Design and Synthesis of Potential Phthalimide-Based Inhibitors of Keap1-Nrf2 Protein-Protein Interaction

Jensan Liu, Ahmed Ali, Longqin Hu
Rutgers, The State University of New Jersey

The Keap1-Nrf2 protein-protein interaction (PPI) is an essential component of a cell's response to oxidative and electrophilic stress. Normally, two Keap1 proteins bind to one Nrf2 protein, leading to the ubiquitination and eventual degradation of the Nrf2 protein. Under stressful conditions, Keap1 undergoes modifications on its cysteine residues, leading to its inability to bind to Nrf2 due to a conformational change. An abundance of Nrf2 then accumulates in the cytoplasm, which then leads to the transcription of many cytoprotective genes. In many cancer cells, the pathway is activated due to mutations in the *KEAP1* and *NRF2* genes. These mutations lead to constitutive expression of the Nrf2-controlled proteins, allowing cancer cells to be especially resilient to oxidative and electrophilic stress. This then, allows cancer cells to proliferate even in harsh and hostile environments where normal cells cannot. Two phthalimide-based inhibitors were designed and synthesized based on a previous direct inhibitor of Keap1-Nrf2 PPI reported by Dr. Hu's group, in an effort to find more potent inhibitors.