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Strategies to Enhance the Photosensitization: Polymerization and D/A Even-Odd Effect

Shunjie Liu+, Haoke Zhang+, Yuanyuan Li+, Junkai Liu, Lili Du, Ming Chen, Ryan T. K. Kwok, Jacky W. Y. Lam, David Lee Phillips and Ben Zhong Tang*

Abstract: A particular challenge in the current design of organic photosensitizers (PSs) with donor-acceptor (D−A) structures is based on trial and error method rather than specific rules. Here we address these challenges by proposing two efficient strategies to enhance the photosensitization efficiency: polymerization−facilitated photosensitization and D/A even−odd effect. Conjugated polymers have been found to exhibit a higher $^1O_2$ generation efficiency than their small molecular counterparts. In addition, PSs with A-D-A structures show enhanced photosensitization efficiency than those with D-A-D ones. Theoretical calculations suggest an enhanced intersystem crossing (ISC) efficiency by these strategies. Both in vitro and in vivo experiments demonstrate that the resulting materials can be used as photosensitizers in image-guided photodynamic anticancer therapy. These guidelines are applicable to other polymers and small molecules to lead to the development of new PSs.

Owing to its spatial−temporal control and noninvasive character, photodynamic therapy (PDT) has recently attracted considerable attention in cancer therapy, and has surpassed the traditional methods such as surgery, chemotherapy and radiotherapy.[1] In PDT, the target cells or bacteria are controllably killed by reactive oxygen species (ROS) produced by photosensitizers (PSs) under illumination. Currently, porphyrin, BODIPY derivatives, phthalocyanines and bacteriochlorin derivatives are the most widely used PSs.[2] However, they exhibit several drawbacks such as reduced fluorescence and singlet oxygen ($^1O_2$) production owing to the strong π-π stacking of their rigid planar structures. To address these issues, luminogens with aggregation-induced emission (AIE) characteristics have recently been developed.[3] AIE luminogens (AIEgens) emit intense fluorescence in the aggregate state due to the mechanism of the restriction of intramolecular motion.[4] In addition, they also exhibit enhanced $^1O_2$ generation in the aggregate state.[5] These features make the nanoparticles of AIEgens particularly suitable as PSs for image-guided PDT.[6]

The common method to improve the photosensitization efficiency of PSs is based on the enhancement of the intersystem crossing (ISC) from the lowest excited state (S_1) to the lowest triplet state (T_1).[7] Thus, approaches to promote ISC is of vital importance for designing efficient PSs. According to the perturbation theory, the rate constant (k_{ISC}) of ISC is given by:[8]

$$k_{\mathrm{ISC}} \propto <{}^1\Psi|\hat{H}_{SO}|{}^3\Psi>/\exp(\Delta E_{ST}^2) \qquad (1)$$

Where $<{}^1\Psi|\hat{H}_{SO}|{}^3\Psi>$ is the spin-orbit coupling (SOC) matrix element, $\hat{H}_{SO}$ is the SOC Hamiltonian and ΔE_{ST} is the energy gap between the singlet and triplet states. This equation suggests that large SOC and small ΔE_{ST} can result in high k_{ISC}. Incorporation of heavy atoms such as bromide, iodine, selenium or platinum, to organic π−conjugated system can enhance SOC to increase k_{ISC}.[9] Alternatively, extending the conjugation length in platinum−containing polymer can also enhance the SOC.[10] However, the presence of heavy atoms may lead to dark toxicity in biological applications.[11] According to Equation (1), another approach to increase k_{ISC} is to reduce ΔE_{ST}, which has been proved by our group and others in designing fluorescent materials with pure organic room-temperature phosphorescence or thermally-activated delayed fluorescence.[12] This way is quite propitious for achieving efficient PSs but has received scant attention owing to the large ΔE_{ST} of the most organic molecules. Recently, strategies of combining different D and A units in conjugated molecules were developed to minimize ΔE_{ST}. This method relies on trial and error discovery of a promising motif followed by extensive tuning of the electronic properties of the D/A units.[9d, 13] Thereby, a convenient yet efficient chemical design strategy to enhance ISC is fascinating and practical.

