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Highly Phototoxic Transplatin-modified Distyryl-BODIPY Photosensitizers for Photodynamic Therapy

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Abstract: We report the synthesis of the first transplatin-BODIPY conjugates for application in photodynamic therapy (PDT). The distyryl BODIPYs containing two iodine atoms were designed to absorb in the red region, easily undergo intersystem crossing for efficient singlet oxygen generation, and additionally offer the possibility for coordination with mono-activated transplatin. We were able to demonstrate that coordination of the BODIPYs with a mono-activated transplatin increases the phototoxic index of the photosensitizers significantly, giving rise to highly phototoxic distyryl BODIPY derivatives, of which one was shown to have the highest ever reported phototoxic index against any cell line. Furthermore, the photophysical mechanism of singlet oxygen generation in distyryl BODIPYs undergoing intramolecular charge transfer was studied experimentally and using time dependent density functional theory.

Introduction

Photodynamic therapy (PDT) is a method for localized control of diseased tissue and is used in oncological and non-oncological therapy settings. With the mechanism of action that is different compared to surgery, radiotherapy, and chemotherapy, PDT offers a variety of advantages. These include non-invasive nature of the treatment even for deep-seated tumors, the ability to be combined with other treatments, lack of cumulative toxicity, the use for inoperable cancers and spatial as well as temporal control of the treatment. Due to the lack of intrinsic or acquired resistance mechanisms of the body against the unique mechanism of cytotoxicity, PDT can be applied repeatedly without compromising antitumor efficacy.^[1-4] Three essential components are needed in PDT: a photosensitizer (PS), light at a specific wavelength and molecular oxygen in the tissue to be treated. These components alone are ideally non-toxic, but applied in combination lead to the generation of reactive oxygen species (ROS), which cause significant cellular damage leading to cell death via apoptosis or necrosis.^[1, 2, 5-8] Once a PS has been administered and has localized in the malignant tissue, the PS is subsequently activated by light through irradiation of the tissue, meaning it is excited from its singlet ground state (S_0) to its short-lived first excited singlet state (S_1) by the absorption of light. The photosensitizer can relax and return to the ground state via internal conversion (IC), a non-radiative process, or by the emission of light (fluorescence). A third pathway called intersystem crossing (ISC) leads to the first

excited triplet state (T_1), thereby the spin of an excited electron is inverted. From the long-lived T_1 the photosensitizer can again relax back to S_0 over two pathways, one radiative (phosphorescence) and one non-radiative (IC/ISC), although both are forbidden by the quantum selection rules.^[1, 2] Alternatively, the photosensitizer transfers its energy onto molecular triplet oxygen (3O_2), leading to the formation of highly reactive singlet oxygen (1O_2), which is believed to be the main agonist to induce oxidative stress amongst all the reactive oxygen species generated during PDT treatment.^[9, 10]

Currently, limitations of PDT are mainly attributed to the lack of long-wavelength absorbance of PSs used in the clinic, as well as reduced cellular uptake of PSs due to aggregation in vivo caused by hydrophobic interactions.^[2] Light penetration through tissue increases with increasing wavelength; endogenous fluorophores, like haemoglobin and melanin, have high absorptions in the visible spectrum below 650 nm. For the highest possible depth of treatment, the PS should therefore absorb light in the *phototherapeutic window* (between 650 and 800 nm).^[11, 12] Absorption of single photons with wavelengths longer than 800 nm does generally not provide enough energy to excite triplet oxygen.^[13] Furthermore, a PS should have a high chemical stability and exhibit a high phototoxic index ($PI = IC_{50}$ in the dark/ IC_{50} in light)^[14], meaning it should be highly toxic when irradiated by light but have low dark toxicity.^[15] To achieve high phototoxicity, the photosensitizer should have high molar extinction coefficients at the irradiated wavelengths, as the extinction coefficient defines how much of the irradiated energy can be absorbed and used for the generation of ROS.^[16] Transitions between pure spin states of different multiplicity (e.g. singlet, triplet) are in principle forbidden by the spin selection rule. However, they can be enabled by the presence of atoms with high atomic number Z ; this phenomenon is known as the *heavy atom effect*.^[17]

BODIPYs are widely known and used as fluorophores but they also exhibit ideal properties for application in PDT. They have a high chemical stability and show high molar extinction coefficients and sharp excitation and emission spectra.^[18] Their photophysical properties can be fine-tuned by various possibilities of synthetic functionalization of the BODIPY core.^[16, 18-21] BODIPYs have been shown by *in vitro* and *in vivo* studies to be capable of acting against a large number of different tumor cells and in most cases display low toxicity in the dark.^[22] Increase of ISC rates of

BODIPYs is achieved in most cases by di-halogenation in the electrophilic positions of the BODIPY core. The first di-iodinated BODIPY has been reported by Yogo *et al.*^[23] in 2005 and di-iodination and di-bromination has since been the standard way to induce the *heavy atom effect* into BODIPY systems, resulting in very high singlet oxygen quantum yields.^[16, 18, 19, 24-26] Condensation reactions of BODIPYs with benzaldehyde derivatives have been carried out extensively in the last two decades. The resulting di-styryl BODIPYs generally absorb in the *phototherapeutic window*.^[16, 18-21, 24]

Often observed in mono- or distyryl BODIPY systems is the formation of intramolecular charge transfer states (ICT states) upon excitation, as summarized in a review by Boens *et al.*^[27]. Thereby an electron is transferred from an electron rich donor moiety to an electron poor acceptor moiety, resulting in a highly polar species. This charge transfer can either occur directly via absorption of light or happen in the picosecond time range after excitation. Direct accessibility to the ICT state becomes more probable with increasing solvent polarity, as polar solvents stabilize this polar state.^[27-30] ICT states are 'weakly emissive' and mostly decay non-radiatively by charge-recombination, thereby partly quenching the fluorescence of the acceptor moiety.^[27, 28, 31] Often encountered as a styryl type substituent is the electron rich dimethylaniline; in these systems, the aniline donor transfers an electron to the BODIPY core acceptor.^[32-34] Aniline substituents lead to larger red-shifts in the absorption spectra than other styryl substituents, which can be explained by the large stabilization of the ICT state in polar solvents. Deniz *et al.* explain that the observed blue-shift at higher pH is a result of decreasing donor characteristics of the protonated aniline substituent.^[34] Recently, the influence of ICT states in BODIPYs on the singlet oxygen quantum yield has become of interest. In 2016, Epelde-Elezcano *et al.* have introduced the concept that the formation of an ICT state and non-radiative deactivation of that state competes with ISC to the excited triplet state, effectively decreasing the singlet oxygen yield.^[35] Several other reports of this phenomenon for have followed; specifically in polar solvents, low ¹O₂ production is observed, as the ICT state is strongly stabilized and probability of reaching T₁ is low.^[36-39]

Coordination of photosensitizers to the *trans*-(NH₃)₂Pt(Cl) unit (synthesized by chloride abstraction from transplatin) has been shown by our group to be highly beneficial for photosensitizer performance *in vitro*. For tetrapyrrolyl-porphyrin,^[14] its Zn(II)-containing analogue,^[40] and a Zn(II) containing tetrapyrrolylporphyrine,^[41] it has been shown that the phototoxic index increases significantly after coordination of one *trans*-bis(amine)platinum-monochloride to each of the pyridyl substituents, and this effect is larger for the *trans* complex than for the one derived from cisplatin. The lower dark toxicity of the *trans* conjugates compared to the *cis* conjugates can be explained by the much lower toxicity of transplatin itself,^[42] as the complex mostly dissociates in the cell, leaving behind relatively innocuous mono-activated transplatin. Additionally, the introduction of charges into the molecule has been shown to greatly enhance the water solubility of otherwise very insoluble photosensitizers that are prone to aggregation. Several BODIPY-platinum conjugates (mainly cisplatin derived) have been reported in literature within the last few years^[43-48]. Heavy atoms can still illicit a (comparably weak) 'intramolecular external heavy-atom effect', even when they are not directly bound to the chromophore.^[49] Coordination of the *cis*-(NH₃)₂Pt(Cl) (synthesized by chloride abstraction from

cisplatin) to a BODIPY was shown to slightly increase the phototoxicity, but even more the dark toxicity, resulting in an unwanted lowered phototoxic index.^[44] One BODIPY-platinum conjugate had to be solubilized with the help of Cremophor EL, as the photosensitizer itself was not soluble enough in water.^[48] It is interesting to note that no BODIPY transplatin-derived conjugates have been reported so far. In this publication, we show the highly beneficial effect of *trans*-bis(amine)platinum-monochloride modification on the phototoxic index of long-wavelength absorbing, low dark toxicity BODIPYs.

Results and Discussion

Di-iodinated BODIPY **1** was used in *Knoevenagel* condensation reactions with aldehydes 1-methyl-5-imidazolecarboxaldehyde, *p*-anisaldehyde, and *p*-dimethylaminobenzaldehyde to give the corresponding novel distyryl BODIPYs **2-4** (Scheme 1), which have been characterized by ¹H-NMR and IR spectroscopy, HR-ESI-MS, elemental analysis and single crystal analysis for **3** and **4** (Figure 1). The two pyrrole-styrene bonds in the **3** are in a *cisoid* conformation on one side and in a *transoid* conformation on the other side. There is only one other structure in the CSD^[50], in which the pyrrole-styrene bond (with no substitution on the vinylenic bond) is in a *cisoid* conformation^[51]. The distyryl BODIPYs were then treated with transplatin (activated *in situ* with AgNO₃ to give [*trans*-Pt(NH₃)₂Cl]NO₃) according to our previously reported procedure.^[14] In all three cases, the pyridyl moiety is coordinated to a Pt(II) center; in BODIPY **2**, both imidazole moieties are additionally coordinated to a platinum center as well, leading to a three-fold platinated complex. The three platinated BODIPYs have been characterized by ¹H-NMR, ¹⁹⁵Pt-NMR and IR spectroscopy, HR-ESI-MS and elemental analysis. Both the imidazole substituted BODIPY **2-tPt** and its non-platinated analogue **2** display a high photo-instability and therefore was protected from light as much as possible. The sensitivity most probably stems from the susceptibility of the imidazole moieties to be oxidized by singlet oxygen that is generated by the PS itself.^[52, 53] The best photosensitizer **3-tPt** with respect to its PDT behaviour and phototoxic index (see below) was then evaluated for its photostability. Its quantum yield of photodegradation was determined relative to zinc phthalocyanine (ZnPc), a benchmark compound in PDT^[54, 55]. The quantum yield of photodegradation of **3-tPt** was 19% relative to the one of the reference compound ZnPc, which shows that **3-tPt** has a better photostability than the benchmark compound (see chapter 4 in the SI). Additionally, we have estimated the partition constants of compounds **3**, **3-tPt**, **4**, and **4-tPt** in *n*-octanol versus a 0.15 M aqueous sodium chloride solution (Table S1).

UV-Vis absorption spectra and fluorescence emission spectra of compounds **2-4** and platinated analogues **2-tPt**, **3-tPt** and **4-tPt** were measured in MeOH (Figure 2). While all six BODIPYs show strong absorption in the *phototherapeutic window*, distinct absorption characteristics of *N,N*-dimethylaniline substituted derivatives **4** and **4-tPt** become apparent with a larger red-shift and broader peaks, while the other BODIPYs show a similar overall shape of the absorption spectrum.

Scheme 1. Overall scheme for the synthesis of transplatin-derived BODIPY conjugates **2-tPt₃**, **3-tPt** and **4-tPt**. Reaction conditions: i) AcOH, piperidine, toluene, 110 °C, 1 h; ii) AcOH, piperidine, toluene, 100 °C, 3 h; iii) AcOH, piperidine, toluene, 100 °C, 3 h; iv) *trans*-Pt(NH₃)₂NO₃Cl, DMF, 55 °C, 65 h; v) *trans*-Pt(NH₃)₂NO₃Cl, DMF, 50 °C, 26 h.

Figure 1. Displacement ellipsoid representations at 50 % probability of **3** (left) and **4** (right). Left: Only one out of two molecules in the asymmetric unit of **3** is displayed for clarity.

