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REVIEW ARTICLE

Insights on Metal-Free Type I Photosensitizers for Photodynamic Therapy

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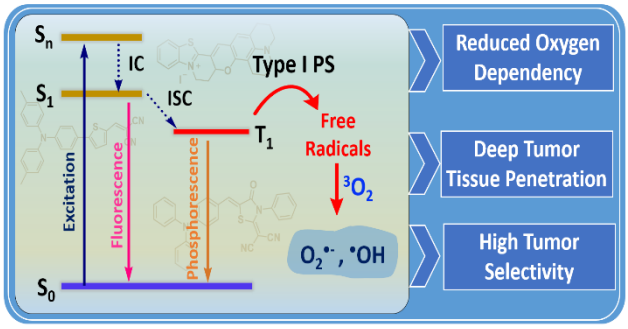
Abstract: Non-invasive treatment techniques have drawn a lot of interest due to the rising need for precise and secure cancer treatment. One such treatment method is photodynamic therapy (PDT), which uses the light irradiation of photosensitizers (PSs) to produce reactive oxygen species (ROS), which kill cancer cells. Most of the conventional photosensitizers used in the PDT process rely on molecular oxygen to produce cytotoxic ROS, known by the name of type II PSs. Because type II PSs requires oxygen to produce ROS, their full potential is not realized in hypoxic tumor tissues. On the other hand, type I PSs can increase the effectiveness of PDT in hypoxic tumor tissues since they rely less on oxygen to produce ROS. Consequently, it has become increasingly crucial to develop type I PSs to treat hypoxic malignancies. Numerous type I PSs of inorganic origin have been developed so far. Nonetheless, certain issues like poor biodegradability and persistent toxicity exist. Type I PSs based on organic compounds were developed in response to these concerns since they are comparatively more biocompatible and biodegradable. Therefore, in this article, we describe recent developments in the development of organic type I PSs for the PDT.



Keywords: *photosensitizer, photodynamic therapy, superoxide anion, hypoxia*.

Contents

1. Introduction

Photodynamic therapy (PDT) is a light-promoted approach that uses functional molecules, known as photosensitizer (PS), to induce cell death via the generation of reactive chemical species.[1] The idea that light and a chemical agent can be combined has a long history. The benefits of sunlight as a therapy were employed in ancient Egypt, China, and India to treat skin cancer, vitiligo, psoriasis, and rickets.[2] The current form of PDT can be traced back to the discoveries made by Oscar Raab in 1900, who found that light and acridine orange together are fatal to paramecia.[3] Researchers have used light and small functional molecules to cure a variety of ailments, particularly cancer, throughout the past century.[4] A major cause of death on a global scale is cancer.[5] Nowadays, cancer patients are usually treated with a combination of multiple approaches including chemotherapy, surgery, and radiation therapy. However, some disadvantages of these traditional treatments include their high invasiveness, lack of selectivity, and serious adverse health effects.[6] In contrast to these traditional treatments, photodynamic therapy (PDT), a recently established therapeutic procedure, has demonstrated excellent prospects for the treatment of cancer with superior safety and therapeutic success.[7] The PDT process is characterized by the conversion of molecular oxygen into reactive oxygen species (ROS) to kill the cancer cells. The photosensitizers (PSs), light, and tissue oxygen are the main components of the photodynamic therapy. Photosensitizers are a key component in the PDT process's effectiveness.

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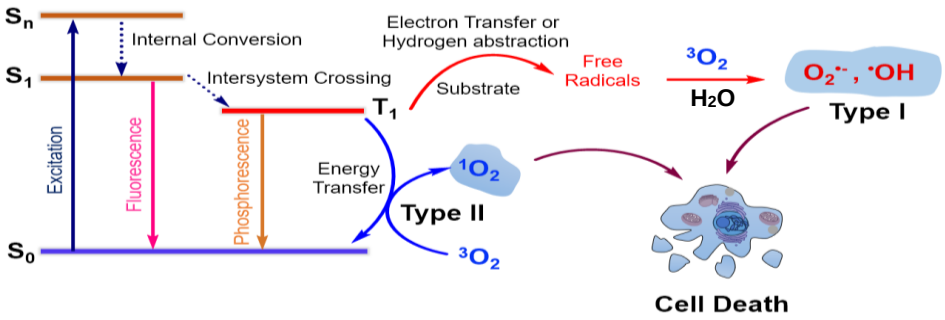


Figure 1. *A schematic representation of PDT mechanisms, type I and II.*

This is due to the fact that PS, when activated by light, releases its excited-state energy or electron into the surrounding tissue oxygen or substrate, resulting in the production of reactive oxygen species (ROS), which kill cancer cells. PDT has the advantage of selectively targeting cancer cells or tissue while preserving normal cells, as PSs introduce cytotoxicity when exposed to specific light types.

