Synthesis and Evaluation of Small Molecule Inhibitors of the PD-1/PD-L1 Protein-Protein Interaction

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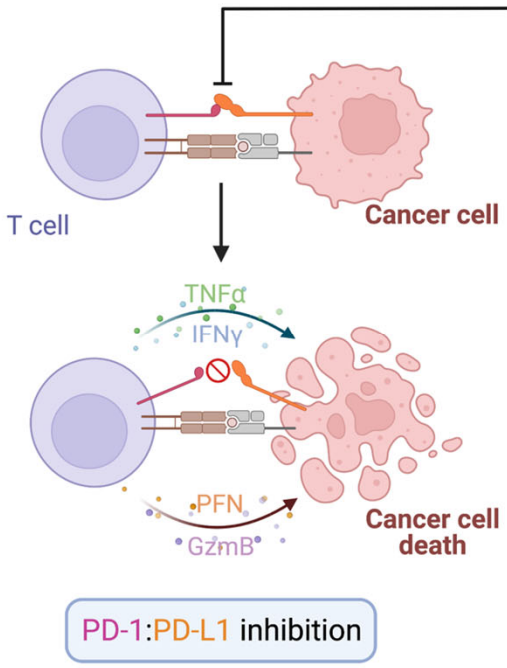
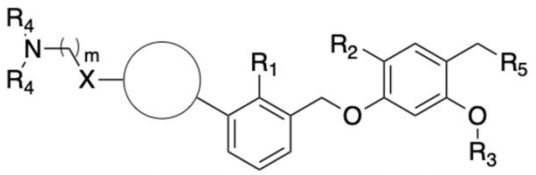
Programmed cell death-1 receptor (PD-1) and programmed cell death-ligand 1 (PD-L1) are extracellular proteins located on T cells and antigen presenting cells, respectively. PD-1/PD-L1 protein-protein interaction (PPI) is normally involved in limiting the generation of autoreactive T cells. However, cancer cells highly express PD-L1 on their surface to escape immune detection. PD-1/PD-L1 PPI inhibitors can prevent cancer cells from evading the immune system. Monoclonal antibodies are the current standard therapy, but have limitations including higher costs and no oral bioavailability, which could be overcome by using small molecule inhibitors. This study aims to synthesize and evaluate three small molecules as inhibitors of the PD-1/PD-L1 PPI to explore the structure-activity relationships of the chemotype. The three target compounds were synthesized in 13 steps with overall yields between 1-6% and characterized by ^{1}H and ^{13}C-NMR spectroscopy and HRMS. Inhibitory activity of the target compounds with reference (LH1461) and control compounds were measured in a homogenous time-resolved fluorescence resonance energy transfer assay. The three synthesized analogs were found to be more potent than the reference compound LH1461 (2,986±43 nM). LH1469 with the ethylene linker and LH1470 with the propylene linker showed an IC_{50} of 574±103 nM and 507±123 nM, respectively. Most notably, LH1468 with the propionyl linker exhibited the best inhibitory activity in this series with an IC_{50} of 89±17 nM. LH1468, with its propionyl linker, could be considered as a potential lead for further optimization. Supported by Rutgers University Foundation, NIH R25ES020721 and the SURF program.





Compound ID	R_3	R_5	X	m	IC_{50} (nM)
LH1461	R_3-B	R_5-B	CO	1	2,986±43
LH1468	R_3-B	R_5-B	CO	2	89±17
LH1469	R_3-B	R_5-B	CH_2	1	574±103
LH1470	R_3-B	R_5-B	CH_2	2	507±123

Proposed Small Molecule Inhibitor Analogs