



# Water-soluble two-photon absorption benzoxazole-based pyridinium salts with the planar cationic parts: crystal structures and bio-imaging



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## ABSTRACT

Six new benzoxazole-based compounds **1–6** of the donor-bridge-accepter (D- $\pi$ -A) type with different anions were obtained by methylation and anion exchange reaction. The single crystals of **1**, **3** and **6** were obtained by slow evaporation of acetonitrile and determined by X-ray crystallography. Ellipsoidal structures of the three compounds showed that the cationic parts all maintained good planarity, which was beneficial for two-photon absorption (2PA) properties and accorded with the results of two-photon excited fluorescence tests. Biological imaging experiments showed water-soluble six compounds had excellent penetrability in living cells and could be located in cytoplasm in one- and two-photon cell imaging. Biological imaging result of compound **6** was more excellent than other compounds, which indicated synergy of anions and cations played a very important role in cell imaging.

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## 1. Introduction

It is necessary to design and synthesize organic materials with larger 2PA cross-sections ( $\delta_{2PA}$ ) because of their potential application, such as photodynamic therapy [1–5], photochemical delivery of biological messengers [6–10], confocal microscopy [11–13], three-dimensional data storage [14–25] and optical power limiting [26]. Among these, two-photon microscopy was a powerful technique for noninvasive live cell imaging, due to two-photon excitation could achieve deeper penetration, less photobleaching and higher spatial resolution compared with one-photon excitation [27]. In two-photon bio-imaging applications, an excellent stain not only requires a high signal-to-noise ratio which depends on large  $\delta_{2PA}$  values, but also demands good biological compatibility which depends on the water solubility. Therefore, design and synthesis of 2PA compounds with

appropriate 2PA cross-sections in water solution is an important way to realize the application in bioimaging. For instance, Wong's group [28] designed and synthesized a 2,7-carbazole dicationic salt (2,7-9E-BHVC) which acted as a two-photon turn-on fluorescent probe for nucleic acid (NA), the effective 2PA cross-sections ( $\delta_{eff}$ ) were 1.67 GM and 30 GM in the absence and presence of NA in phosphate buffer saline solution (PBS), respectively. Zhang's group [29] synthesized four tetraphenylethylene (TPE) salt with different anion group based nanoparticles to apply on 2PA bio-imaging in water solution. The results showed that the sizes, the surface charge and hydrophobic TPE fragment could all facilitate the uptake and interaction with lipid bilayers of cancer cells, thus the nanoparticles showed good permeability to cancer cells. Wang and Zhang [30] synthesized a positive charged water-soluble polythiophene (PTO) that the 2PA cross-section was more than 300 GM in water solution, which could be successfully implied in HeLa cells imaging.

Researchers committed to the application of two-photon materials in biological research because of their intrinsic properties, especially water solubility to avoid organic solvents, which could effectively reduce the toxicity to cells or tissues. However, the larger 2PA cross-sections usually required a large conjugated system by the longer synthetic route, which lowered the solubility in water

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solution and enhanced cost, subsequently. So it was still a challenge to design water-soluble 2PA materials to be applied to bio-imaging. Based on the above, we designed and synthesized six new D- $\pi$ -A type compounds **1–6** based on benzoxazole groups, investigated the influence of different anions on photophysical property, in which the benzoxazole group acted as electron-donor, the pyridine cationic as electron-acceptor. The small molecules **1–6** exhibited excellent solubility and linear, nonlinear optical properties in water, which were successfully carried out the 2PA bio-imaging applications.

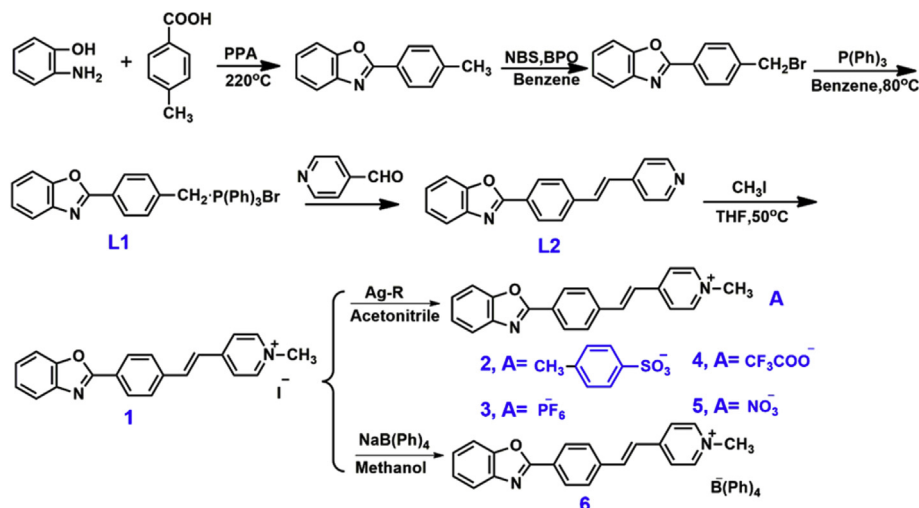
## 2. Experimental section

### 2.1. Materials and instruments

All commercially available chemicals were of analytical grade or chromatographic grade. Every solvent was purified using conventional methods beforehand. IR spectra were recorded with a Nicolet FT-IR NEXUS 870 spectrometer (KBr discs) in the 4000–400  $\text{cm}^{-1}$  region.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker AV 400 Ultrashield spectrometer using  $\text{DMSO-}d_6$  as solvent. Chemical shifts were reported in parts per million (ppm) relative to internal TMS (0 ppm) and coupling constants in Hz. Splitting patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m). The mass spectra were obtained on a Bruker Autoflex III smart beam mass spectrometer. The X-ray diffraction measurements were performed on a CCD area detector using graphite monochromated  $\text{MoK}\alpha$  radiation ( $\lambda = 0.71069 \text{ \AA}$ ) at 298(2) K. Intensity data were collected in the variable  $\omega/2\theta$ -scan mode. The structures were solved by direct methods and difference Fourier syntheses. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were introduced geometrically. Calculations were performed with the SHELXTL-97 program package. CCDC: 1544353 (for **1**), 1535136 (for **3**), 1535139 (for **6**).

