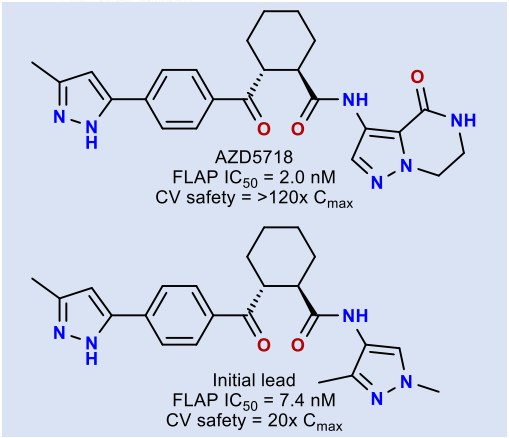
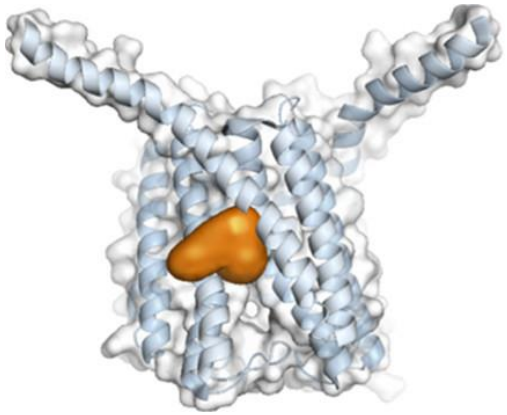
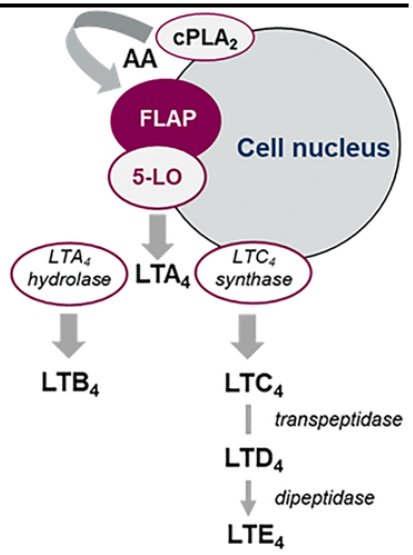
AZD5718



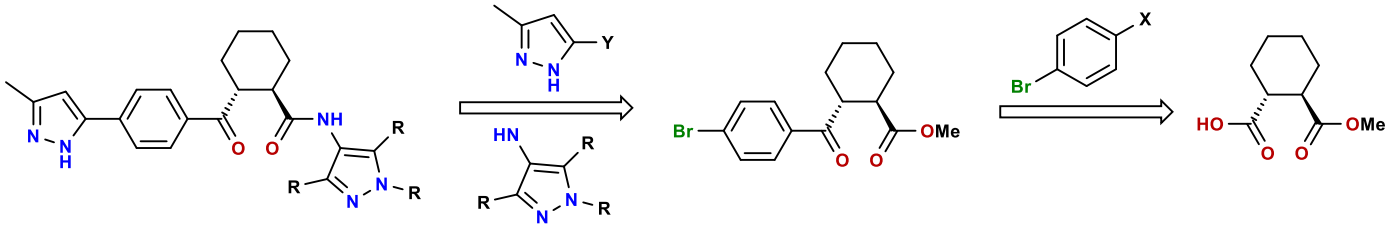
- AZD5718 is a 5-Lipoxygenase activating protein (FLAP) inhibitor and reduces the production of proinflammatory and vasoactive leukotriene
- Reduction in leukotriene production has a therapeutic benefit in the treatment of diseases that involve chronic inflammation such as coronary artery disease.
- The initial lead compound displayed potent FLAP inhibition, however, its preclinical studies showed that it led to increased heart rate, blood pressure, and cardiac contractility in dogs.
- Optimization of the structure to AZD5718 provided a more potent structure with none of the previously observed side effects and a >120x Cmax margin between NOAEL that is currently in phase 2 clinical trials for the treatment of coronary artery disease.



- Leukotrienes are a class of lipid mediators that have pathological effects in inflammatory diseases such as asthma and coronary artery disease.
- They are made through the 5-lipoxygenase pathway, which proceeds through the oxidation of arachidonic acid by 5-lipoxygenase (5-LO).
- The corresponding unstable intermediate leukotriene A_4 (LTA_4) is then converted to Leukotriene B_4 (LTB_4) and Leukotriene D_4 (LTD_4) through the action of a variety of peptidases
- The FLAP protein is critical for the production of leukotrienes, as it facilitates the transfer of arachidonic acid, released from membrane phospholipids, to the active site of 5-LO, initiating the production of leukotrienes.
- Therefore, inhibition of the FLAP protein can lead to reduction in leukotriene formation and ultimately provide a anti-inflammatory effect.
- FLAP inhibitors have been studied in human trials for inflammatory based diseases before, however they did not pass phase 2 trials due to safety concerns, low efficacy or suboptimal ADME properties.



