NOVEL BODIPYs WITH STRONG HEAVY ATOM EFFECT AS DUAL PHOTOSENSITIZERS FOR ANTIMICROBIAL AND ANTICANCER PDT

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INTRODUCTION

Photodynamic therapy (PDT) is a promising regime successfully applied for the treatment of localized cancers and other premalignant or non-malignant dermal lesions, as well as microbial infections. PDT involves the use of a photosensitizer and light of appropriate wavelength to induce oxidative stress leading to the eradication of targeted cells [1]. Boron dipyrromethene (BODIPY) dyes exhibit a number of properties that make them suitable for exploration as PDT agents, including strong absorption coefficient, good stability, chemical robustness, and high structural tunability, which allows affecting their photophysical properties such as absorption and emission wavelengths, solubility and the rate of singlet oxygen generation [2].

SYNTHESIS

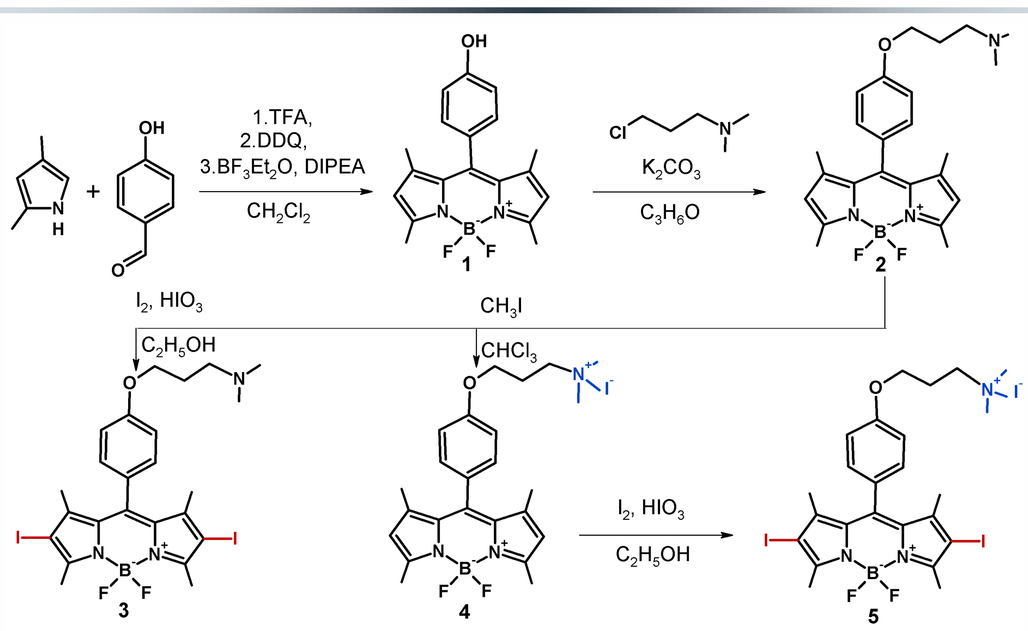

Fig. 1. Synthesis of BODIPY derivatives 2-5.

BODIPY derivative **1** was synthesized from 2,4-dimethylpyrrole and 4-hydroxybenzaldehyde according to the literature procedure [3]. Alkylation reaction with 3-chloro-1-(N,N-dimethyl)-propylamine gave BODIPY analogue (2). In the next steps, BODIPY derivative **2** was iodinated with the mixture of I_2 and HIO_3 (**3**) and methylated using CH_3I (**4**). Finally, BODIPY **4** was iodinated to obtain the derivative **5** with both the cationic group and iodine atoms (Fig.1).

SINGLET OXYGEN GENERATION

The quantum yields of singlet oxygen generation of BODIPYs **2-5** were determined in methanol and ethanol. The relative method, with rose bengal as a reference and 1,3-diphenylisobenzofuran (DPBF) as a chemical quencher for singlet oxygen, was applied. BODIPYs **3** and **5** caused photodecomposition of DPBF with higher rates than rose bengal, indicating that $^1O_2$ was highly produced.

Singlet oxygen generation quantum yields (Φ_Δ) for derivatives 2-5

solvent	**rose bengal**	**2**	**3**	**4**	**5**
methanol	0.81	0.02	**0.90**	0.02	**0.94**
ethanol	0.68	0.02	**0.69**	0.02	**0.97**

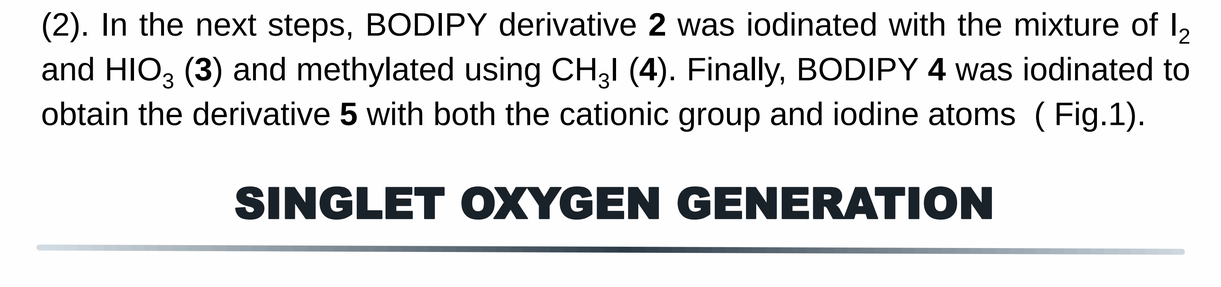

Fig. 4 Changes in the UV-Vis spectra for DPBF and BODIPYs 2-5 mixture in methanol.

