

Review Article

Boron-Fluorine Photosensitizers for Photodynamic Therapy

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Photodynamic therapy (PDT) has been recognized as a promising treatment for cancers and tumors, in which photosensitizer is one of the most important issues. As a class of excellent fluorescent dyes, boron-fluorine derivatives (typically 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene, BODIPY) have preferable ability of generating singlet oxygen and have been under extensive study for PDT sensitizers. In this review, we summarize the recent progress of design and applications of boron-fluorine-based photosensitizers for PDT.

1. Introduction

Cancer is the most deadly killer in the world over the past decade, and almost all of the developed countries spend millions of dollars for research and treatment of cancer every year. Photodynamic therapy (PDT) is an evolving new field of study in the treatment of malignant tumors. Compared to traditional tumor therapy such as surgery, chemotherapy, and radiotherapy, PDT has its unique advantages as follows:

- (1) can be applied to the site which surgery cannot touch;
- (2) can be applied to people who are not suitable for surgery, chemotherapy, and radiotherapy (such as the infirm, the elderly, etc.);
- (3) can be reused safely and effectively;
- (4) does not produce immunosuppression;
- (5) can be used after surgery, chemotherapy, and radiotherapy or used at the same time, with a synergistic effect [1–8].

The mechanism of photodynamic therapy includes a variety of photophysical and photochemical processes [9–12]. Figure 1 depicts the photophysical processes before and after typical photosensitizer molecules were excited. Photosensitizer absorbs light to be excited into the first excited state and then intersystem crossing to excited triplet state. In this process, fluorescence may be observed during the relaxation

from first excited state to ground state, and the energy can also be lost through nonirradiative decay. From the triplet excited state, energy loss through radiation produces phosphorescence with long life time (microseconds), and the energy can also be passed to oxygen nearby to produce reactive oxygen species, including radicals and cytotoxic singlet oxygen $^1\text{O}_2$. The reactive oxygen would kill the cancer cells that photosensitizers accumulated in.

Currently, most studied photosensitizers in the photodynamic therapy of cancer are porphyrin derivatives [14–17], such as porfimer sodium (Photofrin), protoporphyrin IX, and temoporfin. This may be primarily due to the fact that there are a large number of natural porphyrin-based compounds. However, porphyrin has its own shortcomings: first, the molar absorption coefficients of porphyrin derivatives are usually less than $2 \times 10^4 \text{ cm}^{-1} \text{ M}^{-1}$ in the range of 650–900 nm; second, because of their planar structures, porphyrin derivatives tend to aggregate due to strong π - π stacking in concentrated solutions, which can reduce the quantum yield of singlet oxygen [18]; third, porphyrin derivatives are synthetically inaccessible, and it takes great effort to produce large amount of such photosensitizers by conventional organic synthetic strategy. In addition, porphyrin derivatives usually exhibit small stoke shifts, thus limiting their applications in imaging. Therefore, it is of great significance to develop photosensitizers with nonporphyrin chromophore core [19]. Some other chromophores have been

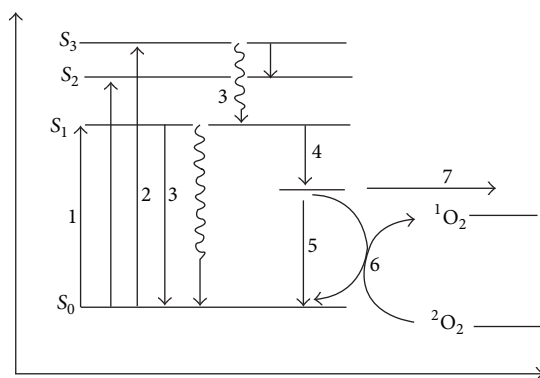


FIGURE 1: Photosensitizer absorbance after physical processes ((1) absorbing light; (2) fluorescence; (3) internal conversion; (4) intersystem crossing; (5) phosphorescence; (6) generating $^1\text{O}_2$; (7) proton or electron transfer).

reported for PDT study, such as phthalocyanine [20–25], squaraine dye [26–31], and perylene diimide [32, 33]; however, these photosensitizers suffer from poor chemical stability and photostability and easily aggregate in a polar environment.

As a class of excellent dyes for applications of sensor and fluorescent imaging, boron-fluorine derivatives (normally 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene, BODIPY) have emerged as a new class of PDT agents over the past decade [34, 35]. Boron-fluorine dyes contain a large number of advantages over other dyes: first, they usually have a large molar absorptive coefficient ($\epsilon > 8 \times 10^4 \text{ cm}^{-1} \text{ M}^{-1}$); second, they have extremely high chemical stability and photostability; third, they have facile availability and can be easily structurally modified to modulate their properties. Therefore, in recent years, the boron-fluorine photosensitizers aroused wide interest of chemists and pharmacologists and are considered to become a new generation of anticancer photosensitizers for clinical use. This review summarizes the design and applications of boron-fluorine photosensitizers.

