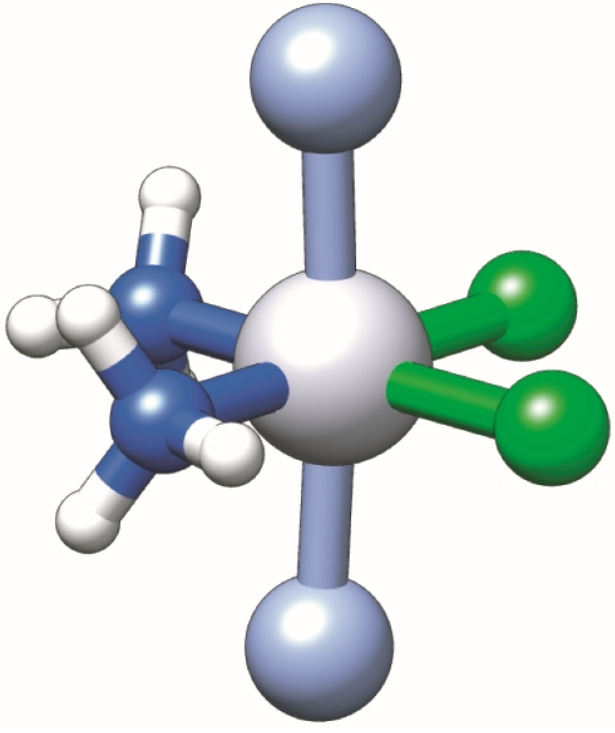

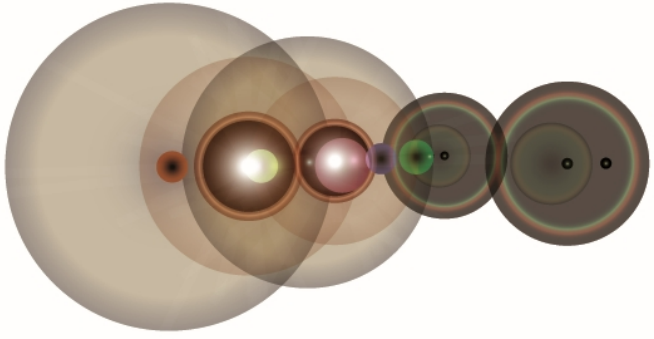

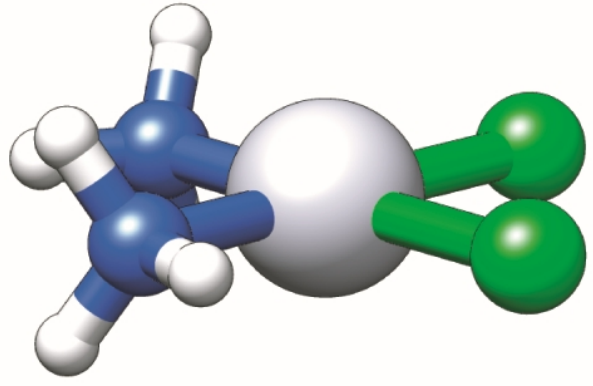

Light-activated
Pt anticancer agents

Anticancer Platinum Agents And Light

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Abstract

Since the discovery of cisplatin, light activation has been employed as a strategy to switch and improve the anticancer effects of platinum compounds. This contribution highlights some of the most representative discoveries obtained in the field of platinum-based photochemotherapy over the years.

1. Introduction

The relationship between Pt anticancer compounds and light dates back to the discovery of cisplatin. After identifying that Pt species were responsible for the abnormal filamentous growth of *E. Coli* bacteria exposed to electric fields [1], Rosenberg and collaborators demonstrated that neutral *cis*-$[PtCl_4(NH_3)_2]$ obtained from UV-irradiated $(NH_4)_2[PtCl_6]$ solutions was highly effective in inhibiting cell division [2,3]. This initial discovery confirmed the potential of Pt complexes as anticancer agents and prompted the identification of cisplatin as lead drug [4–6].
Later, the field focused on other aspects of the biological chemistry of Pt complexes and the use of light was set aside for several years. However, investigators turned back to explore how photochemistry could affect the cytotoxicity profile of Pt agents once the concept of Pt^{IV} prodrugs was introduced to reduce side effects associated with Pt drugs. Part of these efforts were also motivated by the clinical approval of the first photodynamic therapy agent (photofrin) in 1993 [7].

This short review aims at summarizing some of the most important achievements in the development of photoactivatable Pt anticancer agents. Three main sections constitute this contribution. In the first two parts, we discuss the effects of light on the biology of Pt^{II} and Pt^{IV} anticancer complexes. In the third part, we highlight innovative delivery and photochemistry strategies developed to trigger the biological activity of Pt^{IV} compounds. It is worth pointing out that the biological activity of irradiated Pt compounds can

derive either from an enhancement of the effect of the light provoked by the metal species which increases radical production (metal-enhanced phototoxicity) or from the photoactivation of the metal complex itself (photo-enhanced toxicity). In this review the term phototoxicity will encompass both aspects. For a better understanding of the systems described herein, we start with a brief description of the electronic properties of Pt^{II} and Pt^{IV} complexes. To this aim, we return to Rosenberg's original studies and take cisplatin and *cis*-$[PtCl_4(NH_3)_2]$ as representative models.

2. The photochemistry of Pt^{II} and Pt^{IV} complexes

The photochemistry of Pt^{II} and Pt^{IV} complexes of interest in cancer therapy generally involves photodissociation (Pt^{II} and Pt^{IV}) and/or photoreduction (Pt^{IV}) reactions. Such complexes are often non-luminescent and therefore their excited state properties are difficult to characterize via standard spectroscopic techniques. The lack of marked spectroscopic features requires that ultrafast techniques (*e.g.* time-resolved absorption and infrared spectroscopy) are employed for understanding their excited state evolution, as recently reported for a number of Pt^{IV} salts [8,9] and complexes [10], including azido compounds [11,12]. Nonetheless, several pioneering studies are available in the literature of the 60-90s on the photochemistry of Pt complexes with potential in chemotherapy. Conversely, Pt^{II} complexes bearing aromatic diamine ligands of the 2,2'-bipyridine type are highly emissive and their photophysics and photochemistry has been extensively investigated for applications in sensing, catalysis and biology [13].

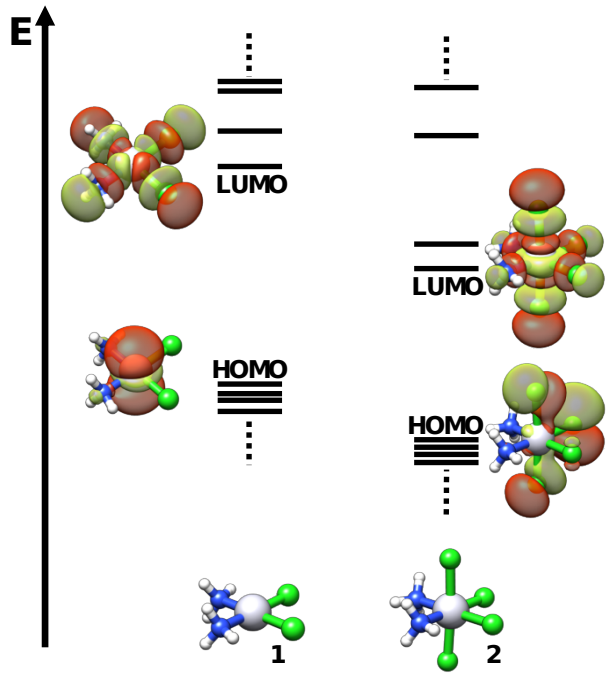


Figure 1 Schematic electronic structure and selected frontiers orbitals of (**1**) *cis*-[$Pt^{II}(NH_3)_2Cl_2$] and (**2**) *cis*-[$Pt^{IV}(NH_3)_2Cl_4$] calculated with DFT (density functional theory) at the SDD level [14]. Atom color code: gray = Pt; green = Cl; blue = N; white = H. HOMO = highest occupied molecular orbital; LUMO = lowest unoccupied molecular orbital.

As shown for *cis*-$Pt^{II}(NH_3)_2Cl_2$ (cisplatin, **1**) and *cis*-[$PtCl_4(NH_3)_2$] (**2**), the electronic structure of Pt^{II} and Pt^{IV} complexes displays LUMOs that have σ-antibonding character (Figure 1). Upon light excitation, these orbitals are populated to afford dissociative excited states that trigger the reactivity of the complexes. Excited states in **1**, **2** and other related systems have ligand-to-metal charge transfer (LMCT) or ligand-field (LF or d-d) nature. LMCT transitions are usually associated with photoreduction and ligand substitution (depending on the ligands), while LF transitions lead to photoisomerization and photoracemization. Another characteristic trait of Pt^{II} and Pt^{IV} complexes such as **1** and **2** is the large HOMO-LUMO energy gap, which results in absorption bands at wavelengths rarely above 400 nm.

