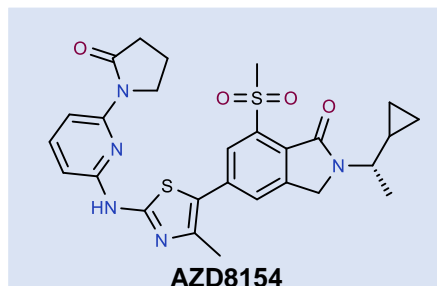


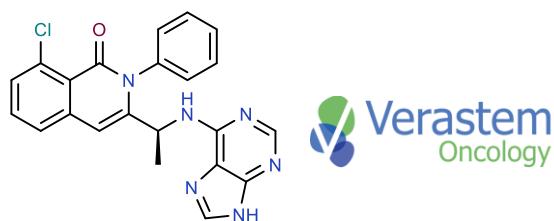
Background

- Dual PI3K γ δ dual Inhibitor for the Treatment of Allergic Asthma
- Long duration of action in the lung
- IH form reduce the systemic toxicity to body
- Phase IIa clinical trial : **NCT04187508**



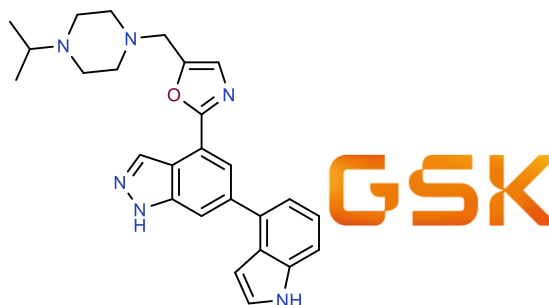
AstraZeneca 

Other PI3K Inhibitor in the Market or Promising in Clinical Trial



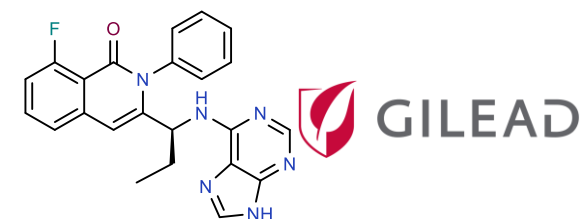
Duvelisib (Copiktra®)

- Indication : chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and follicular lymphoma
- Oral dual PI3K γ δ inhibitor
- Clinical trial of Asthma and Rheumatoid arthritis is hold because of safety issue



Nemoralisib

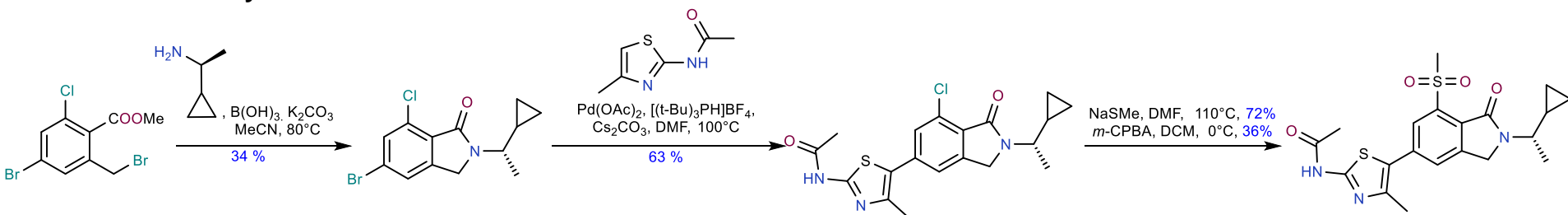
- Clinical trial showed promising data in chronic obstructive pulmonary disease (COPD)
- Inhaled PI3K δ inhibitor
- Under clinical trial for other inflammatory disease



Idelalisib (Zydelig®)

