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Detail Synthetic Study of Infrared Fluorescent Dyes: Design, Synthesis and Chemical Properties of their Photodynamic Therapy Probes

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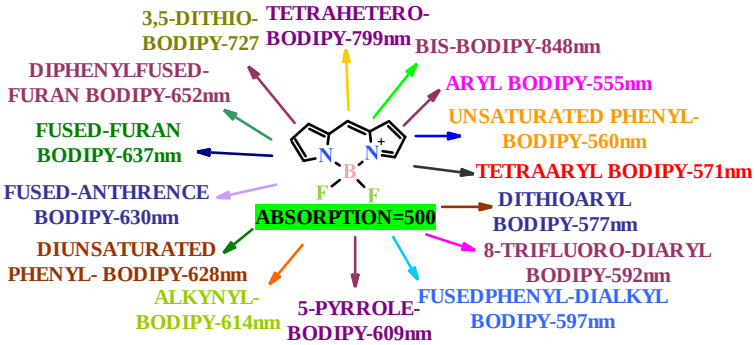
ABSTRACT

Dipyrromethene boron difluoride (BODIPY) derivatives can be used as effective photosensitizers (PS's) to eradicate a broad spectrum of microbes that threaten the global population health. Moreover, these compounds could be used in diagnostic or therapy, controlling the balance between the fluorescence emission and the photodynamic activity. There is still much work to be done in the search for ideal PS's with applications in photodynamic therapy (PDT). To effectively use near infrared region BODIPY dyes for labelling during biological analyses, or as biomarkers in biomedical applications such as imaging diagnosis, a hydrophilic character is usually required. It was found that the introduction of the strong electron-withdrawing group at the *meso* position in the BODIPY skeleton was responsible for the drastic bathochromic shift in the absorption spectrum. Several studies on the development of small molecule fluorescent probes have been performed with short wavelengths and with poor water solubility. There should be new investigations to obtain more information on the mechanisms of photodyna mic action relating to cell damage and experiments in vivo infection models. In order to understand the effect of the substituents, a predictive quantitative structure-activity relationship (QSAR) regression model, based on theoretical holistic molecular descriptors as developed. An even better fluorescent probe would combine the photostability of the BODIPY group with a chromophore that absorbs at longer wavelength that makes for better light penetration in cells and tissues. In this review, we will summarize ideas on different wavelengths and hydroelectric abilities through modifications of molecular structures of the biological probe molecule. BODIPY's materials and chemical modification methods for modulating the optical properties presented here could be versatile for developing efficient photo-responsive bio-related materials to control the biological activities and efficient quenchers on the biotechnological assays with labelled biomolecules.



ABBREVAIATION: BODIPY: 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene, PS: photosensitizers, PDT: photodynamic therapy, QSAR: quantitative structure-activity relationship, NIR: Near-Infrared, ROS: Reactive Oxygen Species, DNA: DeoxyriboNucleic Acid, CRC:, ACQ: aggregation-caused fluorescence quenching, TFA: Tri Fluoroacetic Acid, PET: Photo Electron Transfer, EDG: Electron Donating Groups, HOMO: Highest Occupied Molecular Orbital, LUMO: Lowest Unoccupied Molecular Orbital, BCOD: bicyclo[2.2.2]octadiene, AIE: aggregation-induced emission, TICT: twisted

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intramolecular charge transfer, TPA: Triphenylamine, DMF: *N*,*N*-dimethylformamide, PSMA: Prostate-specific membrane antigen, TBDP: Triple-BODIPY, FRET: Forster or fluorescence Resonance Energy Transfer, EGFR: Estimated Glomerular FiltrationRate, CuAAC: copper (I)-catalyzed alkyne-azide cycloaddition, EGDMA: ethylene glycol dimethacrylate, AIEE: aggregation-induced emission enhancement, BSA: Bovine Serum Albumin, DIBAL: Diisobutylaluminium hydride, GSH: Glutathione, FMM: Functional Molecular Moiety, TEM: Transmission Electron Microscopy.

1. Introduction

1.1 General Characteristics Fluorescence Molecules:

The dipyrromethene boron difluoride (BODIPY) core structure itself is electrically neutral, contributing to the relatively nonpolar nature of the molecule. The advantages of small organic fluorophores over fluorescent proteins are their smaller size, the ease of functionalization to tune the properties for specific experiments, and the possibility of creating any desired fluorescence colour. The ideal organic fluorophore should possess all the desirable chemical and physical characteristics, such as bright fluorescence [due to the combination of a high fluorescence quantum yield (U) with a large molar absorption coefficient (e)],[1] absorption (or fluorescence excitation)/fluorescence emission spectra in the visible or near-infrared (NIR) region, a large Stokes shift (Δv‾), robustness towards light and chemicals, good solubility (especially in water for biological applications), fluorescence lifetimes in the nanosecond range, easy tunability of its properties and a facile synthesis. Boron dipyrromethenes possess low dark (unirradiated) cytotoxicity [although iodinated boron dipyrromethenes may exhibit phototoxicity making them potential photosensitizers in the photodynamic therapy (PDT) of cancers] and excellent resistance to thermal oxidative degradation, to photobleaching, and to acids and bases. Despite the countless fluorescent organic molecules that have been discovered and the commercial availability of many useful and well-established fluorophores, none of the fluorescent dyes happens to meet all the above requirements concurrently.[2] Therefore, the search for the ideal fluorophore continues relentlessly and the development of new, valuable fluorescent molecules presents one of the main challenges in fluorescence research. Moreover, the applications of these far-red and NIR fluorescent dyes for *pH*, metal ion, redox/oxidation species sensing and bio-labelling/bio-imaging will be highlighted, and the sensing mechanisms will also be discussed successively. This review summarizes the attributes of BODIPY derivatives for applications as antimicrobial photosensitizing agents.[3]

1.2 Biological Properties Involved In Bodipy Derivatives:

4,4-difluoro-4-borata-3a-azonia-4a-aza-s-indacene (BODIPY) compounds display excellent photochemical and photophysical properties and mainly used as biological imaging agents, sensitizers for solar cells, optical materials, chemosensors and PDT agents. Most of the BODIPY compounds possess several properties of ideal photosensitizer agents such as good cellular uptake, high singlet oxygen quantum yields, high photostability, and low dark toxicity. In addition, PDT activity of BODIPY compounds can be increased with synthetic modifications.[4] For example, since the BODIPYs are lipophilic, the addition of hydrophilic groups to the core can increase their solubility and bioavailability for PDT applications.

The central carbon of BODIPY is denoted the *meso* position, α-positions are adjacent to the nitrogen atoms, while the others are *β*-positions, which are located in 8, 5-3 and 1-2- 6-7 according to IPUAC nomenclature, respectively.[5] Some of the most important properties of BODIPYs involve high absorption and fluorescence emission in the visible range, low generation of excited triplet state, photochemical stability, chemically robustness and good solubility in organic solvents.[6] These complexes are stable at physiological *pH*, which combined with a low toxicity make them excellent probes for use in biological systems.[5,7,8] Thus, BODIPYs have received substantial interest as fluorophores in bioimaging, biological labeling and fluorescence assays.[8] Also, BODIPYs have been proposed as light-harvesting antennas to improve the absorption of different chromophores.[9]

The versatility of the synthetic pathways to obtain BODIPYs allows manipulating different strategies to find an adequate relation between the structure and the desired spectroscopic and photophysical characteristics. Thus, BODIPY structures have been modified to reduce fluorescence and increase singlet-to-triplet intersystem crossing for applications[10] in photodynamic therapy (PDT). Spin-coupling to heavy atoms is a frequent modification employed to enhance triplet state formation by halogenation reactions. Therefore, the BODIPY fluorophore can be changed into a photosensitizer (PS) by attaching heavy atoms directly on the *s*-indacene ring. This effect produces a long-lived electronically excited triplet state able to produce efficiently reactive oxygen species[11] (ROS).

In the last years, BODIPYs have been proposed as PS with potential applications in killing microbial cells.[12] Moreover, the rigid and extended *π*-conjugation of the BODIPY structure make it a good candidate to be used for bactericidal application in deep tissues since red light can penetrate dipper.[13] Thus, a key factor to improve the efficacy of photo inactivation of microorganisms mediated by BODIPYs is the development of suitable molecular structures with appropriated photo physical and biological properties.[14] Therefore, this review deals with the evolution of these PS's with potential applications in photo killing of microorganisms.

DNA has a key role in vital processes such as mutagenesis, cell death and gene expression; therefore, it is one of the most important pharmacological targets of many anticancer agents. Investigating the interactions of compounds with DNA is crucial to understand their

mechanism of action. Topoisomerases are involved in processes such as replication and transcription of DNA.[15] In anticancer drug research, inhibition of these enzymes has become one of the most common approaches due to high expression of topoisomerases in cancer cells. In addition, the effectiveness of PDT is enhanced with topoisomerase inhibitory effects of photosensitizer agents[16] such as acriflavine and methotrexate.

BODIPY derivatives have been proposed in several potential biomedical applications.[17] BODIPYs absorb strongly in blue-green region with high fluorescence emission, properties that convert them in effective fluorophores in the field of biological labeling.[18] However, BODIPY structures can be conveniently modified by heavy atoms substitution to obtain photosensitizers with applications in photodynamic therapy. Also, external heavy atoms effect can be used to increase the photodynamic activity[19] of these compounds. In recent years, BODIPYs have been proposed as phototherapeutic agents for the photodynamic inactivation of microorganisms.[20] Therefore, BODIPY structures[21] need to be optimized to produce an efficient photocytotoxic activity.[22] In this way, amphiphilic cationic BODIPYs can selectively bind to microbial cells, inducing an effective[23] photo killing of pathogenic microbial cells (Figure 1).

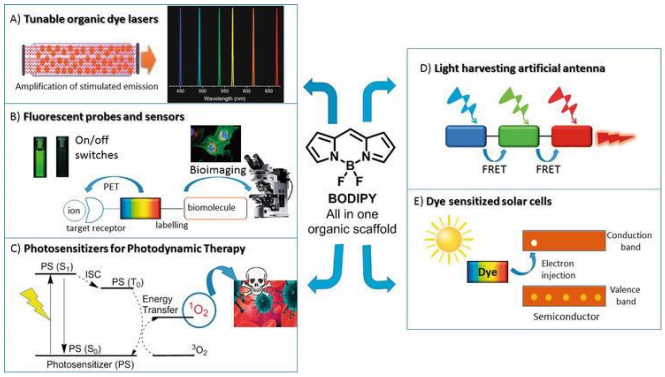


Figure 1. Main application fields of BODIPY.

1.3 Photodynamic Therapy about Bodipy Molecules:

Photodynamic therapy (PDT) is a well-established clinical modality for treating various types of cancers and non-cancerous diseases such as dermatological and cardiovascular illness and age-related macular degeneration[24] PDT utilizes the combination of a photosensitizing drug and oxygen in the presence of light thus induces the generation of reactive oxygen species to damage cancer cells.[25] Photofrin is a photosensitizer agent in clinical trials (Phase I, II and III) [26,27] for CRC but it has several undesirable properties including weak absorption in the red region,[11,28] long-term skin photosensitivity and low photostability.[29] Thus, there is need for the discovery of promising photosensitizer agents for the treatment of CRC with PDT.[30]

Most of the 4,4-difluoro-4-borata-3a-azonia-4a-aza-s-indacene[31] (BODIPY) dyes possess several properties of ideal photosensitizer agents,[32] such as good cellular uptake,[33] high flurosences quantum yields,[34] high photostability and low dark toxicity.[35]

In addition, PDT activity of BODIPY compounds can be increased with synthetic modifications.[36] For example, since the BODIPY's are lipophilic, the addition of hydrophilic groups to the core can increase their solubility and bioavailability[37] (Figure 2).

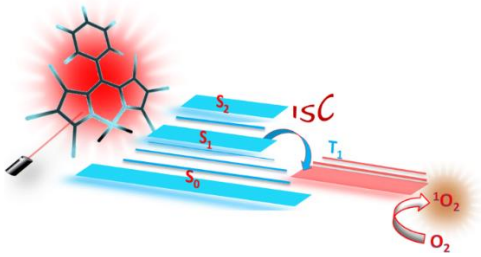


Figure 2. Photodynamic therapy mechanism involved in BODIPY.

In order to increase the efficiency of PDT,[38] photosensitizer agents need to be selective to cancer cells.[39] It is well-known that several cargo vehicles such as liposomes,[40] nanoparticles,[41] microspheres and albumin are used for accumulating photosensitizer agents in cancer cells and improve solubility, stability and bioavailability. Liposomes and nanoparticles play crucial role in the internalization with cell membranes.[42]

1.4. Basic Concepts Present In Bodipy's:

1.4.1. Key Points of Bodipy Molecules:

BODIPY derivatives are 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.[43]

There is a wide chart of commercially available fluorophores spanning the completely ultraviolet-visible region of the electromagnetic spectrum and even reaching the near infrared (NIR). The search for new organic fluorophores is an active task to find molecule with improved photophysical properties[44] and photostability.[45] These are key properties of or any practical application of the detection process (such as the aforementioned bioimaging) since they rule the sensitivity, efficiency, and the operative lifetime (Figure 3). Among them, definitely those chromophores known as borondipyrromethene (BODIPY) are in the forefront of photosensitizers.[46]

The most common uses of BODIPY dyes for photoactive media are in organic lasers, biomedicine[47] (probes and sensors for diagnosis by means of bioimaging and

photosentitizers in photodynamic therapy of cancer), light harvesters and photovoltaic devices[48] (photosensitizers of semiconductors).

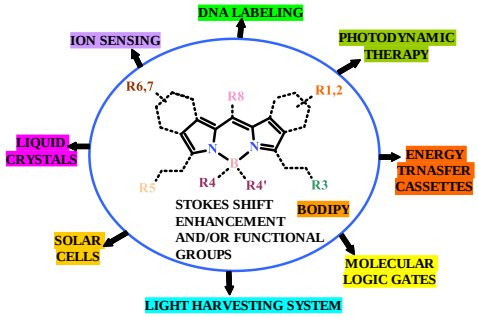


Figure 3. Overall view of BODIPY.

1.4.2. Outlines of Physical Properties of Bodipy's:

Among the multitude of highly fluorescent organic molecules currently available [xanthenes (fluoresceins and rhodamines), cyanines, squaraines, coumarins, acridines, naphthalenes, anthracenes, pyrenes, perylenes, phenanthrenes,[49] the boron complexes of dipyrromethenes (i.e., 4-bora-3a, 4a-diaza-s-indacenes, better known by their registered trademark BODIPY[50] have become an increasingly valuable class of fluorophores.[51] The extremely versatile boron dipyrromethenes (aka boron dipyrrins) usually strongly absorb light in the visible spectral range and are often brightly fluorescent.[52] Their absorption and emission fluroscent peaks tend to be relatively sharp (thus creating pure colors) and are generally separated by a small Stokes shift ($\Delta\nu$–), commonly a few hundred cm^{-1}).[53] The BODIPY core structure itself is electrically neutral, contributing to the relatively nonpolar nature of the molecule. Boron dipyrromethenes possess low dark (unirradiated) cytotoxicity[54] [although iodinated boron dipyrromethenes may exhibit phototoxicity making them potential photosensitizers in the photodynamic therapy (PDT) of cancers] and excellent resistance to thermal oxidative degradation, to photobleaching,[55] and to acids (Figure 4) and bases.[56] From an organic synthesis point of view, the appeal of these dyes can undoubtedly be attributed to their versatile, facile and efficient functionalization chemistry. This allows a practically unlimited structural modification and leads to sophisticated dyes with custom-made (electro) chemical, optical and (photo) physical properties.[57] These properties can be fine-tuned by attachment of suitable groups at the appropriate positions of the core structure.[58] The resultant zwitter ionic species possesses an overall neutral charge.

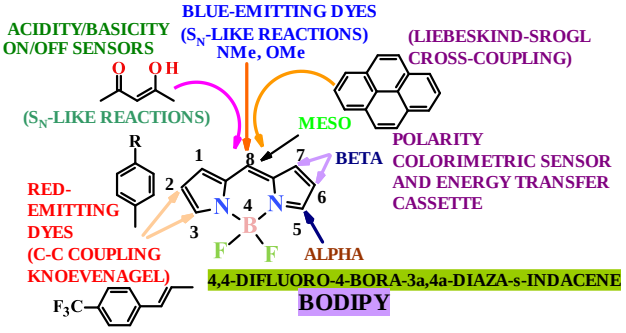


Figure 4. Basic molecular structure of the BODIPY dye.

1.4.3. Fundamental Explanation View of Biological Potent Molecule:

BODIPY dyes were first described by Treibs and Kreuzer in 1968 and have gained ever-growing success in the last few decades.[59] *eg.*, Synthesis of the corresponding dipyrromethene precursor has been reported,[60-65] but this compound is unstable and decomposes above -30 to -40 ℃.[66-70] (Figure 5).

In recent years, fundamental chemistry studies on the BODIPY family have facilitated several promising strategies to efficiently push the absorption and emission of the BODIPY dyes to the far-red and NIR regions.[71]

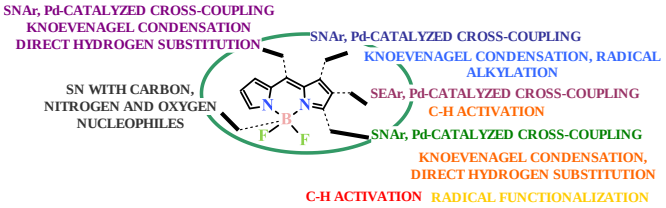


Figure 5. Overview of the different BODIPY post functionalization methods at their preferential site(s) of attack.

1.4.4. Strategies Toward Bodipy-Based Far-Red and NIR Dyes:

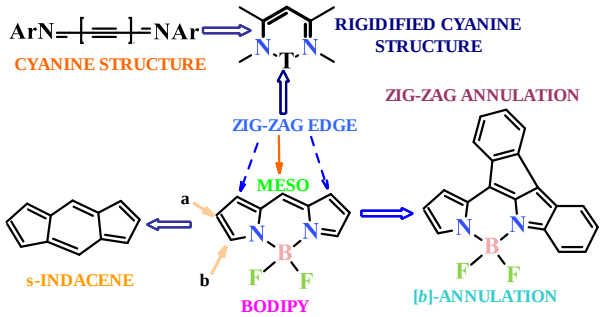
BODIPY is commonly described as a boradiaza-s-indacene by analogy with the all-carbon tricyclic *s*-indacene, and the numbering of substituents follows the rules set for *s*-indacene. This structure can also be considered as an example of "rigidified" mono-methine cyanine, which is generated by the complexation of a dipyrromethene unit to boron trifluoride.

The greatly restricted flexibility leads to unusually high fluorescence quantum yields from the dipyrromethene–boron framework. The π-electrons delocalize along the organic backbone and can be further extended by substitution or fusion of aromatic units to one or both pyrrole fragments. Obtaining dyes with fluorescence in the far-red or NIR spectral region requires the presence of an extended delocalization pathway.

Under these considerations, recent developments in BODIPY chemistry have allowed diverse modifications

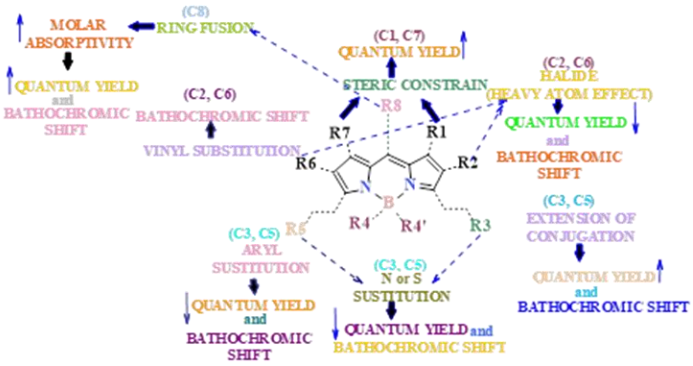
on the core structure to extend the π-conjugation and to generate redshifted BODIPY dyes. These strategies toward far-red and NIR BODIPYs can be summarized and grouped into the following three **(**Figure 6**)** categories: (1) functionalization at the α-, β- and mesosites of the BODIPY core to extend π-conjugation to generate a "push–pull" structure; (2) employment of π-extended pyrrole units instead of the simple pyrrole or fusion of aromatic units to extend the π-conjugation at the [α] bond, [β] bond and the "zig-zag" edge of the BODIPY; (3) replacement of the meso-carbon by an imine type nitrogen atom. We will summarize these synthetic strategies successively and highlight representative examples.

Figure 6. Structural considerations of the bodipy core and the schematicmodification strategies toward far-red and NIR bodipys.



The effects of ten major structural modification strategies[72] will be examined so that their relative effectiveness (Figure 7) can be assessed[73]: (i) aryl substitution, (ii) alkynyl substitution, (iii) styryl substitution, (iv) heteroatom substitution, (v) rigidization with fused-rings, (vi) fused-ring expansion of the p-system, (vii) *b*eta-aromatic ring fusion combined with a-substitution, (viii) the incorporation of an aza-nitrogen atom, (ix) formation of BODIPY dimers, and (x) core modification to form BODIPY analogues.

Figure 7. Structural physical property-position relationship of BODIPYs.



The concepts for the design of NIR fluorescent probes and for bio labelling based on these BODIPY derivatives were also intensively investigated in the last few years.[74]. This review will focus on far-red and NIR BODIPY derivatives nd intend to present a systematic survey of the progress of this type of dye by summarizing the design concept and basic synthetic chemistry.

In view of the importance of BODIPY[75], it is not surprising that many review articles, summarizing the vast amount of knowledge, have appeared. For a comprehensive coverage of the earlier literature, we refer to a number of highly cited texts.[76]

2. Classification Occurred In PDT Molecule of Bodipy:

2.1. Wavelength Importance for Biological Activities in Bodipy Derivatives:

Over the decades, fluorescence imaging techniques have proved to be powerful tools for visualizing cell biology at many levels and for revealing spatiotemporal details about cellular dynamics.[77] They have paved the way for the development of various fluorescent probes, including fluorescent proteins, nanocrystals (quantum dots), and small organic fluorescent dyes, to provide highly sensitive, minimally invasive, and safe detection of cells and tissues.[78] However, such fluorescent systems often suffer from several short comings which impede their potential application as biological probes. In particular, organic dyes commonly suffer from aggregation-caused fluorescence quenching (ACQ) originating from the formation of non-emissive excimers or energy transfer to quenching sites. To avoid the undesirable quenching effects, bulky protective groups have frequently been introduced to the periphery of the fluorescent core. By this approach, high fluorescence efficiencies can be retained in concentrated solutions, because the sterically bulky protective substituents can prevent intermolecular interactions and unfavourable aggregation. Long wavelength light is preferred for living subjects because it causes less photo damage to cells, and penetrates tissues better, while the higher wavelength light is absorbed by the tissues and is converted to heat energy. The bio distribution and cellular uptake of the PS depends on the balance between its hydrophilicity and lipophilicity, as too high lipophilicity would hamper their transport through blood vessel, while a high hydrophilicity would impede its cell membrane penetration. Based up on the above importance of about the wavelengths on biological improving activities of the BODIPY structure derivatives, here we are inserted the chemical sketch of BODIPY molecules with their corresponding wavelengths.

2.2. *α, β,* and Meso-Substituted Bodipy Molecules with Wavelengths:

2.2.1. Aryl-Substituted Bodipy's:

The introduction of aryl substituents has proven to be an effective strategy for achieving a red shift of the main spectral bands.[79] Compared to compound 1, the

absorption of aryl substituented derivatives 2 -6 are shifted to longer wavelengths[78,80] (λ_{max}=544-584nm). In addition, the extended aromatic substituents[81] of 5 and 6 showed red-shifted absorption with maxima at 573 nm and 597 nm, respectively[82,83] (Figure 8, 9).

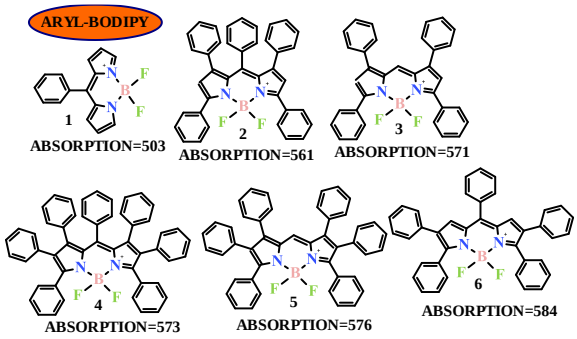


Figure 8. Chemical structure aryl-substituted BODIPYS.

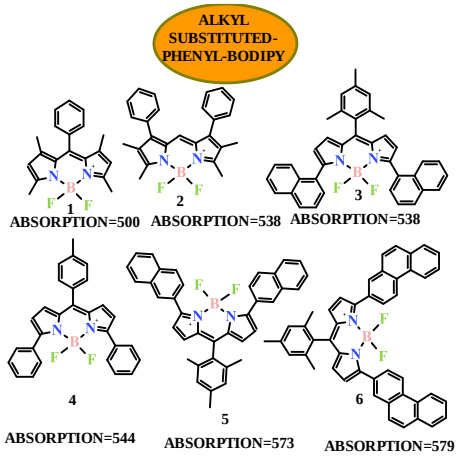


Figure 9. Chemical structure alkyl-phenyl-linked BODIPY's.

2.2.2. Alkenyl and Alkynyl Substituted Bodipys and Related Structures:

2.2.2.1 Alkynyl-Substituted Bodipy's:

Significant red shifts of the main spectral bands can also be obtained by introducing peripheral alkynyl substituents.[84] The 3,5-substituted BODIPY exhibited higher absorption coefficient and fluorescence quantum yield, sharp fluorescence peak,[85] and smaller Stokes shift, compared to the 2,6-substituted BODIPY.[86] These findings revealed that the properties of BODIPY dyes can be finely tuned not only by extended (Figure 10) conjugation but also by means of the position of modification.

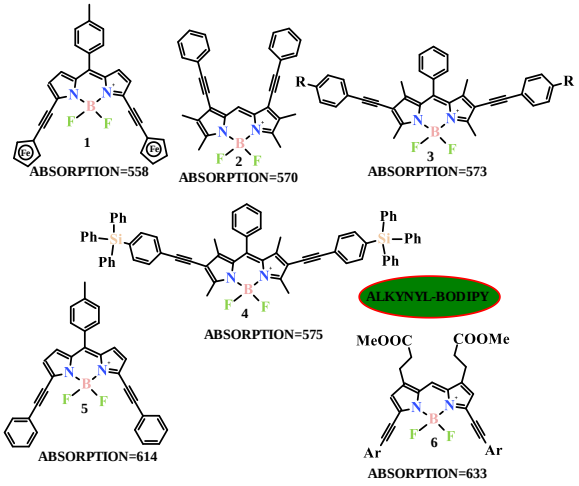


Figure 10. Chemical structure alkynyl-substitution of BODIPY's.

2.2.2.2. Styryl-Linked Bodipy's:

Styryl substituents have proven to be a particularly useful strategy for forming red/NIR region BODIPY dyes. The properties of mono-, di-, multi-*p*-, and meso-*p*-styryl and meso-vinyl substituted BODIPYs will be examined in depth, so that their properties can be compared.[87]

When two styryl substituents are introduced at the 3,5-positions to form Diphenyl-Styryl BODIPY, a narrow and intense absorption band is observed with a maximum at 629 nm.[88] The substitution with electron-donating dimethylamino groups at the para-positions of the phenyl rings of the styryl substituents to form Diphenyl-Styryl BODIPY shifts the emission band to the NIR region.[89] The use of this dye for probe applications has been investigated. *pH*-dependent absorption and fluorescence changes have been observed at the blue end of the visible region due to the presence of two different (Figure 11) protonation states.[90] The fluorescence emission maximum of styryl BODIPY lies at 700 nm in polar solvents such as acetonitrile, due to a CT band associated with the dimethylamino group as the electron donor and the BODIPY core as the electron acceptor.

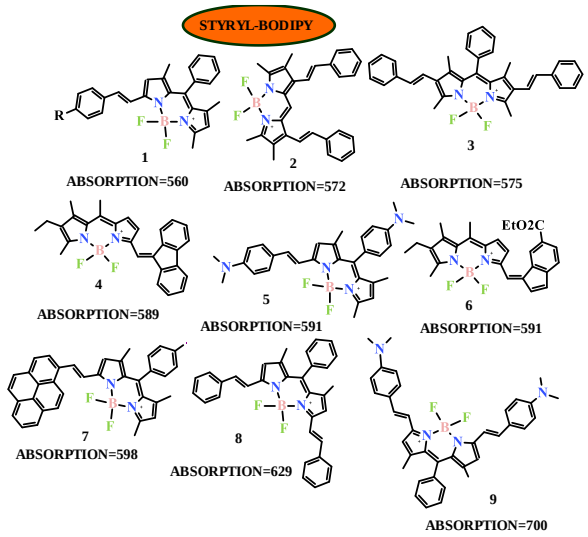


Figure 11. Chemical structure styryl-substitution of BODIPY's.