Herein, we established two strategies to effectively enhance the efficiency of PSs, namely polymerization−facilitated photosensitization[14] and D/A even−odd effect. As shown in Figure 1, several AIEgens based on electron-donating triphenylamine (**T**) and electron-accepting benzothiadiazole (**B**) units were synthesized and well characterized (Supporting Information, Scheme S1−S7). To study the conjugation effect, **TB**, dimer of **TB**, namely **TBTB**, was prepared (Figure 1A). For further comparison, polymer **P1** was prepared. Analysis of the polymer by gel permeation chromatography gave a molecular weight of 2000 g mol^{-1}, suggesting the existence of 5 repeating **TB** units in

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[*] Dr. S. Liu, Dr. H. Zhang, Dr. Y. Li, Mr. J. Liu, Dr. M. Chen, Dr. R. T. K. Kwok, Dr. J. W. Y. Lam, Prof. B. Z. Tang
Department of Chemistry, Hong Kong Branch of Chinese National Engineering Research Center for Tissue Restoration and econstruction, Institute for Advanced Studgy and Department of Chemical and Biological Engineering, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, China
and
HKUST-Shenzhen Research Institute, No.9 Yuexing 1st RD, South Area, Hi-tech Park, Nanshan, Shenzhen 518057, China
E-mail: tangbenz@ust.hk

Prof. B. Z. Tang
Center for Aggregation-Induced Emission,
SCUT-HKUST Joint Research Institute, State Key Laboratory of Luminescent Materials and Devices, South China University of Technology Guangzhou 510640 (China)

Dr. L. Du, Prof. D. L. Phillips
Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong SAR, China.
Dr. L. Du
Institute of Life Sciences, Jiangsu University, Zhenjiang 212013, China

[+] These authors contributed equally to this work

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one polymer chain. Such a length is believed to be longer than the effective conjugated one.[10] On the other hand, to investigate the even−odd effect, four compounds with different relative amount of D and A units were designed and abbreviated as **TBT** with D-A-D structure, **BTB** with A-D-A structure, **TBTBT** with D-A-D-A-D structure and **BTBTB** with A-D-A-D-A structure (Figure 1B).

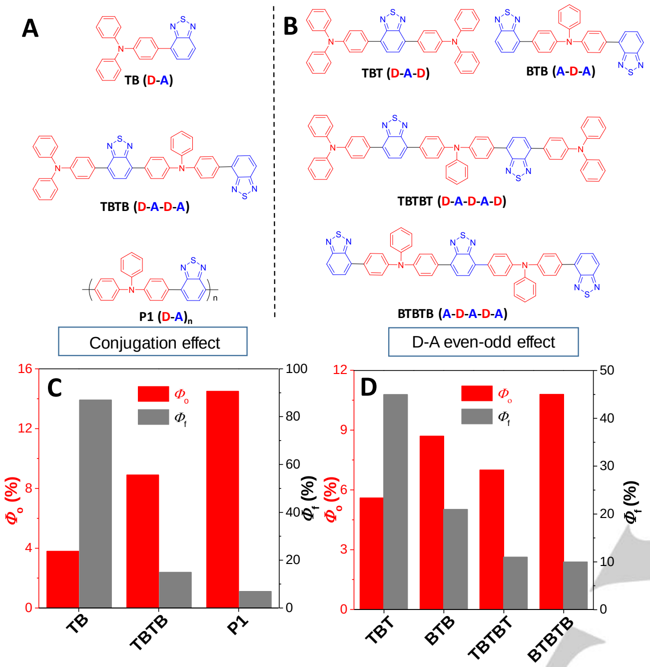

Figure 1. Molecular structures of the new materials and their photosensitization properties. (A and B) Chemical structures. $^1O_2$ quantum yield and fluorescence quantum yield of (C) **TB**, **TBTB** and **P1** and (D) **TBT**, **BTB**, **TBTBT** and **BTBTB**.

