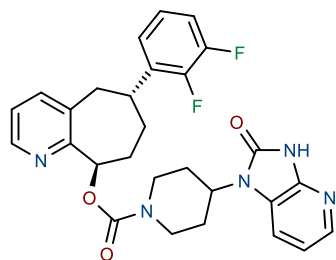
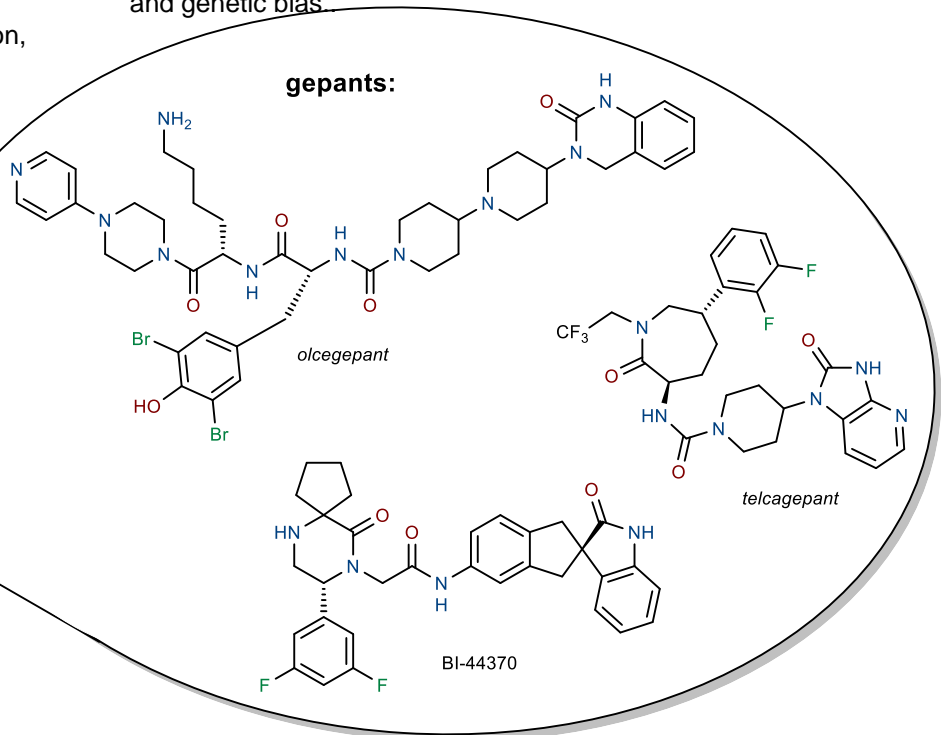
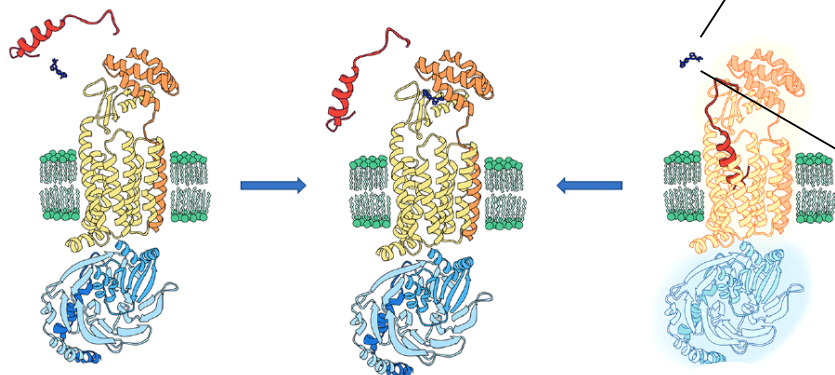
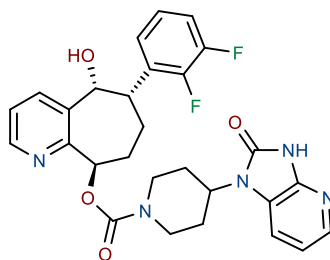


- Calcitonin gene-related peptide (CGRP) is a 37 amino acid neuropeptide (shown below in orange)
- CGRP has been shown to release during migraines, binding to CGRP receptors (trans-membrane protein shown below).
- Early treatments for migraines (triptans), focus action on vasculature dilation, posing serious cardiotoxicity risks and are contraindicated in patients with preexisting conditions.
- CGRP acts on receptors on A $\delta$ -fiber sensory neurons involved in pain perception and satellite glial cells that modulate pain sensitivity and transmission.
- Elevated levels of CGRP may distort normal pain signaling .
- The trigeminal ganglion is outside the BBB, CGRP receptors represent a valuable target, and synthesized CGRP receptor antagonists are called gepants.
- Rimegepant is a newly FDA-approved gepant.
- Migraine attacks are typically characterized by recurrent headaches lasting 4-72 hours.
- It is a leading cause of lost productivity worldwide with strong gender and genetic bias.