Notably, it was discovered that the spectrum of **4** is altered drastically when measured at a low pH; in a solution of 1 M HCl in MeOH, the absorption spectrum of **4(H⁺)₃** (it is assumed that both aniline moieties as well as the pyridyl substituent are

protonated) shows a large blue-shift, an effect which has been observed in other similar BODIPY compounds.^[34]

The singlet oxygen quantum yields of compounds **2–4** and **2-tPt₃**, **3-tPt** and **4-tPt** were determined following the direct method (NIR luminescence monitoring of ¹O₂ phosphorescence emission) and are summarized in Table 1. No signal of ¹O₂ phosphorescence could be detected for *N,N*-dimethylaniline-substituted BODIPYs **4** and **4-tPt** in MeOD-*d*₄, however, a significant quantum yield for singlet oxygen production was observed in acidic medium for compound **4(H⁺)₃** ($\Phi_{\Delta} = 0.24 \pm 0.04$).

Table 1. Overview of photophysical properties. Singlet oxygen quantum yields have been determined by direct method (NIR luminescence monitoring) by comparison to MB ($\lambda_{\text{ex}} = 690$ nm). N.d. = not determined.

Compound	UV-Vis λ_{max} in MeOH [nm] (log ϵ)	Fluorescence Emission λ_{max} in MeOH (λ_{ex}) [nm]	Singlet Oxygen Quantum Yield (Φ_{Δ}) in MeOD- <i>d</i> ₄
2	666 (4.74)	705 (670)	0.24 ± 0.09
3	666 (4.80)	700 (670)	0.40 ± 0.03
4	745 (4.30)	821 (740)	0
2-tPt₃	660 (4.62)	703 (670)	0.07 ± 0.04
3-tPt	676 (4.84)	730 (670)	0.26 ± 0.04
4(H⁺)₃	648 (4.83)	n.d.	0.24 ± 0.04 ^[a]
4-tPt	768 (4.75)	834 (770)	0

[a] Compound measured in 1 M DCl in MeOD-*d*₄.

The question poses itself why *N,N*-dimethylaniline substituted BODIPY **4** does not generate any singlet oxygen; to the best of our knowledge, this compound is the first reported example of a BODIPY that is di-iodinated and does not show any production of singlet oxygen. Furthermore, it is of additional interest why protonation leads to a rise in singlet oxygen generation. The possibility of a charge transfer upon excitation in *N,N*-dimethylaniline substituted BODIPY **4** were investigated by quantum chemical considerations and experimental observations, since for some non-iodinated mono- and distyryl BODIPYs incorporating *N,N*-dimethylaniline substituents, occurrences of intramolecular charge transfer (ICT) have been reported.^[32–34] Thereby, a charge is transferred from the electron rich aniline moieties to the electron deficient BODIPY core. The hypothesis of ICT formation in *N,N*-dimethylaniline-substituted BODIPY **4** has been addressed by TDDFT calculations using a polarizable continuum model (PCM) in MeOH. The same analysis has been conducted for the three-fold protonated species **4(H⁺)₃** and for anisole-substituted BODIPY **3**, both as comparison compounds that do produce singlet oxygen. For all three BODIPYs it was found that the electronic transition corresponding to $S_0 \rightarrow S_1$ is attributed to the HOMO $\rightarrow$ LUMO transition (mixing of the electron density from the HOMO to the LUMO: 99.8% for **4**, 99.7% for **4(H⁺)₃**, 100.4% for **3**).

Figure 2. UV-Vis absorption and fluorescence emission spectra of red region BODIPYs **2–4** and **2-tPt**, **3-tPt** and **4-tPt** in MeOH (1M HCl in MeOH for **4(H⁺)₃**). Fluorescence emission spectra (excited at 670 nm for **2**, **3**, **2-tPt**, and **3-tPt**, at 740 nm for **4** and at 770 nm for **4-tPt**) have been scaled to 1.

The TDDFT spectra (shown in Figure S16) reveal that this transition causes the absorption peak at the highest wavelength, which is also the peak at which the BODIPYs were irradiated for the singlet oxygen quantum yield measurements respectively.

Figure 3. Illustrations of the FMOs of BODIPYs **3**, **4**, and **4(H⁺)₃** calculated with TDDFT. Central row: LUMO. Bottom row: HOMO.

As depicted in the illustrations of the frontier molecular orbitals (FMOs) of BODIPYs **3**, **4** and **4(H⁺)₃** (Figure 3), the HOMO is

delocalized over the entire chromophore in BODIPYs **3** and **4**, while the LUMO is mainly localized on the BODIPY core in both cases. The electron density seems to shift from the electron rich styryl-moieties towards the BODIPY core upon excitation, and such a shift cannot be observed in the protonated species **4(H⁺)₃**. To investigate and compare the magnitude of the electron density shift, each molecule was divided into a donor moiety (both styryl moieties) and an acceptor moiety (BODIPY core and remaining substituents). The electron densities associated with both donor and acceptor in the FMOs were quantified in the ground state (GS) and the excited state (ES). To access such a quantification, the MO-coefficients of each of the orbitals associated with each atom were assigned either to the donor or acceptor moiety. The probability of residence ($|\Psi|^2$) of an electron can thus be calculated from the MO-coefficients which simulate the wavefunction (Ψ). The ground state has been simulated through double occupation of the HOMO while the first excited state can be simulated as single electron occupation of HOMO and LUMO, a simplification which is reasonable, as TDDFT calculations showed that the excitation is associated with an almost pure HOMO-LUMO transition, as discussed above. The shift of electron density associated with the FMOs was estimated as 50% (GS) and 37% (ES) for anisole-substituted BODIPY **3**, 67% (GS) and 46% (ES) for *N,N*-dimethylaniline substituted BODIPY **4**, and 34% (GS) and 30% (ES) for the protonated BODIPY **4(H⁺)₃**. These results show a large shift of electron density upon excitation in BODIPYs **3** and **4**. Evidently, the protonated species **4(H⁺)₃** has much less electron density on the donor-moiety than its unprotonated analogue **4** to begin with, and the electron density does not shift to the acceptor moiety upon excitation in such a degree as for BODIPY **4**. These results suggest that ICT occurs upon excitation in *N,N*-dimethylaniline substituted BODIPY **4** but not in the protonated species **4(H⁺)₃** (Figure 4).

This hypothesis is further supported by experimental evidence; the UV-Vis absorption spectrum of BODIPY **4** revealed a pronounced red-shift with λ_{max} 745 nm, compared to the

absorptions of di-styryl BODIPYs **2** and **3** (both λ_{max} 666 nm). It is plausible that the low energy of the excited state is caused by the large stabilization of the highly polar ICT state in MeOH and other polar solvents.

Figure 4. The formation of an intramolecular charge transfer (ICT) state in BODIPY **4** is switched off upon protonation.

Another indication for the occurrence of an ICT is the additional red-shift of the absorption spectrum after the platination reaction forming BODIPY **4-tPt**, which has an absorption maximum at 768 nm. Through the introduction of a positive charge on the already positively polarized pole of the molecule, a charge transfer becomes more likely and the resulting ICT state is more stabilized, leading to a lower energy transition and red-shifted absorption. Moreover, compound **4** shows the characteristic behavior of ICT probes of a blue-shift upon protonation of the donor moiety.^[34] As shown in Figure 2, the UV-Vis absorption of BODIPY **4** is blue-shifted under acidic conditions; the effect of protonation extends to the ability to generate singlet oxygen. This indicates that the formation of an ICT state and the relaxation thereof competes with ISC (and therefore singlet oxygen production) in compound **4** and this mechanism is switched off upon protonation, allowing the BODIPY to reach the T_1 state.

The computational results show that the first excited state S_1 of anisole-substituted BODIPY **3** has a charge-separated character as well (which has been reported for a similar anisole-substituted BODIPY before^[56]); it is less pronounced than in *N,N*-dimethylaniline substituted BODIPY **4**, and the S_1 of **3** is less stabilized than the S_1 of **4** in MeOH, which is visible in the experimental absorption spectra of these compounds. From this excited state it is still possible for the molecule to reach the triplet state through ISC and to generate singlet oxygen, hence a quantum yield ϕ_Δ of 0.40 ± 0.03 . We suggest that even though compounds **3** and **4** both have first excited singlet states with charge-separated character, *N,N*-dimethylaniline substituted BODIPY **4** mainly relaxes back to the ground state via charge-recombination internal conversion (CR-IC) and therefore does not generate any singlet oxygen, while anisole-substituted BODIPY **3** is able to reach T_1 through ISC. This ISC event can be seen as almost pure spin-flip in nature, as it can still be attributed to the HOMO $\rightarrow$ LUMO transition (mixing of the electron density from the HOMO to the LUMO: 97.5%).

BODIPYs **2**, **3**, **2-tPt**, **3-tPt** and **4-tPt**, which absorb in the red region, were tested in human cancer cells to assess their anti-proliferative properties. BODIPY **4** was not tested due to its low solubility in H_2O , DMF, and DMSO. IC_{50} values of the compounds were determined in the HeLa cell line in the dark as well as after irradiation with light to investigate the phototoxicity. Dose-

response-curves for each compound can be found in Figures S20–S24. All IC_{50} values are shown in Table 2; none of the compounds show significant dark toxicity (> 45 – 100 mM). For application in PDT, photosensitizers with high ratios of dark to light toxicity (phototoxic index, PI) are desired. All five BODIPYs that have been tested have the advantage of low dark toxicity, but platinated compounds **2-tPt** and **3-tPt** show the highest potential, with photocytotoxicities in the sub-micromolar range and PIs greater than 139 for **2-tPt** and greater than 543 for **3-tPt**. To the best of our knowledge, transplatin modified BODIPY **3-tPt** displays the highest PI against any cell line reported for any distyryl-BODIPY so far (see Table S7). Additionally, the compound **3-tPt**, which is the most phototoxic one, was tested in the human cancerous cell line A2780 and the human non-cancerous MRC5 lung fibroblasts (Table S6).

The data for imidazole substituted BODIPYs **2** and **2-tPt** and anisole substituted BODIPYs **3** and **3-tPt** shows that the conjugation of photosensitizers with transplatin increases the photocytotoxicity and therefore the PIs, as reported previously by our group.^[14, 40, 41] Interestingly, the increase in phototoxicity after platination speaks against the expectations, as the decrease in singlet oxygen yields (see Table 2) after the platination would suggest a lower potency of the photosensitizers. We hypothesize that the *trans*-bis(amine)platinum-monochloride unit helps to improve the cell uptake compared with the free ligands. Therefore, the enhanced light toxicity is not caused by the platinum "drug" itself, because this effect would be seen in the dark toxicity only. No judgement can be made for aniline substituted BODIPY **4-tPt**, as its non-platinated analogue could not be tested *in vitro*. The compound displayed a phototoxicity in the micromolar range even though it did not show any singlet oxygen generation. This phenomenon has been observed for a transplatin-phthalocyanine conjugate before.^[41] In order to clarify this issue, BODIPY **4-tPt** was irradiated with light in the presence of the hydroxyl radical sensor aminophenyl fluorescein^[57]. And indeed, the hydroxyl radical promoted breakdown of aminophenyl fluorescein to yield the highly fluorescent fluorescein could be observed in a linear dependency of the light irradiation duration (Figure S15), which proves that **4-tPt** generates hydroxyl radicals upon light irradiation.

Table 2. Anti-proliferative effects of the compounds on cancerous HeLa cells in the dark and upon irradiation. Each of the independent experiments is an average value of quadruplicates. The cells were exposed to LED light at 657 nm for 30 min ($2.52 = J/cm^2$). PI = phototoxic index.

Compound	Dark toxicity [μM]	Light toxicity [μM]	PI
2	> 100	3.55 ± 0.41	> 28
3	> 50	1.530 ± 0.016	> 33
2-tPt	> 45	0.323 ± 0.010	> 139
3-tPt	> 100	0.184 ± 0.002	> 543
4-tPt	> 100	3.855 ± 0.083	> 26

Figure 5. The intracellular localization of compound **3-tPt** in HeLa cells. Cells were incubated with compound **3-tPt** for 3 h in the dark prior to imaging. Confocal images of cells stained with Hoechst 33342 (a), ER-Tracker® (b), 3-tPt (c) and merged image (d) are presented.

The intracellular localization of **3-tPt** was investigated using fluorescence microscopy. HeLa cells were treated with compound **3-tPt** (magenta) and stained with Hoechst 33342 (blue, showing the nucleus) and an additional staining agent (green; MitoTracker® Green, Golgi-ID® Green Assay Kit, or ER-Tracker®) (Figures 5, S25 and S26). The results show that **3-tPt** is taken up by the cancer cells and mainly accumulates in the endoplasmic reticulum (ER); the co-localisation of **3-tPt** and the ER-Tracker® becomes apparent in the merged image in Figure 5, in which the overlay of green and magenta results in a white coloring, especially around the nucleus. No accumulation of **3-tPt** in mitochondria or Golgi was found (Figures S25 and S26).