In principle, the judicious design of a photoactivatable Pt complex must take into account the stability in the dark and toward biological reductants of the prodrug, but also anticipate its photochemistry. In the case of Pt^{II} and Pt^{IV} complexes, this is not trivial and the photoproducts are often a mixture of substitution, reduction and isomerization species.

3. Photoactive Pt^{II} complexes

Direct irradiation of known Pt^{II} anticancer complexes proved to be moderately useful to increase their biologic activity. Brabec and coworkers showed that UV irradiation (up to 5 hours, 365 nm, 4.3 $mW \cdot cm^{-2}$) of carboplatin increased its DNA binding abilities to levels comparable with cisplatin [15]. Similarly, light irradiation (365 nm, 50 min, 1.77 $mW \cdot cm^{-2}$) of the inactive transplatin switched on its antiproliferative activity prompting DNA interstrand and DNA-protein crosslinking [16]. Quiroga, Malina and Bednarski demonstrated that low-energy irradiation at 350 nm (0.12 $mW \cdot cm^{-2}$) of *trans*-diiodido complexes bearing isopropyl, dimethyl or methylamines produced a 1.5–3-fold enhancement in cytotoxicity when compared with dark conditions. On the contrary, no biological effect was found for the *cis* isomer of the isopropylamine derivative under the same conditions [17].

The limited biological effects observed under high energy and long irradiation regimes have hampered the use of light with cisplatin-like drugs. For this reason, research focus was set on to the design of Pt^{II} complexes coordinating photoactive ligands, capable of behaving as PDT photosensitizers for the generation of singlet oxygen and other reactive oxygen species (ROS) upon light excitation. It is worth mentioning that those complexes, in which the coordination of the sensitizer to the metal center resulted in better properties than the individual components combined, are the so-called "dual agents", whereas complexes that release active species after irradiation are named "cage compounds".

3.1. Light-activatable Pt^{II} complexes as PDT agents and/or cage compounds

Brabec, Kašpárková and coworkers studied the mechanism of action of a cisplatin analogue where one of the ammines was substituted by a 1-methyl-7-azaindole moiety (**3**). Compound **3** showed no toxicity in the dark and micromolar IC_{50} values in cisplatin-sensitive ovarian carcinoma (A2780) cells and cisplatin-resistant human prostate adenocarcinoma (LNCaP) cells when irradiated at 365 nm (3.5 $mW \cdot cm^{-2}$). The complex acted as dual antitumoral agent, with phototoxicity arising from the formation of singlet oxygen and DNA interstrand crosslinking [18]. Exploiting the same mechanism, complex **4**, a carboplatin derivative with halo-substituted 7-azaindoles, showed phototoxicity similar to **3** in cisplatin-sensitive and resistant cell lines under irradiation [19].

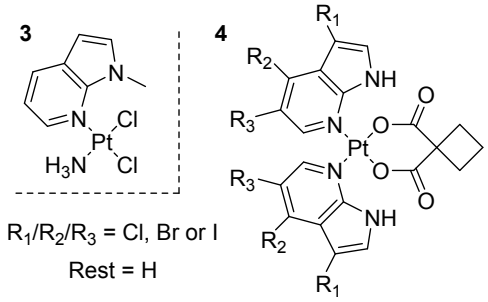


Figure 2 Chemical structure of anticancer azaindole-Pt^{II} complexes.

Chakravarty and coworkers attached Pt^{II} centers to catecholate or diketonate ligands functionalized with fluorescent anthracene and pyrene moieties (Figure 3). In skin keratinocytes HaCaT and breast cancer MCF-7 cells, catecholate complexes **5** and **6** showed increased toxicity in the dark (IC_{50} ~ 30-50 μM) and similar IC_{50} values (5-20 μM) under light irradiation (400-700 nm, 10 $J \cdot cm^{-2}$) compared with their corresponding ligands alone. Data showed phototoxicity arose from apoptosis induced by generation of ROS, whereas the causes of the higher dark toxicity were not conclusive. In the absence of light, neither hydrolysis of the complex nor coordination to 5'-guanosine monophosphate (GMP) was observed in buffer; however, ligand release was confirmed in the dark in the presence of an excess of glutathione (GSH) [20]. Acetylacetonate derivatives **7** and **8** behaved similarly to **5** and **6**; they were stable in solution over 24 hours but released the corresponding ligands when exposed to excess GSH. Due to the presence of pyrene or anthracene, they bound DNA in an intercalative mode and subsequently induced damage upon light irradiation. Complexes **7** and **8** displayed similar phototoxicity values and mechanism of action to those of **5** and **6** in HaCaT cells, inducing apoptosis upon generation of ROS [21].

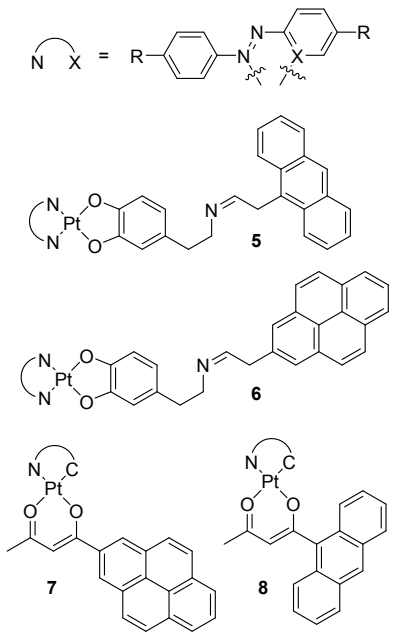


Figure 3 Chemical structure of catecholate- (**5**, **6**) and acetylacetonate-Pt^{II} (**7**, **8**) fluorescent conjugates. **5** and **6**: X=N, R=H; **7** and **8**: X=C, R=OMe.

Chakravarty and coworkers also reported a diammineplatinum complex coordinating curcumin as photoactive moiety. This natural product is a potent anti-inflammatory and anticancer agent, yet prone to hydrolysis and fast metabolization. The Pt^{II} derivative named Platicur (**9**) was designed to protect curcumin from hydrolysis while simultaneously allowing its controlled release and the generation of Pt^{II} species capable of binding DNA upon irradiation with visible light (400–700 nm, 10 J·cm^{-2}). Complex **9** was non-toxic in the dark (IC_{50} > 200 μM) and showed 15 μM IC_{50} in HaCaT cells when irradiated, similarly to curcumin alone, while the value increased to 30 μM in immortalized non-transformed human peripheral lung epithelial (HPL1D) cells [22]. The curcumin derivative **10**, coordinating a diazobenzene ligand instead of ammines, displayed phototoxicity comparable to **9** (11 μM IC_{50} in HaCaT cells, 400-700 nm, 10 J·cm^{-2}) but also presented higher toxicity in the dark (56 μM IC_{50}). Toxicity for these derivatives could be ascribed principally to generation of hydroxyl radicals, although singlet oxygen formation was also observed [21].

Near-infrared (NIR) light (700-1000 nm) penetrates deeper into tissues and causes less damage than visible or UV light. With the aim of developing agents that could be activated in the NIR window, the group of Hart synthesized a NIR light-sensitive (720–740 nm, 3.5 mW·cm^{-2}) prodrug by coordinating the dye IR797 to a Pt diammino fragment (**11**). Under NIR light, **11** behaved as a dual-

agent, generating singlet oxygen and photoreleasing the Pt-aqua complex *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$. Although the compound showed high dark toxicity in cervix and breast cancer C-33 and MCF-7 cells (8-18 μM), IC_{50} values decreased to nanomolar upon light activation (0.14-0.65 μM), corresponding to phototoxicity indexes of 57 and 27 respectively [23].

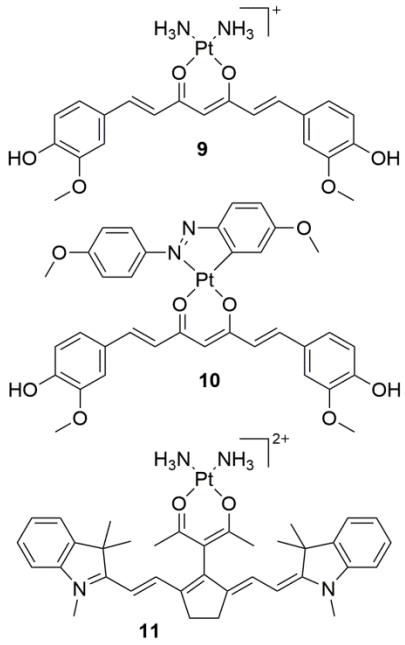


Figure 4 Chemical structure of platicur (**9**), Pt-curcumine acetoacetate (**10**) and NIR active Pt-IR797 conjugate (**11**).

A major limitation of classical PDT systems is the dependency of molecular oxygen to generate reactive oxygen species [7]. This is a fundamental problem in tumors tissues, where oxygen levels are typically much lower than in healthy ones. Adopting an unconventional approach, Palacios and coworkers recently reported a squaramide-based drug precursor (**12**) that displayed phototoxicity only under hypoxic conditions (IC_{50} 69 μM in cisplatin resistant human adenocarcinoma HeLa cells). The squaramide photocleavage mechanism was responsible for the different toxicity. In the absence of oxygen, it generated amino-sulfide fragments that led to the cytotoxic complex **13**. On the contrary, oxidation of these ligands under normoxic conditions led to the generation of non-toxic complex **14** [24].

