Mendeleev Commun., 2027, **37**, just accepted

Mendeleev Communications

Received 10.07.26
Revised 21.10.26

26/8145

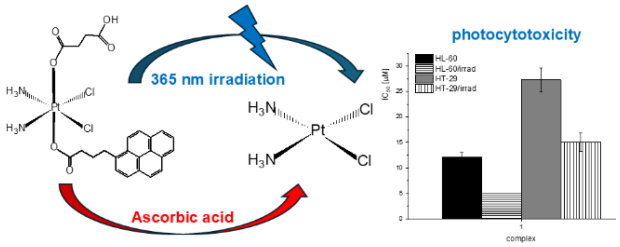
Photoinduced anticancer activity of the pyrenebutyrate Pt^{IV} prodrug of cisplatin

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DOI: 10.71267/mencom.8145

Asymmetrically disubstituted pyrenebutyrate complex of Pt(IV) was examined as cisplatin prodrugs for its anticancer effects in the dark and upon irradiation against leukemic and colorectal cancer cells. The complex exhibited moderate anticancer activity, which increased two to three-fold after being exposed to UV light (365 nm) for 30 minutes The study shows that the cytotoxicity of the studied complex is closely linked to its ability to undergo activation either through chemical reduction by biological reductants or through photoinduced processes.



Keywords: platinum(IV) prodrugs, anticancer agents, cytotoxicity, photoactivation, activation by reduction.

Pt(IV) prodrugs were developed to overcome the limitations of conventional Pt(II) anticancer drugs by exploiting their octahedral geometry and relative kinetic inertness, which enable an activation-by-reduction mechanism in the reducing intracellular environment of cancer cells [1-3]. Upon reduction, Pt(IV) complexes release the active Pt(II) species and, when appropriately functionalized, can simultaneously liberate biologically active axial ligands, creating dual-action therapeutics with enhanced potency and selectivity [4-6]. To achieve a balance between reactivity and pharmacokinetic properties supramolecular delivery approaches have emerged, where functional groups such as pyrene can promote host–guest interactions and targeted transport of Pt(IV) prodrugs [7-9]. In such systems, reductive cleavage of the axial ligands remains essential for releasing the cytotoxic Pt(II) species at the target site, while the pyrene moiety primarily serves as a recognition element for delivery rather than a direct contributor to anticancer activity. With this prospect we have recently reported on pyrenebutyric complexes of Pt(IV) analogs of cisplatin showing rather divers anticancer profiles[9, 10], which can potentially be employed as guest molecules in earlier developed supramolecular capsules with high affinity to pyrene[11].

Significant advances have recently been made in the development of photoresponsive Pt(IV) complexes, highlighting the crucial role of light-induced intracellular processes [12-14]. Pyrene derivatives are particularly appealing because of their extensive π-conjugated systems, intrinsic fluorescence, affinity for cellular membranes, and capacity to bind biological macromolecules through hydrophobic and π–π stacking interactions. In this study, we examine a pyrenebutyrate-functionalized Pt(IV) derivative of cisplatin (compound **1**, Figure 1) and assess its antiproliferative effects against cancer cell lines of diverse origins under both dark conditions and UV irradiation. This was done to find a correlation between the observed light-induced reduction of complex **1** and fundamentally prove the activation-by-reduction hypothesis for Pt(IV) anticancer agents.

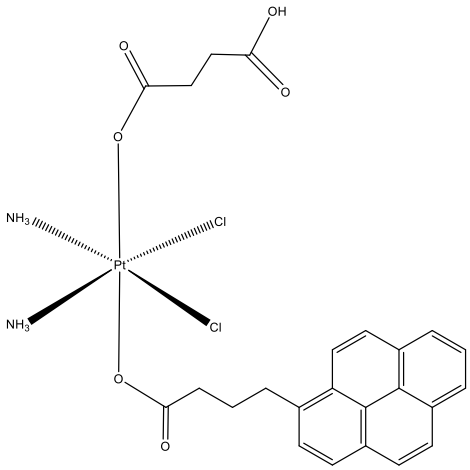


Figure 1 Molecular structure of the studied asymmetrically disubstituted pyrenebutyrate complex of Pt(IV) (**1**).

