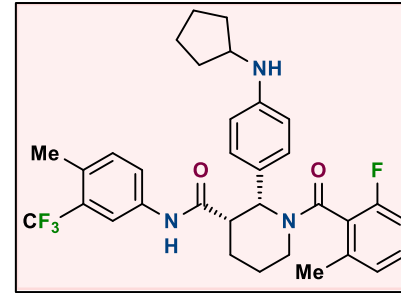


Avacopan

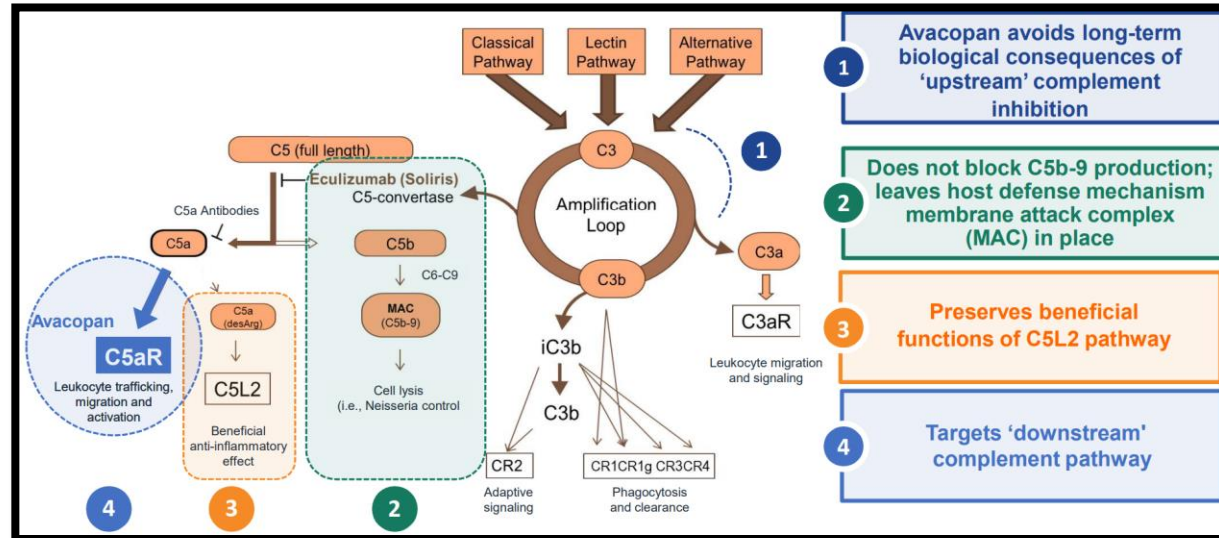
- The initial patent by ChemoCentryx was filed in 2011 as a complement C5a receptor antagonist, and cytochrome P450 3A4 inhibitor for the treatment of anti-neutrophil cytoplasmic autoantibody-associated (ANCA) vasculitis.
- The drug was FDA approved in the United States in October of 2021.
- It is considered a first-in-class drug as it was the only FDA approved orally available complement C5a receptor inhibitor at its time of approval.



