Oral Presentation

Synthesis of New Triazine-Based Ferroptosis Inducers/MMP-Inhibitors for Halting Colon Cancer

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ABSTRACT: Combining ferroptosis with other forms of cancer cell death is new emerging strategy for combating colon cancer. However, ferroptosis induction is seldom studied in tandem with inhibiting MMPs. A combination that is expected to enhance the anticancer therapeutic outcome based on mechanistic studies. The current work introduces hybrid triazines concomitantly inhibit MMP-10/13 and induce ferroptosis bridging their anticancer potentials. The MMPs inhibitory component of the designed scaffold was based on the nonhydroxamate inhibitors model. *s*-Triazine was rationalized as the scaffold core inspired by the FDA-approved ferroptosis inducer altretamine. The ferroptosis electrophilic warheads were installed as Michael acceptors *via* triazole-based spacers. Their reactivity was tuned by incorporating cyano and/or substituted phenyl groups. Initial screening elected the cyanoacrylohydrazides bearing *p*-bromophenyl appendage **9d** as the most promising cytotoxic agent. **9d** surpassed NNGH against MMP-10 and −13 (IC_{50} = 0.16 µM). Ferroptosis studies proved that **9d** depleted the HCT-116 cells GSH by a relative fold decrement of 0.81 with modest GPX4 inhibition inducing HCT-116 cells lipid peroxidation by 1.32 relative fold increment. Docking presumed binding of **9d** to the MMP-10 S1′ pocket and the MMP-13 hydrophobic pocket, as well as covalent interaction with the GPX4 catalytic selenocysteine. **9d** complexed with ferrous oxide nanoparticles induced intracellular iron overload, depleted GSH with a relative fold decrement of 0.12, and triggered lipid peroxidation and ferroptosis by a 3.94 relative fold increment. The complex was 7.5 folds more cytotoxic against HCT-116 cells than its free precursor. Collectively, **9d** could be a lead for tuning MMPs selectivity and ferroptosis induction potential to maximize the benefit of such a combination.

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