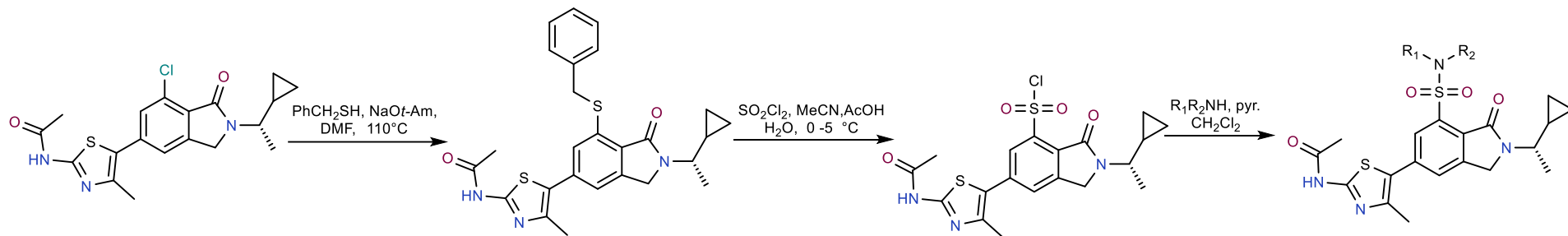
- Indication : CLL
- oral PI3K δ inhibitor

Core Structure synthesis

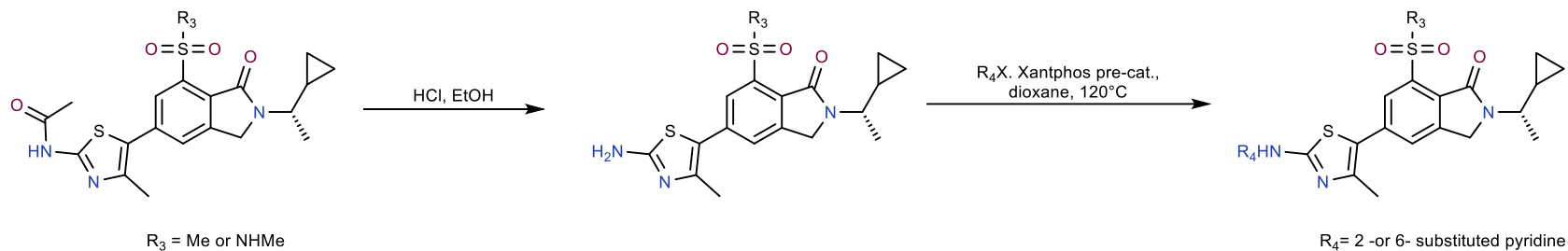


Pemberton, N. *J. Med. Chem.* **2018**, *61*, 5345–5441. <https://doi.org/10.1021/acs.jmedchem.8b00447>
 Perry, M. W. D. *J. Med. Chem.* **2021**, *64*, 8053-8075. <https://doi.org/10.1021/acs.jmedchem.1c00434>