Pingchen, F. *C5aR ANTAGONISTS*: 2011. No. US 2011275639 A1

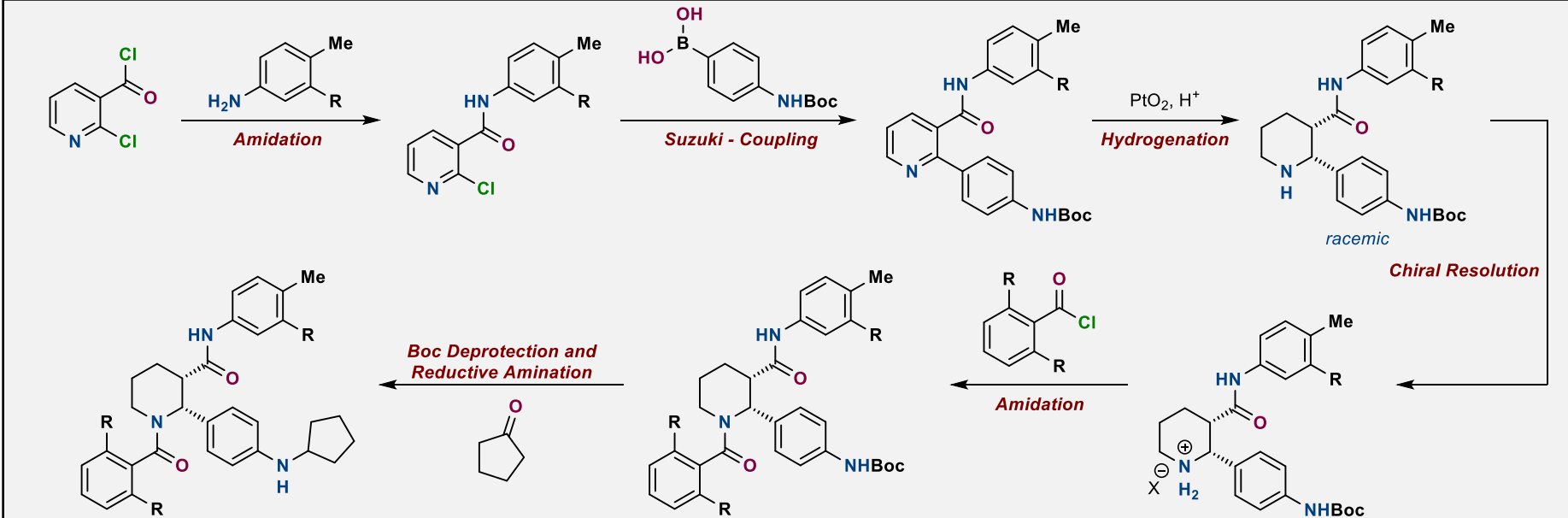
Mechanism of Action

- ANCA-associated vasculitis encompasses a group of disease which are characterized by the destruction and inflammation of small and medium vessels by the attack of the body's own neutrophils.
- Generally, in ANCA-associated vasculitis, there is a loss of tolerance and development of autoantibodies, known as ANCA. After ANCA forms, it can lead to the activation of neutrophils through the binding of PR3 or MPO. This makes the neutrophils adhere to and penetrate the surface of small vessels and release inflammatory mediators such as reactive O₂, cytokines, and NETs. This triggers the alternative complement pathway, forming protein fragment C5a which recruits inflammatory cells by binding C5aR.
- In simpler terms, this disease results in a feedback loop where more neutrophils bind to vessels, releasing more inflammatory mediators, recruiting more neutrophils.