2. PDT Mechanisms

There are primarily two kinds of PDT processes, which are based on the mechanisms that generate ROS.[8] Photoreactions where PSs based on electron transfer generate superoxide anion ($O_2^{\bullet-}$) species are involved in the type I PDT process (Figure 1). On the other hand, if PSs produce singlet oxygen ($^1O_2$) by an energy transfer mechanism, then a PDT process is type II (Figure 1). Though PDT has advanced quickly, its use as a first-choice therapeutic method is limited by the absence of an optimal photosensitizer that can satisfy the cancer treatment requirements. The development of photosensitizers with the necessary characteristics, such as deep tissue penetration, high ROS production ability, near-infrared (NIR) absorption, and tumor selectivity, has been the focus of efforts to improve PDT efficiency.

Most of the PSs developed to date are based on a type II mechanism (Figure 1) in which generated $^1O_2$ is used to kill malignant cells.[9] For the type II PDT approach, a number of PSs of both organic and inorganic origins have been produced; some of these have even been given approval to treat cancer.[1b,9] Low oxygen levels, which result in hypoxia, are a characteristic of tumors. Since type II PS requires oxygen for the generation of singlet oxygen, the type II PDT process exhibits reduced therapeutic efficacy in hypoxic tumor tissues.[10] The oxygen requirement of type II PDT process limits its efficacy, even though it is combined with other reagents to overcome the oxygen deficiency.[11] On the other side, because of its lower oxygen requirement than type II PDT, type I PDT has demonstrated tremendous potential in combating against hypoxic malignancies. When exposed to radiation, type I PS generated excited PS in its singlet state by absorbing light energy. Radiative or non-radiative pathways can return the excited PS to its ground state. Alternatively, to produce PS in its triplet excited state (Figure 1), the singlet excited PS can go through intersystem crossing. This triplet state of PS is converted into an anion radical or a cationic species through electron or proton transfer to biological substrates such as cell membranes or electron-rich molecules. After further interaction with water or molecular oxygen, the anionic radical or cationic species form cytotoxic superoxide anion ($O_2^{\bullet-}$) or hydroxyl radicals ($^{\bullet}OH$).[12] With type I PDT, as opposed to type II PDT, it is possible to improve the therapeutic efficacy against oxygen-depleted (hypoxic) tumors. Consequently, the development of type I photosensitizers, which have a reduced oxygen dependence, is getting attention.

3. Need for type I organic PSs

Type I PS have been developed using different molecular platforms. For instance, TiO_2, because of its charge-separate state formation, have been reported to generate superoxide radical.[13] Metal-complexes of transition metals and inorganic nanocomposites have been developed as a type I PSs.[14]However, the high level of immunotoxicity, low tissue penetration depth, and poor repeatability of these complex materials limit their clinical application. Given these factors, molecules of organic origin are suitable because of their easy preparation, remarkable repeatability, diverse structures, and customizable properties. Thus, there has been a focus on developing type I PSs based on organic compounds in recent years. In this article, we are discussing the type I PSs of organic origin developed for PDT in the last few years.

4. Type I organic PSs

Numerous metal-based compounds have been used as type I photosensitizers in PDT, as was previously mentioned. Unfortunately, most inorganic PSs have a poor rate of biodegradation and may persist in body tissues for extended periods of time, which raises the possibility of long-term toxicity. In contrast, organic molecules are relatively biocompatible in nature, easy to metabolize, and characterized by low toxicity.[15] Nile blue is an organic dye molecule that, with some modifications, has been shown to exhibit ROS generation ability and is employed in photodynamic therapy.[16] In 2018, Peng and colleagues developed a type I photosensitizer molecule **1** (ENBS-B) based on the Nile blue fluorophore (Figure 2).[17] According to the described investigations, **1** has a great capacity to produce $O_2^{\bullet-}$ in a hypoxic environment when exposed to light. Molecule **1** showed strong absorption at ~660 nm and an emission band at ~660 nm. The absorbance of the **1** in the longer wavelength region is useful to get deeper probe penetration as well as to reduce the chances of phototoxicity. According to the authors, light irradiation of **1** produces $O_2^{\bullet-}$, which causes cellular lysosomes and nuclei to break down and causes cancer cells to undergo apoptosis. Though, **1** showed selectivity towards cancer cells due to its biotin unit, its low retention in malignant cells results in an inadequate therapeutic approach. Furthermore, one of the prerequisites for the activation of PSs and the successful completion of the PDT process is the absorption of light by PSs located deep within malignant tissues. This is an important fact because, deep within malignant tissues, most PSs have poor light absorption, which limits their applicability.

