Targeting Cap-Independent Translation in c-MYC mRNA: A Novel Small Molecule Approach for Cancer Therapy

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Cancer remains one of the most significant global health challenges, with the c-MYC proto-oncogene implicated in over 50% of cases, particularly in solid tumors. When dysregulated, c-MYC promotes tumor growth and suppresses the immune response, making it a critical target for cancer therapies. This study explores small molecule therapeutics aimed at inhibiting c-MYC mRNA translation by targeting its Internal Ribosomal Entry Site (IRES), which facilitates cap-independent translation. This previously unexplored approach selectively blocks c-MYC translation in cancer cells that depend on its dysregulation for growth, while sparing normal cells that also rely on c-MYC. High-throughput screening of a fully functional fragment (FFF) library was conducted to identify fragments with specific binding properties. The library was generated using PocketVec, a drug design software that identifies RNA binding pockets and selects fragments to target them. Compounds featuring diazirine and alkyne groups were incubated with c-MYC mRNA, and UV light was used to activate diazirine crosslinking for selective binding. A TAMRA fluorophore was subsequently attached through click chemistry, enabling fluorescence detection of binding interactions. The binding strength was assessed using agarose gel electrophoresis and bioimaging. Results supported the hypothesis that specific functional groups enhance binding affinity, with a dose-response analysis identifying several potential hits. These findings suggest that small molecules can disrupt c-MYC production via the IRES, offering a novel strategy to inhibit tumor growth and overcome limitations of traditional protein-targeting therapies. Future research will focus on optimizing these compounds and evaluating their efficacy in biological systems.

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