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Introductory Chapter: BODIPY Dye, an All-in-One Molecular Scaffold for (Bio)Photonics

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1. Introduction

Dye chemistry has witnessed a renewed interest in the last years. The reason of such impressive growth relies on the modern avenues in organic chemistry, which allow to develop new molecular structures, or decorate the backbone of an available chromophore with the desired substitution pattern, fulfilling the specific requirements of a given application field [1]. In this regard, those organic molecules able to emit fluorescence are receiving a great deal of attention owing to the recent technological advances in high-resolution spectroscopic techniques based on fluorescence. In fact, the Nobel Prize in 2014 was awarded to the development of super-resolution fluorescence microscopy (nanoscopy) [2–4]. Moreover, nowadays, bioimaging has become likely the most successful and widely used technique to monitor biochemical events at real time following the fluorescence emission of probes, sensors, and markers [5].

Actually, there is a wide chart of commercially available fluorophores spanning the whole ultraviolet-visible region of the electromagnetic spectrum and even reaching the near infrared (NIR). Nevertheless, the search for new organic fluorophores is an active task to find molecular structures with improved photophysical properties and photostability. These are key properties for any practical application (such as the aforementioned bioimaging) since they rule the sensitivity and efficiency, and the operative lifetime, respectively, of the detection process. Among them, definitely those chromophores known as borondipyrromethene (BODIPY) are in the forefront. A quick bibliographic search reveals that since their discovery (early 1990s) they have been intensively exploited (almost 1000 publications per year, **Figure 1**). The reason of their success is based on the chemical, photochemical and thermal stability of their boron-dipyrroin core, which provides strong absorption and fluorescence spectral bands [6–8]. Nevertheless, likely the main outstanding characteristic of BODIPYs is their chemical versatility, since their chromophoric core is amenable to a myriad of chemical reactions

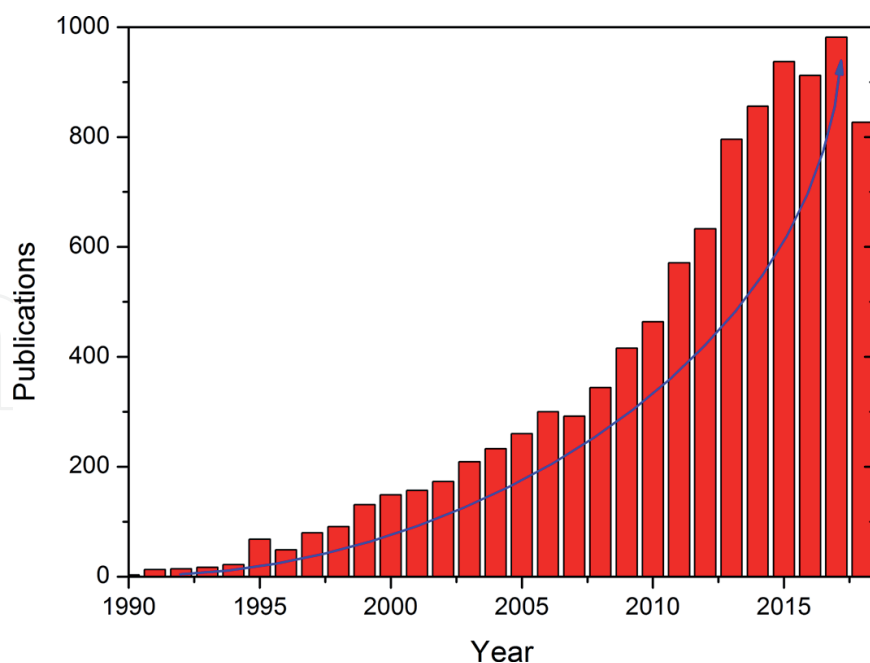


Figure 1. Evolution of the publications dealing with BODIPYs since their first reports (source: SciFinder, September 2018).