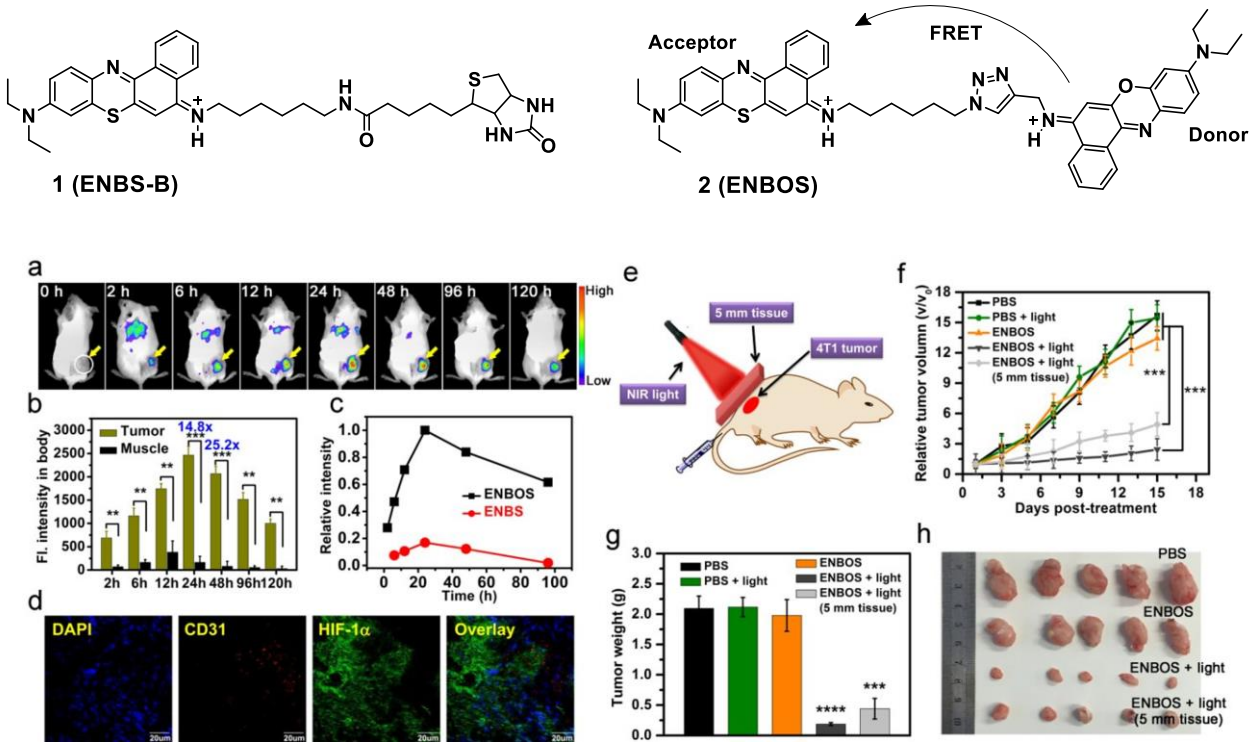


Figure 2. *Structures of 1 (ENBS-B) and 2 (ENBOS). (a) 14T1 tumor-bearing mice's in vivo fluorescence imaging upon an intravenous injection of 1 (ENBOS). (b) Change in ENBOS fluorescence in the tumor and surrounding muscle tissues. (c) Time dependent relative fluorescence of ENBOS and ENBS (without acceptor unit) in 4T1 tumors. (d) Tumor slice immunofluorescence imaging. (e) Diagram showing ENBOS-mediated PDT in deep hypoxic tumor. (f) Relative tumor volume. (g and h) Average tumor weights and associated tumor images. Figures a-e, adapted with permission from ref. 18. Copyright 2019 American Chemical Society.*