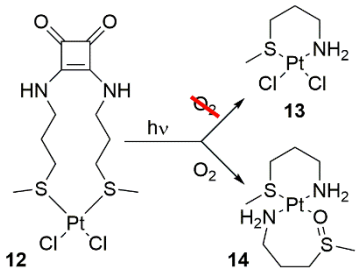


Figure 5 Chemical structure of the squaramide complex **12** and its photoproducts under hypoxic (**13**) or normoxic (**14**) conditions.

3.2. Pt^{II} with heterometallic functional units

Besides the use of photoactive ligands, Pt^{II} agents have been coordinated to other metal scaffolds in order to obtain improved photophysical and photochemical properties.

Chakravarty and coworkers have extensively explored this approach, designing heterobimetallic complexes which combine Pt^{II} centers with photoactive ferrocene and DNA-intercalating N,N,N-pincer ligands. The first generation of this family was based on polypyridyl ligands derived from phenantroline (phen) and dipyridophenazine (dppz) (Figure 6). Phen derivatives **15a** and **15b** showed poor or no cytotoxicity either in the dark or under irradiation (365 nm, 6 W), whereas the dppz chlorido **16a** showed to be toxic in the low micromolar range (2-3 μM IC_{50}) in HeLa and MCF-7 and moderately effective (19 μM IC_{50}) in MCF-10A cells when irradiated (365 nm, 6 W). Compound **16a** however also showed modest toxicity in the dark in HeLa cells (18 μM IC_{50}). Substitution of the chloride by ferrocene (**16b**) translated into higher phototoxicity in MCF-10A cells (13 μM IC_{50}) but lower in HeLa and MCF-7 cells (13-16 μM IC_{50}), whereas dark toxicity decreased in all cases (> 25 μM) [25].

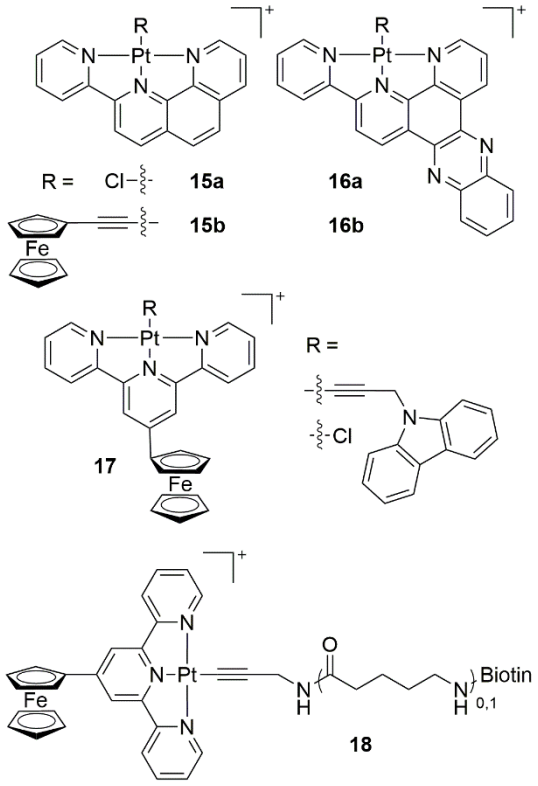


Figure 6 Chemical library of antitumoral ferrocenyl phen (**15**), dppz (**16**) or tpy (**17**, **18**) pincer complexes.

To improve these systems, they prepared complexes with a ferrocene-terpyridine ligand (**17**), selected due to their excellent redox and photophysical properties and the high toxicity of terpyridine-Pt^{II} complexes. They showed good toxicity (10-18 µM IC_{50}) under visible light irradiation (400-700 nm, 2.4 $mW{\cdot}cm^{-2}$) in HaCaT cells and low toxicity (> 65 µM) in the dark. Although entering the cell nucleus, these compounds showed poor DNA intercalating abilities [26]. In a recent study, a biotin unit was attached onto analogue compounds (**18**) to increase the uptake *via* the biotin-specific streptavidin receptors, known to be overexpressed in cancer cells. Despite the high cell uptake, they retained similar dark/light toxicity profiles (IC_{50} 8-17 µM under irradiation, > 50 µM in the dark) in human breast carcinoma cancer cells (BT474) but IC_{50} values under irradiation increased above 40 µM in human normal breast epithelial HBL-100 cells [27].

The combination of platinum with heterometallic functional units has also been exploited to produce effects that go beyond PDT. For instance, several optical or radioactive systems were designed to integrate imaging properties and anticancer activity. The combination of a diamminochloridoplatinate unit with BODIPY led to the development of highly photo-cytotoxic and emissive

theranostic agents (**19a** and **19b**). By monitoring its emission, **19a** was found to preferentially localize in the mitochondria. Both **19a** and **19b** were essentially non-toxic in the dark and induced apoptotic death under irradiation with visible light (400-700 nm, 10 $J \cdot cm^{-2}$) with IC_{50} values of 100-150 nM in HaCaT and 3-6 μM in MCF-7 cells [28]. DNA binding studies with model 9-ethylguanine showed unconventional monosubstitution of one of the ammines instead of the chloride atoms. Guo, He and coworkers proved, with a closely related structure (**20**), that a different linkage between Pt and BODIPY units improved the ROS production and intracellular accumulation when compared to BODIPY alone. This was explained in terms of cell membrane damage after short irradiation periods (5 min, 532 nm, 3.5 $mW \cdot cm^{-2}$). IC_{50} values of separated components were all above 40 μM while the Pt-BODIPY conjugate **20** displayed values in the 4–10 μM range for a number of cancer cell lines upon light activation [29].

The natural emission of an Eu complex upon photodissociation of the Pt center was exploited to build a traceable and controllable cisplatin-delivery molecule (**21**). Complex **21** was non-toxic and non-emissive, but underwent photocleavage upon two-photon excitation (730 nm), simultaneously releasing *cis*-$[Pt(NH_3)_2(H_2O)Cl]^+$ and the emissive Eu unit, allowing to monitor the process. Nonetheless, **21** presented mild dark toxicity in HeLa (22 μM) and A549 (50 μM) cells [30].

Very recently, a novel template was employed to build theranostic compounds with either optical or radiochemical imaging capability, depending on the metal employed. The conjugate consisted of a Pt^{II} center with *trans* geometry and a pincer unit loaded with an emissive rhenium or radioactive technetium tricarbonyl scaffold. The rhenium compound **22a** displayed lower toxicity in the dark (> 60 μM) than after irradiation (350 nm, 2.58 $J \cdot cm^{-2}$), with IC_{50} values between 10 and 20 μM in HeLa and A2780 cisplatin sensitive and resistant cells. The compound did not produce any DNA adduct and cellular damage was attributed to singlet oxygen production. No CO release study was performed but the formation of singlet oxygen was confirmed and quantified. *In vivo* biodistribution of the radioactive technetium analogue **22b** confirmed the great stability of the complex in the bloodstream, with only minor decomposition 1 hour after injection, and accumulation in liver and kidneys [31].

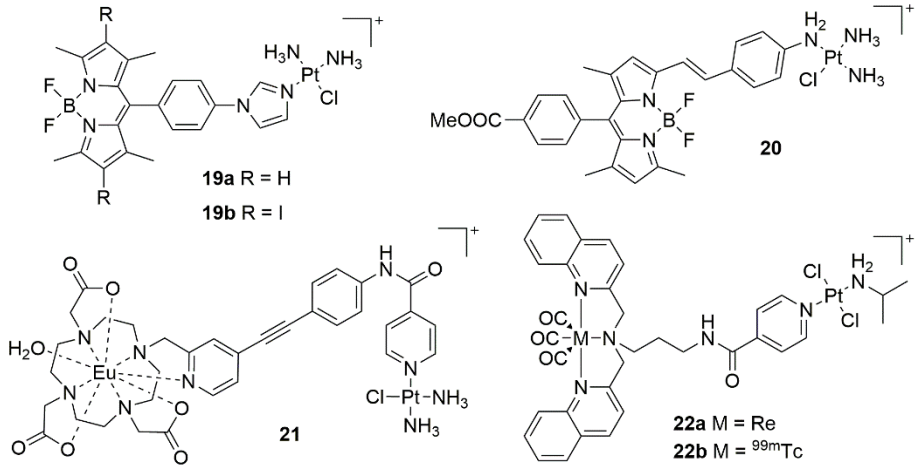


Figure 7 Chemical structure of cisplatin-like BODIPY conjugates (**19** and **20**), Eu-based prodrug for release monitoring (**21**) and theranostic optical and radiolabeled complexes (**22**).