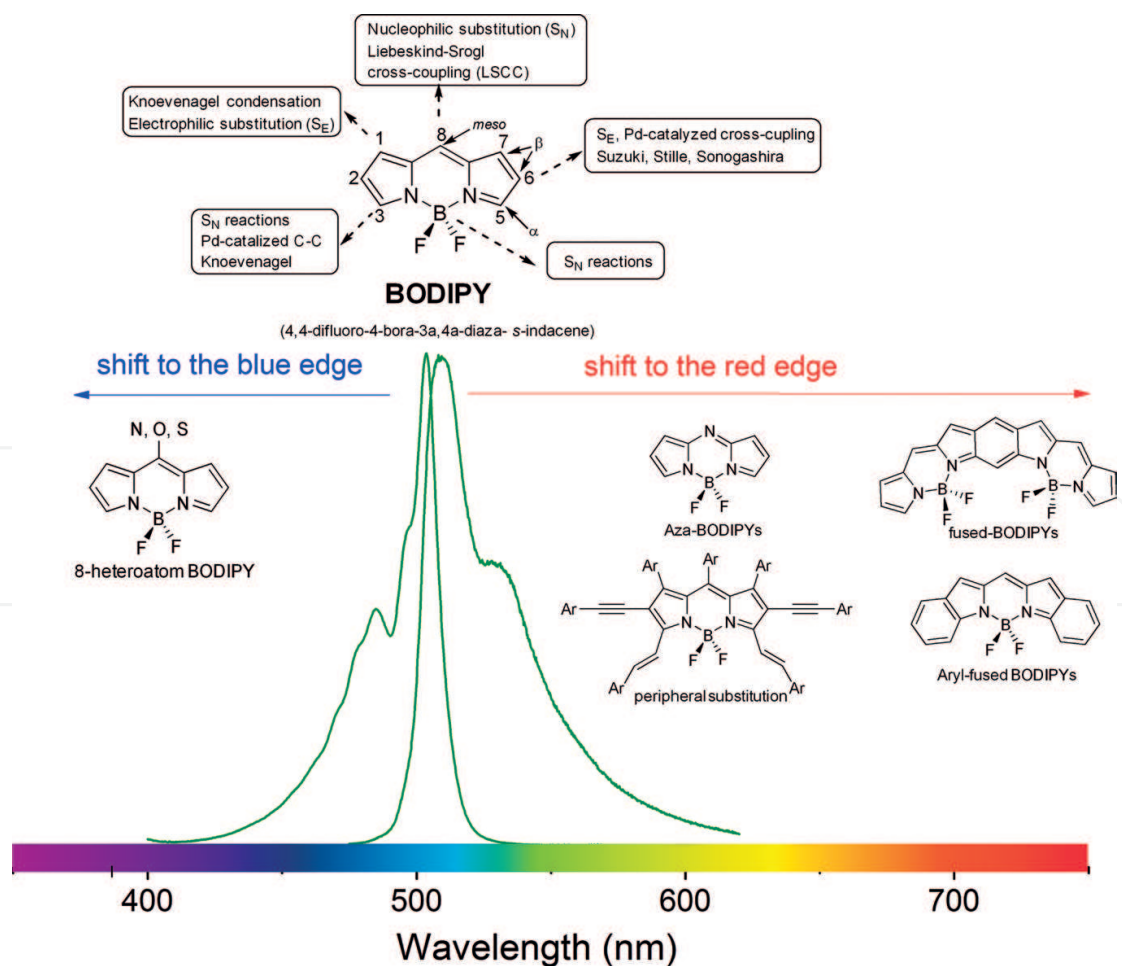


Figure 2. Molecular structure and main organic reactions applied to BODIPYs. The basic absorption and fluorescence bands of BODIPYs and some key structural modifications to achieve pronounced spectral shifts toward both edges of the visible are also included.

