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Abstract

Targeted Protein Degradation with Small Molecules: How PROTACs Work †

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† Presented at the 2nd Molecules Medicinal Chemistry Symposium (MMCS): Facing Novel Challenges in Drug Discovery, Barcelona, Spain, 15–17 May 2019.

Published: 16 December 2019

Abstract: Bivalent degrader molecules (also termed PROTACs) target proteins for degradation through recruitment to E3 ligases. PROTACs are a revolutionary new modality class with therapeutic potential. Formation of a ternary complex between the degrader, the ligase, and the target leads to tagging by ubiquitination and proteasomal degradation of the target protein. In 2015, we disclosed MZ1, a potent degrader made of a ligand we had previously discovered for the E3 ligase von Hippel–Lindau (VHL), and a pan-selective ligand for the BET proteins Brd2, Brd3, and Brd4. We made the unexpected but fascinating observation that MZ1 induces preferential degradation of Brd4 over Brd2 and Brd3—despite engaging BET proteins with the same binary affinity. This demonstrated a now well-established feature of PROTACs: They can achieve a narrower degradation profile in spite of broad target engagement. Our co-crystal structure of a PROTAC ternary complex (VHL:MZ1:Brd4) illuminated the role of cooperative molecular recognition inducing de novo contacts to form a stable ternary. Our work is revealing the structural basis and guiding principles of PROTAC degradation selectivity and mode of action.