2. Boron-Fluorine-Based Photosensitizers

2.1. Halogenated BODIPYs. Introduction of heavy atom is well known to facilitate intersystem crossing (ISC) with minimal energy loss from excited states. Then, the lifetime of the triplet state is increased, and the yield of singlet oxygen is greatly enhanced as a result. Therefore, this strategy has been widely adopted for development of highly effective PDT reagents. BODIPY core chemically reactive, and heavy atoms can be easily added at all positions without disrupting the planarity of the dye. Initially, O'shea et al. introduced bromine atoms at the 2,6-positions of the aza-BODIPY chromophore to produce BODIPY 1-2 (Figure 2) and compared their photophysical and photochemical properties to their nonhalogenated analogies A1-A2 [36, 37]. As proved by X-ray single crystal diffraction, the chromophore core of 1 is still planar with high conjugation degree. Although two bromine atoms were introduced, the planarity of chromophore core was preserved. Their absorption coefficients in visible region

are also nearly consistent before and after introduction of bromine atoms (1 and A1). However, heavy atoms significantly decreased their fluorescent quantum yields, which is beneficial for ISC to excited triplet states to generate singlet oxygen. Using 1,3-diphenylisobenzofuran (DPBF) as trapping reagent, compound 1 is much more effective in generating singlet oxygen at around a hundredfold lower concentration than A1. The presence of other functional groups, like methoxy groups, does not change this tendency. For example, compound 2 shows an increased efficiency of singlet oxygen generation even at a 100-fold lower concentration, compared to A2. It is also the case in cells, and we can ascertain the cellular localization of these photosensitizers by fluorescent imaging technique. Fluorescent imaging by confocal laser scanning microscopy (CLSM) confirmed that the subcellular localization of A1 was exclusive to the cytoplasm with no nuclear localization, and cytotoxicity assay with MRC5-SV40 indicates that these compounds show no dark toxicity up to a concentration of 10^{-4} M , which is essential for PDT. However, upon irradiation by 8 J cm^{-2} light dose, significant light-induced toxicity was observed, with EC_{50} values determined for A1, A2, and 2 as 3.1×10^{-6} , 1.1×10^{-4} , and $3.7 \times 10^{-8} \text{ M}$, respectively. The exceptional light-induced toxicity of 2 was ascribed to the presence of the two bromine heavy atoms, which are directly substituted onto the chromophore core.

Iodine is a heavier atom than bromine and may exert better heavy atom effect to induce efficient singlet to triplet transition. In 2005, Yogo et al. [13] synthesized a simple BODIPY dye A3 and placed two iodine atoms directly on 2,6-positions of the BODIPY core to produce 3 (Figure 3(a)). Introduction of iodine atoms results in significant red-shift of the absorption (around 30 nm) and greatly decreases its fluorescence quantum yield. Compound A3 shows a high fluorescence quantum efficiency (0.70 in methanol). However, the quantum yield decreases to 0.02 in methanol for 3, suggesting that ISC efficiency from singlet excited state to triplet excited state is enhanced by heavy iodine atoms. This is proved by the study of their ability to generate singlet oxygen. From the near-infrared emission spectrum of 3 in methanol, a narrow emission was observed at 1268 nm, which is characteristic of singlet oxygen (Figure 3(b)). Compared to that of Rose Bengal under the same condition, the efficiency of singlet oxygen generation of 3 is 1.34 times greater. Using DPBF as trapping reagent, compound 3 generated singlet oxygen almost equally in all conventional solvents except that in methanol, suggesting that it would offer better flexibility than Rose Bengal because of its poor solubility in nonpolar solvents. Beside that, compound 3 shows much better photostability than Rose Bengal. It is not surprising because typical BODIPY dyes are exceptionally chemically stable and photostable, but this character is quite essential for practical application of PDT reagents. Compound 3 was used for cell photosensitization as shown in Figure 4. HeLa cells were stained by $1 \mu\text{M}$ stock solution and then illuminated with green light ($535 \pm 25 \text{ nm}$, 5 mW/cm^2) for 1 min. Cell viability was assayed through the use of the calcein AM (living cell marker) and EthD-1 (dead cell marker). First, compound 3 shows no dark toxicity, proving that it is safe

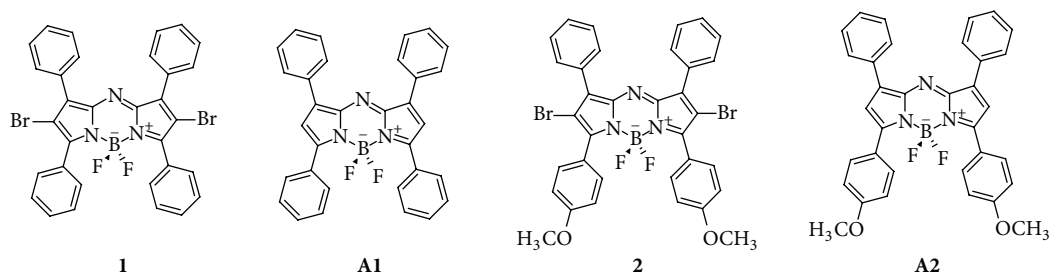


FIGURE 2: Structures of BODIPY 1-2 and A1-A2.

(Figures 4(a)–4(c)). Light illumination induces rapid cellular death (Figures 4(d)–4(f)), suggesting that compound **3** is a potent PDT reagent for cell photosensitization.

To understand the effects of substitution patterns on photosensitizing ability of BODIPY, effectiveness of various iodinated derivatives was investigated to maximize the heavy atom effect (Figure 5), and the position where halogen is placed has a marked effect in the photophysical properties [38].