We further investigated the intracellular ROS levels in HeLa cells that were treated with compound **3-tPt** (at 1 μ M). The cells were irradiated with the same light source as used for the photocytotoxicity assays. The ROS levels were detected using 2',7'-dichlorodihydrofluorescein diacetate (H₂DCF-DA) followed by fluorescence-activated cell sorting (FACS) analysis. The non-fluorescent H₂DCF-DA is converted into fluorescent 2',7'-dichlorodihydrofluorescein (DCF) upon oxidation by intracellular ROS produced by photoactivation of the PS.^[58, 59] ROS levels in cells treated with platinated BODIPY **3-tPt** were significantly higher after light irradiation compared to treatment in the dark or with light irradiation alone (Figure 6). The percentage of cells displaying high ROS levels increases by more than 8-fold upon photoactivation of **3-tPt** compared to treatment with **3-tPt** in the dark (Table S8). The observed phototoxicity of **3-tPt** can therefore be attributed to increased intracellular ROS levels.

Figure 6. Intracellular ROS levels in HeLa cells treated with 1 μ M compound **3-tPt** for 4 h, irradiated with red light for 30 min. The ROS signal is indicated as DCF fluorescence, measured using the BL1 channel (excitation 488 nm, emission 530 nm) on an Attune NxT Cytometer and is plotted against side scatter (SSC). The results are an average of three independent experiments and the error bars represent standard deviation.

Conclusion

We conclude that modification of distyryl BODIPYs with activated transplatin is able to enhance the PI of the compounds versus the non-platinated ones by one order of magnitude. This is achieved by increasing exclusively the photocytotoxicity but not the dark toxicity. Therefore, these transplatin-BODIPY conjugates are very promising candidates for application as photosensitizers in PDT, especially with their advantage of intense absorption in the *phototherapeutic window*. Anisole-substituted BODIPY **3-tPt** is not only the photosensitizer with the highest PI studied in this work but also the distyryl BODIPY with the highest reported PI against any cell line in the literature so far. BODIPY **3-tPt** was evaluated in further cell culture studies and found to accumulate in the ER and no other cellular organelles. HeLa cells that were treated with **3-tPt** were found to display significantly increased intracellular ROS levels upon irradiation with red light, confirming the photoactivatable mechanism of action of BODIPY **3-tPt**. In our experimental and *in silico* studies of the photophysical behaviour of the BODIPYs, we found that *N,N*-dimethylaniline substituted BODIPY **4** exhibits a charge-separated character in the excited

state and we postulate the relaxation from the ICT state to be competing with ISC and therefore singlet oxygen generation.

Experimental Section

All chemicals were of reagent grade and purchased from *Sigma–Aldrich* (Switzerland), *Merck* (Switzerland), *Alfa Aesar* (USA), *Acros Organics* (Belgium), *Honeywell* (USA), or *Fluorochem* (United Kingdom). Reactions were carried out in glass equipment and monitored for completion by analyzing a small sample (after suitable workup) by TLC, UPLC, or UPLC-MS. Solvents for reactions were of p.a. grade. Evaporation of the solvents *in vacuo* was done with the rotary evaporator. Chromatography: *Merck* silica gel 60 (40–63 μm) with the indicated solvent system. Thin layer chromatography (TLC): *Merck* TLC plates silica gel 60 on aluminum with the indicated solvent system; the spots were visualized by UV light (254 and 366 nm). UV-Vis spectra: *Specord® 250 PLUS* spectrophotometer (*Analytic Jena*, Germany); λ_{max} (log ϵ) in nm. Fluorescence emission spectra: *Cary Eclipse* fluorescence spectrophotometer (*Agilent*, USA); λ_{max} in nm. IR spectra: *SpectrumTwo FT-IR Spectrometer* (*Perkin-Elmer*, USA) equipped with a *Specac Golden Gate™* ATR (attenuated total reflection) accessory; applied as neat samples; $1/\lambda$ in cm^{-1} . ^1H -NMR spectra in the indicated solvent; *Bruker AV-400* (400 MHz); δ in ppm rel. to CHCl_3 (δ 7.26), CH_2Cl_2 (δ 5.32), $\text{DMF-}d_7$ (δ 8.04, 2.93, 2.76); J in Hz. ^{11}B -NMR spectra in CDCl_3 ; *Bruker AV-500* (160.42 MHz); d in ppm rel. to BF_3 (δ 0). ^{19}F -NMR spectra in CDCl_3 ; *Bruker AV-500* (107.5 MHz); δ in ppm rel. to CFCl_3 (δ 0). ^{195}Pt -NMR spectra in $\text{DMF-}d_7$; *Bruker AV-500* (107.5 MHz); δ in ppm rel. to K_2PtCl_6 in D_2O (δ 0). Melting point: measured on *Mettler Toledo MP70* melting point system. High-resolution electrospray mass spectra (HR-ESI-MS) were recorded on a *maXis QTOF-MS* instrument (*Bruker Daltonics GmbH*, Bremen, Germany). Samples were dissolved in an appropriate solvent at a concentration of around 1 $\mu\text{mol/mL}$ and measured at continuous flow at 3 $\mu\text{L/min}$. The mass spectrometer was operated in the positive electrospray ionization mode at 4,000 V capillary voltage, -500 V endplate offset, with a N_2 nebulizer pressure of 0.8 bar and dry gas flow of 4 L min^{-1} at 180 $^\circ\text{C}$. MS acquisitions were performed in the mass range from m/z 50 to 2'000 at 20,000 resolution (full width at half maximum) and 1.0 Hz spectra rate. Masses were calibrated between m/z 158 and 1450 or 2721 prior analysis below 2 ppm accuracy, with a 2 μM solution of sodium formate or with a *Fluka* electrospray calibration solution (*Sigma-Aldrich*, Buchs, Switzerland) that has been 100 times diluted with acetonitrile, respectively. Elemental Analysis was performed on a *LECO Truespec CHNS(O)-microanalyser* or on a *LECO TruSpec Micro* system, where the gaseous combustion products of C (CO_2) and H (H_2O) were quantified by means of infrared spectroscopy while nitrogen was measured as N_2 with a thermal conductivity detector. The results were compared with the corresponding values calculated in *ChemDraw Professional 18.0*. Single crystals were obtained from recrystallization by vapor diffusion with indicated solvent and antisolvent systems.^[60] Crystallographic data were collected at 160.0(1) K on a *Rigaku OD XtaLAB Synergy Dualflex* diffractometer equipped with a *Pilatus 200 K* detector and a *PhotonJet Mo K α* ($\lambda = 0.71073 \text{ \AA}$) and *Cu K α* ($\lambda = 1.54184 \text{ \AA}$) source. Suitable crystals were covered with oil (*Infinite V8512*, formerly known as *Paratone N*), mounted on top of a 18 mm Mounted *CryoLoop™* in a *CrystalCap Magnetic™* (*Hampton Research*) and immediately transferred to the diffractometer. The program suite *CrysAlisPro* was used for data collection, multi-scan absorption correction and data reduction.^[61] The structure was solved with direct methods using *SHELXT*^[62] and was refined by full-matrix least-squares methods on F^2 with *SHELXL-2014*.^[63] For these two steps, the GUI *OLEX2* was used (Table S9).^[64] The graphical output was generated with the help of the program *Mercury*.^[65] CCDC 1998711–1998712 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Singlet oxygen quantum yields: The singlet oxygen quantum yields (Φ_Δ) were determined analogously to a method reported by our group^[41] but

with the following divergences: the photosensitizers were dissolved in $\text{MeOD-}d_4$ (1 M DCl in $\text{MeOD-}d_4$ for **4(H*)₃**) and two different concentrations were prepared for each photosensitizer, while the maximum absorption intensities were kept under 1.0. Excitation was performed using a high-power-LED light source (690 nm, FC5-LED-WL, *Prizmatix Ltd.*, Israel) of which the light intensity at the position of the cuvette was measured to be 12.3 mW/cm^2 . Emission spectra were collected from 1050 nm to 1500 nm. The singlet oxygen quantum yields were calculated by comparison with literature reported standard methylene blue (**MB**). Experimental uncertainties of the singlet oxygen quantum yields were calculated by error propagation from the standard errors of the slopes, when plotting the PS absorption intensity versus the singlet oxygen phosphorescence emission intensity of two concentrations of a PS sample. A detailed description of the method can be found in the SI.

List of Supporting Information: Synthetic procedures to yield BODIPYs **5**, **1**, **2**, **3**, **4**, **2-tPt**, **3-tPt** and **4-tPt**, ^1H -, ^{11}B -, ^{19}F - and ^{195}Pt -NMR spectra, computational details, experimental details for singlet oxygen quantum yield measurements, photostability, hydroxyl radical detection, estimation of partition constants, cell culture, photocytotoxicity assays, localization studies, detection of intracellular ROS levels and crystallographic data (including Tables S1 to S9 and Figures S1 to S26).

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Keywords: cancer • intramolecular charge transfer • photophysics • photosensitizer • singlet oxygen

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Entry for the Table of Contents

We have investigated the effect of transplatin coordination to distyryl-BODIPYs with respect to their *in vitro* performance against HeLa cells. The BODIPYs were assessed by analysis of their photophysical properties both experimentally and *in silico*, and by studies of their intracellular behavior, revealing high potential for application in PDT.

Institute and/or researcher Twitter usernames: @RoxanePadrutt, @LordVipin, @SimonKlingler_, @BODIPY_Maker, @UZH_Chemistry

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1 Synthetic Procedures to Yield BODIPYs **5**, **1**, **2**, **3**, **4**, **2-tPt**₃, **3-tPt** and **4-tPt**

BODIPY **5**, analogous to reference [1]:

In a two-necked round bottom flask (500 mL), equipped with a magnetic stirring bar and a septum, 4-pyridinecarboxaldehyde (0.91 g, 8.49 mmol, 1.0 eq.) and 2,4-dimethylpyrrole (1.70 g, 17.5 mmol, 2.1 eq.) were dissolved in CH₂Cl₂ (300 mL). Trifluoroacetic acid (0.2 mL) was added dropwise and the clear yellow soln. was stirred under N₂ at rt under exclusion of light. After 26 h, when TLC reaction control showed full consumption of the 4-pyridinecarboxaldehyde, chloranil (2.10 g, 8.51 mmol, 1.0 eq.) was added to the clear dark red reaction mixture which was subsequently stirred under N₂ at rt. After another 26 h, DiPEA (10 mL) was added, and the black mixture was stirred under N₂ at rt for 30 min. BF₃·Et₂O (46%, 10 mL) was added dropwise over 15 min. After 20 h, the reaction was stopped, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO₂, CH₂Cl₂ to 10% EtOAc in CH₂Cl₂) to afford desired product **5** as red crystals (0.930 g, 2.87 mmol) in a yield of 34%. *R*_f=0.30 (EtOAc/*n*-hexane 1:1); ¹H-NMR (400 MHz, CDCl₃): δ=8.79 (*dd*, *J*=4.3, 1.7, 2H; C^{2'}H, C^{6'}H), 7.32 (*dd*, *J*=4.3, 1.6, 2H; C^{3'}H, C^{5'}H), 6.01 (*s*, 2H; C²H, C⁶H), 2.56 (*s*, 6H; C³CH₃, C⁵CH₃), 1.41 (*s*, 6H; C¹CH₃, C⁷CH₃), see Figure S1; UV-Vis (MeOH): λ_{max} (logε)=310 (3.70), 365 (3.69), 501 (4.88); Fluorescence (EtOH) λ_{ex}=470 nm; λ_{em}=523 nm; HRMS (ESI): *m/z* calcd for C₁₈H₁₉N₃BF₂⁺: 326.16346 [*M*+H]⁺; found: 326.16323.

BODIPY **1**, analogous to reference [2].