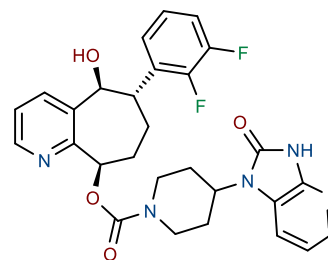
BMS-846372  
CGRP-R Ki = 0.070 nM  
high crystallinity  
low aqueous solubility

small, "helpfully polar" groups introduced



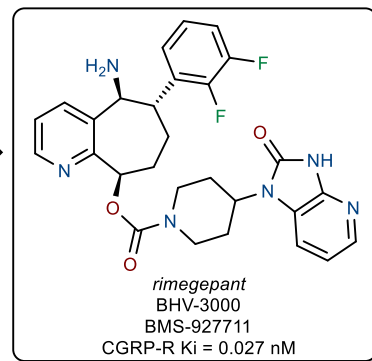
CGRP-R Ki = 4.3 nM

or



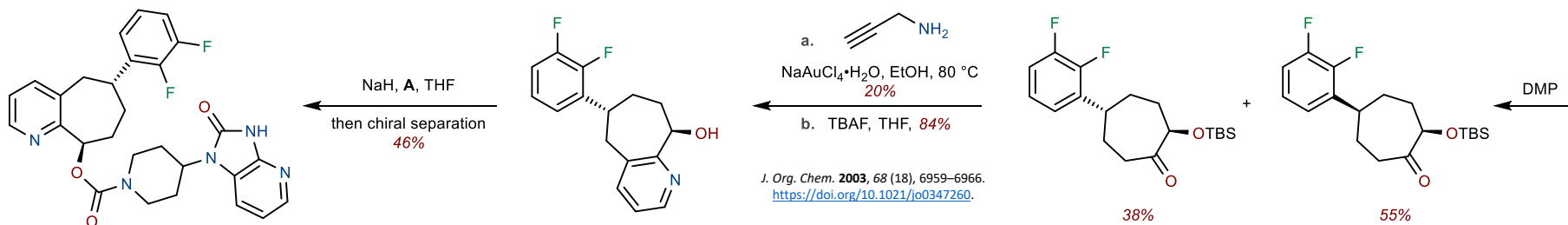
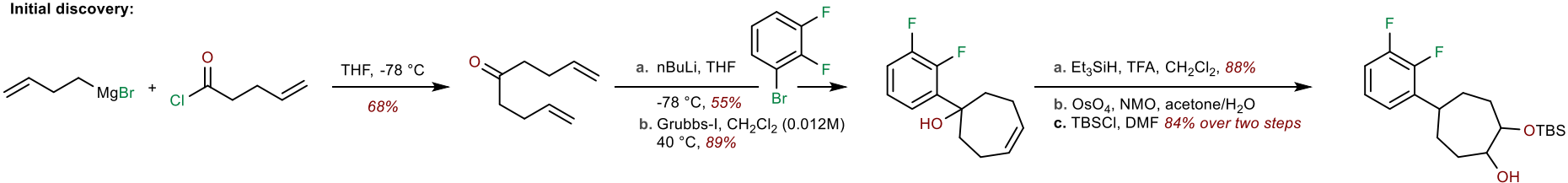
CGRP-R Ki = 0.081 nM

Encouraging initial studies followed by introduction of amine



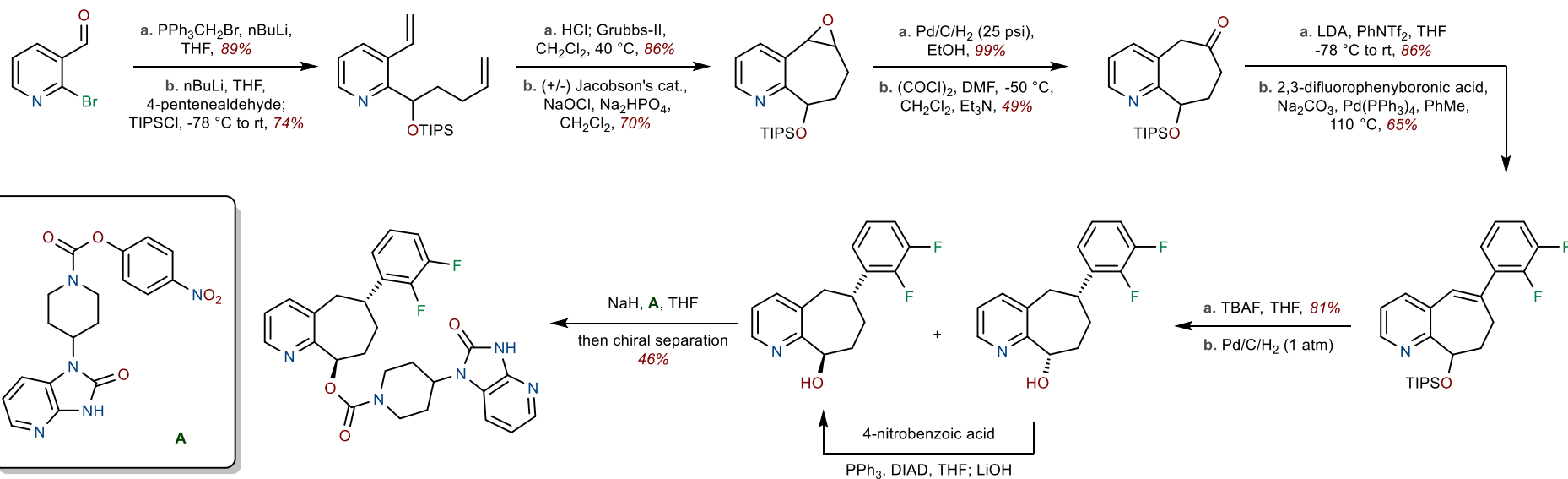
*rimegepant*  
BHV-3000  
BMS-927711  
CGRP-R Ki = 0.027 nM

**Initial discovery:**



BMS-846372

**Second Synthesis:**



A

**Final Route:**

