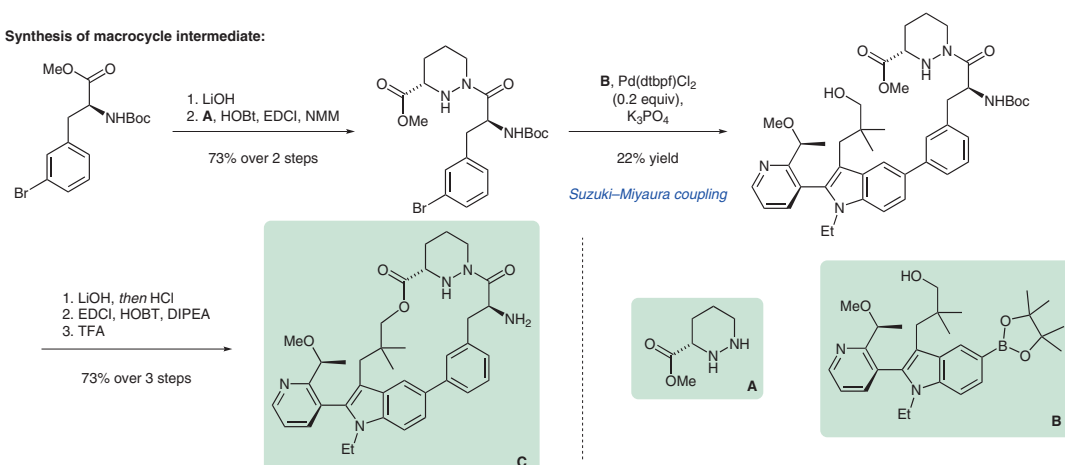


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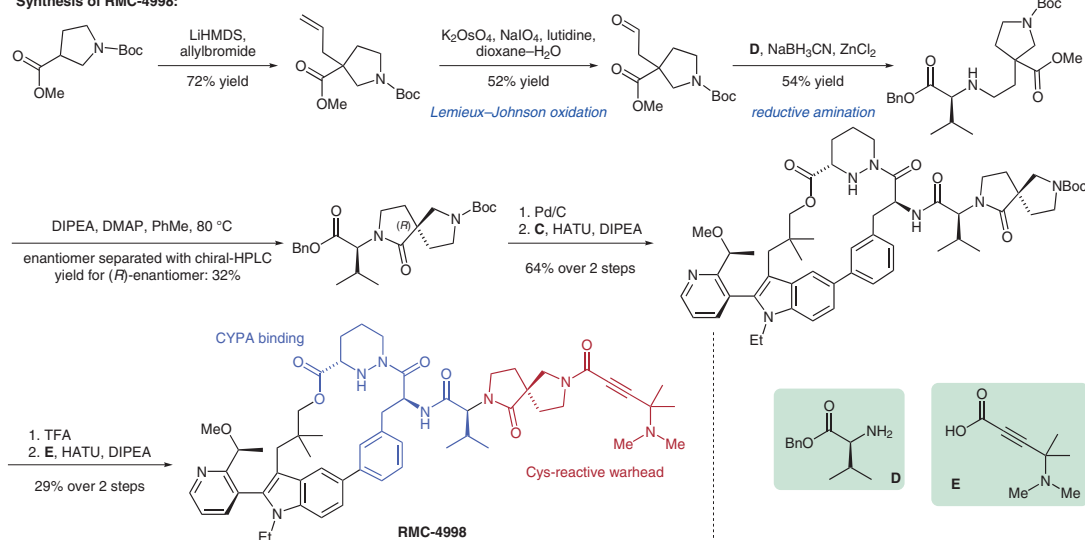
Chemical Remodeling of a Cellular Chaperone to Target the Active State of Mutant KRAS
Science 2023, 381, 794–799, DOI: 10.1126/science.adg9652.

Target Mutant KRAS with Molecular Glue

Synthesis of macrocycle intermediate:



Synthesis of RMC-4998:



Significance: KRAS is considered undruggable due to the lack of binding sites on the protein surface. The authors use a natural product-derived small molecule that binds to cellular chaperone cyclophilin A (CYPA) to form a CYPA:drug:KRAS^{G12C} tricomplex, which deactivates oncogenic signaling and leads to tumor regression in multiple human cancer models.

Comment: The authors based their structural design on sanglifehrin A, a natural product that binds CYPA with high affinity. A SAR study conducted with various Cys-reactive warheads yields RMC-4998 as the lead compound with high potency and selectivity in inhibiting GTP-bound KRAS^{G12C}, blocking its downstream signaling activity.

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