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Synthesis of triphenylphosphonium dibenzothiophene S-oxide derivatives and their effect on cell cycle as photodeoxygenation-based cytotoxic agents

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ABSTRACT

Photodeoxygenation of Dibenzothiophene-S-oxide (DBTO) in UV-A light produces atomic oxygen [$O(^3P)$] and the corresponding sulfide, dibenzothiophene (DBT). Recently, DBTO has been derivatized to study the effect of UV-A light-driven photodeoxygenation in lipids, proteins, and nucleic acids. In this study, two DBTO derivatives with triphenylphosphonium groups were synthesized to promote mitochondrial accumulation. The sulfone analogs of these derivatives were also synthesized and used as fluorescent mitochondrial dyes to assess localization in mitochondria of HeLa cells. These derivatives were then used to study the effect of photodeoxygenation on MDA-MB-231 breast cancer cell line using cell viability assays, cell cycle phase determination tests, and RNA-Seq analysis. The DBTO derivatives were found to significantly decrease cell viability only after UV-A irradiation as a result of generating corresponding sulfides that were found to significantly affect gene expression and cell cycle.

1. Introduction

Chemotherapy remains a popular treatment strategy to manage cancer, but the long-term side-effects associated with conventional cytotoxic chemotherapy continue to be a serious limitation.[1] Targeted chemotherapy, where drugs are activated explicitly at the desired tumor site, has been a more sophisticated way of fighting cancer.[2] Among targeted chemotherapies, the use of photo-pharmacology to activate a small molecule using light, which in this treatment strategy would be to activate a cytotoxic agent allows more spatiotemporal control over the drug's activity.[3,4] Additionally, photo-pharmacology is minimally invasive and aims to improve the quality of treatment by potentially decreasing off-target effects and patient side-effects.[3,4] Photodynamic therapy (PDT) has been an advancing field within photo-pharmacology where porphyrin derivatives are excited by visible light in the presence of oxygen to release singlet oxygen ($^1O_2$).[5] The tumor response to the accumulation of $^1O_2$ leads to cell death, however, PDT depends on the presence of molecular oxygen, which limits its efficacy in hypoxic tumors.[4,6,7] This creates a need for photo-activatable small molecules that lead to cell death on light excitation without being dependent on the availability of molecular oxygen. There is also a need for targeted drug delivery in chemotherapy, which coupled with the use of light can give exclusive control over a small molecule's activity in tumor tissue.

Chemotherapeutic agents have been designed to target mitochondria or the mitochondrial respiratory pathway since the 1980s.[8] This is because cancer cells have altered mitochondrial biology that includes changes in membrane potential, biomass, cell death signaling, redox homeostasis, and metabolic regulation.[9–11] However, these alterations are specific to cancer type and stage, tumor tissue heterogeneity, and microenvironment.[9,12] Designing small molecules or drug delivery agents by incorporating positively charged lipophilic substituents has been favorably used to target mitochondria.[13–17] The difference in mitochondrial membrane potential in cancer cells drives the accumulation of these positively charged small lipophilic molecules in comparison to normal cells.[18] Initiating cell death, which is one of the key anti-cancer drug activities, has been closely linked to mitochondrial bioenergetics, as the release of cytochrome *C* and high proton leak from the inner mitochondrial membrane to the cytosol are some of the prerequisites to cell apoptosis.[19] Synthesizing photo-activatable small molecules that target mitochondria is expected to increase treatment efficiency and improve the landscape for anti-cancer drug discovery.

Photochemistry of aromatic sulfoxides has been explored since the late 1960s to understand the mechanisms involved in photodeoxygenation. In 1967, it was found that dibenzyl sulfoxide on

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