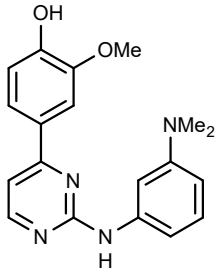
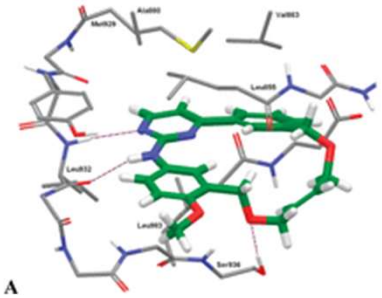
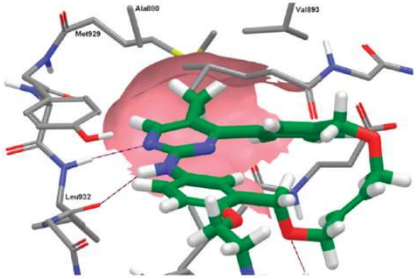
Pacritinib (SB1518)

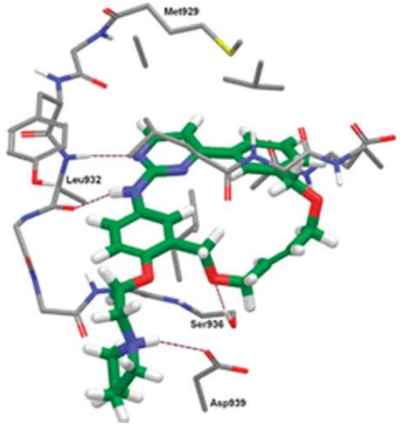
S*BIO™

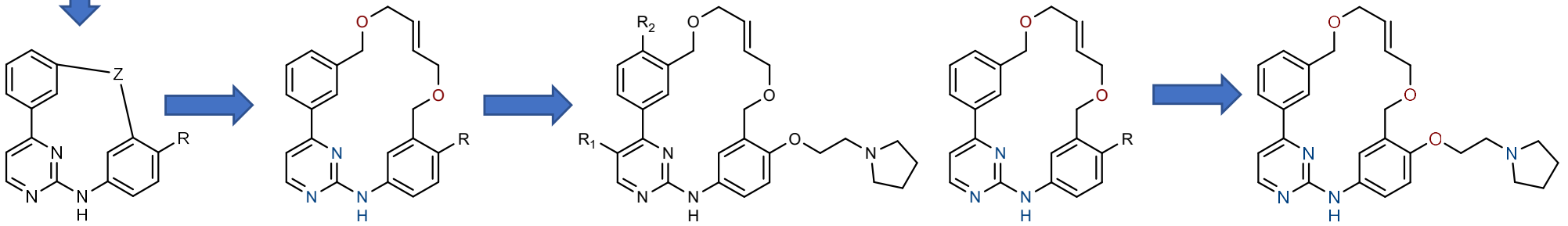
- Inhibits Janus kinase 2 (JAK2) and Fms-like tyrosine kinase 3 (FLT3)
- Approved in February 2022 for treatment of primary and secondary myelofibrosis (MF) in adult patients w/ significantly reduced platelet counts (< 50 x $10^9/L^2$)
  - Provides treatment option for MF patients with severe thrombocytopenia (occurs in ~1/3 of MF patients and carries a poor prognosis)
  - In 2016, the FDA placed a full clinical hold on pacritinib due to concerns over excess deaths and cardiac and hemorrhagic complications in the preliminary results of the PERSIST-1 phase 3 study
- taken twice daily (200 mg)



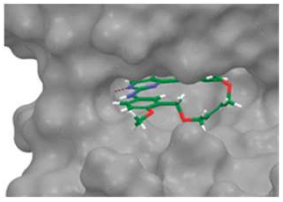








R = OH, OMe



R_1 = Me, R_2 = H
R_1 = H, R_2 = OMe

R =

SAR of aryl rings
Increase solubility

Pacritinib

Kinase	IC_{50} (nM ± s.d.)	Selectivity vs JAK2
JAK1	1280 ± 370	56
JAK2	23 ± 6	1.0
JAK2 (V617F)*	19	0.8
JAK3	520 ± 110	23
TYK2	50 ± 6	2.2
FLT3	22 ± 6	1.0
FLT3 (D835Y)*	6	0.3

"however, these rather ubiquitous pyrimidine-based motifs are heavily patented with very narrow possibilities for developing proprietary compounds"

Leukemia **2011**, *25*, 1751. https://doi.org/10.1038/leu.2011.148 *J. Med. Chem.* **2011**, *54*, 4638. https://doi.org/10.1021/jm200326p

