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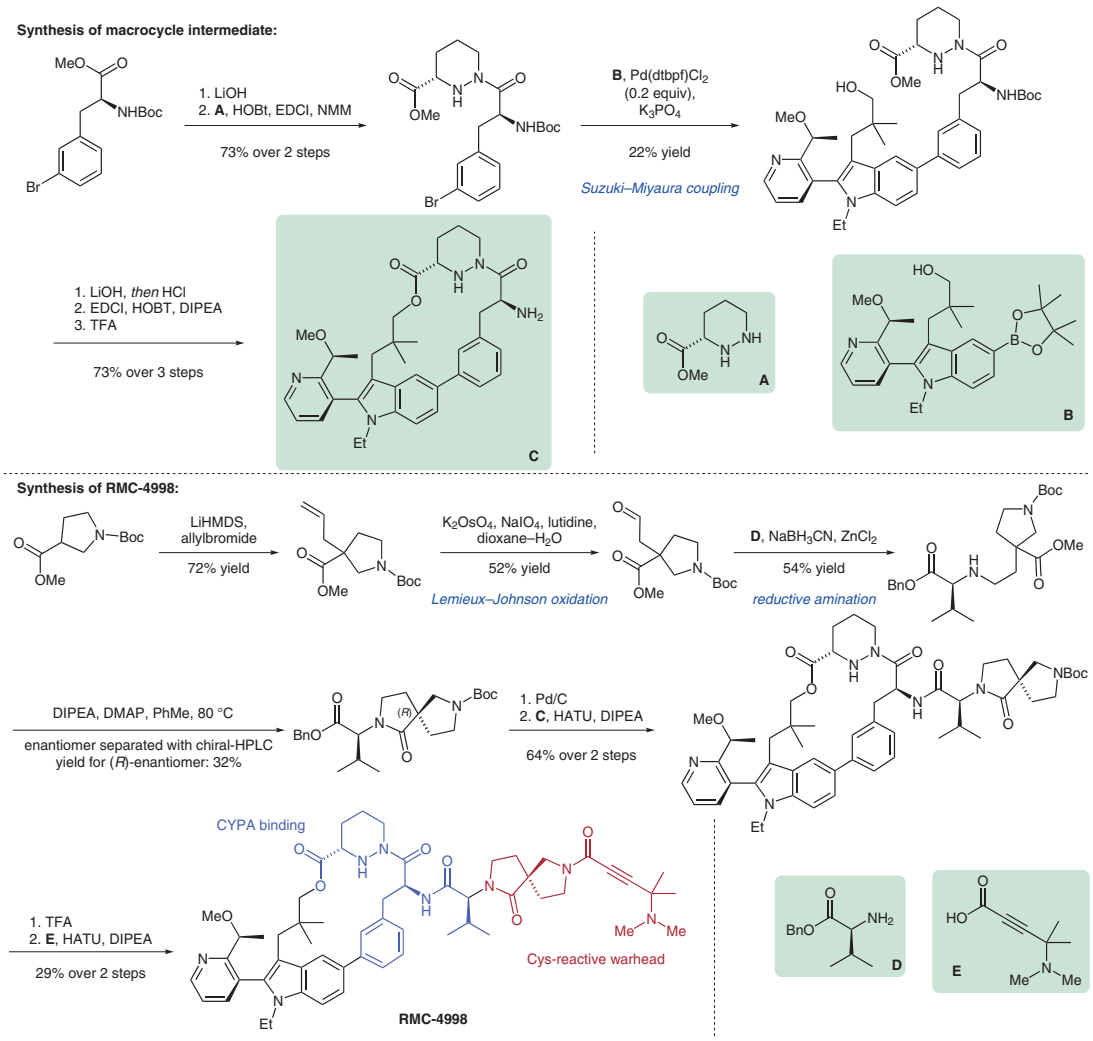
Chemical Remodeling of a Cellular Chaperone to Target the Active State of Mutant KRAS
Science **2023**, *381*, 794–799, DOI: 10.1126/science.adg9652.

Target Mutant KRAS with Molecular Glue



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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Synfacts 2023, 19(11), 1147 Published online: 17.10.2023
DOI: 10.1055/s-0042-1752293; **Reg-No.:** T08823SF

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Category
Innovative Drug Discovery and Development

Key words
KRAS
molecular glue
small-molecule inhibitor
macrocyclization

Synfact of the Month

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