4. Pt^{IV} anticancer complexes and light activation

The need to tackle clinical problems associated with Pt^{II} drugs prompted, in the last 20 years, an increased interest of the scientific community on Pt^{IV} complexes that display hydrolytic inertness. Generally, Pt^{IV} agents do not undergo fast hydrolysis in biological environments (although this dogma has been recently contradicted [32]) and reduce subsequent unspecific toxicity. This family of octahedral compounds incorporates axial ligands into their chemical structure, which help modulating solubility parameters and biological effect in cells, as well as adding molecular and nano-vectors for targeting specifically cancer cells [33–35].

Compared to their Pt^{II} counterparts, octahedral Pt^{IV} complexes require additional steps of activation in which they undergo reductive elimination of ligands, either via inner- or outer-sphere electron-transfer mechanisms [36]. The activation process is thought to be principally triggered inside cells by intracellular reducing agents which are able to convert inert Pt^{IV} complexes into Pt^{II} derivatives. These subsequently form reactive aqua species that generate DNA adducts and induce cell death (Figure 8) [37]. Much of the research carried out on Pt^{IV} complexes has consisted in improving the pharmacological profiles of Pt drugs, elucidating the details of the $Pt^{IV} \rightarrow Pt^{II}$ activation and its biological effects, obtaining promising toxicity profiles *in vitro*, and overcoming drug resistance caused by previous treatments.

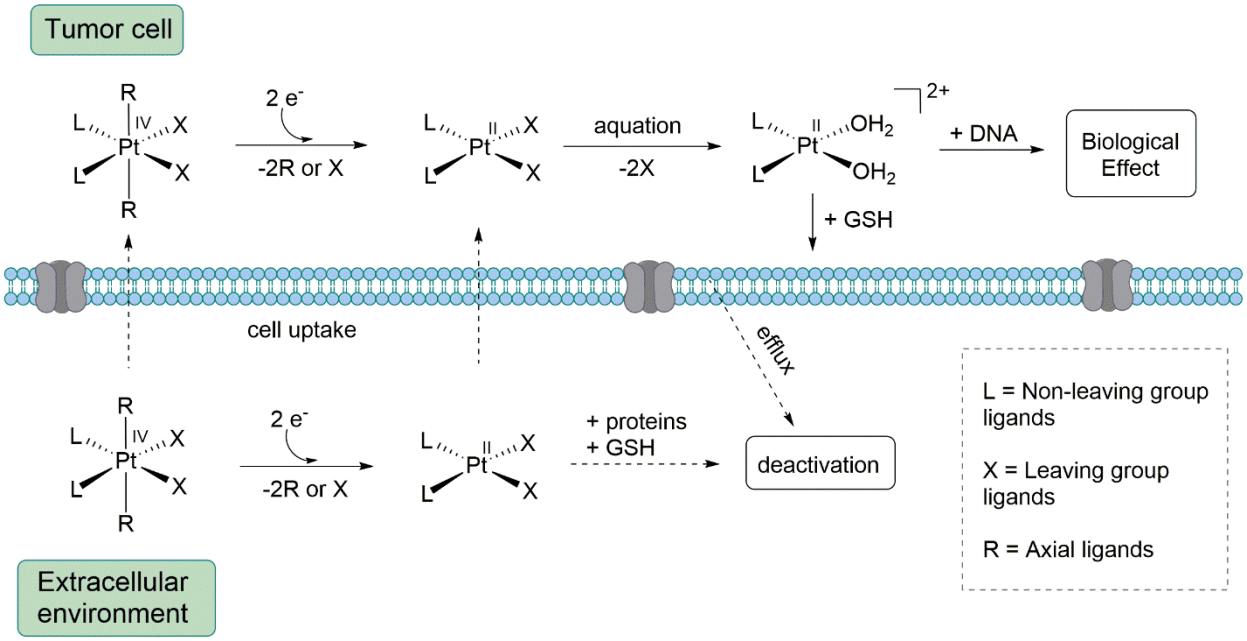


Figure 8 Schematic representation of the activation mechanism of Pt^{IV} prodrugs and their biological action in cells. Scheme adapted from reference [37].

A number of Pt^{IV} prodrugs entered clinical trials with excellent examples represented by Ormaplatin, Iproplatin and Satraplatin (Figure 9) [38–40]. Unfortunately, these three compounds failed to obtain approval by the Food and Drug Administration (FDA) since none of them had anticancer efficacy significantly higher than clinically used Pt^{II} drugs.

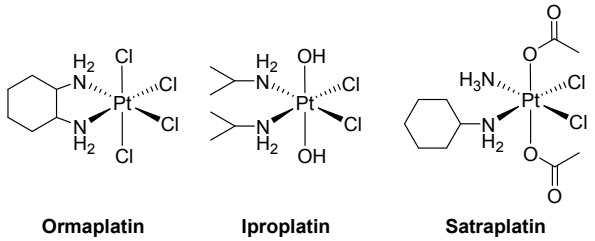


Figure 9 Pt^{IV} prodrugs which entered clinical trials.

Nevertheless, Pt^{IV} complexes remain promising systems to overcome the typical drawbacks of Pt^{II} anticancer drugs and photoactivation has been regarded as an alternative and potentially successful strategy to fine-control the biological effects of Pt^{IV} prodrugs in cancer cells. In the field of photochemotherapy, the initial research focus was to develop stable and non-cytotoxic Pt^{IV} complexes in the dark, capable of reducing cell viability upon light irradiation. More recently, the field interest has aimed at the design of

delivery and targeting approaches and at shifting excitation wavelengths towards the therapeutic window, *e.g.* the red and near infrared part of the spectrum. These aspects are discussed here below through selected and representative examples of Pt^{IV} complexes as prodrugs for active Pt^{II} species.

4.1. Diiodo-Pt^{IV} complexes

In the 1990's, Bednarski's laboratory was the first to investigate the toxicity of Pt^{IV} complexes upon light activation [41,42]. Complexes **23**–**25** bearing iodides as leaving ligands and ethylenediamine (en) as non-leaving group were chosen for their favorable LMCT bands at 380-400 nm ($\varepsilon \approx 1 \times 10^3$ M^{-1} cm^{-1}). Furthermore, the *cis* geometry of iodido ligands in **23**–**25** favored photoreduction with respect to photo-substitution reactions. The chelating ethylenediamine instead reduced the occurrence of photoisomerization reactions, potentially leading to *trans* Pt^{II} species which were known to be inactive.

When irradiated at 410 nm, **23** underwent photodecomposition to generate $[PtCl_2(en)]$ which was then able to platinate DNA. Unfortunately, compound **23** was found to decompose and bind to DNA in the dark as well. Consequently, no differences in toxicity toward human cancer cells (human bladder cancer and melanoma cells, TCCSUP and SK-MEL-24 respectively) were found between samples kept in the dark or light irradiated [42].

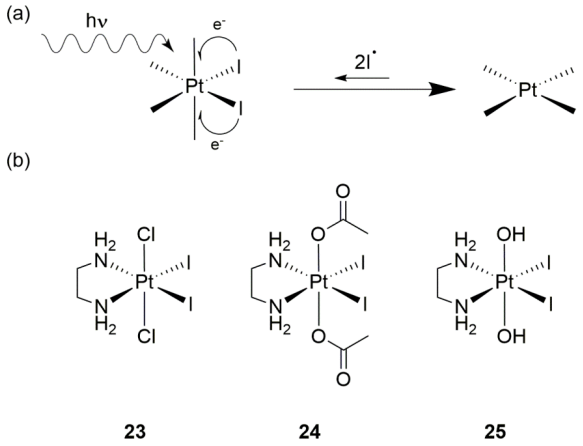


Figure 10 (a) Mechanism proposed for the photoreduction of iodide-based Pt^{IV} compounds. (b) First generation of Pt^{IV} prodrugs based on iodide ligands.

To improve the dark stability of this class of compounds, Bednarski and collaborators changed the axial chlorido ligands of **23** to acetates (**24**) and hydroxides (**25**) [41]. When incubated with cell culture medium, derivatives **24** and **25** decomposed after 6.6 and 46.8 h, respectively. The process was

much faster (≈ 1 h) under light excitation (> 375 nm). Complex **24** afforded 60% of platinated DNA in buffer after 6 h of irradiation, while almost no platination was observed in the dark. On the other hand, **25** did not lead to DNA adducts even after 6 h of light irradiation, suggesting that the photoproducts were likely Pt^{IV} species. Both **24** and **25** displayed higher cytotoxicity against cancer cells (TCCSUP) when irradiated. The different nature of the photoproducts of the two complexes suggested that this photoinduced cytotoxicity derived from different mechanisms of action. Nevertheless, **24** and **25** could kill cancer cells in the low micromolar range also in the dark. In fact, NMR showed that both compounds were rapidly reduced via inner-sphere mechanism by biothiols such *N*-acetylcysteine and GSH [43].
Overall, even if diiodo-Pt^{IV} complexes were deemed as photoactivatable drugs, the proof-of-concept studies conducted by Bednarski and his collaborators demonstrated that light could be used for the activation of Pt^{IV}-based prodrugs, paving the way for the design of new and improved derivatives.