In a two-necked round bottom flask (250 mL), equipped with a magnetic stirring bar, a *Dimroth* condenser, a dropping funnel and a glass stopper, BODIPY **5** (0.12 g, 0.37 mmol, 1.0 eq.) and I_2 (0.19 g, 0.74 mmol, 2.0 eq.) were dissolved in EtOH (130 mL) and the brown soln. was heated to 35 °C and stirred under N_2 until all precipitate dissolved. The mixture was allowed to cool to rt and an aq. soln. of HIO_3 (9 mL, 1.5%) was added dropwise over the course of 10 min, then the reaction mixture was stirred under N_2 and heated to reflux (85 °C bath temp.). After 1 h, TLC reaction control showed full consumption of BODIPY **5** and the mixture was allowed to cool to rt and was then concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (200 mL) and washed with H_2O (2 x 200 mL) and an aq. soln. of KI (3%, 4 x 200 mL). The soln. was concentrated under reduced pressure to afford desired product **1** as dark purple crystals (0.20 g, 0.34 mmol) in a yield of 92%. $R_f=0.50$ (EtOAc/*n*-hexane 1:1); $^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta=8.84$ (*dd*, $J=4.5, 1.4$, 2H; $\text{C}^{2'}\text{H}$, $\text{C}^{6'}\text{H}$), 7.32 (*d*, $J=5.7$, 2H; $\text{C}^{3'}\text{H}$, $\text{C}^{5'}\text{H}$), 2.65 (*s*, 6H; C^3CH_3 , C^5CH_3), 1.42 (*s*, 6H; C^1CH_3 , C^7CH_3), see Figure S2; $^{11}\text{B-NMR}$ (160.42 MHz, CDCl_3): $\delta=0.277$ (*t*, $J=31.83$, 1B; BF_2), see Figure S3; $^{19}\text{F-NMR}$ (107.5 MHz, CDCl_3): $\delta=-146.10$ (1:1:1:1 *q*, $J=31.83$, 2F; BF_2), see Figure S4; UV-Vis (MeOH): λ_{max} ($\log \epsilon$)=390 (3.94), 537 (4.81); Fluorescence (EtOH) $\lambda_{\text{ex}}=500$ nm ; $\lambda_{\text{em}}=564$ nm, (MeOH) $\lambda_{\text{ex}}=535$ nm ; $\lambda_{\text{em}}=563$ nm; HRMS (ESI): m/z calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{BF}_2\text{I}_2^+$: 577.95675 [$M+\text{H}$] $^+$; found: 577.95669.

BODIPY **2**, based on reference [3]:

In a two-necked round bottom flask (25 mL), equipped with a magnetic stirring bar, a *Dimroth* condenser, a septum and activated molecular sieves (4 Å, 6 g), BODIPY **1** (80 mg, 0.14 mmol, 1.0 eq.) was dissolved in degassed toluene (13 mL) and the mixture was stirred under N₂ and under exclusion of light. 1-Methyl-5-imidazolecarboxaldehyde (0.15 g, 1.4 mmol, 9.9 eq.), glacial acetic acid (0.2 mL) and piperidine (0.2 mL) were added, and the dark purple reaction mixture was heated to reflux (110 °C bath temp.). The reaction was stopped after 1 h, when reaction control by TLC showed full conversion of starting material **1**. The molecular sieves were filtered off over a filter paper and washed with EtOAc, and the solvent of the filtrate was removed under reduced pressure. The crude product was purified by column chromatography (SiO₂, 10% MeOH in CH₂Cl₂) under the exclusion of light. After re-dissolution of the product in CH₂Cl₂ and filtration over a filter paper, the filtrate was concentrated under reduced pressure and dried under high vacuum to afford desired product **2** as a dark green, light sensitive solid (56 mg, 0.070 mmol) in a yield of 53%. *R*_f=0.29 (CH₂Cl₂/MeOH 9:1); m.p.: decomposition after heating to 350 °C without melting; ¹H-NMR (400 MHz, CD₂Cl₂): δ=8.82 (dd, *J*=4.3, 1.6, 2H; C^{2'}H, C^{6'}H), 8.13 (d, *J*=16.4, 2H; 2 x C^{3/5/5''}CH), 7.53 (s, 4H; 2 x C^{2''}H, 2 x C^{4''}H), 7.51 (d, *J*=16.4, 2H; 2 x C^{3/5/5''}CH), 7.35 (dd, *J*=4.3, 1.7, 2H; C^{3'}H, C^{5'}H), 3.79 (s, 6H; 2 x NCH₃), 1.50 (s, 6H; C¹CH₃, C⁷CH₃), see Figure S5; IR (neat): 2918w (ν CH₃, C–H), 1622m (ν C=N (conj.)), 1515s (ν C=N (conj.)), 1459m, 1429m, 1407m, 1353s, 1318m, 1272m, 1226w, 1173s, 1157s, 1105s, 1066s (ν aryl–I), 1004s, 944m, 848m, 815s, 791m, 768m, 725m, 654w; UV-Vis (MeOH): λ_{max} (logε)=303 (4.17), 374 (4.50), 442 (3.94), 666 (4.74); Fluorescence (MeOH) λ_{ex}=670 nm ; λ_{em}=705 nm, (EtOH) λ_{ex}=630 nm ; λ_{em}=706 nm; HRMS (ESI): *m/z* calcd for C₂₈H₂₅N₇BF₂I₂⁺: 762.03164 [*M*+H]⁺; found: 762.03173, *m/z* calcd for C₂₈H₂₆N₇BF₂I₂²⁺:

381.52001 $[M+2H]^{2+}$; found: 381.51973; elemental analysis calcd (%) for $C_{28}H_{24}N_7BF_2I_2(H_2O)_2$ (797.19): C 42.19, H 3.54, N 12.30; found: C 43.37, H 3.61, N 12.05.

BODIPY **3**, based on reference [3]:

In a two-necked round bottom flask (100 mL), equipped with a magnetic stirring bar, a *Dimroth* condenser, a septum, and activated molecular sieves (4 Å, 15 g), BODIPY **1** (200 mg, 0.34 mmol, 1.0 eq.) was dissolved in toluene (30 mL) and the mixture was stirred under N_2 and under exclusion of light. *p*-Anisaldehyde (450 mg, 3.30 mmol, 9.5 eq.), glacial acetic acid (0.5 mL) and piperidine (0.5 mL) were added, and the dark purple reaction mixture was heated to reflux (100 °C bath temp.). The reaction was stopped after 3 h, when reaction control by TLC showed full conversion of starting material **1**. The solvent was removed under reduced pressure and the crude product was re-dissolved in CH_2Cl_2 (250 mL) and washed with H_2O (3 x 250 mL). The organic phase was concentrated under reduced pressure and the product was purified twice by column chromatography (SiO_2 , 0.5% MeOH in CH_2Cl_2 and SiO_2 , 0.5% to 3% MeOH in CH_2Cl_2) under the exclusion of light to afford desired product **3** as a dark green solid (180 mg, 0.22 mmol) in a yield of 63%. R_f =0.19 (CH_2Cl_2); m.p.: 269–272 °C; 1H -NMR (400 MHz, CD_2Cl_2): δ =8.81 (d, J =3.8, 2H; $C^2'H$, $C^{6'}H$), 8.19 (d, J =16.6, 2H; 2 x $C^{3/5/4''}CH$), 7.63 (d, J =8.6, 4H; 2 x $C^{3''}H$, 2 x $C^{5''}H$), 7.58 (d, J =16.9, 2H, 2 x $C^{3/5/4''}CH$), 7.35 (d, J =5.4, 2H; $C^{3'}H$, $C^{5'}H$), 6.98 (d, J =8.5, 4H; 2 x $C^{2''}H$, 2 x $C^{6''}H$), 3.87 (s, 6H; 2 x OCH_3), 1.51 (s, 6H; C^1CH_3 , C^7CH_3), see Figure S6; IR (neat): 2920s (ν CH_3 , C–H), 2851m (ν O– CH_3), 2049w, 1740w, 1711w (ν arom. C=C), 1621w (ν C=C conj. to arom. ring), 1597m (ν arom. C=C, conj. C=N), 1569m, 1528m (ν conj. C=N), 1510s (ν arom C=C), 1462s, 1433s, 1415m, 1382m, 1355s, 1321m, 1302m, 1269m, 1258m, 1245s, 1190m, 1165s (ν C–I), 1102s, 1054s, 1031s, 1015s, 988m, 973m, 957m, 937m, 859w, 821m, 807m, 786m, 770m; UV-Vis (MeOH): λ_{max} (log ϵ)=319 (4.36), 379 (4.54), 442 (4.07), 666 (4.80), (CH_2Cl_2): λ_{max} (log ϵ)=321 (4.40), 382 (4.60), 446 (4.15), 671 (4.88), (MeCN): λ_{max} (log ϵ)=318 (4.37), 377 (4.58), 439 (4.11), 660 (4.82). Fluorescence (MeOH) λ_{ex} =670 nm ; λ_{em} =700 nm, (CH_2Cl_2) λ_{ex} =673 nm ; λ_{em} =730 nm; HRMS (ESI): m/z calcd for $C_{34}H_{28}N_3O_2BF_2I_2Na^+$: 836.02242 $[M+Na]^+$; found: 836.02245,

m/z calcd for $C_{34}H_{29}N_3O_2BF_2I_2^+$: 814.04048 $[M+H]^+$; found: 814.04083, m/z calcd for $C_{34}H_{28}N_3O_2BFI_2^+$: 794.03425 $[M-F]^+$; found: 794.03435; elemental analysis calcd (%) for $C_{34}H_{28}N_3O_2BF_2I_2$ (813.23): C 50.22, H 3.47, N 5.17; found: C 50.19, H 3.67, N 5.11. Single crystals were obtained by vapor diffusion (solvent: $CHCl_3$, antisolvent: cyclopentane) following the description in the literature.^[4]

BODIPY **4**, based on reference ^[3]:

In a two-necked round bottom flask (100 mL), equipped with a magnetic stirring bar, a *Dimroth* condenser, a septum and activated molecular sieves (4 Å, 15 g), BODIPY **1** (199 mg, 0.34 mmol, 1.0 eq.) was dissolved in dry toluene (30 mL) and the mixture was stirred under N_2 and under exclusion of light. *p*-Dimethylaminobenzaldehyde (522 mg, 3.5 mmol, 10 eq.), glacial acetic acid (0.5 mL) and piperidine (0.5 mL) were added, and the dark purple reaction mixture was heated to reflux (100 °C bath temp.). The reaction was stopped after 3 h, when reaction control by TLC showed full conversion of starting material **1**. The solvent was removed under reduced pressure and the crude product was dissolved in CH_2Cl_2 (200 mL) and washed with a sat. aq. soln. of $NaHCO_3$ (3 x 200 mL) and H_2O (4 x 200 mL). The organic phase was concentrated under reduced pressure and the product was purified twice by column chromatography (SiO_2 , 0.5% basic MeOH in CH_2Cl_2 and SiO_2 , 2.5% EtOAc in CH_2Cl_2) under the exclusion of light to afford desired product **4** as a dark red solid (94.0 mg, 0.11 mmol) in a yield of 32%. R_f =0.40 (5% EtOAc in CH_2Cl_2); m.p.: decomposition after heating to 350 °C without melting; 1H -NMR (400 MHz, CD_2Cl_2): δ =8.78 (d, J =5.9, 2H; $C^{2'}H$, $C^{6'}H$), 8.22 (d, J =16.0, 2H; 2 x $C^{3/5/4''}CH$), 7.57 (d, J =8.8, 4H; 2 x $C^{3''}H$, 2 x $C^{5''}H$), 7.52 (d, J =16.3, 2H; 2 x $C^{3/5/4''}CH$), 7.35 (d, J =4.4, 2H; $C^{3'}H$, $C^{5'}H$), 6.76 (d, J =9.6, 4H; 2 x $C^{2''}H$, 2 x $C^{6''}H$), 3.06 (s, 12H; 4 x NCH_3), 1.49 (s, 6H; C^1CH_3 , C^7CH_3), see Figure S7; IR (neat): 2916w (ν CH_3 , C–H), 2850w (ν CH_3 , C–H), 2798w (ν NCH_3 , C–H), 1620w (ν C=C conj. to arom. ring), 1585s (ν conj. C=N), 1552w (ν conj. C=N), 1515s (ν arom. C=C), 1483m, 1464m, 1424s, 1385w, 1350s, 1304m, 1261w, 1198w, 1158s, 1102s, 1053s (ν aryl–I), 1013s, 946m, 852w, 808m, 774w, 769w; UV-Vis (MeOH): λ_{max} (log ϵ)=345 (4.32), 431 (4.16), 549 (4.05), 745