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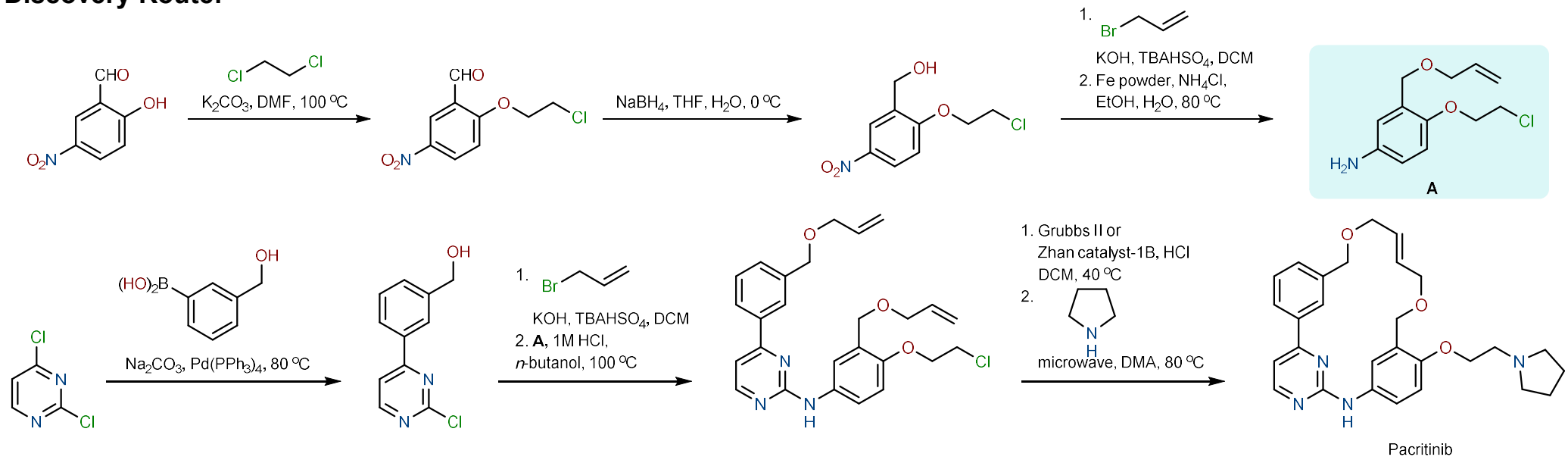
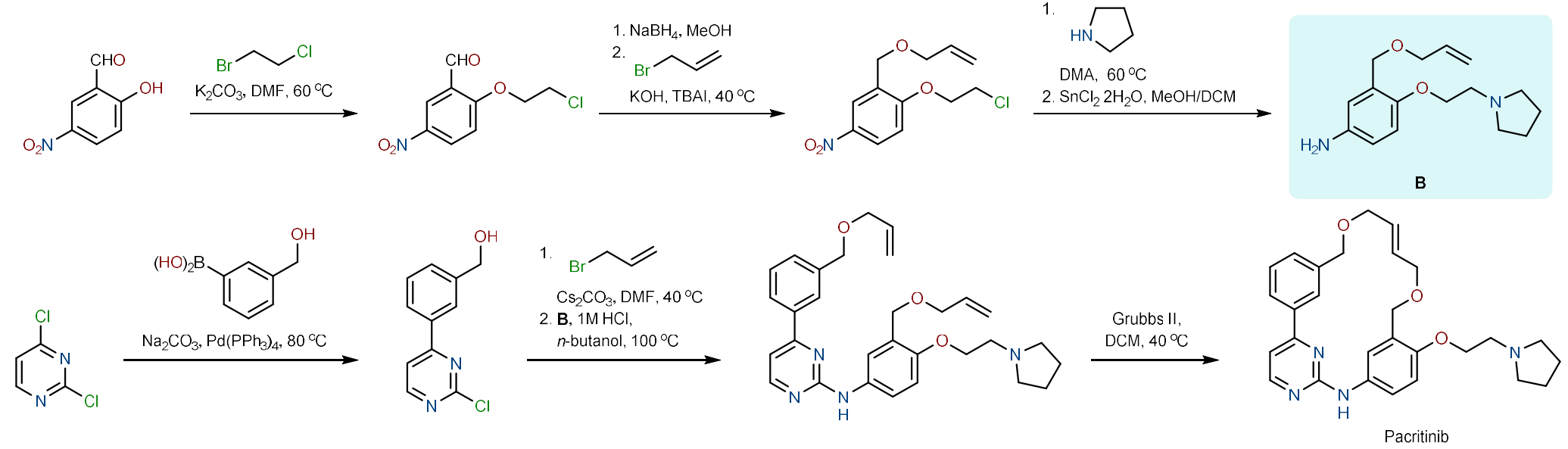
Discovery Route:



Patent Route:



WO2007058627A1