4.2. Diazido-Pt^{IV} complexes

In the early 2000s, Sadler successfully addressed both the dark stability and the biothiol-mediated reduction issues developing azido-based Pt^{IV} complexes [44]. Azides confer stabilization to Pt^{IV} complexes in the cellular reducing environment due to their strong electron-donating nature. The photochemistry of Pt^{IV} complexes coordinating azido ligands was known since the end of 1970s when Vogler *et al*. demonstrated that irradiation of *trans*-$[Pt(N_3)_2(CN)_4]^{2-}$ led to azide elimination and photoreduction to Pt^{II} species [45]. The mechanism proposed involved the formation of azide radicals which were then rapidly converted in molecular nitrogen (Figure 11) [45,46]. Whereas halide radicals are stable in water and can reconvert Pt^{II} to Pt^{IV} (see Figure 10), azido ligands provide a fast and irreversible photoreduction of the Pt^{IV} complexes [47].

The first azido-based compounds investigated by Sadler and collaborators were *cis,trans*-$[Pt(en)(N_3)_2(OH)_2]$ and *cis,trans,cis*-$[Pt(N_3)_2(OH)_2(NH_3)_2]$ (**26** and **27**, Figure 11). The two derivatives behaved similarly in solution, being extremely stable in the dark (up to 90 days) also in the presence of biological reductants like GSH (up to weeks).
Complexes **26** and **27** gave rise to species able to bind to DNA nucleobase models 5’-GMP or to d(GpG) only under irradiation [44,48]. They share similar absorption properties with a LMCT band centered at 256 nm ($\varepsilon \approx 1 \times 10^4$ $M^{-1} \cdot cm^{-1}$) with a tail that reaches the visible region. In the presence of 5’-GMP

and after irradiation at 458 nm, compound **26** afforded the double adduct [Pt(en)(5'-GMP-N7)$_2$]. The same outcome was observed when **26** was incubated with dGpG and irradiated, leading to the formation of the double adduct with the nucleotide. Under irradiation at 458 nm for 3 h, photoproducts of **26** formed platinated GG crosslinks on plasmid DNA and to stop *in vitro* RNA synthesis by RNA polymerase [48]. Of note, **26** and **27** typically absorb up to 350 nm, yet they showed the capability to undergo photoactivation also in the visible region (> 400 nm). Such photoreactivity was rationalized by DFT modeling which determined the presence of weak electronic transitions in the region between 400–500 nm [49].

Both **26** and **27** were active against human bladder cancer cells (including the cisplatin-resistant type) only when irradiated at 366 nm, with IC_{50} values reaching 50 µM [50]. Fluorescence microscopy studies demonstrated also that cell morphology changes were not comparable with the ones provoked by cisplatin, implying a different mechanism of action for the light-activated **26** and **27**.

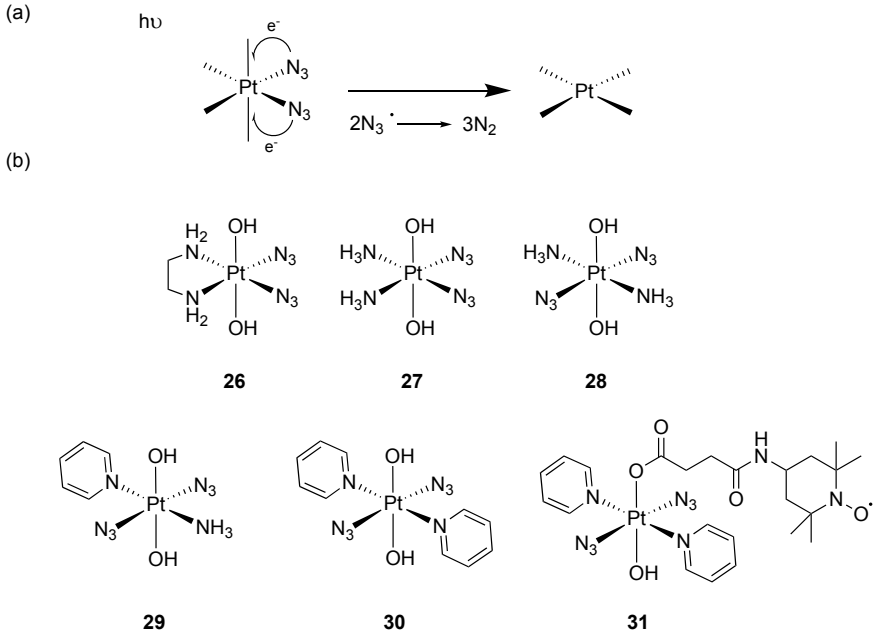


Figure 11 (a) Mechanism proposed for the photoreduction of azido-based Pt^{IV} compounds. (b) Second generation Pt^{IV} prodrugs based on azido ligands.

The Sadler group later studied the photochemistry and the anticancer activity of *trans,trans,trans*-[Pt(N_3)$_2$(OH)$_2$(NH_3)$_2$] (**28**), the *trans* isomer of **27** [51,52]. Complex **28** was stable in the dark but once irradiated at 365 nm in the presence of 5'-GMP afforded the *trans* bis-G adduct [Pt(NH_3)$_2$(5'-GMP-N7)$_2$]. This process was significantly more efficient in comparison to the same

photoreaction performed on **27**. In the case of **28**, more than 75 % of its photoproducts were bound to 5'-GMP after 1 h. Photoactivation of **28** in solution resulted in the formation of *trans*-[$Pt(NH_3)_2(OH_2)_2$] and other photoreduction and photoisomerization products. In the presence of DNA, irradiation of **28** led to interstrand cross-links, as demonstrated for transplatin [16]. In a comparative study, **27**, **28**, cisplatin and transplatin were tested against human keratinocytes (HaCaT cells) and, after irradiation, compound **28** was the most active Pt^{IV} compound so far [51].

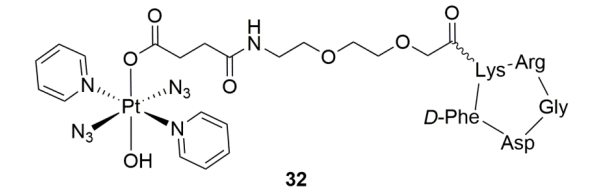
As follow up of the discoveries on **28**, Sadler and collaborators developed two *trans* azido-derivatives (Figure 11) with pyridine (py) ligands, *trans,trans,trans*-[$Pt(N_3)_2(OH)_2(NH_3)(py)$] (**29**) [50] and *trans,trans,trans*-[$Pt(N_3)_2(OH)_2(py)_2$] (**30**) [52]. Pyridines introduced several advantages compared to NH_3 groups: i) they are bulkier, potentially preventing off-target interaction of the Pt^{IV} complex and of its photoproducts; ii) they can promote π-stacking interactions with DNA favoring the binding of the Pt^{IV} complex to their target and iii) they produce a bathochromic shift in the absorption spectrum. Complexes **29** and **30** proved to be very stable in solutions kept in the dark (more than 20 days), even in the presence of reductants such as GSH and ascorbate [52,53]. After irradiation, which can be performed at 365 and 420 nm, photoproducts of both compounds interacted very efficiently (more than the ones of **28**, for instance) with DNA models (*e.g*. 5’-GMP and ct-DNA) [54]. As an example, **30** incubated with DNA and irradiated at 365 nm (4.6 $mW \cdot cm^{-2}$) induced mono- and bifunctional adducts 16-fold more than cisplatin [55].

Recently, thioredoxin (Trx), an important enzyme overexpressed in several cancer cells [56], was proposed as potential target of irradiated **30** (and potentially other Pt^{IV} prodrugs). Photoproducts of the complex could indeed bind to histidine, glutamic acid and glutamine residues of Trx upon irradiation with blue light (460 nm) [57]. In another recent manuscript, Sadler demonstrated that photoproducts of **30** generated by visible light interacted with two neuropeptides giving rise to oxidized or platinated products, with the nature of the species being dependent on the amino acid composition of the peptide [58].

The two pyridine derivatives **29** and **30** have been tested against several cancer cell lines and, to date, remain the lead compounds of this kind in terms of phototoxicity. For example, **29**, while being inactive in the dark, killed A2780 human ovarian carcinoma cells and their cisplatin-resistant version in the low micromolar range (2 and 16 μM, respectively) only when irradiated at

366 nm. These cytotoxicity values, 80-fold higher than the ones obtained with cisplatin, were obtained using a low light dose (5 J·cm^{-2} for 30 min) [54]. Compound **29** proved to be cytotoxic also using irradiation at 420 nm (5 J·cm^{-2}). Upon light-activation, the complex does not kill cancer cells by the same apoptotic mechanism as cisplatin but rather through a different mechanism of cell death, most likely involving autophagy as indicated by changes in the levels of the autophagic proteins LC3B-II and p62. As a matter of fact, a statistically relevant number of mice bearing OE19 (esophagus) tumors treated with **29** and light (420 nm, 100 J·cm^{-2}) survived after the 35th day, while all the controls (no treated and treated in the dark) died in the same time window [59]. It was recently demonstrated that the acute photocytotoxicity of **30** depended on the generation of azide radicals and Pt^{II} photoproducts [60]. In detail, the Sadler group showed by EPR and NMR that light-associated activity of **30** against cancer cells can be switched off by low concentrations (500 μM) of the aminoacid L-tryptophan, which is a well-known mediator of electron transfer in proteins.
Based on the structure activity relationship obtained for complexes **26**–**30**, the same group developed several other azido-based Pt^{IV} prodrugs with diverse ligands (*e.g*. acetate in the axial positions or different N-coordinating ligands in the equatorial positions) [61–63]. The outcome in terms of stability, DNA-binding properties and cytotoxicity (against HaCaT and A2780 cells) in the dark and under irradiation were comparable with the one obtained using **29** and **30** and led to the general conclusion that the *trans* derivatives were more active that their *cis* analogues.

