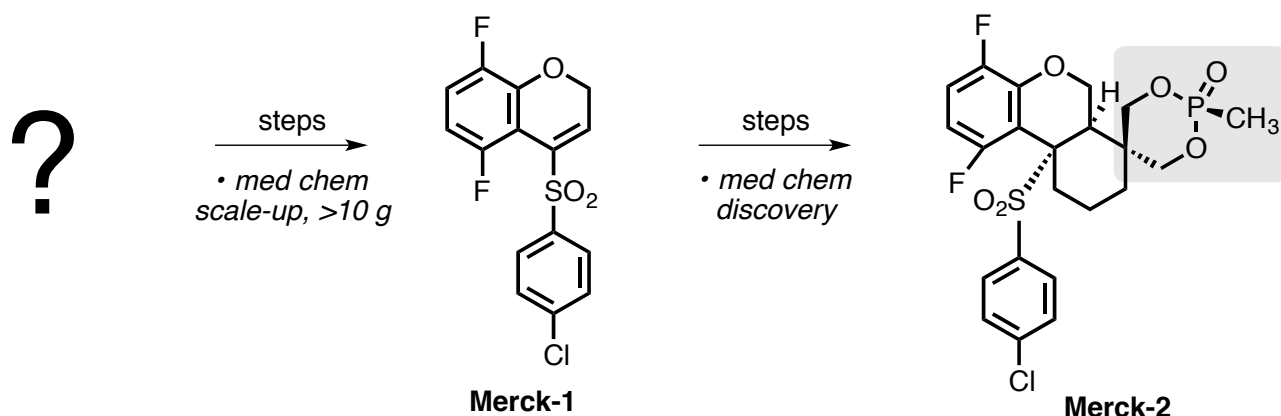


Merck recently disclosed a series of γ -secretase inhibitors (GSIs) that were assessed in a nontransgenic animal model of Alzheimer's disease, demonstrating reduction of amyloid- β in the central nervous system after acute oral dosing. Their most promising compound, **Merck-2**, elaborated upon a previous lead, **Merck-1**. **Merck-1** was the starting point in a medicinal chemistry discovery effort, leading to a new spirocyclic series, including **Merck-2**.

Part 1. Working in teams, propose a retrosynthesis and forward synthesis of **Merck-1** that is *concise and scalable*. All starting materials in your synthesis must be available from any reputable commercial supplier in ≥ 5 g scale.

Part 2. Propose a *medicinal chemistry route* to **Merck-2** and at least 3 other *spirocyclic* analogs (varying the group in gray) using reagents available from a reputable commercial supplier on any scale.

You are only permitted to use a computer to search emolecules.com or vendor websites for commercial availability.



Sund, C., *et al.* (Medivir AB) *Non-Nucleotide Reverse Transcriptase Inhibitors*, World Patent WO2005066131 A1, 21 July 2005.

Xu, R., *et al.*, *Bioorg. Med. Chem. Lett.* **2010**, 20, 2591–2596.

Zhao, Z. *et al.*, *J. Med. Chem.* **2015**, 58, 8806–8817.