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Deubiquitinase-Targeting Chimeras for Targeted Protein Stabilization
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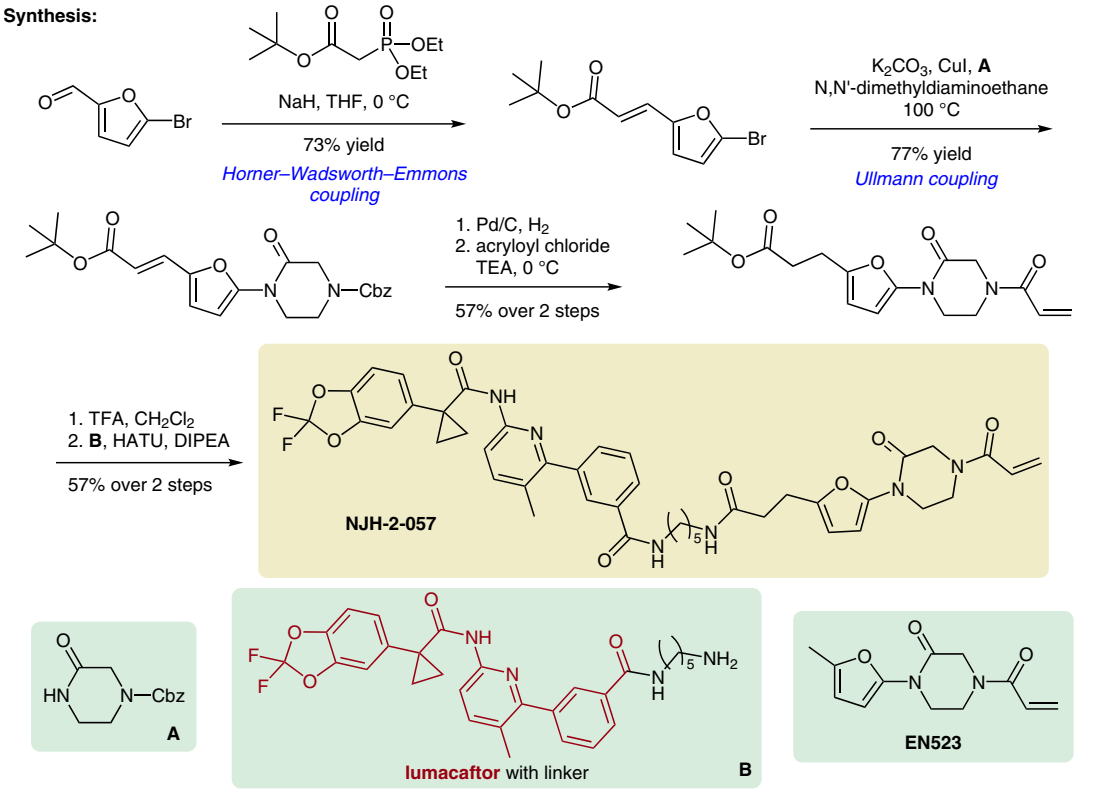
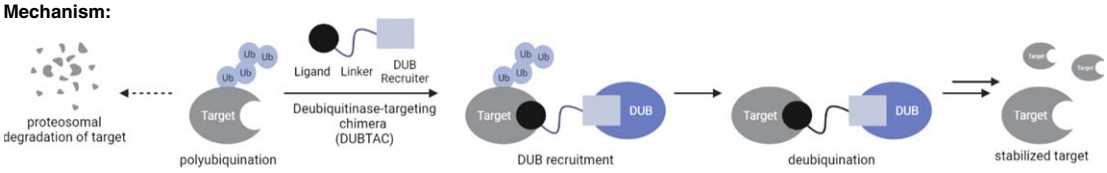
Targeted Protein Stabilization with DUBTACs





Significance: Irregular protein degradation plays a critical role in the pathogenesis of many diseases, such as cystic fibrosis and several forms of cancer. Thus, targeted protein stabilization (TPS) offers a novel therapeutic strategy for such cases. Utilizing an approach analogous to proteolysis-targeting chimeras (PROTACs), Nomura and co-workers developed deubiquitinase-targeting chimeras (DUBTACs) as small-molecule recruiters of the deubiquitinase OTUB1 to stabilize polyubiquitinated proteins of interest tagged for proteasomal degradation.

Comment: Using chemoproteomics, Nomura and co-workers identified OTBU1 as an ideal candidate for recruitment and demonstrated acrylamide **EN523** be a selective ligand for OTBU1 with no loss of activity. DUBTAC **NJH-2-057** was generated by linking **EN523** to the pharmaceutical drug **lumacaftor** to target mutant chloride channel ΔF508-CFTR, the degradation of which is associated with the cystic fibrosis phenotype. In vitro assays demonstrated a dose-dependent and time-responsive restoration of CFTR levels and function, justifying further investigations into DUBTAC-mediated TPS.

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Ullmann coupling

Synfact of the Month