The photophysical data of all compounds are summarized in Table S1. **P1** shows a redder absorption (456 nm) and photoluminescence (PL) (610 nm) in THF than its monomer **TB** (416 and 550 nm), suggestive of its higher conjugation (Figure S1)[15] and potential biological applications. On the other hand, **TBT** and **TBTBT** represent D>A systems and display red-shifted absorption and PL in THF than their A>D counterparts, such as **BTB** and **BTBTB** (Figure S2). Moreover, all the new molecules show blue-shifted but stronger emission in 90% aqueous mixture than in pure THF, demonstrating a twisted intramolecular charge transfer characteristic (Figure S3-S5).[16]

To investigate the ability of these AIEgens to generate $^1O_2$, the $^1O_2$ quantum yield (Φ_o) of their nanoparticles in water was determined using a chemical trapping method by monitoring the absorption of 9,10-anthracenediyl-bis(methylene)dimalonic acid at 378 nm (Figure S6-S8). Interestingly, as shown in Figure 1C, with an increase in conjugation from **TB** to **TBTB** and then to **P1**, the Φ_o increases from 3.8% to 8.9% and then to 14%, accompanying a decreased fluorescence quantum yield (Φ_f) from 87% to 15% and then to 7%. The inverse correlation between Φ_o and Φ_f suggests that the increasing conjugation by polymerization is an effective way to enhance the ISC.[10]

The effect of D-A even-odd effect on the photosensitization is shown in Figure 1D. **BTB** (A-D-A) and **BTBTB** (A-D-A-D-A) exhibit an increased photosensitization efficiency (Φ_o = 8.7% and 10.8%) but a decreased fluorescence quantum yield (Φ_f = 21% and 10%) than **TBT** (D-A-D) and **TBTBT** (D-A-D-A-D) (Φ_o = 5.6% and 7.0%; Φ_f = 45% and 11%). This result indicates that when a luminophore has more A unit than D unit, it shows an enhanced ISC process at the expense of fluorescence quantum yield.[10] Given the widespread use of D-A-D or A-D-A−type luminophores, our finding provides a valuable information for molecular design: fluorescent materials with D-A-D structures show a higher quantum yield, while their A-D-A counterparts are more suitable to serve as efficient PSs. It is noticeable that the improved photosensitization efficiency is independent of the size and shape of these nanoparticles (Figure S9). Furthermore, the same trend in Φ_o variation was observed even when other nanoparticle preparation methods were employed (Figure S10).

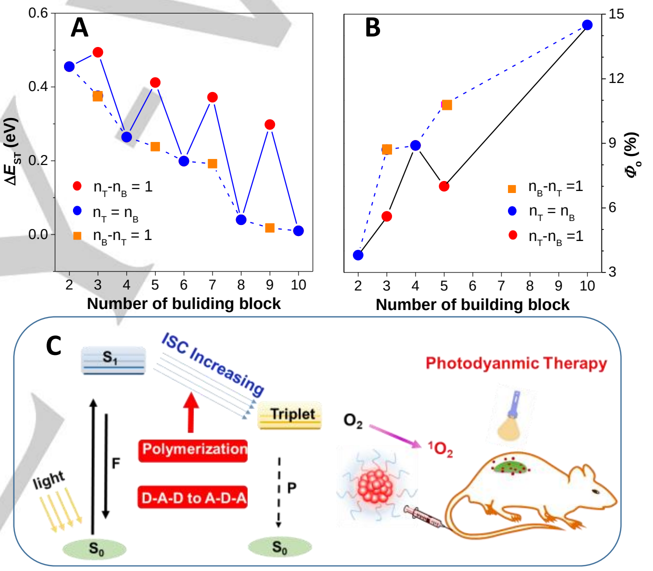

Figure 2. The polymerization and even-odd effect. Dependence of (A) ΔE_{ST} and (B) Φ_o on the number of building block. (C) Enhanced photosensitization for application in PDT. Abbreviation: n_T = number of donor unit, (**T**); n_B = number of acceptor unit, (**B**).

Due to the fact that phosphorescence is not detected in these molecules, it was necessary to apply time-dependent density functional theory (TD-DFT) calculations to estimate the triplet energy. In particular, triplet formation via ISC has an impact on the efficiency of photosensitization.[7] According to Equation (1), we take both ΔE_{ST} and SOC into consideration to study the ISC. First, we investigate the effect of ΔE_{ST} on SOC. The ΔE_{ST} decreases progressively by extending the π-conjugation as the energy of the higher-lying T_n and S_n states decreases gradually to make them get closer to the low-lying state (T_1 and S_1) (Figure S11, Table S2, S3). The increased Φ_o with enhanced conjugation well accounts for the drop in ΔE_{ST}. The decrease of Φ_f from **TB** to **P1** is partially due to the promotion of the ISC,[10] despite the interchain interactions may play also an important role in fluorescence quenching[17]. Similarly, **BTB** and **BTBTB** exhibit a

