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

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By

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Conclusion, and Recommendation

Photocatalysts **1-3** exhibited improved visible-light-driven (400-700 nm, 10 J cm^{-2}) catalytic NADH oxidation (TOF up to *ca*. 697 h^{-1}). Among **1-3**, **3** with higher conjugation showed superior photocytotoxicity against A549 cells (IC_{50} *ca*. 0.8 μM) with low toxicity toward normal HEK-293 cells (IC_{50} = 23.4 μM and >25.0 μM under light and dark, respectively) (**Chapter II**). Incorporation of coumarin 6 in photocatalysts **4-6** shifted the absorption to the green region, and further improved the photocatalytic activity for NADH oxidation (TOFs up to *ca*. 1003.5±24.6 h^{-1}). Photocatalyst **6** exhibited photoinduced (400-700 nm, 10 J cm^{-2}) NADH oxidation potential inside the A549 cancerous cell with excellent photocytotoxicity (400-700 nm, 10 J cm^{-2}) in both normoxic (IC_{50} *ca*. 0.6 μM) and hypoxic conditions (1% O_2) (IC_{50} *ca*. 1.7 μM) while remained nontoxic against Beas2B healthy cells (IC_{50} = >50.0 μM) (**Chapter III**). The incorporation of terpyridine ligands in photocatalysts **7**/**8** further improved photocatalytic NADH oxidation performance, even achieving the highest TOF reported till now (TOFs up to 1084.6±39.4 h^{-1}). This incorporation not only improved NADH photocatalytic activity but also significantly improved the photocytotoxicity of **8** against the MCF-7 cancerous cell line (IC_{50} = 0.3 μM). **8** induced intracellular NADH oxidation and caspase 3/7 activation-mediated apoptotic cell death (**Chapter IV**). Overall, these Ir(III) based photocatalysts showed potential as promising candidates for oxygen-dependent as well as oxygen-independent cancer therapy.

Looking forward, in order to enhance the therapeutic potential for deeply buried tumors, future studies could focus on red-shifting the absorption profile toward the red and near-infrared light region through rational ligand framework design. Further, tumor-targeting moieties (such as glucose, biotin, folic acid, and vitamin B6) may be attached to enhance the

cancer cell selectivity and cellular uptake of the photocatalysts. *In vivo* studies will be crucial to validate the therapeutic potential and biocompatibility of these photocatalysts. Additionally, exploring alternative intracellular electron acceptors under hypoxic conditions other than Fe^{3+}–cytochrome c could help to increase the understanding of the effectiveness of photocatalytic cancer therapy in oxygen-deprived tumors. Exploration of combined treatment strategies (e.g., with ultrasound or immunotherapy) could advance these systems toward clinical application.