

Rational discovery of BRD4 monovalent protein-degraders

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Targeted protein degradation (TPD) using the endogenous ubiquitin (Ub) proteasome system (UPS) is a rapidly growing modality for drug discovery. Strategies for TPD have primarily focused on designing heterobifunctional PROTACs that have utilized ligand binding to well-characterized E3 ligases (e.g., cereblon and VHL). This approach often results in compounds with non-ideal physical properties and in many cases, this can limit their utility as therapeutic agents. Monovalent degraders represent an alternative approach, in which small molecules bind to the target protein and directly induce target degradation by producing conformational or other changes that make the protein susceptible to detection by the cellular quality control and ubiquitin-degradation machinery. These direct degraders display improved physico-chemical properties compared to PROTAC degraders and are not biased towards a preselected E3 ligase. The molecular structures of monovalent degraders are typically designed around a binder for the target protein and a “degradation tail”. However, designing compounds to induce degradation is not well precededented, relies on serendipitous discovery and is often limited by steep structure–activity relationship. Plexium has developed a systematic approach to designing and discovering novel monovalent degraders of therapeutically valuable proteins for the treatment of human cancers.

Here we describe the application of Plexium’s approach to the rational design and discovery of BRD4 monovalent protein-degraders, and the subsequent optimization of both potency and ADME properties. Starting from known BET binders, we identified two series of analogues with potent and deep BRD4 degradation profiles as well as high BRD4-BD2 binding selectivity. Medicinal chemistry optimization focused on increasing potency, and physical properties led to

the discovery of tool compounds, which demonstrate excellent potency in cellular assays as well as good exposure and half-life in mouse models. Finally, mechanistic studies showed that our two series of monovalent degraders promote BRD4 degradation via E3 ligases that are not cereblon or VHL.