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lower ΔE_{ST} than their D>A counterparts. On the other hand, the SOC effect should also be taken into consideration. However, the calculated SOC constants of these molecules are all small (Table S4), which is a common phenomenon observed in pure organic materials.[12a] Collectively, the decrement of ΔE_{ST} plays a major role in improving the ISC efficiency and also Φ_o. To probe the triplet excited state, nanosecond transient absorption experiment was carried out. Polymer **P1** displays a triplet absorption lifetime of 2.68 μs, whereas no data can be obtained from small molecule AIEgens like **TB**, **TBT** and **BTB** (Figure S12). This further suggests the improved ISC by conjugation.[9c, 18]

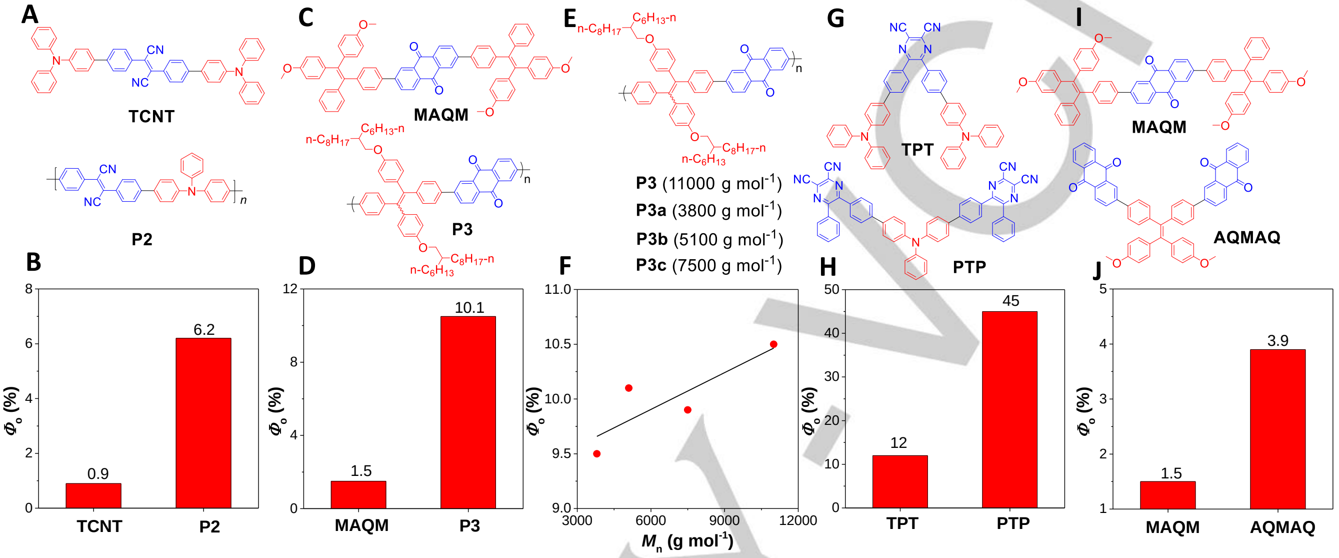

Figure 3. Chemical structures of (A) **TCNT** and **P2**, (C) **MAQM** and **P3**, (E) polymer **P3a-c**, (G)**TPT** and **PTP** and (I) **MAQM** and **AQMAQ**, and (B, D, F, H and J) their respective Φ_o

Extension of the conjugation length or variation of the relative amount of D and A unit plays the same role in improving the photosensitization efficiency. To obtain a full picture, we tried to integrate these two methods into one rule. As shown in Figure 2A, in general, the Φ_o of the same series increases with the extension of conjugation. When the total number of building blocks is even, the Φ_o monotonously increases with increasing the conjugation length. However, in the odd system, the Φ_o depends on the relative amount of D and A unit and AIEgens with more A unit, i. e. n_B-n_T = 1, show higher values than their counterparts with higher D fraction, i. e. n_T-n_B = 1. It is noteworthy that the ΔE_{ST} values obtained by calculation are in good agreement with the experimental data (Figure 2B). This insight provides a design criteria for the selection of PSs to apply in image-guided PDT (Figure 2C).