In this context, Peng and coworkers have developed a FRET (Förster resonance energy transfer)-derived PS, **2** (ENBOS), to achieve enhanced light absorption ability and thus high $O_2^{\bullet-}$ production deep inside the hypoxic tumor tissues (Figure 2).[18] The reported PS was the combination of Nile blue dye (energy donor) and a benzophenothiazine unit (energy acceptor). **2** showed a strong absorption in the region between 600 and 750 nm with a molar absorptivity of 71000 $M^{-1}cm^{-1}$ suggesting its high light absorption ability. First, the authors have demonstrated that the cells loaded with **2** upon NIR light irradiation at a 21% oxygen level result in the significant generation of $O_2^{\bullet-}$. The studies further confirmed the $O_2^{\bullet-}$ generation under hypoxic cellular conditions (2% oxygen level). Furthermore, the reported PS was effectively utilized to initiate ROS ($O_2^{\bullet-}$) production in deep tumorous tissue, supporting this design as a helpful tactic to improve the PDT mechanism's effectiveness. This is confirmed by the data shown in Fig. 2g and 2h, which revealed that this strategy produces prominent inhibition (84%) of tumor growth.

Using the Nile blue molecule, Peng and Kim et al. have reported a PS, **3** (SORgenTAM), as a binary $O_2^{\bullet-}$ photo-generator in the malignant tissue (Figure 3).[19] The reported PS localized in the mitochondria and restrict the intracellular oxygen consumption, making enough O_2 available for the PDT in the cancer cells. The study provides new insights on how to overcome the limitations of the conventional PDT method. Utilizing Nile blue dye, Yi et al. have also recently developed a mitochondrion specific type I PS, **4**, which, when photo activated, changes the activity of the caspase-3 protein, causing apoptotic and pyroptotic cell death (Figure 3).[20] In addition to Nile blue, hemicyanine derivative have also been employed to generate type-I PS.[21]

For a molecule to act as a photosensitizer, it is important that the molecule exhibit a significant intersystem crossing (ISC) process. Because spin orbital coupling can promote the ISC process, heavy atoms are usually incorporated into the molecular structure to achieve efficient ISC crossing and thus the reactive oxygen species generation. However, heavy atoms, due to their toxicity, are not favorable. The alternative to introducing the ISC process is to use an electron donor and electron acceptor architecture.[22] The donor-acceptor molecular system can reduce the energy gap between the singlet excited state (S_1) and triplet excited state (T_1), thus promoting the ISC mechanism. Using this strategy, a variety of type II photosensitizers have been developed. Tang and coworkers reported a type I photosensitizer by employing a donor-acceptor system, **5**, derived from the combination of the phosphindole oxide core and triphenylamine (Figure 4).[23] In **5**, the phosphindole oxide unit is the acceptor part, while triphenylamine is the donor part. Because of the strong electron-accepting ability of the phosphindole oxide core, **5**, upon irradiation, accepts external electrons, causing radical anion formation. This radical anion then transfers the electron to the nearby substrate and leads to the formation of $O_2^{\bullet-}$ species. The in vitro studies suggested that the reported probe localized mainly in the endoplasmic reticulum. As a result, the phototoxicity observed is because of the damage to the endoplasmic reticulum. Further, the in vivo studies validate the working of the reported photosensitizer in the photodynamic therapy. This example clearly demonstrates how the donor-acceptor architecture can be modulated to achieve the generation of type I reactive oxygen species. The AIE (aggregation-induced emission) mechanism in conjunction with donor-acceptor architecture has been extensively utilized in recent years to produce type I ROS species. Radiative decay in the aggregate state of AIE-based PSs is useful to enhance ROS formation, which is one of their advantages.[24] The research group of B. Z. Tang employed this strategy to develop type I PSs. In one of their studies, they have demonstrated the role of AIE in combination with donor-acceptor to obtain type I PS (**6**) with enhanced ROS generation (Figure 4).[25]