(all the chromophoric positions can be functionalized selectively, **Figure 2**) which allows an exhaustive and rich substitution pattern [9]. As a matter of fact, in the bibliography BODIPYs have been claimed as “El Dorado” for organic chemistry or “chameleons” to highlight their versatility [10]. Such functionalization enables the modulation of the photophysical properties or alternatively the induction of new photophysical phenomena. As a consequence, and upon a rational design, BODIPY dyes with absorption and emission along the whole visible region can be attained with improved photonic performance than the benchmark dyes in each spectral region 5 (**Figure 2**), or they can be tailor-made derived to match the requirements of plenty of application fields. All these facts explain and support the unstoppable growth and popularity of these dyes in these last decades (**Figure 1**).

2. Main application fields of BODIPYs

BODIPY dyes are applied in a multitude of diverse (bio)technological fields as photoactive media. Among them likely the most exploited are in organic lasers, biomedicine (probes and sensors for diagnosis by means of bioimaging and photosensitizers in photodynamic therapy of cancer), light harvesters (artificial antennae) and photovoltaic devices (photosensitizers of semiconductors) (**Figure 3**). Hereafter, the fundamentals of each application field with BODIPYs are briefly explained

2.1. Lasers

The high photostability and fluorescence response of BODIPYs make them suitable photoactive media for dye lasers (**Figure 3A**) [11, 12]. After amplification of the stimulated emission, a strong laser emission band can be achieved along the whole visible spectral region just

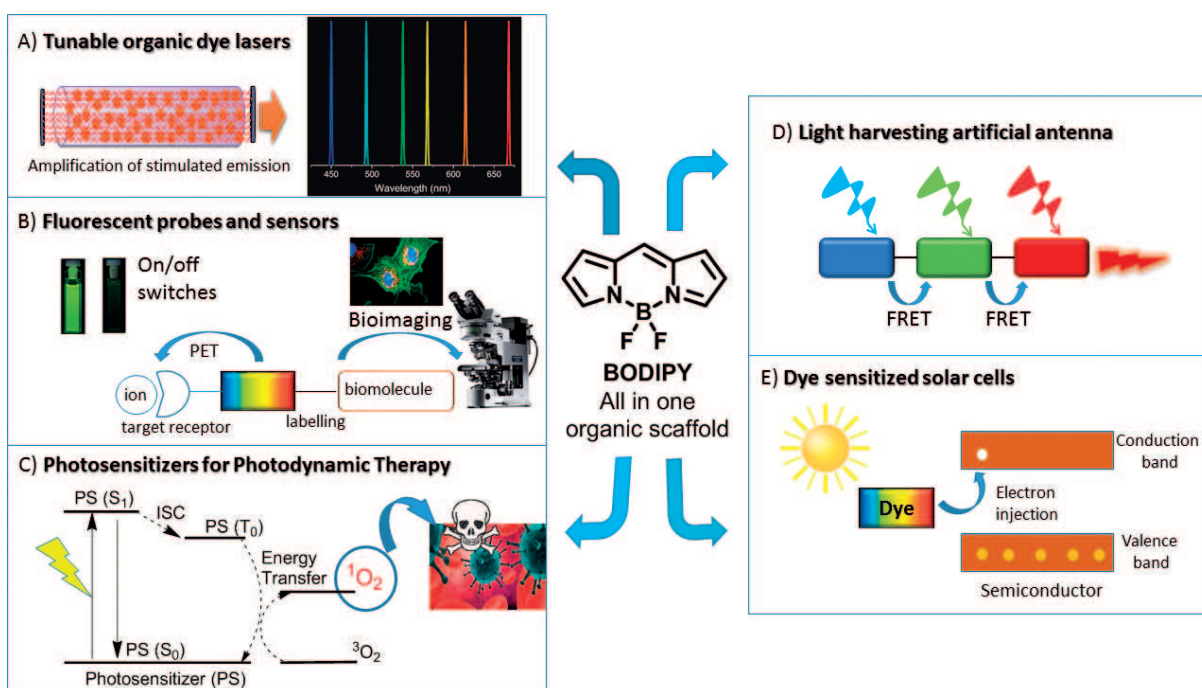


Figure 3. Scheme of the main application fields of BODIPYs.

changing the molecular structure thanks to the claimed chemical versatility of the chromophoric core. The achieved laser signal is highly efficient (even above 50%) and stable, since in some cases no sign of degradation is detected even after prolonged and intense pumping (up to 100,000 pulses). Moreover, the tunable dye lasers based on BODIPYs, even in solid state, display better laser performance than the commercially available organic lasers considered hitherto as benchmarks in each spectral region.

