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Platinum(IV) prodrugs with heavy-atom-free BODIPY in axial position: instant photoactivation, enhanced biosafety and improved phototoxicity

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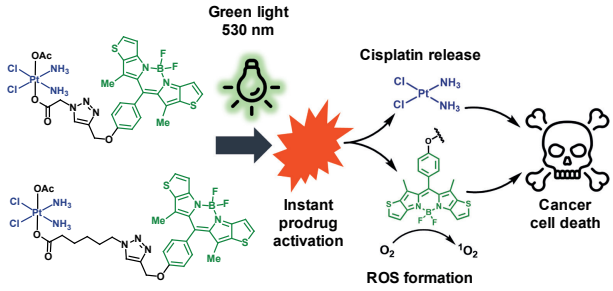
Two new photoactivable Pt^{IV} prodrugs bearing heavy-atom-free BODIPY in the axial position and differing in the linker length were prepared using CuAAC cycloaddition. Under 530 nm green light, both prodrugs produce singlet oxygen and are capable of a rapid cisplatin release in the presence of sodium ascorbate. Investigation of antiproliferative activity demonstrated excellent biosafety of these prodrugs, as well as outstanding phototoxicity under 530 nm low-dose green light.



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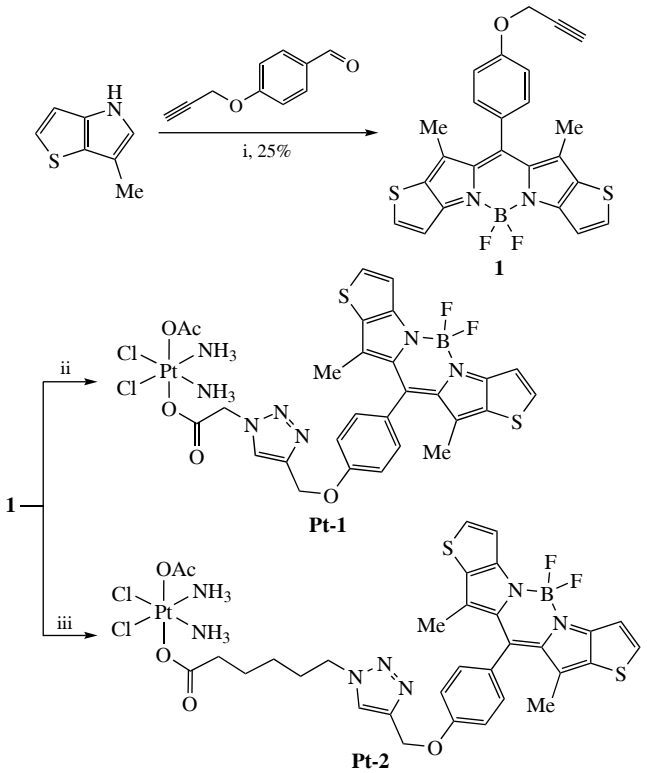
Photodynamic therapy (PDT) is a non-invasive approach to cancer therapy which utilizes non-toxic photosensitizers producing cytotoxically active reactive oxygen species (ROS) under exposure to visible/near-infrared light.[1–3] Despite its local effectiveness, ablative PDT should be combined with chemotherapy to achieve an optimal therapeutic effect. In addition to the ablative effect on the primary tumor site, systemic chemotherapy is necessary to affect metastases, radiating tumor cells, and prevent relapse.[4] Among promising organic photosensitizers, boron-dipyrromethenes (BODIPYs) stand out for their versatility, ease of modification and outstanding photophysical properties.[5–7]

Although the combination of a chemotherapeutic and PDT agent can be highly effective, the separate use of two independent prodrugs has its own disadvantages, such as a different pharmacokinetic profile of drugs, non-uniform drug distribution and difficulties in control over the optimal therapeutic dose.[8,9] To overcome these limitations, multi-action drugs have been proposed. In recent years, several Pt^{IV} prodrugs with the dual chemo/PDT activity have been reported.[10–12] Although this concept is extremely attractive, photoactive Pt^{IV} prodrugs often require considerable light doses and prolonged irradiation time to fully release Pt^{II} drugs, while the prodrug must be stable and non-toxic in the dark and rapidly exert a therapeutic effect upon irradiation; also, the PDT activity and the light response of those prodrugs are often low. Thus, design of Pt^{IV} prodrugs capable of a burst-like cisplatin release and PDT activity is of great interest.

