# Recent developments in design of novel water-soluble BODIPYs and their applications: an updated review

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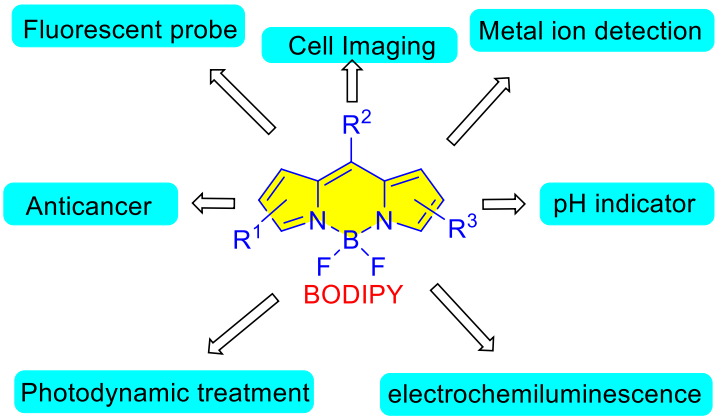
## ABSTRACT

Boron-dipyrromethene (BODIPY) and their derivatives play an important role in the area of organic fluorophore chemistry. The water-soluble boron-dipyrromethene dyes have increasingly received interest, recently. The structural modification of BODIPY core by incorporating different neutral and ionic hydrophilic groups makes it water soluble. The important hydrophilic groups such as quaternary ammonium, sulfonate, oligo-ethylene glycol, dicarboxylic acid, and sugar moieties significantly increased the solubility of these dyes in the water while preserving their photophysical properties. As a result, these fluorescent dyes are utilized in aqueous systems, for applications such as chemosensors, cell imaging, anti-cancer, bio-labelling, biomedicine, metal ion detection, and photodynamic treatment. This review covers most current developments in design and synthesis of water-soluble BODIPY derivatives and their wide applications since 2014.




**Key words**: Boron dipyrromethene, PDT, cell imaging, water soluble

## 1. Introduction

The usage of fluorescence has increased significantly during the past 25 years, in a wide range of modern research. Fluorescence methodology has developed into a very powerful technique that is frequently utilized in the fields of molecular biology, and biochemistry materials

science.[1] Fluorescence is increasingly being used in biological science, which has led to the development and synthesis of organic fluorophores. Boron dipyrromethene (BODIPY) occupies a unique branch in synthetic organic chemistry. However, there are a multitude of well-known synthetic fluorophore, including fluoresceins, rhodamines, cyanines, ethidiumbromide and alexa, that have extensive current applications in fluorescence imaging, as well as in biochemistry and molecular biology, as molecular tagging agents. Although, the low water solubility limits their applications.

Alfred Treibs and Franz-Heinreich Kreuzer invented the first BODIPY in 1968.[2] Comparing the BODIPY molecules to more common organic fluorophores like rhodamines and fluorescein reveals that they have superior optical characteristics.[3] BODIPY and its derivatives, like porphyrins, typically absorb visible light and have quite distinct emission and absorbance peaks. BODIPY is therefore referred to as "porphyrin's little sister." Additionally, the distinctive structure of the BODIPY core makes it compatible with a wide range of reaction conditions, including electrophilic substitution, nucleophilic substitution, condensation reaction, and cross coupling reactions like Suzuki and Sonogashira that are catalyzed by palladium. [4] Additionally, the BODIPY core is easily functionalizable at the α-, β-, and meso positions in addition to fluorine substitution. Due to its exceptional qualities, BODIPY dyes can be used for a variety of purposes, including molecular bio labelling,[5] cell imaging,[6] chemical sensing,[7] and two-photon absorption.[8,9] Scientists have designed fluorescent probes based on BODIPYs for use in environmental, biological, medicinal, and material applications because of their outstanding properties and uses. They have minimal Stokes' shifts, high molar absorption coefficients, and strong fluorescence quantum yields. They have strong chemical and optical stability in both the solid and solution states, are electrically neutral, and are insensitive to solvent polarity. These are quite soluble in the majority of organic solvents. The BODIPY derivative only breaks down in extremely acidic or extremely basic media and is stable in the physiological pH range.[10] Although organic fluorophores based on BODIPY have excellent characteristics and a wide range of applications, they still face numerous difficulties that restrict their use in aquatic environments. Water is an essential component of all living things and is essential for the providing of food, energy, and organic micronutrients. Water soluble BODIPY are currently used for a variety of purposes, including photodynamic treatment, biomacromolecule labelling, chemosensors, and bio-imaging. Therefore, more research is required to enhance their characteristics and resolve this issue. In this review, important applications of water soluble BODIPY are summarized.

2. **Applications of BODIPY:**

**2.1. Cell imaging:**

Fluorescence-based imaging is a particularly sensitive method that is used in a wide range of scientific domains including clinical diagnostics, biochemistry and molecular biology, and materials science. Optical imaging of cells offers significant insight into a number of biological processes. Due to its great sensitivity, specificity, and biocompatibility, fluorescence microscopy is particularly suited for cell-based research. Typically, hydrophilic groups are linked into the chemical structures of water-soluble BODIPY dyes. The important amphiphilic water soluble BODIPYs **1** and **2** have been synthesized by Bardon et.al (Fig. 1).[11]The water solubility of these BODIPYs were achieved by charged groups via phenylene linkers at the 8-position. BODIPY dye **1** contains a dication prepared by alkylating diazabicyclo[2.2.2]octane (DABCO) and BODIPY dye **2** contains a dicarboxylic acid prepared with itaconic acid via Heck coupling reaction condition which was soluble in alkaline water. The butyl groups on the aminophenylene unit balance the oleophilic nature of one end of the molecule with the hydrophilic nature of the other end, resulting in an amphiphilic molecule. Both of these water-soluble dyes exhibit excellent photostability and high-fluorescence quantum yields upon transition from aqueous environment making them attracting for cell labelling applications.[11]

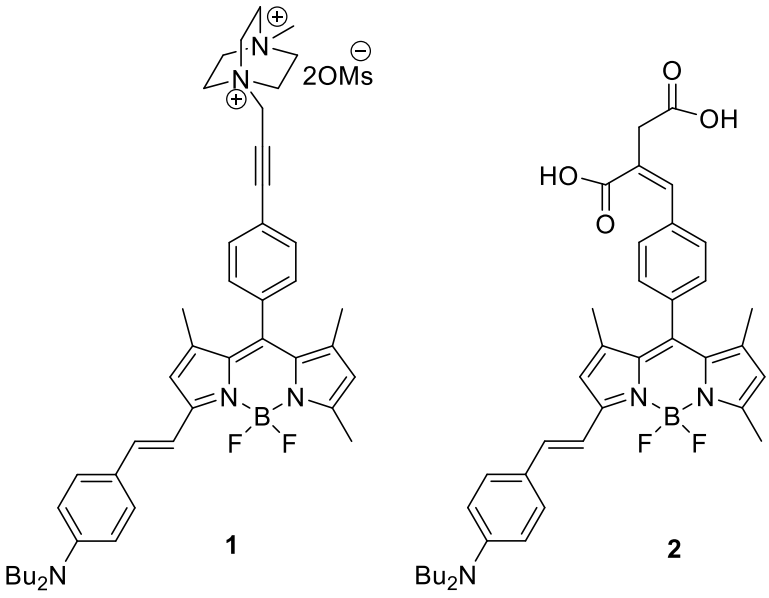



**Fig. 1** BODIPYs as cell-imaging material.

Hypochlorous acid (HOCl), a significant reactive oxygen species (ROS) that is primarily produced by the reaction of hydrogen peroxide and chloride ions catalysed by myeloperoxidase

(MPO), is essential for many important biological processes, including inflammation and immune defence against microorganisms. HOCl also serves as an essential antibacterial agent in the body's natural defensive mechanism. Up to a certain concentration, HOCl is crucial for many cellular processes; but, when concentrations are too high, it can lead to a number of disorders in humans, including renal disease, arthritis, cardiovascular disease, and neuronal degeneration. HOCl is also employed as a home bleach, to clean swimming pools, and to disinfect drinking water. So, it is very desired to have quick, focused, and sensitive HOCl detection in pure aqueous medium. In 2020, Lee and co-workers designed and synthesized the BODIPY-based water-soluble aldoxime functionalised polymeric probe **3** (Fig. 2). This water-soluble macromolecule probe was made utilizing the reversible addition-fragmentation chain transfer (RAFT) technique with hydrophilic DMA and aldehyde-terminated BODIPY methacrylate. BODIPY was used as a signal transducer, and DMA was applied to make the resultant polymer water soluble. The probe **3** was soluble in a variety of organic solvents as well as water. The hydrolytic and photolytic stability of the proposed probe **3** were exceptional, which is encouraging for long-term use. With a very short HOCl detection time, it also demonstrated outstanding selectivity and anti-interference performance in the presence of ROS and RNS. This coloration and fluorescence increase of Probe **3** was brought on by the conversion of aldoxime to nitrile oxide by HOCl oxidation. The author claimed that the synthesized compound is suitable for in vitro imaging of HOCl in human liver cancer cells because to its specific and quick response to HOCl and little cytotoxicity even at high doses.[12]

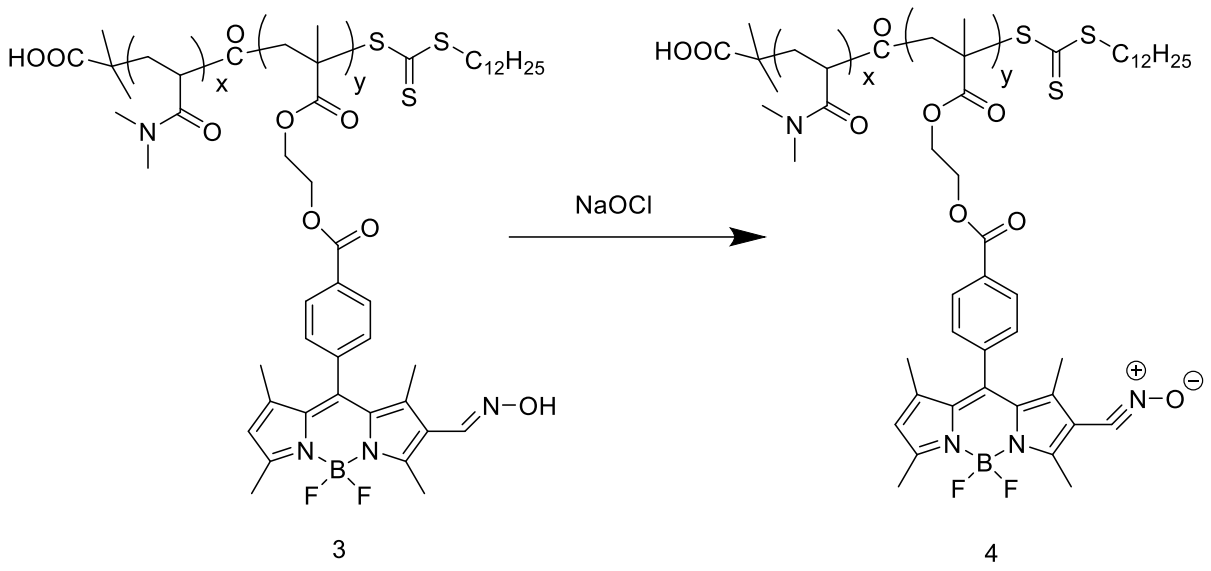
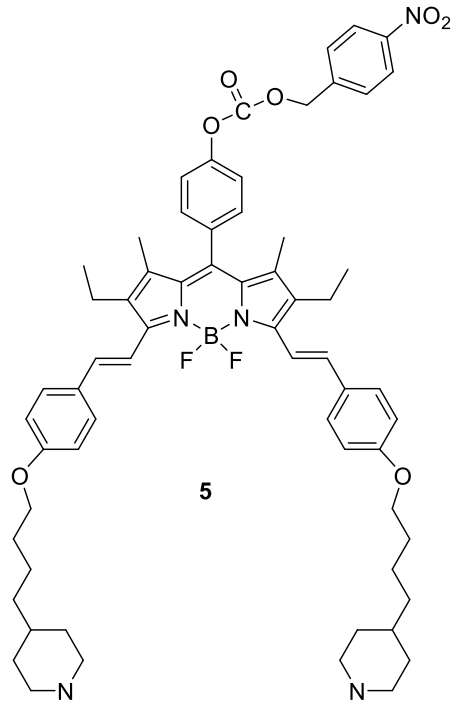



**Fig. 2** BODIPY-based water-soluble aldoxime functionalised polymeric probe.

In 2020, Gorbatov et al. reported a novel water-soluble distyrylsubstituted BODIPY probe **5** for imaging the hypoxic status of human non-small-cell lung cancer A549cells (Fig. 3). The water- solubility and cellular up take was enhanced by due to the orthogonally attached (piperidin-1-yl)alkyl groups by Knoevenagel condensation reaction condition. The UV–VIS absorption spectrum of this distyryl-substituted BODIPY derivative exhibits a strong absorption band centred at 659 nm.[13]




**5**

**Fig. 3** water-soluble distyrylsubstituted BODIPY probe.

The pioneering works of Wang et al demonstrated the water-soluble and membrane permeable BODIPY dye **6** by self-assembled hydrophobin. The Knoevenagel reaction was used to add the carbazole derivative to the 3- and 5-methyl sites. And to improve BODIPY's solubility in non-polar liquids, the decyl was added through carbazole. They showed that the surface modification by HFBI gave HFBI-functionalized BODIPY **6** a good water-solubility. BODIPY with HFBI functionality had a wide intracellular distribution and could cross the nuclear membrane (Fig. 4).[14]