2.2.3. Halophenyl-Unsaturated Bodipy's:

It is worth noting that large Stokes shifts and low FF values are observed for 2,6-distyryl substituted dyes.[91] This is probably related to greater conformational flexibility of the molecular geometry in the excited state, which increases the rate of non radiative decay. Un-substituted BODIPY. The iodine atom at the para-position of the meso-phenyl group of 8-iodophenyl-unsaturated BODIPY appears to have almost no effect on the photophysical properties, since the photophysical values reported are almost the same as those of without halo substituted BODIPY.[90,92] The optical spectra of the bis anthracene derivative 8-iodophenyl-unsaturated

BODIPY contain broad and featureless bands and this dye has a low FF value. The two fluorophores of 8-iodophenyl-unsaturated BODIPY remain in electronic isolation but display fast intramolecular energy transfer.[92] This differs from what has been reported for BODIPY–anthracene energy-transfer cassettes with linking alkynyl moieties.[92] Marked red-shifts are observed for the spectral bands of 8-iodophenyl-unsaturated anthraces BODIPY due to the extension of the *pi*-conjugation system. The higher-energy absorption bands at ca. 430 nm are probably associated primarily with the pyrene moiety. The use of **8** this dye for probe applications (Figure 12) has been investigated. *pH*-dependent absorption and fluorescence changes have been observed at the blue end of the visible region due to the presence of two different protonation states.[93]

The preparation of the tetrastyrylsubstituted BODIPY[94] with four methoxy substituents at the para positions enables the synthesis of dyes with different substituents, such as iodophenyl-tetrastyrylsubstituted BODIPY.[95] These highly colored dyes display outstanding optical properties with the absorption maxima shifting to 700 nm for iodophenyl-tetrastyrylsubstituted BODIPY in dioxane, which was selected to limit aggregation effects and the rate of photodegradation.[96]

Figure 12. Chemical structure halo-styryl-substituted BODIPY's.

It is worth noting that large Stokes shifts and low FF values are observed for 2,6-distyryl substituted dyes.[91] This is probably related to greater conformational flexibility of the molecular geometry in the excited state, which increases the rate of non radiative decay. Un-substituted BODIPY. The iodine atom at the para-position of the meso-phenyl group of 8-iodophenyl-unsaturated BODIPY appears to have almost no effect on the photophysical properties, since the photophysical values reported are almost the same as those of without halo substituted BODIPY.[90,92] The optical spectra of the bis anthracene derivative 8-iodophenyl-unsaturated BODIPY contain broad and featureless bands and this dye has a low FF value. The two fluorophores of 8-iodophenyl-unsaturated BODIPY remain in electronic isolation but display fast intramolecular energy transfer.[92] This differs from what has been reported for BODIPY–anthracene energy-transfer cassettes with linking alkynyl moieties.[92] Marked red-shifts are observed for the spectral bands of 8-iodophenyl-unsaturated anthraces BODIPY due to the extension of the *pi*-conjugation system. The higher-energy absorption bands at ca. 430 nm are probably associated primarily with the pyrene moiety. The use of **8** this dye for probe applications (Figure 12) has been investigated. *pH*-dependent absorption and fluorescence changes have been observed at the blue end of the visible region due to the presence of two different protonation states.[93]

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2.2.4. Hetero-Linked Bodipy's:

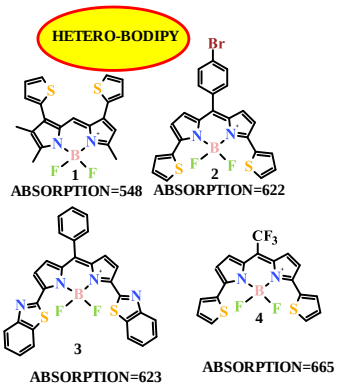


Figure 13. Chemical structure hetero-linked BODIPY'S

BODIPY is to introduce aromatic units at the 3,5-positions (*α*-sites). Direct attachment of phenyl substituents at these two positions can somehow extend the conjugation system, but the bathochromic shift is limited.[97] Heterocyclic aromatic units such as pyrrole (2) and thiophene (3) at the 3,5- positions could induce more significant spectral red shifts; for example, the 3,5-dithienyl BODIPY (3) exhibited a red shift of ~60 nm in absorption and emission compared to the 3,5-diphenyl analogue.[98] Moreover, increasing the number of thiophene rings in the substituents led to a progressive red shift in the absorption/ emission spectrum.[99] Several

unsymmetrical 3,5-dioligothienyl BODIPY dyes (Figure 13) have been synthesized by attaching the additional thiophene units through palladium catalyzed cross-coupling reactions, with the most progressive one substituted thiophene exhibiting an absorption maximum at 548 nm and an emission maximum at 665 nm.

2.2.5. Hetero-Unsaturated-Substitution of Bodipy's:

The introduction of ferrocene moieties to form hetero- unsaturated-BODIPY, results in a large red shift in main absorption band (Figure 14). While the compound is not emissive, since there is substantial charge transfer from electron-rich ferrocene moiety to the BODIPY core.[100] Similarly, no fluorescence is observed for mesoferrocene substituted BODIPY'S.[101] The α-substituted structures of 3,5-ester-unsaturated BODIPY and 3,5-ester-diunsaturated BODIPY[102] result in spectra with typical BODIPY characteristics, such as narrow absorption bands with large molar extinction coefficients.[103] The emission maximum of 3,5-ester-diunsaturated BODIPY is shifted to 671 nm with a relatively high FF value. In the case of β-substituted BODIPY dyes 2,6-ester-unsaturated BODIPY and 2,6-ester-diunsaturated BODIPY, the main absorption and emission bands also exhibit substantial red-shifts, but the bandwidths become broader and there is a decrease in the molar extinction coefficients properties that are not as favorable for many applications as those of the corresponding a-substituted BODIPYs. When compared to the spectra of dyes substituted at the 3,5-positions, the absorption band of the 2,6-substituted (2,6-ester-unsaturated BODIPY) dye are blue-shifted and the emission bands are red-shifted. This is related to the larger Stokes shifts that are observed for 2,6-substituted BODIPY'S.[103]

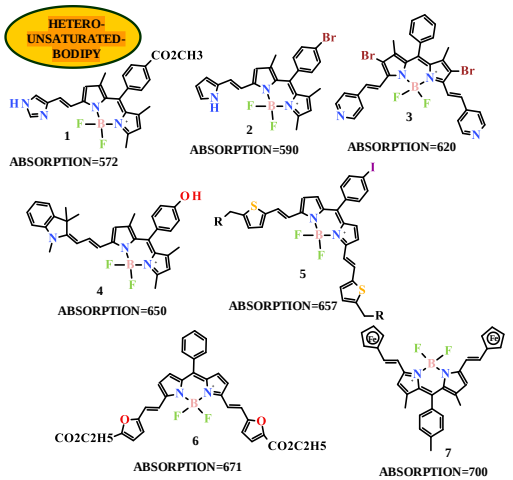


Figure 14. Chemical structure hetero-unsaturation-substituted BODIPY'S.

2.2.6. Halo Substitution of Unsaturated- Bodipy's:

The substitution with electron-donating dimethylamino groups at the para-positions of the phenyl rings of the styryl substituents to form dimethyl amino BODIPY shifts the emission band to the NIR region.[102,104] The use of this dye for probe applications has been investigated. *pH*-dependent absorption and fluorescence changes have been observed at the blue end of the visible region due to the presence of two different protonation states.[104] The main absorption band of pyridyl-substituted dye 3,5-pyrido-BODIPY lies at 620 nm and is further red-shifted upon addition of TFA due to a decrease in the electron-withdrawing properties of the pyridyl groups.[104] Only moderate bathochromic shifts (Figure 15) are observed in the spectra of 2,6-diphenyl BODIPY and 1,7-diphenyl BODIPY, the 2,6- and 1,7-distyrylsubstituted BODIPY analogues of without halo substituted BODIPY.[105]

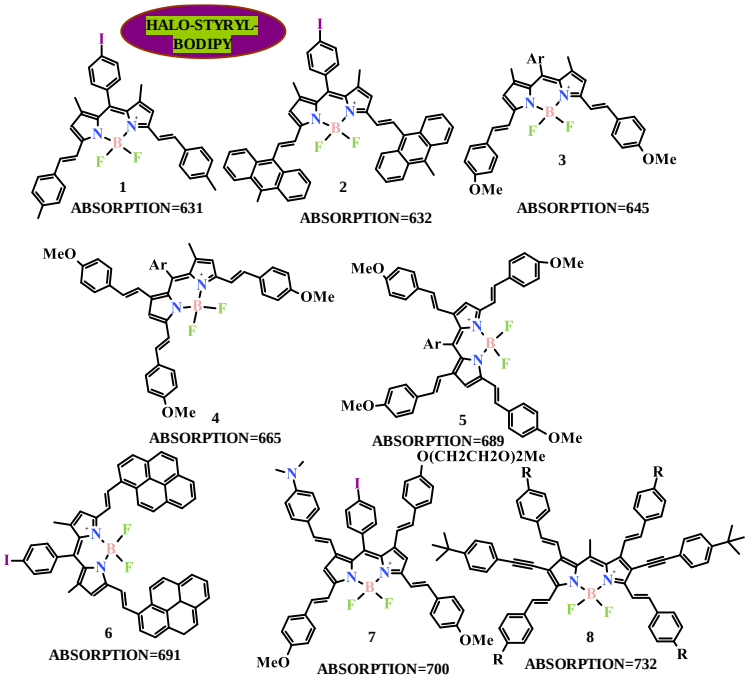


Figure 15. Chemical structure halo-styryl-substituted BODIPY's

It is worth noting that large Stokes shifts and low FF values are observed for 2,6-distyryl substituted dyes. This is probably related to greater conformational flexibility of the molecular geometry in the excited state, which increases the rate of nonradiative decay. The iodine atom at the para-position of the meso-phenyl group of 8-iodophenyl-unsaturated BODIPY appears to have almost no effect on the photophysical properties, since the photophysical values reported are almost the same as those of without halo substituted BODIPY.[106] The optical spectra of the bisanthracene derivative 8-iodophenyl-unsaturated BODIPY contain broad and featureless bands and this dye has a low FF value. The two fluorophores of 8-iodophenyl-unsaturated BODIPY remain in electronic isolation but display fast intramolecular energy transfer.[104] This differs from what has been reported for BODIPY–anthracene energy-transfer cassettes with linking alkynyl moieties.[107] Marked red-shifts are observed for the spectral bands of 8-iodophenyl-unsaturated anthraces BODIPY due to the

extension of the p-conjugation system. The higher-energy absorption bands at ca. 430 nm are probably associated primarily with the pyrene moiety.[108]

2.2.7. Halo Linked Aryl Substitution of Bodipy's:

Although the differing substitution patterns on the pyrrole rings and the electron withdrawing properties of the para-iodo group on the meso-substituent make direct comparison with the classic BODIPY, it is noteworthy that the para-electron-donating group of 3,5-para-methoxyphenyl BODIPY results in an even larger red shift.[109] The introduction of ortho-methoxyphenyl rings onto the BODIPY core at the 3,5-positions to form 3,5-orthomethoxy phenyl-BODIPY results in a decrease in the molar extinction coefficient and FF value, and shortens the wavelengths of the maxima of the main absorption and emission bands.[110] The incorporation of fused-ring-expanded aromatic substituents to form 2,6-*n*-propyl-BODIPY leads to a red-shift of the absorption and emission maxima and an increase in the FF values.[109] The incorporation of electron-donating -OMe groups into the structure of hepta methoxyphenyl-BODIPY results in only small bathochromic shifts. This indicates that there is only a weak interaction between the peripheral phenyl groups and the indacene plane. X-ray structures revealed that the molecules (Figure 16) adopt distorted[112] and ''propeller-like'' conformations having bright fluorescence. The distorted conformations probably inhibit exaction-coupling effects associated with intermolecular aggregation.[113]

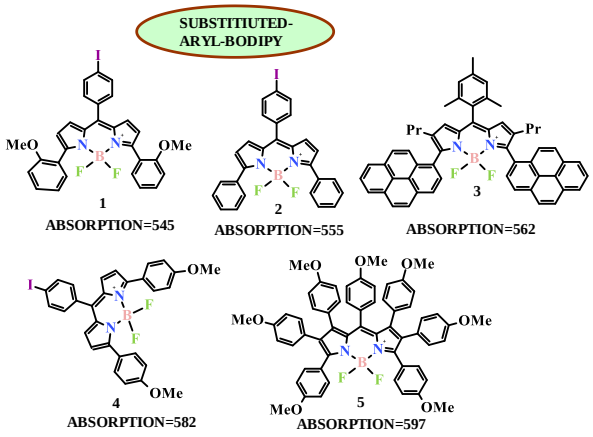


Figure 16. Chemical structure halo-aryl-linked BODIPY's

2.2.8. Alkyl Unsaturated Bodipy's:

The *ALPHA*-substituted structures of mono-unsaturated BODIPY and di-unsaturated BODIPY result in spectra with typical BODIPY characteristics, such as narrow absorption bands with large molar extinction coefficients.[114] The emission maximum of di-unsaturated BODIPY is shifted to 651 nm with a relatively high FF value. In the case of *beta*-substituted BODIPY dyes mono-unsaturated ethyl ester BODIPY and di-unsaturated methyl ester BODIPY, the main absorption and emission bands also exhibit substantial red-shifts, but the bandwidths become broader and there is a decrease in the molar extinction coefficients has a FF value of only 0.054 and thus has properties that are not as favorable for many applications as those of the corresponding *ALPHA*-substituted BODIPYs. When compared to the spectra of dyes substituted at the 3,5-positions, the absorption band of the 2,6-substituted di-unsaturated methylester BODIPY dye are blue-shifted (Figure 17) and the emission bands are red-shifted. This is related to the larger Stokes shifts that are observed for 2,6-substituted BODIPY's.[114]

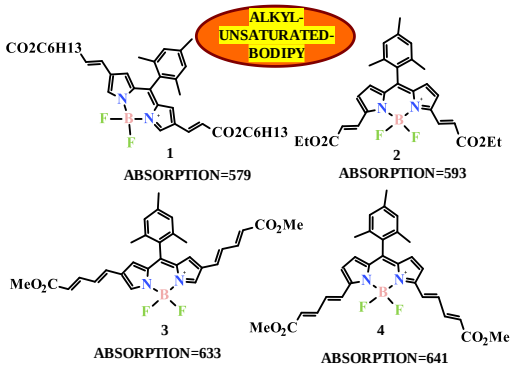


Figure 17. Chemical structure alkyl-unsaturated-substituted BODIPY's

2.2.9. 2,6-Aldehydo-Substituted-Trimethoxy-Styryl Bodipy's:

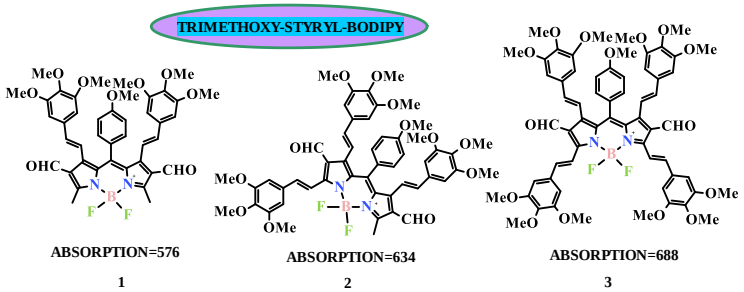


Figure 18. Chemical structure trimethoxy-styryl-substituted BODIPYs.

The parent BODIPY unit has a major absorption peak (S_0-S_1 transition) near 500 nm; however, incorporation of fused aromatic rings and/or aryl substituents.[115] All of these approaches may be useful in certain applications, nevertheless mono- and distyryl modifications seem to offer a greater degree of versatility as (Figure 18) judged by the recent interest,[116] apart from our group.[117] This clearly stems from the following facts: (i) Knoevenagel reaction of the 3- and 5-methyls is in most cases high yielding;[118] (ii) the reaction conditions tolerate the use of a variety of aldehydes with different stereo-electronic characteristics; (iii) strong charge donor

substituents are likely to yield switchable fluorescent molecules with internal charge transfer characteristics useful as chemosensors and molecular logic gates.[119]

2.2.10. 8-Position Unsaturated-Hetero Linked Bodipy's:

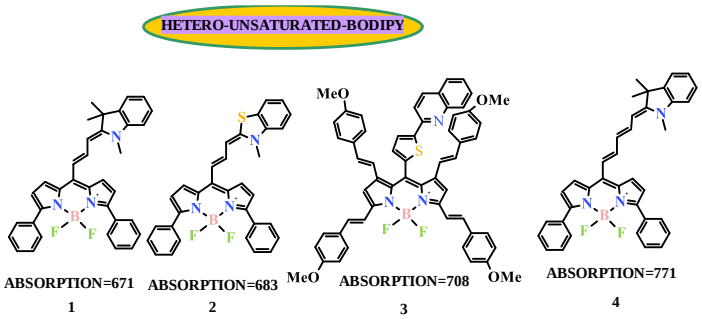


Figure 19. Chemical structure hetero-unsaturation-substituted BODIPYs.

The meso- (thiophen-2-yl) quinoline appended BODIPY has an absorption maximum at 708 nm that does not shift when the solvent polarity is increased.[120] *Meso*-vinylic BODIPYs are weakly fluorescent, particularly in polar solvents, probably due to conformational flexibility associated with the meso-vinyl groups. An extension of the polymethine chain to form (Figure 19) di-unsaturated-Thiazolo-BODIPY leads to a further 100 nm red-shift of the absorption maximum.[121] Interestingly, the main absorption bands of polymethinesubstituted BODIPYs are no longer observed upon protonation and a new peak gains intensity at shorter wavelength. No fluorescence is observed for these protonated species.[121]

2.2.11. Meso-Unsaturated-Styryl Substitution of Bodipy's:

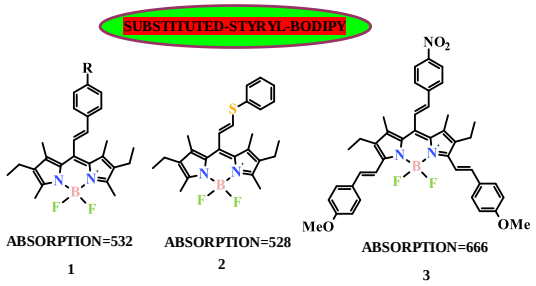


Figure 20. Chemical structure substitution-styryl-substituted BODIPYs.

The fluorescence of the probe is largely quenched in polar solvents due to the PET process. After protonation, a very large fluorescence enhancement (2000-fold) was elicited owing to the inhibition of the PET process.[122] In contrast with what is observed upon substitution at the 3,5-positions, there is almost no shift observed in the main absorption band of meso-styryl dyes and the vinylic thioether.[123] Theoretical calculations have revealed that when substituted phenyl linked (Figure 20) unsaturated BODIPY is further reacted with an aldehyde to form nitro substituted phenyl unsaturated BODIPY, the HOMO and LUMO are mostly localized on the BODIPY and meso-styryl moieties, respectively, in a manner that could facilitate the injection of an electron into the conduction band of TiO_2 in solar cell applications.[124]

2.2.12. 3,5-Position Hetero Atom Linked Phenyl Bodipy's:

The effect of substituting different chalcogen containing groups (O, S, Se, Te), which acted as electron donating groups (EDGs), due to the lone pair on the chalcogen, on sites 3 and 5 (a symmetric site pattern) of the BODIPY core.[125] They found that a red-shift occurred as they moved down the chalcogen group of the periodic table if the same EDGs are added to both sites (Figure 21). This could be due to both the electron donating nature of the substituents or an extension of the π-system. Fron *et al.*, suggested that the red-shift was due to the electronegativity of the chalcogen atom.[123] Others have seen similar trends in other chalcogen substituted fluorophores.[126-128]

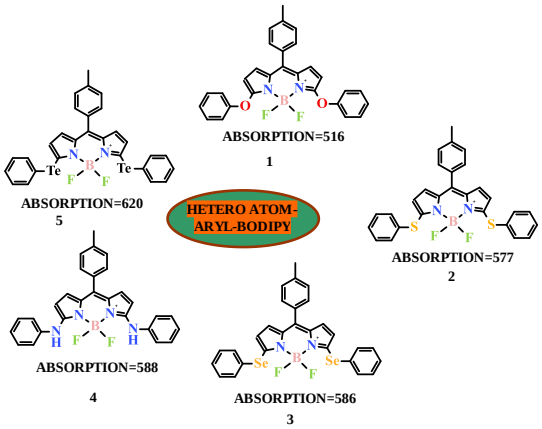


Figure 21. Chemical structure heteroatom-aryl-substituted BODIPY's.

2.2.13. Fused Ring Bodipy's:

Several strategies have been adopted to modify the structure of the BODIPY core to design NIR dyes. Among these, the most efficient approach to expand the π-conjugation of the BODIPY core is *via* fusion of aromatic rings. So far, many novel BODIPY skeletons fused to aromatic hydrocarbons and heterocycles at the *beta*- bond have been reported. This review comprehensively describes the recent advances regarding the development of aromatic [*beta*]-fused BODIPY dyes with the focus on the design and synthesis, the relationships between their photophysical/spectroscopic properties and molecular structures, and the potential applications in bioassays and optoelectronic devices. A molecular approach, a NIR BODIPY dye pyran fused BODIPY bearing 3, 4, 4a-trihydroxanthene moieties was synthesized.[129] The combined extension of conjugation

and restricted bond rotation resulted in a pronounced red shift of the absorption/emission spectra to the NIR region. The new pyran fused BODIPY was stable, non-cytotoxic, and suitable for labelling living cells (Figure 22) for the imaging assay. The meso-hydroxyquinoline fragment of dye can be used as a NIR region chemosensor for metal ions.[130]

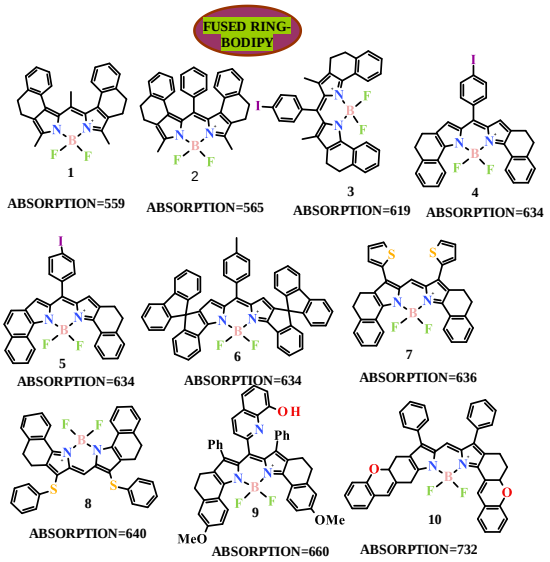


Figure 22. Chemical structure fused ring substituted BODIPY's.

2.2.14. Fused Furan Ring Bodipy's:

The synthesis and photophysicalproperties of new NIR BODIPY dyes by making use of theheavy atom effect. The dyes were designed from the BODIPY fluorophore, KFL-4, due to its high molar extinction coefficient (Figure 23) and long wavelength absorption maximum at 723 nm.[131] To gain insight into the heavy atom effect, attached bromine atoms to the modified BODIPY core using a fast and efficient brominating condition employing bromine and trace iodine in an aromatic electrophilic substitution reaction.[132]

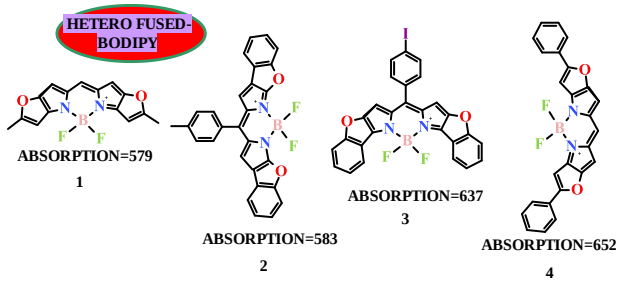


Figure 23. Chemical structure hetero atom ring fused - BODIPYs.

2.2.15. Phenyl Linked-Fused Furan Ring Bodipy's:

A new series of analogues named Keio Fluors[131,133] were prepared with structures similar to those of classic BODIPYs but with furan ring moieties fused at the 2,6- and 3,5-positions. There is a further red-shift of *ca.*, 20 nm due to the introduction of electron-donating methoxysubstituents at the para or ortho-positions to form phenyl-furan fused BODIPY. According to previous reports, the presence of (Figure 24) ortho-methoxyphenyl rings at the 3,5-positions of the BODIPY core tends to have a negative effect on the optical properties, since there is a shortening of the wavelength of the spectral bands, and a decrease in the molar extinction coefficients and FF values. However, the ortho-methoxyphenyl-substituted dye exhibits similar characteristics to other Keio Fluors type dyes, since there is no scope for hindered rotation of the phenyl ring. This means that fine-tuning of the absorption and emission band maxima can be achieved for this series of dyes by attaching substituents at various positions on the phenyl ring.[134]

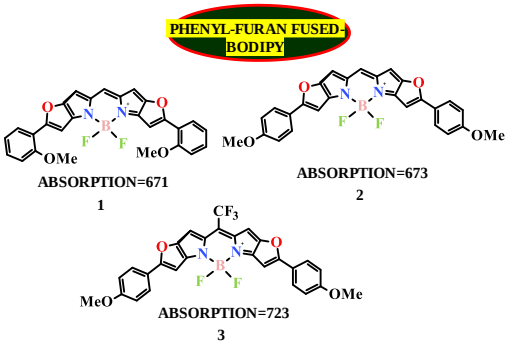


Figure 24. Chemical structure hetero ring fused – BODIPYs

2.2.16. Thiophene Fused-8-Position Substituted-Bodipy's:

BODIPY regulating energy transfer involving the BODIPYs, they can monitor the biorganic- reactions with the changes of emission intensity from the probe with high sensitivity and specificity. Moreover, hetero ring-fused BODIPYs have been synthesized.[135] In particular, thiophene-fused BODIPY's modification with sulfur or iodine elements for receiving the heavy atom effect, the intersystem crossing after photo-excitation to these BODIPYs can be readily induced.[136] Accordingly, the triplet-excited states of the BODIPY's efficiently generate the singlet oxygen via a sensitizing reaction (Figure 25). The superior ability of light absorbing contributes to enhancing the sensitizing efficiency. It should be mentioned that these BODIPY's have sharp spectra of light-absorption and emission from the red-light to the near-infrared region. Based on these optical properties of thiophene-fused BODIPY's.[137]

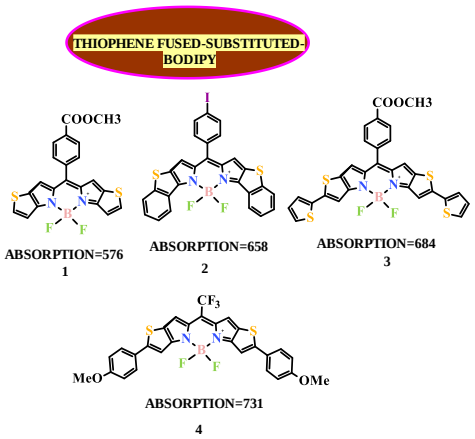


Figure 25. Chemical structure thiophene-fused BODIPY's.

2.2.17. Core Modified-Bodipy:

The absorption bands of *O*-chelated BODIPYs exhibit a significant red shift of ca. 65–80 nm. Narrow emission bands are observed and there is an increase[138] in the FF values relative to the corresponding precursor dye. This is probably due to a decrease in the dihedral angle between the phenyl rings and the BODIPY core (Figure 26). This can be attributed to the BCOD rings blocking the quenching associated with *pi–pi* stacking of the BODIPY core,[139] the absence of rotation of a meso-phenyl group and the *B–O* chelation of the phenyl rings at the 3,5-positions.[140]

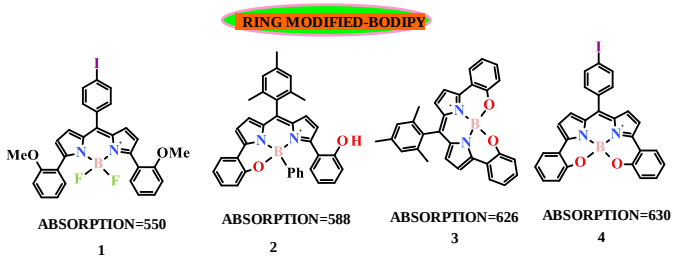


Figure 26. Chemical structure core modified-substituted BODIPYs.

2.2.18. Aryl Fused-Bodipy's:

The free rotation of the aryl substituent at the 3,5-position limits the red shift of the main fluorescent band.[141] Various strategies have been employed to achieve greater degree of uniformity between the *p*-systems of aryl substituents by forming a rigid fused ring system with sp^3 hybridized carbon. In the fused ring BODIPY system, the absorption maximum has a significant red shift. Intense demand for efficient photovaltaic material,[142] organic solar cells and biological applications motivated researchers to synthesize NIR absorbing dyes. Among the strategies to transfer the absorption of BODIPYs to longer wavelength, it is particularly promising to carry out *p*-extension by fusing an aromatic unit (Figure 27) with a *α*- or *β*-bond of a pyrrole[143] polymer. These probes all exhibits marked red shift in the absorption and emission and high (photo) chemical stability due to *pi-pi* accumulation.[144]

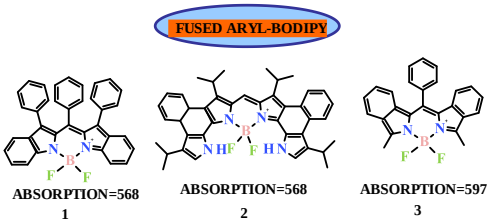


Figure 27. Chemical structure fused aryl substituted BODIPYs.