Recently, V. Venkatesh *et al*. described the nitroxide spin-labelled photoactivatable Pt^{IV} prodrug *trans,trans,trans*-[Pt(N_3)$_2$(OH)(OCOCH$_2$CH$_2$CONH-TEMPO)(py)$_2$] (where TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl) (**31**, Figure 11) [64]. In order to obtain a compound trackable in vivo by EPR and with simultaneous radical-mediated anticancer activity, compound **31** was designed substituting one of the axial hydroxyl of **30** with a functionalized TEMPO radical. EPR experiments showed that light irradiation of **31** with blue light (465 nm, 50 mW) led to the formation of azidyl and nitroxyl radicals in solution and to a corresponding high cytotoxicity towards A2780 human ovarian carcinoma cells (10-fold higher than cisplatin) [64].



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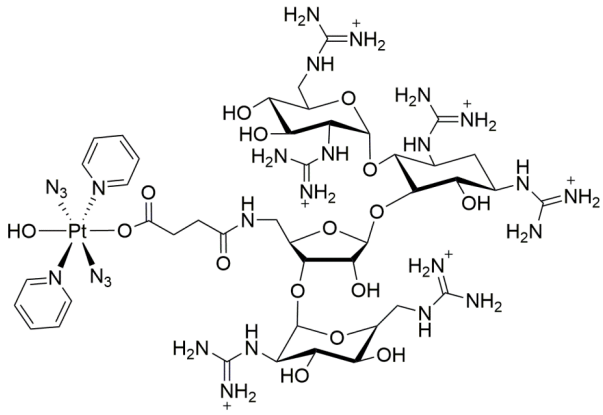

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Figure 12 Azido-Pt^{IV} prodrugs functionalized with targeting ligands for improved cellular uptake.

In a collaborative effort, Marchan and Sadler designed new photoactivatable agents with comparable biological activity of derivative **30** but with improved cellular uptake properties. In the case of compound **32** (Figure 12), for instance, the Pt^{IV} prodrug was conjugated to a cyclic peptide containing the RGD sequence (–Arg–Gly–Asp–), which is selectively recognized by transmembrane glycoproteins ($\alpha_V\beta_3$ and $\alpha_V\beta_3$ integrins) overexpressed in different tumor cells [65]. Complex **33** featured instead a guanidinoglycoside (guanidinoneomycin), known to transport cargos into cells in a selective proteoglycan-dependent manner [66]. In both cases, the metal complexes showed a certain degree of selectivity toward human malignant melanoma cells (SK-MEL-28) and retained the ability to bind the DNA model 5'-GMP upon irradiation with blue light, similarly to **30** [65,66]. These agents highlight how photoactivatable Pt^{IV} scaffolds hold great promise for a double control of platinum-associated anticancer activity: one based on the targeting properties conferred by the chosen axial ligands and the other based on the possibility to selectively generate Pt^{II} species by light excitation.

5. Nanodelivery of photoactivatable Pt prodrugs and innovative photoactivation strategies

Many efforts have been applied to improve the delivery of Pt anticancer complexes by light activation. In a number of systems, octahedral Pt^{IV} complexes were loaded onto polymeric micelles that upon UVA light (365 nm) released cytotoxic Pt^{II} species [67–69]. For instance, Zheng and collaborators described that copolymeric micelles made of monomethoxy poly(ethylene glycol)-block-poly(ε-caprolactone)-block-poly(L-lysine) loaded with **34** (Figure 13) exhibited greater antineoplastic effects than cisplatin in liver hepatocellular carcinoma (HepG2) and ovarian adenocarcinoma (SKOV3) cells after UVA light irradiation (18 mW•cm^{-2}). Upon light excitation, **34** was reduced and Pt^{II} species were released from the polymeric micelles. Uptake studies showed that polymeric encapsulation enhanced the Pt uptake into cells [67].

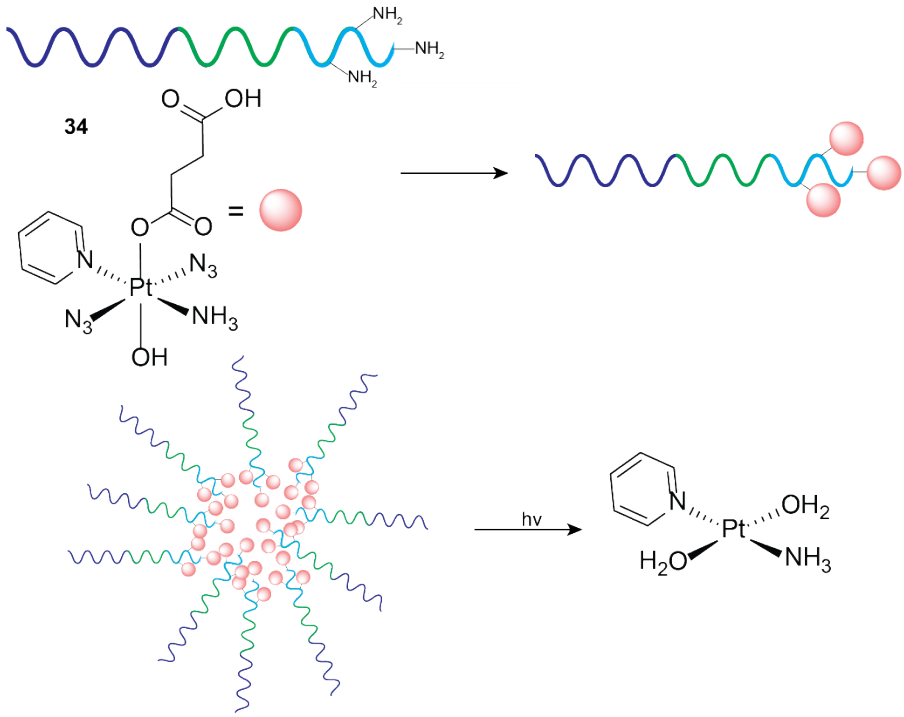

Figure 13 Illustration of Zheng´s nanopolymeric delivery approach [67].

Adopting another approach Huang and coworkers, coordinated one or two hydrophilic amino-functionalized lactose to **35** or **36** respectively (Figure 14), forming self-assembled amphiphilic micelles (one lactose derivative) or vesicles (two lactose derivatives). Lactose-based amphiphiles worked as drug carriers and simultaneously were able to target HepG2 cells that overexpress the asialoglycoprotein receptor, a lectin that can be found in the plasma membrane of liver cells [70]. Upon UVA light activation (10 mW•cm^{-2}), **35** or **36** were photoreduced producing the breakdown of the lactose carriers and the release of the Pt^{II} species. *In vitro* experiments showed that light-irradiated

vesicles generated more Pt-DNA adducts than micelles and that Pt accumulation in HepG2 cells was higher than in cell lines that do not overexpress the asialoglycoprotein receptor. Furthermore, vesicles functionalized with the NIR-absorbing dye Cy7.5 could be traced by fluorescence imaging in mice model. *In vivo* testing on a subcutaneous liver cancer model demonstrated that vesicles accumulated into liver cells causing less system toxicity than cisplatin upon light activation [68].

