Development of Ir(III)-Based Photocatalysts for NADH Oxidation and ROS-mediated Cancer Phototherapy

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Abstract

The global cancer burden is rising at an alarming rate. According to GLOBOCAN 2020 data, the number of cancer-related cases is expected to increase by 47% by 2040 compared to 2020.[1] Although platinum-based chemotherapeutic drugs have been frequently used to treat cancer, these drugs are now facing resistance and also show severe side effects such as nephrotoxicity, neurotoxicity, cardiotoxicity, vomiting, and nausea due to poor selectivity of the drug toward cancer cells over normal cells.[2] So, there is an urgent need for cancer therapy that can overcome these limitations. Photodynamic therapy (PDT) has recently shown promising results in overcoming these limitations.[3] This therapy uses light irradiation to activate the drug at the cancer site selectively.[3] The activation through light irradiation provides high selectivity and reduces off-target toxicity.[3] Even though this therapy offers promising results in treating cancer, its complete dependency on molecular oxygen restricts the therapeutic application of this therapy to normoxia only.[4] Additionally, Photofrin, which is an FDA-approved PDT-based drug, shows side effects like hepatotoxicity and skin irritation.[5] These drawbacks of PDT necessitate a new alternative chemical approach, one of which is photocatalytic cancer therapy (PCT). Unlike PDT, which completely relies on molecular oxygen to generate cytotoxic reactive oxygen species (ROS), PCT employs light and photocatalysts to oxidize intracellular NADH in an oxygen-independent manner.[6] This mechanism enables effective treatment even under hypoxic tumor conditions.[6] The primary objective of this thesis was to shift the light absorption property of the photocatalyst for PCT toward higher wavelengths, particularly into the green light region by suitable molecular engineering. In addition to tuning the light absorption property of photocatalysts, this thesis focused on improving their photocatalytic potential for generating reactive oxygen species (ROS) and oxidizing NADH, under both normoxic and hypoxic conditions.

In this thesis, we have developed cyclometallated Ir(III) photocatalysts having 1,10-phenanthroline and terpyridine derivatives, which exhibited improved in-solution NADH oxidation photocatalytic performance and excellent photo-induced cytotoxicity in visible light (400-700 nm).[7] By changing the cyclometallated ligand to coumarin 6 and making a slight modification in the polypyridyl ligand (phen, dppz, and aip), we were able to shift the absorption of the developed Ir(III)-photocatalysts to the green region.[8] Additionally, this modification resulted in a remarkable enhancement in singlet oxygen quantum yield and NADH photooxidation turnover frequency (TOF). The photocatalysts also showed photoinduced NADH oxidation inside the cancerous cells, along with enhanced photocytotoxicity by targeting the mitochondria of the cancer cells. Notably, these photocatalysts retained efficacy under hypoxic conditions (1% O_2), overcoming a major limitation of traditional photodynamic therapy. We further advanced the design by integrating terpyridine-based ligands, pushing the photocatalytic performance even higher (TOF up to 1084 h^{-1}) and enhancing selectivity and effectiveness in breast and cervical cancer models.[9] All our developed photocatalysts demonstrated light-induced apoptosis in cancer cells *via* mitochondrial depolarization and caspase 3/7 activation while maintaining minimal dark toxicity to normal cells.

This thesis not only expands the chemical space of Ir(III) based photocatalysts for PCT but also contributes valuable insight into the rational design of next-generation photocatalysts for targeted cancer therapy.

References

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