Successive iodination gives rise to a progressive bathochromic shift of the absorption bands. The maximum absorption of compounds **4**, **5**, **6**, and **7** was located at 523, 548, 563, and 581 nm, respectively, with absorption coefficients increasing ($2.2 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$ for **4**; $4.3 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$ for **5**; $4.8 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$ for **6**; $11.6 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$ for **7**) which is advantageous for PDT. However, their fluorescent quantum yields are measured to be 0.034, 0.012, 0.060, and 0.099, which are not consistent with the number of iodine atoms they bear. Using Rose Bengal as reference with a quantum yield for singlet oxygen production of 0.71, the values for compounds **5**, **6**, and **7** are measured to be $0.83 \pm 7\%$, $0.86 \pm 9\%$, and $0.87 \pm 6\%$, respectively. These results indicate that introduction of iodine atoms at 3,5-positions does not produce distinct increase in the efficiency of singlet oxygen generation, which is in good agreement with their photophysical properties. Clearly, iodination at 2,6-positions of BODIPY core is effective in improving their photosensitizing ability. It also gives a clue that 3,5-positions of BODIPY can be suitably functionalized to produce expected PDT reagents with some additional functions, such as extending π -conjugation system to produce Near-infrared (NIR) absorption dyes and introducing affinity groups. Actually, intense absorption in the body's therapeutic window (650–900 nm) is requisite for practical therapy. Increasing the π -conjugation at 3,5-positions of BODIPY chromophore core is one efficient and widely adopted strategy.

Atilgan et al. synthesized a series of BODIPY-based photosensitizers with extended π -system at 3,5-positions (Figure 6) [39]. In consideration of their practical application in aqueous condition, water soluble PEG groups were introduced, which also confer cell permeability and tumor targeting characteristics on photosensitizer [40, 41]. The extended conjugation in these dyes moves the absorption to NIR region (650–680 nm) as expected. Using DPBF as singlet oxygen trapping reagent, these compounds can generate

singlet oxygen under very low concentration level of 9 nM. Among sensitizers **8**–**10**, compound **8** is the most potent one, because it shows the fastest reaction rate to consume DPBF. But the structure-property correlation is not discussed in the context. Evaluation on K562 human erythroleukemia cells was conducted with sensitizer **10** (considering its better solubility characteristics), and the EC_{50} value was less than 200 nM. Beside water solubility issue, PEG can also help to alleviate aggregate formation in aqueous condition. Aggregate would lead to inefficient formation and potential quenching of the triplet state and singlet oxygen. Therefore, compounds **8**–**13** with multiple PEG units may suppress aggregate-induced disadvantages.

Study of **11**–**13** indicates that these compounds are non-cytotoxic in the absence of light. However, upon illumination with red light ($>610 \text{ nm}$), all the compounds become toxic. The photocytotoxicity depends greatly on the substituent and follows the trend **13** ($\text{IC}_{50} = 7 \text{ nM}$) $>$ **12** ($\text{IC}_{50} = 75 \text{ nM}$) $>$ **11** ($\text{IC}_{50} = 330 \text{ nM}$). Compound **13** is the most potent candidate, and its photocytotoxicity is even much higher than that of the most used photosensitizer porfimer sodium ($\text{IC}_{50} = 4600 \text{ ng mL}^{-1}$, in comparison, 11 ng mL^{-1} for that of **13** under the same condition). Compound **13** contains five triethylene glycol chains, which should be responsible for this behavior. To account for the different phototoxicities of **11**–**13**, their aggregation behavior in Dulbecco's modified Eagle's medium (DMEM) was examined by absorption and fluorescence spectroscopic methods. It is found that the Q bands of **11**–**13** remain sharp and intense, proving that they are free from aggregation in the culture medium. Investigation of cellular uptake of the compounds on HT 29 cells indicates that compound **13** shows much stronger intracellular fluorescence throughout the cytoplasm than other compounds, suggesting that it has higher cellular uptake and/or efficiency to emit fluorescence inside the cells. The enhanced uptake may be due to the increased number of triethylene glycol chains. Hence, the highest photocytotoxicity of **13** should be attributed to its low aggregation tendency and high cellular uptake in the biological environment.

In order to release singlet oxygen at the targeted region (e.g., tumor tissue), one possible approach is to deliver the BODIPY sensitizer to targeted cells [42]. Single wall carbon nanotube (SWNT) can be internalized by mammalian cells through endocytosis, while pyrene has strong affinity with SWNT through π - π noncovalent interactions. Compound **14** comprises two pyrene units (Figure 7), which can deliver

