Discovery of Natural, Synthetic, and Repurposed Inhibitors of MTH1 for Therapeutic Management of Breast Cancer

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The human MutT Homolog 1 (MTH1) enzyme plays a pivotal role in maintaining genomic integrity under oxidative stress by sanitizing oxidized nucleotide pools, thereby supporting the survival of cancer cells. Elevated levels of reactive oxygen species (ROS) in tumors render cancer cells highly dependent on MTH1 to prevent the incorporation of damaged nucleotides into DNA. Consequently, MTH1 has emerged as an attractive therapeutic target for selectively inducing cancer cell death. In this study, we employed a comprehensive computational and experimental approach to identify and characterize novel natural, synthetic, and repurposed inhibitors of MTH1. Virtual screening of 3800 FDA-approved drugs highlighted Nilotinib and Lumacaftor as promising MTH1 binders, validated through molecular docking and 500 ns MD simulations. Nilotinib demonstrated strong binding affinity (K_a = 2.5 × 10^4 M^{-1}) and potent inhibitory activity (IC_{50} = 37.2 µM), revealing a previously unrecognized dual mechanism as both a tyrosine kinase and MTH1 inhibitor. A parallel screening of natural compounds identified Resveratrol (RV), Thymoquinone (TQ), and Baicalin (BC) as potent inhibitors. These compounds exhibited high-affinity binding (K_a ranging from 1.0 × 10^5 to 6.2 × 10^5 M^{-1}) and effectively suppressed MTH1 enzymatic activity (IC_{50} values: 18.13 µM for RV, 28.3 µM for TQ, and 34.8 µM for BC). Cellular assays using MCF-7 breast cancer cells demonstrated significant inhibition of proliferation and induction of apoptosis, accompanied by elevated ROS generation and oxidative stress–mediated cytotoxicity. Subsequently, two novel synthetic scaffolds, oxazolone- and thiazolyl-benzenesulfonamide–derived molecules (O29 and DSA5), were designed, synthesized, and structurally characterized via NMR spectroscopy. Docking, MD simulations, and fluorescence binding assays confirmed stable and high-affinity interactions with MTH1, while in vitro enzyme and cell-based assays revealed substantial cytotoxic effects in breast cancer models. Collectively, our findings uncover multiple classes of potent MTH1 inhibitors from repurposed drugs and natural compounds to newly designed scaffolds, demonstrating their mechanistic potential to disrupt tumor redox homeostasis and induce cancer cell death. This integrated approach provides a promising framework for developing MTH1-targeted therapeutics in precision oncology.

Keywords: MTH1 inhibition, oxidative stress, ROS, molecular docking, repurposed drugs, natural compounds, breast cancer, Nilotinib, Resveratrol, Thymoquinone, Baicalin, small-molecule inhibitors.

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