

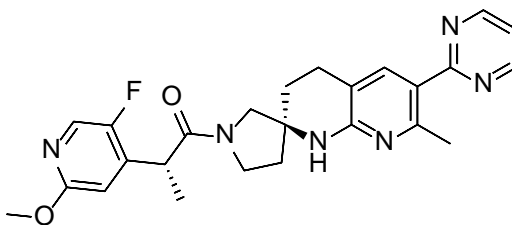
# SYNTHESIS OF MC4R ANTAGONIST PF-07258669: FROM FIRST SYNTHESIS TO DEVELOPMENT OF SCALABLE ROUTE FOR CLINICAL STUDIES

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*Cachexia*, or wasting syndrome, is characterized by loss of weight, muscle atrophy, fatigue and weakness accompanied by significant loss of appetite seen in geriatrics, patients with cancer and other diseases. Inhibition of central MC4R signaling is expected to increase food intake in cachectic patients with underlying chronic disease, leading to increased body weight and functional lean mass. Recently Pfizer has disclosed the discovery of MC4R antagonist PF-07258669 (**1**), possessing a spirocyclic core to optimize MC4R potency. This novel spirocyclic core provides a potency boost through locking in the bioactive conformation; chiral amide provides modulation of properties with improvements in potency through introduction of chiral methyl. This presentation will describe the evolution of synthetic routes to PF-07258669 from the first racemic synthesis to the robust optimized route that delivered hundreds-of-grams of **1** that supplied material to support multiple pre-clinical studies. The challenges encountered and the solutions identified while tackling the synthesis of the novel spirocyclic core and chiral amide will be presented. The development of two separate biocatalytic transformations that set both chiral centers in the molecule in high chiral purity will be described. Additionally, the presentation will show the optimization of sequence consisting of Curtius rearrangement in flow, Wittig olefination and intramolecular Buchwald cyclization to synthesize a key fragment. Finally, the endgame required development of a safe and high-yielding borylation/Suzuki reaction and employed amidation conditions that avoid epimerization. This synthetic route consisting of total of 25 synthetic steps (15 linear) delivered API against tight deadlines.



PF-07258669 (**1**)