liver adenocarcinoma) cancer models, and it was proved to be 1000-fold more cytotoxic than cisplatin, with IC_{50} values in the nanomolar range [43].

Pt(IV) complexes bearing CA4 in the axial position had already been reported before (complexes **X**, **XI**, and **XII**, Fig. 7) but, since CA4 does not possess a carboxylate that could be directly linked to the Pt core, linkers such as carboxylate were attached to it, thus producing a molecule that can be tethered to the OH of Pt(IV) complexes [43,142–144]. However, due to the stability of the bonds between the linker and CA4, the linker remains tethered to CA4 after reduction occurs. This means that such complexes don't release the original CA4 but rather a conjugate CA4-linker [43].

In order to overcome these drawbacks, Schmidt and co-workers recently reported on the synthesis of a panel of complexes based on cisplatin with this antimitotic drug in the axial position (complexes **XIII**, **XIV**, **XV**, **XVI**, **XVII**, **XVIII**, **XIX**, and **XX**, Fig. 7) [43].

Differently from the previously synthesized complexes, in these prodrugs CA4 is bound to the Pt core through a carbonate linker. This way, upon reduction, the carbonate linker is released as CO_2, thus freeing CA4 in its unaltered form [43]. As for the other axial position, it was functionalized with different molecules, all of which were shown to have a synergistic effect in combination with cisplatin: phenylbutyrate (PhB) and valproate (Val) (two histone deacetylase inhibitors), dichloroacetate (DCA) (a pyruvate dehydrogenase kinase inhibitor) and octanoate (Oct) (a molecule that increases DNA methylation) (Fig. 7) [43,111,145–147].

Complexes **XIII**–**XVIII** were synthesized as summarized in Scheme 5 [43]:

First, the hydroxyl moiety of CA4 was activated by making it react with N,N′-disuccinimidyl carbonate (DSC) in the presence of N,N-dimethylpyridine-4-amine (DMAP), obtaining the CA4–DSC derivative. Subsequently, it was reacted with oxoplatin, thus obtaining compound **XIII**, which was exploited to synthesize compounds **XIV**–**XVIII** by making it react with the corresponding anhydride of the desired bioactive molecule.

As for complexes **XIX** and **XX**, they have the CA4 moiety tethered through a glutarate [43]. These two complexes were synthesized following the observation that 3′-OH group of the B-ring of CA4 is not strictly necessary for its interaction with tubulin and that analogues of CA4 with modifications of the OH still exert good cytotoxicity [148].

These complexes were tested for their activity on A2780, A2780R, A375, PC9, HT-29, MCF-7, MDA-MB-231, SK-HEP-1, and RC-124 (human kidney cell line) cell lines. All Pt(IV)-CA4 complexes have IC_{50} values in the low nM range (<10 nM) for all the tested lines (except in HT-29) (Table 3). According to the authors, the improved cytotoxicity of these compounds with regard to cisplatin might be partly explained by their superior cellular accumulation. Indeed, the levels of platinum accumulation of Pt(IV)-CA4 complexes in MDA-MB-231 cells were proved to be from 1.9 to 6.3-fold higher than that of cisplatin [43]. Noteworthy, 1:1 and 2:1 mixtures of CA4 and cisplatin exhibit IC_{50} values similar to that of CA4 alone; this observation opened the discussion on the contribution of cisplatin to the overall activity of these molecules (Table 3) [43].

In *in vivo* studies, on the murine Lewis lung carcinoma (LLC) solid tumor model, complex **XIII** caused a reduction of the tumor weight similar to that of cisplatin (84%) and of a mixture of cisplatin, CA4, and PhB (85%), while complexes **XIV** and **XX** induced a reduction of the tumor mass of 91.5% and 92.6%, respectively (Fig. 8). According to the authors, the higher activity of complex **XIV** compared with complex **XIII** might be explained by the fact that prodrugs with just one bioactive axial ligand are reduced faster than those having two bioactive ligands. Indeed, the rate of reduction of compound **XIII**, measured by HPLC in phosphate buffer with ascorbic acid as the reducing agent, is 9 min, whereas for complex **XIV** it is 210 min. The fast reduction rate of complex **XIII** has been explained as a consequence of the ease of the electron transfer from the reducing agent to the Pt core. However, the authors also suggested that this difference could be explained by taking into account the ability of PhB-bearing complexes to interact in a non-covalent manner with serum albumin through the organic moiety. Indeed, this interaction might render these compounds more stable and bioavailable [43]. These observations, together with the finding that all Pt(IV) complexes are less toxic than cisplatin and a mixture of cisplatin, CA4, and PhB, led the authors to the conclusion that the conjugation of CA4 to the Pt core enhanced the *in vivo* activity of the compounds (Fig. 8) [43].

However, since the cytotoxicity of Pt(IV)-CA4 compounds is very similar to that of CA4, the authors concluded that the small amount of cisplatin released in the cancer cells from these prodrugs doesn't play a crucial role in their cytotoxicity. Contrary, they propose that the main role of the platinum moiety is that of a carrier which is activated by

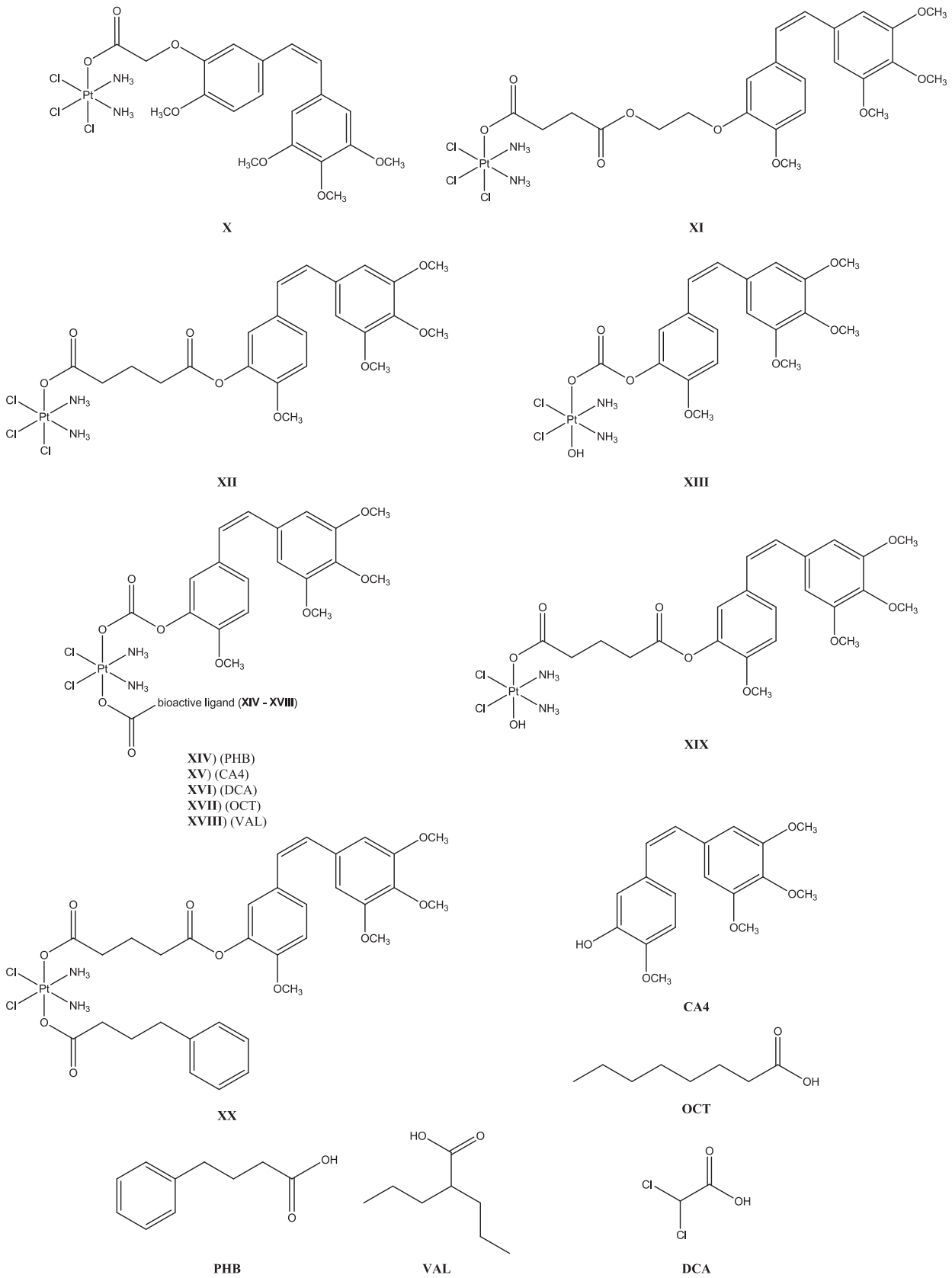
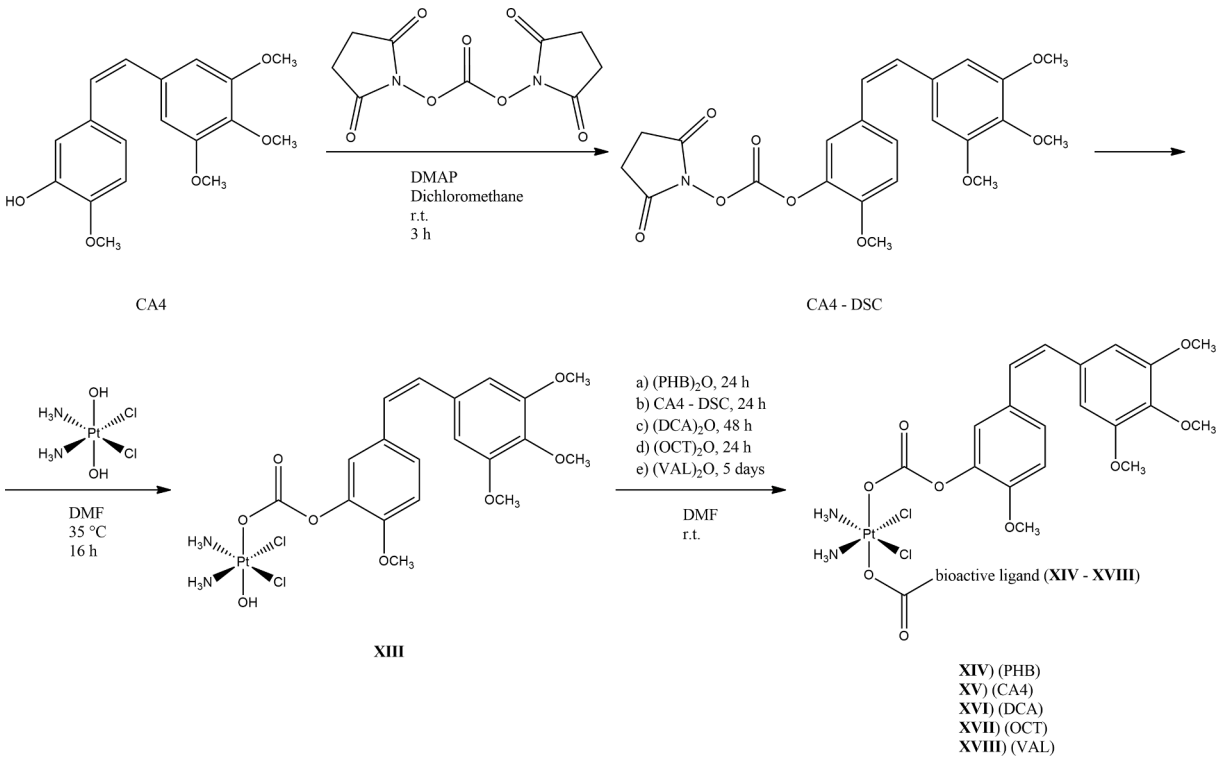


Fig. 7. Molecular structures of complexes **X-XX** and of their axial ligands.