Complex **1** was synthesized from oxoplatin using NHS-activated ester of the pyrene butyric acid, according to a procedure by Erxleben [15, 16]. Its structure was confirmed by IR, NMR and HESI- HRMS analysis that were recently reported by us [10]. In addition to the reported cytotoxicity profile of complex

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1, here we emphasize on the newly observed effect of UV-light irradiation on the toxicity and reactivity of the complex. The comparison of cytotoxicity under dark conditions and following UV irradiation reveals a clear light-induced enhancement of anticancer activity (Figure 2).

Two types of human cancer cell lines of different origin were used in the present study: the leukemic cell line HL-60 (acute promyelocytic leukemia) and the chemoresistant HT-29 cells of colorectal adenocarcinoma. Additionally, reduction of complex **1** was achieved by the irradiation with UV light (365 nm) in DMSO solutions. All experimental details are given below [†] .

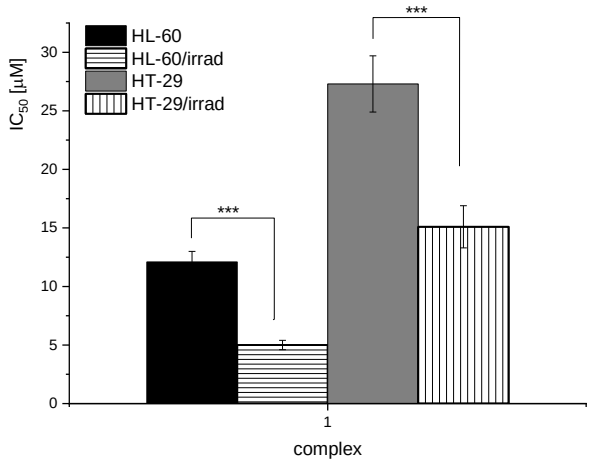


Figure 2 Cytotoxicity of complex **1** under dark conditions and following UV irradiation (365 nm for 30 minutes) against HL-60 and HT-29 cells; *** statistically significant at $p<0.05$.

UV irradiation led to an approximately twofold decrease in the IC_{50} value of the investigated Pt(IV) complex against HT-29 cells, from 27.3 μM to 15.1 μM, thereby confirming its photoresponsive behavior. An even more pronounced effect was observed in HL-60 cells, where complex **1** exhibited a substantial enhancement in cytotoxic activity, with the IC_{50} decreasing to below the lowest concentration tested (<5 μM), corresponding to an estimated photoindex of >2.4. These findings indicate effective photochemical activation of the complex, most likely through reduction of the Pt(IV) center to a more reactive Pt(II) species and/or increased formation of cytotoxic intermediates. Notably, the free pyrenebutyric axial ligand exhibit very low (IC_{50} of 80.1 μM against HL-60 cells) to complete lack of cytotoxicity (IC_{50} > 200 μM against HT-29 cells)[10], which indicates that the observed cytotoxicity of the complexes is caused by the released cisplatin even in dark.

From a biological activity perspective, the behavior of the complex in the presence of bioavailble reducing agents is of critical significance. To investigate this aspect, the reduction of the studied complex was monitored in a water–DMSO medium containing a tenfold excess of ascorbic acid. The release of the pyrenebutyric moiety was tracked by fluorescence spectroscopy, which represents the most sensitive analytical technique for this type of complex. The native fluorescence of the pyrenebutyric group is strongly quenched while coordinated to the platinum center due to heavy element effect. However, the fluorescence signal of the pyrenebutyric fragment becomes evident upon its release. This process typically occurs following the reduction of the octahedral Pt(IV) species to Pt(II), accompanied by the dissociation of the axial ligands. For fluorescence studies, a 10^{-4} M stock solution of compound **1** was prepared in DMSO. This solution was subsequently used to evaluate the stability of the complex in the presence of a tenfold excess of ascorbic acid dissolved in deionized water. The release of the fluorescent pyrenebutyric ligand was monitored over a period of three days. The liberation of the axial pyrenebutyric ligand was followed using its intrinsic fluorescence upon excitation at λ_{exc}= 365 nm.

