Covalent Fragment Screening and Optimization Identifies Chloroacetohydrazide Scaffold as Inhibitors for Ubiquitin C-terminal Hydrolase L1

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The ubiquitin proteasome system (UPS) is a key signaling pathway for protein degradation. Mis-regulation of the UPS is a hallmark of various disease states including neurodegenerative disease and cancer. Ubiquitin C-terminal Hydrolase L1 (UCHL1), a deubiquitinating enzyme, is expressed primarily in the central nervous system under normal physiological conditions. However, UCHL1 is considered an oncogene in various cancers, including melanoma, lung, breast, and lymphoma cancers with its overexpression linked to increased metastatic behavior. Thus, UCHL1 inhibitors could serve as a viable treatment strategy against metastasis. Herein, we describe a covalent fragment screen that identified the chloroacetohydrazide scaffold as a covalent UCHL1 inhibitor. Subsequent optimization provided an improved fragment with single digit micromolar potency against UCHL1 and selectivity over the closely related UCHL3 with efficacy in cellular assays of metastasis. Additionally, we report a ligand-bound crystal structure of our lead molecule in complex with UCHL1, providing insight into the binding mode and information for future optimization.