Scheme 5. Synthetic route for the synthesis of complexes **XIII** – **XVIII** [43].

Table 3
IC_{50} values (nM) of CA4, compound **XIII-XIX** and conjugate CA4-glu on A2780, A2780cis, A375, PC9, HT-29, MCF-7, MDA-MB-231, SK-HEP-1, and RC-124 cell lines (data retrieved from [43]).

Compound	IC_{50}								
	A2780	**A2780cis**	**A375**	**PC9**	**HT-29**	**MCF-7**	**MDA-MB-231**	**SK-HEP-1**	**RC-124**
cisplatin	2410 ± 200	26460 ± 3680	3080 ± 1540	9940 ± 1340	7990 ± 1380	10650 ± 1040	8830 ± 1580	28000 ± 2120	1040 ± 140
CA4 + cisplatin (1:1)	2.40 ± 0.41	2.53 ± 0.31	2.64 ± 0.04	3.33 ± 0.11	415.00 ± 15.56	3.40 ± 0.53	3.55 ± 0.16	4.83 ± 0.56	10.22 ± 0.49
CA4 + cisplatin (2:1)	1.04 ± 0.09	1.11 ± 0.04	1.07 ± 0.35	1.50 ± 0.14	192.30 ± 3.99	1.67 ± 0.22	1.89 ± 0.28	2.49 ± 0.26	4.45 ± 0.37
CA4	2.37 ± 0.44	2.80 ± 0.03	2.02 ± 0.81	4.64 ± 0.49	348.21 ± 14.28	3.14 ± 0.32	3.68 ± 0.58	3.00 ± 0.29	9.31 ± 1.06
XIII	3.61 ± 0.78	4.47 ± 0.64	3.25 ± 1.04	5.82 ± 1.27	211.38 ± 5.62	2.49 ± 0.35	3.51 ± 0.11	4.74 ± 0.18	9.62 ± 1.90
XIV	4.01 ± 0.36	4.52 ± 0.60	3.52 ± 0.85	6.78 ± 0.52	101.96 ± 9.50	2.77 ± 0.08	3.19 ± 0.33	4.02 ± 0.76	11.11 ± 0.84
XV	2.03 ± 0.29	2.46 ± 0.67	1.72 ± 0.78	4.48 ± 0.88	202.79 ± 1.53	1.68 ± 0.23	1.82 ± 0.18	2.42 ± 0.10	5.00 ± 1.28
XVI	3.64 ± 0.18	3.87 ± 0.33	2.47 ± 0.98	5.89 ± 0.65	1100 ± 370	3.33 ± 0.37	3.12 ± 0.37	4.39 ± 0.47	9.73 ± 0.72
XVII	4.18 ± 0.56	4.58 ± 0.85	3.94 ± 0.88	7.18 ± 1.76	139.90 ± 2.54	3.66 ± 0.43	4.37 ± 0.16	5.62 ± 0.81	7.84 ± 0.08
XVIII	5.01 ± 1.19	5.61 ± 1.26	4.34 ± 1.58	9.26 ± 1.41	299.73 ± 7.95	3.91 ± 0.18	4.21 ± 0.35	5.76 ± 0.87	14.46 ± 0.71
CA4-glu	1.78 ± 0.12	1.68 ± 0.05	1.76 ± 0.13	2.29 ± 0.17					
XIX	2.03 ± 0.11	2.45 ± 0.43	2.23 ± 0.66	3.12 ± 0.15					

reduction on the tumor site, and consequently enhances the activity and reduces the toxicity of CA4. Therefore, these compounds might be prodrugs of CA4, rather than multi-action Pt(IV) prodrugs [43].

Other inhibitors of tubulin polymerization have been tethered to the axial position of Pt(IV) complexes. In particular, chalcone (**XXI**) derivatives, have been studied by Huang et al., who synthesized complexes **XXII-XXVII** (Fig. 9) [133]. Indeed, the interest behind chalcone and its analogues derives from their high cytotoxicity against several human cancer cell lines, including multidrug-resistant ones. Their mechanism of action consists of the inhibition of tubulin polymerization through their binding to the colchicine binding site [149–154]. In particular, the chalcone derivative **XXI** is highly cytotoxic against several cancer cell lines and, therefore, it was chosen as an interesting axial ligand for the synthesis of complexes **XXII-XXVII** [133,154–156].

In *in vitro* studies, the Pt(IV) prodrugs **XXII-XXVII** display more potent anticancer activity against the cancer cell lines and lower cytotoxicity against the normal human cell lines than their Pt(II) counterparts. Noteworthy, the cytotoxicity of the complexes grows higher with the elongation of the carbon chain that tethers the axial ligand to the Pt core (Table 4) [133].

Moreover, all the complexes **XXII-XXVII** are more potent than their corresponding Pt(II) counterparts on A549R (cisplatin-resistant) cancer cell line. Similarly, also complexes **XXIV-XXVII** show high activity against this cell line, thus suggesting, according to the authors, a possible use of these prodrugs in the treatment of platinum-resistant tumors (Table 5) [133].

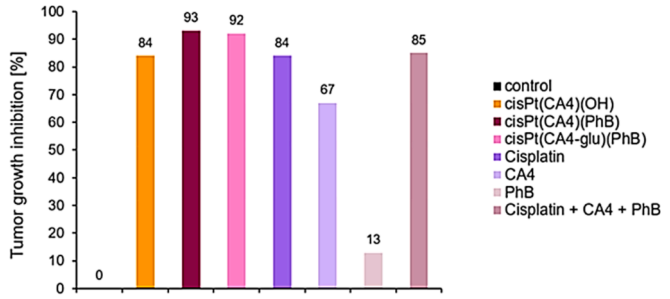


Fig. 8. The graph illustrates the inhibition of tumor growth in *in vivo* studies against the murine Lewis lung carcinoma (LLC) solid tumor model after administration of the compounds reported in Fig. 7 (cisPt(CA4)(OH), **XIII**; cisPt (CA4)(PhB), **XIV**; cisPt(CA4-glu)(PhB), **XX**). Reprinted (adapted) with permission from [43]. Copyright 2021 American Chemical Society.

The authors speculated that the high potency of complexes **XXII** and **XXIII** might derive from their enhanced cellular uptake. Indeed, their uptake in Hep G2 cells is higher than that of cisplatin and results in high levels of cellular platinum. Moreover, both complexes **XXII** and **XXIII** inhibit tubulin polymerization *in vitro*, although this effect is more evident in the case of complex **XXIII**. The synergism between the inhibition of tubulin polymerization together with the ability of the Pt complex to damage the DNA might justify the higher cytotoxicity of these complexes compared with cisplatin [133].

In addition, complexes **XXII** and **XXIII** inhibit cell proliferation and induce apoptosis in Hep G2 cells more effectively than cisplatin. In this frame, complex **XXIII** induces apoptosis more efficiently than complex **XXII**, thus suggesting that the butyl residue in complex **XXIII** improves the anticancer activity more than the propyl carbon chain of complex **XXII**. This hypothesis is further corroborated by the fact that complex **XXIII** induces mitochondrial membrane potential dysfunction in Hep G2 cells more efficiently than complex **XXII**, leading to apoptosis [133].

4. Pt(IV) complexes functionalized with vitamin analogues

4.1. Mitochondria as a target for anticancer drugs

In the last years, mitochondria have emerged as an attractive target for anticancer therapy [157]. Indeed, mitochondria are essential for the life of the cell, providing cellular energy, participating in cellular growth and division and also taking part in apoptosis [158–162]. Anticancer drugs targeting mitochondria cause the destabilization of the mitochondrial outer membrane permeabilization, which leads to the release of apoptosis mediators and ultimately results in cell death [160,163–165].

Among the class of mitochondria targeting agents, there are analogues of Vitamin E, an essential micronutrient with antioxidant properties, such as α-tocopherol succinate (α-TOS) (Fig. 10) [166,167]. This compound targets complex II of the respiratory chain, thus generating superoxide, which results in the destabilization of the mitochondria and apoptotic death. Furthermore, its anticancer action is selective for cancer cells, since they have lower antioxidant defences and esterase activity than normal cells [168]. Indeed, α-TOS displays selective anticancer activity in several cell lines (such as prostate, breast, lung, and colon) by inhibiting the anti-apoptotic proteins Bcl-2 and Bcl-xL and activating Bax, which ultimately results in cell death through