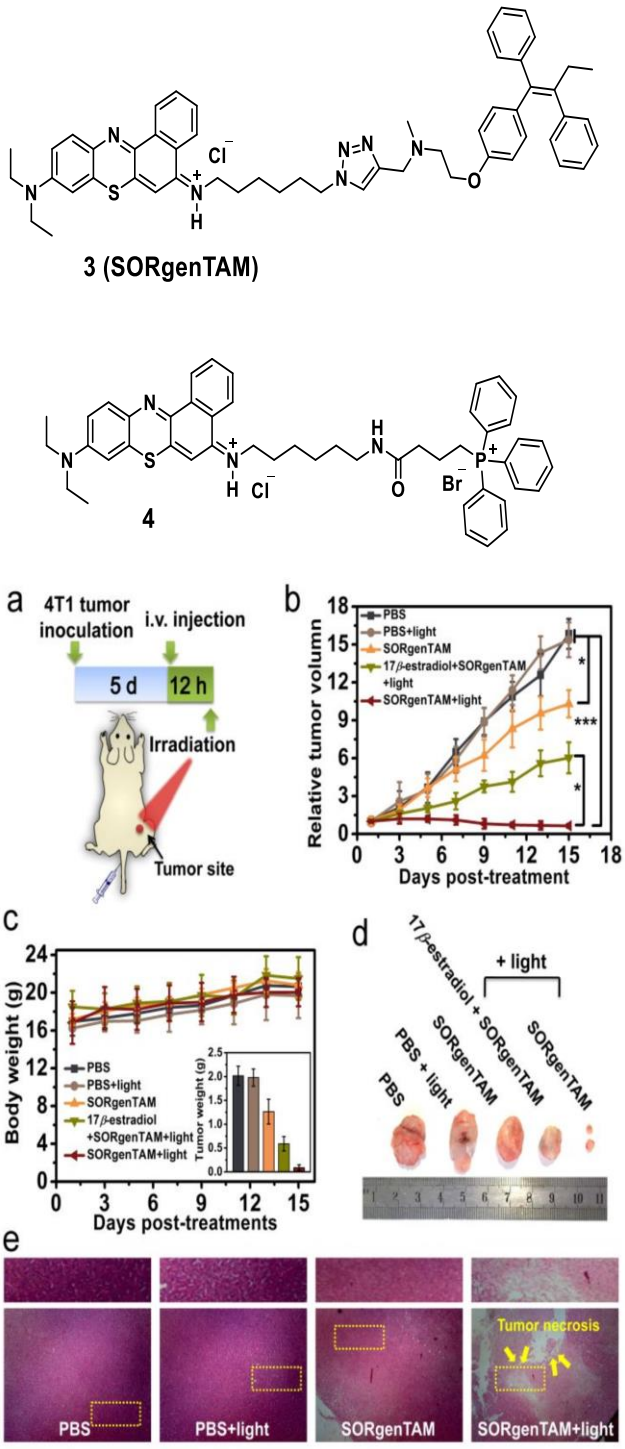


Figure 3. *(a) A schematic representation of the 3 (SORgenTAM) in vivo hypoxic tumor phototherapy experiment. (b) Tumor development in vivo after intravenous injection. (c) Mice's average body weight alterations during the course of the therapy. (d) Mice tumor images with various treatments. (e) Pathological study of tumor tissues obtained 24 hours after different treatments using H&E staining. Figures a-e, adapted with permission from ref. 19. Copyright 2020 American Chemical Society.*

In this particular study, the design of PS (**6**) is derived from the TPA (triphenylamine) donor and styrylpyridine cation acceptor. By using the type I mechanism to target the organelles including mitochondrial and lysosomes, the reported PS was demonstrated to cause cell apoptosis. A number of type I PSs for PDT have been developed by employing this approach.[26] Some of the recently published type 1 PS based on the donor-acceptor framework are given in the table 1.

