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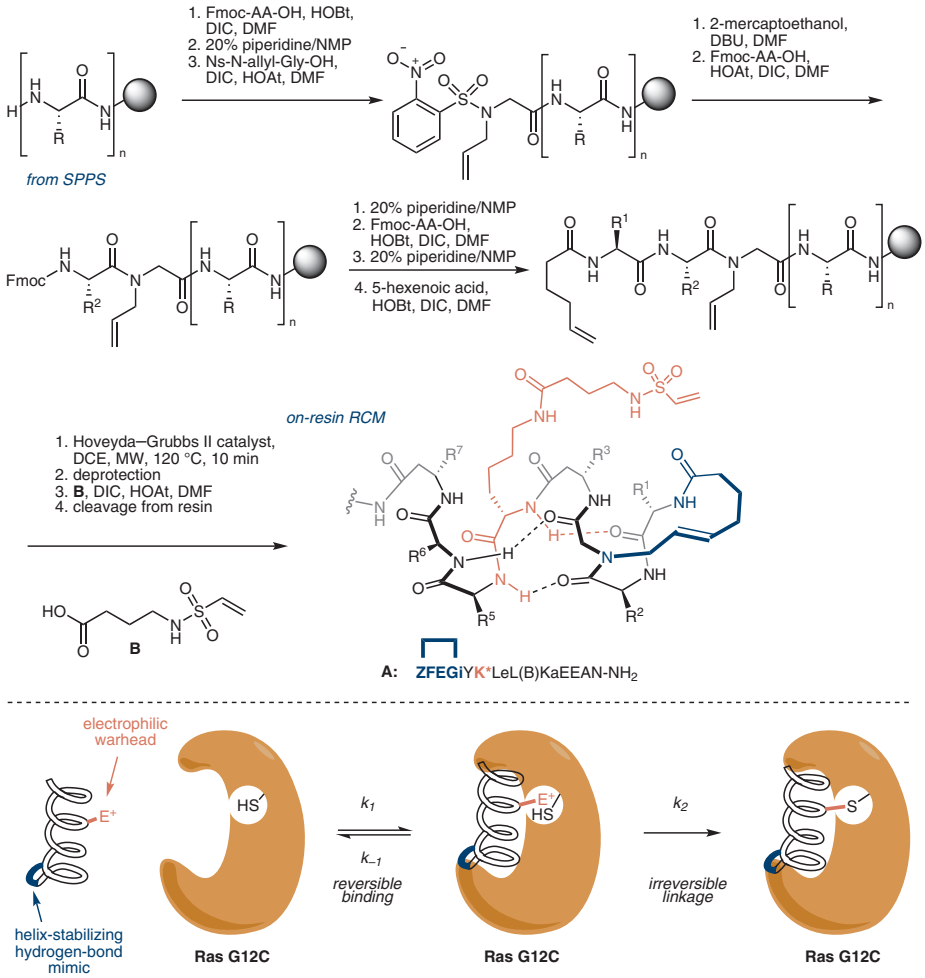
Covalent Targeting of Ras G12C by Rationally Designed Peptidomimetics
ACS Chem. Biol. **2020**, *15*, 1604–1612.

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**.

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Synfacts 2020, 16(08), 0971 Published online: 21.07.2020
DOI: 10.1055/s-0040-1706815; **Reg-No.:** T07620SF

Category
Chemistry in Medicine and Biology

Key words
Ras inhibitors
covalent inhibitors
peptidomimetics
stapled peptides
oncology

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