The Design of Spirooxindole-Pyrrolidinyl Scaffold as an Inhibitor of the MDM2 Protein

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MDM2 amplification occurs in approximately 40 to 60% of human sarcomas such as liposarcoma. MDM2 protein, an E3 ubiquitin-ligase, negatively regulates p53, a tumor suppressor inactivated in almost 50% of cancers. MDM2 amplification renders p53 non-functional. Targeted therapy by inhibiting MDM2 with small molecules, such as spirooxindoles, has emerged as a promising approach for p53 reactivation, minimizing side effects as compared to chemotherapy. I hypothesized that enhancing the spirooxindole-pyrrolidinyl scaffold, by addition of nonpolar functional groups, will improve its binding affinity to MDM2. This was observed through computational modeling. The main binding pocket of MDM2 where p53 binds consists of hydrophobic residues. I modified SAR405838, an MDM2 antagonist that was in clinical trials for liposarcoma by adding an array of nonpolar functional groups to the spirooxindole-pyrrolidinyl scaffold. The average binding affinities of modified molecules were significantly greater than SAR405838, supporting my hypothesis. Nineteen molecules showed more binding affinity than APG-115, another promising spirooxindole. Two new functional groups, 2,5- dichlorotoluene and 2,5-difluorotoluene, that haven't been utilized as MDM2 inhibitors previously were found to work favorably. These molecules showcase potential as inhibitors of MDM2 and in aiding treatment of cancers with MDM2 amplification. Future research will focus on the modification of molecules presented to have favorable pharmacokinetic properties, and testing these molecules in vitro and in vivo with overexpressed MDM2 will help determine how they work and their possible side effects.

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