(4.30), (CH₂Cl₂): $\lambda_{\max}$ (log ϵ)=348 (4.48), 441 (4.34), 552 (4.34), 754 (4.71), (MeCN): $\lambda_{\max}$ (log ϵ)=344 (4.54), 431 (4.39), 546 (4.32), 741 (4.64); Fluorescence (MeOH) λ_{ex} =740 nm ; λ_{em} =821 nm; HRMS (ESI): m/z calcd for C₃₆H₃₅N₅BF₂I₂⁺: 840.10375 [$M+H$]⁺; found: 840.10345, m/z calcd for C₃₆H₃₇N₅BF₂I₂²⁺: 420.55551 [$M+2H$]²⁺; found: 420.55584; elemental analysis calcd (%) for C₃₆H₃₄N₅BF₂I₂ (839.32): C 51.52, H 4.08, N 8.34; found: C 51.25, H 3.98, N 8.29. Single crystals were obtained by vapor diffusion (solvent: CH₂Cl₂, antisolvent: cyclopentane) following the description in the literature.^[4]

BODIPY **2-tPt₃**, based on reference ^[5]:

In a one-necked round bottom flask (5 mL), equipped with a magnetic stirring bar and a *Dimroth* condenser, transplatin (52 mg, 0.17 mmol, 4.2 eq.) and AgNO₃ (29 mg, 0.17 mmol, 4.2 eq.) were dissolved in DMF (2.5 mL) and the light yellow mixture was stirred under N₂ at 55 °C under the exclusion of light. After 24 h, the reaction mixture was allowed to cool down to rt and centrifuged at 6'500 rpm for 5 min. In a two-necked round bottom flask (10 mL) equipped with a magnetic stirring bar, a *Dimroth* condenser and a septum, BODIPY **2** (31 mg, 0.041 mmol, 1.0 eq.) was dissolved in degassed DMF (4.5 mL). The light-yellow supernatant containing the activated transplatin (1.8 mL, corresponding to 3.3 eq.) was added to the soln. and the mixture was stirred under N₂ at 55 °C under the exclusion of light. After 65 h, the dark green reaction mixture was allowed to cool down to rt and poured into CH₂Cl₂ (50 mL). The newly formed dark green precipitate was re-dissolved in DMF (5 mL) and reprecipitated in diethyl ether (50 mL). The precipitate was dried under high vacuum to afford the desired product **2-tPt₃** as a dark green, light sensitive solid with two DMF solvent molecules per product complex (46 mg, 0.024 mmol) in a yield of 59%. m.p.: decomposition after heating to 350 °C without melting; ¹H-NMR (400 MHz, DMF-*d*₇): δ =9.37 (d, J =6.7, 2H; C^{2'}H, C^{6'}H), 8.62 (s, 2H; 2 x C^{2''/4''}H), 8.15 (d, J =16.7, 2H; 2 x C^{3/5/5''}CH), 8.09 (d, J =6.7, 2H; C^{3'}H, C^{5'}H), 8.06 (s, 2H; 2 x C^{2''/4''}H), 7.57 (d,

$J=16.8$, 2H; 2 x $C^{3/5/7}$ CH), 4.65 (s, 6H; 2 x $N^{1'}PtNH_3$), 4.41 (s, 12H; 4 x $N^{3''}PtNH_3$), 4.05 (s, 6H; 2 x NCH_3), 1.59 (s, 6H; C^1CH_3 , C^7CH_3), see Figure S8; ^{195}Pt -NMR (107.5 MHz, DMF- d_7): $\delta=-2306$ (s, 1Pt), -2324 (s, 2Pt), see Figure S9; IR (neat): 3272w (ν NH_3 , N-H), 3120w (ν NH_3 , N-H), 1615m (ν C=C conj. to arom. ring), 1513m (ν arom. C=C), 1466w, 1297s (ν NO_3 , N=O), 1182m, 1103s, 1009m, 952w, 824w, 772w; UV-Vis (MeOH): λ_{max} ($\log \epsilon$)=364 (4.59), 432 (3.91), 660 (4.62); Fluorescence (MeOH) λ_{ex} =670 nm; λ_{em} =703 nm, (DMF) λ_{ex} =344 nm; λ_{em} =689 nm; HRMS (ESI): m/z calcd for $C_{28}H_{42}N_{14}O_3BCl_2F_2I_2Pt_3^{3+}$: 526.66664 [$M-Cl(NO_3)_2$] $^{3+}$; found: 526.66796, m/z calcd for $C_{28}H_{42}N_{13}BCl_3F_2I_2Pt_3^{3+}$: 517.66032 [$M-(NO_3)_3$] $^{3+}$; found: 517.66159; elemental analysis calcd (%) for $C_{28}H_{42}N_{16}O_9BCl_3F_2I_2Pt_3(CHON(CH_3)_2)$ (1888.16): C 21.63, H 3.04, N 13.35; found: C 21.76, H 3.32, N 13.12.

BODIPY **3-tPt**, based on reference [5].

In a one-necked round bottom flask (5 mL), equipped with a magnetic stirring bar, transplatin (13 mg, 0.042 mmol, 1.2 eq.) and $AgNO_3$ (8 mg, 0.047 mmol, 1.4 eq.) were dissolved in dry DMF (0.8 mL) and the light yellow mixture was stirred under N_2 at rt under the exclusion of light. After 26 h, the reaction mixture was allowed to cool down to rt and centrifuged at 6'500 rpm for 5 min. In a two-necked round bottom flask (10 mL) equipped with a magnetic stirring bar, a *Dimroth* condenser and a septum, BODIPY **3** (28 mg, 0.034 mmol, 1.0 eq.) was dissolved in dry DMF (4.5 mL). The light-yellow supernatant containing the activated transplatin was added to the soln. and the mixture was stirred under N_2 at 50 °C under the exclusion of light. After 26 h when reaction control by HPLC showed complete consumption of starting material **3**, the dark green reaction mixture was allowed to cool down to rt and poured into diethyl ether (300 mL). The newly formed dark green precipitate was dried under high vacuum to afford the desired product **3-tPt** as a dark green solid (19 mg, 0.015 mmol) in a yield of 45%. m.p.: decomposition after heating to 350 °C without melting; 1H -NMR (400 MHz, DMF- d_7): $\delta=9.35$ (d,

$J=6.9$, 2H; $C^{2'}H$, $C^{6'}H$), 8.31 (d, $J=17.4$, 2H; 2 x $C^{3/5/4''}CH$), 8.11 (d, $J=4.9$, 2H; $C^{3'}H$, $C^{5'}H$), 7.72 (d, $J=8.9$, 4H; 2 x $C^{3''}H$, 2 x $C^{5''}H$), 7.65 (d, $J=16.5$, 2H; 2 x $C^{3/5/4''}CH$), 7.14 (d, $J=8.6$, 4H; 2 x $C^{2''}H$, 2 x $C^{6''}H$), 4.67 (s, 6H; 2 x N^1PtNH_3), 3.93 (s, 6H; 2 x OCH_3), 1.57 (s, 6H; C^1CH_3 , C^7CH_3), see Figure S10; ^{195}Pt -NMR (107.5 MHz, DMF- d_7): $\delta=-2305$, see Figure S11; IR (neat): 3268w (ν NH₃, N-H), 3186w (ν NH₃, N-H), 3120w (ν NH₃, N-H), 2925w (ν CH₃, C-H), 2836w (ν O-CH₃), 1659m (ν arom. C=C), 1618w (ν C=C conj. to arom. ring), 1598m (ν conj. C=N), 1509s (ν arom. C=C), 1465m, 1434m, 1411m, 1382m, 1352m, 1317m, 1300m, 1265m (ν NO₃, N=O), 1185m, 1165s (ν C-I), 1096s, 1067s, 1029m, 1007s, 959m, 934m, 861w, 820m, 772w; UV-Vis (MeOH): λ_{max} (log ϵ)=320 (4.36), 385 (4.57), 453 (4.10), 676 (4.84); Fluorescence (MeOH) λ_{ex} =670 nm; λ_{em} =730 nm; HRMS (ESI): m/z calcd for $C_{34}H_{34}N_5O_2BClF_2I_2Pt^+$: 1077.01938 [$M-NO_3$] $^+$; found: 1077.02064; elemental analysis calcd (%) for $C_{34}H_{34}N_6O_5BClF_2I_2Pt(CHON(CH_3)_2)(H_2O)$ (1231.95): C 36.07, H 3.60, N 7.96; found: C 35.93, H 3.61, N 8.29.

BODIPY **4-tPt**, based on reference [5]:

In a one-necked round bottom flask (5 mL), equipped with a magnetic stirring bar, transplatin (13 mg, 0.043 mmol, 1.2 eq.) and AgNO₃ (8 mg, 0.047 mmol, 1.3 eq.) were dissolved in dry DMF (0.8 mL) and the light yellow mixture was stirred under N₂ at rt under the exclusion of light. After 26 h, the reaction mixture was allowed to cool down to rt and centrifuged at 6'500 rpm for 5 min. In a two-necked round bottom flask (10 mL) equipped with a magnetic stirring bar, a *Dimroth* condenser and a septum, BODIPY **4** (30 mg, 0.036 mmol, 1.0 eq.) was dissolved in dry DMF (4.5 mL). The light-yellow supernatant containing the activated transplatin was added to the soln. and the mixture was stirred under N₂ at 50 °C under the exclusion of light. After 26 h when reaction control by HPLC showed complete consumption of starting material **4**, the dark red reaction mixture was allowed to cool down to rt and poured into diethyl ether (300 mL). The newly formed black precipitate was dried under high vacuum to afford the desired product **4-tPt** as a black solid (25 mg, 0.021 mmol) in a yield of 58%. m.p.:

decomposition after heating to 350 °C without melting; $^1\text{H-NMR}$ (400 MHz, $\text{DMF-}d_7$): $\delta=9.32$ (d, $J=6.6$, 2H; $\text{C}^{2'}\text{H}$, $\text{C}^{6'}\text{H}$), 8.34 (d, $J=16.1$, 2H; 2 x $\text{C}^{3/5/4''}\text{CH}$), 8.07 (m, 2H; $\text{C}^{3'}\text{H}$, $\text{C}^{5'}\text{H}$), 7.63–7.59 (m, 6H; 2 x $\text{C}^{3''}\text{H}$, 2 x $\text{C}^{5''}\text{H}$, 2 x $\text{C}^{3/5/4''}\text{CH}$), 6.89 (d, $J=8.6$, 4H; 2 x $\text{C}^{2''}\text{H}$, 2 x $\text{C}^{6''}\text{H}$), 4.66 (s, 6H; 2 x N^1PtNH_3), 3.11 (s, 12H; 4 x NCH_3), 1.54 (s, 6H; C^1CH_3 , C^7CH_3), see Figure S12; $^{195}\text{Pt-NMR}$ (107.5 MHz, $\text{DMF-}d_7$): $\delta=-2306$, see Figure S13; IR (neat): 3286w (ν NH_3 , N–H), 3160w (ν NH_3 , N–H), 3105w (ν NH_3 , N–H), 2907w (ν CH_3 , C–H), 2866w (ν NCH_3 , C–H), 2808w, 1662w (ν arom. C=C), 1621w (ν C=C conj. to arom. ring), 1578m (ν conj. C=N), 1513s (ν arom. C=C), 1487w, 1463w, 1424m, 1367w, 1345s, 1292s (ν NO_3 , N=O), 1188w, 1156s, 1095s, 1080s, 1002s, 950m, 942m, 928m, 904w, 852w, 805w, 771m; UV-Vis (MeOH): λ_{max} ($\log \epsilon$)=353 (4.59), 446 (4.44), 563 (4.43), 768 (4.75); Fluorescence (MeOH) λ_{ex} =770 nm ; λ_{em} =834 nm; HRMS (ESI): m/z calcd for $\text{C}_{36}\text{H}_{40}\text{N}_7\text{BClF}_2\text{I}_2\text{Pt}^+$: 1103.08265 [$M-\text{NO}_3$] $^+$; found: 1103.08307, m/z calcd for $\text{C}_{36}\text{H}_{41}\text{N}_7\text{BClF}_2\text{I}_2\text{Pt}^{2+}$: 552.04496 [$M-\text{NO}_3+\text{H}$] $^{2+}$; found: 552.04543; elemental analysis calcd (%) for $\text{C}_{36}\text{H}_{40}\text{N}_8\text{O}_3\text{BClF}_2\text{I}_2\text{Pt}(\text{H}_2\text{O})_{2.5}$ (1210.96): C 35.71, H 3.75, N 9.25; found: C 35.73, H 3.76, N 9.80.