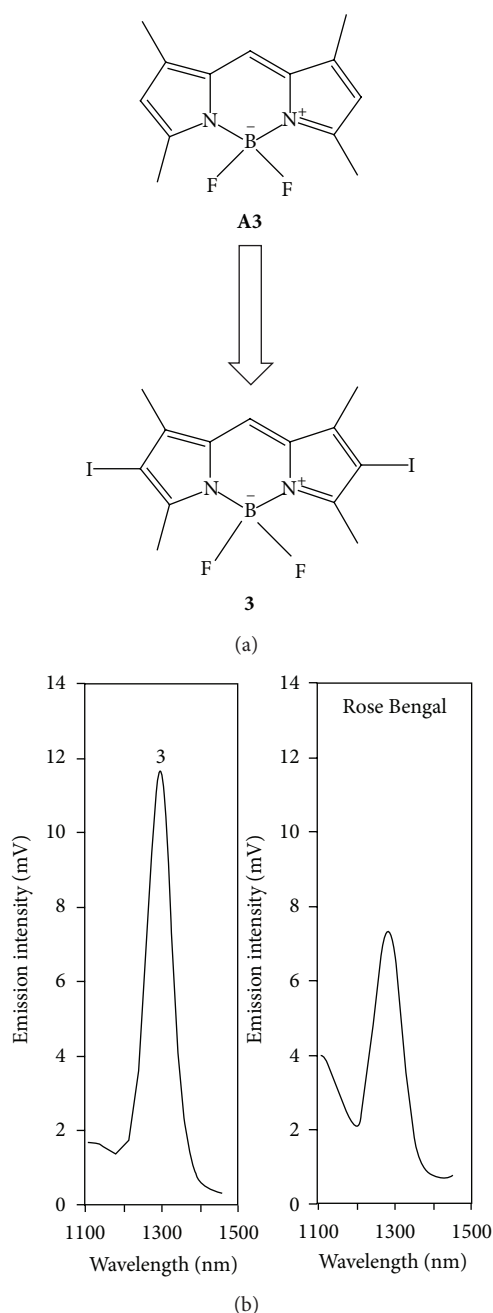


FIGURE 3: (a) Structures of BODIPY A3 and 3. (b) Near-infrared singlet oxygen luminescence emission spectrum of 3 and Rose Bengal in methanol (5×10^{-5} M) excited by an Ar laser light at 514 nm with 100 mW output power. Reprinted with permission from [13] Copyright 2005 American Chemical Society.

the BODIPY sensitizer to mammalian cells functionalized by SWNT. In this way, BODIPY sensitizer can be accumulated in the targeted tumor cells, and selectively killing tumor cells may be realized.

Another strategy is to construct controlled singlet oxygen release by PET (photoinduced electron transfer) modulation of singlet to triplet conversion. By covalent attaching of a substrate-specific receptor to BODIPY dye, therapeutic

property (generation of singlet oxygen) may be reversibly switched off/on. This is realized by introduction of amino units into the BODIPY structure. The neutral form does not generate singlet oxygen efficiently due to the PET process. However, protonation of the amino units can shut down PET, releasing singlet oxygen rapidly upon light irradiation [43].

In tumor tissues, the pH is quite acidic, and intracellular sodium ion concentration is also significantly higher (up to three times) than normal tissues. Therefore, compound 15 is expected to accumulate in tumor cell, because of its high affinity with Na^+ and H^+ (Figure 8). Possible logic system with Na^+ and H^+ as inputs can be constructed by introduction of Na^+ -sensitive (crown ether) and pH-sensitive (pyridine) units (compound 15) [44]. Following the principle of molecular AND logic gates, high concentration of both Na^+ and H^+ ions turns on the output, producing singlet oxygen in significantly high amounts relative to the presence of zero or only one kind of stimuli (high concentration of Na^+ or H^+). As a result, the authors observed cumulative generation of singlet oxygen upon the presence of both stimuli. This approach may not be suitable for in vitro study, because the required concentrations of Na^+ or H^+ are much higher than intracellular levels. But it can be realizable once the sensitizer has extremely high affinity with Na^+ and H^+ . Construction of a polymer bearing a large number of crown ether and pyridine units may be one promising strategy.

2.2. BODIPY Bearing C_{60} . Heavy atoms incorporated into the structure of the sensitizers can improve spin-orbit coupling to facilitate intersystem crossing, but they may potentially arouse increased “dark toxicity.” Beside heavy atoms, efficient ISC of fullerene C_{60} is particularly interesting and more promising for PDT application. Photoexcitation of C_{60} and its derivatives induces a singlet excited state that is transformed to the corresponding triplet excited state via intersystem energy crossing, with nearly quantitative efficiency [45–51].

A few years ago, C_{60} has been found to generate singlet oxygen in biological medium, [52] using hydrophilic molecular micelle-like C_{60} derivatives, in the form of nanosphere structures. C_{60} itself is not an ideal triplet photosensitizer because its absorption in the visible range (at ca. 700 nm) is extremely weak, manifesting a low-lying singlet excited state. But this weak absorption can guarantee intramolecular energy transfer in C_{60} -organic chromophore dyads. 1,1-Dicyanoethylenyl-diphenylaminofluorene was first chosen for such propose, as it can absorb visible light with medium absorption coefficient ($\lambda_{\text{abs}} = 429 \text{ nm}$, $\epsilon = 1.32 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$). Direct detection of singlet oxygen was accomplished by observing its fluorescence emission at 1270 nm during the quenching process [53]. However, the absorption coefficient of 1,1-dicyanoethylenyl-diphenylaminofluorene in visible region is not satisfying for an ideal photosensitizer. Instead, BODIPY derivatives are much more promising. Based on this consideration, Zhao et al. designed a series of C_{60} -based dyads containing BODIPY chromophore (compound 16–20 in Figure 9) [54, 55]. As expected, all these compounds show strong absorption in the visible region (e.g.,