To prove the versatility of the present strategy, different polymers and D/A molecules were designed and examined (Figure 3 and S13-S21, Scheme S8−S16). As shown in Figure 3A, **TCNT** is an AIE−active near−infrared emitting dye for organic light−emitting diode.[19] The Φ_o was enhanced from 0.9% to 6.2% when it was polymerized into polymer **P2** corresponding to a 5.8-fold enhancement (Figure 3B). In addition, if we change both the types of D and A units, the present strategy still works well. For example, **P3** (Φ_o = 10.1%) shows a 5.7-fold enhancement in Φ_o than its small molecule counterpart (Φ_o = 1.5%) (Figure 3C and 3D). On the other hand, the high molecular weight of **P3** (M_w = 11000 g mol^{-1}) motivates us to study the effect of M_w on the photosensitization efficiency. The Φ_o increases gradually by increasing M_w from 3800 to 11000 g mol^{-1} (Figure 3E and 3F). Thus, the polymerization method can precisely increase the photosensitization efficiency of PSs.

Next, we examine the D/A odd effect on the photosensitization efficiency. As shown in Figure 3G, AIE-active **TPT** with D-A-D structure has been successfully used for through−skull three−photon fluorescence imaging of mouse.[20] According to our strategy, **PTP** with an A-D-A structure was designed. As expected, **PTP** exhibits a high Φ_o of 45%, being 2.7-fold higher than that of **TPT** (12%) (Figure 3H). We further varied both the D and A units, as displayed in Figure 3I and 3J, **AQMAQ** with an A-D-A structure showed Φ_o of 3.9%, which was higher than its **MAQM** counterpart (1.5%). Clearly, the D/A conjugated AIEgens demonstrate a stronger photosensitization efficiency when there is more A unit in the molecular structure. Overall, by using this strategy, the Φ_o of low efficient PSs becomes higher and that of high efficient PSs turns into excellent.

The significantly enhanced photosensitization ability and easy synthesis of conjugated polymer **P1** encourages us to evaluate its image-guided PDT of tumor. Due to its hydrophobic character, **P1** is encapsulated by amphiphilic DSPE-PEG$_{2000}$ to endow the resulting nanoparticles (PNPs) with good water dispersibility (Figure S22). Analysis of dynamic light scattering and transmission electron microscopy reveals the good monodispersity of PNPs with a hydrodynamic diameter of about 120 nm (Figure S22). To examine whether the assembled PNPs

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can effectively enter cells, we evaluate the uptake ability of the HeLa cells using a confocal laser scanning microscope. The observation of reticulum-like fluorescence image of HeLa cells suggests the dye may locate at mitochondria (Figure S23).[21] To prove this, colocalization experiment with MitoTracker Green (MTG), a commercial mitochondria-specific imaging agent, was performed. As depicted in Figure 4A, the regions stained with PNPs overlap well with those stained by MTG. The Pearson's coefficient was calculated to be 0.92, indicating the high specificity of PNPs to mitochondria. Moreover, the mitochondrial membrane will be damaged by sensitized $^1O_2$ during PDT and the consequent dysfunction of mitochondria will induce cell apoptosis. As expected, the cell viability decreases with increasing the irradiation time (Figure S24). Importantly, the PNPs show negligible dark toxicity because its non-cationic character to cause no any depolarization of the mitochondrial membrane. This aspect is of importance to avoid the side effect of PSs.[22] To confirm that the cell death is induced by ROS, we used the 2', 7'-dichlorofluorescin diacetate (DCFH-DA) as the indicator to detect the ROS generation in situ. Under white-light irradiation, the DCFH-DA decomposes into dichlorofluorescein (DCF). The fluorescence of the DCF increases and the morphology of the cell changes with the irradiation time (Figure S25). At the same time, we detect ROS generation in HeLa cells after irradiation with 488 nm laser (Figure S26). The signal of ROS increases dramatically at the irradiated part but remains low outside this region. These results suggest that PNPs are promising as PSs for PDT.

