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K-Ras(G12C) Inhibitors Allosterically Control GTP Affinity and Effector Interactions

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Drugging the Undruggable using Irreversible Covalent K-Ras G12C Inhibitors

Synthesis of the inhibitor:

Covalent binding to K-Ras G12C:

Significance: Mutations in the important regulatory signal transduction protein K-Ras are found in approximately 25% of human cancers. Attempts to target this notorious GTPase resulted in many failures and the protein became known as ‘the undruggable’. Shokat and co-workers took advantage of the nucleophilic cysteine of the G12C mutant and developed acrylamide-based inhibitors that bind covalently and irreversibly.

Comment: A library of nearly 500 acrylamides and vinyl sulfonamides was synthesized and tested for K-Ras G12C inhibition. Various aromatic building blocks were combined with the electrophilic portion using amide bond couplings. Based on these discoveries, many companies continued their discovery programs towards K-Ras anticancer drugs. Amgen’s Sotorasib became the first FDA-approved K-Ras G12C inhibitor in May 2021.

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