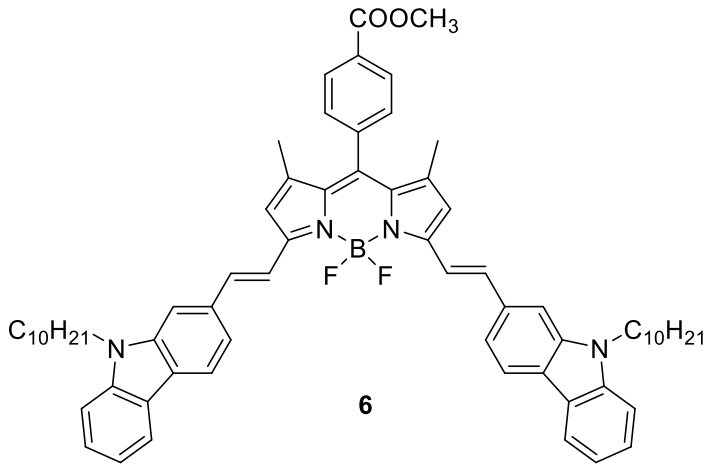



**Fig. 4** HFBI-functionalized BODIPY.

Keyes and co-workers investigated water-soluble naphthyridine substituted BODIPY for cell and tissue imaging (Fig. 5). Two BODIPY compounds (**7**, **8**) with naphthyridine substitutions were compared in terms of their photophysics, cellular localization, and cytotoxicity, as well as their new PEG conjugates (**9**, **10**). In buffered aqueous conditions, the PEGylation compounds were intensely luminous, and PEGylation facilitates chemical absorption by living cells. All of the dyes investigated were nuclear-excluding and localized only within the ER and mitochondria. Finally, all dyes were weakly cytotoxic, IC50 values indicated that cytotoxicity would not be expected at concentrations typically used in fluorescence staining. Apoptosis and necrosis were seen at greater dosages of the BODIPY-VIS dyes (**7**, **8**) and BODIPY-NIR dyes (**9**, **10**) respectively, according to the mechanism of cell death. However, compared to the BODIPY-VIS dyes, the BODIPY-NIR dye demonstrated signs of reduced harmful effects at lower doses acceptable for cell imaging. The additional benefits that the NIR dye localizes in the endoplasmic reticulum and mitochondria and emits outside of the auto fluorescent spectral region as well as the fact that it is not prone to self-quenching make these dyes useful bioimaging tools. They were water soluble, photostable, have high quantum yields, also fully absorbed by the cell and tissue within a short period of time.[15]

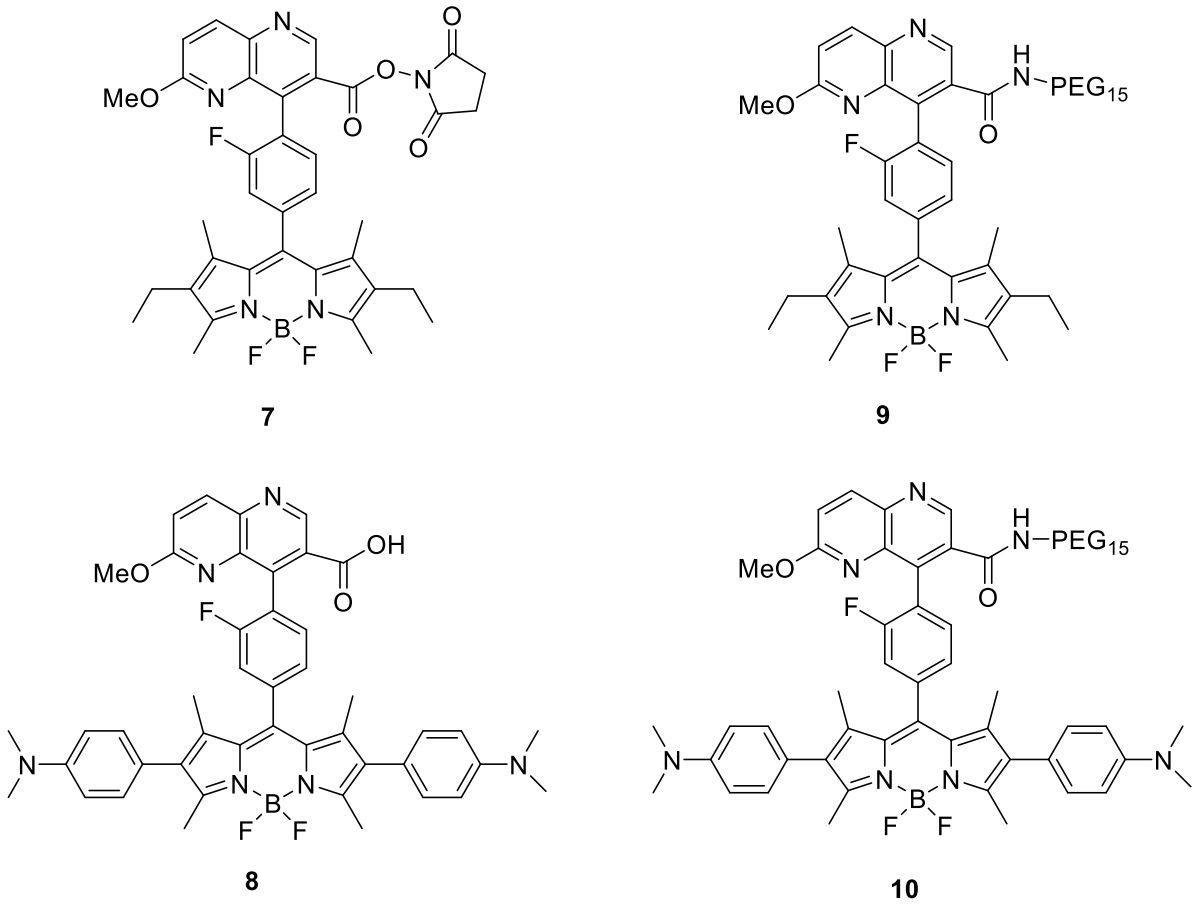



**Fig. 5** naphthyridine substituted BODIPY for cell and tissue imaging.

Kim and co-workers synthesized water-soluble PEGylated BODIPY dyes (**11** and **12**) and investigated their photophysical properties for cellular imaging (Fig. 6). To minimize the tendency to aggregate, bulky di-branched PEG chains were added to the BODIPY core's meso position. In comparison to dye **12**, which includes electron-donating ethyl groups at the positions 2 and 6 of the core, dye **11**, which has no substitutions at those locations, displayed absorption and emission maxima at shorter wavelengths. However, the author reported that BOD-PEG **12** compared to BOD-PEG **11** had greater fluorescence QYs. The PEGylated BODIPY dyes also showed high water solubility and biocompatibility, permeating MCF-7 cells and localizing in the cellular cytoplasm.[16]

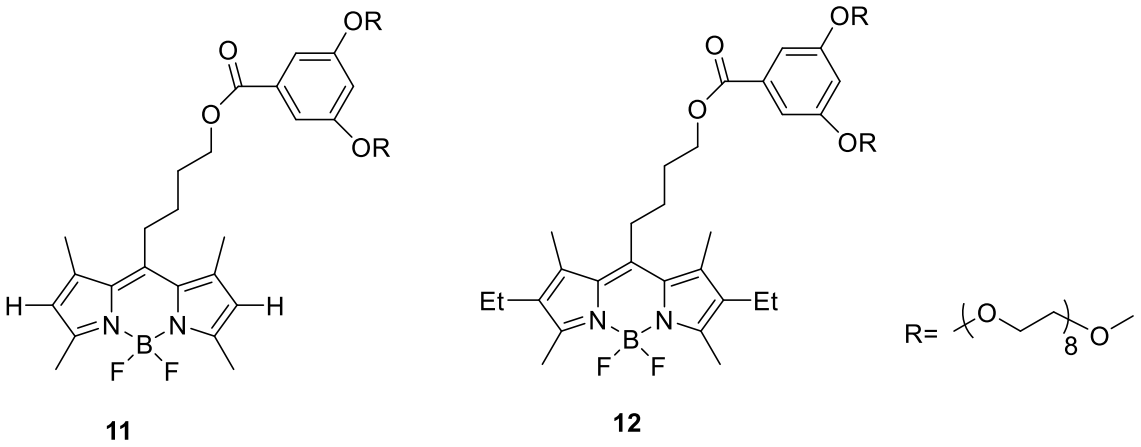


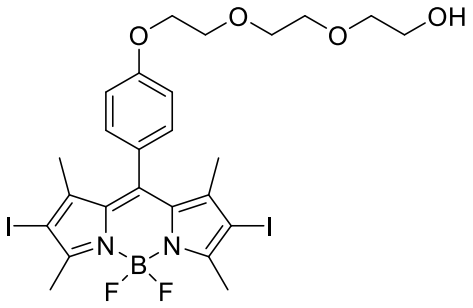

**Fig. 6** PEGylated BODIPY dyes.

### 2.2. Photodynamic treatment (PDT):

The term photodynamic treatment (PDT) was first used in 1904. PDT is a form of phototherapy that contains three non-toxic components: a photosensitizer (PS), a particular wavelength of UV or visible light, and molecular oxygen for tissue destruction. The food and drug administration (FDA) did not, however, approve the first PS agent for PDT therapy until the 1990s. PDT has since been studied as an antineoplastic treatment since it is straightforward, permits highly localized administration, is simple to manage, is less invasive, and has few adverse effects. In addition, various uses for photosensitizers, including those for vascular diseases, dermatology, gastroenterology, and antimicrobial agents, have been discovered. In PDT, the PS molecule is excited by absorbing a photon and changing from its ground state (S0) to a slightly lower energy triplet state (T1), which is then capable of reacting with molecular oxygen through two different mechanisms, Type I and Type II, resulting in the formation of reactive oxygen species (ROS), such as superoxide anion, hydrogen peroxide ($H_2O_2$), and hydroxyl radical (OH•) (Type I), or $^1O_2$. It is claimed that the singlet oxygen produced is mostly to cause for the tissue damage in PDT. One significant factor in the evaluation of photosensitizers is high quantum yield of singlet oxygen production. Due to its stability, large visible-light absorption band, tumor-selectivity, capacity to produce reactive oxygen species, and low toxicity in dark, BODIPY is one of the photosensitizers for PDT. There are several prospects for the use of water-soluble photosensitizers in biological applications. They have a significant binding ability to the phosphate groups of DNA in the blood, which is a hydrophilic system; therefore, they may be injected straight into the patient's bloodstream.

A novel halogenated BODIPY derivative **13** was synthesized by Belfield and co-workers by introducing two iodine substituents as heavy atoms at the 2- and 6-positions along with a

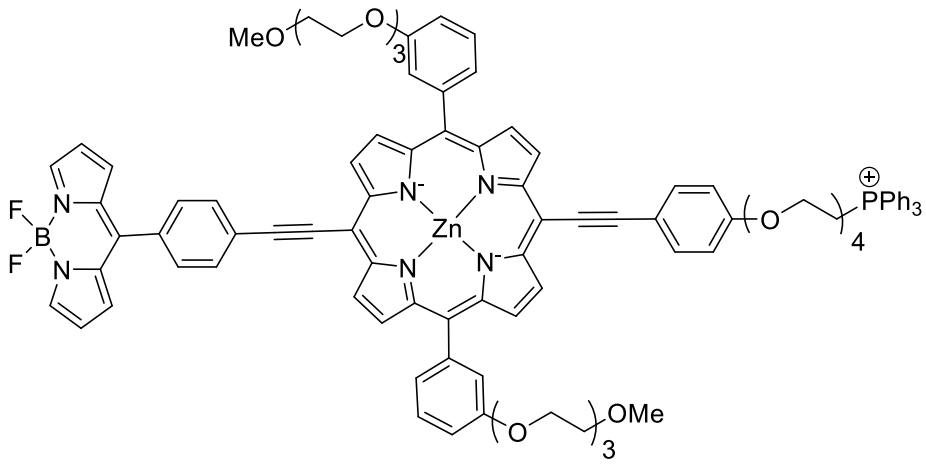
polyethylene glycol chain to increase water solubility (Fig. 7). Unsurprisingly, BODIPY **13** had a low fluorescence quantum efficacy of 0.02 and a high $^1O_2$ QY of 0.93. With an $IC_{50}$ of 10 GM, this heavy atom action resulted in photocytotoxicity being seen in LLC Lewis lung cancer cells.[17]



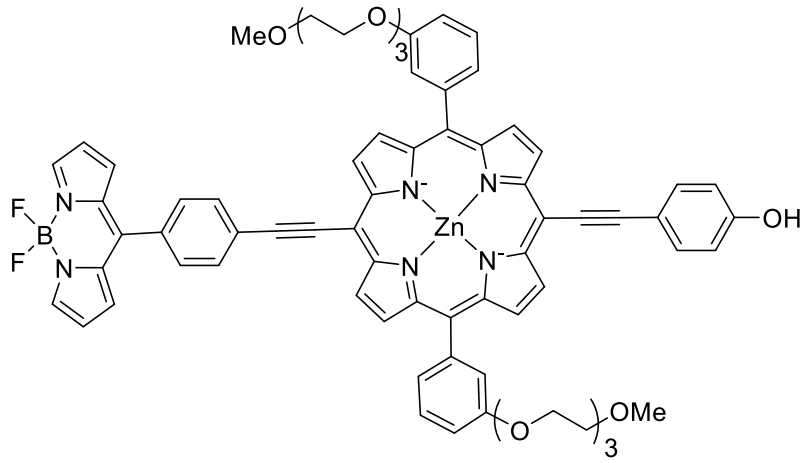

**13**

**Fig. 7** BODIPY for photodynamic treatment.

A novel amphiphilic BODIPY-porphyrin conjugate **14** and its precursor **15** were developed by Xing and co-workers in order to perform TPAPDT (Fig. 8).[18] The hydrophobic BODIPY in Compond **14** is linked to the zinc porphyrin at its meso position via an acetylide linker. Two tri(ethylene glycol) chains and a tetra(ethylene glycol) chain, each conjugated to one of the remaining three meso positions of the zinc porphyrin core, are responsible for some of the hydrophilicity of **14**. Low fluorescence intensity was present in both substances. The relative $^1O_2$ QYs of BODIPY **14** and **15** were determined to be 0.52 and 0.59, respectively, using meso-tetraphenylporphyrin (H2TPP) as a reference. Using the Zscan method, TPA cross-sections (TPCS) were examined. Compound **14** showed larger TPCS than compound **15**, but compound **15** without BODIPY had smaller TPCS. Both two-photon excitation fluorescence emission and two-photon excitation $^1O_2$ production can be improved by using large TPCS. Studies on the in vitro absorption of **14** in human breast cancer MCF-7 cells revealed that it was quicker and more effective than that of **15**. This is explained by the fact that transport across the cell membrane is considerably faster by the more advantageous logP value of **14** as compared to **15**. *in vitro* photocytotoxicity tests revealed that **14**, in accordance with the better cellular uptake tendency, had higher photocytotoxicity than **15**.




**14**




**15**

**Fig. 8** amphiphilic BODIPY-porphyrin conjugate.

The targeting effectiveness can be impacted by the hydrophilicity and length of the peptide linkers used in conjugation. BODIPY was coupled to either a short- or long-EGFR targeting pegylated peptide **16** or **17** (Fig. 9) in a study by Zhao et al. to target the epidermal growth factor receptor (EGFR). On EGFR over expressing Hep2 cells, both conjugates shown more cellular absorption than free BODIPY, as demonstrated in a photocytotoxicity assay and fluorescence imaging investigation. Due to its low water solubility and strong tendency to aggregate as its eleven hydrophobic sites, the long peptide **17** had lesser targeting ability than the short peptide **16** in comparison.[19] With the BODIPY core masked in the hydrophobic pocket, surface Plasmon resonance and docking studies revealed that **17** binds to the lower side of the EGF binding pocket. As contrast to **16**, and it precisely binds to the EGFR, outside of the EGF binding pocket.