2 NMR Spectra of BODIPYs **5**, **1**, **2**, **3**, **4**, **2-tPt**, **3-tPt** and **4-tPt**

Figure S1. $^1\text{H-NMR}$ spectrum of BODIPY **5** in CDCl_3 .

Figure S2. $^1\text{H-NMR}$ spectrum of BODIPY **1** in CDCl_3 .

Figure S3. ^{11}B -NMR spectrum of BODIPY 1 in CDCl_3 .

Figure S4. ^{19}F -NMR spectrum of BODIPY 1 in CDCl_3 .

Figure S5. ¹H-NMR spectrum of BODIPY **2** in CD₂Cl₂.

Figure S6. ¹H-NMR spectrum of BODIPY **3** in CD₂Cl₂.

Figure S7. ¹H-NMR spectrum of BODIPY **4** in CD₂Cl₂.

Figure S8. ¹H-NMR spectrum of BODIPY 2-tPt₃ in DMF-*d*₇.

Figure S9. ¹⁹⁵Pt-NMR spectrum of BODIPY 2-tPt₃ in DMF-*d*₇.

Figure S10. ^1H -NMR spectrum of BODIPY **3-tPt** in DMF- d_7 .

Figure S11. ^{195}Pt -NMR spectrum of BODIPY 3-tPt in $\text{DMF-}d_7$.

Figure S12. ^1H -NMR spectrum of BODIPY 4-tPt in $\text{DMF-}d_7$.

Figure S13. ^{195}Pt -NMR spectrum of BODIPY 4-tPt in $\text{DMF-}d_7$.

3 Experimental Details for Singlet Oxygen Quantum Yield Measurements

The singlet oxygen quantum yields (Φ_{Δ}) were determined analogously to a method reported by our group.^[6] The photosensitizers were dissolved in MeOD-*d*₄ (1 M DCl in MeOD-*d*₄ for **4**(H⁺)₃) and the solutions were placed in a glass cuvette (114F-10-40, 10 mm x 4 mm dimensions, *Hellma Analytics*, Germany). Two different concentrations were prepared for each photosensitizer, while the maximum absorption intensities were kept under 1.0, with the cuvette oriented in a way that the light path equals to 10 mm. The cuvettes containing solutions of the same concentration as used for the corresponding UV-Vis spectroscopy were placed in a CUV-UV/VIS-TC-ABS temperature-controlled Qpod sample compartment (*Avantes*, The Netherlands) and cooled to 20 °C; temperature control was performed with the use of a TC-125 controller (*Quantum Northwest*, USA) and Q-Blue software. Emission spectroscopy was conducted in a custom-built setup.^[6] Excitation was performed using a high-power-LED light source (690 nm, FC5-LED-WL, *Prizmatix Ltd.*, Israel). The light source was connected with an optical fiber (1000 μm core diameter, *Avantes*) to the cuvette holder over a SMA 905 fiber optic connector. The intensity of the light source at the position of the cuvette was measured to be 12.3 mW/cm² using a S310C thermal sensor connected to a PM100USB power meter (*Thorlabs*, Germany). The connection piece used to insert the SMA connector into the cuvette holder was replaced by an in-house custom-built connection piece that allows the fiber to be inserted at a distance of 2.0 cm from the cuvette. The detector (AvaSpec-NIR256-1.7TEC, *Avantes*) was set to 0 °C and connected to the cuvette holder with an optical fiber (600 μm diameter, *Avantes*). Emission spectra were collected at a 90° angle with respect to the excitation beam from 1050 nm to 1500 nm after five averaged measurements each lasting 9 s. All spectra were recorded using AvaSoft 8.9 software from *Avantes* and further processed using Microsoft Office Excel and Origin 2018 software.

The singlet oxygen quantum yields were calculated according to Eq. (1), by comparison with literature reported standard methylene blue (**MB**) that was measured with the same excitation light source, in the same solvent (exception: **4**(H⁺)₃), and is reported in literature in the same solvent.

$$(1) \quad \Phi_{\Delta(x)} = \Phi_{\Delta(\text{std})} \left(\frac{I_{\text{std}}^{\lambda}}{I_x^{\lambda}} \right) \left(\frac{E_x}{E_{\text{std}}} \right)$$

In Eq. (1), the subscript x designates the corresponding photosensitizer and std the standard, respectively. Φ_{Δ} is the singlet oxygen quantum yield. I^{λ} is the light absorption intensity calculated as overlap of the absorption spectrum of either PS or standard and the emission spectrum of the LED light source (I_0). The absorption intensity depends exponentially on absorbance A (Eq. (2)). For A, the measured absorbance values were scaled by a factor of 0.4. E is the integrated emission peak of singlet oxygen at around 1270 nm. For these emission spectra, the integrated values were obtained by applying a manual background correction in Origin.

$$(2) \quad I^{\lambda} = I_0(1 - 10^{-A(\lambda)})$$

Eq. (1) can be rewritten as:

$$(3) \quad \Phi_{\Delta(x)} = \Phi_{\Delta(\text{std})} \left(\frac{S_x}{S_{\text{std}}} \right)$$

In Eq. (3), S designates the slope when E is plotted against I^A for all measured concentrations, with a fixed intercept at 0. Errors of the singlet oxygen quantum yields were calculated by error propagation from the standard errors of S_x and S_{std} .

Figure S14. Examples of singlet oxygen phosphorescence emission spectra with integrated signal (left column: MB, right column: BODIPY 3) at two different concentrations. Bottom row: Plot of absorption intensity I^A versus phosphorescence emission intensity E with linear regression.

4 Determination of Photostability

The photostability of the best photosensitizer **3-tPt** under PDT conditions was determined with the same setup that was used for the determination of the singlet oxygen quantum yield (see previous chapter 3). As comparison, zinc phthalocyanine (ZnPc) was used. Solutions of either ZnPc or **3-tPt** were dissolved in DMF and were stirred during irradiation with the 690 nm LED source. Every minute, the maximum absorption of the photosensitizer around 670 nm was measured. Only initial absorbances were taken into account. The overlap integrals of the LED light source emission together with the absorbance of the respective photosensitizer were calculated as follows:

$$I_{abs} = \int (1 - 10^{-A_{\lambda}}) d\lambda$$

The absorbance values as a function of time were taken relative to the starting absorbance and then the approximately linear decrease of the absorption was determined and compared relative to ZnPc in DMF^[7] as follows:

$$QY_{PS} = QY_{ZnPc} * \frac{I_{abs}(ZnPc)}{I_{abs}(PS)} * \frac{\left(\frac{d(A/A_0)}{dt}\right)_{PS}}{\left(\frac{d(A/A_0)}{dt}\right)_{ZnPc}}$$

These measurements were done in triplicates for ZnPc and **3-tPt**. **3-tPt** had a relative quantum yield of photodegradation of 0.19 ± 0.02 versus ZnPc in DMF.

5 Detection of Hydroxyl Radicals produced by Complex **4-tPt** upon Light Irradiation

The hydroxyl radical sensor aminophenyl fluorescein (APF) was synthesized as described in the literature.^[8] A Varian Cary Eclipse fluorometer was used with the following settings: excitation at 492 nm, emission at 525 nm, slit width: 2.5 nm, averaging time: 1 second.

As a positive control, the Fenton reaction was done: 5 μ M APF and 300 μ M ammonium iron(II) sulfate in PBS buffer were used as a blank (see below). Then, the fluorescence was zeroed again and H₂O₂ was added so that the total H₂O₂ concentration was 300 μ M and the solution was immediately measured (see below).

In order to show the generation of hydroxyl radicals by **4-tPt** upon light irradiation, a 10 mM stock solution of **4-tPt** in DMF was made. 3 μL of this solution were 1000-fold diluted with 3 mL of a PBS solution containing 5 μM APF. The fluorescence intensity was measured for 2 minutes, the mean and the standard deviation of the fluorescence signal were determined. Afterwards, the vertically positioned UV/Vis cuvette was irradiated with the 657 nm LED irradiation setup (see chapter 9) at a distance of 4 cm for 1 and then three times for 10 minutes. After each irradiation, the fluorescence was measured as described before for 2 minutes. The first fluorescence measurement was set to zero.

Figure S15. Fluorescence signal of APF in a PBS solution with 10 μM of **4-tPt** as a function of irradiation time with a 657 nm LED.

6 Estimation of Partition Constants of Compounds **3**, **3-tPt**, **4**, and **4-tPt** between *n*-Octanol and a 0.15 M Sodium Chloride Aqueous Solution

The partition constants (old term: partition coefficient^[9]) of compounds **3**, **3-tPt**, **4**, and **4-tPt** between *n*-octanol and an aqueous 0.15 M sodium chloride solution were estimated as follows (the 0.15 M sodium chloride solution was used in order to suppress hydrolysis of the platinum-chloride bond^[10]). 50 mL of *n*-octanol and 50 mL of an aqueous 0.15 M sodium chloride solution were intensively shaken in a separating funnel and let to equilibrate for 24 hours. About 0.15 mg of compounds **3**, **3-tPt**, **4**, or **4-tPt** were given in a brown glass HPLC vial containing 0.5 mL *n*-octanol saturated with an aqueous 0.15 M sodium chloride solution and 0.5 mL of aqueous 0.15 M sodium chloride solution saturated with *n*-octanol. The closed HPLC vials were vortexed for 30 minutes and then centrifuged^[11]. From the organic phase, three times 10 μ L were removed and diluted with 190 μ L of methanol. From the aqueous phase, three times 10 μ L were removed and diluted with 190 mL of water. The six samples per compound were analyzed by UPLC-ESI-MS, which were recorded on an Acquity Waters system equipped with a PDA detector and an autosampler using an ACQUITY UPLC BEH C18 Gravity 1.7 μ m (2.1 mm $\times$ 50 mm) reverse phase column. The UPLC system was connected to a Bruker Daltonics HCT ESI-MS spectrometer. A total volume of 1 μ L of a sample solution was analysed. A gradient (0 to 0.5 min 5% B, 0.5 to 2 min 30% B, 2 to 4 min 100% B, 4 to 5 min 100% B) of acetoneitrile (solvent B) versus Millipore water containing 0.1% formic acid (solvent A) was applied using a flow rate of 0.3 mL/min. All solvents used were of LCMS grade. Due to the low concentrations, the MS traces had to be used. The logP values have estimated errors of about 20%.

Table S1. logP values (*n*-octanol versus aqueous 0.15 M sodium chloride solution) of compounds **3**, **3-tPt**, **4**, and **4-tPt**. The logP values have estimated errors of about 20%.

Compound	logP value
3	1.12
3-tPt	0.93
4	0.96
4-tPt	0.91

7 Computational Details

All calculations were conducted using density functional theory (DFT) as implemented in the Gaussian16 Revision A.03 suite of *ab initio* quantum chemistry programs. Normal self-consistent field (SCF) and geometry convergence criteria were employed throughout. All structures were optimized in the solution phase using a polarizable continuum model (PCM). Calculations were conducted without using symmetry constraints. Solvated phase calculations were implemented using the SCRF keyword with default parameters and selecting MeOH as the solvent (dielectric constant $\epsilon = 32.613$). Harmonic frequency analysis based on analytical second derivative was used to characterize optimized structures as local minima on the potential energy surface. Calculations were performed using the B3LYP exchange-correlation functionals and the double- ζ DGDZVP basis set by *Wimmer* and co-workers.^[12] ^[13] Optimized structures and molecular orbitals were analyzed by using Chemcraft (version 1.8, build 536b). Time-dependent density functional theory (TDDFT) calculations were performed on the same functionals, basis-set and solution phase PCM. Transition energies and oscillator strengths for electronic excitation to the first 24 excited singlet states, and the first three excited triplet states, were calculated for the simulation of spectra and photophysical analysis. The simulated TDDFT electronic absorption spectra were calculated by using a gaussian line broadening function with a full-width at half maximum (FWHM) value set at a given number (implemented in Chemcraft).

Figure S16. Experimental (top) and TD (bottom) absorption spectra of BODIPYs **3**, **4**, and **4(H⁺)₃**. The simulated TDDFT electronic absorption spectra were calculated by using a gaussian line broadening function with a full-width at half maximum (FWHM) value set at 50 nm for **3** and **4(H⁺)₃** and 100 nm for **4** (implemented in Chemcraft).

