Targeted Nitroisoxazole-Based GPX4 Inhibitor Drug Conjugate for Ferroptosis Induction in Chemoresistant Tumors

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Cancer cells can develop chemoresistance, causing treatment failure in over 90% of metastatic cancer patients. GPX4 inhibitors are promising ferroptosis inducers for chemoresistant tumors but have drawbacks with bioavailability, stability, and selectivity. ML210, utilizing a selective nitroisoxazole group, suffers from poor bioavailability and diminished selectivity in low-molecular-weight analogs. This study aimed to design drug conjugates to enhance the efficacy of a low-molecular-weight ML210 analog. Conjugates were designed with a triphenylphosphonium (TPP) ligand, disulfide-based linker, and nitroisoxazole warhead, with a methoxy polyethylene glycol di-glutamic acid spacer in the redesign. Computational software evaluated solubility, topological polar surface area (TPSA), and lipophilicity at physiological and tumor pH. Results were compared to TPP-DOX, a chemotherapy conjugate. The initial design exhibited high hydrophobicity, increasing the warhead's lipophilicity at pH 7.4 and 6.8 above TPP-DOX while reducing solubility and TPSA near TPP-DOX. The redesign reduced lipophilicity at pH 7.4 to levels around the lone warhead's ($p = 0.39$) and increased lipophilicity from the warhead ($p = 0.003$, without outlier) at pH 6.8. Both were significantly lower than TPP-DOX ($p = 0.003$); TPSA was greater ($p < 0.001$). Solubility remained similar to TPP-DOX ($p = 0.29$). These findings suggest the redesign renders a nitroisoxazole ML210 analog a pharmacologically advantageous ferroptosis inducer, facilitating targeted acidic tumor tissue accumulation and intravenous administration preparation while minimizing side effects. This highlights drug conjugation as an effective, practical strategy to improve the clinical success of nitroisoxazole-based treatments for chemoresistant tumors.

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