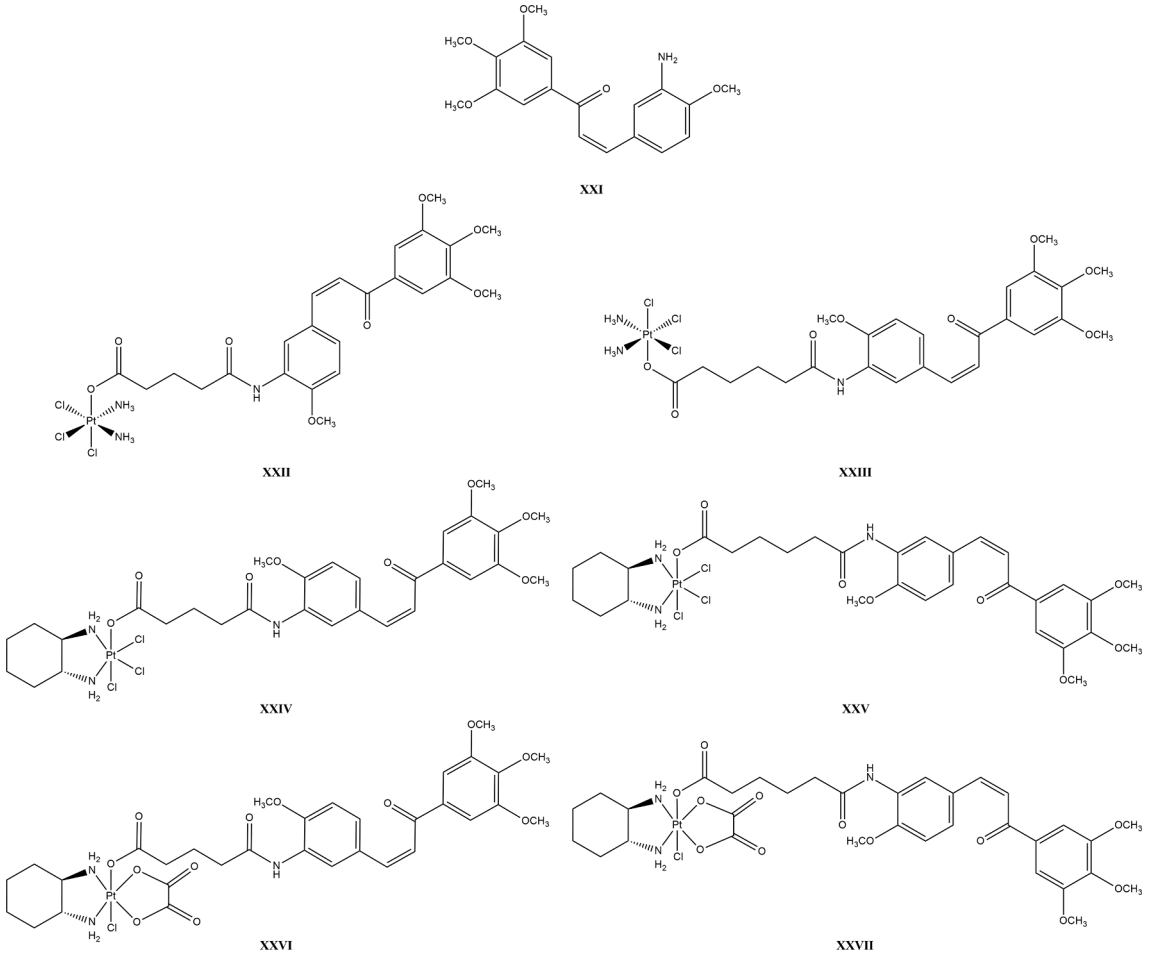


Fig. 9. Molecular structure of compound **XXI** and complexes **XXII-XXVII**.

Table 4
IC_{50} values (μM) of compounds **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, and **XXVII** in Hep G2, SK-OV-3 (human ovarian adenocarcinoma), and NCI-H460 (human lung carcinoma) cancer cell lines and in HL-7702 (normal human liver line) and BEAS-2B (normal human lung line) normal human lines. Data retrieved from [133].

Compound	IC_{50}						
	HepG-2	**SK-OV-3**	**NCI-H460**	**HL-7702**	**BEAS-2B**	**SI**[a]	**SI**[b]
XXI	10.88 ± 2.11	5.46 ± 1.03	8.43 ± 2.17	15.07 ± 2.73	18.43 ± 2.38	1.39	2.18
XXII	2.23 ± 0.39	2.75 ± 1.06	4.65 ± 1.12	24.65 ± 2.13	34.47 ± 3.11	11.05	7.41
XXIV	6.25 ± 1.28	6.78 ± 1.89	5.29 ± 2.07	37.29 ± 3.15	45.43 ± 3.73	5.97	8.59
XXVI	13.12 ± 2.13	9.85 ± 2.54	14.22 ± 2.03	41.22 ± 2.94	44.91 ± 4.01	3.14	3.16
XXIII	0.97 ± 0.25	2.11 ± 0.38	3.66 ± 0.77	33.16 ± 2.51	35.14 ± 2.38	34.19	9.34
XXV	3.81 ± 0.91	5.56 ± 0.67	4.61 ± 1.06	44.61 ± 4.02	41.69 ± 3.05	11.70	9.04
XXVII	10.21 ± 1.01	8.52 ± 1.19	10.38 ± 2.35	48.54 ± 3.61	49.08 ± 2.33	4.75	4.72
cisplatin	9.05 ± 1.23	7.46 ± 1.48	11.21 ± 1.71	8.51 ± 3.61	10.42 ± 1.92	0.94	0.93
dichloro(1R,2R-diaminocyclohexane)platinum(II)	10.50 ± 2.01	9.03 ± 0.81	9.58 ± 1.16	7.61 ± 1.83	8.55 ± 1.36	0.72	0.89
oxaliplatin	15.58 ± 3.13	12.06 ± 1.66	16.09 ± 2.44	10.25 ± 1.95	12.13 ± 2.41	0.66	0.75

[a] SI represents the Selectivity Index, calculated as the ratio between the IC_{50} in HL-7702 cells and the IC_{50} in HepG-2 cells.
[b] SI was calculated as the ratio between the IC_{50} in BEAS-2B cells and the IC_{50} in NCI-H460 cells.

Table 5
IC_{50} values (μM) of compounds **XXI-XXVII** and cisplatin, oxaliplatin and dichloro(1R,2R-diaminocyclohexane)platinum(II) in A549 and A549R cell lines. Data retrieved from [133].

Compound	IC_{50}		
	A549	A549R	RF[a]
XXI	5.61 ± 1.36	6.55 ± 2.08	1.17
XXII	3.69 ± 0.57	4.25 ± 0.34	1.15
XXIV	6.83 ± 1.01	8.23 ± 1.27	1.20
XXVI	10.15 ± 0.38	12.05 ± 2.04	1.19
XXIII	2.42 ± 0.25	3.05 ± 0.53	1.26
XXV	4.50 ± 1.09	6.01 ± 1.15	1.34
XXVII	8.51 ± 1.61	10.29 ± 1.07	1.21
cisplatin	8.59 ± 1.52	42.51 ± 3.15	4.95
dichloro(1R,2R-diaminocyclohexane) platinum(II)	8.65 ± 1.31	21.29 ± 2.68	2.46
oxaliplatin	11.95 ± 1.43	23.76 ± 3.34	1.99

[a] RF represents the resistance factor, calculated as the ratio between the IC_{50} in A549R cells and the IC_{50} in A549 cells.

mitochondria-mediated apoptosis [169–176]. Given these properties and the fact that it has an IC_{50} in the same range of Pt(II) complexes (μM), it is indeed an attractive molecule for the synthesis of novel Pt(IV) complexes [177,178].

4.2. Pt(IV) complexes functionalized with vitamin analogues

With regard to α-TOS, Suntharalingam et al. recently synthesized two Pt(IV) complexes based on cisplatin functionalized with this molecule in the axial position (**XXVIII, XXIX**; Fig. 10) [179].

These two complexes were synthesized by making the anhydride of α-TOS react with the corresponding Pt(IV) derivative (with either an -OH or -OEt moiety, depending on the desired product) in dimethyl formamide (DMF) or a mixture of DMF/ethyl acetate (1:4 v/v) at 50 °C overnight (Scheme 6) [179]:

In *in vitro* studies complex **XXIX** exhibited a cytotoxicity 7–220 times higher than that of cisplatin and a mixture of cisplatin and α-TOS in several cell lines. On the other hand, complex **XXVIII** showed a higher IC_{50} than complex **XXIX** in all the tested cell lines (Table 6). The lower cytotoxicity of complex **XXVIII** compared to complex **XXIX** can be explained in terms of lipophilicity. Indeed, being complex **XXVIII** more lipophilic, it is more prone to undergo detoxification processes by binding to both extra- and intra-cellular proteins [179].

Regarding their cellular uptake, both prodrugs exhibit a 15–20-fold higher cellular uptake in A549 cells compared with cisplatin, probably due to their improved lipophilicity (Fig. 11 A). In addition, the levels of platinum in the nuclear DNA of A549 cells are higher (7–20-fold) in the case of cells exposed to complexes **XXVIII** and **XXIX** than to cisplatin, mixtures of α-TOS and cisplatin and $Pt(IV)(OAc)_2$ (Fig. 11 B). According to the authors, this suggests that Pt(IV)–α-TOS conjugates target nuclear DNA better than both cisplatin and Pt(IV) prodrugs with non-bioactive axial ligands [179].

Moreover, complex **XXIX** possesses the properties of both cisplatin and α-TOS, thus displaying a higher activity than them. Indeed, complex **XXIX**, contrary to cisplatin, complex **XXVIII** and $Pt(IV)(OAc)_2$, is able to decrease Bcl-xL–Bax interactions with a similar potency to free α-TOS in A549 cells. Another distinctive remark of complex **XXIX** with respect to cisplatin is its capability to disrupt mitochondrial function and thus promote apoptosis in cancer cells. Furthermore, complex **XXIX**, contrary to α-TOS, is able to decrease the expression of Bcl-xL, similarly to cisplatin, complex **XXVIII**, and $Pt(IV)(OAc)_2$ [179].

In light of these results, the authors concluded that complex **XXIX** could be considered a promising dual-target anticancer drug which causes damage to the nuclear DNA and disrupts Bcl-xL–Bax interactions, thus leading to mitochondrial dysfunction. Thanks to its ability to target both these pathways, it displays superior cytotoxicity compared with cisplatin [179].

5. Delivery strategies for metal-based anticancer molecules

5.1. The different roles of albumin in human blood

One of the drawbacks of Pt(IV) complexes is that, in some specific cases like in the presence of heme proteins, they can be activated also in healthy cells [62,74,180]. For this reason, enhancing the tumor-targeting abilities of Pt(IV) drugs is of particular importance.

Human serum albumin (HSA) is the most abundant protein in human plasma and is mainly produced in the liver [181–183]. This protein is of great importance in the body, since not only it transports different endogenous molecules (such as fatty acids and steroids), but it is also accountable for the transport of different metal ions in the blood (such as copper, zinc and calcium) [183–187]. However, it also plays a central role in the pharmacokinetics of many drugs, being able to bind molecules such as naproxen, warfarin, chlorpromazine, and ibuprofen, thus affecting their half-life and activity [183,186,187]. Similarly, it is also able to bind metallodrugs, like cisplatin [188–190].