Retrosynthesis:



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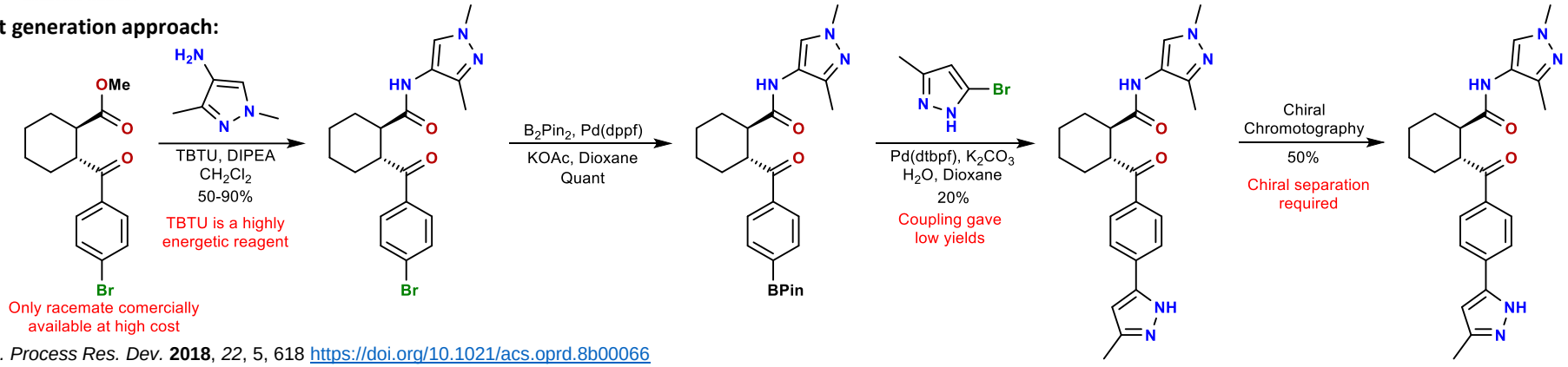
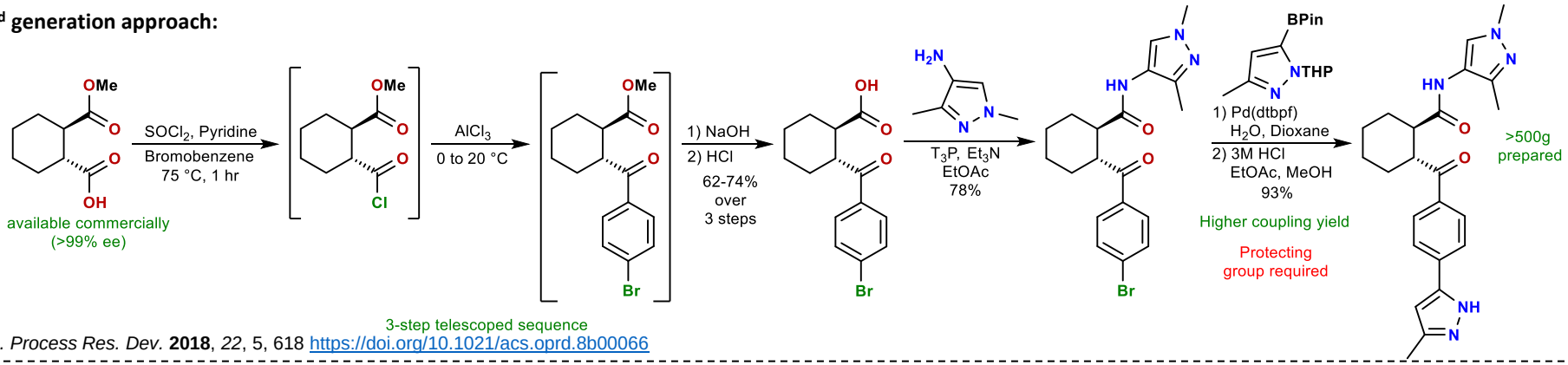
AZD5718

1st generation approach:



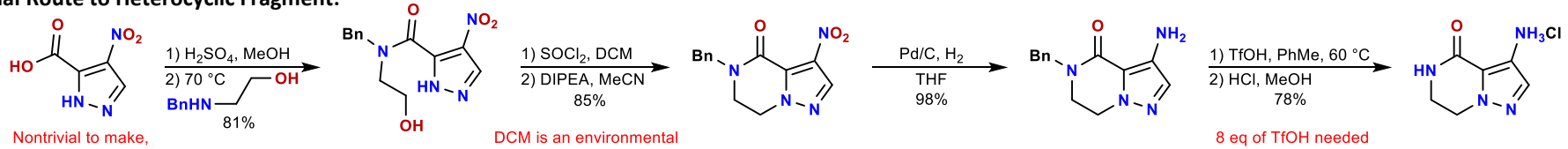
Org. Process Res. Dev. **2018**, *22*, 5, 618 https://doi.org/10.1021/acs.oprd.8b00066

2nd generation approach:

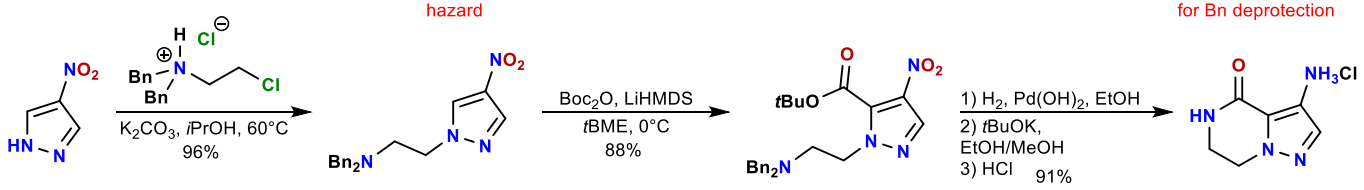


Org. Process Res. Dev. **2018**, *22*, 5, 618 https://doi.org/10.1021/acs.oprd.8b00066

Initial Route to Heterocyclic Fragment:



Process Route:



Org. Process Res. Dev. **2021**, *in press* https://doi.org/10.1021/acs.oprd.0c00533