Table S2. Cartesian coordinates of optimized geometry of BODIPY **3** in the ground state.

Atomic Nr.	X [Å]	Y [Å]	Z [Å]
53	5.4948	-1.778252	-0.111644
53	-5.494696	-1.778574	-0.111233
9	0.00001	0.674319	-1.317894
9	-0.000097	0.787456	0.978902
7	1.25322	-0.998951	-0.086353
7	-1.253164	-0.999057	-0.086488
7	0.00034	-7.393412	0.306474
8	-5.111183	7.013586	-0.116752
6	2.549289	-0.563058	-0.082159
6	3.382756	-1.726109	-0.022959
6	2.581933	-2.866667	0.020141
6	1.225693	-2.390418	-0.013968
6	0.000104	-3.084773	0.025043
6	-2.549257	-0.563241	-0.082164
6	-3.382648	-1.726326	-0.022689
6	-2.581752	-2.866839	0.020389
6	-1.225544	-2.390514	-0.013939
6	2.840411	0.850775	-0.161733
1	2.004234	1.455926	-0.492203
6	4.003113	1.475338	0.169479
1	4.828213	0.88721	0.557957
6	4.266221	2.908333	0.085873
6	5.508918	3.395687	0.537857
1	6.239955	2.696078	0.936895
6	5.837017	4.752867	0.493093
1	6.806434	5.076978	0.854558
6	4.905953	5.669942	-0.019467
6	3.655747	5.204688	-0.480744
1	2.945522	5.924926	-0.877808
6	3.345063	3.854876	-0.428686
1	2.375108	3.53446	-0.797366
6	3.066711	-4.286371	0.07012
1	2.707407	-4.803855	0.963132
1	4.15731	-4.315131	0.08383
1	2.727362	-4.85821	-0.797494
6	0.000174	-4.577073	0.121533
6	0.000208	-5.220651	1.365402
1	0.00018	-4.651404	2.29051
6	0.000292	-6.617767	1.403136
1	0.000319	-7.134411	2.361412
6	0.00031	-6.76767	-0.881997
1	0.000354	-7.405202	-1.764458
6	0.000235	-5.377511	-1.027268
1	0.000216	-4.934499	-2.019078

6	-2.840487	0.850556	-0.161969
1	-2.004455	1.455683	-0.492856
6	-4.003128	1.475099	0.16949
1	-4.828039	0.886985	0.558396
6	-4.266392	2.908052	0.085644
6	-3.345485	3.854554	-0.429438
1	-2.375623	3.534136	-0.798358
6	-3.656303	5.204328	-0.481705
1	-2.946267	5.924536	-0.879164
6	-4.906395	5.669581	-0.02012
6	-5.837213	4.752544	0.492952
6	-5.508983	3.395402	0.537922
1	-6.239829	2.695822	0.937359
6	-3.06646	-4.286562	0.070514
1	-2.726632	-4.858627	-0.796754
1	-4.157064	-4.315387	0.083692
1	-2.70758	-4.803768	0.963864
5	-0.000009	-0.090905	-0.12478
8	5.110597	7.013985	-0.115858
6	6.364304	7.548132	0.33425
1	7.198939	7.130384	-0.238655
1	6.305745	8.62287	0.161513
1	6.513571	7.356904	1.402214
6	-6.364761	7.54774	0.333707
1	-6.306339	8.622446	0.160721
1	-7.199579	7.129819	-0.238803
1	-6.513618	7.356725	1.401766
1	-6.806541	5.076654	0.854658

Table S3. Cartesian coordinates of optimized geometry of BODIPY **4** in the ground state.

Atomic Nr.	X [Å]	Y [Å]	Z [Å]
53	-5.495134	-2.112141	0.090506
53	5.498005	-2.104839	0.092313
9	-0.000516	0.38543	1.253189
9	0.000157	0.445236	-1.046425
7	-1.252555	-1.317424	0.059736
7	1.254422	-1.315804	0.060502
7	0.005246	-7.721137	-0.199762
7	5.184203	6.742183	-0.020969
6	-2.552061	-0.878905	0.050635
6	-3.381466	-2.047921	0.015694
6	-2.579316	-3.187632	-0.005463
6	-1.223477	-2.710115	0.017069
6	0.002321	-3.405372	-0.007211
6	2.553341	-0.875553	0.051655

6	3.384299	-2.04344	0.016185
6	2.583676	-3.184203	-0.005778
6	1.227199	-2.708514	0.017237
6	-2.839535	0.531927	0.097723
1	-1.981446	1.147137	0.340559
6	-4.025789	1.158409	-0.160989
1	-4.883744	0.562601	-0.455063
6	-4.274535	2.587186	-0.109743
6	-5.557031	3.075269	-0.455013
1	-6.329065	2.36776	-0.751373
6	-5.8713	4.42702	-0.43121
1	-6.873531	4.733266	-0.707477
6	-4.900131	5.395378	-0.050911
6	-3.605703	4.908891	0.301133
1	-2.827042	5.600238	0.6018
6	-3.312106	3.555347	0.270089
1	-2.309094	3.247099	0.552247
6	-3.061624	-4.609413	-0.028413
1	-2.706241	-5.141903	-0.914259
1	-4.152259	-4.641214	-0.035872
1	-2.716913	-5.16614	0.846887
6	0.003304	-4.899559	-0.072663
6	0.006578	-5.677686	1.091641
1	0.008434	-5.214467	2.074229
6	0.007366	-7.070541	0.975456
1	0.009839	-7.689776	1.870947
6	0.002163	-6.967661	-1.311948
1	0.000497	-7.503857	-2.259511
6	0.001028	-5.570111	-1.302437
1	-0.00149	-5.020132	-2.2392
6	2.839005	0.535623	0.099216
1	1.980309	1.149661	0.342896
6	4.024265	1.163641	-0.160343
1	4.882658	0.568946	-0.455423
6	4.271289	2.592703	-0.109015
6	3.308053	3.559575	0.272084
1	2.305738	3.249996	0.555266
6	3.599911	4.913496	0.302869
1	2.820618	5.603823	0.604222
6	4.893368	5.401696	-0.050393
6	5.865168	4.434687	-0.432526
6	5.552654	3.082525	-0.456004
1	6.325138	2.376086	-0.753744
6	3.067948	-4.605295	-0.029724
1	2.731192	-5.160589	0.849661
1	4.158536	-4.635443	-0.045829

1	2.706226	-5.1403	-0.911395
5	0.000354	-0.411209	0.078424
7	-5.192354	6.735606	-0.022346
6	-6.529517	7.20408	-0.377617
1	-7.294724	6.791745	0.292336
1	-6.562465	8.29017	-0.297833
1	-6.791383	6.933082	-1.408005
6	4.167046	7.710392	0.382042
1	3.296391	7.684238	-0.28505
1	3.821457	7.531673	1.407989
1	4.590802	8.713202	0.340986
6	6.517921	7.213142	-0.385786
1	6.55058	8.298967	-0.302391
1	7.288525	6.799421	0.276919
1	6.772175	6.945672	-1.419102
6	-4.178418	7.704429	0.387263
1	-4.602393	8.707014	0.343137
1	-3.838688	7.526092	1.415337
1	-3.303936	7.678687	-0.274657
1	6.866478	4.742309	-0.710593

Table S4. Cartesian coordinates of optimized geometry of BODIPY **4(H⁺)₃** in the ground state.

Atomic Nr.	X [Å]	Y [Å]	Z [Å]
53	5.589618	-1.877432	-0.08773
53	-5.394007	-2.272732	-0.158978
9	0.012039	0.378191	-1.292858
9	-0.023787	0.473425	1.002627
7	1.318875	-1.250856	-0.059891
7	-1.186096	-1.352606	-0.090763
7	0.302683	-7.604474	0.304714
7	-5.643555	6.490458	-0.139411
6	2.596699	-0.768881	-0.052616
6	3.478765	-1.897897	-0.014356
6	2.721952	-3.066543	0.01548
6	1.34695	-2.640951	-0.006708
6	0.146774	-3.37718	0.024922
6	-2.494609	-0.971868	-0.090494
6	-3.289402	-2.160548	-0.036945
6	-2.446997	-3.269544	0.00801
6	-1.108312	-2.740402	-0.017705
6	2.826286	0.660004	-0.099812
1	1.948046	1.239394	-0.358078
6	3.984067	1.317042	0.163383
1	4.866591	0.755474	0.447206
6	4.178249	2.76879	0.109471

6	5.478048	3.271781	0.331453
1	6.291005	2.582374	0.541461
6	5.751642	4.637437	0.281129
1	6.766125	4.98481	0.450217
6	4.706274	5.520694	0.012439
6	3.40477	5.061571	-0.199409
1	2.593815	5.75753	-0.400357
6	3.145203	3.693647	-0.152414
1	2.12687	3.358328	-0.318321
6	3.260413	-4.466814	0.043199
1	2.943065	-5.006102	0.939237
1	4.350906	-4.453402	0.040874
1	2.938038	-5.041835	-0.828669
6	0.203474	-4.869398	0.121234
6	0.220931	-5.499768	1.37581
1	0.195561	-4.925524	2.295036
6	0.269484	-6.882521	1.445059
1	0.283495	-7.434766	2.376598
6	0.286687	-7.040728	-0.921754
1	0.315697	-7.711152	-1.771943
6	0.235602	-5.66081	-1.037475
1	0.223034	-5.214718	-2.025629
6	-2.854692	0.429369	-0.184885
1	-2.092374	1.060338	-0.629177
6	-4.004168	0.990308	0.264627
1	-4.726913	0.37429	0.789593
6	-4.37432	2.403963	0.146651
6	-3.671116	3.33163	-0.650141
1	-2.804614	3.023632	-1.225922
6	-4.084725	4.659346	-0.735506
1	-3.534493	5.356902	-1.362278
6	-5.210171	5.073528	-0.020832
6	-5.929883	4.185386	0.777995
6	-5.508748	2.858645	0.851393
1	-6.070971	2.163742	1.468897
6	-2.882806	-4.70505	0.044457
1	-2.542416	-5.254079	-0.837817
1	-3.971453	-4.768052	0.068646
1	-2.506302	-5.223264	0.929824
5	0.028653	-0.38939	-0.10674
7	4.964636	6.983078	-0.056367
6	5.440934	7.557898	1.260338
1	6.41544	7.13617	1.497875
1	5.512803	8.639492	1.151279
1	4.714273	7.296972	2.028357
6	-7.00164	6.633113	-0.791961

1	-6.97671	6.111746	-1.747472
1	-7.753113	6.196353	-0.137319
1	-7.197728	7.694783	-0.93775
6	-5.567178	7.242702	1.171048
1	-5.788946	8.291073	0.972994
1	-6.300658	6.825331	1.858026
1	-4.56073	7.131936	1.57164
6	5.874837	7.361313	-1.205577
1	5.931408	8.448437	-1.249866
1	6.861756	6.939175	-1.027238
1	5.447831	6.960399	-2.123565
1	-6.806187	4.498767	1.336538
1	-4.97442	6.944364	-0.768998
1	4.062672	7.428707	-0.250925
1	0.343271	-8.621258	0.373281

Table S5. Computed absolute energies of optimized geometries of BODIPYs **3**, **4** and **4(H⁺)₃** in the ground state. None of the structures displayed any imaginary frequencies.

	BODIPY 3	BODIPY 4	BODIPY 4(H⁺)₃
Sum of electronic and zero-point energies (Hartree)	-15691.251142	-15730.054402	-15731.309037
Sum of electronic and thermal energies (Hartree)	-15691.209551	-15730.008844	-15731.264313
Sum of electronic and thermal enthalpies (Hartree)	-15691.208607	-15730.007900	-15731.263369
Sum of electronic and thermal free energies (Hartree)	-15691.334241	-15730.143881	-15731.393573

8 Experimental Details on Cell Culture

Human cervical carcinoma cells (HeLa) and non-cancerous MRC5 lung fibroblasts were cultured in DMEM (Gibco) supplemented with 5% fetal calf serum (Gibco), 100 U/mL penicillin, 100 µg/mL streptomycin. Ovarian cancer cell line A2780 were cultured in RPMI 1640 media supplemented with 2 mM Glutamine, 10% fetal calf serum, 100 U/mL penicillin, 100 µg/mL streptomycin. The cells were grown at 37 °C and under a humid atmosphere containing 5% CO₂.