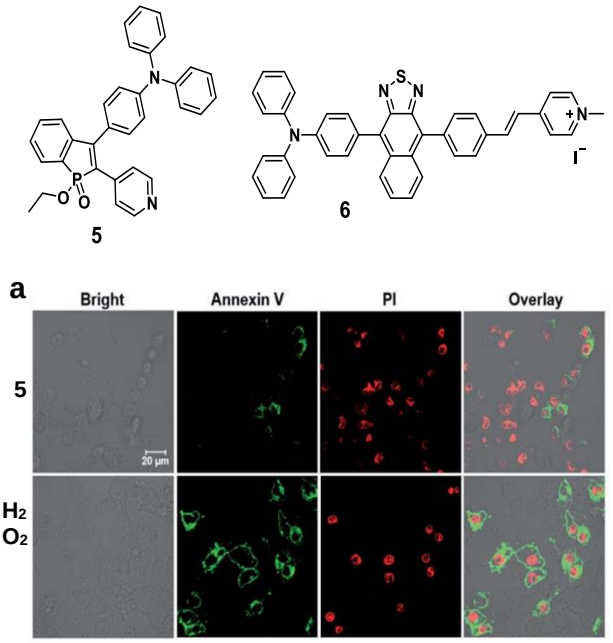
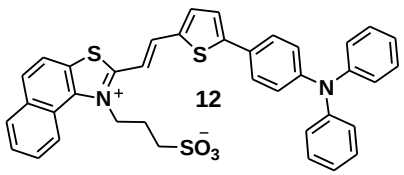
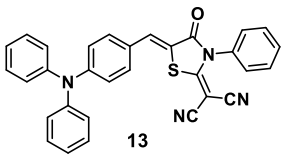
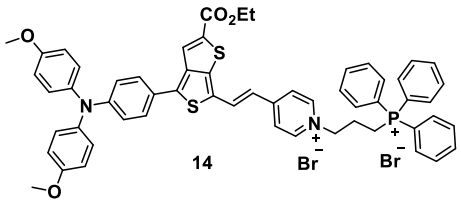
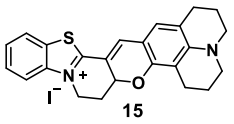
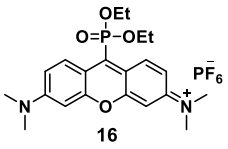


Figure 4. *Structure of 5 and 6. (a) Cell apoptosis analysis after treatment by PDT using **5** as the PS (white light irradiation with 20 mW cm^{-2} for 30 min) and further culturing for 12 h or H_2O_2 for 6 h. Figure 4a, reproduced from Ref. 23 with permission from the Royal Society of Chemistry*.

Table 1. *Recently reported type I organic PSs for the PDT process.*

Molecular structure	References
7	28
8	29
9	30
10	31
11 (n = 3, 6, 10)	32

	33
	34
	35
	36
	37

Supramolecular interactions have attracted a lot of attention in nanomaterials and therapeutics over the past several years because they offer a simple way to control the functional molecules.[27] Supramolecular self-assembled structures have therefore also been investigated as a method of producing reactive oxygen species in photodynamic treatment.[38] In 2018, Yoon and coworkers reported a zinc complex of phthalocyanine-based self-assembled nanostructures as PS for efficient ROS generation via the type I mechanism.[14a] A promising photodynamic action against bacteria was demonstrated by the produced nanostructured PS. Likewise, Yang and coworkers have developed a nano-dimensions based drug delivery system based on the combination of ergosterol and chlorin e6 (PS).[39] The authors have confirmed that the resulting supramolecular system has increased ROS generation ability and, thus, phototoxicity towards cancer cells through the type I PDT process. In another example, pillar[5]arene linked with L-arginine as a host and a Nile blue derivative as a guest employed to generate nano-micelles, which selectively target and release the Nile blue PS in cancer cells.[40] According to the studies, the PS effectively produces type I ROS in a hypoxic environment following release, which results in the death of cancer cells. Moreover, the pillar[5]arene derivative damages the cancer cells' cellmembrane and aids in the apoptotic process. Similar host-guest interactions were employed by Yang et al. to develop type I ROS production to kill cancer cells under hypoxic conditions.[41]

Kida and coworkers demonstrated that amphiphilic rhodamine/fluorescein derivatives in the aqueous medium form supramolecular assemblies that can generate reactive oxygen species (ROS) through the electron transfer mechanism when exposed to visible light (Figure 5).[42] The fundamental idea is that in its self-assembled state, the amphiphilic rhodamine or fluorescein produces a charge-separated (CS) state that can continue into the type I pathway to produce reactive oxygen species (ROS). At the same time, this also suggests an approach to convert type II PS into a type I PS. This is validated by converting fluorescein (Fl-C2) which acts as a type II PS (Figure 5.) into type I PS by using amphiphilic fluoresceine derivative (Fl-C18).[42]