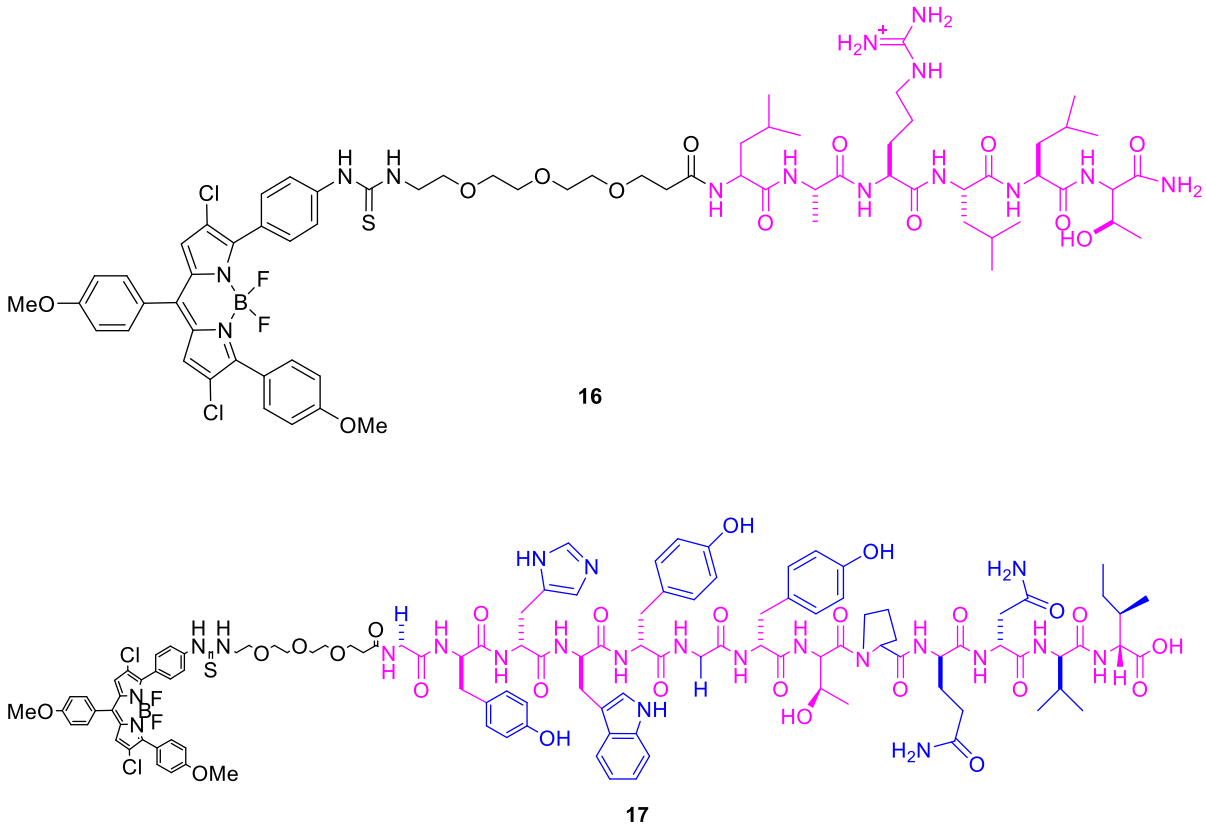
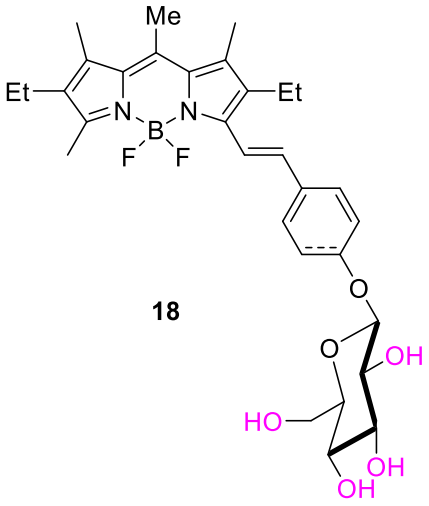


**Fig. 9** BODIPY with EGFR targeting pegylated peptide.

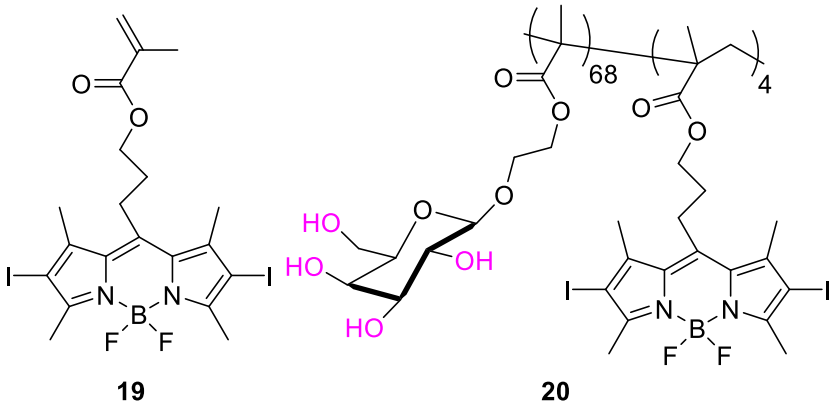
The hydrophilic glycosylated BODIPY was synthesized and studied by Chattopadhyay and co-workers.[20] When used against the A549 cell line, the BODIPY dye **18** with a glycosylated styryl moiety at the C-3 position had the best PDT properties (Fig. 10). The increased sub G1 cell population and modifications in cell shape demonstrated that it specifically promoted reactive oxygen species mediated caspase-8/caspase-3-dependent apoptosis. These results suggested that mitochondria may not be directly implicated in the photo-cytotoxicity of dye **18** coupled with its localisation in the endoplasmic reticulum, as shown by confocal microscopy. Compound **18** was not harmful to normal lung cells and did not cause any dark toxicity in A549 cells.




18

**Fig 10.** hydrophilic glycosylated BODIPY.

Li and co-workers synthesized a macromolecular photosensitizer **20** based on BODIPY that targets tumor cells by using galactose as a ligand for targeted PDT (Fig. 11).[21] Galactose was selected because it binds to asialoglycoprotein (ASGP) receptors that are only expressed in the liver and not in other human tissues. In an aqueous solution, Glycopolymer **20** showed good water solubility. The compound **20** was able to produce $^1O_2$ quickly in an aqueous solution, but when ethanol was employed as a cosolvent, the hydrophobic diiodo-bodipy monomer **19** produced $^1O_2$ to a lesser amount. Targeting to the liver was confirmed by the confocal and flow cytometry investigations, which demonstrated that **20** displayed significantly higher cellular absorption on ASGP-overexpressing HepG2 liver cells than on healthy NIH3T3 cells. This was further confirmed by a photocytotoxicity investigation, which suggested that **20** had no dark cytotoxicity and increased selective killing of HepG2 cancer cells.




19 20

**Fig. 11** Macromolecular photosensitizer.

Turan et al. synthesised water-soluble BODIPY having oligo ethylene glycol moieties (Fig. 12). The quenched BODIPY that only got activated to produce singlet oxygen following glutathione-mediated activation. [22] 2,4-Dinitrobenzenesulfonate was the quencher, and it was connected to a brominated BODIPY **21**, which was embellished with oligoethyleneglycol moieties for better water solubility. A study was conducted to examine the effectiveness in cancer and normal cell lines since cancer cells display high levels of glutathione. In HCT116 cells, the quenched **21** exhibited strong cellular uptake and, intriguingly, significantly stronger photocytotoxicity than the unquenched equivalent. In normal human MRC-5 lung fibroblast cells, **21** did not exhibit photocytotoxic action, suggesting its selectivity against cancer cells with high glutathione expression.

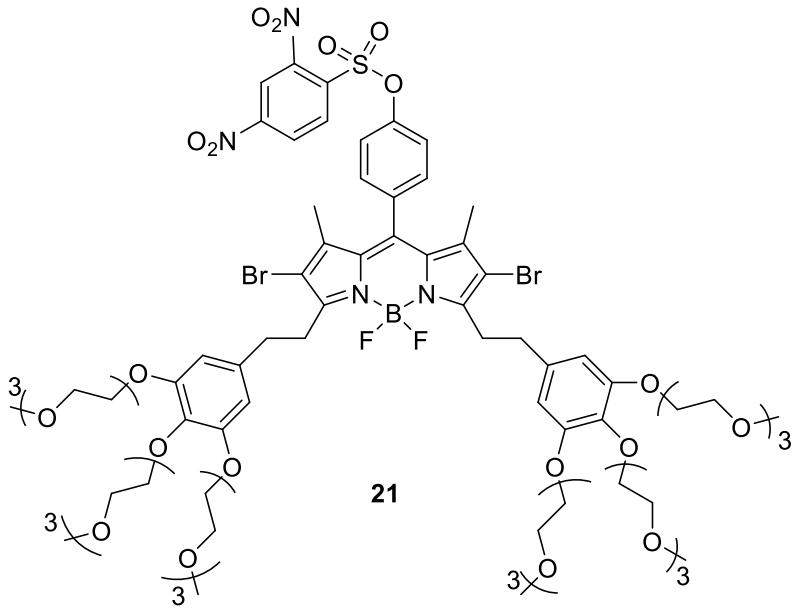



**Fig. 12** BODIPY with oligo ethylene glycol moieties.

A molecular mechanism constructed on a conjugate of $Zn^{2+}$ and terpyridine was presented by Akkaya and colleagues **23**. Compound **23** had additional solubilizing oligo ethylene glycol units suitable for research in physiological conditions, while compound **22** was synthesized for chemical characterisation. [23] In aqueous solutions, the terpyridine unit strongly binds $Zn^{2+}$ ions. In the presence of light, **22** in acetonitrile exhibited very low fluorescence emission intensity and efficiently produced singlet oxygen, whereas the addition of phosphate ions caused a very abrupt increase in emission intensity with a corresponding decrease in singlet oxygen synthesis. Similar to how weakly fluorescent **23** originally produces singlet oxygen to cause apoptosis in K562 cancer cells when exposed to light. After entering apoptosis, **23** interacted with the

exposed phosphotidyl serines in the outer leaflet of the apoptotic cell membranes, switching on a brilliant emission response while also independently turning off singlet oxygen formation.

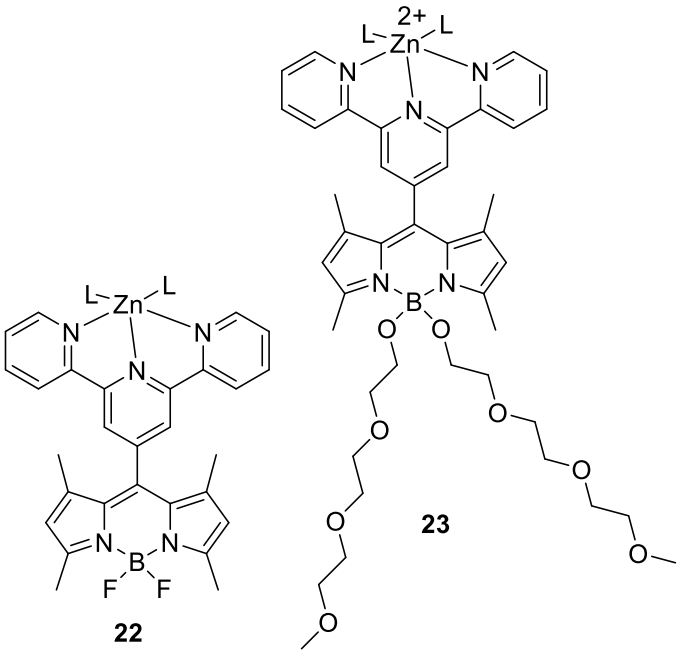
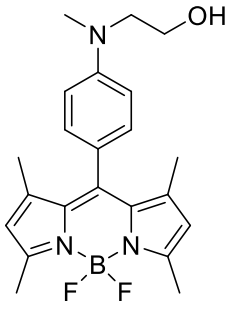



**Fig. 13** BODIPY conjugated with $Zn^{2+}$ and terpyridine.

In order to study the phototoxicity and subcellular localization behaviour of the photosensitizer BODIPY derivative **24** (Fig. 14), Gorbe et al. used the cell lines HeLa (human cervical adenocarcinoma), SCC-13 (squamous carcinoma), HaCaT (immortal human keratinocytes), and MCF-7 (breast cancer). To improve solubility in water, the 2-hydroxyethyl fragment was added to the compound's structure **24**. According to the authors, the **24** exhibits an emission band at 514 nm and has an absorption band at 490 nm. Therefore, BODIPY **24** was discovered to produce singlet oxygen and other ROS upon exposure, suggesting that it may be employed in photodynamic treatment. Additionally, internalization studies were done in these cell lines. When exposed to radiation, it was discovered that 24 was more harmful to SCC-13 and HeLa carcinoma cells than to non-cancerous immortal human keratinocytes HaCaT for the same amount of internalization. Additionally, it was observed that under experimental circumstances, BODIPY **24** was not harmful to cells when there was no light. Despite partial accumulation in the mitochondria, cellular co-localization studies indicated that BODIPY **24** was preferentially localized in the endoplasmic reticulum.[24]




**24**

**Fig. 14** photosensitizer BODIPY.

DNA is one of the most significant pharmacological targets of many anticancer medicines because it plays a crucial role in essential processes like mutagenesis, cell death, and gene expression. Understanding a substance's mode of action requires research into how it interacts with DNA. Topoisomerases are involved in actions including DNA transcription and replication. Due to the high expression of topoisomerases in cancer cells, inhibition of these enzymes has emerged as one of the most popular strategies in the study of anticancer drugs. The topoisomerase inhibitory actions of photosensitizers like acriflavine and methotrexate also increase the efficiency of PDT. Photosensitizer drugs must be focused on cancer cells in order to boost PDT effectiveness. Barut et al. synthesized water soluble BODIPY derivatives **25** and **26** containing 3,4-bis(3-pyridin-3-ylpropoxy)benzyl and 4-(3-pyridin-3-ylpropoxy)benzyl groups (Fig. 15). In order to establish if compounds **25** and **26** are suitable for PDT on HCT-116 cells, the authors investigated into the photochemical, DNA interaction, topoisomerase I and II inhibitory, cytotoxic, phototoxic, and cell death mechanism features of these compounds. On HCT-116 cells, the cytotoxicity and phototoxicity of 6-loaded liposomes (LP6a) and PLGA nanoparticles (NP6a) were also examined. This was done using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT)assay. The compounds **25** and **26** showed strong stability toward irradiation in TBS from the photochemical tests. UV-Vis spectroscopy and viscosity analysis DNA binding tests provided evidence that both chemicals reacted with DNA non-covalently. When exposed to light, both substances strongly cleaved the plasmid DNA of pBR322 to produce singlet oxygen. According to investigations on topoisomerases, the enzymes **25** and **26** were inhibited in a concentration-dependent manner. The substances had strong DNA-topoisomerase I complex binding affinities. Even more so than etoposide, **25** were projected to have a very high affinity for the DNA topoisomerase II complex. The results of the in vitro topoisomerase inhibitory tests were confirmed by the molecular docking investigations. Due to the size of its structure and the induction of apoptosis in HCT-116 cells,

compound **26** had more phototoxic effects than compound **25** in the cell culture studies. A promising photosensitizer agent for Colorectal cancer (CRC) was consequently discovered to exist in compound **26**. In order to increase the bioavailability and uptake of **26** in cells, LP6a and NP6a were created.[25]

