Heavy atom-free BODIPY donor-acceptor dyads as singlet oxygen sensitizers

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The generation of triplet states from the charge-separated excited state (CSS) in electron donor-acceptor complexes is a well-known phenomenon.[1] However, its potential for singlet oxygen ($^1O_2$) photosensitization in biological media has not been realized so far. However, the development of photosensitizers (PS) based on this mechanism will provide a new valuable tool in biomedical applications, particularly in the field of photodynamic therapy (PDT), which utilizes the generation of $^1O_2$ in malignant tissue to cause oxidative stress in cells and prevent growth.[2] Photoinduced electron transfer (PeT) leading to CSS, can be turned on/off by various stimuli allowing for a broad use of corresponding probes as diagnostic tools.[3] The possibility of triplet excited states generation from CSS, and consequently $^1O_2$ production, can bring a radical improvement in the therapeutic potential of PDT treatments by providing a new dimension for the control of the $^1O_2$ generation process. CSS-based photosensitizers have not yet been employed for this purpose, which is in part due to moderate $^1O_2$ generation efficiency of the reported systems and, particularly, due to the considerable synthetic efforts required to access their biocompatible derivatives.[4] In this work we present efficient and readily accessible CSS photosensitizers based on BODIPY donor-acceptor dyads (Fig.1A) and their application as fluorescent labels and PDT agents.

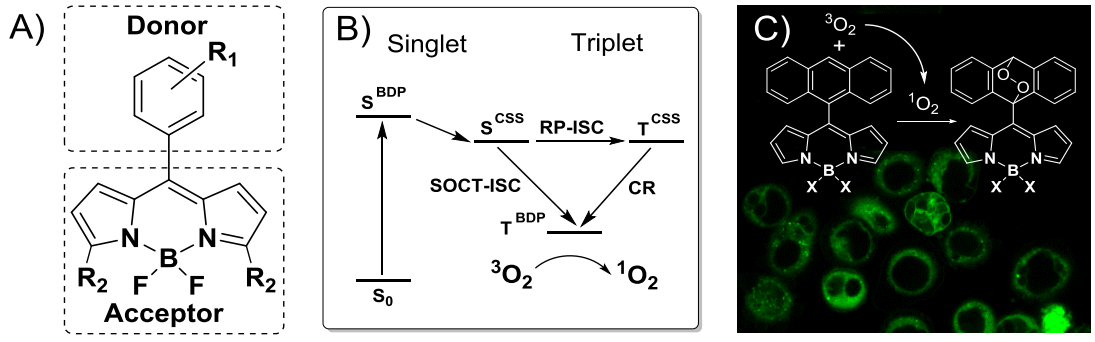

Figure 1. a) BODIPY donor-acceptor dyads, b) pathways for triplet excited states generation, c) fluorescent response of a BODIPY-anthracene dyad upon irradiation of MDA-MB-468 cells due to formation of a fluorescent endoperoxide.

Heavy atom-free BODIPY dyads were designed to produce triplet excited states from charge-separated excited states formed *via* PeT. Two pathways for triplet state generation from CSS yielding the BODIPY triplet state are involved (Fig. 1B): spin-orbit charge transfer intersystem crossing (SOCT-ISC) and radical pair intersystem crossing (RP-ISC). In the

presence of oxygen, dyads generate singlet oxygen with high quantum yields (up to 0.7). Our studies on cancer cells show that thus generated $^1O_2$ induced significant cytotoxic effect on the cells. Median lethal doses (LD_{50}) of the dyads are comparable with those of common PDT sensitizers.

We further optimized the dyads introducing anthracene as an electron donor subunit. The resulting sensitizers were found to show a fluorescence response towards self-sensitized $^1O_2$ in cells. Upon photoexcitation, followed by singlet oxygen ($^1O_2$) generation, formation of highly fluorescent endoperoxides due to cycloaddition of $^1O_2$ with the anthracene subunit takes place. Over the time course of irradiation an increase in fluorescence intensity of the probe can thus be observed. This allows to track morphological changes in the cells, most noticeably "blebbing" of the cell membrane (Fig. 1C), indicating apoptotic behavior. Such a fluorescent response of the sensitizer allows an adjustment of the photon doses required for cell death, making the dyads highly promising new therapeutic and imaging tools.

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