2.2.19. Fused-Bodipy's:

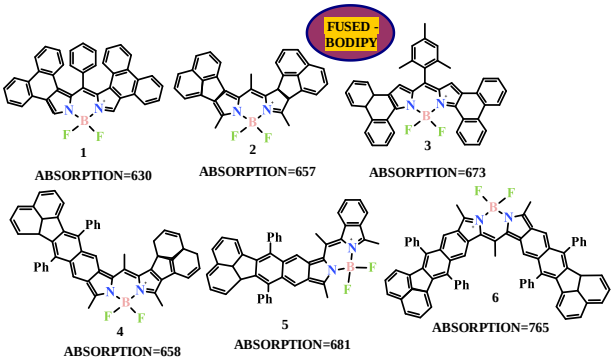


Figure 28. Chemical structure fused BODIPY's.

There is a particularly large red-shift of the spectral bands when acenaphtho groups are fused at the *b*-carbons of the pyrrole moieties to form acenaphtho BODIPY.[145] The phenanthro-fused BODIPY has an intense absorption band at 630 nm with a high molar absorption coefficient and a FF value that is near unity.[146] Trialkyl phenanthro-fused BODIPY has a more intense and red-shifted absorption band (673 nm) than that of phenanthro-fused BODIPY. The emission peaks for dyes diphenyl-anthraces BODIPY and anthraces-phenyl-anthraces BODIPY, which contain a single fluorantho [8,9-*f*]isoindole moiety and either a benzo or acenaphtho fused ring (Figure 28), are observed at similar wavelengths, while the absorption bands lie at 681 and 658 nm, respectively.[147] When two fluorantho [8,9-*f*]-isoindolemoieties are incorporated to form dis phenyl-anthraces BODIPY themain spectral bands lie in the NIR region beyond 750 nm.

2.2.20. Aromatic Fused-Substituted-Bodipy's:

The results in a marked expansion of the *pi*-conjugation system and a shift of the absorption and emission bands to the far-red of the visible region or the NIR region.[148] In contrast to classic BODIPYs, anthracene-BODIPY exhibits a broad envelope of absorption intensity between 500 and 930 nm with maxima at 658, 784 and 867 nm.[149] When an anthracene moiety is fused to the *beta*-positions (Figure 29) of the BODIPY core, there is a remarkable bathochromic shift

of the absorption and emission (924 nm) bands.[150] In a similar manner, the *β*-fused structure of BODIPY PYRROLE linked-anthracene-BODIPY results in a red-shift of the main absorption band to 670 nm.[151]

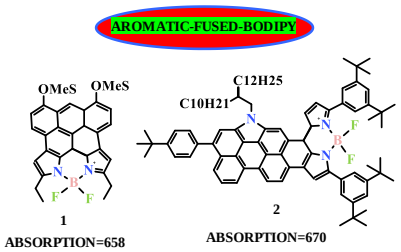


Figure 29. Chemical structure aromatic fused - substituted BODIPY's.

2.2.21. Fused Porphyrin-Bodipy's:

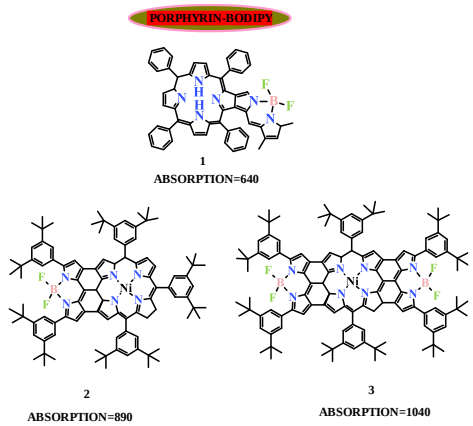


Figure 30. Chemical structure porphyrin- BODIPYs.

Perylene-fused BODIPY dyes exhibit absorption between 600 and 800 nm, as we have reported previously.[152] The absorption spectrum of *β*-Pyrrole linked BODIPY, which has a BODIPY moiety fused at the *β*-pyrrole carbons of a tetraphenyl porphyrin ring, contains four moderately intense bands in the 300– 750 nm region, 640 nm in CH_2Cl_2. porphyrin-fused BODIPY dye is supposed to display enhanced NIR absorption, due to the larger conjugation in the latter.[153] The electron-withdrawing ability of the boron atom can lower the HOMO energy level of the fused dye. In view, of studies have pointed out that a fused BODIPY unit is the most effective building block are reported. So far, for stabilization of the highly electron-rich, *N*-annulated perylene.[150] As a result, the porphyrin-fused BODIPY compound (Figure 30) is expected to be a stable NIR dye in spite of its narrow band gap. Generally speaking, the BODIPY core has relatively high reactivity and can undergo electrophilic substitution.[154] This high reactivity is beneficial to ring-closure reactions, so that fusion of double or even multiple BODIPY units into the porphyrin backbone becomes possible. It also shows the desired photophysical properties and photostability.[155]

2.2.22. Unsaturated-Subsitution-Bodipy's:

The main absorption and emission bands of the benzofused and styryl-substituted BODIPY dye are shifted into the NIR region.[156] The incorporation of a –NMe_2 group onto the styryl group provides a sensor for *pH*. Interestingly, meso-aryl BODIPY displays low fluorescence anisotropy. Many NIR dyes with long polymethine chains, such as styryl dyes, have rather high anisotropies. Low anisotropies can be useful when molecules are used as markers for biological superstructures (Figure 31), since the anisotropy can be modified considerably upon incorporation of the marker into the restricted environment of a biomolecule.[156] A series of asymmetric benzo-fused BODIPYs with alkynyl groups at the *α*-positions, 5-position unsaturated BODIPY's, were recently prepared to provide linkers to other aromatic groups.[157] The introduction of the alkynyl group was achieved with a Sonogashira coupling reaction. In CH_2Cl_2, these dyes exhibit typical BODIPY absorption and emission properties, with bands centered at 612–618 and 625–633 nm, respectively.

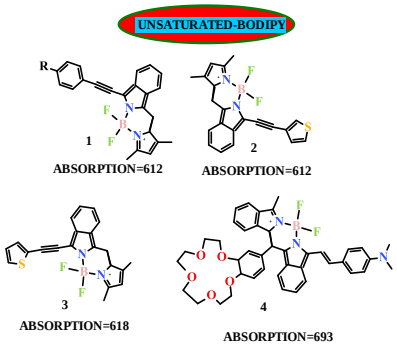


Figure 31. Chemical structure unsaturated-BODIPY

2.2.23. Pyrrole Linked-Bodipy's:

Pyrrole *B*-ring-functionalized pyrrolyl BODIPYs and their *B*-ring unsubstituted analogues were synthesized from easily accessible starting 5-halo-2-formylpyrroles and were characterized by nuclear magnetic resonance,[158] high-resolution mass spectrometry, X-ray analysis, and optical/ electronic properties. In great contrast to the substitution(s) at the other two pyrrolic units, electron-donating substituent(s) at pyrrole B-ring bring significant blue shift of the absorption and emission bands. Cyclic voltammetry and density functional theory calculations indicate that this blue shift may be attributed to the increased highest occupied molecular orbital and the lowest unoccupied molecular orbital energy levels and the overall increase in the energy band gaps.[159] These pyrrolyl BODIPYs generally show intense absorption (centered at 570−624 nm) and fluorescence emission (582−654 nm) in nonpolar solvents. A gradual decrease in the fluorescence intensity was observed for these dyes with the increase in solvent dipolar moment (Figure 32), which combines with the red to far-red absorption/emission, rendering

these pyrrolyl BODIPYs potential applications as environment-sensitive fluorescence probes.[160]

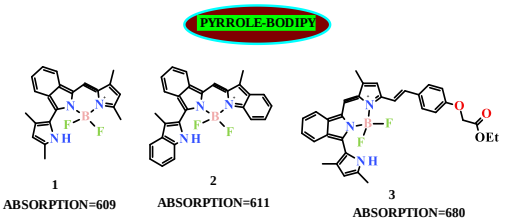


Figure 32. Chemical structure pyrrole ring substituted BODIPY's

2.2.24. Phenyl Ester Unsaturated-Bodipy:

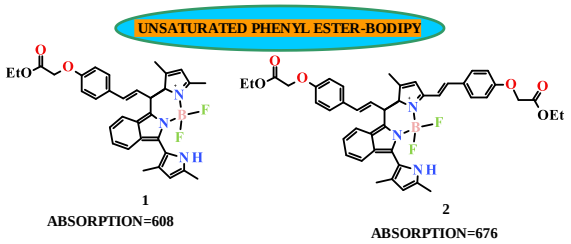


Figure 33. Chemical structure unsaturated phenyl ester-substituted BODIPYs.

This class of BODIPY dye can be achieved by grafting styryl groups onto the BODIPY core to form dyes.[161] These structures demonstrate that a meso-methyl group can not only undergo a Knoevenagel reaction, but can compete with the 3,5-position methyl groups in this regard. In contrast, the meso-substituted BODIPY dye absorbs at 608 nm and emits at 687 nm, and has the largest Stokes shift reported for this series of dyes. This demonstrates that the meso-styryl substituent does not have a significant (Figure 33) effect on the *Pi*-conjugation system of the BODIPY core. There is a 491 torsion angle between the plane of the BODIPY core and that of the meso-styryl ring. In a similar manner,[162] the meso-styryl-substituted BODIPY dye fluoresces only weakly with a quantum yield of less than 0.01.

2.2.25. Important Structures of Bis-Bodipy's:

Red shifts of the absorption bands can also be obtained by forming BODIPY dimers. The properties of directly linked dimers and coplanar fused dimers will be examined in depth. Directly linked bis-BODIPYs, are main spectral band wavelengths are usually observed for directly linked bis-BODIPYs relative to the corresponding monomers. For example, there is almost no red shift of the absorption maxima of the *meso–meso* and *meso-β* linked dyes relative to the corresponding tetramethyl-BODIPY, but a large Stokes shift is observed for the meso–meso linked dye are potentially useful for photodynamic therapy applications due to the interactions between the two BODIPY chromophores (Figure 34) in the excited state.[163-165] The absorption spectrum of the *α–α* linked BODIPY dye is characterized by two major bands at 489 and 562 nm, which is consistent with an exciton splitting effect. The fluorescence emission spectrum of 3,5-linked Bis-BODIPY contains a broad emission band at 650 nm with a Stokes shift of 88 nm with respect to the lowest-energy absorption band.[166-168] The *β–β* linked BODIPY has a typical cyanine-type absorption spectrum.[169, 170] This demonstrates that there is minimal ground-state interaction or excitonic coupling between the two chromophores.

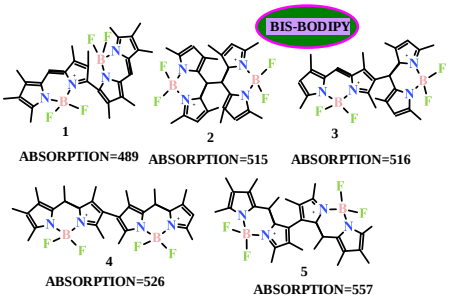


Figure 34. Chemical structure BIS-BODIPY's

2.2.26. Aromatic Fused Bis-Bodipy's:

Typically, *p*-fused bis-BODIPYs exhibit narrow and intense absorption and emission bands in the red/NIR region with high molar absorption coefficients and moderate FF values. This makes these dyes promising candidates for applications (Figure 35) in the NIR region. PPCy derivatives are likely to form excellent NIR fluorophores in aqueous environments, therefore, once appropriate substituents are introduced.[171, 172] PPCy dyes can be synthesized through the condensation reaction of diketopyrrolo-pyrrole with different aromatic acetonitrile groups. They have potentially useful spectroscopic properties such as very intense and narrow absorption bands and strong emission in the NIR region (with absorption bands ranging from 684 to 864 nm), high photostability, and low chemical reactivity.[173-176]

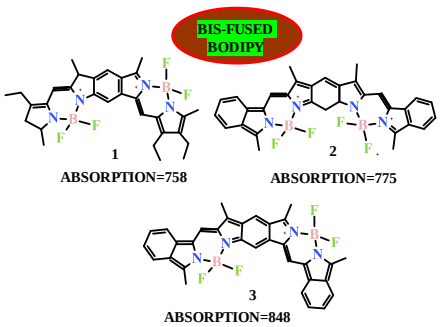


Figure 35. Chemical structure fused- BODIPY's.

3. Synthesis of Aryl Bodipy's:

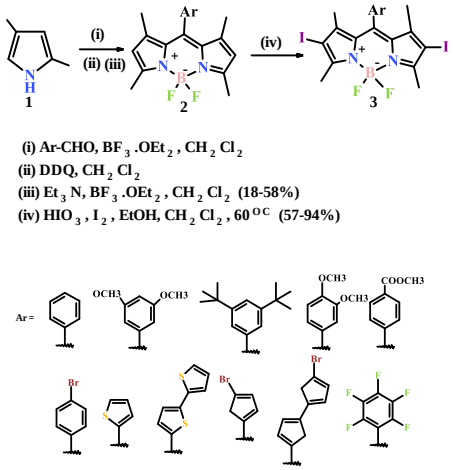
The most straightforward method for extending the electron delocalization of BODIPY is to introduce aromatic units. Direct attachment of phenyl substituents

at which two positions can somehow extend the conjugation system, but the bathochromic shift is limited.

3.1. Meso-Aryl Linked Bodipy's

These 3,5-dimethyl substituted BODIPYs can undergo Knoevenagel condensation reactions with aldehydes to give mono and di-styryl functionalized absorbing BODIPY dyes, within the biological window suitable for PDT.[177-179]

Eleven meso-aryl BODIPYs were synthesized from commercially available 2,4-dimethylpyrrole and the corresponding aryl aldehyde, [178,180] absorption bands 531nm (Scheme 1).



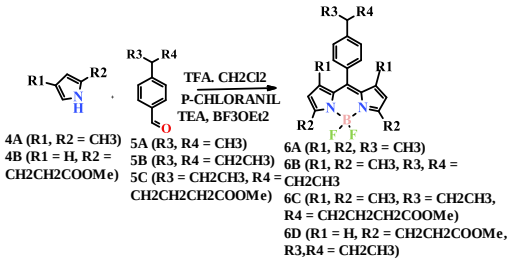
Scheme 1. Syntheses of *meso*-substituted-BODIPY's

A series of twenty-two BODIPY compounds were synthesized, containing various meso-phenyl and mesothienyl groups, and their spectroscopic and structural properties were investigated using both experimental and computational methods. Further functionalization of the BODIPY framework via iodination at the 2,6-pyrrolic positions was explored in order to determine the effect of these heavy atoms on the photophysical and cytotoxicity of the meso-aryl-BODIPYs. Among the series investigated, BODIPYs 2a and 4a bearing electrondonating meso-dimethoxyphenyl substituents showed the highest phototoxicity and dark phototoxicity ratio, and are therefore the most promising for application in PDT.[181]

3.2. Meso-Stubstituted Phenyl BODIPY's

Recently, *Urano et al.*, described BODIPY-based *pH*-activatable probes with tunable *pKa* ranging from 3.8 to 6.0, and used *pH*-activatable probe-antibody conjugates for *in vivo* imaging of cancer cells in mice.[182]

Scheme 2 shows the synthesis of the new BODIPY-based Ph probes **6A–D**. Each pyrrole (**4A, B**) was treated sequentially with a benzaldehyde (**5A–C**) in the presence of a catalytic amount of TFA[183], *p*-chloranil, then TEA and $BF_3.OEt_2$ to afford BODIPY-based *pH* probes **6A–D**.



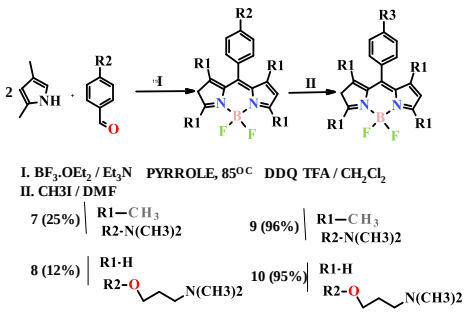
Scheme 2. Synthesis of bodipy-base *pH* probes 6A–D.

New BODIPY-based *pH* probes have been designed with excitation and emission wavelengths suitable for fluorescence microscopy and flow cytometry. These *pH* probes are cell-permeable, selectively label lysosomes, and can be used for noninvasive monitoring of lysosomal *pH* changes during physiological and pathological processes.[184]

3.3. Trimethylamino Linked Phenyl BODIPY's

The development of novel photosensitizer is important to improve the efficacy of PDI. A large number of potential photosensitizers have been proposed for different microorganism.[185]

Cationic BODIPYs **9** and **10** were obtained by methylation of the corresponding non-charged BODIPYs, which were synthetized by acid-catalyzed condensation of corresponding pyrrole and benzaldehyde derivatives and complexation with boron. The two BODIPY's differ by virtue of the substitution pattern at the pyrrole units and the link of the cationic *N*,*N*,*N*-trimethylamino group to the phenylene unit. Compounds **9** and **10** showed similar absorption spectroscopic properties. However, a considerably lower fluorescence emission was found for **9** than **10**, due to the rotation of the phenylene ring that promotes nonradiative decay of the excited state.



Scheme 3. Synthesis of BODIPYs 7-10.

Two cationic BODIPYs 3 and 4 were synthesized by acid-catalyzed condensation of the corresponding pyrrole

and benzaldehyde, followed by complexation with boron and methylation. Compound **9** contains methyl at the 1,3,5 and 7 positions of the *s*-indacene ring and a *N*,*N*,*N*-trimethylamino group attached to the phenylene unit, while 4 is not substituted by methyl groups and the cationic group is bound by an aliphatic spacer. *UV*-visible absorption spectra of these BODIPYs show an intense band at ~500 nm in solvents of different polarities and n-heptane/sodium *bis*(2-ethylhexyl)sulfosuccinate (AOT) / water reverse micelles. Compound **9** exhibits a higher fluorescence quantum yield (FF ¼ 0.29) than 4 (FF ¼ 0.030) in *N*,*N*-dimethylformamide (DMF) due to sterically hindered rotation of the phenylene ring. BODIPYs **9** and **10** induce photosensitized oxidation of 1,3-diphenylisobenzofuran (DPBF) with yields of singlet molecular oxygen of 0.07 and 0.03, respectively. However, the photodynamic activity increases in a microheterogenic medium formed by AOT micelles. Also, both BODIPYs sensitize the photodecomposition of L-tryptophan (trp). In presence of diazabicyclo [2.2.2]octane (DABCO) or *D*-mannitol, a reduction in the photooxidation of Trp was found, indicating a contribution of type I photoprocess. Moreover, the addition of KI produces fluorescence quenching of BODIPYs and reduces the photooxidation of DPBF. In contrast, this inorganic salt increases the photoinduced decomposition of TRP, possibly due to the formation of reactive iodine species. The effect of KI was also observed in the potentiation of the photoinactivation of microorganisms. Therefore, the presence of KI could increase the decomposition of biomolecules induced by these BODIPYs in a biological media, leading to a higher cell photoinactivation.[186]

3.4. *Meso*-Phenyl BODIPY's

A structural modification is often carried out to tune the physical and chemical properties of BODIPY's.[187] Three types of positions *alpha*, *beta* and *meso* (Scheme 4), are available for attaching substituent groups or functional units. The meso substitution is relatively less studied. BODIPY derivatives with a meso-substituted phenyl are particularly interesting since many well-known aromatic reactions can be employed to link another functional molecular moiety (FMM) onto the phenyl which gives a BODIPY-phenyl-FMM dyad for various applications in fluorescent probing, organic solar cell,[188] molecular photo switch and so on (Figure 36).

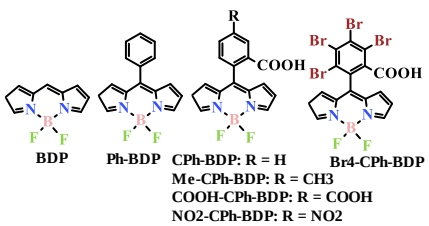
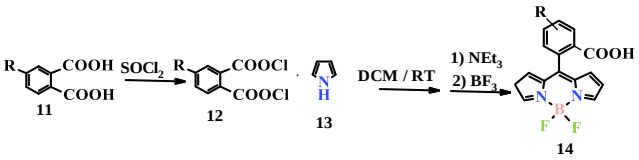


Figure 36. Chemical structures, and synthesis method of bodipy and its phenyl-substituted compounds.

The second method is using a substituent at the ortho position of the phenyl to block the phenyl rotation. The use of the less explored method 2 to make BODIPYs both fluorescent and photoactive in $^1O_2$ generation. Six *m*-carboxyl (meso-phenyl) BODIPY derivatives were synthesized (Scheme 4), and their fluorescence and singlet oxygen generation properties in different solvents were measured.



Scheme 4. Synthesis method of bodipy and its phenyl-substituted compounds.

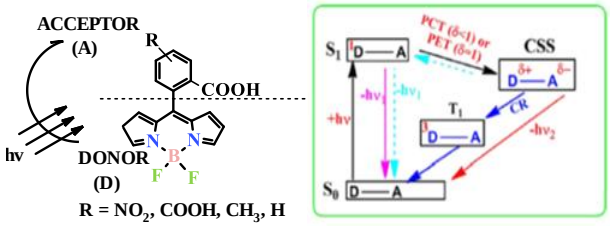


Figure 37. Left: donor-acceptor pairs of the BODIPY's.

The five meso-phenyl substituted BODIPY compounds. We showed that the introduction of a *para*-COOH on the phenyl effectively restricts the rotation and makes the kind of phenyl-BDP compounds highly emissive. In the meantime, the further introduction of a second group NO_2 or COOH on the phenyl strongly enhances PET or PCT, which makes excited triplet state and singlet oxygen formation much more efficient. The results are explained by the presence of photo-induced electron (or charge) transfer from BODIPY core to the phenyl moieties (Figure 37). The method and the mechanism on tuning the fluorescence and photosensitizing properties provide new insights for designing novel photosensitizers in photodynamic therapy of tumor and other applications.[189]

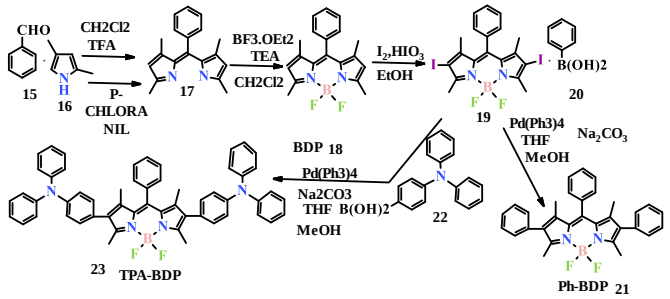
3.5. Triphenylmine BODIPY's

BODIPY-amidothiourea probes can be used for quantitative detection of inorganic F^- ions in aqueous solution with a remarkable detection limit due to a photo induced electron-transfer (PET) process.[190] By using this probe, a simple and user-friendly test strip was fabricated that can be applied to determine the F^- ion content in drinking water. Many BODIPY-based dyes emit red light, which is an attractive attribute in the development of efficient bioimaging systems.

A novel red fluorescent probe based on boron dipyrromethene (BODIPY) was successfully designed

and synthesized, consisting of electron acceptor 1,3,5,7-tetramethyl-8-phenyl-BODIPY (BDP) and electron donor triphenylamine (TPA) units using Suzuki cross-coupling methods. TPA-BDP exploits the advantages of both aggregation-induced emission (AIE) and twisted intramolecular charge transfer (TICT).[191]

It is proposed that fluoride reacts in a nucleophilic displacement reaction at the BDP core which disrupts the structure of TPA-BDP, thereby causing the red fluorescence of TPA-BDP quenched. It is noteworthy that TPA-BDP has been utilized for the fluorescence imaging and fluoride ions detection in living cells with very low cytotoxicity.



Scheme 5. Synthesis of the target TPA-BDP and pH-BDP.

TPA-BDP has a twisted conformation due to the three-bladed propeller-like structure of the triphenylamine units and the twisted conformation will be stabilized in polar solvents, which consequently red-shift the emission spectra (Figure 38). In addition to the bathochromic shift, the emission intensity is decreased as the TICT state is affected by various nonradiative quenching processes.

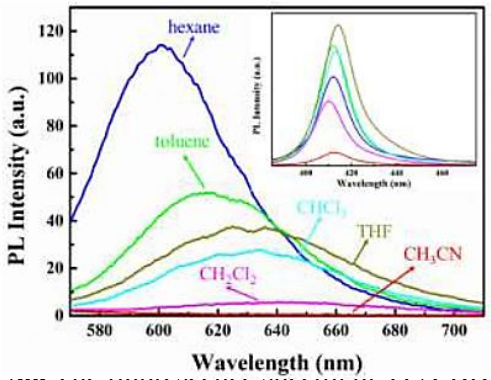


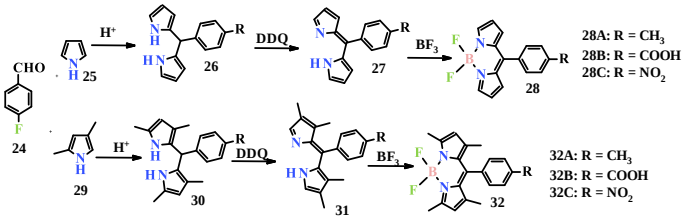
Figure P (10 μm) in different solvents in long-wavelength band at room temperature.

3.6. 8-Substitutedphenyl Linked BODIPY's

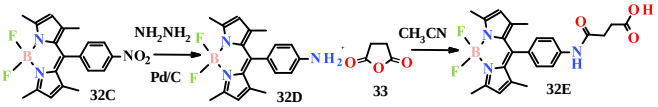
The photostability is one of the fatal properties of BODIPY dyes for their practical applications, especially in electrogenerated chemiluminescence and laser irradiating.[190,192] It is surprising that only a few papers concern the photodegradation of BODIPY dyes[191,193] and the relationship between photostability and the substituents at the skeleton of BODIPY dyes is unclear. In this article, the substituent effects on the photostability.

BODIPY dyes are synthesized in the one-pot reactions: in the first step, dipyrrolemethanes are prepared by the condensation of benzenealdehydes and pyrroles; the second step requires dichlorodicyanobenzoquinone (DDQ) for the oxidation of dipyrrolemethenes; and finally, $BF_3{\cdot}Et_2O$ is employed to coordinate with nitrogen atom. The total synthetic yields are related to the substituents of benzenealdehydes and pyrroles. For the *pi*-substituents at benzene aldehyde, the electron-withdrawing groups.

In this synthesis of two series of BODIPY dyes (**28** and **32**) and researched their spectral properties. Dyes **32** with four methyl groups show much higher fluorescence quantum yields and extinction coefficients than dyes **28**. The X-ray structure analysis of the crystals of **28c** and **32c** is used to reveal that blocking the rotation of 8-phenyl moiety by 1- and 7-methyl groups will suppress the intramolecular vibronic relaxation and internal conversion. The "push–pull" electronic effect caused by methyl groups at 3- and 5-position of BODIPY is another positive factor for the high quantum yields of **32**. The photostability of dyes **28** are higher than that of dyes **32**, and the electron withdrawing *p*-substituents at phenyl moiety of the dyes are beneficial to increasing the photostability. The BODIPY dyes with better photostability present comparatively lower quantum yields in our research.[194]



Scheme 6. Synthetic routes of 28 and 32 (A–C).



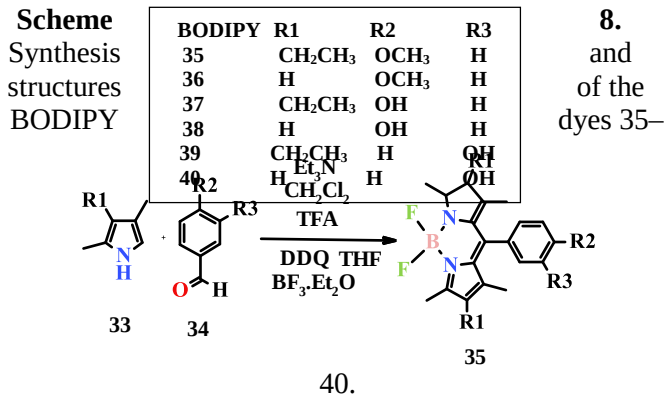
Scheme 7. Synthetic routes of derivatives (32D–E) from 32C.