2.2. Fluorescent probes and sensors

The vast number of synthetic protocols that can be applied in the chromophore of BODIPYs enables labeling of biomolecules with these fluorophores (**Figure 3B**). Thus, bright and stable fluorescent probes can be designed for bioimaging [13]. A high fluorescence response allows an easy and sensible detection of the biomarkers just monitoring the emission under a fluorescence microscope, being the signal also long-lasting owing to the high photostability of the BODIPY-tagged biomolecule.

As aforementioned, the substitution pattern of the chromophore can induce new photophysical processes (such as intramolecular charge transfer, ICT, or photoinduced electron transfer, PET) which are highly sensitive to specific environmental conditions (polarity, acidity) or the presence of certain analytes (ions, molecules) in the surrounding environments, respectively, and hence ideal to develop fluorescent sensors [14, 15]. There are plenty of designs of sensors based on BODIPYs to monitor different environmental properties and detect and quantify molecular species, but likely those called on/off switches show the best performance since the detection process is highly sensitive and can be clearly visualized by the naked eye (**Figure 3B**). Overall, they are based on the induction of a fluorescence-quenching PET process in the BODIPY upon binding a specific receptor (off state). After selective recognition of the target analyte, the PET is suppressed and the bright fluorescence from the chromophore is recovered (on state).

2.3. Photosensitizers in photodynamic therapy

The fluorescent probes are widely applied in biomedicine for diagnosis purposes. However, BODIPYs can be applied for treatment of diseases like cancer [16]. In photodynamic therapy (PDT), organic dyes are used as photosensitizers to generate singlet oxygen, a cytotoxic species able to destroy tumoral cells. Comparing other alternative treatments of cancer, PDT shows advantages since it is noninvasive, with low side effects, the treatment is light-driven and in situ, and, upon absence of light, the photosensitizer is inert. Due to the said chemical versatility of the dipyrroin core, BODIPY dyes are able to generate singlet oxygen via the promotion of the population of their triplet state, and ulterior energy transfer to the ambient triplet oxygen can be designed (**Figure 3C**). Different approaches have been tested to enhance the intersystem crossing probability of BODIPYs in the bibliography, such as grafting heavy atoms (halogens, metals) and promoting ICT processes (orthogonal dimers). Moreover, a suitable balance between singlet oxygen generation and fluorescence response by molecular structural factors allows designing photosensitizers with dual functionality, thus suitable for theragnosis, which means that they are able to generate singlet oxygen and treat, but retaining high enough fluorescence signal for detection by bioimaging [17].

2.4. Artificial antennae

Artificial antennae are bioinspired in the photosynthesis, trying to mimic the efficient light harvesting of solar energy in natural organisms during its conversion into chemical energy [18]. The key process is the excitation energy transfer (EET) which is mediated usually through a Förster long-range mechanism (Förster Resonance Energy Transfer, FRET) [19]. At the molecular level, this can be attempted by the combination of chromophores working at different but complementary spectral regions and able to undergo FRET (spectral overlap to enable the through space dipole–dipole coupling). Moreover, their mutual covalent linkage imposes short distance between energy donor and acceptor boosting the FRET efficiency and eventually promoting other EET mechanism which further contributes to the whole energy transfer. Taking into account that there are BODIPYs available along the whole visible region, the scientific community has been tempted to link them to each other through suitable spacers to customize energy transfer cassettes. These molecular antennae outstand by their broadband absorption, spanning the whole visible, but selective red emission from the last energy acceptor after transport of the light via successive and efficient energy transfer hops from the energy donors (**Figure 3D**). This kind of molecular design is being applied in dye lasers, biomedicine and photovoltaic devices, as explained hereafter in Section 2.5.

