New squaraine dyes for photodynamic therapy

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Photodynamic therapy (PDT) [1]consists in the activation of molecular oxygen under irradiation by light in the presence of photodrugs (photosensitizers, PS) that have been previously selectively accumulated in the target tissues. In comparison with conventional treatment methods, PDT is considered to be a clinical treatment with high safety, few side effects, reliable repeatability, and relatively low cost. The sensitizer, activated by light, reacts with the oxygen present in the tissue, forming highly toxic oxygen radicals (ROS). These species react with biological molecules such as proteins, amino acids, lipids, nucleotides and nucleic acids inducing tissue necrosis/apoptosis or autophagy. Therefore, PS is responsible of PDT efficiency and even if some important developments in PS have been achieved, some problems still exist [2]

The first generation photosensitizer (haematoporphyrin derivative, HPD) is a mixture of porphyrin monomers and oligomers partially purified to produce the commercially available product, Photofrin®, which is a FDA approved photosensitizer. HPD-mediated PDT has several clinical disadvantages, including prolonged skin photosensitivity (4 weeks), relatively low quantum yield of singlet oxygen, and a limited depth of associated tissue damage of 2-5 mm. Consequently, there has been extensive research into the design of improved alternative photosensitizers aimed at overcoming these drawbacks. Quite recently, the interest in finding new PS turned to squaraine compounds[3].

In this work we designed and synthesised a new series of near infra-red absorbing squaraines with different substitution groups in order to investigate how the structure may influence the capacity of these molecules to produce $^1O_2$.The oxygen-generation ability of the new dyes was accessed in vitro by the 1,3-diphenylbenzofuran (DPBF) quenching method [4] envisioning their potential use as sensitizers for PDT. On the most promising squaraines, ROS generation, cytotoxicity, cell death and DNA damage analyses were performed after the photodynamic treatment. Here we present the results obtained along with a structure-activity relationship discussion of these new potential photosensitizers for PDT. In particular, two of these squaraines showed very interesting PDT performances as well as co-localization in mitochondria.

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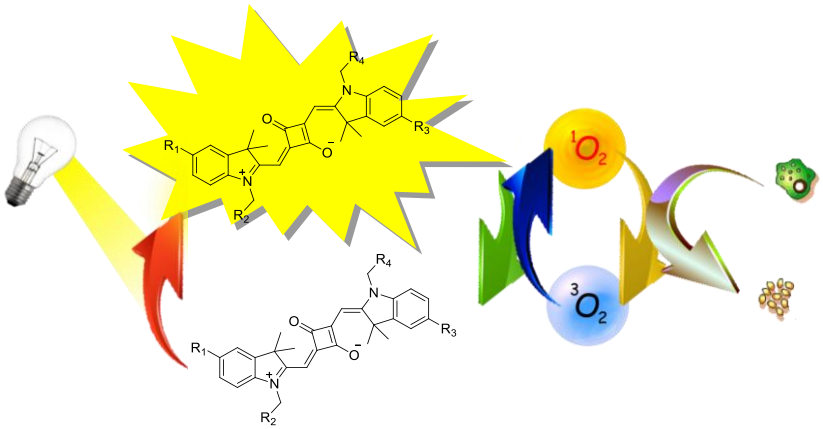

Figure 1.Photodynami mechanism of Squaraines