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Chemical Remodeling of a Cellular Chaperone to Target the Active State of Mutant KRAS
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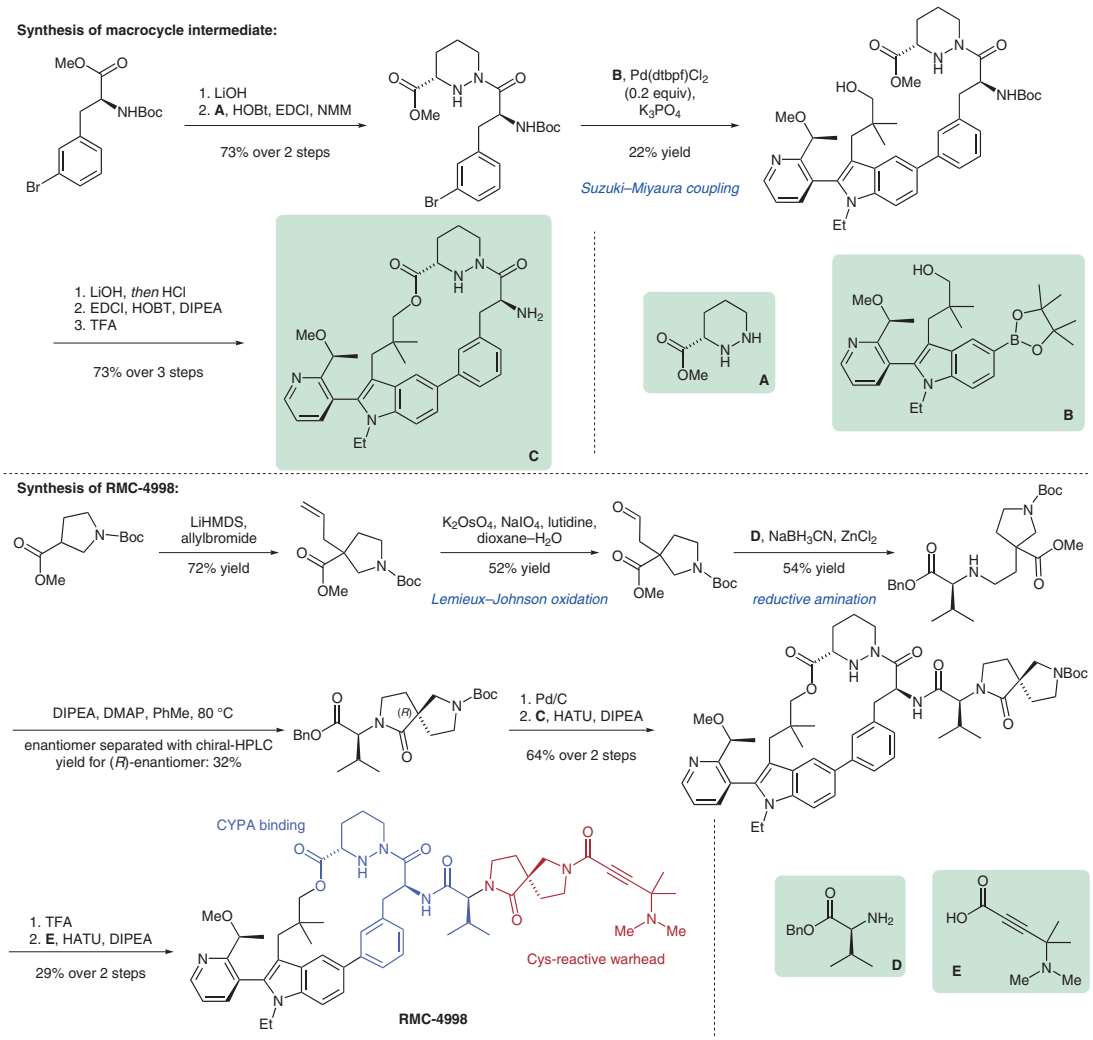
Target Mutant KRAS with Molecular Glue



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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Key words
KRAS
molecular glue
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macrocyclization

Synfact of the Month