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Review

Metal-based BODIPY derivatives as multimodal tools for life sciences

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ABSTRACT

Nowadays, 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene – better known as BODIPY· – is at the forefront of fluorophores for life sciences. Indeed, its high brightness, its tunable excitation and emission wavelengths along with its high chemical and photochemical stability draw more and more the interest of researchers. In the last decade, chemists have taken advantage of the versatility of the synthesis of BODIPY to design sophisticated objects. This review focuses on the different recent studies dealing with the conception of metal-based-BODIPY derivatives for medical purposes. More precisely, emphasis is put on the use of BODIPY derivatives for the elaboration of BODIPY-based theranostics, multimodal imaging probes, and photodynamic therapy sensitizers.

Contents

Abbreviations: acac, acetylacetonate; BMDC, bone marrow derived dendritic cell; BODIPY, boron dipyrromethene, 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene; bpy, 2,2′-dipyridyl; BSA, bovine serum albumin; cat, catechol; CLSM, confocal laser scanning microscopy; CT, computed tomography; DFO, deferoxamine; DOTAGA, 1,4,7,10-tetraaz acyclododecane-1-glutaric acid-4,7,10-triacetic acid; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; dppz, dipyridophenazine; DTPA, diethylene triamine tetracetic acid; DTT, dithiothreitol; FA, folic acid; Fc, ferrocenyl; FDA, food and drug administration; GRPR, gastrin-releasing peptide receptor; HER2, human epithelial growth factor receptor 2; HIF, hypoxia inducing factor; ICP-MS, inductively coupled plasma mass spectrometry; ISC, intersystem crossing; LDH, lactate dehydrogenase; LN, lymph node; LPS, lipopolysaccharide; mAb, monoclonal antibody; MOF, metal–organic framework; MOMIP, monomolecular multimodal imaging probe; MRI, Magnetic Resonance Imaging; NIR, near infrared; NODAGA, 1,4,7-triazacyclononane,1-glutaric acid-4,7-acetic acid; NP, nanoparticle; NPA, *p*-nitrophenylalanine; Oc, octreotide; PACT, photo-activated chemotherapy; PDI, photodynamic inactivation; PDT, photodynamic therapy; PEG, poly(ethylene glycol); PEI, poly(ethylenimine); PeT, photoinduced electron transfer; PET, positron emission tomography; PI, phototoxicity index; ppy, 2-phenylpyridine; PS, photosensitizer; PTT, photothermal therapy; pyda-T, 2,4-diamino-6-(2-pyridyl)-1,3,5-triazine; ROS, reactive oxygen species; sc-DNA, supercoiled DNA; SPECT, single photon emission computed tomography; SPION, superparamagnetic iron oxide nanoparticle; SRIXE, synchrotron radiation induced X-ray emission; SSTR2, somatostatin receptor 2; TCO, *trans*-cyclooctene; TrxR, thioredoxin reductase; Tz, tetrazine; WT, wild-type.

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1. Introduction

This last decade witnessed the advent of "multifunctionality way of life" and research is no exception. A single tool needs to display different applications, to collect numerous information.... In medicine, this trend leads to new fields of research such as "theranostics" or "multimodal imaging". Indeed, it is no longer enough to "simply" conceive a cytotoxic molecule, you need to track it all along its lifetime, and the designed probe should provide information both *in vitro* and *in vivo*. In this context, an increasing number of researchers are developing molecular or nanomolecular objects associating a metal complex to a luminescence probe. The metal complex can play the role of a cytotoxic agent or an imaging probe – scintigraphic probe in case of radioactive metal or Magnetic Resonance Imaging (MRI) probe in case of a paramagnetic one – while the luminophore enables optical imaging and/or can induce a phototoxic sensitization.

Optical imaging is the most used imaging modality in association with these multifunctional objects due to its ease of use, its low cost, and its superiority for *in vitro* studies. Numerous luminescent probes are available, however, for almost 20 years now, BODIPY dyes have turned out to be among the most useful molecules for fluorescent labeling of biomolecules in living cells [1].

Historically, the BODIPY core (Fig. 1) was first synthesized by Treibs and Kreuzer in 1968 [2], but its first use as a fluorescent label for bioactive ligands was reported in 1989 [3]. Since that period, the number of patents related to BODIPY increased steadily while the number of papers increased exponentially until 2015 when it reached a plateau (Fig. 2).

