(A) Chemical structure of VHL-recruiting WDR5 degrader MS67.

(B) (TOP) Overall structure of the VCB-MS67-WDR5 ternary complex displayed in ribbon representation with VHL, Elongin C, Elongin B, and WDR5 colored in gray, pale yellow, cyan, and pale green, respectively. The secondary structure elements for VHL are labeled. The seven β-propellers of WDR5 are also labeled. The simulated annealing Fo-Fc omit map (blue mesh) for MS67 is displayed (contoured at 3.0σ with a carve radius of 2.0 Å).
(BOTTOM LEFT) Overview of the VHL-MS67-WDR5 ternary complex, with VHL, WDR5, and MS67 shown in gray, pale green, and orange, respectively.
(BOTTOM RIGHT) Detailed view of the binding interactions of MS67 with VHL (gray) and WDR5 (pale green) in the VCB-MS67-WDR5 complex. Only amino acids within 4-Å spheres of MS67 are depicted. Water molecules are depicted as pink spheres. Hydrogen bonds are depicted by dashed lines.

(C) Immunoblots for WDR5 and Tubulin posttreatment of MV4;11 cells with the indicated concentrations of MS67, OICR-9429, or MS67N (negative control) for 18 hours. DC50 and Dmax values of MS67 in MV4;11 cells are shown as the means ± SD from three independent experiments.

(D) Immunoblots for WDR5 and Tubulin posttreatment with the indicated concentrations of OICR-9429, MS33, MS67, or MS67N in the indicated PDAC cell lines for 18 hours.

(E) (LEFT) Immunoblot demonstrating enrichment of WDR5 following recombinant expression in BL21 competent E. coli and subsequent affinity-tag and size-exclusion purification. (RIGHT) Mass spectrometry results confirming purified WDR5 protein is free of contamination, fully intact, and at expected molecular weight.

(C) Representative inverse ITC titrations are shown for VCB into MS67 (left), VCB into MS67-WDR5 complex (middle), and WDR5 into degrader MS67 (right) for measuring binding kinetic and determining cooperativity for MS67. The calculated values represent the means ± SD from three independent experiments. First injection has been removed from the fitting.