Herein, we report two novel Pt^{IV} prodrugs with heavy-atom free photosensitizing thienopyrrole-based boron-dipyrromethenes (BODIPY) with a high PDT activity. The ability of novel Pt^{IV} prodrugs to form ROS under green (530 nm) light was estimated, and the Pt^{II} release under irradiation was studied. The influence of the linker length between the Pt^{IV} center and the BODIPY ligand on the photoreduction rate and cytotoxicity was also assessed. This is the first example of Pt^{IV} prodrugs with heavy-atom-free photosensitizing BODIPYs in an axial position as dual-acting prodrugs.

The synthesis of prodrugs consisted of two consecutive stages (Scheme 1; for more details see Online Supplementary Materials, Scheme S1). Principal thienopyrrole-based BODIPY **1** was obtained following literature procedures.[13,14] Platinum(IV) prodrugs **2** and **3** with 2-azidoacetate and 6-azidohexanoate moieties in the axial position, respectively, were obtained *via* acylation of the Pt hydroxy complex $(NH_3)_2Cl_2(AcO)Pt(OH)$. For the key step of conjugation of BODIPY with the oxidized Pt^{IV} core, we used the Cu-catalyzed click reaction with $Cu(MeCN)_4$ as a catalyst and tris[(1-benzyl-4-triazolyl)methyl]-amine as a Cu^{I}-chelating agent.[15] The compounds were characterized by ^{1}H, ^{13}C NMR. For compounds **Pt-1** and **Pt-2**, ^{195}Pt NMR spectra and HRMS were also obtained (see Online Supplementary Materials, Figures S1–S16). In the ^{1}H NMR spectra of both **Pt-1** and **Pt-2** complexes at 8.27 ppm, resonances corresponded to the triazole ring. The broad singlet at 6.50 ppm is a characteristic signal of equatorial NH_3 ligands of the Pt^{IV} complex. Four doublets at 8.05, 7.42, 7.27 and 7.05 ppm correspond to the BODIPY moiety; the singlet at 1.6 ppm corresponds to the 1,7-methyl groups in the BODIPY core. Finally, the stoichiometric relationship between aromatic protons of the BODIPY moiety at 8.05–7.05 ppm, the multiplets of C_2 or C_6 aliphatic chain (at 5.2 and 4.30–1.26 ppm, for **Pt-1** and **Pt-2**, respectively) and the singlet of acetyl in the second axial position confirms the formation of both complexes. In addition, for both



Scheme 1 *Reagents and conditions*: i, CF_3CO_2H, CH_2Cl_2, then DDQ, CH_2Cl_2, then $BF_3 \cdot Et_2O$; ii, $(NH_3)_2Cl_2(AcO)PtOC(O)CH_2N_3$ (**2**), $Cu(MeCN)_4BF_4$, tris[(1-benzyltriazol-4-yl)methyl]amine, DMF, room temperature, 2 h; iii, the same, with $(NH_3)_2Cl_2(AcO)PtOC(O)(CH_2)_5N_3$ (**3**).

prodrugs, a single peak at 1232 ppm in ^{195}Pt NMR spectra verifies the formation of the Pt^{IV} complex with two carboxylate axial ligands.[16]

Photophysical properties of BODIPY **1** and prodrugs **Pt-1** and **Pt-2** were evaluated in $CHCl_3$; all compounds demonstrated absorption at 563 nm and emission at 573 nm (Table 1 and Figures S17, S18). Then, singlet oxygen quantum yields for BODIPY **1** and prodrugs **Pt-1** and **Pt-2** were determined using the singlet oxygen trap DPBF and tetraphenylporphyrin (TPP) as a standard; the obtained values of 0.53–0.56 indicate strong ability of BODIPY **1** and prodrugs **Pt-1** and **Pt-2** to form singlet oxygen under light irradiation and thus to act as PDT agents.