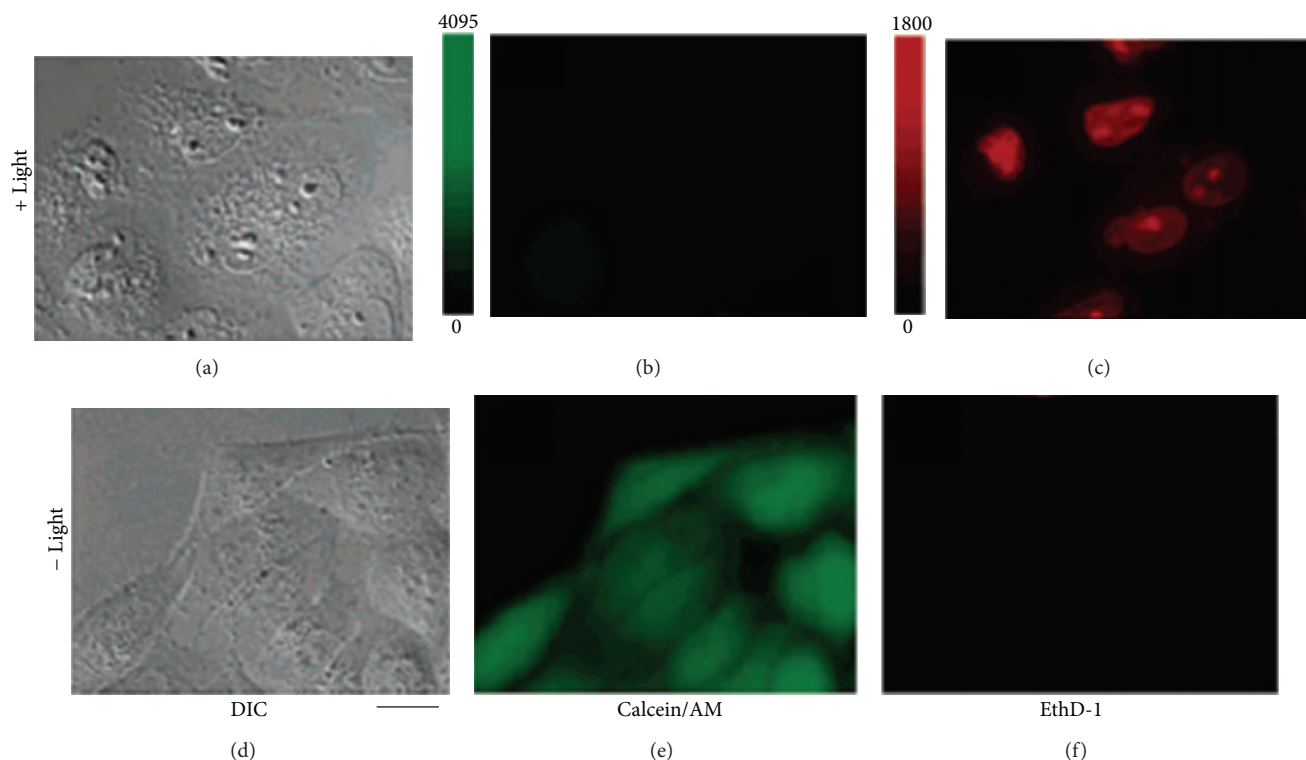


FIGURE 4: Cell photosensitization by **3**. Differential interference contrast and fluorescence and fluorescent images of HeLa cells loaded with calcein AM (living cell marker) and EthD-1 (dead cell marker) before photosensitization (a–c) and after (d–f). Reprinted with permission from [13] Copyright 2005 American Chemical Society.

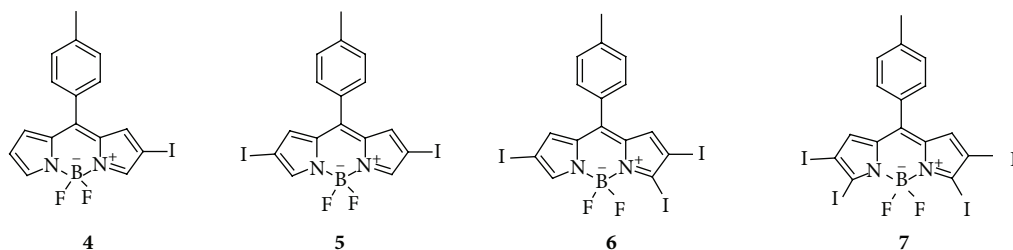


FIGURE 5: Structures of BODIPY **4–7**.

compound **16**, $\lambda_{\text{abs}} = 515 \text{ nm}$, $\epsilon = 7.04 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$). The BODIPY chromophore absorbs visible light and transfers the energy to C_{60} , and then C_{60} acts as intramolecular energy acceptor and spin convertor. Because of its intrinsic capability of ISC, the triplet excited state of C_{60} can be efficiently populated (the triplet excited state of C_{60} upon photoexcitation is close to unity). As a result, these compounds fluoresce weakly with quantum yield 1.0% for **18**, and the energy transfer efficiency is as high as 98.1%. A similar emission property was observed for **19** and **20**. Using 1,5-dihydroxynaphthalene (DHN) as singlet oxygen trapping reagent, photooxidation of DHN by these sensitizers indicates that these dyads are even more potent than traditional organic triplet photosensitizers tetraphenylporphyrin and methylene blue. The quantum yield of singlet oxygen is 0.62 for tetraphenylporphyrin and 0.57 for methylene blue. However, these values increase to 0.85, 0.85, and 0.82 for **18**, **19**, and **20**, respectively. This result

indicates that the number of introduced C_{60} units does not arouse much difference in photosensitizing ability.