Noteworthy, not only albumin accumulates in tumor and inflamed tissues because of leaky blood capillaries and the deficiency of lymphatic drainage (a phenomenon called “enhanced permeability and retention effect”), but it can also be internalized by cancer cells by endocytosis (via macropinocytosis, clathrin-mediated or caveolin-mediated pathway) as an extra source of nutrition [184,191–194]. In light of this, albumin has been proposed as a potential drug carrier for a more

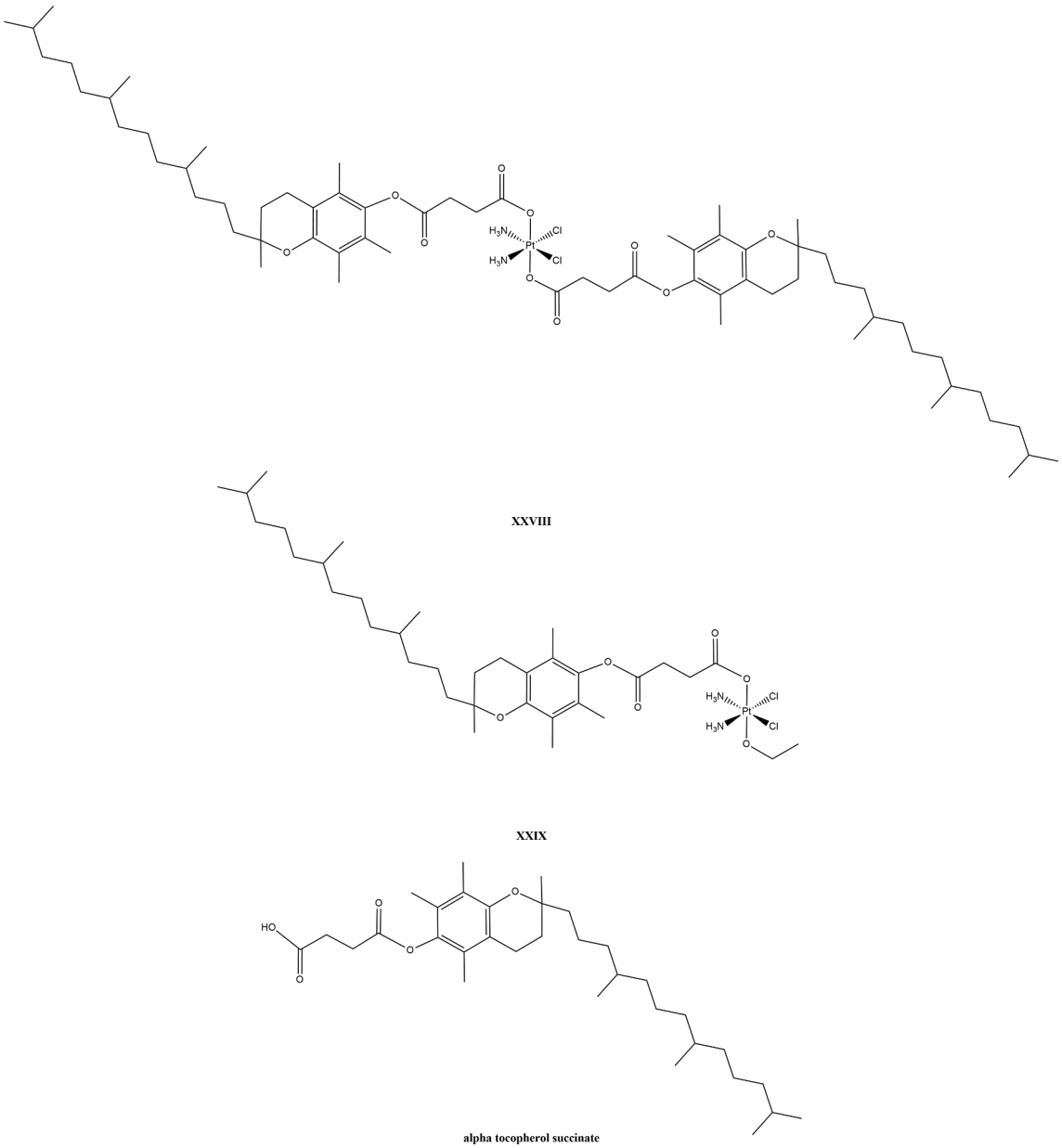


Fig. 10. Molecular structures of complexes **XXVIII**-**XXIX** and of their axial ligands.

selective delivery of antitumor drugs to cancer cells [184].

In this frame, among all proteinogenic amino acids, cysteine is of particular importance due to its platinum affinity mediated by the sulfhydryl group [195]. Although there are different methods to modify this residue, maleimides are particularly interesting because they are selective cysteine thiol binding agents [195,196]. The general scheme of the reaction between maleimide and a cysteine thiolate, which yields a thiosuccinimide bond, is reported below (Scheme 7).

In light of this, a Pt(IV) prodrug bearing a maleimide moiety might be able to bind the free thiol groups in albumin, thus enhancing the tumor-targeting capability compared with classical Pt(II) drugs.

5.2. *Delivery strategies for Pt(IV) complexes*

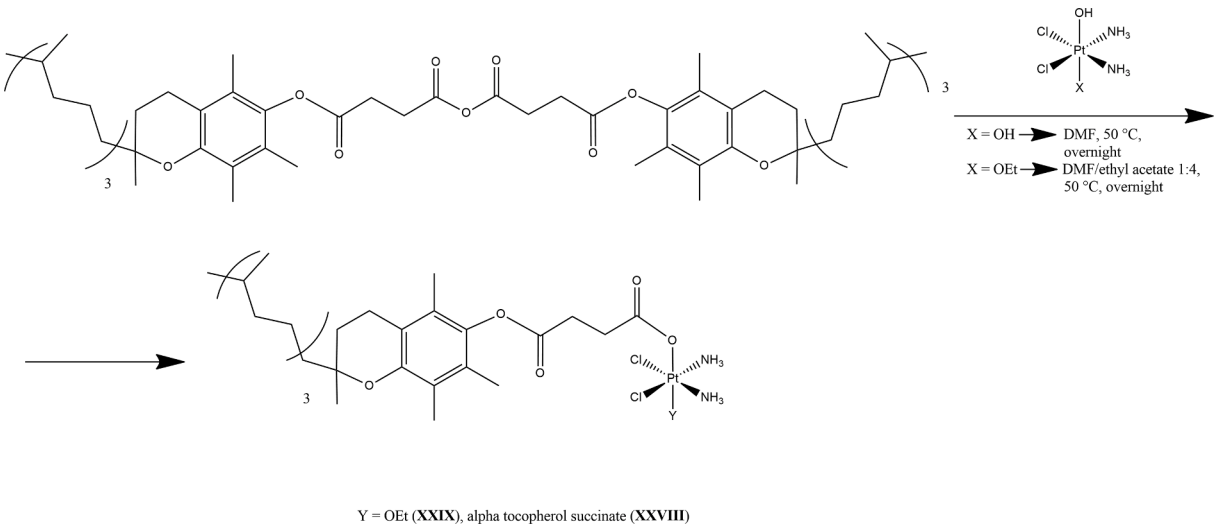
With this regard, Pichler et al. recently reported on the synthesis of a panel of maleimide-functionalized Pt(IV) complexes (**XXX**, **XXXI**; Fig. 12) [38].

Complexes **XXX** – **XXXII** were obtained by making the hydroxido group of the Pt(IV) precursor react with the corresponding maleimide-containing linker in DMF. Complex **XXXII** was synthesized to be used as a reference compound since it doesn't react with thiols [38]. The synthetic route is displayed in Scheme 8.

The interest behind these prodrugs resides in their ability to bind the free thiols groups in proteins (e.g., the Cys34 in HSA) through the maleimide moiety following the mechanism already depicted in Scheme 7. Indeed, complexes **XXX** and **XXXI** promptly react with cysteine, while the succinimide derivative **XXXII** doesn't show any reactivity, thus proving that cysteine binds selectively to the maleimide moiety with respect to the Pt core [38].

Regarding their stability, derivatives **XXX** and **XXXI** undergo slow hydrolysis of the maleimide moiety in aqueous solution, while the succinimide derivative **XXXII** is stable in the same conditions. Noteworthy, contrary to complex **XXXII**, both complexes **XXX** and **XXXI** rapidly bind to albumin in aqueous solution. Indeed, around 80% of maleimide-functionalized Pt(IV) complexes are bound to albumin after 4 h of incubation at a concentration >30 mM, with a 1:1 Pt/albumin molecular ratio [38].

In *in vivo* studies on murine CT-26 colon cancer model, complexes



Scheme 6. Synthetic route for the synthesis of complexes **XXVIII-XXIX** [179].

Table 6
IC_{50} values are (μM) of cisplatin, α-TOS, a mixture of cisplatin and α-TOS, complex **XXVIII**, and complex **XXIX** (Data retrieved from [179]).

Compound	IC_{50}							
	A549	HeLa	A2780	A2780/CP70	PC-3	HCT116	MCF-7	MRC-5
cisplatin	2.5 ± 0.8	1.4 ± 0.3	0.56	6	15.1 ± 0.9	6.6 ± 0.4	18.2 ± 0.5	6.3 ± 0.4
α-TOS	26.9 ± 1.4	25.1 ± 1.0	13.8 ± 1.08	21.7 ± 1.7	37.0 ± 0.1	31.2 ± 1.8	40.5 ± 5.0	28.5 ± 4.2
cisplatin + α-TOS	6.4 ± 0.2	3.4 ± 0.5	4.4 ± 1.2	7.3 ± 0.6	19.2 ± 0.2	17.3 ± 0.9	18.3 ± 0.5	18.8 ± 0.7
XXIX	1.3 ± 0.1	1.9 ± 0.3	0.02 ± 0.01	1.1 ± 0.1	2.5 ± 0.2	1.24 ± 0.01	5.9 ± 0.1	5.3 ± 0.2
XXVIII	13.9 ± 0.1	24.7 ± 0.6	56.4 ± 4.6	>100	>100	>100	>100	80.5 ± 0.6

