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Photodynamic effects induced by *meso*-tris(pentafluorophenyl)corrole and its cyclodextrin conjugates on cytoskeletal components of HeLa cells

Joana F.B. Barata [a], Alicia Zamarrón [b], M. Graça P.M.S. Neves [a, *], M. Amparo F. Faustino [a], Augusto C. Tomé [a], José A.S. Cavaleiro [a], Beate Röder [c], Ángeles Juarranz [b], Francisco Sanz-Rodríguez [b, **]

[a] Department of Chemistry and QOPNA, University of Aveiro, 3810-193 Aveiro, Portugal
[b] Departamento de Biología, Facultad de Ciencias, Universidad Autónoma de Madrid, Canto Blanco, C.P. 28049 Madrid, Spain
[c] Institut für Physik, Photobiophysik, Humboldt- Universität zu Berlin, Newtonstr. 15, D-12489 Berlin, Germany

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ABSTRACT

The aim of this work was to synthesize new corrole β-cyclodextrin conjugates **βCD1** (with one β-cyclodextrin moiety) and **βCD2** (with two β-cyclodextrin moieties) from 5,10,15-tris(pentafluorophenyl) corrole (**TPFC**) and to test *in vitro* the efficacy of these compounds towards tumoral HeLa cells. No dark cytotoxicity was observed for **TPFC** and **βCD1** at the concentration used for PDT cell treatment, even during long incubation periods (24 h). Fluorescence microscopy showed that **TPFC** and **βCD1** accumulate in HeLa cells at lysosomes and in the Golgi apparatus, respectively.

The cell survival after the PDT treatment with visible light was dependent on light exposure level and compound concentration. **βCD1** was able to penetrate efficiently in the cytoplasm of the HeLa cells. In particular, we have analyzed the photodynamic effect of the corrole derivatives on the microtubules of HeLa cells and the morphological alterations on the mitotic spindle. **TPFC** and **βCD1** caused photocytotoxicity in tumoral HeLa cells and induced a rapid metaphase blockage of cells that also showed clearly altered configurations of the mitotic spindle. The results showed that **TPFC** has the highest photosensitizing efficiency on tumoral cells.

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1. Introduction

Photodynamic Therapy (PDT) represents a therapeutic modality currently approved for clinical treatment of several types of cancer and non-oncological diseases. PDT is based on the induction of cell death by the combined effect of visible light, on a compound with photosensitizing properties (photosensitizer, PS), and O_2. The PS is accumulated in the tissue to be treated, and is subsequently activated with visible light. The irradiation is preferentially conducted with the red region of the visible ($\lambda > 600$ nm), because in such wavelength range, the light shows deeper tissue penetration. As a consequence, reactive oxygen species (ROS), such as singlet oxygen ($^1O_2$) are generated, starting a cascade of biochemical events that induces cytotoxicity of neoplastic cells and the regression of tumor [1].

Nowadays PDT is being used for the treatment of endoscopically accessible tumors such as lung, bladder, gastrointestinal and gynecological neoplasms, and also in dermatology for the treatment of non melanoma skin cancers (basal cell carcinoma) and precancerous diseases (e.g. actinic keratosis) [1c].

Tetrapyrrolic derivatives such as porphyrins and analogs are the most widely studied compounds in PDT [2]. In fact, Photofrin® (a purified derivative obtained from hematoporphyrin) and ALA (5-aminolevulinic acid; *in vivo* protoporphyrin IX precursor) are the main compounds used in clinical trials [3].

The cellular targets of PS are numerous, including plasma membrane, mitochondria, Golgi apparatus and lysosomes [4]. Targeting cytoskeleton is an important goal for anti-cancer therapies, since cytoskeleton plays a significant role in the majority of cellular

* Corresponding author.
** Corresponding author.
E-mail addresses: gneves@ua.pt (M. Graça P.M.S. Neves), francisco.sanz@uam.es (Francisco. Sanz-Rodríguez).