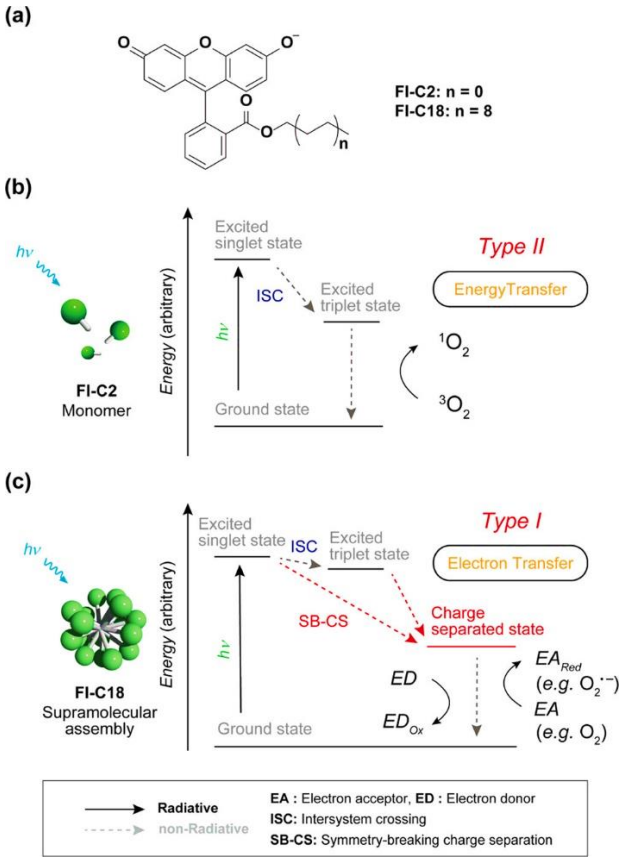


Figure 5. *(a) Molecular structures of fluorescein derivatives. (b) Type II mechanism exhibited by Fl-C2 (monomer state). Type I mechanism displayed by Fl-C18 (assembly state). Adapted with permission from ref. 42b. Copyright 2022 American Chemical Society.*

Kida and colleagues have further utilized the C-S state produced self-assembled organic molecule to develop a type I PS for the PDT process. For this, they have synthesized an amphiphilic rhodamine derivative **17** (Rh19-MA-C18) that, when self-assembled, functioned as type I PS and had a notable PDT effect on malignant cells (Figure 6).[43] The reported PS was developed on rhodamine fluorophore linked to a long alkyl chain to achieve the amphiphilic nature of the molecule. The fluorescence spectrum of **17** in DMSO displayed an emission at 567 nm, while in an aqueous buffer a quenched emission was observed. The behavior in the aqueous buffer was ascribed to the aggregate state of the **17**. This was further suggested by the broad absorption band of **17** in the aqueous buffer. The authors have validated that the self-assembled state of **17** in water with light irradiation (λ_{ex} = 520 nm) can produce $O_2^{\bullet-}$ via type I mechanism. Further, **17** exhibited a good photodynamic effect against cancer cells and on tumor tissue (Figure 7).

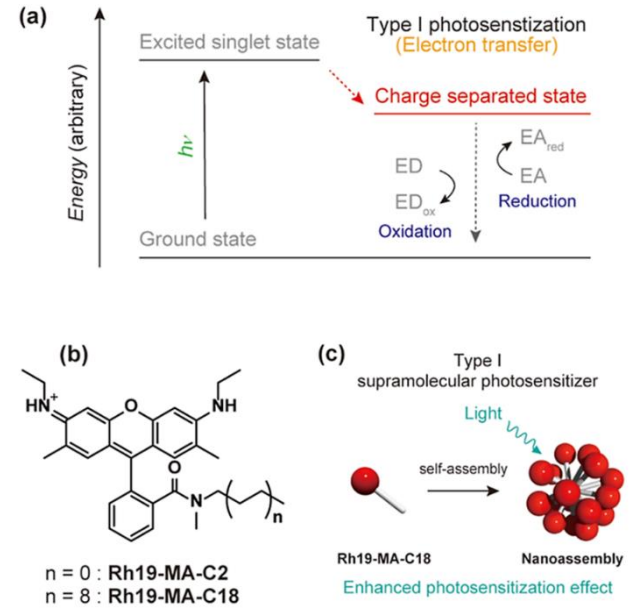


Figure 6. *(a) Mechanism of type I photosensitization based on 17. EA (electron acceptor), EA$_{red}$ (reductant of electron acceptor, ED (electron donor), ED$_{ox}$ (oxidant of electron donor). (b) Structures of 17 (Rh19-MA-C18) and 18 (Rh19-MA-C2). (c) Schematic illustration of supramolecular type I PS based on 17. Adapted with permission from ref. 43. Copyright 2022 American Chemical Society.*