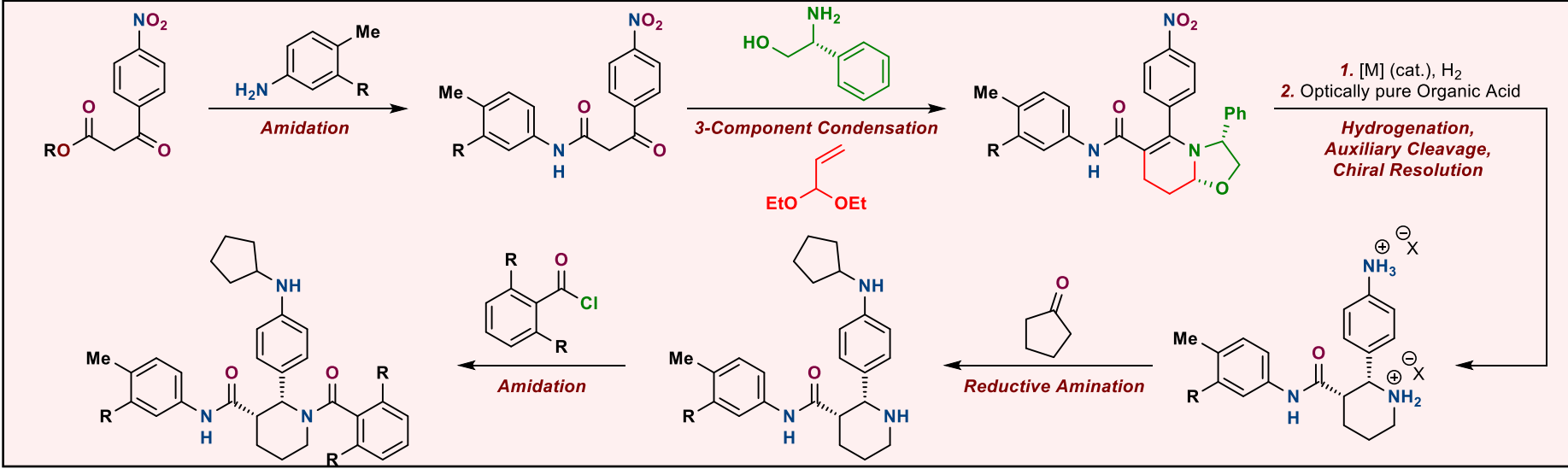


- Avacopan works by blocking C5a-induced upregulation of integrin alpha M on neutrophils, inhibiting C5a-mediated neutrophil activation and migration.
- **Ultimately, it works because it stops the binding of C5a to C5aR.**

General Route 1 Towards the C5a Compounds (Cross Coupling and Pyridine Hydrogenation)

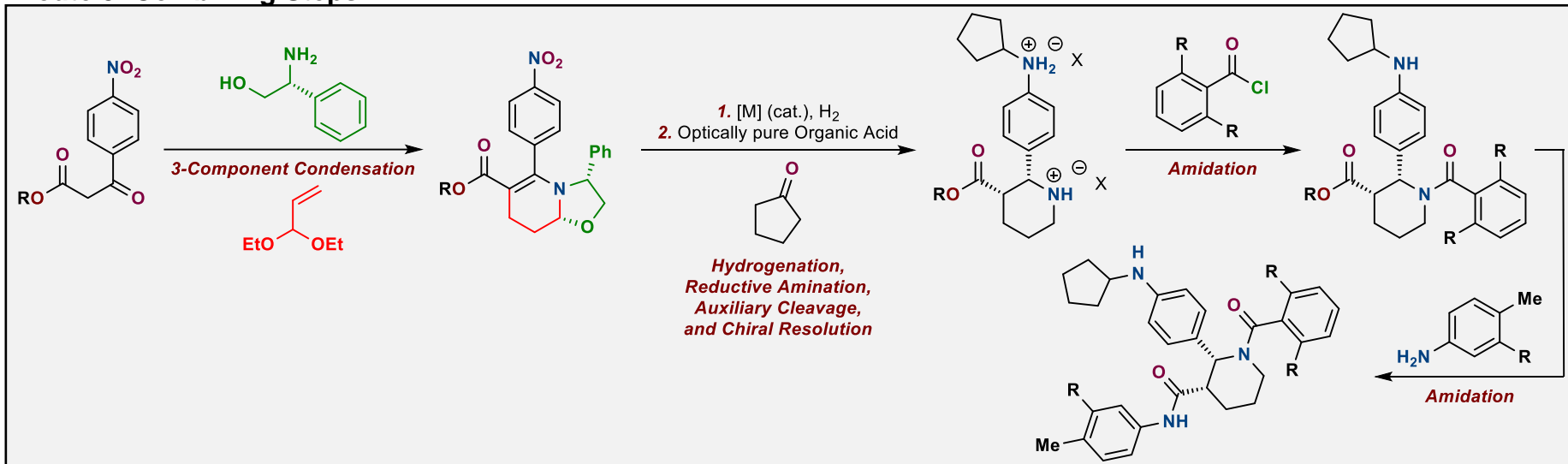


General Route 2 Towards the C5a Compounds (3 Component Coupling to Introduce Chirality and Hydrogenation)



Lee, A. Avacopan: First approval. *Drugs* **2022**, *82*, 79–85. Pub. No. US 2016/0090357 A1

Route 3: Combining Steps



Patented Synthesis of Avacopan