3.7. Meso-Disubstitutedphenyl Linked BODIPY's

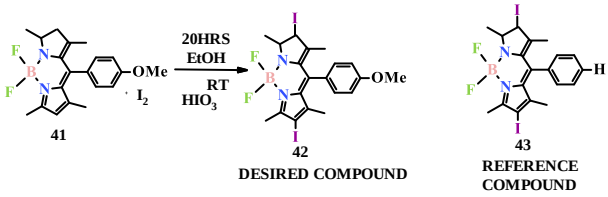
Biological studies investigating apoptotic and autophagic responses have also been performed on four compounds, three of which share a 4-methoxyphenyl moiety as substituent on position 8-(meso), while the 2,6-pyrrole positions are either unsubstituted, or bear two ethyl groups or two iodine atoms; the results of the

phototoxicity studies indicates that substitutions in these positions are critical to the photodynamic efficacy of these compounds.[195] The fourth PS included in the mechanistic studies is a reference molecule, previously synthesized and characterized by *Nagano*, lacking the meso-substituent and bearing two iodine atoms on the pyrrole moiety.[196]

The BODIPY derivatives were synthesized by condensation of aromatic aldehyde and pyrrole following the general methods described by *Akkaya* and *Liu*. Two differently substituted pyrroles, the 2,4-dimethyl pyrrole and the 2,4-dimethyl-3-ethyl pyrrole, were condensed with aromatic aldehydes in CH_2Cl_2 or THF in the presence of catalytic amounts of TFA. The dypyrrolylmethanes thus obtained were subsequently oxidized to dipyrrolylmethenes with DDQ and treated with $BF_3.Et_2O$ in the presence of Et_3N yielding the desired, pure BODIPY's (Scheme 8).



Scheme 8. Synthesis and structures of the BODIPY dyes 35–40.



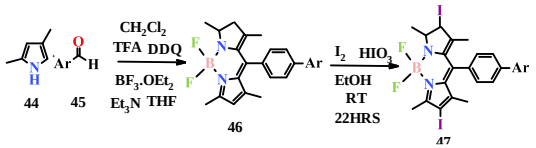
Scheme 9. Iodination of the free 2,6 positions of BODIPY 42 affording compound 43.

Eight BODIPY dyes were synthesized and used as photosensitizers (PS's) on the human colon carcinoma cell line HCT116. In this panel of molecules, the structure varies in the substituents on pyrrole 2, 6 positions and on the phenyl ring at the indacene 8 position. For these compounds relevant physico-chemical parameters, such as singlet oxygen production, fluorescent quantum yield, absorbance profile and a relative rank of lipophilicity were determined. The results indicate that some of these novel PSs are very effective in reducing the growth/viability of HCT116 cells when irradiated with a green LED source, whereas they are practically devoid of activity in the dark, up to 5 lM. To evaluate whether cell death is induced under these conditions, flow cytometric analysis of the percentage of apoptotic and autophagic cells was performed on four molecules, chosen for their efficacy/structural characteristics. The data indicate that phototoxicity likely occurs mainly through apoptotic cell death, whereas autophagy seems to play a minor role in determining cell fate. Furthermore, the relationship between singlet oxygen generation and the PS efficacy is confirmed, thus underscoring the importance of the heavy-atom effect and of the presence of an aryl substituent at dipyrromethene 8-(meso) position. Among the PSs here described, the most efficient BODIPY was successfully tested on three other human cancer cell lines197 of different tissue origin, MCF7 (breast), A2780 and A2780/CP8 (ovary, sensitive and resistant to cisplatin, respectively), yielding IC50 values comparable to those obtained on HCT116.

3.8. Halo Linked-Meso-Substitutedphenyl-BODIPY

The synthesis of a panel of fully characterized BODIPY featuring an aromatic ring on the *meso*-8-position, characterized by the presence of different substituents. These new molecules, together with thirteen BODIPYs,[198] were studied to determine the singlet oxygen ($^1O_2$) production rates, the fluorescent quantum yield and, finally, the relative degree of lipophilicity.

The BODIPY derivatives were synthesized via acid catalysed condensation of the desired aromatic aldehyde (11 different aldehydes were used) with 2,4-dimethylpyrrole in the presence of catalytic amount of trifluoroacetic acid[199] (TFA) Scheme 10.



Scheme 10. Synthetic approach to obtain the iodinated BODIPY series.

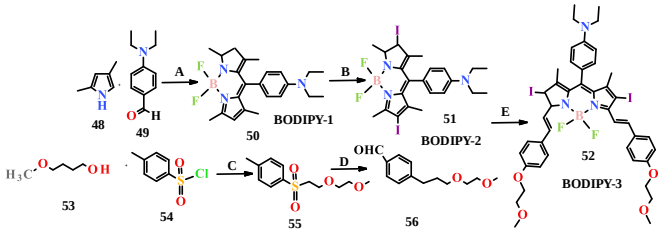
The panel of iodinated BODIPY here reported are shown a very interesting singlet oxygen production rate, in most cases higher than the one obtained with the reference compound Rose Bengal. In agreement with these data a very promising cell-killing effect following irradiation with a green light emitting LED was observed in in vitro assays. The efficacy is undoubtedly correlated to the presence of an aromatic ring on the BODIPY 8-(*meso*) position although none evident indications can be inferred from the presence of electron-withdrawing or electron-donating substituents on the aromatic moiety or according to their position and then their steric hindrance. Actually, the two most active BODIPY's are

methoxyphenyl- and dichlorophenyl-, the former characterized by the presence of a methoxy group on the para position whereas the latter features two chlorine atoms on the ortho, ortho' positions. The complete difference in regio-isomerism and in the electronic effects confirming the absence of correlation between the substituents and the efficacy of the photo-induced action.

3.9. Diethylamino-Phenyl Linked BODIPY's

The fluorescence of TBDP was weak due to the introduction of iodine atom and diethylamine unit. Introduction of iodine is benefit for PDT[200] due to the enhanced intersystem crossing, and the TEG could increase the hydrophilicity of BODIPY and facilitate its self-assembly in aqueous media.[201] An aggregation of BODIPY in water is in favor of photothermal activity upon irradiation.[202]

The TBDP nanoparticles (TBDP NP's) were prepared by a simple precipitation method. Briefly, the TBDP in acetone was dropped into water and then the acetone evaporated to obtain the TBDP NP's. The size of nanoparticles was characterized by transmission electron microscopy (TEM) Scheme 11.



Scheme 11. Synthesis procedure of TBDP. reagents and conditions: (a) 2,4- dimethyl-pyrrole, TFA, 12 h; DDQ, 1 h; Et_3N, BF_3OEt_2, 4 h; (b) NIS, 24 h; (c) TBAC, NaOH; (d) Hydroxybenzaldehyde, acetone, 8 h; (e) toluene, 24 h.

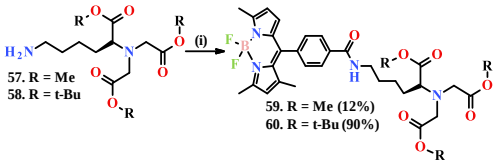
An organic dye TBDP has been designed and synthesized, which can self-assemble into stable organic nanoparticles in physiological condition. TBDP exhibited extremely weak fluorescence and can generate not only singlet oxygen but also heat for synergic photothermal and photodynamic therapy upon laser irradiation. All obtained data from *in vivo* and *in vitro* suggested that the TBDP NPs exhibited a significantly high phototoxicity to inhibit cancer cells effectively.[203] This work highlights the great potential of organic dyes as photosensitizers in biomedical field and cancer treatment.

4. Synthetic Methods of Chain Linked Bodipy's:

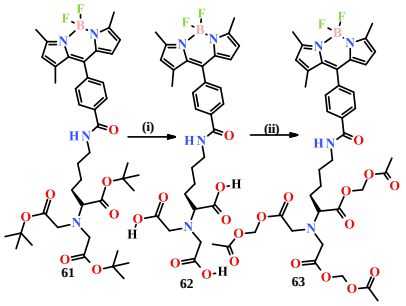
Chain substitution at the 3,5-positions had become an efficient strategy toward π-extended BODIPYs. It was found that the halogen atoms at the 3,5-positions of the BODIPY core showed similar reactivity to heterocyclic imidoyl chlorides. This opens the door for derivatization using transition metal catalyzed coupling reactions. The same group prepared a series of conjugation extended BODIPY dyes bearing polymethine units at the α-position by condensation of 3,5- dimethyl boron dipyrromethene with various hemicyanines, yielding the corresponding mono- and di-substituted derivatives

4.1. Nitrilotriacetic Acid BODIPY Derivatives

The protected NTAs were conjugated to the BODIPY fluorophore,[204] enabling us to detect the compounds in cells. The syntheses of the compounds are shown in Schemes 12 and 13.



Scheme 12. Synthesis of protected NTAS 59 and 60. (a) BODIPY-$COOH_6$, HBTU, DIPEA, CH_3CN.



Scheme 13. Synthesis of the protected NTA 63. (A) 4M HCL in 1,4-dioxane (B) bromomethyl acetate, dipea, DMF, 72% for 2 steps.

Fluorescence labeling of the target molecules using a small molecule-based probe is superior than a method using genetically expressed green fluorescence protein (GFP)[205] in terms of convenience in its preparation and functionalization. Fluorophore-nitrilotriacetic acid (NTA) conjugates with several ester-protecting groups were synthesized and evaluated for their cell membrane permeability by fluorescence microscopy analysis.

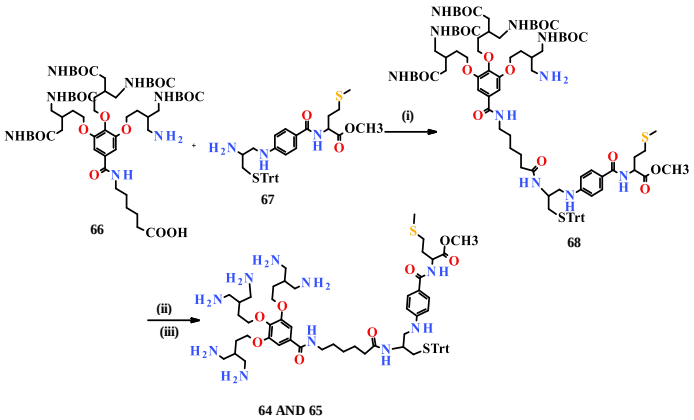
The designed and synthesized fluorescent NTA derivatives,[206] some of which exhibited cell membrane permeability and showed the property of accumulating inside the cells. In this study, acetoxymethyl-protected NTA derivative **63** showed relatively good membrane permeability[207] and was retained inside the cell, because esterases or lipases can readily hydrolyze the acetoxymethyl groups and the resultant negatively charged compound cannot move out of the cell. This derivatization is expected as a method for converting a

non-cell-membrane permeable fluorescent probe to a cell membrane permeable probe.[208]

4.2. Tetrapeptide BODIPY synthesis

Bivalent enzyme inhibitors, in which a surface binding module is linked to an active site binding module through a spacer, are a robust approach for site-selectively delivering a minimally-sized agent to a protein surface to regulate its functions, such as protein–protein interactions (PPIs).

The hydrophobic VI dipeptide moiety was replaced by a 4-amino benzoic acid scaffold. Its methyl ester pro-drug form **67** was found to be active in whole cells at 200 lM, although CVIM itself was inactive. Thus, to decided the replace the CVIM module in 1 with FTI-249 and its corresponding methyl ester form to give **64** and **65**, respectively (Scheme 14). To examine whether these replacements improve membrane penetration of the compounds, they also designed fluorescently- labeled derivatives using the BODIPY chromophore for confocal cell imaging to give 1-BODIPY and 3-BODIPY.

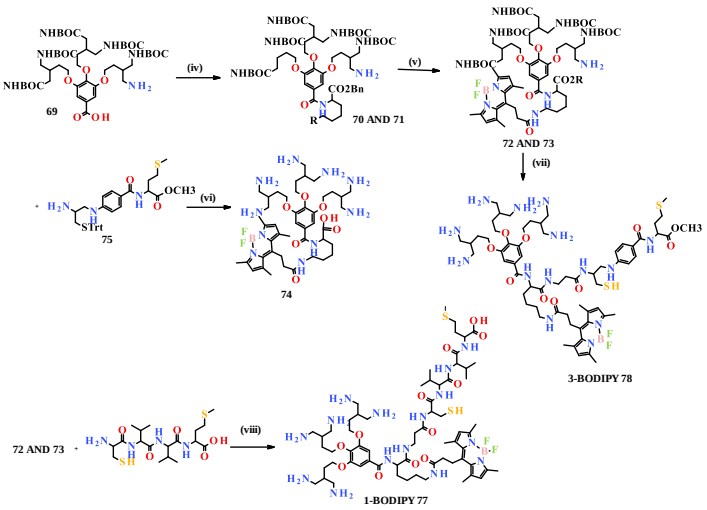


Scheme 14. Reagents and conditions: (I) 5, HOBT, PYBOP, 73%; (II) KOH in MEOH, THEN 30% TFA and 5% TES in dichloromethane, 70%; (III) 50% TFA and 5% TES in dichloromethane, 27%;

The synthetic approach to compounds **64**–**65** and **77**, **78** is shown in Scheme 14. Compounds **64** and **65** were synthesized by coupling reaction[209] of Boc-protected gallate **67**with peptidomimetic **68**, followed by deprotection. To synthesize the BODIPY-containing compounds, the linear alkyl spacer used in **77** and **78** was replaced by a lysyl-β-alanine dipeptide of similar length. Coupling of **69** with x-Fmoc-L-lysine benzyl ester followed by deprotection gave **71**, which was then coupled with BODIPY carboxylic acid using HOBt/PyBOP to afford compound **72**. After removal of the benzyl group by hydrogenation, the resulting free acid **73** was coupled either with protected tetrapeptide BETA-Ala-Cys(Trt)-Val-Leu-Met-OtBu or compound **76** to give protected precursors; these precursors were then deprotected by acid treatment to afford **1-BODIPY**-(**77**) and **3-BODIPY**-(**78**), Scheme-15 respectively .

The results of cell-based assays showed that the peptidomimetic **78** inhibited FTase processing, while the peptidic **77** was inactive. This indicates that peptidomimetic modification is a promising approach for the development of bivalent inhibitors targeting intracellular PPIs.[210] Reduced *in vitro* activity observed for **64** suggests that further structural modifications of the surface module and the peptidomimetic-based anchor module are necessary to improve the activity. The moderate membrane penetration ability of 3- BODIPY observed in the confocal imaging needs to be improved for better cell activity.[211]

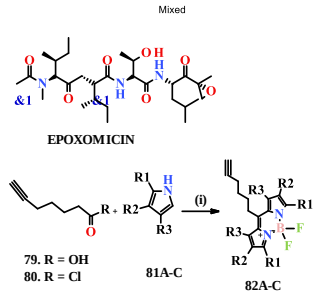
Scheme 15. Reagents and conditions: (IV) H-



LYS(FMOC)-OBN, HOBT, PYBOP, 67%; (V) diethylamine ; BODIPY, HOBT, PYBOP, 99%; (VI) $PD(OH)_2$, 62%; (H) 30% TFA in dichloromethane, 68%; (VII) 13, HOBT, PYBOP, 65%, and THEN 50% TFA and 5% TES in dichloromethane, 20%; (VIII) 14, 65%, and THEN 50% TFA and 5% TES in dichloromethane, 20%.

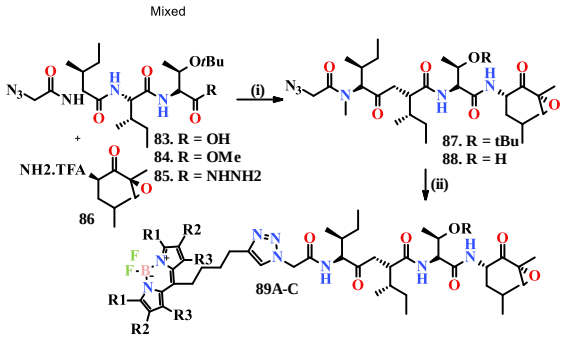
4.3. Acetylene functionalized BODIPY dyes

All three fluorescent epoxomicin analogues revealed bands of labeled proteins, the molecular weight of which correspond to the proteolytically active proteasomal β-subunits.[212] In according to the synthesis of the alkyne functionalized BODIPY dyes commenced with the treatment of 6-heptynoic acid **79** with oxalyl chloride (Scheme 16).



Scheme 16. Synthesis and spectroscopical data of acetylene functionalized BODIPY dyes. Reagents and conditions: (A) oxalylchloride (1.5 Equiv), DMF (CAT.), TOL.3 H; (B) I—1M^2 in DCE, 3A–C (2.1 EQUIV), 2 H 65 ºC; II—BF_3ÆOEt_2 (5 EQUIV), DIPEA (4 EQUIV), 4A 21%, 4B 14%, 4C 26%.

The synthesis of three acetylene functionalized BODIPY dyes is described. These dyes are used to fluorescently modify an azido functionalized epoxomicin analogue employing the Huisgen 1,3-dipolar cycloaddition, resulting in a panel of fluorescent epoxomicin[213] derived proteasome probes. The synthesized azido functionalized epoxomicin analogue **89** (Scheme 17) was produced.



Scheme 17. Synthesis of fluorescent epoxomicin analogues 89a-c. Reagents and conditions: (i) TMS-diazomethane (2 equiv), MeOH/ Tol. (1:1), 15 min, 97%; (ii) hydrazine monohydrate (60 equiv), MeOH, reflux, 37%; (iii) i—t-BuONO, HCl, dioxane/DMF; ii—DiPEA, 8, 11%; (iv) TFA, 30 min; (e) 4a–c, $CuSO_4$ (10 mol %), sodium ascorbate (15 mol %), t-BuOH/Tol./H_2O (1:1:1), 80^{oC}, 12 h, 11a 91%, 11b 82%, 11c 65%, two steps from 83.

The verification of substitution pattern on the core and the flanking pyrroles of the BODIPY not only changes the fluorescence properties of the dye, but also has a dramatic effect on the bioavailability of the fluorophore. The two-step labeling of azido modified target proteins in the proteome using the acetylene functionalized BODIPY dyes are under processing.[214]

4.4. Polynthylene glycol linked-BODIPY's

The lysine of Glu–urea–Lys is more tolerant to structural modification and is utilized to conjugate with imaging prosthetic groups such as bulky optical dyes or radionuclide metal complexes.[215-217] Glu–urea–Lys is the most common scaffold of PSMA-targeted small molecules (Figure 39).

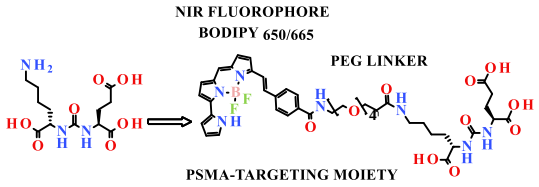
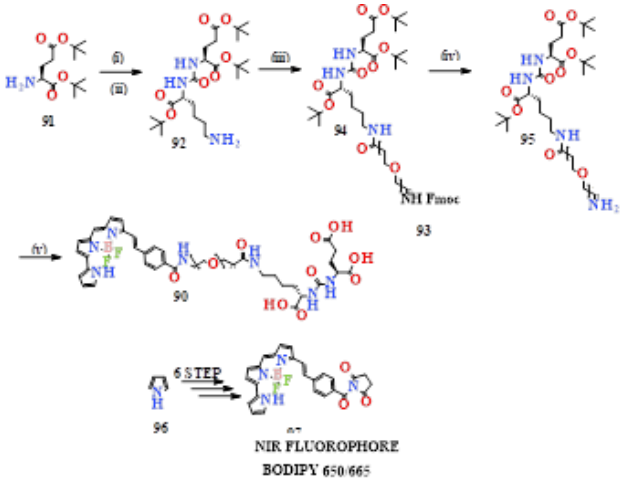


Figure 39. Design of psm-targeted optical imaging agent's base on glu-urea-lys.

Synthesis of the precursor for compound **91** was accomplished as described in Scheme 18. Briefly, the PSMA-binding motif consisting of glutamine and lysine, linked *via* their α-amino groups by a carbonyl forming a urea group, was prepared in two steps from thecommercial (L)-glutamic acid di-*tert*-butyl ester (**92**) by applying a reported synthetic procedure. Amide coupling of compound **93** with PEG linker (Fmoc-15-amino-4,7,10,13-tetraoxapentadecanoic acid) **94** in the presence of 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium3-oxide hexafluorophosphate (HATU) and *N*,*N*diisopropyl ethylamine (DIPEA) was achieved to generate compound **95** in 61% yield. The *Fmoc* group of compound **95** was removed using 20% piperidine in DMF, followed by thehydrolysis of the *tert*-butyl ester (O*t*-Bu) groups using 25% trifluoroacetic acid (TFA) indichloromethane (DCM) to afford compound **90** with a 2-step yield of 40%. *N*Hydroxysuccinimide (NHS) ester of BODIPY650/665 (**97**) was prepared according to the reported method. The BODIPY 650/665 NHS ester **97** was obtained in 6-steps starting from pyrrole and pyrrole aldehyde. The reaction of compound **90** with **97** in thepresence of Tris-HCl buffer in dimethyl sulfoxide



(DMSO) at room temperature for 16 hafforded the final compound **90** in 47% yield.

Scheme 18. Synthesis of Bodipy$_{650/665}$-Labeled PSMA Ligand 97.Reagents And Reaction Condition: (*i*) H-Glu(O*t*bu)-O*t*bu·Hcl, Triphosgene, Et_3N,CH_2Cl_2, –78 ºc To Rt, 12 H, 56% Yield; (*ii*) H_2, 10% Pd/C, Meoh, 4 H; (*iii*) Peg Linker (4), HATU, DIPEA, DMF, 12 Hr, 61% Yield; (*iv*) 20% Piperidine In DMF, RT, 2 Hr And Then 50% TFA In CH_2Cl_2, RT, 2 Hr, 40% Yield In Two Steps; (*v*) Bodipy650/665 NHS Ester (7), Tri-Hcl Buffer, DMSO, RT, 16 Hr, 47% Yield.

The *in vitro* PSMA inhibition assay and cell uptake study showed strong and specific binding for PSMA. As the BODIPY moiety can be applied for optical imaging as well as PET imaging by replacing ^{19}F with radioactive ^{18}F, compound **97** has the potential to be utilized as a NIR imaging probe as well as dual-modality to combine PET and optical imaging.[218]

4.5. Propionic acid-BODIPY

An approach for the development of high affinity BODIPY FL-labeled ligands by using a method of parallel synthesis and screening, which are commonly performed to obtain SAR information quickly in drug discovery. In other words, BODIPY FL-labeled ligands were prepared (Figure 40) by parallel synthesis in two steps: Step 1: ligand of interest is conjugated with various linkers and Step 2: linker-attached ligands are then conjugated to BODIPY FL propionic acid 1, which enabled the preparation of a library of BODIPY FL-labeled ligands with various linker lengths, bulkiness, and polarity. This method as parallel fluorescent (Figure 41) probe synthesis.[219]

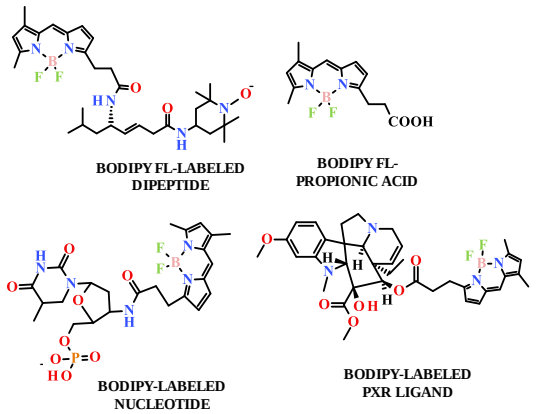


Figure 40. Structure of BODIPY FL propionic acid 1 and BODIPY-labeled fluorescent probes.

A methodology to quickly obtain fluorescent probes with the desired affinity by using a method of parallel synthesis, termed as Parallel-FPS.[220] The parallel synthesis is a widely used technology, but is rarely used in the design and synthesis of fluorescent probes in drug discovery partly due to the limited availability of reagents such as BODIPY FL propionic acid **98**.

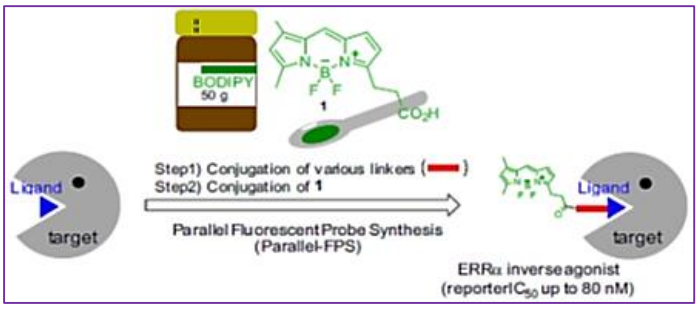
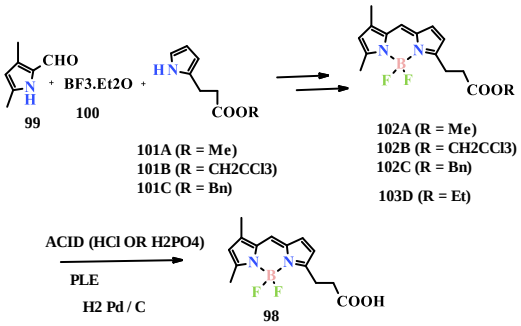
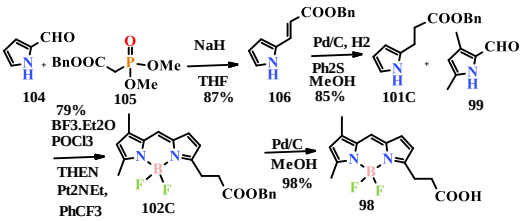


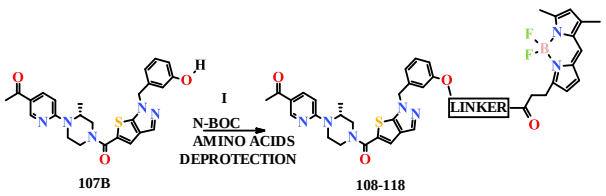
Figure 41. Proposed Scheme to identify fluorescent probe-labeled high-affinity ligands by parallel fluorescent probe synthesis.



Scheme 19. General synthetic route for BODIPY FL propionic acid 98.



Scheme 20. Modified synthetic route for BODIPY FL propionic acid 98.



Scheme 21. Parallel synthesis of BODIPY FL-labeled fluorescent probe for errα.

A methodology for quick development of fluorescent probes with the desired potency for the target of interest by using a method of parallel synthesis, termed as Parallel Fluorescent Probe Synthesis. BODIPY FL propionic acid 1 is a widely used fluorophore, but it is difficult to prepare a large amount of 1, which hinders its use in parallel synthesis. Optimization of a synthetic Scheme enabled us to obtain 50 g of 1 in one batch. With this large quantity of 1 in hand, we performed Parallel-

FPS of BODIPY FL-labeled ligands for estrogen related receptor-a. An initial trial of the parallel synthesis with various linkers provided a potent ligand for ERRa, (**Figure 42**) demonstrating the usefulness of Parallel-FPS221.

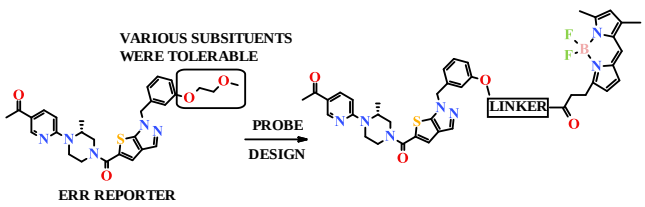
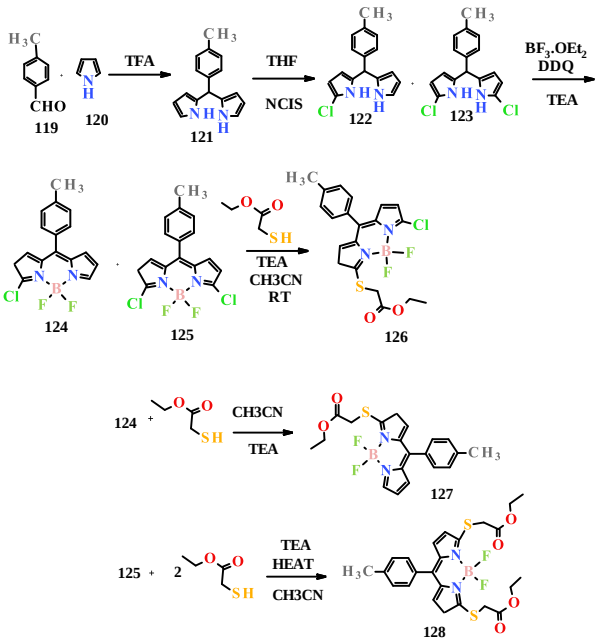


Figure 42. Design of BODIPY fl-labeled fluorescent probe for errα.

4.6. Mono- and dithiosubstituted linked BODIPY's

A pursuit for even better dyes with different properties suitable for various applications is not over. It is particularly important to develop different BODIPY analogues with emission wavelengths tunable from 500 nm to over 700 nm, which can be used as fluorescence FRET pairs with applications in chemistry and biology. One approach to differently substituted BODIPY derivatives include substitution of chlorine on the BODIPY core, which can be facilitated by nucleophiles,[222] or in Pd-catalyzed arylations.[223] Furthermore, *Jiao et al.*, recently introduced a better method for the chlorination and bromination of BODIPY derivatives. However, recent synthetic advances allowed for the nucleophilic substitution on the BODIPY without chlorine substitution,[225] as well as direct CH-arylation reactions, significantly shortening the synthetic pathways towards new dyes.

