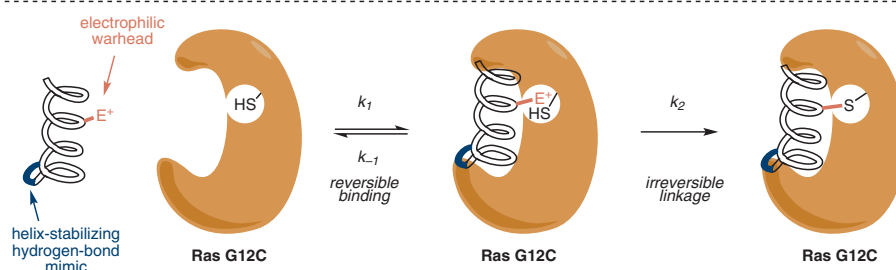
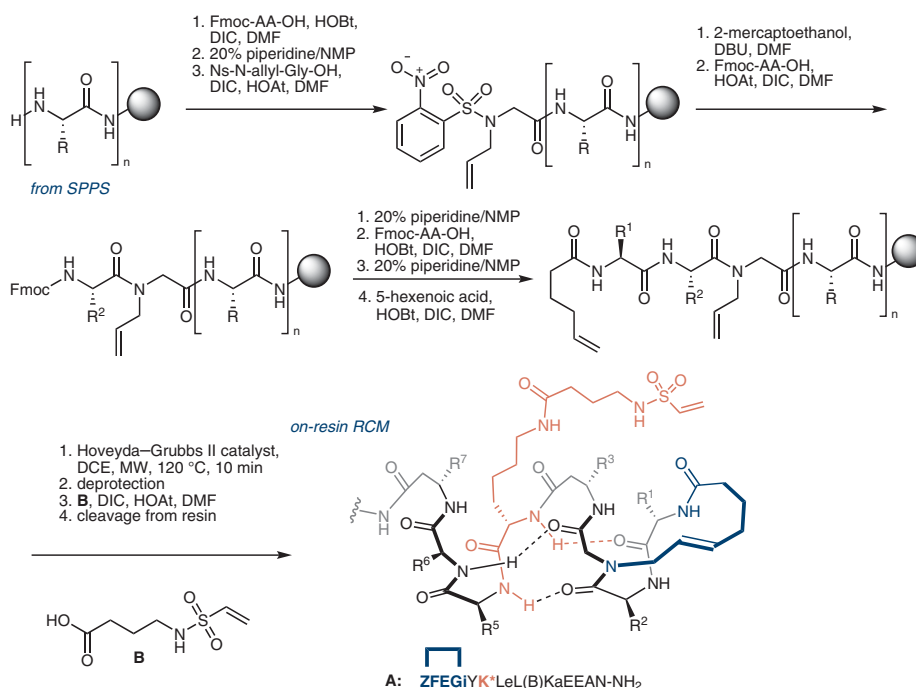


## Covalent Inhibition of Ras G12C with a Stapled Peptidomimetic



**Significance:** Ras proteins are central to several pathways involved in cell proliferation and survival. Dysregulation in Ras signaling is implicated in nearly 30% of all human tumors, and therefore represents an important target in oncology. Bar-Sagi, Arora, and co-workers describe the development of a covalent inhibitor of mutant Ras G12C, using a stapled peptidomimetic scaffold based on the nucleotide exchange factor Son of Sevenless (SoS).

**Comment:** Inhibitor A was synthesized using SPPS and includes an interesting hydrogen-bond surrogate (HBS) motif that is generated from an on-resin ring-closing metathesis of an internal *N*-allyl glycine to an *N*-terminal hexenoic amide. Binding of A to Ras G12C triggers proximity-induced cysteine alkylation of A's sulfonamide motif. Biochemical assays indicate that the G12C mutation is necessary for Ras inhibition and modulation of downstream effects by A.