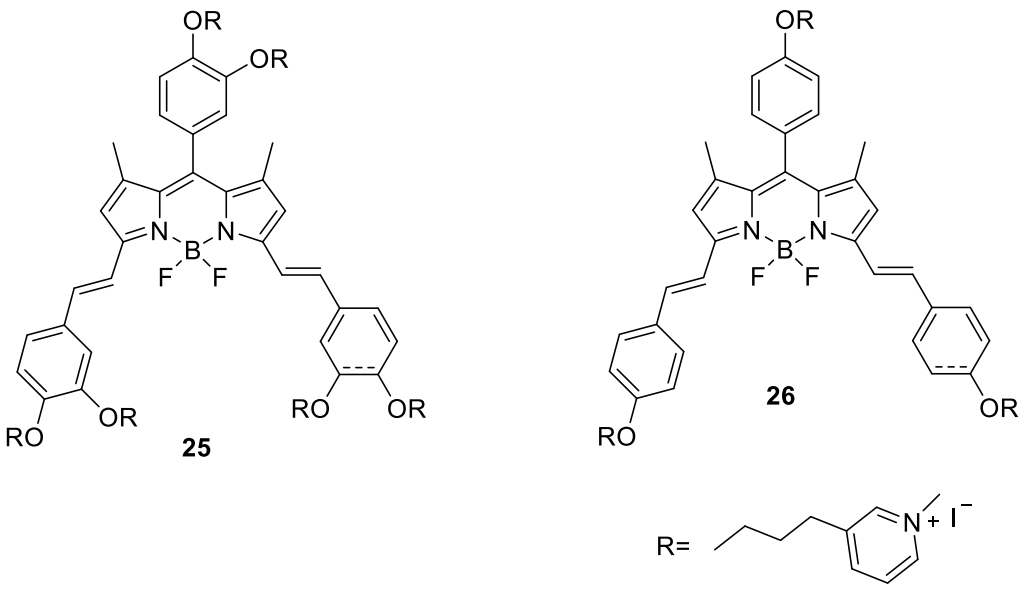



**Fig. 15** BODIPY bearing pyridine and styrene moieties.

A large number of severe chronic infections caused by hard-to-remove bacterial biofilms. To target the bacterial biofilm with precision, Li and co-workers synthesized a water-soluble galactose-decorated cationic (BODIPY)-based photodynamic treatment agent **27** (Fig. 16). These conjugates electrostatically attracted bacteria to form aggregations, which they can then kill by producing a significant amount of reactive oxygen species (ROS) in the presence of visible light without the development of bacterial resistance. Both Gram-positive and Gram-negative bacterial biofilms was efficiently inhibited and eliminated by this drug at the same time. A thorough examination of the antimicrobial process revealed that conjugates may swiftly bind to the surface of bacteria, irreparably damage their membranes, and clearly impede the action of intracellular enzymes all of which contribute to the eventual death of the bacteria. Importantly, these conjugates exhibit negligible cytotoxicity toward A549 cells, no detectable hemolytic activity, and a high selectivity toward bacterial cells as opposed to mammalian cells. The water-soluble galactose-decorated cationic BODIPY **27** offers intriguing insights for the creation of a treatment for bacteria that are resistant to antibiotics. The author claimed that antibiofilm galactose-functionalized cationic photosensitizer based BODIPY exhibited strong bacterial cell selectivity over mammalian cells, negligible cytotoxicity toward A549 cells, and

barely any hemolytic activity. Most importantly, the photosensitizer efficiently inhibited and radiated over 70% of bacterial biofilm at extremely low concentrations without bacterial resistance developing. The innovative photosensitizer had potentially be used as an effective antibacterial agent.[26]

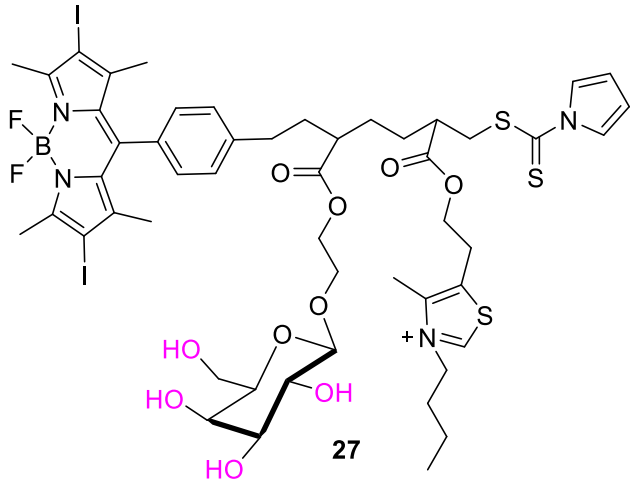



**Fig. 16** water-soluble galactose bearing cationic BODIPY.

Through a facile and efficient click reaction utilizing copper iodide (CuI), several water-soluble BODIPY derivatives with a lactose moiety were synthesized by Kim and co-workers (Fig. 17).[27] The synthetic BODIPY derivatives, photophysical and biological characteristics were thoroughly studied, and the dyes were put to the test as photosensitizers in photodynamic treatment. The effective production of single oxygen species was made possible by the addition of a heavy iodine atom to the BODIPY core. In addition, in the absence of light irradiation, the synthesized BODIPY-based PS agents showed no toxicity to the three cancer cell lines evaluated (HeLa, Huh7, and MCF-7). The halogenated BODIPY derivatives **29** and **30** demonstrated stronger cytotoxic effects against the examined cancer cell lines after LED light irradiation, suggesting their potential as potent photosensitizers for PDT applications. These effects were superior to those of the dye **28**. The tested cell lines, in particular Huh7 cells, effectively absorbed the synthesized compounds. Such efficient cellular uptake is due to interactions between the targeting biomolecule lactose and overexpressed particular receptors on tumor cells, which are recognized by carbohydrate-mediated mechanisms. The study described here made a significant contribution to the field of cancer treatment by offering a straightforward and reliable synthetic method for producing water-soluble BODIPY-based photosensitizers with excellent biocompatibility, adequate tumor-targeting, high cellular transfection, and efficient photodynamic therapeutic properties.[27]

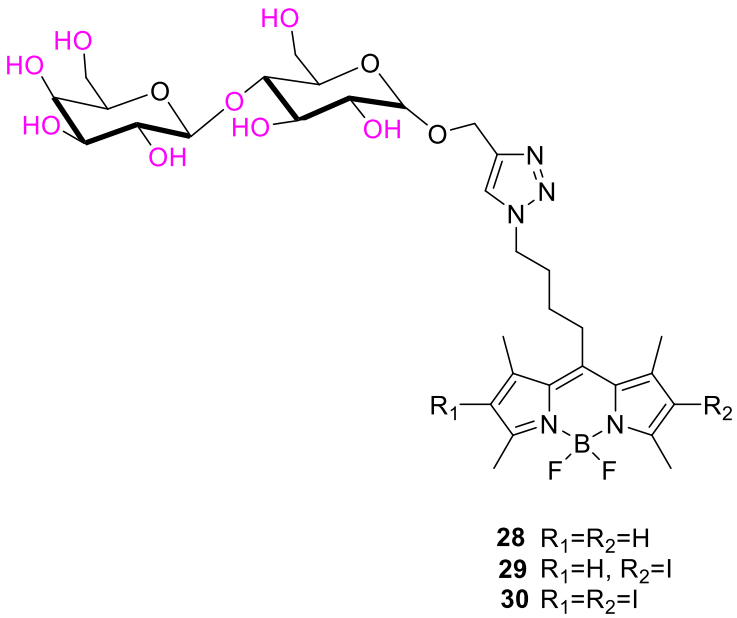



**Fig. 17** water-soluble BODIPY-lactose compounds for PDT.

Ozel and co-workers synthesized novel morpholino based water-soluble derivatives **31, 32** (Fig. 18). Experimental methods were used to evaluate the binding characteristics of **31** and **32** to CT-DNA include absorbance titration, competitive ethidium bromide, viscosity, and electrophoresis tests. According to binding study, compound **31** and **32** inserted with CT-DNA. They stated that the compounds exhibit high binding affinities to CT-DNA based on Kb values of **31** and **32**. Using super-coiled pBR322 plasmid DNA on agarose gel electrophoresis, the DNA-photocleavage activities of **31** and **32** were studied. In the presence of light, compounds **31** and **32** exhibit impressive photocleavage activities via the hydroxyl radical and singlet oxygen pathways. Utilizing UV-Vis absorption spectroscopy, the quenching mechanism of BSA with chemicals was determined. The result showed that a static quenching mechanism may be used by the chemicals to bind to BSA. According to the authors, newly synthesized BODIPY compounds that are water soluble have a great affinity for CT-DNA and BSA and can be successfully cleaved by radiation. The compounds were examined in the presence of various inhibitors such as hydroxyl radical scavenger (DMSO), a singlet oxygen scavenger (NaN3), and superoxide anion radical scavenger (SOD), the reactive oxygen species responsible for DNA photocleavage. It was discovered during the cleavage tests that substances split into supercoiled pBR322 plasmid DNA strands through the hydroxyl radical and singlet oxygen routes. These compounds were therefore promoted as photosensitizers in photodynamic therapy.[28]

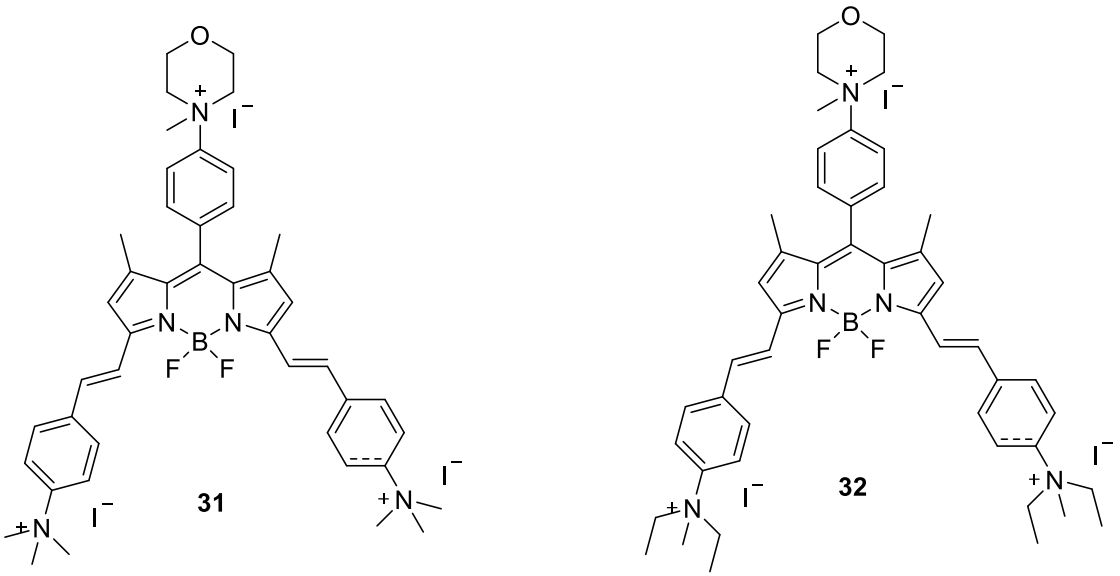



**Fig. 18** BODIPY with DNA-photocleavage activities.

### 2.3. Biomedical Applications:

Senge and co-workers developed a simple and effective method to synthesized highly water-soluble neutral BODIPY **33** by cross-linking them in chitosan-based 3D hydrogel networks (Fig. 19).[29] The synthesized hydrogel is injectable, self-healing, and fluorescent was created utilizing a Schiff reaction. Rheological recovery experiments, as well as macroscopic and microscopic self-healing tests, were used to establish the hydrogel's dynamic nature. Due to the absence of dye aggregation in the hydrogel 3D network, even at high concentrations of cross linker, the fluorescence quantum yield of the novel hydrogels was 14.5 times higher than that of the 3,5-diformyl-BODIPY monomer. Additionally, BDP-CS hydrogel **33,** the fluorescence lifetime at various concentrations proved that the fluorescence dynamics was not follow self-quenching and is consistent with resonance energy transfer. This method of making fluorescent hydrogels by cross-linking BODIPY monomers opens up possibilities for new optical polymer designs and used for biomedical applications, such as an implantable fluorescent hydrogel, along with its attendant improvements in mechanical and photochemical properties and the acceptable values of fluorescent lifetimes.