2.3. BODIPY Dimers. Recently, a new class of BODIPY dimers bis(BF₂)-2,2'-bidipyrins (BisBODIPYs) have been synthesized, and their photophysical properties were compared with those of their corresponding monomers (Figure 10) [56]. The monomers show narrow and intense single absorption band around 530 nm; but the corresponding dimers (**21–24**) exhibit split band maxima at about 490 nm and 560 nm. In particular, the dimers show large Stokes shifts (more than 80 nm) and decreased fluorescence quantum yield. The decreased fluorescence quantum yield is ascribed to the ISC from singlet to triplet excited state. As a result, the quantum yield of production of singlet oxygen is 0.4 in toluene and 0.5 in dichloromethane, pointing to a high

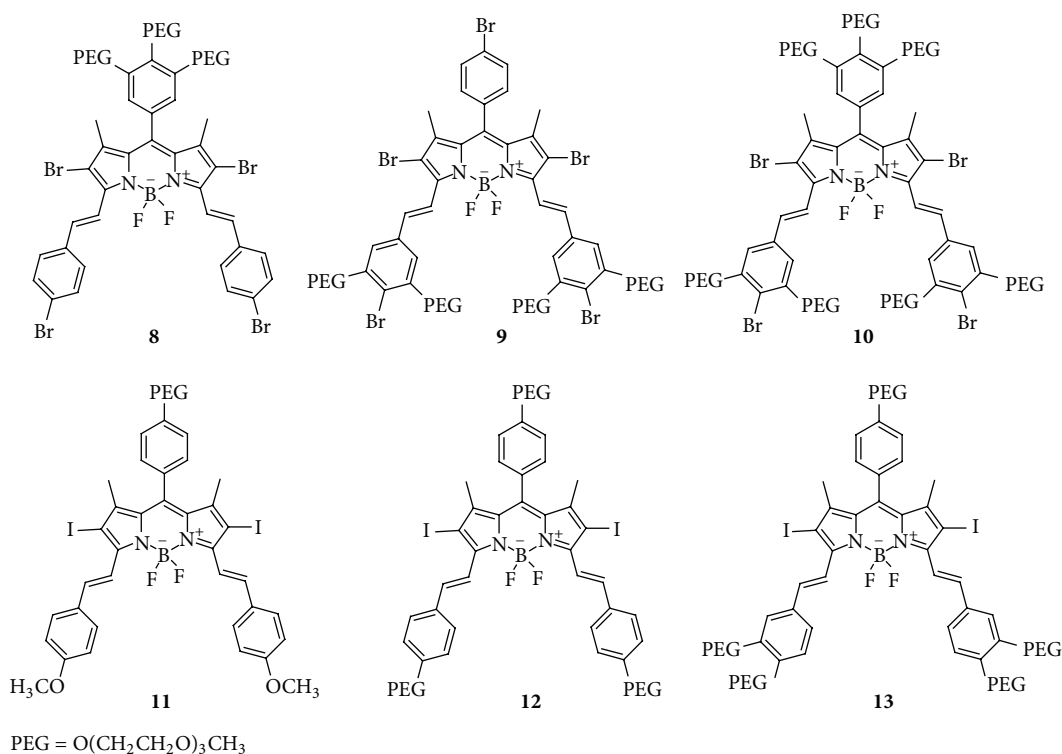


FIGURE 6: Structures of BODIPY 8–13.

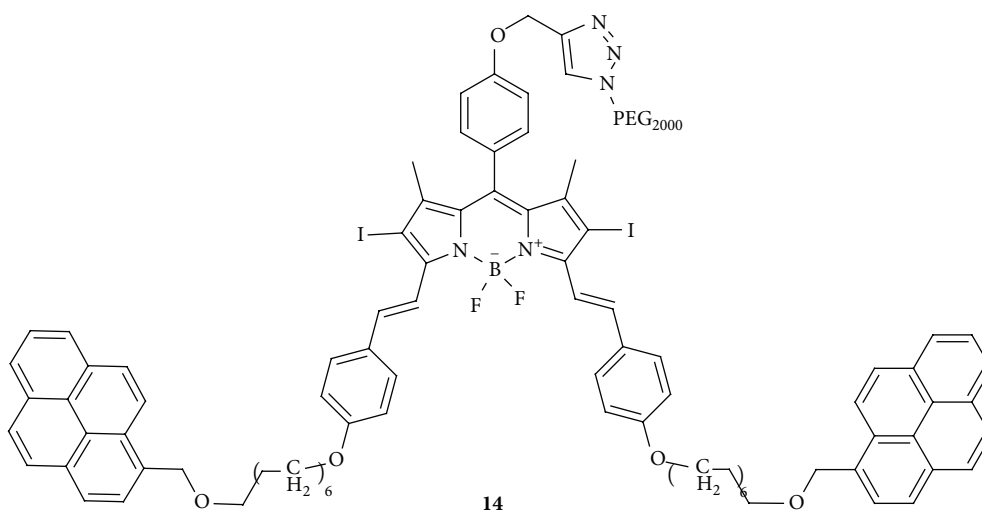


FIGURE 7: Structure of BODIPY 14 with delivery function.

value of triplet yield. In comparison, the values for monomers are less than 0.1. These data indicate that these dimers can be potential singlet oxygen photosensitizers. In order to theoretically explain this behavior, multiconfigurational self-consistent field (MCSCF) techniques (computational chemistry approach) were adopted [57]. The calculations indicate that BODIPY monomer possesses low triplet quantum yield, and the excited state possesses two orbitals with single occupancy. But doubly substituted ones can significantly

enhance S_1 - T_1 coupling. Then, a design principle of orthogonal dimeric chromophore was proposed based on the calculations: the BODIPY dimer should be orthogonally placed. This is proved by the fact that all the dimers synthesized show ideal quantum yield to generate singlet oxygen. In particular for dimers 26 and 27, significant fluorescence emission quantum yields are preserved, opening the possibility for a dual use as therapeutic and imaging agents. As a sacrifice, their singlet oxygen quantum yields are lower than other BODIPY dimers.

