

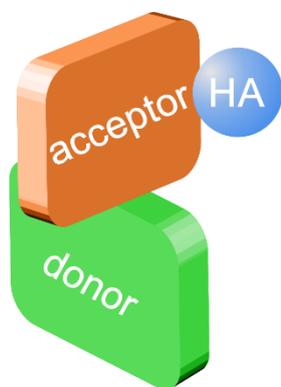


Synergistic enhancement of reactive oxygen species generation *via* combination of heavy atom effect with donor-acceptor architecture in organoboron photosensitizers for photodynamic therapy

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Despite the intensive development of modern medicine, cancer represents one of the most common causes of death worldwide. Currently used treatment methods are associated with a high risk of side effects, caused by low drug selectivity (chemotherapy) or the mutagenic nature of ionizing radiation (radiotherapy). An alternative strategy that is gaining increasing recognition in recent years is PhotoDynamic Therapy - PDT. During the treatment, a photoactive drug (photosensitizer) localizes in the abnormal cell. Then, the photosensitizer is excited to the triplet state upon absorption of visible light emitted by the laser. Subsequently, in this state, it can interact with the oxygen present in cancer cells. These interactions between excited photosensitizer and oxygen molecule may promote the formation of reactive oxygen species ROS that oxidize important biomolecules (*e.g.*, nucleic acids, proteins), which can eventually lead to cell death. Nevertheless, to enable the effective generation of the excited triplet state, the photosensitizer molecule has to be designed appropriately, as this phenomenon ensures the ROS formation, on which the efficacy of the treatment depends. The most common approach relies on the introduction of a heavy atom (HA) within the compound's structure. Nevertheless, the triplet states are characterized by low lifetimes, which limits their probability for interaction with oxygen molecules. Therefore, the recent studies are focused on heavy-atom free photosensitizers with long triplet lifetimes. One of the approaches employs the synthesis of an intramolecular dyad with electron donor and acceptor subunits in nearly perpendicular orientation (DA). This design of the structure facilitates the photoinduced electron transfer within these components, which might result in excited triplet state formation. However, this approach is known for being less effective than photosensitizers with heavy atoms and it may pose challenges on the molecular design level. It should be stressed that though these approaches were developed in parallel, the potential synergy between those two effects was not studied in photosensitizers until very recently.



This study aims to synthesize and characterize novel compounds that integrate two approaches: a donor-acceptor architecture and the incorporation of a heavy atom. The goal is to develop novel photosensitizers with enhanced photocatalytic properties for potential application in PDT.

The conducted literature research, as well as preliminary results, suggest that the synergistic enhancement of ROS formation in donor-acceptor photosensitizers with incorporated heavy atoms occurs. To explore this phenomenon, we propose to synthesize and characterize a series of BODIPY complexes modified with progressively heavier chalcogen atoms (*i.e.*, oxygen, sulfur, selenium). To investigate the impact of the location of the heavy atom on a compound's photoactive properties, these heteroatoms will be introduced on either donor or acceptor moieties separately. Additionally, the compounds with the simultaneous presence of chalcogens on donor (organoboron part) and acceptor

(BODIPY side wings) subunits will be obtained. The research project will involve comprehensive studies on the influence of the heavy atom presence and its positions on the ability to generate ROS upon light irradiation. Additionally, the photosensitizers will be conjugated with monosaccharide (D-mannose) to increase both cellular uptake and selectivity towards cancer cells. These complexes will be subsequently tested *in vitro* for their phototoxicity using normal and cancer cell lines. It should be stressed that the photosensitizers with donor-acceptor-heavy atom design have not yet been studied for their phototoxic properties against cancer cells. Therefore, we believe that this project will contribute to the current understanding and development of next-generation photosensitizers for potential application in PDT.