Synthetic procedure for the preparation of BODIPY dyes is based on the standard procedure for the preparation of the BODIPY core substituted with chlorines, which can be substituted by nucleophiles. However, contrary to previous report, chlorination of dipyrromethane afforded a mixture of mono- and bis-chloro substituted molecules which were not separated, but they were transformed to a mixture of BODIPY derivatives **H-Cl** and **Cl_2** (Scheme 22), which are more stable so it was easier to separate them. Note that chlorination of BODIPY, as reported by *Jiao et al.*, provides chlorinated derivatives in higher yields.



Scheme 22. Synthesis of thioester linked BODIPY'S.

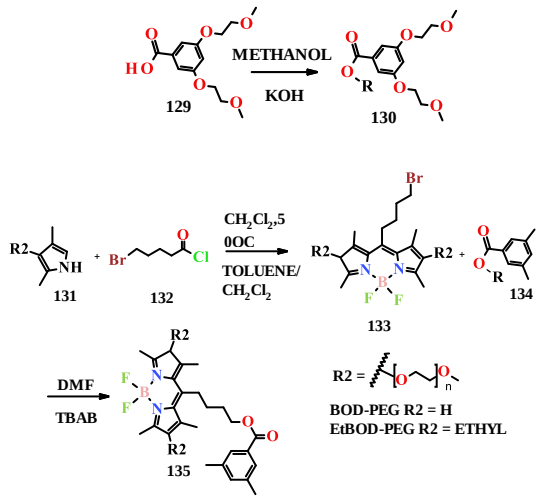
A series of BODIPY dyes, symmetrically or asymmetrically substituted at the 3- and 5- positions was synthesized. Photophysical properties of the dyes were investigated in solvents of different polarity and polarizability. In contrast to majority of BODIPY derivatives, here presented dyes exhibit weak solvatochromic properties that cannot be correlated to solvent polarizability. Substitution of the BODIPY chromophore by -Cl or thioalkyl substituents induces batochromic shifts in both absorption and emission spectra for 50-60 nm and induces higher quantum yields of fluorescence. Thus, the highest Φf was measured for Cl_2 **125**, S-Cl **126** and S2 **128**, whereas H-Cl **124** and H-S **127** are less fluorescent. Similarly to weak solvato chromic properties, Φf, singlet excited state lifetimes, *k*R and *k*NR, are insignificantly affected by changes in solvent polarity/polarizability. Nevertheless, the highest values of Φf and τ were found in solvents of the highest polarizability. The findings were rationalized by TD-DFT computations. Presented study is important for the use of chloro-substituted BODIPY dyes as chemodosimeters for thiols and cystein, as well as for the rational design of new dyes.[225]

4.7. Polyethylene glycol linked BODIPY's

Neutral water-soluble BODIPY dyes, such as PEGylated BODIPY, have an advantage over ionic dyes in that they avoid potential electrostatic interactions between the dyes and biomolecules in biological and medical applications.[226] Thus, the use of PEG to increase the water solubility of BODIPY dyes is a technique still widely used among researchers. It is also well known that PEG possesses several biological and medical advantages

such as long circulation time, satisfactory biocompatibility, and a tendency to accumulate in tumor sites *via* the enhanced permeability and retention (EPR) effect of leaky tumor neovasculature.[227]

The synthesis of the fluorescent BODIPY dyes containing *di*-branched PEG chains. The di-branched PEG chains were prepared according to previously reported methods. First, Williamson etherification between ethyl 3,5-dihydroxybenzoate and tosylated PEG produced di-PEGylated benzoates. Their subsequent hydrolysis yielded di-PEGylated benzoic acid. Meso-1-bromo-butylsubstituted BODIPY dyes were prepared via the condensation of 5- bromovaleryl chloride with either 2,4-dimethyl-3-ethylpyrrole or 2,4-dimethylpyrrole and subsequent complexation with $BF_3{\cdot}OEt_2$ in the presence of triethylamine. Finally, the esterification between the bromine-containing BODIPYs and the carboxyl ends of the di-PEGylated benzoic acid afforded the water-soluble BODIPY dye (Scheme 23).



Scheme 23. Synthesis of peg-functionalized BODIPY fluorescent dyes bod-PEG and etbod-PEG.

A series of water-soluble PEGylated BODIPY dyes (BOD-PEG and EtBOD-PEG) were prepared, and their photophysical properties were investigated. Bulky di-branched PEG chains were introduced at the meso position of the BODIPY core to reduce the aggregation tendencies of the dyes. The dye BOD-PEG, which has no substitutions at positions 2 and 6 of the BODIPY core, exhibited absorption and emission maxima at shorter wavelengths relative to those of EtBOD-PEG, which has electron-donating ethyl groups at the 2 and 6 positions of the core. Notably, the fluorescence QYs of the dyes at 1 μM in water were 0.514 for BOD-PEG and 0.471 for EtBOD-PEG, which are higher than those of other BODIPY-based water-soluble probes reported previously. The PEGylated BODIPY dyes were able to permeate MCF-7 cells and localized in the cellular cytoplasm, exhibiting good water solubility and biocompatibility. This work may provide new strategies for the design and fabrication of highly efficient fluorescent probes in aqueous environments.[228]

5. Heterocycles Linked-Bodipy's:

5.1. Bioconjugation of BODIPY's

This communication focuses on BODIPYs to illustrate those new issues. Compound **137** was used to introduce groups functionalized for bioconjugation, and to study cases in which nucleophilic displacement of F and SNAr reactions can compete (Figure 43). Compound **142** was used to illustrate how SNAr reactions (Scheme 24) in particular can be used to conjugate dyes to proteins while simultaneously (Scheme 25) changing the BODIPY core structure, its fluorescent properties, and enhancing its water solubility.[229]

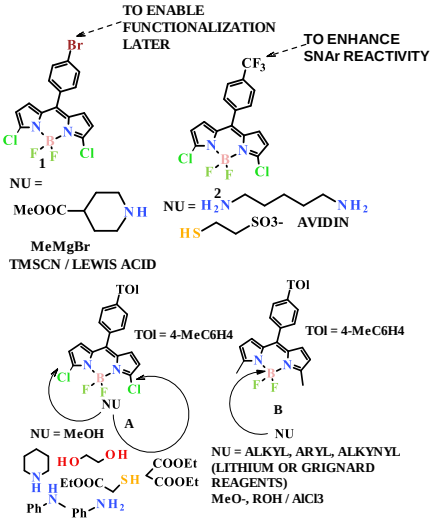
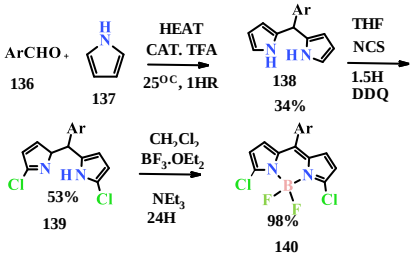
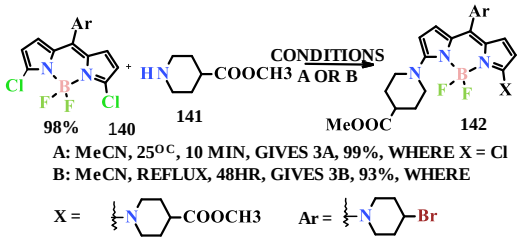


Figure 43. SNAr reactions of BODIPY.



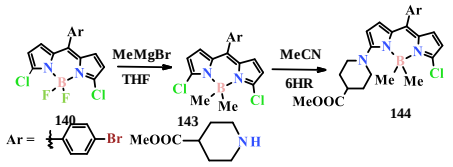
Scheme 24. Synthesis of the 3,5-dichloroBODIPY 140.



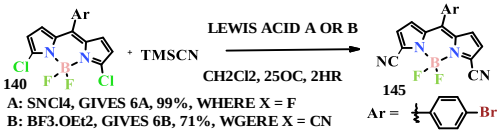
Scheme 25. Mono- and bis-substitution on BODIPY142.

The work described in this paper highlights numerous ways in which the BODIPY core may be modified *via* nucleophilic substitution reactions. In the

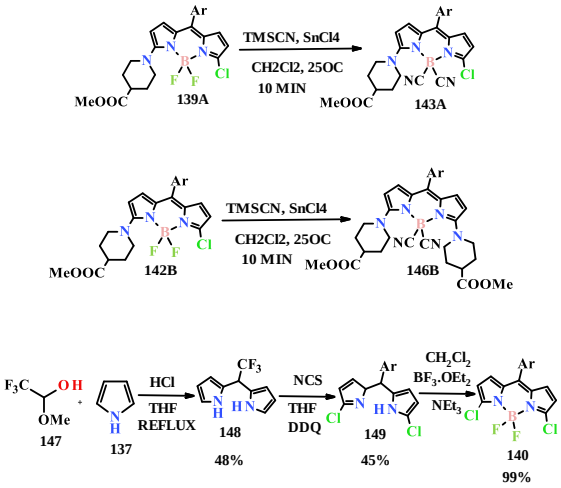
particular case of *SNAr* reactions on compound **142** provides (Scheme 26, 27, 28) a route to label proteins that breaks with well-used approaches involving activation of pendant carboxylic acid functionalities on the dye.



Scheme 26. Syntheses of compound 144 having cyanide substituents.

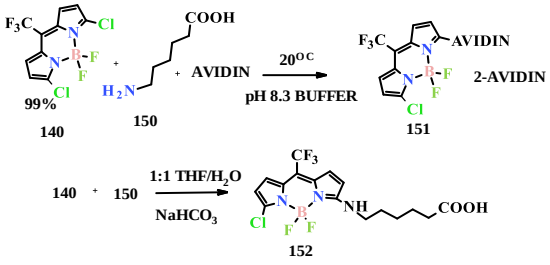


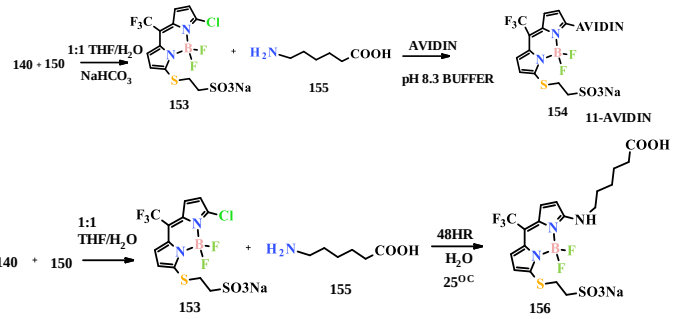
Scheme 27. B-f displacements using cyanide anion in: (A) mono-; and (B) diaminated BODIPY dyes.145



Scheme 28. Synthesis of CF_3-dichloroBODIPY 4.

The new BODIPY systems **140** and **142** were prepared and then used as substrates to explore SNAr and F-B displacement reactions. Chloride was easily displaced from **140** by a piperidine/ester, methylmagnesium bromide selectively displaced fluoride, and cyanide could attack both sites. System **142** readily added soft nucleophiles to the electrophilic carbon atoms, providing a new method for bioconjugation of BODIPYs (Scheme 29) to proteins while also introducing a ^{19}F probe.[230]





Scheme 29. Syntheses of dye avidin conjugates and model compounds.

5.2. Quinone-linked BODIPY's

The Boothman group, the mechanism of action of most *β*-lapachones is related to the destruction of cancer cells with elevated levels of NAD(P)H: quinone oxidoreductase **166** (NQO1).[231] Recently, Ohayon and coworkers[232] have shed some light on the possibility that *b*-lapachones might act non-reversibly as (Figure 44) inhibitors of deubiquitinases.

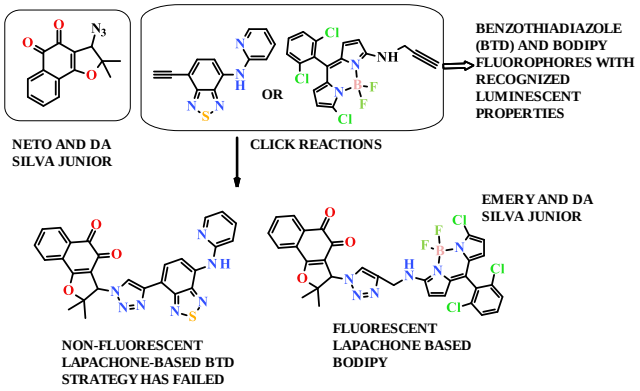
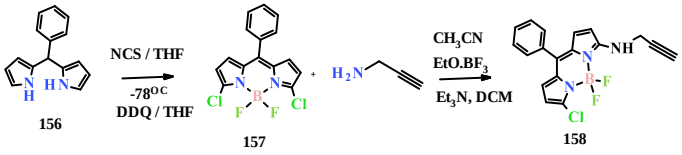


Figure 44. This work: new quinone-based BODIPY hybrids and their antitumor, mechanism of action and subcellular localization studies

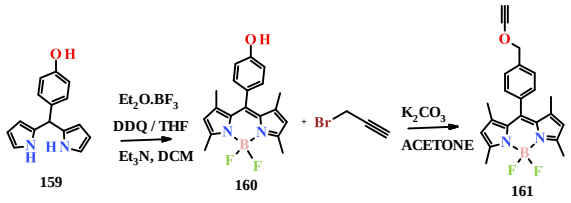
Lapachones are naturally occurring naphthoquinones and among the most studied quinones due their potent antitumor activity.[233] Lately, diverse lapachone derivatives have been reported as potent cytotoxic drugs against different cancer cell lines. In this regard, advances in the synthesis of lapachones with potent antitumor activity (Scheme 30) have been accomplished *via* modification of the A- and C-rings.



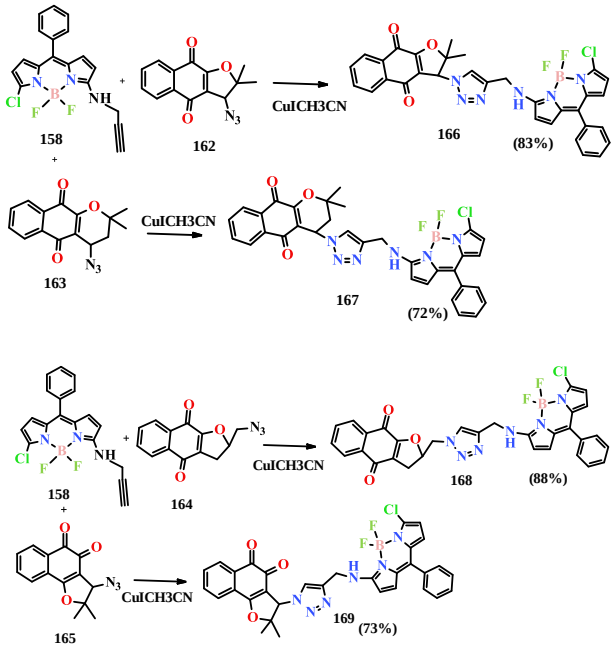
Scheme 30. Preparation of luminescent quinone-based BODIPY via click chemistry: 158

The synthesis of the quinone-based BODIPY hybrids **166–170** was accomplished by a convergent

synthetic route, using a classical copper (I)-catalyzed alkyne-azide cycloaddition (CuAAC) reaction. An alkyne-containing BODIPY and azide-containing quinones to assemble fluorescent, hybrid quinoidal-BODIPY molecules (Scheme 31). Preparation of quinone-containing BODIPYs by the synthesis of boron-dipyrromethene with a terminal alkyne for subsequent CuAAC reaction.

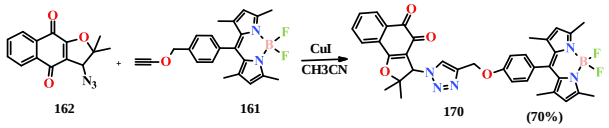


Scheme 31. Synthesis of the clickable BODIPY: 161

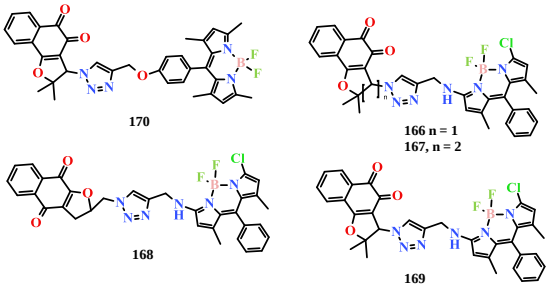


Scheme 32. Synthesis of quinone-based BODIPY hybrids 166–169.

The synthesized and characterized a small collection of novel quinone-based BODIPY hybrids of the natural products lapachol and lawsone (Scheme 32). All compounds were evaluated in cancerous and non-cancerous cell lines, and identified two nor β-lapachone hybrids (**169** and **170**) with potent cytotoxic activity. Mechanistic studies for both compounds suggest that the action of compound **169** may be related to the generation of reactive oxygen species whereas the fluorescent lapachone**170** may exert its cytotoxic action in subcellular lysosomal organelles (**Scheme 33**). This study provides new structure-activity relationships in the preparation of biologically active lapachone derivatives as well as new insights in the potential mechanism (Scheme 34) of action for their cytotoxic activity.[234]



Scheme 33. Synthesis of the quinone-based BODIPY derivative 170.

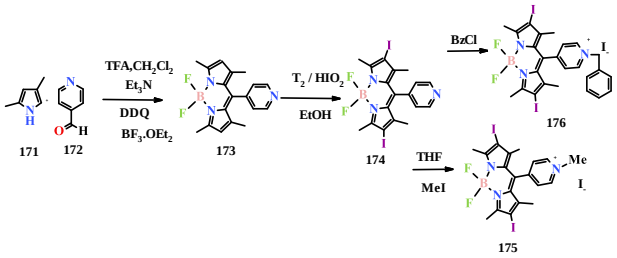


Scheme 34. Overview of lapachone derivatives and the design of quinone-based BODIPY hybrids.

5.3. Pyridine BODIPY's

The basic skeleton of BODIPYs can be further modified through synthetic procedures as needed, exploiting free pyrrole positions, functional groups likely present on the aromatic substituent and the methyls on the 3,5 positions. The water soluble BODIPYs have been reported in which the hydrophilicity was ensured by the presence of sulfonic groups, phosphonates,[235] sulfonated pepdide chains[236] or oligo-ethyleneglycol chains,[237] however, whereas the pegylated BODIPY have been used in PDT, none has been tested as phothosensitizer in antimicrobial PDT.

The photosensitizers obtained that following the standard procedures of BODIPY synthesis which allow a straightforward preparation of several hundread's milligrams of the desired compounds *via* condensation of pyrrole moieties with aldehydes or acyl chloride, followed by a mild oxidation step and complexation with BF_3; all synthetic steps were carried out in the same reaction flask. The insertion of pyridyl-aldehyde on the



dipyrrolylmethene 8-position was envisaged to ensure the molecule with a reaction site easily convertible to the corresponding cationic ammonium salt via straight forward alkylation procedures, thus compounds **175** and **176** were synthesized reacting **174** with two alkylating agent, methyl iodide and benzylchloride, respectively (Scheme 35).

Scheme 35. Synthesis of the BODIPY 173–176.

BODIPYs are recently studied in PDT against cancer cell whereas, to the best of knowledge, no reports have so far appeared about the use of this kind of compounds in PACT. Here in this new view show that manageable cationic BODIPYs, featuring iodine atoms on the 2,6 positions, can be successfully used in *in vitro* PACT irradiating with a green LED source. BODIPY **175** proved to be very effective against S. xylosus and even against the Gram negative *E. coli* under very ‘‘mild’’ conditions, i.e., short incubation time in the dark, limited light dose and low PS concentration, making this molecule a very promising antibacterial PS.[238]

6. Fused-Aryl-Bodipy’s:

Fusion of aromatic units to the BODIPY core has tended to be an efficient strategy to introduce a pronounced bathochromic shift. Aromatic units can be fused at the [*alpha*] bond, [*beta*] bond and the “zig-zag” edge of the BODIPY core. Fusion of aromatic units at all these positions resulted in red shift to their absorption/emission spectra.

6.1. Isothiocyanatophenyl-Fused-BODIPY’s

Tumor cells overexpressing membrane-bound EGFR can be targeted for therapy by combining NIR fluorescent molecules with biological labels. This can be achieved through the facile coupling of biological probes that have intrinsic specificity (binding properties) for the EGFR biomarker (*i.e.*, aptamers, antibodies, or peptides), with (Figure 45) highly fluorescent and nontoxic molecules such as boron dipyrromethenes.[239]

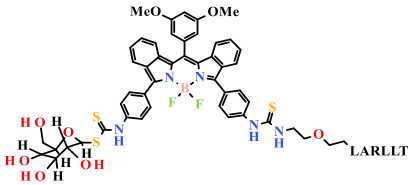
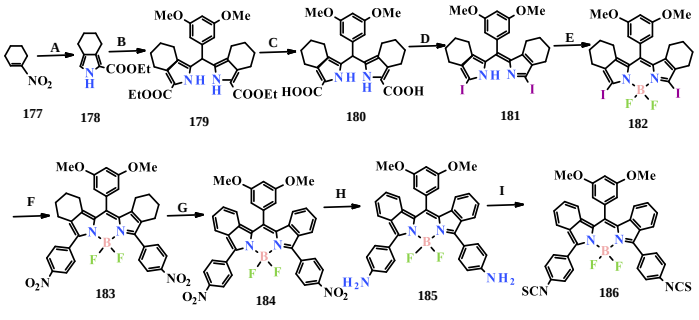


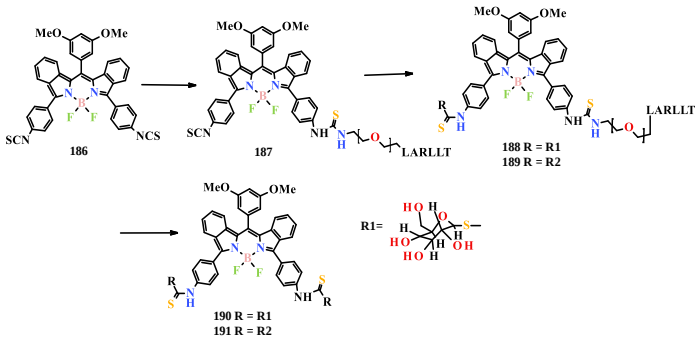
Figure 45. Structure of larllt peptide.

The precursor BODIPY **186** bearing two *p*-isothiocyanatophenyl groups at the 3- and 5-positions was prepared in nine steps as shown in Scheme 36. The synthetic route to BODIPY began with a Barton−Zardreaction.



Scheme 36. Synthesis of Bis(NCS)-Bodipy: Reaction Conditions: (A) Ethyl Isocyanoacetate, DBU, Thf, Rt, Overnight (80%); (B) 3,5-Dimethoxybenzaldehyde, *P*-Toluenesulfonic Acid, N-Tertbutylammonium Iodide, Dichloromethane (DCM), Rt Overnight (84%); (C) 1 M Koh, Thf, Methanol, Reflux For 24 hr, Then 1 M Hcl; (D) I_2, $NaHCO_3$, H_2o/Methanol, Rt For 72 H; (E) $BF_3{\cdot}OEt_2$, Et_3N, DCM, RT for 2 H (68%); (F) 4-Nitrophenylboronic Acid, $Pd(Dppf)Cl_2$, K_2CO_3, THF/Toluene, Reflux For 3 H (73−99%); (G) DDQ, Toluene, Reflux For 1.5 H (54−93%); (H) Hydrazine, Pd/C, Ethanol/THF, Reflux For 3 H; (I) TDP, DCM, Rt Overnight (90%).

Only one of the isothiocyanato groups of BODIPY **187** reacted with formation of a single thiourea bond. Several attempts were explored to elicit peptide diconjugation, including using a larger excess of peptide and varying the reaction time and concentration of reagents, but no di-peptide substituted BODIPY was observed Scheme 37.



Scheme 37. Synthesis of BODIPY conjugates: reaction conditions: (A) 3PEG-LARLLT, ET_3N, DMF, rt for 30 min (90%); (B) R_1−H or R_2−H, Et_3N, DMSO, RT for 30 min (187−83%).

A series of five BODIPY bioconjugates containing an epidermal growth factor receptor (EGFR)-targeted pegylated LARLLT peptide and/or a glucose or biotin ethylene diamine group were synthesized, and the binding capability of the new conjugates to the extracellular domain of EGFR was investigated using molecular modeling, surface plasmon resonance, fluorescence microscopy, competitive binding assays, and animal studies. The BODIPY conjugates with a LARLLT peptide were found to bind specifically to EGFR, whereas those lacking the peptide bound weakly and nonspecifically. All BODIPY conjugates showed low cytotoxicity (IC50 > 94 μM) in HT- 29 cells, both in the dark and upon light activation (1.5 J/cm^2). Studies of nude mice bearing subcutaneous human HT-29 xenografts revealed that only BODIPY conjugates bearing the LARLLT peptide showed tumor localization 24 h after intravenous administration. The results of our studies demonstrate that BODIPY bioconjugates bearing

the EGFR-targeting peptide 3PEG-LARLLT show promise as near-IR fluorescent imaging agents for colon cancers overexpressing EGFR.[240]

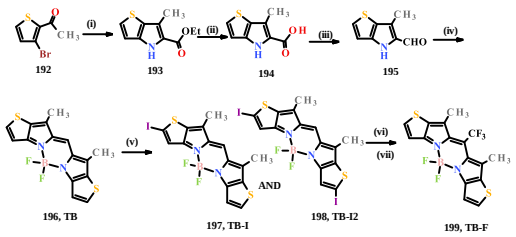
7. Heterocyclic Fused Reaction Methods of Bodipy's:

The excellent features of KFLs made them able to substitute or to complement existing commercially available fluorescent dyes and able to be used as new standard dyes in the vis-NIR region.

7.1. Thiophene-Fused Boron Dipyrromethene Dyes

The synthesis of TB derivatives[241] is outlined in Scheme 38. Until the preparation of the precursors before the ligand formation, all reactions proceeded in good yields.

The development of the thiophene-fused boron dipyrromethene derivatives as efficient light absorbers. The two strategies for the evolution of the optical properties such as the peak positions of absorption wavelengths and molar extinct coefficients were established by the substituent effects.[242]



Scheme 38. Synthetic outlines for Thiophene-Fused BODIPY'S. reagents and conditions: (a) Ethyl Cyanoacetate, CuI, CS_2CO_3, DMSO, 50^{oc}, 4 h, 61%; (b) NaOH, H_2o, Ethanol, reflux, 1 h, 95%; (c) (i) trifluoroacetic acid, 50 ^{o}c, 20 min, (ii) $CH(OEt)_3$ 50^{o}c, 30 min, 70%; (d) (i) $POCl_3$, Dichloromethane, rt, 3 days, (ii) Triethylamine, $BF_3.Et_2O$, rt, 2 days, 10%; (e) N-iodosuccinimide, acetic acid, Chloroform, rt, 24 h, 32% for TB-I, 23% for TB-I2; (f) (i) trifluoroacetic acid, 40^{oc}, 40 min, (ii) trifluoroacetic anhydride, 80^{o}c, 1 h; (g) $BF_3.Et_2O$, Triethylamine, Toluene, 80^{o}c, 2 h, 0.7% (in two steps).

To demonstrate the validity of the TB skeleton for the design of an efficient light absorber. From different point of view, two manners for evolving the optical properties of TB: by employing the heavy atom effect, the peak positions can be shifted to the red-light region. The enhancement of molar extinct coefficients was also obtained. It was found that the introduction of the strong electron-withdrawing group at the *meso* position in the BODIPY[243] skeleton was responsible for the drastic bathochromic shift in the absorption spectrum. Finally, obtained the series of efficient light absorber s for the red light. These compounds have suitable optical properties for generating the light to control photosynthesis and plant growth. Furthermore, thiophene-fused BODIPYs with the efficient light-absorbing ability are promised to be applicable for efficient sensitizers. The materials and chemical modification methods for modulating the optical properties presented here could be versatile for developing efficient photo-responsive bio-related materials to control the biological activities and efficient quenchers on the biotechnological assays with labelled biomolecules.[244]

7.2. Indole BODIPY's

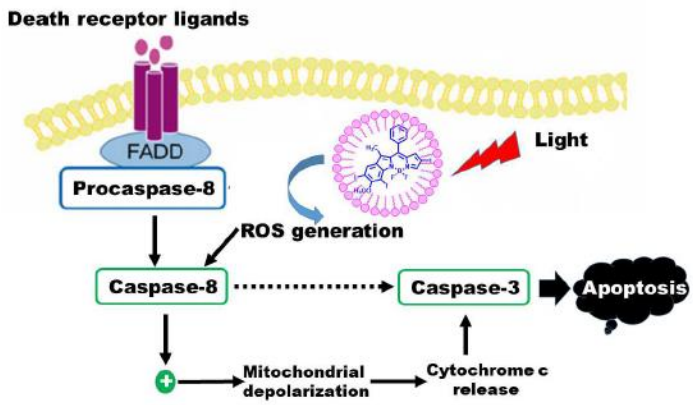
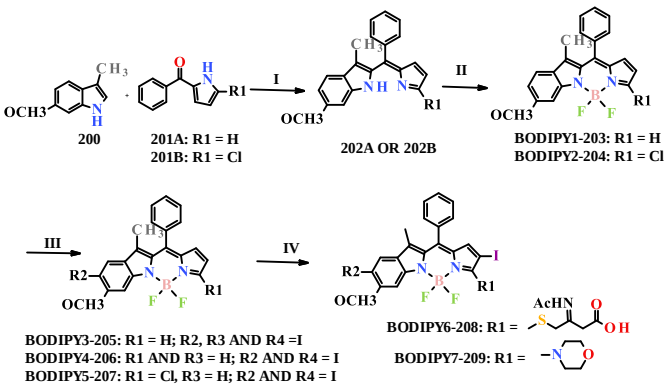


Figure 46. Generate ROS in mitochondria.