9 Irradiation Setup for the Cell Culture

Cells in 96-well plates were irradiated for 30 min with a LED light source (custom build LED light source containing three Starboard, Cree Xlamp XQ-E Photo Red 665 nm LEDs, Cree Inc., USA, mounted on a 10 x 16 cm plate (Figure S16), constant current used = 150 mA) at a distance of 8.80 cm to the light source (light intensity: 1.40 mW/cm², total light dose: 2.52 J/cm²) in a custom build irradiation box containing a side fan to prevent possible cell death induced by heat accumulation due to the LED light source (Figure S17). The emission spectrum of the Photo Red LEDs is given in (Figure S18), which shows that the maximum of the emission is actually at 657 nm.

Figure S17. The mounting position of the LEDs (red circle) on the 10 x 16 cm plated used for the cell irradiation experiments.

Figure S18. The custom build irradiation box containing the LED light source and a 96-well plate at a distance of 8.80 cm to the light source.

Figure S19. The emission spectrum of the used Photo Red LEDs.

10 Experimental Details on Photocytotoxicity Assay

The photocytotoxicity of the photosensitizers was evaluated using a resazurin-based fluorometric cell viability assay. Stock solutions of the photosensitizer (1 mM) were prepared in DMF (in DMSO for **2**) and stored in the dark. Complex **3-tPt** was additionally tried to dissolve in 1% Tween80 in PBS,

unfortunately this was not possible. 100 μL aliquots of cells in growth medium were seeded in 96-well plates (density of 4×10^3 cells/well) and incubated at 37°C and 5% CO_2 . After 24 h of incubation, cells were treated with different concentrations (32 nM – 100 μM) of the test compounds and incubated for 4 h under light exclusion. Post 4 h, the growth medium containing the test compounds were replaced with fresh medium. For light irradiation, the cells were exposed to light at 657 nm for 30 min and it was followed by additional incubation for 72 h.

Post 72 h, the growth medium was replaced with 100 μL of freshly prepared resazurin containing growth medium (0.2 mg/mL final concentration), and cells were incubated at 37°C for 4 h. Subsequently, fluorescence of the resorufin product ($\lambda_{\text{ex}} = 540$ nm) was quantified at 590 nm using a SpectraMax M5 microplate Reader. The reported cytotoxicities have been found with quadruplicate determinations for each drug concentration.

Figure S20. Result of dose-dependent cell viability assays of **2** in HeLa cells. Cells were incubated with **2** for 4 h and subsequently treated with red light (657 nm) for 30 min. Cell viability was determined using resazurin after 72 h.

Figure S21. Result of dose-dependent cell viability assays of **2-tPt₃** in HeLa cells. Cells were incubated with **2-tPt₃** for 4 h and subsequently treated with red light (657 nm) for 30 min. Cell viability was determined using resazurin after 72 h.

Figure S22. Result of dose-dependent cell viability assays of **3** in HeLa cells. Cells were incubated with **3** for 4 h and subsequently treated with red light (657 nm) for 30 min. Cell viability was determined using resazurin after 72 h.

Figure S23. Result of dose-dependent cell viability assays of **3-tPt** in HeLa cells. Cells were incubated with **3-tPt** for 4 h and subsequently treated with red light (657 nm) for 30 min. Cell viability was determined using resazurin after 72 h.

Figure S24. Result of dose-dependent cell viability assays of **4-tPt** in HeLa cells. Cells were incubated with **4-tPt** for 4 h and subsequently treated with red light (657 nm) for 30 min. Cell viability was determined using resazurin after 72 h.

Table S6. Anti-proliferative effects of **3-tPt** on different human cell lines in the dark and upon irradiation. Each of the independent experiments is an average value of quadruplicates. The cells were exposed to light at 657 nm for 30 min. PI = phototoxic index.

Cell line	Dark toxicity [μM]	Light toxicity [μM]	PI
HeLa	> 100	0.184 ± 0.002	> 543
A2780	10.6 ± 1.5	0.180 ± 0.003	59
MRC5	> 100	0.2626 ± 0.019	> 380

Table S7. Phototoxic indexes of distyryl BODIPYs in literature. One compound with highest phototoxic index (PI) listed per paper.

Cell Line	Light Source	Phototoxicity IC ₅₀ [μM]	Dark Toxicity IC ₅₀ [μM]	PI	Reference
HeLa	LED, 657 nm	0.184 ± 0.002	> 100	> 543	this work
HeLa	light-emitting diode, 655 nm	0.0086	> 0.306	> 35	[14]
HeLa	Waldmann PDT 1200 L, 600–720 nm	0.6	105	175	[15]
HeLa	620 nm	2.5	> 2.5	> 1	[16]
HeLa	halogen lamp (300 W) with a red glass filter (Newport, λ > 610 nm)	0.09	> 0.4	> 4	[17]
HT29	> 610 nm	0.042	> 4	> 95	[18]
HCT116	> 625 nm	0.02	4.38	219	[19]
K562	625 nm	0.2	> 0.5	> 2.5	[20]
KB	halogen lamp (300 W) with a red glass filter (Newport, λ > 610 nm)	0.02	> 2	> 100	[21]
A549	Waldmann PDT 1200 L, 600–720 nm	2.3	> 100	> 43	[22]
A549	690 nm	0.7	> 20	> 28	[23]
4T1	660 nm	2	> 100	> 50	[24]
4T1	660 nm	0.036	> 5	> 138	[25]
MDA- MB- 231(+)	CW laser (COMPACT Laser 660 nm, World Star Tech)	1.58	300.5	190	[26]
1121	LED, 635 nm	7.68	16.7	2.2	[27]
MCF-7	halogen lamp (300 W) with a red glass filter (Newport, λ > 610 nm)	0.074	n.d.	n.d.	[28]
MCF-7	LED, 660 nm	0.2	> 5	> 25	[29]

11 Experimental Details on Intracellular Localization Studies

Cellular localization of fluorescent platinated BODIPY **3-tPt** was assessed by fluorescence confocal microscopy. HeLa cells were seeded with a density of 5×10^5 cells mL⁻¹ on a μ -slide 8 wells ibiTreat plate (IBIDI, Germany, 300 μ L per well) in DMEM (Gibco) supplemented with 5 % fetal calf serum (FCS, Gibco) and 100 U mL⁻¹ penicillin and 100 μ g mL⁻¹ streptomycin and were kept for adhering at 37 °C and 5% CO₂ for 24 h. Then, the cells were washed twice with PBS buffer and incubated for 3 h with 1 μ M **3-tPt** in growth medium without FCS and 100 U mL⁻¹ penicillin and 100 μ g mL⁻¹ streptomycin at 37 °C and 5% CO₂. 45 min prior imaging, Hoechst 33342 (1 μ g mL⁻¹), MitoTracker® Green (200 nM, Invitrogen), Golgi-ID® Green Assay Kit (100 μ L per well, Enzo LifeSciences) and ER-Tracker® Green (1 μ M, Invitrogen) were added to the media. The cells were again incubated at 37 °C and 5% CO₂. Then, the cells were washed twice with PBS buffer and the wells were filled with fresh medium (300 μ L per well). The cells were imaged on a Leica SP8 inverse FALCON, equipped with a diode laser (405 nm) and a flexible white light laser source (470–670 nm). The fluorescence was detected with three FLIM capable photon counting hybrid detectors (SMD HyD). The PS was excited with 670 nm, its emission was measured at 690–800 nm; Hoechst was excited with 405 nm, its emission was measured at 415–495 nm, MitoTracker and Golgi stain were excited with 488nm, their emission was recorded at 505–550 nm and ER Tracker was excited with 504 nm and its emission was measured at 514–550 nm.

Figure S25. The intracellular localization of compound **3-tPt** in HeLa cells. Cells were incubated with compound **3-tPt** for 3 h in the dark prior to imaging. Confocal images of cells stained with Hoechst 33342 (a), an additional staining agent (b), **3-tPt** (c) and merged images (d) are presented. 1) Only Hoechst 33342, 2) additional staining agent = ER-Tracker®, 3) additional staining agent = MitoTracker® Green, 4) additional staining agent = Golgi-ID® Green Assay Kit, 5) only Hoechst 33342 and **3-tPt**.

Figure S26. Cross-sections of the intracellular localization of compound **3-tPt** in HeLa cells. Cells were incubated with compound **3-tPt** for 3 h in the dark prior to imaging.

12 Experimental Details on Detection of Intracellular ROS Levels

2 x 10⁵ HeLa cells in 2 mL DMEM supplemented with 5% FBS were seeded on 60 mm dishes. The following day, cells were treated with 1 μM **3-tPt** for 4 hours. Following the incubation, cells were washed with PBS and the medium was subsequently replaced with 2 mL DMEM. Cells were irradiated for 30 min with 657 nm light, as described for the photocytotoxicity assay. After irradiation, H₂DCF-DA was added to the samples to a final concentration of 50 μM and incubated for 30 minutes at 37°C. Cells were washed twice with PBS and collected by trypsinisation. Cells were suspended in 1mL PBS containing 1% FBS. Samples were analysed on an Attune NxT Cytometer (Thermo Fisher Scientific) using BL1 channel (excitation 488 nm, emission 515 nm) to measure DCF fluorescence. Results are expressed as mean percentage of ROS-positive cells over total cell population, obtained from three independent experiments with a minimum of 50 000 cells analysed per condition. The error bars represent standard deviation.

Table S8. Percentage of HeLa cells displaying increased ROS levels after different treatments. The ROS levels were detected using 2',7'-dichlorodihydrofluorescein diacetate (H₂DCF-DA) followed by fluorescence-activated cell sorting (FACS) analysis.

Treatment	Percentage	Standard Deviation
Light	1.16	0.27
3-tPt (1 μM)	7.24	4.99
3-tPt (1 μM) + Light	62.53	6.41

13 Crystallographic Data

Table S9. Crystal data and structure refinement for compounds **3** and **4**.

	BODIPY 3	BODIPY 4
Empirical formula	C ₃₄ H ₂₈ BF ₂ I ₂ N ₃ O ₂	C ₃₆ H ₃₄ BF ₂ I ₂ N ₅
Formula weight	813.2	839.29
Crystal system	Monoclinic	Monoclinic
Space group	P2 ₁ /c	P2 ₁ /c
a [Å]	29.45725(17)	15.6418(2)
b [Å]	10.66212(6)	10.80987(13)
c [Å]	20.51085(13)	20.5026(3)
α [°]	90	90
β [°]	104.9676(6)	108.2863(17)
γ [°]	90	90
Volume [Å ³]	6223.42(7)	3291.62(9)
Z	8	4
Density (calculated) [Mg/m ³]	1.736	1.694
Temperature [K]	160.00(10)	160.00(10)
Wavelength [Å]	1.54184	1.54184
Absorption coefficient [mm ⁻¹]	16.279	15.38
F(000)	3184	1656
Crystal size [mm ³]	0.173 x 0.061 x 0.027	0.067 x 0.061 x 0.011
Crystal description	blue needle	blue plate
Theta range for data collection [°]	3.106 to 79.242	4.543 to 79.394
Index ranges	-37 ≤ h ≤ 37, -12 ≤ k ≤ 12, -25 ≤ l ≤ 26	-19 ≤ h ≤ 19, -10 ≤ k ≤ 13, -26 ≤ l ≤ 26
Reflections collected	170319	43693
Independent reflections	13211 [R(int) = 0.0509]	7087 [R(int) = 0.0470]
Reflections observed	12683	6378
Criterion for observation	I > 2 σ (I)	I > 2 σ (I)
Completeness to theta	99.5 % to 67.684°	99.9 % to 67.684°
Absorption correction	Gaussian	Gaussian
Max. and min. transmission	0.918 and 0.204	0.906 and 0.483
Data / restraints / parameters	13211 / 0 / 801	7087 / 0 / 421
Goodness-of-fit on F ²	1.139	1.078
Final R indices [I > 2 σ (I)]	R1 = 0.0549, wR2 = 0.1341	R1 = 0.0479, wR2 = 0.1251
R indices (all data)	R1 = 0.0562, wR2 = 0.1346	R1 = 0.0525, wR2 = 0.1283
Largest diff. peak / hole [e.Å ⁻³]	2.976 and -1.667	1.583 and -0.920

14 References

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