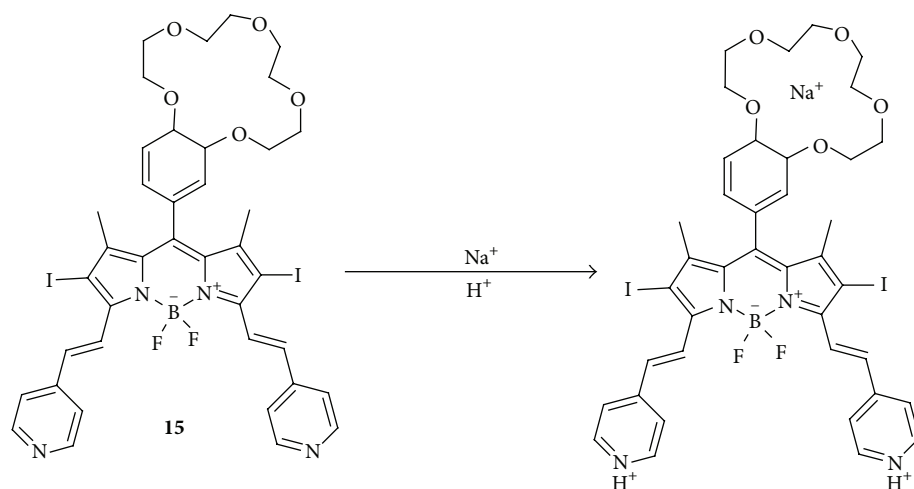
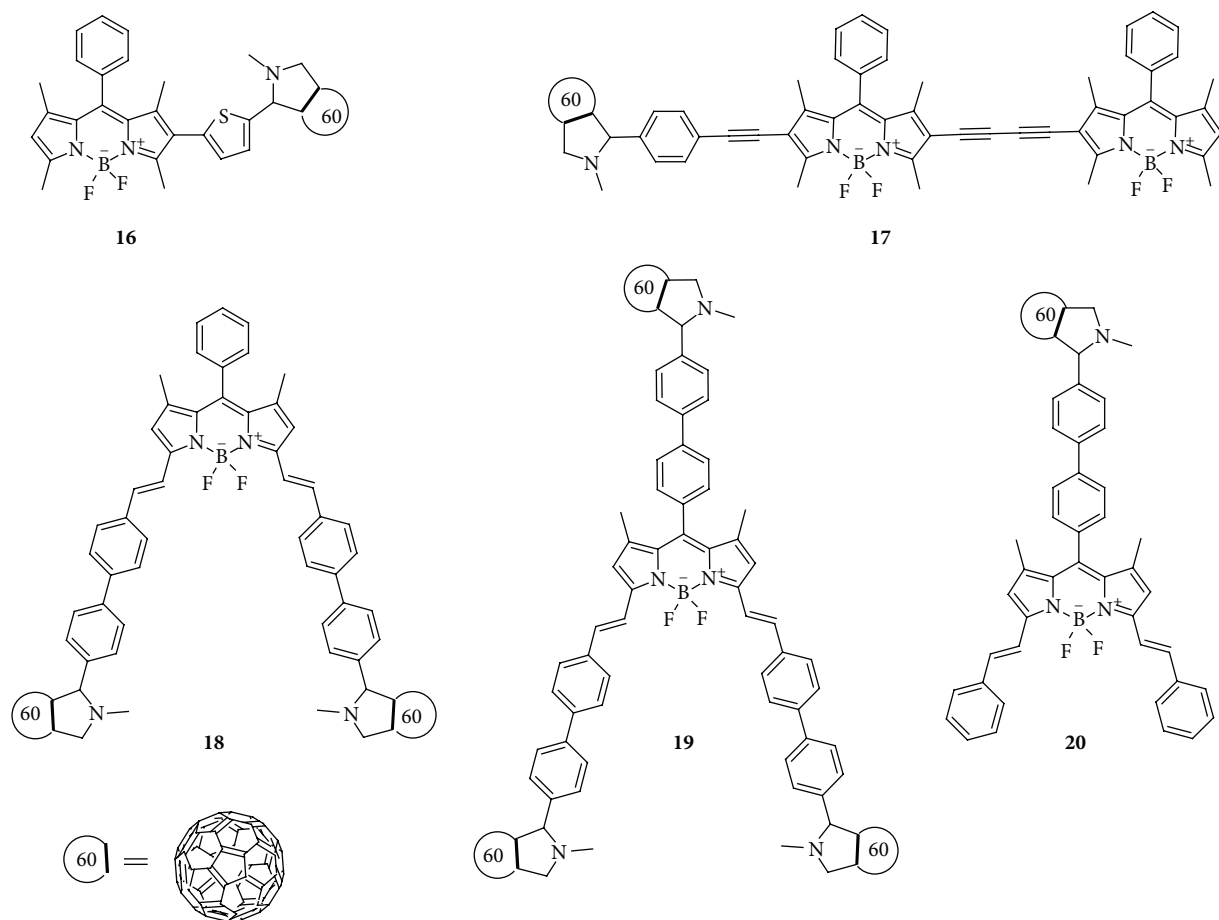


FIGURE 8: PET modulated singlet to triplet conversion.