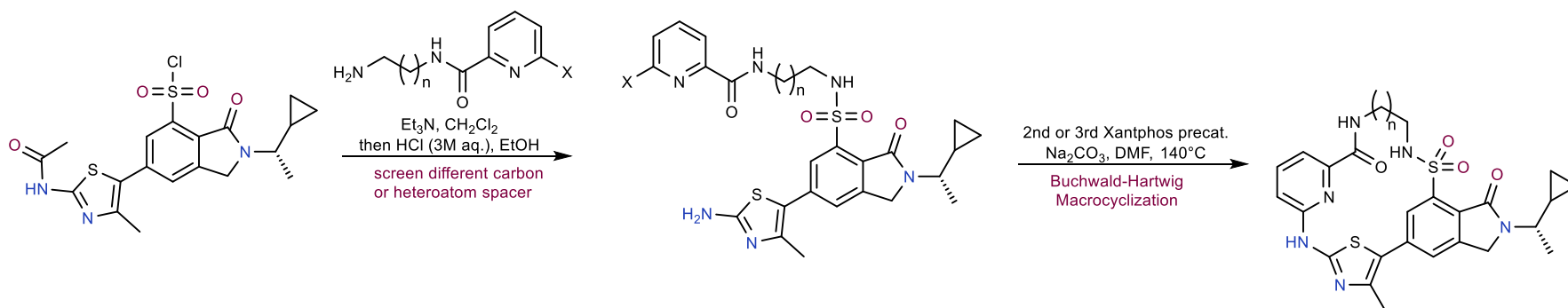
Sulfonamide SAR



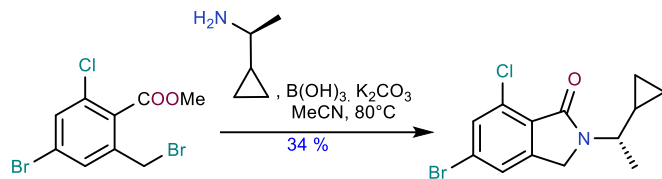
N-heterocycle SAR



Buchwald-Hartwig Reaction for Macrocyclization

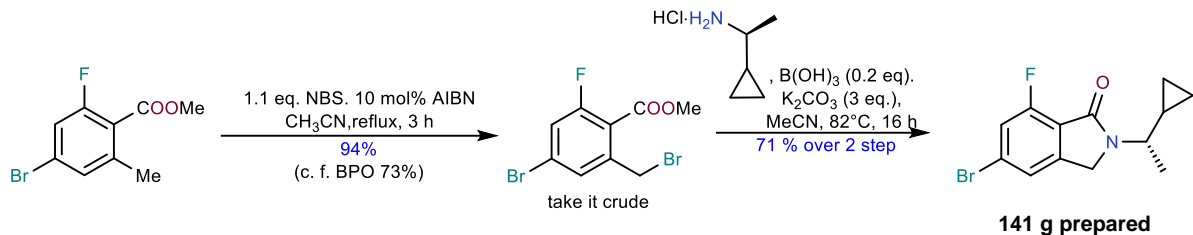


Med. Chem. Route to Key Isoindoline



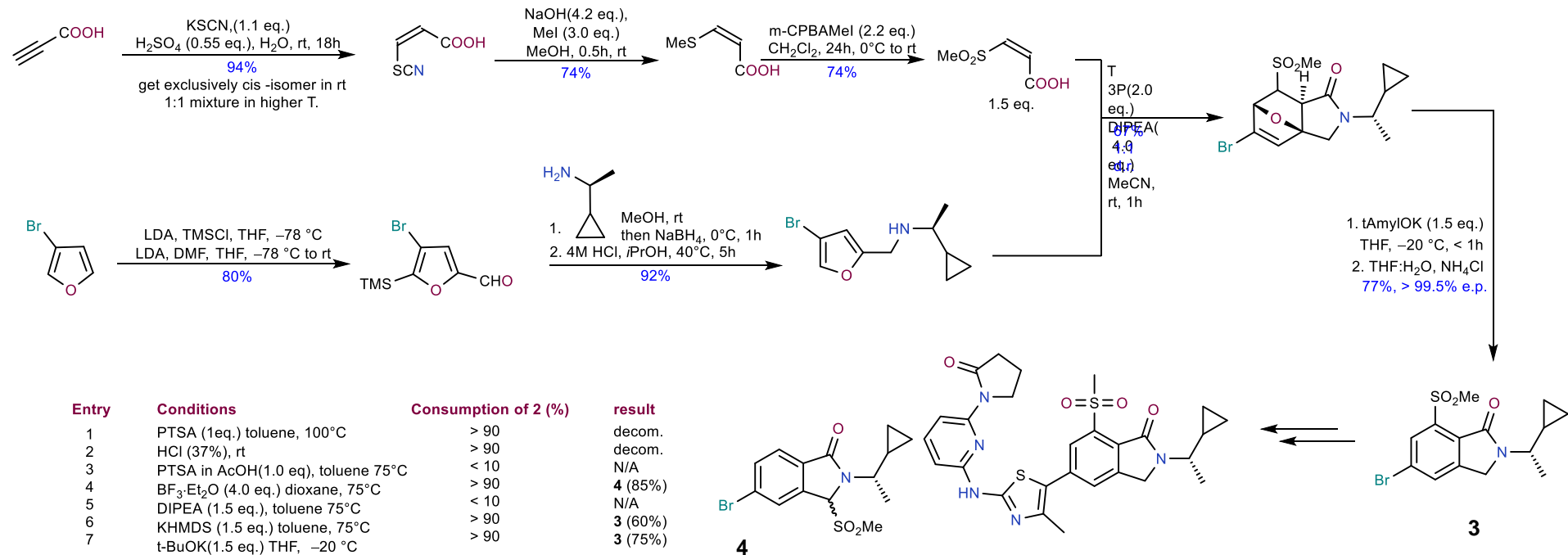
Perry, M. W. D. *J. Med. Chem.* **2021**, *64*, 8053-8075.
<https://doi.org/10.1021/acs.jmedchem.1c00434>

First Generation Process (200 g scale)



Jeffrey, J. L. *Org. Process Res. Dev.* **2022**, *26* 2915–2925. <https://doi.org/10.1021/acs.oprd.2c00240>

IMDA Process



Douglas, J. J. . *Org. Process Res. Dev.* ASAP. <https://doi.org/10.1021/acs.oprd.3c00507>