### 2.2. Synthesis and characterization

Six compounds were prepared according to the synthetic routes showed in Scheme 1. The experiment details and structure characterization data were described in the experimental section and electronic supporting information (ESI). The intermediate **L1** was synthesized efficiently according to our previous work [31].



Scheme 1. Synthetic route to **1–6**.

### 2.2.1. (E)-4-(4-(benzo[d]oxazolyl-2-yl) styryl) pyridine (**L2**)

**L2: L1** (8.00 g, 14.50 mmol), 4-Pyridinecarboxaldehyde (1.28 g, 12.00 mmol),  $\text{K}_2\text{CO}_3$  (4.97 g, 36.00 mmol), 5 drops methyltriethylammonium chloride were added in three-necked flask with 10 mL N, N-Dimethylacetamide and refluxed at 140 °C for 7 h. The reaction mixture was cooled to room temperature and poured into dichloromethane and stirred vigorously, the solid was removed by filtration, the filtrate was washed with saturated brine, then purified with chromatography (Petroleum ether: Ethyl acetate = 5:1) to give 2.50 g of white powder. Yield: 70%.  $^1\text{H}$  NMR: (400 MHz,  $\text{DMSO-}d_6$ ),  $\delta$  (ppm): 8.59 (d,  $J = 8.0 \text{ Hz}$ , 2H), 8.25 (d,  $J = 8.0 \text{ Hz}$ , 2H), 7.90 (d,  $J = 8.0 \text{ Hz}$ , 2H), 7.84–7.80 (t,  $J = 8.0 \text{ Hz}$ , 2H), 7.66 (d,  $J = 16.0 \text{ Hz}$ , 1H), 7.62 (d,  $J = 4.0 \text{ Hz}$ , 2H), 7.47–7.41 (m, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ),  $\delta$  (ppm): 161.96, 150.11, 143.82, 141.55, 139.59, 131.85, 128.30, 127.81, 127.71, 126.00, 125.61, 124.94, 121.04, 119.81, 110.91. MS (ESI):  $m/z$ , found: 299.1105; molecular formula  $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}$ , requires  $[\text{M}+\text{H}]^+$ , 299.1106.

### 2.2.2. (E)-4-(4-(benzo[d]oxazolyl-2-yl) styryl)-1-methylpyridinium iodide (**1**)

**1: L2** (1.16 g, 3.80 mmol) and iodomethane (1.70 g, 14.00 mmol) were dissolved in 40 mL THF and refluxed at 65 °C for 4 h. The mixture was filtered and the solid was washed with THF for 3 times, 1.22 g of yellow product was obtained. Yield: 72%.  $^1\text{H}$  NMR: (400 MHz,  $\text{DMSO-}d_6$ ),  $\delta$  (ppm): 8.92 (d,  $J = 4.0 \text{ Hz}$ , 2H), 8.33–8.27 (m, 4H), 8.10 (d,  $J = 16.0 \text{ Hz}$ , 1H), 7.98 (d,  $J = 8.0 \text{ Hz}$ , 2H), 7.86–7.82 (t,  $J = 8.0 \text{ Hz}$ , 2H), 7.70 (d,  $J = 16.0 \text{ Hz}$ , 1H), 7.50–7.43 (m, 2H), 4.28 (s, 3H).  $^{13}\text{C}$  NMR: (100 MHz,  $\text{DMSO-}d_6$ ),  $\delta$  (ppm): 161.66, 151.91, 150.24, 145.25, 141.49, 139.07, 138.30, 128.80, 127.88, 127.40, 125.86, 125.31, 125.05, 123.84, 119.94, 110.99, 47.05. MS (APCI):  $m/z$ , found: 313.1337; molecular formula  $\text{C}_{21}\text{H}_{17}\text{N}_2\text{O}$ , requires  $[\text{M}+\text{H}]^+$ , 313.1335.

### 2.2.3. (E)-4-(4-(benzo[d]oxazolyl-2-yl) styryl)-1-methylpyridinium 4-methylbenzene sulfonate (**2**)

**2:** An acetonitrile solution of silver *p*-toluenesulfonate (0.15 g, 0.68 mmol) was added to acetonitrile solution of **1** (0.30 g, 0.68 mmol), the mixture was refluxed at 80 °C for 4 h, then the precipitate was removed by filtration. 0.18 g of yellow product was obtained by concentrating filtrate. Yield: 54%.  $^1\text{H}$  NMR: (400 MHz,  $\text{DMSO-}d_6$ ),  $\delta$  (ppm): 8.91 (d,  $J = 8.0 \text{ Hz}$ , 2H), 8.32 (d,  $J = 8.0 \text{ Hz}$ , 2H), 8.27 (d,  $J = 8.0 \text{ Hz}$ , 2H), 8.09 (d,  $J = 16.0 \text{ Hz}$ , 1H), 7.98 (d,  $J = 8.0 \text{ Hz}$ , 2H), 7.86–7.82 (t,  $J = 8.0 \text{ Hz}$ , 2H), 7.69 (d,  $J = 16.0 \text{ Hz}$ , 1H), 7.49–7.43

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