The unprecedented success of BODIPY dyes can be explained by their excellent optical properties. In practice, they display strong absorbance and relatively sharp fluorescence peaks with high quantum yields. Moreover, the extraordinarily rich chemistry they offer played a crucial role in their development [4–6], and consequently they found applications in various domains such as material science [7]. Regarding biological applications, the great stability of BODIPY under physiological conditions and their insensitivity towards pH variations make them a choice candidate for numerous fluorescent labeling purposes. Additionally, their resistance to photobleaching proved to be significantly higher than other classical fluorophores, which is often appreciable for imaging experiments [8]. Through all possible modifications of the BODIPY core, their optical properties are easily tunable as broad post-functionalization is allowed. Thanks to this, numerous different chemical functions have been successfully grafted on BODIPY. However, BODIPY dyes suffer from several drawbacks, notably their high lipophilicity, along with their typical absorption and emission wavelengths located around 500 nm. Indeed, NIR (near-infrared region 650–900 nm) probes are preferred for *in vivo* fluorescence imaging experiments, and water solubility is often a critical parameter for internalization of bioactive compounds. Notwithstanding, great advances have been made to improve water solubility of BODIPY, especially by introducing ionic groups on it [9]. As for the fluorescence properties, numerous modifications of BODIPYs were reported in order to get red-shifted emission. Here, it is noteworthy that the more recent aza-BODIPY family (Fig. 3), first described in 1993 [10], won fame in NIR emission and is currently attracting an increasing interest [11].

All along the 30 past years of constant development, the chemistry of BODIPY has become rich and extensively described. Among the various associations, which have already been studied between them and other classes of molecules, we chose to focus on metal-based BODIPY derivatives and their use as tools for life sciences. The approaches developed in these studies differ from the numerous works dealing with BODIPY sensors for detecting metals in cells [12]. We will also not develop the few metal–BODIPY conjugates, that have been designed as turn-on fluorescent biosensors for selective detection of NO or CO production in cells [13,14]. We believe that the combination between this versatile fluorophore and some metallic complexes has already brought some great advances, and will probably lead to innovative imaging methods and efficient theranostic agents.

This review deals with the association of a metal complex and a BODIPY in the same entity

(1) to take advantage of the unique photophysical properties of BODIPYs to track the fate of metallodrugs or metallodrug candidates *in vitro* or even *in vivo* and possibly get insight into their mechanism of action;
(2) to confer or increase photosensitizing properties to BODIPYs thanks to the heavy atom effect;
(3) to use the physical properties of some metal ions to build up bimodal imaging probes.

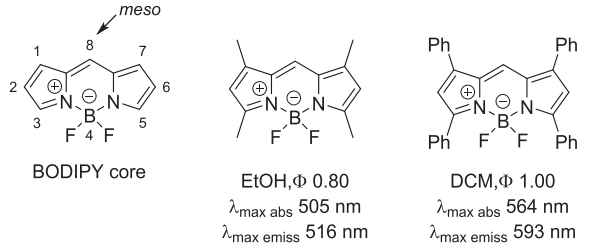

Fig. 1. Structure of the BODIPY core and representative BODIPY derivatives.

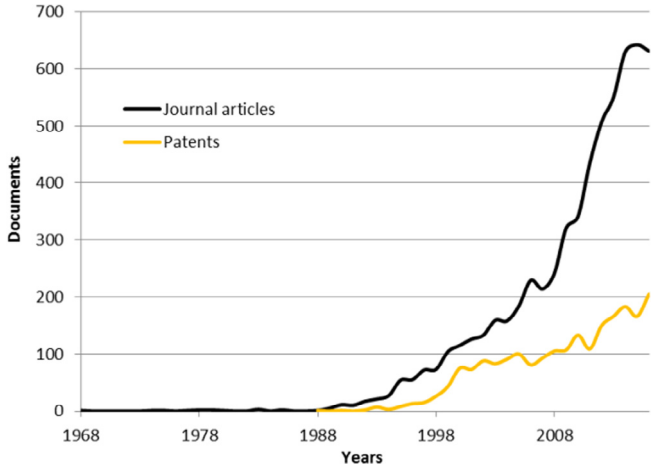

Fig. 2. Occurrence of BODIPY in journal articles and patents between 1968 and 2016 as extracted from the CAS Scifinder™ database on September 8, 2017.

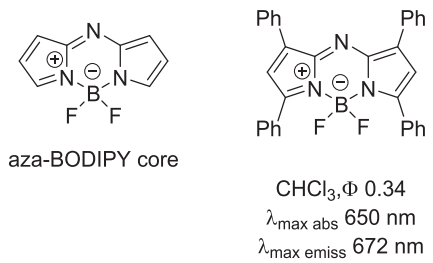

Fig. 3. Structure of aza-BODIPY.