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Development of symmetric *O*-BODIPYs with different optical properties as building blocks for the synthesis of ligands for multimodal imaging

Christian Paul Konken[a,d,*], Günter Haufe[b,c,**], Kathrin Brömmel[d], Bernhard Wünsch[d], Michael Schäfers[a,c,e], Stefan Wagner[a], Verena Hugenberg[f,***]

[a] Department of Nuclear Medicine, University Hospital Münster, Albert-Schweitzer-Campus 1, Building A1, D-48149, Münster, Germany
[b] Organic Chemistry Institute, University of Münster, Corrensstr. 40, D-48149, Münster, Germany
[c] Cells-in-Motion Cluster of Excellence, University of Münster, Waldeyerstr. 15, D-48149, Münster, Germany
[d] Institute for Pharmaceutical and Medicinal Chemistry, University of Münster, Corrensstr. 48, D-48149, Münster, Germany
[e] European Institute for Molecular Imaging, University of Münster, Waldeyerstr. 15, D-48149, Münster, Germany
[f] Institute for Radiology, Nuclear Medicine and Molecular Imaging, HDZ NRW, Georgstr. 11, D-32545, Bad Oeynhausen, Germany

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ABSTRACT

The unique properties and the usually observed high stability of fluorescent dyes based on BODIPYs (boron dipyrromethines) predestinate them for application in medicinal chemistry. Depending on the design of the environment of the boron core, a selective ^{18}F-fluorination is possible. Furthermore, reactive BODIPYs can be used to label bioactive molecules. We synthesized different reactive BODIPYs containing phenyl- and hydroxy substituents on boron as well as mono- and difluorinated counterparts, altering the optical properties of the dyes by rational design of the dipyrromethine ligands. The dyes may directly be used to label bioactive moieties and may be radiolabeled using a previously published protocol.

1. Introduction

Boron dipyrromethine (BODIPY) dyes are fluorescent compounds with easily adjustable optical properties depending on the design of the underlying dipyrromethine core [1,2], which makes them interesting for a broad variety of different applications including chemo- and ionic sensors [3–11], fluorescent switches [12–14], laser dyes [15–18] as well as protein and DNA labeling [2,19–27]. The commercially available dyes, which are optimized for rather specific applications, are usually characterized by comparably high quantum yields [28] and variable Stokes shifts [1,29]. The dye-system offers a variety of possibilities to alter the optical characteristics [1,30–32].

BODIPYs are implemented in medicinal research due to their often displayed favorable stability in a broad range of pH- and polarity values as well as low toxicity [33]. In the past decades radiolabeling of BODIPYs with fluorine-18 gained interest as it is an easy way to get building blocks suitable for dual-labeling of bioactive materials [34–44]. A dual-labeled probe is a bioactive material, which is labeled with two or more (multimodal probe) moieties for the use in at least two imaging modalities (Fig. 1).

In most publications ^{19}F/^{18}F isotopic exchange reactions of fluorine on the boron core of BODIPYs or abstraction of one of the two fluorine atoms followed by substitution with [^{18}F]fluoride are used to yield radiolabeled BODIPYs, while taking advantage of the readily available commercial dyes [36–40,43–45]. Molar activities of the radiolabeled compounds obtained by this approach are low due to the nature of the isotopic exchange reaction. Moreover, most commercially available dyes, which can be applied for radiolabeling, may have inappropriate optical properties for *in vivo* fluorescence imaging applications. Recently, we reported on a BODIPY building block for easy labeling of biomolecules to obtain dual labeled probes for the use in optical imaging and positron emission tomography (PET) [42]. In the present study we addressed the unfavorable optical characteristics of the dye by rational design of the dipyrromethine backbone and optimized it for potential applications in *in vivo* fluorescence imaging. The resulting dyes with a hydroxy substituent on boron may potentially be labeled with [^{18}F]fluoride to obtain building blocks for dual labeling of bioactive molecules. Three generations of different dyes (defined according to their emission characteristics) were prepared; examples are outlined in Fig. 2.

The conspicuous substitution pattern of the hydroxyphenyl BODIPYs (Fig. 2) has its origin in the intended selective ^{18}F-labeling. To

* Corresponding author. Department of Nuclear Medicine, University Hospital Münster, Albert-Schweitzer-Campus 1, Building A1, D-48149, Münster, Germany.
** Corresponding author. Organic Chemistry Institute, University of Münster, Corrensstr. 40, D-48149, Münster, Germany.
*** Corresponding author. Institute for Radiology, Nuclear Medicine and Molecular Imaging, HDZ NRW, Georgstr. 11, D-32545, Bad Oeynhausen, Germany.
E-mail address: paul.konken@uni-muenster.de (C.P. Konken).

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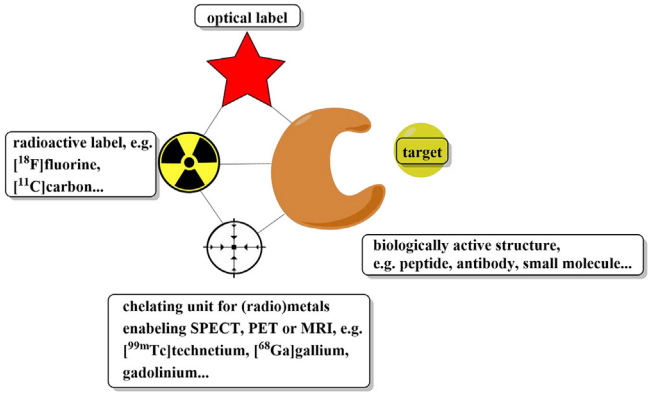

Fig. 1. Multimodal probe.

enable high molar activities of the corresponding [^{18}F]BODIPYs, it is necessary to exchange one particular group by, ideally, nucleophilic substitution. Dichlorophenylborane is one of the few commercially available reagents which can be used directly to introduce the desired boron group into dipyrromethines. The resulting phenyl substituent in the BODIPYs is stabilizing the prepared dyes.

