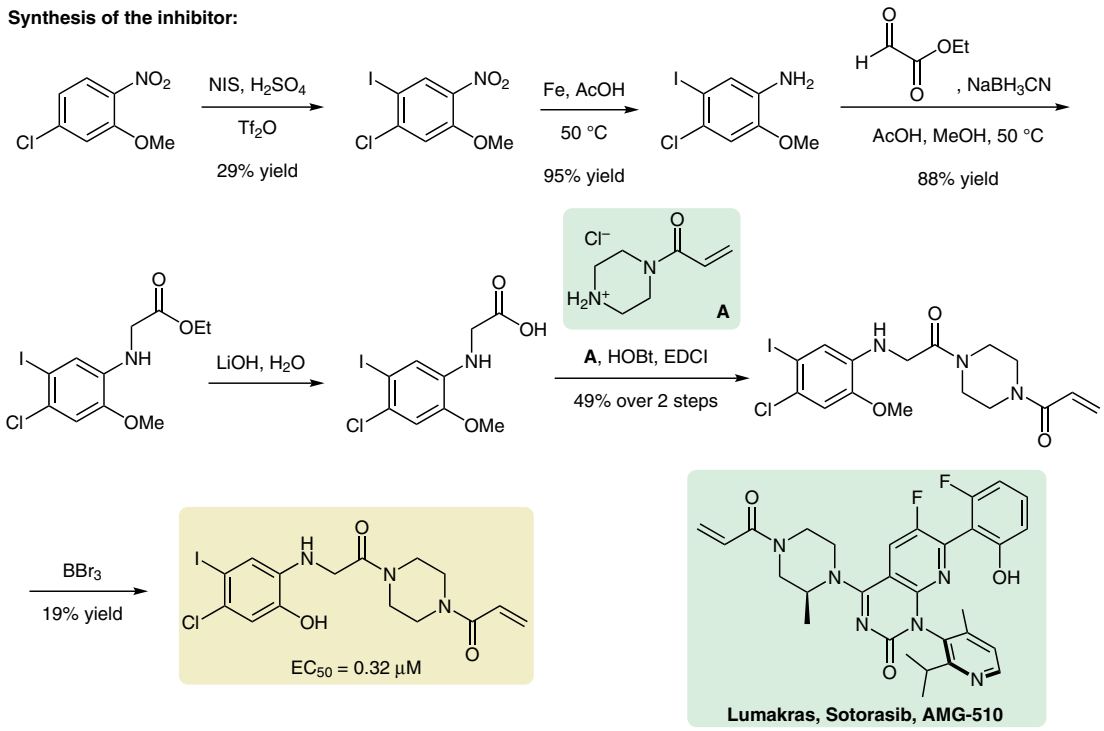
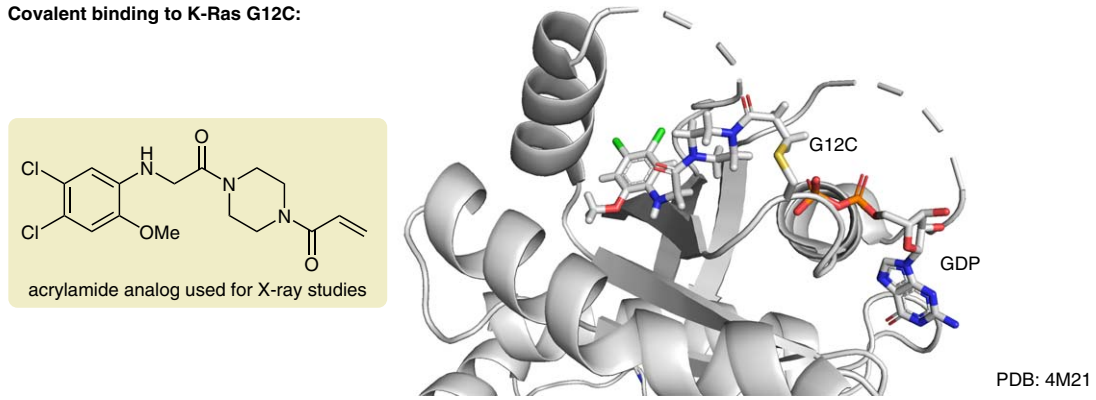
J. M. OSTREM, U. PETERS, M. L. SOS, J. A. WELLS, K. M. SHOKAT* (UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, USA)

K-Ras(G12C) Inhibitors Allosterically Control GTP Affinity and Effector Interactions
*Nature* **2013**, *503*, 548–551, DOI: 10.1038/nature12796.

# Drugging the Undruggable using Irreversible Covalent K-Ras G12C Inhibitors




**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.

**SYNFACTS Contributors:** Dirk Trauner, Klaus-Peter Ruehmann
Synfacts 2021, 17(09), 1055 Published online: 18.08.2021
**DOI:** 10.1055/s-0040-1720791; **Reg-No.:** T08121SF



**Category**
Chemistry in Medicine and Biology

**Key words**
K-Ras
covalent inhibitors
acrylamides
Sotorasib