Mitochondria as the main site of ROS generation, is one of the major PDT targets, in which a rapid apoptotic response is often observed, associated with the activation of apoptotic caspases. Therefore, mitochondria-targeting PDT strategies Figure 46 have been shown to be effective for generating ROS, reducing the dosage needed, the side effects, and drug resistance.[245]

To improve the intersystem crossing efficiency and hence the $^1O_2$ generation efficiencies by introducing iodines in BODIPYs is illustrated in Scheme 39.



Scheme 39. The syntheses of BODIPY'S. i) $POCl_3$, CH_2ClCH_2Cl, 80^{oc}, 2.5h ; ii) BF_3/Et_2O, Et_3N, rt. 30 min; iii) NIS, $AcOH/CHCl_3$ (3:1), rt.; iv) Morpholine or *N*-acetyl-*L*-cysteine, Et_3N, CH_2Cl_2, rt.

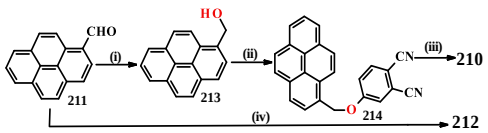
BODIPY3 205 was screened out as the most potential PS due to its good optical properties, high $^1O_2$ efficiency and photostability.[246] In order to improve the insolubility and instability of **BODIPY3 205** in aqueous system, DSPE-PEG2000 was used to trap **BODIPY3 205** into thehydrophobic core of micelles to obtain well-dispersing nano complexes **BODIPY3-PEG3** which has excellent solubility and stability in aqueous media. Moreimportantly, **BODIPY3-PEG3** is able to generate significant $^1O_2$ in living cells andexhibit high light cytotoxicity to three cancer cell lines. The mechanism studiesindicated that **BODIPY3-PEG3** could locate at mitochondria and cause the generationof ROS, which further result in mitochondrial dysfunction and photoinduced apoptosisvia caspase-8 and caspase-3 pathway.[247]

8. Fluorescence Probe Attached Synthetic Methods of Bodipy's:

8.1. Sonogashira Coupling Reaction of BODIPY

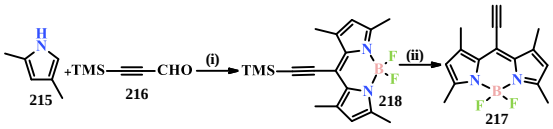
The rationale for such an optimized design[248] was to hope for a better transfer between the two antennas within the dyad by increasing the conjugation between the two antennas. At this stage of the study the yields of transfers were not measured.[251]

The syntheses of pyrene-containing probes **210** and **212** (Scheme 40) were the most straightforward to carry out. Pyrene-Pc **210** was synthesized by reduction of pyrene carboxaldehyde with $NaBH_4$ to afford pyrenyl carbinol **213** that undergoes SNAr with nitrodicyanobenzene to afford pyrenyloxydicyanonobenzene**214**. The latter was subsequently cyclotetramerized in the presence of zinc salt and DBU[249] to afford target **210**. The Pyrene-BODIPY conjugate **212** was synthesized in a three-steps one-pot procedure starting from a TFA-catalyzed condensation of pyrenyl-carbinol and dimethylpyrrole, followed by *p*-chloranil oxidation, deprotonation with triethylamine followed by borylation with BF_3-etherate.[250]



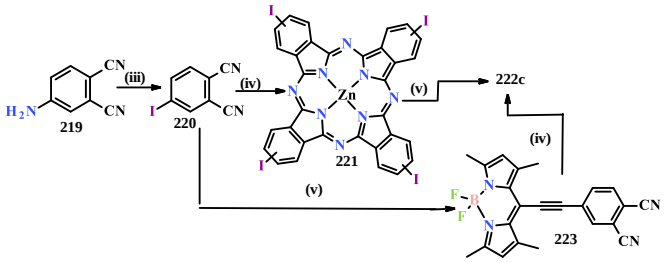
Scheme 40. Synthesis of pyrene-containing targets (1) AND (3) (i) $NaBH_4$, THF, MeOH, yield: 88%; (ii) K_2CO_3, DMSO, yield: 59%; (iii) $Zn(OAc)_2$, DBU, pentanol, yield:17%; (iv) a) dimethylpyrrole, TFA, b) *p*-chloranil, c) NEt_3, d) $BF_3.Et_2O$, yield: 22%.

Pc-BODIPY **222c** was synthesized from alkynyl-BODIPY **217** and tetraiodophthalocyanine $ZnPCI_4$ **221**. The condensation of dimethylpyrrole and trimethylsilylpropynal led to the formation of dipyrromethane that was oxidized, deprotonated and borylated to afford **218** in an overall three- steps one pot procedure. It should be noted that no acid catalyst was necessary in the synthesis of BODIPY **217** (Scheme 41), unlike that of BODIPY **218**. The protective group in **218** was removed to afford unprotected alkynyl-BODIPY **217**. Tetraiodophthalocyanine synthon **221** was synthesized from aminodicyanobenzene as follows: the latter was reacted with sodium nitrite to afford intermediate diazonium salt (none isolated), which reacts withiodide to afford iododicyanobenzene **220**.



Scheme 41. Synthesis of BODIPY- (i) $NaBH_4$, THF, MeOH, yield: 89%; (ii) K_2CO_3, DMSO, yield: 61%.

DBU-catalyzed cyclotetramerization of the latter in refluxing pentanol afforded $ZnPcI_4$ synthon **221**. This synthon was obtained as a mixture of regioisomers that cannot be separated. Subsequent Sonogashira coupling (Cu(I)/Pd(0) catalyzed) between iodinated phthalocyanine **221** and alkynyl-BODIPY **223** afforded BODIPY-Pc conjugate **222c**. It was obtained as a mixture with various degree of functionalization because of incomplete Sonogashira coupling. The mixture was purified by a series of washings with methanol to remove impurities. It was eventually subjected to Sonogashira coupling again, which increased the conjugation rate in BODIPY. Several attempts to separate the different BODIPY-Pc conjugates by standard chromatography on silica failed[252] (Scheme 42).



Scheme 42. Synthesis of synthons, such as BODIPY 223 and $ZnPcI_4$ 222c and subsequent sonogashira coupling between 223 and 222c leading to target 222c. (i) *p*-chloranil, NEt_3, BF_3-Et_2O, yield: 70%; (ii) KF, MeOH, yield: 70% (iii) $NaNO_2$, KI, CH_3OH, yield: 51%; (iv) DBU, $Zn(OAc)_2$, pentanol, yield in 7: 75%; (v) 6, $Pd(PPh_3)_4$, CuI, Et_3N, THF, yield in 2c: 60%; yield in 14: 40%.

Fluorescent Probes aimed at absorbing in the blue/green region of the spectrum and emitting in the green/red have been synthesized (as the form of dyads-

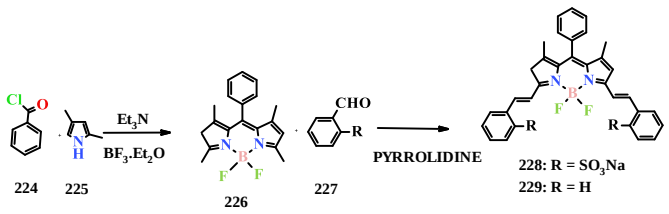
pentads), studied by spectrofluorimetry, and used for cellular imaging.

9. Unsaturated Linked Bodipy's:

9.1. Phenyl Unsaturated Bodipy's

A fluorescent chemosensor consists of an ion-recognition site and a fluorogenic unit for signaling. Spirocyclic rhodamine dye is a widely used platform for ion sensing because its fluorescence is switched on upon interaction with target ion through the transformation from the spirocyclic to the ring-opened form. Indeed, a number of rhodamine-based probes for Fe^{3+} detection have been reported in recent years.[253, 254]

BODIPY dyes have attracted growing attention in the fields of biological imaging, laser dye, optical device, and fluorescent switch, due to their intense absorption in the visible region, excellent photostability, and high fluorescence quantum yield. Moreover, the rich chemistry of BODIPY enables modification of the molecular structure to fine tune the absorption and emission wavelengths. Thus, BODIPY can be derivatized to an NIR-emitting dye by the Knoevenagel condensation of the 3- and 5-methyl groups with aromatic aldehydes Scheme 43.

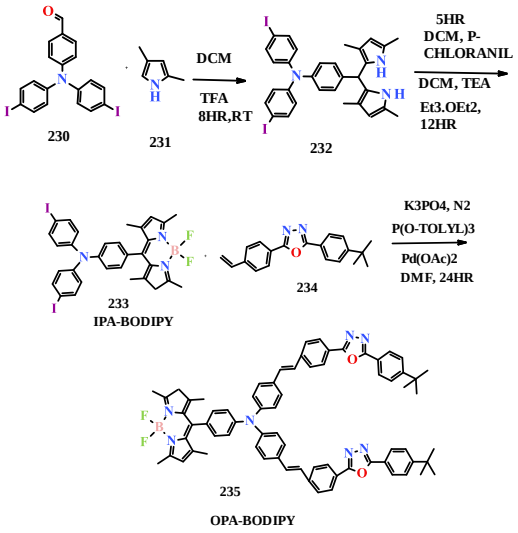


Scheme 43. Synthesis of NIR-fluorescent probe 228 and reference compound 229 via parent BODIPY 226.

BODIPY-based NIR fluorescent Fe^{3+}-probe **228**, readily prepared in two steps, exhibited high solubility and NIR fluorescence quantum yield in aqueous solution. **228** employs two sulfonate groups as the Fe^{3+} recognition units and NIR fluorescent BODIPY as the fluorophore unit. This probe exhibited an excellent fluorescence ON-OFF response toward Fe^{3+} but no response to most of the mono-, di-, and trivalent metal ions including Cr^{3+} and Hg^{2+}, common interfering metal ions for Fe^{3+}. Al^{3+} moderately quenched the fluorescence of **228** without showing the ON-OFF switching at least under the conditions employed. Hence, using an aqueous solution of **228** at 2 μM, one can perform the quantitative analysis of Fe^{3+} of up to 15 μM with a detection limit of 14.2 nM. The ON-OFF switching of B-1fluorescence by Fe^{3+} is reversible, and the NIR fluorescence quenched by Fe^{3+} can be readily recovered by adding reductant VC or stronger chelator EDTA to the fluorescence-silent Fe^{3+}-containing solution. Possessing the high water-solubility, the favorable spectroscopic properties, and the excellent reversible Fe^{3+}-recognition ability, probe **228** should find practical applications in chemical, biological, and environmental analyses.[255]

9.2. Oxadiazole linked phenylamine-BODIPY

A novel red aggregation-induced emission enhancement (AIEE) chromophore named OPA-BODIPY was designed based on 2-[4-(tert-butyl)phenyl]-5-(4-ethenylphenyl)- 1,3,4-oxadiazole and triphenylamine- BODIPY structure. It was synthesized through a new approach utilizing palladium-catalysed Heck reaction. It exhibited deep-red emission in solid state with a wavelength of 614 nm. It had bimodal emission in THF centred at 647 nm and 513 nm, the quantum yield of OPA-BODIPY at 647 nm was 0.11 while that at 513 nm was 0.01. The emission intensity in 90% THF/water mixtures was the strongest and the peak value was about 50 times of that in 10% THF/water, thus OPA-BODIPY performed typical deep-red fluorescence enhancement. The fluorescence intensity of OPA-BODIPY was strengthened continuously with increasing concentration of bovine serum albumin (BSA) which showed OPA-BODIPY could function as bioprobe for BSA (Scheme 44). It was applied to cell imaging and showed a good uptake by MDA-MB- 231 cells which suggested its promising application for biosensors.



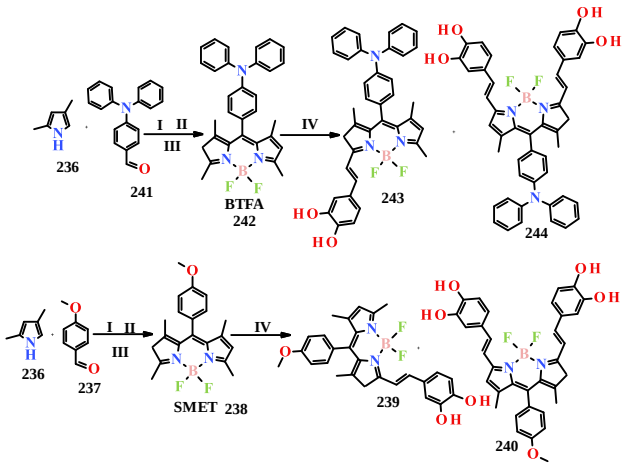
Scheme 44. Synthesis of target compound OPA-BODIPY.

BODIPY could be used as an ideal red-emitting fluorescent material. The AIEE behavior was related to the substituent at the two tentacles of triphenylamine in this triphenylamine-BODIPY construction and comparatively increased in the presence of large conjugated structure. Meanwhile, the emission intensity of OPA-BODIPY located at 628 nm enhanced markedly with the increasing concentration of BSA and gradually reached a stabs turation state which suggested that OPA-BODIPY[256] could be used as bioprobe for BSA.

9.3. Unsaturated Linked Triphenylamine-BODIPY's

BODIPY fluorophores in the literature generally use cyanoacedic acid and carboxylic acid that act as an anchoring moiety localized at C_2, C_6 and C_8 positions of BODIPY core[257,258]. Catechol moiety can also be used as an anchoring group for BODIPY dyes in DSSC application.

Investigated dye molecules consist of an electron donor moiety and one or two anchoring groups (Scheme 45). Here, electron donating moieties which are triphenylamine and methoxyphenyl bound to meso (C_8) position, while the catechol moiety which is the anchoring group attached to both C_3 and C_3-C_5 positions of the BODIPY core *via*., Knoevenagel condensation reaction. In order to evaluate the ground state interaction, linear absorption spectra of the sensitizers were measured both in THF solution and on TiO_2 surface. Linear absorption properties of studied dyes.



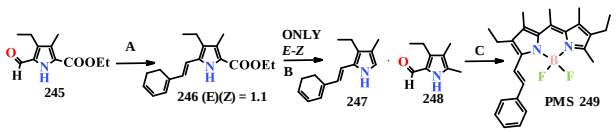
Scheme 45. Synthetic pathway of the BODIPY dyes; (i) cat. trifluoroacetic acid, rt, 12 h; (ii) tetrachloro-1,4-benzoquinone, rt, 12 h; (iii) (1) *N*,*N*-diisopropylethylamine; (2) $BF_3.Et_2O$, rt, 24 h; (iv) 3,4-dihdyroxybenzaldehyde, piperidine, acetic acid, reflux, 6 h.

The goal of this study is to reveal the parameters affecting the photo conversion efficiencies of BODIPY dye sensitized solar cells. Therefore, the effects of electron donating moieties as well as molecular symmetry, on electron injection dynamics and photovoltaic performance were studied. Attachment of the dye to TiO_2 was studied by altering the surface morphology of TiO_2 with fs laser ablation. Four new BODIPY derivatives were designed and sensitized to achieve these goals. Among the sensitized dyes, dye with methoxyphenyl electron donor group and unsymmetrical structure (*i.e.*, one anchoring group at C_3-position) showed the best photovoltaic performance despite of the lower absorption spectra on TiO_2 layer, comparing to the other sensitizers. This dye showed the longer excited state life time in solution and faster electron injection dynamics to TiO_2 as compared to the other sensitizers. Therefore, while designing new chromophores for DSSC applications one should consider not only the light harvesting capability but also the longer excited state lifetime in solution and shorter electron transfer time to TiO_2 on the film of anode electrode. In addition, that increasing the number of the anchoring group on the studied dye molecules may not result better photovoltaic performance. On the other hand, fs laser ablation treatment of the TiO_2 surface enhances the anchoring capability, shortens the electron injection time to TiO_2 conduction band, and therefore, increases the DSSC performance by about 47%. The believe that results are useful while designing new BODIPY chromophores for DSSC applications.[259]

9.4. 3-Styryl-BODIPY's

The photophysical and lasing properties of the dye PMS in air-equilibrated liquid solutions in apolar, polar nonprotic and polar protic solvents, as well as in solid solutions in linear homopolymers of methyl methacrylate (MMA) or in linear copolymers of MMA with the fluorinated monomer 2,2,2-trifluoroethyl methacrylate (TFMA). Taking into account that the rigidity of the matrix is of utmost importance in order to optimize their lasing action, in view of this incorporated the new dye into a crosslinked copolymer of MMA with ethylene glycol dimethacrylate (EGDMA).[260]

Three methods have been reported for the synthesis of 3-styryl-BDP (Scheme 46) dyes: (1) the most used has been the condensation of *p*-dimethylaminobenzaldehyde with 8-aryl-3,5-dimethyl-BDP dyes, taking advantage of the acidity of themethylgroupattachedto the position 3 of the chromophore core; (2) condensation of benzaldehydesor 2-formylpyrroleswith 2-styrylpyrroles, and subsequent formation of the corresponding symmetric or asymmetric BDP dyes with boron trifluoride diethyl etherate; (3) Heck reaction between a 3,5-dichloro-BDP dye and styrene, in the presence of Pd(II).



Scheme 46. Synthesis of the 3-styryl dye pms. reagents and conditions: (a) $PhCH_2PPh_3$, MeONa, THF, Ar, rt, 0.5 h, then 1 in THF, 2 h, then reflux, 1 h; (b) NaOH, EtOH–H_2O, pressure tube, Ar, 80 ◦C, 2 h; (c) $POCl_3$, $CHCl_3$, rt, 12 h, then Et_3N, $BF_3.OEt_2$, rt, 3 hr.

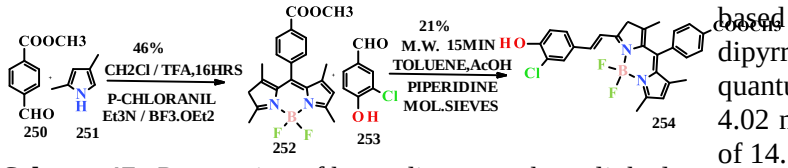
A new BDP **246** dye with a 3-styryl substituent, PMS **249**, has been synthesized with acceptable yield by a method that allows the synthesis of other related dyes with similar conjugated structures. PMS **249** shows higher molar absorption coefficient and oscillator strength than the commercial PM567 dye with similar

fluorescence quantum, if recorded in the same solvent, but the absorption and emission maxima of PMS **249** appear shifted ca. 50 nm, with regard to the corresponding maxima of PM567, as a consequence of the extent of the conjugated system. The electrostatic stabilization of the chromophoric positive charge by the dielectric constant of solvents such as 2,2,2-trifluoroethanol, led to a lasing efficiency as high as ca. 18% in both liquid solution and solid-fluorinated matrices. Laser excitation with 532-nm light of solid solutions of the dye PMS in fluorinated polymeric media, based on MMA with TFMA 9:1 (v/v), gives rise to high photostable laser emission since the system remains at 30% of the initial laser output after 100,000 pump pulses at 10 *Hz* repetition rate in the same position of the sample. To our knowledge, this is the first time that efficient laser emission is described for a 3-styryl-BDP dye. The results presented indicated that appropriate structural modifications in the BDP molecules can yield red emitting fluorophores that laser efficiently and with remarkable photostability when properly incorporated into polymeric matrices, enhancing the feasibility of solid-state organic photonic devices based on BDP dyes.[261]

9.5. *O*-Chlorophenol Unsaturated Linked BODIPY's

The phenol derivative sense the alkaline *pH* range, while the calix[*4*]arene and *o*-chlorophenol derivatives[262] are sensitive in the nearneutral *pH* range. The lack of fluorescence emission of the phenolate formswas attributed to an intramolecular charge transfer (ICT) between the phenolate anion and BODIPY subunits. At lower *pH* a large fluorescence enhancement without spectral shift was observed.[263]

Compound **254** (Scheme 47) was synthesized in 21% yield by microwave-assisted condensation of difluoroboradiaza-sindacene derivative **252** with 3-chloro-4-hydroxybenzaldehyde (**253**) using acetic acid–piperidine as a catalyst. The starting compound **252** was synthesized from methyl 4-formyl benzoate (**250**) and 2,4-dimethylpyrrole (**251**).



Scheme 47. Preparation of borondipyrromethene-linked phenol.

A novel borondipyrromethene-derived *pH* indicator (available as methyl ester (**250**) and sodium salt (**251**)) for the near-neutral *pH* range with ultra bright fluorescence in the red spectral region has been synthesized by linking *o*-chlorophenol to the 3-position of difluoroboradiazaindacene. Absorption and steady-state and time-resolved fluorescence measurements have been used to study the photophysical properties of compound **254**. The fluorescence lifetime (3.8±0.2 ns) and the fluorescence rate constant (kf = (2.6±0.2) × 108 (s−1) of dye **254** are independent of the solvent. In aqueous solution, the water-soluble dye undergoes a reversible protonation–deprotonation reaction (between phenol and phenoxide) in the near-neutral *pH* range responsible for the observed spectroscopic changes. The p*K*a of 7.60 is practically insensitive to low ionic strength. The very high fluorescence quantum yield of the acidic form (0.75) of sodium substituted compound **254** in aqueous solution,[264] the capability of using longer excitation/ emission wavelengths, and the high fluorescence enhancement factor make the new BODIPY derivative an excellent on/off fluorescent *pH* probe.

9.6. Triarylamine linked BODIPY's

Triarylamino groups[265] have been widely investigated as electron donors in DSSCs due to their admirable electron-donating abilities and hole-transport properties. However, the free thermal rotation of the aryl substituent in the excited state of the molecules (Figure 47) may cause serious energy loss,[266] resulting in decreased quantum yields. It is believed that if the phenyl rings in triarylamino groups were locked to limit their free rotation, the performance of the corresponding DSSCs could be improved.

Four donor-π bridge-acceptor structured boron dipyrromethene type sensitizers bearing triarylamine donors with different rigidities were synthesized and applied in dye-sensitized solar cells (Scheme 48). The influence of different triarylamine donors on the optical, electrochemical properties and photovoltaic performances of sensitizers was systematically investigated. It was shown that the photovoltaic performance of boron dipyrromethene type sensitizer-based cell increased with increasing the fluorescence quantum yield and fluorescence lifetime of the corresponding sensitizers, which are believed to be closely related to the rigidities of the donor groups in the molecule. The best performance was realized for the cell based on rigid 9-phenyl-carbazole-substituted boron dipyrromethene sensitizer (*ZH-beta*) with a fluorescence quantum yield of 0.516 and a fluorescence lifetime of 4.02 ns, resulting in a short circuit photocurrent density of 14.10 mA/cm^2 and an overall conversion efficiency of 4.42%, which are fairly good results achieved for boron dipyrromethene type sensitizer-based solar cell.

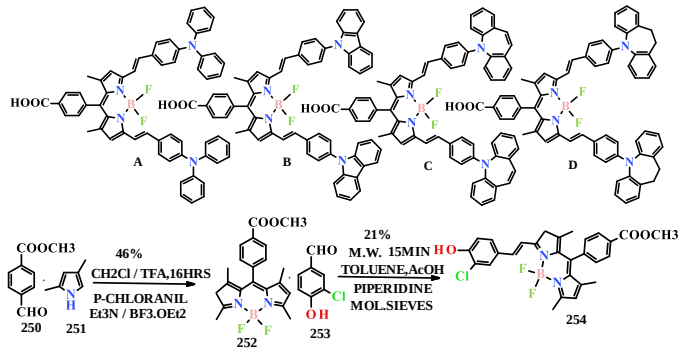
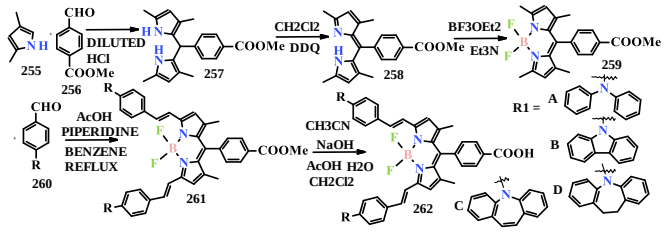


Figure 47. Molecular structure of four BODIPY sensitizers.



Scheme 48. Synthetic route for four BODIPY sensitizers.

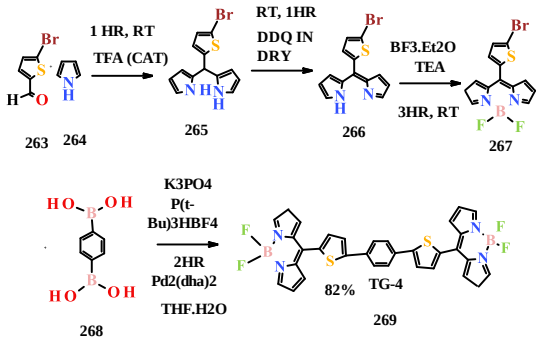
In the study, four BODIPY type sensitizers (ZH-a ~ ZH-d) containing triphenylamine, 9-phenyl-carbazole, 5-phenyl BODIPY type sensitizers which are closely correlated to the electron donor groups in the molecule, have an important influence on the resultant cell performance. The findings obtained in this study can also be employed a new strategy for the future molecular design of high performance BODIPY sensitizers.[267]

10. Preparation of Bis-Bodipy's:

10.1. Thiophene Linked Bis-Bodipy's

Research interest involving BODIPY molecules has grown multi-fold due to their different applications like photovoltaic, biological, photodynamic therapy, molecular rotor, etc. BODIPY molecules are evolving as efficient sensitizers in photovoltaic applications due to their chromophoric nature, high molar extinction coefficient, flexibility in structure modification, and thermal and photo stability.[268]

A synthesized the BODIPY molecule, which made up of two thiophene BODIPY cores comprising a phenyl spacer in between, coded as TG_4 dye molecule. Steady state and time resolved concentration dependent PL reveal that, at very low concentration (nM) TG_4 shows both S1 (first excited state) and S_2 (second excited state) PL269. Importantly, at higher concentration (mM) TG_4 found to exist in aggregated state. Optical absorption and PL studies confirmed that TG_4 exists in mixture of J-/Haggregate state. Moreover, femto second transient absorption (fs-TA) analysis has been studied following 400 nm optical pump, which reveals that the excited single state converted to the mixed aggregated state (Scheme 49).



Scheme 49. Step wise synthetic protocol of TG4 BODIPY 269.

They have carried out steady state and time-resolved PL and fs-TA experiment to study the photophysics of newly synthesized thiophene BODIPY molecule (TG_2). The TG_2 shows optical absorption maxima at 516 nm due to π-π^* electronic transition and broad optical PL band (400-580 nm). Both S1, and S2 PL bands are spectrally resolved in sub nM concentration. However, at relatively higher concentration (even in micro molar concentration), both S_1 and S_2 bands disappear and a red shifted broad PL band appears. The large Stokes shifted and broad PL band at micro molar concentration of TG_2 has been attributed to mixed *J*-/H-aggregated state PL of the dye molecule. Ultrafast TA studies reveal that on photo excitation of aggregated TG_2 and excited singlet are formed within pulse-width limited time (< 120 fs), which eventually convert to the excited mixed aggregated states through IC with in a time constant of ~ 6-8.5 ps.[270]

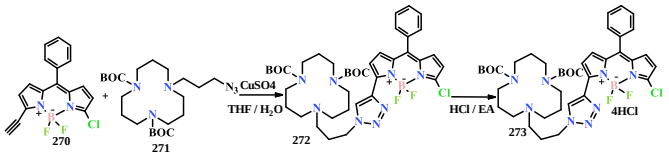
11. Chemical Property Reactions of Bodipy's:

11.1. Triazole linked-BODIPY's

Two fluorescent probes, **272** and **273**, derived from borondipyrromethene (BODIPY) modified with macrocyclic polyamine [12] aneN_3, were synthesized and applied in the discrimination of cysteine (Cys), homocysteine (Hcy), and glutathione (GSH)[271] with absorption and fluorescent spectroscopy in comparison. It was found that Boc-protected **272** showed highly sensitive and selective recognition of GSH over Cys and Hcy; while probe **273** was able to distinguish the three different thiols due to their different reactivities.[272] With its water-solubility, rapid responsiveness, high sensitivity and low cytotoxicity, probe **273** was successfully applied in the fast detection of three biothiols[271,273] in living cells.