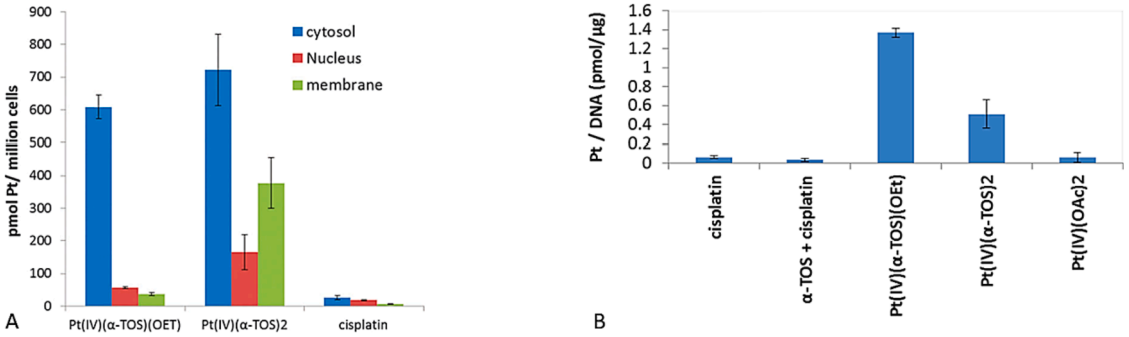
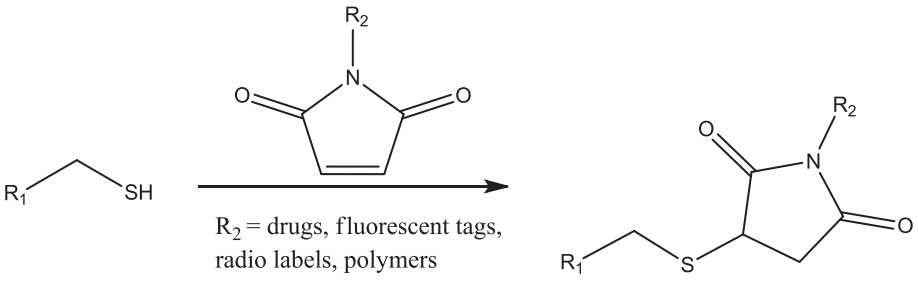
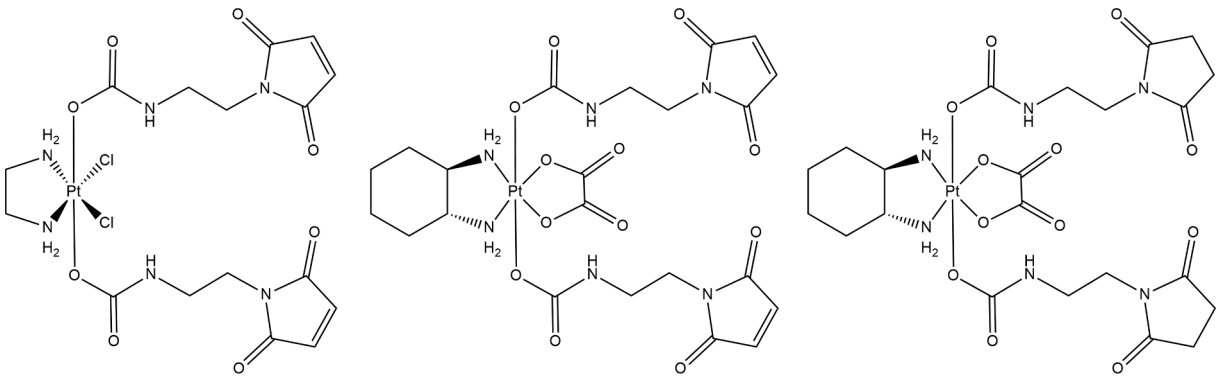


Fig. 11. (A) Cellular uptake studies of cisplatin, complex **XXVIII** (named Pt(IV)(α-TOS)$_2$ in the figure), and complex **XXIX** (named Pt(IV)(α-TOS)(OEt) in the figure) in A549 cells. Reproduced from Ref. [179] with permission from the Royal Society of Chemistry; (B) Graphic illustrating the Pt content in DNA of A549 cells treated with cisplatin, a mixture of cisplatin and α-TOS, complex **XXVIII** (namely Pt(IV)(α-TOS)$_2$ in the picture), complex **XXIX** (namely Pt(IV)(α-TOS)(OEt) in the picture), and Pt(IV)(OAc)$_2$. Reproduced from Ref. [179] with permission from the Royal Society of Chemistry.

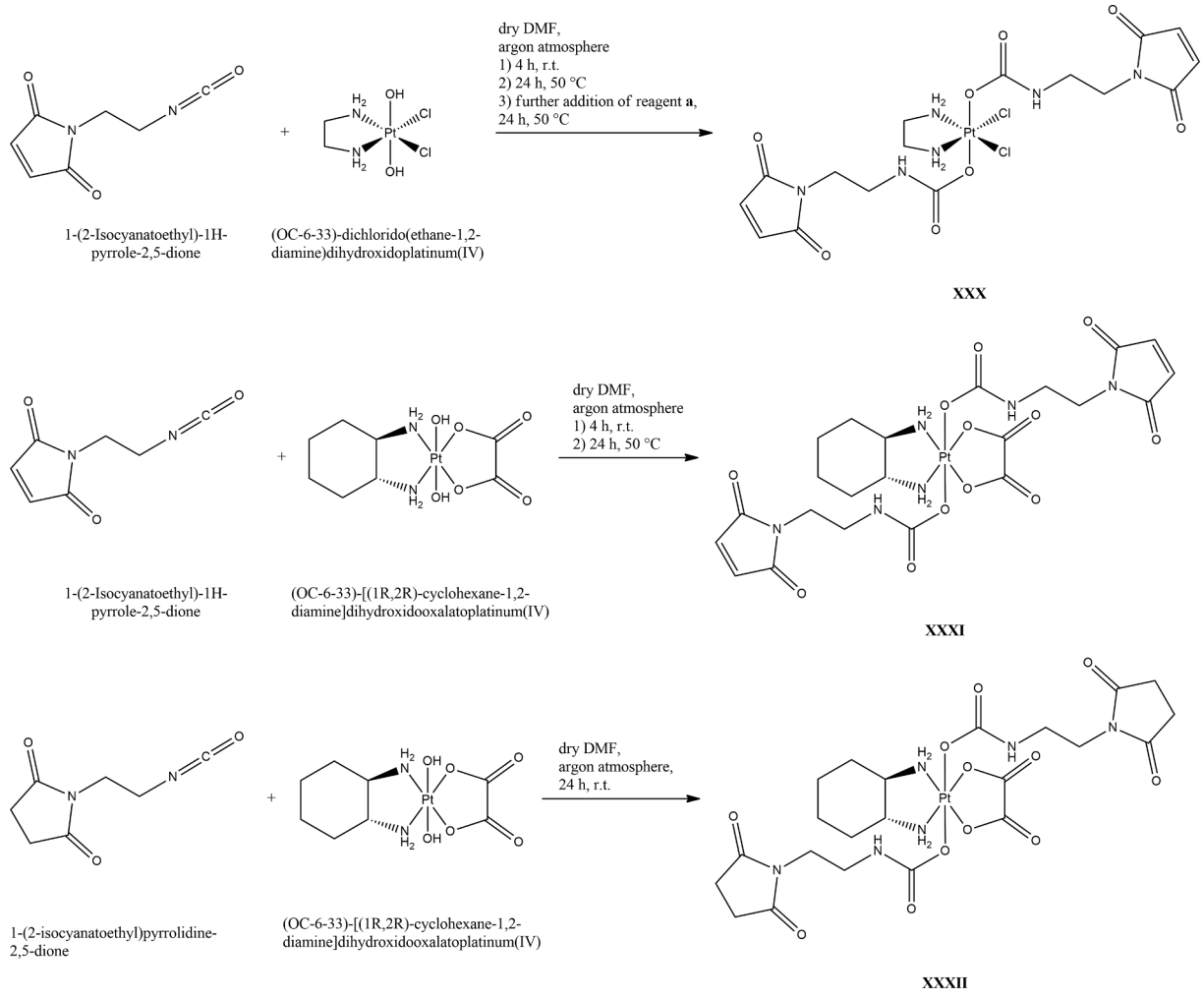


Scheme 7. Reaction mechanism between Cys and a maleimide moiety.



XXX **XXXI** **XXXII**

Fig. 12. Molecular structures of the maleimide-functionalized Pt(IV) complexes (**XXX** and **XXXI**) and of the succinimide functionalized complex (**XXXII**) synthesized by Pichler et al. [38].



Scheme 8. Synthetic route for complexes **XXX** – **XXXII** [38].

XXXI and **XXXII** showed a potent anticancer activity (Fig. 13 A). Noteworthy, complex **XXXI** showed superior anticancer activity compared to complex **XXXII**, suggesting that the bond between complex **XXXI** and albumin either prolongs the plasma half-life of the complex and/or allows a more selective accumulation of this drug in cancer cells [38].

Further studies proved that the ability of complex **XXXI** to bind albumin results in higher levels of drug uptake via endocytosis, followed by its slow reduction and consequent activation inside cancer cells. Indeed, the conjugate complex **XXXI**-albumin rapidly enters cancer cells, yielding 10-fold higher platinum levels than complex **XXXII** (Fig. 13 B). This difference could probably be ascribed to the fact that complex **XXXI**, contrary to oxaliplatin and **XXXII** (which is unable to bind to albumin), enters cancer cells via clathrin- and caveolin-dependent endocytosis. Additional studies unravelled that part of the bioconjugate **XXXI**–albumin accumulates in the lysosomes, where

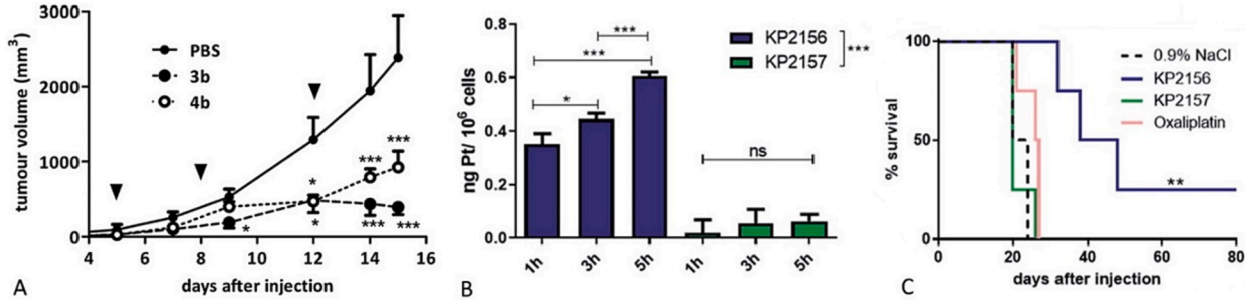


Fig. 13. (A) Graphic illustrating the *in vivo* anticancer activity of **XXXI** (named 3b in the picture) and **XXXII** (named 4b in the picture), which were administered i.v. on days 5, 8, and 12 (indicated by ▼) (Statistical parameters: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$). Reproduced from Ref. [38] with permission from the Royal Society of Chemistry; (B) Cellular uptake studies of complex **XXXI** (named KP2156 in the picture) and of complex **XXXII** (named KP2157 in the picture) (Statistical parameters: *$p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$). Reproduced from Ref. [197] with permission from the Royal Society of Chemistry; (C) Overall survival of CT26-bearing Balb/c mice treated with complex **XXXI** (named KP2156 in the picture), complex **XXXII** (named KP2157 in the picture), and oxaliplatin (Statistical parameters: **$p < 0.01$). Reproduced from Ref. [197] with permission from the Royal Society of Chemistry.

albumin is probably degraded and the prodrug is reduced to oxaliplatin [197].

Moreover, in *in vivo* experiments on CT26 tumor models, complex **XXXI** demonstrated superior activity in comparison with oxaliplatin. This might be due to its improved cellular accumulation and its ability not only to reduce cell proliferation but also to induce apoptosis. Furthermore, at the end of the experiment, the tumors treated with oxaliplatin restarted to progress again (pointing out the resistance of tumor cells to the therapy), whereas complex **XXXI** not only arrested the tumor growth but also induced complete remission of the disease. Noteworthy, this resulted in an enhanced survival rate of animals treated with complex **XXXI** and in the healing of one of them (Fig. 13C). Strikingly, in further experiments this animal showed the development of some sort of antitumor memory or vaccination, as he rejected the novel living administrated CT26 cells [197,198].

