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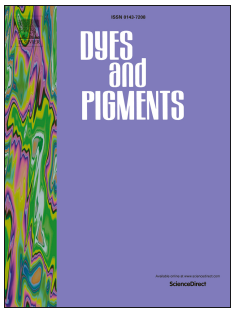

Bromo-pentamethine as mitochondria-targeted photosensitizers for cancer cell apoptosis with high efficiency

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• ARTICLES •

Bromo-pentamethine as mitochondria-targeted photosensitizers for cancer cell apoptosis with high efficiency

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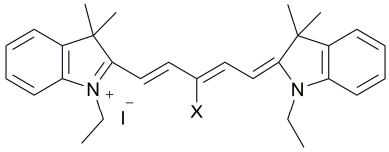
Mitochondria play essential roles in cellular energy supply and produce 90% of reactive oxygen species. A mitochondrial targeted photosensitizer is greatly beneficial to improve the photodynamic therapeutic effect via apoptosis. Herein bromo-pentamethine dyes (λ_{abs} > 650 nm) are designed as mitochondria-localized anticancer photosensitizers. Cell experiments demonstrate that Cy-Br localizes in mitochondria with very low cytotoxicity in dark, and induces cancer cells apoptosis under light with IC_{50} as low as 62 nM, much better than commercial Ce6 (3706 nM). Bromo-group could enhance the quantum yield of reactive oxygen species. The high efficiency might provide a new clue to develop new photosensitizers.

***keyword*: cyanine dye; mitochondria; photosensitizer; photodynamic therapy; cancer cell; apoptosis**

1 Introduction

Compared with traditional cancer therapies, photodynamic therapy (PDT) has attracted more attention due to its selective destruction of tumor cells instead of normal cells.[1] The PDT is comprised of photosensitizer, light, and reactive oxygen species (ROS). It involves the systemic administration of a photosensitizer (PS) which is excited under specific wavelength illumination, and then produce ROS, causing damage to targeted cancer cells. So far, the most widely used photosensitizers including porphyrin and phthalocyanine.[2, 3] Although some of them are used in clinical treatment,[4] there are still exist shortcomings and deficiencies, for example, photofrin, the first case of drug administration approved and the earliest photosensitizer for photodynamic therapy, has drawbacks such as low absorption in red region, and long-lasting skin photosensitivity.[5] An ideal photosensitizer should meet the following criteria: (1) sharp, intense absorption in the biological tissues transparency window (600-900 nm), (2) good solubility in the biological environment, (3) low dark toxicity but strong photocytotoxicity and a high ROS sensitization quantum yield, (4) high specificity for cancer tissues and easily and rapidly to remove out of the body post-treatment.[6-8] These criteria provide a general guideline developing new photosensitizers.

As the primary source of cellular ROS production (up to 90%), mitochondria play essential roles in energy supply and cell apoptosis.[9, 10] Moreover, mitochondria are reported to be susceptible to excessive ROS.[11-13] Hence, a mitochondrial targeted PS delivery system is believed to be have greatly beneficial to improve the cell apoptosis effect. Therefore, new photosensitizes targeting mitochondria and sensitizing in near-infrared wavelength are significant to widen the applicability of PDT.



X=H, Cy-H, λ_{abs}=651 nm X=Cl, Cy-Cl, λ_{abs}=654 nm X=Br, Cy-Br, λ_{abs}=651 nm

Scheme. 1 Molecular structures of pentamethine dyes and their maximum absorption wavelength in DCM.

As pentamethine dyes have long absorption wavelength (>650 nm) that within so-called “phototherapeutic window” (600–900 nm)[14-16], herein three symmetric pentamethines with different halogen groups on the central (meso-) position as photosensitizers (Cy-H, Cy-Cl and Cy-Br) (**Scheme. 1**) have been investigated firstly. The photophysical and photochemical properties of pentamethines showing that the bromo-substituted on the central (meso-) posi-

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