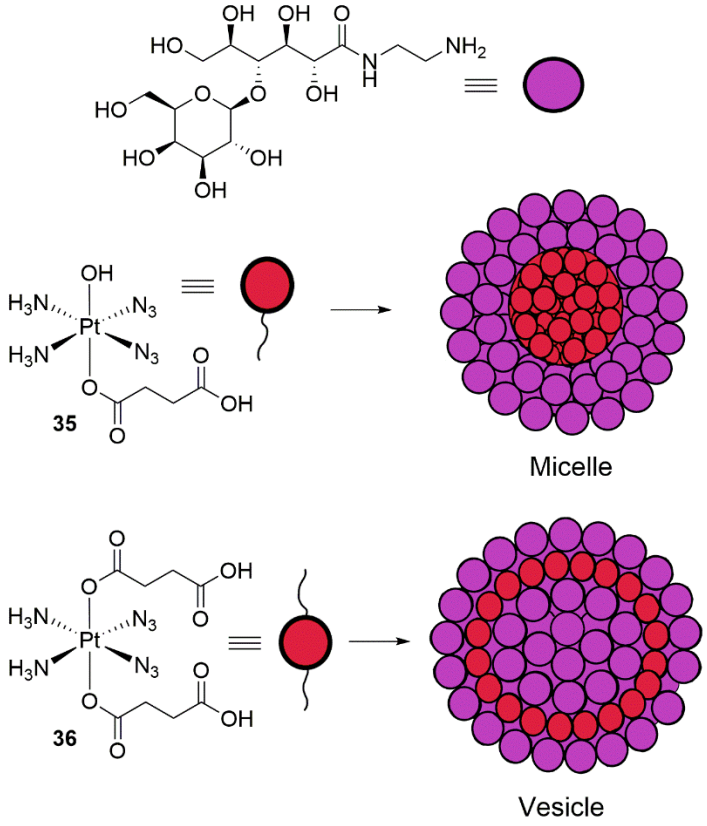

Figure 14 Illustration of Huang´s lactose-based amphiphiles [68].

Sadler´s laboratory exploited the capability of guanosine derivatives to form highly biocompatible hydrogels for the incorporation of compound **37**. The complex was conjugated to a dopamine molecule into a G-quadruplex-based hydrogel by monoborate ester formation (Figure 15). The hydrogel scaffold allowed a slow, sustained and controllable release of cytotoxic Pt^{II} species upon light excitation. The authors showed that under blue light (465 nm 50 $mW \bullet cm^{-2}$), Pt^{II} and Pt^{IV} photoproducts were liberated from the G-quadruplex hydrogel, exhibiting greater toxicity than the parent compound **38** (IC_{50} 3 μM and 74 μM respectively), in cancerous and healthy cells. Notably, the irradiated hydrogel showed 18-fold times greater antiproliferative activity

toward cisplatin resistant A2780 human ovarian carcinoma cells (IC_{50} 3 μM), than for non-cancerous MRC-5 cells (IC_{50} > 50μM) [71].

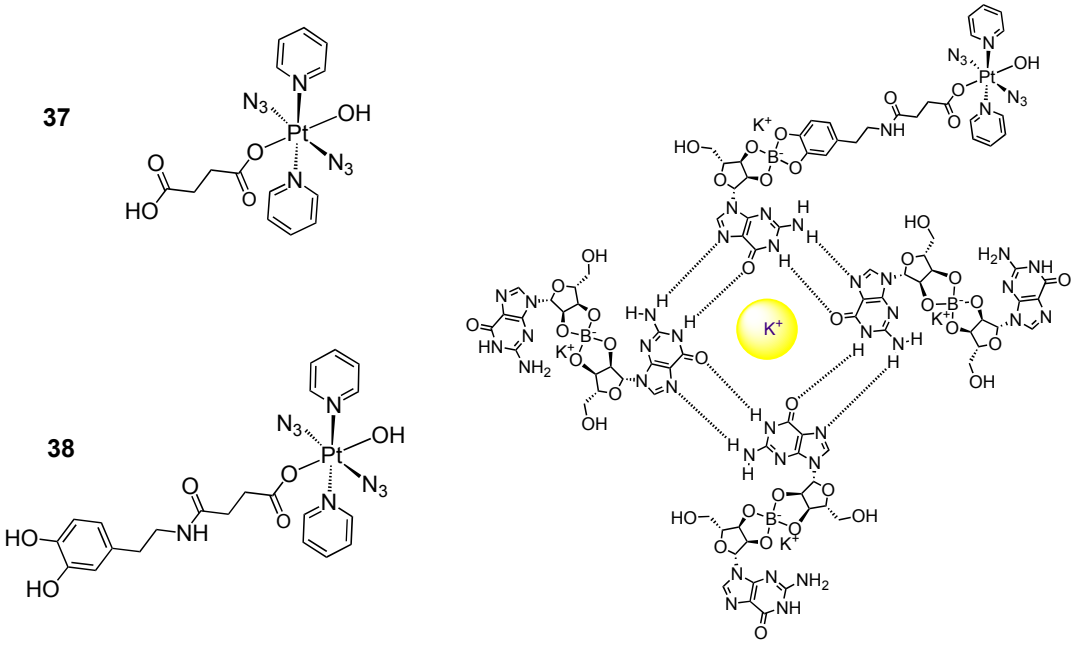

Figure 15 Schematic representation of the Pt^{IV}-guanosine borate hydrogel [71].

Researchers in the field of photoactivatable anticancer Pt agents have investigated a range of nanoscale materials with photophysical features suitable for triggering photochemical reactions at convenient wavelength range, that is the red and NIR region of the spectrum.

The group of Mareque-Rivas designed micelle-encapsulated CdSe@ZnS core-shell quantum dots (QDs) loaded with complex **39** (Figure 16) and the radioactive technetium tricarbonyl complex *fac*-$[^{99m}Tc(OH_2)_3(CO)_3]^+$ for theranostics. Upon 630-nm light excitation (30 mW•cm^{-2}), the nanoscontructs induced the reduction of **39** *via* photoinduced electron transfer, liberating Pt^{II} cytotoxic species. *In vitro* experiments showed that irradiated micelles were active against human prostate cancer PC-3 cells (IC_{50} 25 μM), while no toxicity was observed for dark controls. Moreover, irradiated **39** alone showed no toxic effect of PC-3 cells (IC_{50} ≈ 500 μM) [72]. In a later work, Infante *et al*. showed that the QD-triggered photoreduction of **39** resulted in a different set of photoproducts compared to direct excitation of the metal complex with UVA light [73].

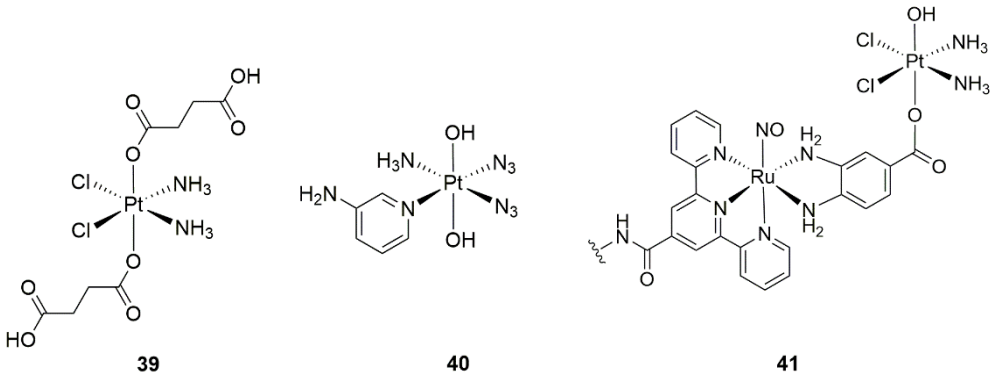

Figure 16: Chemical structure of Pt^{IV} prodrug combined with QDs (**39**), CDs (**40**) and GQDs (**41**).

Carbon Dots (CDs) have been also used as light sensitive carriers for the transport and delivery Pt drugs. Fluorescent CDs functionalized with folic acid and **40** (Figure 16) selectively targeted cancerous cells overexpressing folate receptors, releasing toxic Pt^{II} species under visible light irradiation (> 400 nm, 200 mW•cm^{-2}), and ultimately inducing cell death *via* apoptosis [74]. Similarly, Liu and collaborators loaded the heterobimetallic complex **41** onto folate-functionalized N-doped graphene quantum dots.
In vitro experiments on HeLa, MCF-7 and normal non-cancer HUVEC cell lines showed that these nanoplatforms preferentially accomulated in HeLa cells. Upon NIR light irradiation (808 nm, 1 W•cm^{-2}), **41** showed antiproliferative activity resulting from the synergistic and simultaneous release of NO and Pt^{II} drugs [75].

Photoactivation of Pt^{IV} complexes with near infrared light was also achieved using upconverting nanoparticles (UCNPs), a class of inert nanomaterials that have emerged for their unique emission properties as well as useful tools for imaging in medicine [76]. These nanoscale materials doped with lanthanide ions have the capability to absorb consecutively two or more photons of low energy and undergo non-linear (anti-Stokes) optical processes [76] that lead to shorter-wavelength (visible and UV) light emission. The luminescence profile of UCNPs are suitable for photochemical activation of metal-based anticancer agents.
For example, our group reported earlier that core-shell $NaYF_4$:Yb,Tm@$NaYF_4$ UCNPs loaded with a Pt^{IV} complex functionalized with an amine PEGylated phospholipid (**42** Figure 17a) could be transformed into biologically active Pt^{IV} and Pt^{II} (30%) complexes under 980-nm irradiation (4.9 W•cm^{-2}) for 4 hours [77].