Probes **272** and **273** were synthesized according to the reaction route shown in Scheme50 Acetylyl-5-chlorinated BODIPY **270** was obtained based on a known method[274] and served as starting material in the

subsequent steps. Reaction of **271** with Boc-protected *N*-(3-azidopropyl)-[12] aneN3[275] through copper (I) mediated click cycloaddition reaction resulted in probe **272**. Probe **273** was obtained by deprotection of **272** with hydrogen chloride in ethyl acetate.



Scheme 50. Cycloaddition reaction of BODIPY

In the, probe **273** have exhibit many promising properties such as rapid responsiveness, water-solubility, lower cytotoxicity, superb membrane permeability, and the selectivity to differentiate the three important thiols. Further study on these probes should result in practically useful fluorescent sensors that allow the *in vitro* and *in vivo* detection of thiols.[275]

11.2. Pyran based-BODIPY's

A fluorescent analog of *α*-tocopherol must be able to bind to the *α*-tocopherol transfer proteins to be useful. This criterion, as well as a known maximum molecular length (natural tocopherol) beyond which biological activity is greatly diminished,[276] place restrictions on ligand structure. Our wish to also extend the *UV–vis* absorption to longer wavelength by incorporating greater conjugation meant that a greater portion of the side chain length would be used for the chromophore. Substituted BODIPY fluorophores (Figure 48) absorb at longer wavelengths than the parent ones.

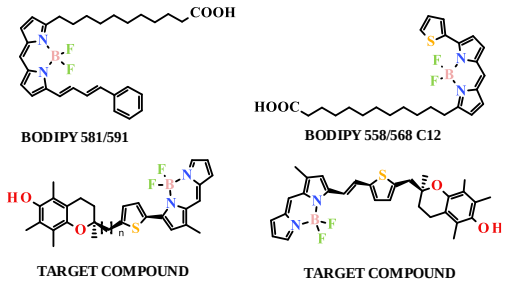
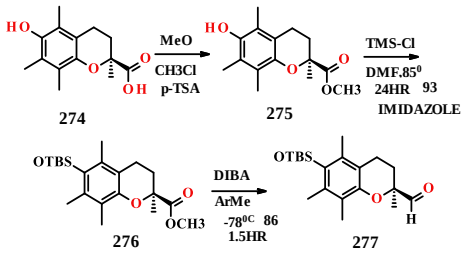


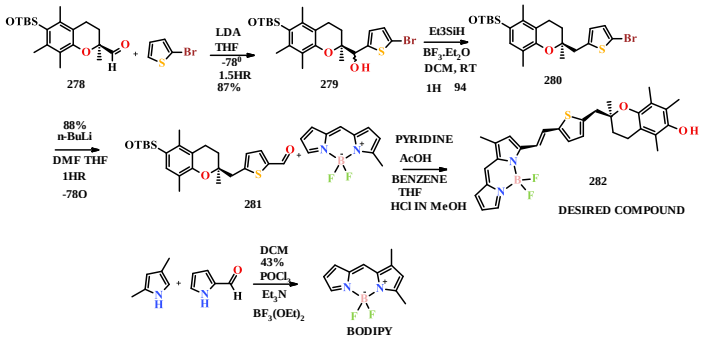
Figure 48. Examples of commercially available long wavelength bodipy structures, and structures of potential targets for similarly *UV/VIS* absorbing BODIPY-*α*-tocopherol analogs.

As with previous syntheses,we chose to incorporate the chromanol into a fluorescent probe using the readily available (*S*)-Trolox, **274**, by first esterification to the methyl ester **275**, followed by protection of the phenol with t-butyldimethylsilyl chloride to give **276**, and reduction of the ester with DIBAL to provide aldehyde, **277** (Scheme 51).



Scheme 51. Synthesis of Trolox aldehyde 277.

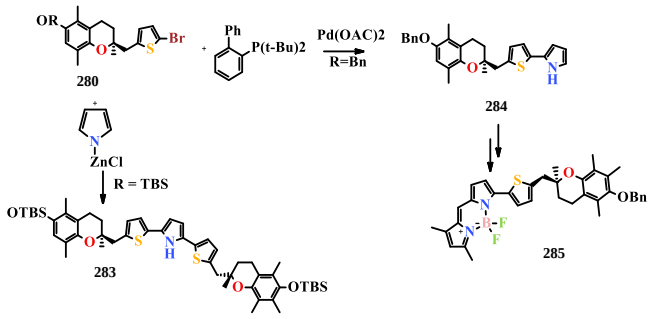
The anion of 2-bromothiopheneadded efficiently to **278**, and the resulting alcohol **279** was deoxygenated using Et_3SiH and $BF_3.Et_2O$ to provide **280** (Scheme52). Literature proceduresuse Et3SiH and trifluoroacetic acid, but this led to decomposition of the starting material. Other attempts at this deoxygenation utilizing hydride agents ($LiAlH_4$, $NaBH_4$ or $NaBCNH_3$) with different Lewis acid ($ZnCl_2$, ZnI_2, $AlCl_3$) failed. Only miniscule amounts of **280** were obtained with a combination of $NaCNBH_3$ and either $ZnCl_2$ or ZnI_2 in dichloroethane.



Scheme 52. Synthesis of target compound-thienyl-ene-BODIPY-toc.

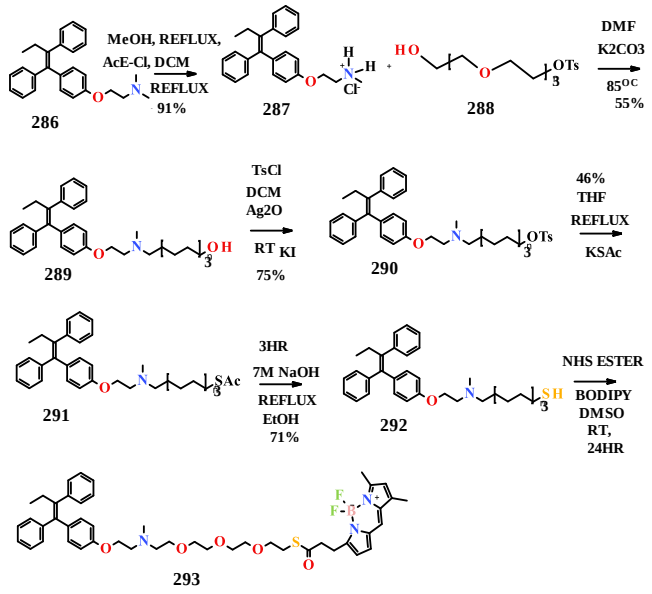
An alternative strategy to produce **282** by performing a Negishi-coupling between **278** and pyrrole using the procedure of Rieth et al.,[277] which would then be elaborated to a terminal BODIPY (Scheme 52), but this only yielded the dimer **281** as seen by ES-MS. When the *O*-benzyl-protected analog **283** was used the coupling reaction yielded only a small amount of product **284** (10.3%).

The fluorescent analog of *α*-tocopherol, thienyl-ene-BODIPY-*α*-Toc, **Target Compound 285**, (Scheme 53) was prepared and shown to binding specifically to human *α*-TTP. The high affinity, high molar absorption coefficient, quantum yield, and photostability, will make this probe a key feature of our studies of the function of *α* -TTP in glia and neurons.[278]



Scheme 53. An alternative route to 1 by coupling pyrrole to thienyl bromide, 10. Only dimer 12 was produce when r = tbs. Yields of TARGET COMPOUND were poor and this benzylated product could not be Deprotected.

11.3. Tamoxifen Conjugated-BODIPY's



Scheme 54. Synthesis of BODIPY FL conjugate of tamoxifen 293.

The synthesis of tamoxifen conjugated with BODIPY FL is outlined in Scheme 54. They have used a traditional conjugation approach to develop the probe compound based on tamoxifen.[277,279] Briefly, the tertiary amine of commercially available tamoxifen was demethylated using α -chloroethyl chloroformate to produce the quaternary ammonium salt[278,280] **293**.

Developing targeted validation probes that can interrogate biology is of interest for both chemists and biologists. The synthesis of suitable compounds provides a means for avoiding the costly labeling of cells with specific antibodies and the bias associated with the interpretation of biological validation experiments. The chemotherapeutic agent, tamoxifen has been routinely used in the treatment of breast cancer for decades. Once metabolized, the active form of tamoxifen (4-hydroxytamoxifen)[281] competes with the binding of estrogens to the estrogen receptors (*ER*). Its selectivity in ER modulation makes it an ideal candidate for the development of materials to be used as chemical probes.[282]

11.4. Guanosine Linked-BODIPY's

BODIPY-modified 20-deoxyguanosine was synthesized for use as a detection reagent for genotoxic compounds (Figure 49). BODIPY-FL is a well known fluorescence reagent whose fluorescent light emission diminishes near a guanine base by a photo-induced electron transfer process.

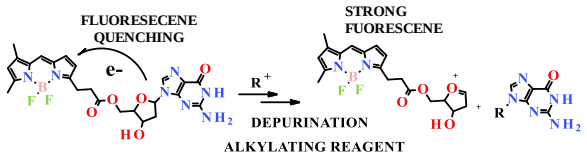
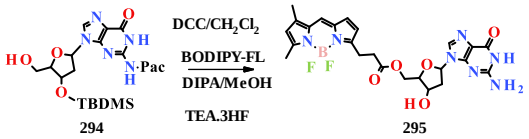


Figure 49. Concept of fluorescence detection of alkylating reagents by BODIPY-modified dg 295.

This property can be used to detect an oligonucleotide sequence and GTPase activities in cells.[284] Given the reactive nature of Dg to mutagenic compounds, the theorised that by attaching the BODIPY to dG at the nearest position, like 50-OH of dG, the expected compound **295** would generally show only weak fluorescence emission.[284] However, once some modifications occur at the guanine bases, the fluorescence of BODIPY will re-emerge (Scheme 55). This fluorescence recovery[285] can efficiently occur when alkylating compounds attack the BODIPY-modified dG, after which the depurination of the modified guanine bases occurs.



Scheme 55. Synthetic procedure for BODIPY-dg 295.

A simple modification of dG with BODIPY-FL could be used as a mutagen detector for oxidative DNA damages and alkylating reagents.[286]

11.5. Lysine-triazole linkage based BODIPY's

Glycolipid photo affinity probes **296** and **297** were designed as shown in Figure 50 to enable covalent crosslinking,[287] subsequent fluorescence detection and isolation of binding proteins. Based on this study, diazirine group would facilitate highly selective

photocross linking of low affinity carbohydrate-binding proteins in complex protein mixtures.[288]

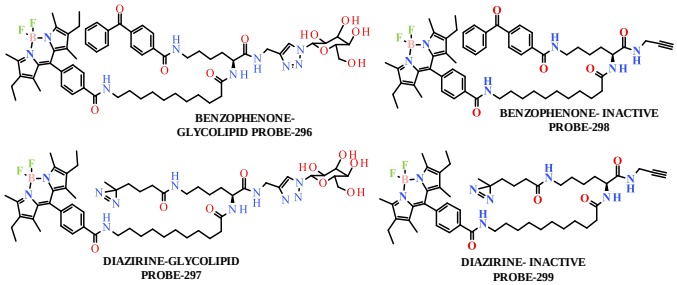
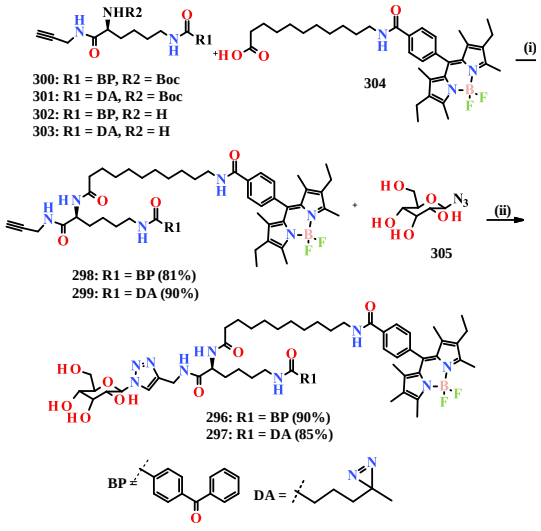


Figure 50. Structures of glycolipid photoaffinity probes 296–297 and the corresponding control probes (inactive probes) 298–299.

The syntheses of **296** and **297** were achieved as shown in Scheme 56. Compound **300** and **301** were synthesized from *N*-Boc-lysine as reported previously.[285,287] Briefly, *N*-Boc-lysine was first acylated using an NHS ester derived from either benzoyl benzoic acid or diazirine carboxylic acid, which was subsequently amidated using propargyl amine. After deprotecting Boc group, BODIPY-conjugated lauric acid **304** was introduced to amine **286** and **287** by amide coupling to yield alkyne-conjugated lipid tail unit **298** and **299**. The sugar head group was introduced to the alkyne-conjugated lipid tail unit under the copper-promoted alkyne–azide cycloaddition (CuAAC) condition **286** using glucosyl azide **305** to provide benzophenone-based glycolipid probe **296** and diazirine-based glycolipid probe **297** in high yield.



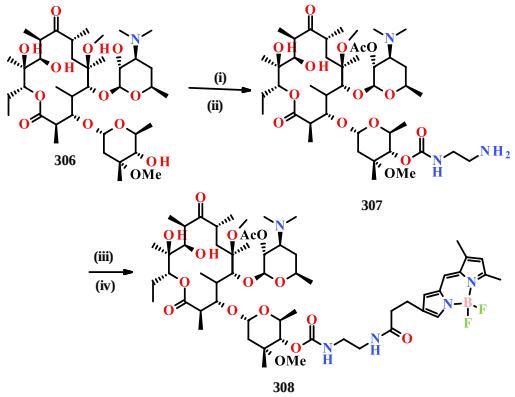
Scheme 56. Structures of glycolipid photoaffinity probes 296–297 and the corresponding control probes (inactive probes) 298–299.

In this research paper, they are evaluated two approaches to distinguish a specific binding protein, in which an inactive probe or a competitive ligand was employed in parallel reactions for comparative analysis. It was found that the comparative analysis involving a competitive ligand was more reliable and that diazirine probe **297** allowed more straightforward detection of a specific carbohydrate-binding protein (i.e., b-glucosidase) than benzophenone probe **296**. These experiments together demonstrated that diazirine-based glycolipid photoaffinity probes **297** would be suitable as a photoaffinity probe to explore specific glycolipid binding proteins.[289]

11.6. Erythromycin probes of BODIPY's

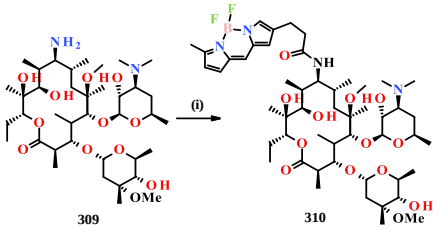
Fluorescent probes that covalently link fluorophores to ribosome inhibitors to probe inhibitor–ribosome interactions and to estimate the location of the inhibitor binding sites.[290] Some of those probes were also successfully used in uHTS to identify small molecules that interact with ribosomes.

The preparation of probe **308** commenced with 6-*O*-methyl-erythromycin[291] (clarithromycin) **306**. The 20-hydroxy group was selectively protected by an acetate group (Scheme 57).



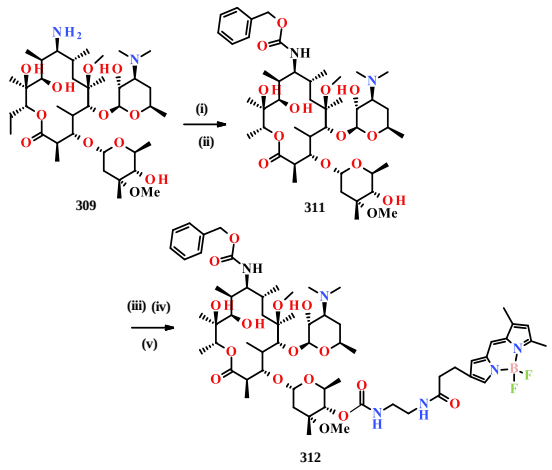
Scheme 57. Preparation of probe 308. reagents and conditions: (a) 1.0 equiv Ac_2O, 3.0 equiv Et_3N, CH_2Cl_2, rt, 16 h; (b) 1.0 equiv CDI, THF, 35 ºC, 12 h, then added 10 equiv $NH_2CH_2CH_2NH_2$, 45 ºC, 1 h; (c) BODIPY-FL propionic acid, succinimidyl ester, DMF, rt, 1 h, 34% from compound 1; (d) MeOH, 60 ºC, 1 h, 33%.

Fluorescent probe **310** was prepared by tethering BODIPY fluorophore to the 9-position of 9-aminoerythromycin **309** (Scheme58), which in turn was prepared from erythromycin A.



Scheme 58. Preparation of probe 38. reagents and conditions: (a) 1.0 equiv BODIPY-FL propionic acid, 1.0 equivsuccinimidyl ester, DMF, rt, 1 h, 62%.

BODIPY probe **312** is a version of probe **308** (Scheme 59) optimized to be more useful in screening due to an increase in the ribosomal off rate as described below. The synthesis involved protecting the amine group of compound **309** with benzyl carbamate and otherwise followed the similar synthesis described for the preparation of fluorescent probe **310**.



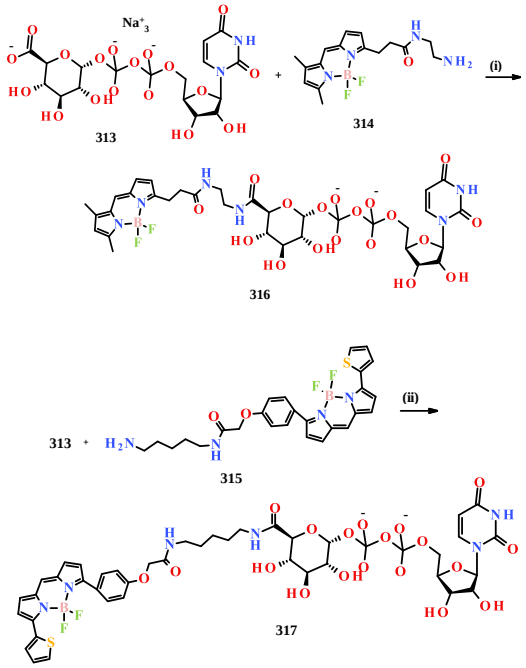
Scheme 59. Preparation of probe 40. reagents and conditions: (a) 1.0 equiv N-(benzyloxycarbonyloxy) succinamide, DMF; (b) 1.2 equiv Ac_2O, 4.0 equiv Et_3N, CH_2Cl_2, rt, 16 h; (c) 2.0 equiv CDI, THF, 35 ºC, 12 h, then added 10 equiv $NH_2CH_2CH_2NH_2$, 45 ºC, 1 h; (d) 1.0 equiv BODIPY-FL propionic acid, 1.0 equivsuccinimidyl ester, DMF, rt, 1 h, 48% from 1; (e) MeOH, 60 ºC, 1 h, 42%.

BODIPY–erythromycin probes of bacterial ribosomes were designed and synthesized by attaching a BODIPY fluorophore to the 4- and 9-positions of the erythromycin structure. The probes exhibited excellent binding affinity to bacterial ribosomes and competed with erythromycin and other drugs whose binding sites are in the same vicinity of the 50S subunit. The synthetic fluorescent probe **310** was successfully adapted in our ultra high-throughput screening (*u*HTS) to identify novel ribosome inhibitors.[292]

11.7. Glucose attached BODIPY's

The diversity of expression of the $P_2Y_{14}R$ and the ubiquitous nature of its endogenous activators, that is, UDP and UDP-sugars, the development of ligands selectively targeting this receptor is a considerable challenge and an important goal for pharmacological studies and potential therapeutic applications.[293]

Thus, chose the structure of **313** as a starting point for designing and building fluorescent probes. The objectives were to facilitate. The availability of such affinity probes and to validate further the previously constructed computational models. The chemical series of hydrophobic P2Y14R antagonist,[292,294] in which a less hydrophobic fluorophore, AlexaFluor 488, in conjugate was optimal, the restriction of choosing a hydrophilic fluorophore was relieved due to the inherent high polarity and hydrophilicity of **313**. Additionally, various BODIPY dyes with built-in reactive amine linkers of varying length are readily available commercially. Two amide-bound conjugates, **316** and MRS4183 **317** (Scheme 60), were docked into a homology model of the hP2Y14R to predict their fit prior to synthesis.



Scheme 60. Synthesis of fluorescent conjugates of 41. Reagents and conditions: (i): HATU, Et_3N, DMF, 23 ºC, 2% yield; (ii) CMP (1.5 equiv), DIPEA (2 equiv), DMF, 0 ºC, 0.3% yield.

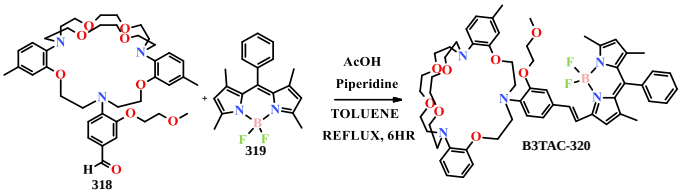
The $P_2Y_{14}R$ is a Gi/o-coupled receptor of the P_2Y family of purinergic receptors that is activated by extracellular UDP and UDP-glucose (UDPG). In an earlier report, that described a $P2Y_{14}R$ fluorescent probe, MRS4174, based on the potent and selective antagonist PPTN, a naphthoic acid derivative. Here, the results of the design, preparation, and activity of an agonist-based fluorescent probe MRS4183 (**317**) and a shorter $P2Y_{14}R$ agonist congener, which contain a UDP-glucuronic acid pharmacophore and BODIPY fluorophores conjugated through diaminoalkyl linkers. The design relied on both docking in a $P2Y_{14}R$ homology model and established structure activity relationship (SAR) of nucleotide analogs.[295]

11.8. 3-Styrylated BODIPY's

The synthesis and spectroscopic properties of a novel red-emitting, fluorogenic K+ probe, B_3TAC, which is also applicable for colorimetric detection of K+ ion. As an ionophore, we selected TAC because of its good

selectivity for K+ and fast response to changes of ion concentration.[296]

The synthetic route to B3TAC is depicted in Scheme 61. **B3TAC-318** was obtained by Knoevenagel-type condensation of TAC-aldehyde (**318**) and 8-phenyl-1,3,5,7-tetramethyl BODIPY (**319**) in a Dean–Stark apparatus with 15% yield.



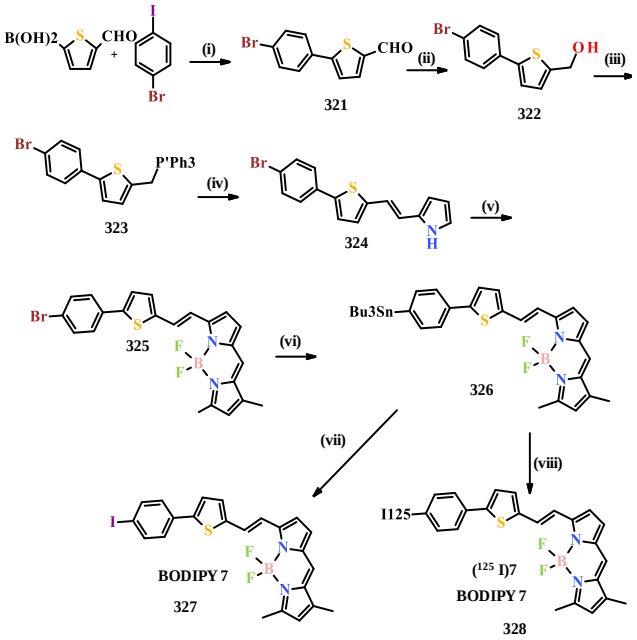
Scheme 61. Synthesis of B3TAC-320 by knoevenagel condensation.

In a developed a red-emitting fluorescent K+ probe, B_3TAC, which also shows a wavelength shift upon binding to K+. The probe was synthesized by conjugating a cryptand-based chelator, 2-triazacryptand [2,2,3]-1-(2-methoxyethoxy)benzene (TAC), to position 3 of the BODIPY fluorophore through a styryl linker. In water–acetonitrile mixed solvent, it responded to K+ in the physiological concentration range with high selectivity over Na+ and other metal ions. B_3TAC is potentially useful for measuring cellular K+ ion concentration, as well as for simple, naked-eye detection of K+ in solution.[297]

11.9. *β*-Amyloid linked BODIPY's

A design strategy for the development[298] of a dual SPECT/fluorescent probe for *alpha*, *beta* plaques in the brain. In this study, the selected boron dipyrromethane (BODIPY), one of the most useful fluorophores.[299]

The target BODIPY derivative[300] was prepared as shown in Scheme 62. The compound **321** was synthesized in a yield of 21.4% by the Suzuki coupling reaction. After reduction of the aldehyde to an alcohol by $NaBH_4$, the desired Wittig reagent 3 was readily prepared from **322** and triphenylphosphine. The compound **322** was produced by a Wittig reaction between **323** and pyrroaldehyde. The key step in the formation of the BODIPY backbone was accomplished by the condensation of pyrrole-2-carboxylaldehyde and **324** at low temperature, followed by the addition of $BF_3.OEt_2$. The bromo compound (**325**) was reacted with bis(tributyltin) using Pd(0) as a catalyst, and the corresponding tributyltin derivative (**326**) was obtained in a yield of 17.0%. The tributyltin derivative (**327**) was readily reacted with iodine in chloroform at room temperature to give the iodo derivative (**328**) in a yield of 20.0%. The radioiodination was achieved by the same iododestannylation reaction using hydrogen peroxide as the oxidant, which produced the desired radioiodinated ligand, **BODIPY7-327**, in a yield of 25% and with greater than 95% radiochemical purity.



Scheme 62. Reagents: (i) dioxane, $(Ph_3P)4Pd$, Na_2CO_3; (ii) MeOH, $NaBH_4$; (iii) $CHCl_3$, Ph_3P–HBr; (iv) MeOH, NaOMe, 2-formylpyrrole; (v) CH_2Cl_2, 3,5-dimethylpyrrole-2- carboxaldehyde, $POCl_3$, Et_3N, $EtOBF_3$; (vi) dioxane, $(Bu_3Sn)_2$, $(Ph_3P)_4Pd$, Et_3N; (vii) $CHCl_3$, I_2; (viii) EtOH, HCl, H_2O_2, [^{125}I]NaI.

The imaging of *β*-amyloid (Ab) aggregates in the brain may lead to the early detection of Alzheimer's disease (AD) and monitoring of the progression and effectiveness of treatment. The purpose of this study was to develop dual modality SPECT and fluorescent probes based on boron dipyrromethane (BODIPY) as a core structure. To designed and synthesized a ^{125}I-labeled derivative of BODIPY (BODIPY7). **BODIPY7-327** had a Ki value of 108 nM for *Ab* aggregates and exhibited peaks of absorption/emission at 606/613 nm. It detected *Ab* plaques in sections of brain tissue from an animal model of AD and displayed low uptake in the brain and high uptake in the liver in normal mice.[301]

11.10. Monoboronic Acid Substituted BODIPY's

A ratiometric carbohydrate sensor consisting of the boron dipyrromethene fluorophore substituted with boronic acid at the 2-position, based upon the strong substituent dependency of the absorbance/fluorescence wavelengths of BODIPY. The substituent is in equilibrium between the boronic acid $B(OH)_2$ and boronate ($B(OH)_3$-) forms, which have different absorbance/fluorescence wavelengths in the visible region (Figure 51**)**.

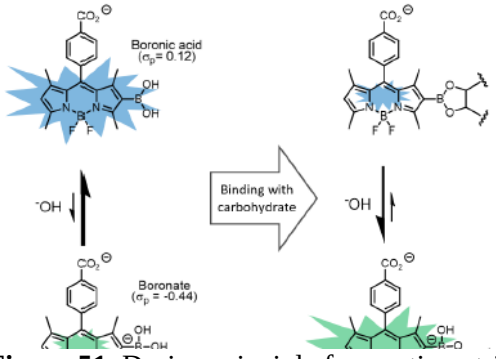
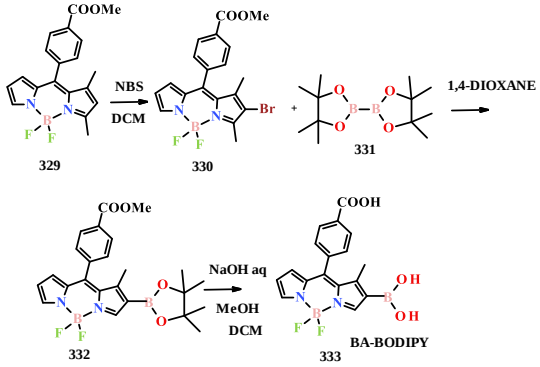


Figure 51. Design principle for a ratiometric carbohydrate sensor based on reaction of carbohydrate diol moiety with monoboronic acid-substituted BODIPY.

Firstly, set out to synthesize BODIPY substituted with boronic acid at the 2-position. 2-Pinacolato-boronic acid-substituted BODIPY has already been reported as an intermediate for coupling reaction,[302] but its fluorometric properties were not given, and the deprotected boronic acid derivative was not reported. According, to synthesized mono-boronic acid-substituted BODIPY (BA-BODIPY) by bromination at the 2-position, followed by conversion of the bromo group to pinacolato-boron and basic deprotection of the cyclic ester (Scheme 63).