FIGURE 9: Structures of BODIPY dyads bearing C₆₀.

2.4. Nonaggregated Boron-Fluorine Dyes. Aggregation due to strong π - π stacking would reduce the quantum yield of generating singlet oxygen. But typical BODIPY dyes have highly planar structure, and they usually pack tightly in concentrated solution, which imposes a limit that current

sensitizers have to be used in dilute solutions. In order to solve this problem, we proposed to use 2-(2'-pyridyl) imidazole derivatives as ligands to coordinate with BF_3 to produce a new class of boron-fluorine dyes (BOPIM, Figure 11) [58]. According to X-ray single crystal diffractions,

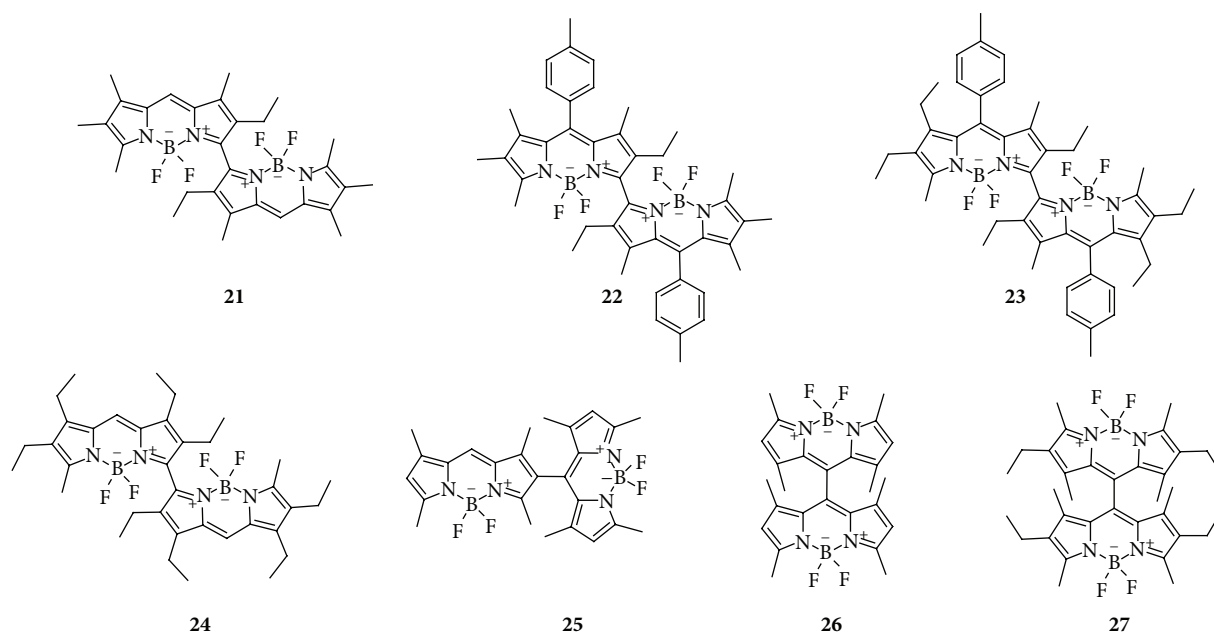


FIGURE 10: Structures of BODIPY dimers.

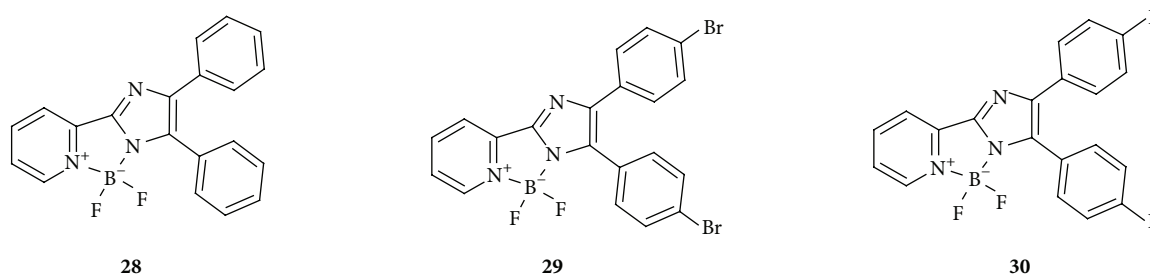


FIGURE 11: Structures of nonaggregated BOPIM dyes.

they form a rigid nonplanar structure through noncovalent intermolecular interactions ($B-F \cdots H$, $B-F \cdots C$, etc.), which inhibits aggregate formation. The nonaggregated mode makes BOPIM 28–30 show similar photophysical properties in aqueous conditions as in conventional organic solvents, and they can generate singlet oxygen under light irradiation. The heavy atom effect is not significant in this case, mainly due to that the halogen atoms are not introduced directly on the chromophore core. The main drawback of this system is that they show medium absorption around 410 nm ($\epsilon < 2 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$). The following work will focus on tuning their absorption to visible region and increasing their absorption coefficients.

3. Outlook

This review summarizes the recent development of boron-fluorine-based photosensitizers. The design comprises introduction of heavy atoms or C_{60} and construction of BODIPY dimers or intermolecular noncovalent bonds to inhibit aggregation. The future research should be to develop clinically

useful BODIPY dyes, especially controllable generation of singlet oxygen at the targeted region.

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