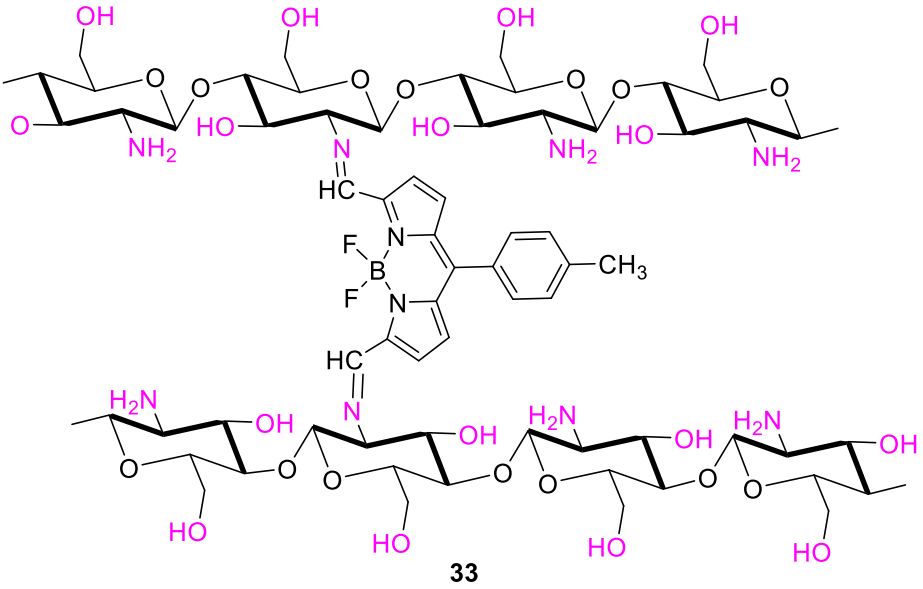



**Fig. 19** Chitosan based BODIPY.

The self-assembly characteristics of the amide-containing bolaamphiphilic BODIPY dye **34** in aqueous conditions were described by Fernandez et al (Fig. 20). The hierarchical self-assembly of the H-type aggregating chromophore, which is temperature-controlled, was proven by the authors. The self-association mechanism in water was discovered to be a highly cooperative process supported by amide-based hydrogen bonds, p-p interactions, and the hydrophobic effect. The production of micelles with a diameter roughly corresponding to the dye molecule's length results from the ensuing rotationally displaced dye arrangement. Individual micelles have been discovered to group together to form larger, spherical nanoparticles, which are most likely stabilized by hydrogen bonds with inserted water molecules from the solvent shell and driven by CH-O interactions with the outer (hydrophilic oligoethyleneglycol chains). Additionally, they asserted that BODIPY dyes **34** were the ability to produce functional materials in aqueous conditions, a capability that is now being used in biological applications.[30]

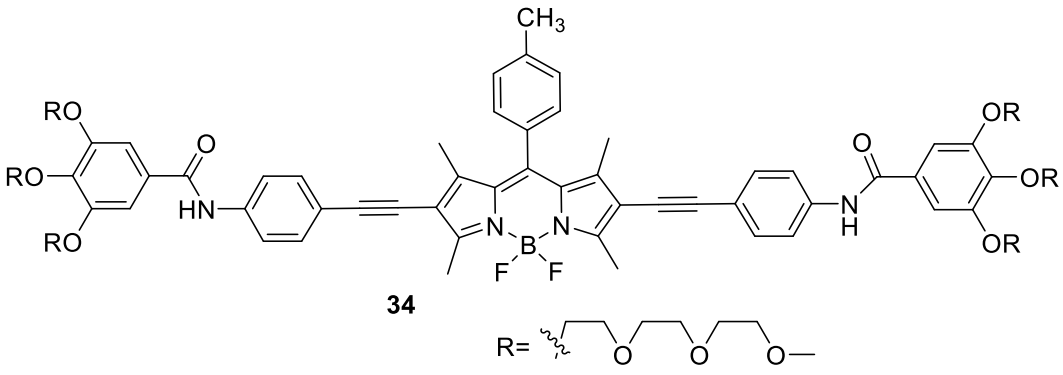



**Fig. 20** H-type aggregating chromophore containing BODIPY.

### 2.4. Anti-cancer:

Because boron-containing drugs currently utilized in BNCT have poor water solubility, they are difficult to detect *in vivo*. To improve the water solubility, selectivity, and targeted fluorescence of boron-containing compounds, Jin and co-workers synthesised the carborane-based water soluble BODIPY **35, 36** in a simple and efficient method (Fig. 21). To improve the solubility and biocompatibility of the carborane polymer, the water-soluble carrier zwitterions was added together with the fluorophore -BODIPY as the target labelling group. The two carborane polymers (**35, 36**) exhibit great biocompatibility was immediately and precisely detected, according to the results of cell imaging. It offers a fresh concept for BNCT research and design. The use of carborane polymers as BNCT agents for the treatment of cancer is significantly impacted by such findings.[31]

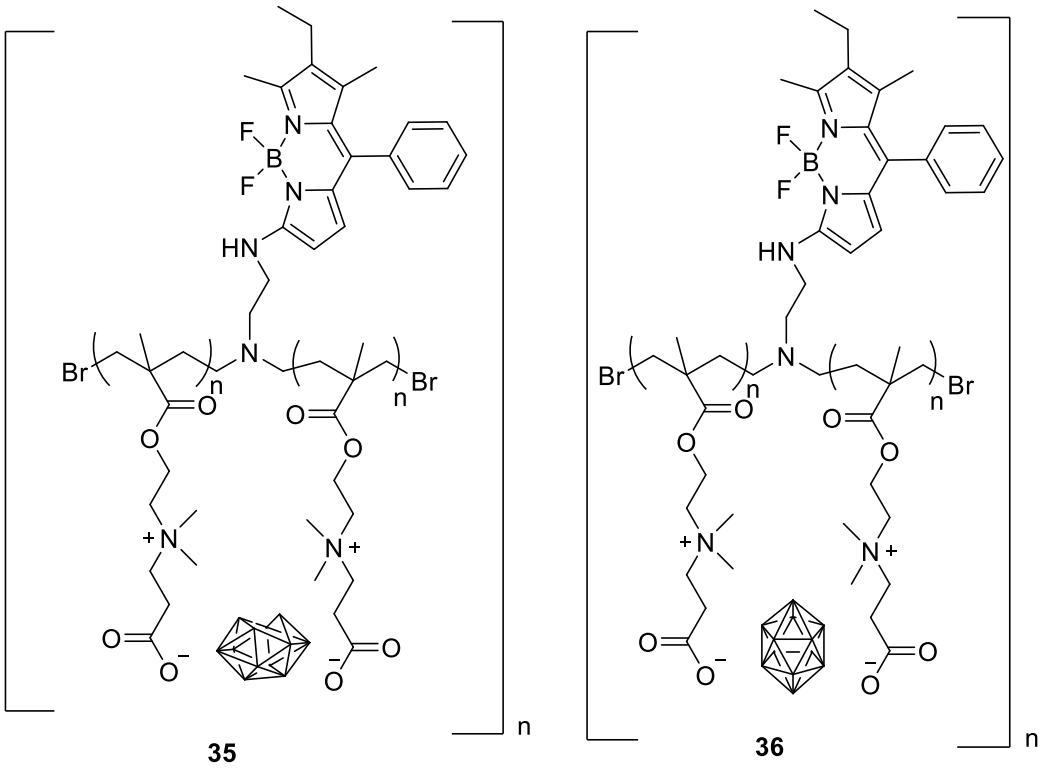



**Fig. 21** BODIPY- carborane complex.

The mitochondria targeted water-soluble thio-glycosylated BODIPYs were synthesized and reported by Kesavan et al. its theranostic properties. The pentafluorophenyldipyrromethane was used to synthesize these neutral thio-glycosylated BODIPYs **37** and **38**. The BODIPYs were highly cytotoxic to HeLa and HaCaT cells, making them candidates for anti-cancer therapy. In these cells, the determined $IC_{50}$ values for BODIPYs remained within the limited range. In HaCaT cells with lower IC50 values, these BODIPYs were more active. [32] A study

on ROS generation in HaCaT cells showed that thioglucosyl substituted BODIPYs have a better capacity for cellular absorption. By using confocal imaging, the dyes' subcellular localisation was made possible by the strong emission of thioglycosylated BODIPYs at 535 nm. These neutral, water-soluble thioglycosylated BODIPYs have been identified as prospective theranostic agents for the treatment of cancer due to their selective mitochondrial localisation.

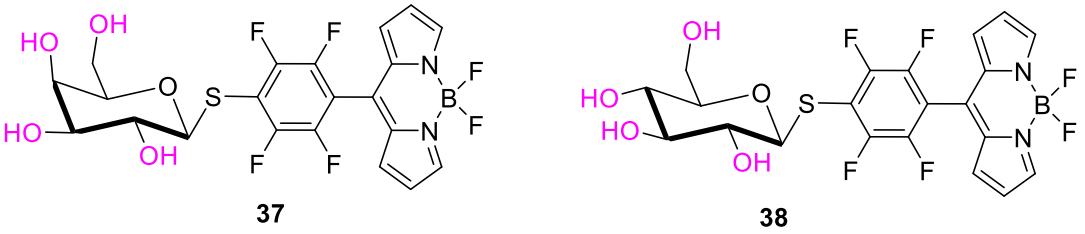



**Fig. 22** BODIPY with theranostic properties.

### 2.5. Bioimaging:

The water-soluble BODIPY photocages were synthesized and high photo release efficiency were described by Weinstain and co-workers. EWGs at the 2,6-positions appear to destabilize the carbocation produced during the photoreaction, according to calculation and in vitro characterization. They were able to get over this barrier by introducing remote sulfonation, which increased water solubility and allowed us to control cellular localisation by changing the amount of sulfonation. The authors compared sets of non-, mono-, and di-MESNA BODIPYs bearing three caged biogenic amines: serotonin, dopamine, and histamine (**39-45**), forming a series of leaving groups with decreased hydrophobicity, to assess the dependence of sulfonated BODIPY PPGs cellular permeability on the nature of the leaving group (Fig. 23). While di-MESNA BODIPY (**39-44**) was entirely cell-impermeable regardless of the polarity of the leaving group, non- and mono-MESNA-BODIPY (**43-45**), cellular permeability was greatly dependent on the polarity of the leaving group. While mono-sulfonated BODIPYs still have the potential to permeate the cellular membrane and can influence intracellular targets, peripherally di-sulfonated BODIPYs are interesting candidates for usage in modulating extracellular proteins and cell-surface receptors. *in vitro* evaluation suggested that EWGs at the 2,6-positions weaken the carbocation produced by the photoreaction. By the introducing remote sulfonation, this increased water solubility and allowed to control cellular localisation by varying the amount of sulfonation. The peripheral sulfonation strategy was applicable to BODIPY fluorophores generally, providing a practical way to confer water-solubility and control cellular permeability.[33]

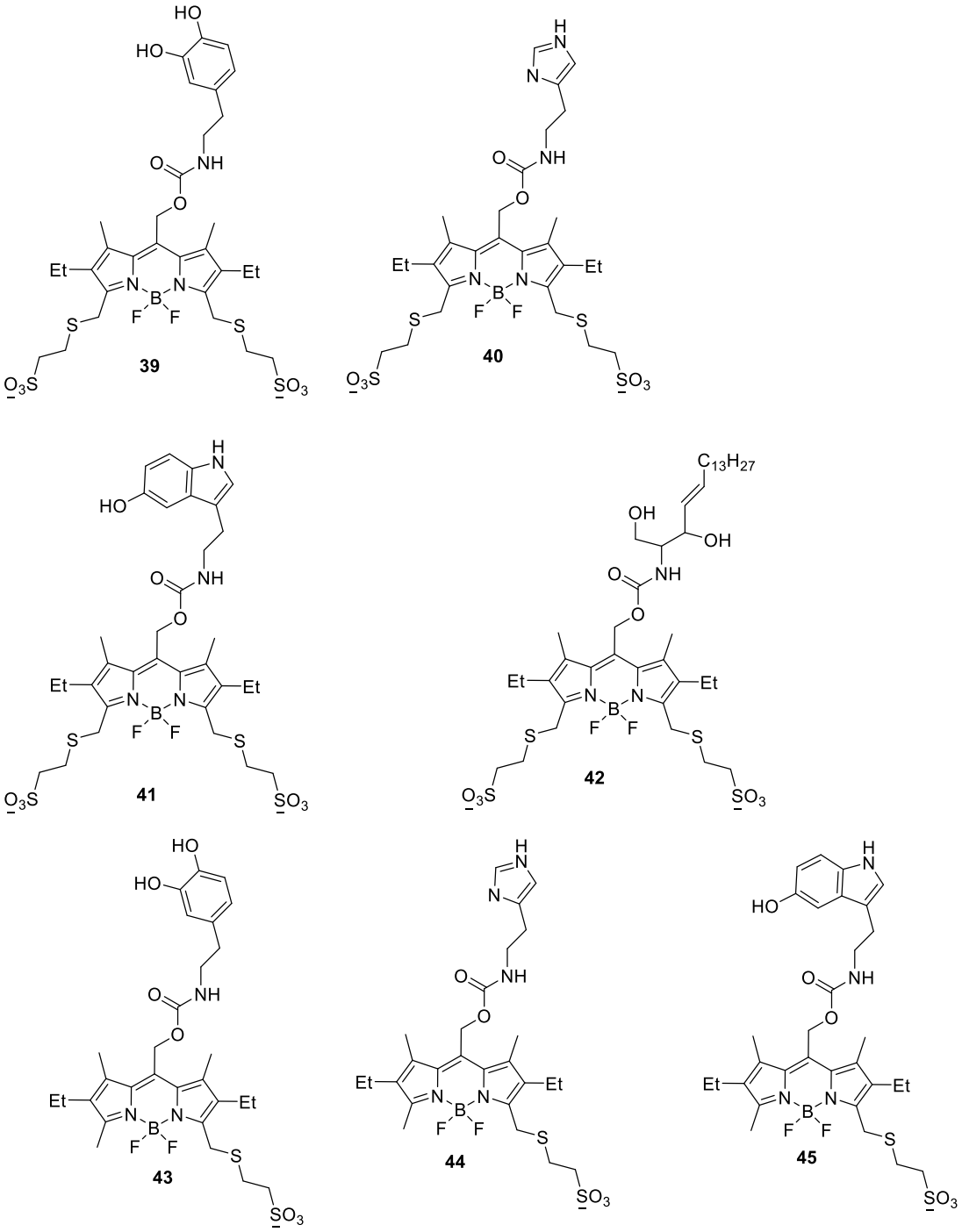



**Fig. 23** BODIPY with three caged biogenic amines.

Muller and co-workers designed and synthesized series of bioconjugatable linker BODIPY probe **46** (Fig. 24). The Excellent fluorescence features, such as high fluorescence quantum yields and narrow absorption and emission bands, are displayed by the synthesized fluorescent dyes. [34] Furthermore, under basic, reductive, or oxidative circumstances, the discovered BODIPY compounds maintain their chemical stability. The synthesized dyes were proven to be adaptable tools and will be very helpful for fluorescently labelling small molecules and

biological targets, enabling the investigation of biological processes, including the development of assays for compound screening, via fluorimetric methods. Sulfonate groups were introduced to the 2- and 6-positions of the BODIPY core to generate water-soluble BODIPY derivatives **46**.