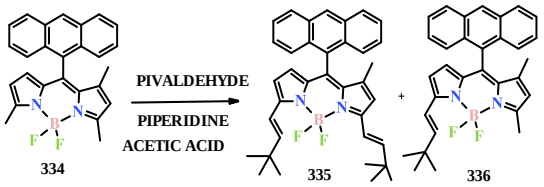
Scheme 63. Synthetic Scheme of BA-BODIPY.

The designed and synthesized a BODIPY-based sensor bearing boronic acid at the 2-position that reacts with carbohydrates to afford a cyclic ester. The resultant change in the equilibrium between the $B(OR)_2$ and $B(OR)_3$- forms, which have different fluorescence peak wavelengths, generates a ratiometric fluorescence response. Although further study will be needed to establish the specificity for various carbohydrates, the core fluorescent scaffold should be available as a basis for the design of practical sensors for clinical diagnosis or biological studies, possibly by introducing selective recognition sites,[303] and a study along this line is currently underway.[304]

11.11. Divinyl BODIPY derivatives

Fluorescence emission maxima of BODIPY dyes via chemical modification of BODIPY core, such as fusion rings to the pyrrolic position to extend *pi*-conjugation,[305] replacement of the 8-carbon atom with a nitrogen atom to form aza-BODIPY dyes,[306] and peripherally substitution.[307]

The synthetic route used to prepare this compound is shown in Scheme 64. The preparation of the target BODIPY **335** required the two starting materials BODIPY **336** and pivaldehyde. The key step involved a Knoevenagel reaction in a mixture of toluene and piperidine leading to the purple disubstituted derivative BODIPY **335** in 48%-isolated yield after careful column chromatography. The red mono-substituted BODIPY **336** was also synthesized in isolated 25% yield at the same time.



Scheme 64. Synthesis of divinyl BODIPY'S by knoevenagel reaction.

The extensive *pi* conjugation is responsible for their red-shifted emission. Cell imaging experiments demonstrated its potential application as a biological fluorescent probe due to its excellent imaging contrast (Figure 52).

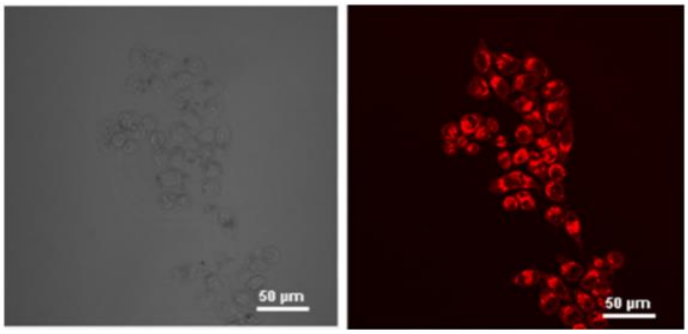


Figure 52. Bright field (left) and intracellular fluorescence image (right) of hela cells after incubation BODIPY 1 (AT 1 µM) for 1 hr.

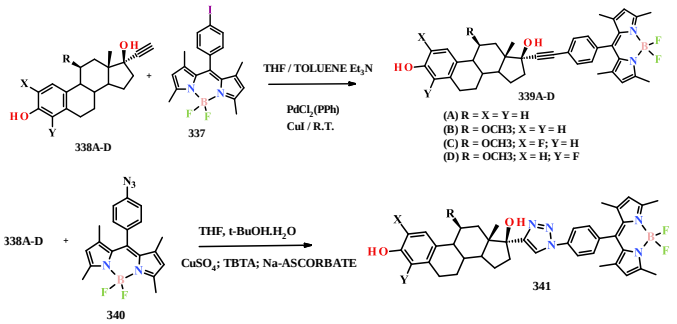
A fluorescent BODIPY **335** has been synthesized by connected two 3,3-dimethyl-1-butenyl substituents to the central BODIPY core through a conjugated tether at the 3,5-positions. Both mono- and difunctionalised derivatives (Figure 52) are accessible. The presence of 3,3-dimethyl-1-butenyl substituents affects the absorption and emission maxima of the BODIPY nucleus, thereby confirming that these units are coupled

electronically. Cell imaging experiments demonstrated that this dyes represent an important addition to the range of strongly absorbing and emitting reagents that could be used as a candidate for bio-related fluorescent bioimaging.[308]

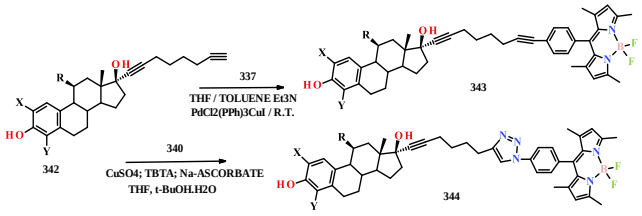
11.12. BODIPY derivatives by using click reactions

These dyes can be radiolabeled with ^{18}F by exchange or substitution of one of the fluorides within the canonical BF_2 dipyrromethene core, rendering them suitable as bimodal PET/fluorescence imaging agents.[309] Furthermore, BODIPYderivatives can generate singlet oxygen providing their potentialuse as photosensitizer in photodynamic therapy (PDT).[310]

The Huisgen 1,3-dipolar cycloaddition reaction, known as the azide/alkyne-‘‘click”-reaction or CuAAC-reaction of organic azides and alkynes, has gained considerable attention in recent years due to its quantitative, robust and orthogonal ligation reaction, suitable for even more sensitive biomolecular ligation.[311] They have been interested in the utilization of copper (I) catalyzedazidealkyne cycloaddition (Click) to assemble conjugates and examine the influence of the 1,2,3-triazole linkage on RBA for the ER. Scheme 65 and 66 show the synthetic methodology for the two 1,2,3-triazole linked BODIPY-EE_2 derivatives.



Scheme 65. Synthesis of 17*β*-estradiol-BODIPY conjugates.

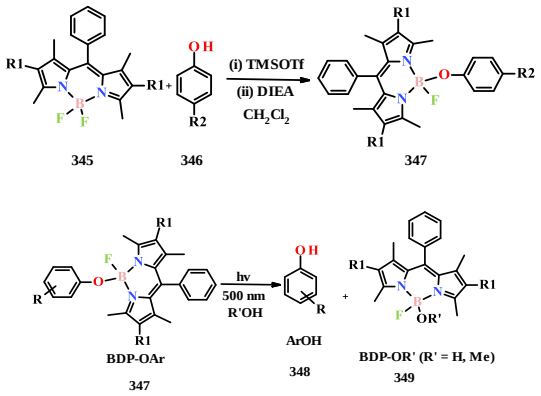


Scheme 66. Synthesis of 17*β*-estradiol-BODIPY conjugates.

In vivo imaging of estrogen receptor (ER) densities in human breast cancer is a potential tool to stage disease, guide treatment protocols and follow-up on treatment outcome. Both positron emission tomography (PET) and fluorescence imaging have received ample attention to detect ligand-ER interaction. In this study, preparation of BODIPY-estradiol conjugates using 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) as fluorescent probe and estradiol derivatives as ligand and established their relative binding affinity (RBA) for the ERa was observed. The synthesis of the conjugates involves attachment of a BODIPY moiety to the C17*α*-position of estradiol using Sonogashira or click reactions of iodo-BODIPY or BODIPY with various 17α-ethynylestradiol (EE_2) derivatives. The highest RBA for the ERa was observed with the EE_2-BODIPY conjugate (**343**) featuring a linear eight carbon spacer chain. Cell uptake studies and *in vivo* imaging experiments in an ER-positive mouse tumor model are in progress.[312]

11.13. Aryloxy BODIPY derivatives

Photoremovable protective groups, or caging groups, enable us to regulate the activities of bioactive molecules in living cells upon photoirradiation. Nevertheless, requirement of UV light for activating caging group is a significant limitation due to its cell toxicity and its poor tissue penetration. Our group previously reported a 500 nm light-activatable caging group based on BODIPY scaffold; however, its uncaging efficiency was lower than those of conventional caging groups. Here we show that the uncaging quantum yield (QY) of BODIPY caging group depends upon the driving (Scheme 67) force of photo-induced electron transfer (P-T). We also found that the uncaging QY increased in less polar solvents.[313]



Scheme 67. General scheme of the uncaging of 4-aryloxy BODIPY derivatives.

Recent research has revealed that exclusive intra- or extracellular localization of a bioactive molecule is crucial for signaling outcome. Thus, BODIPY caging groups would serve as a useful caging scaffold for intracellular uncaging applications. Finally, findings should also be helpful to develop red-shifted BODIPY caging groups that would be (Figure 53) useful for *in vivo* application.[314]

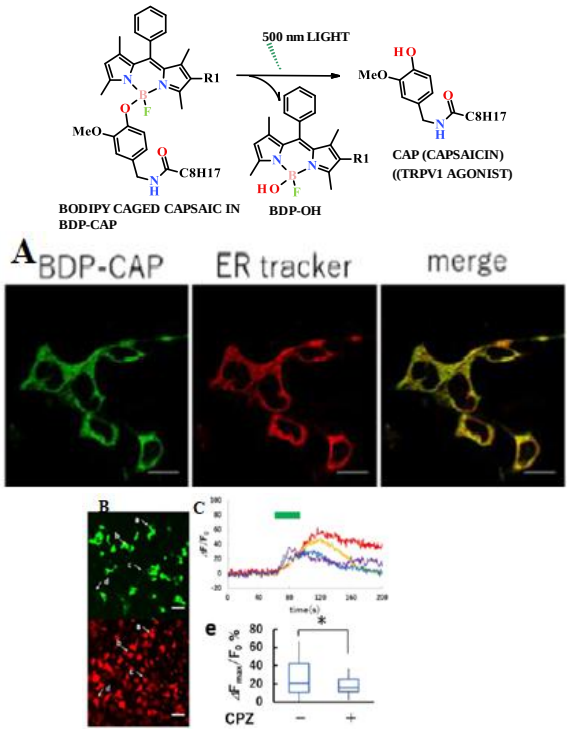


Figure 53. Photoreaction scheme of BDP-CAP and intracellular localizations of BDP-CAP.

11.14. Bis-boronic acid BODIPY's

In the conjugate the sLex-selective boronolectin to BODIPY, a well-known fluorophore for the initial feasibility studies because of its longest-wavelength (kex: 651 nm, kem: 660 nm). As for the conjugation chemistry (Figure 54), a combination of amidation and Huisgen [3+2] cycloaddition reactions.[315]

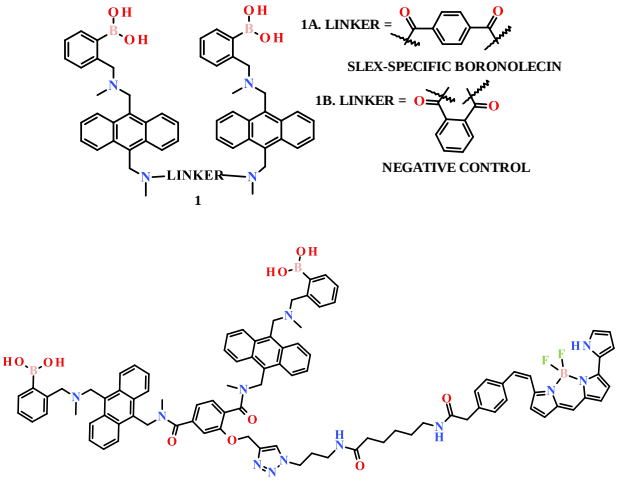
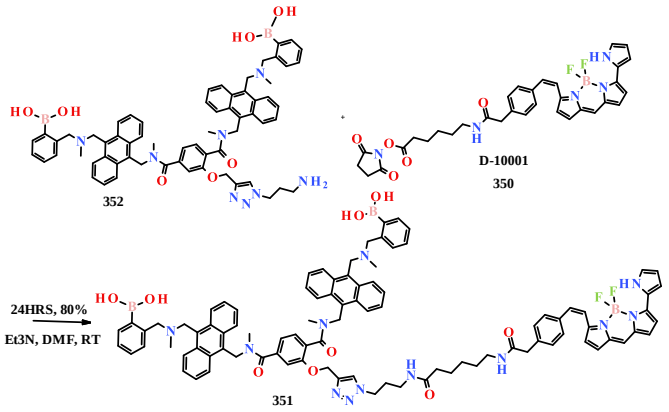


Figure 54. Boronolectin -BODIPY.

Scheme 68 shows the synthesis of the boronolectin-fluorophore conjugate **79**. The fluorescent agent **351** was accomplished in 80% yield by condensation[314] of **352** with a BODIPY succinimidyl ester D-10001 **350** at room temperature.



Scheme 68. Succinimidyl ester BODIPY derivatives.

Carbohydrate-based biomarkers such as sialyl Lewis X are known to correlate with cancer formation and progression[316]. By targeting sialyl Lewis X, have developed a boronolectin-fluorophore conjugate, which was able to selectively label and image xenograft (sc) tumor. This represents the very first example that a small molecule capable of recognizing a carbohydrate biomarker was used for optical imaging application.[317]

Fluorescent quinone-based BODIPY hybrids were synthesised and characterised by NMR analysis and mass spectrometry. The measured their cytotoxic activity against cancer and normal cell lines, performed mechanistic studies by lipid peroxidation and determination of reduced (GSH) and oxidized (GSSG) glutathione, and imaged their subcellular localisation by confocal microscopy. Cell imaging experiments indicated that nor-*β*-lapachone-based BODIPY derivatives might preferentially localise in the lysosomes of cancer cells. These results assert the potential of hybrid quinone-BODIPY derivatives as promising prototypes in the search of new potent lapachone antitumor drugs.

11.15. Phenothiazine Linked Bis-BODIPY

In view, of that Bodipy dyes with (D-*Pi*-A)$_2$ motif were more efficient than congeners with single D-*Pi*-A in hole injection and dark-current suppression.[318] Therefore, the ongoing effort to prepare dye materials that absorb longer wavelengths of radiation led us to modify the structure of BODIPY by extending the p-conjugation to provide new types of D-(*Pi*-A)$_2$ motif dyes in this work are included. On the other hand, phenothiazine (PTZ) was used as the electron donor of sensitizers owing to its electron-rich N and S atoms in the heterocyclic structure and its non-planar butterfly conformation which can sufficiently inhibit molecular aggregation and the formation of intermolecular excimers.[319]

Three 2,6-conjugated Bodipy metal-free organic dyes, UY10 **360**, UY11 **362**, and UY1 **361** with D-(*Pi*-A)$_2$, D-(*Pi*-A)$_2$, and DepeA frameworks, have been

synthesized which contain a rigid alkyl-functionalized phenothiazine (PTZ) core as the donor part and one or double cyanoacetic acid units as acceptor and anchoring part. Their photophysical and electrochemical properties as well as theoretical computation have been extensively investigated. Nano crystalline TiO_2-based dye sensitized solar cells (DSSCs) are fabricated using these dye molecules as light-harvesting sensitizers. Among these dyes, the dye UY11 **362** with De(epepeA)$_2$ framework exhibits the best photovoltaic performance with a short-circuit photocurrent density (*Jsc*) of 11.82 mA cm^{-2}, an open-circuit photovoltage (Voc) of 548 mV and a fill factor (ff) of 0.70, corresponding to an overall conversion efficiency (hr) of 4.52% under AM 1.5 irradiation (100 mW cm^{-2}). The structure-property relationship shows that both conjugated bridge and acceptor play key roles in increasing the efficiency of DSSCs. Electron-rich furan and two cyanoacetic acid-based dye appear to enhance light harvesting capacity and help convey the charge transfer from the excited dye molecules[318,320] to the conduction band of TiO_2 (Figure 55), leading to a higher efficiency of the assembled devices using such a dye. Electrochemical impedance measurements also support the effect on enhancing charge transfer of TiO_2 for dye UY11 **362**.

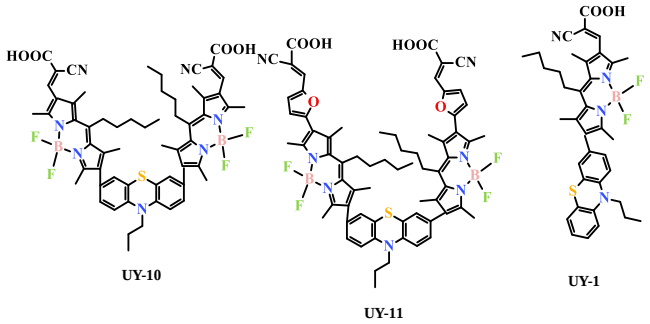
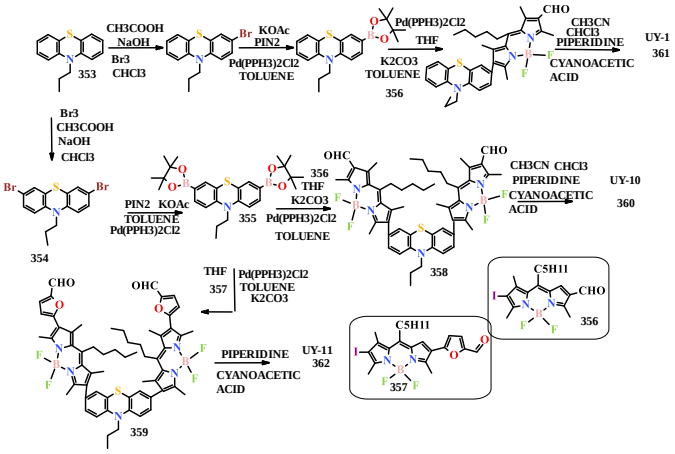


Figure 55. Molecular structure oF BODIPY dyes.

The synthetic routes to new PTZ-based Bodipy dyes are depicted in Scheme 69. The key intermediates, 3,7-dibromo-10-propyl-10*H*-phenothiazine (**354**) were prepared from 10-propyl-10*H*-phenothiazine (**353**) with NBS, similar to published procedures. Afterward, the Miyaura borylation reaction of the compound **354** and commercially available B_2Pin_2 was carried out using KOAc as a base and $Pd(PPh_3)_2Cl_2$ as the catalyst in toluene, resulting in compound **355**. In the next step, palladium-catalyzed Suzuki coupling of **355** with single iodine substituted Bodipy derivatives **356** or **357** provided compound **358** and **359** in 72% and 89%, respectively.



Scheme 69. Phenothiazine BODIPY derivatives.

The importance of optimizing molecular structure is illustrated by the structureeproperty relationship. Double electron-rich furan units and cyanoacetic acid acceptors have been introduced to the PTZ-Bodipy molecular frameto enhance light harvesting efficiency in the excited state and toretard the electron transfer from TiO_2 to the oxidized dye or electrolyte. On the basis of ever increasing consumption of fossil fuels,[321] the provided information confirms and encourages the useof dianchoring architecture for the development of more efficientand stable organic sensitizers in the future.

11.16. 2,6-Diheteroaryl BODIPY's

Triplet energy transfer from PS to surrounding oxygen and its further annihilation generates the singlet oxygen.[322] Very recently, a variety of BODIPY derivatives have been developed mainly to achieve near infra-red absorption and enhanced ISC so that they can be safely used in PDT. Various peripheral substitutions as well as core modifications of BODIPY such as aromatic (Figure 56) and hetero-aromatic ring fusion, iodo or bromo substitution, replacement of *meso* carbon by nitrogen forming aza-BODIPY etc. have been reported for PDT applications.[323] Herein, the point that included the synthesis of hetero-aryl substituted BODIPY derivatives (Figure 57). Near IR absorption (up to 667 nm) and emission (up to 693 nm) with large molar absorption coefficients and high quantum yields are observed. Comparisons of photophysical and electrochemical properties of their isomeric BODIPYs are discussed. Compounds **365** was tested for its ability to accumulate inside cancer cells and for its cytotoic potential.

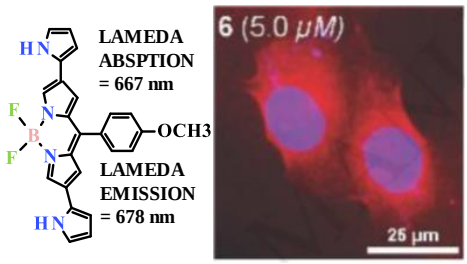


Figure 56. Heteroaryl substituted BODIPYS and their isomers were synthesized and studied: cellular uptake and photocytotoxic properties of 2.6-dipyrrole BODIPY are evaluated on human pancreatic cancer cells.

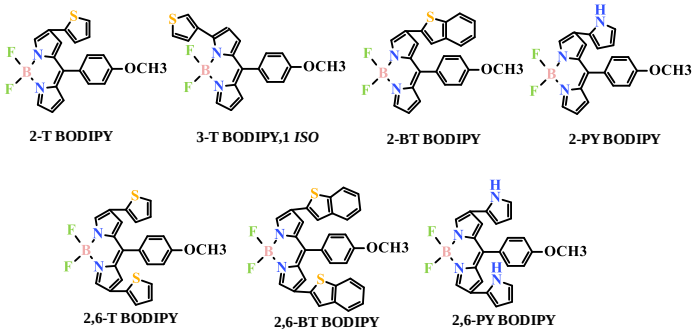
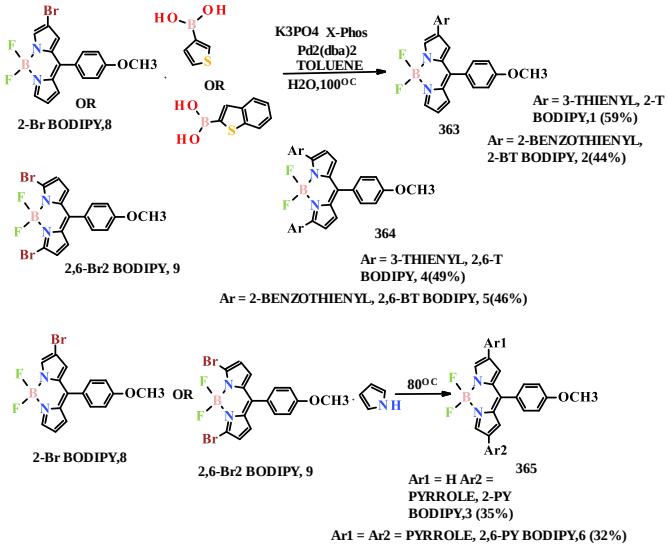


Figure 57. Structure of dipyrrole-BODIPY derivatives.

Derivatives of β substituted heteroaryl BODIPYs, were synthesized. Two synthetic methods, (i) Suzuki coupling or (ii) nuleophilic substitutionby pyrrole were used to synthesize the BODIPYs. Related isomeric BODIPY derivatives (**2 *iso* - 6 *iso***) were synthesized as reported earlier. To afford **363-365** (including their isomers), positional isomers of bromo-BODIPY derivatives were synthesized as shown in Scheme 70.



Scheme 70.DIpyrrole linked BODIPY derivatives.

Synthesis of 2,6-heteroaryl BODIPYs was carried out and their photophysical properties were compared with their positional isomers (-3,5-substituted). In this point of observation slightly more bathochromic shift for 2,6-substituted BODIPY than for 3,5-substitutions. Pyrrole and benzothiophene substitution showed absorption beyond 650 nm and emission upto ˜700 nm. Singlet oxygen production was observed when 2,6-dipyrrolyl BODIPY was used as PS. Further this BODIPY was used in cellular uptake in PANC-1 cells and its photocytotoxicity was studied at different dye concentrations. The IC_{50} was found to be in ~2.4 μ*M*. The strongly believe that knowledge of photophysical and photocytotoxic properties of dipyrrolyl BODIPY will allow us further to design the effective BODIPY based PS for PDT applications.[324]

12.Summary About Importance of Bodipy's Molecule:

BODIPY chemistryallow diverse modification on the core structure. Through these modifications, many characteristics of the parent chromophore can be altered in the desired direction. Despite the progression of this field, the development of BODIPY based Biological properties and radioimaging dyes as well as the advantages of photodyanamic therapy has seen progress. BODIPYs are generally stable and chemically robust, with photophysical properties that facilitate chromatographic purification.

A key factor to improve the efficacy of BODIPY derivatives in PDI involves optimizing the light absorption in the visible region, a long-lived electronically excited triplet state to efficiently produce ROS in a short period of illumination time, and decrease the lipophilicity of the resulting of the *s*-indacene ring for a better transport in biological fluids and cell penetration.

The utilization of fluorescent BODIPYs as photosensitizers for photodynamic therapy, and as boron delivery agents for boron neutron capture therapy offers promise as theranostic agents. Additionally, BODIPY derivatives that absorb and emit in the near *IR* regions of the electromagnetic spectrum and bear radioisotopes suitable for radio-imaging techniques are of great interest. Far-red and near infrared (*NIR*) emissive dyes have advantages in the development of fluorescent probes and labelling for bio-imaging in living systems since fluorescence in the long-wavelength region would generate minimum photo-toxicity to biological components, deep tissue penetration and minimal background from auto-fluorescence by bio-molecules. BODIPY dyes are attractive due to their excellent photo-physical properties and potential for fluorescence-based sensing and bio-imaging applications.

In addition, strong electron donor and acceptor groups can be placed on the chromophore. Thus, numerous research papers have emerged to develop BODIPY-based dyes with absorption and emission in the

long-wavelength spectral region (650–900 nm). In the post functionalization approach, boron dipyrromethenes with reactive functionalities attached directly to the core -halogen or hydrogen atoms, methyl, formyl, or alkylthio groups are used as starting materials for further derivatization. The various synthetic methods towards these starting compounds and their post modification are reviewed. Compounds incorporating the *F*-BODIPY motif have found widespread use in fluorescent molecular probes, photovoltaic devices and photodynamic therapy agents. Accordingly, there is considerable interest in extending and diversifying the *F*-BODIPY framework. *F*-BODIPY's are readily prepared by condensing aldehydes, acyl chlorides or anhydrides with pyrroles and trapping the resulting dipyrrin *in situ* with boron trifluoride. *F*- BODIPY's. The parent dipyrrins are more difficult to handle but have a range of potential applications in dye and porphyrin syntheses, metal ion coordination and supra-molecular chemistry. Methods to enable the functionalization of dipyrrins by temporarily complexing with tin or zinc have been investigated.

More recently, the *F*-BODIPY motif has been envisaged as a means of protecting the dipyrrin, to enable chemical modification and purification before removal of the BF_2 unit to reveal the functionalized dipyrrin. This review summarizes the general strategies to obtain far-red and NIR BODIPY's. Moreover, their applications for fluorescent *pH* probes and imaging or labelling in living systems are highlighted. In this review we describe the numerous post functionalization methodologies of the boron dipyrromethene core designed and realized by research groups around the globe. In *in vivo* bioimaging, NIR fluorescent dyes have obvious advantages over traditional visible dyes, because biological samples have low background fluorescence and a concomitant high signal-to-noise ratio in the NIR region.

Moreover, NIR light can penetrate sample matrices deeply due to low light scattering. Solubility and aggregation characteristics of the dyes can also be modulated as needed. Important properties and applications of a number of substituted BODIPY's made by the methods described in this review are also presented. We discuss the different strategies devised for post derivatization of the BODIPY nucleus at all possible positions *i.e.*, the pyrrole carbons, the *meso*-carbon, and the boron atom and compare them concisely with the standard different functional methodology.

13. Conculsion:

In conclusion, we have successfully explain the designed the BODIPY compounds according to their wavelength absorption region and synthesizing the BODIPY molecules with various reactions conditions of NIR fluorescent probes with tuneable absorption and emission bands over a wide range by including different aromatic as well as the aliphatic substituents and also the natural product rings attached with corresponding BODIPY unit.

14. Future Scope of Bodipy Research:

Numerous in Photodynamic imaging techniques now make it feasible to do things that were not previously possible. Experiments in which interacting proteins are observed inside living cells are now common for dynamically averaged systems, and the field is close to observation of similar events on a single molecule level. Labels can be attached to proteins, for example, antibodies, which accumulate in specific organs for imaging in animals and human subjects. The technological advances in this area are remarkable. However, there is a growing realization that the probes available limit imaging events in cells and whole organisms by fluorescence. For instance, there are few that emit at 800 nm or above, yet living tissues are most transparent to light at and above this wavelength.

BODIPY dyes are notable for their uniquely small Stokes shifts, narrow absorption bands, sharp emissions, high fluorescence quantum yields, and excellent chemical and photostability. The combination of these desirable attributes makes BODIPY fluorophores attractive as tools in a variety of applications, for example, in biochemical labeling, light-emitting devices, supramolecular fluorescent gels, light harvesting systems, and as sensitizers in solar cells.

In the detail view, of the usage of BODIPY as Photosensitizers in a PDT, we expect that the development and optimization of pharmaceutical formulations may increase its solubility in aqueous media and its bioavailability. According to this concept, we are planning to be designing a BODIPY for PDT, some properties of tumor cells should be taken into account, namely the low oxygen concentrations in tumors. In addition of designing, we are interserted to study the different synthetic route of new novel BODIPY derivatives for antitumour photodynamic protocols against infectious diseases and decontamination of surfaces is also a promising strategy to increase its wavelength efficiency and the type of application of BODIPY as biological photodynamic therapy studies.

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16. Conflict of Interests:

The authors declare that there is no conflict of interests.

17. Author Biography:

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