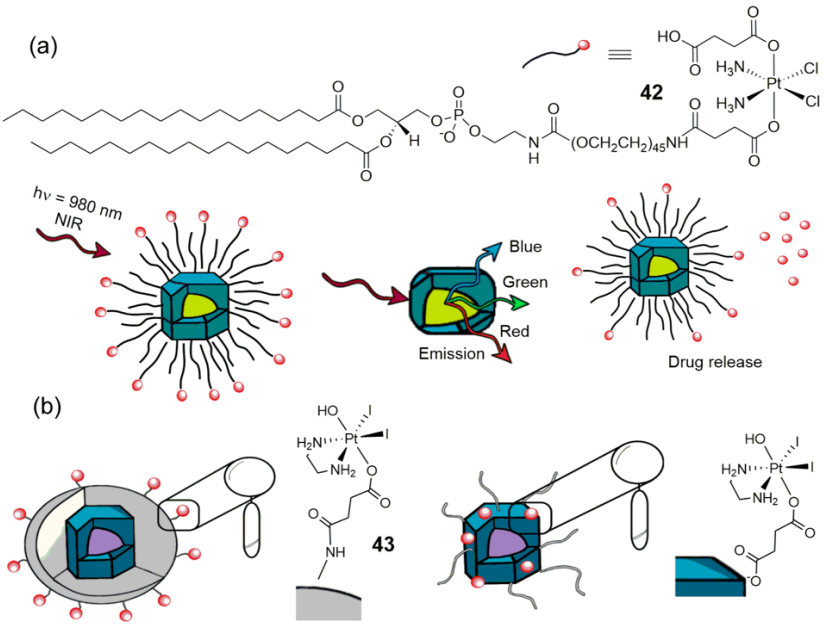

Figure 17: NIR photoactivation of Pt^{IV} prodrug complexes triggered by UCNPs [77,78].

Bednarski and collaborators conjugated light sensitive monocarboxylated diiodido derivatives **43** to $NaGdF_4$:Yb,Er UCNPs employing two different strategies. In one case, UCNPs were functionalized with an aminated silica shell and complexes were covalently attached to the surface *via* amide bonding. In the other case, **43** was attached electrostatically to the surface of the UCNPs by ligand exchange. Results showed that both strategies afforded comparable amount of Pt onto UCNP surfaces. When covalently attached, greater light dependent release of Pt species was observed with respect to electrostatically loaded prodrugs. Besides, covalent UCNP-Pt^{IV} conjugates also showed higher cytotoxicity under dark and upon NIR light irradiation (980 nm, 1.2 $W \bullet cm^{-2}$) in HL60 human leukemia cells, compared to electrostatic loading. XPS measurements demonstrated that in both strategies only around 20% of the Pt on the surface was in the Pt^{IV} oxidation state while 80% was readily transformed to Pt^{II} [78].

Dai et *al.* [79] and Min and *al.* [80] reported that Pt^{IV} azido analogues of **29** and **30** anchored to UCNPs nanomaterials displayed activity *in vitro* and in the former case could also induce tumor reduction *in vivo* upon NIR light irradiation. However, despite having received a high number of citations, these two articles lack key characterization and control experiments and fail in providing substantial evidence on the NIR light activation of Pt^{IV} complexes and its link with the biological effects observed. Furthermore, it is important to stress that UCNP-assisted activation of Pt agents has been achieved so far using rather high excitation intensities and 980-nm light sources, a

wavelength that causes significant water heating and hence can lead to direct damage of biological components [81]. Nd-sensitized UCNPs and 808-nm excitation is currently being investigated as alternative for PDT application to overcome such limitations [82].

Not only nanomaterials can be employed to favor the photochemistry of Pt^{IV} anticancer complexes at more convenient wavelengths, also biomolecule and proteins are effective in such task. In 2017, our group discovered that upon 460-nm light excitation (instead of UVA), selected flavins and flavoproteins are able to photosensitize and photocatalyze the transformation of non-toxic Pt^{IV} prodrugs into cytotoxic Pt^{II} drugs in a bioorthogonal fashion [83]. In these reactions, Pt^{IV} complexes acted as unconventional substrates that interacted with flavin derivatives functioning as photocatalysts in biological environments. In a first work, the rich photoredox features of riboflavin (Rf) [84] were employed to perform selective reduction of **39** (Figure 16) using 2-morpholinoethanesulfonic acid (MES) as sacrificial electron donor [85]. Through this activation approach, Rf can potentially trigger cellular damage in two simultaneous mechanisms: oxidative stress due the photogeneration of ROS by Rf and DNA targeting achieved by the formation of Pt^{II} species in cells. The antiproliferative activity of Rf-activated **39** was tested firstly in PC-3 (human prostate) and later in Capan-1 (pancreatic cancer) cells. Results obtained in PC-3 cells, demonstrated that the catalyst-substrate pair Rf/**39** was not toxic in the dark, while upon blue light irradiation cell viability was reduced to values comparable to cisplatin. On the other hand, Capan-1 cells were tested because they showed high tolerance against singlet oxygen damaging [86–88]. Viability experiments in this cell line suggested that the pair (Rf/**39**) was also effective under regimes in which PDT was not effective, because of the selective photocatalytic activation of the Pt^{IV} substrate [89].
In a second manuscript, we reported that also flavoproteins such as miniSOG (mini Singlet Oxygen Generator) and NOX (NADH oxidase) were able to photocatalytically transform **39** and its analogue **44** into Pt^{II} species in a bioorthogonal manner. Using either MES or NADH as electron donors, miniSOG required blue light activation (460nm, $6 mW \bullet cm^{-2}$) to perform the catalysis. On the contrary, NOX already converted the Pt substrates in dark when NADH was employed, while required light in the case of MES [90].

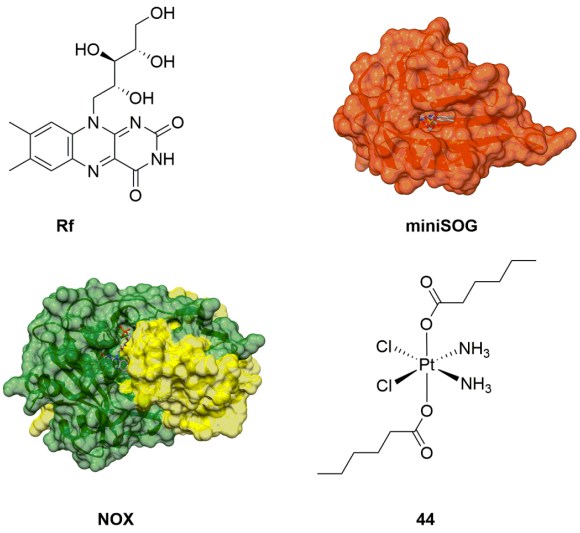

Figure 18: Riboflavin, Rf; mini Singlet oxygen Generator, miniSOG; NADH Oxidase, NOX; flavoproteins and cisplatin prodrug (**44**).

Conclusions

In recent years we have witnessed a remarkable increase of attention on the use of photochemistry as a resource for developing new Pt anticancer agents and drug delivery strategies. In this context, Pt^{IV} azido complexes, developed by Sadler and coworkers, have emerged as the blueprint in the field. Overall, this research area has made significant advances delivering Pt agents with diverse biological activity, cancer cell targeting capability or improved photochemical properties. However, the limited number of *in vivo* studies so far reported on photoactivatable Pt agents is indicative of how much still remains to be done.

For instance, efforts devoted to red-shifting activation wavelengths of Pt complexes can give major contributions to advance the field further and make this class of compounds a tool worth investigating as alternative or synergy for PDT. Novel photoactivatable platforms based on nanomaterials have partially reached this objective (*e.g.* quantum dots and UCNPs), but their sophistication as drug delivery systems might hamper their approval and application for clinical use. Despite their unique photophysical features, UCNP-mediated prodrug activation presently suffers from low photoconversion efficiency and raises concerns for lanthanide leaching.

Flavin-assisted biorthogonal photocatalysis on Pt^{IV} substrates indeed is an advance in term of efficiency and selectivity but is so far restricted to blue light activation, which is not optimal because of the limited light penetration into tissues at these wavelengths [91].

At present, metallodrugs in general appear to suffer from a lack of interest by the pharmaceutical sector. This of course extends to photoactivatable Pt anticancer agents, making difficult to predict what this area of research needs to accomplish in order to deliver the next generation of anticancer drugs. Most likely, the mere synthesis and *in vitro* testing of new Pt compounds that are active against cancer cells upon light irradiation is no longer enough. Therefore, convenient strategies for their light-activation and their implementation into biocompatible delivery systems should be integrated in the design of Pt photoactivatable agents from the beginning. Coupling of Pt prodrugs to tumor targeting vectors such as antibodies or serum proteins can for example reduce non-selective accumulation in to tissues and reduce residual systemic side effects of Pt prodrugs. In addition, incorporation of clinically-approved precursors, ligands, sensitizers or additives in the structures of Pt complexes could ease the drug approval process and hence attract the interest of the pharmaceutical industry. Hopefully, the promising results obtained recently by the Ru PDT agent TLD-1433 in human clinical trials will help the field of Pt photoactivatable anticancer agents to gain new momentum [7].

Acknowledgements

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