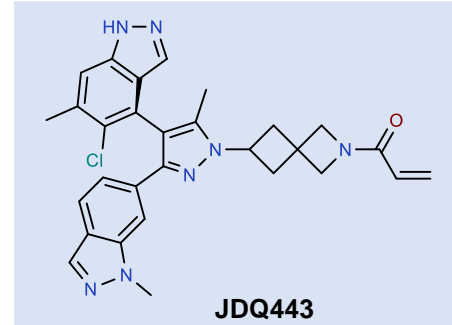
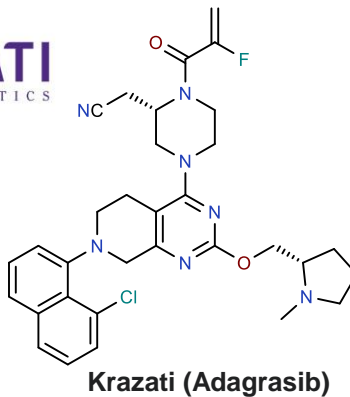
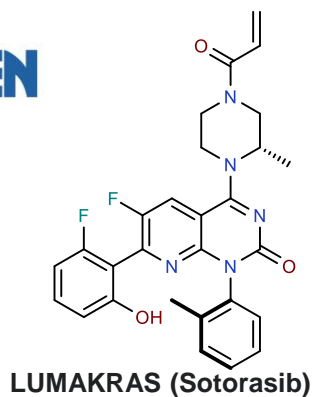


Background

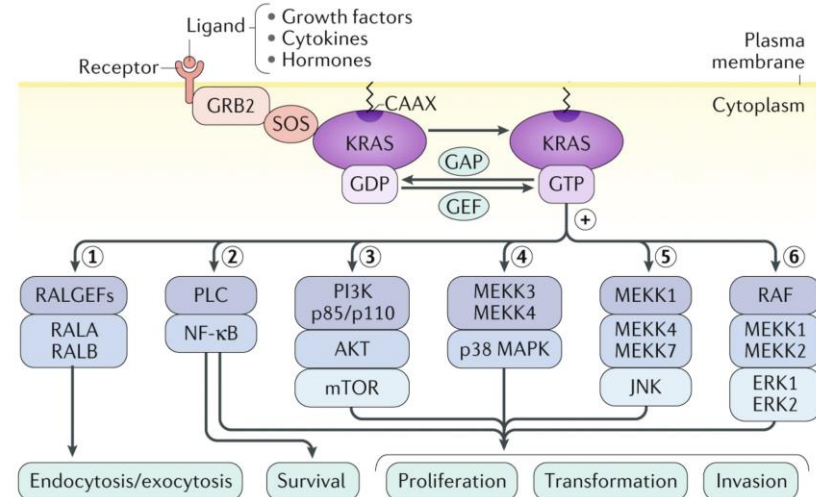
- Rapid emergence of tumor resistance via RAS pathway reactivation has been reported from clinical studies of covalent KRAS^{G12C} inhibitors
- JDQ443 is a novel covalent KRAS^{G12C} inhibitor.
- Structure highlight: Stable atropisomer; 5-methylpyrazole; Spiral azetidine linker; Acrylamide
- Under Phase Ib/II clinical trial (NCT04699188)



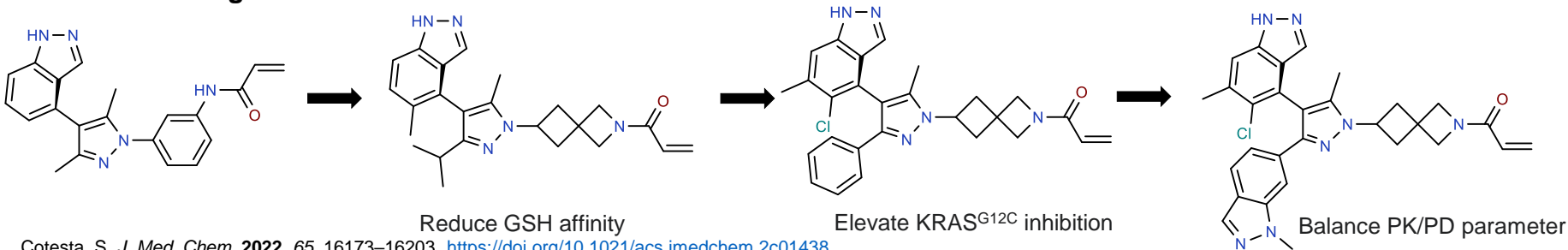
Other KRAS^{G12C} Inhibitor in the Market