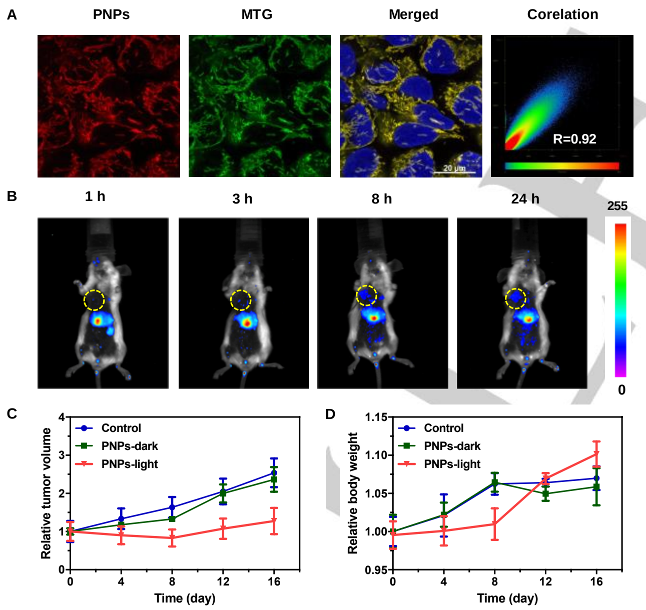

Figure 4. Colocalization with mitochondria-targeting dye MTG. (A) Fluorescence image of HeLa cells stained with PNPs, MTG and Merged image of PNPs, MTG and Hoechst 33258, a nucleus-targeting commercial dye. Scatter plot indicates the overlap coefficient of the cell image stained by PNPs and MTG. Inset: calculated Pearson's correlation coefficient. Excitation: 405 nm (Hoechst 33258) and 488 nm (PNPs and MTG); Emission: 420-450 (Hoechst 33258), 490-530 (MTG) and 570-700 (PNPs) with filter: 530-570 nm. (B)Tumor imaging of mouse after intravenous injection of PNPs at different time. (C) Tumor growth curves and (D) body weight changes of mice in different treatment groups.

Before studying the in vivo image−guided PDT ability of PNPs, we first investigate their use for in vivo fluorescence imaging by intravenous injection of the nanoparticles to xenograft 4T1 tumor-bearing balb/c mice. The fluorescence is gradually strengthened at the tumor site and the fluorescence signal at 24 h is higher than that of the tumor background owing to the enhanced permeability and retention effect (Figure 4B and S27).[23] The tumor is then irradiated with white light for 30 min after 24 h intravenous injection. As control, the mice are administrated with PNPs in dark environment or treated with saline. Results show that the growth of tumor is partly inhibited by treated with PNPs in the presence of light irradiation, indicating the efficient PDT ability of PNPs (Figure 4C). The body weight of mice treated with PNPs + light exceeds that of the control groups due to the efficient PDT (Figure 4D).

To investigate the potential toxicity of PNPs, a single dose of PNPs was injected into mice via veil tail. During a one-month period, the body weight of the treated group increases gradually in a manner similar to that of the control group (Figure S28). After 30 days, the whole blood and liver function are analyzed and no significant difference between the treated and control groups was observed (Figure S29). Although the PNPs mainly accumulate in mononuclear phagocyte system such as liver and spleen[24] (Figure S30), the H&E stain suggests that there is no noticeable tissue damage and inflammatory lesion in these tissues (Figure S31). All the results manifest that the PNPs own good biocompatibility in dark environment and are powerful photosensitizers for photodynamic therapy.

In summary, we have developed two efficient strategies to increase the $^1O_2$ generation of PSs by enhancing the ISC. The singlet oxygen quantum yield of the AIEgens can be increased by 5.8-fold and 2.7-fold via using the polymerization method and D/A even-odd effect, respectively. The observation of polymerization-facilitated photosensitization and D/A even-odd effect in the AIEgens provides insight into establishing a new design framework for PSs. Theoretical analyses demonstrate that the enhanced ISC process mainly results from the lowest singlet state to the low-lying triplet states. By using these strategies, the low efficient PSs become the higher ones and the high efficient PSs turn into excellent ones. The obtained polymer **P1** is promising for application in image-guided photodynamic anticancer therapy. This strategy thus provides an efficient platform for the development of PS for PDT.

Experimental Section

Experimental Details please see supporting information.

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Layout 2:

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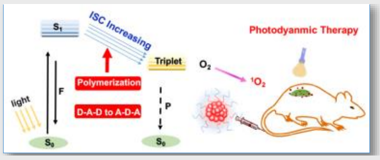

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*Shunjie Liu+, Haoke Zhang+, Yuanyuan Li+, Junkai Liu, Lili Du, Ming Chen, Ryan T. K. Kwok, Jacky W. Y. Lam, David Lee Phillips and Ben Zhong Tang**

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