6. Photoactivatable Pt(IV) complexes

6.1. Light as a means for the activation of Pt(IV) prodrugs

As extensively discussed in chapter 1, the therapeutic applications of Pt(II) drugs are limited by their side effects, caused by their non-specific activation in healthy cells [12,14,23,30,199]. Therefore, a Pt(IV) prodrug capable of releasing its bioactive molecule selectively at the tumor site is highly attractive.

In this frame, another interesting mechanism of activation of Pt(IV) drugs, aside from those aforementioned in the previous chapters, involves the absorption of light. Indeed, the selective reduction of photoactivatable Pt(IV) prodrugs at the tumor site can also be induced by light [49,200]. This way, the bioactive molecules are released *in situ* and, consequently, the diffused side effects related to traditional Pt compounds are reduced [201–203]. Ideally, a photoactivatable Pt(IV) prodrug should be stable and inert during its circulation inside the body but, upon irradiation, it should reduce and consequently release molecules which possess high anticancer activity [49]. These complexes are particularly interesting because nowadays we have at our disposal modern systems, such as lasers and optic fibers, that enable light-delivery to any tissue in the body, thus allowing precise control of the activation of these drugs [204,205].

In the following paragraph, we have reviewed the most recent and prominent complexes in this field, providing examples of complexes both based (**XXXVI**, Fig. 14) and non-based (**XXXIII** and **XXXIV**, Fig. 14) on Pt(II) drugs currently used in clinical practice.

6.2. An overview of the most recent advancements in photoactivatable Pt (IV) complexes

In the last few years, two promising Pt(IV) complexes, namely complex **XXXIII** and complex **XXXIV** (Fig. 14), which bear the π conjugated phterpy ligand (4′-phenyl-2,2′:6′,2″-terpyridine) (Fig. 14) in the equatorial position, have been synthesized. Upon irradiation with visible light the phterpy ligand, acting as an antenna, promotes the reduction and thus the activation of these prodrugs. Moreover, it stabilizes the complexes, allowing the formation of only one photoproduct instead of a mixture of several species [49].

Both these complexes are stable in DMSO in the dark and in physiological-like conditions. However, only complex **XXXIV** is stable also in the presence of the reducing agent GSH at mM concentration. Despite this, after irradiation at 365 nm, both of them are efficiently reduced to complex **XXXV,** with complex **XXXIV** being reduced faster than complex **XXXIII** (Scheme 9). Noteworthy, complex **XXXV** has been suggested to exert its anticancer activity by forming a covalent binding with the DNA [49].

Regarding the stability of these two prodrugs toward reduction, complex **XXXIV** features a more negative reduction potential than its analogue **XXXIII**, possibly because of the enhanced stabilization granted by its axial ligands (i.e., the two acetate groups). Thanks to its higher stability, complex **XXXIV** is also the least cytotoxic in the dark among the two complexes on A2780 and A2780R cell lines. Noteworthy, complex **XXXIV** shows remarkably higher cytotoxicity than cisplatin on both sensitive and resistant A2780 cell lines upon irradiation with light at 365 nm. This suggests the possibility that compound **XXXIV** might be able to overcome platinum resistance in A2780R ovarian cancer cells [49].

Another interesting complex is phorbiplatin (complex **XXXVI**, Fig. 14), a red-light photoactivatable Pt(IV) complex based on oxaliplatin [206]. Authors chose this particular Pt(II) drug as a scaffold due to the fact that tetracarboxylato Pt(IV) complexes are reported to be particularly stable toward reduction [206–209]. The axial position was functionalized with pyropheophorbide a (PPA) (Fig. 14), an highly efficient photo-absorber in the red-light region (around 650 nm) which has already been used in photodynamic therapy as photosensitizers [210–218]. Indeed, PPA was reported to be able to kill cancer cells by inducing ROS production upon irradiation [219].

Phorbiplatin was synthesized as depicted in the picture below (Scheme 10):

PPA was reacted with *N*-hydroxysuccinimide (NHS) and 1-ethyl-3-(-3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) in DMSO overnight at room temperature, thus yielding the activated ester of PPA. This derivative was then reacted with $[Pt(DACH)(OH)_2(ox)]$ in DMSO at 60 °C overnight, giving (after purification) the target compound

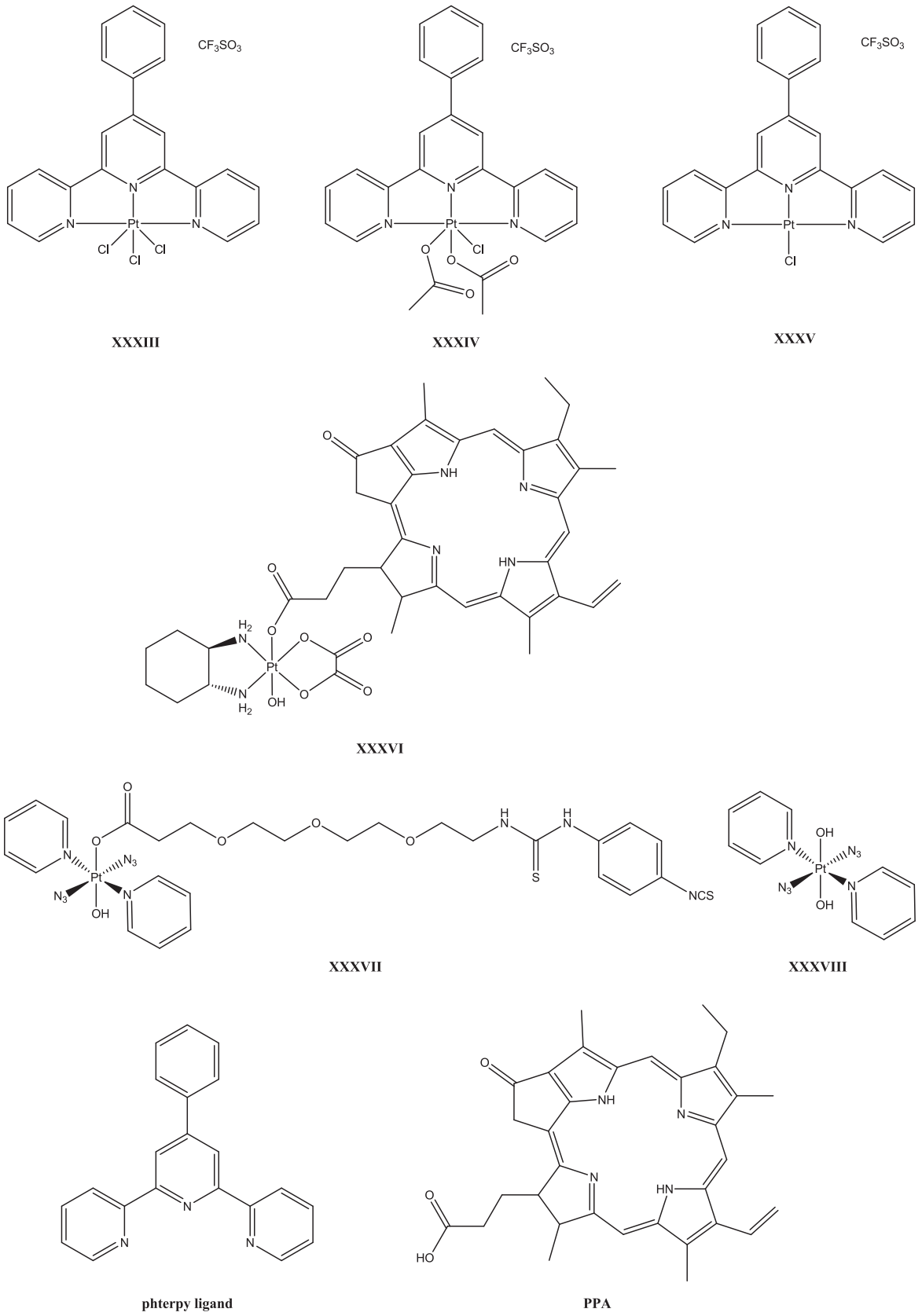
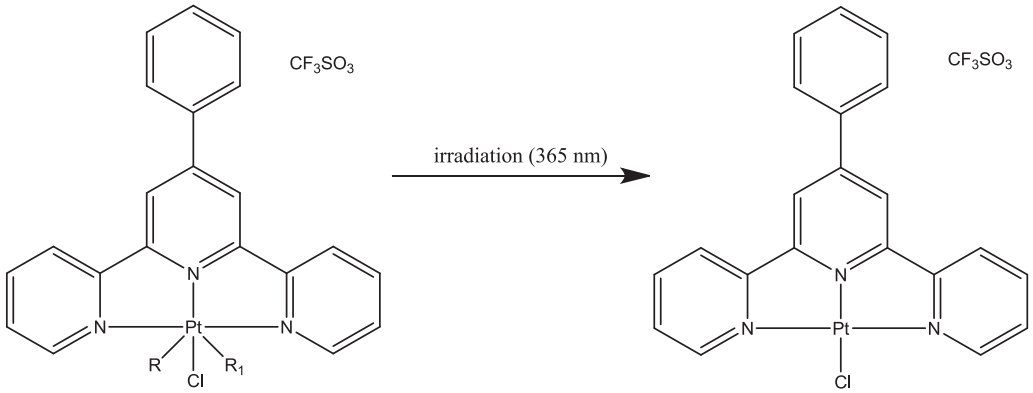