2.5. Photosensitizers in solar cells

Photovoltaic devices usually feature inorganic semiconductors, where an electron is promoted from the valence band to the semiconductor band upon irradiation, thus converting sunlight into electricity. In this regard, one of the main drawbacks is their low absorption of the solar spectrum, which is limited to the NIR region, and low efficiency. One way to circumvent this limitation is by means of organic dyes since their light absorption ability is much better. Thus, the role of these photosensitizers is to absorb light and afterward inject an electron into the conduction band of the conductor (dye-sensitized solar cells, **Figure 3E**) [20, 21]. To this aim dyes should have a push-pull character (chromophore decorated with electron donors and acceptors) to enable an ulterior electron transfer upon excitation. Moreover, the antennae described in Section 2.4 are ideal for these devices since they ensure an efficient light harvesting of the sunlight (both in efficiency owing to the high absorption coefficient of BODIPYs and in spectral interval since all the incoming light from the UV–Vis–NIR can be absorbed simultaneously) and, after choosing a suitable red-emitting BODIPY subunit able to promote electron transfer, activate the semiconductor with a better exploitation of the sunlight.

The aforementioned fields are the most tested ones with BODIPYs, but other areas of interest are tackled also successfully, such as materials science (self-assembly, or grafting the dye to nanoparticles, polymers, graphene, etc.) [22], electrochemistry (light-emitting diodes based on electroluminescence, photocatalyst and photochemical reactions overall) [23] or chirality (as optically active compounds able to absorb or emit selectively circularly polarized light of specific handedness) [24]. Even theoretical chemists have been attracted by the boom of BODIPYs, and many computational studies can be found in the bibliography to unravel their excited state dynamics [25].

Of course, BODIPYs have some drawbacks, mainly their low Stokes shift and poor water solubility. However, even those limitations can be easily overcome after suitable structural modifications. Indeed, BODIPYs endowed with high Stokes shift [26], and improved solubility [27] are now readily available to reduce the reabsorption/reemission effects at high optical densities and enable their solubility in the physiological media.

Therefore, BODIPYs can be described as an all-in-one scaffold where different functionalities can be added to the chromophore simultaneously and different non-interfering chromophoric positions, being the right choice for any application field or device demanding an organic dye.

This book aims to describe the state-of-art related to BODIPYs and provides an overview of their chemical versatility and tunable photophysical and electrochemical properties, and degradation mechanisms upon irradiation or external factors, to explore their performance as stable fluorescent sensors and biomarkers, or for electrochemical purposes. Costero et al. report the design of BODIPYs for chemosensing of anions, cations and neutral molecules in solution, gas phase and even in the solid state using nanoparticles. They also describe the ongoing mechanisms allowing the recognition of the target analyte. Related to this topic, Dokyoung et al. revisit the synthetic approaches to develop blue-emitting BODIPYs and their viability as fluorescent probes and sensors. They highlight the possibility of these fluorophores to label biomolecules (like proteins) or to detect metals, amino acids (like cysteine) or gases (like phosgene). Afterward, Heiden et al. report the electrochemical properties of BODIPY. They prove their ability to electrogenerate chemiluminescence and claim the key role of this chromophore in photochemistry and photocatalysis owing to their tunable redox activity. Finally, Yuriy et al. overview the degradation mechanisms and kinetics of BODIPYs in acid and basic media via spectroscopic techniques and computational simulations. They enlarge the study to dipyrinates and bis-dipyrinates, owing to their structural similarity with the dipyrin core of BODIPYs. Indeed, BODIPY is named in the literature as the “little sister” of porphyrins.

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