The Discovery and Characterization of CFT-18442: A Potent, Selective, and Orally Bioavailable Degrader of BRAF V600E

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BRAF mutations occur in approximately 15% of all cancers, and approximately >70% of BRAF mutations are V600E mutations. Despite the clinical success of approved small molecule inhibitors of BRAF V600E (vemurafenib, dabrafenib and encorafenib), resistance has developed, necessitating the need for alternative therapeutics capable of addressing these escape mechanisms. A Bifunctional Degradation Activating Compound (BiDAC^{TM}) offers the potential for a fundamental improvement over current BRAF inhibitors by degrading mutant BRAF V600E, which can address many forms of resistance to BRAF inhibition. Here we report the discovery of CFT-18442, a cereblon-based BiDAC degrader that is capable of selectively and potently degrading mutant BRAF V600E. In vitro, CFT-18442 demonstrates superior growth inhibitory activity relative to inhibitors in both BRAFi-sensitive A375 melanoma cells (V600E) and BRAFi-resistant A375 cells (V600E + NRAS Q61K mutation). In vivo, oral dosing of CFT-18442 in the A375 and A375 (NRAS Q61K) cell-derived xenograft models led to robust tumor growth inhibition in both settings. The medicinal chemistry campaign, which focused on the improvement of in vivo pharmacokinetics, led to the identification of CFT-18442 with desirable in vivo oral exposure, highlighting the potential to realize high oral bioavailability with this class of beyond rule of 5 (bRo5) compounds through rational linker design.