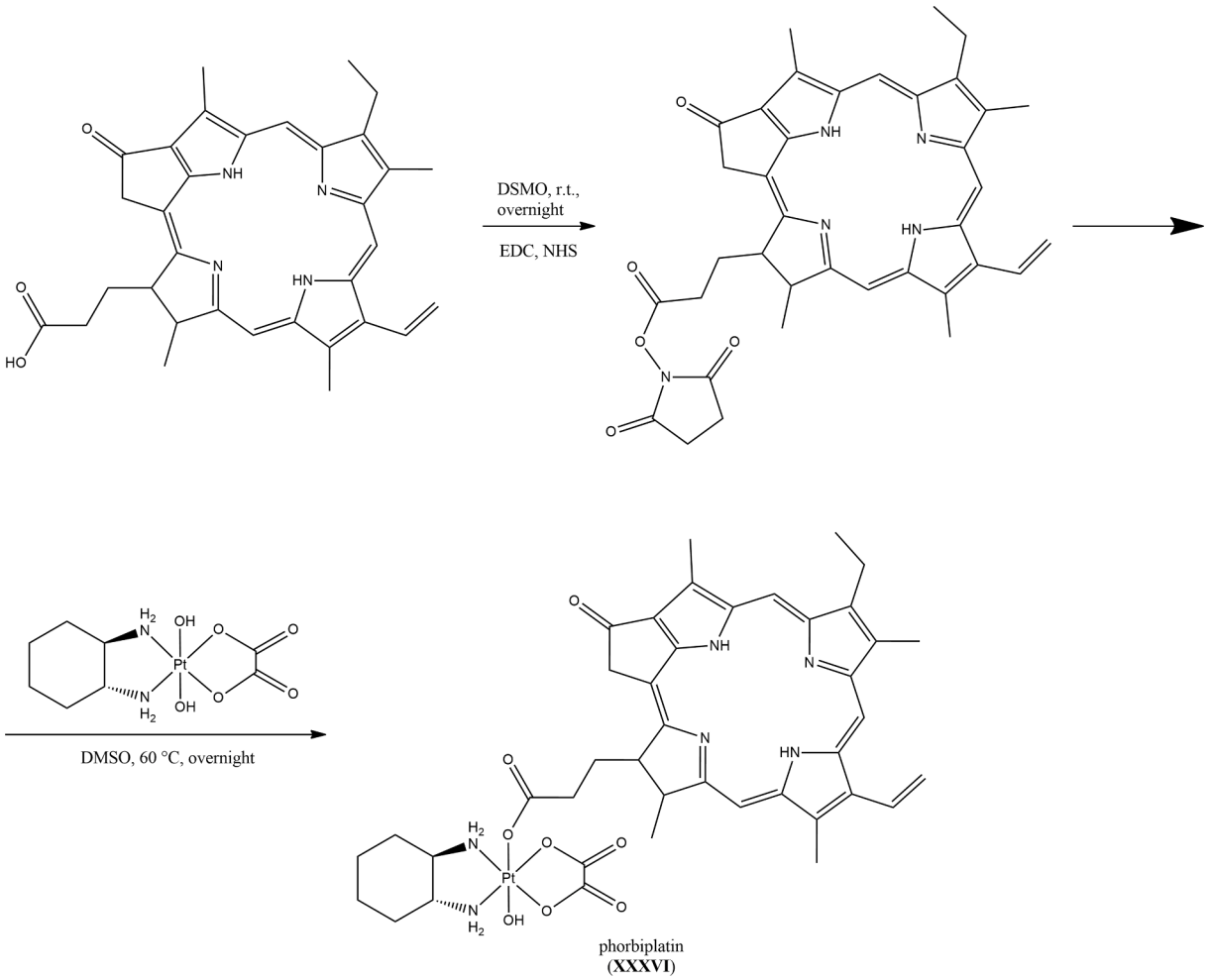
Fig. 14. Molecular structures of complexes **XXXIII-XXXVIII**, phterpy ligand e PPA.



R, R_1 = Cl (complex **XXXIII**)
R, R_1 = OAc (complex **XXXIV**)

XXXV

Scheme 9. Photo-reductive activation of complexes **XXXIII** and **XXXIV**.



Scheme 10. Synthetic route of phorbiplatin (**XXXVI**) [206].

(namely, phorbiplatin) (Scheme 10) [206].

Phorbiplatin, which is stable in the dark also in the presence of cellular reducing agents, was tested for its cytotoxicity against A2780 and A2780R and MCF-7 cancer cell lines (Table 7) [206,220].

This complex is non-toxic in the dark but, upon irradiation with red light, it displays a potent activity in A2780 cells. Moreover, it was cytotoxic also on A2780R and MCF-7 cells. In contrast, oxaliplatin is much less cytotoxic toward A2780R cells both in the dark, and under irradiation, proving that light has a minimum effect on its activity. On the other hand, PPA has low cytotoxicity in the dark but it becomes very active upon irradiation [206].

Therefore, compared with oxaliplatin, phorbiplatin displays a 523-

Table 7
IC_{50} values (μM) of phorbiplatin (complex **XXXVI**), PPA and oxaliplatin (data retrieved from [206]).

Cell Line	Condition	IC_{50}			IC_{50} oxaliplatin/ IC_{50} complex XXXVI
		oxaliplatin	PPA	phorbiplatin, XXXVI	
A2780	in the dark	76 ± 4	>10	>10	
	under irradiation (650 nm)	68 ± 9	0.34 ± 0.05	0.13 ± 0.01	523
A2780cisR	in the dark	162 ± 9	>10	>10	
	under irradiation (650 nm)	185 ± 8	0.23 ± 0.01	0.19 ± 0.01	974
MCF-7	in the dark	110 ± 4.3	>10	>10	
	under irradiation (650 nm)	78.6 ± 8.7	0.20 ± 0.02	0.044 ± 0.004	1786
4T1	in the dark	8.7 ± 0.9	>10	>10	
	under irradiation (650 nm)	7.6 ± 1.3	0.16 ± 0.02	0.13 ± 0.004	58
MRC-5	in the dark	122 ± 5.2	>10	>10	

fold, 974-fold and 1786-fold increased phototoxicity, respectively, in A2780, A2780R and MCF-7 cell lines. This may derive from its more efficient accumulation in cancer cells, which could be a consequence of its enhanced lipophilicity (Fig. 15A) and might suggest the ability of phorbiplatin to overcome the resistance against conventional Pt drugs. In addition, phorbiplatin is non-toxic in MRC-5 cells (normal human lung fibroblasts cell line) in the dark, thus highlighting its safety [206,221–224].

In addition, in *in vivo* studies, irradiated phorbiplatin was more active against the growth of breast tumor than oxaliplatin, PPA and a mixture of PPA and oxaliplatin (Fig. 15B). Noteworthy, treatment with phorbiplatin did not cause a significant change in the body weight of the mice, thus highlighting once again its safety (Fig. 15C) [206].

A possible photoreduction mechanism for this prodrug was also proposed. According to this mechanism, upon irradiation phorbiplatin is reduced to oxaliplatin, which damages DNA, and PPA, which generates ROS. In this frame, PPA is proposed to ease the transfer of an electron from a reducing agent (like ascorbate) to the Pt core, thus facilitating the reduction of the prodrug [206].

The figure below presents the proposed mechanism of photoreduction more in detail (Scheme 11). First, phorbiplatin, thanks to irradiation, is excited to its singlet excited state (**2**). Then, through intersystem crossing (ISC), the singlet excited state (**2**) is converted into a triplet excited state (**3**). Consequently, the triplet excited PPA moiety (**3**) is reduced (accepting an electron from a donor like ascorbate), thus forming a Pt(IV) complex which contains ground state PPA π radical anion (**4**). This radical further reduces the Pt core (yielding him an electron), forming a Pt(III) complex (**5**) or (**6**). Lastly, the Pt(III) complex is reduced to its corresponding Pt(II) counterpart [206,225]. According to the authors, the pathway via **5** is more stable, and thus more likely to occur, than the one via **6** [206].

Another interesting photoactivatable Pt(IV) complex is complex **XXXVII** (Fig. 14). It was designed with the aim to increase the tumor-targeting capability of Pt(IV) compounds and, therefore, to decrease the systemic toxicity of Pt drugs. Indeed, thanks to its isothiocyanate group it is capable of binding to the lysine residues of proteins and, therefore, it can be exploited for protein-mediated delivery of the photoactivatable complex **XXXVIII**, which is the precursor of complex **XXXVII** [226]. The Pt(IV)-based azido complex **XXXVIII**, was chosen as a basis for complex **XXXVII** due to its inertness and lack of toxicity in the presence of bio-reductants [227].

Both complexes **XXXVII** and **XXXVIII**, are stable in the dark but readily activate upon irradiation with blue light (420 nm) [226].

Complex **XXXVII** was conjugated to the side chain of lysine of myoglobin (the NH_2 pendant in Scheme 12) by making this protein react with 5 equivalents of complex **XXXVII** (Scheme 12). Interestingly, no apo-myoglobin was found in the sample, demonstrating that myoglobin retains its heme group during the linking process. Moreover, the ratio of complex **XXXVII**/myoglobin determined through UV–vis spectroscopy was 5.6, which is in good accordance with the one calculated in ESI-MS analysis (4.4) [226].

The conjugate between myoglobin and complex **XXXVII** is stable in the dark, but promptly photo-decomposes upon irradiation with blue light. Although less effective, green light (520 nm) is also able to cause