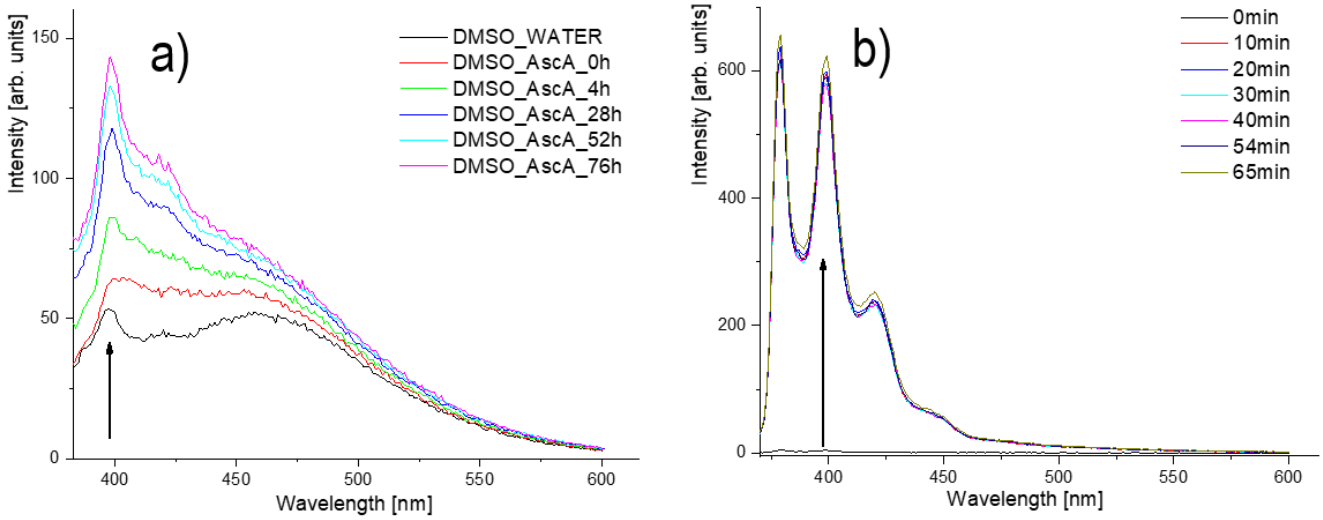


Figure 3 Fluorescence enhancement of complex **1** (λ_{ex} = 365 nm) upon a) addition of 10-fold excess of ascorbic acid in DMSO-water solution and measured at different time intervals in the course of 3 days; and b) irradiation of DMSO solutions with UV flashlight (365 nm, 10 W) and measured at different time interval in the course of 65 minutes. Note that before starting irradiation the complex is virtually non fluorescent.

[†] All cell lines were obtained from the German Collection of Microorganisms and Cell Cultures (DSMZ GmbH, Braunschweig, Germany). The cytotoxic effect of complex **1** was assessed through the MTT colorimetric assay after 72 hours of treatment. In vitro irradiation experiments were performed 4 hours after treatment of the cancer cells with the tested compounds and using Alonefire SV140 365nm UV Flashlight Strong 60W for 30 minutes at a distance of 22 cm to cover the whole plate. Control cells were exposed to light simultaneously and used as a reference for the estimation of the survival rate of the cells treated with the Pt(IV) complex upon irradiation. The irradiation of DMSO solutions of complex **1** were caried out in quartz cuvettes using an Alonefire SV143 UV flashlight (365 nm, 10 W) positioned 22 cm from the samples. Fluorescence measurements were recorded at selected time intervals on a "Cary Eclipse" spectrophotometer (Varian, Australia).

The fluorescence increase of complex **1** upon reaction with ascorbic acid or UV-light irradiation (Figure 3) clearly indicate distinct kinetics; fluorescence intensity of the former case increases only threefold in the course of three days, whereas UV-light exposure leads to abrupt increase in the first 10 minutes indicating fast and supposedly complete release of the pyrenebutyric fragment. This fact demonstrates that UV-light irradiation is more efficient tool for reduction of the studied Pt(IV) complex and release of the fluorescent axial pyrenebutyric ligand.

In summary it can be concluded that the investigated pyrenebutyrate Pt(IV) analog of cisplatin displayed markedly enhanced photocytotoxicity upon UV irradiation, confirming its efficient photoactivation. While moderate anticancer activity was observed in the dark, light exposure significantly reduced IC_{50} values, with the most pronounced effect detected in HL-60 leukemia cells, where almost threefold increase in potency was achieved. The strong correlation between fluorescence-detected ligand release and enhanced cytotoxicity indicates that irradiation promotes rapid conversion of the Pt(IV) prodrugs into biologically active Pt(II) species. These findings highlight the potential of pyrenebutyrate-functionalized Pt(IV) complexes as promising photoactivatable anticancer agents with improved therapeutic efficacy upon light activation.

This work was supported by the National Science Fund of Bulgaria (grant number КП-06-Н59/9).

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Received: 10th July 2026; Com. 26/8145