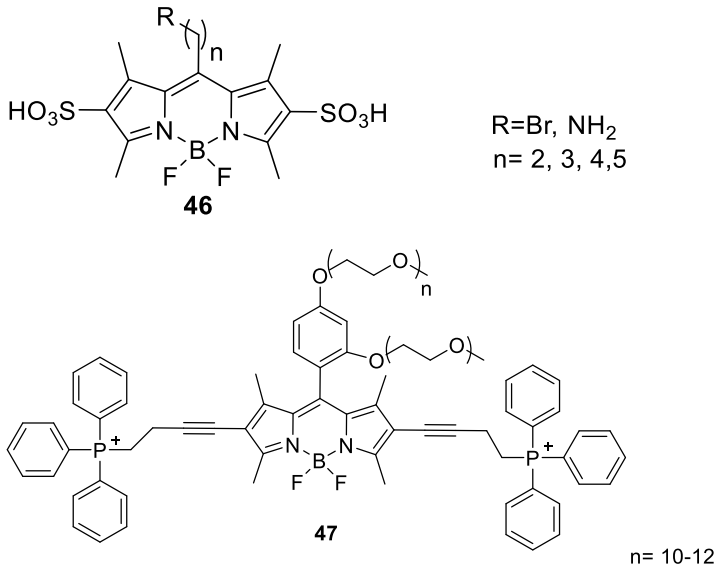



**Fig. 24** BODIPY-Fluorescent dye complexes.

Mitochondria targeting BODIPY based fluorescent probe **47** was designed and synthesized by Belfield and co-workers (Fig. 24).[35] In the Probe **47**, a BODIPY platform that acts as the fluorophore, two TPP groups that target mitochondria, and two PEG groups that make the compound more water soluble, ensure biocompatibility, and inhibit rotational freedom and non-radiative decay.[35] **47** possesses many desirable characteristics of a fluorescent mitochondrial targeting probe, including high water solubility, high fluorescence quantum yield, solvent independent photophysical properties, pH insensitivity, good photostability, low cytotoxicity, and excellent mitochondrial targeting traits, according to photophysical characterization, quantitative photostability studies, cell viability assessments, and fluorescence microscopy experiments.

High-fluorescence, water-soluble probes that can handle the demands of current, target-specific recognition assay. Werz and co-workers designed and synthesized series of water soluble based glyco-BODIPY (**48-51**). Complex, hemiacetal-equipped glycans with a pure hydroxyl functionality that the authors reported, like Gb3, also serve as compatible and integrable oligosaccharides. A single additional synthetic step enabled a sequential red-shift in the absorption, enhancing compatibility with multicolour labelling assay. Due to their wide variety

of solubilities, glycoconjugates were modified structurally throughout the synthesis process, turning them into uncharged, hydrophilic labels for click chemistry-mediated ligations and probes for target-specific photodynamic treatment. The constructed glycoconjugates, regardless of the incorporated sugar moiety, exhibit generally solvent-independent fluorescence effective, preserving all of the spectroscopic benefits of the BODIPY motif. Confocal imaging research revealed a variety of GlycoBODIPYs' applications for cellular studies and illustrated their powerful chiral activity for particular cellular applications.[36]

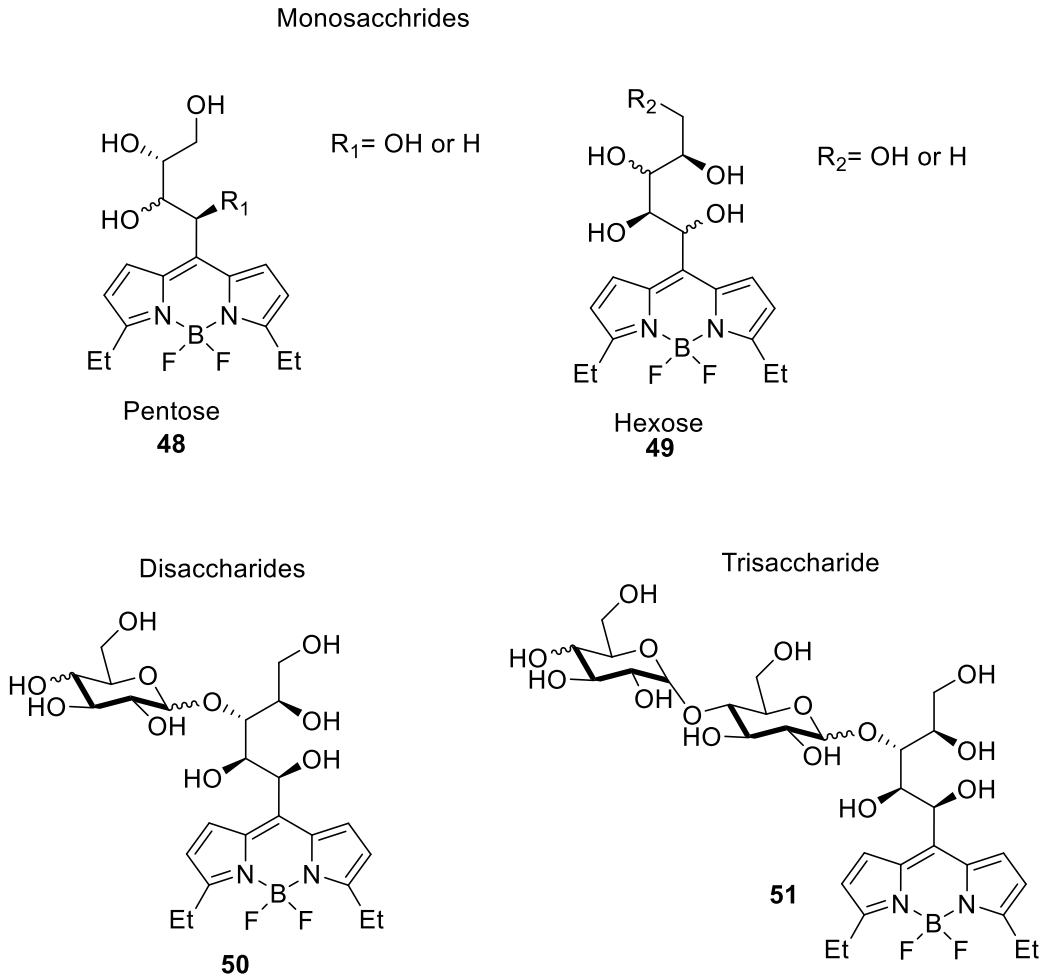
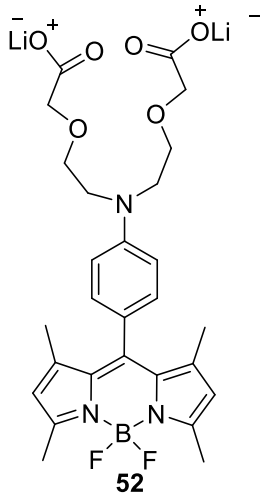



**Fig. 25** Glyco-BODIPY complexes.

### 2.6. Metal ion detection:

Maity et al. developed BODIPY derivative **52**, which is extremely water soluble and can detect $Cd^{2+}$ preferentially to other metal ions in aqueous media (Fig. 26). The frontier molecular orbitals of the chemosensor before and after binding with $Cd^{2+}$ (from DFT experiments) suggested useful information to build turn-on sensing mechanism. Hence, the chemosensor

serves as a superb fluorimetric probe with notable selectivity and specificity towards $Cd^{2+}$ up to submicromolar level. The competitive binding experiment demonstrated that no impact on the selectivity towards $Cd^{2+}$ from the other ecologically and physiologically relevant metal ions. The sensor's reversibility and reuse were proved by performing several cycles with alternate additions of $Cd^{2+}$ and $S^{2-}$. The sensing probe's OFF/ON/OFF behaviour presents an opportunity to build an INHIBIT logic gate using [$Cd^{2+}$] and [$S^{2-}$] as the two inputs. Additionally, cell research showed that the probe **52** was capable of reliably detecting intracellular $Cd^{2+}$. The authors claimed that this sensing technique unquestionably offers a foundation to construct a BODIPY-based chemosensor to track other environmentally hazardous toxic heavy metal ions in an aqueous media.[37]



**52**

**Fig. 26** BODIPY complex for $Cd^{2+}$ ion detection.

Common metal ions in naturally occurring aquatic environments and organisms include $Fe^{3+}$ and $Fe^{2+}$ have great importance for life process. So, it was very essential to develop water-soluble fluorescence sensors for detecting $Fe^{2+/}Fe^{3+}$ ions. Small molecular fluorescent monomers were designed and synthesized by Cheng and colleagues (Fig. 27).[38] Then, using the RAFT process, they were co-polymerized with methacrylic acid. It was discovered that fluorescent BODIPY-based polymers (**53-56**) had the ability to selectively recognize $Fe^{3+.}$ These polymers containing the BODIPY moiety at the end of the polymer chains were easily dissolved in water because to the presence of the polymethacrylic acid chain. The BODIPYs exhibited a low detection limit and were sensitive at detecting $Fe^{3+}$. These fluorescent polymer sensors displayed good temperature stability and a high fluorescence quantum yield. As a result, the authors proposed a unique technique for water-soluble fluorescent polymer sensors for $Fe^{2+/}Fe^{3+}$ ions.

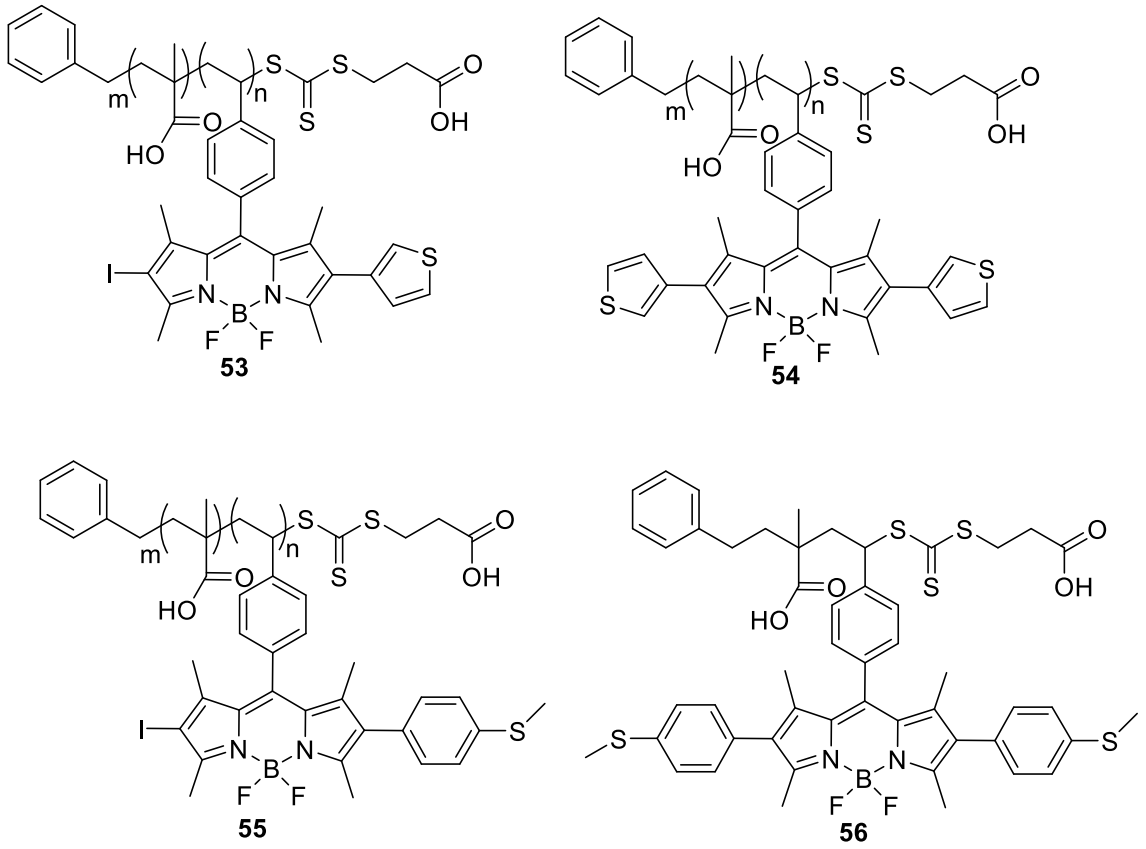



**Fig. 27** BODIPY complex for $Fe^{2+/}Fe^{3+}$ ion detection.

By adding hydrophilic carboxyl and amide chains, Cheng and co-workers used the reversible addition-fragmentation chain transfer polymerization (RAFT) polymerization technique to produce the water-soluble BODIPY polymers **57-59** (Fig. 28).[39] Small molecular fluorescent monomers were added to the end of the main chain after the main monomers of methacrylic acid (MAA) and methacrylamide (MAM) were employed as the primary monomers. Due to the presence of sufficiently long hydrophilic carboxyl and amide chains, the polymers were water soluble. These fluorescent probes have a very low detection limit and a high sensitivity to $Fe^{2+/}Fe^{3+}$, strong selectivity, and anti-interference of other ions. These probes, according to the authors, could be effective sensors for differentiating between $Fe^{2+}$ and $Fe^{3+}$.

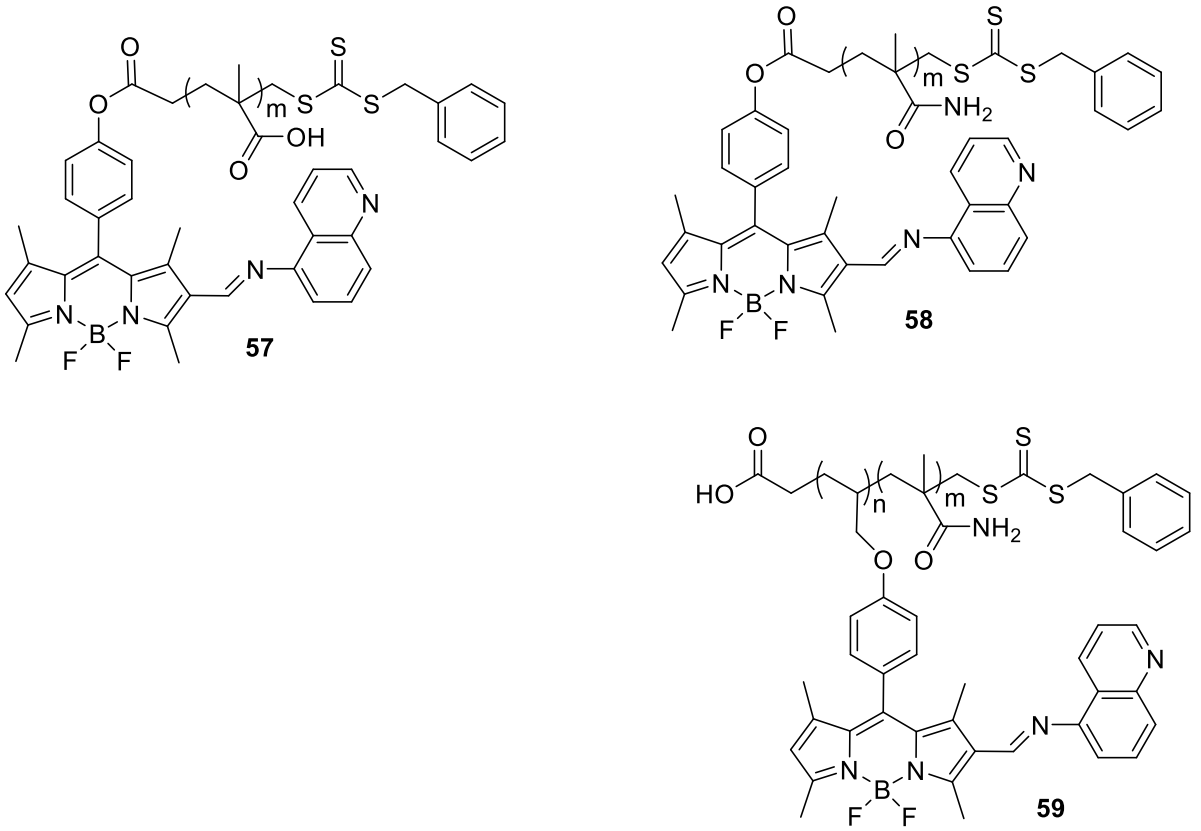
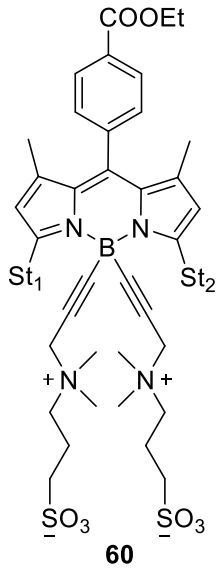
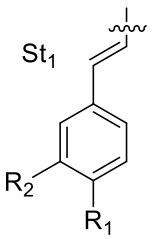


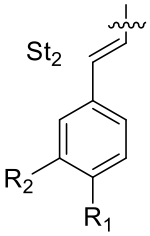

**Fig. 28** BODIPY-methacrylic acid and methacrylamide conjugates.

### 2.7. pH indicator:

To adequately visualize various cellular activities, the intracellular pH must be accurately determined. Ulrich and co-workers synthesize water soluble Red-NIR emissive BODIPY derivatives **60** with alterations of their absorption and emission properties in selected ranges of pH. By gradually modifying the substituents near the tertiary aniline derivatives or the phenol subunits that were selected as the protonation sites, the pH sensitive ranges were selected.[40] These products were developed owing of their unusual electrical characteristics. Additionally, the addition of sulfobetaine functionalities at the boron centre of these pH-responsive BODIPYs provided useful fluorescent dyes in aqueous conditions, for which steric hindrance and electrostatic repulsions hinder their non-emissive aggregation. So, both water (and EtOH) and saline solutions were used to conduct the absorption and emission spectrophotometric experiments and determine their pKa values.