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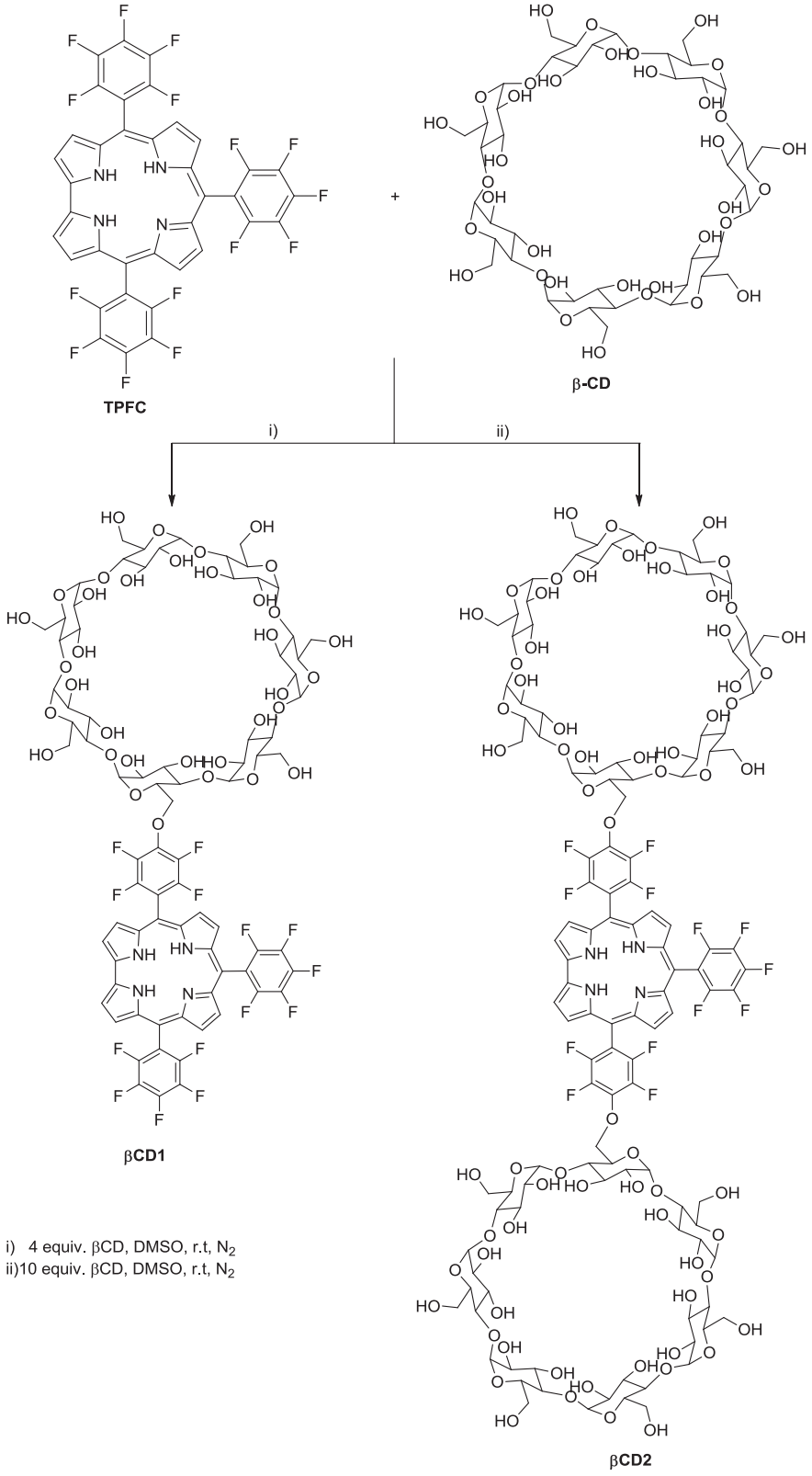
processes related with tumoral progression, such as cell motility, division and perturbation of cytoskeletal components, which can lead to the cell killing [5]. It has been reported that several PSs, including porphyrins, in combination with light can alter the microtubules (MTs) causing a blockage of cell cycle in metaphase–anaphase transition, leading to cell death by mitotic catastrophe [6].

In recent years, another member of the porphyrinoid family (the



Scheme 1. Synthesis of corrole-β-cyclodextrin conjugates.

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