Hydrolytic stability is a highly important parameter of Pt^{IV} prodrugs since less stable complexes are more prone to hydrolysis in bloodstream and side binding with proteins, which hinders *in vivo* antitumor activity.[17,18] The stability of prodrugs **Pt-1** and **Pt-2** (Figure 1) in the dark was evaluated in the 60 : 30 : 10 DMSO/MeOH/H_2O mixtures within 24 h; the probes at different time points were analyzed by LCMS. The level of **Pt-1** and **Pt-2** complexes in solutions was evaluated by the peak area in the 898–908 and 954–964 *m/z* ranges, respectively, which corresponds to the $([M - HF] + H)^+$ ion. In the absence of NaAsc, both complexes were quite stable in aqueous conditions with 5–10% of the starting Pt^{IV} prodrug decay in the first 24 h.

To achieve the optimal combined effect of PDT and photoactivatable chemotherapy, photoactive Pt^{IV} prodrugs should be resistant to reduction in the absence of light, while rapidly

Table 1 Photophysical properties of BODIPY **1** and prodrugs **Pt-1** and **Pt-2**.

Compound	λ_{abs}/nm	λ_{fl}/nm[a]	F_D
BODIPY **1**	563	573	0.56
Pt-1	563	573	0.56
Pt-2	563	573	0.53

[a] Fluorescence spectra were obtained at λ_{ex} = 525 nm.

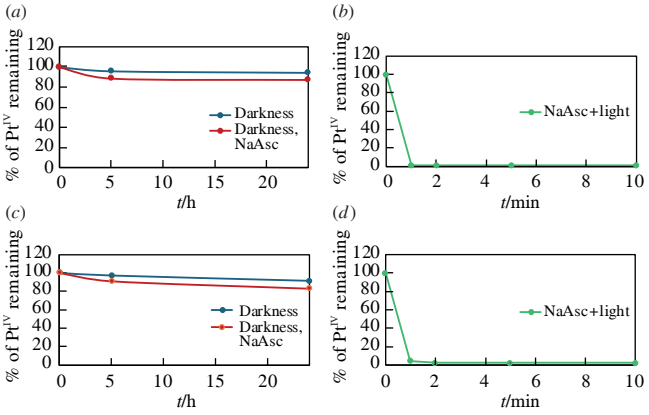


Figure 1 (*a*) **Pt-1** decay in the darkness in the absence and in the presence of sodium ascorbate (NaAsc). (*b*) **Pt-1** photoreduction under 530 nm (3.8 mW cm^{-2}) in the presence of excess NaAsc. (*c*) **Pt-2** decay in the darkness in the absence and in the presence of sodium ascorbate (NaAsc). (*d*) **Pt-2** photoreduction under 530 nm (3.8 mW cm^{-2}) in the presence of excess NaAsc.

releasing cytotoxic species under irradiation.[10] Thus, the reduction rate of **Pt-1** and **Pt-2** was assessed in the presence of NaAsc. Over 24 h, ~15% of **Pt-1** and **Pt-2** were reduced, while most of the initial complexes remained intact, which implies a high stability of prodrugs against premature hydrolysis.