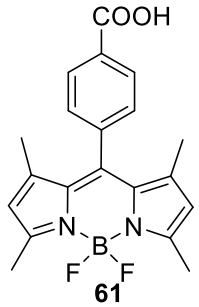




| $R_1$ | $R_2$ | $R_3$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| a | OH | Cl | – | – |
| b | $NMe_2$ | H | OH | H |
| c | $NEt_2$ | OMe | $NEt_2$ | OMe |
| d | $NMe_2$ | OMe | $NMe_2$ | OMe |
| e | $NMe_2$ | H | $NMe_2$ | H |

**Fig. 29** BODIPY as pH indicator.

### 2.8. Probe for analytical Applications:

In the process known as electrochemiluminescence (ECL), radical species generated at electrodes interact to create excited states that release energy in the form of light. ECL has grown to be used in many analytical applications, such as biological studies, cancer detection, and cell surface characterization. ECL provides benefits over conventional detecting methods in these situations since it doesn't need a light source. Ding and co-workers reported a comparison investigation of the electrochemiluminescence of organic-soluble BODIPY **61** and water-soluble BODIPY **62** (Fig. 30). The mechanics of ECL light emission were investigated using a combination of UV-visible, fluorescence, and spooling ECL spectroscopy. The excited states of analyte dimers, known as excimers, were shown to be crucial in the production of ECL. When TPrA was utilized as a reductive coreactant, the ECL intensities were markedly increased.[41]



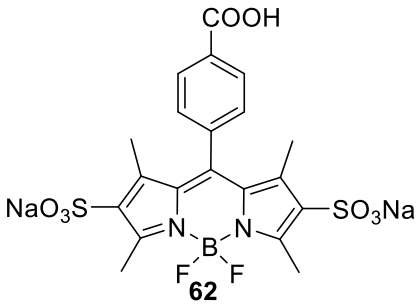




**Fig. 30** BODIPY as analytical probes.

### 2.9. Probe for peroxynitrite detection:

Reactive oxygen (ROS) and nitrogen species (RNS), the redox-active species, are closely linked to some human diseases, including cancer, neurodegenerative diseases, cardiovascular diseases, diabetes mellitus, and gastrointestinal disorders. Cells may have a complex regulatory system in place to maintain their redox balance. Peroxynitrite ($ONOO^-$), a by-product of the diffusion-controlled interaction between superoxide radicals and nitric oxide, has drawn particular interest among ROS and RNS because of its particularly powerful oxidizing capacity and reactive nucleophilic nature. Currently, it was shown that $ONOO^-$ plays a key role in the stimulation of calcium signalling, which is what causes skeletal muscle hypertrophy. Therefore, it is crucial to develop procedures that are accurate and practical for detecting ONOO- in biological samples. Recently, Na and co-workers designed and synthesized water-soluble BODIPY probes **63** and **64** (Fig. 31) for the detection of peroxynitrite ($ONOO^-$). The fact that Ac-Phe-OH **64a** was specifically removed from Ac-Phe-BODIPY **64** by ONOO- over other ROS and RNS is more significant than the fact that Ac-Phe-OH **64a** was a derivative of acetylated L-phenylalanine and has lower toxicity and greater biocompatibility. According to ESI-MS analysis and $^1H$ NMR spectroscopic studies, the mechanism was proved that the cleavage of the phenol ester bond of Ac-Phe-BODIPY occurs. Moreover, esterifying Ac-Phe-OH with BODIPY-OH increased the water solubility.[42]

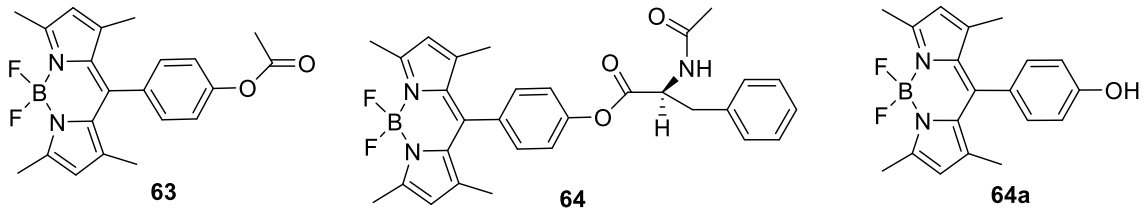



**Fig. 31** BODIPY for peroxynitrite detection.

### 2.10. Turn-on fluorescent Probe:

a. Probe for hypochlorite:

Myeloperoxidase (MPO)-catalyzed chloride ion peroxidation is the primary source of HClO production in leukocytes. As the primary microbicidal mediator in the human immune system, HClO is critical in the destruction of several diseases and germs that invade the body. Therefore, it is important to maintain a level of HClO that is well-balanced for cellular processes and innate host defence. Pathological processes include neurodegeneration, arthritis, renal disease, atherosclerosis, osteoarthritis, lung damage, rheumatoid arthritis, and cancer are

all associated with abnormal levels of HClO. For this reason, it is crucial to quickly detect HClO in live cells. To this end, Kim et al. synthesised BODIPY-based water-soluble fluorescent probe **65** that performed as a highly sensitive and selective HOCl/$OCl^-$ detection in aqueous buffer solution (Fig. 32).[43] When treated with HOCl in aqueous solution, Probe **65** exhibits a selective "off-on" fuorescence-based response and has high water solubility. This sort of water-soluble probe was developed by the author and uses a catechol moiety as a redox-responsive receptor group for targeted HOCl/$OCl^-$ detection in aqueous conditions.

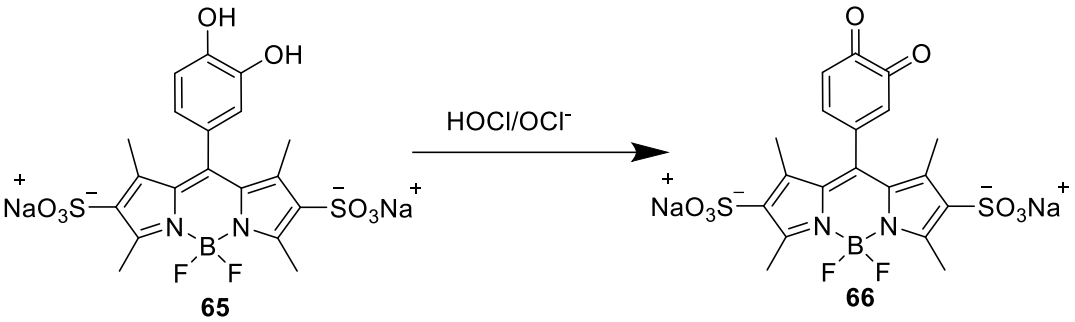



**Fig. 32** BODIPY as a probe for hypochlorite detection.

Soni et al. developed and synthesized the PTZ-BODIPY Probe **67**, a sensitive and highly water-soluble fluorescent chemosensor for the detection of $OCl^-$ in solution and solid phase (Fig. 33).[44] The BODIPY core was added carboxylic acid functional groups in order to make the probe water soluble. A branched ethylene glycol moiety was also introduced to the PTZ moiety to improve the probe's aqueous solubility and prevent fluorescence quenching from aggregation. The selective stimulation of the BODIPY was found to start the reductive PET from the PTZ moiety to BODIPY, which led to the quenching of the BODIPY fluorescence, according to steady-state and time-resolved fluorescence measurements. In presence of NaOCl, the fluorescence was restored. According to selectivity study, Probe **67** was detecting selectively $OCl^-$ than other competing ROS, cations, and anions. Cytotoxicity studies showed that the probe **67** was non-toxic. Consequently, the probe was implicated in a biological application.[44]

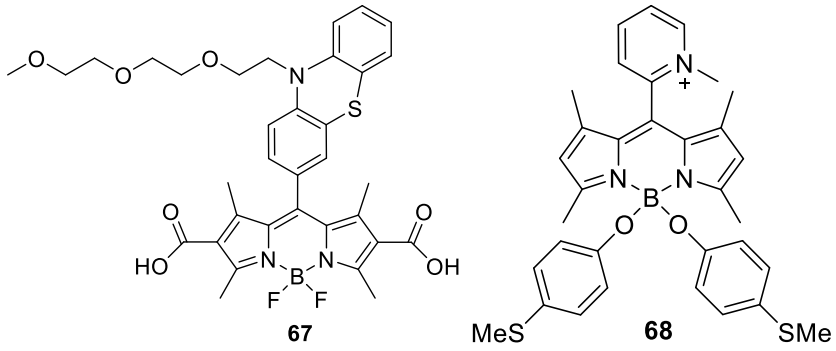
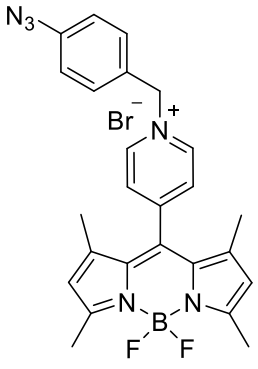



**Fig. 33** PTZ-BODIPY Probe for hypochlorite detection.

Zhao and co-workers designed and synthesized water-soluble BODIPY dye **68** for quick and selective detection of hypochlorous acid (Fig. 33).[45] In order to make the BODIPY core more water soluble, the pyridinium salt was added and the 4-methylmercaptophenoxy was chosen as the responsive site by oxidizing thioether. Low intrinsic fluorescence was present in probe **68**. After adding HClO, the probe soon demonstrated an impressive fluorescent response and generated a significant fluorescence increase of up to 100-fold. The author claimed that probe **68** was successfully applied to image HClO in living cells.

b. Probe for Gasotransmitters ($H_2S$):

Gasotransmitters, which are endogenously generated gaseous molecules that diffuse extensively and have a variety of physiological and pathological effects on living things, include nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide ($H_2S$). Reactive sulfur, which includes hydrogen sulfide ($H_2S$) gas, is thought to be the body's third major gasotransmitter after nitric oxide (NO) and carbon monoxide. The water-soluble "Turn-On" fluorescence probe for $H_2S$ was reported by Zhang et al.[46] Through the quaternization procedure, meso-pyridinium-4-yl functionalized BODIPY dye fragments were widely quenched, and the pyridinium unit led to increased water solubility. Regeneration of fluorescence occurs when the pyridinium's N-substituent was eliminated. Due to the photoinduced electron-transfer (PET) mechanism, BODIPY-based probe **69** has a very low fluorescence quantum yield and is soluble in water. $H_2S$ was added to probe **69**, and this caused a substantial fluorescence improvement. To distinguish $H_2S$ from other frequent analytes and medically necessary thiol-containing amino acids, probe **69** demonstrates good selectivity. The probe was successfully employed to find $H_2S$ in live cells and had a minimal level of toxicity.

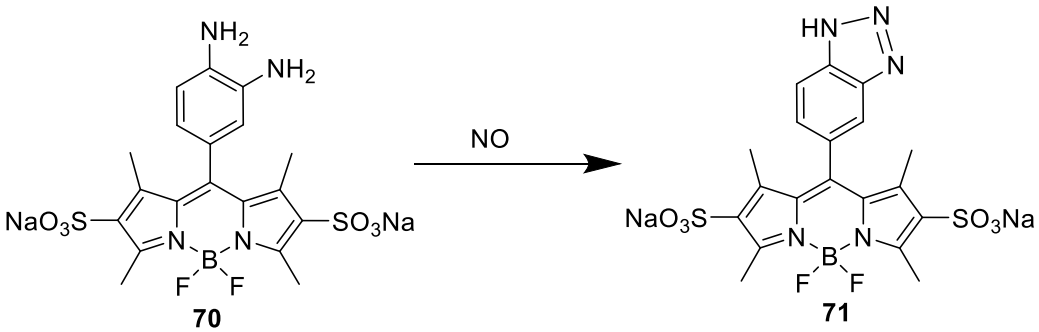



**69**

**Fig. 34** BODIPY as a probe for Gasotransmitters.

c. Probe for NO:

A novel water-soluble BODIPY dye with two sulphonate groups has been reported, and the release behaviour of NO has been carefully observed using the CE-LIF (capillary electrophoresis with laser induced fluorescence detection) approach. The turn-on fluorescent probe**70** fast increases the fluorescence to 540-fold when NO is present in an aqueous solution (Fig. 35).[47] The o-diamino aromatic moiety serves as the NO trapping domain while the BODIPY core acts as a fluorophore. The solubility of in water was significantly enhanced by the addition of two sodium sulfonate groups to the BODIPY backbone. The corresponding triazole**71** was formed after trapping NO in water, the PET process is suppressed. Additionally, although being extremely water soluble, the probe was not entered the cell plasma through the cell membrane. This concept was used to simultaneously quantify and retain NO in a single cell, according to reports. To understand the physiological and pathological roles of such a transitory molecule, it was therefore advantageous to research the release behaviour of gasotransmitters (NO).[47]




**70** **71**

**Fig. 35** BODIPY as a probe for Gasotransmitters.

**Conclusions:**

In recent years, the use of water-soluble BODIPYs have received significant interests. It has been reported that several water-soluble BODIPY dyes having charged as well as neutral

hydrophilic groups with quaternary ammonium, sulfonates, phosphonates, carboxylates, oligoethyleneglycols, and sugar moieties. By affixing hydrophilic sterically hindered groups, it is possible to increase the fluorescence quantum yields and reduced the aggregation of the BODIY dyes in water. These water-soluble BODIPY derivatives have numerous potential uses in photodynamic therapy, chemosensors, bio-labelling of bio-macromolecules, cell imaging, metal ion detection, pH sensor and other fields. However, the optical properties and biocompatibility of the water-soluble BODIPY dyes need to be optimized through logical molecular design in order to further enhance the performance of these molecules in applications. The unique advantages of NIR in biological applications, make the development of water soluble BODIPYs having high fluorescence in the NIR rang, a significant research area.