1.1. Strategies to red-shift the optical characteristics of BODIPY dyes

BODIPY fluorophores are subject of numerous research areas, the dyes share the general structure outlined in Fig. 3.

While R^3-R^5 and R^7-R^9 may be the whole bandwidth of organic substituents, R^1 and R^2 are fluorine atoms in most recent publications aside from a few exceptions. The bridge X may be a CH or CR^6 moiety (classic BODIPY dyes) or a nitrogen atom (aza-BODIPYs). A nitrogen atom in the bridge position causes a bathochromic shift of approximately 100 nm in excitation and emission wavelength compared to a classical BODIPY with a CH or CR^6 and a similar substitution pattern [1].

Since the first synthesis of a BODIPY dye by Treibs and Kreutzer in 1968 (**A** in Fig. 4) an myriad number of functionalized dyes were prepared and published [46].

Despite the large number of dyes, the synthesis of the unsubstituted BODIPY (**B** in Fig. 4) was only successful in 2009, realized by three independent research groups at the same time [47–49]. This fact underlines the lability of the unsubstituted dipyrromethine ligand.

To induce a bathochromic shift of the excitation and emission wavelength in the fluorophores, three general strategies are commonly used:

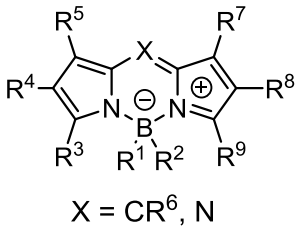

Fig. 3. General structure of BODIPY dyes.

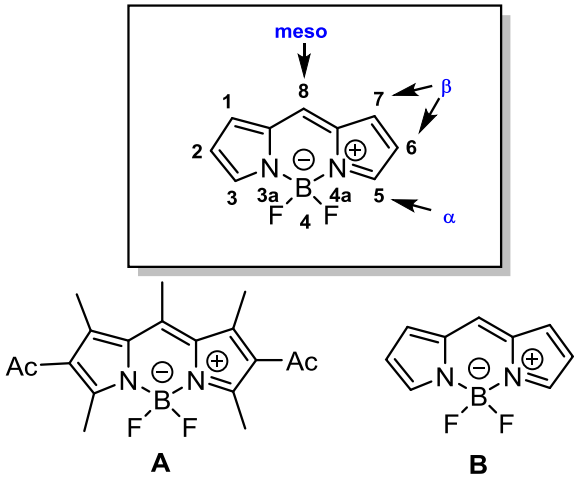

Fig. 4. IUPAC recommendation for BODIPYs regarding the numbering, first BODIPY dye (A) and unsubstituted BODIPY (B).

1 Increasing the relative electron density of the dipyrromethine ligand, e.g. by electron rich substituents like methoxy or similar groups, preferably at the α or β positions (Fig. 4).
2 Enlarging the conjugated π-system.
3 Favoring planarity of the ligand by annulation of aromatic/non-aromatic systems to the core structure.

For the preparation of the desired hydroxyphenyl-BODIPYs the commonly used synthesis strategies applied for BODIPYs with a BF_2-unit, such as electrophilic aromatic substitution at the core or Knoevennagel condensation with electron deficient methyl-groups, are not applicable for hydroxyphenyl-BODIPYs due to the less stable B-*O*-bond. This results in the necessity to prepare the dipyrromethine ligand before the final complexation of the boron species or to change the boron substitution pattern after complexation with borontrifluoride diethyletherate. The last-mentioned preparation approach (fluorine

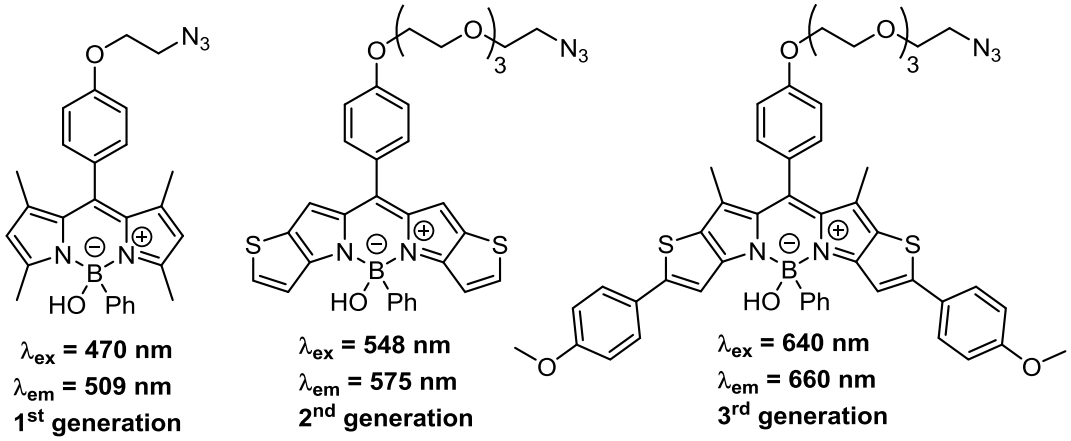

Fig. 2. Exemplary BODIPY dyes discussed in this manuscript.