SPECTRAL PROPERTIES

The normalized absorption and fluorescence spectra of BODIPY derivatives **2-4** in methanol are presented in Fig 2. The electronic absorption spectra of BODIPY **2-4** in methanol are presented in Fig 3. The introduction of iodine atoms to the BODIPY core caused a bathochromic shift of the absorption band by 32 nm.

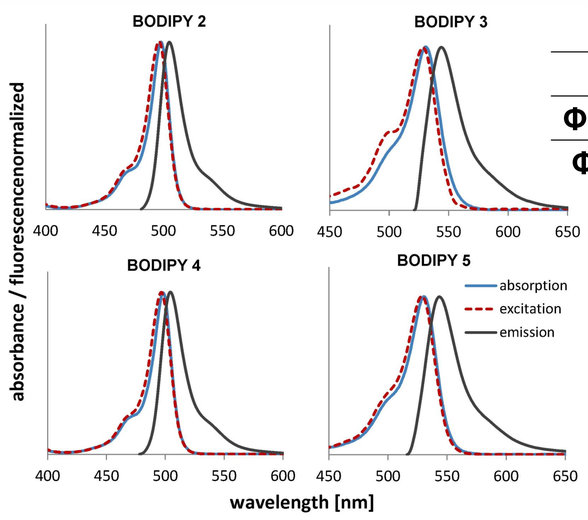

Fig. 2 Absorption and emission bands of BODIPYs 2-5.

BODIPY	**2**	**3**	**4**	**5**
λ_{max}	498	530	498	530
Φ_F in MeOH	0.69	0.02	0.70	0.02
Φ_F in EtOH	0.61	0.02	0.60	0.02

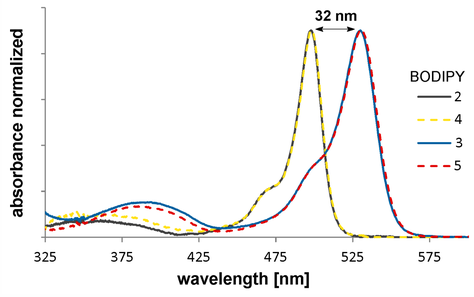

Fig. 3 UV-Vis spectra of BODIPYs 2-5.

ANTIMICROBIAL ACTIVITY

In vitro photodynamic antimicrobial activity studies of BODIPY derivatives **2-5** were performed on Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli* strains.

Log_{10} reductions of *S. aureus* and *E. coli* treated with BODIPYs 2-5

BODIPY	conditions	**2**	**3**	**4**	**5**
		2.5 µM	**0.25 µM**	**2.5 µM**	**0.25 µM**
S. aureus	Light	4.1 ± 0.6	3.9 ± 0.6	>5.8 ± 0.2	>5.6 ± 0.4
	Dark	-0.03±0.06	0.05±0.12	0.05 ± 0.2	0.2 ± 0.3
		500 µM			**5 µM**
E. coli	Light	1.7 ± 0.2	>5.4 ± 0.3	>5.3 ± 0.3	>5.3 ± 0.4
	Dark	0.1 ± 0.2	0.3 ± 0.4	>1.9 ± 0.1	0.3 ± 0.1

ANTICANCER ACTIVITY

In vitro photodynamic anticancer activity studies of BODIPY derivatives **2-5** were performed on human androgen-sensitive prostate adenocarcinoma cell line (LNCaP).

The IC_{50} values [µM] of BODIPYs 2-5 against prostate adenocarcinoma cell line

BODIPY	**2**	**3**	**4**	**5**	**5 hypoxia**
non-irradiated	9.7±1.4	>2	>10	>0.06	>10
irradiated	3.3±1.5	**0.048±0.012**	>10	**0.019±0.004**	>10

CONCLUSIONS

Novel BODIPYs with dimethylaminopropoxyphenyl substituents and their cationic and iodinated derivatives were synthesized and characterized using mass spectrometry, UV-Vis spectrophotometry, and various NMR techniques. Subsequent photochemical studies allowed evaluating their absorption and emission properties and the singlet oxygen generation ability. *In vitro* photodynamic activity studies were performed on human androgen-sensitive prostate adenocarcinoma cells and two bacterial strains (Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli*). It was found that the introduction of iodine atoms into the BODIPY core caused significant enhancement of singlet oxygen production, which is considered the main cytotoxic agent in PDT. BODIPY derivative possessing both a positive charge and iodine atoms revealed the highest activity towards all studied cells [4].

REFERENCES

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