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Impact of structural A_3B^{3+}-design of a Zn(II) porphyrin photosensitizer on the photoinactivation of *Candida albicans*: ZnMVanTriM-2-PyP^{3+} *vs.* ZnTM-2-PyP^{4+}

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Antimicrobial resistance (AMR) represents a rising menace for the public health. In this context, photodynamic inactivation (PDI) has emerged as a therapeutic option that uses the activation of photosensitizers (PSs) by light to generate reactive oxygen species (ROS), which impact simultaneously multiple cellular targets, minimizing AMR. PS biological efficiency is improved by structural changes that yield an amphiphilic character, allowing PS interactions with cell membranes with the least compromise to PS solubility in biological fluids. Water-soluble tetracationic Zn(II)-porphyrins (ZnA_4P^{4+}) derived from A_4-type *meso*-2-*N*-alkylpyridylporphyrins (alkyl = Me to *n*Hex) are potent PSs. These ZnA_4P^{4+} PSs showed photodynamic activity against cancer cells, bacteria, fungi, and parasites [1-4]. The combination of both (i) positive charged moieties (2-*N*-alkylpyridyl groups) and (ii) a d^{10} central metal, such as Zn(II) in ZnA_4P^{4+}, gives rise to a class of PSs with desirable photophysical, photochemical, and biological properties. Additionally, PS lipophilicity may be tailored through *N*-alkyl side-chain, improving cell uptake and controlling subcellular distribution [1-4]. Inspired by ZnA_4P^{4+}, a new tricationic A_3B-type ZnP prototype (ZnMVanTriM-2-PyP^{3+}, ZnA_3BP^{3+}; A= 2-*N*-methylpyridyl and B= *O*-methylvanillin) was designed by replacing one cationic 2-*N*-alkylpyridyl group (A) by a neutral *O*-methylvanillin group (B) (Fig. 1). ZnA_3BP^{3+} was designed, prepared, fully characterized, and investigated as PS for PDI of *Candida albicans* as a pathogenic model, using the 2-*N*-tetramethylpyridyl analog (ZnTM-2-PyP^{4+}, ZnA_4P^{4+}) as positive control. Partition coefficient (log P_{ow}) measurements confirmed the considerably higher lipophilicity of ZnA_3BP^{3+} with respect to the ZnA_4P^{4+} analog. PDI assays against *C. albicans* yeasts showed that ZnA_3BP^{3+} totally eradicated the yeasts in doses much lower than those of its ZnA_4P^{4+} counterpart. These results indicate, as proof of concept, that ZnA_3BP^{3+} may represent a structurally viable platform for further chemical derivatization and development of a new class of water-soluble ZnPs for PDI-based antimicrobial therapy.

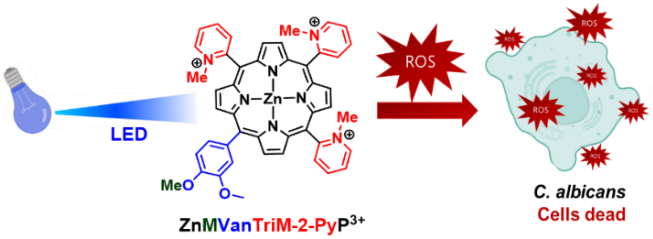

Figure 1. Photodynamic inactivation of *Candida albicans* using a ZnA_3BP^{3+}-based PS (ZnMVanTriM-2-PyP^{3+}) resulting in the generation of reactive oxygen species (ROS) that lead to cell death.

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