Mechanism of Action



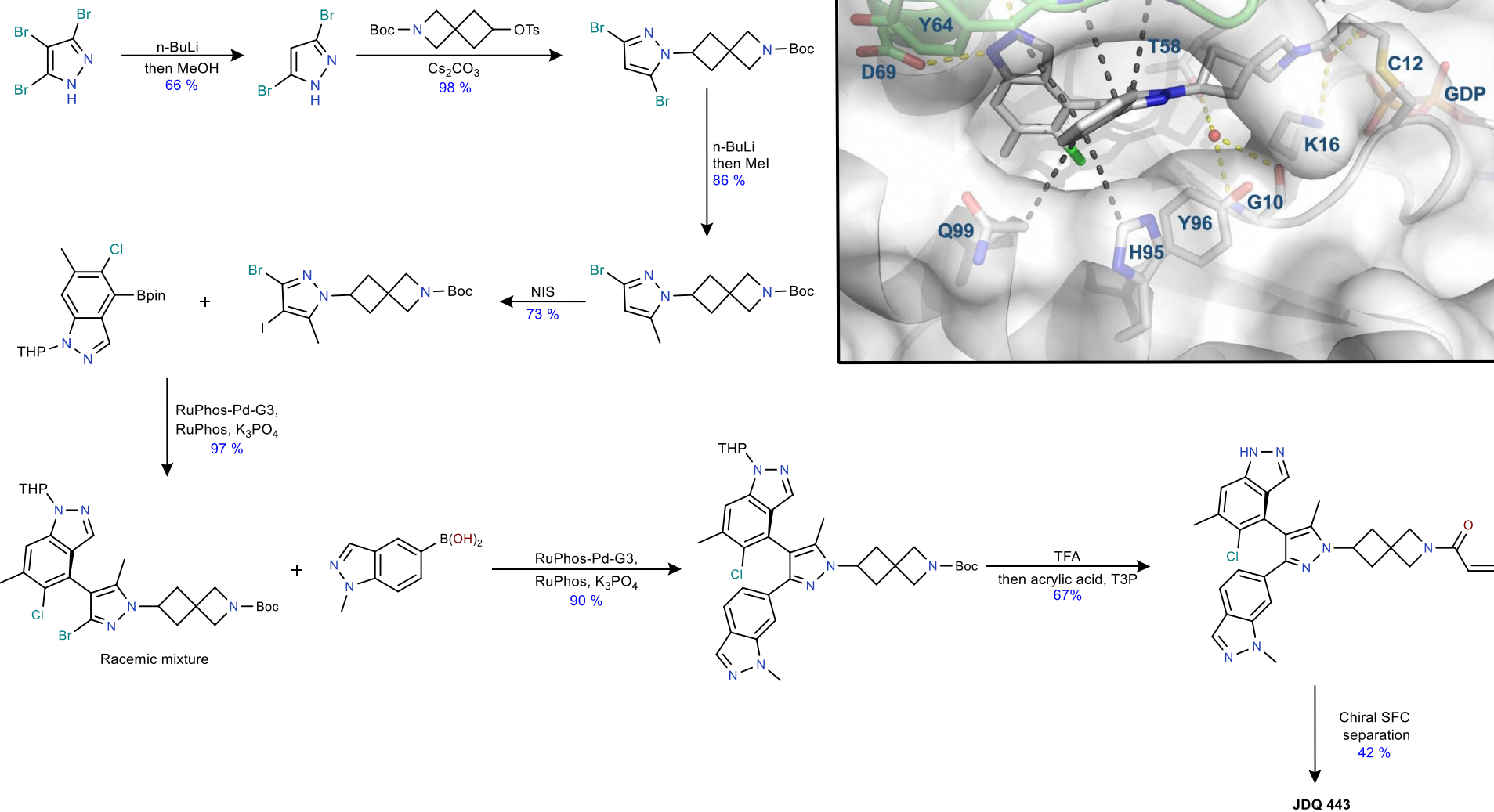
Structure Design



Cotesta, S. *J. Med. Chem.* **2022**, *65*, 16173–16203. <https://doi.org/10.1021/acs.jmedchem.2c01438>

Buscail, L. *Nat Rev Gastroenterol Hepatol.* **2020**, *17*, 153–168. <https://doi.org/10.1038/s41575-019-0245-4>

Synthesis



Cocrystal structure of KRAS^{G12C} with JDQ443