Considering high F_D values of **Pt-1** and **Pt-2**, we expected that no photoreduction would occur under irradiation in the absence of the reducing agent. In the previous reports on Pt^{IV} prodrugs with triplet photosensitizers in the axial position, photoreduction was observed only when NaAsc was present in the solution.[10,19] Thus, the light-responsive behavior of the **Pt-1** and **Pt-2** prodrugs was studied under 530 nm light (3.8 mW cm^{-2}) in the presence of 10 equiv. NaAsc. Both prodrugs **Pt-1** and **Pt-2** demonstrated a burst-like instantaneous light-induced reduction with all prodrugs reduced in less than a minute under low-dose irradiation. Considering that the observed photoreduction behavior of **Pt-1** and **Pt-2** is in line with the previously obtained results on photoreduction of Pt^{IV} prodrugs with triplet photosensitizing BODIPYs, we assumed the formation of the radical anion by the reaction of the excited BODIPY moiety with the electron donor sodium ascorbate.[10,19] It is important to note that the reduction in the dark and photodegradation of the prodrugs was accompanied by the accumulation of cisplatin in the solution, which was detected as the cisplatin–DMSO adduct $[Pt(NH_3)_2Cl(DMSO)]^+$ (*m/z* = 342.0100) (Figures S19, S20).[20,21] Thus, both prodrugs are capable of a light-induced release of cisplatin, in addition to the impressive PDT activity.

Then, the antiproliferative activity of BODIPY **1** and Pt^{IV} complexes **Pt-1** and **Pt-2** was evaluated on the breast adenocarcinoma Sk-Br-3 cell line (Table 2). Cells were incubated in the dark for 1 h and irradiated with low-dose green light (530 nm, 3.8 mW cm^{-2}, 4 min 20 s), the control group was incubated in the dark. In the absence of light, **Pt-1** and **Pt-2** were

Table 2 Antiproliferative activity of **Pt-1** and **Pt-2** prodrugs, BODIPY **1** and cisplatin on the breast adenocarcinoma Sk-Br-3 cell line in the dark and under 530 nm green light irradiation [3.8 mW cm^{-2}, 4 min 20 s, light (+)].

Compound	IC_{50}/μM		PI[a]
	without light (–)	with light (+)	
Pt-1	>20	2.4 ± 0.5	>8
Pt-2	>20	2.6 ± 0.6	>8
BODIPY **1**	>20	0.035 ± 0.007	>571
Cisplatin	13.0 ± 3.0	–	–

[a] Phototoxicity index, IC_{50} [light (–)]/IC_{50} [light(+)].

not toxic in concentrations of <20 μM, indicating improved biosafety as compared to cisplatin which demonstrated IC_{50} in the dark in concentrations of 13 μM. Moreover, under low-dose light irradiation, phototoxicity of both **Pt-1** and **Pt-2** prodrugs surpassed cisplatin cytotoxicity almost 6-fold with IC_{50} in concentrations of 2.4 and 2.6 mM, respectively (see Table 2 and Figure S21). Notably, the difference in the linker length had little to no impact on phototoxicity. Expectedly, BODIPY **1** demonstrated an outstanding phototoxicity with IC_{50} in concentrations of 19 nM, which aligns with the previously published data.[13] Nevertheless, both Pt^{IV} prodrugs **Pt-1** and **Pt-2** demonstrated improved biosafety as compared to cisplatin, combined with increased cytotoxicity under green light.

To conclude, we have designed and synthesized two new Pt^{IV} complexes with a heavy-atom-free BODIPY photosensitizer in the axial position. Both **Pt-1** and **Pt-2** are capable of a gradual cisplatin and axial ligand release in reducing environment, while under ambient green light irradiation, an almost instant photoreduction occurs, which is accompanied by a release of the cisplatin adduct. An outstanding green light-induced ROS-generating ability of **Pt-1** and **Pt-2** Pt^{IV} prodrugs was confirmed *in vitro*. In the MTT assay all studied compounds demonstrated great biosafety, and a 10–1000-fold increase in phototoxicity under low-dose green light irradiation.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7776.

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