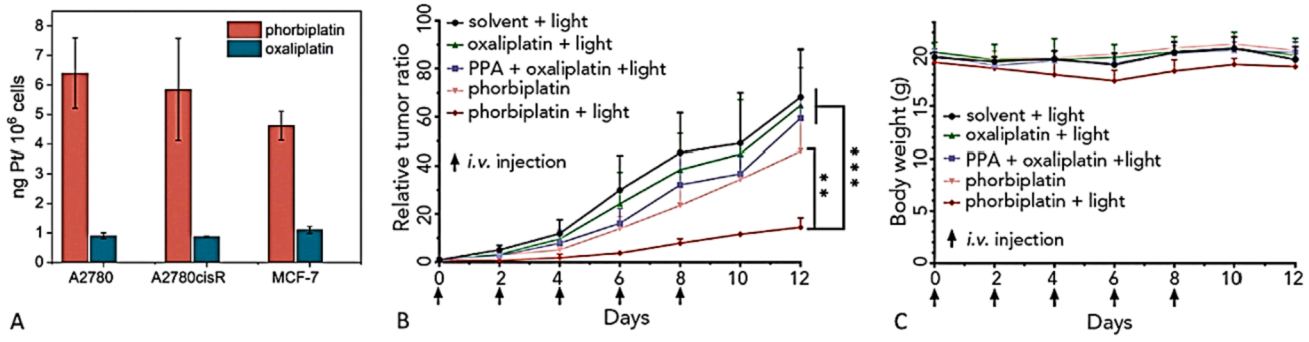
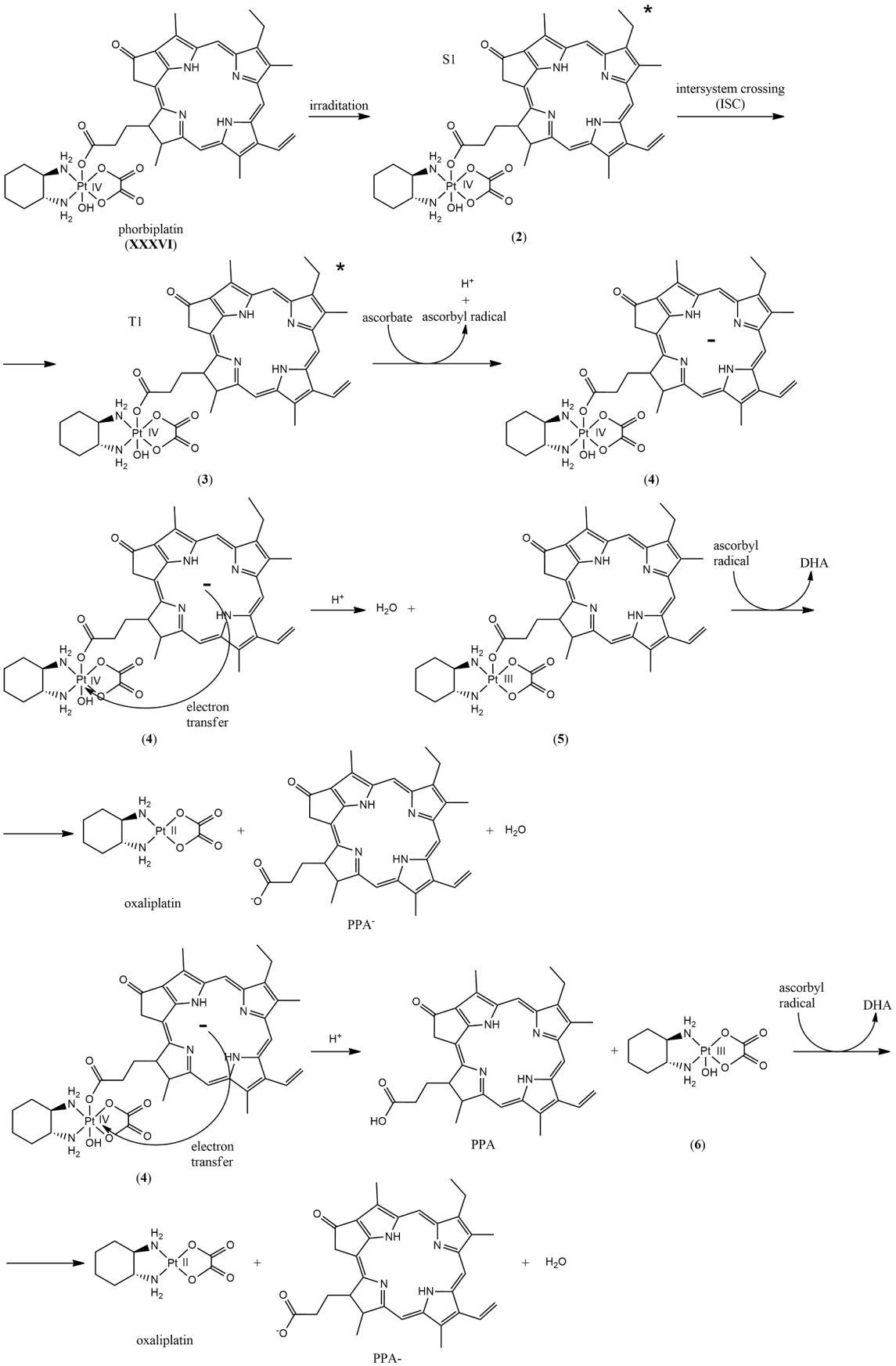
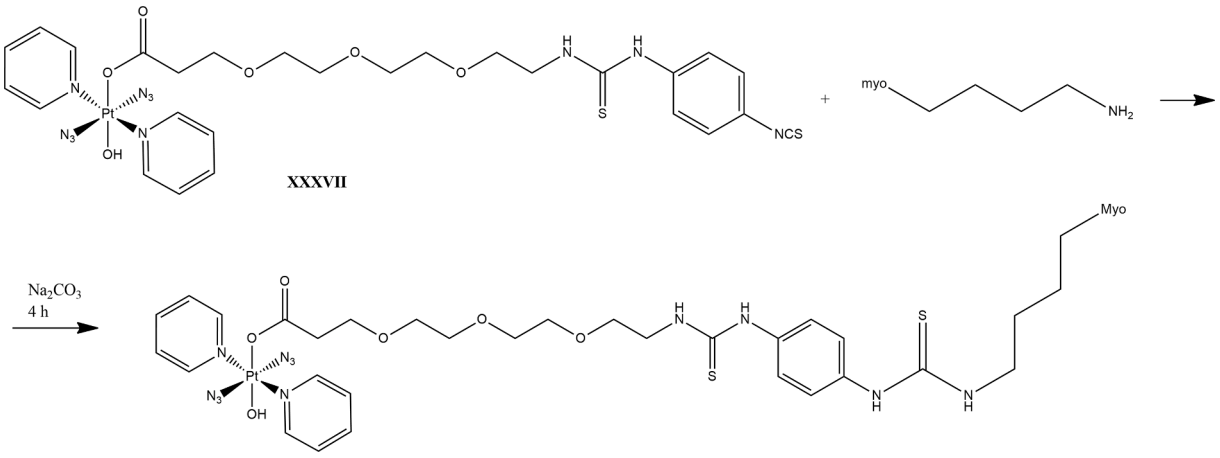


Fig. 15. (A) Studies on the cellular accumulation of Pt after treatment of A2780, A2780R and MCF-7 cell lines with phorbiplatin (**XXXVI**) or oxaliplatin. Reprinted from Chem, Vol 5, Zhigang Wang, Na Wang, Shun-Cheung Cheng, Kai Xu, Zhiqin Deng, Shu Chen, Zoufeng Xu, Kai Xie, Man-Kit Tse, Peng Shi, Hajime Hirao, Chi-Chiu Ko, Guangyu Zhu, Phorbiplatin, a Highly Potent Pt(IV) Antitumor Prodrug That Can Be Controllably Activated by Red Light, Pages No 3151–3165. Copyright (2019), with permission from Elsevier.; (B) Growth and relative tumour volumes of 4T1 tumours treated with various compounds (indicated in the figure). The arrows indicate when complex administration and irradiation took place. (Statistical parameters: $^{**}p < 0.01$, $^{***}p < 0.001$). Reprinted from Chem, Vol 5, Zhigang Wang, Na Wang, Shun-Cheung Cheng, Kai Xu, Zhiqin Deng, Shu Chen, Zoufeng Xu, Kai Xie, Man-Kit Tse, Peng Shi, Hajime Hirao, Chi-Chiu Ko, Guangyu Zhu, Phorbiplatin, a Highly Potent Pt(IV) Antitumor Prodrug That Can Be Controllably Activated by Red Light, Pages No 3151–3165., Copyright (2019), with permission from Elsevier.; (C) Changes in the body weight of the mice treated with various compounds (indicated in the figure). The arrows indicate when complex administration and irradiation took place. Reprinted from Chem, Vol 5, Zhigang Wang, Na Wang, Shun-Cheung Cheng, Kai Xu, Zhiqin Deng, Shu Chen, Zoufeng Xu, Kai Xie, Man-Kit Tse, Peng Shi, Hajime Hirao, Chi-Chiu Ko, Guangyu Zhu, Phorbiplatin, a Highly Potent Pt(IV) Antitumor Prodrug That Can Be Controllably Activated by Red Light, Pages No 3151–3165., Copyright (2019), with permission from Elsevier.



Scheme 11. Schematic representation of the authors' proposed reduction mechanism of phorbiplatin by ascorbate and promoted by light irradiation (DHA: dehydroascorbic acid) [206].



Scheme 12. Conjugation of complex **XXXVII** to myoglobin (abbreviated as myo in the figure) [226].

photo-activation of this conjugate. Noteworthy, native myoglobin doesn't undergo photo-decomposition under the same conditions, thus suggesting a possible interaction between the heme group and complex **XXXVII** during the photo-decomposition [226].

To characterize the conjugate between complex **XXXVII** and myoglobin, the authors made myoglobin react with 1 equivalent of complex **XXXVII**, in order to form the adduct 1:1. Analysis performed on this sample suggests that several lysine residues in the myoglobin protein are susceptible to being modified by complex **XXXVII**. Irradiation of this sample with blue light led to photo-decomposition of the conjugate through two different pathways. The first one goes through the loss of the azido moieties and the OH group, whereas the second leads to the release of complex **XXXVIII**. In the second pathway, the released complex **XXXVIII** can further be photoactivated, leaving the PEG isothiocyanate moiety tethered to myoglobin [226,228].

Subsequently, the authors synthesized a photoactivatable Pt(IV)-antibody conjugate, which could be employed for selective cancer phototherapy. In particular, complex **XXXVII** was conjugated to the Her2-targeting monoclonal antibody trastuzumab by making this antibody react with 5 equivalents of the complex. Trastuzumab is a monoclonal antibody employed in clinic to treat Her2-positive breast and gastric tumor and was chosen for this reaction due to its ability to form stable conjugates with chemotherapeutics through its lysine residues [226,229]. In this case, the ratio between complex **XXXVII** and trastuzumab is ca. 0.6. The lower ratio in the case of trastuzumab compared with myoglobin is partly due to the gentler reaction conditions employed for the antibody (especially with regard to the pH of the solution and the incubation time), which are necessary to prevent its denaturation. In particular, when conjugating the complex with myoglobin the pH of the solution is 8.5–9 and the incubation time is 4 h. On the other hand, in the conjugation with trastuzumab the pH of the solution is 8.5 and the incubation time is 2 h [226].

7. Conclusions

To sum up, in this review we have discussed some of the most recent and interesting progress made in the field of Pt(IV) complexes. Indeed, because of the several drawbacks of Pt(II) drugs, cancer therapy highly needs novel molecules capable of overcoming their limitations. In particular, in this review we have reported complexes functionalized in the axial positions with molecules with different mechanisms of action, ranging from COX-targeting drugs to mitochondria-targeting agents and tubulin polymerization inhibitors. Furthermore, in order to give a wider overview of the strategies that can be exploited with these complexes, we have also reviewed some of the most recent examples of Pt(IV) complexes with delivering and photoactivation properties. Moreover, we have reported the rationale behind their design, as well as their activity and mechanism of action. In light of this, we can conclude that Pt(IV) complexes hold great potential in cancer therapy but further studies are required to refine their structure and obtain a molecule which could effectively replace the traditional Pt(II) drugs. In this frame, Pt(IV) complexes with delivery (chapter 5) and photoactivatable properties (chapter 6) represent a very interesting field for future research, capable of providing new drugs that could overcome the limitations of traditional Pt-based drugs. Nonetheless, the other classes of Pt(IV) prodrugs described in this review hold great potential as well. However, in order to overcome the drawbacks of the already existing complexes and synthesize drugs with new and improved features, it is necessary to link to the axial position of Pt(IV) complexes novel molecules with different biological targets and anticancer mechanisms.

In conclusion, although this review isn't exhaustive of all the literature on this topic, we still believe that it may provide useful insights, thus helping researchers to find new ideas to develop innovative drugs.

CRediT authorship contribution statement

Carlo Marotta: Conceptualization, Data curation, Writing – original draft. **Ester Giorgi:** Data curation. **Francesca Binacchi:** Data curation. **Damiano Cirri:** Data curation, Writing – original draft. **Chiara Gabbiani:** Conceptualization, Supervision. **Alessandro Pratesi:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

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

Data will be made available on request.

Acknowledgements

This work is supported by the Università di Pisa under the "PRA – Progetti di Ricerca di Ateneo" (Institutional Research Grants) - Project no. PRA_2022_12" New challenges of transition metal and lanthanide complexes in the perspective of green chemistry" funded to A.P.

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