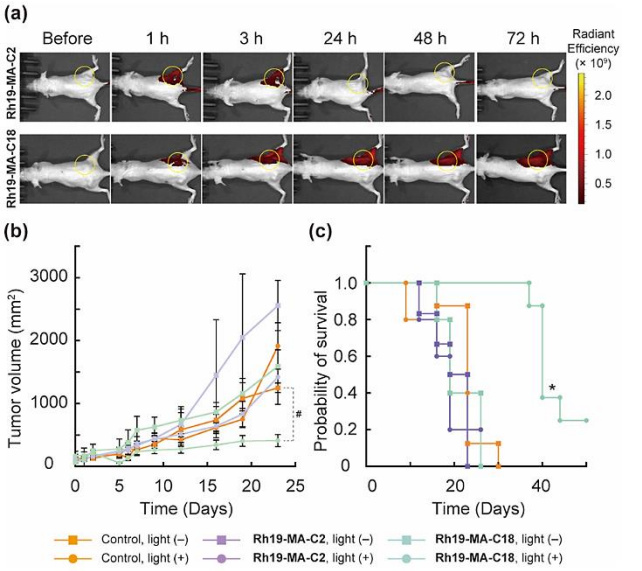


Figure 7. *(a) In vivo fluorescent images of the dye distribution after injection of Rh19-MA-C18 (17) and Rh19-MA-C2 (18). (b) Tumor volume analysis (each group ≥ n = 5). (c) Survival probability after injection of Rh19-MA-C18 (17) and Rh19-MA-C2 (18). Adapted with permission from ref. 43. Copyright 2022 American Chemical Society.*

Using PC9 tumor-bearing mice in in vivo tests, it was demonstrated that Rh19-MA-C18 (17) worked well for PDT. Following injection, fluorescence signals were recorded (Figure 7a), demonstrating Rh19-MA-C18's excellent bioretention and supporting its usefulness for PDT in deep tissue. The study split the mice into six groups and looked at the PDT effect of Rh19-MA-C18 on tumor cells. The findings demonstrated that while tumor size expanded under various circumstances, Rh19-MAC18 (17) and light were able to decrease it (Figure 7b and c). Mice survival rates were also markedly increased by Rh19-MA-C18 (17)-based PDT, with some mice surviving for as long as 50 days. This study highlights the possibility of supramolecular nano-assembly as a practical method for the development of type I PS for the photodynamic therapy. This finding additionally presents the possibility that type II PS can be easily converted into type I PS through simple chemical changes.

5. Conclusion

Photodynamic therapy is a potential method for treating cancer that has seen substantial development and application in clinical practice due to its noninvasiveness and excellent therapeutic selectivity. A wide range of inorganic based compounds have been extensively explored as PSs for PDT. Nevertheless, inorganic photosensitizers are associated with many disadvantages including toxic nature of heavy metal ions and low biodegradation. In contrast, organic PSs have the potential to address such issues with promising clinical applications. As described earlier, PSs developed on type I mechanisms are less oxygen-dependent because of the disproportionation reaction, are the preferable choices in the PDT process as tumor tissues are characterized by oxygen deficiency. Because of these reasons, in recent times, attention has been given to developing organic molecules-based type I PSs for the PDT process. To date, several approaches have been developed to generate organic molecules derived type I PSs for the PDT process. For instance, introducing the donor-acceptor groups in the PS design to enhance the intersystem crossing (ISC) is one of the useful strategies to develop type I PSs. A number of organic type I PSs have been developed using this approach. Moreover, mechanisms such as AIE have combined with the donor-acceptor architecture to obtain type I PSs. Nonetheless, visible light activates the majority of type I PSs, irrespective of their organic or inorganic origin. This limits their therapeutic efficacy as well as their broader use. Additionally, working of the PSs for the tumor region deep inside the tissues is another concern as the visible light has limited tissue permeability. Therefore, developing organic type I PSs for PDT activated by NIR light is of great significance as it can offer deep tissue penetration. Likewise, low energy nature of NIR light is beneficial to minimize the harmful effect on the normal tissues. Further, tumor selectivity is another concern as it can lead to the accumulation of the PSs in normal tissues. Overcoming these challenges is crucial to maximizing the benefits of PDT and requires the integration of additional cancer treatment strategies.

Author Contribution Declaration

Roopa: article design, reviewplan and manuscript draft manuscript; **Kumar**: supervision, review and editing.

Data Availability Declaration

There are no new data were created hence data sharing is not applicable.

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