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**Conflict of Interest**:

There are no conflicts to declare.

**References**

1. (a) M. Bates, B. Huang, G. T. Dempsey and X. Zhuang, Multicolor super-resolution imaging with photo-switchable fluorescent probes, *Science*, 2007, **317**, 1749-1753. (b) Z. Shi, X. Han, W. Hu, H. Bai, B. Peng, L. Ji, Q. Fan, L. Li and W. Huang, Bioapplications of small molecule Aza-BODIPY: from rational structural design to in vivo investigations, *Chem. Soc. Rev.*, 2020, **49**, 7533-7567. (c) J. Michel Merkes, T. Ostlender, F. Wang, F. Kiessling, H. Sun and S. Banala, Tuning the optical properties of BODIPY dyes by N-rich heterocycle conjugation using a combined synthesis and computational approach, *New J. Chem.*, 2021, **45**, 19641-19645. (d) A. Blázquez-Moraleja, L. Maierhofer, E. Mann, R. Prieto-Montero, A. Oliden-Sánchez, L. Celada, V. Martínez-Martínez and M. D. C. J. L. Chiara, Acetoxymethyl-BODIPY dyes: a universal platform for the fluorescent labeling of nucleophiles,*Org. Chem. Front.*, 2022, **9**, 5774-5789. (e) S. Wu, L. Gai, Z. Zhou and H. Lu, Recent advances in zig-zag-fused BODIPYs, *Org. Chem. Front.*, 2022, **9**, 5989-6000. (f) M. D. Matveeva, D. I. Zhilyaev, A. R. Miftyakhova, P. Chulkin, P. Janasik, L. G. Voskressensky, G. Talarico and I. V. Efimov, Synthesis and photophysical properties of novel oxadiazole substituted BODIPY fluorophores, *New J. Chem.*, 2022, **46**, 5725-5729. (g) I. V. Efimov, A. R.

Miftyakhova, M. D. Matveeva, D. I. Zhilyaev, P. Czulkin, P. Janasik, G. Talarico and L. G. Voskressensky, Synthesis and photophysical properties of 1,7-aroyl BODIPYs: an experimental and theoretical study, *New J. Chem.*, 2022, **46**, 19291.

2. A. Treibs and F. H. Kreuzer, Difluorboryl-Komplexe von Di- und Tripyrrylmethenen, *Justus Liebigs Ann Chem*., 1968, **718**, 208-223.
3. G. Ulrich, R. Ziessel and A. Harriman, The chemistry of fluorescent bodipy dyes: Versatility unsurpassed, *Angew Chemie - Int Ed*., 2008, **47**, 1184-1201.
4. A. Loudet and K. Burgess, BODIPY dyes and their derivatives: Syntheses and spectroscopic properties, *Chem Rev*., 2007, **107**, 4891-4932.
5. M. Sameiro and T. Gonçalves, Fluorescent labeling of biomolecules with organic probes, *Chem Rev*., 2009, **109**, 190-212.
6. L. Jiao, J. Li, S. Zhang, C. Wei, E. Hao and M. G. H. Vicente, A selective fluorescent sensor for imaging Cu2+ in living cells, *New J Chem*., 2009, **33**, 1888-1893.
7. L. Zeng, E. W. Miller, A. Pralle , E. Y. Isacoff and C. J. Chang, A selective turn-on fluorescent sensor for imaging copper in living cells, *J Am Chem Soc*., 2006, **128**, 10-11.
8. Q. Zheng, G. S. He and P. N. Prasad, A novel near IR two-photon absorbing chromophore: Optical limiting and stabilization performances at an optical communication wavelength, *Chem Phys Lett*., 2009, **475**, 250-255.
9. D. Zhang, Y. Wang, Y. Xiao, S. Qian and X. Qian, Long-wavelength boradiazaindacene derivatives with two-photon absorption activity and strong emission: versatile candidates for biological imaging applications, *Tetrahedron*., 2009, **65**, 8099-8103.
10. M. Wang, M. G. H. Vicente, D. Mason and P. Bobadova-Parvanova, Stability of a Series of BODIPYs in Acidic Conditions: An Experimental and Computational Study into the Role of the Substituents at Boron, *ACS Omega*., 2018, **3**, 5502-5510.
11. K. M. Bardon, S. Selfridge and D.S. Adams, Synthesis of Water-Soluble Far-Red-Emitting Amphiphilic BODIPY Dyes, *ACS Omega*., 2018, **3**, 13195-13199.
12. U. Haldar, R. Sharma, B. Ruidas and H. Lee, Toward rapid and selective detection of hypochlorous acid in pure aqueous media and its application to cell imaging: BODIPY-derived water-soluble macromolecular chemosensor with high sensitivity, *Dye Pigment*., 2020, **172**, 107858.
13. S. A. Gorbatov, D. Y. Uvarov, A. M. Scherbakov, I. V. Zavarzin , Y. A. Volkova and A. Romieu, A novel water-soluble BODIPY dye as red fluorescent probe for imaging

hypoxic status of human cancer cells, *Mendeleev Commun*., 2020, **30**, 750-752.

14. K. Wang, Y. Xiao and Y. Wang, Self-assembled hydrophobin for producing water-soluble and membrane permeable fluorescent dye, *Sci Rep*., 2016, **6**, 1-11.
15. R. D. Moriarty, A. Martin and K. Adamson, The application of water soluble, mega-Stokes-shifted BODIPY fluorophores to cell and tissue imaging, *J Microsc*., 2014, **253**, 204-218.
16. I. W. Badon, J. Lee, T. Pegarro Vales, B. K. Cho and H. J. Kim, Synthesis and photophysical characterization of highly water-soluble PEGylated BODIPY derivatives for cellular imaging, *J Photochem Photobiol A Chem*., 2019, **377**, 214-219.
17. B. Kim, B. Sui, X. Yue, S. Tang, M. G. Tichy and K. D. Belfield, In Vitro Photodynamic Studies of a BODIPY-Based Photosensitizer, *European J Org Chem*., 2017, **2017**, 25-28.
18. T. Zhang, R. Lan and L. Gong, An Amphiphilic BODIPY-Porphyrin Conjugate: Intense Two-Photon Absorption and Rapid Cellular Uptake for Two-Photon-Induced Imaging and Photodynamic Therapy, *ChemBioChem*., 2015, **16**, 2357-2364.
19. N. Zhao, T. M. Williams and Z. Zhou, Synthesis of BODIPY-Peptide Conjugates for Fluorescence Labeling of EGFR Overexpressing Cells, *Bioconjug Chem*., 2017, **28**, 1566-1579.
20. N. Shivran, M. Tyagi and S. Mula, Syntheses and photodynamic activity of some glucose-conjugated BODIPY dyes, *Eur J Med Chem*., 2016, **122**, 352-365.
21. Z. Lu, X. Zhang and Z. Wu, BODIPY-based macromolecular photosensitizer with selective recognition and enhanced anticancer efficiency, *RSC Adv*., 2014, **4**, 19495-19501.
22. I. S. Turan, F. P. Cakmak, D. C. Yildirim, R. Cetin-Atalay and E. U. Akkaya, Near-IR absorbing BODIPY derivatives as glutathione-activated photosensitizers for selective photodynamic action, *Chem - A Eur J*., 2014, **20**, 16088-16092.
23. I. S. Turan, G. Gunaydin, S. Ayan and E. U. Akkaya, Molecular demultiplexer as a terminator automaton, *Nat Commun*., 2018, **9**, 1-8.
24. M. Gorbe, A. Barba-Bon and C. De La Torre, Synthesis and in Vitro Evaluation of a Photosensitizer-BODIPY Derivative for Potential Photodynamic Therapy Applications, *Chem - An Asian J*., 2015, **10**, 2121-2125.
25. B. Barut, C.Ö. Yalçın and S. Sari, Novel water soluble BODIPY compounds: Synthesis, photochemical, DNA interaction, topoisomerases inhibition and photodynamic activity properties, *Eur J Med Chem*., 2019, 183.

26. X. Dai, X. Chen and Y. Zhao, A Water-Soluble Galactose-Decorated Cationic Photodynamic Therapy Agent Based on BODIPY to Selectively Eliminate Biofilm, *Biomacromolecules*., 2018, **19**, 141-149.
27. M. Lan, S. Zhao, W. Liu, C. S. Lee, W. Zhang and P. Wang, Photosensitizers for Photodynamic Therapy, *Adv Healthc Mater*., 2019, **8**,
28. Z. Biyiklioglu, B. Barut and A. Özel, Synthesis, DNA/BSA binding and DNA photocleavage properties of water soluble BODIPY dyes, *Dye Pigment*., 2018, **148**, 417-428.
29. S. Belali, G. Emandi and A. A. Cafolla, Water-soluble, neutral 3,5-diformyl-BODIPY with extended fluorescence lifetime in a self-healable chitosan hydrogel, *Photochem Photobiol Sci*., 2017, **16**, 1700-1708.
30. A. Rödle, M. Lambov, C. Mück-Lichtenfeld, V. Stepanenko and G. Fernández, Cooperative nanoparticle H-type self-assembly of a bolaamphiphilic BODIPY derivative in aqueous medium, *Polymer (Guildf)*., 2017, **128**, 317-324.
31. C. Shao, G. Lian and G. Jin, Nido-carborane encapsulated by BODIPY zwitterionic polymers: Synthesis, photophysical properties and cell imaging, *J Saudi Chem Soc*., 2021, **25**, 101345.
32. P. E. Kesavan, V. Pandey, M. K. Raza, S. Mori and I. Gupta, Water soluble thioglycosylated BODIPYs for mitochondria targeted cytotoxicity, *Bioorg Chem*., 2019, **91**, 103139.
33. D. Kand, P. Liu and M. X. Navarro, Water-Soluble BODIPY Photocages with Tunable Cellular Localization, *J Am Chem Soc*., 2020, **142**, 4970-4974.
34. F. Heisig, S. Gollos, S. J. Freudenthal, A. El-Tayeb, J. Iqbal and C. E. Müller, Synthesis of BODIPY derivatives substituted with various bioconjugatable linker groups: A construction kit for fluorescent labeling of receptor ligands, *J Fluoresc*., 2014, **24**, 213-230.
35. B. Sui, S. Tang, A. W. Woodward, B. Kim and K. D. Belfield, A BODIPY-Based Water-Soluble Fluorescent Probe for Mitochondria Targeting, *European J Org Chem*., 2016, **16**, 2851-2857.
36. L. J. Patalag, S. Ahadi, O. Lashchuk, P. G. Jones, S. Ebbinghaus and D. B. Werz, GlycoBODIPYs: Sugars Serving as a Natural Stock for Water-soluble Fluorescent Probes of Complex Chiral Morphology, *Angew Chemie*., 2021, **133**, 8848-8853.
37. A. Maity, U. Ghosh, D. Giri, D. Mukherjee, T. K. Maiti and S. K. Patra, A water-soluble BODIPY based ‘OFF/ON’’ fluorescent probe for the detection of Cd 2+ ions with high

selectivity and sensitivity, *Dalt Trans*., 2019, **48**, 2108-2117.

38. S. He, L. Xiao, L. Marin, Y. Bai and X. Cheng, Fully-water-soluble BODIPY containing fluorescent polymers prepared by RAFT method for the detection of Fe3+ ions, *Eur Polym J*., 2021, **150**, 110428.
39. S. He, L. Marin and X. Cheng, Novel water soluble polymeric sensors for the sensitive and selective recognition of Fe3+/Fe2+ in aqueous media, *Eur Polym J*. 2022, **162**, 110891.
40. A. Sutter, M. Elhabiri and G. Ulrich, Fluorescent pH-Responsive Probes Based on Water-Soluble Boron-Dipyrromethene (BODIPY) Derivatives, Featuring Long-Wavelength Emission, *Chem - A Eur J*., 2018, **24**, 11119-11130.
41. P. Chauhan, K. Chu, N. Yan and Z. Ding, Comparison study of electrochemiluminescence of boron-dipyrromethene (BODIPY) dyes in aprotic and aqueous solutions, *J Electroanal Chem*., 2016, **781**, 181-189.
42. X. Zhao, N. Li and F. Liu, Synthesis and Application of Water-Soluble Reaction-Based Boron-Dipyrromethene (BODIPY) Probes for Fluorescent Detection of Peroxynitrite with High Selectivity, *Chinese J Org Chem*., 2020, **40**, 4339-4343.
43. J. Kim and Y. Kim, A water-soluble sulfonate-BODIPY based fluorescent probe for selective detection of HOCl/OCl− in aqueous media, *Analyst*., 2014, **139**, 2986-2989.
44. D. Soni, N. Duvva and D. Badgurjar, Hypochlorite-Mediated Modulation of Photoinduced Electron Transfer in a Phenothiazine–Boron dipyrromethene Electron Donor–Acceptor Dyad: A Highly Water Soluble "Turn-On" Fluorescent Probe for Hypochlorite, *Chem - An Asian J*., 2018, **13**, 1594-1608.
45. Y. Jin, M. Lv and Y. Tao, A water-soluble BODIPY-based fluorescent probe for rapid and selective detection of hypochlorous acid in living cells, *Spectrochim Acta - Part A Mol Biomol Spectrosc*., 2019, **219**, 569-575.
46. J. Zhang , F. Peng, X. Dong and W. Zhao, Water-soluble BODIPY derivative as a highly selective "turn-on" fluorescent probe for hydrogen sulfide in living cells, *Chem Lett*., 2015, **44**, 1524-1526.
47. Z. X. Zhang, X. F. Guo, H. Wang and H. S. Zhang, Capillary Electrophoresis Strategy to Monitor the Released and Remaining Nitric Oxide from the Same Single Cell Using a Specially Designed Water-Soluble Fluorescent Probe, *Anal Chem*., 2015, **87**, 3989-3995.